(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 October 2013 (31.10.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/160728 A1

(51) International Patent Classification:
C07D 491/06 (2006.01) *A61P 25/28* (2006.01)
C07C 233/06 (2006.01) *A61K 31/55* (2006.01)
C07C 309/73 (2006.01)

(21) International Application Number:
PCT/IB2012/052084

(22) International Filing Date:
26 April 2012 (26.04.2012)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicants *(for all designated States except US)*: **ALMA MATER STUDIORUM - UNIVERSITA' DI BOLOGNA** [IT/IT]; Via Zamboni 33, 40126 Bologna (IT). **FONDAZIONE ISTITUTO ITALIANO DI TECNOLOGIA** [IT/IT]; Via Morego 30, 16163 Genova (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CAVALLI, Andrea** [IT/IT]; Via Galletta 8/A, 40068 San Lazzaro di Savena (BO) (IT). **ROSINI, Michela** [IT/IT]; Via I. Alpi 7, 40013 Castel Maggiore (BO) (IT). **SIMONI, Elena** [IT/IT]; Via Mario Conti 53/a, 40068 San Lazzaro di Savena (BO) (IT). **REGGIANI, Angelo M.** [IT/IT]; Via Privata Palme 89, 16036 Recco (GE) (IT). **MELCHIORRE, Carlo** [IT/IT]; Via Faenza 17, 40139 Bologna (IT).

(74) Agents: **SPADARO, Marco** et al.; Cantaluppi & Partners S.r.l., Viale Della Tecnica 205, 00144 Roma (IT).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

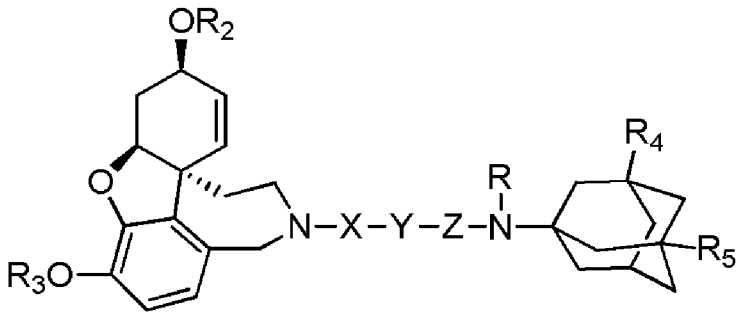
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *with amended claims and statement (Art. 19(1))*

(54) **Title**: DUAL TARGETING COMPOUNDS FOR THE TREATMENT OF ALZHEIMER'S DISEASE



(I)

(57) **Abstract**: Compounds of formula (I) wherein the groups are as defined in the description, are used as medicaments, in particular for the treatment of a disease selected from the group consisting of: cognitive impairment, memory dysfunction, neurodegenerative disorders and related dementia, Alzheimer's disease, Parkinson's disease, neuropsychiatric behavior associated with Alzheimer's disease, pain, depression, attention deficit hyperactivity disorder and for pharmacological addictive substance or intoxicant therapy; and for the neuroprotection from NMDA toxicity.

WO 2013/160728 A1

DUAL TARGETING COMPOUNDS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

The present invention refers to the field of medicinal chemistry, in particular compounds for the treatment of neurological disorders, in particular of Alzheimer's disease. More in particular, it refers to multi-target compounds obtained by the combination of Galantamine and Memantine, as well as to their preparation, their use as medicaments and compositions containing them.

BACKGROUND OF THE INVENTION

Alzheimer's disease (AD) is a progressive neurological disorder characterized by deterioration of cognitive function, dementia, memory loss, and altered behavior.

Despite massive investments by the pharmaceutical industry, there are few, if any, effective treatments for AD.

Although AD was once thought to result from a cholinergic deficit alone, it has been shown that other neurotransmitters, including dopamine, noradrenalin, serotonin, and glutamate are reduced or dysregulated in AD. Currently, the neurotransmitter systems most studied in the pathogenesis of AD are the cholinergic and the glutamatergic (Palmer, A. M.; Gershon, S. Is the neuronal basis of Alzheimer's disease cholinergic or glutamatergic? *FASEB J* **1990**, 4, 2745-52), and approved drugs for the treatment of AD are four acetylcholinesterase (AChE) inhibitors – Donepezil, Galantamine, Rivastigmine, and Tacrine (almost no longer used in the clinical practice) – and one noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, Memantine.

According to the cholinergic hypothesis of AD, the loss of cholinergic functions in the central nervous system (CNS) contributes significantly to the cognitive decline associated with AD (Bartus, R. T.; Dean, R. L., 3rd; Beer, B.; Lippa, A. S. The cholinergic hypothesis of geriatric memory dysfunction. *Science* **1982**, 217, 408-14). Moreover, although the relationship between cholinergic depletion, amyloidogenesis, and τ-phosphorylation is complex, it appears that cholinergic reduction may increase the production of β-amyloid and may induce τ-phosphorylation. On the other hand, the glutamatergic hypothesis of AD states that glutamate-related excitoxic mechanisms involving the NMDA receptor lead to neurodegeneration and cell death (Bleich, S.; Romer, K.; Wiltfang, J.; Kornhuber, J. Glutamate and the glutamate receptor system: a target for drug action. *Int J Geriatr Psychiatry* **2003**, 18, S33-40). Synaptic stimulation

through NMDA receptors is important for learning and memory functions, but excess glutamate can cause excitotoxicity and neurodegeneration (Michaels, R. L.; Rothman, S. M. Glutamate neurotoxicity in vitro: antagonist pharmacology and intracellular calcium concentrations. *J Neurosci* **1990**, 10, 283-92).

In this scenario, treatment strategies may address impairments in both systems by combining an inhibitor of the AChE enzyme, able to improve the cholinergic tone, with an NMDA receptor antagonist, able to contrast the glutamate-induced neurodegeneration. However, this combination therapy, presents some drawbacks. Other than facing the cumbersome administration of two separate drugs, which is an additional problem for elder patients affected by Alzheimer and for people caring them, different pharmacokinetics of the respective drugs can impact on different pharmacodynamic. In practice, the clinician should face and manage a combination therapy with two different ADME curves (Absorption Distribution Metabolism Excretion).

An innovative alternative to cumbersome drug combinations are drugs that can hit multiple targets – the so-called multitarget drugs (MTD).

The strategy of targeting two or more proteins at the same time with a single compound can provide therapeutic effects superior to those of a selective drug (Cavalli, A.; Bolognesi, M. L.; Minarini, A.; Rosini, M.; Tumiatti, V.; Recanatini, M.; Melchiorre, C. Multi-target-directed ligands to combat neurodegenerative diseases. J Med Chem 2008, 51, 347-72; Zimmermann, G. R.; Lehar, J.; Keith, C. T. Multi-target therapeutics: when the whole is greater than the sum of the parts. Drug Discov Today 2007, 12, 34-42; Morphy, R.; Rankovic, Z. Fragments, network biology and designing multiple ligands. Drug Discov Today 2007, 12, 156-60; Hopkins, A. L. Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol 2008, 4, 682-90). This can be explained by the number of potential benefits offered by the use of MTDs over cocktails or multicomponent drugs. The advantages of MTDs can be summarized as follows: 1) reduced uncertainty in clinical development since predicting the pharmacokinetics of a single compound is much easier than with a drug cocktail, overcoming the problem of different bioavailability, pharmacokinetics and metabolism; 2) certainty on the pharmacodynamics; 3) improved efficacy due to the synergistic effect of simultaneously inhibiting multiple targets; 4) improved safety by decreasing the side effects related to the load of a drug cocktail (reduced risk of drug-drug interactions); this is particularly relevant for drug metabolism, where the competition of different drugs for the same

metabolic enzyme affect their toxicity. All these considerations are of particular relevance as one of the major contributions to attrition rate in drug development continues to be the drug candidate's pharmacokinetic profiling.

Another important advantage is a simplified therapeutic regimen and improved compliance, which is particularly important for elderly AD patients and their caregivers (Small, G.; Dubois, B. A review of compliance to treatment in Alzheimer's disease: potential benefits of a transdermal patch. Curr Med Res Opin 2007, 23, 2705-13). With this regard, a key issue is that AD patients are susceptible to a wide range of concomitant medical conditions (co-morbidity), including hypertension, vascular diseases, and diabetes, which can often be associated. Thus, problems associated with polypharmacy in the geriatric population have been recognized as critical in recent years. These problems primarily consist of drug interactions which occur more frequently in this population because of the co-existence of chronic disease and impaired organ functions. Two drugs that themselves are safe cannot be assumed to be safe in combination, particularly in elderly patients. It follows that the number of drugs administered simultaneously should be reduced as much as possible, since advanced age is an unpredictable risk factor for drug treatment (Turnheim, K. (2003). When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp. Geront.* 38, 843-853). As such, MTDs are strongly favored over combination therapy with respect to the complexity of interactions between polypharmacy, comorbidity, altered pharmacodynamic sensitivity, and changes in pharmacokinetics in the elderly. The clinical use of MTDs can also simplify the therapeutic regimen (Youdim, M.B., and Buccafusco, J.J. (2005). CNS Targets for multi-functional drugs in the treatment of Alzheimer's and Parkinson's diseases. *J Neural Transm* 112, 519-537). Compliance with prescribed medication regimens is essential for effective treatment. Non-compliance represents a general problem, but is especially challenging for forgetful AD patients and their caregivers (Small, G., and Dubois, B. (2007). A review of compliance to treatment in Alzheimer's disease: potential benefits of a transdermal patch. *Curr. Med. Res. Opin. 23*, 2705-2713). Consequently, a simplified MTD regimen may increase treatment adherence. All the above mentioned advantages are not available with drug cocktails.

The multitarget ligand strategy is an innovative approach to the development of novel drug candidates for the treatment of complex neurological disorders, especially in view

of the fact that the major basic processes involved in neurodegenerative diseases are multifactorial in nature (Cavalli, A.; Bolognesi, M. L.; Minarini, A.; Rosini, M.; Tumiatti, V.; Recanatini, M.; Melchiorre, C. Multi-target-directed ligands to combat neurodegenerative diseases. J Med Chem **2008**, 51, 347-72). Such a strategy is thus based on the concept that a single multifunctional compound can be deployed to hit multiple targets that cooperate in the neurodegenerative process underlying AD and other neurodegenerative diseases, and therefore would prevent unwanted compensation among interacting pathogenic pathways. Indeed, the multitarget compounds could represent a practical alternative to the use of drug combinations. Since most of the neurodegenerative mechanisms are shared by many neuronal disorders, such multitarget compounds may also be used as medications for other illnesses.

One problem connected to multitarget compounds is that many of them are inefficient in terms of their binding energy per unit of molecular weight. This is because they contain groups that are only important for one of the targets, being merely tolerated by the others. This results in an unbalanced profile (Morphy, R., and Rankovic, Z. (2007). Fragments, network biology and designing multiple ligands. *Drug Discov. Today* 12, 156-160; Morphy, R. (2006). The influence of target family and functional activity on the physicochemical properties of pre-clinical compounds. *J Med Chem* 49, 2969-2978). The consequent optimization of activities is not an easy task. In fact, a multitarget compound is to be considered as a new chemical entity, with its own pharmacological profile, therefore it's efficacy on the targets of the parent compounds is not predictable a priori, and the complete process of drug development must be faced.

Galantamine is a reversible cholinesterase inhibitor. Unlike other inhibitors, it also enhances acetylcholine transmission by sensitizing postsynaptic nicotinic receptors (possibly via α7) (Samochocki, M.; Hoffle, A.; Fehrenbacher, A.; Jostock, R.; Ludwig, J.; Christner, C.; Radina, M.; Zerlin, M.; Ullmer, C.; Pereira, E. F.; Lubbert, H.; Albuquerque, E. X.; Maelicke, A. Galantamine is an allosterically potentiating ligand of neuronal nicotinic but not of muscarinic acetylcholine receptors. *J Pharmacol Exp Ther* **2003**, 305, 1024-36). This dual action increases Galantamine's effect on cholinergic input with respect to classical AChE inhibitors, leading to increased efficacy against memory loss. Moreover, Galantamine has also been shown to augment central glutamatergic transmission via indirect action on the nicotinic receptor pathway (Santos,

M. D.; Alkondon, M.; Pereira, E. F.; Aracava, Y.; Eisenberg, H. M.; Maelicke, A.; Albuquerque, E. X. The nicotinic allosteric potentiating ligand Galantamine facilitates synaptic transmission in the mammalian central nervous system. *Mol Pharmacol* **2002**, 61, 1222-34; Moriguchi, S.; Marszalec, W.; Zhao, X.; Yeh, J. Z.; Narahashi, T. Mechanism of action of Galantamine on N-methyl-D-aspartate receptors in rat cortical neurons. *J Pharmacol Exp Ther* **2004**, 310, 933-42). Many reports have shown that activation of α7 nicotinic receptors located on presynaptic glutamatergic neurons stimulates glutamate release and increases the NMDA receptor activity on postsynaptic neurons (McGehee, D. S.; Heath, M. J.; Gelber, S.; Devay, P.; Role, L. W. Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. *Science* **1995**, 269, 1692-6). Since glutamate has a positive action on memory function (mainly through NMDA receptors), this indirect action further increases the efficacy of Galantamine on memory loss.

Abundant patent literature exists on Galantamine. For example, US 5777108 discloses Galantamine derivatives as acetylcholinesterase inhibitors for the treatment of neurodegenerative disorders, such as Alzheimer's disease and WO 0174339 refers to the use of Galantamine for the treatment of neuropsychiatric behavior associated with Alzheimer's disease. Other derivatives of Galantamine for the treatment of neurodegenerative diseases, in particular Alzheimer, are disclosed in US 2004023984 and WO 9740049A1. Of note, WO 2008/022365 relates to the use of Galantamine and its derivatives for controlling the effect of toxic organic phosphorous compounds.

Methods of preparation of Galantamine and derivatives are disclosed in WO 1996012692, US 6797819, and US 6043359.

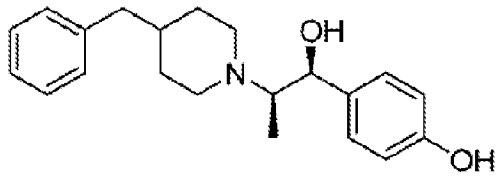
Memantine is an NMDA receptor antagonist that, unlike other antagonists, has a beneficial effect on Alzheimer's patients without significant side effects (Lipton, S. A. Pathologically activated therapeutics for neuroprotection. *Nat Rev Neurosci* **2007,** 8, 803-8). A process for the manufacture of Memantine and intermediate products is disclosed in WO 2009115334A2.

Although at a first glance the two drugs appear to have some opposing mechanisms, a closer examination reveals that working together Galantamine and Memantine provide a more normal neurophysiologic response in patients with AD (Geerts, H.; Grossberg, G. T. Pharmacology of acetylcholinesterase inhibitors and N-methyl-D-aspartate receptors for combination therapy in the treatment of Alzheimer's disease. *J Clin Pharmacol* **2006**,

46, 8S-16S). Multiple neurotransmitters are involved in AD and the most studied systems are the cholinergic and glutamatergic. Due to the complexity of the interaction between the two systems, it is difficult to predict the pharmacological profile of a drug acting on both of them.

Particularly relevant in the context of the present invention is the role of the NMDA receptors in neurodegeneration, and in particular of the NR2B subunit of said receptors. NMDA receptors play a pivotal role in synaptic transmission and neural plasticity. These receptors are hetero-oligomeric channels comprising two major types of subunits, termed NR1 and NR2 (A-D) subunits. The pharmacological and functional properties of NMDA receptors are highly dependent on the NR2 isoform(s) present in the receptor. NR2B subunit containing receptors have been implicated in modulating functions, such as learning, memory processing, attention, emotion, mood, and pain perception, as well as been involved in a number of human disorders. Such disorders include, for example, cognitive impairment, neurodegenerative disorders, such as AD and Parkinson's disease, pain, depression, attention deficit hyperactivity disorder, and addiction.

Ifenprodil is the prototype for NMDA receptor antagonists which display a high degree of selectivity for NR2B-containing receptors.



Ifenprodil

This compound, together with its congener Eliprodil, is recognized as the template for the development of new generations of selective antagonists of the NR2B-containing receptors (Chazot P.L. "The NMDA receptor NR2B Subunit: a valid therapeutic target for multiple CNS pathology" *Current Medicinal Chemistry*, 2004, 11, 399-396).

Compounds selectively targeting the NR2B subunit containing receptors are generally known. For example, US2003229096 (A1) discloses a broad variety of substituted imidazol-pyridazine derivatives that are NMDA receptor subtype selective blockers, which are said to be useful in the therapy of CNS disorders.

Combinations of Memantine and Galantamine are already known in the art, as discussed in "Rationale for combination therapy with Galantamine and Memantine in Alzheimer's disease" (Grossberg G. T.; Edwards, K. R.; Zhao, Q. *J Clin Pharmacol* **2006**, 46, 17S-26S).

US2010227852A1 discloses a drug combination therapy comprising 1-amminocyclohexane derivative such as Memantine and an acetylcholinesterase inhibitor (AChEI) such as Galantamine.

EP1397138B1 discloses combinations of Galantamine with Memantine for treating a dependence on addictive substances or narcotics. The only disclosed compound which contains both the Galantamine and the adamantine moiety is (-)-(6-O-demethyl)-6-O-[(adamantan-1-yl)carbonyl]galantamine (P11149).

US20030199493 discloses derivatives and analogues of Galantamine. In particular the compound of example 192 (SPH-1517) is structurally similar to the compounds of the present invention, which, however, differ from it in the presence of two methyl groups on the adamantane residue, providing therefore a Memantine residue. Also, only the SPH-1517 compound anticholinergic activity as Galantamine analogue is disclosed and no mention is made to the NMDA receptor as a possible pharmacological target of the same compound. The person of ordinary skill in the art would not recognize any contribution for targeting the NMDA receptor in the adamantane residue of the compound SPH-1517. As a matter of fact, this residue is an aliphatic scaffold with no specific pharmacological target.

WO2004037234 discloses a combination therapy of 1-amminocyclohexane derivatives and acetylcholinesterase inhibitors (AChEI) for the treatment of dementia associated with disorders of the central nervous system, e.g. Alzheimer's disease. In a specific embodiment, the 1-amminocyclohexane derivative is Memantine and the AChEI is Galantamine. Compared to the combination disclosed in this document, the compounds of the present invention provide the advantages above mentioned for being multitarget drugs and the further effect of being specifically active on the NMDA receptor containing the NR2B subunit. None of these issues is addressed in the mentioned document.

Although the concept of MTDs is well-known in the art, and a combination therapy of Galantamine and Memantine is currently in clinical practice, a combination of the two drugs in one single MTD compound is still unknown.

RECTIFIED SHEET (RULE 91) ISA/EP

WO2005030332A2 discloses Galantamine and derivatives thereof, however, none of the disclosed compounds presents the adamantane moiety.

There is still the need of a drug for Alzheimer's disease which is effective in combining the stimulation of the cholinergic system with the suppression of the glutamate neurotoxicity, providing molecules which are endowed with neuroprotective profile. Particular interest is on the attempt of broadening the window of efficacy of the AChEI drugs, by contrasting the progressive neurodegeneration responsible of their decline in efficacy. The neuroprotective profile achieved through the activity on the NR2B subunit containing NMDA receptors can broaden the temporal window in which AChEI drugs can provide beneficial effects on memory and cognition.

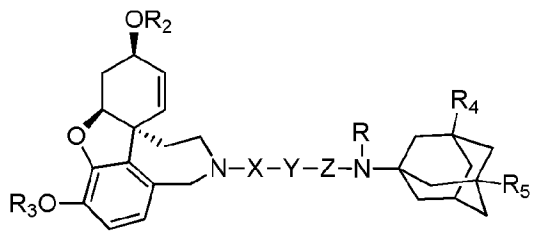
SUMMARY OF THE INVENTION

It has now been found that multitarget compounds obtained by the combination of Galantamine and Memantine achieve the pharmacological profile of a drug combination in a single new chemical entity.

In particular, it has been found that said compounds have an unexpected activity on the 2B subunit of the NMDA receptor, which has been shown to be the actual modulator of neuroprotection and its selective antagonism in the family of NMDA receptor subunits is a desirable pharmacological target (Chazot P.L. "The NMDA receptor NR2B Subunit: a valid therapeutic target for multiple CNS pathology" *Current Medicinal Chemistry,* 2004, 11, 389-396).

Therefore, the claimed compounds achieve neuroprotection from NMDA toxicity mainly thanks to their activity on said subunit.

The compounds of the present invention have the general formula (I):



(I)

wherein:

X is $(CH_2)_m$ and m is comprised between 2 and 12;

Y is selected from the group consisting of NR_1, where R_1 is H, a protecting group, preferably Boc, Fmoc, Cbz, or C_1-C_4 alkyl ; O, S, SO, SO_2, S-S, $O(CH_2)_pO$, wherein p is comprised between 1 and 6; a cyclic hydrocarbon having from 3 to 8 carbon atoms, an aromatic hydrocarbon having from 6 to 10 carbon atoms; a heterocyclic ring having from 3 to 7 members; or Y is absent.

Z is selected from the group consisting of $(CH_2)_n$, wherein n is comprised between 2 and 12, C=O and $CH_2O(CH_2)_2$, or Z is absent;

R is H, C_1-C_4 alkyl or a protective group, such as Boc, Fmoc, Cbz.

R_2 is H, C_1-C_4 alkyl, the residue of a pharmaceutically acceptable acid.

R_3 is C_1-C_4 alkyl, preferably methyl;

R_4 and R_5, the same or different, are C_1-C_4 alkyl, preferably methyl.

The present invention comprises also the pharmaceutically acceptable salts of the compounds of formula (I).

Other than the sterical configuration of the Galantamine residue, which remains set in the present invention, the compounds of formula (I) may have additional chiral carbon atoms, therefore, enantiomers, racemates, diastereoisomers and mixtures thereof are comprised in the present invention.

A further object of the present invention are methods for the preparation of the compounds of formula (I).

A further object of the present invention are compounds useful as intermediates in the synthesis of the compounds of formula (I).

It is also an object of the present invention the use of said compounds of general formula (I) in the preparation of a medicament useful in the treatment of a disease selected from the group consisting of: cognitive impairment, memory dysfunction, neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease, and related dementia, neuropsychiatric behavior associated with Alzheimer's disease, pain, depression, attention deficit hyperactivity disorder, and for pharmacological addictive substance or intoxicant therapy, in particular the therapy of alcoholism, and the same compounds for the treatment of said diseases.

It is also an object of the present invention a method for the treatment of a disease selected from the group consisting of: cognitive impairment, memory dysfunction, neurodegenerative disorders, such as Alzheimer disease and Parkinson's disease, and related dementia, neuropsychiatric behavior associated with Alzheimer's disease, pain, depression, attention deficit hyperactivity disorder and for pharmacological addictive substance or intoxicant therapy, in particular the therapy of alcoholism, by administering the compounds of general formula (I) to a patient in need thereof.

A preferred embodiment is a method for the treatment of Alzheimer's disease by administering the compounds of general formula (I) to a patient in need thereof.

Another preferred embodiment is a method for the treatment of alcoholism by administering the compounds of general formula (I) to a patient in need thereof.

