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

(57) Abrégé/Abstract:
This invention relates to methods and compositions for treating central nervous system (CNS) disorders with cognitive impairment. In particular, it relates to the use of inhibitors of synaptic vesicle glycoprotein 2A (SV2A), alone or in combination with valproate, in treating central nervous system (CNS) disorders with cognitive impairment 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, amyotrphic lateral sclerosis and cancer-therapy-related cognitive impairment.

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

(57) Abstract: This invention relates to methods and compositions for treating central nervous system (CNS) disorders with cognitive impairment. In particular, it relates to the use of inhibitors of synaptic vesicle glycoprotein 2A (SV2A), alone or in combination with valproate, in treating central nervous system (CNS) disorders with cognitive impairment 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 (aMCl), Age- Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, amyotrphic lateral sclerosis and cancer-therapy-related cognitive impairment.

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METHODS AND COMPOSITIONS FOR IMPROVING COGNITIVE FUNCTION

Field of the Invention

[0001] This invention relates to methods and compositions for treating central nervous system (CNS) disorders with cognitive impairment. In particular, it relates to the use of inhibitors of synaptic vesicle glycoprotein 2A (SV2A), alone or in combination with valproate, in treating central nervous system (CNS) disorders with cognitive impairment 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, amyotrphic lateral sclerosis and cancer-therapy-related cognitive impairment.

Background of the Invention

[0002] Cognitive ability may decline as a normal consequence of aging or as a consequence of a CNS disorder.

[0003] 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] Other central nervous system (CNS) disorders, such as dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS) and cancer-therapy-related cognitive impairment, are also associated with cognitive impairment.

[0006] There is, therefore, a need for effective treatment for central nervous system (CNS) disorders with cognitive impairment and to improve cognitive function in patients diagnosed with age-related cognitive impairment, MCI, amnestic MCI, AAMI, ARCD, dementia, AD, prodromal AD, PTSD, schizophrenia, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, and similar central nervous system (CNS) disorders with cognitive impairment or at risk of developing them.

Summary of the Invention

[0007] In accordance with a first aspect of the present invention, there is provided a method for treating 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 a central nervous system (CNS) disorder with cognitive impairment, or at risk thereof, the method comprising the step of administering to said subject a therapeutically effective amount of an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof. In some embodiments of this aspect of the invention, the methods 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 said CNS disorder with cognitive impairment 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 said CNS disorder with cognitive impairment in said subject.

[0008] In some embodiments of this aspect of the invention, the CNS disorder with cognitive impairment 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 this aspect of the invention, the MCI is amnestic MCI. In some embodiments of this aspect of the invention, the CNS disorder with cognitive impairment is dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS) or cancer-therapy-related cognitive impairment. In one embodiment of this aspect of the invention, the subject that suffers such a CNS disorder or cognitive impairment is a human patient.

[0009] The SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof that is useful in the methods and compositions of this aspect of the invention include those disclosed in, for example, United States (U.S.) Patent Application 12/580,464, 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 thereof may be used in the methods and compositions of this aspect of the invention. In other embodiments, the SV2A inhibitor is selected from the group of SV2A inhibitors referred to in International Patent Applications WO2010/144712; WO2010/002869; WO2008/132139; WO2007/065595; WO2006/128693; WO2006/128692; WO2005/054188; WO2004/087658; WO2002/094787; WO2001/062726; U.S. Patents 7,465,549; 7,244,747; 5,334,720; 4,696,943; 4,696,942; U.S. Patent Application Publication Numbers 20090312333; 20090018148; 20080081832; 2006258704; and UK Patent Numbers 1,039,113; and 1,309,692 or their pharmaceutically acceptable salts, hydrates, solvates, or polymorphs. 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 thereof. In other embodiments, the SV2A inhibitor is brivaracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof. In other embodiments, the SV2A inhibitor is seletracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0010] In other embodiments of this aspect of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof can be administered at doses as disclosed, for example, in 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 other embodiments of this aspect of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is administered every 12 or 24 hours at a daily dose of about 0.1 to 0.2 mg/kg, or about 0.01 to 2.5 mg/kg, or about 0.1 to 2.5 mg/kg, or about 0.4 to 2.5 mg/kg, or about 0.6 to 1.8 mg/kg, or about 0.04 to 2.5 mg/kg, or about 0.06 to 1.8 mg/kg, or about 2.0 to 4.0 mg/kg, or about 2.0 to 3.0 mg/kg, or about 3.0 to 4.0 mg/kg, or about 0.2 to 0.4 mg/kg, or about 0.2 to 0.3 mg/kg, or about 0.3 to 0.4 mg/kg, or about 0.001 - 5 mg/kg, or about 0.001 - 0.5 mg/kg, or about 0.01 - 0.5 mg/kg.

[0011] In accordance with a second aspect of the present invention, there is provided a method for treating 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 a central nervous system (CNS) disorder with cognitive impairment, or at risk thereof, the method comprising the step of administering to said subject a therapeutically effective amount of an SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate, or polymorph in combination with valproate or an analog, derivative or pharmaceutically acceptable

salt thereof. In some embodiments of this aspect of the invention, the methods 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 said CNS disorder with cognitive impairment 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 said CNS disorder with cognitive impairment in said subject.

[0012] In some embodiments of this aspect of the invention, the SV2A inhibitor and/or valproate 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.

[0013] In some embodiments of this aspect of the invention, the CNS disorder with cognitive impairment 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 this aspect of the invention, the MCI is amnestic MCI. In some embodiments of this aspect of the invention, the CNS disorder with cognitive impairment is dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia or cancer-therapy-related cognitive impairment. In one embodiment, the subject that suffers such cognitive impairment is a human patient.

[0014] The SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof that is useful in the methods and compositions of this aspect of the invention include those disclosed in, for example, United States (U.S.) Patent Application 12/580,464, 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. However, any SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof may be used in the methods

and compositions of this aspect of the invention. In other embodiments, the SV2A inhibitor is selected from the group of SV2A inhibitors referred to in International Patent Applications WO2010/144712; WO2010/002869; WO2008/132139; WO2007/065595; WO2006/128693; WO2006/128692; WO2005/054188; WO2004/087658; WO2002/094787; WO2001/062726; U.S. Patents 7,465,549; 7,244,747; 5,334,720; 4,696,943; 4,696,942; U.S. Patent Application Publication Numbers 20090312333; 20090018148; 20080081832; 2006258704; and UK Patent Numbers 1,039,113; and 1,309,692 or their pharmaceutically acceptable salts, hydrates, solvates, or polymorphs. 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 thereof. In other embodiments, the SV2A inhibitor is brivaracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof. In other embodiments, the SV2A inhibitor is seletracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0015] In other embodiments of this aspect of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof that is administered in combination with valproate or its analog, derivative or pharmaceutically acceptable salt can be administered at doses as disclosed, for example, in 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 other embodiments of this aspect of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof that is administered in combination with valproate or its analog, derivative or pharmaceutically acceptable salt is administered every 12 or 24 hours at a daily dose of about 0.01 to 1 mg/kg, or about 0.001 to 1 mg/kg, or about 0.1 mg/kg to 5 mg/kg, or about 0.05 mg/kg to 0.5 mg/kg.

[0016] In certain embodiments of this aspect of the invention, valproate or an analog, derivative or pharmaceutically acceptable salt thereof that is administered in combination with the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is administered at a daily dose such that the subject maintains a blood total valproate level of 0.5 to 5 μg/ml plasma.

[0017] In other embodiments of this aspect of the invention, the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate, or polymorph and the valproate or its analog, derivative or pharmaceutically acceptable salt are administered simultaneously, or sequentially, or in a single formulation or in separate formulations packaged together. In other embodiments of this aspect of the invention, the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate, or polymorph and the valproate or its analog, derivative or pharmaceutically acceptable salt are administered via different routes. As used herein, "combination" includes administration by any of these formulations or routes of administration.

[0018] In accordance with a third aspect of the present invention, there is provided a pharmaceutical composition comprising a SV2A inhibitor or a pharmaceutically acceptable salt thereof. In certain embodiments of this aspect of the invention, the SV2A inhibitor is present in an amount of 0.07 – 60 mg, 0.07 – 350 mg, 25 – 60 mg, 25 – 125 mg, 50 – 250 mg, 5 – 140 mg, 0.7 – 180 mg, 125 – 240 mg, 3 - 50 mg, or 3 – 60 mg. . In other embodiments of this aspect of the invention, the SV2A inhibitor is present in an amount of 0.05 - 35 mg.

[0019] In accordance with a fourth aspect of this invention, there is provided a pharmaceutical composition comprising an SV2A inhibitor or a pharmaceutically acceptable salt thereof in combination with valproate or an analog, derivative or pharmaceutically acceptable salt thereof. In some embodiments of this aspect of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt thereof is present in an amount of 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 other embodiments, the amount of the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate,

solvate or polymorph thereof 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.

[0020] In accordance with a fifth aspect of the present invention, there is provided a method for treating 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 a central nervous system (CNS) disorder with cognitive impairment, or at risk thereof, the method comprising the step of administering to said subject a therapeutically effective amount of levetiracetam or a pharmaceutically acceptable salt thereof. In some embodiments of this aspect of the invention, the methods 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 said CNS disorder with cognitive impairment in said subject. In other embodiments of this aspect of invention, the methods alleviate, ameliorate, or slow the progression, of one or more symptoms associated with said CNS disorder with cognitive impairment in said subject.

[0021] In some embodiments of this aspect of the invention, the CNS disorder with cognitive impairment 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 this aspect of the invention, the MCI is amnestic MCI. In some embodiments of this aspect of the invention, the CNS disorder with cognitive impairment is dementia, Alzheimer's Disease (AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia or cancer-therapy-related cognitive impairment. In one embodiment, the subject that suffers such cognitive impairment is a human patient.

[0022] In certain embodiments of this aspect of the invention, the levetiracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is

administered every 12 or 24 hours at a daily dose of about 1 to 2 mg/kg, or about 0.1 to 2.5 mg/kg, or about 0.4 to 2.5 mg/kg, or about 0.6 to 1.8 mg/kg, or about 2.0 to 3.0 mg/kg, or about 3.0 to 4.0 mg/kg, or about 2.0 to 4.0 mg/kg, or about 0.1 - 5 mg/kg, or about 70 to 140 mg, or about 7 to 180 mg, or about 25 – 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 - 350 mg.

[0023] In certain embodiments of this aspect of the invention, the levetiracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is administered every 12 or 24 hours at a daily dose according to one of the daily dose ranges indicated as "+" listed in Table 1 or Table 2.

[0024] In accordance with a sixth aspect of the present invention, there is provided a method for treating 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 a central nervous system (CNS) disorder with cognitive impairment, or at risk thereof, the method comprising the step of administering to said subject a therapeutically effective amount of brivaracetam or a pharmaceutically acceptable salt thereof. In some embodiments of this aspect of the invention, the methods 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 said CNS disorder with cognitive impairment in said subject. In other embodiments of this aspect of invention, the methods alleviate, ameliorate, or slow the progression, of one or more symptoms associated with said CNS disorder with cognitive impairment in said subject.

[0025] In some embodiments of this aspect of the invention, the CNS disorder with cognitive impairment 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 this aspect of the

invention, the MCI is amnestic MCI. In some embodiments of this aspect of the invention, the CNS disorder with cognitive impairment is dementia, Alzheimer's Disease (AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia or cancer-therapy-related cognitive impairment. In one embodiment, the subject that suffers such cognitive impairment is a human patient.

[0026] In certain embodiments of this aspect of the invention, the brivaracetam or the pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is administered every 12 or 24 hours at a daily dose of about 0.1 to 0.2 mg/kg, or about 0.01 to 2.5 mg/kg, or about 0.04 to 2.5 mg/kg, or about 0.06 to 1.8 mg/kg, or about 0.2 to 0.4 mg/kg, or about 7 to 15 mg, or about 0.7 to 180 mg, or about 2.5 to 180 mg, or about 4.0 to 130 mg, or about 14 to 30 mg.

[0027] In certain embodiments of this aspect of the invention, the brivaracetam or the pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is administered every 12 or 24 hours at a daily dose of at least 0.1 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, or 2.0 mg; but no more than a daily dose of 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, or 35 mg. In other embodiments, the brivaracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is administered every 12 or 24 hours at a daily dose of at least 0.0015 mg/kg, 0.0075 mg/kg, 0.01 mg/kg, 0.015 mg/kg, 0.02 mg/kg, or 0.03 mg/kg; but no more than a daily dose of 0.5 mg/kg, 0.4 mg/kg, 0.3 mg/kg, 0.2 mg/kg, 0.15 mg/kg, 0.1 mg/kg, 0.05 mg/kg, or 0.04 mg/kg.

[0028] In certain embodiments of this aspect of the invention, the brivaracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is administered every 12 or 24 hours at a daily dose according to one of the daily dose ranges indicated as "+" listed in Table 3 or Table 4. For example, the brivaracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof may be administered every 12 or 24 hours at a daily dose of 0.1 - 35 mg, 0.5 - 35 mg, 0.75 - 35 mg, 1.0 - 35 mg, 1.5 - 35 mg, 2.0 - 35 mg, 0.1 - 30 mg, 0.1 - 25 mg, 0.1 - 20 mg, 0.1 - 15 mg, 0.1 - 10 mg, 0.1 - 5 mg, 0.1 - 2.5 mg, 0.0015 - 0.5 mg/kg, 0.0075 - 0.5 mg/kg, 0.01 - 0.5 mg/kg, 0.015 - 0.5 mg/kg, 0.02 - 0.5 mg/kg, 0.03 - 0.5 mg/kg, 0.0015 - 0.4 mg/kg, 0.0015 - 0.3 mg/kg, 0.0015 - 0.2 mg/kg,

0.0015 - 0.15 mg/kg, 0.0015 - 0.1 mg/kg, 0.0015 - 0.05 mg/kg, or 0.0015 - 0.04 mg/kg.

[0029] In accordance with a seventh aspect of the present invention, there is provided a method for treating 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 a central nervous system (CNS) disorder with cognitive impairment, or at risk thereof, the method comprising the step of administering to said subject a therapeutically effective amount of selectracetam or a pharmaceutically acceptable salt thereof. In some embodiments of this aspect of the invention, the methods 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 said CNS disorder with cognitive impairment in said subject. In other embodiments of this aspect of invention, the methods alleviate, ameliorate, or slow the progression, of one or more symptoms associated with said CNS disorder with cognitive impairment in said subject.

[0030] In some embodiments of this aspect of the invention, the CNS disorder with cognitive impairment 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 this aspect of the invention, the MCI is amnestic MCI. In some embodiments of this aspect of the invention, the CNS disorder with cognitive impairment is dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia or cancer-therapy-related cognitive impairment. In one embodiment, the subject that suffers such cognitive impairment is a human patient.

[0031] In certain embodiments of this aspect of the invention, the seletracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is administered every 12 or 24 hours at a daily dose of at least 0.1 mg, 0.5 mg, 0.75

mg, 1.0 mg, 1.5 mg, or 2.0 mg; but no more than a daily dose of 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, or 35 mg. In other embodiments, the seletracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is administered every 12 or 24 hours at a daily dose of at least 0.0015 mg/kg, 0.0075 mg/kg, 0.01 mg/kg, 0.015 mg/kg, 0.02 mg/kg, or 0.03 mg/kg; but no more than a daily dose of 0.5 mg/kg, 0.4 mg/kg, 0.3 mg/kg, 0.2 mg/kg, 0.15 mg/kg, 0.1 mg/kg, 0.05 mg/kg, or 0.04 mg/kg.

[0032] In certain embodiments of this aspect of the invention, the seletracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof is administered every 12 or 24 hours at a daily dose according to one of the daily dose ranges indicated as "+" listed in Table 5 or Table 6. For example, the seletracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof may be administered every 12 or 24 hours at a daily dose of 0.1 - 35 mg, 0.5 - 35 mg, 0.75 - 35 mg, 1.0 - 35 mg, 1.5 - 35 mg, 2.0 - 35 mg, 0.1 - 30 mg, 0.1 - 25 mg, 0.1 - 20 mg, 0.1 - 15 mg, 0.1 - 10 mg, 0.1 - 5 mg, 0.1 - 2.5 mg, 0.0015 - 0.5 mg/kg, 0.0075 - 0.5 mg/kg, 0.01 - 0.5 mg/kg, 0.015 - 0.5 mg/kg, 0.02 - 0.5 mg/kg, 0.03 - 0.5 mg/kg, 0.0015 - 0.4 mg/kg, 0.0015 - 0.3 mg/kg, 0.0015 - 0.2 mg/kg, 0.0015 - 0.15 mg/kg, 0.0015 - 0.1 mg/kg, 0.0015 - 0.05 mg/kg, or 0.0015 - 0.04 mg/kg.

Brief Description of the Drawings

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

[0034] **FIG. 2** depicts the effects of administering levetiracetam on the spatial memory retention of six aged-impaired rats (AI) in a Morris Water Maze (MWM) test. Three treatment conditions were employed: vehicle control, levetiracetam (5

mg/kg/day) and levetiracetam (10 mg/kg/day). The AI rats were trained for two consecutive days, with a one-time treatment prior to the training trials per day. 24 hours later, the AI rats were tested. The time the AI rats, 24 hours after treatment with the different conditions and two days of training, spent swimming in the target quadrant or the target annulus in a memory retention trial is used as a measure of spatial memory retention. The target quadrant refers to the quadrant of the maze (which is a circular pool) where the escape platform is placed during the training trials. The target annulus refers to the exact location of the escape platform during the training trials.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[0057] **FIG. 17A** shows the difference between the control (placebo) subjects and the aMCI subjects treated with placebo or with levetiracetam (125 mg twice a

day for two weeks) in their performance of the Verbal Paired Associates Test – Delayed Recall.

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

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

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

Detailed Description of the Invention

[0061] 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.

[0062] 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).

[0063] 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).

[0004] 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).

[0005] The singular forms "a," "an," and "the" include the plurals unless the context clearly dictates otherwise.

