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(54) **Title**: ARYLALKYLPIPERAZINES FOR USE AS NEUROPROTECTIVE AGENTS

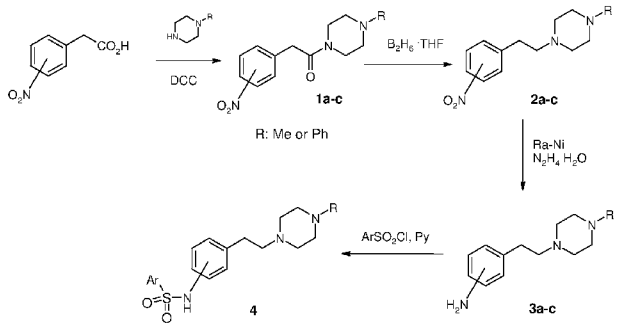
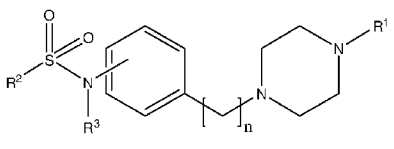


Figure1



A

(57) **Abstract**: A compound of the general formula A or a or a pharmaceutically acceptable salt or solvate thereof, wherein: R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6- C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1C_6- (halo)alkyl, C_1C_6-(halo)- alkoxy and/or $COOR^3$; R^2 is selected from the group consisting of: C_6-C_{10}-aryl and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$ amino, C_1C_6- alkylamino, CrC6-dialkyl- amino, C_1-C_6-(halo)alkyl, C_1C_6-(halo)alkoxy and/or $COOR^3$; R^3 is independently at each occurrence selected from the group consisting of hydrogen and C_1-C_2-alkyl; and n is an integer from 1 to 10 inclusive.

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ARYLALKYLPIPERAZINES FOR USE AS NEUROPROTECTIVE AGENTS

Field of the Invention

The present invention relates to novel arylpiperazines, in particular novel arylsulphonamide arylpiperazines, including the synthesis thereof and their applicability for use in the treatment or prophylaxis of a disease, in particular for use as neuroprotective agents, in treatment of neurological and neuropsychiatric disorders and in the treatment of diseases associated with, accompanied by or caused by mitochondrial stress.

Background of the Invention

N-arylpiperazines are known in the art for having high affinity to numerous ligands suitable for different G protein coupled receptors (GPCRs) (Sukalovic et al., 2005).

Many N-arylpiperazines are biologically active and the N-arylpiperazine subunit can be found in pharmacologically compounds related to serotonin ligands, calcium blockers, antipsychotic drugs, antihypertensive drugs, and acetylcholinesterase inhibitory activity.

In particular N-arylpiperazines are known to have antipsychotic or antidepressant properties, and are capable of interacting with dopamine and serotonin receptor ligands or acetylcholinesterase inhibitors (Caccia, 2007).

Moreover, various compounds with N-arylpiperazine moiety have been found to exhibit direct neuroprotective effects in vitro (Druse et al., 2005; Koprivica et al., 2011; Park et al., 2011; Park et al., 2009). One such arylpiperazine derivative, aripiprazole, a second generation antipsychotic and partial agonist of D2 dopamine receptor, was found to increase the levels of neuroprotective brain-derived neurotrophic factor (BDNF) and antiapoptotic Bcl-2 protein whilst at the same time reducing the proapoptotic action of glycogen synthase kinase 3β in SH-SY5Y cells (Park et al., 2009). Aripiprazole has also been found to protect PC12 neuronal cell line from N-methyl-4-phenylpyridinium-induced oxidative stress (Park et al., 2011), as well as rat embryonic cortical neurons and rat dopaminergic neurons in mesencephalic cultures from glutamate-induced toxicity (Koprivica et al., 2011; Matsuo et al., 2010).

Another arylpiperazine derivative, buspirone, which is a serotonin agonist, has been found to protect fetal rhombencephalic rat neurons from ethanol-induced apoptosis through activation of Akt (Druse et al., 2005).

In the USA, each year more than 60,000 new cases of Parkinson's are diagnosed. In the UK, it is estimated to affect 100-180 people per 100,000 head of the population. As the incidence of Parkinson's increases with aging, with 2-4% of those over the age 60 being affected, with the increase of ageing population the number of Parkinson's disease sufferers is likely to rise. The main treatments provide symptomatic relief only. The most commonly used first line of treatment for Parkinson's is the administration of L-dopa (levodopa). This may be administered in combination with a peripheral decarboxylase inhibitor such as carbidopa, which prolongs the effects of L-dopa by slowing the conversion of L-dopa to dopamine in the blood stream. However, long-term use of L-dopa causes abnormal hyperkinetic involuntary movements (dyskinesia) as a significant side effect. In fact, at least 40% of Parkinson's sufferers treated with L-dopa and a peripheral decarboxylase inhibitor develop dyskinesia within 5 years. Alternatively, dopamine agonists may be used which, whilst effective, may cause nausea, vomiting and psychiatric complications.

The causes of L-dopa induced dyskinesia are currently unknown. It is thought that a priming phenomenon occurs which causes the abnormal movements associated with dyskinesia. The therapeutic strategies for treatment therefore involve both preventing this priming process from occurring, as well as avoiding the expression of dyskinesia in patients where priming has occurred.

Muscarinic and glutamatergic antagonist, amantadine, is the only clinically approved treatment for dyskinesia reduction, but high doses are require, it is poorly tolerated and has been found to be ineffective in the long term. There is thus a need for an effective regime for inhibiting or treating dyskinesia, which can be carried out without affecting anti-Parkinson's treatments.

Possible treatments, which have been employed in the treatment of Parkinson's include opioid antagonists (e.g. naloxone) and agonists (e.g. morphine), alpha-2 adrenoceptor antagonists (idozoxan, fipamezole), 5-HT1a receptor agonists (sarizotan), 5-HT2a/c receptor antagonists (quetiapine), cannabinoid receptor agonists (e.g. nabilone), magnesium sulphate, 3,4-methylenedioxymethamphetamine

(ecstasy), nicotine and the anti-convulsant, levatiracetam. However, none of the above treatments have been effective or useful in late stage clinical trials.

Disclosure of the Invention

In summary herein are presented a group of novel N-arylpiperazines with neuroprotective properties.

The inventors had identified N-{4-[2-(4-phenyl-piperazin-1-yl)ethyl]-phenyl}-picolinamide (1) and N-{3-[2-(4-phenyl-piperazin-1-yl)ethyl]-phenyl}-picolinamide (2) in their previous research of synthesized dopaminergic ligands with an arylpiperazine moiety as the most active in preventing mitochondrial damage and apoptosis induced by nitric oxide and 6-hydroxy dopamine in SH-SY5Y cells (Tovilovic et al., 2012, Tovilovic et al., 2013).

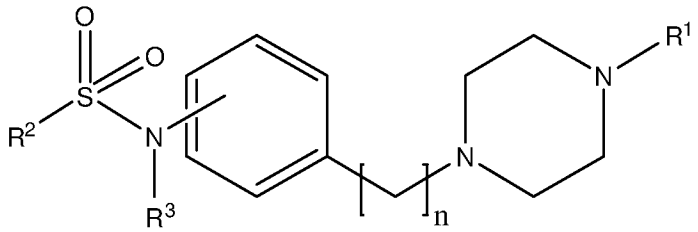
It has been discovered since, by the inventors, that those arylpiperazines modulate apoptotic and autophagic responses induced by neurotoxin 6-OHDA in human SH-SY5Y neuron-like cells. In rat model of EAE the described compounds demonstrated BBB penetrability and in vivo activity against induced neuropathy.

Starting from the structural scaffolding of arylpiperazines N-{4-[2-(4-phenyl-piperazin-1-yl)ethyl]-phenyl}-picolinamide (1) and N-{3-[2-(4-phenyl-piperazin-1-yl)ethyl]-phenyl}-picolinamide (2), bioisosteric heteroaryl sulphonamides were prepared and their cytoprotective activity was determined in a primary culture of neuronal cells.

The sulphonamide moiety was chosen because it is not associated with any toxicity and is known to be present in a wide range of compounds for the treatment of various diseases.

Among tested sulphonamides N-{4-[2-(4-phenyl-piperazin-1-yl)ethyl]-phenyl}-picolinsulphonamide and N-{3-[2-(4-phenyl-piperazin-1-yl)ethyl]-phenyl}-nicotinsulphonamide appeared as most interesting candidates for further research.

A first aspect of the invention relates to a compound of the general formula A



A

or a or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$;

R^2 is selected from the group consisting of: C_6-C_{10}-aryl and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$ amino, C_1-C_6-alkylamino, C_1-C_6-dialkyl- amino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)alkoxy and/or $COOR^3$;

R^3 is independently at each occurrence selected from the group consisting of: hydrogen and C_1-C_2-alkyl; and

n is an integer from 1 to 10 inclusive.

Preferably, a given moiety is substituted with one, two, three, four, or five independently selected substituents.

Preferably R^1 is selected from the group consisting of: C_1-C_6-alkyl, phenyl, and nitrogen-containing C_6-heteroaryl, each optionally substituted with halogen, hydroxyl, C_1-C_6-(halo)alkyl, and/or C_1-C-(halo)alkoxy.

More preferably R^1 is phenyl, optionally substituted with halogen, hydroxyl, and/or C_1-C_6-alkoxy.

Preferably R^2 is selected from the group consisting of: phenyl and C_1-C_6-heteroaryl, each optionally substituted with halogen, hydroxyl, amino, C_1-C_6-(halo)alkyl, and/or C_1-C_6-(halo)alkoxy.

More preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy.

Still more preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, and pyridazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy.

Yet more preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, and 3-pyridyl. The phenyl group may optionally be substituted with halogen, amino, and/or C_1-C_6-alkoxy. The 2-pyridyl or 3- pyridyl group may optionally be substituted with halogen, hydroxyl, amino, and/or C_1-C_6-alkoxy, preferably being monosubstituted in the ortho-position.

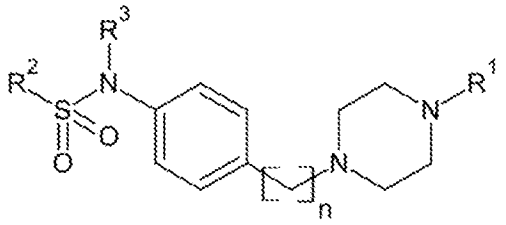
Preferably R^3 is hydrogen.

Preferably n is an integer from 1 to 6 inclusive. More preferably n is 2.

Preferably R^1 is phenyl, which is optionally substituted with halogen, hydroxyl, and/or C_1-C_6-alkoxy; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy; and n is 2.

Still more preferably, R^1 is an unsubstituted phenyl; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with hydroxyl; R^3 is hydrogen; and n is 2.

In one alternative the invention relates to a compound of the general formula I.



I

or a or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$;

R^2 is selected from the group consisting of: C_6-C_{10}-aryl and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$ amino, C_1-C_6-alkylamino, C_1-C_6-dialkyl- amino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)alkoxy and/or $COOR^3$;

R^3 is independently at each occurrence selected from the group consisting of: hydrogen and C_1-C_2-alkyl; and

n is an integer from 1 to 10 inclusive.

Preferably, a given moiety is substituted with one, two, three, four, or five independently selected substituents.

Preferably R^1 is selected from the group consisting of: C_1-C_6-alkyl, phenyl, and nitrogen-containing C_6-heteroaryl, each optionally substituted with halogen, hydroxyl, C_1-C_6-(halo)alkyl, and/or C_1-C_6-(halo)alkoxy.

More preferably R^1 is phenyl, optionally substituted with halogen, hydroxyl, and/or C_1-C_6-alkoxy.

Preferably R^2 is selected from the group consisting of: phenyl and C_1-C_6-heteroaryl, each optionally substituted with halogen, hydroxyl, amino, C_1-C_6-(halo)alkyl, and/or C_1-C_6-(halo)alkoxy.

More preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy.

Still more preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, and pyridazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy.

Yet more preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, and 3-pyridyl. The phenyl group may optionally be substituted with halogen, amino, and/or C_1-C_6-alkoxy. The 2-pyridyl or 3- pyridyl group may optionally be substituted with halogen, hydroxyl, amino, and/or C_1-C_6-alkoxy, preferably being monosubstituted in the ortho-position.

Preferably R^3 is hydrogen.

Preferably n is an integer from 1 to 6 inclusive. More preferably n is 2.

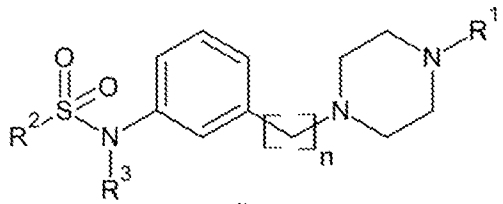
Preferably R^1 is phenyl, which is optionally substituted with halogen, hydroxyl, and/or C_1-C_6-alkoxy; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy; and n is 2.

Still more preferably, R^1 is an unsubstituted phenyl; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with hydroxyl; R^3 is hydrogen; and n is 2.

Still more preferably R^1 is unsubstituted phenyl; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, pyridazinyl, each unsubstituted or

substituted with hydroxyl; R^3 is hydrogen; and n is 2.

In one alternative the invention relates to a compound of the general formula II.



II

or a or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$;

R^2 is selected from the group consisting of: C_6-C_{10}-aryl and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$ amino, C_1-C_6-alkylamino, C_1-C_6-dialkyl- amino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)alkoxy and/or $COOR^3$;

R^3 is independently at each occurrence selected from the group consisting of: hydrogen and C_1-C_2-alkyl;

and n is an integer from 1 to 10 inclusive.

Preferably, a given moiety is substituted with one, two, three, four, or five independently selected substituents.

Preferably R^1 is selected from the group consisting of: C_1-C_6-alkyl, phenyl, and nitrogen-containing C_6-heteroaryl, each optionally substituted with halogen, hydroxyl, C_1-C_6-(halo)alkyl, and/or C_1-C_6-(halo)alkoxy.

More preferably R^1 is phenyl, optionally substituted with halogen, hydroxyl, and/or C_1-C_6-alkoxy.

Preferably R^2 is selected from the group consisting of: phenyl and C_1-C_6-heteroaryl, each optionally substituted with halogen, hydroxyl, amino, C_1-C_6-(halo)alkyl, and/or C_1-C_6-(halo)alkoxy.

More preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy.

Still more preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, and pyridazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy.

Yet more preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, and 3-pyridyl. The phenyl group may optionally be substituted with halogen, amino, and/or C_1-C_6-alkoxy. The 2-pyridyl or 3- pyridyl group may optionally be substituted with halogen, hydroxyl, amino, and/or C_1-C_6-alkoxy, preferably being monosubstituted in the ortho-position.

Preferably R^3 is hydrogen.

Preferably n is an integer from 1 to 6 inclusive. More preferably n is 2.

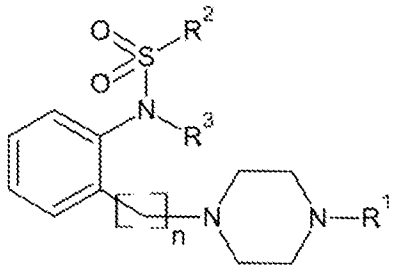
Preferably R^1 is phenyl, which is optionally substituted with halogen, hydroxyl, and/or C_1-C_6-alkoxy; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy; and n is 2.