It is also an object of the present invention the use of the compounds of general formula (I) for the neuroprotection from NMDA toxicity as well as a method for the treatment of said toxicity by administering said compounds to a patient in need thereof.

Another object of the present invention are pharmaceutical compositions comprising an effective dose of at least one compound of formula (I).

The compounds of the present invention provide the advantages of 1) reduced uncertainty in clinical development since predicting the pharmacokinetics of a single compound is much easier than with a drug cocktail, overcoming the problem of different bioavailability, pharmacokinetics and metabolism; 2) certainty on the pharmacodynamics; 3) improved efficacy due to the synergistic effect of simultaneously inhibiting multiple targets; 4) improved safety by decreasing the side effects related to the load of a selective drug or drug cocktail (reduced risk of drug-drug interactions). They also provide the advantage of achieving neuroprotection by specifically targeting the 2B subunit of the NMDA receptor.

The above objects of the present invention will be described in the detail also through some preferred embodiments and by means of examples.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The compounds of the present invention can be also defined as MultiTarget Drugs (MTD), in that they combine in their molecule two different drugs.

Basically, the compounds of formula (I) can be schematized as

G-L-M

wherein, G is the part of the Galantamine molecule, L is a linker and M is the part of the Memantine molecule.

In the context of the present invention and if not differently explicitly specified, the following terms have the following meaning.

"Protective group" is as normally acknowledged by the person of ordinary skill in the art of organic synthesis. Here, it protects NH function through a temporarily link to a position of a molecule during the course of a synthetic path. The protective group does not take part to the reaction and can be easily released from the molecule, In this context, Boc is tert-butyl carbamate, Fmoc is 9-fluorenylmethyl carbamate, Cbz is benzyl carbamate, "C_1-C_4 alkyl" is methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, ter-butyl. See for example Protective groups in organic synthesis, T.W. Greene, P.G.M. Wuts, *Third Edition* (1999), Wiley Interscience.

"Leaving group" is a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage. See for example Smith, March. Advanced Organic Chemistry 6th ed. (501-502).

"Cyclic hydrocarbon having from 3 to 8 carbon atoms" is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, a polycyclic ring, such as bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[3.2.1]octane, bicyclo[4.1.1]octane, bicyclo[3.3.0]octane, which can optionally contain one or more carbon-carbon unsaturated bonds, except aromatic rings, and can optionally be substituted by a C_1-C_4 alkyl or a C_2-C_4 alkenyl or a C_2-C_4 alkyinyl.

"Aromatic hydrocarbon having from 6 to 10 carbon atoms" is phenyl or naphthtyl, which can optionally be substituted by a C_1-C_4 alkyl or a C_2-C_4 alkenyl or a C_2-C_4 alkyinyl.

"Heterocyclic ring having from 3 to 7 members" means a carbocyclic ring wherein at least one ring member is one or more heteroatom selected from the group consisting of N, O, S. Said heterocyclic ring can contain one or more unsaturated bonds between each of carbon atom or heteroatom. Said heterocyclic ring can optionally be substituted by a C_1-C_4 alkyl or a C_2-C_4 alkenyl or a C_2-C_4 alkyinyl. Examples of said rings are

oxazine, aziridine, piperidine, piperazine, pyridine, pyrimidine, furane, thiopene, imidazole, oxazole, pyrane.

The term "pharmaceutically acceptable acid" means an acid that forms an ester with the hydroxy group on the Galantamine hydroxy group. This ester maintains or improves the biological properties of the starting compound. Examples of improvement are enhances solubility, enhanced bioavailability, taste masking, or complementary pharmacological activity. Methods for the preparation of said esters are well-known in the art and are part of the common general knowledge of the person skilled in organic chemistry. Examples of said acids are organic acids, such as formic acid, acetic acid, propionic acid, butyric acid, pentanoic acid, hexanoic acid, heptanoic acid, decanoic acid, oxalic acid, succinic acid, malonic acid, glutaric acid, adipic acid, pimelic acid methansulfonic acid, salicylic acid, succinic acid, citric acid; inorganic acids, such as chloridric acid, bromidric acid, sulfuric acid, phosphoric acid. The term "pharmaceutically acceptable salt" means a salt that maintains or improves the biological properties of the starting compound. Examples of improvement are enhances solubility, enhanced bioavailability, taste masking, or complementary pharmacological activity. Examples of methods for the preparation of said salts include the following: addition of inorganic acids (e.g., chloridric acid, bromidric acid, sulfuric acid, phosphoric acid, and similar) or organic (e.g., acetic acid, ossalic acid, maleic acid, methansulfonic acid, salicylic acid, succinic acid, citric acid, and similar), and the free base of the starting compound. The compounds of the present invention, have to be considered, if not differently specified, as comprising their pharmaceutically acceptable salts. Examples of this kind of salts are: formate, acetate, propionate, butiyric, pentanoate, hexanoate, heptanoate, decanoate, oxalate, succinate, malonate, glutarate, adipate, pimelate, methansulfonate, salicylate, succinate, citrate, tartrate; chloride, bromide, sulfate, phosphate. For a general reference, see also P. Heinrich Stahl, Camille G. Wermuth (Eds.) Handbook of Pharmaceutical Salts, Properties, Selection and Use, Wiley-VCH, 2008.

The compounds of the present invention contain at least one chiral carbon, therefore, if not differently specified, they will be considered as comprising the individual isomer(s) or mixtures thereof, which may be racemic or of other kind. Methods for the stereochemistry determination and stereoisomer separation are known in the art (see for instance, Chapter 4 in "Advanced Organic Chemistry" IV Edition L. March, John Wiley and Sons, New York, 1992).

A first group of preferred compound of formula (I) are those wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y and Z are absent.

A second group of preferred compound of formula (I) are those wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y and Z are absent and R is H.

A third group of preferred compound of formula (I) are those wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y and Z are absent and R is CH_3.

A fourth group of preferred compound of formula (I) are those wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is absent, Z is C=O and R is H.

A fifth group of preferred compound of formula (I) are those wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is $O(CH_2)_pO$, wherein p is comprised between 1 and 6, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

A sixth group of preferred compound of formula (I) are those wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is S, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

A seventh group of preferred compound of formula (I) are those wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is O, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

An eigth group of preferred compound of formula (I) are those wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is NH, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

The following compounds are preferred:

a) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethyl)carbamate;

b) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(3-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)propyl)carbamate;

c) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(4-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)butyl)carbamate;

d) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(5-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)pentyl)carbamate;

e) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(6-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)hexyl)carbamate;

f) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(7-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)heptyl)carbamate;

g) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(8-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)octyl)carbamate;

h) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(9-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)nonyl)carbamate;

i) (4aS,6R,8aS)-11-(2-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

j) (4aS,6R,8aS)-11-(3-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)propyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

k) (4aS,6R,8aS)-11-(4-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)butyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

l) (4aS,6R,8aS)-11-(5-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)pentyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol

m) (4aS,6R,8aS)-11-(6-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)hexyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

n) (4aS,6R,8aS)-11-(7-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)heptyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

o) (4aS,6R,8aS)-11-(8-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)octyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

p) (4aS,6R,8aS)-11-(9-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)nonyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

q) (4aS,6R,8aS)-11-(3-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)propyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

r) (4aS,6R,8aS)-11-(4-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)butyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

s) (4aS,6R,8aS)-11-(5-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)pentyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

t) (4aS,6R,8aS)-11-(6-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)hexyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

u) (4aS,6R,8aS)-11-(7-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)heptyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

v) (4aS,6R,8aS)-11-(8-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)octyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

w) (4aS,6R,8aS)-11-(10-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)decyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

x) 3-((4aS,6R,8aS)-3,6-dimethoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)-N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)propanamide;

y) 4-((4aS,6R,8aS)-3,6-dimethoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)-N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)butanamide;

z) N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)-5-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)pentanamide

aa)N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)-6-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)hexanamide;

bb)*tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(2-(2-(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethoxy)ethoxy)ethyl)carbamate;

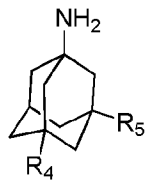
cc)*tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(2-(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethoxy)ethyl)carbamate;

dd) (4aS,6R,8aS)-11-(2-(2-(2-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethoxy)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

ee) (4aS,6R,8aS)-11-(2-(2-(2-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol.

The invention furthermore provides processes for the preparation of compounds of general formula (I).

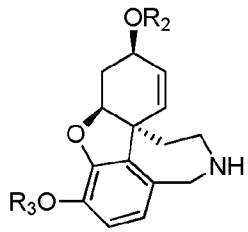
In a general perspective, the compounds of formula (I) can be prepared starting from a Memantine derivative M



wherein R_4 and R_5 are as defined above for formula (I).

A linker L of formula D-X-Y-Z-NR-E, wherein X, Y, Z and R are as defined above for formula (I), D and E are a leaving group is reacted with M to give an intermediate M-X-Y-Z-NR-E.

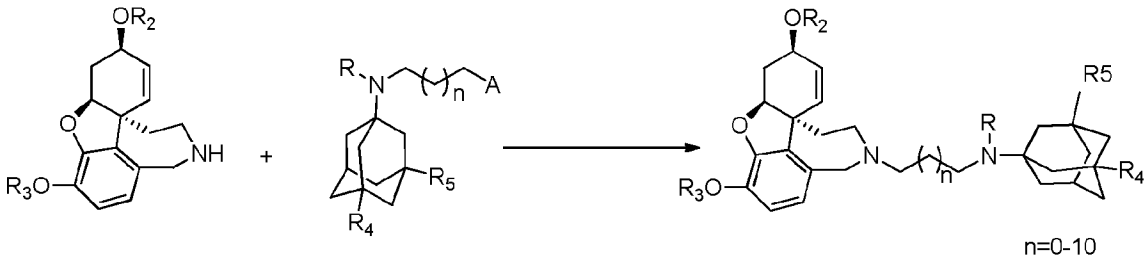
The intermediate M-X-Y-Z-NR-E is then reacted with a des-methyl-galanthamine derivative G



wherein R_2 and R_3 are as defined above for formula (I), to give the compounds of formula (I).

The intermediate M-X-Y-Z-NR-E is novel, hence is a further object of the present invention.

For the preparation of the compounds of formula (I), according to the present invention, wherein X is $(CH_2)_m$ as defined above, Y and Z are absent, the general synthesis can be described by the following reaction:



(II)

wherein R, R_2, R_3, R_4 and R_5, are as defined above for formula (I), n is an integer comprised between 0 and 10 and A is an activated alcohol group.

The compound of formula (II) is novel, hence is a further object of the present invention.

In case R is H, a first building block M-L-A, wherein M is Memantine, L is an alkylene chain (namely X as defined above) and A is an activated alcohol group, is obtained by reacting Memantine with a halo-alcohol of the desired length, followed by protection of the nitrogen atom on the Memantine moiety and, finally, activating the alcoholic function.

Within the scopes of the present invention, activated alcohol group is well understood by the person of ordinary skill in the art and means an alcohol function (OH), wherein the hydrogen atom is substituted by another functional group so to provide a good

leaving group. Examples of activating groups are tosyl, mesyl. To provide a good leaving group the alcohol function can also be converted into halogenous groups (Br, Cl, I) according to the general procedures. Finally, the M-L-A building block is reacted with N-desmethyl Galantamine to provide the desired compound. The N-protecting group on the Memantine moiety can be released.

Alternatively, the alcohol can be converted into aldehyde directly *via* Swern oxidation or after esterification following reduction with DIBAL. Then, the M-L-aldehyde can be connected to the Galantamine scaffold through reductive amination, this latter synthetic route is applicable only to obtain compounds of formula (I) wherein R=H and R= C_1-C_4 alkyl.

For the preparation of the compounds of formula (I), according to the present invention, wherein X is $(CH_2)_m$ as defined above, Y and Z are absent and R is C_1-C_4, the synthetic route is the same as above, wherein R is H, except, in the starting building block M-L-A, wherein M is N-C_1-C_4-Memantine, most preferably N-methyl-Memantine. In this synthetic route, there is no need to protect the nitrogen atom on the Memantine moiety.

Generally, a salt of Memantine, for example chloride, is dissolved in a suitable solvent, such as dimethyl formamide, tetrahydrofuran or dioxane. Then the appropriate halo-alcohol is added to the vigorously stirred solution of Memantine. Suitable halo-alcohols are for example bromo-, chloro or iodo-alcohol. The reaction is carried out at the presence of a base, for example a base derived from an alkaline metal, such as K_2CO_3, NaOH, KOH, Na_2CO_3; inorganic base in general can be used, under adequate stirring conditions and at a temperature above room temperature, for example ranging from 60°C to 110°C, for example 80°C, and for a time spanning from 12 h to 48 h. The stoichiometry of the reaction is according to the type of reaction, however the molar ratios can be varied depending on other conditions, such as the solvent, the temperature, reaction time and other compounds present in the reaction mixture. After completion of reaction, the solvent is removed, for example by vacuum-evaporation. Completion of reaction is checked by ordinary means, such as chromatography, for example thin layer chromatography, gaschromatography; spectroscopy, for example IR or NMR. The residue is re-dissolved in a suitable medium, such as water and extracted with a suitable amount of an organic solvent immiscible with water, such as CH_2Cl_2, for a sufficient number of times. The collected organic layers are concentrated to yield the

RECTIFIED SHEET (RULE 91) ISA/EP

crude *N*-alkylated Memantine derivative which, if desired, is further purified by flash chromatography.

As a second step, the N-alkylated Memantine is dissolved into a suitable solvent, for example a mixture of an organic solvent and water, for example THF/H_2O (1:1 or other convenient ratios) and treated with a base, preferably an alkaline carbonate, for example Na_2CO_3 and a protecting group is introduced on the nitrogen of the Memantine moiety. A preferred example of protecting group is di-*tert*-butyl dicarbonate (BOC). General methods used to protect the nitrogen as carbamate:: Methyl and Ethyl carbamate, 9-Fluorenylmethyl Carbamate (Fmoc group), 9-(2-Sulfo)fluorenylmethyl Carbamate, 9-(2,7-Dibromo)fluorenylmethyl Carbamate, Tetrabenzofluorenylmethyl carbamate (Tbfmoc group), 2-Chloro-3-indenylmethyl Carbamate (Climoc group), Benzinden3-ylmethyl Carbamate (Bimoc group), 2,7-Di-t-butyl[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc Group), 1,1 Dioxobenzothiophene-2-ylmethylcarbamate(Bsmoc Group), 2-Furanylmethyl carbamate, 2,2,2-Trichloethyl carbamate (Troc Group), 2-Trimethylsilylethyl carbamate (Teoc group), 2-Phenylethyl carbamate (hZ group), 1-(1-Adamantyl)-1-methylethyl carbamate (Adpoc group), 2-Haloethyl Carbamate,1,1-Dimethyl carbamate-2,2-dibromoethyl carbamate (DB-*t*-BOC group),1,1-Dimethyl-2,2,2-trichloroethyl carbamate (TCBOC group),1-methyl-1-(4-biphenylyl)ethyl carbamate (Bpoc group), 1-(3,5-Di-*t*-butylphenyl)-1-methylethyl carbamate (*t*-Bumeoc group), 2-(2'-and 4'-Pyridyl)ethyl carbamate (Pyoc group), 2,2-Bis(4'-nitrophenyl)ethyl carbamate (Bnpeoc group), *N*-(2-Pivaloylamino)-1,1-dimethylethyl carbamate, 2-[(2-Nitrophenyl)dithio]-1-phenylethyl carbamate (NpSSPeoc group), 2-(N,N-Dicyclohexylcarboxamido)ethyl carbamate, 1-Adamantyl carbamate (1-Adoc group), 2-Adamantyl carbamate (2-Adoc group),Vinyl carbamate (Voc group), Allyl carbamate (Aloc or Alloc group), 1-Isopropylallyl carbamate (Ipaoc group), cinnamyl carbamate (Coc group), 4-Nitrocinnamyl carbamate (Noc group), 3-(3'-Pyridyl)prop-2-enyl carbamate (Paloc group), 8-Quinolyl carbamate, N-Hydroxypiperdinyl carbamate, Alkyldithio carbamate, benzyl carbamate (Cbz group) and miscelloneus benzyl carbamates such as *p*-Methoxybenzyl carbamate (Moz group), *p*-Nitrobenzyl carbamate (PNZ group), p-halobenzyl carbamate, 4-Methylsulfinylbenzyl carbamate (Msz group), 9-Anthrylmethyl carbamate, Diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-Methylsulfonylethyl carbamate, [2-(1,3-Dithianyl)methyl carbamate (Dmoc group). (Protective groups in organic synthesis, T.W. Greene, P.G.M. Wuts, *Third Edition* (1999), Wiley Interscience). The resultant mixture is allowed to stir

at room temperature for a time sufficient to completion of the reaction, for example overnight. The solvent is removed, preferably in vacuo, yielding a residue which is subsequently dissolved in water and extracted with an organic solvent, such as AcOEt, for a sufficient number of times. The extracts are gathered, washed, for example with brine, dried over Na_2SO_4 or other desiccant agents, concentrated, and purified. Flash chromatography is a suitable purification technique.

As a third step, the OH group at the end of the alkyl chain is activated for the final step, when the Galantamine moiety is added. This activation is conventional and well known to the person of ordinary skill in the art. For example, p-TsCl (p-tosyl chloride) is added to a mixture of the appropriate alcohol, a base, such as Et_3N (triethylamine) and DMAP (dimethylaminopyridine) in catalytical amounts in a dry organic solvent, such as CH_2Cl_2 under inert atmosphere (for example N_2) with stirring at low temperature, such as 0°C. The stirring is then continued at room temperature after 30 minutes for until completion of the reaction. Then, the reaction is quenched, for example with saturated NH_4Cl aqueous solution and extracted with an organic solvent, such as AcOEt. Combined extracts are washed, for example with brine, dried over Na_2SO_4,or other desiccant, and evaporated. The tosylate derivative is then purified by ordinary means, such as flash chromatography.

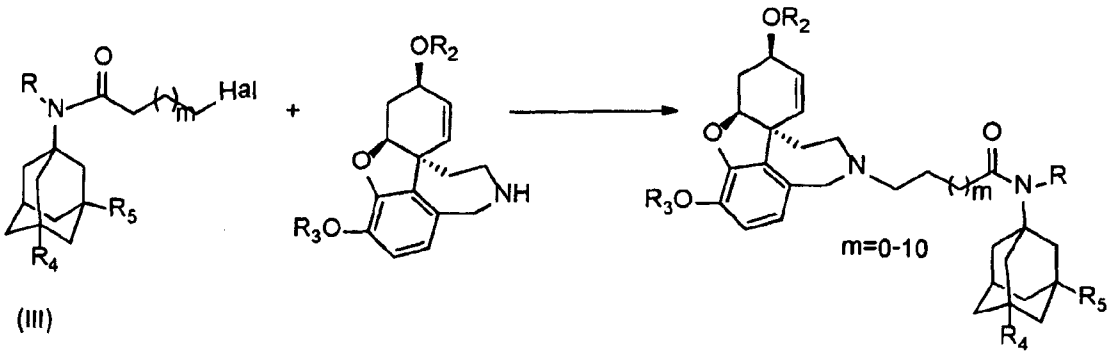
Finally, the building block M-L-A is treated with N-desmethyl galantamine and a suitable base, for example Et_3N in a reaction solvent, such as CH_3CN for example is stirred at a temperature ranging from 60 °C to 90 °C, for a time sufficient to completion of the reaction. After elimination of the solvent, the residue is purified by conventional means, for example flash chromatography.

If desired, the protecting groups on nitrogen are removed by well-known methods. For example, HCl 4M in dioxane is added to the Boc derivative at low temperature, for example 0 °C, and the solution is allowed to stir at room temperature for a sufficient time. After removing the solvent the obtained residue is purified as usual, for example by flash chromatography.

All the reactions are preferably carried out in a closed vessel, such as a pressure tube or a sealed reactor.

According to the present invention, the amido compounds, corresponding to the compounds of formula (I) wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is absent, Z is C=O can be prepared following the general synthesis

RECTIFIED SHEET (RULE 91) ISA/EP



(III)

wherein R, R_2, R_3, R_4 and R_5, are as defined above for formula (I), m is an integer comprised between 0 and 10, Hal is an halogen atom.

The compound of formula (III) is novel, hence is a further object of the present invention.

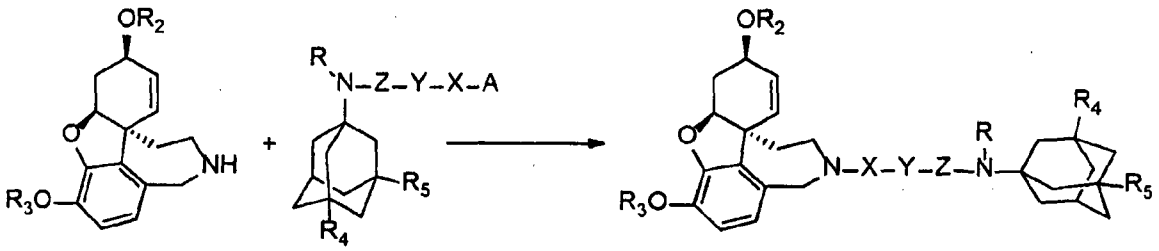
As starting step, Memantine is treated with a halo-acyl chloride of the desired length. The reduction of the amido functionality with $LiAlH_4$ represents a further synthetic route.

To a solution of Memantine salt, preferably a hydrochloride and a base, for example a carbonate of alkali metal, such as K_2CO_3 in a suitable solvent, for example acetonitrile, the appropriate acylating agent is added. The reaction is left, preferably under stirring, until completion of the reaction, which is checked by ordinary means. After removing the solvent, for example by vacuum evaporation, the crude is purified by ordinary techniques, such as flash chromatography.

The intermediate of the preceding step is reacted with des-methyl-Galantamine at the presence of an organic base, such as a trialkyl amine, preferably triethylamine, and a suitable catalyst, for example KI, in an appropriate solvent, such as CH_3CN. The reaction mixture is kept at high temperature, the boiling point of the solvent is convenient, or lower temperature, for example 80°C until completion of the reaction, The reaction is conveniently carried out in a closed vessel. At the end, the solvent is removed as usual and the residue is purified by conventional technique, for example flash chromatography.

According to the present invention, compounds of formula (I), wherein X is $(CH_2)_m$ and m is comprised between 2 and 12; Y is O or $O(CH_2)_pO$, wherein p is comprised between 1 and 6; Z is $(CH_2)_n$, wherein n is comprised between 1 and 12 can be prepared following the general synthesis:

RECTIFIED SHEET (RULE 91) ISA/EP



(IV)

wherein R, R_2, R_3, R_4 and R_5, are as defined above, A is an activated alcohol group.

The compound of formula (IV) is novel, hence is a further object of the present invention.

Starting from the suitable di-alcohol and transforming one end hydroxyl group into an activated hydroxyl group, as explained above and with conventional procedures, for example by reacting with tosyl chloride. The reaction is carried out in the presence of a base, for example an organic base, for example a trialkyl amine, preferably triethyl amine, and a catalyst used in such a kind of reactions, for example DMAP (dimethylaminopyridine) in dry organic solvent, such as CH_2Cl_2 and in a inert atmosphere (argon or nitrogen) with stirring at low temperature, conveniently 0°C, then raising the temperature to about room temperature until completion of the reaction. The reaction is then quenched, for example with saturated NH_4Cl aqueous solution and the whole mixture is extracted with an immiscible or partially miscible organic solvent, for example ethyl acetate. The organic extract is washed with brine, dried with conventional means, for example over Na_2SO_4, and, following solvent removal, the crude is purified by conventional means, such as flash chromatography.

