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(54) Title: ADAMANTANE COMPOUNDS

(57) Abstract: The present invention relates to new multi-functional compounds that are useful in the treatment of neurodegenerative diseases, such as Alzheimer's disease, to the preparation of the compounds, and to compositions including the compounds. The present invention also relates to the use of the compounds, as well as compositions including the compounds, in treating or preventing neurodegenerative diseases.

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Adamantane compounds

Field of the invention

The present invention relates to new multi-functional compounds that are useful in the treatment of neurodegenerative diseases, such as Alzheimer's disease, to the preparation of the compounds, and to compositions including the compounds. The present invention also relates to the use of the compounds, as well as compositions including the compounds, in treating or preventing neurodegenerative diseases.

Background of the invention

Neurodegenerative diseases, such as Alzheimer's disease (also referred to herein as AD), Parkinson's disease and Huntington's disease, remain an intractable health problem in the elderly. Dementia (including its most common form, Alzheimer's disease) is now the second leading cause of death in Australia, and no cure exists.

These diseases are multi-faceted with a number of contributing pathological alterations including: protein misfolding and β -amyloid aggregation with plaque formation; oxidative stress and reactive oxygen species (ROS) generation; dysregulation of autophagy, which limits the recycling of misfolded proteins; dysregulation of metal metabolism; and lowering of acetylcholine levels.

While the precise role of ROS in neurodegeneration is unclear, evidence does suggest that redox-active metals and ROS are involved. Notably, Alzheimer's disease is a disease of advancing age, and as iron levels also increase as a function of age, this may lead to increased ROS generation.

In addition, senile plaques have remarkably high iron, copper and zinc levels, and copper and zinc ions are known to facilitate β -amyloid aggregation by modulating amyloid peptide conformation. The role of iron in Alzheimer's disease is further supported by the fact that expression of amyloid precursor protein (APP) is up-regulated by increased cellular iron (as APP plays an integral role in iron efflux from neuronal cells).

These data led to the assessment of various iron chelators for treatment of Alzheimer's disease. One such chelator (clioquinol; CQ) binds copper and zinc ions, is

able to cross the Blood Brain Barrier (BBB) and clinically attenuates cognitive loss. However, clioquinol is associated with myelinopathies and does not decrease brain β -amyloid.

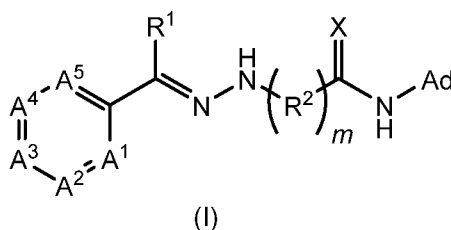
Therefore, there is still a need for agents that are effective in treating and/or
5 preventing neurodegenerative diseases.

Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood, regarded as relevant, and/or combined with other pieces of prior art by a skilled person
10 in the art.

Summary of the invention

The present inventors have found that the issues with current agents used in neurodegenerative therapy could be overcome by developing one multifunctional agent that is able to target the main hallmarks of neurodegenerative diseases.

15 In a first aspect, the present invention relates to a compound of formula (I):

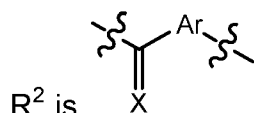


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ad is an adamantane moiety,

X is selected from O and S,

20 m is 0 or 1,



wherein Ar is selected from aryl and heteroaryl, which aryl and heteroaryl groups are optionally substituted,

R^1 is selected from H, alkyl and heteroaryl,

A¹, A², A³, A⁴ and A⁵ are independently selected from CH and N, and

the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group.

5 Ar may be a 5- or 6-membered aryl or heteroaryl group. Ar may be a 6-membered aryl group. Ar may not be substituted.

R¹ may be H. R¹ may be C₁ to C₃ alkyl (i.e., methyl, ethyl or propyl). R¹ may be a heteroaryl group (e.g., pyridine). Preferably, R¹ is H or C₁ to C₃ alkyl.

The aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be substituted. At least
10 one of the substituents may be OH (e.g., one or more of A¹, A², A³, A⁴ and A⁵ may be C-OH). The aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be substituted with one or more additional substituents (i.e., additional to OH). The aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be substituted with one additional substituent such as OH. The one additional substituent may be halogen (e.g., bromine, chlorine or fluorine). The one
15 additional substituent may be an alkyl group (e.g., C₁ to C₃ alkyl). The one additional substituent may be a heteroalkyl group e.g., O-alkyl (such as OCH₃, OCH₂CH₃) or OCF₃. The aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be substituted with two additional substituents, which may be the same or different (e.g., two halogens, which may be the same or different, two OH groups, or one alkyl group and one heteroalkyl
20 group).

One of A¹, A², A³, A⁴ and A⁵ may be N i.e., the aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be a heteroaryl group. The heteroaryl group may not be further substituted. Alternatively, the heteroaryl group may be substituted with one or more substituents. The one or more substituents may be independently selected from OH, an
25 alkyl group (e.g., methyl or ethyl) and a heteroalkyl group (e.g., CH₂OH or CH₂CH₂OH).

The N and/or OH substituents may be situated on the aromatic ring containing A¹, A², A³, A⁴ and A⁵ such that the compound of formula (I) is able to chelate metal ions (e.g., iron, copper and zinc). Therefore, A¹ may be selected from N and C-OH. Preferably, A¹ is C-OH.

30 The aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be fused (e.g., at A² and A³, or A⁴ and A⁵) to an aryl group, to give a bicyclic aryl or heteroaryl group (e.g.,

naphthyl or quinoline). The bicyclic aryl or heteroaryl group may be substituted with one or more substituents selected from OH, alkyl and heteroalkyl.

In a second aspect, the present invention relates to a pharmaceutical composition including a compound of formula (I) (according to the first aspect of the invention) together with a pharmaceutically acceptable carrier, diluent or excipient.

Compounds and pharmaceutical compositions according to the present invention may be suitable for treating and/or preventing neurodegenerative diseases. Accordingly, in another aspect, the present invention relates to a method of treating and/or preventing a neurodegenerative disease in a subject, the method including administering to the subject an effective amount of a compound of formula (I) according to the first aspect of the invention or a pharmaceutical composition according to the second aspect of the invention.

In a further aspect the present invention relates to the use of a compound of formula (I) according to the first aspect of the invention or a pharmaceutical composition according to the second aspect of the invention in the manufacture of a medicament for treating and/or preventing a neurodegenerative disease.

In a further aspect the present invention relates to the use of a compound of formula (I) according to the first aspect of the invention or a pharmaceutical composition according to the second aspect of the invention for the treatment and/or prevention of a neurodegenerative diseases in a subject.

In another aspect the present invention relates to a compound of formula (I) according to the first aspect of the invention or a pharmaceutical composition according to the second aspect of the invention for use in the treatment and/or prevention of a neurodegenerative diseases in a subject.

The neurodegenerative disease may be selected from dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease and Friedreich's ataxia.

The compounds of formula (I) may be used in therapy alone or in combination with one or more other therapeutic agents, for example, as part of a combination therapy.

Further aspects of the present invention and further embodiments of the aspects described in the preceding paragraphs will become apparent from the following description, given by way of example and with reference to the accompanying drawings.

Brief description of the drawings

5 **Figure 1.** Effect of adamantane compounds 1-27 on ^{59}Fe release from SK-N-MC cells. Results are expressed as the mean $\pm$ SD of three independent experiments. *** $p < 0.001$ versus the control. $^{\circ}p < 0.05$, $^{\circ\circ}p < 0.01$, $^{\circ\circ\circ}p < 0.001$ versus DFO. ### $p < 0.001$ versus CQ. $^{\bullet\bullet}p < 0.001$ versus DFO. $^{\bullet\bullet\bullet}p < 0.001$ versus Dp44mT.

10 **Figure 2.** Effect of adamantane hydrazones on ^{59}Fe uptake from ^{59}Fe -transferrin ($^{59}\text{Fe}_2\text{-Tf}$) by SK-N-MC neuroepithelioma cells. Results are expressed as the mean $\pm$ SD of three independent experiments. *** $p < 0.001$ versus the control. $^{\circ}p < 0.05$, $^{\circ\circ}p < 0.01$, $^{\circ\circ\circ}p < 0.001$ versus DFO.

15 **Figure 3.** Effects of 1-8 and 20-27 on iron-mediated oxidation of ascorbate. Compounds 9-18 were not assayed due to their poor aqueous solubility. Results are mean $\pm$ SD (3 experiments). *** $p < 0.001$ versus the control.

Figure 4. The effect of 1, 2, 11, 13, 15, 20-21, 23-24 on the inhibition of Cu(II)-mediated aggregation of $\text{A}\beta_{1-40}$. Results are presented as mean $\pm$ S.E.M. (three experiments) using quadruplicates in each experiment. *** $p < 0.001$ versus $\text{A}\beta + \text{Cu(II)}$; ### $p < 0.001$ versus $\text{A}\beta$.

20 **Figure 5.** Inhibition of NMDAR-mediated calcium influx into human astrocytes by selected adamantane compounds at 25 μM . Error bar represents mean percentage inhibition $\pm$ SEM. Abbreviations are: MEM (Memantine), NIMO (Nimodipine). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus MK-801; $^{\bullet}p < 0.05$, $^{\bullet\bullet}p < 0.01$, $^{\bullet\bullet\bullet}p < 0.001$ versus Memantine.

25 **Figure 6.** Inhibition of VGCC-mediated calcium influx into human astrocytes by selected adamantane compounds at 25 μM . Error bar represents mean percentage inhibition $\pm$ SEM. Abbreviations are: MEM (Memantine), NIMO (Nimodipine). *** $p < 0.001$ versus NIMO.

Detailed description of the embodiments

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations
5 constitute various alternative aspects of the invention.

Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centres, it will be understood that, unless otherwise specified, all of the optical isomers and mixtures thereof are encompassed. Compounds with two or more asymmetric elements can also be present as mixtures of
10 diastereomers. In addition, compounds with carbon-carbon double bonds may occur in *Z* and *E* forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified. Where a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Recited compounds are further intended to
15 encompass compounds in which one or more atoms are replaced with an isotope, i.e., an atom having the same atomic number but a different mass number. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include ^{11}C , ^{13}C , and ^{14}C .

Compounds according to the formula provided herein, which have one or more
20 stereogenic centres, have an enantiomeric excess of at least 50%. For example, such compounds may have an enantiomeric excess of at least 60%, 70%, 80%, 85%, 90%, 95%, or 98%. Some embodiments of the compounds have an enantiomeric excess of at least 99%. It will be apparent that single enantiomers (optically active forms) can be obtained by asymmetric synthesis, synthesis from optically pure precursors,
25 biosynthesis or by resolution of the racemates, for example, enzymatic resolution or resolution by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example, a chiral HPLC column.

Certain compounds are described herein using a general formula that includes variables such as A^1 , A^2 , A^3 and R^1 . Unless otherwise specified, each variable within
30 such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence.

Therefore, for example, if a group is shown to be substituted with 0, 1 or 2 R*, the group may be unsubstituted or substituted with up to two R* groups and R* at each occurrence is selected independently from the definition of R*. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable
5 compounds, i.e., compounds that can be isolated, characterized and tested for biological activity.

A "pharmaceutically acceptable salt" of a compound disclosed herein is an acid or base salt that is generally considered in the art to be suitable for use in contact with the tissues of human beings or animals without excessive toxicity or carcinogenicity,
10 and preferably without irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids.

Suitable pharmaceutically acceptable salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric,
15 sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, benzenesulfonic, ethane disulfonic, 2-hydroxyethylsulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pamoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alkanoic (such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is any integer from 0 to 6, i.e., 0, 1, 2, 3, 4, 5 or 6), and the like. Similarly,
20 pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminium, lithium and ammonium. A person skilled in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein. In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical
25 method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Generally, the use of non-aqueous media, such as ether, ethyl acetate, ethanol, isopropanol or acetonitrile, is preferred.

It will be apparent that each compound of formula (I) may, but need not, be
30 present as a hydrate, solvate or non-covalent complex. In addition, the various crystal

forms and polymorphs are within the scope of the present invention, as are prodrugs of the compounds of formula (I) provided herein.

A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a subject or patient, to produce a compound of formula (I) provided herein. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, carboxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, carboxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, phosphate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved *in vivo* to generate the parent compounds.

A "substituent" as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, heteroalkyl group, haloalkyl group or other substituent described herein that is covalently bonded to an atom, preferably a carbon or nitrogen atom, that is a ring member. The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated substituents, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound, i.e., a compound that can be isolated, characterized and tested for biological activity. When a substituent is oxo, i.e., =O, then two hydrogens on the atom are replaced. An oxo group that is a substituent of an aromatic carbon atom results in a conversion of -CH- to -C(=O)- and a loss of aromaticity. For example a pyridyl group substituted by oxo is a pyridone. Examples of suitable substituents are alkyl (including haloalkyl e.g., CF₃), heteroalkyl, halogen (for example, fluorine, chlorine, bromine or iodine atoms), C(O)OH, C(O)H, OH, =O, SH, SO₃H, NH₂, NH-alkyl, =NH, N₃ and NO₂ groups.

The term "alkyl" refers to a saturated, straight-chain or branched hydrocarbon group that contains from 1 to 20 carbon atoms, preferably from 1 to 10 carbon atoms,

for example a *n*-octyl group, especially from 1 to 6, i.e., 1, 2, 3, 4, 5, or 6, carbon atoms. Specific examples of alkyl groups are methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *n*-hexyl and 2,2-dimethylbutyl.

The term "heteroalkyl" refers to an alkyl group as defined above that contains one
5 or more heteroatoms selected from oxygen, nitrogen and sulphur (especially oxygen and nitrogen). Specific examples of heteroalkyl groups are methoxy, trifluoromethoxy, ethoxy, *n*-propyloxy, *iso*-propyloxy, butoxy, *tert*-butoxy, methoxymethyl, ethoxymethyl, -CH₂CH₂OH, -CH₂OH, methoxyethyl, 1-methoxyethyl, 1-ethoxyethyl, 2-methoxyethyl or 2-ethoxyethyl, methylamino, ethylamino, propylamino, *iso*-propylamino, dimethylamino,
10 diethylamino, *iso*-propyl-ethylamino, methylamino methyl, ethylamino methyl, di-*iso*-propylamino ethyl, methylthio, ethylthio, *iso*-propylthio, enol ether, dimethylamino methyl, dimethylamino ethyl, acetyl, propionyl, butyryloxy, acetyloxy, methoxycarbonyl, ethoxycarbonyl, propionyloxy, acetylamino, propionylamino, carboxymethyl, carboxyethyl, carboxypropyl, *N*-ethyl-*N*-methylcarbamoyl and *N*-methylcarbamoyl.
15 Further examples of heteroalkyl groups are nitrile, *iso*-nitrile, cyanate, thiocyanate, *iso*-cyanate, *iso*-thiocyanate and alkylnitrile groups.

The term "aryl" refers to an aromatic group that contains one or more rings containing from 6 to 14 ring carbon atoms, preferably from 6 to 10 (especially 6) ring carbon atoms. Examples are phenyl, naphthyl and biphenyl groups.

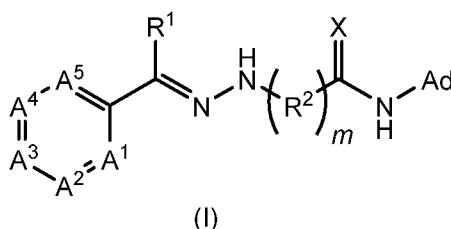
20 The term "heteroaryl" refers to an aromatic group that contains one or more rings containing from 5 to 14 ring atoms, preferably from 5 to 10 (especially 5 or 6) ring atoms, where one or more of the ring atoms are replaced with one or more (preferably 1, 2, 3 or 4) oxygen, nitrogen, phosphorus or sulfur ring atoms (preferably O, S or N). Examples are pyridine, imidazole, thiazole, *iso*-thiazole, 1,2,3-triazole, 1,2,4-triazole,
25 oxadiazole, thiadiazole, indole, indazole, tetrazole, pyrazine, pyrimidine, pyridazine, oxazole, isoxazole, triazole, tetrazole, isoxazole, indazole, benzimidazole, benzoxazole, benzisoxazole, benzthiazole, pyridazine, quinoline, isoquinoline, pyrrole, purine, carbazole, acridine, and *iso*-quinoline groups.

The expression "halogen" or "halogen atom" as used herein means fluorine,
30 chlorine, bromine, or iodine.

The term "optionally substituted" refers to a group in which one, two, three or more hydrogen atoms have been replaced independently of each other by, for example, halogen (for example, fluorine, chlorine, bromine or iodine atoms), C(O)OH, C(O)H, OH, =O, SH, =S, SO₃H, NH₂, NH-alkyl, =NH, N₃ or NO₂ groups. This expression also refers to a group that is substituted by one, two, three or more alkyl or heteroalkyl groups. These groups may themselves be substituted. For example, an alkyl group substituent may be substituted by one or more halogen atoms (i.e., may be a haloalkyl group). The term "haloalkyl" refers to an alkyl group (as defined above) that is substituted by one or more halogen atoms (as also defined above). Specific examples of haloalkyl groups are trifluoromethyl, dichloroethyl, dichloromethyl and iodoethyl.

As used herein a wording defining the limits of a range of length such as, for example, "from 1 to 5" means any integer from 1 to 5, i. e. 1, 2, 3, 4 and 5. In other words, any range defined by two integers explicitly mentioned is meant to comprise and disclose any integer defining said limits and any integer comprised in said range.

As discussed above, the present invention relates to a compound of formula (I):

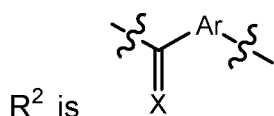


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ad is an adamantane moiety,

X is selected from O and S,

m is 0 or 1,



R^1 is selected from H, alkyl and heteroaryl,

A¹, A², A³, A⁴ and A⁵ are independently selected from CH and N, and

the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group.

5 R¹ may be H. R¹ may be C₁ to C₃ alkyl (i.e., methyl, ethyl or propyl). R¹ may be a heteroaryl group (e.g., pyridine). Preferably, R¹ is H or C₁ to C₃ alkyl.

Ar may be a 5- or 6-membered aryl or heteroaryl group. Ar may be a 6-membered aryl group. Ar may not be substituted.

The aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be substituted. At least
10 one of the substituents may be OH (e.g., one or more of A¹, A², A³, A⁴ and A⁵ may be C-OH). The aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be substituted with one or more additional substituents (i.e., additional to OH). The aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be substituted with one additional substituent such as OH. The one
15 additional substituent may be halogen (e.g., bromine, chlorine or fluorine). The one additional substituent may be an alkyl group (e.g., C₁ to C₃ alkyl). The one additional substituent may be a heteroalkyl group e.g., O-alkyl (such as OCH₃, OCH₂CH₃) or OCF₃. The aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be substituted with two additional substituents, which may be the same or different (e.g., two halogens, which may be the same or different, two OH groups, or one alkyl group and one heteroalkyl
20 group).

One of A¹, A², A³, A⁴ and A⁵ may be N i.e., the aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be a heteroaryl group. The heteroaryl group may not be further substituted. Alternatively, the heteroaryl group may be substituted with one or more substituents. The one or more substituents may be independently selected from OH, an
25 alkyl group (e.g., methyl or ethyl) and a heteroalkyl group (e.g., CH₂OH or CH₂CH₂OH).

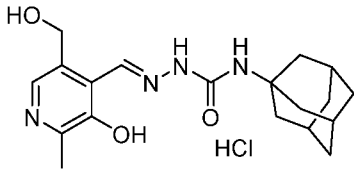
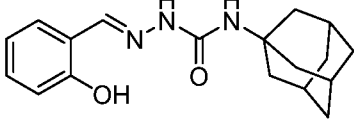
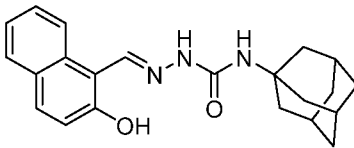
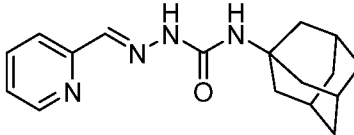
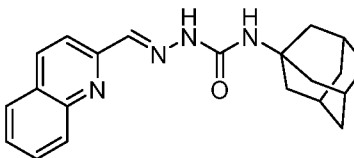
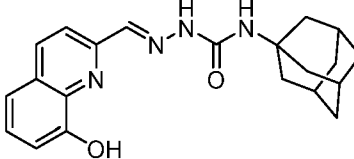
The N and/or OH substituents may be situated on the aromatic ring containing A¹, A², A³, A⁴ and A⁵ such that the compound of formula (I) is able to chelate metal ions (e.g., iron, copper and zinc). Therefore, A¹ may be selected from N and C-OH. Preferably, A¹ is C-OH.