Still more preferably, R^1 is an unsubstituted phenyl; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with hydroxyl; R^3 is hydrogen; and n is 2.

Still more preferably R^1 is an unsubstituted phenyl; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, and 3-pyridyl, each optionally substituted with

hydroxyl, with phenyl preferably being unsubstituted and 2-pyridyl and 3- pyridyl preferably being unsubstituted or monosubstituted in the ortho- position; R^3 is hydrogen; and n is 2.

In one alternative the invention relates to a compound of the general formula III.



III

or a or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$;

R^2 is selected from the group consisting of: C_6-C_{10}-aryl and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$ amino, C_1-C_6-alkylamino, C_1-C_6-dialkyl- amino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)alkoxy and/or $COOR^3$;

R^3 is independently at each occurrence selected from the group consisting of: hydrogen and C_1-C_2-alkyl; and

n is an integer from 1 to 10 inclusive.

Preferably, a given moiety is substituted with one, two, three, four, or five independently selected substituents.

Preferably R^1 is selected from the group consisting of: C_1-C_6-alkyl, phenyl, and nitrogen-containing C_6-heteroaryl, each optionally substituted with halogen, hydroxyl, C_1-C_6-(halo)alkyl, and/or C_1-C_6-(halo)alkoxy.

More preferably R^1 is phenyl, optionally substituted with halogen, hydroxyl, and/or C_1-C_6-alkoxy.

Preferably R^2 is selected from the group consisting of: phenyl and C_1-C_6-heteroaryl, each optionally substituted with halogen, hydroxyl, amino, C_1-C_6-(halo)alkyl, and/or C_1-C_6-(halo)alkoxy.

More preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy.

Still more preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, and pyridazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy.

Yet more preferably R^2 is selected from the group consisting of: phenyl, 2-pyridyl, and 3-pyridyl. The phenyl group may optionally be substituted with halogen, amino, and/or C_1-C_6-alkoxy. The 2-pyridyl or 3- pyridyl group may optionally be substituted with halogen, hydroxyl, amino, and/or C_1-C_6-alkoxy, preferably being monosubstituted in the ortho-position.

Preferably R^3 is hydrogen.

Preferably n is an integer from 1 to 6 inclusive. More preferably n is 2.

Preferably R^1 is phenyl, which is optionally substituted with halogen, hydroxyl, and/or C_1-C_6-alkoxy; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy; and n is 2.

Still more preferably, R^1 is an unsubstituted phenyl; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with hydroxyl; R^3 is hydrogen; and n is 2.

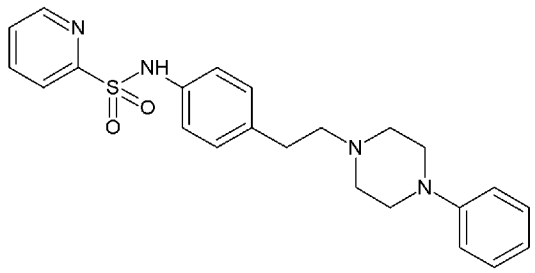
More preferably, the compound according to the invention is selected from the group consisting of:

N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
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N-{4-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{3-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{2-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{4-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide,
N-{3-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide,
N-{2-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide,
N-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{2-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{2-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
N-{2-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
N-{4-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-benzsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-benzsulphonamide,

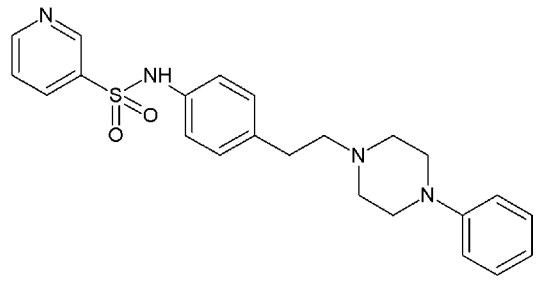
N-{2-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-benzsulphonamide,
N-{4-[2-(4-methyl piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{2-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{4-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide, and
N-{2-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide,

and pharmaceutically acceptable salts or solvates thereof.

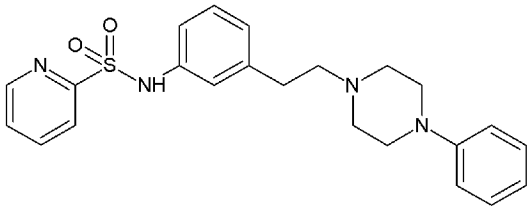
Most preferably, the compound of the general formula A, I, II or III is selected from the group consisting of: N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridyl-sulphonamide (IIIa), N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridyl-sulphonamide (IIIb) N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridyl-sulphonamide (IIa), N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridyl-sulphonamide (IIb) N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridyl-sulphonamide (Ia) and N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridyl-sulphonamide (Ib) or a pharmaceutically acceptable salt or solvate thereof.



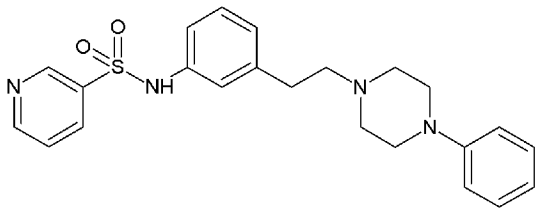
Ia



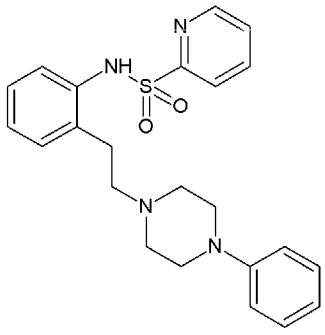
Ib



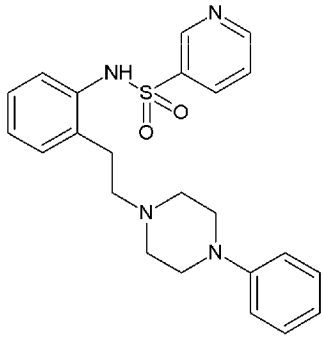
IIa



IIb



IIIa

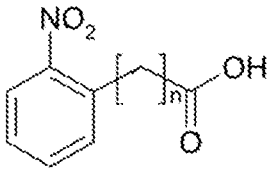


IIIb

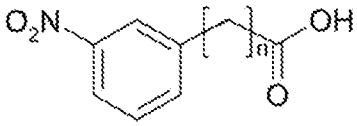
Preferably, the compounds of the general formula A, I, II or III have neuroprotective activity. In particular, the compounds of the general formula A, I, II or III are preferably capable of protecting human neuroblastoma cells from oxidative stress induced by 6-hydroxy dopamine.

According to a second aspect of the present invention there is provided a process for the manufacture of a compound of the general formula A, I, II or III, which comprises the steps of:

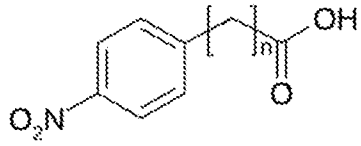
(i) reacting an arylcarboxylic acid of general formula IV a), IV b), or IV c)



IVa)

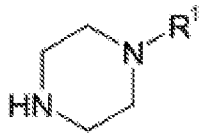


IVb)



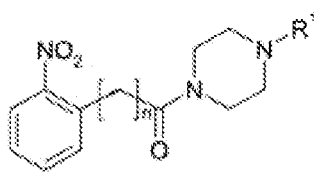
IVc)

with an amine of general formula V

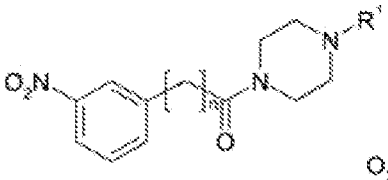


V

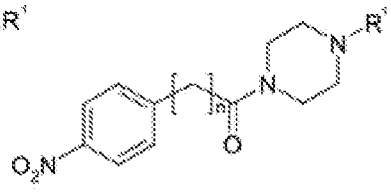
to give a compound of general formula VIa), VIb), or VIc);



VIa)



VIb)



VIc)

(ii) reducing said compound of formula VI a), VI b) or VI c) with a suitable reducing agent;

(iii) hydrogenating the product of step (ii);

(iv) reacting the product of step (iii) with a arylsulphonic acid chloride of the general formula R^2SO_2Cl; and

(v) optionally isolating the resulting compound of formula A, I, II, or III,

wherein:

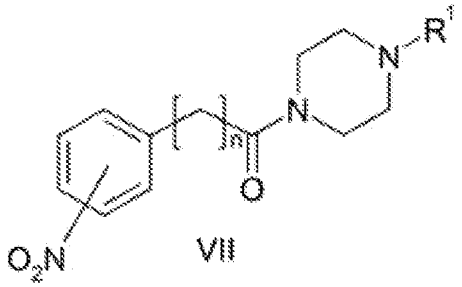
R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$;

R^2 is selected from the group consisting of: C_6-C_{10}-aryl and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$ amino, C_1-C_6-alkylamino, C_1-C_6-dialkyl- amino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)alkoxy and/or $COOR^3$;

R^3 is independently at each occurrence selected from the group consisting of: hydrogen and C_1-C_2-alkyl; and

n is an integer from 0 to 9 inclusive.

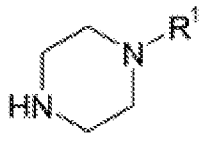
Preferably the arylcarboxylic acid of step (i) has the general formula VII



VII

wherein R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$; and n is an integer from 0 to 9 inclusive.

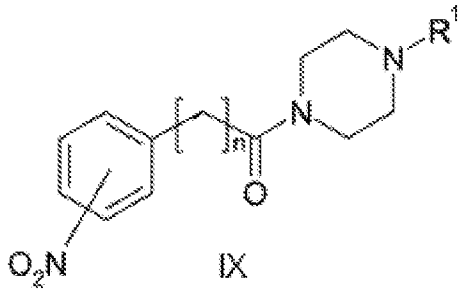
Preferably the amine of step (i) has the general formula VIII



VIII

wherein R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$.

Preferably the reaction product of step (i) has the general formula IX



IX

wherein R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$.

More preferably R^1 is phenyl, R^2 is selected from phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, and pyrazinyl, each optionally substituted with hydroxyl; R^3 is hydrogen at each occurrence; and n is 1.

Suitable reducing agents for use in the reduction step (ii) include but are not limited to diborane (B_2H_6), lithium aluminium hydride (LAH; $LiAlH_4$), and diisobutylaluminium hydride (DIBAL).

Suitable catalysts for hydrogenating the nitro group (NO_2) in step (iii) include but are not limited to transition metals of groups 8, 9, 10 and 11 of the periodic table, in particular nickel (e.g. Raney nickel), platinum, palladium, rhodium, and ruthenium.

According to a third aspect of the present invention there is provided a pharmaceutical composition comprising one or more compounds of the general formula A, I, II or III

as described above and pharmaceutically acceptable excipients, adjuvants, diluents and/or carriers.

Suitable excipients include but are not limited to; disintegrators, binders, fillers, and lubricants.

Suitable disintegrators include but are not limited to; agar-agar, algins, calcium carbonate, cellulose, colloid silicon dioxide, gums, magnesium aluminium silicate, methylcellulose, and starch.

Suitable binders include but are not limited to hydroxymethyl cellulose, hydroxypropylcellulose, microcrystalline cellulose, and polyvinylpyrrolidone.

Suitable fillers include but are not limited to calcium carbonate, calcium phosphate, tribasic calcium sulphate, calcium carboxymethylcellulose, cellulose, dextrin, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrins, maltose, sorbitol, starch, sucrose, sugar, and xylitol.

Suitable lubricants include but are not limited to agar, ethyl laureate, ethyl oleate, glycerin, glyceryl palmitostearate, glycols, hydrogenated vegetable oil, magnesium oxide, mannitol, poloxamer, sodium benzoate, sodium lauryl sulphate, sodium stearyl, sorbitol, stearates, and talc.

Suitable adjuvants include but are not limited to buffer substances, colorants, consistency-improving agents, diluents, emollients, flavour-improving agents, preservatives, salts for varying the osmotic pressure, solubilisers, stabilisers, wetting and emulsifying agents, masking agents and antioxidants.

Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting-point wax, cocoa butter, water, alcohols, polyols, glycerol, vegetable oils and the like.

The pharmaceutical composition may also comprise at least one further active agent, which may include one or more further organic or inorganic molecule.

The composition may be used alone, without further medication. Alternatively, the composition may be used in combination with other medicaments, such as medicaments for treating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, ALS, stroke, and age-related macular degeneration.

Mitochondria are cellular organelles composed of two membranes. An inner mitochondrial membrane (IMM), which is organized into so-called cristae, is surrounded by an outer membrane, which encloses the entire organelle. The space surrounded by the IMM is called matrix and harbours the majority of the mitochondrial proteins, as well as the mitochondrial genome. Between the two membranes, there is an inter-membrane space.

The most prominent function of mitochondria is their role in the regulation of cellular metabolism and, most importantly, in the oxidative phosphorylation, a central step in the production of energy in the form of ATP. The content of mitochondria differs according to the cell type. Cells which have high energy consumption, such as muscle and nerve cells, are particularly rich in mitochondria.

A problem in the process of oxidative phosphorylation is that a small part of the electrons transported in the respiratory chain is responsible for the formation of reactive oxygen species (ROS) such as the dioxide anion (O_2^-.), also known as superoxide and hydrogen peroxide (H_2O_2). ROS lead to propagation of free radicals and can oxidize cellular lipids, nucleotide bases, and proteins. For example, O_2^- can react with nitric oxide (NO) to form toxic compounds such as peroxy nitrite ($ONOO^-$). Inhibition of components of the mitochondrial respiratory chain may ultimately lead to apoptosis of cells.

A state where cells, e.g. human cells, produce increased amounts of oxidants, e.g. ROS, leading to an increased release of free radicals and resulting in cellular degeneration is referred to as oxidative or mitochondrial stress. Mitochondrial stress seems to be involved in several disorders, including neurodegenerative and cardiovascular diseases.

According to a fourth aspect of the present invention there is provided a compound of the general formula A, I, II or III for use as a medicament. In one alternative for use as a human medicament, in another alternative for use as a veterinary medicament.

In one alternative the medicament is for use as a neuroprotective agent.

In another alternative the medicament is for use in the treatment or prophylaxis of neurological and neuropsychiatric disorders.

In a further alternative the medicament is for use in the treatment or prophylaxis of diseases, disorders or conditions associated with, accompanied by or caused by mitochondrial stress.

In yet another alternative the medicament is for use in the treatment of a neurodegenerative disorder. Preferably, said neurodegenerative disorder is selected from amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease, stroke, and age-related macular degeneration.

In another alternative the medicament is for use in the treatment of pathological conditions related to mitochondrial dysfunction and dysfunction of serotonin and dopamine transmitter systems. The medicament acts on the dopamine and serotonin receptors and the antiapoptotic property of the medicament is mediated through mitochondrial dysfunction.

According to a fifth aspect of the present invention there is provided a compound of the general formula A, I, II or III for use in the treatment or prophylaxis of a disease.

In one alternative the compound is for use as a neuroprotective agents.

In another alternative the compound is for use in the treatment or prophylaxis of neurological and neuropsychiatric disorders.

In a further alternative the compound is for use in the treatment or prophylaxis of diseases, disorders or conditions associated with, accompanied by or caused by mitochondrial stress.