[0006] The term "including" is used to mean "including but not limited to". "Including" and "including but not limited to" are used interchangeably.

[0007] 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 of such agents may render them suitable as "therapeutic agents" in the methods and compositions of this invention.

[0008] 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).

[0009] "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.

[0071] 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. *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.

[0072] 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. Other tests known in the art may also be used to assess cognitive function, such as novel object recognition and odor recognition tasks.

[0073] 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.

[0074] "Promoting" cognitive function refers to affecting impaired cognitive function so that it more closely resembles the function of a normal, unimpaired subject. Cognitive function may be promoted to any detectable degree, but in humans preferably is promoted sufficiently to allow an impaired subject to carry out daily activities of normal life at the same level of proficiency as a normal, unimpaired subject.

[0075] 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 the same level of proficiency as an aged-matched normal, unimpaired subject or as a young adult subject.

[0076] "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.

[0077] "Improving" cognitive function includes promoting cognitive function and/or preserving cognitive function in a subject.

[0078] "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, unimpairmed 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).

[0079] "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 amestic MCI and non-amnestic MCI), Age-Associated Memory Impairment (AAMI), and Age-related Cognitive Decline (ARCD).

[0080] "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.

[0081] "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).

[0082] 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).

[0083] "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.).

[0084] "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.

[0085] 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.

[0086] Vascular dementia is caused by strokes. Symptoms overlap with those of AD, but without the focus on memory impairment.

[0087] 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.

[0088] 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.

[0089] "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.

[0090] "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.

[0091] "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.

[0092] "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.

[0093] "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 with CNS disorders with cognitive impairment, such as age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnestic MCI, dementia, Alzheimer's Disease (AD), prodromal AD, PTSD, schizophrenia, amyotrophic lateral sclerosis (ALS) or cancer therapy-related cognitive impairment. 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).

[0094] "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.

[0095] "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 absorbtion, 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.

[0096] 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.

[0097] As used herein, administration of an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof and valproate or an analog, derivative or pharmaceutically acceptable salt thereof "in combination" or "together" includes simultaneous administration and/or administration at different times, such as sequential administration. It also includes administration in a single formulation or in separate formulation packaged together.

[0098] The term "simultaneous administration," as used herein, means that the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate, or polymorph and valproate or its analog, derivative or pharmaceutically acceptable salt, are administered with a time separation of no more than about 15 minutes, and in some embodiments no more than about 10 minutes. When the drugs are administered simultaneously, the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate, or polymorph and valproate or its analog, derivative or pharmaceutically acceptable salt,, may be contained in the same dosage (e.g., a unit dosage form comprising both the SV2A inhibitor and the valproate) or in discrete dosages (e.g., the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate, or polymorph, is contained in one dosage form and the valproate or its analog, derivative or pharmaceutically acceptable salt, is contained in another dosage form).

[0099] The term "sequential administration" as used herein means that the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate, or polymorph are

valproate or its analog, derivative or pharmaceutically acceptable salt, are administered with a time separation of more than about 15 minutes, and in some embodiments more than about one hour, or up to 12 hours. Either the SV2A inhibitor or the valproate may be administered first. For sequential administration, he SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate, or polymorph, and valproate or its analog, derivative or pharmaceutically acceptable salt, may be contained in discrete dosage forms, optionally contained in the same container or package.

[0100] 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 a CNS disorder with cognitive impairment. 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.

[0101] "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.

[0102] "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.

[0103] "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.

[0104] 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 valproate. 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 valproate.

[0105] "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 compounds. The acid addition salt form of a compound that occurs in its free form as a base can be obtained by treating said free base form with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclic, salicylic, p- aminosalicylic, pamoic and the like. See, e.g., WO 01/062726.

Description of Methods of the Invention

[0106] The methods of this invention comprise administration of an SV2A inhibitor or a pharmaceutically acceptable salt thereof. The methods of this invention further comprise administration of an SV2A inhibitor or a pharmaceutically acceptable salt thereof in combination with administration of valproate or a pharmaceutically acceptable salt thereof. The agents or compounds of the SV2A inhibitor or the valproate and their pharmaceutically acceptable salts also include hydrates, solvates,

polymorphs, and prodrugs of those agents, compounds, and salts.

Methods of Assessing Cognitive Impairment

[0107] Animal models serve as an important resource for developing and evaluating treatments for CNS disorders with cognitive impairment. Features that characterize cognitive impairment in animal models typically extend to cognitive impairment in humans. Efficacy in such animal models is, thus, expected to be predictive of efficacy in humans. The extent of cognitive impairment in an animal model for a CNS disorder, and the efficacy of a method of treatment for said CNS disorder may be tested and confirmed with the use of a variety of cognitive tests.

[0108] A Radial Arm Maze (RAM) behavioral task is one example of a cognitive test, specifically testing spacial memory (Chappell *et al. Neuropharmacology* 37: 481-487, 1998). The RAM apparatus consists of, *e.g.*, eight equidistantly spaced arms. A maze arm projects from each facet of a center platform. A food well is located at the distal end of each arm. Food is used as a reward. Blocks can be positioned to prevent entry to any arm. Numerous extra maze cues surrounding the apparatus may also be provided. After habituation and training phases, spatial memory of the subjects may be tested in the RAM under control or test compound-treated conditions. As a part of the test, subjects are pretreated before trials with a vehicle control or one of a range of dosages of the test compound. At the beginning of each trial, a subset of the arms of the eight-arm maze is blocked. Subjects are allowed to obtain food on the unblocked arms to which access is permitted during this initial "information phase" of the trial. Subjects are then removed from the maze for a delay period, *e.g.*, a 60 second delay, a 15 minute delay, a one-hour delay, a two-hour delay, a six hour delay, a 24 hour delay, or longer) between the information phase and the subsequent "retention test," during which the barriers on the maze are removed, thus allowing access to all eight arms. After the delay period, subjects are placed back onto the center platform (with the barriers to the previously blocked arms removed) and allowed to obtain the remaining food rewards during this retention test phase of the trial. The identity and configuration of the blocked arms vary across trials. The number of "errors" the subjects make during the retention test phase is tracked. An error occurs in the

trial if the subjects entered an arm from which food had already been retrieved in the pre-delay component of the trial, or if it re-visits an arm in the post-delay session that had already been visited. A fewer number of errors would indicate better spatial memory. The number of errors made by the test subject, under various test compound treatment regimes, can then be compared for efficacy of the test compound in treating CNS disorders with cognitive impairment.

[0109] Another cognitive test that may be used to assess the effects of a test compound on the cognitive impairment of a CNS disorder model animal is the Morris water maze. A water maze is a pool surrounded with a novel set of patterns relative to the maze. The training protocol for the water maze may be based on a modified water maze task that has been shown to be hippocampal-dependent (de Hoz *et al.*, *Eur. J. Neurosci.*, 22:745-54, 2005; Steele and Morris, *Hippocampus* 9:118-36, 1999). The subject is trained to locate a submerged escape platform hidden underneath the surface of the pool. During the training trial, a subject is released in the maze (pool) from random starting positions around the perimeter of the pool. The starting position varies from trial to trial. If the subject does not locate the escape platform within a set time, the experimenter guides and places the subject on the platform to "teach" the location of the platform. After a delay period following the last training trial, a retention test in the absence of the escape platform is given to assess spatial memory. The subject's level of preference for the location of the (now absent) escape platform, as measured by, *e.g.*, the time spent in that location or the number of crossings of that location made by the mouse, indicates better spatial memory, *i.e.*, treatment of cognitive impairment. The preference for the location of the escape platform under different treatment conditions, can then be compared for efficacy of the test compound in treating CNS disorders with cognitive impairment.

[0110] 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); or the Benton Visual Retention Test. *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. Another example of a cognitive test in humans is the explicit 3-alternative forced choice task. In this test, subjects are presented with color photographs of common objects consisting of a mix of three types of image pairs: similar pairs, identical pairs and unrelated foils. The second of the pair of similar objects is referred to as the "lure". These image pairs are fully randomized and presented individually as a series of images. Subjects are instructed to make a judgment as to whether the objects seen are new, old or similar. A "similar" response to the presentation of a lure stimulus indicates successful memory retrieval by the subject. By contrast, calling the lure stimulus "old" or "new" indicates that correct memory retrieval did not occur.

[0111] 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

[0112] 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 or polymorth thereof, alone or in combination with valproate or an alalog, derivative or pharmaceutically acceptable salt thereof. 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 age-related cognitive impairment. 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.

[0113] 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).

[0114] 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.

[0115] 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.

[0116] 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

[0117] This invention also provides methods and compositions for treating dementia using an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorth thereof, alone or in combination with valproate or an alalog, derivative or pharmaceutically acceptable salt 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.

[0118] 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.

[0119] 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

[0120] 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 polymorth thereof, alone or in combination with valproate or an alalog, derivative or pharmaceutically acceptable salt 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.

[0121] 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).

[0122] 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.

[0123] 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.

[0124] 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

[0125] This invention additionally provides methods and compositions for treating schizophrenia using an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorth thereof, alone or in combination with valproate or an alalog, derivative or pharmaceutically acceptable salt 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. In certain embodiments, treatment comprises alleviation, amelioration or slowing the progression, of one or more symptoms associated with schizophrenia. 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 schizophrenia. The dose of the composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications.

[0126] Cognitive impairments are also 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.

[0127] 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.

[0128] 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.

[0129] 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, as well as human subjects with schizophrenia, using a variety of cognitive tests known in the art, as discussed above.

Amyotrophic Lateral Sclerosis (ALS)

[0130] This invention additionally provides methods and compositions for treating ALS using an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorth thereof alone or in combination with valproate or a an alalog, derivative or pharmaceutically acceptable salt thereof. 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.

[0131] 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.

[0132] 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

[0133] 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 polymorth thereof, alone or in combination with valproate or an alalog, derivative or pharmaceutically acceptable salt thereof. 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 preventing or slowing the progression, of 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.

[0134] 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).

[0135] 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.

[0136] 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.

[0137] 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.

SV2A Inhibitor

[0010] "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).

[0011] "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.) 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.

[0140] 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 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.

[0141] 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.

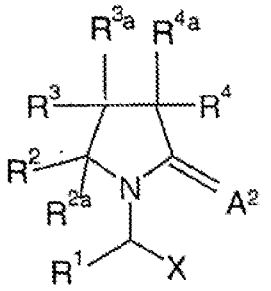
[0142] In some embodiments of this invention, the SV2A inhibitor is levetiracetam or salts, solvates, hydrates, polymorphs or prodrugs thereof. Levetiracetam refers to the International Union of Pure and Applied Chemistry (IUPAC) name of the compound (2S)-2-(2-oxopyrrolidin-1-yl) butanamide). Levetiracetam 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).

[0143] 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 :

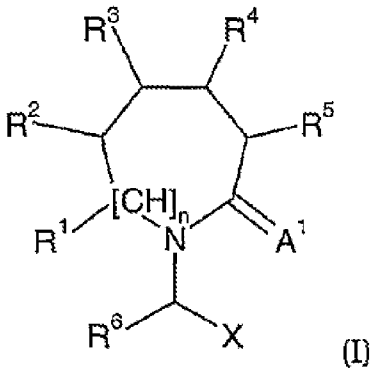
(2S)-2-[(4S)-4-(2, 2-difluorovinyl)-2-oxopyrrolidinyl]butanamide;

(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,

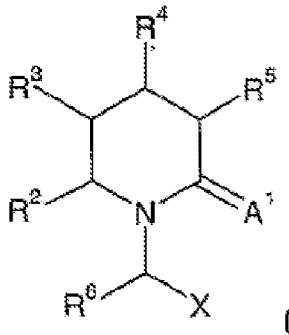
each optionally substituted by one or more substituents selected from halogen, alkyl, substituted alkyl, alkoxy, nitro, amino, acyl and phenyl.

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.

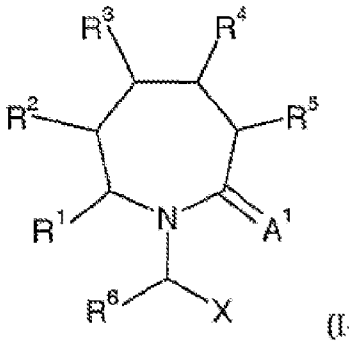
According to a preferred embodiment, a compound of formula I is as defined above wherein n represents 0. The compound is a 6-ring structure (2-thioxo- or 2-oxo-piperidinyl derivative) wherein R^1 is not existent since n=0, and is depicted by the formula (I-A).



(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=1, R^3 and R^4 are the same or different and each is independently hydrogen, halogen, nitro, nitrooxy, cyano, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, acyl derivative, sulfonyl derivative or sulfinyl derivative;

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

R^6 is hydrogen, alkyl, aryl or-CH_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=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 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, 1-propynyl, cyclopropylethynyl, 3- methyl-1-butynyl, 1-butynyl, 2,2-difluoropropyl, 2-chloro-2,2-difluoroethyl, 2-bromo-2,2- difluoroethyl and 2-iodo-2,2-difluoroethyl.

According to yet another preferred embodiment, the compound is as defined above wherein R^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-(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-[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,

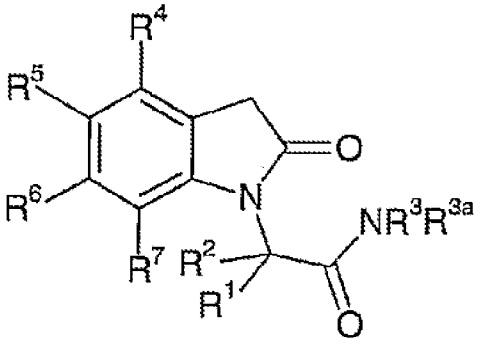
2-(2-oxo-5-phenyl-1-piperidinyl]butanamide,

(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,



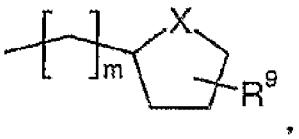
(I)

wherein

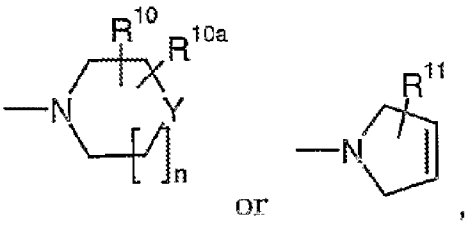
R^1 is hydrogen,

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,

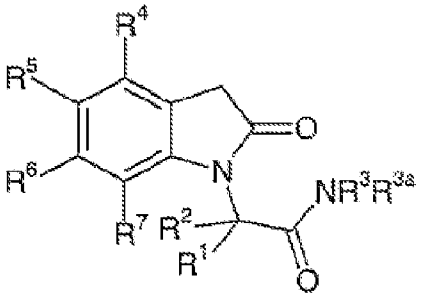
R^{15} is aryl or heterocycle,

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)

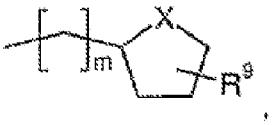
wherein

R^1 is hydrogen,

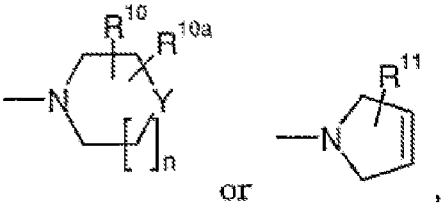
R^2 is hydrogen or C1-20-alkyl,

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



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^b- pyridinyl in which R^b 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.

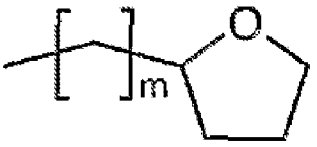
Generally, R^3 is hydrogen; C1-6-alkyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, hydroxy, alkoxy, alkoxycarbonyl or alkylamino; C5-7-cycloalkyl; (hydroxymethyl) cyclohexenyl; phenyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, C1-4-alkyl,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

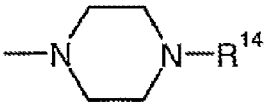
Generally, R^{3a} is hydrogen, C1-4-alkyl or a group of formula



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.

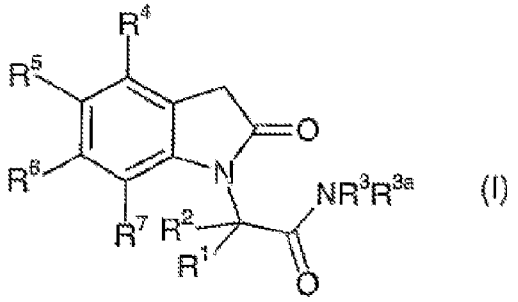
Preferably, R^6 is hydrogen, methyl or Cl. More preferably, R^6 is hydrogen.

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,



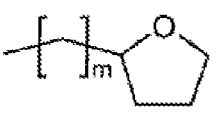
(I)

wherein R^1 is hydrogen,

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

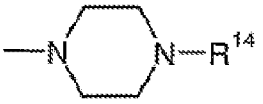
R^3 is hydrogen; C1-6-alkyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, hydroxy, alkoxy, alkoxycarbonyl or alkylamino ; C5-7-cycloalkyl ; (hydroxymethyl) cyclohexenyl; phenyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, C1-4-alkyl, hydroxy,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

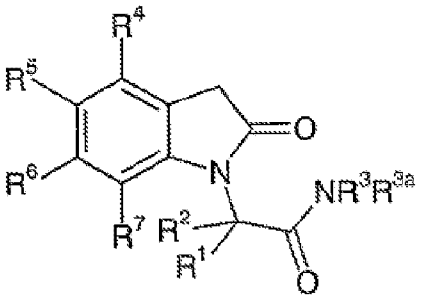
V is unsubstituted C1-4-alkylene,

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-dihydro-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.

