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(54) Titre : UTILISATION DE DERIVES DE LA 1,4-BIS (3-AMINOALKYL) PIPERAZINE POUR LE TRAITEMENT DE
MALADIES NEURODEGENERATIVES
(54) Title: USE OF 1,4-BIS (3-AMINOALKYL) PIPERAZINE DERIVATIVES IN THE TREATMENT OF
NEURODEGENERATIVE DISEASES

(57) **Abrégé/Abstract:**

Use of 1,4-bis (3-aminoalkyl) piperazine derivatives as defined in formula I or II for the manufacture of a pharmaceutical composition intended for the treatment of neurodegenerative diseases, related neurodegenerative diseases, developmental diseases or cancer. The instant invention is also directed to some specific 1,4-bis (3-aminoalkyl) piperazine derivatives and pharmaceutical composition including them.



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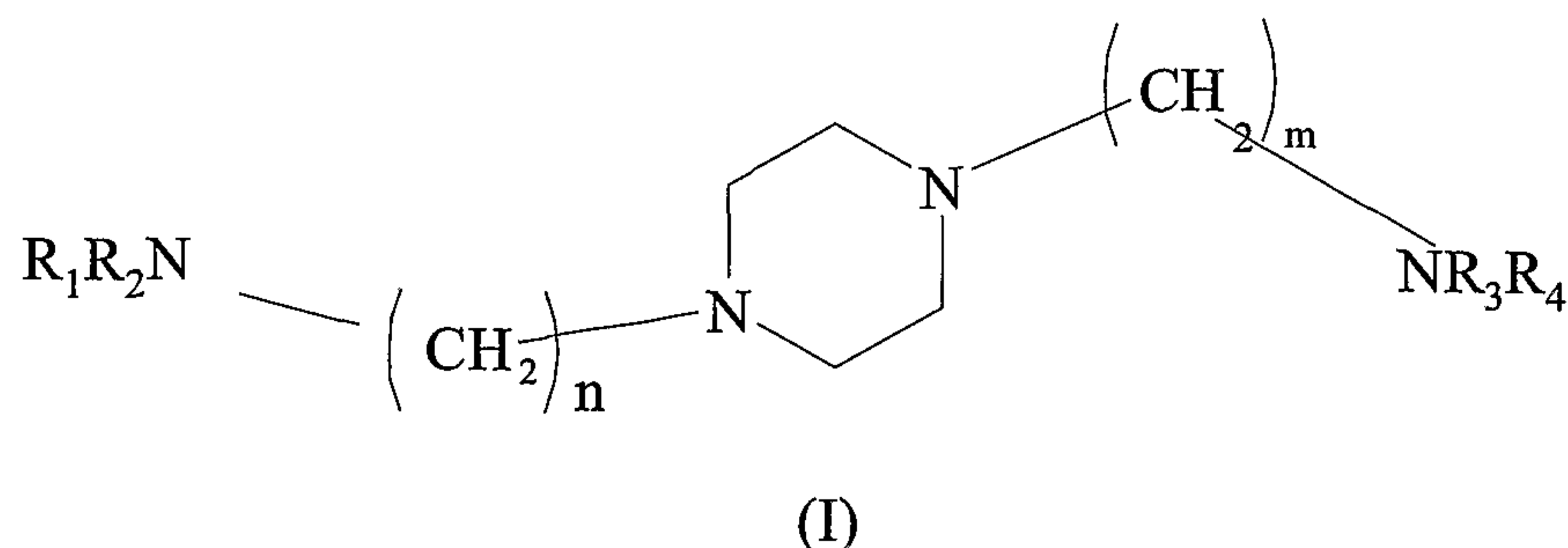
(54) **Title:** USE OF 1,4-BIS (3-AMINOALKYL) PIPERAZINE DERIVATIVES IN THE TREATMENT OF NEURODEGENER-
ATIVE DISEASES

(57) **Abstract:** Use of 1,4-bis (3-aminoalkyl) piperazine derivatives as defined in formula I or II for the manufacture of a pharma-
ceutical composition intended for the treatment of neurodegenerative diseases, related neurodegenerative diseases, developmental
diseases or cancer. The instant invention is also directed to some specific 1,4-bis (3-aminoalkyl) piperazine derivatives and pharma-
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WO 2006/051489 A1

USE OF 1,4-BIS (3-AMINOALKYL) PIPERAZINE DERIVATIVES IN THE TREATMENT OF NEURODEGENERATIVE DISEASES

The present invention relates to the use of 1,4-bis(3-aminoalkyl)piperazine derivatives of formula (I)



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for the manufacture of pharmaceutical compositions intended for the treatment of neurodegenerative diseases, for example a disease distinguished by related disorders with APP dysfunction, and in particular Alzheimer's disease. The present invention also relates to some of said 1,4-bis(3-aminoalkyl)piperazine derivatives to their preparation and their use in therapy.

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Alzheimer's disease is a progressive neurological disease that affects brain functions, including short-term memory loss, inability to reason, and the deterioration of language and the ability to care for oneself. An estimated 3% of people between the ages of 65 and 74 have Alzheimer's disease, rising to about half those age 85 and over. Currently, Alzheimer's disease is incurable.

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WO 02/37118 discloses means for detecting pathological transformation of the APP protein and their uses in diagnostic and therapeutic applications in degenerative pathologies such as Alzheimer disease.

20

Some of the compounds of formula (I) are already known, namely various compounds of formula (I) are useful for their antimalarial properties in : "Trypanothione reductase inhibition/trypanocidal activity relationship in a 1,4-bis(3-aminopropyl)piperazine series" B. Bonnet *et al*, *Bioorganic & Medicinal Chemistry* 8 (2000) 95-103, "Synthesis and *in vitro* and *in vivo* Antimalarial Activity of N-(7-chloro-4-quinolyl)-1,4-bis(3-aminopropyl)piperazine derivatives" A. Ryckebusch *et al*, *J. Med. Chem.* (2003), 46, 542-557, "Synthesis and antimalarial evaluation of new 1,4-bis(3-aminopropyl)piperazine derivatives" A. Ryckebusch *et al*, *Bioorganic & Medicinal*

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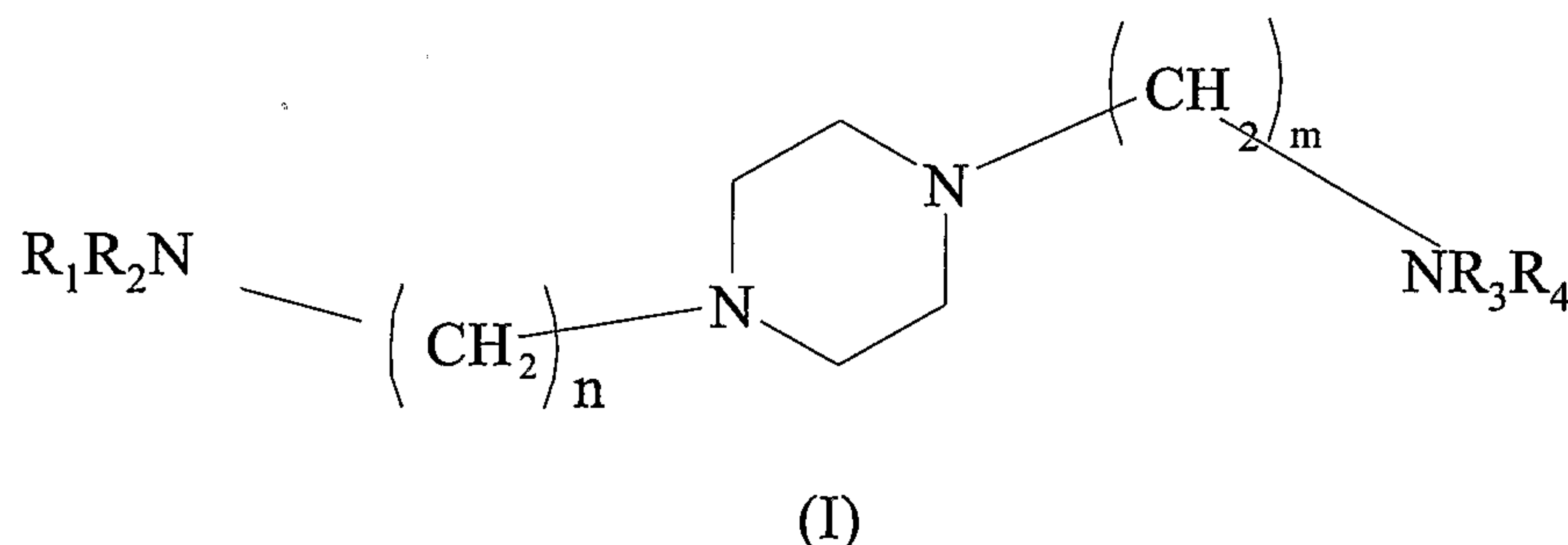
Chemistry Letters 13 (2003) 3783-3787 and in "Design, Synthesis and antimalarial activity of novel quinoline-based, zinc metallo-aminopeptidase inhibitors" M.Flipe *et al*, *Bioorganic & Medicinal Chemistry Letters* 13 (2003) 2659-2662.

Unexpectedly, the inventors discovered that the molecules according to the present invention could be used to rectify the metabolism of the Amyloid Protein Precursor (APP) on three essential points:

- 1) increasing the carboxy-terminal fragments of APP (APP-CTFs) which all in common possess the last 50 aminoacids of APP, and especially those having potential physiological activities, such as the α -stubs (APP-CTF alpha) and the γ -stubs (APP-CTF gamma or AICD for APP intra cellular domain),
- 2) decreasing the production of the neurotoxic by-products of APP, i.e. β -amyloid ($A\beta$) peptides, especially in their form x-42,
- 3) without modifying the APP expression and in absence of neurotoxicity.

Therefore, the 1,4-bis(3-aminoalkyl)piperazine derivatives as described herein are useful in the treatment of all diseases where a dysfunction of the APP metabolism occurs. The Alzheimer's disease is one said disease.

