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(54) Title: A NEW COMBINATION OF (A) AN ALPHA-4-BETA-2 -NEURONAL NICOTINIC AGONIST AND (B) A GSK3 INHIBITOR

(57) Abstract: The present invention related to a combination of (a) a $\alpha 4 \beta 2$ -neuronal nicotinic agonist and (b) a GSK3 inhibitor. The invention further relates to pharmaceutical compositions comprising said combination and to methods of treating CNS disorders in mammals by administering said combination. The invention further relates to a kit comprising the combination and use of said kits in treatment of CNS disorders such as dementia and/or Alzheimer's Disease.

WO 2009/017455 A1

**A new combination of (a) an α 4 β 2-neuronal
nicotinic agonist and (b) a GSK3 inhibitor**

FIELD OF THE INVENTION

The present invention relates to a combination of (a) an α 4 β 2-nicotinic agonist and (b) a GSK3 inhibitor. The invention further relates to pharmaceutical compositions comprising
5 said combination and to methods of treating CNS disorders in mammals by administering said combination. The invention further relates to a kit comprising the combination and use of said kit in treatment of CNS disorders such as dementia and/or Alzheimer's Disease.

Glycogen synthase kinase 3 (GSK3) is a serine / threonine protein kinase composed of two
10 isoforms (α and β), which are encoded by distinct genes but are highly homologous within the catalytic domain. GSK3 is highly expressed in the central and peripheral nervous system. GSK3 phosphorylates several substrates including tau, β -catenin, glycogen synthase, pyruvate dehydrogenase and elongation initiation factor 2b (eIF2b). Insulin and growth factors activate protein kinase B, which phosphorylates GSK3 on serine 9 residue
15 and inactivates it.

Alzheimer's Disease (AD) dementias, and taupathies.

AD is characterized by cognitive decline, cholinergic dysfunction and neuronal death, neurofibrillary tangles and senile plaques consisting of amyloid- β deposits. The sequence
20 of these events in AD is unclear, but are believed to be related. Glycogen synthase kinase 3 β (GSK3), previously known as Tau kinase I selectively phosphorylates the microtubule associated protein Tau at sites that are hyperphosphorylated in AD brains.

Hyperphosphorylated tau has lower affinity for microtubules and accumulates as paired helical filaments. This results in depolymerization of microtubules, which leads to dying
25 back of axons and neuritic dystrophy. The paired helical filaments are the main components that constitute neurofibrillary tangles and neurophil threads in AD brains. In addition to AD, neurofibrillary tangles are consistently found in other CNS diseases such as amyotrophic lateral sclerosis, parkinsonism-dementia of Gaum, corticobasal degeneration, dementia pugilistica and head trauma, Down's syndrome, postencephalatic

parkinsonism, progressive supranuclear palsy, Niemann-Pick's Disease and Pick's Disease.

GSK3 has been proposed as the link between the two neuropathological hallmarks of Alzheimer's disease, the extracellular amyloid- β and the neurofibrillary tangles made of hyperphosphorylated tau. Addition of amyloid- β to primary hippocampal cultures results in hyperphosphorylation of tau and a paired helical filaments-like state via induction of GSK3 activity, followed by disruption of axonal transport and neuronal death (Imahori and Uchida., J. Biochem 121:179-188, 1997). GSK3 preferentially associates with neurofibrillary tangles and has been shown to accumulate in the cytoplasm of pre-tangle neurons in AD brains. GSK3 protein levels are also increased by 50% in brain tissue from AD patients (Pei, et al., J. Neuropathol. Exp. Pathol. 58: 1010-1019, 1999). Furthermore, GSK3 phosphorylates pyruvate dehydrogenase, a key enzyme in the glycolytic pathway and prevents the conversion of pyruvate to acetyl-Co-A (Hoshi et al., PNAS 93:2719-2723, 1996). Acetyl-Co-A is critical for the synthesis of acetylcholine, a key neurotransmitter in cognitive functions. Accumulation of amyloid- β is an early event in AD. GSK3 Tg mice show increased levels of amyloid- β in brain. Also, PDAPP mice fed with lithium show decreased amyloid- β levels in hippocampus and decreased amyloid plaque area (Su et al., Biochemistry 2004, 43:6899-6908). Thus, GSK3 inhibition may have additional disease modification effects through reduction of amyloid- β levels as well as the tau pathology associated with AD and the other - diseases referred to above.

Chronic and Acute Neurodegenerative Diseases

Growth factor mediated activation of the PI3K /Akt pathway has been shown to play a key role in neuronal survival. The activation of this pathway results in GSK3 β inhibition.

Recent studies (Bhat et. al., PNAS 97:11074-11079 (2000)) indicate that GSK3 activity is increased in cellular and animal models of neurodegeneration such as cerebral ischemia or after growth factor deprivation. For example, the active site phosphorylation was increased in neurons vulnerable to apoptosis, a type of cell death commonly thought to occur in chronic and acute degenerative diseases such as cognitive disorders, Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, Huntington's Disease and HIV

dementia and traumatic brain injury; and as in ischemic stroke. Lithium was neuroprotective in inhibiting apoptosis in cells and in the brain at doses that resulted in the inhibition of GSK3. Thus GSK3 inhibitors could be useful in attenuating the course of neurodegenerative diseases.

5

Bipolar Disorders (BD)

Bipolar Disorders are characterised by manic episodes and depressive episodes. Lithium has been used to treat BD based on its mood stabilising effects. The disadvantage of lithium is the narrow therapeutic window and the danger of overdosing that can lead to
10 lithium intoxication. The discovery that lithium inhibits GSK3 at therapeutic concentrations has raised the possibility that this enzyme represents a key target of lithium's action in the brain (Stambolic et al., Curr. Biol. 6:1664-1668, 1996; Klein and Melton; PNAS 93:8455-8459, 1996; Gould et al., Neuropsychopharmacology, 1:32-8, 2004). GSK3 inhibitor has been shown to reduce immobilisation time in forced swim test,
15 a model to assess depressive behaviour (O'Brien et al., J Neurosci 2004, 24:66791-6798) GSK3 has been associated with a polymorphism found in bipolar II disorder (Szczepankiewicz et al., Neuropsychobiology. 2006;53(1):51-6). Inhibition of GSK3 β may therefore be of therapeutic relevance in the treatment of BD as well as in AD patients that have affective disorders.

20

Schizophrenia

Accumulating evidence implicates abnormal activity of GSK3 in mood disorders and schizophrenia. GSK3 is involved in signal transduction cascades of multiple cellular processes, particularly during neural development. Kozlovsky et al (Am J Psychiatry 2000
25 May; 157(5):831-3) found that GSK3 levels were 41% lower in the schizophrenic patients than in comparison subjects. This study indicates that schizophrenia involves neurodevelopmental pathology and that abnormal GSK3 regulation could play a role in schizophrenia. Furthermore, reduced β -catenin levels have been reported in patients exhibiting schizophrenia (Cotter et al., Neuroreport 9:1379-1383 (1998)). Atypical
30 antipsychotics such as olanzapine, clozapine, quetiapine, and ziprasidone, inhibit GSK3 by

increasing ser9 phosphorylation suggesting that antipsychotics may exert their beneficial effects via GSK3 inhibition (Rosborough et al., Int J Neuropsychopharmacol, 4:1-13 2006).

5 The neuronal nicotinic agonists are known to provide benefits in the area of the treatment and/or prevention of central nervous system (CNS) disorders. Compounds having agonist or partial agonist activity against the alpha-4/beta-2, or $\alpha 4/\beta 2$, receptor ($\alpha 4\beta 2$ -neuronal nicotinic agonist) modulate neuronal nicotinic receptors in the patient's brain. As such, the compounds have the ability to express neuronal nicotinic pharmacology, and in particular,
10 to act as neuronal nicotinic agonists.