In a closed vessel the appropriate activated alcohol is added to a solution of a Memantine salt, preferably hydrochloride, and a base (K_2CO_3 for example) in a suitable solvent, for example dimethylformamide (DMF). The reaction mixture is warmed (for example about 80°C) for a suitable time (typically 48 hours), until completion. The solvent is removed and the residue is worked properly, for example is taken up with water and extracted with an organic solvent (such as CH_2Cl_2). The crude is finally purified by usual means, for example flash chromatography.

The intermediate compound obtained in the previous step is dissolved in a reaction medium (for example THF/H_2O) and treated with an alkali carbonate, for example sodium, and a suitable protecting group for the nitrogen, di-*tert*-butyl dicarbonate is

RECTIFIED SHEET (RULE 91) ISA/EP

preferred. The resultant suspension is allowed to stir at room temperature, for example overnight. The solvent is then removed yielding a residue which is dissolved in water and extracted with an organic solvent, such as AcOEt. The gathered extracts are combined, washed with brine, dried, for example over Na_2SO_4, concentrated by evaporation, and purified as usual, for example by flash chromatography.

The primary alcohol is activated according to conventional methods, for example with tosyl chloride, as described above.

Finally, the reaction with des-methyl-Galantamine is carried out as above described. If desired, the N-protecting group is removed.

In view of the complementary pharmacology of Galantamine and Memantine, the two activities combined into a single dual-target molecule produce a significant synergy against the main AD hallmarks, i.e. memory loss, cognition loss, and neuronal death.

A further object of the present invention is a pharmaceutical composition comprising at least one compound of Formula (I) as an active ingredient, in an amount such as to produce a significant therapeutic effect. The amount of active ingredient can be determined by the skilled person resorting to methods of dose finding conventionally adopted in the pharmaceutical industry. By way of example, the dosage can range from 0.01 µg/kg to 1 mg/kg. Unitary dosages can provide a dose of active ingredient varying from 1 to 50 mg. The compositions covered by the present invention are entirely conventional and are obtained with methods which are common practice in the pharmaceutical industry, such as, for example, those illustrated in *Remington's Pharmaceutical Science Handbook, Mack Pub. N.Y.* – last edition. According to the administration route chosen, the compositions will be in solid or liquid form, suitable for oral, parenteral or intravenous administration. The compositions according to the present invention contain, along with the active ingredient, at least one pharmaceutically acceptable vehicle or excipient. These may be particularly useful formulation coadjuvants, e.g. solubilising agents, dispersing agents, suspension agents, and emulsifying agents.

The following examples illustrate the invention without limiting it.

PREPARATIONS AND EXAMPLES

In the following section, exemplary preparations of intermediate compounds are given. It is intended that the skilled reader can adapt or modify the synthetic routes in order to obtain the compounds of the present invention.

Chemical reagents were purchased from Sigma Aldrich, Fluka (Italy) and TCI-Europe. N-desmethyl galantamine was purchased from Synfine research.

Solvents were RP grade. Dichloromethane was distilled from calcium chloride. Dry dimethylformamide and triethylamine were used as supplied.

The structures of the unknown compounds were unambiguously assessed by MS(EI), ^{1}H NMR and ^{13}C NMR.

Nuclear magnetic resonance spectra (NMR) were recorded at 400 MHz on Varian VXR 400 spectrometers and reported in parts per million.

UPLC-MS analyses were run on a Waters ACQUITY UPLC-MS instrument consisting of a SQD Single Quadropole Mass Spectrometer equipped with an electrospray ionization interface and a photodiode array detector. The analyses were performed on an ACQUITY UPLC BEH C18 column (50x2.1mmID, particle size 1.7µm) with a VanGuard BEH C18 pre-column (5x2.1mmID, particle size 1.7µm). The mobile phases were 10mM NH_4OAc at pH 5 adjusted with AcOH (A) and 10mM NH_4OAc in MeCN-H2O (95:5) at pH 5 (B). Electrospray ionization in positive and negative mode was used in the mass scan range 100-500Da.

Column chromatography purifications were performed under "flash conditions" using Sigma Aldrich silica gel grade 9385, 230-400 mesh.

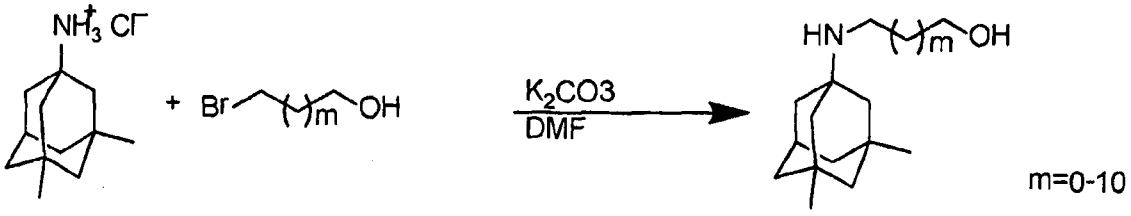
TLC were performed on 0.20 mm silica gel 60 F254 plates (Merck, Germany), which were visualized by exposure to ultraviolet light and potassium permanganate stain. Reactions involving generation or consumption of amine were visualized by using bromocresol green spray (0.04% in EtOH made blue by NaOH) following heating of the plate.

Preparation I

General synthesis of Compounds of Formula (I) wherein X is $(CH_2)_m$, as defined above, Y and Z are absent, R is H.

Step 1

RECTIFIED SHEET (RULE 91) ISA/EP



(IIa)

In a pressure tube (Sigma Aldrich, ACE pressure tube) the appropriate bromo-alcohol was added to a vigorously stirred solution of Memantine hydrochloride (0.500 g, 2.32 mmol) and K_2CO_3 (0.8 g, 5.75 mmol) in DMF (10 mL). The reaction mixture was stirred at 80°C for 48 hours. After evaporating the solvent, the residue was taken up with water and extracted with CH_2Cl_2 (3 x 10 mL). The collected organic layers were concentrated to yield crude *N*-alkylated Memantine derivative which was further purified by flash chromatography.

m=2(ES129) 4-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)butan-1-ol. It was synthesized from 4-bromo-1-butanol (0.251 mL, 2.78 mmol). Elution with CH_2Cl_2/MeOH/33% aqueous ammonia (9:1:0.16) afforded **ES129** as a waxy solid: 0.501 g (86%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.80 (s, 6H), 1.04-1.12 (AB m, 2H), 1.22-1.30 (m, 8H), 1.46-1.47 (m, 2H), 1.54-1.66 (m, 4H), 2.09-2.11 (m, 1H), 2.59 (t, *J*=4.8 Hz, 2H), 3.52, (t, *J*=5.2 Hz, 2H), 3.85 (br s exchangeable with D_2O, 1 H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 29.95, 30.12, 30.15, 32.34, 32.80, 40.15, 40.72, 42.84, 48.39, 50.79, 52.59, 62.41.

m=3(ES91) 5-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)pentan-1-ol. It was synthesized from 5-bromo-1-pentanol (0.464 g, 2.78 mmol). Elution with CH_2Cl_2/MeOH/33% aqueous ammonia (9:1:0.15) afforded **ES91** as foam solid: 0.560 g (91%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.83 (s, 6H), 1.11-1.12 (AB m, 2H), 1.25-1.34 (m, 8H), 1.40-1.44 (m, 2H), 1.50-1.60 (m, 6H), 2.13-2.14 (m, 1H), 2.47 (br s exchangeable with D_2O, 1H), 2.61 (t, *J*=6.8 Hz, 2H), 3.62 (t, *J*=6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 23.49, 29.97, 30.19, 30.25, 32.29, 32.35, 40.36, 40.79, 42.91, 48.44, 50.85, 52.83, 62.15.

m=4(ES92) 6-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)hexan-1-ol. It was synthesized from 6-bromo-1-esanol (0.37 mL, 2.78 mmol). Elution with CH_2Cl_2/MeOH/33% aqueous ammonia (9:1:0.15) afforded **ES92** as a foam solid: 0.577 (89%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.11-1.12 (AB m, 2H), 1.22-1.39 (m,

12H), 1.49-1.58 (m, 6H), 2.13-2.14 (m, 1H), 2.51 (br s exchangeable with D_2O, 1H), 2.59 (t, *J*=7.6 Hz, 2H), 3.61 (t, *J*=6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.64, 27.21, 29.66, 30.17, 30.26, 30.44, 32.35, 32.65, 40.46, 40.70, 42.88, 48.34, 50.82, 52.93, 62.40.

m=5(ES93) 7-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)heptan-1-ol. It was synthesized from 7-bromo-1-eptanol (0.427 mL, 2.78 mmol). Elution with CH_2Cl_2/MeOH/33% aqueous ammonia (9:1:0.15) afforded **ES93** as a foam solid: 0.626 g (92%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.09-1.121(AB m, 2H), 1.19-1.36 (m, 14H), 1.42-1.47 (m, 4H), 1.52-1.56 (m, 2H), 2.11-2.13 (m, 1H), 2.51 (br s exchangeable with D_2O, 1H), 2.55 (t, *J*=7.6 Hz, 2H), 3.6 (t, *J*=6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.77, 27.43, 29.31, 30.16, 30.78, 32.26, 32.71, 40.51, 41.03, 42.49, 48.71, 50.89, 52.22, 61.93.

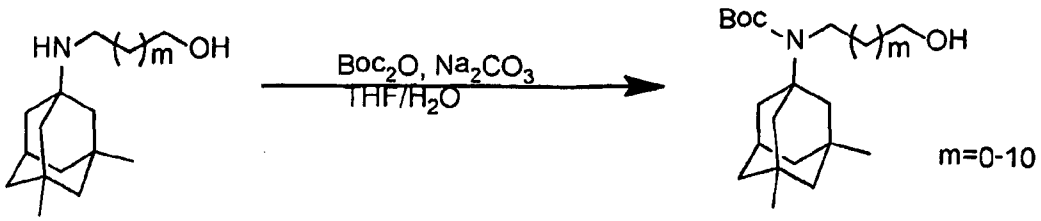
m=6(ES105) 8-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)octan-1-ol. It was synthesized from 8-bromo-1-octanol (0.477 mL, 2.78 mmol). Elution with CH_2Cl_2/MeOH/33% aqueous ammonia (9:1:0.1) afforded **ES105** as a foam solid: 0.613 g (86%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.11-1.12 (AB m, 2H), 1.21-1.36 (m, 16H), 1.43-1.57 (m, 6 H), 2.12-2.14 (m, 1H), 2.51 (br s exchangeable with D_2O, 1H), 2.53-2.57 (m, 2H), 3.59 (t, *J*=6.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.68, 27.38, 29.31, 29.42, 30.17, 30.24, 30.63, 32.30, 32.70, 40.54, 40.85, 42.91, 48.53, 50.86, 52.53, 57.81, 62.42.

m=7(ES152) 9-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)nonan-1-ol. It was synthesized from 9-bromo-1-nonanol (0.620 g, 2.78 mmol). Elution with CH_2Cl_2/MeOH/33% aqueous ammonia (9:1:0.1) afforded **ES152** as a foam solid: 0.671 g (90%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.10-1.11 (AB m, 2H), 1.21-1.29 (m, 14H), 1.45-1.49 (m, 4H), 1.53-1.57 (m, 6H), 2.12-2.14 (m, 1H), 2.51 (br s, 1H), 2.55 (t, *J*=7.6 Hz, 2H), 3.60 (t, *J*=6.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.75, 25.79, 27.47, 29.34, 29.41, 29.44, 29.52, 30.28, 30.82, 32.32, 32.77, 40.59, 40.99, 42.97, 48.68, 50.91, 52.42, 62.53.

In this Preparation I, all intermediates (IIa) are novel, except the ones wherein m is 0, 1 or 2, which are commercially available. Therefore, these intermediates are a further object of the present invention.

Step 2

RECTIFIED SHEET (RULE 91) ISA/EP



(IIb)

The appropriate secondary amine (1 eq.) was dissolved in THF/H_2O (1:1) and treated with Na_2CO_3 (2.5 eq.) and di-*tert*-butyl dicarbonate (1.5 eq). The resultant suspension was allowed to stir at room temperature overnight. The solvent was then removed in vacuo yielding a residue which was dissolved in water and extracted with AcOEt (3×15 mL). The extracts were combined, washed with brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography.

m=2(ES134) ***tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(4-hydroxybutyl)carbamate.** It was synthesized from **ES129** (0.250 g, 0.99 mmol). Elution with petroleum ether/AcOEt (6:4) afforded **ES134** as a foam solid: 0. 280 g (80%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 6H), 1.10-1.13 (AB m, 2H), 1.22-1.33 (m, 4H), 1.43 (s, 9H) 1.46-1.54 (m, 4H), 1.68-1.71 (AB m, 4H), 1.89-1.90 (m, 2H), 2.10-2.12 (m, 1H), 3.24 (t, *J*=8.4 Hz, 2H), 3.63(t, *J*=6.0 Hz, 2H).^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.99, 28.58, 29.97, 30.47, 30.67, 32.78, 39.43, 42.63, 43.19, 46.96, 50.48, 57.98, 62.39, 79.10, 155.36.

m=3(ES96) ***tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(5-hydroxypentyl)carbamate.** It was synthesized from **ES91** (0.300 g, 1.13 mmol). Elution with petroleum ether/ AcOEt (7:3) afforded **ES96** as a foam solid: 0.360 g (87%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85 (s, 6H), 1.12-1.14 (AB m, 2H), 1.24-1.37 (m, 6H), 1.45 (s, 9H) 1.48-1.60 (m, 4H), 1.70-1.73 (AB m, 4H+1 H exchangeable with D_2O), 1.92-1.93 (m, 2H), 2.13-2.15 (m, 1H), 3.21 (t, *J*=8.0 Hz, 2H), 3.62 (t, *J*=6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 23.27, 28.59, 30.47, 30.67, 31.43, 32.35, 32.76. 39.37, 42.65, 43.58, 46.89, 50.49, 57.97, 62.71, 78.89, 155.21.

m=4(ES94) ***tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(6-hydroxyhexyl)carbamate.** It was synthesized from **ES92** (0.400 g, 1.43 mmol). Elution with petroleum ether/ AcOEt (6:4) afforded **ES94** as a foam solid: 0.410 g (75%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85 (s, 6H), 1.09-1.17 (AB m, 2H), 1.22-1.29 (m, 4H), 1.34-1.41 (m, 4H), 1.42-1.52 (m, 11H), 1.58-1.61 (m, 4H), 1.70-1.77 (AB m, 4H), 2.13-2.15 (m, 1H), 3.21 (t, *J*=8.0 Hz, 2H), 3.64 (t, *J*=6.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ

25.46, 26.90, 28.59, 30.47, 30.67, 31.72, 32.73, 32.76, 39.35, 42.67, 43.58, 46.87, 50.51, 57.95, 62.78, 78.79, 155.19.

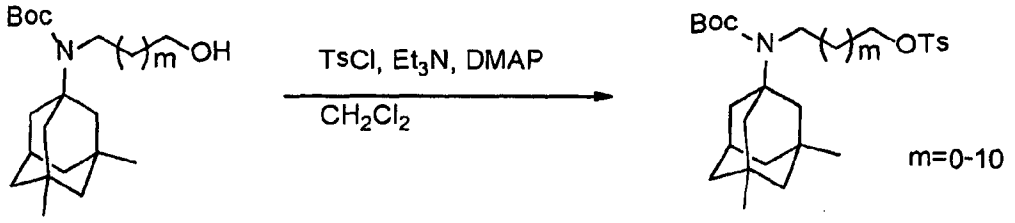
m=5(ES99) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(7-hydroxyheptyl)carbamate. It was synthesized from **ES93** (0.480 g, 1.64 mmol). Elution with petroleum ether/ AcOEt (7:3) afforded **ES99** as a foam solid: 0.530 g (83%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85 (s, 6H), 1.09-1.14 (AB m, 2H), 1.22-1.37 (m, 10H), 1.43-1.49 (m, 10H), 1.53-1.58 (m, 2H), 1.70-1.73 (AB m, 4H), 1.92-1.93 (m, 2H), 2.13-2.15 (m, 1H), 2.29-2.31 (m, 1H), 3.21 (t, *J*=8.0 Hz, 2H), 3.62 (t, *J*=6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.69, 27.05, 28.55, 29.07, 30.46, 30.62, 31.59, 32.60, 32.71, 39.28, 42.63, 43.63, 46.80, 50.47, 57.89, 62.61, 78.73, 155.10.

m=6(ES109) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(8-hydroxyoctyl)carbamate. It was synthesized from **ES105** (0.380 g, 1.24 mmol). Elution with petroleum ether/ AcOEt (7.5:2.5) afforded **ES109** as a foam solid: 0.430 g (85%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 6H), 1.05-1.14 (AB m, 2H), 1.17-1.34 (m, 12H), 1.39-1.57 (m, 13H) 1.67-1.74 (AB m, 4H), 1.89-1.90 (2H), 2.09-2.12 (m, 1H), 3.17 (t, *J*=7.6 Hz, 2H), 3.60 (t, *J*=6.4 Hz, 2H).^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.64, 27.06, 28.59, 29.29, 29.39, 30.47, 30.68, 31.69, 32.72, 32.76, 39.32, 42.67, 43.71, 46.84, 50.51, 57.92, 62.93, 78.72, 155.13.

m=7(ES153) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(9-hydroxynonyl)carbamate. It was synthesized from **ES152** (0.600 g, 1.87 mmol). Elution with petroleum ether/ AcOEt (8:2) afforded **ES153** as a foam solid: 0.650 g (82%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.80 (s, 6H), 1.05-1.14 (AB m, 2H), 1.17-1.34 (m, 14H), 1.39-1.57 (m, 13H) 1.67-1.74 (AB m, 4H), 1.89-1.90 (2H), 2.09-2.12 (m, 1H), 3.17 (t, *J*=7.6 Hz, 2H), 3.60 (t, *J*=6.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.69, 27.10, 28.57, 29.25, 29.30, 29.55, 30.46, 30.67, 31.71, 32.73, 32.74, 39.30, 42.67, 43.71, 46.82, 50.51, 57.91, 62.90, 78.68, 155.10.

In this Preparation I, all intermediates (IIb) are novel. Therefore, these intermediates are a further object of the present invention.

Step 3



(IIc)

p-TsCl (1 eq.) was added to a mixture of the appropriate alcohol (1 eq.), Et_3N (2 eq.), and DMAP (cat.) in dry CH_2Cl_2 (0.1 M) under N_2 atmosphere with stirring at 0°C. The stirring was continued at room temperature for 3.5 hours. After completion, the reaction was quenched with saturated NH_4Cl aqueous solution and extracted with AcOEt (3 x 10 mL). Combined extracts were washed with brine, dried over Na_2SO_4, and evaporated. The tosylate derivative was then purified by flash chromatography.

m=2(ES137) 4-((*tert*-butoxycarbonyl)((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)butyl 4-methylbenzenesulfonate. It was synthesized from **ES134** (0.090 g, 0.26 mmol). Elution with petroleum ether/ AcOEt (9:1) afforded **ES137** as an oil: 0.110 g (85%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 6H), 1.08-1.13 (AB m, 2H), 1.18-1.33 (m, 4H), 1.40 (s, 9H), 1.43-1.49 (m, 4H), 1.67-1.71 (m, 4H), 1.85-1.86 (m, 2H), 2.10-2.11 (m, 1H), 2.42 (s, 3H), 3.18 (t, *J*=8.0 Hz, 2H), 4.00 (t, *J*=6.4 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 7.76 (d, *J*=8.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.60, 26.55, 27.69, 28.54, 28.56, 30.44, 30.64, 32.77, 39.37, 42.60, 42.63, 42.91, 46.88, 50.44, 58.06, 70.29, 79.06, 127.83, 129.79, 133.17, 144.67, 155.05.

m=3(ES97) 5-((*tert*-butoxycarbonyl)((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)pentyl 4-methylbenzenesulfonate. It was synthesized from **ES96** (0.180 g, 0.492 mmol). Elution with petroleum ether/ AcOEt (9:1) afforded **ES97** as an oil: 0.250 g (98%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.11-1.14 (AB m, 2H), 1.24-1.29 (m, 4H), 1.33-1.46 (m,4H), 1.44 (s, 9H), 1.64-1.71 (m, 6H), 1.90-1.91 (m, 2H), 2.13-2.14 (m, 1H), 2.45 (s, 3H), 3.18 (t, *J*=7.6 Hz, 2H), 4.02 (t, *J*=6.4 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 7.78 (d, *J*=8.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.58, 22.97, 28.56, 30.45, 30.64, 31.01, 32.75, 39.35, 42.62, 43.30, 46.86, 50.46, 57.97, 70.45, 78.87, 127.80, 129.79, 133.15, 144.63, 155.05.

m=4(ES104) 6-((*tert*-butoxycarbonyl)((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)hexyl 4-methylbenzenesulfonate. It was synthesized from **ES94** (0.710 g, 1.945 mmol). Elution with petroleum ether/ AcOEt (9:1) afforded **ES104** as an oil: 0.900 g (87%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.80 (s, 6H), 1.07-1.36 (m, 12H), 1.40 (s, 9H), 1.58-1.68 (m, 6H), 1.86-1.87 (m, 2H), 2.08-2.10 (m, 1H), 2.40 (s, 3H), 3.13 (t, *J*=8.0 Hz, 2H), 3.97 (t, *J*=6.0 Hz, 2H), 7.30 (d, *J*=7.6 Hz, 2H), 7.74 (d, *J*=7.6 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.59, 25.16, 26.51, 28.57, 28.85, 30.46, 30.65, 31.50, 32.74,

RECTIFIED SHEET (RULE 91) ISA/EP

39.34, 42.64, 43.48, 46.84, 50.46, 57.93, 70.50, 127.80, 129.78, 133.16, 144.61, 155.06.