In yet another alternative the compound is for use in the treatment of a neurodegenerative disorder. Preferably, said neurodegenerative disorder is selected from amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease),

Alzheimer's disease, Parkinson's disease, stroke, and age-related macular degeneration.

In another alternative the compound is for use in the treatment of pathological conditions related to mitochondrial dysfunction and dysfunction of serotonin and dopamine transmitter systems. The compound acts on the dopamine and serotonin receptors and the antiapoptotic property of the medicament is mediated through mitochondrial dysfunction.

According to a sixth aspect of the present invention there is provided a compound of the general formula A, I, II or III for use in a method of treatment or prophylaxis of a disease.

In one alternative the compound is for use in a method as a neuroprotective agent.

In another alternative the compound is for use in a method of treatment or prophylaxis of neurological and neuropsychiatric disorders.

In a further alternative the compound is for use in a method of treatment or prophylaxis of diseases, disorders or conditions associated with, accompanied by or caused by mitochondrial stress.

In yet another alternative the compound is for use in a method of treatment of a neurodegenerative disorder. Preferably, said neurodegenerative disorder is selected from amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease, stroke, and age-related macular degeneration.

In another alternative the compound is for use in a method of treatment of pathological conditions related to mitochondrial dysfunction and dysfunction of serotonin and dopamine transmitter systems. The compound acts on the dopamine and serotonin receptors and the antiapoptotic property of the medicament is mediated through mitochondrial dysfunction.

According to a seventh aspect of the present invention there is provided a method for manufacturing a medicament intended for the treatment or prophylaxis of a disease, characterised in that a compound of the general formula A, I, II or III is used.

In one alternative the medicament intended for use as a neuroprotective agent.
In another alternative the medicament intended for use in the treatment or prophylaxis of neurological and neuropsychiatric disorders.

In a further alternative the medicament intended for use in the treatment or prophylaxis of diseases, disorders or conditions associated with, accompanied by or caused by mitochondrial stress.

In yet another alternative the medicament is for use in the treatment of a neurodegenerative disorder. Preferably, said neurodegenerative disorder is selected from amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease, stroke, and age-related macular degeneration.

In another alternative the medicament is for use in the treatment of pathological conditions related to mitochondrial dysfunction and dysfunction of serotonin and dopamine transmitter systems. The medicament acts on the dopamine and serotonin receptors and the antiapoptotic property of the medicament is mediated through mitochondrial dysfunction.

According to an eighth aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the general formula A, I, II or III as described above and pharmaceutically acceptable excipients, adjuvants, diluents and/or carriers for use in the treatment or prophylaxis of a disease.

In one alternative the pharmaceutical composition is for use as a neuroprotective agent.

In another alternative the pharmaceutical composition is for use in the treatment or prophylaxis of neurological and neuropsychiatric disorders.

In a further alternative the pharmaceutical composition is for use in the treatment or prophylaxis of diseases, disorders or conditions associated with, accompanied by or caused by mitochondrial stress.

In yet another alternative the pharmaceutical composition is for use in the treatment of a neurodegenerative disorder. Preferably, said neurodegenerative disorder is selected from amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease, stroke, and age-related macular degeneration.

In another alternative the pharmaceutical composition is for use in the treatment of pathological conditions related to mitochondrial dysfunction and dysfunction of serotonin and dopamine transmitter systems. The pharmaceutical composition acts on the dopamine and serotonin receptors and the antiapoptotic property of the medicament is mediated through mitochondrial dysfunction.

According to an ninth aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the general formula A, I, II or III as described above and pharmaceutically acceptable excipients, adjuvants, diluents and/or carriers for use in a method of treatment or prophylaxis of a disease.

In one alternative the pharmaceutical composition is for use as a neuroprotective agents.

In another alternative the pharmaceutical composition is for use in a method of treatment or prophylaxis of neurological and neuropsychiatric disorders.

In a further alternative the pharmaceutical composition is for use in a method of treatment or prophylaxis of diseases, disorders or conditions associated with, accompanied by or caused by mitochondrial stress.

In yet another alternative the pharmaceutical composition is for use in a method of treatment of a neurodegenerative disorder. Preferably, said neurodegenerative disorder is selected from amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease, stroke, and age-related macular degeneration.

In another alternative the pharmaceutical composition is for use in a method of treatment of pathological conditions related to mitochondrial dysfunction and dysfunction of serotonin and dopamine transmitter systems. The pharmaceutical

composition acts on the dopamine and serotonin receptors and the antiapoptotic property of the medicament is mediated through mitochondrial dysfunction.

According to a tenth aspect of the present invention there is provided a method of treatment of a disease or condition of the human or animal body comprising administering a therapeutically effective amount of a compound of the general formula A, I, II or III or a pharmaceutical composition as described above.

In one alternative the method of treatment or prophylaxis is of neurological and neuropsychiatric disorders.

In a further alternative the method of treatment or prophylaxis is of diseases, disorders or conditions associated with, accompanied by or caused by mitochondrial stress.

In yet another alternative the method of treatment or prophylaxis is of treatment of a neurodegenerative disorder. Preferably, said neurodegenerative disorder is selected from amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease, stroke, and age-related macular degeneration.

In particular, the compound of general formula A, I, II, or III, or a pharmaceutical composition comprising a compound of general formula A, I, II, or III, is for use in the treatment of a disease, disorder or condition associated with, accompanied by or caused by mitochondrial stress.

The present invention also relates to a method for the treatment of a disease, disorder or condition associated with, accompanied by or caused by mitochondrial stress, comprising administering a pharmaceutically effective amount of a of formula A, I, II or III to a subject in need thereof.

Definitions

A pharmaceutically acceptable salt relates to salts or complexes of a compound of formula A, I, II, or III. Examples of such salts include, but are not limited to, base addition salts formed by reaction of a compound of formula A, I, II, or III, with an organic or inorganic base, e.g. ammonia or a hydroxide, carbonate or bicarbonate of a metal cation, which is preferably selected from alkali metals (e.g. sodium, potassium

or lithium), and alkaline earth metals (e.g. calcium or magnesium), or with an organic primary, secondary or tertiary alkyl amine. Also encompassed are acid addition salts formed with inorganic acids (e.g. hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid), as well as salts formed with organic acids, e.g. aliphatic monocarboxylic and dicarboxylic acids, aromatic acids, and sulfonic acids. Non-limiting examples of such acids include acetic acid, benzoic acid, (+)-camphor-10- sulfonic acid, citric acid, gluconic acid, lactic acid, methanesulfonic acid, propionic acid, oxalic acid, succinic acid, tartric acid, trifluoroacetic acid, and triphenylacetic acid.

A pharmaceutically acceptable solvate may be for example a hydrate.

The term (halo)alkyl as used herein relates to an alkyl group which optionally contains at least one halogen, e.g. F, Cl, Br or I substituent up to perhalogenation.

The term alkyl as used herein relates to a monovalent linear or branched, saturated or unsaturated hydrocarbon moiety, consisting of carbon and hydrogen atoms, wherein the number of carbon atoms is defined by a subscript number, e.g. C_1-C_{12}. Non-limiting examples of alkyl moieties include methyl, ethyl, ethenyl, ethynyl, ethinyl, propyl, isopropyl, allyl, n-butyl, isobutyl, tert-butyl, butenyl, hexyl, octyl, and dodecyl.

The term cycloalkyl means a monovalent saturated or partially unsaturated carbocyclic moiety, preferably consisting of one or two rings. Non-limiting examples include cyclopropyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexadienyl, decalinyl, norbornyl.

The term aryl as used herein relates to an unsaturated aromatic carbocyclic group of from 6 to 10 carbon atoms having a single ring or two condensed rings. Non-limiting examples of aryl moieties include phenyl and naphthyl.

The term heteroaryl as used herein relates to a monocyclic radical of 5 to 7 ring atoms containing one, two, or three ring heteroatoms selected from nitrogen, oxygen, and sulphur, the remaining ring atoms being carbon. Non-limiting examples of heteroaryl moieties include furanyl, imidazolyl, isoxazolyl, oxazolyl, pyridyl, pyridazinyl, pyrazinyl, thiazolyl, and thiophenyl.

The term alkoxy as used herein relates to a moiety of the formula -OR, wherein R is an alkyl moiety as defined herein. Non-limiting examples of alkoxy moieties include methoxy, ethoxy, and isopropoxy.

The term substituted as used herein means that one or more functional groups, substituents, are attached to one or more carbon atoms of an alkyl, cycloalkyl, aryl, or heteroaryl moiety as defined herein.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

All compatible combinations of the embodiments described above are explicitly disclosed herein as if each combination was specifically and individually recited.
Any sub-titles herein are included for convenience only, and are not to be construed as limiting the disclosure in any way.

The invention will now be further described with reference to the following non-limiting Figures and Examples. Other embodiments of the invention will occur to those skilled in the art in the light of these.

The disclosure of all references cited herein, inasmuch as it may be used by those skilled in the art to carry out the invention, is hereby specifically incorporated herein by cross- reference.

Description of the Figures

Figure 1 illustrates Scheme 1, the synthetic route and chemical structures N-{4-[2-(4-aryl-piperazin-1-yl)-ethyl]-phenyl}-arylsulphonamides, N-{3-[2-(4-aryl-piperazin-1-yl)-ethyl]-phenyl}-arylsulphonamides and N-{2-[2-(4-aryl-piperazin-1-yl)-ethyl]-phenyl}-arylsulphonamides;

Figure 2 illustrates Scheme 2 the synthetic route and chemical structures of the N-{4-[2-(4-aryl-piperazin-1-yl)-methyl]-phenyl}-arylsulphonamides, N-{3-[2-(4-aryl-piperazin-1-yl)-methyl]-phenyl}-arylsulphonamides and N-{2-[2-(4-aryl-piperazin-1-yl)-methyl]-phenyl}-arylsulphonamides;

Figure 3 illustrates Table 1 illustrating the chemical structure and binding affinity of the some new arylpiperazine-sulphonamides for the D_2 DA and 5-HT_{1A} receptors;

Figure 4 illustrates the effect of compounds 1 and 2 on motor clinical scores;

Figure 5 illustrates the viability of rat ventral mesencephalic cells in culture following administration of proteasomal inhibitor lactacystin (5μM) using MTT assay. Compound 4h (4207) and 4f (4295) are protective against the effect of lactacystin in this model; and

Figure 6 illustrates the viability of ventral mesencephalic neurones using calcein AM assay. Low to medium concentrations of compound 4h (4207) and 4f (4295) reversed cell death in response to 5 μM lactacystin.

Examples

Synthesis and characterization of N-arylpiperazine derivatives

Overview

Synthetic route and chemical structures of the compounds synthesized in the present study are shown in Figure 1 and Figure 2. Acylation of N-phenylpiperazine using nitrophenylacetic acid gave rise to 2-(nitrophenyl)-1-(4-phenyl-piperazin-1-yl)-ethanones (1a-c). Amides 1a-c were converted to 1-nitro-phenethyl-4-phenyl-piperazines 2a-c using diborane in tetrahydrofuran (THF). Nitro compounds 5a-c were obtained by direct alkylation of arylpiperazines with corresponding nitrobenzyl halides (Figure 2). Reduction of nitro compounds 2a-c and 5a-c by Ra-Ni/hydrazine provided anilines 3a-c and 6a-c. Target compounds 4a-c and 7a-c were obtained by condensation of anilines 3a-c and 6a-c with corresponding aromatic sulphonyl chloride in presence of pyridine in N-Dimethylformamide (DMF). All compounds were characterized by NMR spectroscopy and mass spectroscopy.

General

A Stuart SMP10 apparatus (Bibby Sterlin Ltd, Stone, UK) was used to determine melting points, presented here as uncorrected. 1H-NMR (at 300 MHz) and 13C-NMR (at 50 MHz) spectra were recorded on a Bruker AC300 (Bruker, Karlsruhe, Germany) with CDCl3 as a solvent, and, unless otherwise stated, are reported in ppm using tetramethylsilane as the internal standard. The mass spectra were determined by field desorption mass spectroscopy on a Finnigan Mat 8230 mass spectrometer (Finnigan, Bremen, Germany). For analytical thin-layer chromatography Merck (Darmstadt, Germany) F-256 plastic-backed thin-layer silica gel plates were used. Chromatographic purifications were performed on Merck-60 silica gel columns, 230-400 mesh ASTM, under medium pressure (dry column flash chromatography). All reagents and solvents used herein were obtained from Aldrich and were used without further purification. Solutions were routinely dried over anhydrous MgSO4 prior to evaporation.

A library of several hundred new arylpiperazines has been synthesized and screened for neuroprotective activity. Synthesis arylpiperazines containing heteroaryl sulphonamide fragments as a part of molecule is shown in Figures 1 and 2.

Example 1:

2-(Nitro-phenyl)-1-(4-phenyl-piperazin-1-yl)-ethanones (1a-c):

1-Phenylpiperazine (10.75 g, 10.12 mL, 66.24 mmol), *o-*, *m-* or *p*-nitrophenylacetic acid (12 g, 66.24 mmol) and triethylamine (7.37g, 10.14 mL, 72.87 mmol) were

dissolved in 200 ml DMF dry. The obtained solution was cooled to 10°C with an ice bath, a PPAA solution (72.70 mmol, 42.5 mL, 50% solution in DMF) was dropwise added and the reaction mixture (orange solution) was left with stirring, at RT overnight. The reaction mixture was poured onto ice/water. The pH of the suspension was adjusted to 8 with 10% Na_2CO_3 solution (from acidic range). The precipitate was filtrated, washed with water and crystallized from acetone to give the expected product.

Yield: 2-(2-Nitro-phenyl)-1-(4-phenyl-piperazin-1-yl)-ethanone (1a): 17.2 g white crystals; mp 140-141°C, 2-(3-Nitro-phenyl)-1-(4-phenyl-piperazin-1-yl)-ethanone (1b): 12.5 g; white crystals; mp 124-126 ºC and 2-(4-Nitro-phenyl)-1-(4-phenyl-piperazin-1-yl)-ethanone (1c): 19.0 g; white crystals; mp 147-150 ºC.

Example 2:

1-[2-(Nitro-phenyl)-ethyl]-4-phenyl-piperazines (2a-c):

To a suspension of 2-(2-nitro-phenyl)-1-(4-phenyl-piperazin-1-yl)-ethanone (1a) or 2-(3-nitro-phenyl)-1-(4-phenyl-piperazin-1-yl)-ethanone (2a) or 2-(4-nitro-phenyl)-1-(4-phenyl-piperazin-1-yl)-ethanone (3a) (15 g, 46.1 mmol) in 300 ml dry THF, a diborane solution (1 M in THF, 118 mL, 118 mmol) was added dropwise while cooling externally in an ice-water bath. The ice bath was removed after the addition of diborane was completed and the reaction mixture was heated with a heat-gun to seeding. After spontaneous boiling stops the reaction mixture was refluxed for an additional 2 h. After cooling down to RT water (35 ml) was added drop wise followed by 5.5 M HCl (70 ml). The reaction mixture was refluxed for another 60 min and was left to cool down to RT. The reaction mixture was concentrated under vacuum and the resulting solution was treated with 10% $NaHCO_3$ solution to pH~8. The product was extracted with ethyl acetate, washed with water and brine and evaporated to dryness to give yellow oil. Trituration with hexane gave the product.