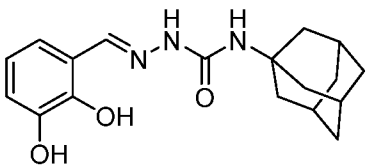
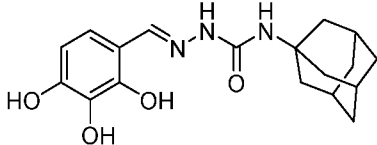
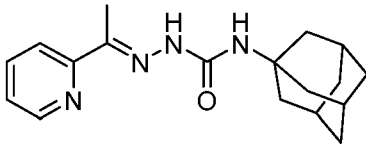
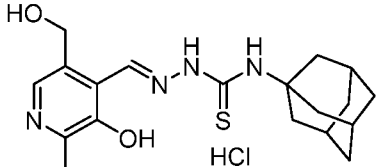
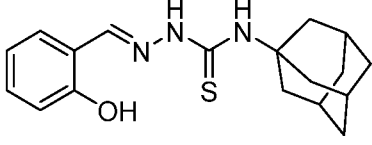
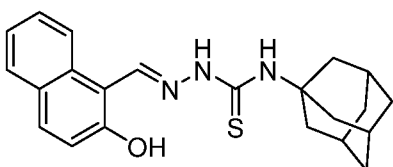
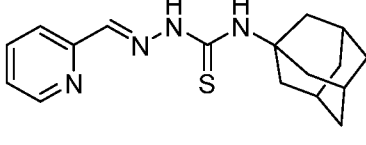
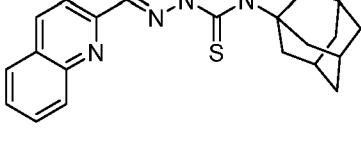
30 The aromatic ring containing A¹, A², A³, A⁴ and A⁵ may be fused (e.g., at A² and A³ or A⁴ and A⁵) to an aryl group, to give a bicyclic aryl or heteroaryl group (e.g.,

naphthyl or quinoline). The bicyclic aryl or heteroaryl group may be substituted with one or more substituents selected from OH, alkyl and heteroalkyl.

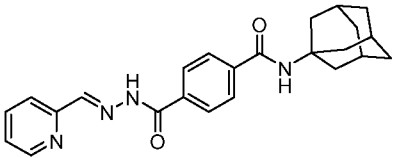
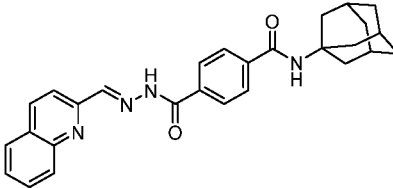
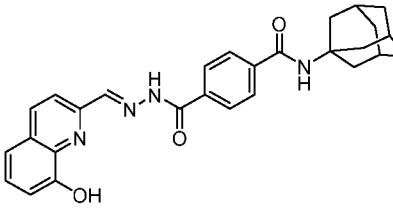
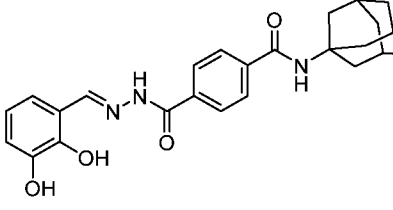
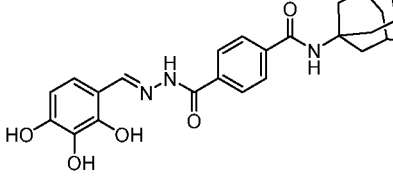
Specific examples of the compounds of the present invention are given in Table 1, below.

5 *Table 1. Examples of compounds of the present invention.*

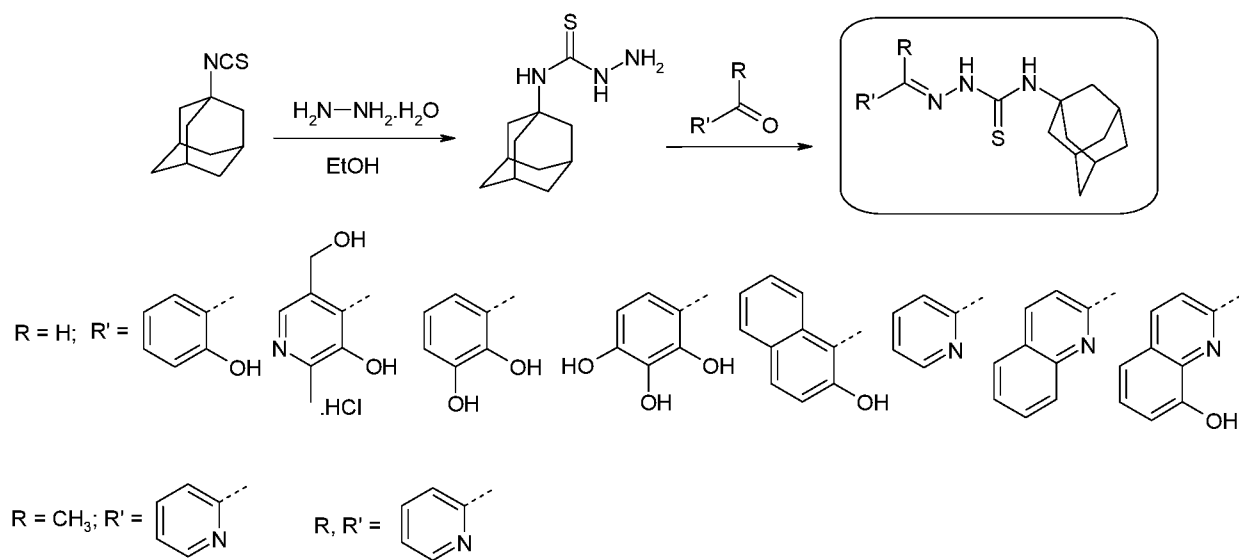
Compound	Structure
1	
2	
3	
4	
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Compound	Structure
7	
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Compound	Structure
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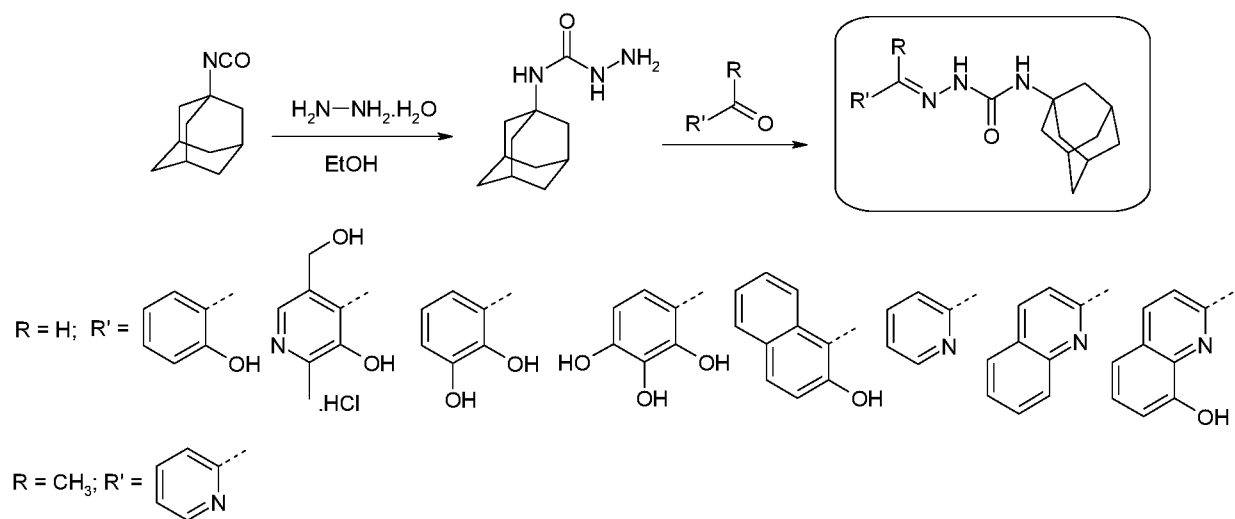
Compound	Structure
23	
24	
25	
26	
27	

The compounds of the present invention can be synthesised by any suitable method known to a person skilled in the art. One general synthesis is given below in Schemes 1, 2 and 3.

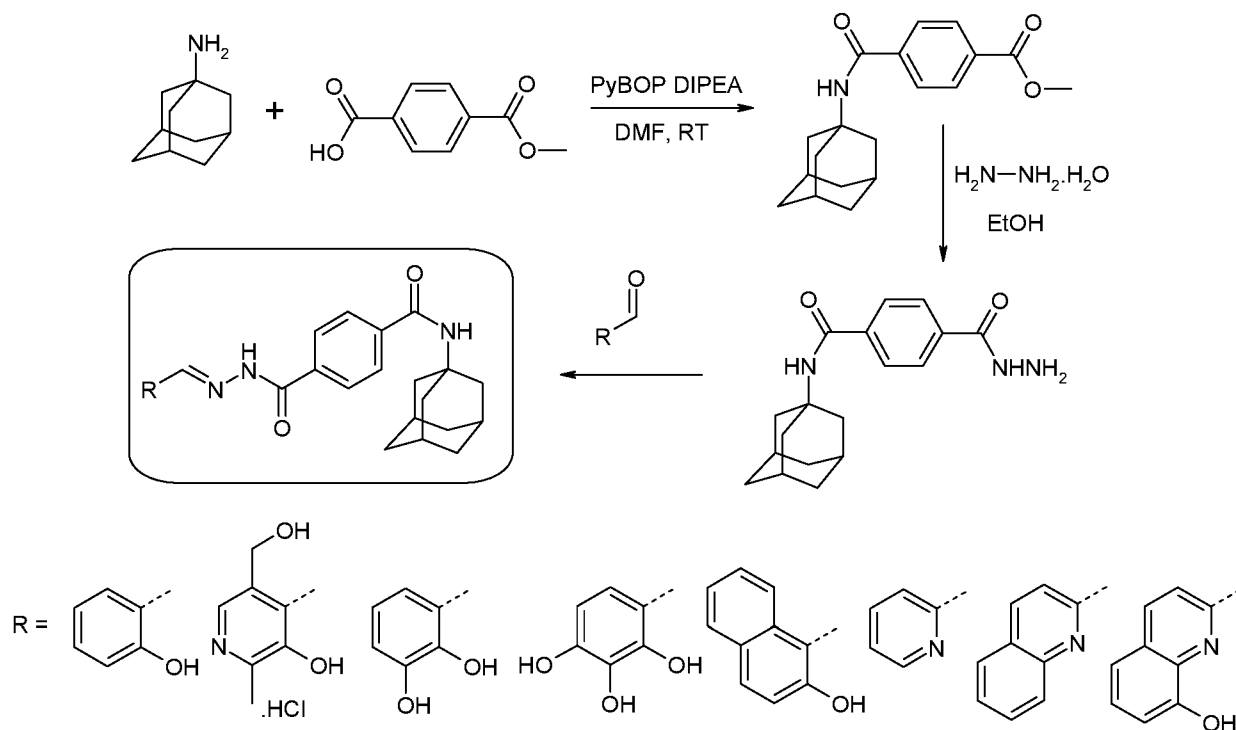


Scheme 1

5



Scheme 2



Scheme 3

The compounds of the present invention are multifunctional agents that may be effective in treating and/or preventing a number of neurodegenerative disorders. The compounds of the present invention may achieve this by targeting the main hallmarks (such as protein misfolding and β -amyloid aggregation with plaque formation, oxidative stress and ROS generation, dysregulation of autophagy, and dysregulation of metal metabolism) of neurodegenerative disorders.

As discussed above, increased iron, copper and/or zinc levels are thought to lead to β -amyloid aggregation with plaque formation, and ROS generation. Without wishing to be bound by theory, the present inventors postulate that the compounds of the present invention (in particular, the hydrazone/thiosemicarbazone moieties, in conjunction with the N or C-OH functionality on the aromatic ring) may be effective metal chelators. Therefore, the compounds of the present invention may be effective at preventing or ameliorating the aggregation of β -amyloid, and may also inhibit production of ROS, resulting in prevention or amelioration of ROS-induced cell death. Particularly preferred in this regard are compounds having a “hard” donor atom (such as O) at A¹ (e.g., in the form of a C-OH group), as such compounds strongly chelate Fe³⁺, thereby

preventing reduction of Fe^{3+} to Fe^{2+} (Fe^{2+} is the iron species that is considered to be responsible for the aetiologies involved in neurodegenerative disorders).

The present inventors also postulate that the depletion of iron (*via* chelation of the metal) may induce pro-survival autophagy (specifically, beneficial clearing of protein
5 aggregates).

Further, calcium influx has been found to be higher in neuronal cells of patients with Alzheimer's disease, resulting in elevated intracellular calcium levels. Calcium overload can induce the aggregation of β -amyloid *via* increasing levels of APP. Trans-membrane proteins such as *N*-methyl-D-aspartate receptor (NMDAR) and voltage-
10 gated calcium channel (VGCC) are the main regulators of calcium influx and efflux from cells. The present inventors postulate that, by including a memantine analogue in the compounds of the present invention, NMDAR and/or VGCC antagonism can be achieved, resulting in reduction of calcium influx.

In the brain, acetylcholine (a neurotransmitter) is produced in several locations,
15 including the basal forebrain. Acetylcholine-producing cells in the basal forebrain are damaged in the early stages of Alzheimer's disease, which may contribute to the memory impairments that are an early symptom of the disease. The present inventors postulate that, by including in the compounds of the present invention a moiety (such as the benzoyl group) that acts as a cholinesterase inhibitor, the decrease in acetylcholine
20 levels that occurs *via* this pathway can be mitigated.

The compounds of the present invention are also highly lipophilic, which contributes to their blood-brain barrier (BBB) permeability.

The present inventors have also found that the absence of substitution on the nitrogen atom adjacent to the adamantane moiety results in the compounds of the
25 present invention having lower cytotoxicity compared with compounds that are substituted at this position. Thus, while compounds having substitution at this nitrogen atom may be useful in anti-cancer therapy, they would not be expected to be useful in other therapies (e.g., for treatment of neurodegenerative disorders), due to their cytotoxicity.

30 The therapeutic use of compounds of formula (I), their pharmaceutically acceptable salts, solvates or hydrates and also formulations and pharmaceutical

compositions (including mixtures of the compounds of formula (I)) are within the scope of the present invention. Accordingly, the present invention also relates to pharmaceutical compositions including a therapeutically effective amount of the compounds of formula (I), or its pharmaceutically acceptable salt, solvate or hydrate thereof, and one or more pharmaceutically acceptable excipients.

Pharmaceutical compositions may be formulated for any appropriate route of administration including, for example, topical (for example, transdermal or ocular), oral, buccal, nasal, vaginal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (for example, intravenous), intramuscular, spinal, intracranial, intrathecal, intraocular, periocular, intraorbital, intrasynovial and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions in a form suitable for oral use or parenteral use are preferred. Suitable oral forms include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Aqueous suspensions contain the active ingredient(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as naturally-occurring phosphatides (for example, lecithin), condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate. Aqueous suspensions may also comprise one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil

such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and/or flavouring agents may be added to provide palatable oral preparations. Such suspensions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as olive oil or arachis oil, a mineral oil such as liquid paraffin, or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides such as sorbitan monoleate, and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide such as polyoxyethylene sorbitan monoleate. An emulsion may also comprise one or more sweetening and/or flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavouring agents and/or colouring agents.

A composition may further include one or more components adapted to improve the stability or effectiveness of the applied formulation, such as stabilizing agents, suspending agents, emulsifying agents, viscosity adjusters, gelling agents, preservatives, antioxidants, skin penetration enhancers, moisturizers and sustained release materials. Examples of such components are described in Martindale – The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and Martin (ed.), Remington's Pharmaceutical Sciences. Formulations may comprise microcapsules, such as hydroxymethylcellulose or gelatin-microcapsules, liposomes, albumin microspheres, microemulsions, nanoparticles or nanocapsules.

A pharmaceutical composition may be formulated as inhaled formulations, including sprays, mists, or aerosols. For inhalation formulations, the compounds provided herein may be delivered via any inhalation methods known to a person skilled in the art. Such inhalation methods and devices include, but are not limited to, metered
5 dose inhalers with propellants such as CFC or HFA or propellants that are physiologically and environmentally acceptable. Other suitable devices are breath operated inhalers, multidose dry powder inhalers and aerosol nebulizers. Aerosol formulations for use in the subject method typically include propellants, surfactants and co-solvents and may be filled into conventional aerosol containers that are closed by a
10 suitable metering valve.

Inhalant compositions may comprise liquid or powdered compositions containing the active ingredient that are suitable for nebulization and intrabronchial use, or aerosol compositions administered via an aerosol unit dispensing metered doses. Suitable liquid compositions comprise the active ingredient in an aqueous, pharmaceutically
15 acceptable inhalant solvent such as isotonic saline or bacteriostatic water. The solutions are administered by means of a pump or squeeze-actuated nebulized spray dispenser, or by any other conventional means for causing or enabling the requisite dosage amount of the liquid composition to be inhaled into the patient's lungs. Suitable formulations, wherein the carrier is a liquid, for administration, as for example, a nasal
20 spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

Pharmaceutical compositions may also be prepared in the form of suppositories such as for rectal administration. Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug.
25 Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Pharmaceutical compositions may be formulated as sustained release formulations such as a capsule that creates a slow release of modulator following administration. Such formulations may generally be prepared using well-known technology and administered by, for example, oral, rectal or subcutaneous implantation,
30 or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable. Preferably, the formulation provides a relatively constant level of modulator release. The amount of modulator contained

within a sustained release formulation depends upon, for example, the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

For the prevention and/or treatment of the conditions discussed herein, the dose of the biologically active compound according to the invention may vary within wide limits and may be adjusted to individual requirements. Active compounds according to the present invention are generally administered in a therapeutically effective amount. Preferred doses range from about 0.1 mg to about 140 mg per kilogram of body weight per day (e.g., about 0.5 mg to about 7 g per patient per day). The daily dose may be administered as a single dose or in a plurality of doses. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between about 1 mg to about 500 mg of an active ingredient.

However, it will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination (i.e., other drugs being used to treat the patient), and the severity of the particular disorder undergoing therapy.

The terms "therapeutically effective amount" or "effective amount" refer to an amount of the compound of formula (I) that results in an improvement or remediation of the neurodegenerative disease.

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability and BBB permeability, such that the preferred oral dosage forms discussed above can provide therapeutically effective levels of the compound *in vivo*.

The compounds of the present invention are preferably administered to a patient (for example, a human) orally or parenterally, and are present within at least one body fluid or tissue of the patient. Accordingly, the present invention further provides methods for treating and/or preventing neurodegenerative diseases.

As used herein, the term "treatment" encompasses both disorder-modifying treatment and symptomatic treatment. It refers to therapeutic treatment, i.e., after the onset of symptoms, in order to reduce the severity and/or duration of symptoms, and/or to cure the condition or disorder. As used herein, the term "prevention" encompasses prophylactic treatment, i.e., before the onset of symptoms, in order to prevent, delay or reduce the severity of symptoms and/or the condition or disorder.

Patients may include but are not limited to primates, especially humans, domesticated companion animals such as dogs, cats, horses, and livestock such as cattle, pigs, sheep, and poultry, with dosages as described herein.

Compounds of the present invention may be useful for the treatment and/or prevention of neurodegenerative diseases in a subject. Accordingly, the present invention also relates to a method of treating or preventing neurodegenerative diseases in a patient including administration to the patient of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt, solvate or hydrate thereof. The present invention also relates to the use of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt, solvate or hydrate thereof, for treating or preventing neurodegenerative diseases. The present invention also provides a pharmaceutical composition for use in treating or preventing neurodegenerative diseases, in any of the embodiments described in the specification. The present invention also relates to the use of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or hydrate thereof, for the manufacture of a medicament for treating or preventing neurodegenerative diseases.

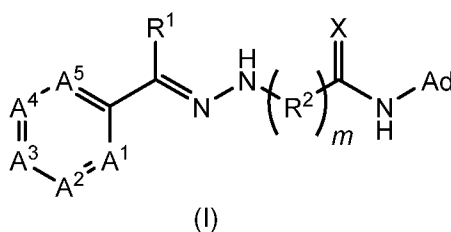
The present invention also relates to a compound of formula (I), or a pharmaceutically acceptable salt, solvate or hydrate thereof, when used in a method of treating or preventing neurodegenerative diseases. The present invention also relates to a composition having an active ingredient for use in treating or preventing neurodegenerative diseases, wherein the active ingredient is a compound of formula (I), or a pharmaceutically acceptable salt, solvate or hydrate thereof. The present invention also relates to the use of a pharmaceutical composition containing a compound of the formula (I), or a pharmaceutically acceptable salt, solvate or hydrate thereof, in treating or preventing neurodegenerative diseases, such as described above. In one

embodiment, the compound of formula (I) is essentially the only active ingredient of the composition. In one embodiment, the neurodegenerative disease is selected from dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease and Friedreich's ataxia.

It is also within the present invention that the compounds according to the invention are used as or for the manufacture of a diagnostic agent, whereby such diagnostic agent is for the diagnosis of the disorders and conditions which can be addressed by the compounds of the present invention for therapeutic purposes as disclosed herein.

For various applications, the compounds of the invention can be labelled by isotopes, fluorescence or luminescence markers, antibodies or antibody fragments, any other affinity label like nanobodies, aptamers, peptides etc., enzymes or enzyme substrates. These labelled compounds of this invention are useful for mapping the location of receptors *in vivo*, *ex vivo*, *in vitro* and *in situ* such as in tissue sections *via* autoradiography and as radiotracers for positron emission tomography (PET) imaging, single photon emission computerized tomography (SPECT) and the like, to characterize those receptors in living subjects or other materials. The labelled compounds according to the present invention may be used in therapy, diagnosis and other applications such as research tools *in vivo* and *in vitro*, in particular the applications disclosed herein.