Accordingly, the present invention relates to the use of a compound represented by the following formula (I)



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in which n and m are identical or different and independently represent an integer of greater than or equal to 2, particularly ranging from 2 to 8, more preferably ranging from 2 to 6, more particularly being 2, 3 or 4, the resulting hydrocarbon chain optionally comprising one or more heteroatoms selected among oxygen, nitrogen and sulphur, and

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in which R_1 , R_2 , R_3 and R_4 , independently the ones of the others, represent

- a hydrogen atom,
- a (C₁-C₇)alkyl group, straight or branched, saturated or unsaturated,
- a (C₁-C₇)alkylcarbonyl group,
- an aryl group,
- 5 - an aralkyl group, where the aryl group is attached to a (C₁-C₄)alkylene bridging moiety,
- a heteroaryl group,

where each (C₁-C₇)alkyl group can be possibly substituted by one or more identical or different groups chosen among a halogen, the cyano group, the hydroxy group, the nitro group, the amino group, a (C₁-C₇)alkylamino group, a (C₁-C₇)alkoxy group, a tertbutoxycarbonylamino group, a HO-(C₁-C₈)alkyl- group, a H₂N-(C₁-C₈)alkyl- group, a HO-(C=O)- group, a (C₁-C₈)alkyl-O-(C=O)- group, a (C₁-C₈)alkyl-(C=O)- group, a (C₁-C₈)alkyl-(C=O)-(C₁-C₈)alkyl- group, a HSO₃(C₁-C₈)alkyl- group, a H₂N-(C=O)- group and a H₂N-(C=O)-(C₁-C₈)alkyl- group,

15 where the aryl group is selected among the groups benzyl, phenyl, biphenyl, anthryl, phenylbenzyl, fluorenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl and indanyl,

where the heteroaryl group is an aromatic monocycle, an aromatic bicycle, an aromatic tricycle, or a bicycle or a tricycle of which one or two of the cycles is aromatic and the other cycle(s) is or are partially hydrogenated, from C₅ to C₁₄ comprising within the cyclic system one, two or three heteroatoms, identical or different, selected among oxygen, nitrogen and sulphur, and

25 where each one of these aryl or heteroaryl groups comprises possibly one or more substitutions, identical or different, chosen among a halogen, the hydroxy group, a (C₁-C₇)alkyl group, a (C₁-C₇)alkoxy group, a (C₇-C₁₃) arylalkoxy group, the cyano group, the nitro group, the amino group, a (C₁-C₇)alkylamino group, a HO-(C₁-C₈)alkyl- group, a H₂N-(C₁-C₈)alkyl- group, a HO-(C=O)- group, a (C₁-C₈)alkyl-O-(C=O)- group, a (C₁-C₈)alkyl-(C=O)- group, a (C₁-C₈)alkyl-(C=O)-(C₁-C₈)alkyl- group, a HSO₃(C₁-C₈)alkyl- group, a H₂N-(C=O)- group and a H₂N-(C=O)-(C₁-C₈)alkyl- group,

30 where (R₁ and R₂) and/or (R₃ and R₄), independently of one another, can possibly form an aromatic or partially or totally hydrogenated C₄ to C₁₄ monocycle,

optionally comprising within the cyclic system one, two or three heteroatoms, identical or different, selected among oxygen, nitrogen and sulphur,

provided that at most two of the radicals chosen among R₁, R₂, R₃ and R₄ simultaneously represent a hydrogen atom and that (R₁ and R₂) or (R₃ and R₄) do not simultaneously represent a hydrogen atom,

or their salts with pharmaceutically acceptable acids,

for the manufacture of a pharmaceutical composition intended for the treatment of neurodegenerative diseases, related neurodegenerative diseases, developmental diseases or cancer.

In one particular variant of the present invention the heteroaryl group is different from an acridin group or an acridin derivative. In another variant the heteroaryl group is different from an aromatic tricycle.

The use of derivatives of formula (I) is more particularly intended for the treatment of neurodegenerative diseases or related neurodegenerative diseases where APP and its catabolic products are a cause or a risk factor for the development of the pathology.

The derivatives of formula (I) can be used for treatment or prevention. Among neurodegenerative diseases Alzheimer's disease, Down syndrome, amyloid angiopathies, dementia with Lewy bodies and Parkinson's disease may be cited. Indeed, for this two last diseases, important amyloid deposits are always observed in the neocortex of patients with sporadic DLB (Dementia with Lewy Body), and DLB is considered as a continuum of PD (Parkinson's Disease) (McKeith IG *et al.* Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* **1996**; 47: 1113-1124; McKeith *et al.* Dementia with Lewy bodies. *Lancet Neurol* **2004**;3:19-28 and Emre M. Dementia in Parkinson's disease: cause and treatment. *Curr Opin Neurol* **2004**; 17:399-404). Therefore, correcting the risk factor due to APP dysfunction is likely to inhibit the conversion of PD into DLB. APP is also a ubiquitous protein, found in all cell types, and a member of a large family involving APP like proteins, or other proteins with a similar catabolism regulated at the surface membrane (Notch, ErbB, N- and E-Cadherine, LRP, Syndecan, ...) (De Strooper B. (2003) Aph-1, Pen-2, and Nicastrin with Presenilin generate an active γ -Secretase complex. *Neuron* 38, 9-12). Therefore, the derivatives of formula (I) may also be used for the treatment of pathologies such as cancer. Together, correcting the metabolic cleavage of

the C-terminal part of APP and/or APP-like proteins and/or other proteins with structural or conformational homologies with the C-terminal fragments of APP₁ concerns pathologies related to amyloidopathies, tauopathies, synucleopathies as well as developmental diseases and cancer.

5 The compounds of formula (I) can comprise one or more asymmetrical carbon atoms. They can thus exist in the form of enantiomers or of diastereoisomers. These enantiomers, diastereoisomers, as their mixtures, including the racemic mixtures form part of the invention.

10 The compounds of the invention may exist in the form of free bases or of addition salts with pharmaceutically acceptable acids.

 Suitable pharmaceutically acceptable salts of compounds of formula (I) include base addition salts and where appropriate acid addition salts. Suitable physiologically acceptable base addition salts of compounds of formula (I) include alkali metal or alkaline metal salts such as sodium, potassium, calcium, and magnesium salts, and ammonium salts, formed with amino acids (e.g. lysine and arginine) and organic bases (e.g. procaine, phenylbenzylamine, ethanolamine diethanolamine and N-methyl glucosamine).

15 Suitable acid addition salts may be formed with organic acid and inorganic acids e.g. hydrochloric acid.

20 The compounds of formula (I) and or salts thereof may form solvates (e.g. hydrates) and the invention includes all such solvates.

 The term (C₁-C₇)alkyl as used herein refers to a straight or branched-chain hydrocarbon radical of one to seven carbon atoms and cyclized manifestations thereof unless otherwise indicated. Included within the scope of this term are such moieties as methyl, ethyl, isopropyl, n-butyl, t-butyl, t-butylmethyl, cyclopropyl, N-propyl, pentyl, cyclopentyl, n-hexyl, cyclohexyl, cyclohexylmethyl, 2-ethylbutyl etc.

25 The term halogen refers to a fluorine, a chlorine, a bromine or an iodine atom.

 Fluorine and chlorine are preferred halogen atoms in the framework of the present invention.

30 The term (C₁-C₇)alkoxy refers to alkoxy radical made up of an oxygen radical bearing a saturated straight or branched chain hydrocarbon radical of one to seven carbon atoms. Included within the scope of this term are methoxy, ethoxy, propoxy, n-butoxy,

isobutoxy, sec-butoxy, t-butoxy, n-pentoxy, isopentoxy, sec-pentoxy, t-pentoxy... and the like.

Among the compound of formula (I) defined above, the compounds for which the use is preferred may be given in details as follows.

5

A first class of such compounds of formula (I), hereinafter referring to compounds of formula (Ia), is such that R_1 and R_3 are hydrogen atoms and R_2 and R_4 are identical and different from a hydrogen atom.

Among this first class of compounds of formula (Ia), the compounds for which the therapeutic use is the most preferred are characterized in that R_2 and R_4 are selected among

- a chloroquinolinyl group such as 7-chloroquinolin-4-yl,
- a pyridinylmethyl group, such as the pyridin-3-ylmethyl,
- a benzyl group possibly substituted one or twice on the phenyl group by a group chosen among an atom of halogen and a methoxy group such as 4-methoxybenzyl, 3,4-dimethoxybenzyl, 4-chlorobenzyl and 4-fluorobenzyl,
- a quinolinylmethyl group, such as quinolin-4-ylmethyl, and,
- a (C_1-C_7) alkyl group, such as cyclopropylmethyl, isobutyl, 2-ethylbutyl and heptyl.

20

A second class of such compounds of formula (I), hereinafter referring to compounds of formula (Ib), is such that R_1 and R_3 are hydrogen atoms and R_2 and R_4 are different and do not represent a hydrogen atom.

Among this second class of compounds of formula (Ib), the compounds for which the therapeutic use is the most preferred are characterized in that R_2 is a heteroaryl group such as 7-chloroquinolin-4-yl and the R_4 group is a (C_1-C_7) alkyl group such as a cyclopropylmethyl group, a isobutyl group, a tertibutylmethyl group and a cyclohexylmethyl group.

25

A third class of such compounds of formula (I), hereinafter referring to compounds of formula (Ic), is such that R_1 is a hydrogen atom, R_2 is different from a hydrogen atom and R_3 and R_4 are identical and different from a hydrogen atom.

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Among this third class of compounds of formula (Ic), the compounds for which the therapeutic use is the most preferred are characterized in that R_3 and R_4 represent a

(C₁-C₇)alkyl group such as an isobutyl group or a cyclopropylmethyl group or form with the nitrogen atom a saturated or unsaturated heterocycle like for example an aziridine, an azetidine, a pyrrolidine, a piperidine or an azepane and R₂ represents a group chosen among

- 5 - a benzimidazol group such as the benzimidazol-2-yl group,
- a pyrimidin group such as the pyrimidin-2-yl group,
- a pyrazinyl group such as the pyrazin-2-yl group,
- a purin group such as the purin-6-yl group,
- a quinolinyl group,
- 10 - a chloroquinolinyl group such as the 7-chloroquinolin-4-yl group,
- an acridin group such as the 6-chloro-2-methoxyacridin-9-yl group,
- a benzyl group possibly substituted one or several times on the phenyl group by a group chosen among an atom of halogen and a methoxy group such as the 4-methoxybenzyl group, the 3,4-dimethoxybenzyl group, the 4-chlorobenzyl group and the
- 15 4-fluorobenzyl group,
- a pyridinylmethyl group such as the pyridin-4-ylmethyl group, and,
- a thiazolylmethyl group such as the thiazol-2-ylmethyl group.

20 In one particular variant of the present invention, R₂ is a group different from an acridin or an acridin derivative. In an another variant it is different from an aromatic tricycle.

25 A fourth class of such compounds of formula (I), hereinafter referring to compounds of formula (Id), is such that R₁ is a hydrogen atom and R₂, R₃ and R₄ are different the ones from the others and do not represent a hydrogen atom.

A fifth class of such compounds of formula (I), hereinafter referring to compounds of formula (II), is such that R₁, R₂, R₃ and R₄ are identical.