Yield: 1-[2-(2-Nitrophenyl)-ethyl]-4-phenyl-piperazine (2a): 12.7 g yellow powder; mp 74-75°C, 1-[2-(3-Nitrophenyl)-ethyl]-4-phenyl-piperazine (2b): Yield: 9.5 g; white crystals; mp 88-90 ºC and 1-[2-(4-Nitrophenyl)-ethyl]-4-phenyl-piperazine (2c): 14.0 g; white crystals; mp 137-140 ºC.

Example 3:

1-[2-(Nitro-phenyl)-methyl]-4-phenyl-piperazines (5a-c):

1-Phenylpiperazine (10.75 g, 10.12 mL, 66.24 mmol), *o-, m-* or *p*-nitrobenzyl chloride (11.3 g, 66.24 mmol) and sodium carbonate (6.93g, 66.24 mmol) were resuspend in 100 ml DMF dry. The obtained solution was brought to 60 ºC and left with stirring overnight. The reaction mixture was poured onto ice/water. The precipitate was filtrated, washed with water and crystallized from ethanol to give the expected product. Yield: 1-[2-(2-Nitrophenyl)-methyl]-4-phenyl-piperazine (6a): 15.7 g yellow powder; mp 102-105ºC, 1-[2-(3-Nitrophenyl)-methyl]-4-phenyl-piperazine (6b): Yield: 16.5 g; white crystals; mp 128-130 ºC and 1-[2-(4-Nitrophenyl)-methyl]-4-phenyl-piperazine (6c): 18.0 g; white crystals; mp 169-170 ºC.

Example 4:

[2-(4-Phenyl-piperazin-1-yl)-ethyl]-phenylamines (3a-c) and [2-(4-Phenyl-piperazin-1-yl)-methyl]-phenylamines (6a-c):

To a ethanol solution of 1-[2-(2-Nitrophenyl)-ethyl]-4-phenyl-piperazine (2a) or 1-[2-(3-Nitrophenyl)-ethyl]-4-phenyl-piperazine (2b) or 1-[2-(4-Nitrophenyl)-ethyl]-4-phenyl-piperazine (2c) (110 ml, 3 g, 9.36 mmol) and hydrazine hydrate (5.0 ml) were successively added, Ra/Ni (0.5-0.7 g). The reaction mixture was stirred at rt for 3 h and for 1 h at 50 ºC. The suspension was filtrated over a bed of Celite and the filtrate was evaporated in a vacuum. The residue was taken in ethyl acetate and washed with water/bicarbonate solution, water and brine. After being evaporated the oily residue was crystallized from ethyl acetate.

Yield: 2-[2-(4-Phenyl-piperazin-1-yl)-ethyl]-phenylamine (3a): 2.53g , pink crystals; mp 101-103ºC; 3-[2-(4-Phenyl-piperazin-1-yl)-ethyl]-phenylamine (3b): 2.3 g; mp 105-108 ºC; white crystals; 4-[2-(4-Phenyl-piperazin-1-yl)-ethyl]-phenylamine (3c): 2.8 g; white crystals; mp 202-205 ºC 2-[2-(4-Phenyl-piperazin-1-yl)-methyl]-phenylamine (6a): 2.23g , pink crystals; mp 131-134ºC; 3-[2-(4-Phenyl-piperazin-1-yl)-methyl]-phenylamine (6b): 2.13 g; mp 172-175 ºC; white crystals; and 4-[2-(4-Phenyl-piperazin-1-yl)-methyl]-phenylamine (6c): 2.38 g; white crystals; mp 223-224 ºC.

Example 5:

N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide (4d):

2-Pyridinesulfonyl chloride*, 0.37 g* (2.2 mmol), was added to the solution of 560 mg of 2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml),

each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from methanol to give 480 mg of product, mp: 233-235°C.

^{1}H NMR (300 MHz, *DMSO-d$_6$*) δ ppm: 10.15 (brs, 1H, NH), 8.82 (ddd, *J* = 4.7 Hz, *J* =1.7 Hz, *J* =0.9 Hz, 1H, Ar-H), 8.06 (td, *J* = 7.8 Hz, *J* = 1.7 Hz, 1H, Ar-H), 7.87 (dt, *J* = 7.9 Hz, *J* = 0.9 Hz, 1H, Ar-H), 7.70 (ddd, *J* = 7.7 Hz, *J* =4.7 Hz, *J* = 1.1 Hz, 1H, Ar-H), 7.34-7.25 (m, 3H, Ar-H), 7.19 (td, *J* = 7.5 Hz, *J* = 1.4 Hz, 1H, Ar-H), 7.12 (td, *J* = 7.5 Hz, *J* = 1.7 Hz, 1H, Ar-H), 7.03 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.91 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1H, Ar-H), 6.87 (t, *J* = 7.3 Hz, 1H, Ar-H), 3.90-3.80 (m, 2H, -CH_2-), 3.65-3.55 (m, 2H, -CH_2-), 3.34-3.29 (m, 4H, -CH_2-), 3.18-3.13 (m, 4H, -CH_2-); ^{13}C NMR (100 MHz, *DMSO- d$_6$*) δ ppm:156.88, 150.18, 149.49, 138.76,134.54, 133.85, 130.17, 129.06, 127.42, 127.36, 126.95, 126.85, 124.53, 122.33, 119.89, 115.86, 55.10, 50.54, 45.27, 24.66; HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_4O_2S$: 423.1855, found 423.1845.

Example 6:

N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide (4e):

2-Pyridinesulfonyl chloride (prepared according to the method described in US2007/60623), *0.37 g* (2.2 mmol), was added to the solution of 560 mg of 3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from methanol to give 460 mg of product, mp: 210-212°C.

^{1}H NMR (300 MHz, *DMSO- d$_6$*) δ ppm: 10.63 (s, 1H, NH), 8.72 (ddd, *J* = 4.6 Hz, *J* =1.6 Hz, *J* =0.9 Hz, 1H, Ar-H), 8.06 (td, *J* = 7.6 Hz, *J* = 1.7 Hz, 1H, Ar-H), 7.99 (dt, *J* = 8.1 Hz, *J* = 1.1 Hz, 1H, Ar-H), 7.640 (ddd, *J* = 7.3 Hz, *J* =4.7 Hz, *J* = 1.3 Hz, 1H, Ar-H), 7.26 (dd, *J* = 8.5 Hz, *J* = 7.4 Hz, 2H, Ar-H), 7.18 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.04 (brs, 1H, Ar-H), 7.03-6.99 (m, 3H, Ar-H), 6.94 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.86 (t, *J* = 7.2 Hz, 1H, Ar-H), 3.83-3.80 (m, 2H, -CH_2-), 3.62-3.59 (m, 2H, -CH_2-), 3.25-3.14 (m, 6H, -CH_2-), 3.06-3.00 (m, 2H, -CH_2-); ^{13}C NMR (100 MHz, *DMSO-d$_6$*□□□ ppm: 156.47, 150.29, 149.71, 138.87, 138.18, 138.04, 129.44, 129.24, 127.54, 124.27, 122.66, 120.41, 120.09, 118.45, 116.08, 55.89, 50.64, 45.50, 29.31; FD-MS: *m/z* (%):

422.7 $[M]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_4O_2S$: 423.1855, found 423.1867.

Example 7:

N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide (4f):

2-Pyridinesulfonyl chloride, *0.37 g* (2.2 mmol), was added to the solution of 560 mg of 4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from methanol to give 520 mg of product, mp: 125-127°C.

^1H NMR (300 MHz, *DMSO- d_6*) δ ppm: 10.58 (s, 1H, NH), 8.71 (ddd, *J* = 4.8 Hz, *J* =1.7 Hz, *J* =0.9 Hz, 1H, Ar-H), 8.05 (td, *J* = 7.7 Hz, *J* = 1.7 Hz, 1H, Ar-H), 7.96 (dt, *J* = 7.9 Hz, *J* = 1.0 Hz, 1H, Ar-H), 7.64 (ddd, *J* = 7.4 Hz, *J* =4.7 Hz, *J* = 1.2 Hz, 1H, Ar-H), 7.25 (dd, *J* = 8.6 Hz, *J* = 7.3 Hz, 2H, Ar-H), 7.12-7.11 (m, 4H, Ar-H), 6.99 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.85 (t, *J* = 7.3 Hz, 1H, Ar-H), 3.82-3.78 (m, 2H, $-CH_2-$), 3.59-3.56 (m, 2H, $-CH_2-$), 3.30-3.24 (m, 2H, $-CH_2-$), 3.19-3.09 (m, 4H, $-CH_2-$), 3.02-2.97 (m, 2H, $-CH_2-$); ^{13}C NMR (100 MHz, *DMSO- d_6*) δ ppm: 156.35, 150.06, 149.50, 38.68, 136.16, 132.54, 129.20, 129.02, 127.31, 122.37, 120.32, 119.88, 115.87, 55.80, 50.46, 45.26, 28.39; FD-MS: *m/z* (%): 422.6 $[M]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_4O_2S$: 423.1855, found 423.1867.

Example 8:

N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide hydrochloride (4g):

3-Pyridinesulfonyl chloride (prepared according to the method described in US2006/217387 A1), *0.37 g* (2.2 mmol), was added to the solution of 560 mg of 2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from dilute ethanol as hydrochloride salt, yield was 530 mg of product, mp: 175-176°.

^{1}H NMR (300 MHz, *DMSO- d_6*) δ ppm: 8.80-8.78 (m, 2H, Ar-H), 8.05 (ddd, *J* = 8.1 Hz, *J* =2.3 Hz, *J* =1.6 Hz, 1H, Ar-H), 7.59 (ddd, *J* = 8.0 Hz, *J* =4.8 Hz, *J* = 0.7 Hz, 1H, Ar-H), 7.22 (dd, *J* = 8.7 Hz, *J* = 7.3 Hz, 2H, Ar-H), 7.17 (dd, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H, Ar-H), 7.13-7.01 (m, 3H, Ar-H), 6.96 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.79 (t, *J* = 7.3 Hz, 1H, Ar-H), 3.30-3.27 (m, 4H, -CH_2-), 2.72-2.69 (m, 4H, -CH_2-), 2.61-2.56 (m, 4H, -CH_2-); ^{13}C NMR (100 MHz, *DMSO- d_6*) δ ppm:153.03, 150.69, 146.76, 137.20, 136.00, 135.38, 134.35, 130.70, 128.87, 127.00, 125.10, 124.28, 123.66, 118.86, 115.37, 58.56, 52.39, 47.37, 28.77; ESI-MS: *m/z* (%): 423.22 $[M+H]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_4O_2S$: 423.1855, found 423.1873.

Example 9:

N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide hydrochloride (4h):

3-Pyridinesulfonyl chloride, *0.37 g* (2.2 mmol), was added to the solution of 560 mg of 3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from dilute ethanol as hydrochloride salt, yield was 590 mg of product, mp: 158-159°C.

^{1}H NMR (300 MHz, *DMSO- d_6*) δ ppm: 8.87 (dd, *J* = 2.4 Hz, *J* =0.7 Hz, 1H, Ar-H), 8.77 (dd, *J* = 4.8 Hz, *J* =1.6 Hz, 1H, Ar-H), 8.12 (ddd, *J* = 8.1 Hz, *J* =2.4 Hz, *J* =1.6 Hz, 1H, Ar-H), 7.59 (ddd, *J* = 8.1 Hz, *J* =4.8 Hz, *J* = 0.8 Hz, 1H, Ar-H), 7.24 (dd, *J* = 8.7 Hz, *J* = 7.3 Hz, 2H, Ar-H), 7.20 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.04 (t, *J* = 1.6 Hz, 1H, Ar-H), 7.00-6.93 (m, 4H, Ar-H), 6.83 (t, *J* = 7.3 Hz, 1H, Ar-H), 3.40-3.33 (brs, 4H, -CH_2-), 3.26-2.20 (m, 4H, -CH_2-), 3.15-3.10 (m, 2H, -CH_2-), 2.93-2.87 (m, 2H, -CH_2-); ^{13}C NMR (100 MHz, *DMSO- d_6*) δ ppm:163.00, 153.48, 149.74, 147.03, 138.85, 137.27, 135.65, 134.71, 129.51, 129.03, 124.98, 124.31, 120.73, 119.74, 118.80, 115.80, 56.36, 50.93, 45.87, 29.79; FD-MS: *m/z* (%): 422.5 $[M]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_4O_2S$: 423.1855, found 423.1873.

Example 10:

N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide hydrochloride (4i):

3-Pyridinesulfonyl chloride, *0.37 g* (2.2 mmol), was added to the solution of 560 mg of 4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from dilute ethanol as hydrochloride salt, yield was 620 mg of product, mp: 177-178°C.

^1H NMR (300 MHz, *DMSO- d_6*) δ ppm: 8.84 (dd, *J* = 2.4 Hz, *J* =0.7 Hz, 1H, Ar-H), 8.76 (dd, *J* = 4.8 Hz, *J* =1.6 Hz, 1H, Ar-H), 8.09 (ddd, *J* = 8.1 Hz, *J* =2.4 Hz, *J* =1.6 Hz, 1H, Ar-H), 7.59 (ddd, *J* = 8.1 Hz, *J* =4.8 Hz, *J* = 0.8 Hz, 1H, Ar-H), 7.19 (dd, *J* = 8.7 Hz, *J* = 7.3 Hz, 2H, Ar-H), 7.13 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.00 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.92 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.76 (t, *J* = 7.2 Hz, 1H, Ar-H), 3.13-3.09 (brs, 4H, -CH_2-), 2.71-2.66 (m, 2H, -CH_2-), 2.60-2.53 (m, 6H, -CH_2-); ^{13}C NMR (100 MHz, *DMSO- d_6*) δ ppm:153.37, 150.85, 146.99, 135.74, 134.78, 134.63, 129.46, 128.85, 124.28, 120.97, 118.78, 115.29, 59.10, 52.41, 47.88, 31.69; FD-MS: *m/z* (%): 422.5 $[M]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{23}H_{27}N_4O_2S$: 423.1855, found 423.1840.

Example 11:

N-{2-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide (7d):

2-Pyridinesulfonyl chloride, *0.37 g* (2.2 mmol), was added to the solution of 530 mg of 2-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from methanol to give 580 mg of product, mp: 225-226°C.

^1H NMR (300 MHz, *DMSO- d_6*) δ ppm: 11.37 (brs, 1H, NH), 10.44 (brs, 1H, NH), 8.80 (ddd, *J* = 4.7 Hz, *J* = 1.6 Hz, *J* = 0.8 Hz, 1H, Ar-H), 8.07 (td, *J* = 7.8 Hz, *J* =1.7 Hz, 1H, Ar-H), 7.91 (dt, *J* = 7.9 Hz, *J* = 0.8 Hz, 1H, Ar-H), 7.85 (dd, *J* = 7.3 Hz, *J* = 1.7 Hz, 1H, Ar-H), 7.70 (ddd, *J* = 7.6 Hz, *J* = 4.7 Hz, *J* = 1.1 Hz, 1H, Ar-H), 7.37-7.31 (m, 3H, Ar-H), 7.26 (dd, *J* = 8.4 Hz, *J* = 7.5 Hz, 2H, Ar-H), 7.15 (dd, *J* = 7.5 Hz, *J* = 1.8 Hz, 1H, Ar-H), 6.98 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.86 (t, *J* = 7.3 Hz, 1H, Ar-H), 4.48 (s, 2H, -CH_2-), 3.80-3.77 (brs, 2H, -CH_2-), 3.44-3.20 (brs, 6H, -CH_2-); ^{13}C NMR (100 MHz, *DMSO- d_6*) δ ppm:156.61, 150.15, 149.37, 138.91, 136.23, 133.06, 130.38, 129.07, 127.53,

127.04, 126.85, 125.80, 122.38, 119.90, 115.86, 54.11, 50.37, 45.22; FD-MS: *m/z* (%): 408.6 $[M]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_4O_2S$: 409.1698, found 409.1685.