In a first embodiment, the present invention relates to a compound of formula (I):

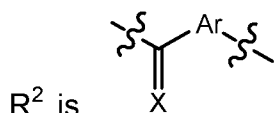


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ad is an adamantane moiety,

X is selected from O and S,

m is 0 or 1,



R^1 is selected from H, alkyl and heteroaryl,

A^1 , A^2 , A^3 , A^4 and A^5 are independently selected from CH and N, and

- 5 the aromatic ring containing A^1 , A^2 , A^3 , A^4 and A^5 is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group.

In a second embodiment, the present invention relates to a compound of formula (I) according to the first embodiment, wherein m is 0.

- 10 In a third embodiment, the present invention relates to a compound of formula (I) according to the first embodiment, wherein m is 1.

In a fourth embodiment, the present invention relates to a compound of formula (I) according to the first or third embodiments, wherein Ar is a 5- or 6-membered aryl or heteroaryl group.

- 15 In a fifth embodiment, the present invention relates to a compound of formula (I) according to the fourth embodiment, wherein Ar is a 6-membered aryl group.

In a sixth embodiment, the present invention relates to a compound of formula (I) according to the first, third or fifth embodiments, wherein Ar is not substituted.

- 20 In a seventh embodiment, the present invention relates to a compound of formula (I) according to any of the first to sixth embodiments, wherein R^1 is H.

In an eighth embodiment, the present invention relates to a compound of formula (I) according to any of the first to sixth embodiments, wherein R^1 is C_1 to C_3 alkyl.

In a ninth embodiment, the present invention relates to a compound of formula (I) according to the eighth embodiment, wherein R^1 is methyl, ethyl or propyl.

- 25 In a tenth embodiment, the present invention relates to a compound of formula (I) according to the first, second or third embodiments, wherein R^1 is a heteroaryl group.

In an eleventh embodiment, the present invention relates to a compound of formula (I) according to the tenth embodiment, wherein R^1 is pyridine.

In a twelfth embodiment, the present invention relates to a compound of formula (I) according to any of the first to eleventh embodiments, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted.

In a thirteenth embodiment, the present invention relates to a compound of formula (I) according to the twelfth embodiment, wherein at least one substituent is OH.

In a fourteenth embodiment, the present invention relates to a compound of formula (I) according to the thirteenth embodiment, wherein one or more of A¹, A², A³, A⁴ and A⁵ is C-OH.

In a fifteenth embodiment, the present invention relates to a compound of formula (I) according to the thirteenth or fourteenth embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with one or more additional substituents.

In a sixteenth embodiment, the present invention relates to a compound of formula (I) according to the fifteenth embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with one additional substituent.

In a seventeenth embodiment, the present invention relates to a compound of formula (I) according to the sixteenth embodiment, wherein the one additional substituent is OH.

In an eighteenth embodiment, the present invention relates to a compound of formula (I) according to the fifteenth embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with two additional substituents.

In a nineteenth embodiment, the present invention relates to a compound of formula (I) according to the eighteenth embodiment, wherein the two additional substituents are different to each other.

In a twentieth embodiment, the present invention relates to a compound of formula (I) according to the eighteenth embodiment, wherein the two additional substituents are the same as each other.

In a twenty-first embodiment, the present invention relates to a compound of formula (I) according to any of the eighteenth to twentieth embodiments, wherein the two additional substituents are selected from OH, an alkyl group and a heteroalkyl group.

In a twenty-second embodiment, the present invention relates to a compound of formula (I) according to any of the first to twenty-first embodiments, wherein one of A¹, A², A³, A⁴ and A⁵ is N to give a heteroaryl group.

5 In a twenty-third embodiment, the present invention relates to a compound of formula (I) according to the twenty-second embodiment, wherein the heteroaryl group is substituted with one or more substituents.

In a twenty-fourth embodiment, the present invention relates to a compound of formula (I) according to the twenty-third embodiment, wherein the one or more substituents are independently selected from OH, an alkyl group and a heteroalkyl group.
10

In a twenty-fifth embodiment, the present invention relates to a compound of formula (I) according to the twenty-fourth embodiment, wherein the alkyl group is methyl or ethyl.

In a twenty-sixth embodiment, the present invention relates to a compound of formula (I) according to the twenty-fourth embodiment, wherein the heteroalkyl group is CH₂OH or CH₂CH₂OH.
15

In a twenty-seventh embodiment, the present invention relates to a compound of formula (I) according to any of the first to twenty-sixth embodiments, wherein A¹ is selected from N and C-OH.

20 In a twenty-eighth embodiment, the present invention relates to a compound of formula (I) according to the twenty-seventh embodiment, wherein A¹ is C-OH.

In a twenty-ninth embodiment, the present invention relates to a compound of formula (I) according to any of the first to twenty-eighth embodiments, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is fused to an aryl group to give a bicyclic aryl or heteroaryl group.
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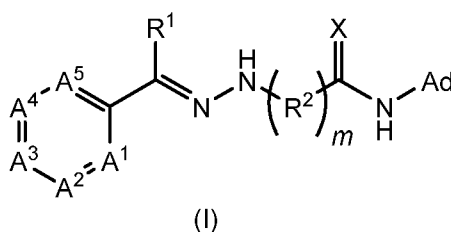
In a thirtieth embodiment, the present invention relates to a compound of formula (I) according to the twenty-ninth embodiment, wherein the bicyclic aryl or heteroaryl group is naphthyl or quinoline.

In a thirty-first embodiment, the present invention relates to a compound of formula (I) according to the twenty-ninth or thirtieth embodiment, wherein the bicyclic
30

aryl or heteroaryl group is substituted by one or more substituents selected from OH, alkyl and heteroalkyl.

In a thirty-second embodiment, the present invention relates to a compound of formula (I) according to any of the twenty-ninth to thirty-first embodiments, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is fused to the aryl group at A² and A³ or A⁴ and A⁵.

In a thirty-third embodiment, the present invention relates to a pharmaceutical composition including a compound of formula (I):

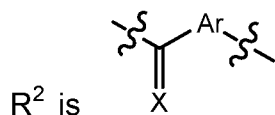


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ad is an adamantane moiety,

X is selected from O and S,

m is 0 or 1,



and heteroaryl groups are optionally substituted,

R¹ is selected from H, alkyl and heteroaryl,

A¹, A², A³, A⁴ and A⁵ are independently selected from CH and N, and

the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group,

together with a pharmaceutically acceptable carrier, diluent or excipient.

In a thirty-fourth embodiment, the present invention relates to a pharmaceutical composition according to the thirty-third embodiment, wherein the composition is suitable for parenteral or oral administration.

In a thirty-fifth embodiment, the present invention relates to a pharmaceutical composition according to the thirty-third or thirty-fourth embodiment, wherein m is 0.

In a thirty-sixth embodiment, the present invention relates to a pharmaceutical composition according to the thirty-third or thirty-fourth embodiment, wherein m is 1.

5 In a thirty-seventh embodiment, the present invention relates to a pharmaceutical composition according to the thirty-third, thirty-fourth or thirty-sixth embodiment, wherein Ar is a 5- or 6-membered aryl or heteroaryl group.

10 In a thirty-eighth embodiment, the present invention relates to a pharmaceutical composition according to the thirty-seventh embodiment, wherein Ar is a 6-membered aryl group.

In a thirty-ninth embodiment, the present invention relates to a pharmaceutical composition according to the thirty third, thirty-fourth, thirty-sixth or thirty-eighth embodiment, wherein Ar is not substituted.

15 In a fortieth embodiment, the present invention relates to a pharmaceutical composition according to any of the thirty-third to thirty-ninth embodiments, wherein R^1 is H.

In a forty-first embodiment, the present invention relates to a pharmaceutical composition according to any of the thirty-third to thirty-ninth embodiments, wherein R^1 is C_1 to C_3 alkyl.

20 In a forty-second embodiment, the present invention relates to a pharmaceutical composition according to the forty-first embodiment, wherein R^1 is methyl, ethyl or propyl.

25 In a forty-third embodiment, the present invention relates to a pharmaceutical composition according to any of the thirty-third to thirty-ninth embodiments, wherein R^1 is a heteroaryl group.

In a forty-fourth embodiment, the present invention relates to a pharmaceutical composition according to the forty-third embodiment, wherein R^1 is pyridine.

30 In a forty-fifth embodiment, the present invention relates to a pharmaceutical composition according to any of the thirty-third to forty-fourth embodiments, wherein the aromatic ring containing A^1 , A^2 , A^3 , A^4 and A^5 is substituted.

In a forty-sixth embodiment, the present invention relates to a pharmaceutical composition according to the forty-fifth embodiment, wherein at least one substituent is OH.

5 In a forty-seventh embodiment, the present invention relates to a pharmaceutical composition according to the forty-sixth embodiment, wherein one or more of A¹, A², A³, A⁴ and A⁵ is C-OH.

10 In a forty-eighth embodiment, the present invention relates to a pharmaceutical composition according to the forty-sixth or forty-seventh embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with one or more additional substituents.

In a forty-ninth embodiment, the present invention relates to a pharmaceutical composition according to the forty-eighth embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with one additional substituent.

15 In a fiftieth embodiment, the present invention relates to a pharmaceutical composition according to the forty-ninth embodiment, wherein the one additional substituent is OH.

In a fifty-first embodiment, the present invention relates to a pharmaceutical composition according to the forty-eighth embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with two additional substituents.

20 In a fifty-second embodiment, the present invention relates to a pharmaceutical composition according to the fifty-first embodiment, wherein the two additional substituents are different to each other.

25 In a fifty-third embodiment, the present invention relates to a pharmaceutical composition according to the fifty-first embodiment, wherein the two additional substituents are the same as each other.

In a fifty-fourth embodiment, the present invention relates to a pharmaceutical composition according to the fifty-first, fifty-second or fifty-third embodiments, wherein the two additional substituents are selected from OH, an alkyl group and a heteroalkyl group.

In a fifty-fifth embodiment, the present invention relates to a pharmaceutical composition according to any of the thirty-third to fifty-fourth embodiments, wherein one of A¹, A², A³, A⁴ and A⁵ is N to give a heteroaryl group.

5 In a fifty-sixth embodiment, the present invention relates to a pharmaceutical composition according to the fifty-fifth embodiment, wherein the heteroaryl group is substituted with one or more substituents.

10 In a fifty-seventh embodiment, the present invention relates to a pharmaceutical composition according to the fifty-sixth embodiment, wherein the one or more substituents are independently selected from OH, an alkyl group and a heteroalkyl group.

In a fifty-eighth embodiment, the present invention relates to a pharmaceutical composition according to the fifty-seventh embodiment, wherein the alkyl group is methyl or ethyl.

15 In a fifty-ninth embodiment, the present invention relates to a pharmaceutical composition according to the fifty-seventh, wherein the heteroalkyl group is CH₂OH or CH₂CH₂OH.

In a sixtieth embodiment, the present invention relates to a pharmaceutical composition according to any of the thirty-third to fifty-ninth embodiments, wherein A¹ is selected from N and C-OH.

20 In a sixty-first embodiment, the present invention relates to a pharmaceutical composition according to the sixtieth embodiment, wherein A¹ is C-OH.

25 In a sixty-second embodiment, the present invention relates to a pharmaceutical composition according to any of the thirty-third to sixty-first embodiments, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is fused to an aryl group to give a bicyclic aryl or heteroaryl group.

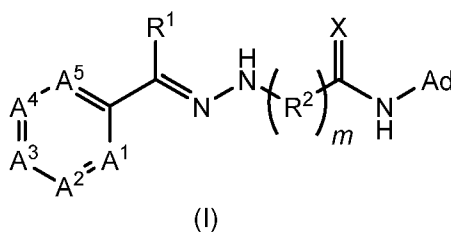
In a sixty-third embodiment, the present invention relates to a pharmaceutical composition according to the sixty-second embodiment, wherein the bicyclic aryl or heteroaryl group is naphthyl or quinoline.

30 In a sixty-fourth embodiment, the present invention relates to a pharmaceutical composition according to the sixty-second or sixty-third embodiment, wherein the

bicyclic aryl or heteroaryl group is substituted by one or more substituents selected from OH, alkyl and heteroalkyl.

In a sixty-fifth embodiment, the present invention relates to a pharmaceutical composition according to the sixty-second, sixty-third or sixty-fourth embodiments, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is fused to the aryl group at A₂ and A³ or A⁴ and A⁵.

In a sixty-sixth embodiment, the present invention relates to a method of treating and/or preventing a neurodegenerative disease in a subject, the method including administering to the subject an effective amount of a compound of formula (I):

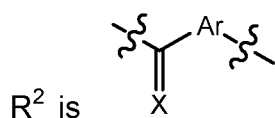


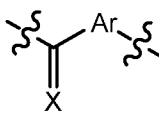
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ad is an adamantane moiety,

X is selected from O and S,

m is 0 or 1,



*R*² is , wherein Ar is selected from aryl and heteroaryl, which aryl and heteroaryl groups are optionally substituted,

*R*¹ is selected from H, alkyl and heteroaryl,

A¹, A², A³, A⁴ and A⁵ are independently selected from CH and N, and

the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group.

In a sixty-seventh embodiment, the present invention relates to a method according to the sixty-sixth embodiment, wherein the neurodegenerative disease is

selected from dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease and Friedrich's ataxia.

In a sixty-eighth embodiment, the present invention relates to a method according to the sixty-sixth or sixty-seventh embodiment, wherein m is 0.

5 In a sixty-ninth embodiment, the present invention relates to a method according to the sixty-sixth or sixty-seventh embodiment, wherein m is 1.

In a seventieth embodiment, the present invention relates to a method according to the sixty-sixth, sixty-seventh or sixty-ninth embodiment, wherein Ar is a 5- or 6-membered aryl or heteroaryl group.

10 In a seventy-first embodiment, the present invention relates to a method according to the seventieth embodiment, wherein Ar is a 6-membered aryl group.

In a seventy-second embodiment, the present invention relates to a method according to the sixty-sixth, sixty-seventh, sixty-ninth or seventy-first embodiment, wherein Ar is not substituted.

15 In a seventy-third embodiment, the present invention relates to a method according to any of the sixty-sixth to seventy-second embodiments, wherein R^1 is H.

In a seventy-fourth embodiment, the present invention relates to a method according to any of the sixty-sixth to seventy-second embodiments, wherein R^1 is C_1 to C_3 alkyl.

20 In a seventy-fifth embodiment, the present invention relates to a method according to the seventy-fourth embodiments, wherein R^1 is methyl, ethyl or propyl.

In a seventy-sixth embodiment, the present invention relates to a method according to any of the sixty-sixth to seventy-second embodiments, wherein R^1 is a heteroaryl group.

25 In a seventy-seventh embodiment, the present invention relates to a method according to the seventy-sixth embodiment, wherein R^1 is pyridine.

In a seventy-eighth embodiment, the present invention relates to a method according to any of the sixty-sixth to seventy-seventh embodiments, wherein the aromatic ring containing A^1 , A^2 , A^3 , A^4 and A^5 is substituted.

In a seventy-ninth embodiment, the present invention relates to a method according to the seventy-eighth embodiment, wherein at least one substituent is OH.

In an eightieth embodiment, the present invention relates to a method according to the seventy-ninth embodiment, wherein one or more of A¹, A², A³, A⁴ and A⁵ is C-OH.

5 In an eighty-first embodiment, the present invention relates to a method according to the seventy-ninth or eightieth embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with one or more additional substituents.

In an eighty-second embodiment, the present invention relates to a method according to the eighty-first embodiment, wherein the aromatic ring containing A¹, A²,
10 A³, A⁴ and A⁵ is substituted with one additional substituent.

In an eighty-third embodiment, the present invention relates to a method according to the eighty-second embodiment, wherein the one additional substituent is OH.

In an eighty-fourth embodiment, the present invention relates to a method
15 according to the eighty-second embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with two additional substituents.

In an eighty-fifth embodiment, the present invention relates to a method according to the eighty-fourth embodiment, wherein the two additional substituents are different to each other.

20 In an eighty-sixth embodiment, the present invention relates to a method according to the eighty-fourth embodiment, wherein the two additional substituents are the same as each other.

In an eighty-seventh embodiment, the present invention relates to a method according to any of the eighty-fourth to eighty-sixth embodiments, wherein the two
25 additional substituents are selected from OH, an alkyl group and a heteroalkyl group.

In an eighty-eighth embodiment, the present invention relates to a method according to any of the sixty-sixth to eighty-seventh embodiments, wherein one of A¹, A², A³, A⁴ and A⁵ is N to give a heteroaryl group.

In an eighty-ninth embodiment, the present invention relates to a method according to the eighty-eighth embodiment, wherein the heteroaryl group is substituted with one or more substituents.

5 In a ninetieth embodiment, the present invention relates to a method according to the eighty-ninth embodiment, wherein the one or more substituents are independently selected from OH, an alkyl group and a heteroalkyl group.

In a ninety-first embodiment, the present invention relates to a method according to the ninetieth embodiment, wherein the alkyl group is methyl or ethyl.

10 In a ninety-second embodiment, the present invention relates to a method according to the ninetieth embodiment, wherein the heteroalkyl group is CH₂OH or CH₂CH₂OH.

In a ninety-third embodiment, the present invention relates to a method according to the any of the fifty-sixth to seventy-ninth embodiments, wherein A¹ is selected from N and C-OH.

15 In a ninety-fourth embodiment, the present invention relates to a method according to the ninety-third embodiment, wherein A¹ is C-OH.

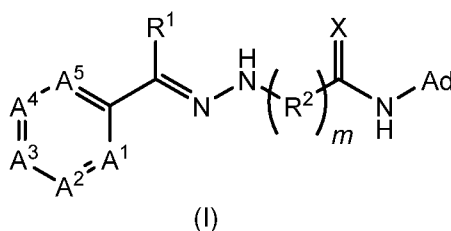
20 In a ninety-fifth embodiment, the present invention relates to a method according to any of the sixty-sixth to ninety-fourth embodiments, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is fused to an aryl group to give a bicyclic aryl or heteroaryl group.

In a ninety-sixth embodiment, the present invention relates to a method according to the ninety-fifth embodiment, wherein the bicyclic aryl or heteroaryl group is naphthyl or quinoline.

25 In a ninety-seventh embodiment, the present invention relates to a method according to the ninety-fifth or ninety-sixth embodiment, wherein the bicyclic aryl or heteroaryl group is substituted by one or more substituents selected from OH, alkyl and heteroalkyl.

30 In a ninety-eighth embodiment, the present invention relates to a method according to any of the ninety-fifth to ninety-seventh embodiments, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is fused to the aryl group at A² and A³ or A⁴ and A⁵.

In a ninety-ninth embodiment, the present invention relates to a method of treating and/or preventing a neurodegenerative disease in a subject, the method including administering to the subject an effective amount of a pharmaceutical composition including a compound of formula (I):



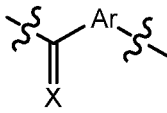
5

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ad is an adamantane moiety,

X is selected from O and S,

m is 0 or 1,

10 R^2 is , wherein Ar is selected from aryl and heteroaryl, which aryl and heteroaryl groups are optionally substituted,

R^1 is selected from H, alkyl and heteroaryl,

A^1 , A^2 , A^3 , A^4 and A^5 are independently selected from CH and N, and

15 the aromatic ring containing A^1 , A^2 , A^3 , A^4 and A^5 is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group,

together with a pharmaceutically acceptable carrier, diluent or excipient.

20 In a one hundredth embodiment, the present invention relates to a method according to the ninety-ninth embodiment, wherein the neurodegenerative disease is selected from dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease and Friedreich's ataxia.

In a one hundred and first embodiment, the present invention relates to a method according to the ninety-ninth or one hundredth embodiment, wherein *m* is 0.

In a one hundred and second embodiment, the present invention relates to a method according to the ninety-ninth or one hundredth embodiment, wherein m is 1.

In a one hundred and third embodiment, the present invention relates to a method according to any of the ninety-ninth, one hundredth or one hundred and second
5 embodiments, wherein Ar is a 5- or 6-membered aryl or heteroaryl group.

In a one hundred and fourth embodiment, the present invention relates to a method according to the one hundred and third embodiment, wherein Ar is a 6-membered aryl group.

In a one hundred and fifth embodiment, the present invention relates to a method
10 according to any of the ninety-ninth, one-hundredth, one hundred and second or one hundred and fourth embodiments, wherein Ar is not substituted.

In a one hundred and sixth embodiment, the present invention relates to a method according to any of the ninety-ninth to one hundred and fifth embodiments, wherein R^1 is H.

15 In a one hundred and seventh embodiment, the present invention relates to a method according to any of the ninety-ninth to one hundred and fifth embodiments, wherein R^1 is C_1 to C_3 alkyl.

In a one hundred and eighth embodiment, the present invention relates to a method according to the one hundred and seventh embodiments, wherein R^1 is methyl,
20 ethyl or propyl.

In a one hundred and ninth embodiment, the present invention relates to a method according to any of the ninety-ninth to one hundred and fifth embodiments, wherein R^1 is a heteroaryl group.

In a one hundred and tenth embodiment, the present invention relates to a
25 method according to the one hundred and ninth embodiment, wherein R^1 is pyridine.

In a one hundred and eleventh embodiment, the present invention relates to a method according to any of the ninety-ninth to one hundred and tenth embodiments, wherein the aromatic ring containing A^1 , A^2 , A^3 , A^4 and A^5 is substituted.