The neuronal nicotinic agonists described herein may be used in methods for preventing and/or treating a central nervous system disorder (CNS) in a subject susceptible to such a disorder. For example, an effective amount of a neuronal nicotinic agonists effective for
15 providing some degree of prevention of the progression of a CNS disorder (i.e., provide protective effects), amelioration of the symptoms of a CNS, and amelioration of the reoccurrence of a CNS, can be administered to a patient in need thereof.

The neuronal nicotinic agonists can be used to treat and/or prevent those types of conditions and disorders for which other types of neuronal nicotinic compounds have been
20 proposed as therapeutics.

The neuronal nicotinic agonists are useful in the treatment of a variety of CNS disorders, for example neurodegenerative disorders, neuroinflammatory disorders, cognitive disorders such as Alzheimer's Disease, Cognitive Deficit in Schizophrenia, or any disorder mentioned below.

25

SUMMARY OF THE INVENTION

This invention relates to compositions comprising a pharmaceutical combination of (a) an $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a GSK3 inhibitor useful for the treatment of CNS disorders, such as those disorders defined below.

The inventions also relates to said combination, wherein the $\alpha 4\beta 2$ -neuronal nicotinic agonist is N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, and pharmaceutically-acceptable salts, solvates or solvated salts thereof, and the GSK3 inhibitor is one of the compounds mentioned below.

5 A second aspect of the invention relates to a pharmaceutical composition comprising a combination comprising (a) a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a second therapeutic agent, which is a GSK3 inhibitor, together with a pharmaceutically-acceptable vehicle, carrier or diluent. One embodiment of the invention relates to one pharmaceutical composition comprising both agents (a) and (b). Another
10 embodiment relates to a two separate pharmaceutical compositions, one for (a) and one for (b).

A third aspect of the invention relates to a kit comprising a dosage unit of a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and a dosage unit of a second therapeutic agent, which is a GSK3 inhibitor, optionally with instructions for use.

15 A fourth aspect of the invention relates to a method for treating CNS disorders, such as those disorders defined below, in a subject in need thereof comprising administering simultaneously, sequentially, concomitantly or separately, to said subject (a) a therapeutically effective amount of a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a therapeutically effective amount of a second therapeutic agent,
20 which is a GSK3 inhibitor, wherein the amounts of (a) and (b) are together synergistically effective in the treatment.

DETAILED DESCRIPTION OF THE INVENTION

Combination

25 A first aspect of the invention relates to a combination comprising (a) a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a second therapeutic agent, which is a GSK3 inhibitor. In one embodiment of the invention the combination comprises the group of compounds (a) and (b) as defined below.

$\alpha 4\beta 2$ -neuronal nicotinic agonist useful in the combination of the present invention are those described in US 6,603,011 and US 6,958,399, which are hereby incorporated by reference. Particular nicotinic agonists are compounds N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine, (4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine and (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, metabolites or prodrugs and pharmaceutically-acceptable salts, cocrystals, solvates or solvated salts of any of the foregoing. The preparation of these compounds is described in said US patents.

Other $\alpha 4\beta 2$ -neuronal nicotinic agonist useful in the combination of the present invention are those described in WO2008/057938, for example compound 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane and pharmaceutically-acceptable salts, solvates or solvated salts of any of the foregoing.

Suitable GSK3 inhibitors useful in the combination of the present invention and the preparation thereof are described in patent applications WO 03/004472, WO 03/055492, WO 03/082853, WO 06/001754, WO 07/040436, WO 07/040438, WO 07/040439 and WO 07/040440, WO08/002244 and WO08/992245, which are hereby incorporated by reference.

Particular GSK inhibitors are compounds selected from the group comprising 3-[7-(2-morpholin-4-ylethoxy)quinazolin-4-yl]-2-oxo-1,3-dihydroindole-5-carbonitrile;
3-[7-(2-methoxyethoxy)quinazolin-4-yl]-2-oxo-1,3-dihydroindole-5-carbonitrile;
3-[7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl]-2-oxo-1,3-dihydroindole-5-carbonitrile;
3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-2-oxo-1,3-dihydroindole-5-carbonitrile;
2-hydroxy-3-[5-(4-methylpiperazine-1-carbonyl)pyridin-2-yl]-1H-indole-5-carbonitrile;
1-[(4-methoxyphenyl)methyl]-3-(5-nitro-1,3-thiazol-2-yl)urea;
2-hydroxy-3-[5-[(4-phenylpiperazin-1-yl)methyl]pyridin-2-yl]-1H-indole-5-carbonitrile;
2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile;
2-hydroxy-3-[5-(4-methylpiperazin-1-yl)sulfonylpyridin-2-yl]-1H-indole-5-carbonitrile;
2-hydroxy-3-[5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl]-1H-indole-5-carbonitrile;
3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-5-nitro-1H-indol-2-ol;

- 2-hydroxy-3-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile;
[6-(2-hydroxy-5-nitro-1H-indol-3-yl)pyridin-3-yl]-(4-methylpiperazin-1-yl)methanone;
2-hydroxy-3-[5-(1-piperidylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile;
2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-6-carbonitrile;
5 2-hydroxy-3-[5-(4-methylpiperazin-1-yl)sulfonylpyridin-2-yl]-1H-indole-6-carbonitrile;
3-fluoro-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-2-oxo-1H-indole-6-carbonitrile;
[4-[5-(4-methoxyphenyl)-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl]phenyl]-(4-methylpiperazin-1-yl)methanone;
3-(4-methoxyphenyl)-N-(2-morpholin-4-ylethyl)-5,7-diazabicyclo[4.3.0]nona-1,3,5,8-
10 tetraene-9-carboxamide;
3-(4-chlorophenyl)-N-(2-morpholin-4-ylethyl)-5,7-diazabicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carboxamide;
5-fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine;
15 [4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;
[4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]phenyl]-phenyl-methanone;
N-(3-methoxypropyl)-8-[4-(trifluoromethyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-
20 1,3,5,7-tetraene-5-carboxamide;
5-(4-methoxyphenyl)-8-[4-(1-piperidylmethyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene;
N-(3-methoxypropyl)-8-[4-(morpholin-4-ylmethyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene-5-carboxamide;
25 [4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]phenyl]-pyridin-2-yl-methanone;
[4-[[4-(3-cyclohexyl-2-methyl-imidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;
[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;
30

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]pyrimidin-2-amine;

4-(2,3-dimethylimidazol-4-yl)-5-fluoro-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine;

5 [4-[5-(4-chlorophenyl)-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl]phenyl]-(4-methylpiperazin-1-yl)methanone;

N-(3-methoxypropyl)-8-[3-(2,2,3,3-tetrafluoropropoxymethyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene-5-carboxamide;

10 [4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-pyridin-2-yl-methanone;

[4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]-pyridin-2-yl-methanone;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine;

15 [4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;

4-(2,3-dimethylimidazol-4-yl)-5-fluoro-N-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]pyrimidin-2-amine;

20 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(4-methylsulfonylphenyl)pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine;

[4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-2-(trifluoromethoxy)phenyl]-(4-methylpiperazin-1-yl)methanone;

25 5-fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;

azetidin-1-yl-[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]methanone;

30 5-fluoro-N-[3-methyl-4-(morpholin-4-ylmethyl)phenyl]-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-amine;