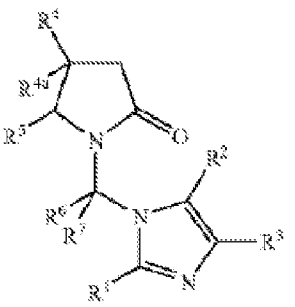
In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: 2-(5-iodo-2-oxo-2,3-dihydro-1H-indol-1- yl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl) acetamide ; 2- (5, 7-dibromo- 2-oxo-2, 3-dihydro-1H-indol-1-yl)acetamide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

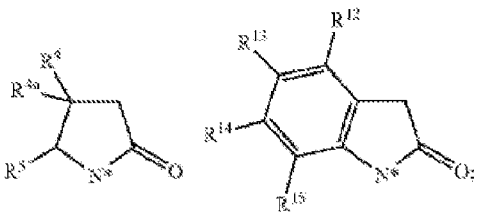


wherein R^1 is hydrogen, C_{1-20} alkyl, C_{3-8} cycloalkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, guanidine, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, aryl or heterocycle;

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;

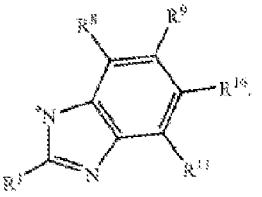
R^{12} is hydrogen or halogen;

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;

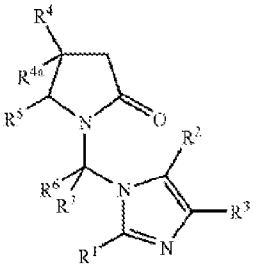
with the proviso that R^4 is different from hydrogen when represents a group of formula



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)

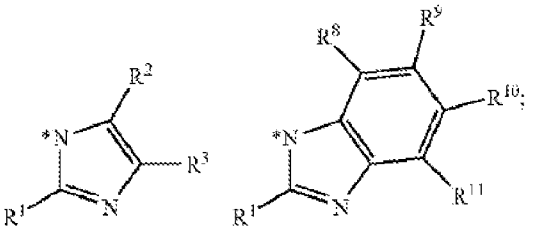


wherein R^1 is hydrogen, C_{1-20} alkyl, C_{3-8} cycloalkyl, halogen, hydroxy, ester, amido, cyano, nitro, amino, guanidine, alkylthio, alkylsulfonyl, alkylsulfinyl, aryl or heterocycle;

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

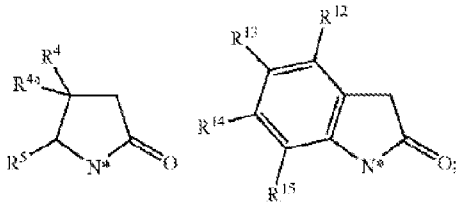


R^4 is hydrogen, C_{1-20} alkyl, C_{2-12} alkenyl or aryl;

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;

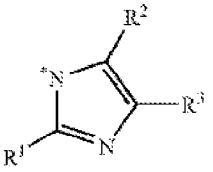
R^{12} is hydrogen or halogen;

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

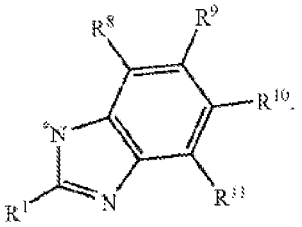
R^{14} is hydrogen;

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.

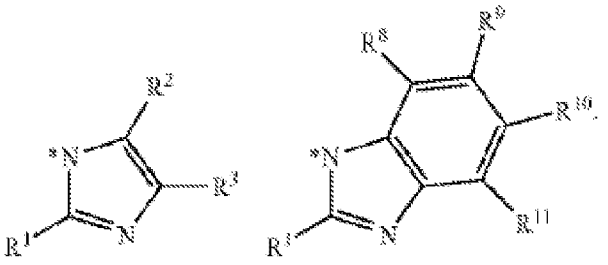
Usually, R^5 is hydrogen.

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



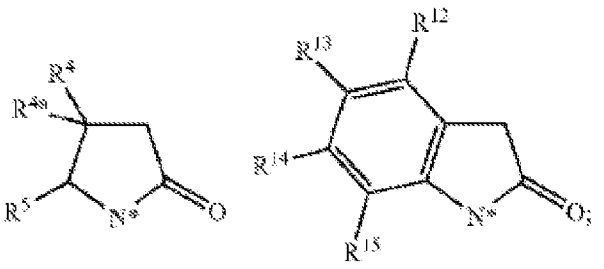
Usually, R^8 is hydrogen.

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;

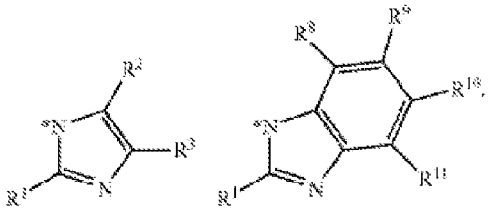
R^5 is hydrogen;

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



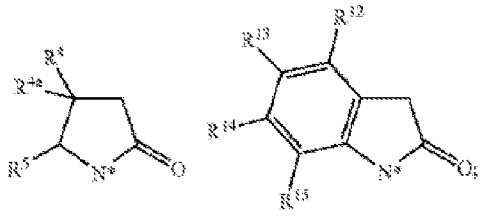
R^8 is hydrogen;

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



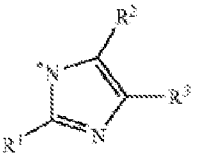
R^{12} is selected from hydrogen or halogen;

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

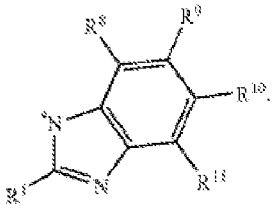
R^{14} is hydrogen;

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

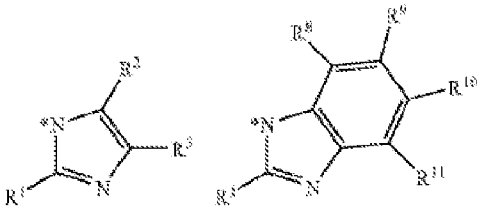
R^1 is selected from hydrogen; methyl; ethyl; i-propyl; n-propyl; cyclopropyl; n-butyl; i-butyl; t-butyl; 1-ethylpropyl; 2,4,4-trimethylpentyl;

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;

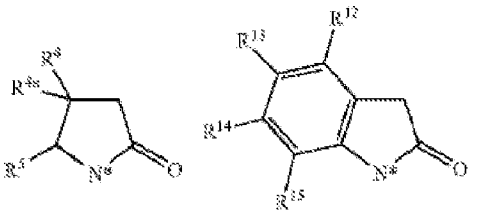
R^{10} is selected from methyl; hydrogen; trifluoromethyl; fluoro; cyano; or methoxy;

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;

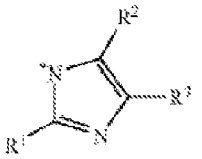
R^{15} hydrogen;

R^6 is selected from hydrogen; azidomethyl;

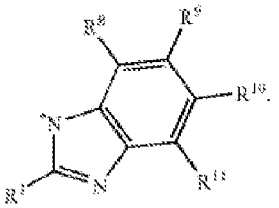
R^7 is hydrogen;

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



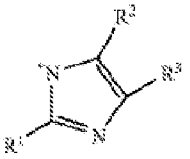
In a more preferred embodiment, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

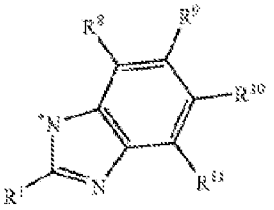
R^1 is selected from hydrogen; methyl; ethyl; i-propyl; n-propyl; n-butyl;methylthio; nitro; cyano; amino; chloro; or 1H-pyrrol-2-yl;

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;

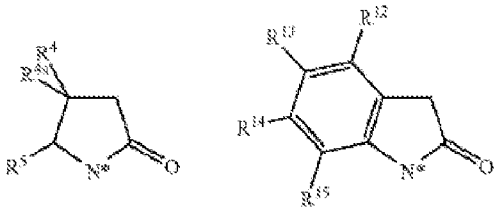
R^{11} is hydrogen;

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;

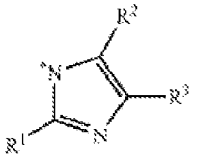
R^{14} is hydrogen;

R^{15} hydrogen;

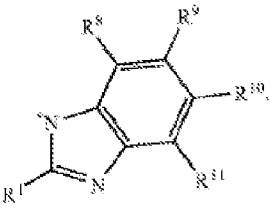
R^6 is hydrogen;

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;

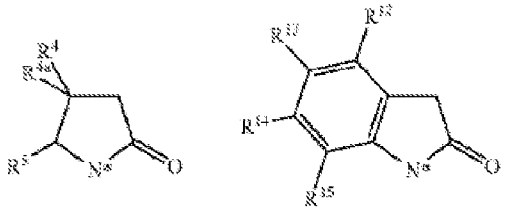
R^3 is hydrogen;

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-(1H-imidazol-1-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,4,5-trifluorophenyl)pyrrolidin-2-one; 1-[(2-nitro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin-- 2-one; 1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-2-carbonitrile; 1-[(2-

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

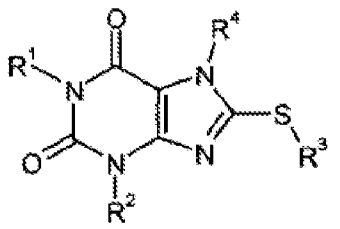
In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: 1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one; (-)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-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

phenylpyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one; 4-(3-fluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3,5-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,3,4-trifluorophenyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,4,5-trifluorophenyl)pyrrolidin-2-one; 1-[(2-nitro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin-- 2-one; 1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-2-carbonitrile; 1-[(2-amino-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(5-chloro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin- -2-one; (+)-1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; (-)-1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; 1-[(2-chloro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin- -2-one; 1-[(2-chloro-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; (+)-1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile; 5-bromo-1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 5-chloro-1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 1-(1H-imidazol-1-ylmethyl)-5-methyl-1,3-dihydro-2H-indol-2-one; 1-[(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]-1H-imidazole-5-carbo- nitrile.

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

v) International Patent Application WO 2007/065595:

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



(I)

wherein

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

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

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

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

R^5 is C2-4 alkyl;

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

R^7 is C1-4 alkyl;

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

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

The term "alkyl", as used herein, is a group which represents saturated, monovalent hydrocarbon radicals having straight (unbranched) or branched moieties, or combinations thereof, and containing 1-8 carbon atoms, preferably 1-6 carbon atoms; more preferably alkyl groups have 1-4 carbon atoms. Alkyl moieties may optionally be substituted by 1 to 5 substituents independently selected from the group consisting of hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl, acyl, aryl or heterocycle. Alkyl moieties may be optionally

substituted by a cycloalkyl as defined hereafter. Preferred alkyl groups are methyl, cyanomethyl, ethyl, 2-ethoxy-2-oxoethyl, 2- methoxyethyl, n-propyl, 2-oxopropyl, 3-hydroxypropyl, 2-propynyl, n-butyl, i-butyl, n-pentyl, 3-pentyl, n-hexyl, cyclohexylmethyl, benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, 4-(aminosulfonyl)benzyl, 1- phenylethyl, 2-phenylethyl, (3,5-dimethylisoxazol-4-yl)methyl or (5-nitro-2-furyl)methyl. More preferred alkyl groups are methyl, ethyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3- hydroxypropyl, 2-propynyl, n-butyl, 3-pentyl, n-hexyl, benzyl, 3-bromobenzyl, 3- methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, (3,5-dimethylisoxazol-4-yl)methyl or (5-nitro- 2-furyl)methyl. Most preferred alkyl groups are methyl, ethyl, 3-methoxybenzyl, 3- nitrobenzyl or (5-nitro-2-furyl)methyl.

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

The term "aryl" as used herein, is defined as a phenyl group optionally substituted by 1 to 4 substituents independently selected from halogen, amino, nitro, alkoxy or aminosulfonyl. Preferred aryl groups are phenyl, 2-bromophenyl, 3-bromophenyl, 4- bromophenyl, 3-methoxyphenyl, 3-nitrophenyl, 3-aminophenyl or 4-(aminosulfonyl)phenyl.

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

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

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

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

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

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

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

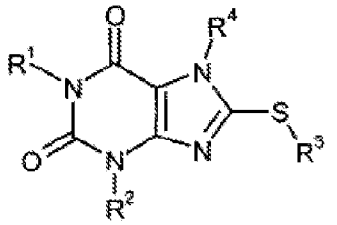
Generally R^4 is C_{1-8} alkyl optionally substituted by alkoxycarbonyl, C_{3-6} cycloalkyl, aryl or heterocycle. Usually R^4 is C_{1-8} alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl 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 $-CHR^5R^6$ 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 $-CHR^5R^6$, 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-

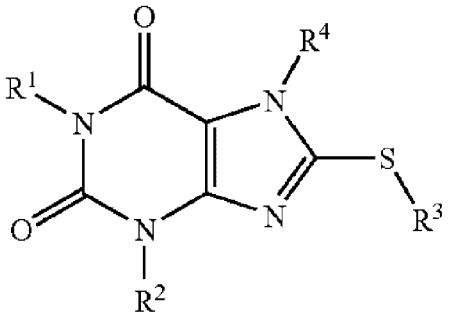
yl)thio]butanoate; 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8- yl]thio}butanamide; 2-[(7-butyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8- yl)thio]butanamide; 7-(3-bromobenzyl)-8-[(1-ethylpropyl)thio]-3-methyl-3,7-dihydro-1 H- purine-2,6-dione; ethyl 2-{8-[(3-bromobenzyl)thio]-1 ,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;

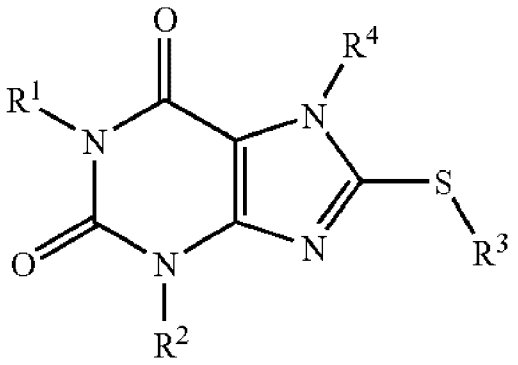
R.sup.7 is C.sub.1-4 alkyl;

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;

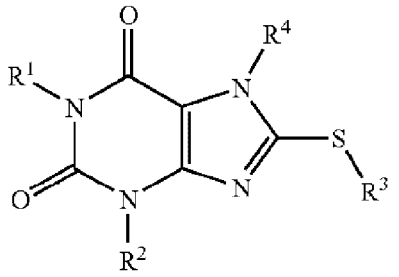
R.sup.5 is hydrogen or C.sub.1-4 alkyl;

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]but-anoate; 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;

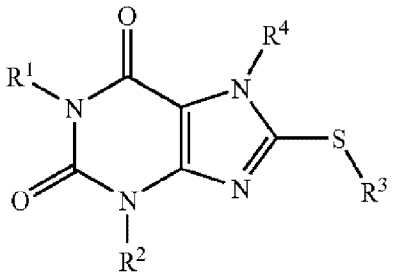
R.sup.4 is C.sub.1-8 alkyl optionally substituted by alkoxycarbonyl, C.sub.3-6 cycloalkyl, aryl or heterocycle;

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;

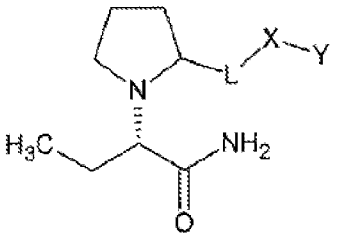
R.sup.5 is hydrogen or C.sub.1-4 alkyl;

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

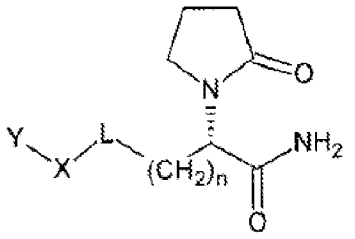
R.sup.7 is C.sub.1-4 alkyl;

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

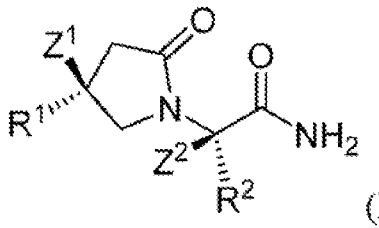
n of Formula 2 and L, X, and Y of Formulas 1 and 2 are defined as follows: a) n is an integer with a value of 0 to 8; b) L is one of the group consisting of CH2, CO, NHCO, NHCOO, CONH, NH, O, or S, and combinations thereof; c) X is an end group, an aromatic group, an aryl group, or a saturated, unsaturated, 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.

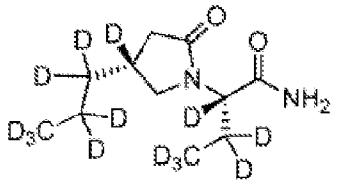
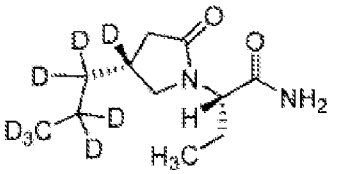
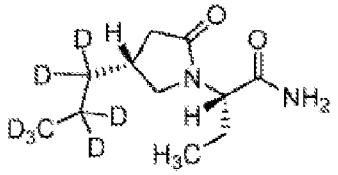
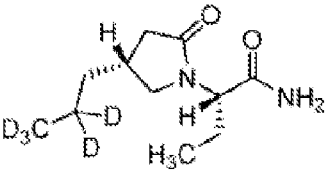
One embodiment of this invention provides compounds of Formula I wherein R1 is selected from CD3CH2CH2-, CD3CD2CH2-, CD3CH2CD2-, CH3CH2CD2-, CH3CD2CD2-, CD3CD2CD2- or CH3CH2CH2-. In a more specific embodiment, R1 is CD3CD2CD2- or

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.