In a one hundred and twelfth embodiment, the present invention relates to a method according to the one hundred and eleventh embodiment, wherein at least one substituent is OH.

5 In a one hundred and thirteenth embodiment, the present invention relates to a method according to the one hundred and twelfth embodiment, wherein one or more of A¹, A², A³, A⁴ and A⁵ is C-OH.

10 In a one hundred and fourteenth embodiment, the present invention relates to a method according to the one hundred and twelfth or one hundred and thirteenth embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with one or more additional substituents.

In a one hundred and fifteenth embodiment, the present invention relates to a method according to the one hundred and fourteenth embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with one additional substituent.

15 In a one hundred and sixteenth embodiment, the present invention relates to a method according to the one hundred and fifteenth embodiment, wherein the one additional substituent is OH.

20 In a one hundred and seventeenth embodiment, the present invention relates to a method according to the one hundred and fourteenth embodiment, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with two additional substituents.

In a one hundred and eighteenth embodiment, the present invention relates to a method according to the one hundred and seventeenth embodiment, wherein the two additional substituents are different to each other.

25 In a one hundred and nineteenth embodiment, the present invention relates to a method according to the one hundred and seventeenth embodiment, wherein the two additional substituents are the same as each other.

30 In a one hundred and twentieth embodiment, the present invention relates to a method according to any of the one hundred and seventeenth to one hundred and nineteenth embodiments, wherein the two additional substituents are selected from OH, an alkyl group and a heteroalkyl group.

In a one hundred and twenty-first embodiment, the present invention relates to a method according to any of the ninety-ninth to one hundred and twentieth embodiments, wherein one of A¹, A², A³, A⁴ and A⁵ is N to give a heteroaryl group.

5 In a one hundred and twenty-second embodiment, the present invention relates to a method according to the one hundred and twenty-first embodiment, wherein the heteroaryl group is substituted with one or more substituents.

In a one hundred and twenty-third embodiment, the present invention relates to a method according to the one hundred and twenty-second embodiment, wherein the one or more substituents are independently selected from OH, an alkyl group and a
10 heteroalkyl group.

In a one hundred and twenty-fourth embodiment, the present invention relates to a method according to the one hundred and twenty-third embodiment, wherein the alkyl group is methyl or ethyl.

15 In a one hundred and twenty-fifth embodiment, the present invention relates to a method according to the one hundred and twenty-third embodiment, wherein the heteroalkyl group is CH₂OH or CH₂CH₂OH.

In a one hundred and twenty-sixth embodiment, the present invention relates to a method according to any of the ninety-ninth to one hundred and twenty-fifth embodiments, wherein A¹ is selected from N and C-OH.

20 In a one hundred and twenty-seventh embodiment, the present invention relates to a method according to the one hundred and twenty-sixth embodiment, wherein A¹ is C-OH.

In a one hundred and twenty eighth embodiment, the present invention relates to a method according to any of the ninety-ninth to one hundred and twenty-seventh
25 embodiments, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is fused to an aryl group to give a bicyclic aryl or heteroaryl group.

In a one hundred and twenty-ninth embodiment, the present invention relates to a method according to the one hundred and twenty-eighth embodiment, wherein the bicyclic aryl or heteroaryl group is naphthyl or quinoline.

30 In a one hundred and thirtieth embodiment, the present invention relates to a method according to the one hundred and twenty-eighth or one hundred and twenty-

ninth embodiment, wherein the bicyclic aryl or heteroaryl group is substituted by one or more substituents selected from OH, alkyl and heteroalkyl.

In a one hundred and thirty-first embodiment, the present invention relates to a method according to any of the one hundred and twenty eighth to one hundred and thirtieth embodiments, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is fused to the aryl group at A² and A³ or A⁴ and A⁵.

The nature of the present invention shall now be illustrated by the following non-limiting Examples.

Examples

10 Experimental Details

Materials and methods

All chemicals used for synthesis were purchased from Sigma-Aldrich and used as received without further purification. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded on a Bruker Advance 400 NMR spectrometer using DMSO-*d*₆ as a solvent. (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), *N,N*-diisopropylethylamine (DIPEA), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and other biochemicals were purchased from Sigma-Aldrich. Elemental analysis was performed on a Thermo Scientific Flash 2000 CHNS/O analyser. Electrospray ionization mass spectrometry (ESI-MS) measurements were performed on a Bruker amaZon SL mass spectrometer in enhanced resolution mode.

Synthesis of 1-Adamantylsemicarbazide

1-Adamantylisocyanate (10 g, 56.42 mmol) was refluxed for 2 h with an excess of hydrazine hydrate (15 g, 300 mmol) in ethanol (100 mL). Water (200 mL) was then added to the reaction mixture. The resultant precipitate was collected by filtration, washed with water and dried *in vacuo* to obtain 1-adamantylsemicarbazide as a white solid (11.5 g). Yield: 99%. ¹H NMR: δ ppm (DMSO-*d*₆) 1.61 (6H, t, 3×CH₂), 1.87 (6H, d, 3×CH₂), 1.99 (3H, m, 3×CH), 4.04 (2H, s, NH₂), 5.90 (1H, s, NH), 6.88 (1H, s, NH-N).

General procedure for the preparation of compounds 1-9:

To a solution of 1-adamantylsemicarbazide (5 mmol) in absolute ethanol (25 mL), 1.05 equivalents of the desired aldehyde or ketone (5.25 mmol) followed by glacial acetic acid (10 drops), were added and refluxed for 60 min. The precipitate formed was collected by filtration at room temperature and washed with adequate amounts of ethanol and dried *in vacuo*.

1

White solid (1.57 g). Yield: 80%. ^1H NMR: δ ppm (DMSO- d_6) 1.64 (6H, t, $3\times\text{CH}_2$), 1.99 (6H, d, $J = 2.0$ Hz, $3\times\text{CH}_2$), 2.05 (3H, m, $3\times\text{CH}$), 2.61 (3H, s, CH_3), 4.73 (2H, s, CH_2), 6.65 (1H, s, NHCO), 8.17 (1H, s, CH), 8.33 (1H, s, $\text{CH}=\text{N}$), 11.25 (1H, s, NH-N), 12.62 (1H, bs, OH). ^{13}C NMR: δ ppm (DMSO- d_6) 14.8, 29.3, 36.4, 41.4, 50.9, 58.7, 129.3, 129.9, 135.0, 136.4, 142.2, 152.4. ESI-MS in CH_3OH : found mass: 359.07, Calc. mass for $\text{C}_{19}\text{H}_{27}\text{N}_4\text{O}_3$: 359.20 $[\text{M}+\text{H}]^+$. Anal. Calc. for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_3\cdot\text{HCl}$ (%): C 57.79, H 6.89, N 14.19. Found (%): C 57.18, H 7.04, N 14.10.

2

White solid (1.10 g). Yield: 70%. ^1H NMR: δ ppm (DMSO- d_6) 1.64 (6H, t, $3\times\text{CH}_2$), 1.98 (6H, d, $J = 2.4$ Hz, $3\times\text{CH}_2$), 2.04 (3H, m, $3\times\text{CH}$), 6.05 (1H, s, NHCO), 6.81-6.86 (2H, m, CH), 7.15-7.20 (1H, m, CH), 7.60 (1H, dd, $J = 7.6$ and 1.6 Hz, CH), 8.11 (1H, s, $\text{CH}=\text{N}$), 10.11 (1H, s, NH-N), 10.15 (1H, s, OH). ^{13}C NMR: δ ppm (DMSO- d_6) 29.4, 36.5, 42.1, 50.3, 116.5, 119.7, 120.9, 126.8, 130.7, 137.6, 154.3, 156.4. ESI-MS in CH_3OH : found mass: 314.00, Calc. mass for $\text{C}_{18}\text{H}_{24}\text{N}_3\text{O}_2$: 314.18 $[\text{M}+\text{H}]^+$. Anal. Calc. for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_2$ (%): C 68.98, H 7.40, N 13.41. Found (%): C 69.03, H 7.46, N 13.50.

3

Yellow solid (1.15 g). Yield: 63%. ^1H NMR: δ ppm (DMSO- d_6) 1.65 (6H, t, $3\times\text{CH}_2$), 1.99 (6H, d, $J = 2.0$ Hz, $3\times\text{CH}_2$), 2.05 (3H, m, $3\times\text{CH}$), 6.11 (1H, s, NHCO), 7.18 (1H, d, $J = 7.2$ Hz, CH), 7.36 (1H, t, $J = 5.6$, CH), 7.53 (1H, t, $J = 5.6$ Hz, CH), 7.83 (2H, t, $J = 7.6$ Hz, CH), 8.40 (1H, d, $J = 7.2$ Hz, CH), 8.78 (1H, s, $\text{CH}=\text{N}$), 10.09 (1H, s, NH-N), 11.53 (1H, bs, OH). ^{13}C NMR: δ ppm (DMSO- d_6) 29.6, 36.5, 42.3, 50.7, 110.7, 119.1, 122.7, 123.8, 127.9, 128.6, 129.3, 131.9, 139.5, 154.0, 156.9. ESI-MS in CH_3OH :

found mass: 364.07, Calc. mass for $C_{22}H_{26}N_3O_2$: 364.20 $[M+H]^+$. Anal. Calc. for $C_{22}H_{25}N_3O_2$ (%): C 72.70, H 6.93, N 11.56. Found (%): C 72.54, H 6.97, N 11.66.

4

White solid (0.74 g). Yield: 50%. 1H NMR: δ ppm (DMSO- d_6) 1.65 (6H, t, $3\times CH_2$),
5 2.01 (6H, d, $J = 3.0$ Hz, $3\times CH_2$), 2.05 (3H, m, $3\times CH$), 6.16 (1H, s, NHCO), 7.32-7.35
(1H, ddd, $J = 9.0, 6.0$ and 1.5 Hz, CH), 7.79-7.83 (1H, dt, $J = 10.0, 10.0$ and 2.0 Hz,
CH), 7.88 (1H, s, CH=N), 7.97 (1H, d, $J = 9.5$ Hz, CH), 8.54 (1H, d, $J = 10.0$ Hz, CH),
10.48 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.6, δ 36.6, 42.2, 50.7, 120.1, 124.1,
137.1, 140.2, 149.8, 154.2. ESI-MS in CH_3OH : found mass: 299.00, Calc. mass for
10 $C_{17}H_{23}N_4O$: 299.18 $[M+H]^+$. Anal. Calc. for $C_{17}H_{21}N_4O$ (%): C 68.43, H 7.43, N 18.78.
Found (%): C 68.40, H 7.42, N 18.87.

5

Yellow crystals (1.1 g). Yield: 63%. Single crystals suitable for X-ray diffraction
were obtained from the ethanol mother liquor. 1H NMR: δ ppm (DMSO- d_6) 1.66 (6H, t,
15 $3\times CH_2$), 2.05 (9H, m, $3\times CH_2$ and $3\times CH$), 6.27 (1H, s, NHCO), 7.60 (1H, t, $J = 7.0$ Hz,
CH), 7.76 (1H, t, $J = 7.0$ Hz, CH), 7.97 (1H, d, $J = 7.5$ Hz, CH), 8.04 (1H, s, CH=N), 8.15
(1H, d, $J = 8.5$ Hz, CH), 8.34 (1H, d, $J = 9.0$ Hz, CH), 10.65 (1H, s, NH=N). ^{13}C NMR: δ
ppm (DMSO- d_6) 29.6, 36.6, 42.2, 50.8, 118.1, 127.4, 128.2, 128.5, 129.3, 130.5, 136.9,
140.4, 147.9, 154.2, 154.5. ESI-MS in CH_3OH : found mass: 349.00, Calc. mass for
20 $C_{21}H_{25}N_4O$: 349.20 $[M+H]^+$. Anal. Calc. for $C_{21}H_{24}N_4O\cdot 0.5H_2O$ (%): C 70.56, H 7.05, N
15.67. Found (%): C 70.51, H 7.32, N 15.12.

6

Light yellow solid (1.37 g). Yield: 69%. 1H NMR: δ ppm (DMSO- d_6) 1.65 (6H, t,
 $3\times CH_2$), 2.06 (9H, m, $3\times CH_2$ and $3\times CH$), 6.26 (1H, s, NHCO), 7.08 (1H, dd, $J = 7.0$ and
25 1.5 Hz, CH), 7.40 (2H, m, CH), 8.08 (1H, s, CH=N), 8.12 (1H, d, $J = 9.0$ Hz, CH), 8.26
(1H, d, $J = 8.5$ Hz, CH), 9.73 (1H, s, OH), 10.69 (1H, s, NH=N). ^{13}C NMR: δ ppm
(DMSO- d_6) 29.4, 36.5, 42.1, 50.6, 112.5, 118.2, 128.2, 129.0, 136.7, 138.5, 140.2,
152.3, 153.7, 154.1. ESI-MS in CH_3OH : found mass: 365.00, Calc. mass for
 $C_{21}H_{25}N_4O_2$: 365.20 $[M+H]^+$. Anal. Calc. for $C_{21}H_{24}N_4O_2$ (%): C 69.21, H 6.64, N 15.37.
30 Found (%): C 68.76, H 6.69, N 15.15.

7

White crystals (0.89 g). Yield: 54%. ^1H NMR: δ ppm (DMSO- d_6) 1.64 (6H, t, $3\times\text{CH}_2$), 1.97 (6H, d, $J = 2.0$ Hz, $3\times\text{CH}_2$), 2.04 (3H, m, $3\times\text{CH}$), 6.02 (1H, s, NHCO), 6.63 (1H, t, $J = 8.0$ Hz, CH), 6.75 (1H, dd, $J = 7.5$ and 1.5 Hz, CH), 7.03 (1H, dd, $J = 8.0$ and 1.5 Hz, CH), 8.10 (1H, s, CH=N), 9.35 (2H, bs, OH), 10.07 (1H, s, NH=N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.6, 36.6, 42.3, 50.5, 116.5, 117.5, 119.6, 121.5, 138.7, 145.3, 146.1, 154.4. ESI-MS in CH_3OH : found mass: 329.93, Calc. mass for $\text{C}_{18}\text{H}_{24}\text{N}_3\text{O}_3$: 330.18 $[\text{M}+\text{H}]^+$. Anal. Calc. for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_3$ (%): C 65.63, H 7.04, N 12.76. Found (%): C 65.52, H 7.01, N 12.77.

8

White solid (0.92 g). Yield: 53%. Single crystals for X-ray diffraction analysis were grown in ethanol. ^1H NMR: δ ppm (DMSO- d_6) 1.64 (6H, t, $3\times\text{CH}_2$), 1.96 (6H, d, $J = 2.0$ Hz, $3\times\text{CH}_2$), 2.04 (3H, m, $3\times\text{CH}$), 5.94 (1H, s, NHCO), 6.33 (1H, d, $J = 7.5$ Hz, CH), 6.84 (1H, d, $J = 7.5$ Hz, CH), 7.94 (1H, s, CH=N), 8.38 (1H, bs, OH), 9.67 (1H, bs, OH), 9.33 (1H, bs, OH), 9.84 (1H, s, NH=N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.6, 36.6, 42.4, 50.5, 108.1, 113.2, 118.5, 133.3, 140.8, 146.7, 148.1, 154.5. ESI-MS in CH_3OH : found mass: 346.00, Calc. mass for $\text{C}_{18}\text{H}_{24}\text{N}_3\text{O}_4$: 346.15 $[\text{M}+\text{H}]^+$. Anal. Calc. for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_4\cdot(\text{EtOH})_{0.5}(\text{H}_2\text{O})$ (%): C 59.05, H 7.30, N 10.87. Found (%): C 59.39, H 7.17, N 10.88.

9

White solid (1.29 g). Yield: 83%. ^1H NMR: δ ppm (DMSO- d_6) 1.66 (6H, bs, $3\times\text{CH}_2$), 2.04 (9H, m, $3\times\text{CH}_2$ and $3\times\text{CH}$), 2.27 (3H, s, CH_3), 6.29 (1H, s, NHCO), 6.35 (1H, m, CH), 7.80 (1H, t, $J = 7.2$ Hz, CH), 8.01 (1H, d, $J = 7.2$ Hz, CH), 8.56 (1H, d, $J = 4.4$ Hz, CH), 9.44 (1H, s, NH=N). ^{13}C NMR: δ ppm (DMSO- d_6) 12.1, 29.4, 36.5, 42.1, 50.4, 120.1, 123.8, 136.9, 145.2, 148.9, 154.4, 155.6. ESI-MS in CH_3CN : found mass: 335.18 (100%), Calc. mass for $\text{C}_{18}\text{H}_{24}\text{N}_4\text{ONa}$: 335.18 $[\text{M}+\text{H}]^+$. Anal. Calc. for $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}$ (%): C 69.20, H 7.74, N 17.93. Found (%): C 69.33, H 7.71, N 17.94.

Synthesis of the thiosemicarbazide precursor

1-Adamantylthiosemicarbazide was prepared by refluxing 1-adamantylisothiocyanate (10 g, 56.42 mmol) with excess hydrazine hydrate (15 g, 300

mmol) in ethanol (100 mL) for 60 min. The precipitate formed was collected by filtration, washed with ethanol followed with water and dried in air to give a product as white solid (11.5 g). Yield: 99%. ^1H NMR: δ ppm (DMSO- d_6) 1.63 (6H, t, $3\times\text{CH}_2$), 2.04 (3H, m, $3\times\text{CH}$), 2.17 (6H, d, $J = 1.6$ Hz, $3\times\text{CH}_2$), 4.50 (2H, s, NH_2), 7.42 (1H, bs, NHCS), 8.39 (1H, s, NH-N).

Synthesis of thiosemicarbazone compounds

Thiosemicarbazones **10-19** were synthesized following the general procedure used for preparation of compounds **1-9** stated above.

10

Yellow solid (1.87 g). Yield: 87%. ^1H NMR: δ ppm (DMSO- d_6) 1.66 (6H, t, $3\times\text{CH}_2$), 2.08 (3H, m, $3\times\text{CH}$), 2.25 (6H, d, $J = 2.0$ Hz, $3\times\text{CH}_2$), 2.62 (3H, s, CH_3), 4.75 (2H, s, CH_2), 7.92 (1H, s, NHCS), 8.20 (1H, s, OH), 8.50 (1H, s, $\text{CH}=\text{N}$), 12.13 (1H, s, OH). ^{13}C NMR: δ ppm (DMSO- d_6) 15.4, 29.4, 36.3, 41.0, 54.1, 59.4, 129.7, 136.0, 137.2, 142.6, 152.3. ESI-MS in CH_3OH : found mass: 375.13 (100%), Calc. mass for $\text{C}_{19}\text{H}_{27}\text{N}_4\text{OS}$: 375.19 $[\text{M}-\text{Cl}]^+$. Anal. Calc. for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_2\text{S}\cdot\text{HCl}$ (%): C 55.53, H 6.62, N 13.63, S 7.80. Found (%): C 55.48, H 6.63, N 13.67, S 7.73.

11

White solid (1.28 g). Yield: 78%. ^1H NMR: δ ppm (DMSO- d_6) 1.65 (6H, t, $3\times\text{CH}_2$), 2.07 (3H, m, $3\times\text{CH}$), 2.26 (6H, d, $J = 3.0$ Hz, $3\times\text{CH}$), 6.81-6.88 (2H, m, CH), 7.19-7.24 (1H, m, CH), 7.47 (1H, s, NHCS), 7.67 (1H, dd, $J = 9.5$ and 4.0 Hz, CH), 8.37 (1H, s, $\text{CH}=\text{N}$), 10.02 (1H, bs, OH), 11.28 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.5, 36.4, 41.5, 53.4, 116.6, 119.8, 120.8, 126.3, 131.6, 138.9, 157.0, 175.0. ESI-MS in CH_3OH : found mass: 352.10 (100%), Calc. mass for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{OSNa}$: 352.15 $[\text{M}+\text{Na}]^+$. Anal. Calc. for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{OS}$ (%): C 65.62, H 7.02, N 12.75, S 9.73. Found (%): C 65.40, H 7.01, N 12.90, S 9.68.

12

Yellow solid (1.20 g). Yield: 63%. ^1H NMR: δ ppm (DMSO- d_6) 1.67 (6H, t, $3\times\text{CH}_2$), 2.09 (3H, m, $3\times\text{CH}$), 2.29 (6H, m, $3\times\text{CH}_2$), 7.19 (1H, d, $J = 8.8$ Hz, CH), 7.37 (1H, t, $J = 7.6$ Hz, CH), 7.43 (1H, s, NHCS), 7.53 (1H, t, $J = 7.2$ Hz, CH), 7.84 (2H, dd, $J = 7.6, 2.0$ Hz, $2\times\text{CH}$), 8.64 (1H, d, $J = 8.0$ Hz, CH), 8.89 (1H, s, $\text{CH}=\text{N}$), 10.66 (1H, bs,

OH), 11.34 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.5, 36.4, 41.4, 53.4, 111.1, 118.7, 123.8, 128.1, 128.7, 129.3, 131.7, 141.0, 157.3, 175.0. ESI-MS in CH_3OH : found mass: 402.13 (100%), Calc. mass for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{OSNa}$: 402.16 $[\text{M}+\text{Na}]^+$. Anal. Calc. for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{OS}$ (%): C 69.62, H 6.64, N 11.07, S 8.45. Found (%): C 69.69, H 6.59, N 11.26, S 8.39.