5-fluoro-N-[4-(morpholin-4-ylmethyl)phenyl]-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;

5-fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-amine;

5 [4-[[5-fluoro-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;

5-[5-fluoro-2-[[4-(4-methylpiperazin-1-yl)sulfonylphenyl]amino]pyrimidin-4-yl]-1-(oxan-4-yl)imidazole-2-carbonitrile;

5-fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;

5-fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine;

[4-[[5-fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;

15 N-(2-cyanoethyl)-3-[5-(4-methoxyphenyl)-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl]benzamide;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-methylsulfonyl-3-(trifluoromethyl)phenyl]pyrimidin-2-amine;

20 azetidin-1-yl-[4-[8-[4-(morpholin-4-ylmethyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-5-yl]phenyl]methanone;

8-[4-(morpholin-4-ylmethyl)phenyl]-N-pyridin-3-yl-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene-5-carboxamide;

2-[3-[8-[4-(4-methylpiperazine-1-carbonyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-5-yl]phenoxy]acetonitrile;

25 5-fluoro-N-(4-methylsulfonylphenyl)-4-[3-propan-2-yl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;

5-fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-propan-2-yl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;

30 [4-[[5-fluoro-4-[3-propan-2-yl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;

4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(4-methylsulfonylphenyl)pyrimidin-2-amine;
4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]pyrimidin-2-amine;
4-[[4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;
4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine;
5-(4-methoxyphenyl)-8-(3-methylsulfonylphenyl)-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene;
[4-[5-(3-fluoro-4-methoxy-phenyl)-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl]phenyl]-(4-methylpiperazin-1-yl)methanone;
5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-methylsulfonylpyridin-3-yl)pyrimidin-2-amine;
(2,6-dimethylmorpholin-4-yl)-[4-[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]methanone;
[5-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]-(4-methylpiperazin-1-yl)methanone;
5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(1-morpholin-4-ylethyl)phenyl]pyrimidin-2-amine;
5-fluoro-N-(4-methylsulfonylphenyl)-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;
azetidin-1-yl-[2-chloro-4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]methanone;
azetidin-1-yl-[4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-2-methyl-phenyl]methanone;
azetidin-1-yl-[5-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]pyridin-2-yl]methanone;
azetidin-1-yl-[4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-2-(trifluoromethoxy)phenyl]methanone;

azetidin-1-yl-[3-chloro-5-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]pyridin-2-yl]methanone;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[6-(morpholin-4-ylmethyl)pyridin-3-yl]pyrimidin-2-amine;

5 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-propan-2-ylsulfonylpyridin-3-yl)pyrimidin-2-amine;

azetidin-1-yl-[3-chloro-5-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]methanone;

N-(6-ethylsulfonylpyridin-3-yl)-5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-amine;

10 3-chloro-5-[[5-fluoro-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]-(4-methylpiperazin-1-yl)methanone;

5-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-N-methyl-N-propan-2-yl-pyridine-2-carboxamide;

15 N-ethyl-5-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-N-methyl-pyridine-2-carboxamide;

3-[4-[8-[4-(morpholin-4-ylmethyl)phenyl]2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene-5-carbonyl]piperazin-1-yl]propanenitrile;

[3-chloro-5-[[5-fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]-(4-methylpiperazin-1-yl)methanone;

20 [3-chloro-5-[[5-fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]-(1-piperidyl)methanone;

azetidin-1-yl-[3-chloro-5-[[5-fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]methanone;

25 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[6-(4-methylpiperazin-1-yl)sulfonylpyridin-3-yl]pyrimidin-2-amine;

N-[6-[(4,4-difluoro-1-piperidyl)methyl]pyridin-3-yl]-5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(oxan-4-yl)pyrimidin-2-amine;

1-[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-1-piperidyl]ethanone;
 [4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-1-piperidyl]-phenyl-methanone;
 5 1-[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-1-piperidyl]-2-phenyl-ethanone;
 benzyl 4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]piperidine-1-carboxylate;
 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(1-methylsulfonyl-4-piperidyl)pyrimidin-2-amine;
 10 N-[1-(benzenesulfonyl)-4-piperidyl]-5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-amine;
 5-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-N,N-dimethyl-pyridine-2-sulfonamide; an isomer, a metabolite , a prodrug or a
 15 pharmaceutically acceptable salt thereof, or a solvate or a solvate of a pharmaceutically acceptable salt thereof.

One embodiment of the invention relates to a combination comprising (a) a first therapeutic agent, which is N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine,
 20 (4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine and (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, metabolites or prodrugs and pharmaceutically-acceptable salts, solvates or solvated salts of any of the foregoing and (b) a second therapeutic agent, which is a compounds selected from the group comprising
 25 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile;
 [4-[[5-fluoro-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl)-(4-methylpiperazin-1-yl)methanone;
 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-propan-2-ylsulfonylpyridin-3-yl)pyrimidin-2-amine;

5 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine; as a free base, an isomer, a metabolite or a prodrug or a pharmaceutically acceptable salt thereof.

A particular GSK3 inhibitor is 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile as a free base, an isomer, a metabolite, a prodrug or a
10 pharmaceutically acceptable salt thereof.

In one embodiment of the invention the combination comprises the (a) a first therapeutic agent, which is N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine, (4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine and (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, metabolites or prodrugs and pharmaceutically-acceptable salts, solvates or solvated salts of any of the foregoing and (b) 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile; or

20 (a) a first therapeutic agent, which is N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine, (4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine and (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, metabolites or prodrugs and pharmaceutically-acceptable salts, solvates or solvated salts of any of the foregoing and (b) [4-[[5-fluoro-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone; or

(a) a first therapeutic agent, which is N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine, (4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine and (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, metabolites or prodrugs and pharmaceutically-acceptable salts,
30

solvates or solvated salts of any of the foregoing and (b) 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine; or

(a) a first therapeutic agent, which is N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine, (4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine and (2S)-(4E)-N-

5 methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, metabolites or prodrugs and pharmaceutically-acceptable salts, solvates or solvated salts of any of the foregoing and (b) 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]pyrimidin-2-amine;

(a) a first therapeutic agent, which is N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine, (4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine and (2S)-(4E)-N-
10 methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, metabolites or prodrugs and pharmaceutically-acceptable salts, solvates or solvated salts of any of the foregoing and (b) 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-propan-2-ylsulfonylpyridin-3-yl)pyrimidin-2-amine;

15 (a) a first therapeutic agent, which is N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine, (4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine and (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, metabolites or prodrugs and pharmaceutically-acceptable salts, solvates or solvated salts of any of the foregoing and (b) 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine; as a free base,
20 an isomer, a metabolite or a prodrug or a pharmaceutically acceptable salt thereof.

For use in medicine, pharmaceutically-acceptable salts may be useful in the preparation of the compounds used in the combination of the invention. Suitable pharmaceutically-

25 acceptable salts of the compounds described herein include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically-acceptable acid such as hydrochloric acid, sulfuric acid, methanesulphonic acid and fumaric acid. Furthermore, where the compounds carry an acidic moiety, suitable pharmaceutically-acceptable salts thereof may include alkali metal

salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The expression "pharmaceutically-acceptable salts" includes any pharmaceutically-acceptable salt, including both pharmaceutically-acceptable acid addition salts and

5 pharmaceutically-acceptable cationic salts. The expression "pharmaceutically-acceptable cationic salts" is intended to include but is not limited to such salts as the alkali metal salts, (e.g. sodium and potassium), alkaline earth metal salts (e.g., calcium and magnesium), aluminium salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine) and choline. The expression "pharmaceutically-acceptable acid
10 addition salts" is intended to include but is not limited to such salts as the hydrochloride, hydrobromide and sulfate salts.