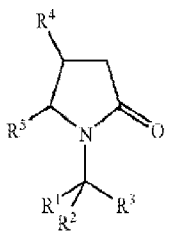
The R and Z variables as described above may be selected and taken together to provide more specific embodiments of this invention. For example, in one embodiment, R1 is CD3CH2CH2-, CD3CD2CH2-, CD3CH2CD2-, CH3CH2CD2-, CH3CD2CD2-, CD3CD2CD2- or CH3CH2CH2-; and R2 is selected from CH3CH2-, CD3CH2-, CH3CD2-,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

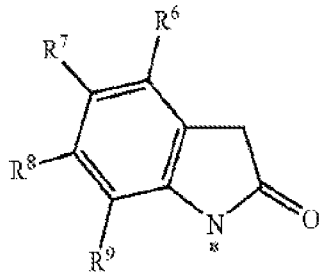
2-chloro-1H-benzimidazol-1-yl.

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.

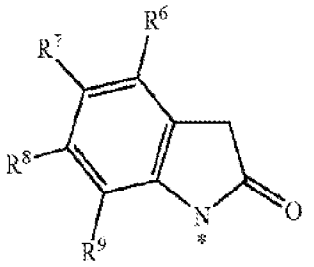
R4 in formula (I) is selected from the group comprising or consisting of hydrogen; C1-12 alkyl optionally substituted by halogen or C1-4 alkoxy; C2-12 alkenyl optionally substituted by halogen; C2-12 alkynyl optionally substituted by halogen.

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;

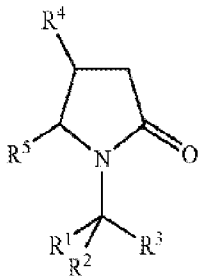
1H-pyrrol-1-yl;

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;

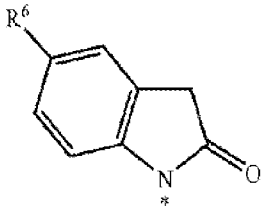
R2 is hydrogen;

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.

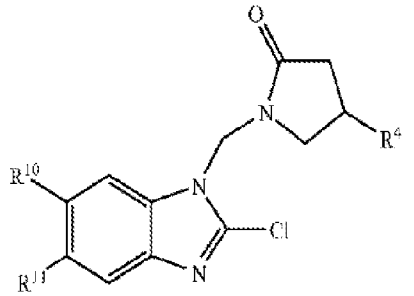
In this embodiment, most specific moieties R3 are selected from 5-bromo-1H-imidazol-4-yl; 5-chloro-1H-imidazol-4-yl; 1H-imidazol-5-yl; 4-bromo-1-methyl-1H-imidazol-5-yl; 4-chloro-1-methyl-1H-imidazol-5-yl; 1H-pyrazol-4-yl.

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

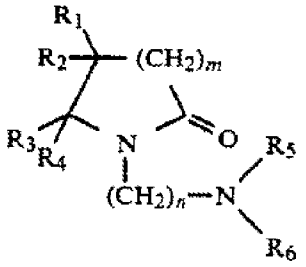
The present invention relates to the novel compound (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

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;

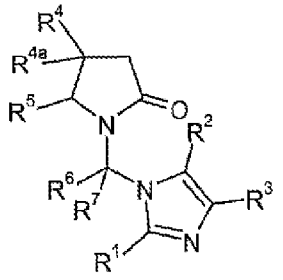
n represents an integer from 1-2, preferably 1.

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,



(I)

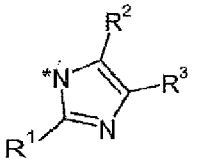
wherein

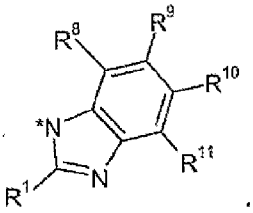
RI is hydrogen, CI-20 alkyl, C3 23 cycloalkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, guanidine, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, aryl or heterocycle; R2 is

hydrogen, C1 20 alkyl, alkoxy, amino, halogen, hydroxy, ester, amido, nitro, cyano, carbamate, or aryl;

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

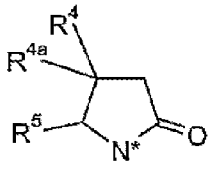
or R2 and R3 can form together with the imidazole ring the following 1H-benzimidazole cycle

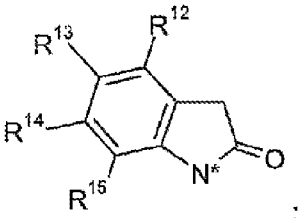




;

R4 is hydrogen, C1-20 alkyl, C2-12 alkenyl,C2-12 alkynyl, aryl, azido, alkoxycarbonylamino, arylsulfonyloxy or heterocycle; R4a is hydrogen or C1-20 alkyl; or R4 and R4a can form together a C3-8 cycloalkyl ; R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle





;

R6 is hydrogen or C1 20 alkyl ; R7 is hydrogen; or R6 and R7 are linked together to form a C3-6 cycloalkyl ; R8 is hydrogen, halogen, nitro, cyano, C1 20 alkyl or alkoxy ; R9 is hydrogen, C1-20 alkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl ;

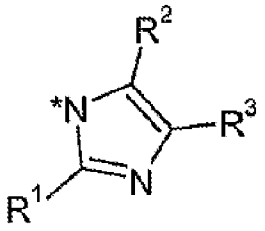
RIO is hydrogen, C1 20 alkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl ;

RI l is hydrogen, halogen, nitro, cyano, C1 20 alkyl or alkoxy ; R12 is hydrogen or halogen;

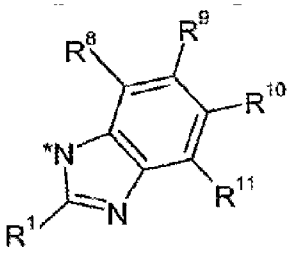
R13 is hydrogen, nitro, halogen, heterocycle, amino, aryl, C1-20 alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen; R14 is hydrogen, C1-20 alkyl or halogen;

R15 is hydrogen, C1 20 alkyl or halogen;

with the proviso that R4 is different from hydrogen when

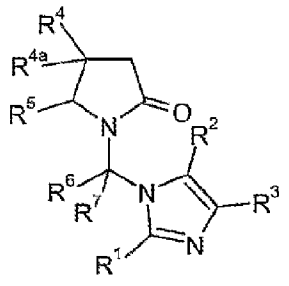


N represents a group of formula



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

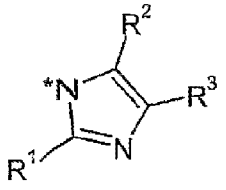
In a preferred embodiment, the invention concerns a compound having the formula I, their tautomers, geometrical isomers (including cis and trans, Z and E isomers), enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts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

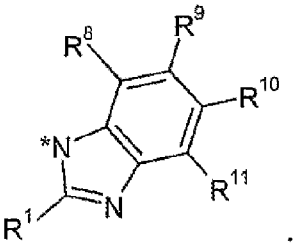


(I)

wherein

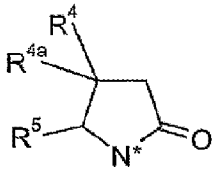
RI is hydrogen, C1-20 alkyl, C3-8 cycloalkyl, halogen, hydroxy, ester, amido, cyano, nitro, amino, guanidine, alkylthio, alkylsulfonyl, alkylsulfinyl, aryl or heterocycle; R2 is hydrogen, C1 20 alkyl, halogen, cyano, ester, carbamate or amido; R3 is hydrogen, cyano, C 1 20 alkyl, halogen or ester; or R2 and R3 can form together with the imidazole ring the following 1H- benzimidazole cycle

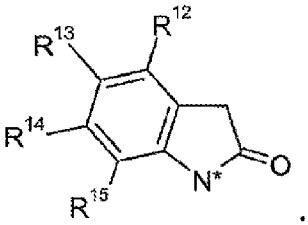




; R4 is hydrogen, C1 20 alkyl, C2 12 alkenyl or aryl; R4a is hydrogen;

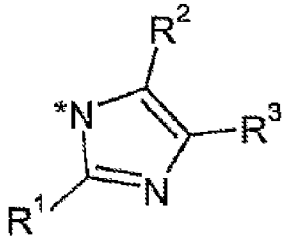
R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle



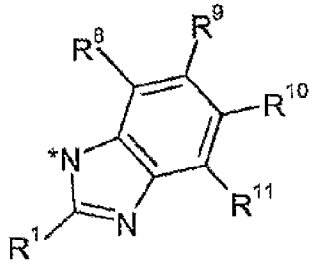


;

R6 is hydrogen or C 1 20 alkyl ; R7 is hydrogen; or R6 and R7 are linked together to form a C3-6 cycloalkyl ; R8 is hydrogen; R9 is hydrogen, C 1-20 alkyl, halogen or alkoxy; RIO is hydrogen, C1 20 alkyl, halogen or cyano; R11 is hydrogen; R12 is hydrogen or halogen; R13 is hydrogen, halogen, heterocycle or C1 20 alkyl ; R14 is hydrogen; R15 is hydrogen; with the proviso that R4 is different from hydrogen when



represents a group of formula



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

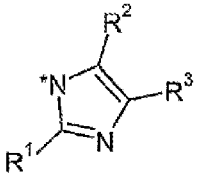
Usually, R5 is hydrogen.

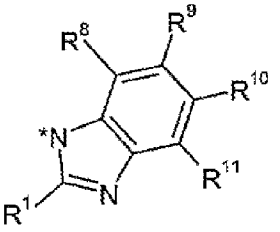
Usually, R6 is hydrogen or Cl-1~0 alkyl unsubstituted or substituted by hydroxy or azido. Preferably, R6 is hydrogen or azidomethyl. More preferably R6 is hydrogen.

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





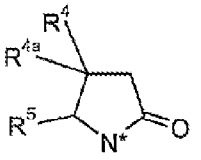
Usually, R8 is hydrogen.

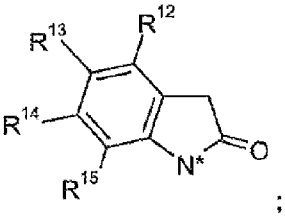
Usually, R9 is hydrogen; halogen ; 1-3 alkyl or alkoxy. In some embodiments, R9 is hydrogen; methyl; chloro or methoxy. In some embodiments R9 is hydrogen.

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





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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.

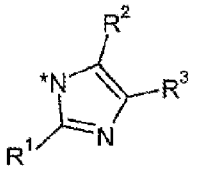
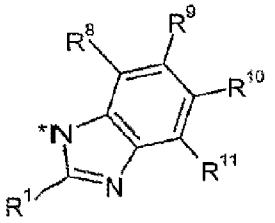
In a general embodiment of the invention, the compounds of formula I, or pharmaceutically acceptable salts thereof, are those wherein

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;

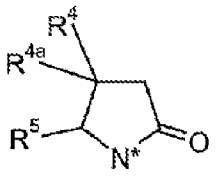
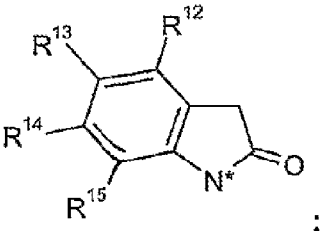
R4a is hydrogen; R5 is hydrogen; R6 is selected from hydrogen or C 1-10 alkyl unsubstituted or substituted by hydroxy or azido;

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

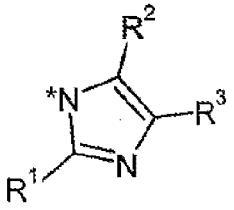
R8 is hydrogen; R9 is selected from hydrogen; halogen; C1-3 alkyl ; alkoxy ;

R10 is selected from hydrogen; halogen; cyano or Cil alkyl unsubstituted or substituted by halogens; or alkoxy ; R l is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle

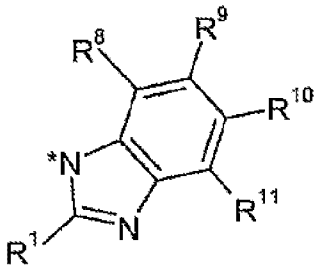



;

R12 is selected from hydrogen or halogen; R13 is selected from hydrogen; CI-3 alkyl ; halogen ; thiazolyl unsubstituted or substituted by alkyl groups, such as methylthiazolyl; R14 is hydrogen; R15 is hydrogen; with the proviso that R4 is different from hydrogen when

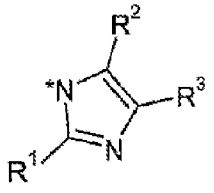


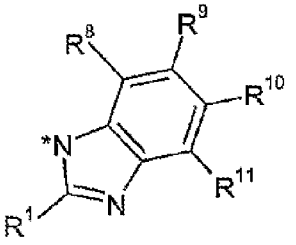
represents a group of formula



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

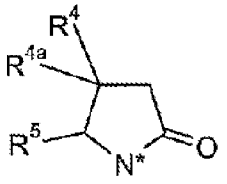


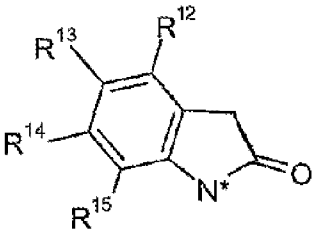


R8 is hydrogen; R9 is selected from hydrogen; methyl; choro ; methoxy;

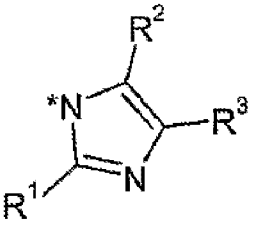
R10 is selected from methyl; hydrogen; trifluoromethyl; fluoro; cyano; or methoxy; R is hydrogen; R4 is selected from hydrogen; n-propyl ; 2,2-difluorovinyl ; phenyl; 3- chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl ; 3,5-difluorophenyl ; 3,4- difluorophenyl; 3-chloro-4-fluorophenyl ; 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

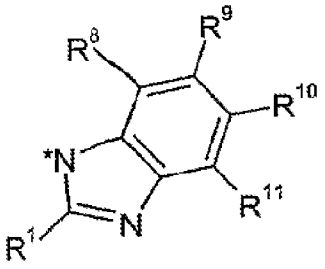




R12 is selected from hydrogen; chloro; fluoro; R13 is selected from hydrogen; chloro; bromo; methyl; R14 is hydrogen; R15 hydrogen; R6 is selected from hydrogen; azidomethyl; R7 is hydrogen; or R6 and R7 are linked to form a cyclopropyl ; with the proviso that R4 is different from hydrogen when



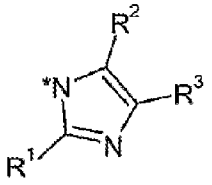
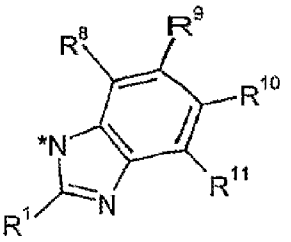
represents a group of formula



.

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

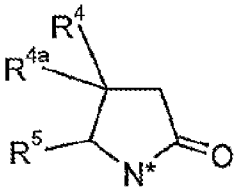
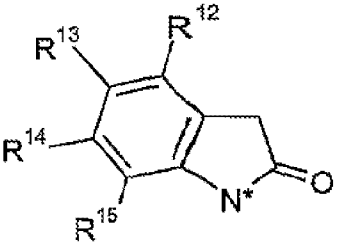
RI is selected from hydrogen; methyl; ethyl; i-propyl ; n-propyl ; n-butyl; methylthio; nitro; cyano ; amino; chloro ; or lH-pyrrol-2-yl ; R2 is selected from hydrogen; chloro; cyano; R3 is selected from hydrogen; cyano; or R2 and R3 can form together with the imidazole ring the following 1H- benzimidazole cycle

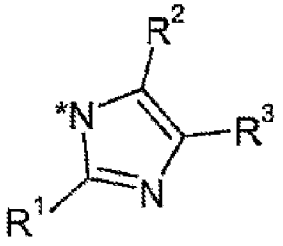
R8 is hydrogen; R9 is hydrogen;

R10 is selected from hydrogen ; trifluoromethyl ; fluoro ; cyano;

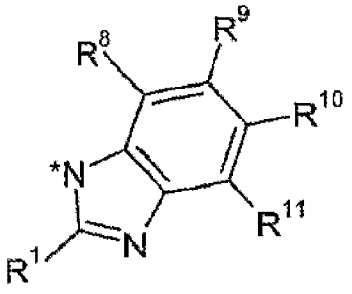
R11 is hydrogen; R4 is selected from hydrogen; n-propyl ; 2, 2-difluorovinyl ; phenyl; 3- chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl ; 3, 5-difluorophenyl ; 3,4- difluorophenyl ; 3-chloro-4-fluorophenyl; 2,3, 4-trifluorophenyl ; 2,4, 5-trifluorophenyl ; 2,3, 5-trifluorophenyl; 3,4, 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



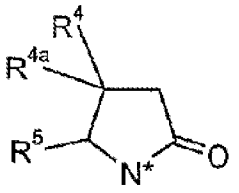
R11 represents a group of formula

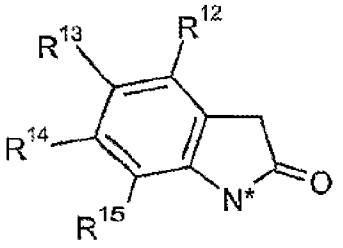


In one embodiment of the invention, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

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-onc; 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-onc; 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- (lH-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.

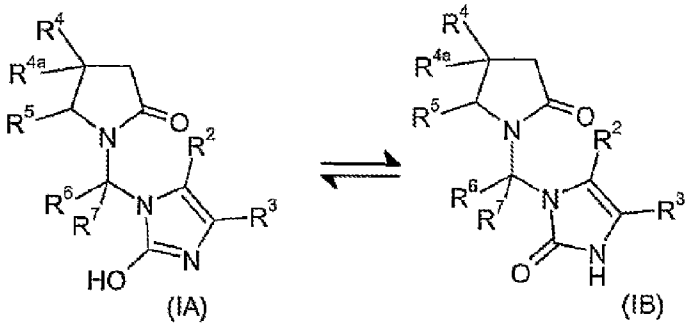
Compounds of the formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

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.

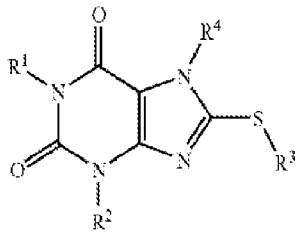
Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

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.