30 In the framework of the invention, n and m are possibly identical and more preferably equal to 2 or 3 or 4.

 More particularly, these compounds may be chosen among:

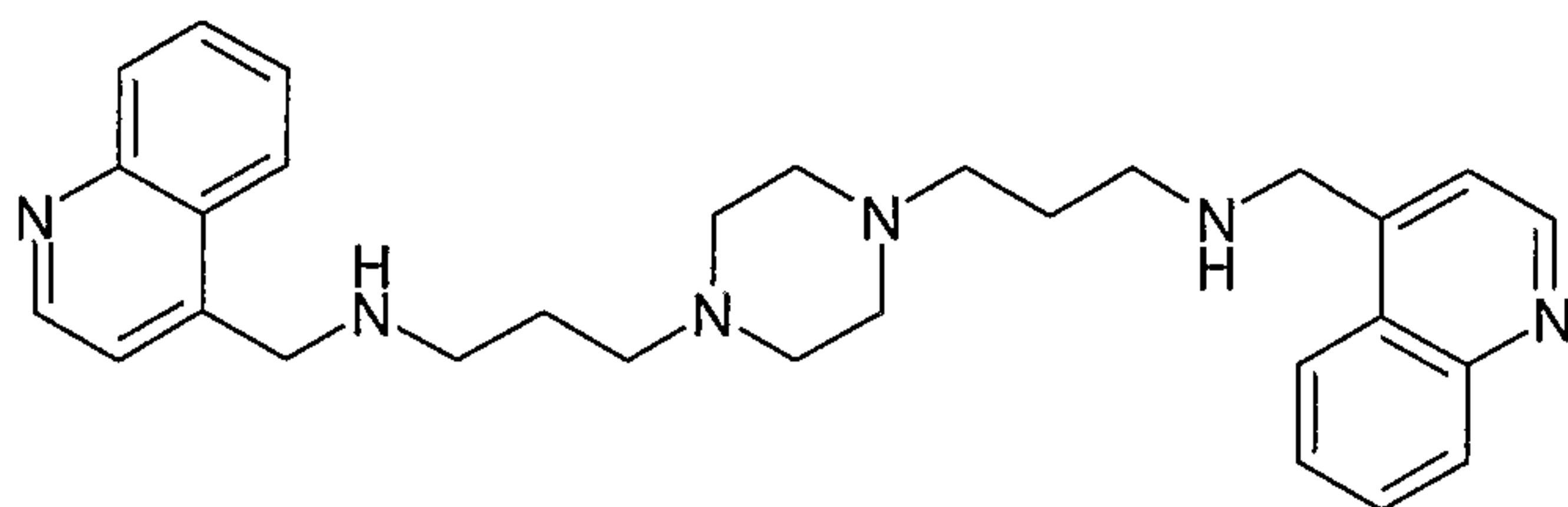
- 1,4-bis{3-[N-(7-chloroquinolin-4-yl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(pyrid-3-ylmethyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(3,4-dimethoxybenzyl)amino]propyl}piperazine,
- 1,4-bis{3-[4-chlorobenzyl)amino]propyl}piperazine,
- 5 - 1,4-bis{3-[N-(quinol-4-ylmethyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(4-methoxybenzyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(cyclopropylmethyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(isobutyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(2-ethylbutyl)amino]propyl}piperazine,
- 10 - 1,4-bis{3-[N-(*n*-heptyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(4-fluorobenzyl)amino]propyl}piperazine,
- N⁴-[3-(4-{3-[(cyclopropylmethyl)amino]propyl}piperazino)propyl]-7-chloroquinolin-4-amine,
- N⁴-[3-(4-{3-(isobutylamino)propyl}piperazino)propyl]-7-chloroquinolin-4-
- 15 amine,
- N⁴-[3-(4-{3-(*tert*-pentylamino)propyl}piperazino)propyl]-7-chloroquinolin-4-amine,
- N⁴-[3-(4-{3-(cyclohexylmethylamino)propyl}piperazino)propyl]-7-chloroquinolin-4-amine,
- 20 - N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-benzimidazol-2-amine,
- N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-pyrimidin-2-amine,
- N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-pyrazin-2-amine,
- 25 - N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-purine-6-amine,
- N⁴-[3-{4-[3-(diisobutylamino)propyl]piperizano}propyl]-7-chloroquinolin-4-amine,
- N⁴-[3-(4-{3-[di(cyclopropylmethyl)amino]propyl}piperizano)propyl]-7-chloroquinolin-4-amine,
- 30 - N⁴-[3-(4-{3-[di(cyclopropylmethyl)amino]propyl}piperizano)propyl]-6-chloro-2-methoxyacridin-9-amine,

- N⁴-[3-(4-{3-[diisobutylamino]propyl}piperizano)propyl]-4-benzyloxyamine,
- N⁴-[3-(4-{3-[diisobutylamino]propyl}piperizano)propyl]-4-pyridinylmethylamine,
- 5 - N⁴-[3-(4-{3-[diisobutylamino]propyl}piperizano)propyl]-4-fluorobenzylamine,
- N⁴-[3-(4-{3-diisobutylamino]propyl}piperizano)propyl]-4-chlorobenzylamine,
- N⁴-[3-(4-{3-[diisobutylamino]propyl}piperizano)propyl]-2-thiazolylmethylamine,
- 10 - N¹-[3-(4-3-[(7-chloro-4-quinolyl)amino]propylpiperizano)propyl]-N¹-cyclopropyl-methylcyclopropane-1-carboxamide,
- *Tert*-butyl-N-3-[[3-(4-3-[(7-chloro-4-quinolyl)amino]propylpiperazino)propyl](cyclopropylmethyl)amino]-3-oxopropylcarbamate,
- 15 - 5-{[3-(4-[3-(7-chloro-4-quinolyl)amino]propylpiperazino)propyl](cyclopropylmethyl)amino}pentanenitrile,
- *Tert*-butyl-N-3-{[3-(4-[3-(7-chloro-4-quinolyl)amino]propylpiperazino)propyl](cyclopropylmethyl)amino}propylcarbamate,
- 1,4-bis(3-[diisobutylamino]propyl)piperazine, and
- 20 - 1,4-bis(3-[dicyclopropylmethylamino]propyl)piperazine.
- 1,4-bis{2-[4-chlorobenzyl)amino]ethyl}piperazine,
- 1,4-bis{2-[4-fluorobenzyl)amino]ethyl}piperazine,
- 1,4-bis{4-[4-chlorobenzyl)amino]butyl}piperazine,
- 1,4-bis{4-[4-fluorobenzyl)amino]butyl}piperazine,
- 25 - *N*-(7-chloro-quinolin-4-yl)-*N*-3-[4-(3-pyrrolidin-1-yl-propyl)piperazin-1-yl]propylamine
- *N*-(7-chloro-quinolin-4-yl)-*N*-3-[4-(3-piperidin-1-yl-propyl)piperazin-1-yl]propylamine
- *N*-3-[4-(3-azepan-1-ylpropyl)piperazin-1-yl]propyl-*N*-(7-chloro-4-quinolyl)-amine
- 30 - {3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-(6-methyl-1*H*-benzimidazol-2-yl)-amine

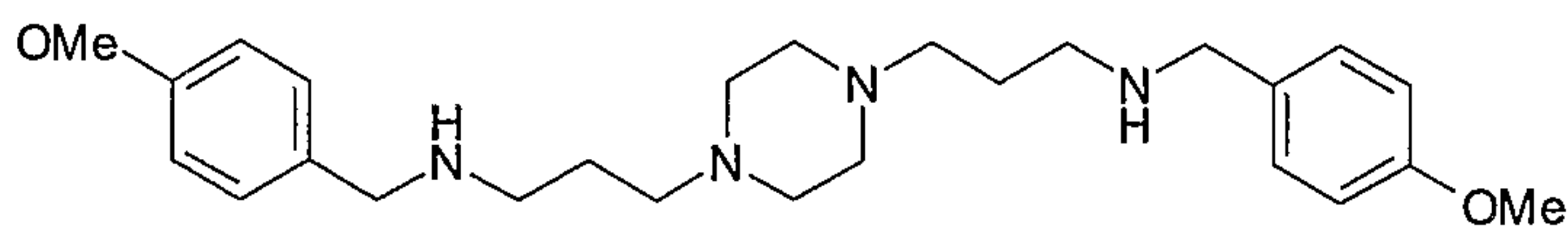
- {3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-(6-methoxy-1*H*-benzimidazol-2-yl)-amine
- (1*H*-Benzimidazol-2-yl)-{3-[4-(3-pyrrolidin-1-yl-propyl)-piperazin-1-yl]-propyl}-amine
- 5 - (1*H*-Benzimidazol-2-yl)-{3-[4-(3-isobutylamino-propyl)-piperazin-1-yl]-propyl}-amine
- 1,4-bis{3-[*N*-(1*H*-Benzimidazol-2-yl)amino]propyl}piperazine
- 1,4-bis{3-[*N*-(anthr-9-ylmethyl)amino]propyl}piperazine
- 1,4-bis{3-[*N*-(Benzyl)amino]propyl}piperazine
- 10 - 1,4-bis{3-[*N*-(4-nitrobenzyl)amino]propyl}piperazine
- 1,4-bis{3-[*N*-(napht-2-ylmethyl)amino]propyl}piperazine
- 1,4-bis{3-[*N*-(4-phenylbenzyl)amino]propyl}piperazine
- 1,4-bis{3-[*N*-(3,4-dibenzyloxybenzyl)amino]propyl}piperazine
- 1,4-bis{3-[*N*-(fluoren-2-ylmethyl)amino]propyl}piperazine
- 15 - 1,4-bis{3-[*N*-(benzofur-2-ylmethyl)amino]propyl}piperazine
- 1,4-bis{3-[*N*-(quinol-2-ylmethyl)amino]propyl}piperazine

Some compounds pertaining to anyone of said herabove defined formula (Ia) to (Id) and (II) form part of the invention.