The pharmaceutically-acceptable cationic salts containing free carboxylic acids can be readily prepared by reacting the free acid form with an appropriate base. Typical bases are sodium hydroxide, sodium methoxide and sodium ethoxide.

15 The pharmaceutically-acceptable acid addition salts containing free amine groups can be readily prepared by reacting the free base form with the appropriate acid.

Suitable salts for the GSK inhibitor may be, but are not limited to, hydrochloride, fumarate, tartrate, citrate, edisylate and phosphate.

20 Examples of further suitable pharmaceutically acceptable salts include inorganic acid addition salts such as chloride, bromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate, benzoate,
25 hydroxybenzoate, edisylate, orotate, R-mandelate and ascorbate; salts with amino acids such as lysine monohydrochloride, aspartate and glutamate. The salts may be in some cases hydrates or ethanol solvates. Representative salts are provided as described in U.S. Pat. No. 5,597,919 to Dull et al., U.S. Pat. No. 5,616,716 to Dull et al. and U.S. Pat. No. 5,663,356 to Ruecroft et al., each herein incorporated by reference.

The synthesis of salts of (2S)-(4E)-N-methyl-5-(3-(5-isopropoxypyridin)yl)-4-penten-2-amine can be accomplished by combining (2S)-(4E)-N-methyl-5-(3-(5-isopropoxypyridin)yl)-4-penten-2-amine with various inorganic and organic acids in appropriate solvents, as exemplified in U.S. Patent No. 6,432,954 and PCT WO06/053082, each incorporated by reference. The hemigalactarate salt of (2S)-(4E)-N-methyl-5-(3-(5-isopropoxypyridin)yl)-4-penten-2-amine can be prepared using the techniques set forth in U.S. Patent No. 6,958,399, as noted above herein incorporated by reference. The synthesis of 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane is described in WO2008/057938, which is herein incorporated by reference.

In the context of this specification the expression "pharmaceutically-acceptable salts" also includes solvates, hydrates or solvated or hydrated salts thereof.

The active agents of the composition described herein can be co-administered simultaneously or may be administered separately, concomitantly or sequentially in any order, or as a single pharmaceutical composition.

Pharmaceutical compositions

A second aspect of the invention relates to a pharmaceutical composition comprising a combination comprising (a) a therapeutically effective amount of a first therapeutic agent, which is $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a therapeutically effective amount of a second therapeutic agent, which is a GSK3 inhibitor, together with a pharmaceutically-acceptable vehicle, carrier or diluent.

One embodiment of the invention relates to one pharmaceutical composition comprising both agents (a) and (b). Another embodiment relates to two separate pharmaceutical compositions, one for agent (a) and one for agent (b).

The composition may be administered in a standard manner such as orally, parenterally, transmucosally (e.g., sublingually or via buccal administration), topically, transdermally, rectally, via inhalation (e.g., nasal or deep lung inhalation). Parenteral administration

includes, but is not limited to intravenous, intraarterial, intraperitoneal, subcutaneous or intramuscular.

For buccal administration, the composition can be in the form of tablets or lozenges formulated in conventional manner. For example, tablets and capsules for oral

5 administration can contain conventional excipients such as binding agents (e.g., syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (e.g., lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (e.g., magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (e.g., potato starch or sodium starch glycollate), or wetting agents
10 (e.g., sodium lauryl sulfate). Tablets may be coated according to methods well known in the art.

Such compositions can also be formulated as suppositories for rectal administration, e.g., containing conventional suppository bases, such as cocoa butter or other glycerides.

Compositions for inhalation typically can be provided in the form of a solution,
15 suspension, or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant, such as dichlorodifluoromethane or trichlorofluoromethane. Typical topical and transdermal formulations comprise conventional aqueous or nonaqueous vehicles, such as eye drops, creams, ointments, lotions, and pastes, or are in the form of a medicated plaster, patch, or membrane.
20 Additionally, compositions described herein can be formulated for parenteral administration by injection or continuous infusion. Formulations for injection can be in the form of suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulation agents, such as suspending, stabilizing, and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle (e.g.,
25 sterile, pyrogen-free water) before use.

A composition in accordance with the present invention also can be formulated as a depot formulation. Such long acting formulations can be administered by implantation (e.g., subcutaneously or intramuscularly) or by intramuscular injection. Accordingly, the compounds of the invention can be formulated with suitable polymeric or hydrophobic

materials (e.g., an emulsion in an acceptable oil), ion exchange resins, or as sparingly soluble derivatives (e.g., a sparingly soluble salt).

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various
5 excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch, and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc may be used to form tablets. Solid compositions of a similar
10 type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols.

Alternatively, the composition described herein can be incorporated into oral liquid formulations such as aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs,
15 for example. Moreover, formulations containing these compounds can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid formulations can contain conventional additives, such as suspending agents, such as sorbitol syrup, synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin,
20 glucose/sugar syrup, gelatin, hydroxyethylcellulose, hydroxypropylmethylcellulose, aluminium stearate gel, emulsifying agents, such as lecithin, sorbitan monooleate, or acacia; nonaqueous vehicles (which can include edible oils), such as almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol; and preservatives, such as methyl or propyl p-hydroxybenzoate and sorbic acid. The liquid forms in which the
25 compositions described herein may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

When aqueous suspensions and/or elixirs are desired for oral administration, the
30 compounds described herein can be combined with various sweetening agents, flavouring

agents, colouring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerine and various like combinations thereof. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium
5 carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

The combinations described herein can also be administered in a controlled release formulation such as a slow release or a fast release formulation. Such controlled release formulations of the combinations described herein may be prepared using methods well known to those skilled in the art. The method of administration will be determined, by the
10 attendant physician or other person skilled in the art after an evaluation of the patient's condition and requirements.

Kit

A third aspect of the invention relates to a kit comprising a dosage unit of a first
15 therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and a dosage unit of a second therapeutic agent, which is a GSK3 inhibitor, optionally with instructions for use. One embodiment relates to a kit as described above wherein the first therapeutic agent is (2S)-(4E)-N-methyl-5-[3-(5-isopropoxy-pyridin-2-yl)-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, metabolites or prodrugs and pharmaceutically-
20 acceptable salts, thereof.

Another embodiment relates to a kit as described above wherein the second therapeutic agent is any of the GSK3 inhibiting compounds selected from 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile;
[4-[[5-fluoro-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl)-(4-methylpiperazin-1-yl)methanone;
25 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine;
5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-propan-2-ylsulfonylpyridin-3-yl)pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine; as a free base, an isomer, a metabolite or a prodrug or
5 a pharmaceutically acceptable salt thereof.

Method of treatment

A fourth aspect of the invention relates to a method for treating CNS disorders such as, but not limited to, those discussed herein, including neurodegenerative disorders,
10 neuroinflammatory disorders, cognitive disorders, or any disorder mentioned below, in a subject in need thereof comprising administering simultaneously, sequentially, concomitantly or separately, to said subject (a) a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a second therapeutic agent, which is a GSK3 inhibitor, wherein the amounts of (a) and (b) are together synergistically effective in the treatment.