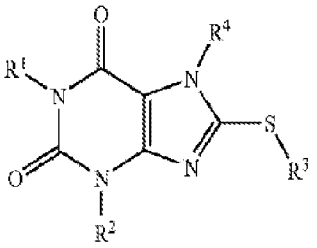
Generally R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl, C3-6 cycloalkyl, aryl or heterocycle. Usually R4 is C1-8 alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl or ethoxycarbonyl. 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

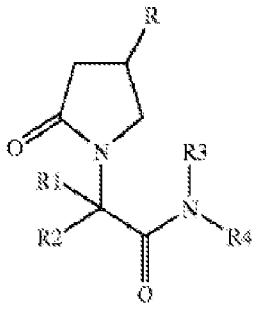
In some embodiments, the compound includes optionally substituted N-alkylated 2-oxo-pyrrolidine derivatives. In some embodiments, those compounds are alkyl amides derivatives substituted on the positions 4 and/or 5 of the pyrrolidone ring. Examples of optionally substituted N-alkylated 2-oxo-pyrrolidine 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.

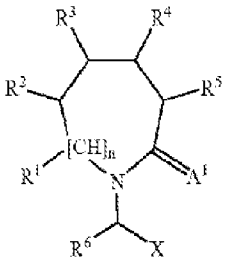
An example of such an acetam compound includes, but is not limited to, a compound of formula I wherein R, R1, R2, R3 and R4 are hydrogen, 2-oxo-pyrrolidineacetamide, known by the generic name piracetam as described in UK Patents Nos. 1,039,113 and 1,309,692.

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-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-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.

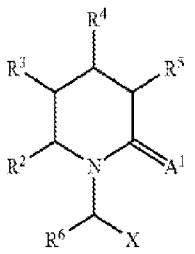
The invention also includes within its scope prodrug forms of the compounds of formula I and Its various sub-scopes and sub-groups.

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.

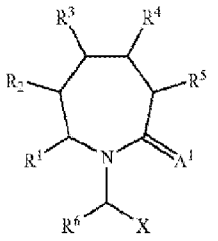
According to one embodiment, the present invention relates to a compound of formula I as defined above wherein n represents 0. The compound is a 6-ring structure (2-thioxo- or 2-oxo-piperidinyl derivative) wherein R<1 > is not existent since n=0, and is depicted by the formula (I-A).

(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,

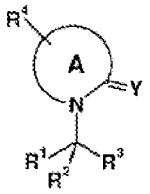
2-(2-oxo-5-phenyl-1-piperidinyl]butanamide,

(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;

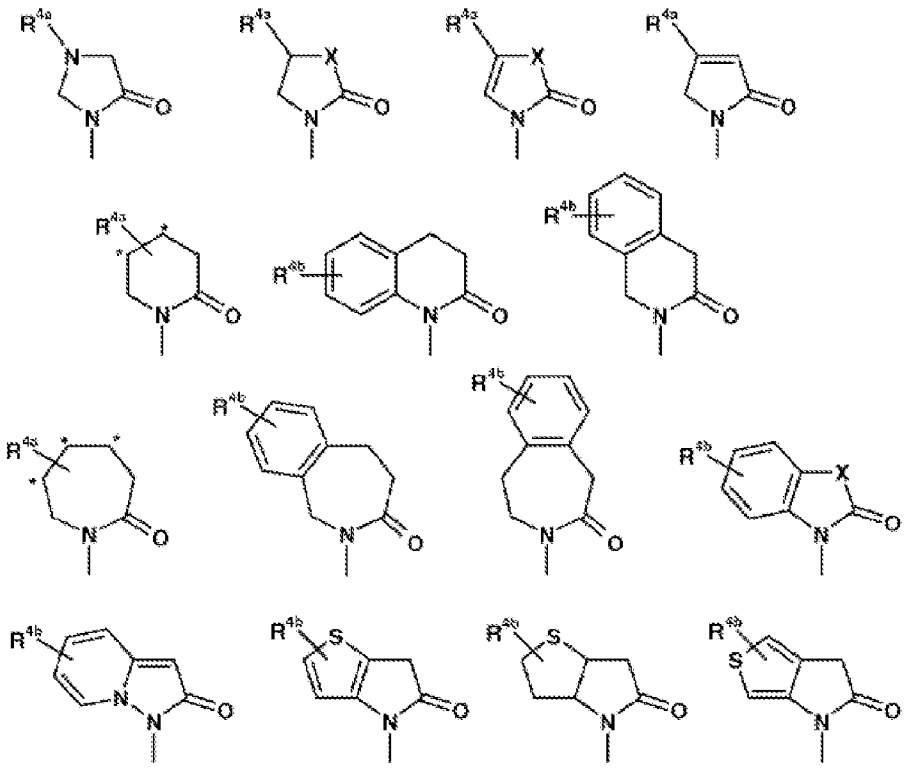
In some embodiments the compounds are as follows:

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.

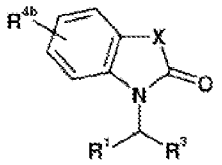
In a specific embodiment, when R^ is -CONR5R6 and R^ is C-µg alkyl, the carbon atom to which R-I and R^ are attached is preferably in the "S"-configuration.

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)

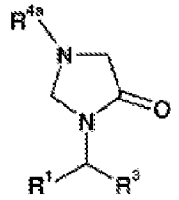
wherein

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

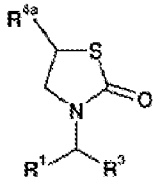
R1 is hydrogen or C-|.g alkyl, preferably hydrogen, methyl or ethyl; in a more specific embodiment R^ is ethyl.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl, preferably R^ is -CONH2.

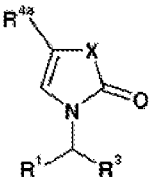
R^a is either hydrogen or an aryl; with the proviso that 2-(5-oxoimidazolidin-1-yl)acetamide is excluded. Preferably R^a is an aryl, e.g. a phenyl which may be substituted preferably by halogen, nitro, alkoxy, in particular by nitro.

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;

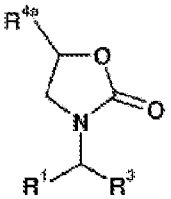
R1 is hydrogen or C-|.g alkyl, preferably hydrogen, methyl or ethyl; in a more specific embodiment R^ is ethyl.

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)

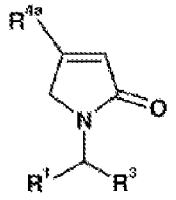
wherein

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

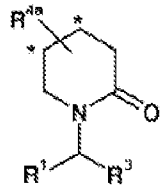
R1 is hydrogen or C-|.g alkyl, in particular hydrogen, methyl or ethyl.

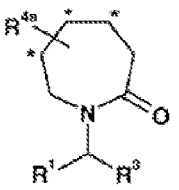
R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; in particular R^ is -CONH2

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)

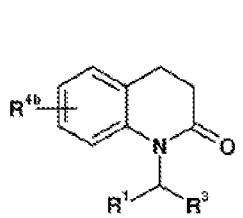

(I-D2)

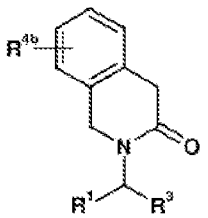
wherein

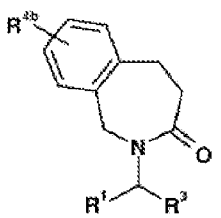
R-I is hydrogen or C-|.g alkyl, in particular hydrogen; R3 is an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl. In one embodiment, R^ is 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. In a more specific embodiment, R^ 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)

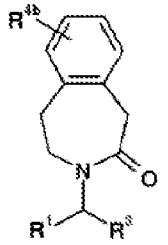
wherein

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

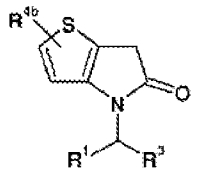
R-I is hydrogen or C-|.g alkyl, preferably hydrogen;

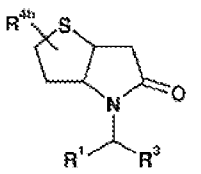
R3 is an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl; more specifically R^ is 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. More specifically R^ is 1 H-imidazol-4-yl or imidazo[1 ,2- a]pyridin-3-yl.

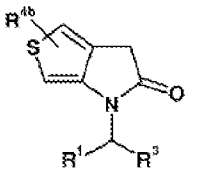
R^b is hydrogen; halogen; nitro; cyano; C-1.4 alkyl optionally substituted by halogen; C-1.4 alkoxy optionally substituted by halogen; specifically R^ is hydrogen, halogen or cyano,.

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 claims 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.

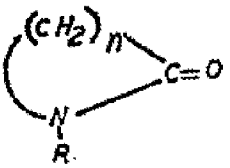
The invention also includes within its scope pro-drug forms of the compounds of formula (I) and its various sub-scopes and sub-groups.

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-onc; 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;

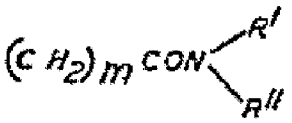
1-(1 H-imidazol-5- ylmethyl)-6-propylazepan-2-one; 1-(1 H-imidazol-4-ylmethyl)-4-propylazepan-2-one; 4- (1 H-imidazol-4-ylmethyl)-4,6-dihydro-5H-thieno[3,2-b]pyrrol-5-one; 2-(5-oxo-5,6-dihydro- 4H-thieno[3,2-b]pyrrol-4-yl)acetamide; 4-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3- yl]methyl}-4,6-dihydro-5H-thieno[3,2-b]pyrrol-5-one; 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:



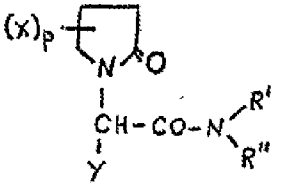
wherein N is a whole number of from 3 to 5 and R represents a



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:

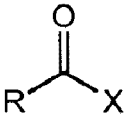


wherein X is a hydrogen atom or an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms, p is a whole number of from 1 to 6, Y is a hydrogen atom or an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms or a cycloalkyl radical and R' and R", which may be the same or different, 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.

Valproate

[0144] In some embodiments, an SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate or polymorph is administered in combination with valproate or its analog, derivative or pharmaceutically acceptable salt.

[0145] Analogs and derivatives of valproate useful for the methods and compositions of this invention include compounds of the formula:



wherein, independently for each occurrence:

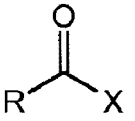
X is -OH, C_{1-10} alkoxy, -O-alkali metal, $-N(R^1)_2$, -SH, or $-S-C_{1-10}$ alkyl;

R is a straight chain or branched C_{1-30} alkyl; and

R^1 is H, C_{1-10} alky, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, or aralkyl;

provided that R may be unsubstituted or substituted by one or more -OH, C_{1-10} alkoxy, $-N(R^1)_2$, -SH, $-S-C_{1-10}$ alkyl, or aryl.

[0146] In other embodiments, analogs and derivatives of valproate useful for the methods and compositions of this invention include compounds of the formula:



wherein, independently for each occurrence:

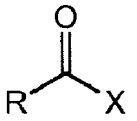
X is -OH, C_{1-10} alkoxy, -O-alkali metal, $-N(R^1)_2$, -SH, or $-S-C_{1-10}$ alkyl;

R is $CH[(CH_2)_2CH_3]_2$; and

R^1 is H, C_{1-10} alky, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, or aralkyl;

provided that R may be unsubstituted or substituted by one or more -OH, C_{1-10} alkoxy, $-N(R^1)_2$, -SH, $-S-C_{1-10}$ alkyl, or aryl.

[0147] In other embodiments, analogs and derivatives of valproate useful for the methods and compositions of this invention include compounds of the formula:



wherein, independently for each occurrence:

X is -OH, -O-alkali metal, -SH, or - NH_2; and

R is $CH[(CH_2)_2CH_3]_2$.

[0148] Methods for making the compounds of formula may be found in, for example, U.S. Patent Nos.: 4,558,070; 4,595,695; 4,654,370; 4,895,873; 4,913,906; 5,017,613; 5,019,398; 5,049,586; 5,162,573; 5,440,023; 5,856,569; 6,131,106 and 6,610,326.

[0149] Other names and descriptions of valproate are also envisioned herein, such as Depakote, Valrelease, 2-propylpentanoate, valproic acid, VPA and sodium valproate.

Methods of Treating CNS Disorders with Cognitive Impairment with the Administration of an SV2A Inhibitor

[0150] In one aspect, the invention provides methods and compositions for treating 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 a central nervous system (CNS) disorder with cognitive impairment (e.g., age-related cognitive impairment, MCI, amnestic MCI, dementia, AD, prodromal AD, PTSD, schizophrenia, ALS and cancer therapy-related cognitive impairment), or the risk thereof in a subject in need thereof by administering an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof. In some embodiments, the SV2A inhibitor is administered in combination with valproate or an analog, derivative or pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof. In some embodiments, the SV2A inhibitor is selected from the group consisting of levetiracetam, seletracetam, and brivaracetam or derivatives or analogs or pharmaceutically acceptable salts, or solvates, or hydrates, or polymorphs, or prodrugs

thereof. 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 other embodiments, the SV2A inhibitor is brivaracetam 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 other embodiments, the SV2A inhibitor is seletracetam 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 CNS disorder with cognitive impairment 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 with cognitive impairment is dementia, post traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS) or cancer-therapy-related cognitive impairment. 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.

[0151] The use of the SV2A inhibitors and its pharmaceutically acceptable salt, hydrate, solvate or polymorph in combination with valproate or its analog, derivative or pharmaceutically acceptable salt reduces the amount of valproate necessary for the treatment of CNS disorders involving cognitive dysfunction and other affective disorders, including MCI, amnestic MCI, AAMI, ARCE, dementia, AD, PTSD, schizophrenia, ALS or cancer-therapy-related cognitive impairment. In one embodiment, the subject that suffers such cognitive impairment is a human patient, and thus reduce the side effects caused by valproate without diminishing efficacy. Further, the efficacy of a combination of the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate or polymorph and valproate or its analog, derivative or pharmaceutically acceptable salt exceeds the efficacy of either drug administered alone at its optimal dose and thus is an improved treatment for CNS disorders with cognitive impairment.

[0152] 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.

[0153] As used herein, administration of an SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate or polymorph and valproate or its analog, derivative or pharmaceutically acceptable salt "in combination" includes simultaneous administration and/or administration at different times, such as sequential administration. Simultaneous administration of the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate or polymorph and valproate or its analog, derivative or pharmaceutically acceptable salt can optionally be combined with supplemental doses of the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate or polymorph and/or valproate or its analog, derivative or pharmaceutically acceptable salt. Simultaneous administration of drugs encompasses administration as co-formulation or, alternatively, as separate compositions.

[0154] In accordance with this invention, the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate or polymorph, alone or in combination with valproate or its analog, derivative or pharmaceutically acceptable salt 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 or its pharmaceutically acceptable salt, hydrate, solvate and polymorps, alone or in combination with valproate or its analog, derivative or pharmaceutically acceptable salt, can be administered to a subject via

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CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 247

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THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 247

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

Claims

1. Use of levetiracetam, brivaracetam, or seletracetam, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, for treating cognitive impairment associated with a central nervous system (CNS) disorder, for delaying or slowing the progression of said cognitive impairment, or for reducing the rate of decline of cognitive function associated with said CNS disorder, in a subject having or at risk of having said cognitive impairment or decline of cognitive function,

wherein the CNS disorder is amnestic mild cognitive impairment, dementia, prodromal Alzheimer's Disease, post-traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS), or cancer-therapy related cognitive impairment, and

wherein the levetiracetam, brivaracetam, or seletracetam, or the pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, is formulated for administration at a daily dose of about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.12 mg, about 0.14 mg, about 0.16 mg, about 0.18 mg, about 0.2 mg, about 0.22 mg, about 0.24 mg, about 0.26 mg, about 0.28 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 1.2 mg, about 1.4 mg, about 1.6 mg, about 1.8 mg, about 2 mg, about 2.2 mg, about 2.4 mg, about 2.6 mg, about 2.8 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, about 20 mg, about 22 mg, about 25 mg, about 28 mg, about 30 mg, about 35 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about 140 mg, about 150 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 250 mg, about 280 mg, about 300 mg, about 325 mg, or about 350 mg.

2. The use according to claim 1, wherein the levetiracetam, brivaracetam, or seletracetam, or the pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, is formulated for extended release.

3. The use according to claim 1 or 2, wherein the levetiracetam, brivaracetam, or

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seletracetam, or the pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, is formulated for administration every 12 hours.

4. The use according to claim 1 or 2, wherein the levetiracetam, brivaracetam, or seletracetam, or the pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, is formulated for administration every 24 hours.

5. A pharmaceutical composition for treating cognitive impairment associated with a central nervous system (CNS) disorder, for delaying or slowing the progression of said cognitive impairment, or for reducing the rate of decline of cognitive function associated with said CNS disorder, in a subject having or at risk of having said cognitive impairment or decline of cognitive function, said pharmaceutical composition comprising levetiracetam, brivaracetam, or seletracetam, and a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing,

wherein the CNS disorder is amnestic mild cognitive impairment, dementia, prodromal Alzheimer's Disease, post-traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS), or cancer-therapy related cognitive impairment, and

wherein the levetiracetam, brivaracetam, or seletracetam, or the pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, is present in an amount of about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.12 mg, about 0.14 mg, about 0.16 mg, about 0.18 mg, about 0.2 mg, about 0.22 mg, about 0.24 mg, about 0.26 mg, about 0.28 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 1.2 mg, about 1.4 mg, about 1.6 mg, about 1.8 mg, about 2 mg, about 2.2 mg, about 2.4 mg, about 2.6 mg, about 2.8 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, about 20 mg, about 22 mg, about 25 mg, about 28 mg, about 30 mg, about 35 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about 140 mg, about 150 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 250 mg, about 280 mg, about 300 mg, about 325 mg, or about 350 mg.

