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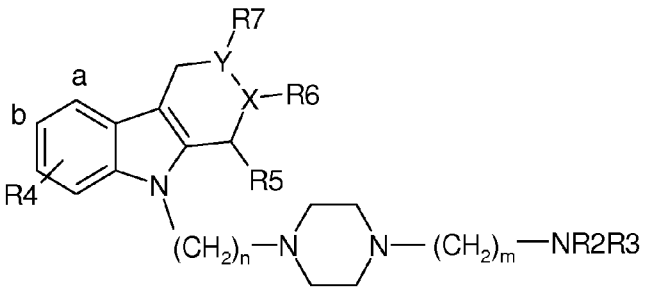
(54) Title: NEW N_a-SUBSTITUTED CARBOLINE COMPOUNDS USABLE FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES



(III)

(57) Abstract: The present invention relates to a compound according to Formula (III) or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or polymorph thereof and its use.

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NEW N_a-SUBSTITUTED CARBOLINE COMPOUNDS USABLE FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

TECHNICAL FIELD

The present invention relates to new compounds and the use thereof for the treatment of a disease related to a dysfunction of the Amyloid Precursor Protein (APP) and/or of a disease related to a modification of tau protein. An example of such disease is Alzheimer's disease (AD).

BACKGROUND OF THE INVENTION

AD is a progressive neurodegenerative disorder that gradually damages the neurons in regions of the brain involved in memory, learning and reasoning.

The diagnostic of AD is currently post mortem and consists in checking the presence of extracellular accumulation of amyloid β (Aβ) peptides forming amyloid deposits in the brain parenchyma. AD is currently incurable. AD is a multifactorial disease. The cause for most Alzheimer's cases is still essentially unknown (except for 1% to 5% of cases where genetic mutations have been identified).

Several competing hypotheses exist trying to explain the cause of AD.

On the one hand it has been proposed that amyloid beta (Aβ) deposits are the fundamental cause of the disease. Support for this postulate comes from the location of the Alzheimer genetic mutation located on *APP* gene, for the APP on chromosome 21, together with the fact that people with Trisomy 21 (Down Syndrome), who have an extra copy of the APP gene, almost universally exhibit AD by 40 years of age. APOE4, the major genetic risk factor for AD, also leads to excess amyloid buildup in the brain before AD symptoms arise. Thus, the amyloid cascade hypothesis places the amyloid production, oligomerization, aggregation and synaptoxicity at the center of Alzheimer etiopathogenesis. Further evidence comes from the finding that transgenic mice, which express a mutant form of the human *APP* gene, develop fibrillar amyloid deposits and Alzheimer's-like brain pathology with spatial learning deficits.

On the other hand, AD is also known as a tauopathy. In tauopathies, abnormally and hyperphosphorylated tau protein isoforms aggregate into fibrillar structures within neurons to form the so-called neurofibrillary tangles (NFTs). The precise mechanism of tangle formation is not completely understood but mutations of *tau* gene - also called

MAPT for microtubule-associated protein tau - are associated with the development of a tauopathy named Frontotemporal Dementia with Parkinsonism linked to chromosome 17.

Neurodegeneration results in the progressive loss of structure or function of neurons, leading to their death. Many neurodegenerative diseases, including Parkinson's (PD), Alzheimer's, Huntington's (HD) diseases, amyotrophic lateral sclerosis (ALS) with frontotemporal demential, inclusion body myopathy with Paget's bone disease and frontotemporal dementia (IBMPFD) occur as a result of neurodegenerative processes. As research progresses, many similarities appear relating these diseases to each other in terms of common physiopathological hallmarks from the subcellular level to the clinical symptoms observed in patients. Noteworthy, the whole spectrum of these neurodegenerative diseases are associated to the accumulation and aggregation of unfolded or mis-folded proteins such as synuclein, amyloid peptide, microtubule-associated protein tau, huntingtin, TDP-43, FUS/TLS etc.

The degradation of altered or pathologically mis-folded proteins is a complex phenomenon, which takes many cellular paths and is likely deregulated in a large number of pathologies. At the crossroads of cellular systems of protein degradation such as endosome/lysosome, endoplasmic reticulum associated-degradation, autophagy and ubiquitin-proteasome system, VCP (Valosin Containing Protein), also referred as p97 or CDC48, is a new therapeutic target for the treatment of neurodegenerative diseases and cancers. VCP is a member of AAA+/ATPase enzyme family (ATPases are associated with various cellular activities) and is involved in a growing number of cellular mechanims: cellular division, organelle biogenesis, nucleus membrane formation, DNA repair, transport and vesicules fusion, protein degradation and suppression of protein aggregates. It is associated with cofactors such as with HSP90, Ufd1 or Npl4. Its importance has been demonstrated in several diseases. In particular, mutations in *VCP/p97* gene have been shown to be linked to IBMPFD and some familial ALS. Moreover, several neurodegenerative diseases are associated to protein degradation dysfunction (Nixon RA, Yang DS, Lee JY. Autophagy, 2008, 4, 590-99). The possible linkage of VCP to the AD-relevant protein Tau was recently proposed (Dolan PJ, Jin YN, Hwang W, Johnson GV. FEBS Lett, 2011, 585, 3424-9 Abisambra JF1, Jinwal UK, Blair LJ, O'Leary JC 3rd, Li Q, Brady S, Wang L, Guidi CE, Zhang B, Nordhues BA, Cockman M, Suntharalingham A, Li P, Jin Y, Atkins CA, Dickey CA.J Neurosci. Tau accumulation activates the unfolded protein response by impairing endoplasmic reticulum-associated degradation. 2013 May 29;33(22):9498-507. doi:

10.1523/JNEUROSCI.5397-12.2013). VCP/p97, which is essential for the maturation of ubiquitin containing autophagosomes, is a potential therapeutic target of choice for the treatment of neurodegenerative diseases.

Document WO 2006/051489 describes the use of 1,4-bis(3-aminoalkyl) piperazine derivatives in the treatment of neurodegenerative diseases, particularly in the treatment of AD. The compounds disclosed in the afore-mentioned document are able to a) increase the carboxy-terminal fragments of APP (APP-CTFs) which all in common possess the last 50 amino acids of APP, and especially those having potential physiological activities, such as the α-stubs (APP-CTF alpha) and the ε-stubs (APP-CTF gamma or AICD for APP intra cellular domain), b) increase the soluble fragment sAPPα, c) decrease the production of neurotoxic by-products of APP, *i.e.* β-amyloid (Aβ) peptides, especially in their form x-42 and d) without modifying the APP expression and in the absence of neurotoxicity.

An object of the present invention is to provide new compounds that can be useful as drugs, especially for the treatment of diseases related with APP disorder, for the treatment of tauopathies and more particularly for the treatment of neurodegenerative diseases such as AD, Lewy body disease, Down syndrome, amyloid angiopathy, PD, ALS, frontotemporal lobar degeneration and IBMPFD.

Another object of the present invention is to provide compounds having an effect on Tau pathology.

Another object of the present invention is to provide compounds having a biological activity in at least one of the afore-mentioned mechanisms a) to d) as regard to β-amyloid (Aβ) peptides and the afore-mentioned mechanisms as regards tau pathology.

Another object is to provide compounds useful as drugs, especially for the treatment of the afore-mentioned diseases, said compounds having an improved efficiency and/or an improved solubility and/or an improved toxicity and/or an improved *in vivo* stability and/or an improved biodisponibility and/or said compounds being easier to synthesize at an industrial scale.

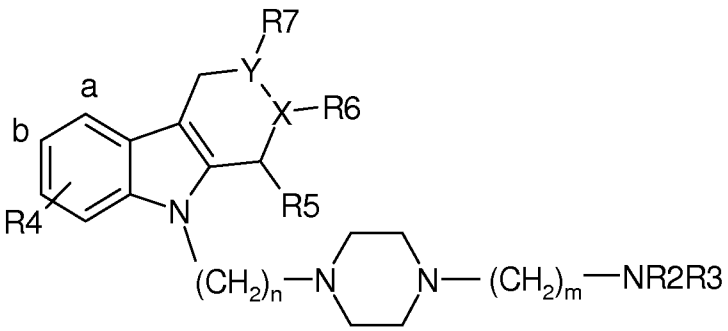
Another object of the present invention is to provide compounds that can be active, when orally administered.

Another object of the invention is to provide compounds able to interact and/or react with VCP/p97.

Another object of the present invention is to provide a pharmaceutical composition comprising the compounds of the present invention. Advantageously, this composition can be orally administered.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a compound according to Formula (III) The present invention provides a compound according to Formula (III):



(III)

in which

- **n** is an integer equal to 2 or superior to 2;
- **R4** is selected from F, Cl, H, O-CH_3, and -CH_3;
- **R5** is selected from H, CH_3 and a phenyl group;
- **X** and **Y** are selected from the group consisting of carbon atom and nitrogen atom, with the proviso that **X** is a nitrogen atom when **Y** is a carbon atom and **X** is a carbon atom, when **Y** is a nitrogen atom;
- **R6** and **R7** are independently selected from the group consisting of an hydrogen atom, an alkyl group, a COO**R8** group, wherein **R8** is a linear or branched alkyl group having from 2 to 10 carbon atoms, with the proviso that when **Y** is a carbon atom, **R6** is a hydrogen atom and when **X** is a carbon atom, **R7** is an hydrogen atom;
- **m** is an integer equal to 2 or superior to 2; and
- **R2** and **R3** are selected independently one from another from the groups consisting of:

- linear or branched (C_1-C_{12}) alkyl; linear or branched (C_2-C_{12}) alkenyl; linear or branched (C_2-C_{12}) alkynyl; said alkyl group, alkenyl group or alkynyl group may be substituted with at least one substituent selected from halogen, cycloalkyl, hydroxyl, alkoxy, amino, acylamino, aroylamino, heteroaroylamino and carboxy groups;
- heteroaroylamino;
- (C_2-C_6) heterocycloalkyl comprising in the cycle an oxygen atom and/or a nitrogen atom;

- benzyl optionally substituted with an alkyl group, halogen, an ether group and/or an amino group; or

R2 and **R3** form together with the nitrogen atom carrying them a saturated or unsaturated (C_2-C_7) heterocycle.

or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or polymorph thereof.

The compounds according to the invention are able to increase APP-CTF alpha and AICD, as previously mentioned. They can be therapeutically efficient without involving cell toxicity.

The compounds of the invention can be easily synthesized and at low cost.

The compounds according to the invention are also active on VCP/p97 and thus are multi-target drugs.

DETAILED DESCRIPTION OF THE INVENTION

According to the invention, **m** and **n** may be identical or different from one another. **m** and **n** can be equal to 2 or to any integer superior to 2. They may also be different and each equal to an integer equal to 2 or superior to 2. Advantageously, **m** and **n** are independently selected from 2 and 3. Advantageously, **m** and **n** are identical and are both equal to 2 or 3.