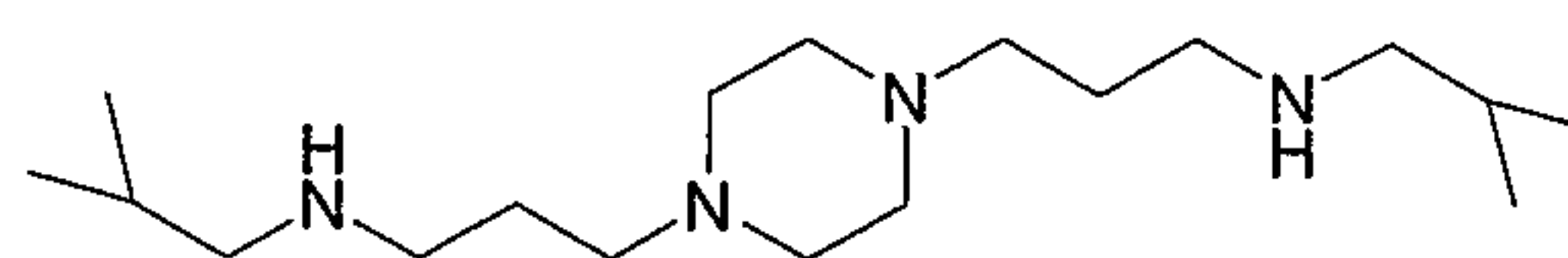
20 More specifically, the instant invention is also directed to the following compounds (1) to (21):



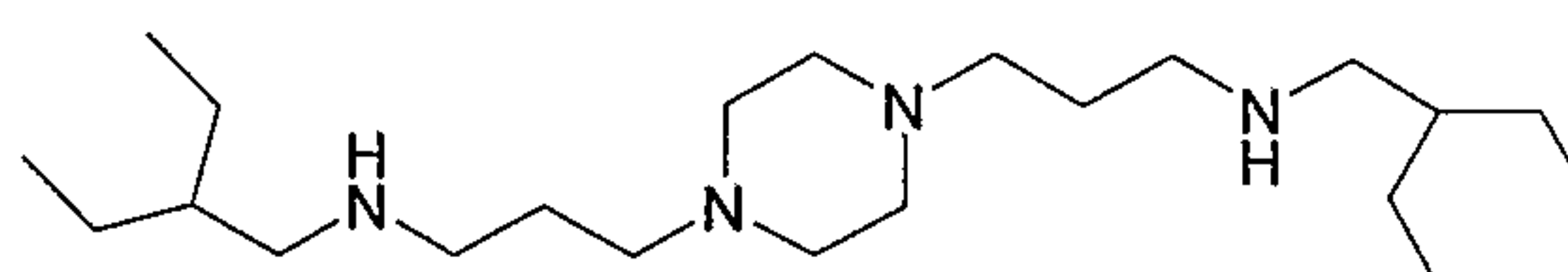
(1)



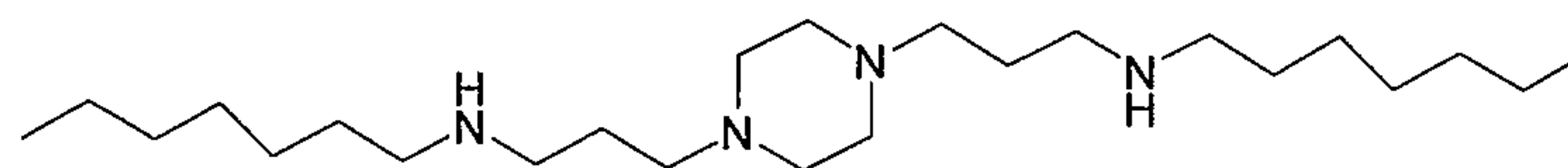
(2)



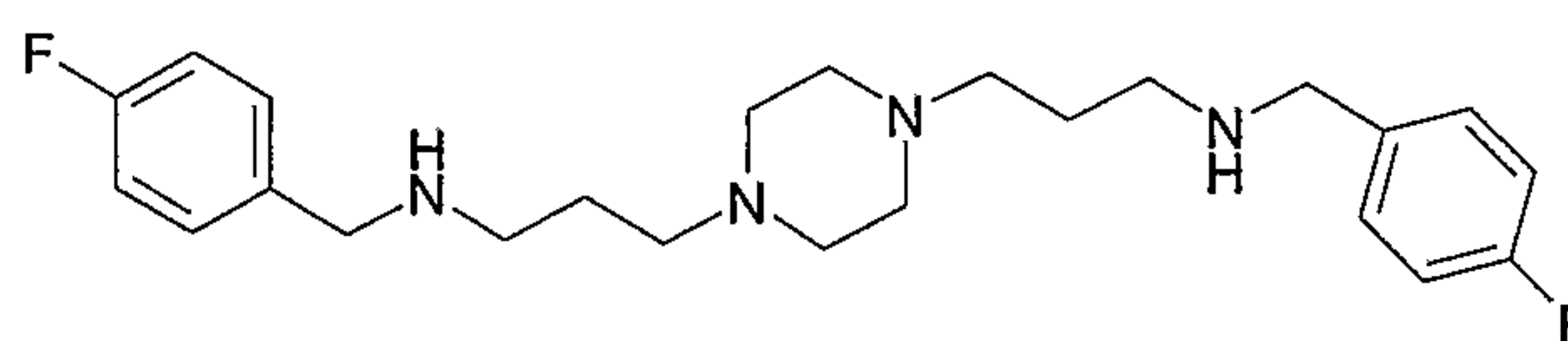
(3)



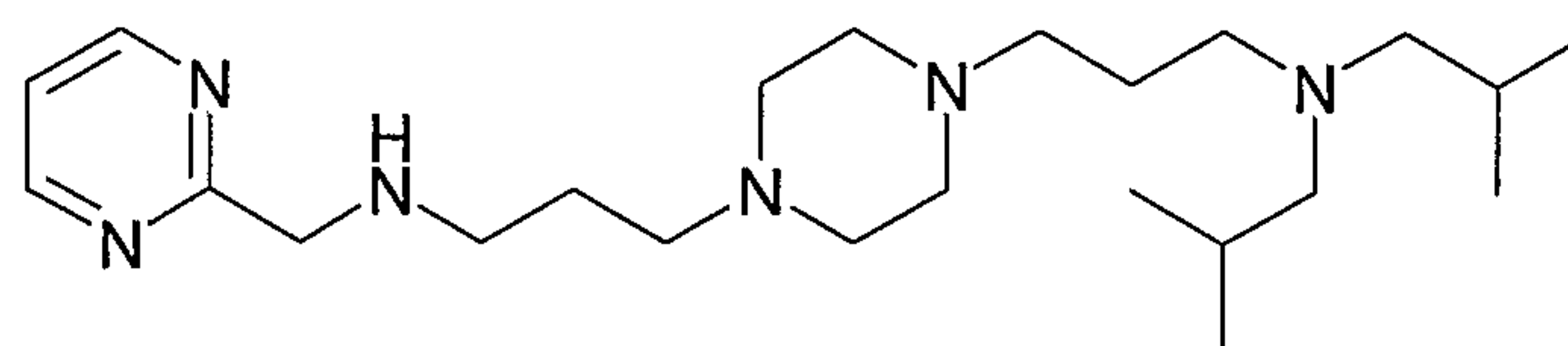
(4)



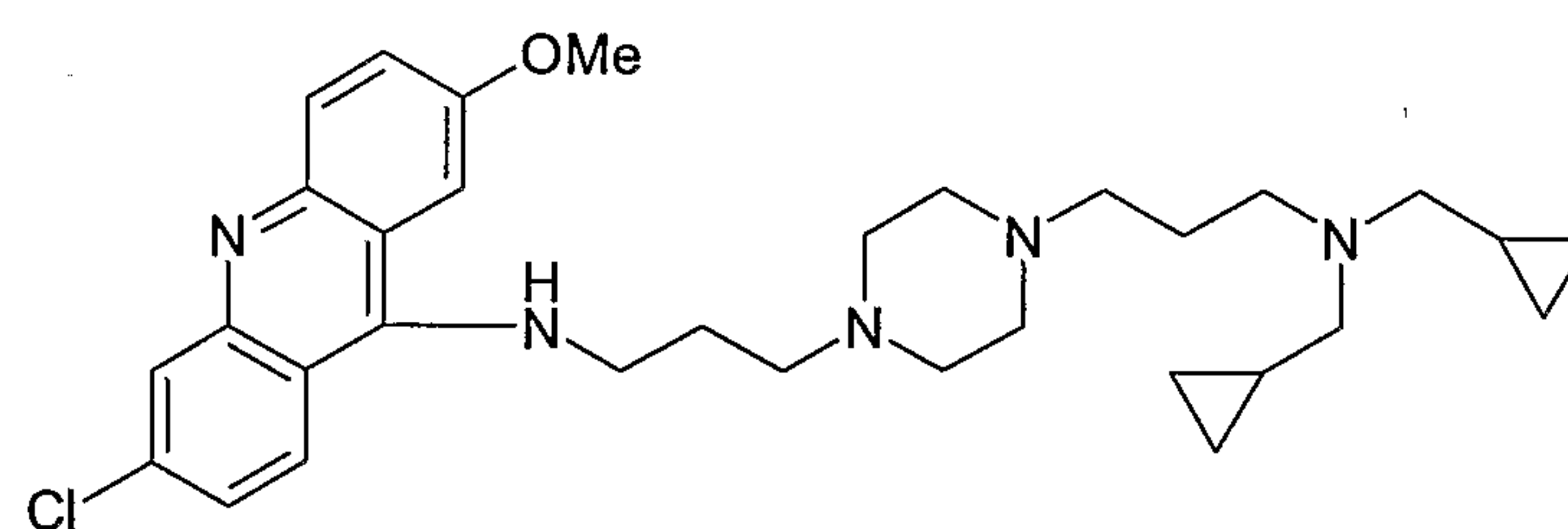
(5)



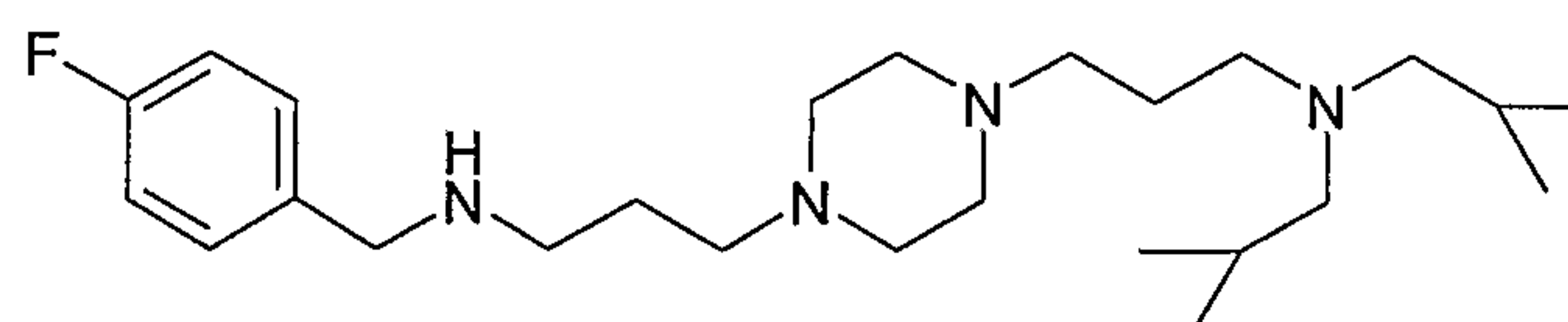
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(7)

