Anavex 1-41 (1-(5,5-diphenyltetrahydrofuran-3-yl)-N,N-dimethylmethanamine hydrochloride) presents a mixed pharmacological activity involving the modulation of both sigma-1 and muscarinic components showing prominent anti-amnesic, anti-depressant at low sigma-1 agonistic doses. In addition, it presents mixed pharmacological activity involving the modulation of sodium and chloride channels.

Donepezil ((RS)-2-[(1-benzyl-4-piperidyl)methyl]- 5,6-dimethoxy-2,3-dihydroinden-1-one) is an acetylcholine esterase inhibitor having non-selective sigma-1 agonistic activity. Donepezil is also an agonist of muscarinic and nicotinic receptors, and is a marketed drug used in the palliative treatment of Alzheimer's disease.

Other molecules having Sig-1R affinity are known but they either lack subtype selectivity over Sig-2R or they have high affinity for other receptors sites as do Anavex 1-41 and 2-73, and donepezil.

Drugs having poor selectivity (*i.e.* modulating the activity of multiple receptors) are more susceptible to inducing deleterious side effects, in particular to patients who are already under other medications.

There is therefore still a need for new selective modulators, especially agonists, of sigma-1 receptor activity of therapeutic value for the treatment and/or prevention of sigma-1 receptor related diseases, especially neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic lateral sclerosis.

SUMMARY

The present disclosure encompasses compounds of general Formula I, their pharmaceutically acceptable salts and solvates as well as methods of use of such compounds or compositions comprising such compounds as modulators, especially agonists of sigma-1 receptor activity.

In one aspect, the present disclosure provides a compound of Formula I:

membered heterocyclyl group, which is fused to a 5- or 6-membered aryl group and which is optionally substituted by one or more substituents independently selected from C1-C3 alkyl, preferably methyl, and wherein the resulting heterocyclic moiety is optionally substituted by one or more substituents independently selected from halogen, preferably fluoro.

In one embodiment, the compound of Formula I is not one, more or all of the following:

N-[3-[benzyl(methyl)amino]propyl]-4-chlorobenzamide;

N-[3-[benzyl(methyl)amino]propyl]benzamide;

N-[3-[benzyl(methyl)amino]propyl]-4-fluorobenzamide;

N-[3-[benzyl(methyl)amino]propyl]-4-bromobenzamide;

N-[3-[benzyl(methyl)amino]propyl]-4-methoxybenzamide;

N'-benzyl-N-[(4-chlorophenyl)methyl]-N'-methylpropane-1,3-diamine; and

N-[3-[benzyl(methyl)amino]propyl]-4-chlorobenzenesulfonamide.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as disclosed herein or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

In another aspect, the present disclosure provides a compound as disclosed herein or a pharmaceutically acceptable salt or solvate thereof for use as a medicament.

The present disclosure also relates to the use of the above compounds or their pharmaceutically acceptable salts and solvates as modulators of sigma-1 receptor activity, preferably as agonists of sigma-1 receptors.

The present disclosure further provides the use of a compound according to the present disclosure or a pharmaceutically acceptable salt or solvate thereof as a medicament. Preferably, the medicament is used for the treatment

and/or prevention of sigma-1 related diseases.

In yet another aspect, the present disclosure provides a use of a compound as disclosed herein or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating and/or preventing a sigma-1 receptor related disease.

In a further aspect, the present disclosure provides a use of a compound as disclosed herein or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the diagnosis of a sigma-1 receptor related disease.

In another aspect, the present disclosure provides a diagnostic imaging composition comprising a compound as disclosed herein or a pharmaceutically acceptable salt or solvate thereof and at least one pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

DETAILED DESCRIPTION OF THE INVENTION