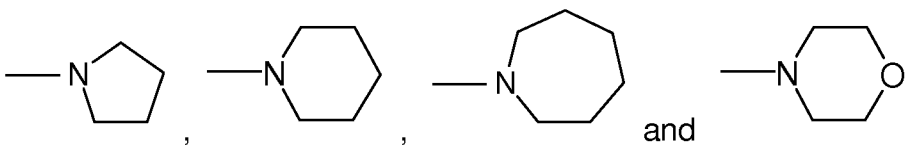
According to one embodiment, **R2** and **R3** are identical and are selected from (C_1-C_{12}) alkyls.

R2 and **R3** may be identical and either isobutyl or methyl groups. These compounds are particularly *in vitro active*.

R4 is advantageously selected from H, Cl, F and CH_3.

Advantageously, **R4** is attached to the carbon atom in position **b**.

R2, **R3** and the nitrogen atom carrying them may form one of the following heterocyclic groups:



and

Accordingly, **R2**, **R3** and the nitrogen atom carrying them may form a pyrrolidinyl group.

According to one particular embodiment of the invention, **R6** or **R7** are selected from H and $-CH_2CH_2CH_3$. Preferably, **R6** or **R7** is $-CH_2CH_2CH_3$.

According to one other embodiment of the invention which may be combined with any one of the previous embodiment(s), **X** is N.

According to one other embodiment of the invention which may be combined with any one of the previous embodiment(s), except the embodiment in which **X** is N, **Y** is N.

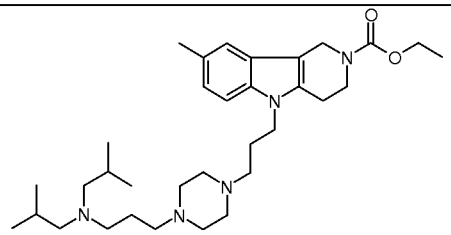
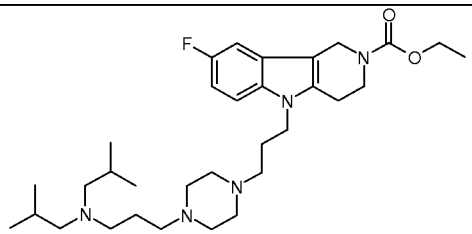
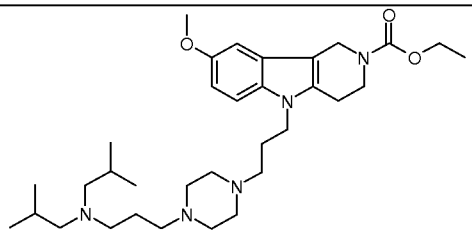
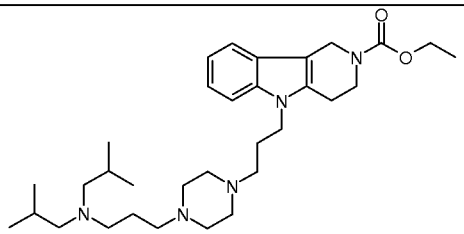
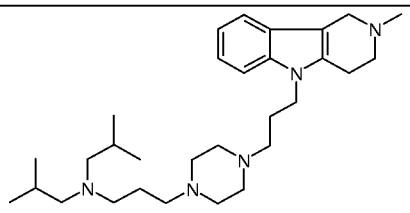
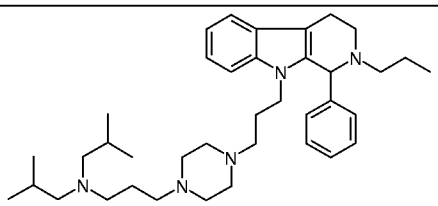
According to one embodiment, **R5** may be H or a phenyl group.

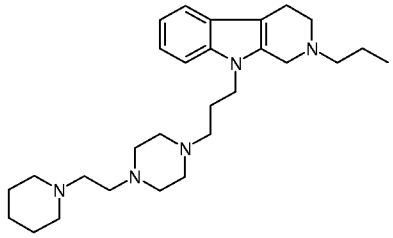
In one specific embodiment, preferred compounds of the invention and pharmaceutically acceptable salts, solvates, clathrates, hydrates or polymorphs thereof are those wherein **R4**, **R5**, **n**, **m**, **R2** and **R3** are as defined above with respect to Formula (III) or any of its embodiments, and wherein **R6** and **R7** are independently selected from H, linear C1-C4-alkyl or COO**R8**, wherein **R8** is a linear C1-C3-alkyl group, preferably **R6** and **R7** are independently selected from H, methyl, $-CH_2CH_2CH_3$ or COO**R8**, wherein **R8** is ethyl, with the proviso that **R6** can only be a hydrogen atom when **X** is a carbon atom, and **R7** can only be a hydrogen atom when **Y** is a carbon atom.

In one variant of this embodiment, **X** is N, **Y** is C, **R7** is H**,** and **R6** is linear C1-C4-alkyl preferably $CH_2CH_2CH_3$. Particularly preferred compounds of this variant are those wherein **R4** is H, and/or **R5** is H or phenyl, and/or **m** is 2 or 3, and/or **R2** and **R3** are both isobutyl or **R2**, **R3** and the nitrogen atom carrying them form a piperidinyl moiety, and/or **n** is 3. Other particularly preferred compounds of this variant are those wherein **R2** and **R3** are both isobutyl and **m** is 3, or **R2**, **R3** and the nitrogen atom carrying them form a piperidinyl moiety and **m** is 2.

In another variant of this embodiment, **X** is C, **Y** is N, **R6** is H, and **R7** is linear C1-C4-alkyl or COO**R8**, wherein **R8** is a linear C1-C3-alkyl group, preferably **R7** is methyl or COO**R8**, wherein **R8** is ethyl. Particularly preferred compounds of this variant are those wherein **R4** is preferably attached to the carbon atom in position **b** and selected from the group consisting of F, H, O-CH_3, CH_3, and/or **R5** is H, and/or **m** is 3, and/or **R2** and **R3** are both isobutyl, and/or **n** is 3.

The present invention also relates to a compound selected from the group consisting of:

Compound no.	Structure	Name
3.3a		5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-8-methyl-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate
3.3b		5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-8-fluoro-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate
3.3c		5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-8-methoxy-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate
3.3d		5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate
3.5a		5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-2-methyl-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole
3.4a		*N,N*-diisobutyl-3-[4-(3-(1-phenyl-2-propyl-1,2,3,4-tetrahydro-pyrido[3,4-*b*]indol-9-yl)propyl)piperazin-1-yl]propylamine

3.4b		1-[2-(piperidin-1-yl)ethyl]-4-(3-(2-propyl-1,2,3,4-tetrahydro-pyrido[3,4-*b*]indol-9-yl)propyl)piperazine

The present invention also relates to the compounds of Formula (III) for their use as a medicament, especially for their use as a medicament in the treatment of a disease selected from the group consisting of tauopathies, amyloidopathies and synucleopathies and more particularly neurodegenerative diseases, related neurodegenerative diseases, developmental diseases or cancer and, for example, Alzheimer's disease, Paget's disease of bone, familial amyotrophic lateral sclerosis, Lewy body disease, Down syndrome, amyloid angiopathy, Parkinson's disease, amyotrophic lateral sclerosis (ALS), frontotemperal degeneration and frontotemporal lobar dementia.

Paget's disease of bone, frontotemporal dementia, familial amyotrophic lateral sclerosis and Alzheimer's disease are diseases already known as diseases linked with VCP/p97 modifications, in particular modifications of VCP/p97 localisation or activity (Bartolome F1, Wu HC, Burchell VS, Preza E, Wray S, Mahoney CJ, Fox NC, Calvo A, Canosa A, Moglia C, Mandrioli J, Chiò A, Orrell RW, Houlden H, Hardy J, Abramov AY, Plun-Favreau H. Pathogenic VCP mutations induce mitochondrial uncoupling and reduced ATP levels.Neuron. 2013 Apr 10;78(1):57-64. doi: 10.1016/j.neuron.2013.02.028).

The present invention also relates to a pharmaceutical composition comprising as an active ingredient, a compound according to the invention and a pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

The pharmaceutical composition according to the invention may be in a dosage form suitable for oral administration (including sublingual administration), for parenteral administration (such as intravenous, intramuscular or subcutaneous injection or intravenous infusion), intracisternal or intraperitoneal administration for topical administration (including ocular, transdermal and mucosal administration such as intranasal administration), by a skin patch, an inhalator, an implant or a suppository. The composition according to the present invention may be liquid, like for example, a syrup. The composition of the invention may also be a powder which can be diluted with water, for example, prior to use. It may also be solid or semi-solid depending on the carrier, diluent, adjuvant and/or excipient used for the preparation of the composition

according to the invention. The person skilled in the art is able to select carrier, diluent, adjuvant and/or excipient according to the most suitable method of administration. For example, the person skilled in the art may refer to the latest edition of Remington's Pharmaceutical Sciences.

Examples of dosage forms that can be used according to the invention include, but are not limited to, tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, creams, lotions, soft and hard gelatin capsules, suppositories, drops, sterile injectable solutions and sterile packaged powders that may be reconstituted before use, for administration as a bolus and/or for continuous administration. Carriers, excipients, diluents and/or adjuvants are selected according to the method of administration. They may be selected from lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, gelatin, , microcrystalline cellulose gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The pharmaceutical composition can optionally contain other substances which are commonly used in pharmaceutical formulations, such as lubricants, wetting agents, emulsifying and suspending agents, dispersing agents, disintegrating agents, stabilizing agents, isotonic agents, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, perfuming agents, coloring agents, antibacterial agents and/or antifungal agents such as parabens, chlorobutanol, phenol, sorbic acid, dispensing agents, flow regulators, release agents, etc. The composition may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein. For example, the composition according to the present invention may comprise nanoparticles carrying at least one compound of the invention. The compound according to the invention may be inside the nanoparticle or outside thereof, for example, linked to the surface thereof.

The pharmaceutical compositions of the invention may be in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. In general, such a unit dosage will contain from 1mg to 600mg of at least one compound of the invention. For example, a unit dosage may contain 2mg, 50mg, 100mg or 200mg of at least one compound according to the

invention. For example one, two or three unit dosages may be administered per day, with about 6 hours between two administrations.

Depending on the use of the composition for prevention or treatment and depending on the route of administration, the active compound of the invention will usually be administered in a daily amount equal to 0.1mg/Kg or superior to 0.1mg/kg and inferior to 50mg/kg or equal to 50mg/kg, for example about 0.5, 1, 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 mg, per kilogram body weight of the patient, and it may be administered as a single daily dose, or divided into one or more daily doses, for example two or three daily doses,.