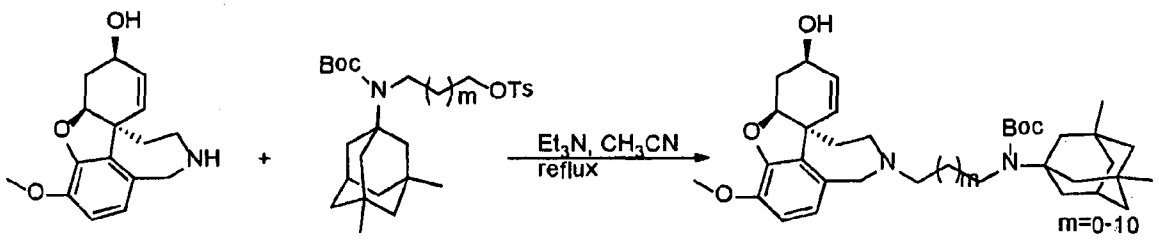
m=5(ES102) 7-((*tert*-butoxycarbonyl)((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)heptyl 4-methylbenzenesulfonate. It was synthesized from **ES99** (0.530 g, 1.349 mmol). Elution with petroleum ether/ AcOEt (9.2:0.8) afforded **ES102** as an oil: 0.720 g (98%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 6H), 1.07-1.39 (m, 14H), 1.41 (s, 9H), 1.58-1.62 (m, 2H), 1.65-1.72 (m, 4H), 1.88-1.89 (m, 2H), 2.10-2.11 (m, 1H), 2.41 (s, 3H), 3.14 (t, *J*=8.0 Hz, 2H), 3.98 (t, *J*=6.0 Hz, 2H), 7.31 (d, *J*=7.9 Hz, 2H), 7.75 (d, *J*=7.9 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.60, 25.38, 26.91, 28.59, 28.71, 28.75, 30.47, 30.67, 31.62, 32.76, 39.34, 42.67, 43.60, 46.85, 50.50, 57.92, 70.56, 78.73, 127.82, 129.76, 133.19, 144.60, 155.10.

m=6(ES110) 8-((*tert*-butoxycarbonyl)((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)octyl 4-methylbenzenesulfonate. It was synthesized from **ES109** (0.380 g, 0.934 mmol). Elution with petroleum ether/ AcOEt (9:1) afforded **ES110** as an oil: 0.460 g (88%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.08-1.37 (m, 16H), 1.45 (s, 9H), 1.60-1.67 (m, 2H), 1.70-1.77 (m, 4H), 1.92-1.93 (m, 2H), 2.12-2.15 (m, 1H), 2.45 (s, 3H), 3.19 (t, *J*=7.6 Hz, 2H), 4.01 (t, *J*=6.8 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 7.79 (d, *J*=8.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.58, 25.25, 26.99, 28.60, 28.79, 28.96, 29.11, 30.48, 30.67, 31.69, 32.76, 39.34, 42.67, 43.66, 46.85, 50.51, 57.92, 70.60, 78.69, 127.82, 129.76, 133.23, 144.57, 155.10.

m=7(ES155) 9-((*tert*-butoxycarbonyl)((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)nonyl 4-methylbenzenesulfonate. It was synthesized from **ES153** (0.370 g, 0.877 mmol). Elution with petroleum ether/AcOEt (9.5:0.5) afforded **ES155** as an oil: 0.490 g (97%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.82 (s, 6H), 1.06-1.40 (m, 18H), 1.42 (s, 9H), 1.56-1.63 (m, 2H), 1.68-1.74 (m, 4H), 1.90-1.91 (m, 2H), 2.11-2.12 (m, 1H), 2.43 (s, 3H), 3.17 (t, *J*=8.0 Hz, 2H), 4.00 (t, *J*=6.4 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 7.75 (d, *J*=8.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.61, 25.30, 27.10, 28.60, 28.80, 28.86, 29.22, 29.40, 30.49, 30.69, 31.74, 32.77, 39.34, 42.69, 43.71, 46.86, 50.52, 57.93, 70.63, 76.67, 76.98, 77.30, 78.71, 127.85, 129.76, 133.24, 144.57, 155.13.

In this Preparation I, all intermediates (IIc) are novel. Therefore, these intermediates are a further object of the present invention.

Examples 1-6



In a pressure tube (Sigma Aldrich, ACE pressure tube) a mixture of the appropriate activated alcohol (1.2 eq), N-desmethyl galantamine (1 eq) and Et_3N (2 eq) in CH_3CN (0.1 M) was stirred at 80°C for 48 hours. After evaporating the solvent, the residue was purified by flash chromatography.

Example 1

m=2; *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(4-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)butyl)carbamate. It was synthesized from **ES137** (0.80 g, 0.158 mmol). Elution with CH_2Cl_2/CH_3OH (9:1) afforded the compound of interest as a waxy solid: 0.066 g (83%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 6H), 1.05-1.12 (m, 2H), 1.20-1.32 (AB m, 4H), 1.41-1.50 (m+s, 14H), 1.65-1.72 (AB m, 4H), 1.88 (m, 2H), 1.95-2.04 (m, 2H), 2.08-2.10 (m, 1H), 2.42-2.49 (m, 2H), 2.64-2.67 (m, 1H), 3.12-3.21 (m, 3H), 3.29-3.36 (m, 1H), 3.75-3.82 (s+d, *J*=16.0 Hz, 4H), 4.08-4.12 (m+d, *J*=16.0 Hz, 2H), 4.57 (br m, 1H), 5.97 (dd, J_1=10.2 Hz, J_2=4.3 Hz 1H), 6.06 (d, *J*=10.4 Hz, 1H), 6.57 (d, *J*=8.4, 1H), 6.62 (d, *J*=8.0, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.98, 28.60, 29.52, 29.95, 30.47, 30.67, 32.76, 32.95, 39.33, 42.65, 43.56, 46.85, 48.41, 50.49, 51.49, 53.39, 55.87, 57.67, 57.97, 62.06, 78.79, 88.72, 111.12, 121.94, 126.92, 127.57, 129.45, 133.12, 144.05, 145.79, 155.08. UPLC/MS: Purity 100%, r.t = 2.72 min.MS (ESI+):m/z 607.46 $[M+H]^+$.

Example 2

m=3; *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(5-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)pentyl)carbamate. It was synthesized from **ES97** (0.180 g, 0.34 mmol). Elution with CH_2Cl_2/CH_3OH (9:1) afforded compound of interest as a waxy solid: 0.170 g (96%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.12-1.13 (AB m, 2H), 1.19-1.27 (m, 4H), 1.33-1.36 (m, 2H), 1.44-1.54 (m+s, 14H), 1.69-1.76 (AB m, 4H), 1.92-1.93 (m, 2H), 1.98-2.05 (m, 2H), 2.13-2.14 (m, 1H), 2.35 (br s, exchangeable with D_2O, 1H), 2.45-2.51 (m, 2H), 2.66-2.71 (m, 1H), 3.17-3.22 (m, 3H), 3.29-3.36 (m, 1H), 3.78-3.83 (s+d,

J=16.0 Hz, 4H), 4.11-4.14 (m+d, J=16.0 Hz, 2H), 4.61 (br m, 1H), 5.98 (dd, J_1=10.4 Hz, J_2=4.2 Hz, 1H), 6.09 (d, J=9.2 Hz, 1H), 6.61 (d, J=8 Hz, 1H), 6.66 (d, J=8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.92, 27.17, 28.59, 29.94, 30.48, 30.67, 31.65, 32.76, 32.98, 39.35, 42.66, 43.63, 46.87, 48.38, 50.50, 51.52, 53.21, 55.85, 57.75, 57.93, 62.03, 78.75, 88.68, 111.12, 121.94, 126.91, 127.56, 129.38, 133.12, 144.04, 145.78, 155.10. UPLC/MS: Purity 100%. MS (ESI+):m/z 621.62 $[M+H]^+$.

Example 3

m=4; *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(6-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)hexyl)carbamate. It was synthesized from **ES104** (0.280 g, 0.524 mmol). Elution with CH_2Cl_2/CH_3OH (9:1) afforded the compound of interest as a waxy solid: 0.190 g (68%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.82 (s, 6H), 1.06-1.14 (AB m, 2H), 1.18-1.35 (m, 9H), 1.43-1.52 (m+s, 13H), 1.67-1.74 (AB m, 4H), 1.90 (m, 2H), 1.96-2.07 (m, 2H), 2.11-2.12 (m, 1H), 2.33 (br s, exchangeable with D_2O, 1H), 2.40-2.50 (m, 2H), 2.65-2.69 (m, 1H), 3.13-3.20 (m, 3H), 3.30-3.37 (m, 1H), 3.77-3.82 (s+d, J=15.6 Hz, 4H), 4.10-4.13 (m+d, J=15.6 Hz, 2H), 4.59 (br m, 1H), 5.98 (dd, J_1= 15.2, Hz, J_2= 4.8 Hz 1H), 6.07 (d, J=10.04 Hz, 1H), 6.59 (d, J=8.4, 1H), 6.64 (d, J=8.4, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ27.39, 27.44, 27.77, 28.84, 29.91, 30.18, 30.73, 30.92, 32.03, 33.01, 33.19, 39.61, 42.91, 43.91, 47.12, 48.64, 50.75, 51.77, 56.11, 58.03, 58.16, 62.30, 78.99, 111.34, 122.21, 127.18, 127.80, 129.68, 133.39, 144.28, 144.02, 155.39. UPLC/MS: Purity 100%. MS (ESI+):m/z 635.64 $[M+H]^+$.

Example 4

m=5; *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(7-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)heptyl)carbamate. It was synthesized from **ES102** (0.290 g, 0.53 mmol). Elution with CH_2Cl_2/CH_3OH (9:1) afforded the compound of interest as a waxy solid: 0.230 g, (81%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.11-1.13 (AB m, 2H), 1.19-1.35 (m, 11 H), 1.43-1.53 (m+s, 13H), 1.69-1.76 (AB m, 4H), 1.92-1.93 (m, 2H), 1.98-2.05 (m, 2H), 2.13-2.14 (m, 1H), 2.44-2.51 (m, 2H), 2.66-2.71 (m, 1H), 3.15-3.21 (m+t, J=8.0, 3H), 3.30-3.37 (m, 1H), 3.80-3.83 (s+d, J=15.2 Hz, 4H), 4.11-4.15 (m+d, J=15.2 Hz, 2H), 4.61 (br m, 1H), 6.00 (dd, J_1= 10.4 Hz, J_2= 4.4 Hz, 1H), 6.09 (d, J=9.2 Hz, 1H), 6.61 (d, J=8.4, 1H), 6.66 (d, J=8.4, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.14, 27.42, 28.60, 29.34, 29.66, 29.94, 30.48, 30.68, 31.71, 32.76, 32.90, 39.33, 42.67, 43.69, 46.85, 48.38, 50.51, 51.46, 55.85, 57.75, 57.92, 62.04, 78.69, 88.71, 111.12, 121.98,

126.91, 127.57, 129.35, 133.13, 144.05, 145.77, 155.11. UPLC/MS: Purity 100%. MS (ESI+):m/z 649.66 $[M+H]^+$.

Example 5

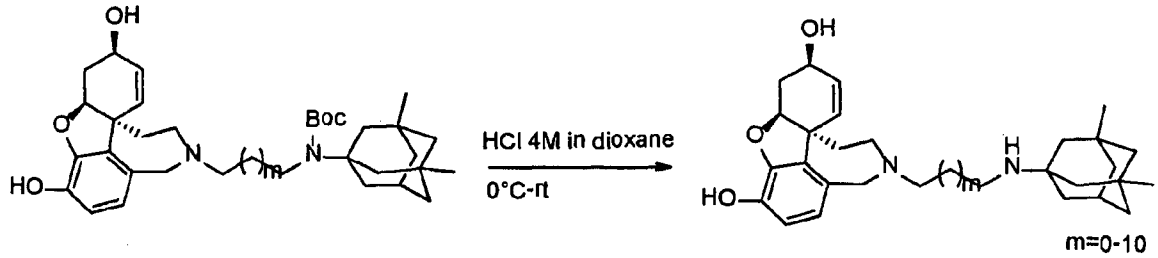
m=6; *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(8-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)octyl)carbamate. It was synthesized from **ES110** (0.210 g, 0.374 mmol). Elution with CH_2Cl_2/CH_3OH (9.25:0.75) afforded the compound of interest as a waxy solid: 0.190 g (92%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.08-1.17 (AB m, 2H), 1.21-1.37 (m, 13 H), 1.41-1.53 (m+s, 13H), 1.70-1.77 (AB m, 4H), 1.92-1.93 (m, 2H), 1.98-2.09 (m, 2H), 2.13-2.15 (m, 1H), 2.41-2.54 (m, 2H), 2.65-2.70 (m, 1H), 3.15-3.23 (m, 3H), 3.32-3.38 (m, 1H), 3.79-3.84 (s+AB d, *J*=14.8 Hz, 4H), 4.11-4.15 (m+AB d, *J*=15.2 Hz, 2H), 4.60 (br m, 1H), 6.00 (dd, J_1= 10, Hz, J_2= 4.4 Hz, 1H), 6.09 (d, *J*=9.0 Hz, 1H), 6.61 (d, *J*=8.4, 1H), 6.66 (d, *J*=8.4, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.07, 27.37, 28.60, 28.94, 29.28, 29.96, 30.48, 30.67, 31.71, 32.75, 32.91, 39.33, 42.68, 43.70, 46.85, 48.38, 50.52, 51.57, 55.78, 55.83, 55.88, 57.91, 62.03, 78.66, 88.64, 88.71, 111.12, 121.96, 126.94, 127.55, 129.38, 133.14, 144.03, 145.78, 155.10. UPLC/MS: Purity 100%. MS (ESI+):m/z 663.70$[M+1]^+$.

Example 6

m=7; *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(9-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)nonyl)carbamate. It was synthesized from **ES155** (0.200 mg, 0.347 mmol). Elution with CH_2Cl_2/CH_3OH (9:1) afforded the compound of interest as a waxy solid: 0.160 g (83%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.08-1.17 (AB m, 2H), 1.20-1.37 (m, 15 H), 1.41-1.55 (m+s, 13H), 1.70-1.77 (AB m, 4H), 1.92-1.93 (m, 2H), 1.98-2.05 (m, 2H), 2.13-2.15 (m, 1H), 2.44-2.51 (m, 2H), 2.66-2.71 (m, 1H), 3.16-3.22 (m+t, *J*=8.0, 3H), 3.32-3.39 (m, 1H), 3.81-3.84 (s+AB d, *J*=15.2 Hz, 4H), 4.12-4.16 (m+AB d, *J*=15.2 Hz, 2H), 4.61 (br m, 1H), 6.00 (dd, J_1= 10.4, Hz, J_2= 4.8 Hz, 1H), 6.08 (d, *J*=10.0 Hz, 1H), 6.61 (d, *J*=8.4, 1H), 6.66 (d, *J*=8.4, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.13, 27.33, 27.35, 28.60, 29.31, 29.48, 29.58, 29.66, 29.93, 30.49, 30.68, 31.75, 32.76, 32.83, 39.33, 42.68, 43.73, 46.84, 48.36, 50.52, 51.43, 55.86, 57.92, 62.03, 78.68, 88.69, 111.14, 122.04, 126.86, 127.61, 129.80, 133.12, 144.09, 145.78, 155.12. UPLC/MS: purity 99%. MS (ESI+): m/z 677.7$[M+1]^+$.

Examples 7-12

Deprotection of nitrogen



HCl 4M in dioxane (1 mL) was carefully added to the appropriate Boc derivative (1 eq.) at 0 °C and the solution was allowed to stir at room temperature for 2 hours. After removing the solvent the obtained residue was purified by flash chromatography.

Example 7

m=2; (4aS,6R,8aS)-11-(4-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)butyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol. It was synthesized from the compound of Example 1 (0.066 g, 0.109 mmol). Elution with CH_2Cl_2/CH_3OH/33% aqueous ammonia (9:1:0.1) afforded the compound of interest as a waxy solid: 0.050 g (91%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.08-1.16 (AB m, 2H), 1.25-1.37 (m, 9 H), 1.52-1.61 (m, 6H), 1.98-2.09 (m, 2H), 2.13-2.14 (m, 1H), 2.48-2.58 (m, 2H), 2.61-2.71 (m, 3H), 3.19-3.33 (2H), 3.82 (AB d, *J*=15.2, 1H), 3.83 (s, 3H), 4.10-4.13 (m+AB d, *J*=15.2 Hz, 2H), 4.60 (br m, 1H), 6.00 (dd, J_1=10.4, Hz, J_2=4.8 Hz, 1H), 6.07 (d, *J*=10.4 Hz, 1H), 6.63 (d, *J*=8.0, 1H), 6.66 (d, *J*=8.0, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.27, 27.91, 29.67, 29.92, 30.06, 30.16, 32.37, 33.01, 40.28, 42.70, 47.69, 48.32, 50.65, 51.46, 51.81, 55.85, 57.62, 62.02, 88.71, 111.19, 122.14, 126.75, 127.70, 128.80, 133.13, 144.17, 145.83. UPLC/MS: Purity 97%, r.t = 3.00 min.MS (ESI+):m/z 507.35 $[M+H]^+$.

Example 8

m=3; (4aS,6R,8aS)-11-(5-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)pentyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol It was synthesized from compound of Example 2 (0.170 g, 0.274 mmol). Elution with CH_2Cl_2/CH_3OH/33% aqueous ammonia (9:1:0.1) afforded the compound of interest as a waxy solid: 0.095 g (66%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.11-1.21 (AB m, 2H), 1.26-1.35 (m, 11 H), 1.46-1.52 (m, 6H), 1.98-2.03 (m, 2H), 2.13-2.14 (m, 1H), 2.42-2.50 (m, 2H), 2.59 (t, *J*=7.6, 2H), 2.66-2.71 (m, 1H), 3.16-3.17 (1H), 3.33-3.34 (m, 1H), 3.79 (AB d, *J*=15.2, 1H), 3.83 (s, 3H), 4.10-4.13 (m+AB d, *J*=15.2 Hz, 2H), 4.60 (br m, 1H), 6.00 (dd, J_1=10.4, Hz, J_2=4.8 Hz, 1H), 6.08 (d, *J*=10.0 Hz, 1H), 6.60 (d, *J*=8.4, 1H), 6.65 (d, *J*=8.4, 1H). ^{13}C-NMR

($CDCl_3$, 100 MHz) δ 25.14, 27.25, 29.94, 30.17, 30.23, 32.37, 32.94, 40.43, 42.85, 48.41, 50.79, 51.52, 55.88, 57.76, 62.07, 88.71, 111.13, 121.97, 126.96, 127.53, 129.52, 133.14, 144.03, 144.77. UPLC/MS: Purity 97%, MS (ESI+):m/z 521.58 $[M+H]^+$.

Example 9

m=4; (4aS,6R,8aS)-11-(6-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)hexyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol. It was synthesized from the comound of Example 3 (0.160 g, 0.252 mmol). Elution with CH_2Cl_2/CH_3OH/33% aqueous ammonia (9:1:0.1) afforded the compound of interest as a waxy solid: 0.075 g (56%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.09-1.15 (AB m, 2H), 1.18-1.37 (m, 11H), 1.42-1.54 (m, 8H), 1.98-2.04 (m, 2H), 2.13-2.14 (m, 1H), 2.42-2.51 (m, 2H), 2.60 (t, *J*=7.6, 2H), 2.66-2.71 (m, 1H), 3.16-3.17 (1H), 3.31-3.33 (m, 1H), 3.79 (AB d, *J*=16.0, 1H), 3.83 (s, 3H), 4.10-4.13 (m+AB d, *J*=16.0 Hz, 2H), 4.60 (br m, 1H), 6.00 (dd, J_1=10.4, Hz, J_2=4.8 Hz, 1H), 6.08 (d, *J*=10.0 Hz, 1H), 6.60 (d, *J*=8.4, 1H), 6.65 (d, *J*=8.4, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 22.66, 26.67, 27.21, 27.38, 29.67, 29.94, 30.14, 30.21, 31.89, 32.38, 32,95, 33.66, 40.45, 42.80, 47.95, 48.41, 50.74, 51.50, 53.66, 55.85, 55.88, 57.77, 62.07, 88.70, 111.11, 121.97, 126.97, 127.51, 129.56, 133.15, 144.00. 145.76. UPLC/MS: Purity 100%. MS (ESI+):m/z 535.59 $[M+H]^+$.

Example 10

m=5; (4aS,6R,8aS)-11-(7-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)heptyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol. It was synthesized from the compound of Example 4 (0.130 g, 0.200 mmol). Elution with CH_2Cl_2/CH_3OH (9:1) afforded the compound of interest as a waxy solid: 0.070 g (64%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.08-1.15 (AB m, 2H), 1.23-1.34 (m, 15H), 1.44-1.51 (m, 6H), 1.94-2.07 (m, 2H), 2.13 (br m, 1H), 2.40-2.52 (m, 2H), 2.57 (t, *J*=7.2 Hz, 2H), 2.66-2.69 (m, 1H), 3.14-3.18 (1H), 3.31-3.37 (m, 1H), 3.79 (AB d, *J*=15.2, 1H), 3.83 (s, 3H), 4.09-4.15 (m+AB d, *J*=15.2 Hz, 2H), 4.60 (br m, 1H), 5.99 (dd, J_1=10.4, Hz, J_2=4.8 Hz, 1H), 6.08 (d, *J*=10.0 Hz, 1H), 6.61 (d, *J*=8.4, 1H), 6.65 (d, *J*=8.4, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.35, 27.50, 27.55, 27.72, 29.40, 29.91, 30.05, 30.16, 32.14, 32.72, 33.19, 38.29, 40.36, 42.46, 45.58, 48.64, 50.41, 51.74, 56.11, 57.25, 58.02, 62.31, 88.94, 111.37, 122.21, 127.21, 127.77, 129.74, 133.39, 144.25, 146.01. UPLC/MS: Purity 100%. MS (ESI+):m/z 549.6$[M+H]^+$.

Example 11

m=6; (4aS,6R,8aS)-11-(8-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)octyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol. It was synthesized from the compound of Example 5 (0.160 g, 0.241 mmol). Elution with CH_2Cl_2/CH_3OH (9:1) afforded the compound of interest as a waxy solid: 0.093 g (68%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 6H), 1.14-1.15 (AB m, 2H), 1.22-1.37 (m, 13H), 1.43-1.53 (m, 7H), 1.64-1.68 (m, 4H), 1.98-2.05 (m, 2H), 2.16-2.17 (m, 1H), 2.43-2.49 (m, 2H), 2.66-2.70 (m, 2H), 3.16-3.17 (m, 1H), 3.29-3.35 (m, 1H), 3.79 (AB d, *J*=15.2, 1H), 3.83 (s, 3H), 4.10-4.15 (m+AB d, *J*=15.2 Hz, 2H), 4.61 (br m, 1H), 6.00 (dd, J_1=10.4, Hz, J_2= 4.8 Hz, 1H), 6.08 (d, *J*=10.0 Hz, 1H), 6.61 (d, *J*=8.4, 1H), 6.66 (d, *J*=8.4, 1H). ^{13}C-NMR($CDCl_3$, 100 MHz) δ 27.27, 27.30, 27.40, 29.25, 29.51, 29.66, 29.94, 30.06, 32.42, 32.97, 40.18, 42.48, 46.21, 50.43, 51.46, 55.84, 55.90, 58.60, 62.07, 88.74, 111.12, 121.97, 126.97, 127.53, 129.51, 133.15, 144.01, 145.77, 177.21. UPLC/MS: Purity 100%. MS (ESI+):m/z 563.43 $[M+H]^+$.