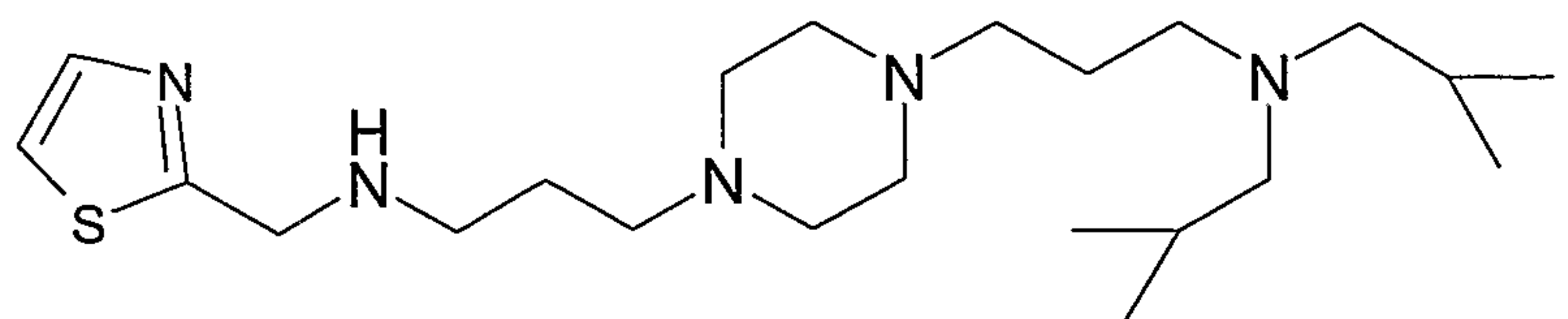


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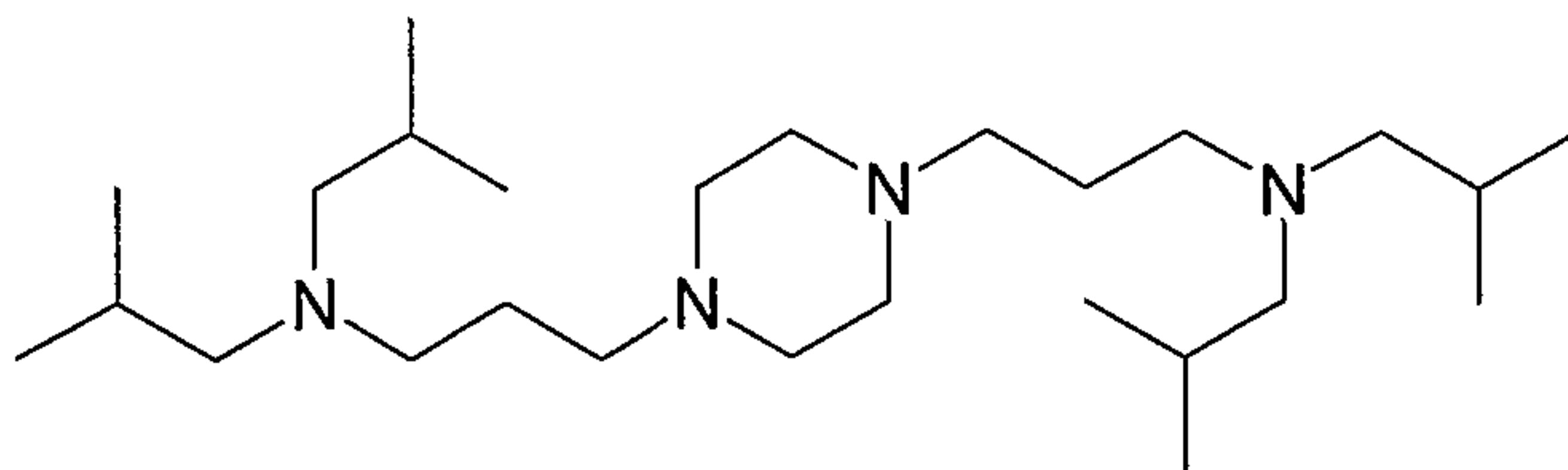


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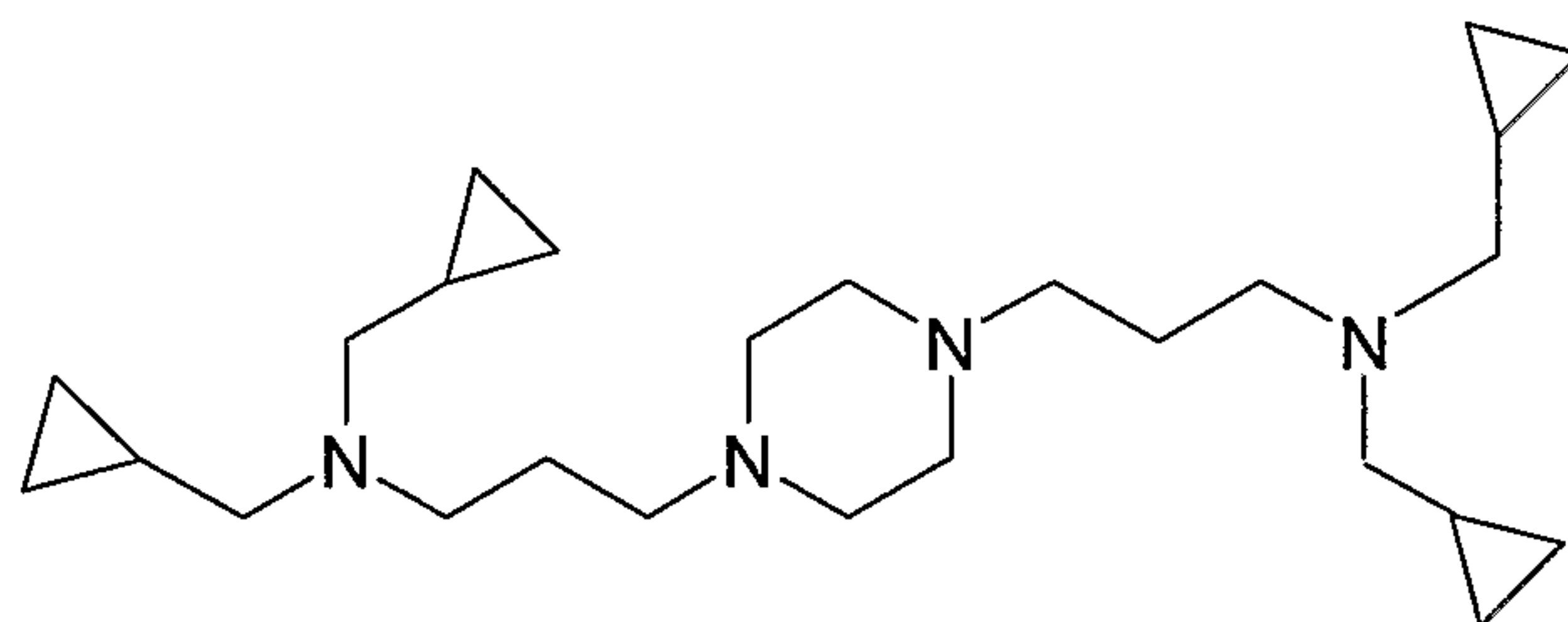
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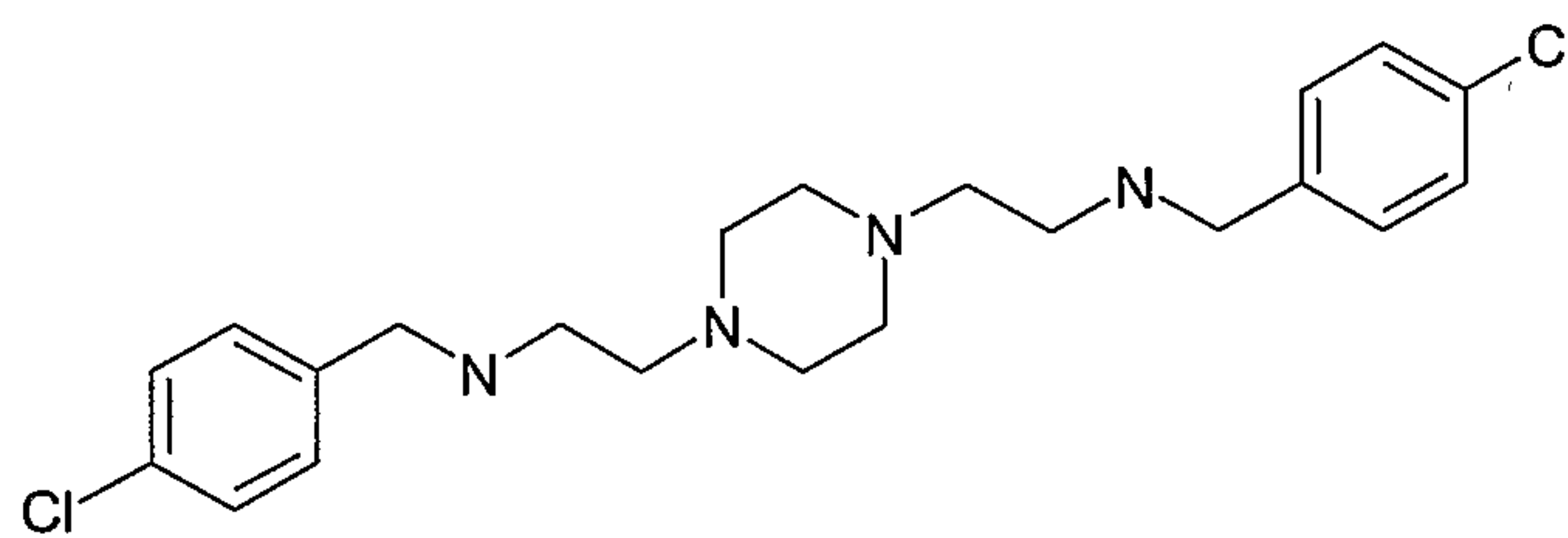
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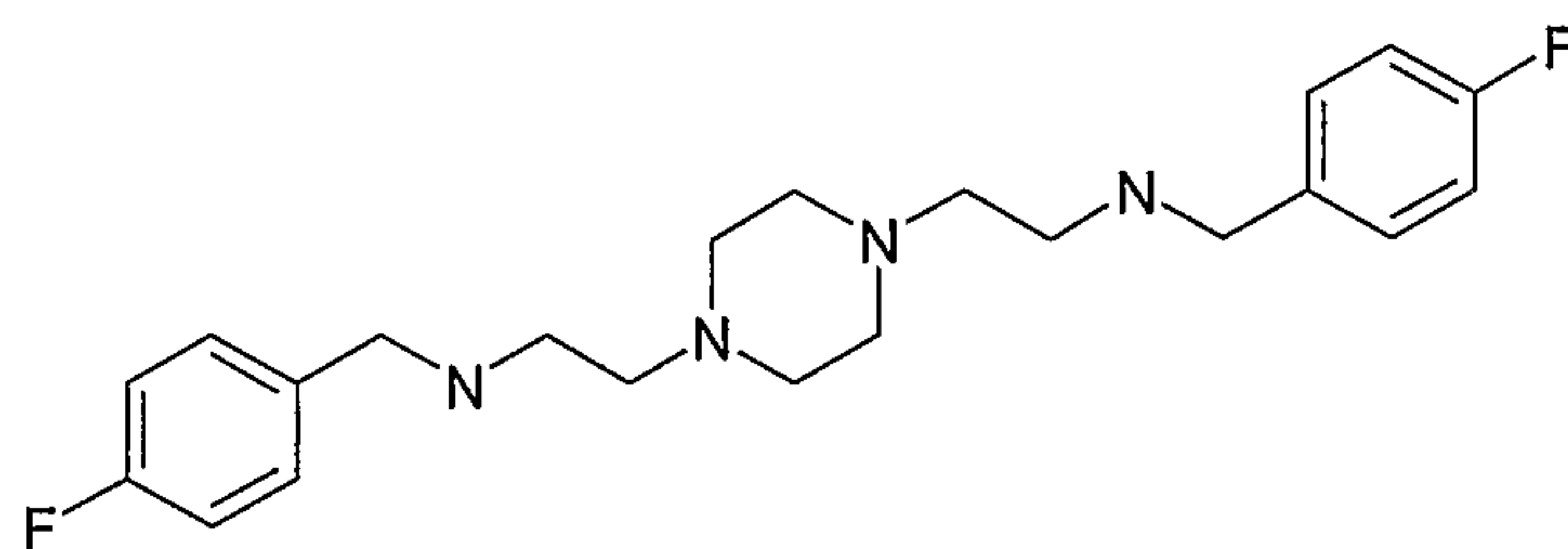
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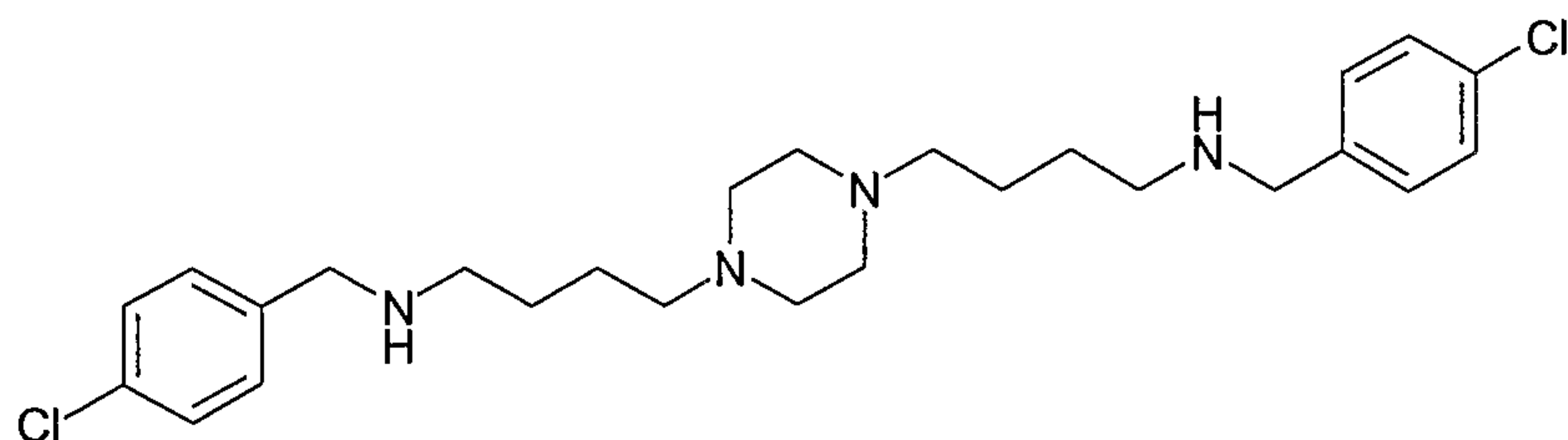
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(13)