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6. Use of levetiracetam, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for treating cognitive impairment associated with a central nervous system (CNS) disorder, for delaying or slowing the progression of said cognitive impairment, or for reducing the rate of decline of cognitive function associated with said CNS disorder, in a subject having or at risk of having said cognitive impairment or decline of cognitive function,

wherein the CNS disorder is amnestic mild cognitive impairment, dementia, prodromal Alzheimer's Disease, post-traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS), or cancer-therapy related cognitive impairment, and

wherein the levetiracetam, or the pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated for administration every 12 hours at a daily dose of about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, about 20 mg, about 22 mg, about 25 mg, about 28 mg, about 30 mg, about 35 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about 140 mg, about 150 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 250 mg, about 280 mg, about 300 mg, about 325 mg, or about 350 mg.

7. Use of levetiracetam, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for treating cognitive impairment associated with a central nervous system (CNS) disorder, for delaying or slowing the progression of said cognitive impairment, or for reducing the rate of decline of cognitive function associated with said CNS disorder, in a subject having or at risk of having said cognitive impairment or decline of cognitive function,

wherein the CNS disorder is amnestic mild cognitive impairment, dementia, prodromal Alzheimer's Disease, post-traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS), or cancer-therapy related cognitive impairment, and

wherein the levetiracetam, or the pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated for administration every 24 hours at a daily dose of about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, about 20 mg, about 22 mg, about 25 mg, about 28 mg, about 30 mg, about 35 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about

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140 mg, about 150 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 250 mg, about 280 mg, about 300 mg, about 325 mg, or about 350 mg.

8. Use of brivaracetam, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for treating cognitive impairment associated with a central nervous system (CNS) disorder, for delaying or slowing the progression of said cognitive impairment, or for reducing the rate of decline of cognitive function associated with said CNS disorder, in a subject having or at risk of having said cognitive impairment or decline of cognitive function,

wherein the CNS disorder is amnestic mild cognitive impairment, dementia, prodromal Alzheimer's Disease, post-traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS), or cancer-therapy related cognitive impairment, and

wherein the brivaracetam, or the pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated for administration every 12 hours at a daily dose of about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.12 mg, about 0.14 mg, about 0.16 mg, about 0.18 mg, about 0.2 mg, about 0.22 mg, about 0.24 mg, about 0.26 mg, about 0.28 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 1.2 mg, about 1.4 mg, about 1.6 mg, about 1.8 mg, about 2 mg, about 2.2 mg, about 2.4 mg, about 2.6 mg, about 2.8 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, about 20 mg, about 22 mg, about 25 mg, about 28 mg, about 30 mg, or about 35 mg.

9. Use of brivaracetam, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for treating cognitive impairment associated with a central nervous system (CNS) disorder, for delaying or slowing the progression of said cognitive impairment, or for reducing the rate of decline of cognitive function associated with said CNS disorder, in a subject having or at risk of having said cognitive impairment or decline of cognitive function,

wherein the CNS disorder is amnestic mild cognitive impairment, dementia, prodromal Alzheimer's Disease, post-traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS), or cancer-therapy related cognitive impairment, and

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wherein the brivaracetam, or the pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated for administration every 24 hours at a daily dose of about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.12 mg, about 0.14 mg, about 0.16 mg, about 0.18 mg, about 0.2 mg, about 0.22 mg, about 0.24 mg, about 0.26 mg, about 0.28 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 1.2 mg, about 1.4 mg, about 1.6 mg, about 1.8 mg, about 2 mg, about 2.2 mg, about 2.4 mg, about 2.6 mg, about 2.8 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, about 20 mg, about 22 mg, about 25 mg, about 28 mg, about 30 mg, or about 35 mg.

10. Use of seletracetam, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for treating cognitive impairment associated with a central nervous system (CNS) disorder, for delaying or slowing the progression of said cognitive impairment, or for reducing the rate of decline of cognitive function associated with said CNS disorder, in a subject having or at risk of having said cognitive impairment or decline of cognitive function,

wherein the CNS disorder is amnestic mild cognitive impairment, dementia, prodromal Alzheimer's Disease, post-traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS), or cancer-therapy related cognitive impairment, and

wherein the seletracetam, or the pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated for administration every 12 hours at a daily dose of about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.12 mg, about 0.14 mg, about 0.16 mg, about 0.18 mg, about 0.2 mg, about 0.22 mg, about 0.24 mg, about 0.26 mg, about 0.28 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 1.2 mg, about 1.4 mg, about 1.6 mg, about 1.8 mg, about 2 mg, about 2.2 mg, about 2.4 mg, about 2.6 mg, about 2.8 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, about 20 mg, about 22 mg, about 25 mg, about 28 mg, about 30 mg, or about 35 mg.

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11. Use of seletracetam, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for treating cognitive impairment associated with a central nervous system (CNS) disorder, for delaying or slowing the progression of said cognitive impairment, or for reducing the rate of decline of cognitive function associated with said CNS disorder, in a subject having or at risk of having said cognitive impairment or decline of cognitive function,

wherein the CNS disorder is amnestic mild cognitive impairment, dementia, prodromal Alzheimer's Disease, post-traumatic stress disorder (PTSD), schizophrenia, amyotrophic lateral sclerosis (ALS), or cancer-therapy related cognitive impairment, and

wherein the seletracetam, or the pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated for administration every 24 hours at a daily dose of about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.12 mg, about 0.14 mg, about 0.16 mg, about 0.18 mg, about 0.2 mg, about 0.22 mg, about 0.24 mg, about 0.26 mg, about 0.28 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 1.2 mg, about 1.4 mg, about 1.6 mg, about 1.8 mg, about 2 mg, about 2.2 mg, about 2.4 mg, about 2.6 mg, about 2.8 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 14 mg, about 16 mg, about 18 mg, about 20 mg, about 22 mg, about 25 mg, about 28 mg, about 30 mg, or about 35 mg.

12. The use according to any one of claims 1 and 6-11, wherein the CNS disorder is dementia.

13. The use according to claim 12, wherein the dementia is Alzheimer's disease (AD).

14. The pharmaceutical composition according to claim 5, wherein the CNS disorder is dementia.

15. The pharmaceutical composition according to claim 14, wherein the dementia is Alzheimer's disease (AD).

16. The use according to claim 10 or 11, wherein the seletracetam, or the pharmaceutically

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acceptable salt, hydrate, or solvate thereof, is formulated for extended release.

17. The use according to claim 6 or 7, wherein the levetiracetam, or the pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated for extended release.

18. The use according to claim 8 or 9, wherein the brivaracetam, or the pharmaceutically acceptable salt, hydrate, or solvate thereof, is formulated for extended release.

19. The pharmaceutical composition according to claim 5, wherein the levetiracetam, brivaracetam, or seletracetam, or the pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, is formulated for extended release.

20. The pharmaceutical composition according to claim 5, wherein the levetiracetam, brivaracetam, or seletracetam, or the pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, is formulated for administration every 12 hours.

21. The pharmaceutical composition according to claim 5, wherein the levetiracetam, brivaracetam, or seletracetam, or the pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, is formulated for administration every 24 hours.

22. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 10 mg.

23. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 12 mg.

24. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 14 mg.

25. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 16 mg.

26. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 18 mg.

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27. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 20 mg.

28. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 22 mg.

29. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 25 mg.

30. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 28 mg.

31. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 30 mg.

32. The use according to any one of claims 1 and 8-11, wherein the daily dose is about 35 mg.

33. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 100 mg.

34. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 120 mg.

35. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 140 mg.

36. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 150 mg.

37. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 160 mg.

38. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 180 mg.

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39. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 200 mg.

40. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 220 mg.

41. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 240 mg.

42. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 250 mg.

43. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 280 mg.

44. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 300 mg.

45. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 325 mg.

46. The use according to any one of claims 1, 6, and 7, wherein the daily dose is about 350 mg.

47. The pharmaceutical composition according to claim 5, wherein the amount is about 10 mg.

48. The pharmaceutical composition according to claim 5, wherein the amount is about 12 mg.

49. The pharmaceutical composition according to claim 5, wherein the amount is about 14 mg.

50. The pharmaceutical composition according to claim 5, wherein the amount is about 16 mg.

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51. The pharmaceutical composition according to claim 5, wherein the amount is about 18 mg.

52. The pharmaceutical composition according to claim 5, wherein the amount is about 20 mg.

53. The pharmaceutical composition according to claim 5, wherein the amount is about 22 mg.

54. The pharmaceutical composition according to claim 5, wherein the amount is about 25 mg.

55. The pharmaceutical composition according to claim 5, wherein the amount is about 28 mg.

56. The pharmaceutical composition according to claim 5, wherein the amount is about 30 mg.

57. The pharmaceutical composition according to claim 5, wherein the amount is about 35 mg.

58. The pharmaceutical composition according to claim 5, wherein the amount is about 100 mg.

59. The pharmaceutical composition according to claim 5, wherein the amount is about 120 mg.

60. The pharmaceutical composition according to claim 5, wherein the amount is about 140 mg.

61. The pharmaceutical composition according to claim 5, wherein the amount is about 150 mg.

62. The pharmaceutical composition according to claim 5, wherein the amount is about 160 mg.

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63. The pharmaceutical composition according to claim 5, wherein the amount is about 180 mg.

64. The pharmaceutical composition according to claim 5, wherein the amount is about 200 mg.

65. The pharmaceutical composition according to claim 5, wherein the amount is about 220 mg.

66. The pharmaceutical composition according to claim 5, wherein the amount is about 240 mg.

67. The pharmaceutical composition according to claim 5, wherein the amount is about 250 mg.

68. The pharmaceutical composition according to claim 5, wherein the amount is about 280 mg.

69. The pharmaceutical composition according to claim 5, wherein the amount is about 300 mg.

70. The pharmaceutical composition according to claim 5, wherein the amount is about 325 mg.

71. The pharmaceutical composition according to claim 5, wherein the amount is about 350 mg.

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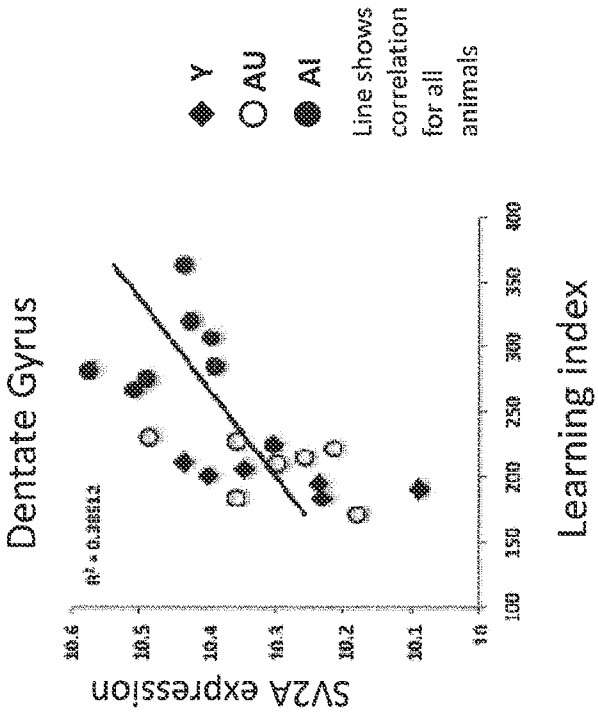

Dentate Gyrus
SV2A expression
Learning index
Y
AU
AI
Line shows correlation for all animals
Correlations:
All r= 0.62
Aged: r = 0.61

FIG. 1

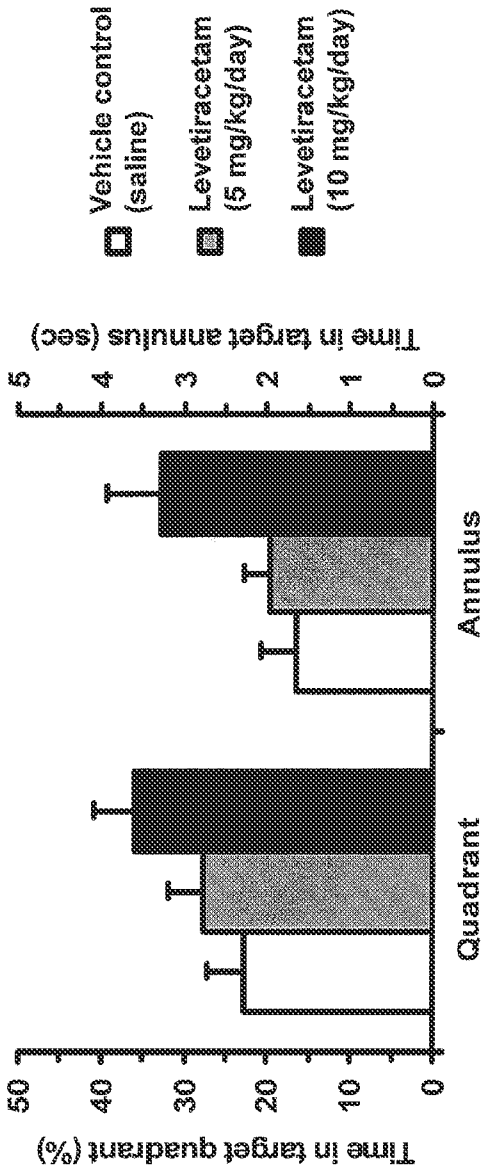
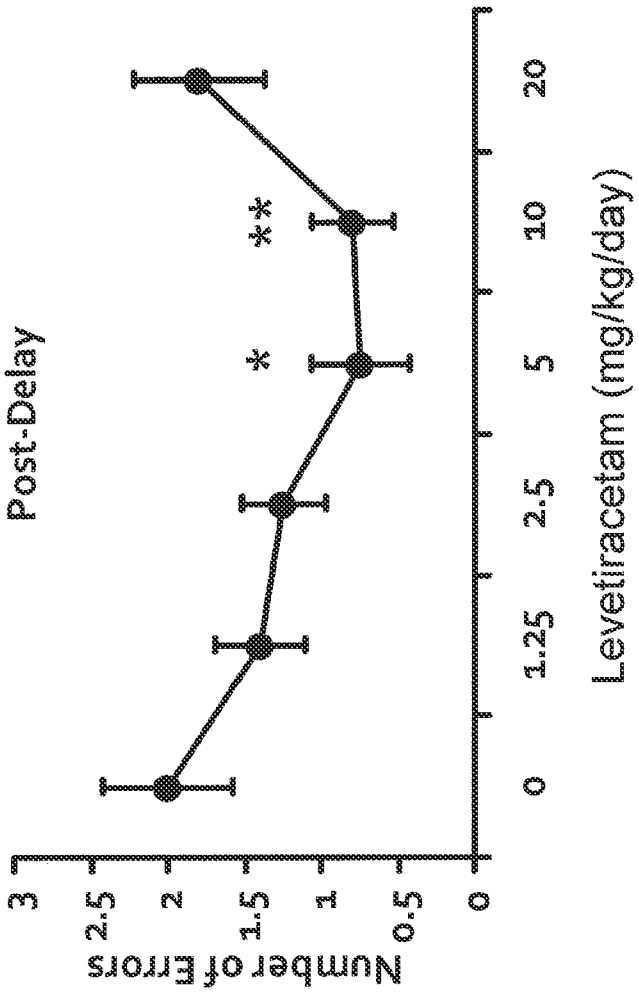

Vehicle control (saline)
Levetiracetam (5 mg/kg/day)
Levetiracetam (10 mg/kg/day)
Time in target annulus (sec)
0
1
2
3
4
5
Annulus
Quadrant
Time in target quadrant (%)
0
10
20
30
40
50

FIG. 2



* t(9) = 2.18, p = 0.057
** t(9) = 2.37, p = 0.042

FIG. 3

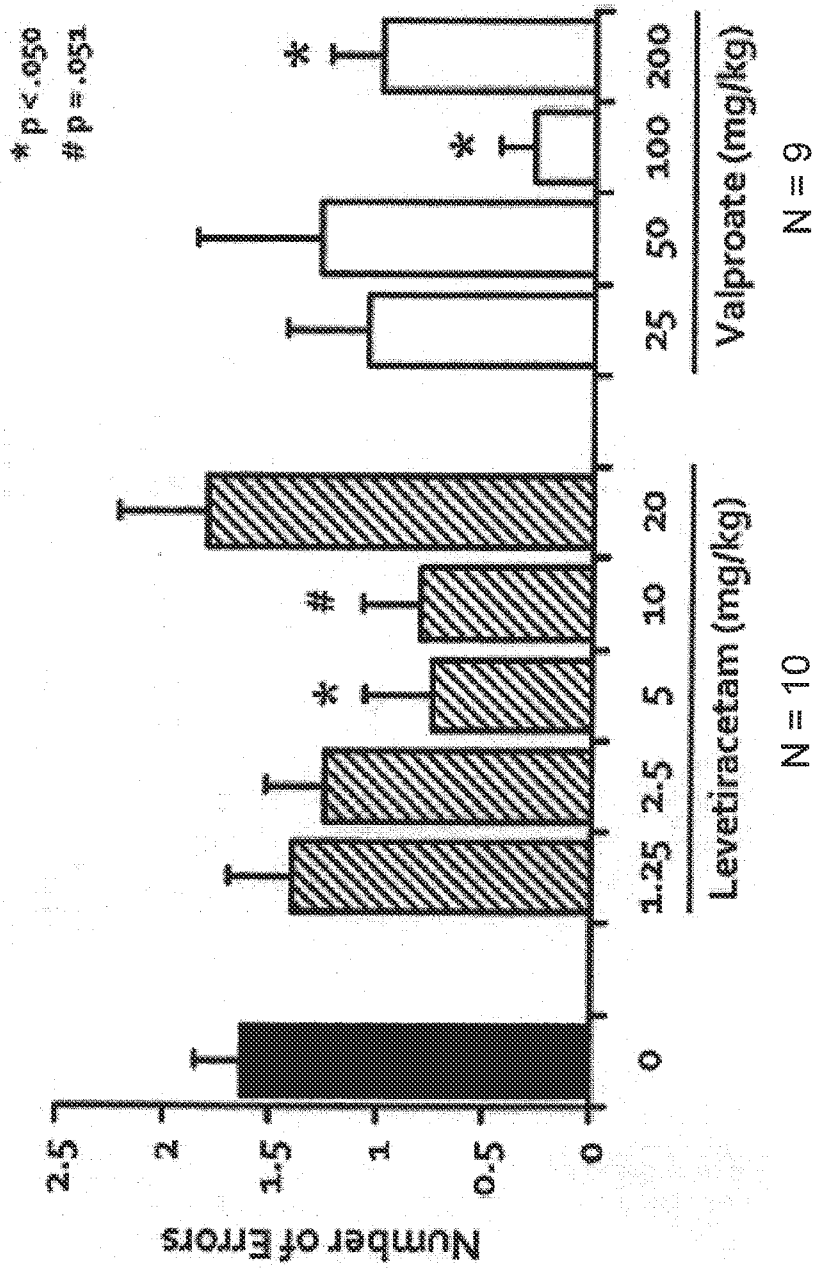

* p < .050
# p = .051
Number of Errors
2.5
2
1.5
1
0.5
0
0
1.25
2.5
5
10
20
Levetiracetam (mg/kg)
N = 10
25
50
100
200
Valproate (mg/kg)
N = 9