DEFINITIONS

According to the present invention, the term “alkyl group” means a saturated aliphatic hydrocarbon group which may be straight (linear) or branched and having advantageously 1 to 12 carbon atoms in the chain. Preferably, when not specified, an alkyl group according to the invention may have 1 to 12, preferably 1 to 10, more preferably 1 to 6 carbon atoms and even more preferably 1, 2, 3 or 4 carbon atoms.

The term “alkenyl group” refers to an aliphatic hydrocarbon group which may be straight (linear) or branched and which comprises at least one double bond between two carbons. The alkenyl group may have advantageously 2 to 12 carbon atoms in the chain. Preferably, when not specified, an alkenyl group according to the invention may have 2 to 12, preferably 2 to 10, more preferably 2 to 6 carbon atoms and even more preferably 2, 3 or 4 carbon atoms. The alkenyl group may have only one double bond.

The term “alkynyl group” refers to an aliphatic hydrocarbon group which may be straight (linear) or branched and comprising at least one triple bond between two carbons. The alkynyl group may have advantageously 2 to 12 carbon atoms in the chain. Preferably, when not specified, an alkynyl group according to the invention may have 2 to 12, preferably 2 to 10, more preferably 2 to 6 carbon atoms and even more preferably 2, 3 or 4 carbon atoms. The alkynyl group may comprise only one triple bond.

The term “branched” means that one or more lower alkyl groups, alkenyl groups or alkynyl groups selected from methyl, ethyl, ethenyl, ethynyl, propyl, propenyl, propynyl and butyl, butenyl and butynyl are attached to one carbon of a linear alkyl, alkenyl or alkynyl chain. When at least two lower alkyl groups are attached to one carbon atom of the aforementioned linear chain, they may be attached on the same carbon atom or not. Advantageously, when the two (or more) lower alkyl, alkylenyl or

alkynyl groups are attached to the same carbon atom of the linear alkyl chain, they may be attached to the free-end carbon atom of the linear chain, i.e. the carbon atom ending the molecule of the invention. According to the present invention, a "branched alkyl group" may be for example, isobutyl, isopentyl, isohexyl, isoheptyl, isooctyl, isononyl, isodecyl, isoundecanyl or isododecanyl group.

The alkyl, alkenyl and alkynyl group may be substituted with one or more "alkyl group substituent" which may be identical or different and include, for example, halogen, cycloalkyl, hydroxyl, alkoxy, amino, acylamino, aroylamino groups.

The term "halogen" refers to a halogen atom and advantageously represents F, Cl and Br atoms.

The term "cycloalkyl" refers to saturated and unsaturated cyclic, bicyclic, tricyclic and polycyclic hydrocarbon groups having preferably for each cyclic group 3 to 12 carbon atoms. Preferably, according to the present invention, the cycloalkyls are saturated cycles.

The term "alkoxy" refers to an **R**-O, wherein **R** is an alkyl group as previously defined, an alkyl group substituted by an alkyl group substituent as herein defined, an alkenyl group as herein defined or an alkenyl group substituted by an alkyl group substituent as herein defined.

The term "amino" refers to any group having the following formula **RR'**N- wherein **R** and **R'** are, independently from one another, selected from an hydrogen atom, an alkyl group as previously defined, an alkyl group substituted by an "alkyl group substituent" as herein defined, an alkenyl group as previously defined, an alkenyl group substituted by an "alkyl group substituent", an alkynyl group or an alkynyl group substituted by an "alkyl group substituent".

The term "acylamino" refers to any group having the formula **R**CON- wherein **R** is an alkyl group as previously defined, an alkyl group substituted by an "alkyl group substituent" as herein defined, an alkenyl group as previously defined, an alkenyl group substituted by an "alkyl group substituent", an alkynyl group or an alkynyl group substituted by an "alkyl group substituent".

The term "aroylamino" means a φCON, wherein φ is an aromatic group, such as for example, a phenyl group; φ may also be polycyclic.

The term "heteroaroylamino" refers to any group φ'CON-, wherein φ' is an aromatic group eventually polycyclic, comprising in at least one cycle thereof an oxygen atom or a nitrogen atom or a sulfur atom as a heteroatom.

The term "carboxy groups" refers to any **R**COO- group wherein R is an alkyl group as previously defined, an alkyl group substituted by an "alkyl group substituent" as herein defined, an alkenyl group as previously defined, an alkenyl group substituted by an "alkyl group substituent", an alkynyl group or an alkynyl group substituted by an "alkyl group substituent".

An "ether group" is, according to the present invention, a **R**O**R'** group wherein **R** and **R'** are different or identical and are selected from alkyl, alkenyl and alkynyl groups as previously defined, alkyl groups substituted by an "alkyl group substituent" as herein defined, alkenyl groups as previously defined and alkenyl groups substituted by an "alkyl group substituent". **R** and **R'** may form a cycle thereby forming a cyclic ether. According to the invention, **R** or **R'** is attached to one carbon of the benzyl group.

The term "pharmaceutically acceptable" means suitable for use in contact with the cells of a living organism, especially a mammal and more especially a human being, without undue toxicity, irritation, immune response or the like and providing a reasonable benefit/risk balance.

The term "pharmaceutically acceptable salt(s)" refers to any salt obtained from a compound of the invention, said salt having a slightly similar biological activity compared to the biological activity of said compound of the invention. Salts according to the present invention may be obtained from organic and inorganic acids or bases. Pharmaceutically acceptable salts are for example reviewed in "Berge, *et al* ((1997) J. pharm. Sd, vol 66, 1).

Suitable pharmaceutically acceptable salt may be selected from hydrochlorides, sulfates, bisulfates and/or phosphates.

The term "treatment" and derived terms mean reversing, alleviating, stopping or preventing the disorder and/or at least one symptom linked to said disorder. The term "treatment" also refers to a prophylactic treatment which can delay the onset of the above-mentioned diseases.

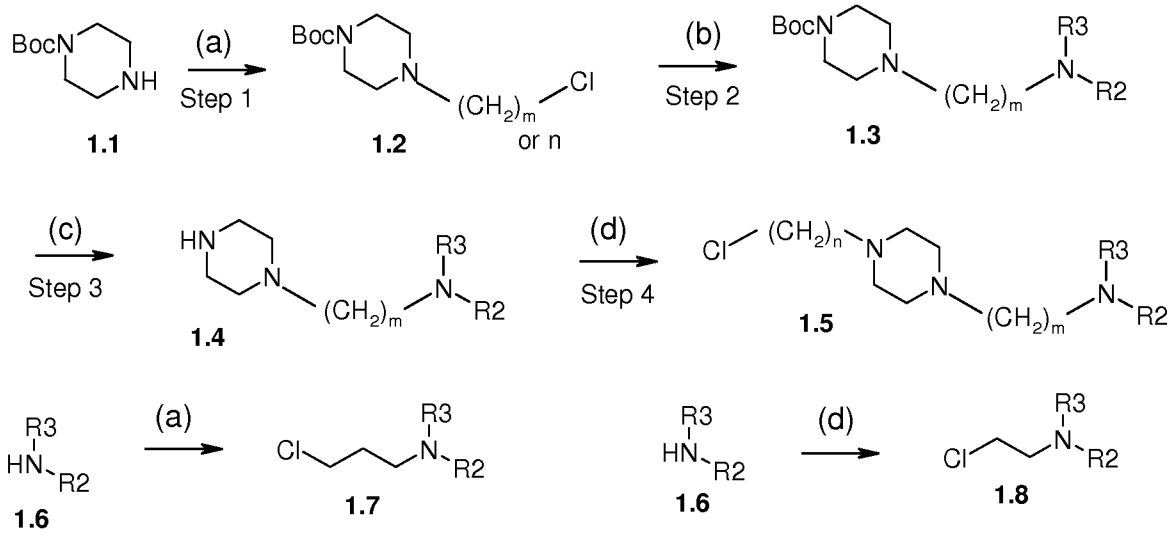
The compounds of the present invention may be used for the treatment of any living organism, more especially a mammal and more particularly a human and more particularly a human over 65 years old.

EXPERIMENTAL PART

CHEMICAL PART

In the further mentioned general schemes, **n**, **m**, **R2**, **R3**, **R4**, **R5**, **R6** and **R7** refer to the values and groups as defined above, respectively.

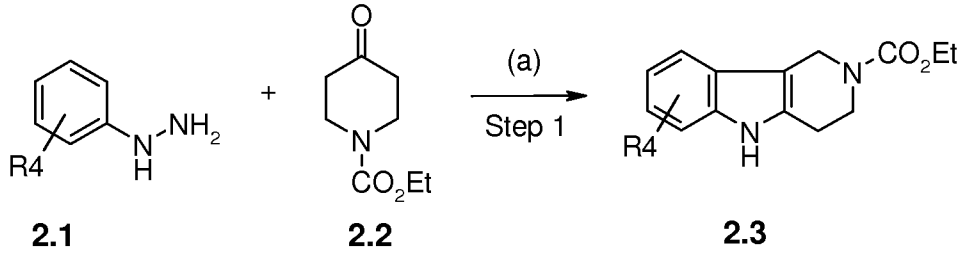
Scheme 1: Preparation of intermediates chloroalkyl-piperazine derivatives



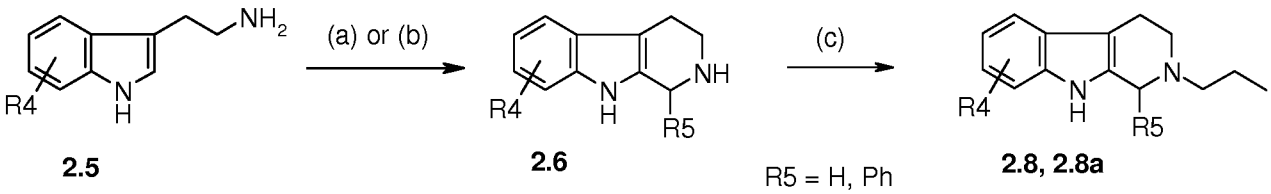
Reagents: (a): 1-bromo-3-chloropropane or 1-bromo-2-chloroethane, K_2CO_3, NaI, acetonitrile, rt (rt : room temperature); (b): HNR_2R_3, diisopropylethylamine, NaI, CH_3CN, reflux; (c): TFA, CH_2Cl_2, rt; (d): (i): 3-bromo-1-propanol or 2-bromoethanol, EtOH, reflux; (ii): $SOCl_2$, CH_2Cl_2, 0°C→ reflux.

Scheme 2: Preparation of intermediates tricycle derivatives

Scheme 2a: beta and gamma carbolines intermediates



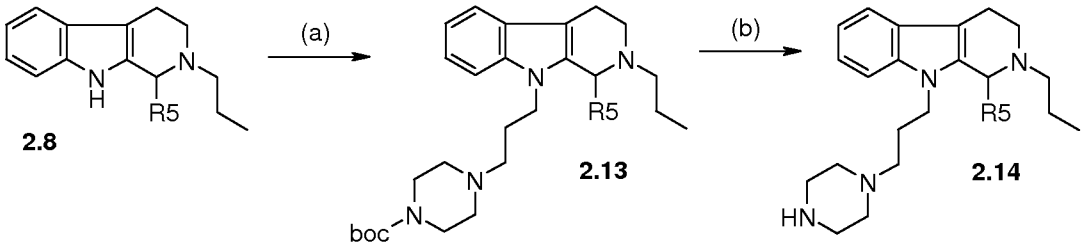
Reagents: (a): EtOH, with or without HCl, reflux.