15 Neurodegenerative Disorder(s) include, but are not limited to Alzheimer's Disease (AD), Dementia, Cognitive Deficit in Schizophrenia (CDS), Mild Cognitive Impairment (MCI), Age-Associated Memory Impairment (AAMI), Age-Related Cognitive Decline (ARCD), Cognitive Impairment No Dementia (CIND), Multiple Sclerosis (MS), Parkinson's Disease
20 (PD), post encephalitic parkinsonism, parkinsonism-dementia of Gaum, head trauma, Huntington's Disease, Amyotrophic Lateral Sclerosis (ALS), motor neuron diseases (MND), Multiple System Atrophy (MSA), Corticobasal Degeneration, Progressive Supranuclear Paresis, Guillain-Barré Syndrome (GBS), and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Dementia includes, but is not limited to, Down
25 syndrome, vascular dementia, dementia with Lewy bodies, HIV dementia, Frontotemporal dementia Parkinson's Type (FTDP), Pick's Disease, Niemann-Pick's Disease, traumatic brain injury (TBI), dementia pugilistica, Creutzfeld-Jacob Disease and prion diseases.

Neuroinflammatory Disorder(s) include but are not limited to Multiple Sclerosis (MS),
30 Parkinson's disease, Multiple System Atrophy (MSA), Corticobasal Degeneration,

Progressive Supranuclear Paresis, Guillain-Barré Syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP). Multiple sclerosis (MS) includes Relapse Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), and Primary Progressive Multiple Sclerosis (PPMS).

5

Cognitive Disorder(s) include but are not limited to

- a) Dementia, including but not limited to Alzheimer's Disease (AD), Down syndrome, vascular dementia, Parkinson's Disease (PD), postencephalatic parkinsonism, dementia with Lewy bodies, HIV dementia, Huntington's Disease, amyotrophic lateral sclerosis
- 10 (ALS), motor neuron diseases (MND), Frontotemporal dementia Parkinson's Type (FTDP), progressive supranuclear palsy (PSP), Pick's Disease, Niemann-Pick's Disease, corticobasal degeneration, traumatic brain injury (TBI), dementia pugilistica, Creutzfeld-Jacob Disease and prion diseases;
- b) Cognitive Deficit in Schizophrenia (CDS);
- 15 c) Mild Cognitive Impairment (MCI);
- d) Age-Associated Memory Impairment (AAMI);
- e) Age-Related Cognitive Decline (ARCD);
- f) Cognitive Impairment No Dementia (CIND);
- g) Addictions such as nicotine addiction.

20

The invention further relates to therapies for the treatment of:

Attention-Deficit and Disruptive Behavior Disorder(s) including but not limited to attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) and affective disorders.

25

Another embodiment of the invention relates to a method for treating dementia in Alzheimer's Disease, cognitive deficit in schizophrenia, mild cognitive impairment and age-associated memory impairment.

One embodiment of the invention relates to a method for treating CNS disorders wherein the cognitive disorder is dementia, Cognitive Deficit in Schizophrenia (CDS), Mild Cognitive Impairment (MCI), Age-Associated Memory Impairment (AAMI), Age-Related Cognitive Decline (ARCD) or Cognitive Impairment No Dementia (CIND).

5

Another embodiment of the invention relates to a method for treating CNS disorders, wherein the disease is Cognitive Deficit in Schizophrenia.

Yet another embodiment of the invention relates to a method for treating CNS disorders, wherein the dementia is Frontotemporal dementia (FTD), Frontotemporal dementia Parkinson's Type (FTDP), progressive supranuclear palsy (PSP), Pick's Disease, Niemann-Pick's Disease, corticobasal degeneration, traumatic brain injury (TBI) or dementia pugilistica.

10

Yet a further embodiment of the invention relates to a method for treating CNS disorders, wherein the dementia is Alzheimer's Disease (AD), Down's syndrome, vascular dementia, Parkinson's Disease (PD), postencephalatic parkinsonism, dementia with Lewy bodies, HIV dementia, Huntington's Disease, amyotrophic lateral sclerosis (ALS), motor neuron diseases (MND, Creutzfeld-Jacob's disease or prion diseases).

15

20

One embodiment of the invention relates to a method for treating Alzheimer's Disease.

Another embodiment of the invention relates to a method for treating CNS disorders, wherein the use is in the delay of the disease progression of Alzheimer's Disease.

25

Another embodiment of the invention relates to a method for treating Bipolar Disorders.

One embodiment of the invention relates to the methods mentioned above wherein the first therapeutic agent is (2S)-(4E)-N-methyl-5-[3-(5-isopropoxy-pyridin)yl]-4-penten-2-amine

or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, metabolites or prodrugs and pharmaceutically-acceptable salts, thereof.

Another embodiment of the invention relates to the methods mentioned above wherein the second therapeutic agent is any of the GSK3 inhibiting compounds mentioned above or a compound selected from 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile;

[4-[[5-fluoro-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-propan-2-ylsulfonylpyridin-3-yl)pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine; as a free base, an isomer, a metabolite or a prodrug or a pharmaceutically acceptable salt thereof.

One embodiment of the invention relates to a method of treating CNS disorders, such as those disorders defined above, in a subject in need thereof using the kit as described above.

Another embodiment of the invention relates to a method of treating CNS disorders, such as those disorders defined above, in a subject in need thereof using the pharmaceutical composition comprising the combination comprising (a) a therapeutically effective amount of a first therapeutic agent, which is an $\alpha\beta 2$ -neuronal nicotinic agonist and (b) a therapeutically effective amount of a second therapeutic agent, which is a GSK3 inhibitor.

One embodiment of the invention relates to the use of the combination comprising (a) a therapeutically effective amount of a first therapeutic agent, which is an $\alpha\beta 2$ -neuronal nicotinic agonist and (b) a therapeutically effective amount of a second therapeutic agent,

which is a GSK3 inhibitor, for the manufacturing of a medicament for use simultaneously, sequentially, concomitantly or separately, in therapy.

Another embodiment of the invention relates to the use of the combination comprising (a) a therapeutically effective amount of a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal
5 nicotinic agonist and (b) a therapeutically effective amount of a second therapeutic agent, which is a GSK3 inhibitor, for the manufacturing of a medicament for use simultaneously, sequentially, concomitantly or separately, for the treatment of CNS disorders, such as those disorders defined above.

10 A further embodiment of the invention relates to a pharmaceutical composition comprising the combination comprising (a) a therapeutically effective amount of a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a therapeutically effective amount of a second therapeutic agent, which is a GSK3 inhibitor, for use simultaneously, sequentially, concomitantly or separately, for treatment of CNS disorders, such as those
15 disorders defined above, particularly for Alzheimer's Disease, mild to moderate dementia of the Alzheimer's type, attention deficit disorder, attention deficit hyperactivity disorder, mild cognitive impairment, age-associated memory impairment, schizophrenia, and cognitive dysfunction in schizophrenia.

20 **Dosages**

The effective dose of the $\alpha 4\beta 2$ -neuronal nicotinic agonist and the GSK3 inhibitor in the combinations according to the present invention may vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder as well as the potency of the selected specific compound, the mode of administration, the age and weight
25 of the patient, and the like. Determining a dose is within the skill of the ordinary artisan.

Typically, the effective dose of nicotinic agonists generally requires administering the compound in an amount of less than 5 mg/kg of patient weight. Often, the nicotinic agonists are administered in an amount from less than about 1 mg/kg patient weight to less
30 than about 100 μ g/kg of patient weight, and occasionally between about 10 μ g/kg to less

than 100 µg/kg of patient weight. The foregoing effective doses typically represent that amount administered as a single dose, or as one or more doses administered over a 24 hours period.