Example 12:

N-{3-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide (7e):

2-Pyridinesulfonyl chloride, *0.37 g* (2.2 mmol), was added to the solution of 530 mg of 3-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from methanol to give 590 mg of product, mp: 228-231 °C.

^1H NMR (300 MHz, *DMSO- d_6*) δ ppm: 10.51 (s, 1H, NH), 8.71 (ddd, *J* = 4.7 Hz, *J* = 1.7 Hz, *J* = 0.9 Hz, 1H, Ar-H), 8.04 (td, *J* = 7.7 Hz, *J* =1.7 Hz, 1H, Ar-H), 7.94 (dt, *J* = 7.9 Hz, *J* = 1.0 Hz, 1H, Ar-H), 7.63 (ddd, *J* = 7.6 Hz, *J* = 4.7 Hz, *J* = 1.2 Hz, 1H, Ar-H), 7.20 (dd, *J* = 8.7 Hz, *J* = 7.3 Hz, 2H, Ar-H), 7.15 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.10 (t, *J* = 1.6 Hz, 1H, Ar-H), 7.03 (ddd, *J* = 8.0 Hz, *J* = 2.1 Hz, *J* = 1.0 Hz, 1H, Ar-H), 6.96-6.91 (m, 3H, Ar-H), 6.76 (t, *J* = 7.2 Hz, 1H, Ar-H), 3.39 (s, 2H, $-CH_2-$), 3.08-3.05 (brs, 4H, $-CH_2-$), 2.38-2.35 (brs, 4H, $-CH_2-$); ^{13}C NMR (100 MHz, *DMSO- d_6*) δ ppm:156.12, 150.13, 149.39, 138.69, 137.88, 130.31, 129.45, 129.04, 127.39, 127.08, 122.93, 122.55, 121.19, 119.84, 115.86, 57.91, 49.86, 45.02; FD-MS: *m/z* (%): 408.6 $[M]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_4O_2S$: 409.1698, found 409.1708.

Example 13:

N-{4-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide (7f):

2-Pyridinesulfonyl chloride, *0.37 g* (2.2 mmol), was added to the solution of 530 mg of 4-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from methanol to give 670 mg of product, mp: 178-179 °C.

^{1}H NMR (300 MHz, *DMSO- d_6*) δ ppm: 10.86 (s, 1H, NH), 8.72 (ddd, *J* = 4.9 Hz, *J* = 1.6 Hz, *J* = 0.9 Hz, 1H, Ar-H), 8.04 (ddd, *J* = 7.9 Hz, *J* =1.5 Hz, *J* =1.0 Hz, 1H, Ar-H), 7.66 (ddd, *J* = 7.0 Hz, *J* =4.7 Hz, *J* = 1.6 Hz, 1H, Ar-H), 7.51 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.24 (dd, *J* = 8.6 Hz, *J* = 7.3 Hz, 2H, Ar-H), 7.21 (d, *J* = 8.6 Hz, 2H, Ar-H), 6.94 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.84 (t, *J* = 7.3 Hz, 1H, Ar-H), 4.23 (s, 2H, -CH_2-), 3.77-3.73 (m, 2H, -CH_2-), 3.28-3.10 (m, 6H, -CH_2-); ^{13}C NMR (100 MHz, *DMSO- d_6*) δ ppm:156.32, 150.16, 149.42, 138.84, 138.76, 132.33, 129.03, 127.49, 124.47, 122.37, 119.81, 119.11, 115.83, 57.71, 49.89, 45.06; FD-MS: *m/z* (%): 408.6 $[M]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_4O_2S$: 409.1698, found 409.1689.

Example 14:

N-{2-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide hydrochloride (7g):

3-Pyridinesulfonyl chloride, *0.37 g* (2.2 mmol), was added to the solution of 530 mg of 2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from dilute ethanol as hydrochloride salt, yield was 590 mg of product, mp: 222-224°C

^{1}H NMR (300 MHz, *DMSO- d_6*) δ ppm: 11.00 (brs, 1H, NH), 10.49 (brs, 1H, NH), 8.99 (d, *J* =1.9 Hz, 1H, Ar-H), 8.87 (m, 3H, Ar-H), 8.61 (ddd, *J* = 8.0 Hz, *J* = 1.9 Hz, *J* = 1.5 Hz, 1H, Ar-H), 8.14 (ddd, *J* = 8.1 Hz, *J* = 2.4 Hz, *J* = 1.6 Hz, 1H, Ar-H), 7.98 (ddd, *J* = 8.0 Hz, *J* = 5.6 Hz, *J* = 0.7 Hz, 1H, Ar-H), 7.86-7.83 (m, 1H, Ar-H), 7.66 (ddd, *J* = 8.1 Hz, *J* = 4.9 Hz, *J* = 0.8 Hz, 1H, Ar-H), 7.39-7.36 (m, 2H, Ar-H), 7.25 (dd, *J* = 8.6 Hz, *J* = 7.4 Hz, 2H, Ar-H), 6.97 (dd, *J* = 8.7 Hz, *J* = 0.7 Hz, 2H, Ar-H), 6.95-6.92 (m, 1H, Ar-H), 6.85 (t, *J* = 7.3 Hz, 1H, Ar-H), 4.33 (s, 2H, -CH_2-), 3.85-3.70 (brs, 2H, -CH_2-), 3.40-3.10 (brs, 6H, -CH_2-); ^{13}C NMR (100 MHz, *DMSO- d_6*) δ ppm:153.59, 149.35, 147.09, 146.25, 143.23, 141.31, 139.93, 135.86, 13579, 134.94, 133.24, 130.59, 129.08, 127.27, 126.88, 126.67, 126.13, 124.36, 119.94, 115.89, 53.85, 50.43, 45.23; FD-MS: *m/z* (%): 408.5 $[M]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_4O_2S$: 409.1698, found 409.1712.

Example 15:

N-{3-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide hydrochloride (7h):

3-Pyridinesulfonyl chloride, *0.37 g* (2.2 mmol), was added to the solution of 530 mg of 3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from dilute ethanol as hydrochloride salt, yield was 590 mg of product, mp: 166-168°C.

^1H NMR (300 MHz, *DMSO- d_6*) δ ppm: 10.43 (s, 1H, NH), 8.84 (dd, *J* = 2.4 Hz, *J* = 0.8 Hz, 1H, Ar-H), 8.78 (dd, *J* = 4.8 Hz, *J* =1.6 Hz, 1H, Ar-H), 8.07 (ddd, *J* = 8.1 Hz, *J* = 2.4 Hz, *J* = 1.6 Hz, 1H, Ar-H), 7.59 (ddd, *J* = 8.1 Hz, *J* = 4.8 Hz, *J* = 0.8 Hz, 1H, Ar-H), 7.24-7.31 (m, 3H, Ar-H), 7.08 (brt, *J* = 1.6 Hz, 1H, Ar-H), 7.04-7.00 (m, 2H, Ar-H), 6.92 (dd, *J* = 8.8 Hz, *J* = 0.9 Hz, 2H, Ar-H), 6.77 (t, *J* = 7.2 Hz, 1H, Ar-H), 3.41 (s, 2H, $-CH_2-$), 3.08-3.05 (brs, 4H, $-CH_2-$), 2.38-2.35 (brs, 4H, $-CH_2-$); ^{13}C NMR (100 MHz, *DMSO- d_6*) δ ppm:153.39, 150.91, 147.02, 139.36, 136.96, 135.50, 134.63, 129.05, 128.82, 125.26, 124.21, 120.85, 119.62, 118.71, 115.28, 61.49, 52.29, 48.07; FD-MS: *m/z* (%): 408.6 $[M]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_4O_2S$: 409.1698, found 409.1694.

Example 16:

N-{4-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide hydrochloride (7i):

3-Pyridinesulfonyl chloride, *0.37 g* (2.2 mmol), was added to the solution of 530 mg of 4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenylamine (2.0 mmol) in 5.0 ml dry pyridine, reaction mixture was stirred at room temperature for 2 h, whereupon diluted with 100 ml ethyl acetate and extracted 2 times with 8% $NaHCO_3$ (50 ml) and H_2O (50 ml), each. Organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Obtained products ware purified by recrystallized from dilute ethanol as hydrochloride salt, yield was 610 mg of product, mp: 177-179°C.

^1H NMR (300 MHz, *DMSO- d_6*) δ ppm: 10.46 (s, 1H, NH), 8.86 (dd, *J* = 7.2 Hz, *J* = 0.5 Hz, 1H, Ar-H), 8.77 (dd, *J* = 4.8 Hz, *J* =1.6 Hz, 1H, Ar-H), 8.10 (ddd, *J* = 8.1 Hz, *J* = 2.2 Hz, *J* = 1.7 Hz, 1H, Ar-H), 7.59 (ddd, *J* = 8.1 Hz, *J* = 4.8 Hz, *J* = 0.6 Hz, 1H, Ar-H), 7.21 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.18 (dd, *J* = 8.6 Hz, *J* = 7.4 Hz, 2H, Ar-H), 7.06 (d,

J = 8.5 Hz, 2H, Ar-H), 6.89 (d, J = 7.9 Hz, 2H, Ar-H), 6.75 (t, J = 7.2 Hz, 1H, Ar-H), 3.40 (s, 2H, -CH_2-), 3.09-3.06 (brs, 4H, -CH_2-), 2.44-2.41 (brs, 4H, -CH_2-); ^{13}C NMR (100 MHz, *DMSO- d_6*) δ ppm:153.37, 150.91, 146.96, 135.77, 134.60, 134.43, 129.74, 128.79, 124.25, 120.60, 118.66, 115.25, 61.24, 52.39, 48.05; ESI-MS: *m/z* (%): 409.2 $[M+H]^+$ (100); HR-MS: *m/z* $[M+H]^+$ calcd. for $C_{22}H_{25}N_4O_2S$: 409.1698, found 409.1683.

Among synthesized sulphonamides N-{3-[2-(4-phenyl-piperazin-1-yl)ethyl]-phenyl}-picolinsulphonamide (4e) and N-{3-[2-(4-phenyl-piperazin-1-yl)ethyl]-phenyl}-nicotinsulphonamide (4h) appeared as most interesting candidates for further in vivo investigation.

Biological Data

In a series of studies it was shown that the newly synthesized N-{4-[2-(4-phenyl-piperazin-1-yl)ethyl]-phenyl}-picolinamide (1) and N-{3-[2-(4-phenyl-piperazin-1-yl)ethyl]-phenyl}-picolinamide (2) with arylpiperazine moiety possessed some activity at dopaminergic D2 receptors (discussed below) as well as being most active in preventing mitochondrial damage and apoptosis induced by nitric oxide (NO) in SH-SY5Y cells (Tovilovic et al., 2012). Similarly these novel arylpiperazines modulated the apoptotic and autophagic responses induced by 6-OHDA in human SH-SY5Y neuron-like cells.

In a parallel field, a number of key studies using rodent models of experimental autoimmune encephalomyelitis (EAE) have demonstrated the potential value of these compounds as potent anti-inflammatory agents. Since in this study it was shown that the 2 compounds significantly reduced motor disability due to neuropathy induced by EAE in vivo, this therefore demonstrates good blood brain barrier penetrability (see Figure 4). Thus a variety of approaches have suggested that these compounds bring about neuroprotective effects that might be of great value in Parkinson's disease.

Figure 4 illustrates the effect of compounds 1 and 2 on motor clinical scores (Rats were evaluated daily and graded by a blinded investigator according to the following scale: grade 0 = no signs; grade 1 = limp tail; grade 2 = hind limb weakness sufficient to impair righting; grade 3 = paraplegia) following IV administration of 70 microgram myelin basic protein suspended in Freund's adjuvant. The top panel compares clinical

score against time. In the bottom panel the area under the curves for the duration of the experimental observation is compared.

Finally, it should be noted that newly described arylpiperazine 1 and 2 are a partial dopaminergic agonist with moderate affinity towards dopamine D2 receptors. However, the neuroprotective activity of those two compounds ware apparently independent of dopamine receptor binding (Tovilovic et al., 2012). Chemical proteomics study revealed NAD(P)H dehydrogenase (Quinone) (NQO1) as putative mitochondrial target for these compounds.

From a range of sulphonsmides synthesized, we have identified 2 interesting compounds: 4298 and 4207, which possess little or no affinity for dopamine D2 receptors but high affinity for 5-HT1a receptors (Ki values: 6.42 and 6.88 nM respectively, see Figure 3). The rationale for choosing these compounds is that there would be little if any confounding effects due to activation or antagonism of dopamine receptors. These compounds will have interesting characteristics that would make them suitable for further investigation in neuroprotection investigations as well as in modulating the symptoms of neurological and neuropsychiatric diseases.

Compounds 4298 and 4208 as well as 4295 (which had high affinity for D2 receptor: Ki value=4.43 nM) were tested against lactacystin (5μM) cytotoxicity on rat primary ventral mesencephalic neurones. All compounds markedly protected the dopaminergic neurons against 5μM lactacystin (see Figure 5) in an MTT assay. The compounds 4207 which possessed little or no dopaminergic activity offered most protection against lactacystin.

When 4207 and 4295 (no D2 affinity vs. high D2 affinity) were tested against 5 μM lactacystin in calcein AM fluorescence assay, both compounds were able to afford protection at concentrations ranging from 0.1 to 1 μM, suggesting that the protective effect of N-arylpiperazine heteroaryl sulphonamides were not related activation of D2 receptors. However, at higher concentrations ranging from 10 to 100 μM neuroprotection was reversed, indicating a bimodal concentration response relationship (see Figure 6).

The present invention relates to of formula A, I, II or III and pharmaceutically acceptable salts or solvates thereof and, in particular, to their activity as 5-

hydroxytryptamine 1A (5-HT1A) receptor subtype ligands, to their stereo chemical isomers and to their use for the treatment of pathological conditions for which the pharmacological properties inherent in these compounds is indicated. In particular, 5-HT1A receptor has been a major target for neurobiological research and drug development due to its implication in many pathophysiological processes. 5-HT1A ligands may find use in the treatment of several diseases such as anxiety, depression, schizophrenia, sexual dysfunction, cognitive deficits resulting from neurodegenerative diseases like Alzheimer's disease, nausea and vomiting, sleep disorders, pain, obesity, pain, addiction, withdrawal and in the treatment of prostate cancer. More recent evidence now indicates that 5-HT1A ligands act in other disease states and conditions by virtue of their ability to inhibit the release of glutamate (Choi et al., 2013). 5-HT1A ligands may be used to treat conditions arising from the dysfunction of the glutamate neurotransmitter system or the aberrant release of glutamate.

Therefore, the present invention relates to medicaments in which the ligands comprising an active ingredient derivative or a salt thereof represented by formula A, I, II or III and pharmaceutically acceptable salts or solvates thereof for treatment of patients suffering from disorders of the central and/or peripheral nervous system in which 5-HT1A and/or dopamine D2 receptor subtype activity play an important role. Thus, ligands incorporating the above chemical moiety might be useful as therapeutic or prophylactic agent for a variety of disorders where a therapeutic role following the binding of the ligands (described in this invention) to 5-HT1A and or D2 receptor has been described.