2.5 **2.6** **2.8, 2.8a**

Reagents: (a): (R5=H) HCHO 37%, CH_3CO_2H, CH_3OH, rt; (b): (R5=Ph) PhCHO, TFA, CH_2Cl_2, rt (rt=room temperature); (c): iodopropane, K_2CO_3, acetonitrile, reflux.

Scheme 2b : alkylpiperazine beta and gamma carbolines

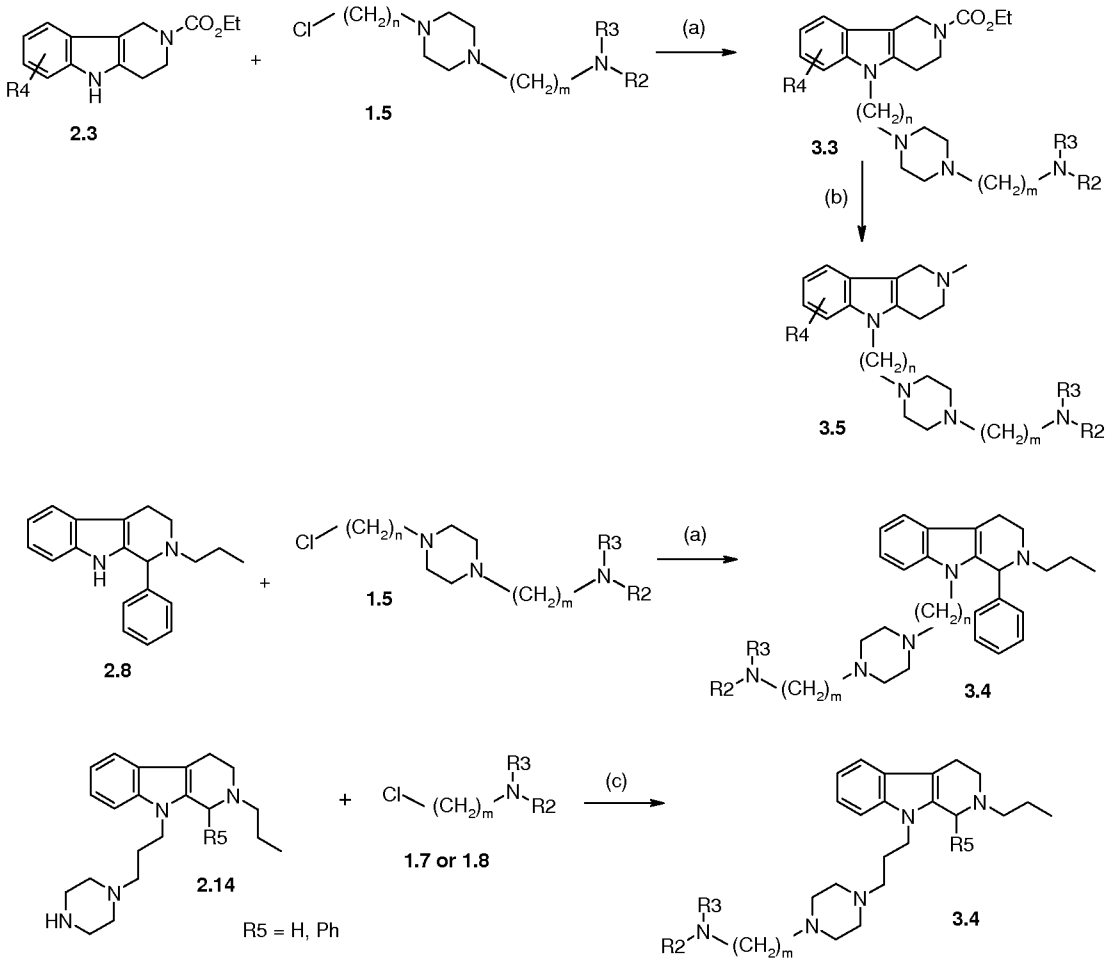


2.8 **2.13** **2.14**

Reagents: (a): NaH, DMF, 70°C (Procedure D'); (b): HCl 8%, MeOH.

Scheme 3: Preparation of compounds of the invention

Scheme 3a: Amino side chain on the B-ring of tricyclic compounds



Reagents: (a): NaH, DMF, 50-70°C (Procedure E); (b): $LiAlH_4$, THF, rt (c): NaI, K_2CO_3, acetonitrile, reflux (Procedure E2).

1. General

^1H-, and ^{13}C spectra were recorded on a 300 MHz Bruker spectrometer. Chemical shifts (δ) are given in ppm relative to the internal standard solvent. LC/MS chromatograms were recorded on a Waters Alliance 2695 system (X-Terra column, ionization mass spectrometer). For some compounds mass spectra were recorded on a MALDI-TOF Voyager-DE-STR (Applied Biosystems) apparatus.

2. General procedure A: Preparation of intermediates chloroalkylpiperazine derivatives (compound 1.5): Scheme 1

Step 1: Preparation of *tert*-butyl 4-(3-chloropropyl)piperazine-1-carboxylate (compound 1.2)

To a stirred solution of *tert*-butyl piperazine-1-carboxylate (**1.1**) (10 g, 53.7 mmol) in acetonitrile (125 mL) was added 1-bromo-3-chloropropane (21.13 g, 134.2 mmol, 2.5 eq), potassium carbonate (7.4 g, 53.7 mmol, 1eq) and sodium iodide (8.05 g, 53.7 mmol, 1 eq). The mixture was stirred for 24h at room temperature and the solvent was evaporated. The residue was solubilised again in CH_2Cl_2 and basified with 1M NaOH solution. Two layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was dried with $MgSO_4$ and evaporated under reduced pressure to give the compound **1.2** with a good purity, which was directly used for the next step without purification. MALDI-TOF *m/z* 263.10-265.14 $[M+H]^+$

Step 2: Preparation of compounds 1.3

To a stirred solution of *tert*-butyl 4-(3-chloropropyl)piperazine-1-carboxylate (**1.2**) (11.35 g, 43.3 mmol, 1 eq) in CH_2Cl_2 (400 mL) was added the amine (5 eq), *N,N*-diisopropylethylamine (5.6 g, 43.3 mmol, 1 eq) and sodium iodide (6.5 g, 43.3 mmol, 1eq). The mixture was warmed to reflux and stirred for 24h. The solvent was then evaporated. The residue was solubilised again in CH_2Cl_2 and alkalinized with 1M NaOH solution. Two layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The crude was purified by chromatography on silica gel (CH_2Cl_2/MeO:95/5) to give the corresponding compounds **1.3.**

Example 1: Preparation of 4-(3-(*N,N*-diisobutylamino)propyl)piperazine-1-*tert*-butylcarboxylate (compound 1.3a)

Compound **1.3a** was synthesized according to the procedure described by using *N,N*-diisobutylamine (27.96 g, 5 eq). Yield: 73%. MALDI-TOF *m/z* 356.30 $[M+H]^+$

Example 2: Preparation of 4-(3-(*N,N*-dibenzylamino)propyl)piperazine-1-*tert*-butylcarboxylate (compound 1.3b)

Compound **1.3a** was synthesized according to the procedure described by using *N,N*-dibenzylamine (42.7g, 5 eq). Yield: 49%. LCMS *m/z* 424.30 $[M+H]^+$

Example 3: Preparation of 4-(3-(pyrrolidin-1-yl)propyl)piperazine-1-*tert*-butyl carboxylate (compound 1.3c)

Compound **1.3c** was synthesized according to the procedure described by using pyrrolidine (15.4 g, 5 eq). Yield: 80%. LCMS *m/z* 298.3 $[M+H]^+$

Step 3: Preparation of compounds 1.4

To a stirred solution of **1.3** (15 mmol) in CH_2Cl_2 (80 mL) at room temperature was added trifluoroacetic acid (22.2 mL, 290 mmol, 20 eq). The reaction mixture was stirred overnight and the solvent was removed by evaporation. The residue was basified by using a mixture of saturated $NaHCO_3$ solution and 6M NaOH solution (100/10 v/v), and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give the amine **1.4**.

Example 1: Preparation of *N,N*-diisobutyl-3-(piperazin-1-yl)propylamine (compound 1.4a)

Compound **1.4a** was synthesized from compound **1.3a** according to the procedure described. Yield: 96%. MALDI-TOF *m/z* 256.32 $[M+H]^+$

Example 2: Preparation of *N,N*-dibenzyl-3-(piperazin-1-yl)propylamine (compound 1.4b)

Compound **1.4b** was synthesized from compound **1.3b** according to the procedure described. Yield: 96%. MALDI-TOF *m/z* 324.08 $[M+H]^+$

Example 3: Preparation of 3-(piperazin-1-yl)propylpyrrolidine (compound 1.4c)

Compound **1.4c** was synthesized from compound **1.3c** according to the procedure described. Yield: 90%. LCMS *m/z* 198.3 $[M+H]^+$

Step 4: Preparation of chloroalkylpiperazine derivatives 1.5

To a stirred solution of **1.4** (1 eq) in ethanol at room temperature was added 1-bromoalkyl-1-ol (1.7 eq), potassium carbonate (3 eq) and sodium iodide (1eq). The reaction mixture was warmed to reflux and stirred for 24h. Mineral salts were removed by filtration and the filtrate was concentrated under reduced pressure. The crude was solubilised in CH_2Cl_2, filtered again to remove residual mineral salts and evaporated.

The crude alcohol derivative was solubilised in CH_2Cl_2 and cooled to 0°C. Thionylchloride (6 eq) was then added dropwise. After 2h of stirring at reflux and overnight at room temperature, the solvent was evaporated. The resulting crude was solubilised in a mixture of CH_2Cl_2 and water. The aqueous layer was alkalinized and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, evaporated and purified by chromatography on silica gel (CH_2Cl_2/MeOH:90/10) to give the chloroalkyl piperazine derivatives **1.5a-d**.