13

White solid (1.05 g). Yield: 67%. ^1H NMR: δ ppm (DMSO- d_6) 1.67 (6H, bs, $3\times\text{CH}_2$), 2.09 (3H, bs, $3\times\text{CH}$), 2.29 (6H, bs, $3\times\text{CH}_2$), 7.39 (1H, m, CH), 7.56 (1H, s, NH), 7.84 (1H, m, CH), 7.99 (1H, d, $J = 8.1$ Hz, CH), 8.12 (1H, s, CH=N), 8.58 (1H, d, $J = 4.6$ Hz, CH), 11.54 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.5, 36.4, 41.3, 53.7, 120.4, 124.7, 137.2, 142.1, 150.0, 153.4, 175.3. ESI-MS in CH_3OH : found mass: 315.11 (100%), Calc. mass for $\text{C}_{17}\text{H}_{23}\text{N}_4\text{S}$: 315.16 $[\text{M}+\text{H}]^+$. Anal. Calc. for $\text{C}_{17}\text{H}_{22}\text{N}_4\text{S}$ (%): C 64.93, H 7.05, N 17.82, S 10.20. Found (%): C 65.20, H 7.07, N 18.11, S 10.22.

14

Light grey solid (1.45 g). Yield: 80%. ^1H NMR: δ ppm (DMSO- d_6) 1.68 (6H, t, $3\times\text{CH}_2$), 2.10 (3H, m, $3\times\text{CH}$), 2.33 (6H, d, $3\times\text{CH}_2$), 7.64 (1H, m, CH), 7.66 (1H, s, NHCS), 7.77 (1H, t, $J = 8.0$ Hz, CH), 7.99 (2H, t, $J = 7.6$ Hz, $2\times\text{CH}$), 8.12 (1H, d, $J = 8.8$ Hz, CH), 8.26 (1H, s, CH=N), 8.37 (1H, d, $J = 8.4$ Hz, CH), 11.71 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.5, 36.4, 41.2, 53.8, 118.0, 127.7, 128.3, 128.4, 129.3, 130.5, 137.0, 142.2, 147.9, 153.9, 175.3. ESI-MS in CH_3OH : found mass: 387.12 (100%), Calc. mass for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{SNa}$: 387.16 $[\text{M}+\text{Na}]^+$. Anal. Calc. for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{S}$ (%): C 69.20, H 6.64, N 15.37, S 8.80. Found (%): C 69.19, H 6.57, N 15.55, S 8.71.

15

Light yellow solid (1.40 g). Yield: 73%. ^1H NMR: δ ppm (DMSO- d_6) 1.67 (6H, t, $3\times\text{CH}_2$), 2.09 (3H, m, $3\times\text{CH}$), 2.32 (6H, d, $J = 2.0$ Hz, $3\times\text{CH}_2$), 7.10 (1H, dd, $J = 7.6$ and 1.6 Hz, CH), 7.38 (2H, m, $2\times\text{CH}$), 7.66 (1H, s, NHCS), 8.09 (1H, d, $J = 8.4$ Hz, CH), 8.28 (2H, m, CH merged with CH=N), 9.91 (1H, s, OH), 11.79 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.5, 36.3, 41.2, 53.8, 112.7, 118.1, 118.3, 128.6, 129.2, 136.9, 138.7, 142.0, 151.8, 153.9, 175.3. ESI-MS in CH_3OH : found mass: 403.11 (100%), Calc. mass for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{OSNa}$: 403.16 $[\text{M}+\text{Na}]^+$. Anal. Calc. for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{OS}$ (%): C 66.29, H 6.36, N 14.72, S 8.43. Found (%): C 66.27, H 6.32, N 14.98, S 8.34.

16

White solid (1.65 g). Yield: 95%. ^1H NMR: δ ppm (DMSO- d_6) 1.65 (6H, t, $3\times\text{CH}_2$), 2.07 (3H, m, $3\times\text{CH}$), 2.26 (6H, d, $J = 2.0$ Hz, $3\times\text{CH}_2$), 6.64 (1H, t, $J = 7.6$ Hz, CH), 6.79 (1H, dd, $J = 7.6$ and 1.6 Hz, CH), 7.11 (1H, d, $J = 8.0$ Hz, CH), 7.44 (1H, s, NHCS), 8.37 (1H, s, CH=N), 8.99 (1H, bs, OH), 9.55 (1H, bs, OH), 11.25 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.5, 36.4, 41.5, 53.4, 116.6, 116.9, 119.7, 121.3, 139.6, 145.8, 146.1, 175.0. ESI-MS in CH_3OH : found mass: 368.10 (100%), Calc. mass for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_2\text{SNa}$: 368.14 $[\text{M}+\text{Na}]^+$. Anal. Calc. for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_2\text{S}\cdot(\text{H}_2\text{O})_{0.25}$ (%): C 61.78, H 6.77, N 12.01, S 9.16. Found (%): C 61.56, H 6.80, N 12.09, S 9.09.

17

Light grey solid (0.75 g). Yield: 46%. ^1H NMR: δ ppm (DMSO- d_6) 1.65 (6H, t, $3\times\text{CH}_2$), 2.07 (3H, m, $3\times\text{CH}$), 2.25 (6H, d, $J = 2.0$ Hz, $3\times\text{CH}_2$), 6.33 (1H, d, $J = 8.8$ Hz, CH), 6.97 (1H, d, $J = 8.4$ Hz, CH), 7.35 (1H, s, NHCS), 8.25 (1H, s, CH=N), 8.48 (1H, s, OH), 9.03 (1H, bs, OH), 9.53 (1H, s, OH), 11.08 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.5, 36.4, 41.5, 53.3, 108.3, 113.1, 117.5, 133.3, 140.8, 147.2, 148.7, 174.5. ESI-MS in CH_3OH : found mass: 384.09 (100%), Calc. mass for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_3\text{SNa}$: 384.14 $[\text{M}+\text{Na}]^+$. Anal. Calc. for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_3\text{S}$ (%): C 59.81, H 6.41, N 11.63, S 8.87. Found (%): C 59.98, H 6.40, N 11.68, S 8.83.

18

White solid (0.88 g). Yield: 54%. ^1H NMR: δ ppm (DMSO- d_6) 1.67 (6H, bs, $3\times\text{CH}_2$), 2.09 (3H, m, $3\times\text{CH}$), 2.29 (6H, d, $J = 2.4$ Hz, $3\times\text{CH}_2$), 2.40 (3H, s, CH_3), 7.40 (1H, ddd, $J = 7.4, 4.9, 1.1$ Hz, CH), 7.75 (1H, s, NHCS), 7.84 (3H, td, $J = 7.8, 1.8$ Hz, CH), 8.01 (1H, d, $J = 8.1$ Hz, CH), 8.60 (1H, m, CH), 10.16 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 12.9, 29.5, 36.4, 41.2, 53.6, 120.5, 124.5, 137.2, 148.0, 149.2, 155.1, 176.0. ESI-MS in CH_3CN : found mass: 329.14 (100%), Calc. mass for $\text{C}_{18}\text{H}_{25}\text{N}_4\text{S}$: 329.18 $[\text{M}+\text{H}]^+$. Anal. Calc. for $\text{C}_{18}\text{H}_{24}\text{N}_4\text{S}$ (%): C 65.82, H 7.36, N 17.06, S 9.76. Found (%): C 65.93, H 7.40, N 17.45, S 9.78.

19

White solid (1.50 g). Yield: 77%. ^1H NMR: δ ppm (DMSO- d_6) 1.66 (6H, bs, CH_2), 2.09 (3H, bs, CH), 2.28 (6H, bs, CH_2), 7.50 (1H, m, $2\times\text{CH}$), 7.58 (1H, m, CH), 7.80 (1H, s, NHCS), 8.00 (3H, m, $3\times\text{CH}$), 8.59 (1H, d, $J = 3.9$ Hz, CH), 8.83 (1H, d, $J = 4.2$ Hz,

CH), 13.28 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 28.4, 35.3, 39.93, 52.8, 122.9, 123.3, 124.2, 126.5, 136.8, 137.0, 139.6, 147.5, 147.9, 150.5, 154.6, 174.2. ESI-MS in CH_3CN : found mass: 392.14 (100%), Calc. mass for $\text{C}_{22}\text{H}_{26}\text{N}_5\text{S}$: 392.19 $[\text{M}+\text{H}]^+$. Anal. Calc. for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{S}$ (%): C 67.49, H 6.44, N 17.89, S 8.19. Found (%): C 67.63, H 6.38, N 18.04, S 8.13.

Preparation of the 1-adamantyl containing amide intermediate

Mono-methyl terephthalate (4.7 g, 26.1 mmol) and PyBOP (15 g, 28.9 mmol) were dissolved in DMF and stirred at room temperature. After 15 min, 1-adamantylamine (4.0 g, 26.44) and DIPEA (3.8 g, 29.5 mmol) were added and stirring was continued overnight. The addition of water to the reaction mixture resulted in the formation of a white precipitate, which was filtered off, washed with copious amounts of water and dried to get the amide intermediate. Yield: 98%. ^1H NMR: δ ppm (DMSO- d_6) 1.65 (6H, t, CH_2), 2.07 (9H, m, $3\times\text{CH}_2$ and $3\times\text{CH}$), 3.87 (1H, s, CH_3), 7.83 (1H, s, NH), 7.87 (2H, d, $J = 8.0$ Hz, CH), 7.98 (2H, d, $J = 8.0$ Hz, CH).

Preparation of the 1-adamantyl containing hydrazide intermediate

The amide intermediate (8 g, 25.6 mmol) was refluxed with an excess of hydrazine hydrate (10 g, 200 mmol) in ethanol for 2 h. The desired hydrazide precipitate was collected by filtration, washed with copious amounts of ethanol and dried in air. White solid. Yield: 90%. ^1H NMR: δ ppm (DMSO- d_6) 1.66 (6H, t, CH_2), 2.05 (9H, m, $3\times\text{CH}_2$ and $3\times\text{CH}$), 4.52 (2H, s, NH_2), 7.69 (1H, s, NH), 7.81 (2H, d, $J = 6.8$ Hz, CH), 7.84 (2H, d, $J = 6.8$ Hz, CH), 7.87 (1H, s, NH- NH_2).

General procedure for the preparation of compounds 20-27:

The hydrazone ligands were prepared in good yield by refluxing the hydrazide intermediate (4 mmol) with the appropriate aldehyde (4.2 mmol) in absolute ethanol (20 mL) in the presence of catalytic amounts of glacial acetic acid (8 drops) for 2 h. The resulting precipitate was filtered off, washed with ethanol and dried in vacuo.

20

Yellow solid (1.26 g). Yield: 63%. ^1H NMR: δ ppm (DMSO- d_6) 1.67 (6H, t, $3\times\text{CH}_2$), 2.07 (3H, m, $3\times\text{CH}$), 2.10 (6H, d, $3\times\text{CH}_2$), 2.65 (3H, s, CH_3), 4.79 (2H, s, CH_2), 7.84 (1H, s, CH), 7.93 (2H, d, $J = 8$ Hz, CH), 8.11 (2H, d, $J = 12$ Hz, CH), 8.22 (1H, s, $\text{CH}=\text{N}$), 9.17 (1H, s, NHCO), 13.17 (1H, bs, OH), 13.43 (1H, s, NHN). ^{13}C NMR: δ ppm

(DMSO- d_6) 14.9, 29.5, 36.7, 41.4, 52.4, 58.5, 127.5, 128.2, 128.4, 129.2, 133.3, 137.7, 140.1, 143.4, 144.2, 153.6, 162.9, 165.7. ESI-MS in CH_3CN : found mass: 463.07, Calc. mass for $C_{26}H_{31}N_4O_4$: 463.24 $[M-Cl]^-$. Anal. Calc. for $C_{26}H_{30}N_4O_4 \cdot HCl$ (%): C 62.58, H 6.26, N 11.23. Found (%): C 62.63.18, H 6.30, N 11.31.

5 21

White solid (1.10 g). Yield: 66%. 1H NMR: δ ppm (DMSO- d_6) 1.68 (6H, t, $3 \times CH_2$), 2.07 (3H, m, $3 \times CH$), 2.10 (6H, d, $J = 2.0$ Hz, $3 \times CH_2$), 6.94 (2H, t, $J = 8.4$ Hz, CH), 7.30 (1H, t, $J = 7.0$ Hz, CH), 7.56 (1H, d, $J = 7.0$ Hz, CH), 7.77 (1H, s, CH=N), 7.91 (2H, d, $J = 8$ Hz, CH), 7.96 (2H, d, $J = 8$ Hz, CH), 8.68 (1H, s, NH), 11.25 (1H, s, OH), 12.18 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.4, 36.6, 41.3, 52.2, 116.9, 119.1, 119.8, 127.9, 128.0, 130.0, 132.0, 135.0, 139.4, 149.1, 158.0, 162.6, 165.8. ESI-MS in CH_3CN : found mass: 418.21 (30%), Calc. mass for $C_{25}H_{28}N_3O_3$: 418.21 $[M+H]^+$, found mass: 857.00 (100%), Calc. mass for $C_{50}H_{54}N_6O_6Na$: 857.40 $[2M+Na]^+$. Anal. Calc. for $C_{25}H_{27}N_3O_3 \cdot 0.5H_2O$ (%): C 70.40, H 6.62, N 9.85. Found (%): C 70.83, H 6.60, N 9.98.

15 22

Yellow solid (1.38 g). Yield: 73%. 1H NMR: δ ppm (DMSO- d_6) 1.68 (6H, t, $3 \times CH_2$), 2.08 (3H, m, $3 \times CH$), 2.11 (6H, d, $J = 2.0$ Hz, $3 \times CH_2$), 7.24 (1H, d, $J = 8.0$ Hz, CH), 7.43 (1H, t, $J = 7.0$ Hz, CH), 7.63 (1H, t, $J = 7.0$, CH), 7.77 (1H, s, CH=N), 7.90-7.97 (4H, m, CH), 8.03 (2H, m, CH), 8.25 (1H, d = 9.0 Hz, CH=N), 9.52 (1H, s, NHCO), 12.26 (1H, s, OH), 12.73 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.4, 36.6, 41.3, 52.2, 109.0, 119.4, 121.2, 124.1, 127.8, 128.1, 128.3, 132.1, 134.8, 139.6, 147.7, 158.6, 162.4, 165.8. ESI-MS in CH_3CN : found mass: 468.20 (30%), Calc. mass for $C_{29}H_{30}N_3O_3$: 468.23 $[M+H]^+$, found mass: 957.00 (100%), Calc. mass for $C_{58}H_{58}N_6O_6Na$: 957.43 $[2M+Na]^+$. Anal. Calc. for $C_{29}H_{29}N_3O_3$ (%): C 74.50, H 6.25, N 8.99. Found (%): C 74.70, H 6.30, N 9.02.

23

White solid (1.10 g). Yield: 69%. 1H NMR: δ ppm (DMSO- d_6) 1.67 (6H, t, CH_2), 2.06 (3H, m, CH_2), 2.09 (6H, m, CH), 7.44 (1H, t, $J = 6.0$ Hz, CH), 7.77 (1H, s, CH), 7.90-7.99 (6H, m, CH), 8.51 (1H, s, CH=N), 8.62 (1H, s, NHCO), 12.11 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.4, 36.6, 41.3, 52.2, 120.5, 125.0, 128.0, 135.3, 137.4, 139.4, 148.9, 150.0, 153.7, 163.2, 165.8. ESI-MS in CH_3CN : found mass: 403.07 (35%),

Calc. mass for $C_{24}H_{27}N_4O_2$: 403.21 $[M+H]^+$, found mass: 826.93 (100%), Calc. mass for $C_{48}H_{52}N_8O_4Na$: 827.40 $[2M+Na]^+$. Anal. Calc. for $C_{24}H_{26}N_4O_2$ (%): C 71.62, H 6.51, N 13.92. Found (%): C 71.57, H 6.48, N 13.94.

24

5 Light brown solid (1.13 g). Yield: 60%. 1H NMR: δ ppm (DMSO- d_6) 1.67 (6H, t, CH_2), 2.07 (3H, m, CH), 2.10 (6H, d, $J = 2.0$ Hz, CH), 7.65 (1H, t, $J = 6.0$ Hz, CH), 7.78 (1H, m, CH=N), 7.82 (1H, d, $J = 6.0$ Hz, CH), 7.93 (2H, d, $J = 6.4$ Hz, CH), 8.05 (2H, d, $J = 6.4$ Hz, CH), 8.14 (1H, dd, $J = 12.0$ and 7.6 Hz, CH), 8.44 (1H, d, $J = 6.8$ Hz, CH), 8.65 (1H, s, NHCO), 12.27 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.4, 36.5,
10 41.3, 52.2, 118.0, 118.2, 127.9, 128.0, 128.4, 128.5, 129.4, 129.4, 130.5, 135.3, 137.3, 139.5, 147.9, 148.8, 154.2, 163.4, 165.8. ESI-MS in CH_3CN : found mass: 453.13 (75%), Calc. mass for $C_{28}H_{29}N_4O_2$: 453.23 $[M+H]^+$, found mass: 926.93 (100%), Calc. mass for $C_{56}H_{56}N_8O_4Na$: 927.43 $[2M+Na]^+$. Anal. Calc. for $C_{28}H_{28}N_4O_2 \cdot 1.5H_2O$ (%): C 70.13, H 6.52, N 11.68. Found (%): C 70.04, H 6.38, N 11.76.

15 25

Light yellow solid (1.4 g). Yield: 75%. 1H NMR: δ ppm (DMSO- d_6) 1.67 (6H, t, CH_2), 2.07 (3H, m, CH), 2.10 (6H, d, $J = 2.0$ Hz, CH), 7.14 (1H, d, $J = 7.0$ Hz, CH), 7.44-7.50 (2H, m, CH), 7.81 (1H, s, CH=N), 7.93 (2H, d, $J = 8.0$ Hz, CH), 8.01 (2H, d, $J = 8.0$ Hz, CH), 8.36 (1H, d, $J = 8.0$ Hz, CH), 8.69 (1H, s, NHCO), 9.87 (1H, s, OH), 12.33 (1H,
20 s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.4, 36.5, 41.3, 52.2, 112.6, 118.2, 118.3, 128.0, 128.1, 128.9, 129.3, 137.1, 138.6, 139.5, 148.8, 152.1, 152.1, 153.9, 163.4, 165.8. ESI-MS in CH_3CN : found mass: 469.22 (100%), Calc. mass for $C_{28}H_{29}N_4O_3$: 469.22 $[M+H]^+$. Anal. Calc. for $C_{28}H_{28}N_4O_3 \cdot H_2O$ (%): C 69.12, H 6.21, N 11.51. Found (%): C 69.36, H 6.26, N 11.40.

25 26

White solid (1.27 g). Yield: 73%. 1H NMR: δ ppm (DMSO- d_6) 1.67 (6H, t, CH_2), 2.07 (3H, m, CH), 2.11 (6H, d, $J = 2.0$ Hz, CH_2), 6.75 (1H, t, $J = 8.0$ Hz, CH), 6.89 (1H, d, $J = 2.0$ Hz, CH), 6.99 (1H, d, $J = 3.0$ Hz, CH), 7.81 (1H, s, CH=N), 7.93 (2H, d, $J = 8.0$ Hz, CH), 8.01 (2H, d, $J = 8.0$ Hz, CH), 8.66 (1H, s, NHCO), 9.29 (1H, s, OH), 11.56
30 (1H, s, OH), 12.23 (1H, s, NH-N). ^{13}C NMR: δ ppm (DMSO- d_6) 29.4, 36.5, 41.3, 52.2, 117.9, 119.2, 120.5, 127.9, 128.0, 134.9, 139.4, 146.1, 146.6, 149.8, 162.6, 165.8. ESI-

MS in CH₃CN: found mass: 456.13 (30%), Calc. mass for C₂₅H₂₇N₃O₄Na: 456.19 [M+Na]⁺, found mass: 888.80 (100%), Calc. mass for C₅₀H₅₄N₆O₈Na: 889.39 [2M+Na]⁺. Anal. Calc. for C₂₅H₂₇N₃O₄·H₂O (%): C 66.50, H 6.47, N 9.31. Found (%): C 66.52, H 6.48, N 9.14.

5 27

Light grey solid (1.32 g). Yield: 73%. ¹H NMR: δ ppm (DMSO-d₆) 1.67 (6H, t, CH₂), 2.07 (3H, m, CH), 2.09 (6H, d, J = 2.0 Hz, CH₂), 6.39 (1H, d, J = 3.0 Hz, CH), 6.79 (1H, d, J = 3.0 Hz, CH), 7.79 (1H, s, CH=N), 7.89 (2H, d, J = 7.0 Hz, CH), 7.97 (2H, d, J = 7.0 Hz, CH), 8.49 (1H, s, NHCO), 8.53 (1H, s, OH), 9.51 (1H, s, OH), 11.50 (1H, s, OH), 12.05 (1H, s, NH-N). ¹³C NMR: δ ppm (DMSO-d₆) 29.4, 36.5, 41.3, 52.2, 117.9, 119.2, 120.5, 127.9, 128.0, 134.9, 139.4, 146.1, 146.6, 149.8, 162.6, 165.8. ESI-MS in CH₃CN: found mass: 450.13 (30%), Calc. mass for C₂₅H₂₈N₃O₅: 450.20 [M+H]⁺, found mass: 920.60 (100%), Calc. mass for C₅₀H₅₄N₆O₁₀Na: 921.38 [2M+Na]⁺. Anal. Calc. for C₂₅H₂₇N₃O₅·2H₂O (%): C 61.84, H 6.44, N 8.65. Found (%): C 62.18, H 6.24, N 8.76.