For human patients, the effective dose of the nicotinic agonists generally requires

5 administering the nicotinic agonist in an amount of at least about 1, often at least about 10, and frequently at least about 25 mg/ 24 hr./ patient. For human patients, the effective dose of the nicotinic agonists requires administering the nicotinic agonist which generally does not exceed about 500, often does not exceed about 400, and frequently does not exceed about 300 mg/ 24 hr./ patient. In addition, administration of the effective dose is such that
10 the concentration of the nicotinic agonist within the plasma of the patient normally does not exceed 500 ng/mL, and frequently does not exceed 100 ng/mL.

Suitable daily doses of the GSK3 inhibitor in the treatment of a mammal, including man are approximately 0.01 to 250 mg/kg bodyweight at per oral administration and about
15 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician.

20 The term "therapeutically-effective amount" as used herein refers to a sufficient amount of the compound to treat CNS disorders or conditions at a reasonable risk/benefit ratio applicable to any medical treatment.

The term "treating" as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more
25 symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of "treating" as defined herein.

The term "disorder", unless stated otherwise, has the same meaning as the terms "condition" and "disease" and are used interchangeably throughout the description and claims.

The term “agent” means the compounds comprised in the combination of the present invention, i.e. an GSK inhibitor or a nicotinic agonist.

“Synergy” means an improved effect of the two agents in the combination, which is greater than the expected additive effect of the individual agents.

5

Examples

EXAMPLE 1 (Prophetic)

A pharmaceutical composition is prepared by combining $\alpha 4\beta 2$ -neuronal nicotinic agonist and a GSK3 inhibitor in a pharmaceutically-acceptable carrier. The composition contains
10 respective amounts of the $\alpha 4\beta 2$ -neuronal nicotinic agonist and the GSK3 inhibitor to deliver on a daily basis a therapeutically-effective amount of each ingredient. The composition is administered to a patient on a daily, twice daily, three times daily, or four times daily basis.

15 EXAMPLE 2 (Prophetic)

A pharmaceutical composition is prepared by combining (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane or a pharmaceutically acceptable salt thereof with 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carbonitrile as a free base or a
20 pharmaceutically acceptable salt thereof in a pharmaceutically-acceptable carrier. The composition contains respective amounts of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane or a pharmaceutically acceptable salt thereof and 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carbonitrile as a free base or a
25 pharmaceutically acceptable salt thereof to deliver on a daily basis a therapeutically-effective amount of each ingredient. The composition is administered to a patient on a daily, twice daily, three times daily, or four times daily basis.

EXAMPLE 3 (Prophetic)

Biological tests for assessing effects of combinations of a neuronal nicotinic agonist and a GSK3 inhibitor.

- 5 Interaction design: Interactive effects of drug combinations are tested by co-administering varying doses of the neuronal nicotinic agonist, for example (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane or a pharmaceutically acceptable salt thereof, with the GSK3 inhibitor, for example 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carbonitrile as a free base or a pharmaceutically acceptable salt thereof and then
10 conducting various biological tests (e.g. antipsychotic tests) to determine the existence of interactions (positive or negative). The dose range used for combination studies includes doses of the neuronal nicotinic agonist known to be active in cognitive-enhancement tests (when tested alone) as well as doses below the threshold for activity (sub-threshold doses).
15 Similarly, for the GSK inhibitor, the dose range includes doses in which the GSK inhibitor alone is active as well as sub-threshold doses.

In/ex vivo testing:**Interactive effects of drugs on Long-term potentiation**

- 20 Various drugs, including muscarinic and nicotinic selective compounds affect long term potentiation (LTP) in the hippocampus (HPC). LTP is an electrophysiological phenomenon that has been shown to be strongly linked to cognitive function in the living organism (Lynch MA, *Physiol Rev* 84:87-136, 2004). Therefore, compounds that decrease the induction of LTP impair memory and compounds that restore LTP function improve
25 cognitive performance.

Nicotinic agonists have been shown to facilitate the induction of LTP in normal and impaired animal models (Wang et al, *Eur J Neurosci* 23:1111-1119, 2006; Yamazaki, *Eur. J Neurosci* 22:845-860, 2005). GSK inhibitors have also been shown to improve LTP induction and facilitate synaptic plasticity (Hooper et al., *Eur J Neurosci* 25:81-86, 2007).

The effect of the compounds are tested in both an ex vivo and in vivo setting. The latter consists of electrodes being placed in the anaesthetized rodent brain, more specifically the hippocampus and a small current is used to induce LTP. Different LTP variables such as induction and maintenance measured in the absence and presence of compounds.

- 5 In the ex vivo setting, brain tissue is dissected out and used as a slice preparation and LTP is measured in similar fashion to that described above.

Interactive effects of drugs on Novel Object Recognition

Potentialiation of drug-induced enhancement of novel object recognition (NOR):

- 10 Various classes of drugs (e.g. $\alpha 4\beta 2$) have been shown to improve performance of the NOR task in rodents. Drugs that enhance NOR performance may have therapeutic potential in CNS disorders with cognitive deficits including dementias (e.g. Alzheimer's disease) and psychoses (e.g. schizophrenia). Drugs that interact to additively or synergistically improve cognitive performance in NOR in rodents may have surprising activity in human diseases.
- 15 Both nicotinic agonists (Levin et al, Psychopharmacol 183:523-539, 2006) and GSK (Hernandez et al, J Neurochem 83:1529-1533, 2002) have been shown to modulate cognitive function in rodents. The interactive effects of a GSK inhibitor and $\alpha 4\beta 2$ nicotinic agonists on novel object recognition are tested in a mouse NOR model. Mice are allowed to explore first two identical objects (object A) during the sample period. Then 15 minutes
- 20 later mice were allowed to explore another copy of object A and a second different object (B). Rodents preferentially explore novel objects over familiar objects unless they have forgotten the familiar object. In this version of the test, mice generally show no preference for the novel object by 15 minutes. Therefore, drugs that induce preferential exploration of object B over object A supports drug-induced enhancement of memory function. Drugs
- 25 were administered so that maximal plasma concentrations occurred at the time the sample period.

- It is contemplated that the combination of (a) a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a second therapeutic agent, which is a GSK3 inhibitor
- 30 provide synergistic or additive effects in treating CNS disorders such as neurodegenerative

disorders, neuroinflammatory disorders, cognitive disorders, dementia, Alzheimer's Disease, cognitive deficit in schizophrenia, mild cognitive impairment and age-associated memory impairment or any disorder mentioned herein.

Through combination of a disease modifying and symptomatic treatment the overall
5 efficiency of the treatment will be enhanced.

Compositions and methods described herein may offer advantages over previous methods for treating neurodegenerative disorders. The method of treatment described herein may permit reduced quantities of these agents to be used and, therefore may permit improved management of disease symptoms such as reduction of disease-related side effects. A
10 further advantage of this synergistic or additive effect may be a faster onset of the therapeutic action of the single compounds.

CLAIMS

1. A combination comprising (a) a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a second therapeutic agent, which is a GSK3 inhibitor.

5 2. A pharmaceutical composition comprising a combination comprising (a) a therapeutically effective amount of a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a therapeutically effective amount of a second therapeutic agent, which is a GSK3 inhibitor, together with a pharmaceutically-acceptable vehicle, carrier or diluent.

10

3. The pharmaceutical composition according to claim 2, wherein the first therapeutic agent is (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, or a pharmaceutically-acceptable salt thereof.