Example 1: Preparation of *N,N*-diisobutyl-3-(4-(3-chloropropyl)piperazin-1-yl)propylamine (compound 1.5a)

Compound **1.5a** was synthesized according to the procedure described by using *N,N*-diisobutyl-3-(piperazin-1-yl)propylamine (**1.4a**) and 3-bromopropanol. Yield: 60%. MALDI-TOF *m/z* 332.3-334.3 $[M+H]^+$

Example 2: Preparation of *N,N*-dibenzyl-3-(4-(3-chloropropyl)piperazin-1-yl)propylamine (compound 1.5b)

Compound **1.5b** was synthesized according to the procedure described by using *N,N*-dibenzyl-3-(piperazin-1-yl)propylamine (**1.4b**) and 3-bromopropanol. Yield: 63%. LCMS *m/z* 400.24-402.23 $[M+H]^+$

Example 3: Preparation of 3-(4-(3-chloropropyl)piperazin-1-yl)propylpyrrolidine (compound 1.5c)

Compound **1.5c** was synthesized according to the procedure described by using 3-(piperazin-1-yl)propylpyrrolidine (**1.4c**) and 3-bromopropanol. Yield: 30%. LCMS *m/z* 274.4-275.2 $[M+H]^+$

Example 4: Preparation of *N,N*-diisobutyl-3-(4-(2-chloroethyl)piperazin-1-yl)propylamine (compound 1.5d)

Compound **1.5d** was synthesized according to the procedure described by using *N,N*-diisobutyl-3-(piperazin-1-yl)propylamine (**1.4a**) and 2-bromoethanol. Yield: 40%. MALDI-TOF *m/z* 318.1-320.1 $[M+H]^+$

Preparation of 3-chloro-*N,N*-diisobutylpropylamine (compound 1.7)

To a stirred solution of *N,N*-diisobutylamine (**1.6**) (3 g, 23,2 mmol) in acetonitrile (150 mL) was added 1-bromo-3-chloropropane (10.90 g, 69.6 mmol, 3 eq), potassium carbonate (6.4 g, 46.4 mmol, 2 eq). The mixture was stirred for 24h at room temperature. The mineral was filtered and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH: 90/10) gave the compound **1.7**. Yield 18%. LCMS *m/z* 206.1 $[M+H]^+$.

Preparation of 2-chloro-*N,N*-diisobutylethylamine 1.8

To a stirred solution of *N,N*-diisobutylamine (**1.6**) (3 g, 23,2 mmol) in acetonitrile (50 mL) at room temperature was added 2-bromoethanol (4.35 g, 34.8 mmol, 1.5 eq), potassium carbonate (6.4 g , 46.4 mmol, 2 eq). The reaction mixture was refluxed for 24h. Mineral salts were removed by filtration and the filtrate was concentrated under reduced pressure. The crude was solubilised in CH_2Cl_2, filtered again and evaporated.

The crude alcohol derivative was solubilised in CH_2Cl_2 and cooled to 0°C. Thionylchloride (13.8 g, 116 mmol, 5 eq) was then added dropwise. After stirring overnight at room temperature, the solvent was evaporated. The product purified by chromatography on silica gel (CH_2Cl_2/MeOH:90/10) to give compound **1.8**. Yield 37%. LCMS *m/z* 192.6 $[M+H]^+$.

3. General procedure B: Preparation of intermediates tricycle gamma-carboline derivatives (compounds 2.3 and 2.4): Scheme 2a

Step 1: Preparation of compounds 2.3

N-carbethoxy-4-piperidone **2.2** (1 eq) and appropriate phenylhydroxylamine or phenylhydrazine **2.1** (1 eq) were dissolved in absolute ethanol at room temperature, and 12N HCl solution can be added. The reaction mixture was stirred at reflux for 2h or overnight then cooled to room temperature. Treatment of resulting mixture according a suitable procedure gave the corresponding products.

Example 1: Preparation of ethyl 1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (compound 2.3a)

Compound **2.3a** was synthesized according to the procedure described by using *N*-carbethoxy-4-piperidone and phenylhydrazine. The resulting mixture was cooled to room temperature and filtered. Yield 90%. LCMS *m/z* 245.12 $[M+H]^+$

Example 2: Preparation of ethyl 8-methoxy-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (compound 2.3b)

Compound **2.3b** was synthesized according to the procedure described by using *N*-carbethoxy-4-piperidone and 4-methoxyphenylhydrazine at reflux for 2h. After evaporation of solvent, the residue was hydrolysed with water and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, evaporated and purified by preparative TLC (CH_2Cl_2/MeOH:98/2). Yield 93%. LCMS *m/z* 275.37 $[M+H]^+$

Example 3: Preparation of ethyl 8-methyl-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (compound 2.3c)

Compound **2.3c** was synthesized according to the procedure described by using *N*-carbethoxy-4-piperidone and 4-methylphenylhydrazine at reflux overnight. The resulting mixture was cooled to room temperature and filtered. Yield 98 %. LCMS *m/z* 259.15 $[M+H]^+$

Example 4: Preparation of ethyl 8-fluoro-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (compound 2.3d)

Compound **2.3d** was synthesized according to the procedure described by using *N*-carbethoxy-4-piperidone and 4-fluorophenylhydrazine at reflux for 2h. After evaporation of solvent, the residue was hydrolysed by water and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and evaporated and purified by preparative TLC (CH_2Cl_2/MeOH:98/2). Yield 75%. LCMS *m/z* 263.23 $[M+H]^+$

4. General procedure C: Preparation of intermediates tricycle beta-carboline derivatives (compounds 2.6, 2.8 and 2.8a): Scheme 2a

Example 1 - Preparation of 1-phenyl-2,3,4,9-tetrahydro-*1H*-beta-carboline (2.6b)

To a stirred solution of tryptamine (5 g, 31.2 mmol) in dichloromethane (70 mL) was added trifluoroacetic acid (3.6 mL, 46.8 mmol, 1.5 eq), and benzaldehyde (4 mL, 46.8 mmol, 1.5 eq). The mixture was stirred for 48h at room temperature and the solvent was evaporated. The residue was washed with diethyl ether, ethyl acetate and filtered to give the compound **2.6b** with a good purity, which was directly used for the next step without purification. Yield : 71 %. LCMS *m/z* 249.13 $[M+H]^+$

Preparation of 1-phenyl-2-propyl-2,3,4,9-tetrahydro-*1H*-pyrido[3,4-b]indole (compound 2.8)

To a stirred solution of compound **2.6b** (1.00 g, 4.0 mmol) in acetonitrile (50 mL) was added 1-iodopropane (0.8 mL, 2 eq), potassium carbonate (1.65 g, 3eq). The mixture was stirred for 3 days at room temperature, the mineral was filtered. The solvent was evaporated. The crude was purified by chromatography on silica gel (cyclohexane/ethyl acetate:9.5/0.5). Yield 60%; LCMS *m/z* 291.0 $[M+H]^+$**.**

Preparation of 2-propyl-2,3,4,9-tetrahydro-*1H*-pyrido[3,4-b]indole (compound 2.8a)

To a stirred solution of commercially available 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole **2.6a** (2.50 g, 14.5 mmol) in acetonitrile (100 mL) and methanol (20 mL) was added 1-iodopropane (2.0 mL, 21.8 mmol, 1.5 eq), potassium carbonate (3.00 g, 21.8 mmol, 1.5 eq). The mixture was refluxed for 24h, and the mineral was filtered. The solvent was evaporated. The crude product was purified by chromatography on silica gel (CH_2Cl_2/methanol:99.8/0.2). Yield 68%; LCMS *m/z* 215.0 $[M+H]^+$

5. General procedure D': Preparation of intermediates tricycle beta- and gamma-carboline derivatives (compounds 2.13, 2.14): Scheme 2b

Preparation of *tert*-butyl 4-(3-(2-propyl-1,2,3,4-tetrahydro-pyrido[3,4-*b*]indol-9-yl)propyl)piperazine -1-carboxylate (compound 2.13a)

To a solution of 2-propyl-2,3,4,9-tetrahydro-*1H*-pyrido[3,4-b]indole **2.8a** (1.50 g, 7.0 mmol) in THF (20 mL) at 0°C was added sodium hydride (0.67 g, 28.0 mmol). The solution was stirred for 30 mn and *tert*-butyl 4-(3-chloropropyl)piperazine-1-carboxylate **1.2** (2.02 g, 7.7 mmol) added. After refluxing for 24h, the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH: 95/5) gave the compound **2.13a**. Yield 76%. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.12 (t, 3H, J= 7.4 Hz), 1.60 (s, 9H), 1.83 (m, 2H), 2.05 (m, 2H), 2.45 (m, 6H), 2.80 (t, 2H, J= 7.8 Hz), 2.95-3.10 (m, 4H), 3.60 (m, 4H), 3.92 (s, 2H), 4.20 (t, 2H, J= 6.8 Hz), 7.22 (t, 1H, J= 7.1 Hz), 7.30 (t, 1H, J= 8.1 Hz), 7.50 (d, 1H, J= 8.1 Hz), 7.62 (d, 1H, J= 7.6 Hz). LCMS *m/z* 341.1 $[M+H\text{-}Boc]^+$.

Preparation of 1-(3-(2-propyl-1,2,3,4-tetrahydro-pyrido[3,4-*b*]indol-9-yl)propyl) piperazine trihydrochloride (compound 2.14a)

To a stirred solution of *tert*-butyl 4-(3-(2-propyl-1,2,3,4-tetrahydro-pyrido[3,4-*b*]indol-9-yl)propyl)piperazine-1-carboxylate **2.13a** (900 mg, 2.1 mmol) in MeOH (50 mL) at room temperature was added HCl 8% (10 mL). The reaction mixture was stirred overnight and the solvent was removed by evaporation. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/MeOH (saturated with gaseous NH_3): 90/10) gave the compound **2.14a**. Yield 95%. ^{1}H NMR (300 MHz, MeOD) δ = 1.10 (t, 3H, J= 6.4 Hz), 1.96 (m, 2H), 2.40 (m, 2H), 2.60 (m, 4H), 3.20 (m, 6H), 3.30-3.45 (m, 4H), 3.70 (m, 2H),4.20 (t, 2H, J= 7.5 Hz), 4.64 (s, 2H), 7.10 (t, 1H, J= 8.1 Hz), 7.25 (t, 1H, J= 8.2 Hz), 7.50 (m, 2H). LCMS *m/z* 341.10 $[M+H]^+$.

6. General procedures E and E2: Synthesis of compounds of the invention - Scheme 3

General procedure E: To a solution of compounds **2.3c-d, 2.8** (1 eq) and *N,N*-diisobutyl-3-(4-(3-chloropropyl)piperazin-1-yl)propylamine **1.5a** (1.1 eq) in DMF (7 mL) at room temperature was added sodium hydride (8 eq). After being stirred for 24h at 70°C, the solvent was removed under reduced pressure. The compounds **3.3** and **3.4**

were obtained by purification of the crude by preparative TLC (CH_2Cl_2/MeOH/NH_4OH:90/10/2).

General procedure E2: To a solution of tricyclic compounds **2.14a** (1 eq) in acetonitrile (20 mL) was added the desired derivative **1.7** or **1.8** (2 eq), K_2CO_3 (5 eq) and NaI (1eq). After refluxing for 24h , the solvent was removed under reduced pressure. The residue was solubilised in a mixture of CH_2Cl_2 and 1M NaOH solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and concentrated. The crude was purified by column chromatography on silica gel (CH_2Cl_2/MeOH:90/10) gave the compounds **3.4**.