Effect of Compounds 1-27 on Mobilising Cellular ⁵⁹Fe

The ability of compounds **1-27** to mobilise ⁵⁹Fe from SK-N-MC neuroepithelioma cells prelabelled with ⁵⁹Fe₂-transferrin (⁵⁹Fe₂-Tf) was determined by standard techniques.¹ A monolayer of SK-N-MC cells was prelabelled with ⁵⁹Fe₂-Tf (0.75 μM) in complete MEM media for 3 h at 37°C. The cells were then washed four times with ice-cold PBS and then incubated with medium alone (control) or medium containing compounds **1-27** (25 μM) for 3 h at 37°C. After incubation, the overlying medium containing mobilised ⁵⁹Fe was separated using a Pasteur pipette without affecting the cell monolayer. PBS (1 mL) was added to the cells, which were then removed from the plate using a plastic spatula. Radioactivity was measured in both the cells and supernatant using a γ-scintillation counter (Wallac Wizard², PerkinElmer). The well characterized chelators, DFO, Dp44mT and clioquinol (CQ; 25 μM) were included as positive controls.²

Effect of Compounds 1-27 at Preventing Cellular ⁵⁹Fe Uptake

The ability of compounds **1-27** to prevent the cellular uptake of ⁵⁹Fe from the Fe transport protein, ⁵⁹Fe₂-Tf, were performed using standard procedures.^{3,4} A monolayer

of SK-N-MC neuroepithelioma cells was incubated with $^{59}\text{Fe}_2\text{-Tf}$ (0.75 μM) and compounds **1-27** (25 μM) in complete MEM media for 3 h at 37°C. The media was then removed and cells were washed four times with ice-cold PBS. Subsequently, cells were incubated with Pronase (1 mg/mL; Sigma-Aldrich) for 30 min at 4°C. The monolayer of cells was then detached from the plate using a plastic spatula and centrifuged at 14,000 rpm for 3 min at 4°C. The supernatant that contain membrane-bound ^{59}Fe was removed and the cell pellet containing internalized ^{59}Fe was resuspended in 1 mL of PBS. The levels of ^{59}Fe in both the supernatant and cell suspension were measured on a γ -scintillation counter. Internalized ^{59}Fe uptake was calculated as a percentage of the control (medium alone). The well characterized chelators, DFO, Dp44mT and CQ (25 μM) were included in this study as positive controls.^{3,4}

Effect of Compounds 1-27 on Cellular Proliferation

The effect of compounds **1-27** on the cellular proliferation of SK-N-MC cells was determined by the MTT assay using standard techniques.^{5,6} The SK-N-MC neuroepithelioma cells were seeded in 96-well microtiter plates at 1.5×10^4 cells/well. Stock solutions of compounds were prepared in DMSO (20 mM) and diluted further in complete MEM media so that the final DMSO concentration was <0.5% (v/v). After 24 h, cells were incubated with compounds at a range of concentrations (0.20 – 100 μM) and incubated for 72 h at 37°C in a humidified atmosphere containing 5% CO_2 and 95% air. After this incubation, 10 μL of MTT (5 mg/mL) was added to each well and further incubated for 2 h at 37°C. The cells were dissolved in 100 μL of DMSO and the plates were read at 570 nm using a scanning multi-well spectrophotometer. The half maximal inhibitory concentration (IC_{50}) was defined as the concentration of the compound required to decrease the absorbance to 50% of the untreated control.

Acetylcholinesterase (AChE) inhibition assay

The ability of compounds **1-27** to inhibit AChE was measured using standard procedure.^{7,8} Stock solutions of the compounds were prepared in DMSO (10 mM). Working solutions were prepared by dissolving 12.5 μL of chelator or DMSO (control) in 997.5 μL of freshly prepared HEPES buffer (50 mM, 150 mM, NaCl; pH 8). The chelator (206 μL) was added to a cuvette containing 238 μL of DTNB (3 mM in HEPES buffer) and 37.5 μL of AChE at a concentration of 0.26 U/mL and incubated for 15 min. After the addition of 12.5 μL of AChI (15 mM), the enzymatic reaction was followed by

measuring the absorbance at 405 nm for the first 5 min using UV-vis spectrophotometer in kinetic mode to calculate initial rate of the reaction. A slope (m) was calculated from each kinetic graph. The percentage of enzymatic activity was calculated using formula given below.

5
$$\% \text{ activity} = 100 - [m_{\text{sample}}/m_{\text{control}}]$$

Where m_{sample} is the slope of obtained from the sample and m_{control} is the slope obtained from the control (DMSO) reaction. Each experiment was carried out in triplicate.

Ascorbate Oxidation Assay

10 The ability of the iron complexes of compounds 1-27 to redox cycle and mediate the oxidation of ascorbate was evaluated.^{3,9} The assay was carried out in phosphate buffer (10 mM, pH = 7.4) containing an excess of sodium citrate (500 μ M) and 10% acetonitrile due to poor solubility of iron complexes in the buffer alone. Freshly prepared ascorbic acid (100 μ M) was incubated with FeCl₃ alone (10 μ M, control), the iron
15 complexes of compounds 1-27 (10 μ M) or FeCl₃ (10 μ M) in the presence of the positive or negative controls, EDTA or DFO (10 μ M), respectively.¹⁰ The absorbance was measured at 265 nm after a 10 and 40 min incubation at room temperature and the change in absorbance between these two time points was used to calculate the percentage of ascorbate oxidation relative to control (100%).

20 Inhibition of Cu(II)-Mediated A β ₁₋₄₀ Aggregation

Turbidimetric assay was carried out by following a standard protocol with minor modification.¹¹ Briefly, a synthetic A β ₁₋₄₀ (1 mg) purchased from China peptide (Shanghai, China) was dissolved in DMSO (50 μ L) and then in Milli-Q water (910 μ L) was added just prior to the experiment to provide a 250 μ M solution. HEPES (4-(2-
25 hydroxyethyl)-1-piperazineethanesulfonic acid) buffer was prepared (20 mM, NaCl, 150 mM) in Milli-Q water and the pH was adjusted to 6.6 to maximize copper binding with A β ₁₋₄₀. The HEPES buffer was then was passed through Chelex resin to remove trace metal ions and filtered using a 0.2 μ m PES membrane filter (Millipore).

Stock solutions of DTPA, Dp44mT, and the selected adamantane analogues
30 were prepared in DMSO (10 mM) and diluted further with HEPES buffer (20 mM HEPES, 150 mM NaCl, pH 6.6) to a final concentration of 50 μ M. A stock solution of

Cu(II) (250 μ M; ICP grade, Sigma-Aldrich) was also prepared in HEPES buffer. Solutions of Cu(II) (5 μ L) and A β ₁₋₄₀ (5 μ L) were added to HEPES buffer (15 μ L) in a 384-well plate, which was then incubated with the ligands (25 μ L) in a final volume of 50 μ L. The final concentrations of the agents, Cu(II) and A β ₁₋₄₀ were 25 μ M each. The solutions were incubated for 2 h/37°C and absorbance measured at 405 nm using a FluoStar Omega Plate Reader (BMG Labtech, Ortenberg, Germany).

NMDAR and VGCC Inhibition

To measure NMDAR activity, a modified protocol was used,¹² where primary human astrocytes were loaded (~1 h at RT) with 3.5 μ g/mL Fura-2-AM in loading solution containing 135 mM NaCl, 5 mM KCl, 1 mM MgCl₂, 1 mM CaCl₂, 5 mM glucose, and 10 mM HEPES (pH 7.4). Probenicid was dissolved in 1 M NaOH and added to the loading solution at a final concentration of 4 mM to prevent dye leakage. After a 1 h incubation, the loading solution was removed and replaced with HBSS containing 50 mM glycine. Addition of selected adamantane compounds was undertaken 30 min prior to the addition of NMDA (100 μ M). The calcium influx experiments were subsequently performed using a Fluostar Optima Fluorometer (NY, USA). The wavelengths selected were 340 nm for excitation, and emission was set at 520 nm. Fluorescence was measured *via* orbital scanning of 10 locations at a 3 mm radius every 0.5 s. Baseline fluorescence was measured during the first 10 seconds of the experiment, followed by injection of NMDA (in HBSS), and readings were further taken for an additional 90 s. A solution of HBSS not containing NMDA was also used as a negative control. Experiments were repeated in triplicate using three different cellular preparations.

To measure KCl-mediated Ca²⁺ influx, primary human astrocytes were incubated (~1 h at room temperature) with 3.5 μ g/ml Fura-2-AM (in DMSO), as previously described with minor modification.¹² The adamantane compounds were incubated for 30 min at 37°C and used immediately after incubation. After 10 s into the reading, 10 μ L of 140 mM KCl in depolarisation solution, containing 5.4 mM NaCl, 140 mM KCl, 10 mM NaHCO₃, 1.4 mM CaCl₂, 0.9 mM MgSO₄, 5.5 mM glucose monohydrate, 0.6 mM KH₂PO₄, 0.6 mM Na₂HPO₄, and 20 mM HEPES (pH 7.4), was added. The calcium influx experiments were subsequently performed using Fluostar Optima Fluorometer (NY, USA). The wavelengths selected were 340 nm for excitation, and emission was set at

520 nm. Experiments were repeated in triplicate using three different cellular preparations.

Results

Effect of Compounds 1-27 on ^{59}Fe Release from Prelabelled cells

5 As iron-loading is one of the hallmarks of AD¹¹ and is partly responsible for the generation of increased amounts of ROS and β -amyloid aggregation¹², chelators to bind cellular iron and induce iron release were developed. The results were compared with three positive controls, namely: **(1)** Dp44mT, a thiosemicarbazone chelator with high iron mobilization efficacy;¹³ **(2)** DFO, the classical iron chelator employed in
10 neurodegenerative diseases;¹⁴ and **(3)** CQ, an iron chelator that has been used in clinical trials for AD.¹⁵

As shown in Figure 1, the incubation of cells with control medium alone results in only minimal amounts of cellular ^{59}Fe release ($5 \pm 1\%$ of total cellular iron) from prelabelled SK-N-MC cells, whereas Dp44mT and CQ could mediate significantly ($p <$
15 0.001) higher amounts of ^{59}Fe release (i.e., $40 \pm 3\%$ and $42 \pm 2\%$ of total cellular iron, respectively). In contrast, the well known iron chelator, DFO, could release only moderate amounts of intracellular ^{59}Fe ($15 \pm 1\%$) from cells. Interestingly, the novel adamantane analogues (compounds 1-9) having no benzene linker mediated low to moderate levels of cellular ^{59}Fe release (5 - 19%). Among them, compounds 1 and 2
20 demonstrated the greatest activity at mobilizing ^{59}Fe , resulting in the release of $18 \pm 2\%$ and $19 \pm 1\%$ of intracellular ^{59}Fe , respectively. These results were similar to that observed with the gold-standard iron chelator, DFO, but were significantly ($p < 0.001$) less than that of Dp44mT or CQ.

In terms of compounds 10-19, 11 and 15 demonstrated marked ability to promote
25 ^{59}Fe mobilization, releasing $39 \pm 4\%$ and $36 \pm 3\%$ of total cellular ^{59}Fe , respectively. Hence, their activities were comparable ($p > 0.05$) to that of Dp44mT and CQ, but significantly ($p < 0.001$) higher than that of DFO. Interestingly, compounds 13 and 16 released $26 \pm 2\%$ and $23 \pm 2\%$ of cellular ^{59}Fe , respectively. This activity was significantly ($p < 0.01$) lower than Dp44mT and CQ, but slightly and significantly ($p <$
30 0.01) higher than DFO. Compounds 10 ($16 \pm 6\%$) and 12 ($15 \pm 2\%$) showed ^{59}Fe release that was comparable ($p > 0.05$) to that of DFO. However, compounds 14, 17, 18 and 19 resulted in less ^{59}Fe release from cells than that induced by DFO.

Compounds 20-27 having a benzene linker showed variable ^{59}Fe mobilization ranging from low to high ^{59}Fe release (6-41% of cellular Fe). Most of these compounds exhibited significantly ($p < 0.05$) higher or comparable levels of cellular ^{59}Fe release to that of DFO. Among these agents, compound 23 displayed the highest ^{59}Fe mobilization activity, releasing $40 \pm 4\%$ of cellular ^{59}Fe . Hence, this compound had comparable activity to the positive controls, Dp44mT and CQ, but significantly ($p < 0.001$) higher efficacy than DFO. In addition, analogue 22 released comparable ($p > 0.05$) levels of cellular ^{59}Fe ($16 \pm 3\%$) to that mediated by DFO. However, the analogues 24 and 25 did not mediate appreciable ^{59}Fe release relative to the control (i.e., only 6-7% of cellular ^{59}Fe).

In these ^{59}Fe release studies, the compounds 11, 15, 20, 21 and 23 were demonstrated to be the most active amongst all the novel adamantane analogues. We observed no linear relationship ($R^2 < 0.3$) between ^{59}Fe release and anti-proliferative activity (i.e., IC_{50} values). Hence, cellular Fe release mediated by these compounds may not be an important factor in terms of the anti-proliferative activity observed (Table 2 below).

Effect of Compounds 1-27 at Preventing Cellular ^{59}Fe Uptake

Iron uptake into brain cells is predominantly mediated by the binding of the blood iron transport protein, transferrin ($\text{Fe}_2\text{-Tf}$), to the transferrin receptor 1 (TfR1).¹⁶ Considering the increased levels of iron in AD,¹¹ inhibition of iron uptake from transferrin by iron chelators would be a beneficial strategy for the treatment of AD. This is suggested by positive results in the treatment of this condition using a number of different chelators, such as DFO, CQ and PBT2, in clinical trials.¹⁷ The potency of the novel adamantane based chelators (compounds 1-27) at inhibiting ^{59}Fe uptake from the iron transport protein, $^{59}\text{Fe}_2\text{-Tf}$, was compared with the positive control chelators, Dp44mT, DFO and CQ. The results are shown in Figure 2.

As described previously, the positive control, Dp44mT, effectively inhibited ^{59}Fe uptake from $^{59}\text{Fe}_2\text{-Tf}$ to $6 \pm 1\%$ of the control.¹⁵ On the other hand, the classical chelator, DFO, showed markedly less activity compared to Dp44mT, as demonstrated previously,⁵ reducing ^{59}Fe uptake from $\text{Fe}_2\text{-Tf}$ to $85 \pm 4\%$ of the control. Another iron chelator, CQ, also significantly ($p < 0.001$) inhibited ^{59}Fe uptake to $26 \pm 6\%$ of the control. As displayed in Figure 2, compounds 1-9 were found to be less effective than

positive controls, Dp44mT and CQ. However, some compounds, including 1 and 2, were found to be significantly ($p < 0.01-0.05$) more effective than DFO at preventing ^{59}Fe uptake to $60 \pm 8\%$ and $41 \pm 4\%$ of the control, respectively.

In terms of compounds 10-19, agents 11, 13 and 15 showed significantly ($p < 0.001-0.01$) higher efficacy than DFO by reducing ^{59}Fe uptake to $29 \pm 5\%$, $59 \pm 7\%$ and $45 \pm 4\%$ of the control, respectively. Compounds 20-27 having a benzene linker showed a diverse response ranging from low to high activity (19-95% of the control) at inhibiting ^{59}Fe uptake from $^{59}\text{Fe}_2\text{-Tf}$. Compounds 22, 24, 25, 26 and 27 displayed low activity at inhibiting ^{59}Fe uptake, but were comparable ($p > 0.05$) to DFO. As shown in Figure 2, compounds 20 and 21 moderately reduced ^{59}Fe uptake to $46 \pm 5\%$ and $66 \pm 2\%$ of the control, respectively, which was significantly ($p < 0.01$) more effective than DFO. Among all novel adamantane compounds tested here, compound 23 exhibited the greatest ability to inhibit ^{59}Fe uptake from $^{59}\text{Fe}_2\text{-Tf}$, reducing it to 19% of the control. This activity was similar to that exhibited by CQ, but significantly ($p < 0.001$) higher than DFO.

In summary, compounds 2, 11, 15, 20 and 23 were found to be the best among all adamantane analogues in terms of reducing ^{59}Fe uptake from $^{59}\text{Fe}_2\text{-Tf}$. However, as demonstrated for ^{59}Fe efflux, no linear correlation ($R^2 < 0.3$) was observed between the inhibition of ^{59}Fe uptake and cellular proliferation (IC_{50} ; Table 2). This suggests that the inhibition of ^{59}Fe uptake by these compounds may not be the major factor affecting cellular proliferation.

Effect of Compounds 1-27 on Cellular Proliferation

The human SK-N-MC neuroepithelioma cell line was chosen for these initial cellular proliferation studies as it is a neural cell line that has been used as a preliminary model for AD.^{20,21} Furthermore, it is a well characterised cell line for examining the effect of iron chelating agents.^{3,22-24} For comparison, the well-known iron chelators, DFO and Dp44mT, were included, as their anti-proliferative activity is well described in this cell-type.^{4,15} In these studies, Dp44mT and DFO displayed IC_{50} values of $0.007 \pm 0.001 \mu\text{M}$ and $16.60 \pm 1.32 \mu\text{M}$, respectively (Table 2). Compounds 8, 9, 10, 17 and 24, demonstrated very low anti-proliferative activity and had IC_{50} values greater than $100 \mu\text{M}$. In contrast, all the other analogues decreased cellular viability in a dose-dependent manner with IC_{50} values ranging from $0.07-77.9 \mu\text{M}$. Notably, compounds 1-9 and 20-27 are semicarbazones and hydrazones, respectively, and showed generally low anti-

proliferative activity, with IC₅₀ values that ranged between 1.96-77.9 µM (Table 2). On the other hand, thiosemicarbazone compounds 10-19 showed a wide range of activity, having IC₅₀ values ranging from 0.07 to >100 µM. Compound 19 was somewhat atypical and showed the highest anti-proliferative activity of 0.07 µM (Table 2).

5

Relative to the positive control compounds (Table 2), eleven of the twenty-seven adamantane compounds exhibited relatively less cytotoxicity (IC₅₀ = 21.08–100 µM) than DFO (16.6 µM) and Dp44mT (0.007 µM). In fact, the activity of these eleven adamantane analogues was at least 0.2–5.0-fold and 3000-14,000-fold less cytotoxic than DFO and Dp44mT, respectively. Sixteen other compounds were relatively more cytotoxic than DFO, but significantly ($p < 0.001$) less cytotoxic than Dp44mT.

In summary, of the adamantane analogues, compounds 8, 9, 10, 17 and 24 did not cause 50% of cell death even at the highest concentration employed (100 µM), suggesting that these compounds were relatively non-toxic, and thus, are compatible for treatment of neural cells.

15

Table 2. Cytotoxicity of compounds 1-27 Against SK-N-MC Neuroepithelioma Cells as Determined by the MTT Assay. Results are mean $\pm$ SD (3 experiments).

Compound	IC ₅₀ (µM)
Dp44mT	0.007 $\pm$ 0.001
DFO	16.60 $\pm$ 1.32
1	77.87 $\pm$ 2.62
2	23.43 $\pm$ 2.81
3	5.96 $\pm$ 0.25
4	63.41 $\pm$ 5.92
5	28.23 $\pm$ 1.87
6	10.07 $\pm$ 0.85
7	8.29 $\pm$ 1.08
8	>100
9	>100
10	>100
11	6.40 $\pm$ 1.94
12	3.05 $\pm$ 1.08
13	0.15 $\pm$ 0.02
14	2.71 $\pm$ 0.95
15	8.08 $\pm$ 2.66
16	5.01 $\pm$ 0.75
17	>100
18	0.87 $\pm$ 0.15
19	0.07 $\pm$ 0.02

Compound	IC ₅₀ (μM)
20	10.19 ± 1.91
21	7.03 ± 0.86
22	1.96 ± 0.40
23	40.24 ± 4.86
24	>100
25	21.08 ± 2.73
26	8.01 ± 1.09
27	14.30 ± 3.67

Acetylcholinesterase (AChE) inhibition assay

Since acetylcholinesterase (AChE) is considered as a viable therapeutic target for the symptomatic improvement in AD with several agents already being utilized in the clinics²⁵, we evaluated *in vitro* inhibitory activities of all novel compounds 1-27 against isolated AChE. In these studies, the activities of the adamantane analogues were compared with the well-known AChE inhibitors, tacrine and donepezil, which were used as positive controls.²⁶ The inhibition of AChE was expressed as IC₅₀ values in Table 3.

As expected, the positive controls, tacrine and donepezil, showed potent inhibition of AChE with the IC₅₀ values of 0.13 ± 0.02 μM and 0.07 ± 0.01 μM, respectively. All novel compounds, except 10 and 24, showed very low inhibitory activity when tested at 50 μM. Unfortunately, precipitation of these agents at higher concentrations prevented the determination of their IC₅₀ values. Among all analogues, compounds 10 and 24 displayed moderate and dose dependent inhibitory activity with IC₅₀ values of 13 ± 2 μM and 31 ± 2 μM, respectively. In summary, this study demonstrated that compounds 10 and 24 have the potential to act as mild AChE inhibitors.