(14)

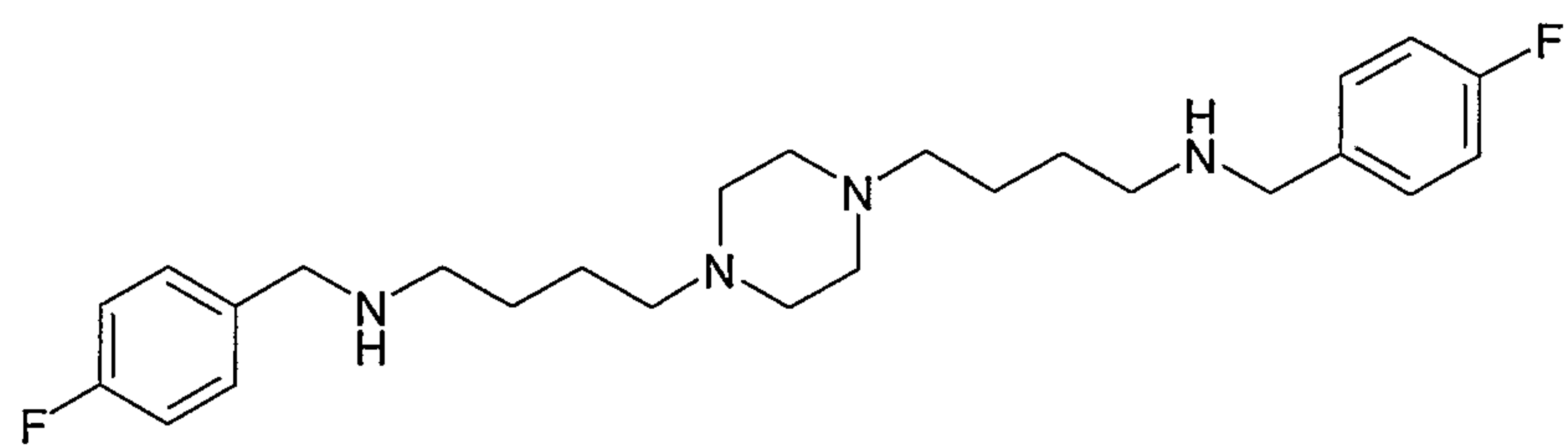


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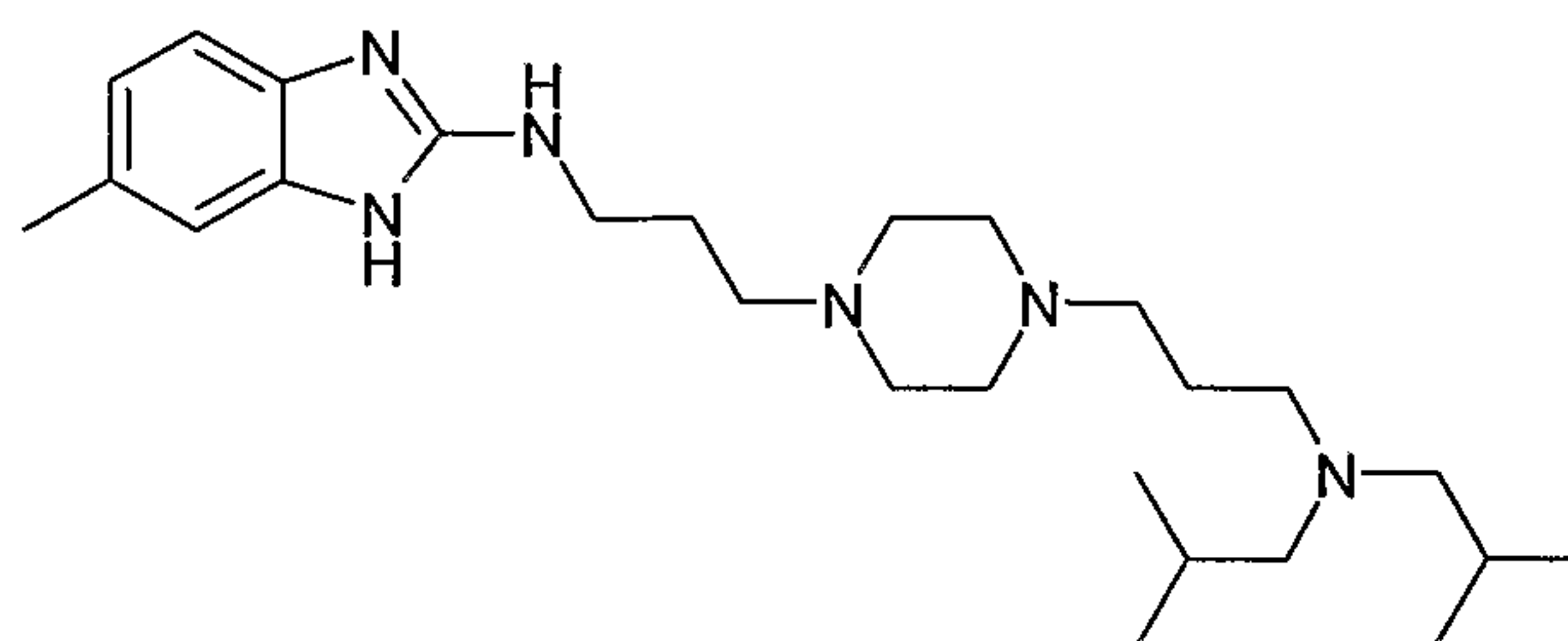
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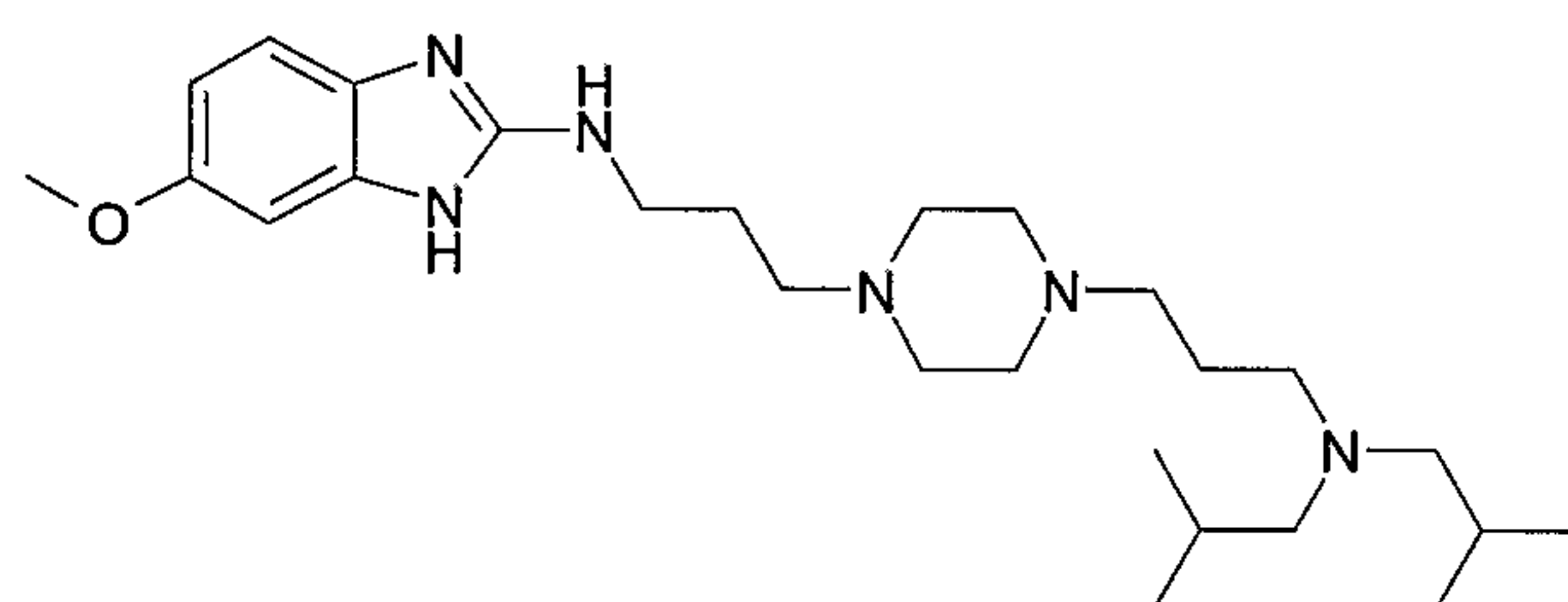