15

4. The pharmaceutical composition according to claim 2, wherein the second therapeutic agent is selected from

3-[7-(2-morpholin-4-ylethoxy)quinazolin-4-yl]-2-oxo-1,3-dihydroindole-5-carbonitrile;

3-[7-(2-methoxyethoxy)quinazolin-4-yl]-2-oxo-1,3-dihydroindole-5-carbonitrile;

20

3-[7-[2-(2-methoxyethoxy)ethoxy]quinazolin-4-yl]-2-oxo-1,3-dihydroindole-5-carbonitrile;

3-[7-(3-morpholin-4-ylpropoxy)quinazolin-4-yl]-2-oxo-1,3-dihydroindole-5-carbonitrile;

2-hydroxy-3-[5-(4-methylpiperazine-1-carbonyl)pyridin-2-yl]-1H-indole-5-carbonitrile;

1-[(4-methoxyphenyl)methyl]-3-(5-nitro-1,3-thiazol-2-yl)urea;

25

2-hydroxy-3-[5-[(4-phenylpiperazin-1-yl)methyl]pyridin-2-yl]-1H-indole-5-carbonitrile;

2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile;

2-hydroxy-3-[5-(4-methylpiperazin-1-yl)sulfonylpyridin-2-yl]-1H-indole-5-carbonitrile;

2-hydroxy-3-[5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl]-1H-indole-5-carbonitrile;

3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-5-nitro-1H-indol-2-ol;

30

2-hydroxy-3-[5-(pyrrolidin-1-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile;

- [6-(2-hydroxy-5-nitro-1H-indol-3-yl)pyridin-3-yl]-(4-methylpiperazin-1-yl)methanone;
2-hydroxy-3-[5-(1-piperidylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile;
2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-6-carbonitrile;
2-hydroxy-3-[5-(4-methylpiperazin-1-yl)sulfonylpyridin-2-yl]-1H-indole-6-carbonitrile;
5 3-fluoro-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-2-oxo-1H-indole-6-carbonitrile;
[4-[5-(4-methoxyphenyl)-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl]phenyl]-(4-methylpiperazin-1-yl)methanone;
3-(4-methoxyphenyl)-N-(2-morpholin-4-ylethyl)-5,7-diazabicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carboxamide;
10 3-(4-chlorophenyl)-N-(2-morpholin-4-ylethyl)-5,7-diazabicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carboxamide;
5-fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-amine;
[4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;
15 [4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]phenyl]-phenyl-methanone;
N-(3-methoxypropyl)-8-[4-(trifluoromethyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene-5-carboxamide;
20 5-(4-methoxyphenyl)-8-[4-(1-piperidylmethyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene;
N-(3-methoxypropyl)-8-[4-(morpholin-4-ylmethyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene-5-carboxamide;
[4-[[5-fluoro-4-(2-methyl-3-propan-2-yl-imidazol-4-yl)pyrimidin-2-yl]amino]phenyl]-pyridin-2-yl-methanone;
25 [4-[[4-(3-cyclohexyl-2-methyl-imidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;
[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]pyrimidin-2-amine;
4-(2,3-dimethylimidazol-4-yl)-5-fluoro-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine;
5 [4-[5-(4-chlorophenyl)-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl]phenyl]-(4-methylpiperazin-1-yl)methanone;
N-(3-methoxypropyl)-8-[3-(2,2,3,3-tetrafluoropropoxymethyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene-5-carboxamide;
[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-pyridin-2-yl-methanone;
10 [4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]-pyridin-2-yl-methanone;
5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine;
15 [4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;
4-(2,3-dimethylimidazol-4-yl)-5-fluoro-N-[4-[(4-methylpiperazin-1-yl)methyl]phenyl]pyrimidin-2-amine;
5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(4-methylsulfonylphenyl)pyrimidin-2-amine;
20 2-amine;
5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine;
[4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-2-(trifluoromethoxy)phenyl]-(4-methylpiperazin-1-yl)methanone;
25 5-fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;
azetidin-1-yl-[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]methanone;
5-fluoro-N-[3-methyl-4-(morpholin-4-ylmethyl)phenyl]-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-amine;
30

5-fluoro-N-[4-(morpholin-4-ylmethyl)phenyl]-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;

5-fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-amine;

5 [4-[[5-fluoro-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;

5-[5-fluoro-2-[[4-(4-methylpiperazin-1-yl)sulfonylphenyl]amino]pyrimidin-4-yl]-1-(oxan-4-yl)imidazole-2-carbonitrile;

5-fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;

5-fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine;

[4-[[5-fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;

15 N-(2-cyanoethyl)-3-[5-(4-methoxyphenyl)-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl]benzamide;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-methylsulfonyl-3-(trifluoromethyl)phenyl]pyrimidin-2-amine;

20 azetidin-1-yl-[4-[8-[4-(morpholin-4-ylmethyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-5-yl]phenyl]methanone;

8-[4-(morpholin-4-ylmethyl)phenyl]-N-pyridin-3-yl-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene-5-carboxamide;

2-[3-[8-[4-(4-methylpiperazine-1-carbonyl)phenyl]-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-5-yl]phenoxy]acetonitrile;

25 5-fluoro-N-(4-methylsulfonylphenyl)-4-[3-propan-2-yl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;

5-fluoro-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]-4-[3-propan-2-yl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;

30 [4-[[5-fluoro-4-[3-propan-2-yl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;

- 4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(4-methylsulfonylphenyl)pyrimidin-2-amine;
4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]pyrimidin-2-amine;
4-[[4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]-(4-methylpiperazin-1-yl)methanone;
4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine;
5-(4-methoxyphenyl)-8-(3-methylsulfonylphenyl)-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene;
[4-[5-(3-fluoro-4-methoxy-phenyl)-2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl]phenyl]-(4-methylpiperazin-1-yl)methanone;
5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-methylsulfonylpyridin-3-yl)pyrimidin-2-amine;
(2,6-dimethylmorpholin-4-yl)-[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl]methanone;
[5-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]-(4-methylpiperazin-1-yl)methanone;
5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(1-morpholin-4-ylethyl)phenyl]pyrimidin-2-amine;
5-fluoro-N-(4-methylsulfonylphenyl)-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-amine;
azetidin-1-yl-[2-chloro-4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]phenyl]methanone;
azetidin-1-yl-[4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-2-methyl-phenyl]methanone;
azetidin-1-yl-[5-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]pyridin-2-yl]methanone;
azetidin-1-yl-[4-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]-2-(trifluoromethoxy)phenyl]methanone;

azetidin-1-yl-[3-chloro-5-[[4-(2,3-dimethylimidazol-4-yl)-5-fluoro-pyrimidin-2-yl]amino]pyridin-2-yl]methanone;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[6-(morpholin-4-ylmethyl)pyridin-3-yl]pyrimidin-2-amine;

5 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-propan-2-ylsulfonylpyridin-3-yl)pyrimidin-2-amine;

azetidin-1-yl-[3-chloro-5-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]methanone;

N-(6-ethylsulfonylpyridin-3-yl)-5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-amine;

10 3-chloro-5-[[5-fluoro-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]-(4-methylpiperazin-1-yl)methanone;

5-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-N-methyl-N-propan-2-yl-pyridine-2-carboxamide;

15 N-ethyl-5-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-N-methyl-pyridine-2-carboxamide;

3-[4-[8-[4-(morpholin-4-ylmethyl)phenyl]2,7,9-triazabicyclo[4.3.0]nona-1,3,5,7-tetraene-5-carbonyl]piperazin-1-yl]propanenitrile;

3-chloro-5-[[5-fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]-(4-methylpiperazin-1-yl)methanone;

20 3-chloro-5-[[5-fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]-(1-piperidyl)methanone;

azetidin-1-yl-[3-chloro-5-[[5-fluoro-4-[3-methyl-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]pyridin-2-yl]methanone;

25 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[6-(4-methylpiperazin-1-yl)sulfonylpyridin-3-yl]pyrimidin-2-amine;

N-[6-[(4,4-difluoro-1-piperidyl)methyl]pyridin-3-yl]-5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(oxan-4-yl)pyrimidin-2-amine;

1-[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-1-piperidyl]ethanone;

[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-1-piperidyl]-phenyl-methanone;

5 1-[4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-1-piperidyl]-2-phenyl-ethanone;

benzyl 4-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]piperidine-1-carboxylate;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(1-methylsulfonyl-4-piperidyl)pyrimidin-2-amine;

10 N-[1-(benzenesulfonyl)-4-piperidyl]-5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-amine; and

5-[[5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]pyrimidin-2-yl]amino]-N,N-dimethyl-pyridine-2-sulfonamide; or a pharmaceutically acceptable salt thereof.