Table 3. *In vitro* Acetylcholinesterase Inhibition Assay Results for compounds 1-27. Results are mean or mean $\pm$ SD (3 experiments).

Compound	IC ₅₀ (μ M)
1	> 50
2	> 50
3	> 50
4	> 50
5	> 50
6	> 50
7	> 50
8	> 50
9	> 50
10	13 $\pm$ 2
11	> 50
12	> 50
13	> 50
14	> 50
15	> 50
16	> 50
17	> 50
18	> 50
19	> 50
20	> 50
21	> 50
22	> 50
23	> 50
24	31 $\pm$ 2
25	> 50
26	> 50
27	> 50

Ascorbate oxidation

5 Metal-promoted oxidative stress is thought to be significant in the pathogenesis of AD particularly considering the high concentration of metal ions in β -amyloid plaques, i.e., concentrations $\sim$ 1 mM.²⁷ Therefore, the assessment of the anti-oxidant activity of the adamantane analogues is essential in terms of their development as new drugs for AD treatment.²⁸ To examine this property, the Fe(III) complexes of the adamantane
10 analogues were assessed in terms of their activity to catalyse ascorbate oxidation *via* iron-mediated Fenton chemistry.^{3,9} In these studies, ascorbate was used as a substrate

because of its abundance in neurons and its strong anti-oxidant potential to protect these cells from oxidative stress.²⁹⁻³¹ For comparison, the well-known, redox-active and redox-inactive Fe(III) complexes of EDTA and DFO were included as positive and negative controls, respectively. The results are shown in Figure 3.

5 In accordance with previously published results,^{30,31} the EDTA iron complex markedly accelerated the oxidation of ascorbate to 436% of the control. In contrast, the redox inactive Fe(III)-DFO complex significantly ($p < 0.001$) reduced ascorbate oxidation, decreasing to 17% relative to the control, confirming its anti-oxidative behaviour.

10 Interestingly, none of the iron complexes derived from compounds 1-8 and 20-27 showed increased ascorbate oxidation. However, many of these compounds significantly ($p < 0.001$) inhibited ascorbate oxidation relative to the control. Notably, the iron(III) complexes of compounds 1, 25 and 26 did not display marked ascorbate oxidation with activities that were comparable to the control (100%). In conclusion, this
15 study demonstrated that all the adamantane analogues form redox inactive Fe complexes and have appropriate properties for AD treatment.

Inhibition of Cu(II)-Mediated A β ₁₋₄₀ Aggregation

Senile plaque formation associated with A β aggregation is a common hallmark of AD,³⁴ where the presence of trace of metal ions, particularly Cu(II), has been found to
20 accelerate the aggregation process.³⁵ Thus, chelation therapy has been proposed to be a beneficial strategy to sequester such metal ions, and thus, reverse the aggregation process.³⁵ To investigate whether the adamantane compounds could inhibit Cu(II)-mediated aggregation of A β , the turbidity assay was utilised.¹¹ In this assay, the A β ₁₋₄₀ isoform was investigated due to its high abundance in cerebrospinal fluid.¹¹ The assay
25 was carried out by incubating equimolar (25 μ M) amounts of A β ₁₋₄₀ and Cu(II) in the presence or absence of selected adamantane ligands (25 μ M) in HEPES buffer (pH 6.6) for 1 h. The assay was performed at mildly acidic conditions (pH 6.6) because Cu(II) can promote A β aggregation at this pH,³⁶ as well as to mimic the acidosis conditions found in the cerebrum of AD brains.³⁷ Copper chelators, such diethylenetriamine
30 pentaacetic acid (DTPA) and Dp44mT, were included as positive controls.¹¹

As shown in Figure 4, co-incubation of Cu(II) with A β ₁₋₄₀ significantly ($p < 0.001$) enhanced A β ₁₋₄₀ aggregation with respect to A β ₁₋₄₀ alone. Both positive controls, DTPA and Dp44mT, significantly ($p < 0.001$) inhibited Cu(II)-mediated A β ₁₋₄₀ aggregation. All novel adamantane compounds examined showed significant ($p < 0.001$) inhibition of Cu(II)-mediated A β ₁₋₄₀ aggregation. As these adamantane compounds successfully inhibited Cu(II)-mediated A β ₁₋₄₀ aggregation, they demonstrated therapeutic potential for AD treatment.

NMDAR and VGCC Inhibition

As NMDAR-mediated calcium influx increases intracellular calcium levels and leads to excitotoxicity in AD,¹² we screened selected adamantane compounds for their inhibitory activity on NMDAR in human astrocytes using a reported protocol.¹² Both memantine and MK-801, which are NMDAR antagonist, were utilized as positive controls, while nimodipine (NIMO), that acts selectively as an antagonist for VGCC, was used as a negative control.¹² The results are shown in Figure 5.

As previously reported,¹² both MK-801 and memantine showed potential inhibition of NMDAR-mediated calcium influx. However, NIMO, a VGCC antagonist, did not show any inhibitory effects against NMDAR-mediated calcium influx. Interestingly, the selected adamantane compounds examined showed similar or decreased inhibition of NMDAR-mediated calcium influx compared to memantine. The inhibition activity of 1, 2, 11, 13 and 15 were found to be significantly ($p < 0.001-0.05$) lower than both memantine and MK-801. On the other hand, compounds 20, 21, 23 and 24 exhibited comparable activity to memantine, but significantly ($p < 0.01-0.05$) decreased activity relative to MK-801.

To further assess the selectivity of these adamantane agents, their ability to inhibit VGCC was examined. The results are shown in Figure 6. Human astrocytes were incubated with selected adamantane compounds (25 μ M) in the presence of KCl that activates VGCC for calcium influx. In these experiments, NIMO was used as positive control, while memantine and MK-801 were included as negative controls. As previously reported, NIMO potently inhibited VGCC-mediated calcium influx, whereas MK-801 and memantine did not show any inhibitory effects. The selected adamantane analogues examined showed significantly ($p < 0.001$) decreased inhibition of VGCC compared to

NIMO. Amongst all analogues, 13 and 15 showed moderate inhibition of VGCC-mediated calcium influx (31% and 39%, respectively).

In summary compounds 20, 21, 23 and 24 showed potential to act as NMDAR antagonists to inhibit Ca-mediated excitotoxicity in AD.

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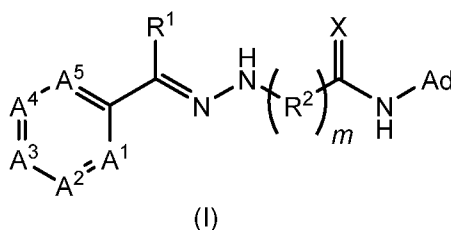
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CLAIMS

1. A compound of formula (I):

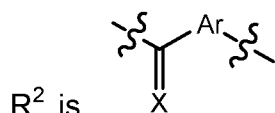


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

- 5 Ad is an adamantane moiety,

X is selected from O and S,

m is 0 or 1,



- 10 R^1 is selected from H, alkyl and heteroaryl,

A^1 , A^2 , A^3 , A^4 and A^5 are independently selected from CH and N, and

the aromatic ring containing A^1 , A^2 , A^3 , A^4 and A^5 is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group.

- 15 2. The compound of claim 1, wherein *m* is 0.
3. The compound of claim 1, wherein *m* is 1.
4. The compound of claim 1 or claim 3, wherein Ar is a 5- or 6-membered aryl or heteroaryl group.
5. The compound of claim 4, wherein Ar is a 6-membered aryl group.
- 20 6. The compound of any one of claims 1 or 3 to 5, wherein Ar is not substituted.
7. The compound of any one of the preceding claims, wherein R^1 is H.
8. The compound of any one of claims 1 to 6, wherein R^1 is C_1 to C_3 alkyl.

9. The compound of claim 8, wherein R¹ is methyl, ethyl or propyl.
10. The compound of any one of claims 1 to 3, wherein R¹ is a heteroaryl group.
11. The compound of claim 10, wherein R¹ is pyridine.
- 5 12. The compound of any one of the preceding claims, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted.
13. The compound of claim 12, wherein at least one substituent is OH.
14. The compound of claim 13, wherein one or more of A¹, A², A³, A⁴ and A⁵ is C-OH.
- 10 15. The compound of claim 13 or claim 14, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with one or more additional substituents.
16. The compound of claim 15, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with one additional substituent.
17. The compound of claim 16, wherein the one additional substituent is OH.
- 15 18. The compound of claim 15, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is substituted with two additional substituents.
19. The compound of claim 18, wherein the two additional substituents are different to each other.
20. The compound of claim 18, wherein the two additional substituents are the
20 same as each other.
21. The compound of any one of claims 18 to 20, wherein the two additional substituents are selected from OH, an alkyl group and a heteroalkyl group.
22. The compound of any one of the preceding claims, wherein one of A¹, A², A³, A⁴ and A⁵ is N to give a heteroaryl group.
- 25 23. The compound of claim 22, wherein the heteroaryl group is substituted with one or more substituents.
24. The compound of claim 23, wherein the one or more substituents are independently selected from OH, an alkyl group and a heteroalkyl group.
25. The compound of claim 24, wherein the alkyl group is methyl or ethyl.

26. The compound of claim 24, wherein the heteroalkyl group is CH₂OH or CH₂CH₂OH.

27. The compound of any one of the preceding claims, wherein A¹ is selected from N and C-OH.

5 28. The compound of claim 27, wherein A¹ is C-OH.

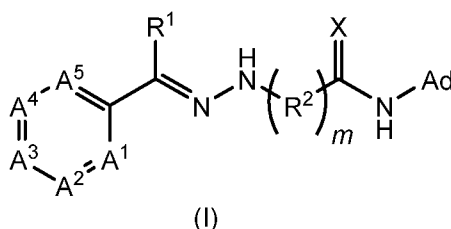
29. The compound of any one of the preceding claims, wherein the aromatic ring containing A¹, A², A³, A⁴ and A⁵ is fused to an aryl group to give a bicyclic aryl or heteroaryl group.

30. The compound of claim 29, wherein the bicyclic aryl or heteroaryl group is
10 naphthyl or quinoline.

31. The compound of claim 29 or claim 30, wherein the bicyclic aryl or heteroaryl group is substituted by one or more substituents selected from OH, alkyl and heteroalkyl.

32. The compound of any one of claims 29 to 31, wherein the aromatic ring
15 containing A¹, A², A³, A⁴ and A⁵ is fused to the aryl group at A² and A³ or A⁴ and A⁵.

33. A pharmaceutical composition including a compound of formula (I):

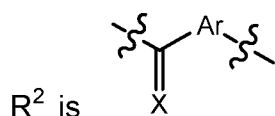


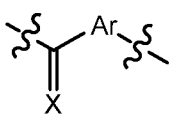
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ad is an adamantane moiety,

20 X is selected from O and S,

m is 0 or 1,



R² is , wherein Ar is selected from aryl and heteroaryl, which aryl and heteroaryl groups are optionally substituted,

R¹ is selected from H, alkyl and heteroaryl,

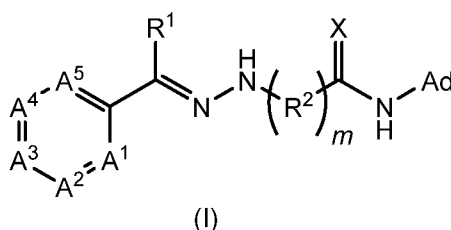
A^1 , A^2 , A^3 , A^4 and A^5 are independently selected from CH and N, and

the aromatic ring containing A^1 , A^2 , A^3 , A^4 and A^5 is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group,

5 together with a pharmaceutically acceptable carrier, diluent or excipient.

34. The pharmaceutical composition of claim 33, wherein the composition is suitable for parenteral or oral administration.

35. A method of treating and/or preventing a neurodegenerative disease in a subject, the method including administering to the subject an effective amount of a
10 compound of formula (I):

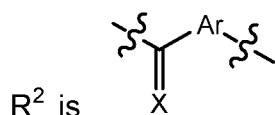


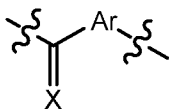
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ad is an adamantane moiety,

X is selected from O and S,

15 m is 0 or 1,



R^2 is , wherein Ar is selected from aryl and heteroaryl, which aryl and heteroaryl groups are optionally substituted,

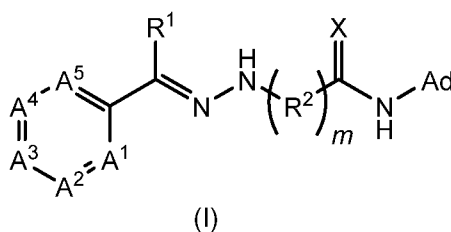
R^1 is selected from H, alkyl and heteroaryl,

A^1 , A^2 , A^3 , A^4 and A^5 are independently selected from CH and N, and

20 the aromatic ring containing A^1 , A^2 , A^3 , A^4 and A^5 is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group.

36. The method of claim 35, wherein the administration is selected from parenteral or oral administration.

37. Use of an effective amount of a compound of formula (I):

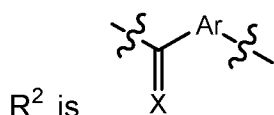


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ad is an adamantane moiety,

5 X is selected from O and S,

m is 0 or 1,



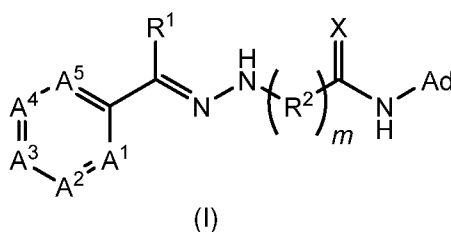
R^1 is selected from H, alkyl and heteroaryl,

10 A^1 , A^2 , A^3 , A^4 and A^5 are independently selected from CH and N, and

the aromatic ring containing A^1 , A^2 , A^3 , A^4 and A^5 is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group,

15 in the preparation of a medicament for the treatment of a neurodegenerative disorder.

38. Use of an effective amount of a compound of formula (I):

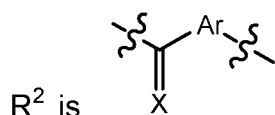


or a pharmaceutically acceptable salt or prodrug thereof, wherein:

Ad is an adamantane moiety,

20 X is selected from O and S,

m is 0 or 1,



R^1 is selected from H, alkyl and heteroaryl,

5 A^1 , A^2 , A^3 , A^4 and A^5 are independently selected from CH and N, and

the aromatic ring containing A^1 , A^2 , A^3 , A^4 and A^5 is optionally substituted with one or more substituents independently selected from halogen, OH, alkyl and heteroalkyl, and is optionally fused to an aryl group,

for the treatment of a neurodegenerative disorder.

10 39. The method of claim 35 or claim 36, or the use of claim 37 or claim 38, wherein the neurodegenerative disease is selected from dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease and Friedrich's ataxia.