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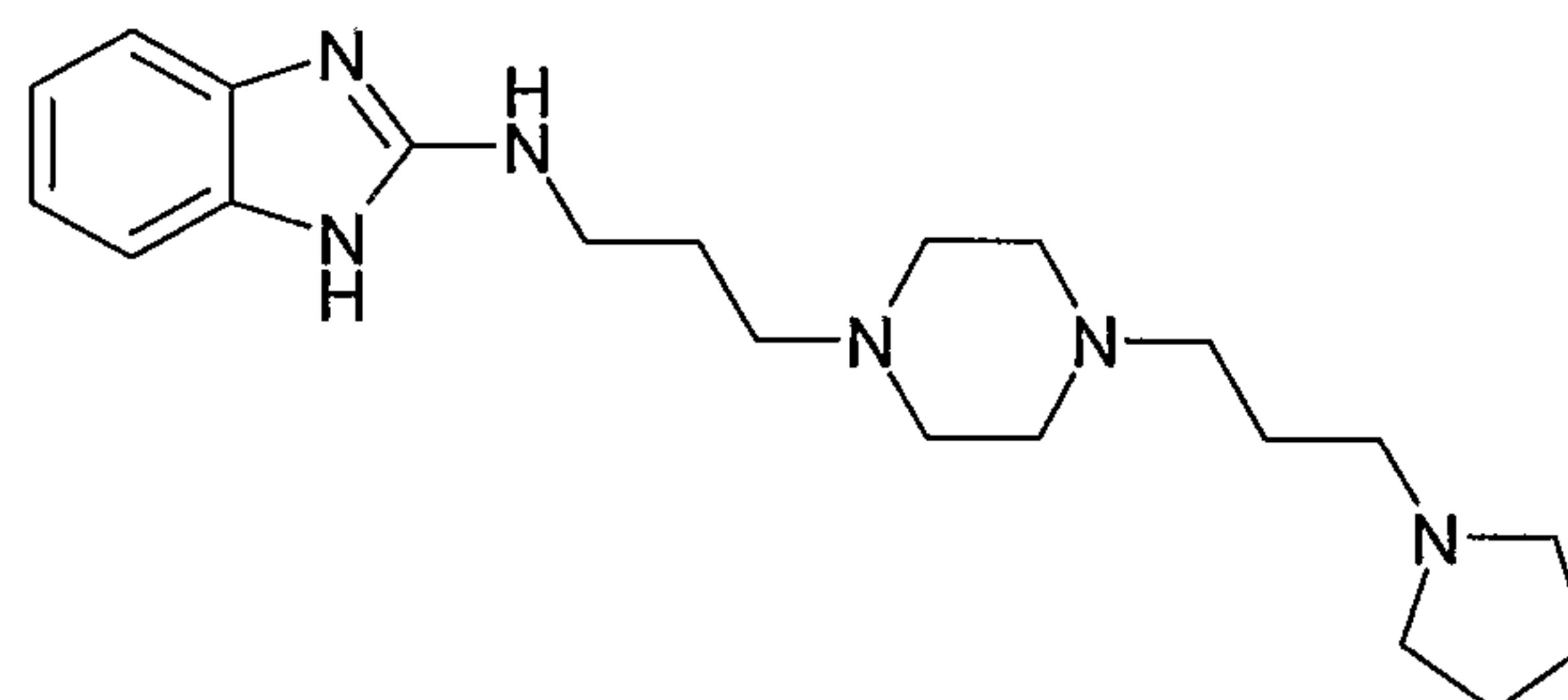


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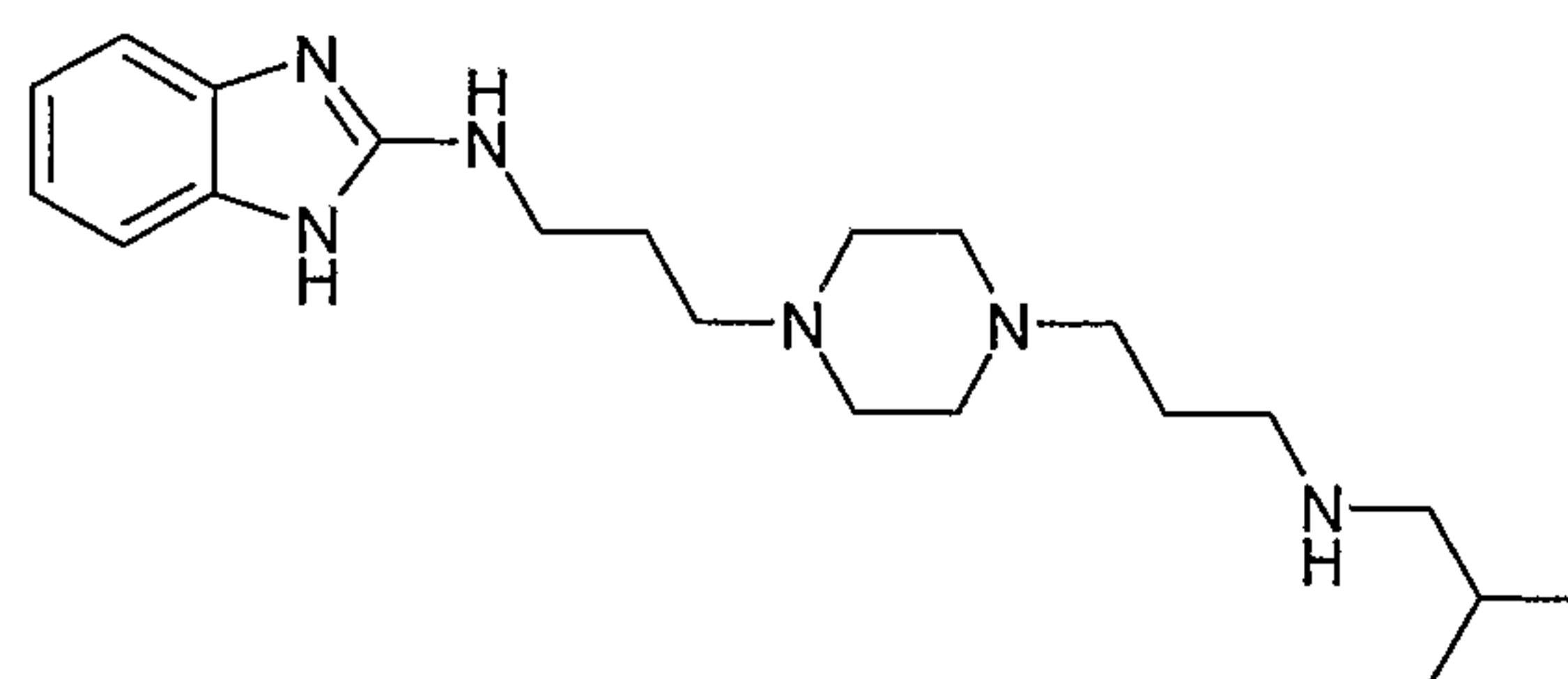
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(18)

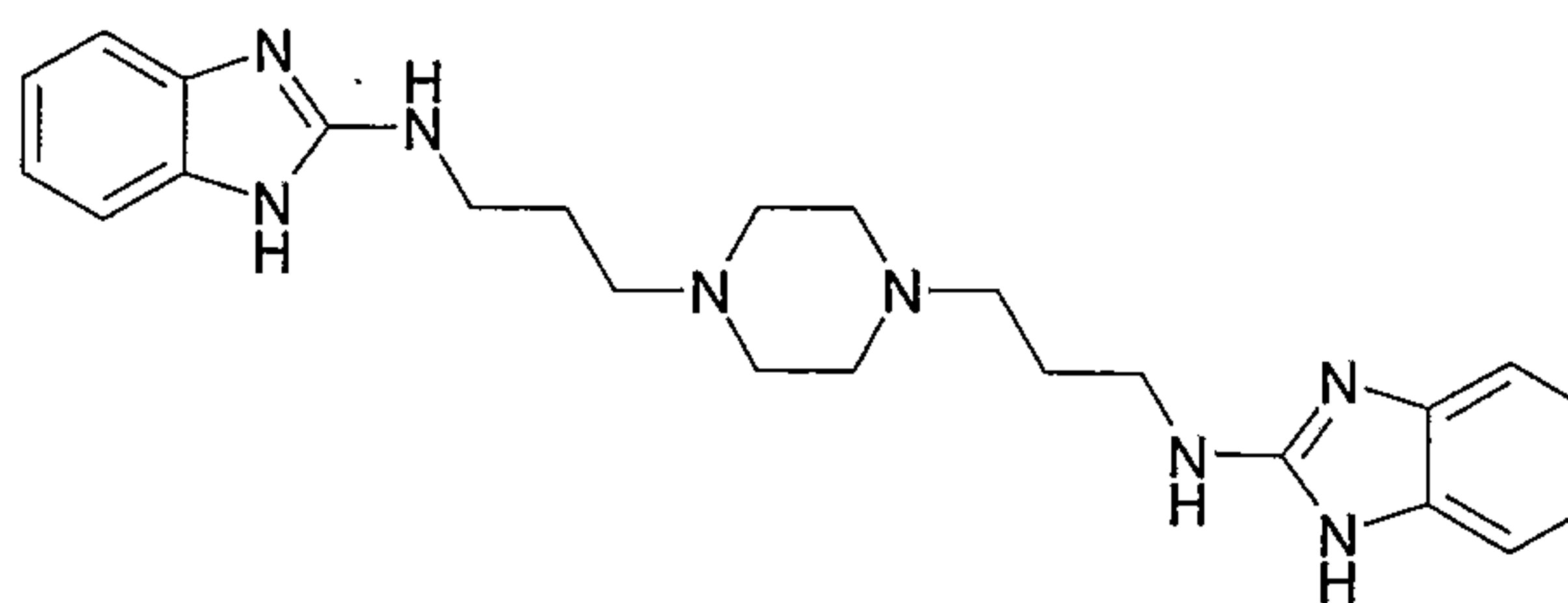


(19)