Example 1: Synthesis of 5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-8-methyl-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate (compound 3.3a)

Compound **3.3a** was synthesized according to the procedure E by using 8-methyl-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate **2.3c** (142 mg, 0.55 mmol) and *N,N*-diisobutyl-3-(4-(3-chloropropyl)piperazin-1-yl)propylamine **1.5a** (200 mg, 0.6 mmol). Yield 20%. ^{1}H NMR (MeOD, 300 MHz) δ = 0.89 (d, 12H, *J* = 6.6 Hz), 1.30 (t, 3H, *J* = 6.9 Hz), 1.55-1.76 (m, 5H), 1.85-1.93 (m, 2H), 2.07 (d, 4H, *J* = 7.2 Hz), 2.25 (t, 2H, *J* = 7.2 Hz), 2.26-2.71 (m, 13H), 2.83 (t, 2H, *J* = 6.0 Hz), 4.07 (t, 2H, *J* = 6.0 Hz), 4.18 (q, 2H, *J* = 6.0 Hz), 4.62 (s, 2H), 6.94 (d, 1H, *J* = 9.0 Hz), 7.17 (s, 1H), 7.23 (d, 1H, *J* = 6.0 Hz); LCMS *m/z* 554.51 $[M+H]^+$

Example 2: Synthesis of 5-(3-(4-(3-(N,N-diisobutylamino)propyl)piperazin-1-yl)propyl)-8-fluoro-1,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole-2-ethylcarboxylate (compound 3.3b)

Compound **3.3b** was synthesized according to the procedure E by using 8-fluoro-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate **2.3d** (200 mg, 0.76 mmol) and *N,N*-diisobutyl-3-(4-(3-chloropropyl)piperazin-1-yl)propylamine **1.5a**. Yield 35%. ^{1}H NMR (MeOD, 300 MHz) δ = 0.89 (d, 12H, *J* = 6.6Hz), 1.30 (t, 3H, *J* = 6.9 Hz), 1.54-1.77 (m, 4H), 1.88 (m, 2H), 2.07 (d, 4H, *J* = 7.2 Hz), 2.25 (t, 2H, J = 7.2 Hz), 2.26-2.71 (m, 10H), 2.85 (t, 2H, J = 5.4Hz), 3.84 (t, 2H, J = 5.4Hz), 4.10 (t, 2H, *J* = 6.6 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.60 (s, 2H), 6.86 (td, 1H, *J*= 9.0 Hz, *J* = 2.4 Hz), 7.06 (dd, 1H, *J*= 9.6 Hz, *J*= 2.4 Hz), 7.31 (dd, 1H, *J*= 8.7 Hz, *J*= 4.2 Hz). LCMS *m/z* 558.57 $[M+H]^+$

Example 3: Synthesis of 5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-8-methoxy-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate (compound 3.3c)

Compound **3.3c** was synthesized according to the procedure E by using 8-methoxy-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate **2.3b** (200 mg, 0.75 mmol) and *N,N*-diisobutyl-3-(4-(3-chloropropyl)piperazin-1-yl)propylamine **1.5a**. Yield 41%. ^{1}H NMR (MeOD, 300 MHz) δ = 0.88 (d, 12H, *J*= 6.5Hz), 1.30 (t, 3H, *J*= 6.7 Hz), 1.55-1.75 (m, 4H), 1.90 (m, 2H), 2.08 (d, 4H, *J* = 7.0 Hz), 2.25 (t, 2H, J = 7.3 Hz), 2.33-2.55 (m, 8H), 2.83 (t, 2H, J = 5.7Hz), 3.33 (s, 2H), 3.61-3.90 (m, 7H), 4.07 (t, 2H, *J* = 6.7 Hz), 4.19 (q, 2H, J = 7.2 Hz), 4.61 (s, 2H), 6.75 (dd, 1H, *J*= 8.8 Hz, *J*= 2.1 Hz), 6.89 (d, 1H, *J*= 2.0 Hz), 7.24 (d, 1H, *J*= 8.7 Hz). LCMS *m/z* 570.58 $[M+H]^+$.

Example 4: Synthesis of 5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate (compound 3.3d)

The compound **3.3d** was synthesized according to the procedure E by using 1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate **2.3a** (200 mg, 0.78 mmol) and *N,N*-diisobutyl-3-(4-(3-chloropropyl)piperazin-1-yl)propylamine **1.5a**. Yield 45%. ^{1}H NMR (MeOD, 300 MHz) δ = 0.90 (d, 12H, *J*= 6.6Hz), 1.30 (t, 3H, *J*= 6.5 Hz), 1.65-1.80 (m, 4H), 2.00-2.21 (m, 6H), 2.40-2.70 (m, 10H), 2.83 (t, 2H, J = 5.7Hz), 2.91 (s, 2H), 3.55-3.75 (m, 4H), 3.85 (t, 2H, *J* = 6.7 Hz), 4.50 (q, 2H, J = 7.2 Hz), 4.61 (s, 2H), 7.10-7.50 (m, 4H). LCMS *m/z* 540.38 $[M+H]^+$.

Example 5: Synthesis of 5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-2-methyl-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (compound 3.5a)

To a stirred solution of compound **3.3d** (200 mg, 0.37 mmol) in THF (30 mL), $LiAlH_4$ was added (30 mg, 0.74 mmol). The mixture was stirred for 16h, and water was added (10 mL). The solvent was evaporated. The crude product was purified by chromatography on silica gel (CH_2Cl_2/methanol:99.8/0.2). Yield 55%. ^{1}H NMR (MeOD, 300 MHz) δ = 0.95 (d, 12H, *J*= 6.7Hz), 1.60-1.75 (m, 4H), 2.09 (d, 4H, *J*= 6.8Hz), 2.30-2.70 (m, 19H), 2.90 (m, 4H), 3.70 (m, 2H), 4.20 (t, 2H, *J* = 6.7 Hz), 6.90-7.25 (m, 4H). LCMS *m/z* 482.57 $[M+H]^+$.

Example 6: Synthesis of *N,N*-diisobutyl-3-[4-(3-(1-phenyl-2-propyl-1,2,3,4-tetrahydro-pyrido[3,4-*b*]indol-9-yl)propyl)piperazin-1-yl]propylamine (compound 3.4a)

Compound **3.4a** was synthesized according to the procedure E by using 1-phenyl-2-propyl-2,3,4,9-tetrahydro-*1H*-pyrido[3,4-b]indole **2.8** (300 mg, 1.03 mmol) and *N,N*-diisobutyl-3-(4-(3-chloropropyl)piperazin-1-yl)propylamine (**1.5a**) (375 mg, 1.13 mmol). Yield 46%. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 0,97 (m, 15H, CH_3); 2,00 (m, 8H, CH, CH_2); 3,40 (m, 26H, NCH_2); 6,20 (s, 1H, H_1); 7,30 (m, 2H, H_5, H_8); 7,60 (m, 7H, H_6, H_7, H_{Ar}); 9,5 (s, 2H, $2NH^+$); 10,6 (s, 1H, NH^+); 12,8 (s, 1H, NH^+). LCMS *m/z* 586.6 $[M+H]^+$.

Example 7: Synthesis of 1-[2-(piperidin-1-yl)ethyl]-4-(3-(2-propyl-1,2,3,4-tetrahydro-pyrido[3,4-*b*]indol-9-yl)propyl)piperazine (compound 3.4b)

Compound **3.4b** was synthesized according to the procedure E2 by using 1-(3-(2-propyl-1,2,3,4-tetrahydro-pyrido[3,4-*b*]indol-9-yl)propyl) piperazine **2.14a** (200 mg, 0.59 mmol) and commercial 2-chloroethylpiperidine (110 mg, 0.74 mmol). Yield 26%. ^{1}H NMR (300 MHz, MeOD) δ = 1.00 (t, 3H, J= 7.2 Hz), 1.48 (m, 2H), 1.55-1.78 (m, 6H), 1.90 (m, 2H), 2.32 (t, 2H, J= 6.8 Hz), 2.40-2.65 (m, 18H), 2.80-2.90 (m, 4H), 3.75 (s, 2H), 4.10 (t, 2H, J= 6.8 Hz), 7.01 (t, 1H, J= 7.1 Hz), 7.10 (t, 1H, J= 8.1 Hz), 7.34 (d, 1H, J= 8.1 Hz), 7.41 (d, 1H, J= 7.7 Hz).). LCMS *m/z* 452.1 $[M+H]^+$.

BIOLOGICAL RESULTS

Cell cultures and transfections to test activity on Aβ1–40 and Aβ1–42 secretion

Human neuroblastoma cell line SKNSH-SYSY (ATCC® Catalog No. CRL-2266TM), HEK (ATCC® CRL-1573™) and COS-1 (ATCC® CRL-1650™) cells were maintained in Dulbecco's modified Eagle medium (DMEM, GIBCO BRL) supplemented with 10% fetal calf serum, 2 mM L-glutamine, 1 mM non-essential amino acids, 50 units/ml penicillin/streptomycin (Invitrogen, France) in a 5% CO_2 humidified incubator at 37°C. APP695 cDNA was subcloned into eukaryotic expression vector pcDNA3 (Invitrogen), allowing for a G418 (Invitrogen) selection of clones. This APP cDNA coding for the 695 amino acid long isoform was transfected into SKNSH-SYSY cells using the ethyleneimine polymer ExGen 500 (Euromedex) according to the manufacturer's instructions. The cells expressing APP (SKNSH-SYSY APP^{WT}) were selected by the addition of 200 µg/ml G418 in the cell medium. To quantify Aβ which released in the cell culture medium, the collected medium was spun at 200×g to eliminate the cell debris.