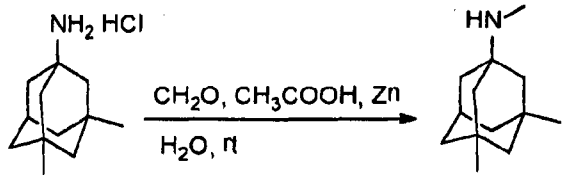
Example 12

m=7; (4aS,6R,8aS)-11-(9-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)nonyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol. It was synthesized from the compound of Example 6 (0.095 g, 0.138 mmol). Elution with CH_2Cl_2/CH_3OH (9:1) afforded the compound of interest as a waxy solid: 0.060 (75%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85 (s, 6H), 1.11-1.14 (AB m, 2H), 1.26-1.59 (m, 25 H), 1.98-2.09 (m, 2H), 2.16-2.17 (m, 1H), 2.40-2.53 (m, 2H), 2.60-2.71 (m, 3H), 3.15-3.18 (m, 1H), 3.21-3.37 (m, 1H), 3.79 (AB d, *J*=15.2, 1H), 3.83 (s, 3H), 4.10-4.14 (m+AB d, *J*=15.2 Hz, 2H), 4.61 (br m, 1H), 6.00 (dd, J_1= 10.4 Hz, J_2= 4.8 Hz, 1H), 6.10 (d, *J*=10.0 Hz, 1H), 6.61 (d, *J*=8.4, 1H), 6.65 (d, *J*=8.4, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.35, 27.45, 29.40, 29.48, 29.52, 29.95, 30.12, 30.19, 32.40, 32.98, 40.56, 42.76, 48.41, 50.70, 51.50, 55.87, 57.82, 62.07, 88.71, 111.10, 121.95, 126.98, 127.51, 129.62, 133.15, 143.10, 145.77. UPLC/MS: purity 99%. MS (ESI+): m/z 577.6$[M+1]^+$.

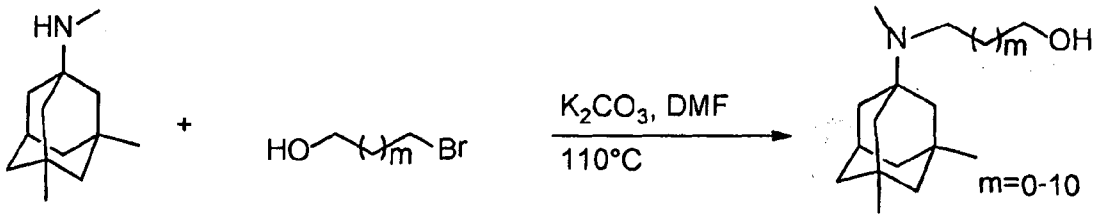
Preparation II

General synthesis of Compounds of Formula (I) wherein X is $(CH_2)_m$, as defined above, Y and Z are absent, R is C1-C4 alkyl, preferably methyl.

Step 1



(1R,3R,5S,7R)-N,3,5-trimethyladamantan-1-amine. To a solution of Memantine hydrochloride (0.720 g, 3.33 mmol) in dioxane/H_2O (1:1) was sequentially added glacial acetic acid (0.382 ml, 6.66 mmol), Zn duster (0.436 g, 6.66 mmol), and 35% aqueous formaldehyde (0.833 ml, 16.65 mmol). The mixture was allowed to stir at 30 °C for 2 days. Then, saturated NH_4Cl aqueous solution was added (5 mL), the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH/ 33% aqueous NH3 9:1:1.8) to achieve the desired compound as a white solid (0.480 g, 75%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.76 (s, 6H), 1.04-1.05 (AB m, 2H), 1.15-1.23 (m, 8H), 1.40-1.41 (m, 2H), 2.05-2.07 (m, 1H), 2.26 (s, 3H), 2.75 (br s, exchangeable with D_2O, 1H).



(IIIa)

In a pressure tube (Sigma Aldrich, ACE pressure tube) the appropriate Bromo-alcohol (1.2 eq.) was added to a vigorously stirred solution of N,3,5-trimethyladamantan-1-amine (0.270 g, 1.40 mmol) and K_2CO_3 (0.484 g, 3.50 mmol) in DMF (4 ml). The reaction mixture was stirred at 80°C for 48 hours. After evaporating the solvent, the residue was taken up with water and extracted with CH_2Cl_2 (3 × 10 mL). The crude was purified by flash chromatography.

m=2 ES122; 6-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(methyl)amino)hexan-1-ol. It was synthesized from 6-bromo-1-esanol (0.308 mL, 1.68 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:1.5) afforded **ES122** as a waxy solid: 0.370 g (90%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.80 (s, 6H), 1.00-1.10 (AB m, 2H), 1.21-1.38 (M, 12H), 1.43-1.56 (m, 6H), 2.09-2.12 (m, 1H), 2.21 (s, 3H), 2.30-2.38 (m, 2H),

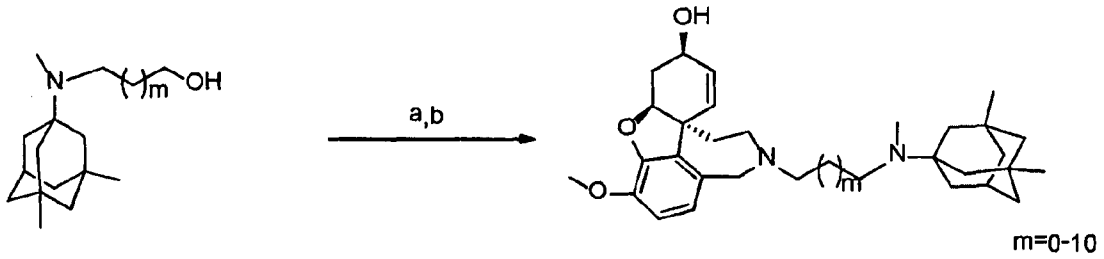
3.57 (t, *J* =6.8 Hz, 2H).). ^{13}C-NMR($CDCl_3$, 100 MHz) δ 25.54, 27.38, 29.05, 30.16, 30.53, 32.30, 32.65, 33.76, 36.71, 42.91, 44.36, 49.58, 50.82, 57.32, 62.59.

m=3 ES128; 7-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(methyl)amino)heptan-1-ol. It was synthesized from 7-bromo-1-eptanol (0.258 mL, 1.68 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:1.4) afforded **ES128** as a waxy solid: 0.375 g (87%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.75 (s, 6H), 0.95-1.03 (AB m, 2H), 1.18-1.47 (m, 19H), 2.03-2.05 (m, 1H), 2.11 (s, 3H), 2.25-2.29 (m, 2H), 3.16 (br s, exchangeable with D_2O, 1H), 3.49 (t, *J* =6.8 Hz,3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.94, 27.86, 29.16, 30.36, 30.79, 32.23, 32.55, 33.99, 36.73, 43.32, 44.81, 49.99, 51.28, 56.80, 62.60.

m=4 ES132; 8-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(methyl)amino)octan-1-ol. It was synthesized from 8-bromo-1-octanol (0.288 mL, 1.68 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:1.5) afforded **ES132** as a waxy solid : 0.410 g (91%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.77 (s, 6H), 0.98-1.06 (AB m, 2H), 1.20-1.26 (m, 14H), 1.33-1.39 (m, 2H), 1.46-1.49 (m, 6H), 2.06-2.07 (m, 1H), 2.14 (s, 3H), 2.28-2.32 (m, 2H), 2.75 (br s, exchangeable with D_2O, 1H), 3.52 (t, *J* =6.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.94, 27.86, 29.16, 30.36, 30.79, 32.23, 32.55, 33.99, 36.73, 43.32, 44.81, 49.99, 51.28, 56.80, 62.60.

In this Preparation II, all intermediates (IIIa) are novel. Therefore, these intermediates are a further object of the present invention.

Examples 13-15



a) TsCl, DMAP, Et_3N, CH_2Cl_2, rt. b) des-methyl-galantamine, Et_3N, CH_3CN, 80°C.

p-TsCl (1 eq.) was added to a mixture of the appropriate alcohol (1 eq.), Et_3N (2 eq.), and DMAP (cat.) in dry CH_2Cl_2 (0.1 M) under N_2 atmosphere with stirring at 0°C. The stirring was continued at room temperature for 3.5 hours. The reaction was quenched with saturated NH_4Cl aqueous solution and extracted with AcOEt (3 x 10 mL). The extract was washed with brine prior to drying over Na_2SO_4, and solvent evaporation.

The crude was then transferred into a pressure tube (Sigma Aldrich, ACE pressure tube) and added with des-methyl-Galantamine (0.5 eq.), and Et_3N (2 eq.) in CH_3CN, with stirring at 80°C for 48 hours. After evaporating the solvent, the residue was purified by flash chromatography.

Example 13

m=2; (4aS,6R,8aS)-11-(6-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)hexyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-enzo[2,3]benzofuro[4,3-cd]azepin-6-ol. It was synthesized from **ES122** (0.210 g, 0.716 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.15) afforded the compound of interest as a waxy solid: 0.085 g (43%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 6H), 1.08-1.17 (AB m, 2H), 1.24-1.33 (m, 9H), 1.38-1.52 (m, 7H), 1.60-1.65 (m, 3H), 1.98-2.07 (m, 2H), 2.19 (br m, 1H), 2.35 (s, 3H), 2.41-2.53 (m, 4H), 2.67-2.71 (m, 1H), 3.11-3.18 (m, 1H), 3.31-3.38 (m, 1H), 3.80 (AB d, J =16 Hz, 1H) 3.83 (s, 3H), 4.10-4.14 (m+AB d, J =16 Hz, 2H), 4.61 (br m, 1H), 6.00 (dd, J_1= 10.0 Hz, J_2= 4.8 Hz, 1H), 6.09 (d, J=10.0 Hz, 1H), 6.61 (d, J=8.4 Hz, 1H), 6.66 (d, J=8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.36, 27.20, 27.38, 27.51, 28.63, 29.94, 30.14, 30.38, 32.48, 32.91, 33.64, 36.45, 41.26, 42.07, 42.67, 44.02, 47.15, 48.41, 49.69, 50.60, 51.48, 55.88, 55.94, 57.78, 62.07, 88.71, 111.13, 121.99, 126.98, 127.52, 129.52, 133.14, 144.01, 145.76. UPLC/MS: Purity 92%, r.t = 1.91 min.MS (ESI+):m/z 549.45$[M+H]^+$.

Example 14

m=3; (4aS,6R,8aS)-11-(6-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)heptyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-enzo[2,3]benzofuro[4,3-cd]azepin-6-ol. It was synthesized from **ES128** (0.190 g, 0.618 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.15) afforded the compound of interest as a waxy solid: 0.084 g (49%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.82 (s, 6H), 1.03-1.08 (AB m, 2H), 1.22-1.36 (m, 14H), 1.40-1.49 (m, 5H), 1.52-1.55 (m, 2H), 1.95-2.00 (m, 2H), 2.12-2.18 (m, 1H), 2.25 (s, 3H), 2.37-2.48 (m, 4H), 2.67-2.67 (m, 1H), 3.11-3.15 (m, 1H), 3.28-3.31 (m, 1H), 3.78 (AB d, J =16 Hz, 1H) 3.83 (s, 3H), 4.07-4.11 (m+AB d, J =16 Hz, 2H), 4.57 (br m, 1H), 5.97 (dd, J_1= 10.0 Hz, J_2= 4.8 Hz 1H), 6.09 (d, J=9.6 Hz, 1H), 6.61 (d, J=8.4 Hz, 1H), 6.66 (d, J=8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.32, 27.54, 29.49, 29.65, 29.94, 30.18, 30.50, 32.33, 32.93, 33.73, 36.69, 42.88, 44.33, 48.40, 49.64, 50.79, 51.48, 55.86, 57.76, 62.07, 88.71,

111.11, 121.97, 126.99, 127.51, 129.53, 133.15, 144.00, 145.75. UPLC/MS: Purity 98%, r.t = 2.09 min.MS (ESI+):m/z 563.48$[M+H]^+$.

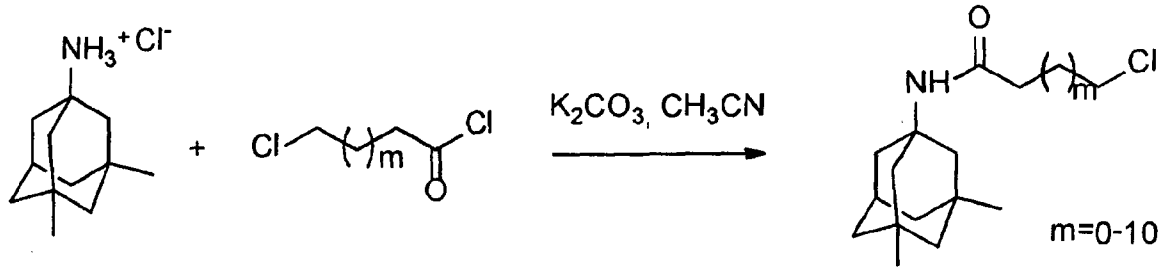
Example 15

m=4; (4aS,6R,8aS)-11-(6-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)octyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-enzo[2,3]benzofuro[4,3-cd]azepin-6-ol. It was synthesized from **ES132** (0.160 g, 0.499 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.15) afforded the compound of interest as a waxy solid: 0.075 g (52%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 6H), 1.01-1.13 (AB m, 2H), 1.25-1.31 (m, 16H), 1.38-1.46 (m, 5H), 1.47-1.50 (m, 2H), 1.94-2.02 (m, 2H), 2.10-2.11 (m, 1H), 2.19 (s, 3H), 2.31-2.38 (m, 4H), 2.40-2.77 (m, 1H), 3.11-3.15 (m, 1H), 3.28-3.32 (m, 1H), 3.78 (AB d, J =16 Hz, 1H) 3.83 (s, 3H), 4.07-4.11 (m+AB d, J =16 Hz, 2H), 4.58 (br m, 1H), 5.97 (dd, J_1= 10.0 Hz, J_2= 5.2 Hz 1H), 6.07 (d, J=10.0 Hz, 1H), 6.58 (d, J=8.4 Hz, 1H), 6.63 (d, J=8.4 Hz, 1H). ^{13}C-NMR($CDCl_3$, 100 MHz) δ 27.45, 29.54, 29.95, 30.24, 30.62, 32.23, 32.98, 33.90, 37.02, 43.08, 44.74, 48.41, 49.70, 50.99, 51.51, 55.87, 57.81, 62.08. UPLC/MS: Purity 94%, r.t = 2.09 min.MS (ESI+):m/z 577.5 $[M+H]^+$.

Preparation III

General synthesis of Compounds of Formula (I) wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is absent, Z is C=O and R is H,

Step 1



(IIIb)

To a vigorously stirred solution of Memantine hydrochloride (0.300 g, 1.40 mmol) and K_2CO_3 (0.480 g, 3.5 mmol) in CH_3CN the appropriate acylating agent was added dropwise. The reaction was stirred at room temperature for 4 hours. After evaporating the solvent the crude was purified by flash chromatography.

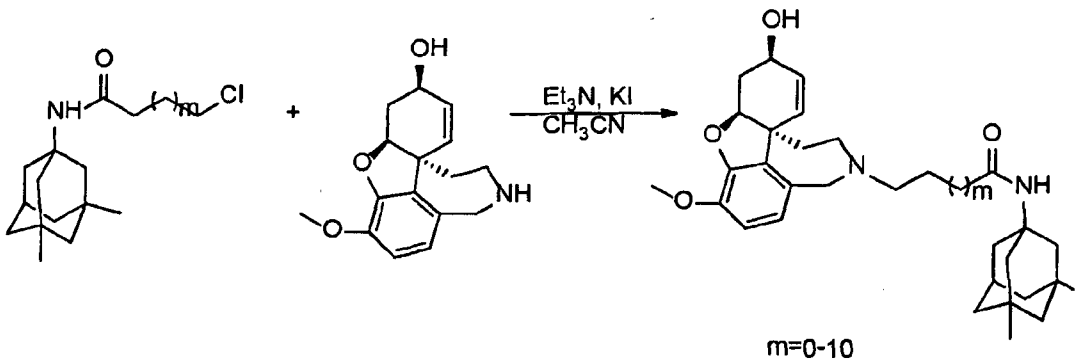
m=1; ES113; 4-chloro-N-((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)butanamide. It was synthesized from 4-chlorobutanoyl chloride (0.16 mL, 1.40 mmol). Elution with petroleum ether/ AcOEt (8.5:1.5) afforded **ES113** as a oil: 0.340 g (86%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.79 (s, 6H), 1.06-1.14 (AB m, 2H), 1.20-1.25 (m, 2H), 1.30-1.34 (m, 2H), 1.55-1.59 (AB m, 4H), 1.77-1.78 (m, 2H), 1.98-2.05 (m, 2H), 2.07-2.10 (m, 1H), 2.22 (t, *J*=7.2 Hz, 2H), 3.54 (t, *J*=6.4 Hz, 2H), 5.28 (br s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.17, 30.01, 32.32, 34.07, 40.15, 42.60, 44.54, 47.56, 50.53, 53.54, 170.78.

m=2; ES82; 5-chloro-N-((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)pentanamide. It was synthesized from 5-chloropentanoyl chloride (0.18 mL, 1.40 mmol). Elution with petroleum ether/ AcOEt (8.5:1.5) afforded **ES82** as a oil: 0.380 g (91%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 6H), 1.07-1.16 (AB m, 2H), 1.23-1.26 (m, 2H), 1.32-1.35 (m, 2H), 1.56-1.63 (AB m, 4H), 1.68-1.80 (m, 6H), 2.07-2.11 (m, 3H), 3.50 (t, *J*=6.4 Hz, 2H), 5.18 (br s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 22.97, 30.10, 31.91, 32.33, 35.56, 40.19, 42.63, 44.66, 47.61, 50.55, 53.44, 171.46.

m=3; ES114; 6-chloro-N-((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)esanamide. It was synthesized from 6-chloroesanoyl chloride (0.21 mL, 1.40 mmol). Elution with petroleum ether/ AcOEt (8.5:1.5) afforded **ES114** as a oil: 0.370 g (85%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.79 (s, 6H), 1.06-1.14 (AB m, 2H), 1.21-1.34 (AB m, 4H), 1.37-1.44 (m, 2H), 1.53-1.62 (m, 6H), 1.70-1.77 (m, 4H), 1.98-2.08 (m, 3H), 3.46-3.49 (m, 2H), 5.31 (br s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 24.88, 26.35, 30.07, 32.29, 37.26, 40.14, 42.62, 44.79, 47.56, 50.55, 53.33, 171.87.

In this Preparation III, all intermediates (IIIa) are novel. Therefore, these intermediates are a further object of the present invention.

Examples 16-18



m=0-10

A mixture of the chloride derivative (1.2 eq.), des-methyl-Galantamine (1 eq.), Et_3N (2 eq.) and KI (cat.) in CH_3CN (0.1M) was stirred at 80°C for 48 hours in a pressure tube (Sigma Aldrich, ACE pressure tube). After evaporating the solvent, the residue was purified by flash chromatography.

Example 16

m=1; 4-((4aS,6R,8aS)-3,6-dimethoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)-N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)butanamide. It was synthesized from **ES113** (0.070 g, 0.247 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.02) afforded the compound of interest as a waxy solid: 0.070 g (65%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.83 (s, 6H), 1.13-1.15 (AB m, 2H), 1.26-1.38 (AB m, 4H), 1.61 (br m, 4H), 1.72-1.79 (m, 4H), 1.98-2.04 (m, 2H), 2.11-2.14 (m, 3H), 2.47-2.55 (m, 3H), 2.65-2.70 (m, 1H), 3.11-3.18 (m, 1H), 3.31-3.38 (m, 1H), 3.77 (AB d, J =16 Hz, 1H) 3.83 (s, 3H), 4.09-4.14 (m+AB d, J =16 Hz, 2H), 4.60 (br m, 1H), 5.57 (br s,1H), 6.00 (dd, J_1= 10.0 Hz, J_2= 4.8 Hz, 1H), 6.09 (d, J=10.0 Hz, 1H), 6.61 (d, J=8.4 Hz, 1H), 6.66 (d, J=8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 22.92, 30.05, 32.30, 33.04, 35.24, 40.17, 42.63, 47.60, 48.33, 50.56, 51.52, 53.25, 58.81, 55.89, 55.96, 57.60, 61.98, 88.68, 111.24, 122.04, 126.82, 127.65, 129.01, 133.10, 144.11, 145.82, 172.01. UPLC/MS: Purity 96%. MS (ESI+):m/z 521.38 $[M+H]^+$.

Example 17

m=2; N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)-5-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)pentanamide It was synthesized from **ES82** (0.070 g, 0.235 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.02) afforded the compound of interest as a waxy solid: 0.070 g (67%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.83 (s, 6H), 1.11-1.19 (AB m, 2H), 1.24-1.47 (AB m, 4H), (m, 4H), 1.49-1.60 (m, 5H), 1.62-1.80 (br m, 2H), 1.98-2.09 (m, 2H), 2.11-2.14 (m, 3H), 2.44-2.54 (m, 2H), 2.65-2.70 (m, 1H), 3.13-3.17 (m, 1H), 3.31-3.37 (m, 1H), (AB d, J =15.6 Hz, 1H) 3.83 (s, 3H), 4.09-4.14 (m+AB d, J =15.6 Hz, 2H), 4.60 (br m, 1H), 5.12 (br s, 1H), 6.00 (dd, J_1= 9.6 Hz, J_2= 5.2 Hz, 1H), 6.08 (d, J=10.0 Hz, 1H), 6.60 (d, J=8.0 Hz, 1H), 6.65 (d, J=8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 23.51, 26.87, 30.12, 32.34, 32.99, 37.50, 40.21, 42.63, 47.65, 48.38, 50.57,

51.60, 53.34, 55.92, 57.67, 62.05, 88.72, 111.18, 121.96, 126.94, 127.57, 129.38, 133.15, 144.07, 145.81, 171.97. UPLC/MS: Purity 100%. MS (ESI+):m/z 535.42 $[M+H]^+$.

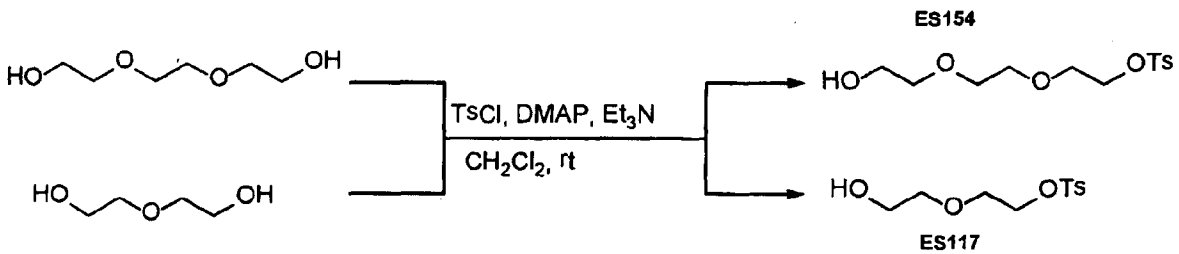
Example 18

m=3; N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)-6-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)hexanamide. It was synthesized from **ES114** (0.070 g, 0.224 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.02) afforded the compound of interest as a waxy solid: 0.080 g (78%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.83 (s, 6H), 1.07-1.14 (AB m, 2H), 1.18-1.38 (AB m, 4H), 1.48-1.66 (m, 10H), 1.81 (br m, 2H), 1.96-2.06 (m, 4H), 2.12 br (m, 1H), 2.41-2.54 (m, 3H), 2.41-2.54 (m, 1H), 3.14-3.18 (m, 1H), 3.27-3.37 (m, 1H), 3.77 (AB d, *J* =16 Hz, 1H) 3.83 (s, 3H), 4.09-4.14 (m+AB d, *J* =16 Hz, 2H), 4.60 (br m, 1H), 5.23 (br s, 1H), 6.00 (dd, J_1= 10.0 Hz, J_2= 4.8 Hz, 1H), 6.09 (d, *J*=10.0 Hz, 1H), 6.61 (d, *J*=8.4 Hz, 1H), 6.66 (d, *J*=8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.54, 26.84, 27.08, 29.63, 30.04, 32.30, 32.85, 37.52, 40.15, 42.62, 47.58, 48.35, 50.55, 51.43, 53.30, 55.81, 55.87, 57.65, 62.01, 61.99, 88.67, 111.18, 121.98, 126.91, 127.53, 129.25, 133.09, 144.01, 145.74, 172.17. UPLC/MS: Purity 100%. MS (ESI+):m/z 549.45 $[M+H]^+$.