FIG. 4

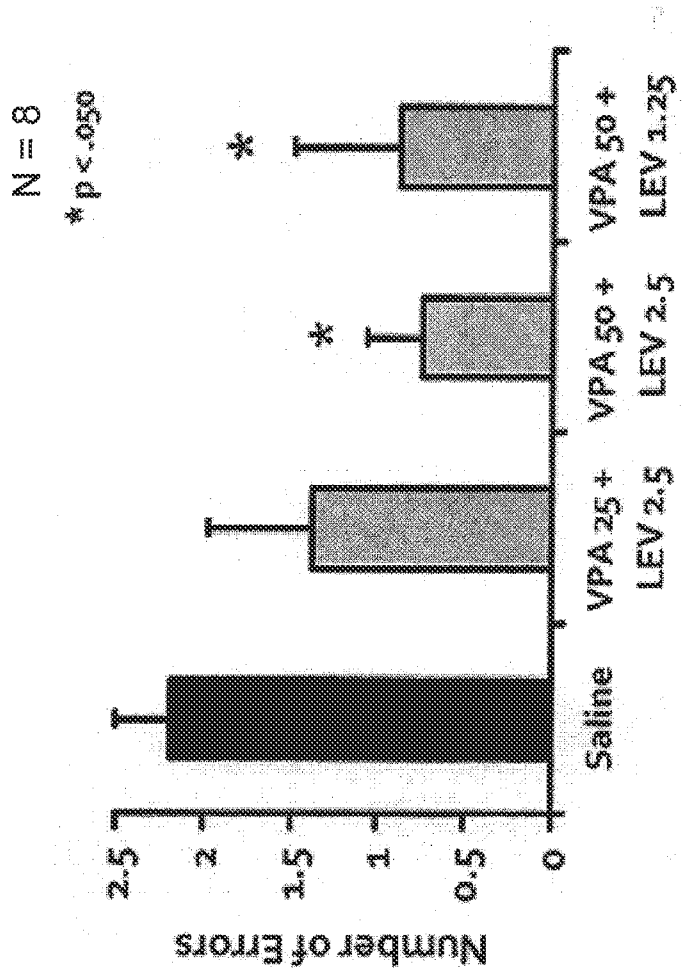

N = 8
* p <.050
Number of Errors
2.5
2
1.5
1
0.5
0
Saline
VPA 25 + LEV 2.5
VPA 50 + LEV 2.5
VPA 50 + LEV 1.25
*
*
*

FIG. 5

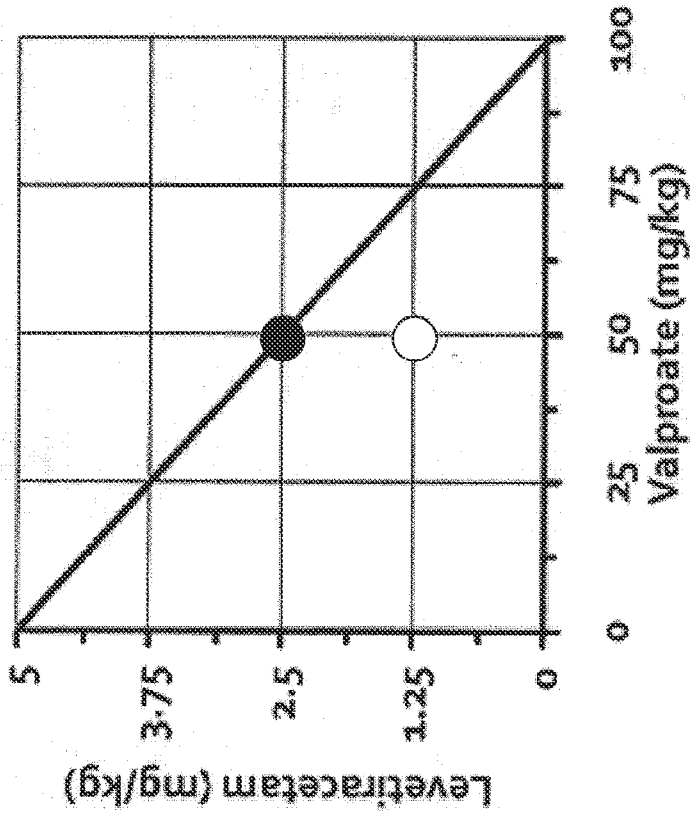

Levetiracetam (mg/kg)
5
3.75
2.5
1.25
0
0
25
50
75
100
Valproate (mg/kg)

FIG. 6

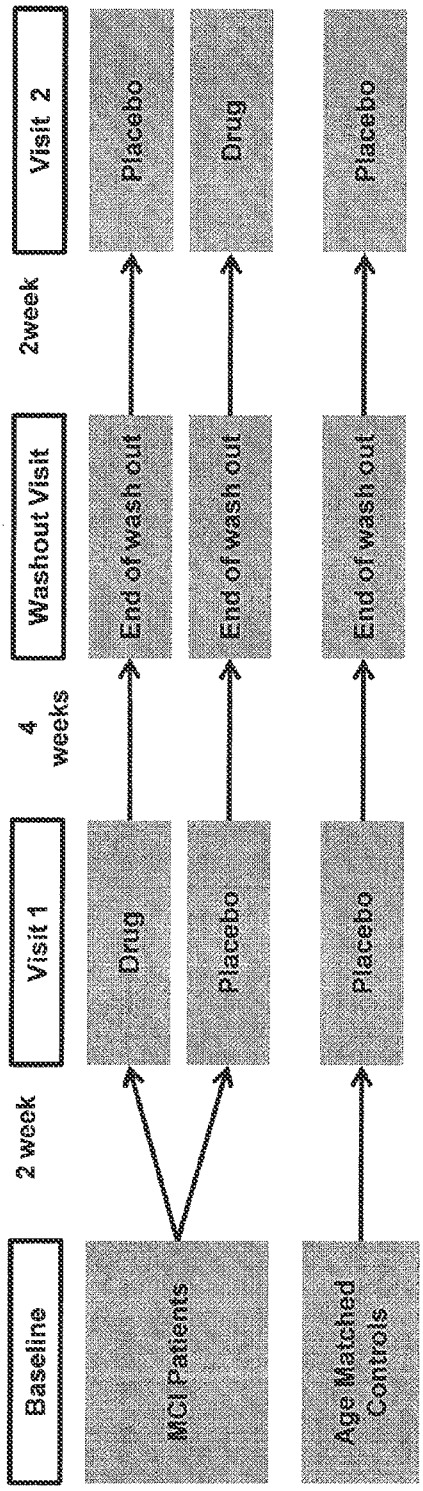
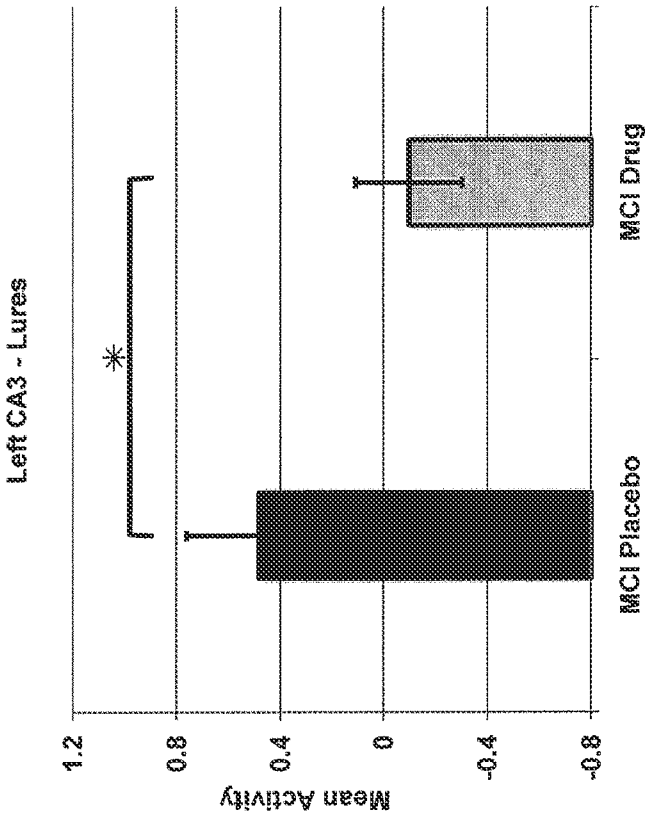
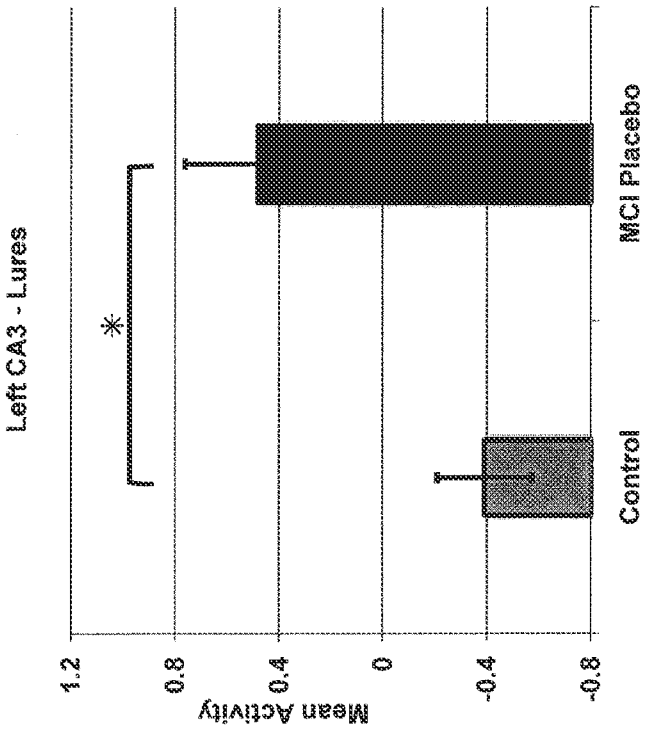

Baseline
2 week
Visit 1
4 weeks
Washout Visit
2week
Visit 2
MCI Patients
Drug
Placebo
End of wash out
Placebo
Age Matched Controls
Placebo
End of wash out
Drug
Drug
End of wash out
Placebo

FIG. 7



*Paired samples t-test: t = 2.276, p = 0.037

FIG. 8B



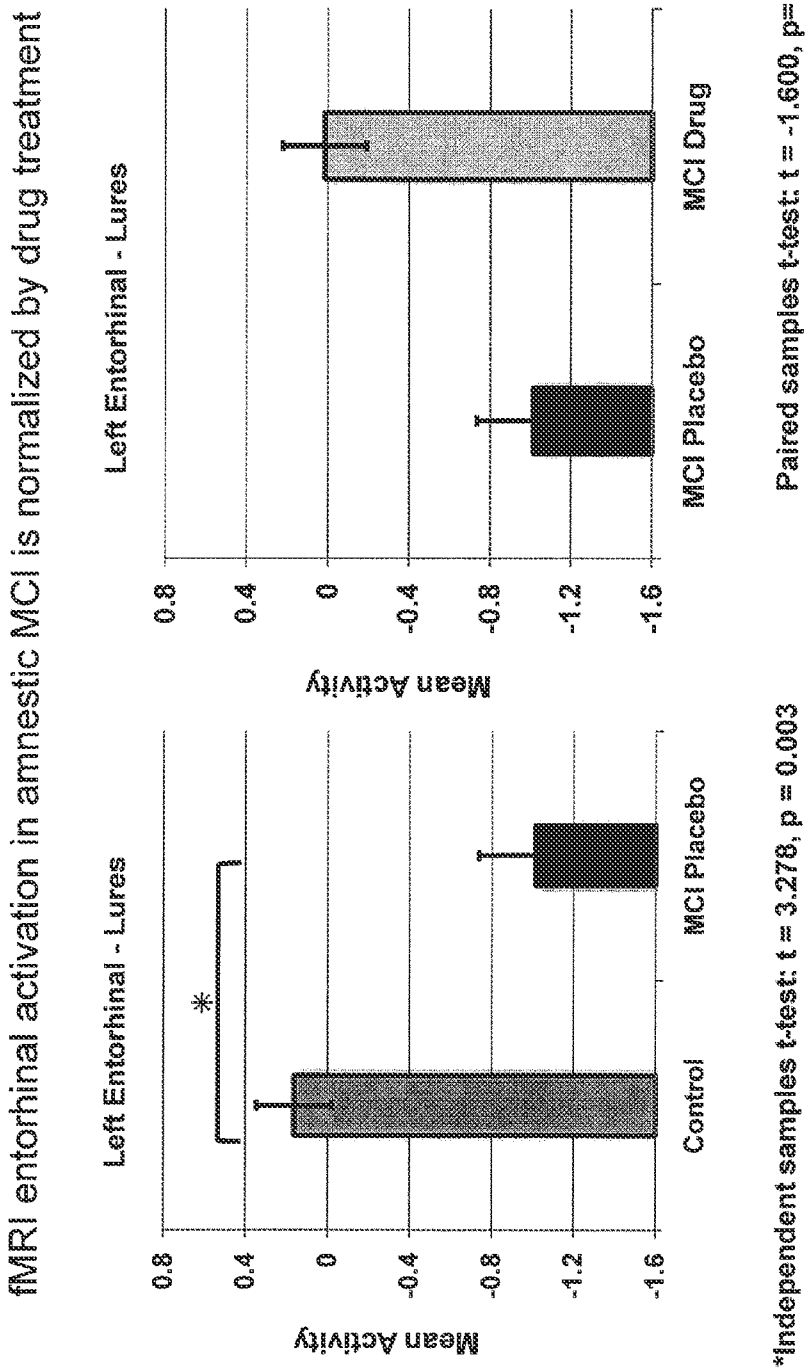
*Independent samples t-test: t = -2.636, p = 0.013

FIG. 8A

Left CA3 Lures

Group	Mean Activity	Standard Error
Control	-0.39129	0.182628
MCI Placebo	0.48440	0.277487
MCI Drug	-0.09653	0.205892

FIG. 8C



*Independent samples t-test: t = 3.278, p = 0.003

FIG. 9A

Paired samples t-test: t = -1.600, p= 0.129

FIG. 9B

Left Entorhinal Lures

Group	Mean Activity	Standard Error
Control	0.16444	0.143864
MCI Placebo	-1.01273	0.329062
MCI Drug	0.016291	0.411762

FIG. 9C

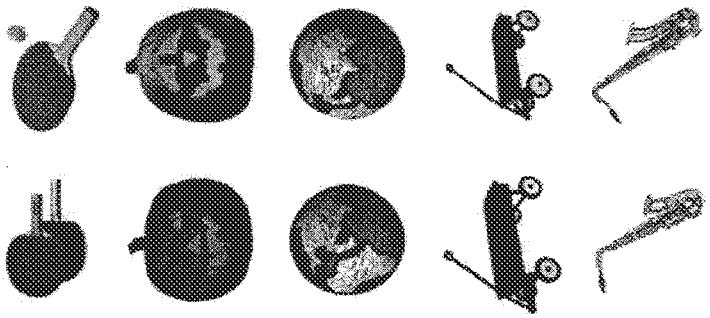


FIG. 10B

FIG. 10A

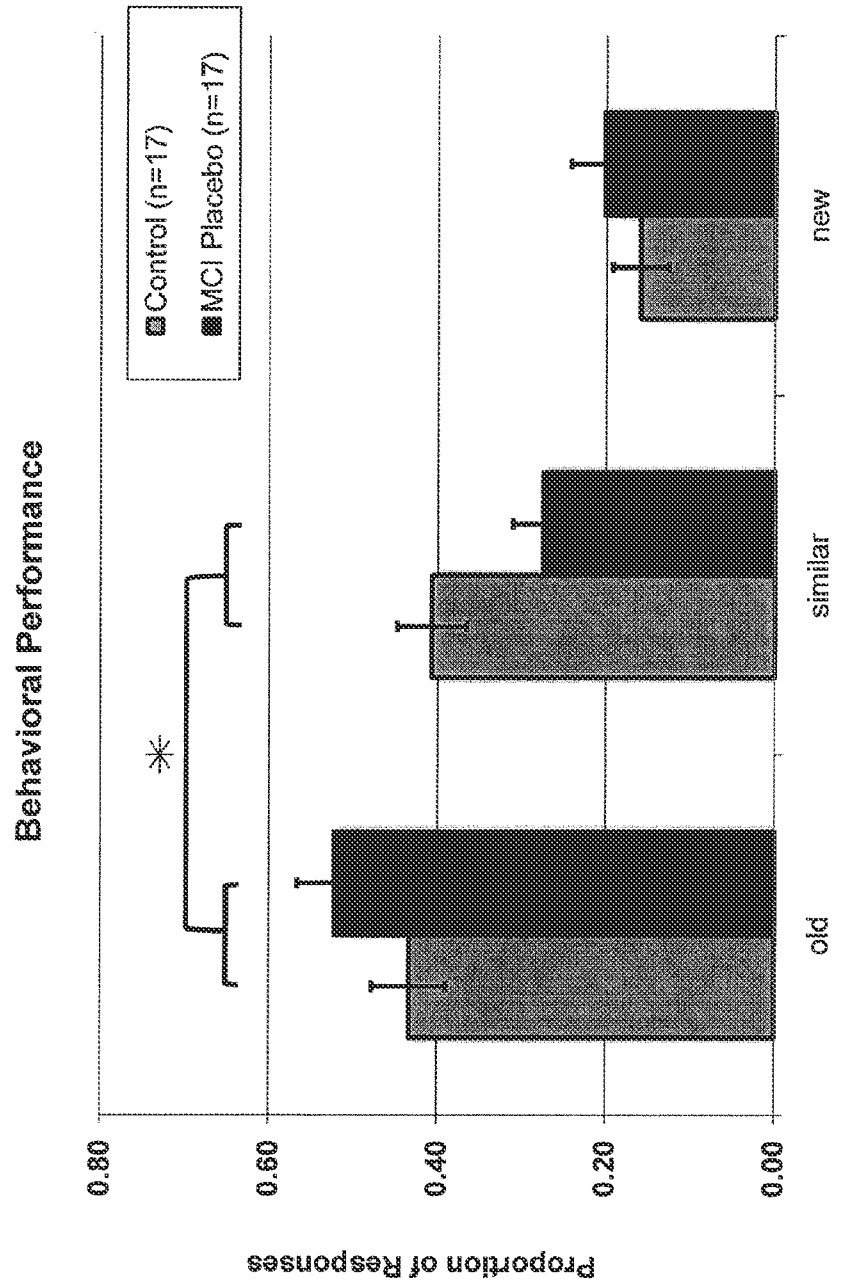

Behavioral Performance
Control (n=17)
MCI Placebo (n=17)
*
0.80
0.60
0.40
0.20
0.00
Proportion of Responses
old
similar
new
Control vs. MCI Placebo by Old vs. Similar: F= 7.687, p = 0.009