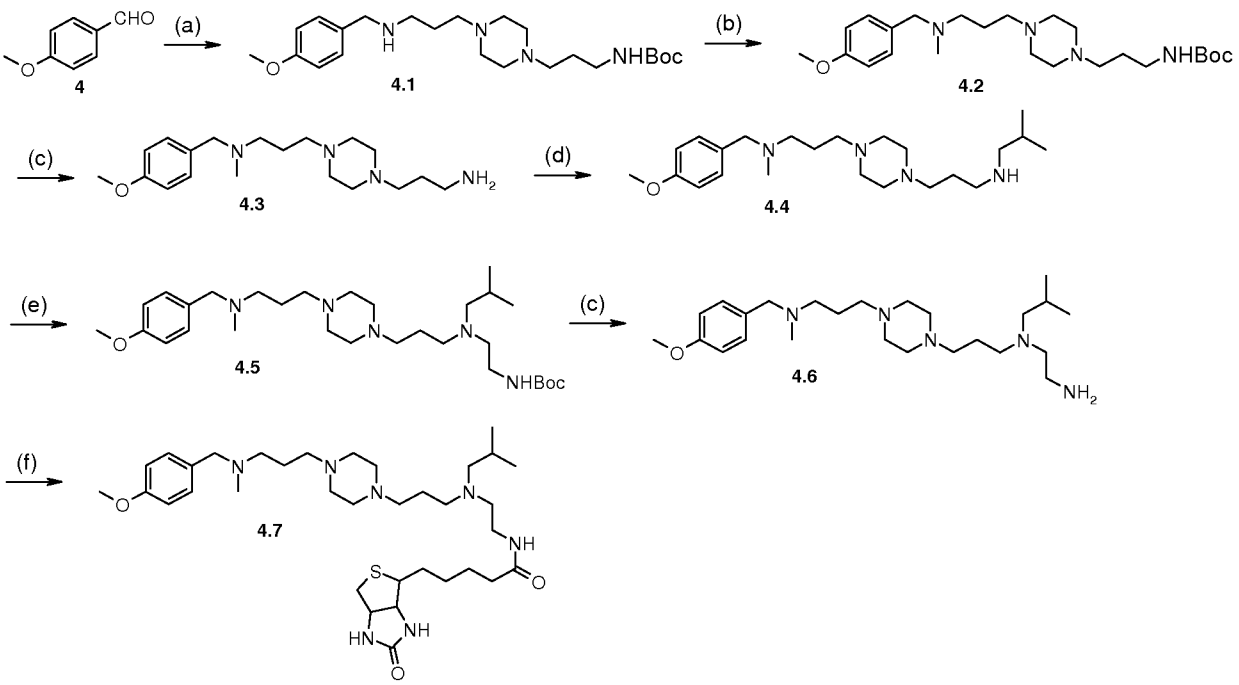
The concentrations of secreted $A\beta_{1-40}$ and $A\beta_{1-42}$ were determined using the Human Aβ (1–40) Assay Kit (IBL) or the INNOTEST™ beta-Amyloid (1– 42) ELISA Kit (Innogenetics), according to manufacturer's instructions. The results were expressed as IC_{50}, i.e. the concentration able to decrease to 50% the basal amount of secreted Aβ peptide 1-40 and 1-42.

Quantifications of APP-CTFs and AICD

After treatment, SY5Y-APP^{WT} cells were scrapped and lysed in 1× Lysis Buffer (250 mM NaCl, 50 mM Tris, pH 8.8, 5 mM EDTA, 2.5% Triton X-100, 1% Deoxycholate, 0.1% SDS). For the Western blotting, an equal amount of total proteins (20 ìg/lane) was loaded on a 16.5% Tris–Tricine or 8–16% Tris–Glycine polyacrylamide gel.
SDS–polyacrylamide gel electrophoresis (PAGE) was performed using the Criterion™ Tris-Tricine-precast or Bis-Tris-precast criterion gels (Bio-Rad Bioresearch division). Proteins were transferred to a 0.2 cm^2 nitrocellulose membrane (Hybond, Amersham Biosciences) at 2.5 mA/cm2 per gel using the Criterion™ Blotter system (Amersham Biosciences), according to the manufacturer's instructions. Proteins were reversibly stained with Ponceau Red in order to check the quality of the transfer of protein. The membranes were blocked in 25 mM Tris–HCl pH 8.0, 150 mM NaCl, 0.1% Tween-20 (v/v) and 5% (w/v) of skimmed milk for 30 min. Membranes were incubated overnight at 4℃ with appropriate dilution of the primary antibodies, and were incubated for 1 h at room temperature with secondary antibody. The immunoreactive complexes were revealed using the ECL™ Western Blotting kit and LAS-3000 Chemiluminescence Camera acquisition system (FujiFilm). Quantifications were calculated with Image J software (NIH) and the data were collected using Excel Software (Microsoft). The loading variations between Western blot lanes were normalized according to the tubulin signal. Quantification of CTFα and AICD were compared to control conditions (considered as 100 in arbitrary units) and are presented for two concentrations of the drug: 1 and 10µM.

VCP affinity evaluation

Biotinylated-Probe synthesis 4.7



Reagents: (a) : *tert*-butyl 3-(4-(3-aminopropyl)piperazin-1-yl)propylcarbamate, $NaBH_4$, MeOH (b) : HCO_2H, HCHO, EtOH, reflux; (c): TFA, CH_2Cl_2, rt; (d) : isobutyraldehyde, $NaBH_4$, MeOH, rt ; (e) : $OHCCH_2NHBoc$, $NaBH(OAc)_3$, CH_2Cl_2, rt; (f) : triethylamine, Biotine-OSu, DMF, rt.

Preparation of *tert*-butyl 3-(4-(3-(4-methoxybenzylamino)propyl)piperazin-1-yl)propyl carbamate (compound 4.1)

To a stirred solution of *tert*-butyl 3-(4-(3-aminopropyl)piperazin-1-yl)propylcarbamate (2.7 g, 10 mmol) in methanol (10 mL) at room temperature, in presence of 3A molecular sieves and under inert atmosphere, was added 4-methoxybenzaldehyde **4** (3.0 g, 11 mmol). The mixture was stirred for 16h and cooled to 0°C by using an ice-bath and then $NaBH_4$ (0.95 g, 25 mmol) was added in small portions. After additional 30 minutes of stirring, the mixture was filtered over celite. The filtrate was evaporated; the concentrate was dissolved in CH_2Cl_2 and alkalinized with 1M NaOH solution. Two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated. Crude compound **4.1** was used for the next step without purification. ^1H NMR (MeOD, 300 MHz) δ: 1.45 (s, 9H), 1.82-1.61 (m, 4H), 2.65-2.30 (m, 12H), 2.70 (t, 2H, *J* = 6.1 Hz), 3.10 (t, 2H, *J* = 5.9 Hz), 3.49 (s, 2H), 3.80 (s, 3H), 6.91 (m, 2H), 7.28 (m, 2H)). LCMS *m/z* 421.45 $[M+H]^+$.

Preparation of *tert*-butyl 3-(4-(3-(N-(4-methoxybenzyl)-N-methylamino)propyl)piperazin-1-yl)propylcarbamate (compound 4.2)

To a stirred solution of *tert*-butyl 3-(4-(3-(4-methoxybenzylamino)propyl)piperazin-1-yl)propyl carbamate **4.1** (3.9 g, 10 mmol) in ethanol (50mL) at room temperature, was added formic acid (0.65 mL, 17 mmol) and formaldehyde 37% (0.35 mL, 5 mmol). The solution was refluxed for 4h and hydrolyzed with 1M NaOH solution (10 mL). The mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated. Purification by chromatography on silica gel (eluent: CH_2Cl_2/MeOH/NH_3 95/5 v/v) yielded compound **4.2**. Yield 49%. ^{1}H NMR (MeOD, 300 MHz) δ: 1.47 (s, 9H), 1.83-1.61 (m, 4H), 2.23 (s, 3H), 2.65-2.37 (m, 14H), 3.10 (t, 2H, *J* = 6.6 Hz), 3.49 (s, 2H), 3.80 (s, 3H), 6.90 (d, 2H, *J* = 8.7 Hz), 7.24 (d, 2H, *J* = 8.7 Hz).

Preparation of 3-(4-(3-(*N*-(4-methoxybenzyl)-N-methylamino)propyl)piperazin-1-yl)propylamine (compound 4.3)

To a stirred solution of *tert*-butyl 3-(4-(3-(*N*-(4-methoxybenzyl)-N-methylamino)propyl)piperazin-1-yl)propylcarbamate **4.2** (3.9 g, 10 mmol) in CH_2Cl_2 (50 mL) at room temperature was added TFA (7.7 mL, 100 mmol). The reaction mixture was stirred overnight and the solvent was removed by evaporation. The residue was alkalinized with a mixture of saturated $NaHCO_3$ solution and 6M NaOH solution (80/20 v/v, 50 mL), and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give the corresponding unprotected product **4.3**, which was directly used for next step without purification. Yield 98 %. ^{1}H NMR (MeOD, 300 MHz) δ: 1.82-1.61 (m, 4H), 2.22 (s, 3H), 2.80-2.33 (m, 16H), 3.48 (s, 2H), 3.80 (s, 3H), 6.90 (d, 2H, *J* = 8.7 Hz), 7.24 (d, 2H, *J* = 8.7 Hz).

Preparation of 3-(4-(3-isobutylaminopropyl)piperazin-1-yl)-*N*-(4-methoxybenzyl)-*N*-methylpropan-1-amine (compound 4.4)

To a stirred solution of 3-(4-(3-(*N*-(4-methoxybenzyl)-*N*-methylamino)propyl)piperazin-1-yl)propylamine **4.3** (3.3 g, 10 mmol) in methanol (100 mL) at room temperature, in presence of 3A molecular sieves and under inert atmosphere, was added isobutyraldehyde (1.0 mL, 11 mmol). The mixture was stirred for 16h and cooled to 0°C and then $NaBH_4$ (1.0 g, 25 mmol) was added in small portions. After additional 30 minutes of stirring, the mixture was filtered over celite. The filtrate was evaporated; the concentrate was dissolved in CH_2Cl_2 and alkalinized with 1M NaOH solution. Two

layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated. Purification by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 90/10 v/v) gave the corresponding product **4.4**. Yield 58%. ^{1}H NMR (MeOD, 300 MHz) δ: 0.92 (d, 6H, *J* = 6.6 Hz), 1.87-1.63 (m, 4H), 2.18 (s, 3H), 2.68-2.23 (m,16H), 3.44 (s, 2H), 3.76 (s, 3H), 6.87 (d, 2H, *J* = 8.7 Hz), 7.22 (d, 2H, *J* = 8.7 Hz). LCMS *m/z* 391.41 $[M+H]^+$.

Preparation of *tert*-butyl 2-(isobutyl(3-(4-(3-(*N*-(4-methoxybenzyl)-*N*-methylamino)propyl)piperazin-1-yl)propyl)amino)ethylcarbamate (compound 4.5)

To a stirred solution of 3-(4-(3-isobutylaminopropyl)piperazin-1-yl)-*N*-(4-methoxybenzyl)-*N*-methylpropan-1-amine **4.4** (360 mg, 0.92 mmol) in CH_2Cl_2 (20 mL), at room temperature and under inert atmosphere were added CHO-CH_2-NHBoc (220 mg, 1.38 mmol) and $NaBH(OAc)_3$ (293 mg, 1.38 mmol). The mixture was stirred for 24h and 1N NaOH solution (15 mL) was added. After additional 15 minutes of stirring, the resulting mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, evaporated and purified by chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 95/5 v/v) to give corresponding substituted product **4.5**. Yield 71%. ^{1}H NMR (MeOD, 300 MHz) δ: 0.92 (d, 6H, *J* = 6.6Hz), 1.46 (s, 9H), 1.92-1.72 (m, 4H), 2.18 (d, 2H, *J* = 6.9Hz), 2.23 (s, 3H), 2.81-2.50 (m, 14H), 3.13 (m, 2H), 3.50 (s, 2H), 3.81 (s, 3H), 6.90 (d, 2H, *J* = 7.8 Hz), 7.25 (2H, *J* = 7.8 Hz). LCMS *m/z* 534.58 $[M+H]^+$.