Preparation IV

General synthesis of compounds of formula (I), wherein X is $(CH_2)_m$ and m is comprised between 2 and 12; Y is O or $O(CH_2)_pO$, wherein p is comprised between 1 and 6; Z is selected from the group consisting of $(CH_2)_n$, wherein n is comprised between 1 and 12; R is H, C_1-C_4 alkyl or a protective group, such as Boc, Fmoc, Cbz.

Step 1



p-TsCl (1.2 eq.) was added dropwise to a mixture of the appropriate di-alcohol, Et_3N (1 eq.), and DMAP (cat.) in dry CH_2Cl_2 (0.01 M) under N_2 atmosphere with stirring at 0°C. The stirring was continued at room temperature for 4 hours. The reaction was quenched with saturated NH_4Cl aqueous solution and the whole was extracted with AcOEt. The

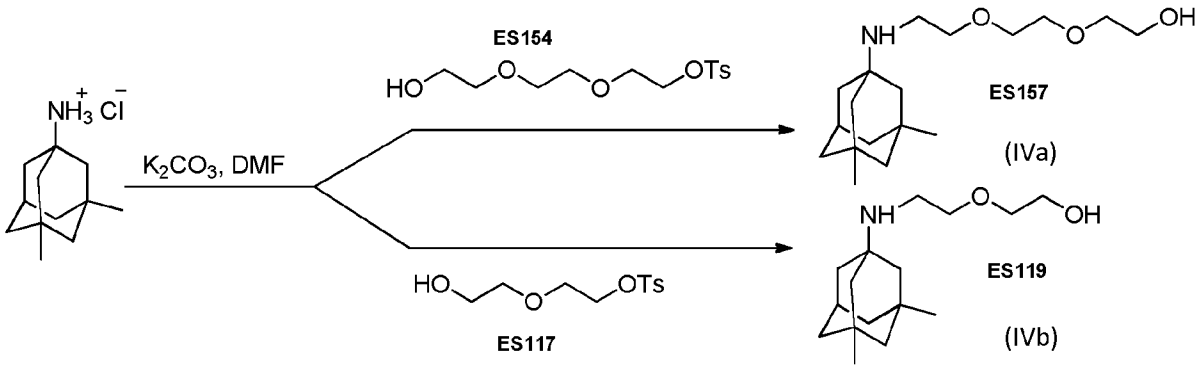
extract was washed with brine, dried over Na_2SO_4, and, following solvent evaporation, the crude was purified by flash chromatography.

ES154; 2-(2-(2-hydroxyethoxy)ethoxy)ethyl 4-methylbenzenesulfonate. It was synthesized from triethylene glycol (1.000 g, 6.66 mmol). Elution with petroleum ether/ AcOEt (2:8) afforded **ES154** as a waxy solid: 0.450 g (22%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H), 2.99 (br s, exchangeable with D_2O, 1H), 3.40-3.63 (m, 10H), 4.02 (t, *J*=4.8 Hz, 2H), 7.21 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.48, 42.73, 61.39, 68.47, 69.24, 70.06, 70.42, 71.12, 72.46, 127.79, 129.81, 132.71, 144.87.

ES117; 2-(2-hydroxyethoxy)ethyl 4-methylbenzenesulfonate. It was synthesized from diethylene glycol (1.000 g, 9.42 mmol). Elution with petroleum ether/ AcOEt (5:5) afforded **ES117** as a waxy solid: 0.850 g (35%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.26 (br s, exchangeable with D_2O, 1H), 2.30 (s, 3H), 3.54 (t, *J*=5.6 Hz, 2H), 3.65-3.70 (m, 4H), 4.20 (t, *J*=4.8 Hz, 2H), 7.35 (d, *J*=8.4 Hz, 2H), 7.80 (d, *J*=8.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.58, 61.56, 68.51, 69.20, 72.47, 127.91, 129.83, 132.90, 144.95.

Step 2

Synthesis of compounds ES157, ES119



In a pressure tube (Sigma Aldrich, ACE pressure tube) the appropriate activated alcohol (1.2 eq.) was added to a vigorously stirred solution of Memantine hydrochloride (1 eq) and K_2CO_3 (2.5 eq) in DMF (0.1 M). The reaction mixture was stirred at 80°C for 48 hours. After evaporating the solvent, the residue was taken up with water and extracted with CH_2Cl_2 (3 x 10 mL). The crude was purified by flash chromatography.

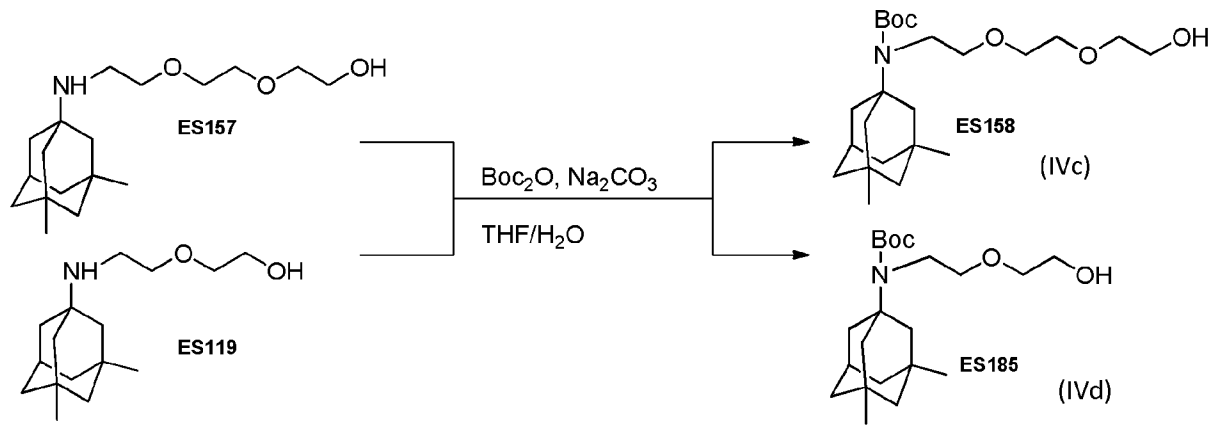
ES157; 2-(2-(2-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethoxy)ethanol. It was synthesized from **ES154** (0.450 g, 1.48 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.13) afforded **ES157** as a waxy solid: 0.230 g (60%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.73 (s, 6H), 0.97-1.07 (AB m, 2H), 1.10-1.20 (m, 8H), 1.31-1.38 (m, 2H), 2.02-2.03 (br m, 1H), 2.60-2.70 (m, 2H), 3.48-3.67 (m, 10H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 30.05, 32.26, 40.00, 40.90, 42.50, 42.91, 48.59, 50.85, 51.94, 52.28, 61.18, 69.87, 70.56, 71.23.

ES119; 2-(2-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethanol. It was synthesized from **ES117** (0.210 g, 0.81 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.13)afforded **ES119** as a waxy solid: 0.160 g (88%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.77 (s, 6H), 1.04-1.08 (AB m, 2H), 1.17-1.26 (m, 8H), 1.42-1.43 (m, 2H), 2.04-2.08 (br m, 1H), 2.72 (t, *J*=5.2 Hz, 2H), 3.08 (br m, exchangeable with D_2O, 1H), 3.50-3.57 (m, 4H).3.62-3.64 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 30.06, 30.21, 32.31, 40.28, 40.76, 42.85, 48.46, 50.81, 52.39, 61.57, 71.06, 72.59.

In this Preparation IV, all intermediates (IVa) and (IVb) are novel. Therefore, these intermediates are a further object of the present invention.

Step 3

Synthesis of compounds ES158, ES185.



The appropriate secondary amine (1 eq.) was dissolved in THF/H_2O (1:1) and treated with Na_2CO_3 (2.5 eq.) and di-*tert*-butyl dicarbonate (1.5 eq). The resultant suspension was allowed to stir at room temperature overnight. The solvent was then removed in vacuo yielding a residue which was dissolved in water and extracted with AcOEt (3 × 15

mL). The extracts were combined, washed with brine, dried over Na_2SO_4, concentrated by evaporation, and purified by flash chromatography.

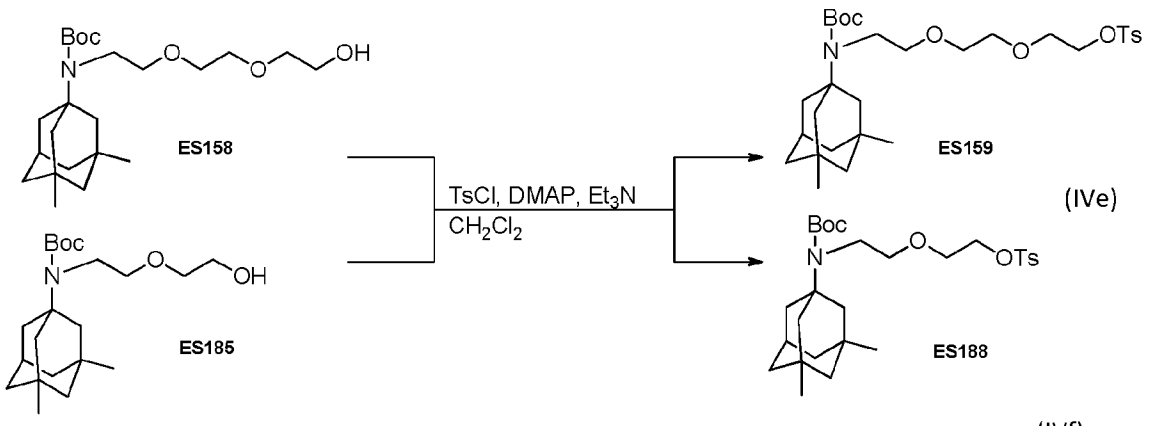
ES158; *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(2-(2-(2-hydroxyethoxy)ethoxy)ethyl)carbamateethanol. It was synthesized from **ES157** (0.230 g, 0.740 mmol). Elution with petroleum ether/ AcOEt (5:5) afforded **ES158** as a waxy solid: 0.160 g (53%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.78 (s, 6H), 1.01-1.05 (AB m, 2H), 1.16-1.28 (AB m, 4H), 1.38 (s, 9H), 1.65-1.68 (AB m, 4H), 1.85 (br m, 2H), 2.06-2.07 (m, 1H), 3.40-3.52 (m, 4H), 3.53-3.59 (m, 6H), 3.66 (t, *J*=4.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.52, 30.43, 30.62, 32.77, 39.23, 42.51, 42.57, 46.79, 50.44, 58.03, 61.62, 70.36, 70.43, 70.91, 72.52, 79.23, 154.99.

ES185; *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(2-(2-hydroxyethoxy)ethyl)carbamate. It was synthesized from **ES119** (0.160 g, 0.599 mmol). Elution with petroleum ether/ AcOEt (5:5) afforded **ES185** as a waxy solid: 0.140 g (64%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.82 (s, 6H), 1.09-1.11 (AB m, 2H), 1.21-1.33 (AB m, 4H), 1.43 (s, 9H), 1.70-1.78 (AB m, 4H), 1.90 (br m, 2H), 2.11-2.14 (m, 1H), 3.46-3.52 (m, 4H), 3.53-3.55 (m, 2H), 3.70 (t, *J*=4.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.55, 30.47, 30.67, 32.81, 39.40, 42.62, 46.92, 50.48, 58.08, 61.86, 70.99, 72.10, 79.36, 155.15.

In this Preparation IV, all intermediates (IVc) and (IVd) are novel. Therefore, these intermediates are a further object of the present invention.

Step 4

Synthesis of compounds ES159, ES188.



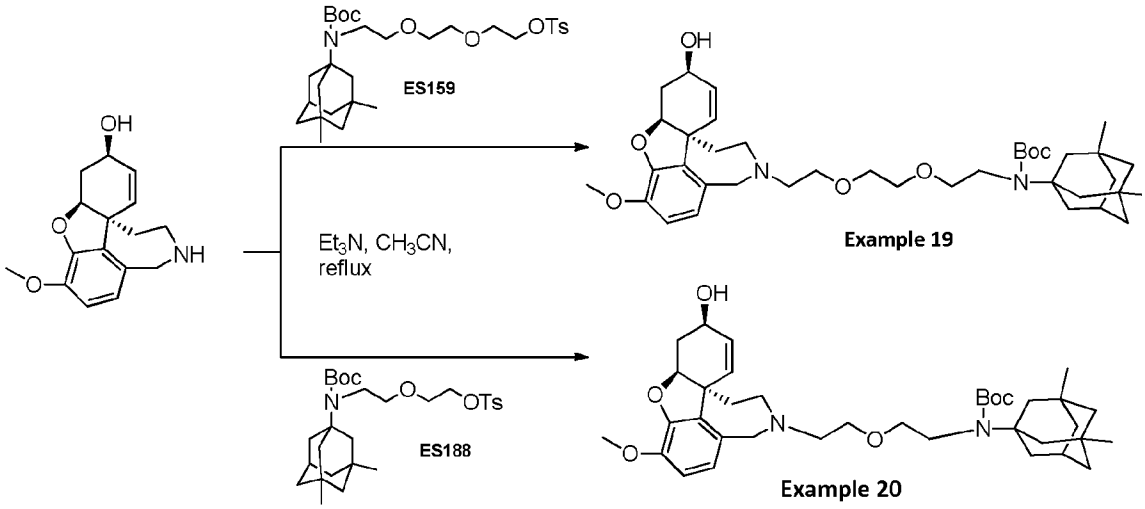
p-TsCl (1 eq.) was added to a mixture of the appropriate alcohol (1 eq), Et_3N (2 eq.), and DMAP (cat.) in dry CH_2Cl_2 (0.1 M) under N_2 atmosphere with stirring at 0°C. The stirring was continued at room temperature for 3.5 hours. The reaction was quenched with saturated NH_4Cl aqueous solution and the whole was extracted with AcOEt. The extract was washed with brine prior to drying over Na_2SO_4, and solvent evaporation. The tosylate activated derivative was then purified by flash chromatography.

ES159; 5-((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)-2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl 4-methylbenzenesulfonate. It was synthesized from **ES158** (0.160 g, 0.390 mmol). Elution with petroleum ether/AcOEt (7:3) afforded **ES159** as a waxy solid: 0.120 g (55%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.79 (s, 6H), 1.06-1.07 (AB m, 2H), 1.18-1.30 (AB m, 4H), 1.40 (s, 9H), 1.70-1.78 (AB m, 4H), 1.87 (br m, 2H), 2.06-2.09 (m, 1H), 2.40 (s, 3H), 3.40 (br m, 4H), 3.47-3.54 (m, 4H), 3.64 (t, *J*=4.8 Hz, 2H), 4.11 (t, *J*=5.2 Hz, 2H), 7.29 (d, *J*=8.0 Hz, 2H), 7.74 (d, *J*=8.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.60, 28.54, 30.47, 30.65, 32.79, 39.22, 42.57, 42.59, 46.77, 50.47, 58.04, 68.70, 69.14, 70.29, 70.72, 71.00, 79.16, 127.92, 129.78, 132.96, 144.75, 154.94.

ES188; 2-(2-((*tert*-butoxycarbonyl)((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethyl 4-methylbenzenesulfonate. It was synthesized from **ES185** (0.140 g, 0.38 mmol). Elution with petroleum ether/AcOEt (8:2) afforded **ES188** as a waxy solid: 0.180 g (91%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.82 (s, 6H), 1.07-1.08 (AB m, 2H), 1.18-1.31 (AB m, 4H), 1.41 (s, 9H), 1.70-1.78 (AB m, 4H), 1.87 (br m, 2H), 2.01-2.10 (m, 1H), 2.42 (s, 3H), 3.37 3.39 (m, 4H), 3.60 (t, *J*=4.8 Hz, 2H), 4.12 (t, *J*=4.8 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 7.75 (d, *J*=8.4 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.61, 28.54, 30.44, 30.67, 32.81, 39.27, 42.50, 42.60, 46.79, 50.45, 58.07, 68.42, 69.12, 71.10, 79.26, 127.92, 129.79, 133.02, 144.76, 154.96.

In this Preparation IV, all intermediates (IVe) and (IVf) are novel. Therefore, these intermediates are a further object of the present invention.

Examples 19-20



In a pressure tube (Sigma Aldrich, ACE pressure tube) a mixture of the appropriate activated alcohol (1 eq), des-methyl-Galantamine (1 eq) and Et_3N (2 eq) in CH_3CN (0.1 M) was stirred at 80°C for 48 hours. After evaporating the solvent, the residue was purified by flash chromatography.

Example 19

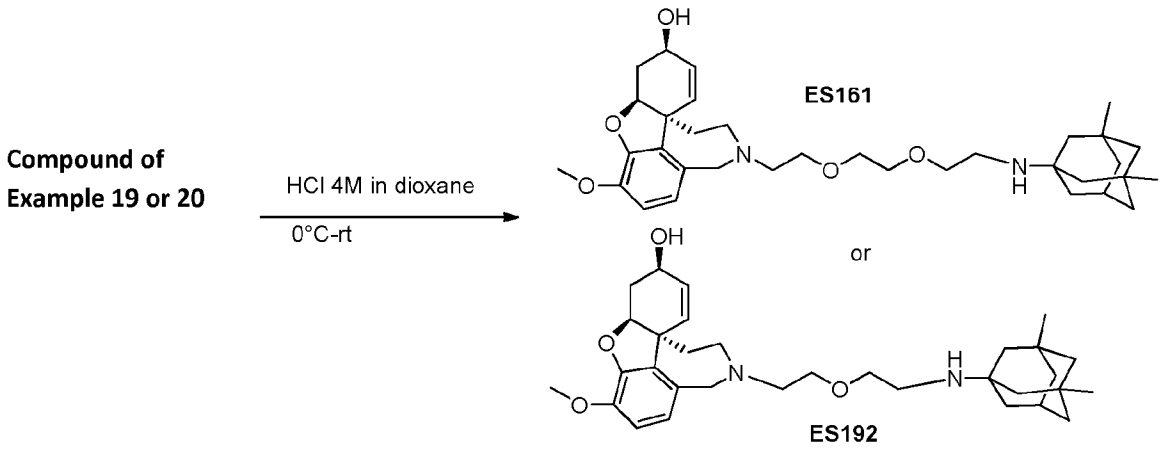
***tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(2-(2-(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethoxy)ethoxy)ethyl)carbamate.** It was synthesized from **ES159** (0.120 g, 0.212 mmol). Elution with CH_2Cl_2/CH_3OH (9:1) afforded the compound of interest as a waxy solid: 0.080 g (57%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.80 (s, 6H), 1.03-1.01 (AB m, 2H), 1.18-1.31 (AB m, 4H), 1.42 (s, 9H), 1.46-1.49 (m, 1H), 1.69 (AB m, 4H), 1.89 (br m, 2H), 1.94-2.09 (m, 3H), 2.61-2.67 (m, 1H), 2.71 (t, *J*=4.8 Hz, 2H), 3.15-3.19 (m, 1H), 3.35-3.39 (m, 1H), 3.40-3.43 (m, 4H), 3.53-3.59 (m, 6H), 3.79 (s, 3H), 3.83 (d, *J*=15.2 Hz, 1H), 4.09-4.11 (m, 1H), 4.15 (d, *J*=15.6 Hz, 1H), 4.60 (br m, 1H), 5.96 (dd, J_1=10.0, J_2=4.4 Hz, 1H), 6.00 (d, *J*=10.0 Hz, 1H), 6.57 (d, *J*=8.4 Hz, 1H), 6.62 (d, *J*=8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.56, 29.93, 30.47, 30.67, 32.81, 32.95, 39.23, 42.61, 46.78, 48.41, 50.48, 51.91, 55.87, 57.98, 58.06, 62.03, 69.34, 70.44, 70.98, 79.14, 88.69, 111.14, 122.12, 126.84, 127.60, 128.65, 129.36, 133.12, 144.11, 145.83, 154.94.

Example 20

***tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(2-(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethoxy)ethyl)carbamate.** It was synthesized from **ES188** (0.180 g, 0.345

mmol). Elution with CH_2Cl_2/CH_3OH (9.5:0.5) afforded **COMPOUND OF INTEREST** as a waxy solid: 0.115 g (53%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.82 (s, 6H), 1.09-1.10 (AB m, 2H), 1.20-1.33 (AB m, 4H), 1.42 (s, 9H), 1.47-1.51 (m, 1H), 1.69 (AB m, 4H), 1.90-1.91 (br m, 2H), 1.95-2.11 (m, 3H), 2.63-2.64 (m, 1H), 2.67-2.71 (m, 2H), 3.15-3.19 (m, 1H), 3.36-3.40 (m, 1H), 3.42-3.45 (m, 4H), 3.48-3.56 (m, 2H), 3.80 (s, 3H), 3.83 (d, *J*=15.2 Hz, 1H), 4.10-4.11 (m, 1H), 4.16 (d, *J*=15.6 Hz, 1H), 4.58 (br m, 1H), 5.97 (dd, J_1=10.0, J_2=4.4 Hz, 1H), 6.00 (d, *J*=10.0 Hz, 1H), 6.57 (d, *J*=8.4 Hz, 1H), 6.62 (d, *J*=8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.57, 29.93, 30.47, 30.68, 32.81, 33.00, 39.28, 42.61, 46.81, 48.41, 50.48, 50.72, 51.91, 53.39, 55.88, 58.02, 58.08, 62.04, 69.01, 70.90, 79.17, 88.71, 111.14, 122.06, 126.85, 127.61, 129.40, 133.12, 144.12, 145.80, 154.98.

Examples 21-22



HCl 4M in dioxane (1 mL) was carefully added to the appropr derivative (1 eq.) at 0 °C and the solution was allowed to stir at room temperature for 2 hours. After removing the solvent the obtained residue was purified by flash chromatography.