Brain serotonin (5-HT) plays a major role in a number of physiological processes and pathological conditions. Serotonin neurotransmission is involved in the mood regulation, impulse control, vigilance and sleep, eating, sexual behaviour, and cognitive functions, such as memory and learning (Maes and Meltzer, 1995; Overstreet et al., 1998; King et al., 2008; Newman-Tancredi and Klevan, 2011). In addition, serotonin is important in the modulation of anxiety and fear, as well as impulsiveness in suicidal and other violent acts (Dourish, 1987; Murphy, 1990; Fuller, 1991; Lesch, 1991; Lemonde et al., 2003; Akimova et al., 2009). In the periphery, serotonin plays an important role in the gastro-intestinal functioning (Gershon, 2004, 2005).

Therefore, based on the extensive role serotonin following activation of 5-HT1A receptors (Lucki, 1998), the compounds described in this invention will be useful in the following indications:

Mood disorders: depression and anxiety

There is considerable evidence for the role of aberrant serotonin transmission in depression and anxiety (Akimova et al., 2009; Blier and Mansari, 2013). In several experimental paradigms ligands activating the 5-HTIA receptor have been shown to be effective in reducing anxiety and depression (Jann, 1998). Therefore, the disclosed compounds, acting through 5-HT1A receptors are likely to be invaluable for the treatment of depressive disorders, including the sub-type disorders major depressive disorder and dysthymic disorder, and for the treatment of generalized anxiety disorders (GAD). In addition, combination treatment with SSRIs and the disclosed compounds might also have beneficial effects in treatment resistant major depressive disorders (Papakostas et al., 2005) by enhancing the therapeutic potential of SSRIs in treatment of depression (Cittrome, 2012).

Furthermore, due to activity profile and similarity with buspirone, a non-benzodiazepine anxiolytic acting on 5-HT1A and D2 receptor, the compounds described in this invention are likely to have anxiolytic properties and will thus be useful for treatment of generalized anxiety disorders.

Recently the presence of a new subtype of depression has been hypothesized: Stressor-precipitated, cortisol-induced, serotonin-related, anxiety/aggression-driven depression. Patients suffering from this subtype of depression, exhibit impaired serotonin synthesis and reduced 5-HT1A receptor sensitivity (van Praag, 1997). As specific therapeutic agents selective 5-HT1A agonists and cortisol or CRH antagonists are proposed. Prophylactically, maintenance treatment with 5-HT1A agonists seems indicated as well as psychological interventions to increase the stressor threshold.

Bipolar Depression

Aripiprazole (Abilify) is a new antipsychotic undergoing phase III clinical trials for type I bipolar disorder as an adjunct to mood stablizers such lithium or valproate. This

agent, which possesses unique capabilities compared to other antipsychotic agents, especially because of its partial dopaminergic agonistic activity. Moreover, like the other atypical agents, aripiprazole is an antagonist of the 5-HT2A receptor, and an agonist of the 5-HT1A receptor. Aripiprazole is well recognized for its capacity to potentiate antidepressants in the treatment of unipolar depression. Furthermore, it is well known that treatment of bipolar estate with mood stabilizers can markedly affect the expression of 5-HT1A receptors (Nugent et al., 2013). The similarity of action profile of the current disclosed compounds suggest a beneficial effect for in this indication either directly of as adjunct to mood stabilizers.

Social Phobia

Buspirone has been investigated as an alternative therapy to monoamine oxidase inhibitors for treatment of social phobia as it lacks the potentially serious side effects associated with those compounds. One open-label study reported positive findings in a group of patients currently receiving SSRI therapy with the addition of buspirone (30–60 mg/day) (Van Ameringen et al., 1996). Therefore, the disclosed compounds either alone or in combination with SSRI may be efficacious for this indication.

Obsessive compulsive disorder (OCD)

SSRIs such clomipramine, fluoxetine, sertraline, paroxetine, and fluvoxamine are commonly and successfully used in the treatment of OCD. However, while 50 to 70% of OCD patients respond to one of these medications, their symptoms are rarely eliminated (Stanley and Turner, 1995). In a few cases of intractable OCD combination of sertraline and buspirone resulted in dramatic improvements in OCD treatment (Menkes, 1995). Some trials have also reported successful treatment of OCD (Jenike et al., 1991; Pato et al., 1991) following buspirone treatment. Therefore, it is feasible that combination of 5-HT1A agonist disclosed herein would have enhance the benefits of SSRIs in the treatment of OCD.

Attention deficit hyperactivity disorder (ADHD)

In many neuropsychiatric syndromes, including ADHD and schizophrenia, functioning of the ascending serotonergic system is impaired. Experimental evidence from isolation reared rats suggest that 5-HT1A receptor binding site densities were

significantly reduced by 22% in the prelimbic cortex, and significantly increased by between 10 and 50% in the motor cortex, somatosensory cortex, dentate gyrus and CA fields of the hippocampus (Preece et al., 2004).

Schizophrenia

Schizophrenia has two components: positive symptoms, which include delusion, hallucination and excitation and negative symptoms, which include social withdrawal and apathy. The commonly used drugs for this indication do not fully address the need for treatment of the negative symptoms of this disorder. Several patent application using animal and clinical studies have suggested that combination of D2 receptor blockade and 5-HT1A activation could markedly reduce both the negative and positive symptoms of schizophrenia (NeuroSearch, WO09095438, 2009; WO1004080, 2010).

Furthermore, long term treatment with commonly used drugs may lead to extrapyramidal side effects such as tardive dystonia/dyskinesia. Clinical trials with buspirone have suggested that tartive dyskinesia may be effectively reduced by 5-HT1A activation (Moss, et al., 1993). Due to the proposed efficacy of the disclosed compounds on the 5-HT1A receptor and affinity for D2 receptors, the disclosed compounds may also be beneficial in targeting the extrapyramidal symptoms such as tardive dyskinesia, acute dystonia.

Movement disorders: Parkinson's disease and levodopa-induced dyskinesia

It has been shown that methyledioxymethamphetamine (MDMA) can markedly reduce levodopa-induced dyskinesia in a primate model of Parkinson's disease (PD) (Iravani et al., 2003). This effect is brought about by direct stimulation of 5-HT1A receptors (Iravani et al., 2006). Several 5-HT1A agents including sarizotan and tandisparone showed some efficacy in reducing levodopa-induced dyskinesia (Kannari et al., 2002; Goetz et al., 2007). Clinical trials with fetal ventral mesencephalic tissue grafts have shown some successes in the treatment of PD, however it can result in graft-induced dyskinesias (GIDs) similar to that observed

following long-term symptomatic treatment of PD patients with levodopa. It is suggested that GIDs occur due to an underlying dysfunction in serotonergic neurotransmission (Politis 2010a-c, 2011a-b). Following the administration of buspirone in transplanted PD patients affected by GID; marked attenuation of GID was reported, indicating buspirone may be effective in the treatment of GIDs.

Neurogenesis

Serotonin is believed to play an important role in cognition, and serotonin receptors may provide a novel target for future anti-dementia therapeutics. Several lines of evidence suggest that cognitive decline might result from progressive loss hippocampal neurons and induction of neurogenesis might be a valuable avenue to explore in combatting progressive cell loss that occur in cognitive decline (Song et al., 2012). There is evidence that 5-HT1A receptors are involved in the mechanism of neurogenesis (Fuss et al., 2013). Understanding the contributions of adult neurogenesis to hippocampal function will provide new insight into the fundamental aspects of brain plasticity, which can be used to guide therapeutic interventions to replace neural populations damaged by disease or injury (Song et al., 2012). Accordingly, it has been shown that 5-HT1A receptors activation in vitro promotes neurogenesis (Klempin et al., 2010). Also, activation of 5-HT1A receptor by selective 5-HT1A agonist, 8-OH-DPAT increased neurogenesis and survival of late differentiating cells in the dentate gyrus and in the olfactory bulb (Soumier et al., 2010). Patent Number 7,678,808 entitled, "5HT Receptor Mediated Neurogenesis." The patent prodided coverage for treating depression with buspirone, a 5HT1A agent, in combination with melatonin, by initiating neurogenesis cascade. Buspirone and melatonin are the two active agents in BCI-952, a compound that was selected by BrainCells' platform and that demonstrated proof-of-concept in a clinical study.

Neuroprotection: Alzheimer's disease, Parkinson's disease, Huntington's disease and Multiple sclerosis, traumatic brain injury, stroke

In rat primary hippocampal cultures, and in rat in vivo middle cerebral artery occulusion model of stroke, novel 5-HT1A agonists have been shown to possess a neuroprotective effect (Valhondo et al., 2013). It has been proposed the neuroprotective mechanisms of 5-HT1A receptors are thought to be the result of

neuronal hyperpolarization via the activation of G protein-coupled inwardly rectifying K+ channels upon binding to both pre- and post-synaptic 5-HT1A receptors. Hyperpolarization results in inhibition of neuron firing and reduction of glutamate release.

Glutamate is the predominant neurotransmitter in the central nervous system and it plays an important role in neuroplasticity. As such, excessive extracellular levels of glutamate (excitotoxicity) have been associated With the pathophysiology of both acute neurodegenerative disorders such as stroke, transient ischemic attack and spinal/brain trauma, as Well as chronic neurodegenerative disorders such as epilepsy, Alzheimer's Disease, amyotrophic lateral sclerosis, Huntington's Disease, Parkinson's Disease, AIDS dementia and retinal diseases. Compounds Which inhibit or attenuate the release of glutamate represent potential neuroprotective agents for the treatment of ischemia resulting from stroke, transient ischemic attack, brain/ spinal trauma and fetal hypoxia (Koroshetz and Moskowitz, 1996).

Activation of 5-HT1A receptors inhibit the excessive release of glutamate (Rylander, 2012). In addition to therapeutic applications in the field of psychiatry, more recent preclinical studies have suggested that 5-HT1A receptor ligands have also pronounced neuroprotective properties. 5-HT1A ligands have been proven to be effective in anxiety and depression. In addition to therapeutic applications in the field of psychiatry, more recent preclinical studies have suggested that 5-HT1A receptor ligands have also pronounced neuroprotective properties.

Neuroprotection: role of 5-HT1A as an anti-inflammatory agent

Activation of 5-HT1A receptors play a prominent role in modulation of the immune system action (Idova and Davydova, 2010). 5-HT is required for optimal accessory function of monocytes and macrophages, acting through 5-HT1A receptors. The observation 5-HT acting on 5-HT1A receptors inhibits proliferation of T cells in response can be taken as a modulatory role of 5-HT1A receptors on immune response (Mossner et al., 1998). Indeed, 5-HT1A receptors might be involved in the pathogenesis of multiple sclerosis and in experimental autoimmune encephalitis (EAE) models (Pedotto et al., 2001). In our preliminary experiments using a group of compounds disclosed herein, significant reduction in EAE-induced disability was

observed in the rat.

Spinocerebellar ataxia - (Machado-Joseph disease)

Spinocerebellar ataxia are clinically heterogeneous group of disorders. Patients exhibit usually a slowly progressive cerebellar syndrome with various combinations of oculomotor disorders, dysarthria, dysmetria/kinetic tremor, and/or ataxic gait. They can present also with pigmentary retinopathy, extrapyramidal movement disorders (parkinsonism, dyskinesias, dystonia, chorea), pyramidal signs, cortical symptoms (seizures, cognitive impairment/behavioral symptoms), peripheral neuropathy (Manto, 2005). The cerebellum receives a prominent serotonergic innervation, consequently targeting 5-HT1 receptors is likely to be beneficial in the treatment of ataxias. Several studies have evaluated buspirone for ataxia treatment. On mild to moderate ataxia, buspirone, a 5-HT1A agonist displayed efficacy in reducing global ataxia (Lou et al., 1995; Trouillas et al., 1995). Consequently, the compounds disclosed herein are likely to be efficacious in this pathology.

Sleep disorders

5-HT is involved in the regulation of sleep. Various 5-HT1A agonists such as tandospirone (Suzuki et al., 1995) and buspirone (Wilson et al., 2005) have been efficacious in treatment of insomnia, therefore compounds with similar property might have an important therapeutic value.

Pain

The serotonergic system is highly involved in the regulation of affective, homeostatic and pain related mechanisms (Milan, 1995; Ossipov et al., 2010). Recently, it has been reported that novel 5-HT1A agonist have antinoceptive property in various rodent pain models (Valhondo et al., 2013). In a clinical study model of trigeminal neuralgia (recurrent, severe shooting pain in the area of trigeminal nerve which can be brought about by light touches such as chewing, talking brushing teeth), 5-HT1A agonists reduced mechanical allodynia (Kanai et al., 2006). It has been suggested that in analgesia, 5-HT1A receptor activation has a differential effect compared opioids: stimulation of peripheral nociceptors initially produces pain as a first-order

effect, but also sets out hypoalgesia as a second-order effect which with repeated administration this second-order hypoalgesia counteracts the first-order pain and remarkably develops into increasingly powerful analgesia (Colpaert, 2006). Thus agents acting as 5-HT1A agonist, including those addressed in this disclosure might be beneficial in the treatment of neuropathic pain and in particular as adjunct therapy to opioid analgesics such as tramadol (Berrocoso et al., 2007).

Age-related macular degeneration

Age-related macular degeneration (AMD) is a painless eye condition that generally leads to the gradual loss of macula (photoreceptor (rods and cones) involved in central vision but can sometimes cause a rapid irreversible vision loss in older age. AMD is the leading cause of visual impairment in the UK, affecting up to 500,000 people to some degree. For reasons that are unclear, AMD tends to be more common in women than men. It is also more common in white people and people of Chinese ethnicity than people from other ethnic groups. Age is one of the most important risk factors for AMD. The condition is most common in people over 50 and it's estimated that one in every 10 people over 65 have some degree of AMD (Sharma et al., 2014). The products of oxidative stress trigger chronic low-grade inflammation (pathophysiological parainflammation) process in AMD patients. Microglial activation induces photoreceptor cells injury and leads to the development of dry AMD (Nita et al., 2014).

In rats, retinal exposure to blue causes severe photo-oxidative damage and consequently can model features of AMD, including photoreceptor and retinal pigment epithelium degeneration, choriocapillaris atrophy, and retinal remodeling (Marc et al., 2008). In this model 5-HT1A receptor agonists such as 8-hydroxy-DPATand buspirone were shown to 5-HT1A agonists provided potent and complete functional and structural protection. Protection was inhibited by treatment with WAY-100635, confirming the requirement for activating the 5-HT1A receptor in initiating this survival pathway. Consequently, agents acting as 5-HT1A agonist, including those addressed in this disclosure might be beneficial in the treatment of AMD.

Cerebrovascular disorders

5-HT1A agonists have hypotensive effects so they may utility in the treatment of high blood pressure (Kubo et al., 1995). Furthermore these agents are likely to be useful for the prophylaxis and therapy of cerebral disorders (e.g. migraine), in particular in geriatrics, and for the control of the sequelae of cerebral infarcts (apoplexia cerebri), such as stroke and cerebral ischaemias.