FIG. 11

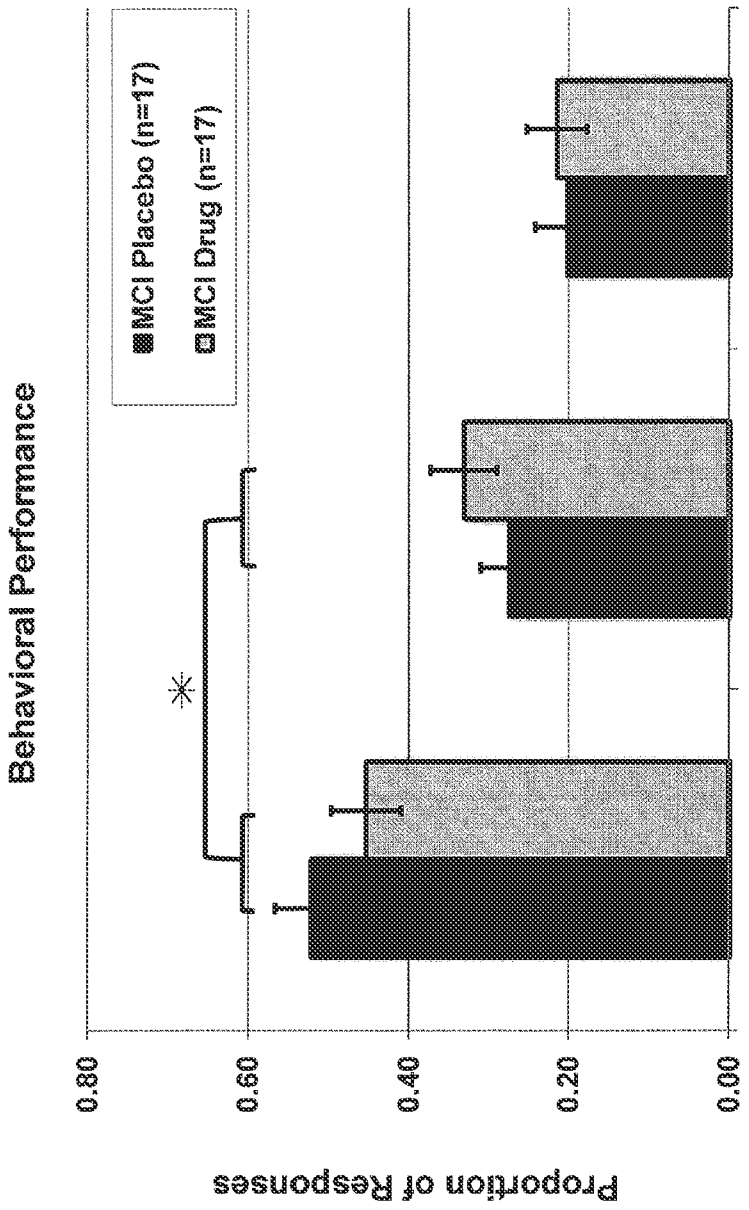

Behavioral Performance
MCI Placebo (n=17)
MCI Drug (n=17)
Proportion of Responses
0.80
0.60
0.40
0.20
0.00
old
similar
new
MCI Drug vs. MCI Placebo by Old vs. Similar: F = 5.028, p = 0.039

FIG. 12

Behavioral Performance

Control Subjects	Proportion of Responses	Standard Error
Old	0.433676	0.04426
Similar	0.406771	0.04135
New	0.159553	0.03312
MCI Placebo Subjects	Proportion of Responses	Standard Error
Old	0.52262	0.04871
Similar	0.27549	0.03956
New	0.20188	0.04528
MCI Drug Subjects	Proportion of Responses	Standard Error
Old	0.45361	0.04825
Similar	0.33144	0.04592
New	0.21494	0.04202

FIG. 13

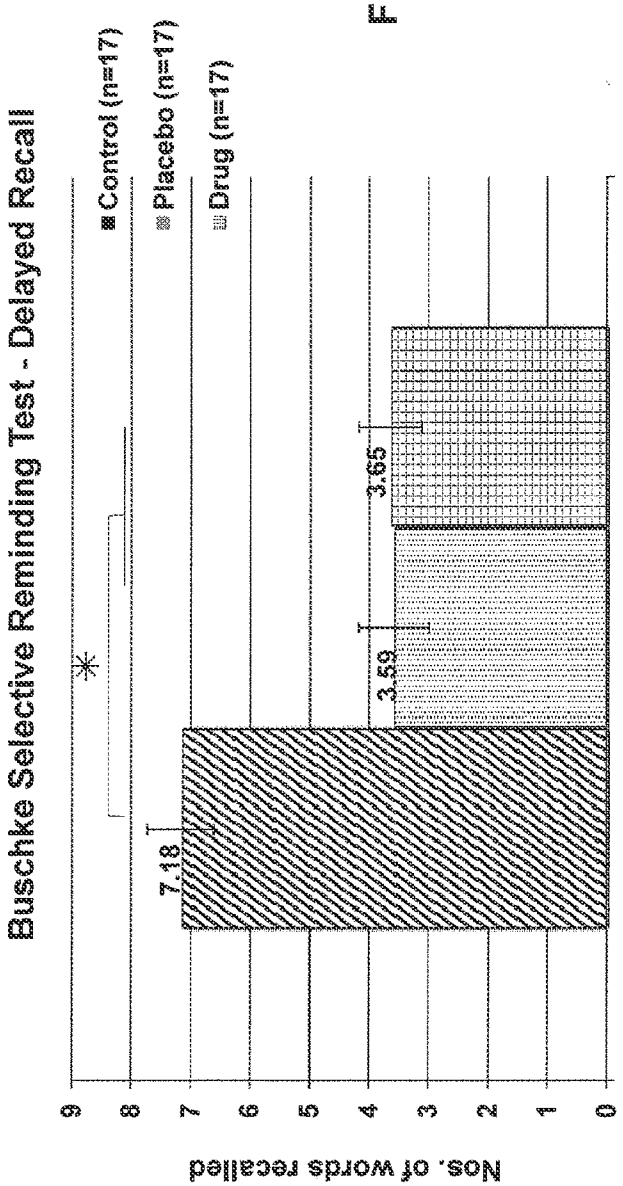


FIG. 14A

Group	Mean	Standard Error	Delayed (p-value)
Control	7.18	0.56	Control vs. Placebo: <0.001
MCI Placebo	3.59	0.59	Control vs. Drug: < 0.001
MCI Drug	3.65	0.53	Placebo vs. Drug: 0.887

FIG. 14B

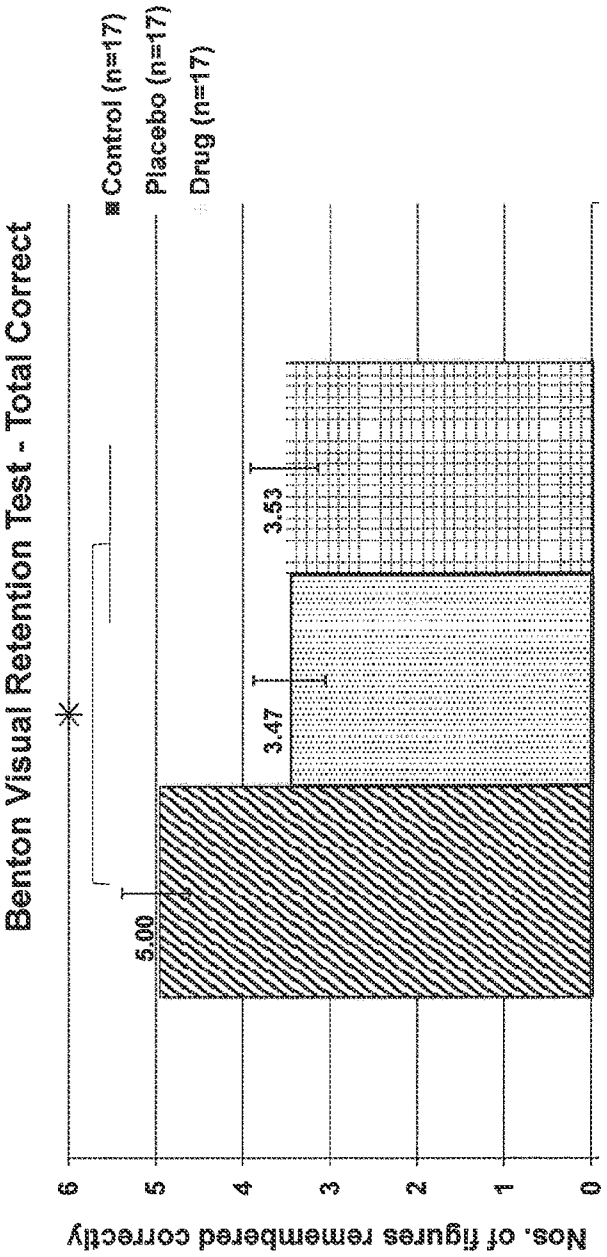


FIG. 15A

Group	Mean	Standard Error	Total Correct (p-value)
Control	5.00	0.38	Control vs. Placebo: 0.011
MCI Placebo	3.47	0.41	Control vs. Drug: 0.011
MCI Drug	3.53	0.38	Placebo vs. Drug: 0.805

FIG. 15B

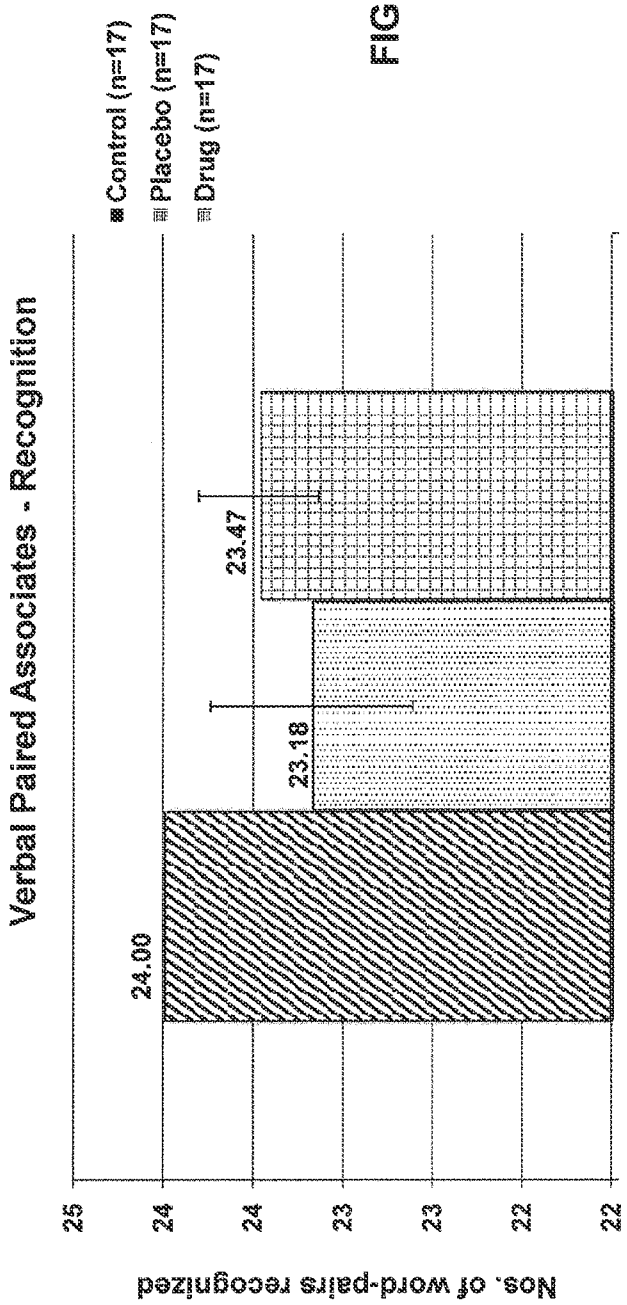


FIG. 16A

Group	Mean	Standard Error	Recognition (p-value)
Control	24.00	0.00	Control vs. Placebo: 0.154
MCI Placebo	23.18	0.56	Control vs. Drug: 0.122
MCI Drug	23.47	0.33	Placebo vs. Drug: 0.428

FIG. 16B

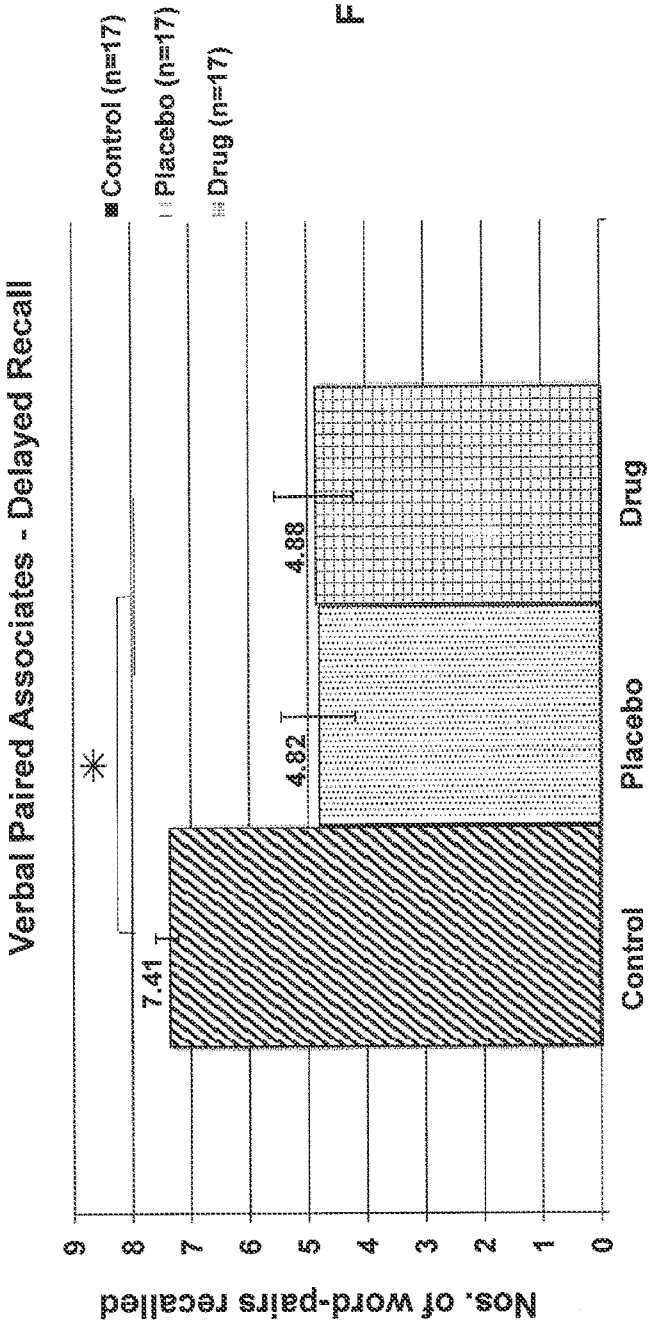


FIG. 17A

Group	Mean	Standard Error	Delayed Recall (p-value)
Control	7.41	0.19	Control vs. Placebo: <0.001
MCI Placebo	4.82	0.63	Control vs. Drug: 0.001
MCI Drug	4.88	0.67	Placebo vs. Drug: 0.848

FIG. 17B

Study Status

	Control subjects	MCI subjects	Total subjects
Participated in screening	26	32	58
Screening failures	4	9	13
Enrolled	22	23	45
Removed or withdrew from study	5	6	11
Total subjects used in analysis	17	17	34

FIG. 18A

Characteristics of Study Samples

	Control Subjects	MCI Subjects	p
N	17	17	
Sex (M/F)	9/8	6/11	0.307
Age (yrs)	69.3 (7.0)	72.9 (8.9)	0.201
Education (yrs)	15.9 (2.6)	15.8 (2.9)	0.951
Race (Caucasian/African American)	17/0	14/3	0.074
Hispanic or Latino (y/n)	0/17	1/16	0.317

FIG. 18B