Example 21

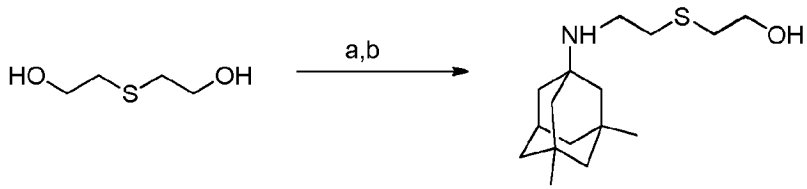
(4aS,6R,8aS)-11-(2-(2-(2-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethoxy)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol. It was synthesized from the compound of Example 19 (0.080 g, 0.120 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.05) afforded **THE COMPOUND OF INTEREST** as a waxy solid: 0.060 g (88%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.08-1.16 (AB m, 2H), 1.26-1.37 (m, 8H), 1.51-1.54 (m, 3H), 1.98-2.09 (m, 2H), 2.15 (br m, 1H), 2.66-2.70 (m, 1H), 2.74 (t,

J=5.8 Hz, 2H), 2.83 (t, *J*=4.8 Hz, 2H), 3.21-3.25 (m, 1H), 3.38-3.44 (m, 1H), 3.54-3.67 (m, 8H), 3.83 (s, 3H), 3.88 (d, *J*=15.2 Hz, 1H), 4.13-4.15 (m, 1H), 4.18 (d, *J*=15.2 Hz, 1H), 4.60 (br m, 1H), 6.00 (dd, J_1=10.4, J_2=5.2 Hz, 1H), 6.08 (d, *J*=10.4 Hz, 1H), 6.61 (d, *J*=8.0 Hz, 1H), 6.65 (d, *J*=8.4 Hz, 1H). ^{13}C-NMR($CDCl_3$, 100 MHz) δ 29.92, 30.12, 30.18, 32.38, 32.91, 40.05, 40.29, 42.77, 47.95, 48.40, 50.72, 51.83, 55.87, 57.89, 62.03, 68.99, 70.04, 70.16, 70.27, 88.68, 111.17, 122.21, 126.80, 127.63, 129.22, 133.14, 144.12, 145.82. UPLC/MS: purity 99%. MS (ESI+): m/z 567.5 $[M+1]^+$.

Example 22

(4aS,6R,8aS)-11-(2-(2-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol It was synthesized from compound of Example 20 (0.115 g, 0.184 mmol). Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.05) afforded **THE COMPOUND OF INTEREST** as a waxy solid: 0.085 g (88%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 6H), 1.11-1.01 (AB m, 2H), 1.24-1.33 (m, 4H), 1.36-1.45 (AB m, 4H), 1.54-1.62 (m, 3H), 1.98-2.11 (m, 2H), 2.20 (br m, 1H), 2.66-2.71 (m, 1H), 2.76 (t, *J*=5.2 Hz, 2H), 2.90 (t, *J*=4.8 Hz, 2H), 3.34-3.39 (m, 2H), 3.53-3.62 (m, 2H), 3.71-3.72 (m, 2H), 3.83 (s, 3H), 3.95 (d, *J*=15.2 Hz, 1H), 4.14-4.17 (m+d, *J*=15.2 Hz, 2H), 4.61 (br m, 1H), 6.00-6.08 (m, 2H), 6.65-6.67 (m, 2H).^{13}C-NMR ($CDCl_3$, 100 MHz) δ 30.06, 32.58, 40.34, 42.55, 48.35, 50.50, 51.54, 55.87, 57.30, 62.00, 88.70, 111.27, 122.38, 126.52, 127.86, 133.10, 144.28, 145.83. UPLC/MS: Purity 95%, r.t = 2.24 min.MS (ESI+):m/z 523.35 $[M+H]^+$.

Synthesis of compound ES194

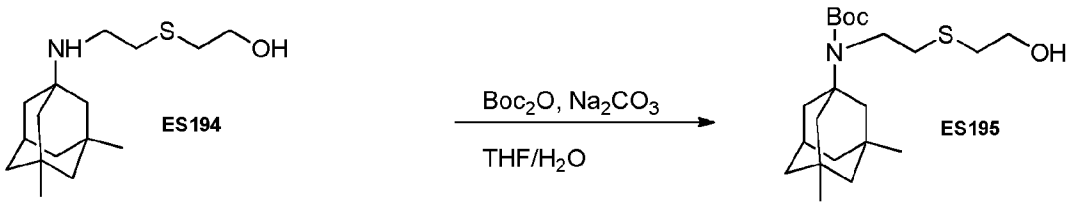


a) TsCl, DMAP, Et_3N, CH_2Cl_2, rt. b) memantine hydrochloride, K_2CO_3, DMF, 80°C.

ES194. **2-((2-(((1s,3s,5R,7S)-3-methyladamantan-1-yl)amino)ethyl)thio)ethanol**. p-TsCl (1 eq.) was added to a mixture of tiodietilenglicole (0.500 mg, 1 eq.), Et_3N (1.140 mL, 2 eq.), and DMAP (cat.) in dry CH_2Cl_2 (0.1 M) under N_2 atmosphere with stirring at 0°C. The stirring was continued at room temperature for 3.5 hours. The reaction was quenched with saturated NH_4Cl aqueous solution and extracted with AcOEt (3 x 10 mL).

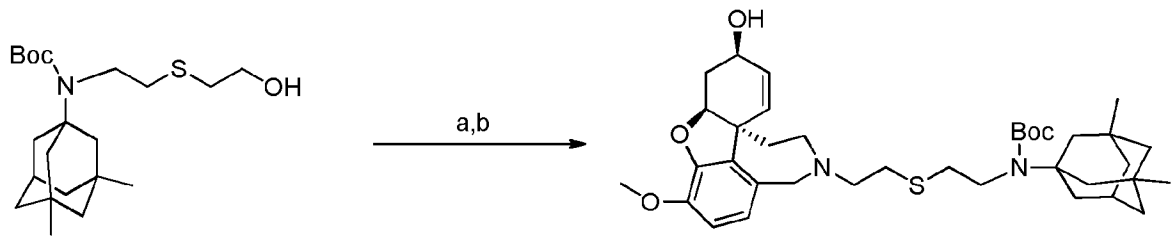
The extract was washed with brine prior to drying over Na_2SO_4, and solvent evaporation. The crude was then transferred into a pressure tube (Sigma Aldrich, ACE pressure tube) and added with Memantine hydrochloride (0.441 g, 0.5 eq.), and K_2CO_3 (2 eq.) in DMF, with stirring at 80°C for 36 hours. After evaporating the solvent, the residue was purified by flash chromatography. Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.14) afforded **ES194** as a waxy solid: 0.250 g (435%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.76 (s, 6H), 1.03-1.04 (AB m, 2H), 1.15-1.24 (m, 8H); 1.41 (br m, 2H), 2.05-2.06 (m, 1H), 2.60-2.72 (m, 4H), 3.29 (br s, exchangeable with D_2O, 1H), 3.64-3.70 (m, 4H).

Synthesis of compounds ES195.



ES195 ***tert*-butyl ((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)(2-((2-hydroxyethyl)thio)ethyl)carbamate. ES194** (0.250 g, 1 eq.) was dissolved in THF/H_2O (1:1) and treated with Na_2CO_3 (2.5 eq.) and di-*tert*-butyl dicarbonate (0.140 g, 1.5 eq). The resultant suspension was allowed to stir at room temperature overnight. The solvent was then removed in vacuo yielding a residue which was dissolved in water and extracted with AcOEt (3 × 15 mL). The extracts were combined, washed with brine, dried over Na_2SO_4, concentrated by evaporation, and purified by flash chromatography. Eluting with petroleum ether/ AcOEt (8:2) afforded **ES195** as a waxy solid: 0.220 g (65%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.81 (s, 6H), 1.08-1.11 (AB m, 2H), 1.22-1.32 (AB m, 4H), 1.43 (s, 9H), 1.67 (AB m, 4H), 1.88 (br m, 2H), 2.10-2.12 (m, 1H), 2.54 (t, *J*=8.0 Hz, 2H), 2.72 (t, *J*=6.0 Hz, 2H), 3.40 (t, *J*=8.0 Hz, 2H), 3.71 (t, *J*=5.6 Hz, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.57, 30.40, 30.62, 31.82, 32.81, 34.92, 39.52, 42.54, 43.92, 47.04, 50.39, 58.26, 60.84, 79.60, 154.98.

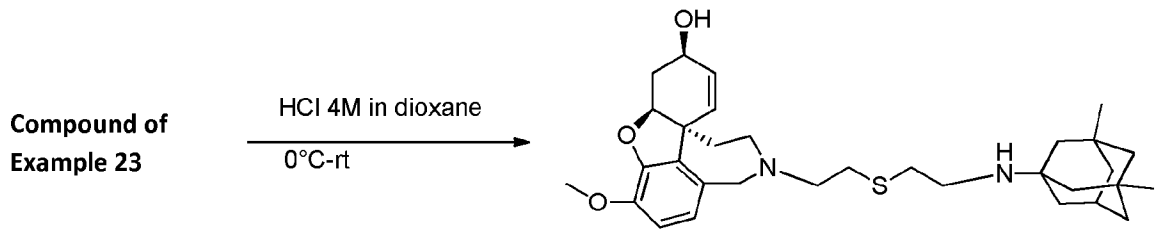
Example 23



a) TsCl, DMAP, Et_3N, CH_2Cl_2, rt. b) des-methyl-galantamine, Et_3N, CH_3CN, 80°C.

tert-butyl **((1r,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(2-((2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethyl)thio)ethyl)carbamate.** p-TsCl (1 eq.) was added to a mixture of **ES 195** (0.100 g, 1 eq.), Et_3N (2 eq.), and DMAP (cat.) in dry CH_2Cl_2 (0.1 M) under N_2 atmosphere with stirring at 0°C. The stirring was continued at room temperature for 3.5 hours. The reaction was quenched with saturated NH_4Cl aqueous solution and extracted with AcOEt (3 x 10 mL). The extract was washed with brine prior to drying over Na_2SO_4, and solvent evaporation. The crude was then transferred into a pressure tube (Sigma Aldrich, ACE pressure tube) and added with des-methyl-Galantamine (0.5 eq.), and Et_3N (2 eq.) in CH_3CN, with stirring at 80°C for 48 hours. After evaporating the solvent, the residue was purified by flash chromatography. Elution with CH_2Cl_2/CH_3OH (9.5:0.5) afforded the compound of interest as a waxy solid: 0.075 g (90%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 6H), 1.12 (AB m, 2H), 1.25-1.36 (AB m, 4H), 1.46 (s, 9H), 1.51-1.55 (m, 1H), 1.71 (AB m, 4H), 1.90-1.91 (br m, 2H), 1.98-2.04 (m, 2H), 2.14-2.15(m, 1H), 2.54-2.58 (m, 2H), 2.66-2.77 (m, 5H), 3.15-3.19 (m, 1H), 3.38-3.43 (m, 3H), 3.82 (s, 3H), 3.83 (d, *J*=15.2 Hz, 1H), 4.14 (m, 1H), 4.18 (d, *J*=15.6 Hz, 1H), 4.61 (br m, 1H), 6.01 (dd, J_1=10.0, J_2=4.4 Hz, 1H), 6.03 (d, *J*=10.0 Hz, 1H), 6.61 (d, *J*=8.4 Hz, 1H), 6.65 (d, *J*=8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 28.60, 29.66, 29.92, 30.10, 30.43, 30.65, 32.55, 32.82, 33.05, 39.54, 42.58, 44.02, 47.04, 48.41, 50.41, 51.59, 55.89, 57.47, 58.23, 62.03, 79.37, 88.68, 111.16, 121.95, 126.77, 127.68, 129.25, 133.07, 144.17, 145.90, 154.83.

Example 24



(4aS,6R,8aS)-11-(2-((2-(((1r,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)ethyl)thio)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol.

HCl 4M in dioxane (1 mL) was carefully added to COMPOUND OF EXAMPLE 23 (0.075 g, 1 eq.) at 0 °C and the solution was allowed to stir at room temperature for 2 hours. After removing the solvent the obtained residue was purified by flash chromatography. Elution with CH_2Cl_2/CH_3OH/ 33% aqueous ammonia (9:1:0.05) afforded the compound of interest as a waxy solid: 0.055 g (88%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.82 (s, 6H), 1.04-1.13 (AB m, 2H), 1.19-1.27 (m, 8H), 1.43 (br s, 2H), 1.48-1.51 (m, 1H), 1.98-2.04 (m, 2H), 2.09-2-11(m, 1H), 2.59-2.75 (m, 8H), 3.15 (m, 1H), 3.18 (m, 1H), 3.36-3.42 (m, 1H), 3.60-3.64 (m, 1H), 3.72-3.76 (m, 1H), 3.81 (s, 3H), 3.82 (d, *J*=15.2 Hz, 1H), 4.10-4.17 (m+d, *J*=15.2 Hz, 2H), 4.58 (br m, 1H), 5.99 (dd, J_1=10.0, J_2=4.4 Hz, 1H), 6.05 (d, *J*=10.0 Hz, 1H), 6.58 (d, *J*=8.4 Hz, 1H), 6.63 (d, *J*=8.4 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 29.67, 29.86, 29.93, 30.25, 30.30, 32.37, 33.00, 33.68, 39.65, 41.27, 42.85, 42.97, 48.41, 49.00, 49.04, 50.91, 51.70, 52.25, 55.89, 57.38, 62.03, 71.11, 72.29, 88.69, 111.17, 121.94, 126.74, 127.69, 129.15, 133.07, 144.20, 145.90. UPLC/MS: purity 95%. MS (ESI+): m/z 539.32 $[M+1]^+$.

Biological results

1) Evaluation of compound binding affinity at NMDA Glutamate receptors

In order to evaluate [^{3}H] MK-801 binding parameters, saturation binding studies were performed. Aliquots of rat brain cortex (40 µg) were incubated in the presence of increasing radioligand concentrations ranging from 0.3 to 68 nM. Scatchard analysis of saturation binding data demonstrated the radioligand labelled an homogenous population of binding sites with an affinity constant value of 4.0 nM and a maximum density of binding sites of 955 fmol/mg of proteins.

The activity of the new compounds towards NMDA glutamate receptors were evaluated by competition binding assays. Aliquots of rat brain cortex membranes (40 µg proteins) were incubated with 3 nM [^{3}H] MK-801 and two different concentrations of each compounds (100 nM and 10 µM). In parallel, Memantine, Ifenprodil and dextromethorphan were tested as standard compounds. Based on the obtained preliminary data, the most promising compounds showing the higher % of binding inhibition, were tested at 6 concentrations. Isotherms were analyzed by nonlinear regression using PRISM (GraphPad Software, San Diego, CA) to generate IC_{50} values. They were transformed into Ki values according to Cheng-Prussof (Cheng-Prusoff 1973): Ki = IC_{50}/(1+L/Kd), where L is the radioligand concentration, and K_d is the dissociation constant. The % of binding inhibition at 10 µM or the Ki values of the compounds are reported in Table 1.

TABLE 1

Compound	Ki (µM)	% of [^{3}H] MK-801binding inhibition at 10 µM
EXAMPLE 8	24.3 ± 3.2	
EXAMPLE 2	15.9 ± 2.7	
EXAMPLE 4		27.52 ± 1.617
EXAMPLE 10	10.1 ± 2.1	
EXAMPLE 9		37.49 ± 1.79
EXAMPLE 3		39.73 ± 2.39
EXAMPLE 11	4.99 ± 0.20	
EXAMPLE 5		33.45 ± 4.01
EXAMPLE 18		33.87 ± 4.73

Compound	Ki (μM)	% of [^{3}H] MK-801binding inhibition at 10 μM
EXAMPLE 17		21.65 ± 2.95
EXAMPLE 16		30.46 ± 3.25
EXAMPLE 13		22.2 ± 3.9
EXAMPLE 14		31.6 ± 2.8
EXAMPLE 15		39.3 ± 3.2
EXAMPLE 1		43.7 ± 6.6
EXAMPLE 6	32.3 ± 0.3	
EXAMPLE 12	4.63 ± 1.54	
EXAMPLE 21	13.1 ± 2.9	
Memantine	1.16 ± 0.07	
Galantamine		8.60 ± 0.40
Ifenprodil	3.08 ± 0.76	
Dextromethorphan	0.207 ± 0.021	

2) Determination of compound inhibitory effect on rat acetylcholinesterase (AChE)

In order to evaluate AChE kinetic parameters in rat brain, Km and Vmax for the enzyme was calculated by Michaelis-Menten equation.

Aliquots of enzyme preparation (10 μg) were incubated in the presence of different acetylthiocholine iodide (ACTHI) substrate concentrations ranging from 0.025 to 2.5 mM

and 0.25 mM dithiobisnitrobenzoate (DTNB). The enzyme activity was measured quantifying the increase of absorbance at 412 nm due to the yellow colour produced from the reaction of ACTHI with the DTNB ion.

Screening of the new compounds as AChE inhibitors was performed evaluating the ability of two selected concentrations of each compounds (100 nM and 10 μM) to inhibit the enzyme activity at a specific substrate concentration, corresponding to Km. Activities of the synthetized compounds were compared with the inhibitory activity shown by the known standard inhibitor Galantamine. Based on the data obtained from the screening, the IC_{50} value of the compounds, showing the higher % of enzyme activity inhibition, was evaluated. Aliquots of brain homogenates (containing 10 μg of proteins) were incubated with five different compound concentrations and the AChE activity was quantified as above described. The IC_{50} values of the compounds towards AChE activity are reported in Table 2.

TABLE 2

Determination of IC_{50} value of the compounds towards AChE activity.

Compound	IC_{50} (nM ± SEM)
EXAMPLE 8	4.31 ± 0.25
EXAMPLE 2	250.7 ± 25.7
EXAMPLE 4	63.5 ± 5.9
EXAMPLE 10	1.79 ± 0.06
EXAMPLE 9	1.16 ± 0.03
EXAMPLE 3	344.9 ± 58.9
EXAMPLE 11	5.36 ± 0.77
EXAMPLE 5	510 ± 68
EXAMPLE 18	11.3 ± 1.6
EXAMPLE 17	369 ± 7.6
EXAMPLE 16	55.7 ± 10.3
EXAMPLE 13	1.03 ± 0.18

Compound	IC_{50} (nM ± SEM)
EXAMPLE 14	1.33 ± 0.12
EXAMPLE 15	0.52 ± 0.05
EXAMPLE 1	1380 ± 120
EXAMPLE 6	368.3 ± 89.3
EXAMPLE 12	2.32 ± 0.50
EXAMPLE 21	80.9 ± 12.8
Galantamine	2550 ± 690
Memantine	8.50% ± 1.30 at 10 µM

3) [^{3}H] ifenprodil binding assay on rat cortex

Ifenprodil, a heterocyclic amino alcohol, is an atypical noncompetitive antagonist, which selectively binds to and inhibits NR2B-containing NMDA receptors (Carter et al.,1990; Mott et al., 1998; Williams, 2001). Owing to its subunit selectivity [^{3}H]ifenprodil has been extensively used as a ligand in receptor-binding studies on NR2B-containing NMDA receptor complexes (Chenard & Menniti, 1999).

In order to evaluate [^{3}H] ifenprodil binding parameters, saturation binding studies were performed. Aliquots of rat brain cortex (100 µg) were incubated in the presence of increasing radioligand concentrations ranging from 0.5 to 100 nM. Scatchard analysis of saturation binding data demonstrated the radioligand labelled an homogenous population of binding sites with an affinity constant value of 28.0 ± 1.8 nM and a maximum density of binding sites of 1508 ± 321 fmol/mg of proteins.

The activity of the new compounds towards NR2B/NMDA glutamate receptors were evaluated by competition binding assays. Aliquots of rat brain cortex membranes (100 µg proteins) were incubated with 10 nM [^{3}H] ifenprodil and two different concentrations of each compounds (100 nM and 100 µM). In parallel, eliprodil and ifenprodil were tested as standard compounds. Based on the obtained preliminary data, the most promising compounds showing the higher % of binding inhibition were tested at 6 concentrations. Isotherms were analyzed by nonlinear regression using PRISM

(GraphPad Software, San Diego, CA) to generate IC_{50} values. They were transformed into Ki values according to Cheng-Prussof (Cheng-Prusoff 1973): Ki = IC_{50}/(1+L/Kd), where L is the radioligand concentration, and K_d is the dissociation constant. The % of binding inhibition at 100 µM or the Ki values of the compounds are reported in Table 3.

TABLE 3

Compound	Ki (µM)	% of [^{3}H] ifenprodil inhibition at 100 µM
EXAMPLE 8	40.9 ± 5.6	
EXAMPLE 2		33 ± 9
EXAMPLE 4		70 ± 9
EXAMPLE 10	10.95 ± 3.44	
EXAMPLE 9	4.6 ± 0.7	
EXAMPLE 3	1.93 ± 0.36	
EXAMPLE 11	2.9 ± 1.0	
EXAMPLE 5		38 ± 4
EXAMPLE 18	9.76 ± 4.48	
EXAMPLE 17		27 ± 4
EXAMPLE 16		46 ± 10
EXAMPLE 13	5.25 ± 1.6	
EXAMPLE 14		46 ± 17
EXAMPLE 15		43 ± 15
EXAMPLE 1		36 ± 6
EXAMPLE 6		16.4 ± 2.5
EXAMPLE 12		21.3 ± 4.8
EXAMPLE 21		8.15 ± 1.87
Eliprodil	0. 54 ± 0.07	
Ifenprodil	0.029 ± 0.003	
Galantamine		21.8 ± 4.8
Memantine		23.3 ± 5.6

4) Evaluation of NMDA toxicity in SHSY-5Y cells

Cell culture, pharmacological treatments and MTS assay.

SHSY-5Y cells were maintained in DMEM/F12 medium supplemented with 15% fetal bovine serum, 1% non-essential amino acids, 2 mM L-glutamine and penicillin/streptomycin in humidified atmosphere (5% CO_2) at 37 °C.

Cells were seeded in 96-well microplates (5.000 cells/well); the day after, cells were incubated with NMDA, in the absence or in the presence of different compound concentrations. The NMDA receptor antagonists/AChE inhibitor were added for 5 min prior to addition of NMDA, in order to determine the inhibition of NMDA-mediated cell toxicity. In parallel classical NMDA receptor antagonist (Eliprodil and Ifenprodil) and AChE inhibitor (Galantamine) were used as standard compounds.

Following incubation times, cell viability was determined using the MTS assay according to manufacturer's instruction. The dehydrogenase activity in active mitochondria reduces 3-(4, 5-dimethylthiazol-2-yl)-5- (3-carboxy methoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) to the soluble formazan product. The absorbance of formazan at 490 nM was measured in a colorimetric assay with an automated plate reader.

Within an experiment, each condition was assayed in duplicate or triplicate and each experiment was performed at least three times. The results were calculated by subtracting the mean background from the values obtained from each test condition and were expressed as the percentage of the control (untreated cells).

Student's *t*-test was used to evaluate whether differences between the experimental groups and the control were statistically significant.

Preliminary experiments were carried out to characterize the effects of NMDA on cell viability; SHSY-5Y cells were incubated with different NMDA concentrations (ranging from 50 µM to 5 mM) for 1, 3, 6 or 24 hours in non complete medium. After 1 hour of treatment NMDA was able to significantly decrease cell viability only at the highest concentration. On the contrary, when cells were exposed to NMDA for 3, 6, or 24 hours, a significant decrease of cells viability was observed at 500 µM, 1 mM and 5 mM.

Based on these data, all the other experiments were carried out exposing cells to 500 μM NMDA for 6 hours.

The IC_{50} values of the compounds toward NMDA-induced toxicity in SHSY-5Y cells are reported in Table 4.