Endocrinology and gynaecology

Full or partial agonists of 5-HT1A receptors facilitate HPA excitability and, at higher doses, directly stimulate ACTH secretion (Korneyev, 1997). Furthermore, the use in endocrinology and gynecology is described, e.g. for the treatment of acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome or undesired puerperal lactation. For example, prolactin responses to buspirone challenges were examined in seven women with late luteal phase dysphoric disorder (LLPDD) and the same number of healthy controls. The responses were found to be blunted during the follicular phase in the women with LLPDD (characterized by depressed or labile mood, anxiety, irritability, anger, and other symptoms occurring exclusively during the 2 weeks preceding menses) suggesting that 5-HT1A receptor subsensitivity might be an important trait in LLPDD sufferers (Yatham, 1993) that could be effectively treated with 5-HT1A agonist.

Dermatology

Atopic dermatitis can be aggravated by mental stress and activation of 5-HT1A receptor subtype, has been shown to significantly inhibit stress-induced degranulation of mouse dermal mast cells (Kawana et al., 2010). Inhibition of stress-induced mast cell degranulation may be one of the mechanisms underlying the clinical efficacy. Therefore, 5-HT1A agonists are likely to be useful in the clinical management of stress-associated aggravation of atopic dermatitis.

Gastroenterology

5-HT1A receptor agonists appear to be broad spectrum antiemetic agents (Wolff et al., 1997; Alfieri et al., 1995; Wolff et al., 1995; Lucot, 1997). Consequently the

compounds reported here are likely to be useful in the treatment of emesis as well as prevention of disorders of the gastrointestinal tract associated with unnecessary or undesirable gastric acid secretion including peptic ulcer gastric and duodenal ulcers, gastritis, gastroesophogeal reflux disease, gastric dispepsia, and Zollinger-Ellison syndrome.

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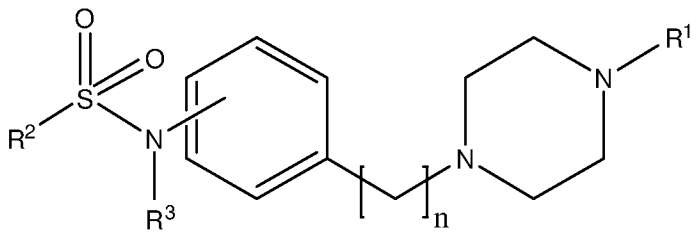
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Claims

1. A compound of the general formula A



A

or a or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$;

R^2 is selected from the group consisting of: C_6-C_{10}-aryl and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$ amino, C_1-C_6-alkylamino, C_1-C_6-dialkyl- amino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)alkoxy and/or $COOR^3$;

R^3 is independently at each occurrence selected from the group consisting of: hydrogen and C_1-C_2-alkyl; and

n is an integer from 1 to 10 inclusive.

2. A compound as claimed in Claim 1 wherein a given moiety is substituted with one, two, three, four, or five independently selected substituents.

3. A compound as claimed in Claim 1 or Claim 2 wherein R^1 is selected from the group consisting of: C_1-C_6-alkyl, phenyl, and nitrogen-containing C_6-heteroaryl, each

optionally substituted with halogen, hydroxyl, C_1-C_6-(halo)alkyl, and/or C_1-C_6-(halo)alkoxy.

4. A compound as claimed in any preceding claim wherein R^1 is phenyl, optionally substituted with halogen, hydroxyl, and/or C_1-C_6-alkoxy.

5. A compound as claimed in any preceding claim wherein R^2 is selected from the group consisting of: phenyl and C_1-C_6-heteroaryl, each optionally substituted with halogen, hydroxyl, amino, C_1-C_6-(halo)alkyl, and/or C_1-C_6-(halo)alkoxy.

6. A compound as claimed in any preceding claim wherein R2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy.

7. A compound as claimed in any preceding claim wherein R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, and pyridazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy.

8. A compound as claimed in any preceding claim wherein R^2 is selected from the group consisting of: phenyl, 2-pyridyl, and 3-pyridyl. The phenyl group may optionally be substituted with halogen, amino, and/or C_1-C_6-alkoxy. The 2-pyridyl or 3- pyridyl group may optionally be substituted with halogen, hydroxyl, amino, and/or C_1-C_6-alkoxy, preferably being monosubstituted in the ortho-position.

9. A compound as claimed in any preceding claim wherein R^3 is hydrogen.

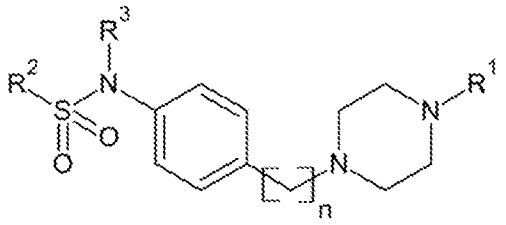
10. A compound as claimed in any preceding claim wherein n is an integer from 1 to 6 inclusive.

11. A compound as claimed in any preceding claim wherein n is 2.

12. A compound as claimed in Claim 1 or Claim 2 wherein R^1 is phenyl, which is optionally substituted with halogen, hydroxyl, and/or C_1-C_6-alkoxy; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with halogen, hydroxyl, amino and/or C_1-C_6-alkoxy; and n is 2.

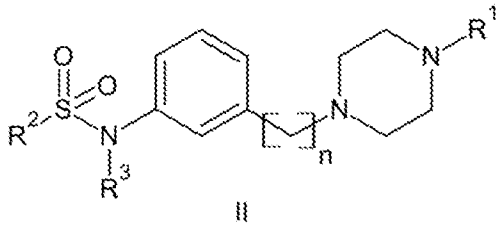
13. A compound as claimed in Claim 1 or Claim 2 wherein R^1 is an unsubstituted phenyl; R^2 is selected from the group consisting of: phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrazinyl, each optionally substituted with hydroxyl; R^3 is hydrogen; and n is 2.

14. A compound as claimed in any preceding claim wherein the general formula A comprises a compound of the general formula I.



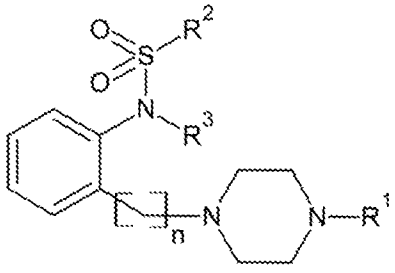
I

15. A compound as claimed in any preceding claim wherein the general formula A comprises a compound of the general formula II.



II

16. A compound as claimed in any preceding claim wherein the general formula A comprises a compound of the general formula III.



III

17. A compound as claimed in Claim 1 wherein the compound is selected from the group consisting of:

N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
N-{4-[2-(4-Phenyl-piperazin-1-yl)-methyl]-phenyl}-benzsulphonamide,
N-{3-[2-(4-Phenyl-piperazin-1-yl)-methyl]-phenyl}-benzsulphonamide,
N-{2-[2-(4-Phenyl-piperazin-1-yl)-methyl]-phenyl}-benzsulphonamide,
N-{4-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{3-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{2-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{4-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide,
N-{3-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide,
N-{2-[2-(4-phenyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide,
N-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{2-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-benzsulphonamide,
N-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{2-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridylsulphonamide,
N-{4-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
N-{2-[2-(4-methyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridylsulphonamide,
N-{4-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-benzsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-benzsulphonamide,
N-{2-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-benzsulphonamide,
N-{4-[2-(4-methyl piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{2-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-2-pyridylsulphonamide,
N-{4-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide,
N-{3-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide, and

N-{2-[2-(4-methyl-piperazin-1-yl)-methyl]-phenyl}-3-pyridylsulphonamide,

and pharmaceutically acceptable salts or solvates thereof.

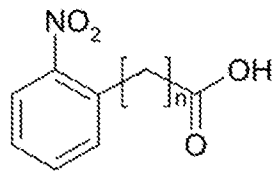
18. A compound as claimed in Claim 1 wherein the compound is selected from the group consisting of: N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridyl-sulphonamide, N-{2-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridyl-sulphonamide, N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridyl-sulphonamide, N-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridyl-sulphonamide, N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-2-pyridyl-sulphonamide, and N-{4-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-3-pyridyl-sulphonamide, and pharmaceutically acceptable salts or solvates thereof.

19. A compound as claimed in any preceding claim having neuroprotective activity.

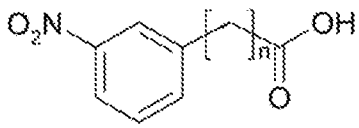
20. A compound as claimed in any preceding claim being capable of protecting human neuroblastoma cells from oxidative stress induced by 6-hydroxy dopamine.

21. A method for the manufacture of a compound as claimed in any preceding claim, which comprises the steps of:

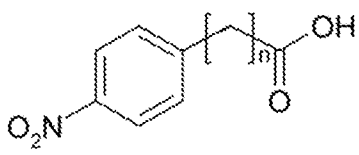
(i) reacting an arylcarboxylic acid of general formula IV a), IV b), or IV c)



IVa)

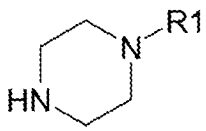


IVb)

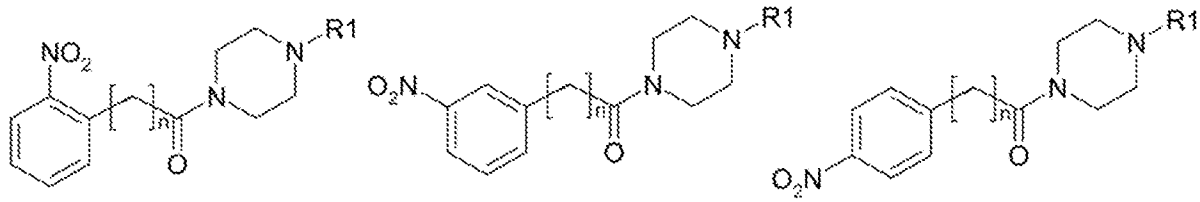


IVc)

with an amine of general formula V



to give a compound of general formula VIa), VIb), or VIc);



VIa) VIb) VIc)

(ii) reducing said compound of formula VI a), VI b) or VI c) with a suitable reducing agent;

(iii) hydrogenating the product of step (ii);

(iv) reacting the product of step (iii) with a arylsulphonic acid chloride of the general formula R^2SO_2Cl; and

(v) optionally isolating the resulting compound of formula A, I, II, or III,

wherein:

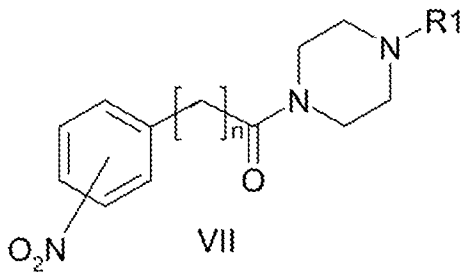
R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$;

R^2 is selected from the group consisting of: C_6-C_{10}-aryl and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$ amino, C_1-C_6-alkylamino, C_1-C_6-dialkyl- amino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)alkoxy and/or $COOR^3$;

R^3 is independently at each occurrence selected from the group consisting of: hydrogen and C_1-C_2-alkyl; and

n is an integer from 0 to 9 inclusive.

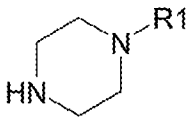
22. A method as claimed in Claim 21 wherein the arylcarboxylic acid of step (i) has the general formula VII



VII

wherein R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$; and n is an integer from 0 to 9 inclusive.

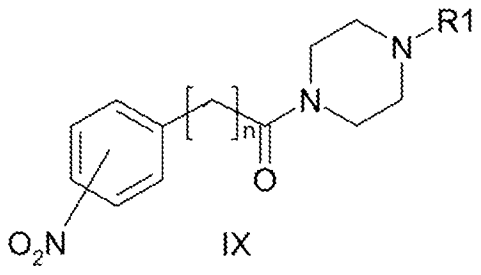
23. A method as claimed in Claim 21 or Claim 21 wherein the amine of step (i) has the general formula VIII



VIII

wherein R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$.

24. A method as claimed in any of claims 21 to 23 wherein the reaction product of step (i) has the general formula IX



IX

wherein R^1 is selected from the group consisting of: C_1-C_{12}-alkyl, C_3-C_{12}-cycloalkyl, C_6-C_{10}-aryl, and C_5-C_7-heteroaryl; each optionally substituted with halogen, hydroxyl, $OCOR^3$, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_1-C_6-(halo)alkyl, C_1-C_6-(halo)- alkoxy and/or $COOR^3$.

25. A method as claimed in Claim 24 wherein R^1 is phenyl, R^2 is selected from phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, and pyrazinyl, each optionally substituted with hydroxyl; R^3 is hydrogen at each occurrence; and n is 1.

26. A pharmaceutical composition comprising one or more compounds as claimed in any of claims 1 to 20 and pharmaceutically acceptable excipients, adjuvants, diluents and/or carriers.

27. A pharmaceutical composition as claimed in Claim 26 comprising at least one further active agent.

28. A compound as claimed in any of claims 1 to 20 for use as a medicament.

29. A compound as claimed in any of claims 1 to 20 for use in the treatment or prophylaxis of a disease.

30. A compound as claimed in any of claims 1 to 20 for use in a method of treatment or prophylaxis of a disease.

31. A method for manufacturing a medicament intended for the treatment or prophylaxis of a disease, characterised in that a compound as claimed in any of claims 1 to 20 is used.

32. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 20 and pharmaceutically acceptable excipients, adjuvants, diluents and/or carriers for use in the treatment or prophylaxis of a disease.

33. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 20 and pharmaceutically acceptable excipients, adjuvants, diluents and/or carriers for use in a method of treatment or prophylaxis of a disease.

34. A method of treatment of a disease or condition of the human or animal body comprising administering a therapeutically effective amount of a compound as claimed in any of claims 1 to 20 or a pharmaceutical composition as described above.

35. A compound as substantially described herein.

36. A method for the manufacture of a compound as substantially described herein.

37. A pharmaceutical composition as substantially described herein.

]

38. A compound for use as a medicament as substantially described herein.

39. A compound for use in the treatment or prophylaxis of a disease as substantially described herein.

40. A compound for use in a method of treatment or prophylaxis of a disease as substantially described herein.

41. A method for manufacturing a medicament intended for the treatment or prophylaxis of a disease as substantially described herein.

42. A pharmaceutical composition for use in the treatment or prophylaxis of a disease as substantially described herein.

43. A pharmaceutical composition for use in a method of treatment or prophylaxis of a disease as substantially described herein.