15

5. The pharmaceutical composition according to claim 2, wherein the second therapeutic agent is 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carbonitrile as a free base or a pharmaceutically acceptable salt thereof.

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6. A kit comprising a dosage unit of a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and a dosage unit of a second therapeutic agent, which is a GSK3 inhibitor, optionally with instructions for use.

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7. A method for treating CNS disorders in a subject in need thereof comprising administering to said subject (a) a therapeutically effective amount of a first therapeutic agent, which is an $\alpha 4\beta 2$ -neuronal nicotinic agonist and (b) a therapeutically effective amount of a second therapeutic agent, which is a GSK3 inhibitor.

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8. The method according to claim 7, wherein the first therapeutic agent is (2*S*)-(4*E*)-N-methyl-5-[3-(5-isopropoxy-pyridin-2-yl)-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-

diazabicyclo[3.3.0]octane, or a pharmaceutically-acceptable salt thereof and the second therapeutic agent is a compound defined in claim 4.

9. The method according to claim 7, wherein the first therapeutic agent is (2S)-(4E)-N-methyl-5-[3-(5-isopropoxy-pyridin-2-yl)-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, or a pharmaceutically-acceptable salt thereof and the second therapeutic agent is 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile;

[4-[[5-fluoro-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-

yl]amino]phenyl)-(4-methylpiperazin-1-yl)methanone;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-propan-2-ylsulfonylpyridin-3-yl)pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine; as a free base, an isomer, a metabolite or a prodrug or a pharmaceutically acceptable salt thereof as a free base or a pharmaceutically acceptable salt thereof..

10. The method according to any one of claims 7 to 9, wherein the CNS disorder is dementia.

11. The method according to claim 10, wherein the dementia is selected from Alzheimer's Disease, mild to moderate dementia of the Alzheimer's type, attention deficit disorder, attention deficit hyperactivity disorder, mild cognitive impairment, age-associated memory impairment, schizophrenia, and cognitive dysfunction in schizophrenia.

12. The method according to claim 10, wherein the CNS disorder is Bipolar Disorders.

13. The method according to any one of claims 7 to 12, using the kit according to claim 6.

14. Use of a pharmaceutical composition comprising a combination of (a) a therapeutically effective amount of a first therapeutic agent, which is an $\alpha 4\beta 2$ - neuronal nicotinic agonist and (b) a therapeutically effective amount of a second therapeutic agent, which is a GSK3 inhibitor for prevention and/or treatment of CNS disorders.

15. Use of a pharmaceutical composition comprising a combination of (a) a therapeutically effective amount of a first therapeutic agent, which is (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, or a pharmaceutically-acceptable salt thereof and (b) a therapeutically effective amount of a second therapeutic agent, which is a compound defined in claim 4 for prevention and/or treatment of CNS disorders.

16. Use of a pharmaceutical composition comprising a combination of (a) a therapeutically effective amount of a first therapeutic agent, which is (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine or 3-(5-chloro-2-furoyl)-3,7-diazabicyclo[3.3.0]octane, or a pharmaceutically-acceptable salt thereof and (b) a therapeutically effective amount of a second therapeutic agent is, which is 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carbonitrile; [4-[[5-fluoro-4-[3-(oxan-4-yl)-2-(trifluoromethyl)imidazol-4-yl]pyrimidin-2-yl]amino]phenyl)-(4-methylpiperazin-1-yl)methanone; 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-methylpyridin-3-yl)pyrimidin-2-amine; 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(4-methylpiperazin-1-yl)sulfonylphenyl]pyrimidin-2-amine; 5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-(6-propan-2-ylsulfonylpyridin-3-yl)pyrimidin-2-amine;

5-fluoro-4-[2-methyl-3-(oxan-4-yl)imidazol-4-yl]-N-[4-(morpholin-4-ylmethyl)phenyl]pyrimidin-2-amine; as a free base, an isomer, a metabolite or a prodrug or a pharmaceutically acceptable salt thereof as a free base or a pharmaceutically acceptable salt thereof for prevention and/or treatment of CNS disorders.

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17. The use according to any one of claims 14 to 16, wherein the CNS disorder is dementia.

18. The use according to claim 17, wherein the dementia is selected from Alzheimer's
10 Disease, mild to moderate dementia of the Alzheimer's type, attention deficit disorder, attention deficit hyperactivity disorder, mild cognitive impairment, age-associated memory impairment, schizophrenia, and cognitive dysfunction in schizophrenia.

19. The use according to any one of claims 14 to 16, wherein the CNS disorder is Bipolar
15 Disorders.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2008/050898

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 0007600 A1 (R.J. REYNOLDS TOBACCO COMPANY), 17 February 2000 (17.02.2000) --	1-19
Y	WO 03082853 A1 (ASTRAZENECA AB), 9 October 2003 (09.10.2003) --	1-19
Y	WO 2007040438 A2 (ASTRAZENECA AB), 12 April 2007 (12.04.2007) --	1-19
Y	WO 2007040440 A1 (ASTRAZENECA AB), 12 April 2007 (12.04.2007) --	1-19

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

3 November 2008

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2008/050898

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006001754 A1 (ASTRAZENECA AB), 5 January 2006 (05.01.2006) --	1-19
A	US 20040214835 A1 (CALDWELL, WILLIAM SCOTT ET AL), 28 October 2004 (28.10.2004) -- -----	1-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2008/050898

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7-19
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 7-19 relate to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic
.../...
2. ☒ Claims Nos.: 1-2, 6-7, 10-14 and 17-19
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Present claims 1-2, 6-7, 10-14 and 17-19 relate to a combination of compounds defined by reference to a desirable
.../...
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2008/050898

Box II.1

methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.

Box II.2

characteristic or property, namely (a) a first therapeutic agent, which is an alpha-4-beta-2-neuronal nicotinic agonist and (b) a second therapeutic agent, which is GSK3 inhibitor.

The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

The search for the concept of an alpha-4-beta-2-neuronal nicotinic agonist or GSK3 inhibitor will retrieve a pertinent document only if these concepts are described with these specific terms in a reference. Specific solutions previously known and falling under these concepts, but failing to mention this fact, are not likely to be revealed in such a search.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in claims 3-5, 8-9, and 15-16.

International patent classification (IPC)**A61K 31/4439** (2006.01)**A61K 31/00** (2006.01)**A61K 31/4412** (2006.01)**A61P 25/00** (2006.01)**A61P 25/28** (2006.01)**Download your patent documents at www.prv.se**

The cited patent documents can be downloaded at www.prv.se by following the links:

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Use the application number as username.

The password is **QGFOUYKMPO**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/08/2008

International application No.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

30/08/2008

International application No.

PCT/SE2008/050898

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