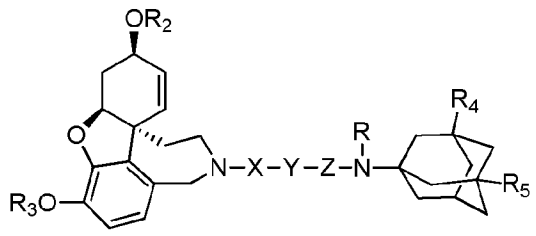
TABLE 4

Compound	IC_{50} (nM) vs 500μM NMDA
Eliprodil	0.23
Ifenprodil	0.73
Galantamine	746.7
Memantine	718
EXAMPLE 10	0.21
EXAMPLE 9	0.28
EXAMPLE 18	0.37

In light of the above reported results, the present series of molecules, which show a dual AChE/NR2B mechanism, are able to contrast the NMDA-induced neurotoxicity in neuroblastoma cell lines. This profile is rather unexpected and not fully justified by the molecular data. In fact, while the molecules were micromolar binders of the 2B subunit of the NMDA receptor, they were able to contrast the NMDA-induced neurodegeneration at a subnanomolar level, concentrations much lower than the concentration at which Memantine is able to revert the neurotoxicity by NMDA. Therefore, the ability of the Galantamine fragment to interact with other receptor systems involved in neurodegeneration (likely nicotinic receptors) could be responsible for the remarkable pharmacological profile of the present series of compounds. We can therefore summarize that the present series of dual AChE/NR2B inhibitors show activities against the biological targets for which these compounds were designed (i.e. AChE, NMDAR, NR2B), along with an unexpected and remarkable neuroprotective profile, as assessed by cell-based experiments.

CLAIMS

1. Compounds of formula (I)



(I)

wherein:

X is $(CH_2)_m$ and m is comprised between 2 and 12;

Y is selected from the group consisting of NR_1, where R_1 is H, a protecting group, or C_1-C_4 alkyl; O, S, SO, SO_2, S-S, $O(CH_2)_pO$, wherein p is comprised between 1 and 6; a cyclic hydrocarbon having from 3 to 8 carbon atoms, an aromatic hydrocarbon having from 6 to 10 carbon atoms; a heterocyclic ring having from 3 to 7 members; or Y is absent;

Z is selected from the group consisting of $(CH_2)_n$, wherein n is comprised between 1 and 12, C=O and $CH_2O(CH_2)_2$, or Z is absent;

R is H, C_1-C_4 alkyl or a protective group;

R_2 is H, C_1-C_4 alkyl, the residue of a pharmaceutically acceptable acid;

R_3 is C_1-C_4 alkyl;

R_4 and R_5, the same or different, are C_1-C_4 alkyl;

their pharmaceutically acceptable salts;

their enantiomers, racemates, diastereoisomers and mixtures.

2. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y and Z are absent.

3. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y and Z are absent and R is H.

4. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y and Z are absent and R is CH_3.

5. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is absent, Z is C=O and R is H.

6. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is $O(CH_2)_pO$, wherein p is comprised between 1 and 6, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

7. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is S, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

8. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is O, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

9. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is NH, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

10. A compound according to claim 1, selected from the group consisting of:

a) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethyl)carbamate;

b) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(3-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)propyl)carbamate;

c) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(4-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)butyl)carbamate;

d) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(5-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)pentyl)carbamate;

e) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(6-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)hexyl)carbamate;

f) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(7-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)heptyl)carbamate;

g) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(8-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)octyl)carbamate;

h) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(9-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)nonyl)carbamate;

i) (4aS,6R,8aS)-11-(2-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol; +

j) (4aS,6R,8aS)-11-(3-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)propyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

k) (4aS,6R,8aS)-11-(4-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)butyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

l) (4aS,6R,8aS)-11-(5-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)pentyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol

m) (4aS,6R,8aS)-11-(6-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)hexyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

n) (4aS,6R,8aS)-11-(7-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)heptyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

o) (4aS,6R,8aS)-11-(8-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)octyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

p) (4aS,6R,8aS)-11-(9-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)nonyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

q) (4aS,6R,8aS)-11-(3-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)propyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

r) (4aS,6R,8aS)-11-(4-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)butyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

s) (4aS,6R,8aS)-11-(5-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)pentyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

t) (4aS,6R,8aS)-11-(6-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)hexyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

u) (4aS,6R,8aS)-11-(7-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)heptyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

v) (4aS,6R,8aS)-11-(8-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)octyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

w) (4aS,6R,8aS)-11-(10-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)decyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

x) 3-((4aS,6R,8aS)-3,6-dimethoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)-N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)propanamide;

y) 4-((4aS,6R,8aS)-3,6-dimethoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)-N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)butanamide;

z) N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)-5-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)pentanamide

aa) N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)-6-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)hexanamide;

bb) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(2-(2-(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethoxy)ethoxy)ethyl)carbamate;

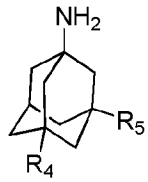
cc) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(2-(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethoxy)ethyl)carbamate;

dd) (4aS,6R,8aS)-11-(2-(2-(2-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethoxy)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

ee) (4aS,6R,8aS)-11-(2-(2-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol.

11. A process for the preparation of the compounds of claim 1, comprising

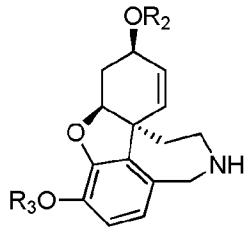
a) the reaction of the compound M



wherein R_4 and R_5 are as defined in claim 1,

with a compound of formula D-X-Y-Z-NR-E, wherein X, Y, Z and R are as defined in claim 1, D and E are a leaving group, to give the compound M-X-Y-Z-NR-E;

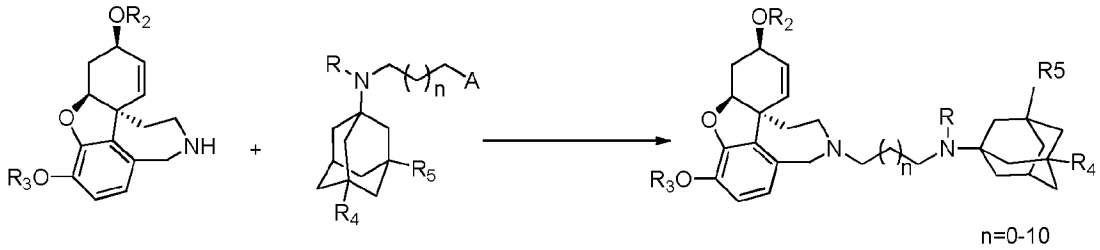
b) the reaction of the compound M-X-Y-Z-NR-E with a des-methyl-galanthamine derivative G



wherein R_2 and R_3 are as defined in claim 1.

12. The compound of M-X-Y-Z-NR-E for use as intermediate in the process of claim 11.

13. A process for the preparation of compounds of claim 1, wherein X is $(CH_2)_m$ as defined above, Y and Z are absent; R-R_5 are as defined above comprising the following reaction:

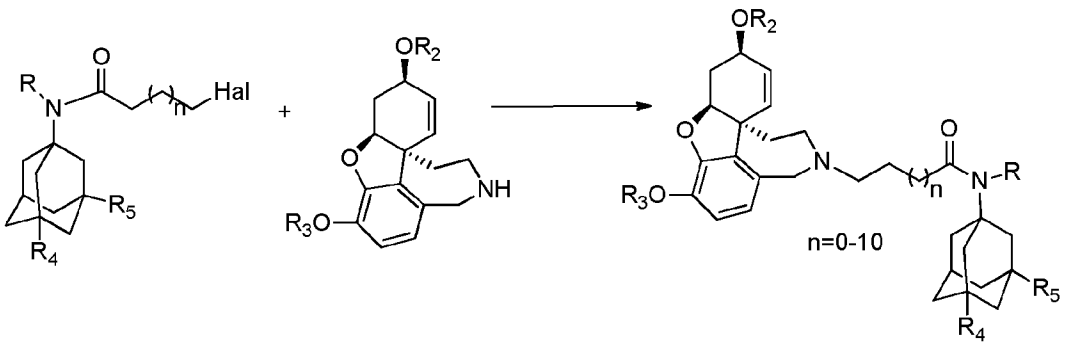


(II)

wherein R, R_2, R_3, R_4 and R_5 are as defined in claim 1, n is an integer between 0 and 10, and A is an activated alcohol group.

14. The compound of formula (II) as described in claim 13, with the proviso that when R is H, n is an integer selected from the group consisting of 0, 1, and from 5 to 10 as intermediate in the process of claim 13.

15. A process for the preparation of compounds of claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is absent, Z is C=O, R-R_5 are as defined above comprising the following reaction:

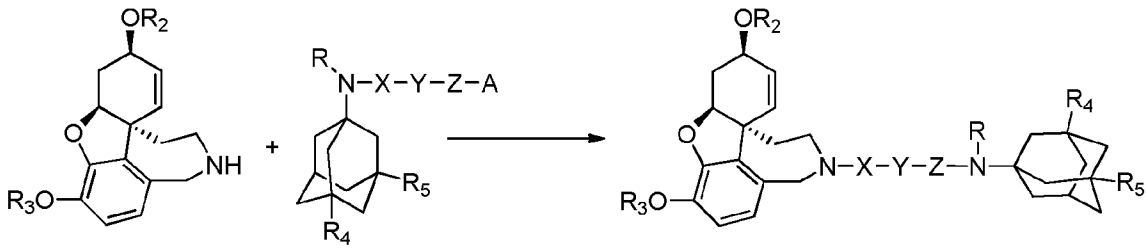


(III)

wherein R, R_2, R_3, R_4 and R_5 are as defined in claim 1, n is an integer between 0 and 10, and Hal is a halogen atom.

16. The compound of formula (III) as described in claim 15 as intermediate in the process of claim 15.

17. A process for the preparation of compounds of claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12; Y is O or $O(CH_2)_pO$, wherein p is comprised between 1 and 6; Z is $(CH_2)_n$, wherein n is comprised between 1 and 12, R-R_5 are as defined above, comprising the following reaction:



(IV)

wherein R, R_2, R_3, R_4 and R_5 are as defined in claim 1, A is an activated alcohol group.

18. The compound of formula (IV) as described in claim 17 as intermediate in the process of claim 17.

19. A pharmaceutical composition comprising at least a compound of any one of claims 1-10.

20. The compounds of any one of claims 1-10 for use as medicaments.

21. The compounds according to claim 20 wherein said medicament is for the treatment of a disease selected from the group consisting of: cognitive impairment, memory dysfunction, neurodegenerative disorders and related dementia, Alzheimer's disease, Parkinson's disease, neuropsychiatric behavior associated with Alzheimer's disease, pain, depression, attention deficit hyperactivity disorder and for pharmacological addictive substance or intoxicant therapy.

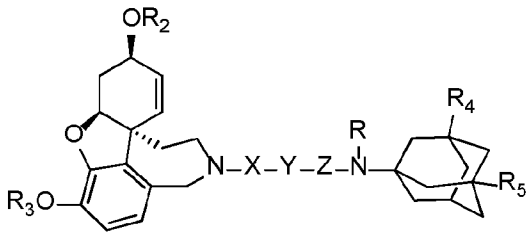
22. The compounds according to claim 21 wherein the disease is Alzheimer's disease.

23. The compounds according to claim 21 wherein the disease is alcoholism.

24. The compounds of any one of claims 1-10 for use as medicaments for the neuroprotection from NMDA toxicity.

AMENDED CLAIMS
received by the International Bureau on 27 February 2013 (27.02.2013)

1. Compounds of formula (I)



(I)

wherein:

X is $(CH_2)_m$ and m is comprised between 2 and 12;

Y is selected from the group consisting of NR_1, where R_1 is H, a protecting group, or C_1-C_4 alkyl; O, S, SO, SO_2, S-S, $O(CH_2)_pO$, wherein p is comprised between 1 and 6; a cyclic hydrocarbon having from 3 to 8 carbon atoms, an aromatic hydrocarbon having from 6 to 10 carbon atoms; a heterocyclic ring having from 3 to 7 members; or Y is absent;

Z is selected from the group consisting of $(CH_2)_n$, wherein n is comprised between 1 and 12, C=O and $CH_2O(CH_2)_2$, or Z is absent;

R is H, C_1-C_4 alkyl or a protective group;

R_2 is H, C_1-C_4 alkyl, the residue of a pharmaceutically acceptable acid;

R_3 is C_1-C_4 alkyl;

R_4 and R_5, the same or different, are C_1-C_4 alkyl;

their pharmaceutically acceptable salts;

their enantiomers, racemates, diastereoisomers and mixtures.

2. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y and Z are absent.

3. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y and Z are absent and R is H.

AMENDED SHEET (ARTICLE 19)

4. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y and Z are absent and R is CH_3.

5. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is absent, Z is C=O and R is H.

6. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is $O(CH_2)_pO$, wherein p is comprised between 1 and 6, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

7. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is S, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

8. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is O, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

9. Compounds according to claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is NH, Z is $(CH_2)_n$, wherein n is comprised between 1 and 12.

10. A compound according to claim 1, selected from the group consisting of:

a) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethyl)carbamate;

b) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(3-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)propyl)carbamate;

c) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(4-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)butyl)carbamate;

d) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(5-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)pentyl)carbamate;

e) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(6-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)hexyl)carbamate;

AMENDED SHEET (ARTICLE 19)

f) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(7-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)heptyl)carbamate;

g) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(8-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)octyl)carbamate;

h) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(9-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)nonyl)carbamate;

i) (4aS,6R,8aS)-11-(2-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol; +

j) (4aS,6R,8aS)-11-(3-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)propyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

k) (4aS,6R,8aS)-11-(4-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)butyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

l) (4aS,6R,8aS)-11-(5-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)pentyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol

m) (4aS,6R,8aS)-11-(6-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)hexyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

n) (4aS,6R,8aS)-11-(7-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)heptyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

o) (4aS,6R,8aS)-11-(8-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)octyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

p) (4aS,6R,8aS)-11-(9-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)nonyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

AMENDED SHEET (ARTICLE 19)

q) (4aS,6R,8aS)-11-(3-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)propyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

r) (4aS,6R,8aS)-11-(4-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)butyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

s) (4aS,6R,8aS)-11-(5-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)pentyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

t) (4aS,6R,8aS)-11-(6-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)hexyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

u) (4aS,6R,8aS)-11-(7-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)heptyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

v) (4aS,6R,8aS)-11-(8-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)octyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

w) (4aS,6R,8aS)-11-(10-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(methyl)amino)decyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

x) 3-((4aS,6R,8aS)-3,6-dimethoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)-N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)propanamide;

y) 4-((4aS,6R,8aS)-3,6-dimethoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)-N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)butanamide;

AMENDED SHEET (ARTICLE 19)

z) N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)-5-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)pentanamide

aa) N-((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)-6-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)hexanamide;

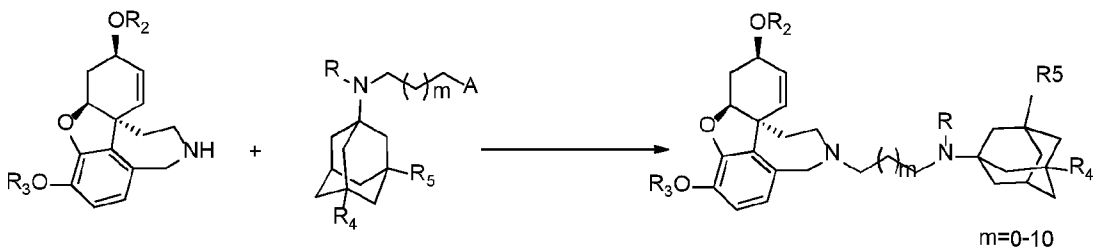
bb) *tert*-butyl ((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)(2-(2-(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethoxy)ethoxy)ethyl)carbamate;

cc) *tert*-butyl ((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)(2-(2-((4aS,6R,8aS)-6-hydroxy-3-methoxy-5,6,9,10-tetrahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-11(12H)-yl)ethoxy)ethyl)carbamate;

dd) (4aS,6R,8aS)-11-(2-(2-(2-(((1R,3R,5S,7R)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethoxy)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol;

ee) (4aS,6R,8aS)-11-(2-(2-(((1R,3R,5S,7S)-3,5-dimethyladamantan-1-yl)amino)ethoxy)ethyl)-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzo[2,3]benzofuro[4,3-cd]azepin-6-ol.

13. A process for the preparation of compounds of claim 1, wherein X is $(CH_2)_m$ as defined above, Y and Z are absent; R-R_5 are as defined above comprising the following reaction:



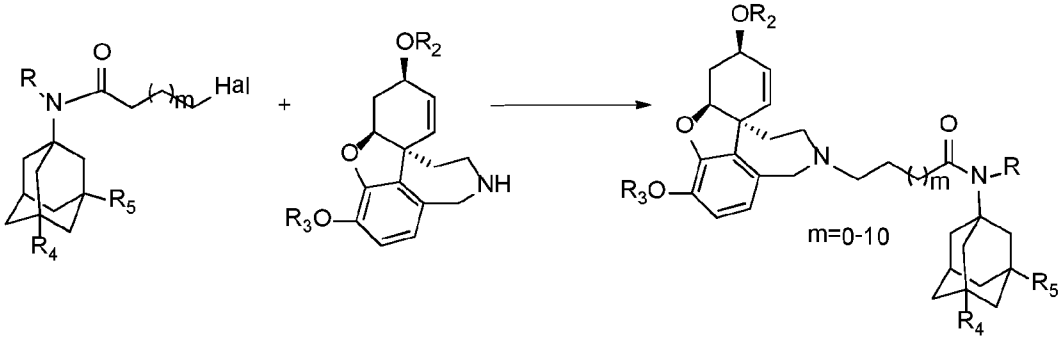
(II)

wherein R, R_2, R_3, R_4 and R_5 are as defined in claim 1, m is an integer between 0 and 10, and A is an activated alcohol group.

AMENDED SHEET (ARTICLE 19)

14. The compound of formula (II) as described in claim 13, with the proviso that when R is H, m is an integer selected from the group consisting of 0, 1, and from 5 to 10 as intermediate in the process of claim 13.

15. A process for the preparation of compounds of claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12, Y is absent, Z is C=O, R-R_5 are as defined above comprising the following reaction:

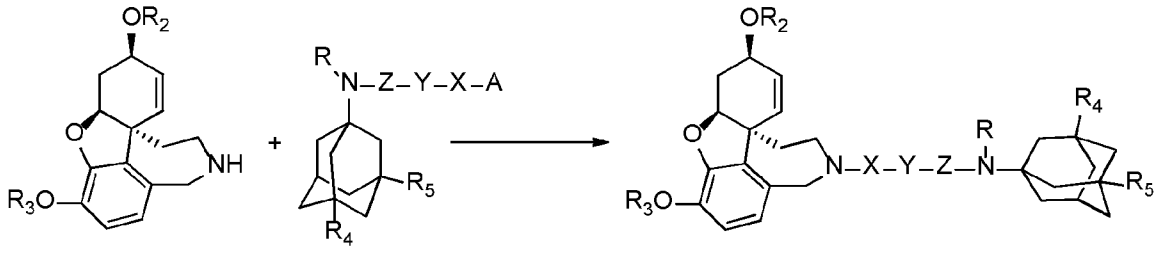


(III)

wherein R, R_2, R_3, R_4 and R_5 are as defined in claim 1, m is an integer between 0 and 10, and Hal is a halogen atom.

16. The compound of formula (III) as described in claim 15 as intermediate in the process of claim 15.

17. A process for the preparation of compounds of claim 1, wherein X is $(CH_2)_m$ and m is comprised between 2 and 12; Y is O or $O(CH_2)_pO$, wherein p is comprised between 1 and 6; Z is $(CH_2)_n$, wherein n is comprised between 1 and 12, R-R_5 are as defined above, comprising the following reaction:



(IV)

AMENDED SHEET (ARTICLE 19)

wherein R, R_2, R_3, R_4 and R_5 are as defined in claim 1, A is an activated alcohol group.

18. The compound of formula (IV) as described in claim 17 as intermediate in the process of claim 17.

19. A pharmaceutical composition comprising at least a compound of any one of claims 1-10.

20. The compounds of any one of claims 1-10 for use as medicaments.

21. The compounds according to claim 20 wherein said medicament is for the treatment of a disease selected from the group consisting of: cognitive impairment, memory dysfunction, neurodegenerative disorders and related dementia, Alzheimer's disease, Parkinson's disease, neuropsychiatric behavior associated with Alzheimer's disease, pain, depression, attention deficit hyperactivity disorder and for pharmacological addictive substance or intoxicant therapy.

22. The compounds according to claim 21 wherein the disease is Alzheimer's disease.

23. The compounds according to claim 21 wherein the disease is alcoholism.

24. The compounds of any one of claims 1-10 for use as medicaments for the neuroprotection from NMDA toxicity.

STATEMENT UNDER ARTICLE 19 (1)

Dear Sirs,

we refer to the letter requesting an amendment under Art.19 PCT.

Claims 11 and 12 have been cancelled in response to the objections raised by the Examiner in the Written Opinion accompanying the International Search Report of 20.07.2012, where said claims have been regarded as unclear.

The corresponding paragraphs in the description may be cancelled accordingly.

Following the cancellation of claims 11 and 12, the Applicant respectfully believes that the Examiner's objections will be overcome.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/052084

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/06 C07C233/06 C07C309/73 A61P25/28 A61K31/55
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/019166 A2 (NEUROMOLECULAR INC [US]; WENT GREGORY T [US]; WASLEY JAN W F [US]; LIP) 3 March 2005 (2005-03-03) figure 5	18
A	WO 03/101458 A1 (LUNDBECK & CO AS H [DK]; THOMSEN LARS LYKKE [DK]; PEDERSEN ANDERS GERS) 11 December 2003 (2003-12-11) page 3, line 17 claims 1,9,11,15	1-24
A	EP 1 397 138 B1 (HF ARZNEIMITTELFORSCH GMBH [DE]) 5 January 2005 (2005-01-05) cited in the application claims 1-2	1-24

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 July 2012	20/07/2012

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/052084

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005019166 A2	03-03-2005	EP 1638931 A2	29-03-2006
		US 2005124701 A1	09-06-2005
		WO 2005019166 A2	03-03-2005
WO 03101458 A1	11-12-2003	AT 414519 T	15-12-2008
		AU 2003227516 A1	19-12-2003
		BR 0311375 A	15-03-2005
		DK 1509232 T3	23-02-2009
		EP 1509232 A1	02-03-2005
		ES 2314200 T3	16-03-2009
		JP 2005528431 A	22-09-2005
		MX PA04011762 A	31-03-2005
		NZ 536603 A	29-06-2007
		PT 1509232 E	07-01-2009
		SI 1509232 T1	30-04-2009
		WO 03101458 A1	11-12-2003
EP 1397138 B1	05-01-2005	AR 034493 A1	25-02-2004
		AT 286397 T	15-01-2005
		AU 2002323873 B2	16-11-2006
		BR 0211008 A	26-10-2004
		CA 2450787 A1	27-12-2002
		CN 1527711 A	08-09-2004
		CZ 20033390 A3	17-03-2004
		DE 10129265 A1	02-01-2003
		EP 1397138 A2	17-03-2004
		ES 2236551 T3	16-07-2005
		HK 1063292 A1	27-05-2005
		HU 0400865 A2	28-07-2004
		IL 159345 A	11-02-2009
		JP 2005500298 A	06-01-2005
		MX PA03011825 A	07-03-2005
		NZ 529944 A	23-02-2007
		PL 367207 A1	21-02-2005
		PT 1397138 E	29-04-2005
		SK 15652003 A3	06-04-2004
		TW I325320 B	01-06-2010
		UA 76753 C2	16-02-2004
		US 2004192683 A1	30-09-2004
		WO 02102388 A2	27-12-2002
		ZA 200309232 A	21-07-2004