44. A method of treatment of a disease or condition of the human or animal body as substantially described herein.

Scheme 1

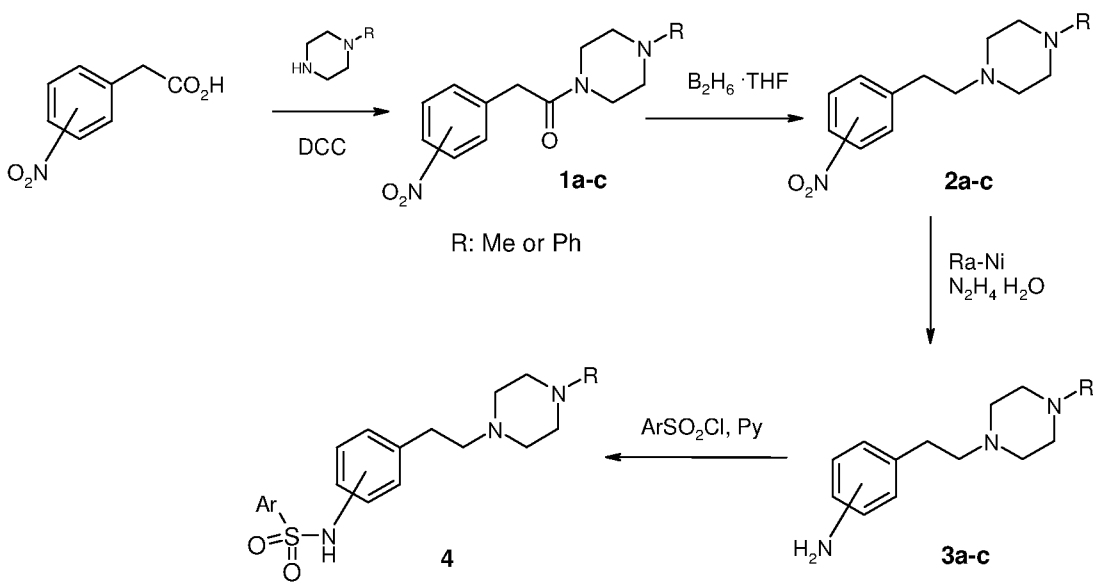


Figure1

Scheme 2

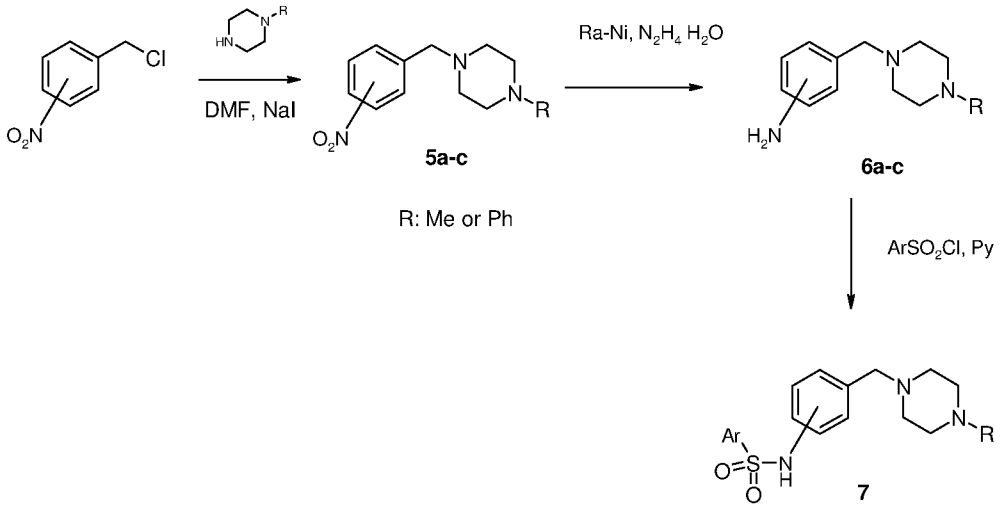
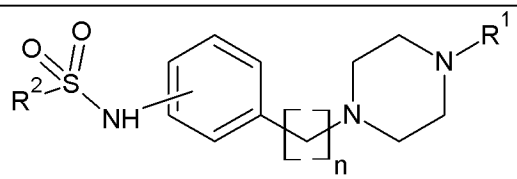


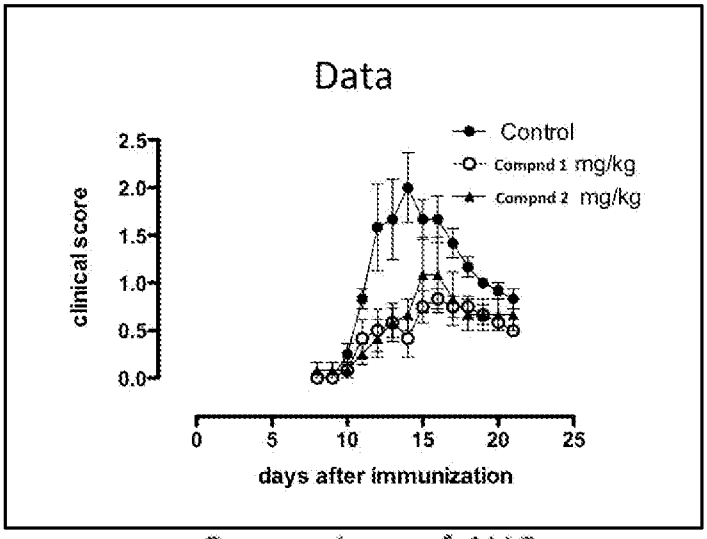
Figure 2



compd.	substitution pattern	R^1	R^2	n	receptor Ki (nM)	
					Dopamine D_2	Serotonin 5-HT_{1A}
4a	1,2	Phenyl	Phenyl	2	>1000	559.6
4b	1,3	Phenyl	Phenyl	2	>1000	17.5
4c	1,4	Phenyl	Phenyl	2	214.8	>1000
4d	1,2	Phenyl	2-Pyridyl	2	>1000	536.9
4e (4298)	1,3	Phenyl	2-Pyridyl	2	>1000	6.42
4f (4295)	1,4	Phenyl	2-Pyridyl	2	4.43	818.1
4g	1,2	Phenyl	3-Pyridyl	2	>1000	536.9
4h (4207)	1,3	Phenyl	3-Pyridyl	2	1036	6.88
4i (4206)	1,4	Phenyl	3-Pyridyl	2	4.90	372.9
4j	1,2	Methyl	Phenyl	2	>1000	>1000
4k	1,3	Methyl	Phenyl	2	>1000	>1000
4l	1,4	Methyl	Phenyl	2	>1000	>1000
4m	1,2	Methyl	2-Pyridyl	2	>1000	>1000
4n	1,3	Methyl	2-Pyridyl	2	>1000	641.1
4o	1,4	Methyl	2-Pyridyl	2	621.8	>1000
4p	1,2	Methyl	3-Pyridyl	2	>1000	>1000
1q	1,3	Methyl	3-Pyridyl	2	>1000	392.2
4r	1,4	Methyl	3-Pyridyl	2	584.2	>1000
7a	1,2	Phenyl	Phenyl	1	>1000	>1000
7b	1,3	Phenyl	Phenyl	1	>1000	>1000
7c	1,4	Phenyl	Phenyl	1	>1000	632.9
7d	1,2	Phenyl	2-Pyridyl	1	>1000	>1000
7e	1,3	Phenyl	2-Pyridyl	1	168.3	>1000
7f	1,4	Phenyl	2-Pyridyl	1	252.3	828.9
7g	1,2	Phenyl	3-Pyridyl	1	>1000	>1000
7h	1,3	Phenyl	3-Pyridyl	1	312.4	410.2
7i	1,4	Phenyl	3-Pyridyl	1	535.4	383.4
7j	1,2	Methyl	Phenyl	1	>1000	>1000
7k	1,3	Methyl	Phenyl	1	>1000	>1000
7l	1,4	Methyl	Phenyl	1	>1000	>1000
7m	1,2	Methyl	2-Pyridyl	1	>1000	>1000
7n	1,3	Methyl	2-Pyridyl	1	>1000	>1000
7o	1,4	Methyl	2-Pyridyl	1	>1000	>1000
7p	1,2	Methyl	3-Pyridyl	1	>1000	>1000
7q	1,3	Methyl	3-Pyridyl	1	>1000	>1000
7r	1,4	Methyl	3-Pyridyl	1	>1000	>1000

The affinity of the new compounds for cloned human D_2 DA and $5HT_{1A}$ receptors was evaluated in *in vitro* binding assays using [^{3}H]spiperone for labeling D_2 DA receptors and [^{3}H]8-OH-DPAT for labeling $5HT_{1A}$ receptors.

Figure 3


Data
Control
Compnd 1 mg/kg
Compnd 2 mg/kg
clinical score
2.5
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
25
days after immunization

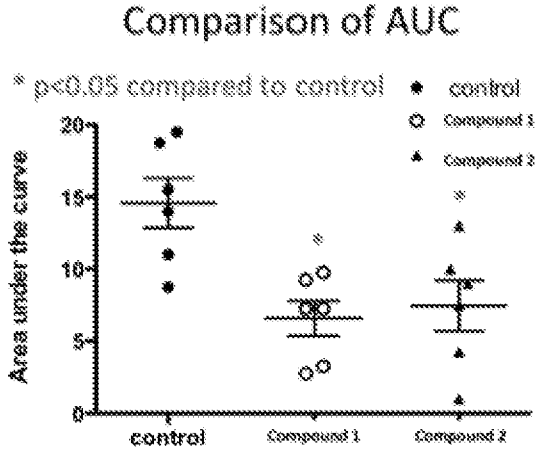

Comparison of AUC
* p<0.05 compared to control
control
Compound 1
Compound 2
Area under the curve
20
15
10
5
0
control
Compound 1
Compound 2

Figure 4

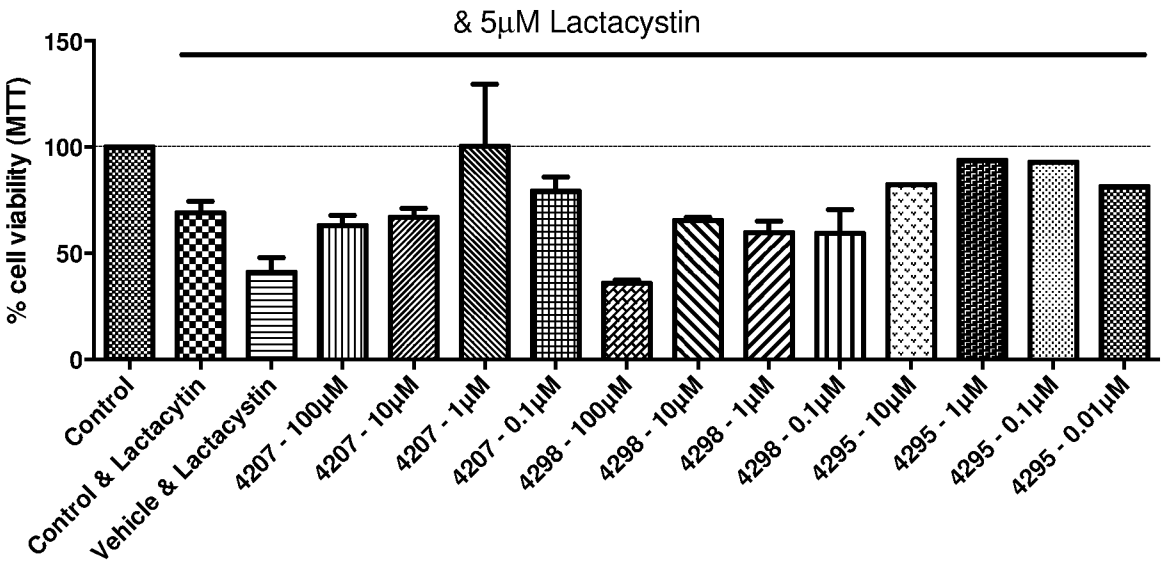

& 5µM Lactacystin
% cell viability (MTT)
150
100
50
0
Control
Control & Lactacytin
Vehicle & Lactacystin
4207 - 100µM
4207 - 10µM
4207 - 1µM
4207 - 0.1µM
4298 - 100µM
4298 - 10µM
4298 - 1µM
4298 - 0.1µM
4295 - 10µM
4295 - 1µM
4295 - 0.1µM
4295 - 0.01µM

Figure 5

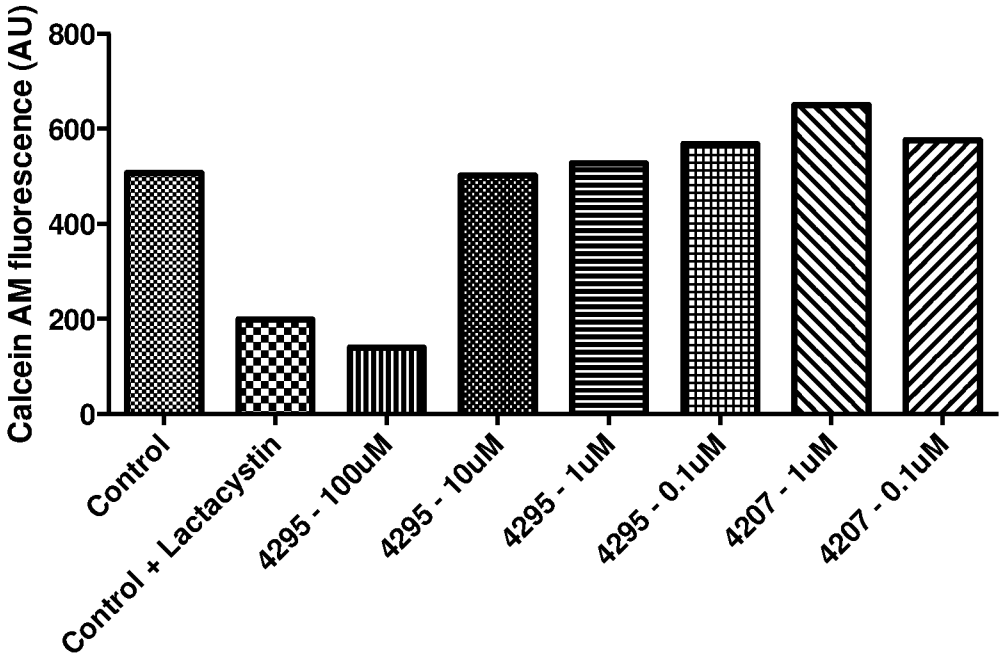

Calcein AM fluorescence (AU)
800
600
400
200
0
Control
Control + Lactacystin
4295 - 100uM
4295 - 10uM
4295 - 1uM
4295 - 0.1uM
4207 - 1uM
4207 - 0.1uM

Figure 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/052822

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/71 A61K31/496 A61P25/00
ADD.

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)
C07D A61K A61P

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

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

EPO-Internal, WPI Data, 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.
X	WO 2004/041793 A1 (WARNER LAMBERT CO [US]; CHO STEPHEN SUNG YONG [US]; DAVIS JAMIE MARIE) 21 May 2004 (2004-05-21) page 1, paragraph 1 examples 77,84 examples 355-499 claims -----	1-44
X	DATABASE Chemcats [Online] 15 September 2014 (2014-09-15), XP002751848, Database accession no. 1711816420 CAS Registry numbers: 1172551-93-7; 1172035-64-1;1171851-33-4;1172287-57-8;1171911-34-4;1171571-00-8; 1171494-45-3;1171431-34-7; 1170575-69-5;1171791-25-5;1171755-27-3 ----- -/--	1-44

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 December 2015	11/01/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stix-Malaun, Elke

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/052822

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	DATABASE Chemcats [Online] 1 January 2015 (2015-01-01), XP002751849, Database accession no. 1080065424 abstract -----	1-44
Y	WO 03/029233 A1 (RICHTER GEDEON VEGYESZET [HU]; GALAMBOS JANOS [HU]; NOGRADI KATALIN [H) 10 April 2003 (2003-04-10) examples claims -----	1-44
Y	WO 2012/069428 A1 (NOSCIRA SA [ES]; PALOMO NICOLAU FRANCISCO [ES]; SANCHEZ-QUESADA JORGE) 31 May 2012 (2012-05-31) examples claims -----	1-44

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2015/052822

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		WO 03029233 A1	10-04-2003
WO 2012069428 A1	31-05-2012	EP 2643299 A1	02-10-2013
		JP 2013542973 A	28-11-2013
		US 2014005195 A1	02-01-2014
		WO 2012069428 A1	31-05-2012