Preparation of *N'*-isobutyl-*N'*-(3-(4-(3-(*N*-(4-methoxybenzyl)-*N*-methylamino)propyl) piperazin-1-yl)propyl)ethane-1,2-diamine (compound 4.6)

To a stirred solution of *tert*-butyl 2-(isobutyl(3-(4-(3-(*N*-(4-methoxybenzyl)-*N*-methylamino)propyl) piperazin-1-yl)propyl)amino)ethylcarbamate **4.5** (0.5 g , 1 mmol) in CH_2Cl_2 (30 mL) at room temperature was added TFA (0.8 mL, 10 mmol). The reaction mixture was stirred overnight and the solvent was removed by evaporation. The residue was alkalinized with a mixture of saturated $NaHCO_3$ solution and 6M NaOH solution (80/20 v/v, 10mL), and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to give the corresponding unprotected product **4.6**, which was directly used for next step without purification. Yield 98 %. ^{1}H NMR (MeOD, 300 MHz) δ: 0.92 (d, J = 6.9Hz), 2.19-2.00 (m, 3H), 2.72 (s, 3H), 3.55-3.07 (m, 12H), 3.76 (s, 3H), 4.32-4.14 (m, 2H), 7.32 (d, J=9 Hz, 2H). LCMS *m/z* 434.50 $[M+H]^+$.

Preparation of *N*-(2-(isobutyl(3-(4-(3-(*N*-(4-methoxybenzyl)-*N*-methylamino)propyl) piperazin-1-yl)propyl)amino)ethyl)-5-(2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (compound 4.7)

To a solution of *N'*-isobutyl-*N'*-(3-(4-(3-(*N*-(4-methoxybenzyl)-*N*-methylamino)propyl)piperazin-1-yl)propyl)ethane-1,2-diamine **4.6** (0.3 g, 0.64 mmol) in DMF (10 mL) at room temperature was added triethylamine (1.4 mL, 9.6 mmol) and then Biotine-OSu (219 mg, 0.64 mmol). After being stirred for 24h at room temperature, the solvent was removed under reduced pressure. Purification of the crude by preparative TLC (eluent: CH_2Cl_2/MeOH/NH_3 90/10/2 v/v) gave compound **4.7**. Yield 63 %. ^{1}H NMR (MeOD, 300 MHz) δ: 0.88 (d, J = 6.6Hz, 6H), 1.81-1.10 (m, 12Hz), 2.19-2.15 (dd, J = 7.4Hz, J= 2.1Hz, 4H), 2.22 (s, 3H), 2.93-2.30 (m, 20H), 3.28-3.12 (m, 2H), 3.49 (s, 2H), 3.79 (s, 3H), 4.30-4.36 (m, 1H), 4.51-4.45 (m, 1H), 6.87 (d, J= 6.6Hz, 2H), 7.22 (d, J= 6.6Hz, 2H). LCMS *m/z* 660.85 $[M+H]^+$.

VCP interaction assay

Physical interaction between HIS-tagged valosin-containing protein/p97 (VCP/p97) (TebuBio) and biotinylated probe **4.7** was investigated by Enzyme-Linked Assay (ELA) based on HIS-Select® High Sensitivity Nickel coated plates, used following manufacturer's recommendations (Sigma Aldrich). Other chemical compounds were tested in competition with the biotinylated probe **4.7** in this system. Briefly, nickel beads were incubated overnight at 4°C with 2% casein blocking solution. After a three-time rinse with wash buffer (0.05% Tween20 in phosphate buffer saline), HIS-tagged VCP/p97 protein (5µg/ml in PBS) was incubated with nickel beads for 90 min at 25°C. Then, the plate was washed three times. Chemical compounds (60µM) were incubated 10 min at 25°C before addition of biotinylated probe **4.7** (20µM) 30 min at 25°C. After five washes, streptavidin-peroxidase (2µg/ml) was added during 1 h at 25°C, followed by the peroxidase substrate addition 30 min at rt. Reaction was stopped with 0.5M H_2SO_4 solution and the optical density was read at 450 nm using a microplate reader (VICTOR X4 Wallac, 2030-0040, PerkinElmer). Competition efficiency was quantified by the loss of signal compared to the control condition.

The biological activities of selected compounds of the invention are given in the following Table I.

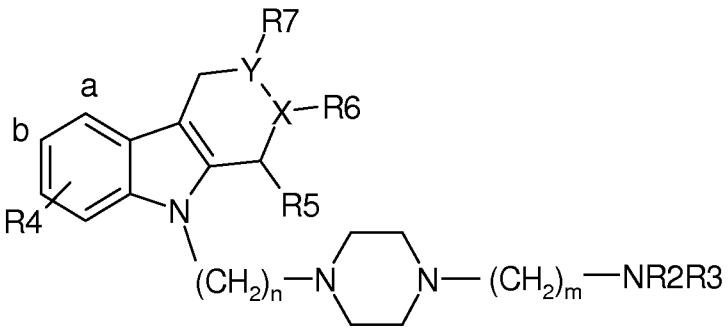
Table I

Compound no	$A\beta_{1-40}$ IC_{50}, (μM)	$A\beta_{1-42}$ IC_{50}, (μM)	AICD (10μM)	CTFα (10μM)	VCP
3.3a	10	>10			
3.4a	1	5	8889	169	100%
3.4b	1	10			

a: results in arbitrary units compared to a control (no active ingredient added) with a value of 100

CLAIMS

1. A compound according to Formula (III):



(III)

in which

- **n** is an integer equal to 2 or superior to 2;
- **R4** is selected from F, Cl, H, O-CH_3, and -CH_3;
- **R5** is selected from H, CH_3 and a phenyl group;
- **X** and **Y** are selected from the group consisting of carbon atom and nitrogen atom, with the proviso that **X** is a nitrogen atom when **Y** is a carbon atom and **X** is a carbon atom, when **Y** is a nitrogen atom;
- **R6** and **R7** are independently selected from the group consisting of an hydrogen atom, an alkyl group, a COO**R8** group, wherein **R8** is a linear or branched alkyl group having from 2 to 10 carbon atoms, with the proviso that when **Y** is a carbon atom, **R6** is a hydrogen atom and when **X** is a carbon atom, **R7** is an hydrogen atom;
- **m** is an integer equal to 2 or superior to 2; and
- **R2** and **R3** are selected independently one from another from the groups consisting of:

- linear or branched (C_1-C_{12}) alkyl; linear or branched (C_2-C_{12}) alkenyl; linear or branched (C_2-C_{12}) alkynyl; said alkyl group, alkenyl group or alkynyl group may be substituted with at least one substituent selected from halogen, cycloalkyl, hydroxyl, alkoxy, amino, acylamino, aroylamino, heteroaroylamino and carboxy groups;
- heteroaroylamino;
- (C_2-C_6) heterocycloalkyl comprising in the cycle an oxygen atom and/or a nitrogen atom;
- benzyl optionally substituted with an alkyl group, halogen, an ether group and/or an amino group; or

R2 and **R3** form together with the nitrogen atom carrying them a saturated or unsaturated (C_2-C_7) heterocycle.

or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or polymorph thereof.

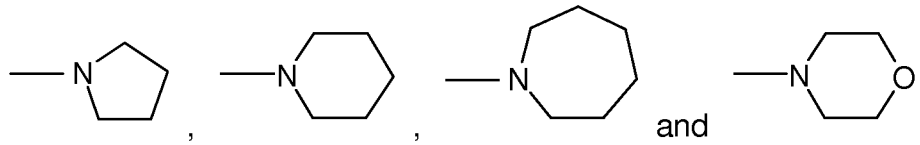
2. A compound according to claim 1, wherein **n** and **m** are selected from 2 and 3 and preferably are identical.

3. A compound according to claim 1 or 2, wherein **R2** and **R3** are identical and are selected from (C_1-C_{12}) alkyls.

4. A compound according to claim 3, wherein **R2** and **R3** are identical and either isobutyl or methyl groups.

5. A compound according any of claims 1 to 4, wherein **R4** is attached to the carbon atom in position b and is preferably selected from F, Cl, H and OCH_3.

6. A compound according to any of claims 1, 2 and 5, wherein **R2**, **R3** and the nitrogen atom carrying them form one of the following heterocyclic groups:



, , and

7. A compound according to claim 6, wherein **R2** and **R3** and the nitrogen atom carrying them form a pyrrolidinyl group.

8. A compound according to any of claims 1 to 7, wherein **R6** or **R7** are selected from H and -$CH_2CH_2CH_3$.

9. A compound according to any of claims 1 to 8, wherein **X** is N.

10. A compound according to any of claims 1 to 9, wherein **R5** is H or a phenyl group.

11. A compound according to claim 1 wherein said compound is selected from:

5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-8-methyl-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate,

5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-8-fluoro-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate,

5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-8-methoxy-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate,

5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-2-ethylcarboxylate,

5-(3-(4-(3-(*N,N*-diisobutylamino)propyl)piperazin-1-yl)propyl)-2-methyl-1,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole,

N,N-diisobutyl-3-[4-(3-(1-phenyl-2-propyl-1,2,3,4-tetrahydro-pyrido[3,4-*b*]indol-9-

yl)propyl)piperazin-1-yl]propylamine, and

1-[2-(piperidin-1-yl)ethyl]-4-(3-(2-propyl-1,2,3,4-tetrahydro-pyrido[3,4-*b*]indol-9-yl)propyl)piperazine.

12. A compound according any of claims 1 to 11 for use as medicament.

13. A compound according to any of claims 1 to 11 for use as a medicament in the treatment of a disease selected from the group consisting of tauopathies, amyloidopathies and synucleopathies.

14. A compound according to any of claims 1 to 11 for use according to claim 13, wherein said disease is a neurodegenerative disease, a related neurodegenerative disease or a developmental disease.

15. A compound according to any of claims 1 to 11 for use according to any of claims 13 and 14, wherein said disease is selected from the group consisting of Alzheimer's disease, Paget's disease of bone, familial amyotrophic lateral sclerosis (ALS), Lewy body disease, Down syndrome, amyloid angiopathy, Parkinson's disease, amyotrophic lateral sclerosis (ALS), frontotemporal degeneration, and frontotemporal lobar dementia.

16. A pharmaceutical composition comprising as an active ingredient, a compound according to any of 1 to 11 and a pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/063772

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P25/28 A61P25/16
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2014	18/08/2014

Name and mailing address of the ISA/	Authorized officer
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