Figure 1

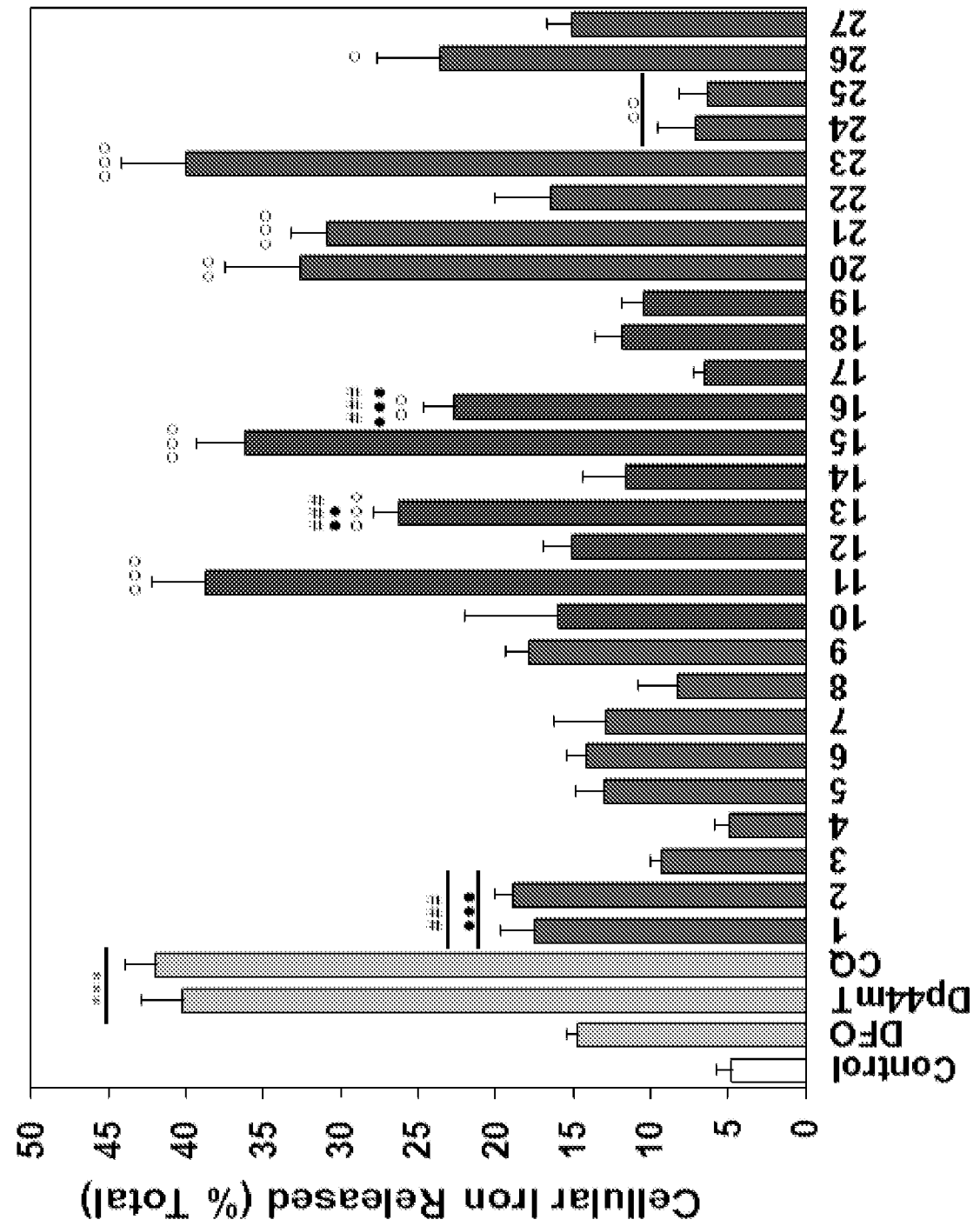


Figure 2

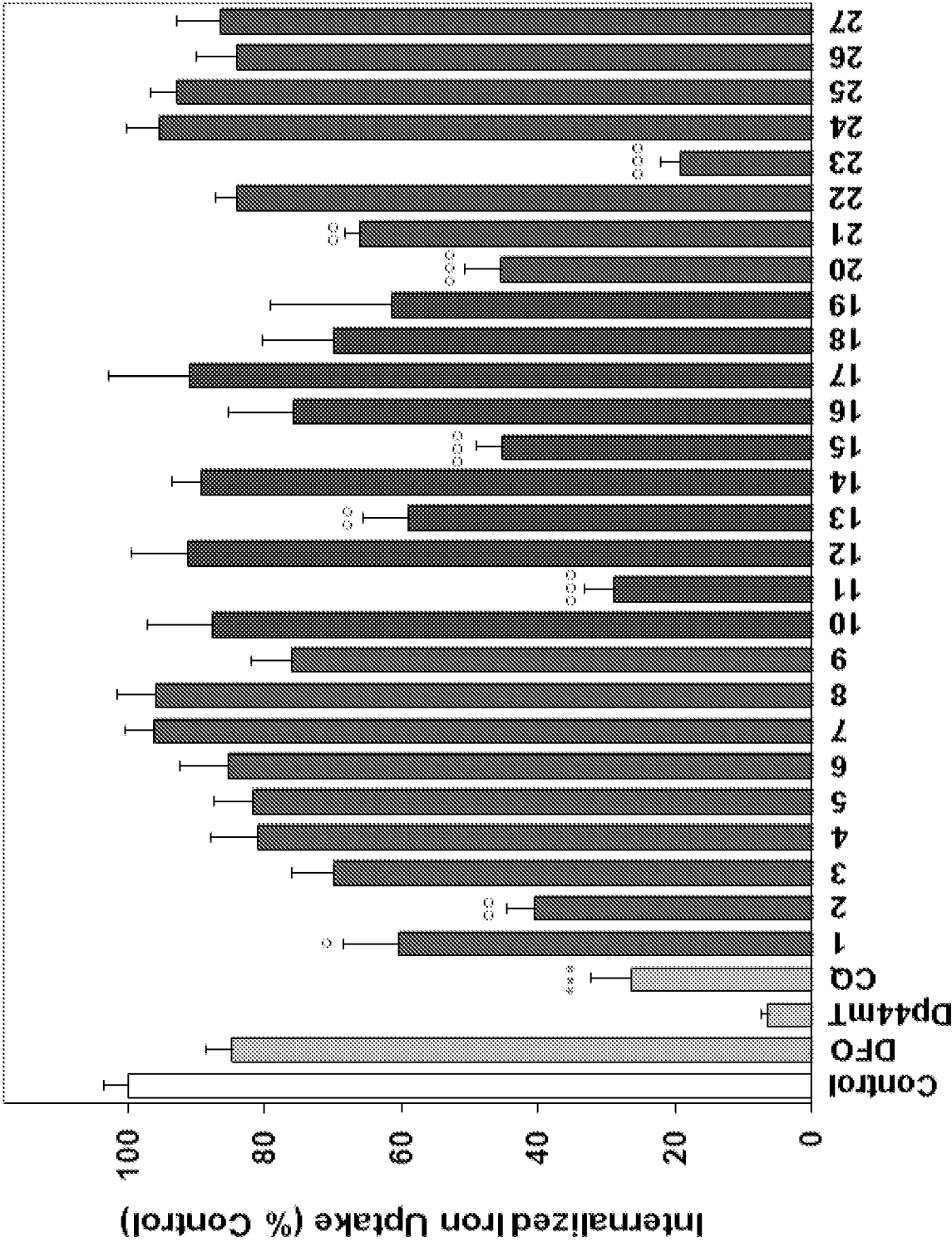


Figure 3

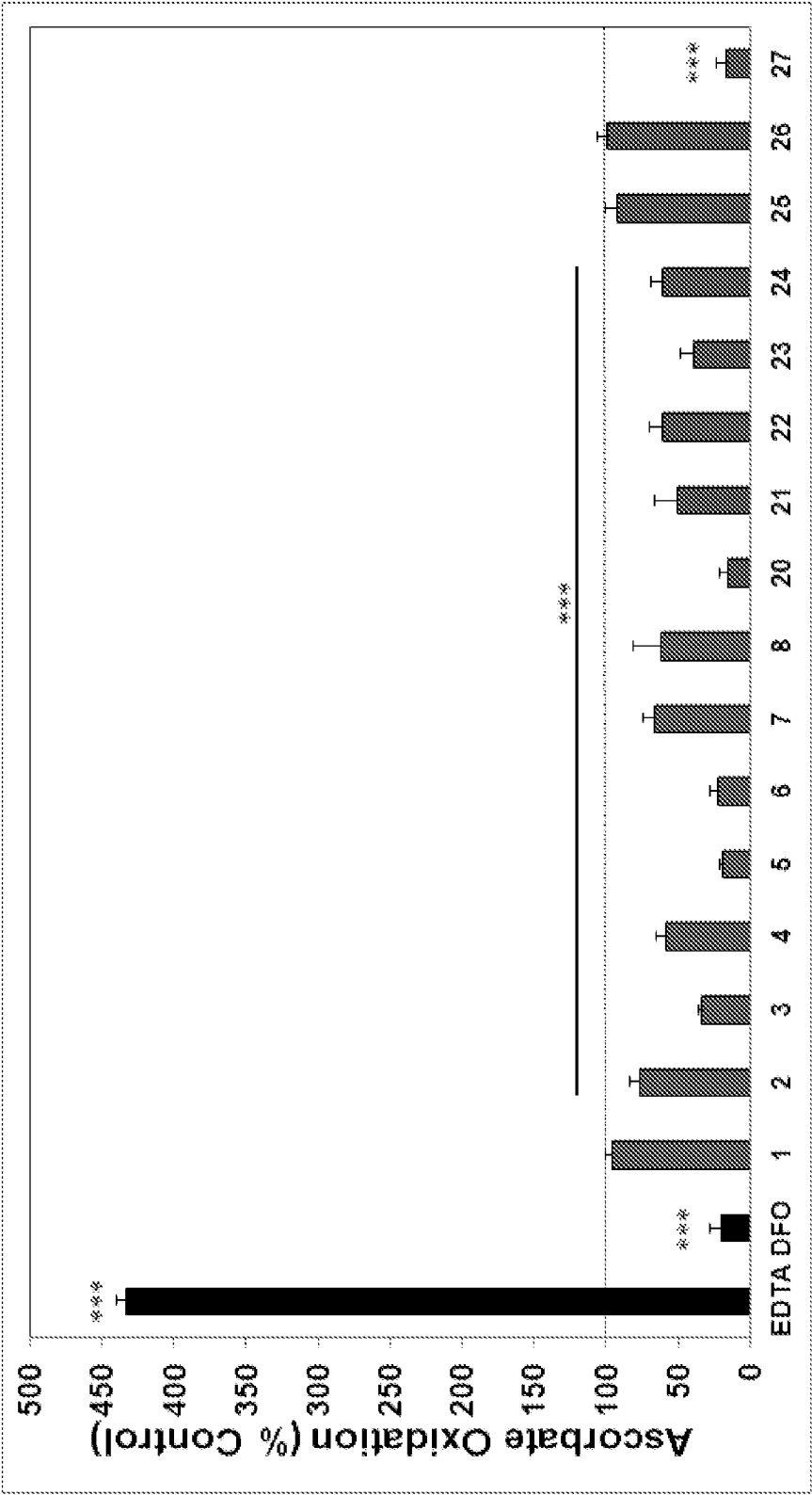


Figure 4

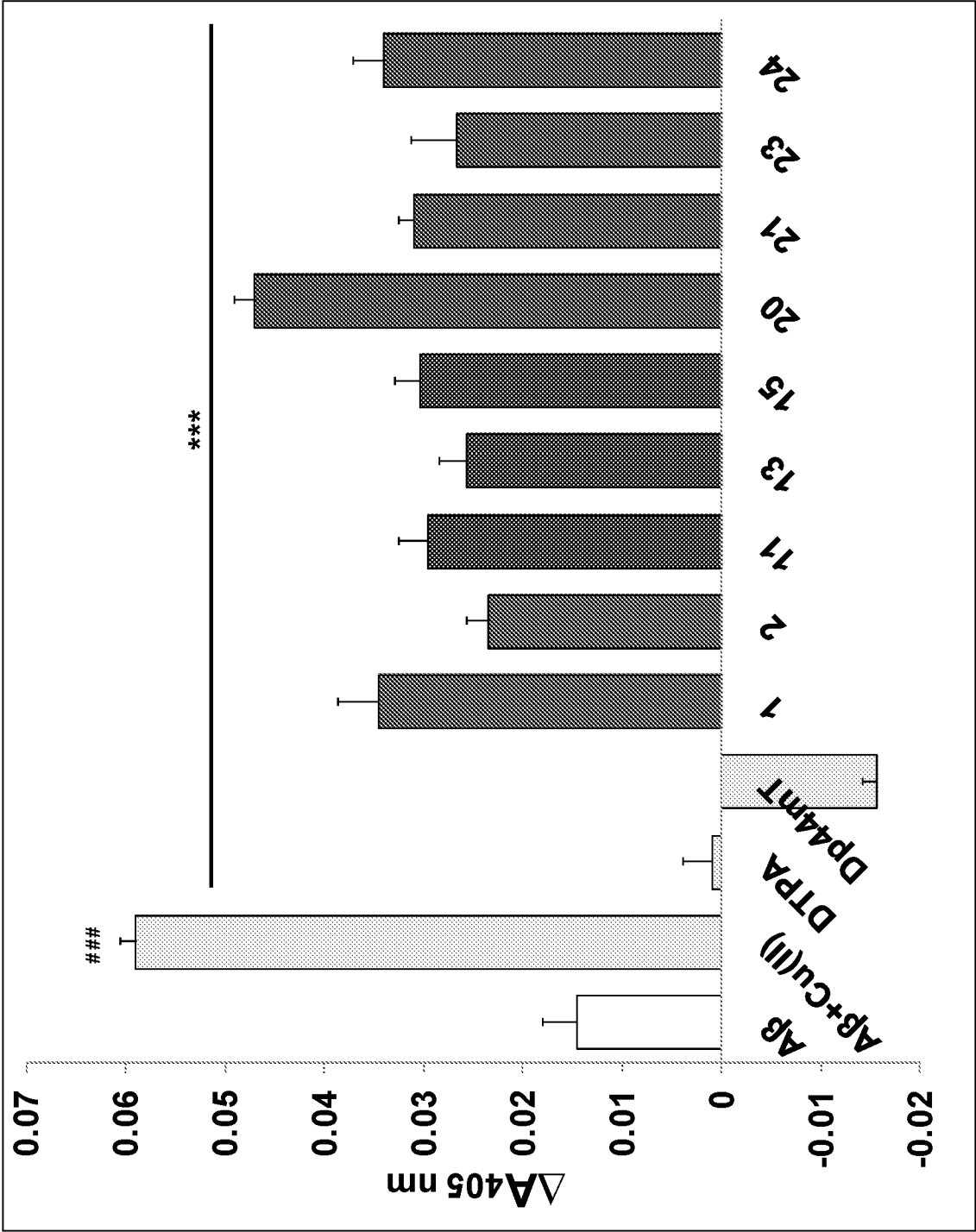


Figure 5

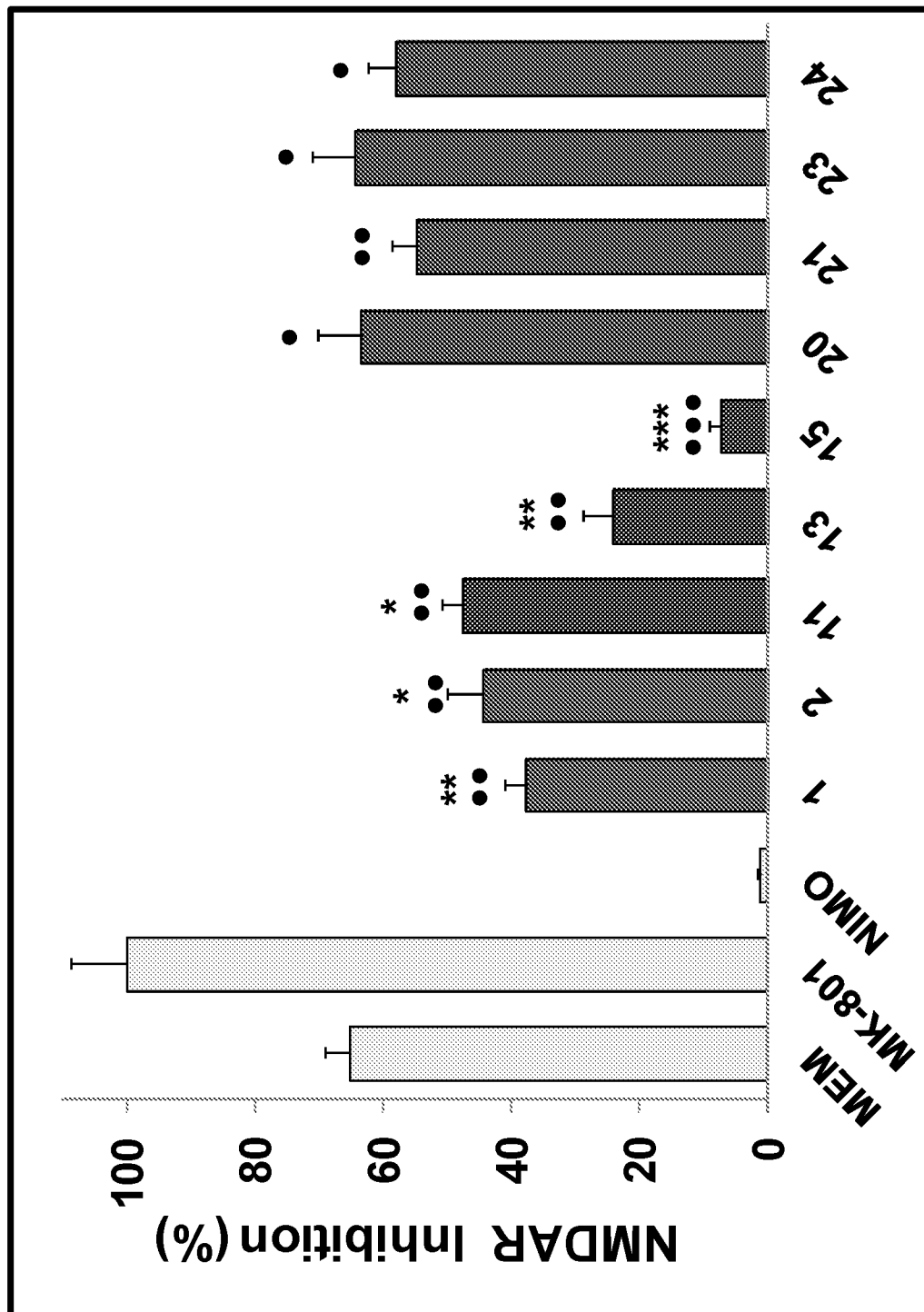
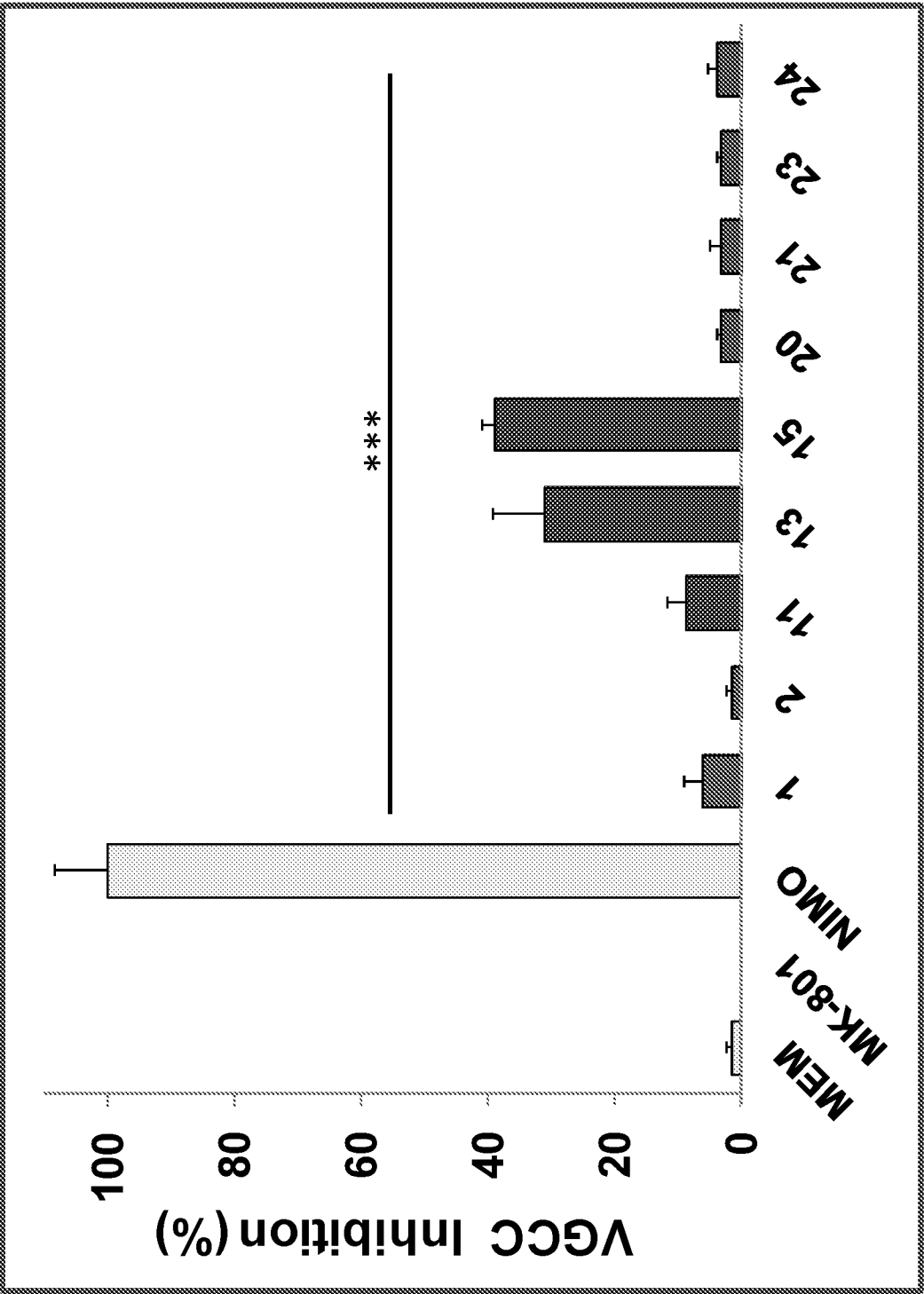


Figure 6



INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2017/050604

A. CLASSIFICATION OF SUBJECT MATTER

C07C 281/08 (2006.01) C07C 337/08 (2006.01) C07C 251/24 (2006.01) C07D 215/12 (2006.01) C07D 215/26 (2006.01)
C07D 213/65 (2006.01) C07D 213/53 (2006.01) A61K 31/175 (2006.01) A61K 31/4704 (2006.01)
A61K 31/4402 (2006.01) A61K 31/166 (2006.01) A61K 31/44 (2006.01)

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)

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)

STN: Chemical Abstracts Registry and CAPLUS - Substructure searches based on compounds of formula (I).

Patentscope: Applicant search with IPC marks C07D and C07C. Inventor search with IPC marks C07D and C07C.

Espacenet: Applicant search with IPC marks C07D and C07C and keywords adamantane or adamantyl or semicarbazone or thiosemicarbazone. Inventor search with IPC marks C07D or C07C.

Applicant/ Inventors names were also searched in internal databases provided by IP Australia.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"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
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Date of the actual completion of the international search 9 August 2017		Date of mailing of the international search report 09 August 2017	
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustalia.gov.au		Authorised officer James Cochrane AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262256192	

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2017/050604
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	B. PRESCOTT et al., "4-(1-Adamantyl)-3-Thiosemicarbazones as Potential Chemotherapeutic Agents." Antimicrobial Agents and Chemotherapy, 1969, Vol. 9, pp. 275-279. Abstract; p.277, compounds listed in Table 1; and p. 278, Table 2 and column 2, lines 15-37.	1, 2, 7, 12-16, 18, 20-21 and 27-34
X	D. L. KLAYMAN et al., "2-Acetylpyridine Thiosemicarbazones. 1. A New Class of Potential Antimalarial Agents." Journal of Medicinal Chemistry, 1979, Vol. 22, No. 7, pp. 855-862. Abstract; p. 856-857, compound 57, Table 1; p. 858, compound 84, Table 2; p.860-861, compounds 119-129 and 131-133, Table 3; and p. 859, Biological Method.	1, 2, 7-12, 22-24, 27, 33 and 34
X	N. GOKHALE et al., "Synthesis And Evaluation Of Novel Thiosemicarbazone Derivatives As Anticancer Agents." International Journal of Pharmaceutical Sciences and Research, 2015, Vol. 6, Issue 4, pp. 1792-1804. Abstract; compounds TSC-6, TSC-12 and TSC-15 (Table, 2, p.1801-1802); pharmaceutical compositions (Tables 3 and 4, p. 1803).	1, 2, 7, 12, 22-23, 29, 30, 32 and 33
X	US 4,440,771 A (Scovill et al.) 03 April 1984 Abstract; claims 1, 2, 17, 28, 35, 41 and 47, in particular the formula disclosed therein.	1, 2, 8-9, 27, 29, 32 and 33-34
X	US 3,406,180 A (Sallay et al.) 15 October 1968 Abstract; column 4, Example VII, N-adamantany-2-benzylidenehydrazine-1-carbothioamide, lines 60-69 and claim 11.	1, 2, 7 and 33-34
X	V. OPLETALOVA et al., "Thiosemicarbazones and their antimycobacterial effects." Ceska a Slovenska Farmacie, 2013, Vol. 62(2), pp.78-83. Abstract; compound 6o (N-adamantan-1-yl-2-(1-(pyrazin-2-yl)ethylidene)hydrazine-1-carbothioamide) (p. 80, Fig 3); Experimental part (p. 81, lines 1-27).	1, 2, 8, 9, 22 and 33
X	JP 54119029 A (Meiji Seika Kaisha Ltd.) 14 September 1979 Abstract; compounds 4 (N-adamantany-2-benzylidenehydrazine-1-carbothioamide) and 18 (N-adamantan-1-yl-2-(1-phenylethylidene)hydrazine-1-carbothioamide) (Table 1, p 176); pharmaceutical compositions are also disclosed (abstract, Tables 2-4, p. 178-180).	1, 2, 7-9 and 33-34
X	CAS RN 348586-31-2; STN entry date: 26 Jul 2001; 2-[(2,4-dihydroxyphenyl)methylene]-N-tricyclo[3.3.1.1 ^{3,7}]dec-1-yl-hydrazinecarboxamide. Whole document.	1, 2, 7, 12-17 and 27-28
X	351329-68-5; STN entry date: 14 Aug Dec 2001; 2-[(4-hydroxy-3,5-dimethoxyphenyl)methylene]-N-tricyclo[3.3.1.1 ^{3,7}]dec-1-yl-hydrazinecarboxamide Whole document.	1, 2, 7, 12-15, 18, 20 and 21
X	CAS RN: 327104-85-8; STN entry date: 14 Mar 2001; 2-[[3-hydroxy-6-(hydroxymethyl)-2-methyl-4-pyridinyl]methylene]-N-tricyclo[3.3.1.1 ^{3,7}]dec-1-yl-hydrazinecarboxamide. Whole document.	1, 2, 7, 12-15, 18-19 and 21-28
Form PCT/ISA/210 (fifth sheet) (July 2009)		

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/AU2017/050604	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 4,440,771 A	03 April 1984	US 4440771 A	03 Apr 1984
US 3,406,180 A	15 October 1968	US 3406180 A	15 Oct 1968
JP 54119029 A	14 September 1979	None	
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2009)			