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(20)

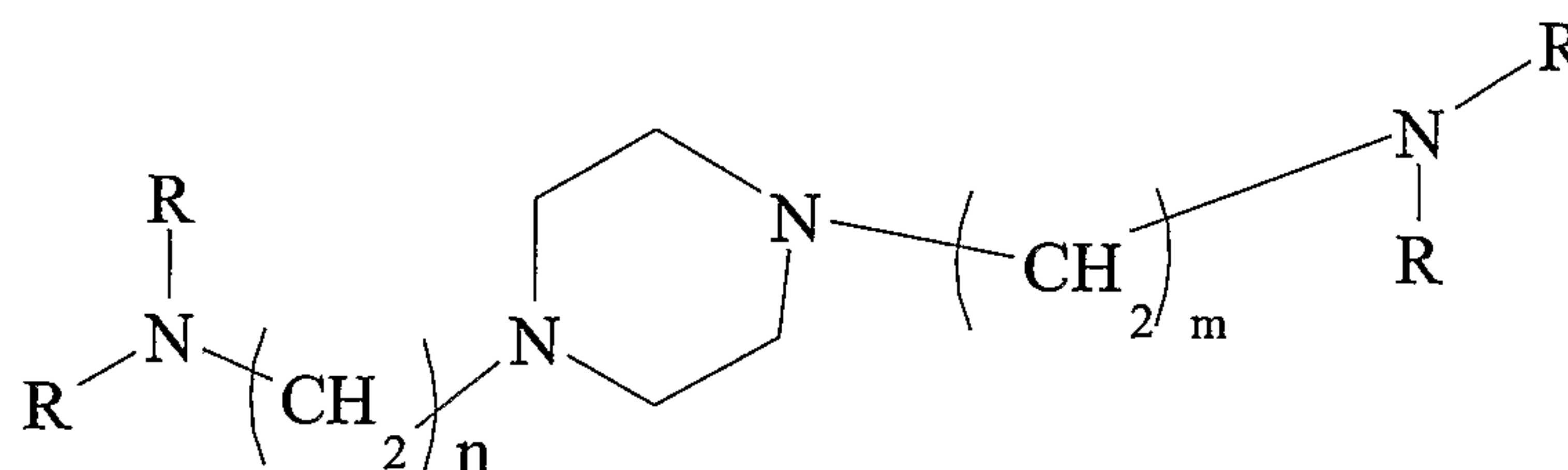


(21)

and their salts with pharmaceutically acceptable acids.

5 According to a further aspect of the invention, compounds of formula (II) hereinafter defined are also encompassed within the scope of the invention.

Therefore, the invention further relates to compounds of general formula (II)



(II)

10 in which n and m are identical or different and independently represent an integer of greater than or equal to 2, particularly ranging from 2 to 8, more preferably ranging from 2 to 6, more particularly being 2, 3 or 4, the resulting hydrocarbon chain optionally comprising one or more heteroatoms selected among oxygen, nitrogen and sulphur, and,

15 in which R is selected among

- a (C₃-C₈)alkyl group, straight or branched, saturated or unsaturated,
- an aralkyl group,
- an aryl group or,
- a heteroaryl group,

20 where the group (C₃-C₈)alkyl can be possibly substituted by one or more identical or different groups chosen among a halogen, the cyano group, the hydroxy group, the nitro group, the amino group, a group (C₁-C₇)alkylamino, a group (C₁-C₇)alkoxy, a tertbutoxycarbonylamino group, a HO-(C₁-C₈)alkyl- group, a H₂N-(C₁-C₈)alkyl- group, a HO-(C=O)- group, a (C₁-C₈)alkyl-O-(C=O)- group, a (C₁-C₈)alkyl-(C=O)- group, a (C₁-

C₈)alkyl-(C=O)-(C₁-C₈)alkyl- group, a HSO₃(C₁-C₈)alkyl- group, a H₂N-(C=O)- group and a H₂N-(C=O)-(C₁-C₈)alkyl- group,

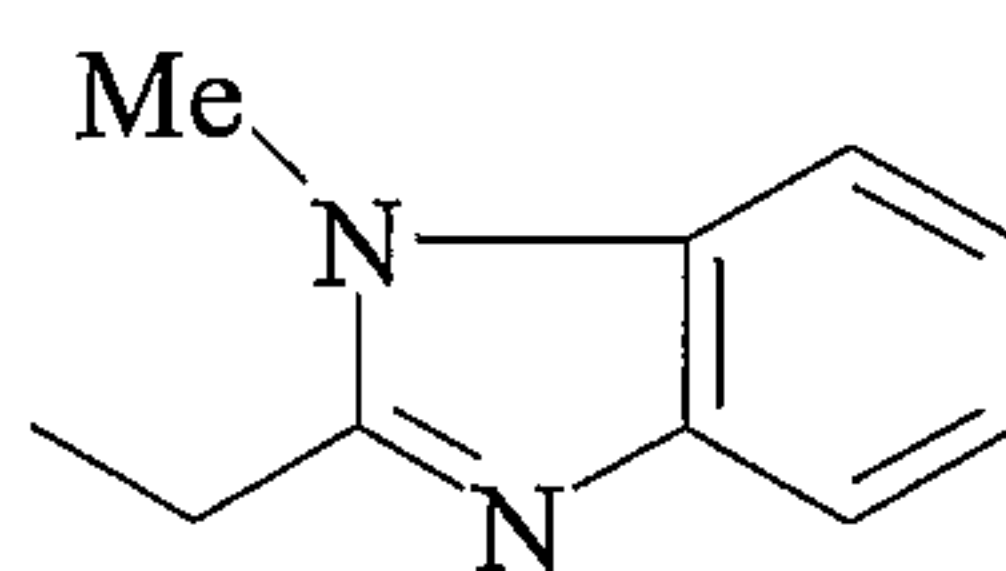
where the aryl group is selected among the groups benzyl, phenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl or indanyl,

5 where the heteroaryl group is an aromatic monocycle, an aromatic bicycle, or a bicycle of which one of the cycles is aromatic and the other cycle is partially hydrogenated, from 5 to 12 links comprising within the cyclic system one, two or three heteroatoms, identical or different, selected among oxygen, nitrogen and sulphur and,

where each one of these groups aryl or heteroaryl comprises possibly one or
10 more substitutions, identical or different, chosen among a halogen, the hydroxy group, a (C₁-C₇)alkyl group, a (C₁-C₇)alkoxy group, the cyano group, the nitro group, the amino group, a (C₁-C₇)alkylamino group, a HO-(C₁-C₈)alkyl- group, a H₂N-(C₁-C₈)alkyl- group, a HO-(C=O)- group, a (C₁-C₈)alkyl-O-(C=O)- group, a (C₁-C₈)alkyl-(C=O)- group, a (C₁-C₈)alkyl-(C=O)-(C₁-C₈)alkyl- group, a HSO₃(C₁-C₈)alkyl- group, a H₂N-(C=O)- group and
15 a H₂N-(C=O)-(C₁-C₈)alkyl- group,

where (R₁ and R₂) and/or (R₃ and R₄), independently of one another, can possibly form an aromatic or partially hydrogenated C₅ to C₁₄ monocycle, optionally comprising within the cyclic system one, two or three heteroatoms, identical or different, selected among oxygen, nitrogen and sulphur,

20 provided that compounds for which R represents a n-hexyl group or R represents a



group are excluded,

and their salts with pharmaceutically acceptable acids.

25 In one particular variant of the present invention the heteroaryl group is different from an acridin group or and acridin derivative. In another variant the heteroaryl group is different from an aromatic tricycle.

In the framework of the invention, n and m are possibly identical and more preferably equal to 2 or 3 or 4.

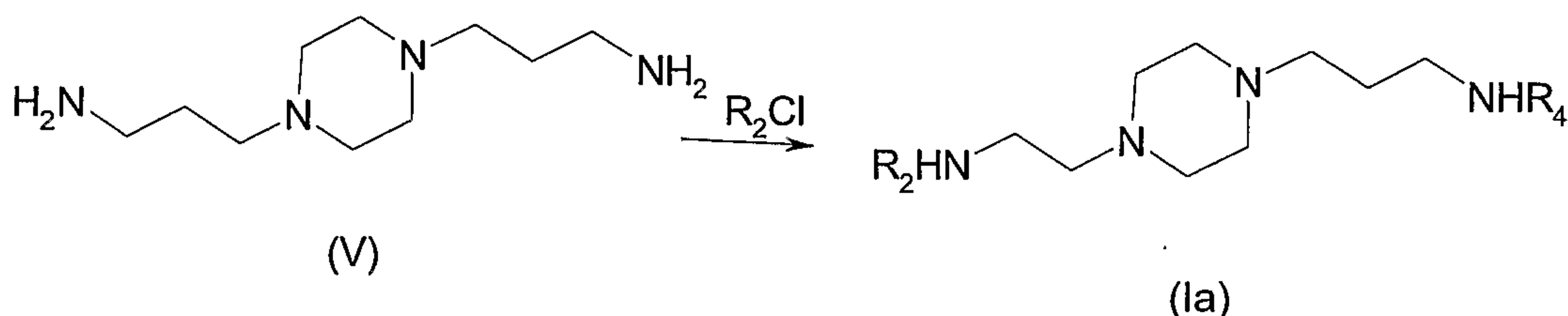
A "protective group" Pg means a group which makes it possible on the one hand to protect a reactive function such as a hydroxy or an amine during a synthesis and on the other hand to regenerate the intact reactive function at the end of the synthesis. Examples of protective groups as well as the methods of protection and deprotection are given in Protective groups in Organics Synthesis, Green and At, 2nd ED (John Wiley & Sons, Inc, New York).

A "leaving group" can easily be cleaved of a molecule by rupture of heterolytic bindings, with departure of an electronic pair. This group can thus be replaced easily by another group during a substitution reaction for example. Such groups therefore are, for example the halogens, or activated hydroxy groups such as a mesyl, tosyl, triflate, acetyl, etc. Examples of leaving groups as references related to said preparations are given in "Advances Organic Chemistry", J.March, 3rd Edition, Wiley Interscience, p 310-316.

The following schemes exemplify the preparation of compounds of formula (I) wherein n is equal to m and is equal to 3. Compounds of formula (I) wherein n and m are different from said definition may be prepared starting from the corresponding 1,4-bis(3-aminoalkyl)piperazine instead of compound of formula (V) as defined beneath.

The compounds of general formula (Ia) can be prepared according to scheme 1 below.

20

Scheme 1((Ia); $R_1 = R_3 = H$, $R_2 = R_4 \neq H$)

According to this process, a derivative of formula (V), namely 1,4-bis(3-aminopropyl)piperazine can be reacted with a compound of formula R_2Cl , for example in the presence of K_2CO_3 , for example in a solvent DMF, for example at a temperature ranging between 80 and 160°C, to obtain a compound of formula (Ia).

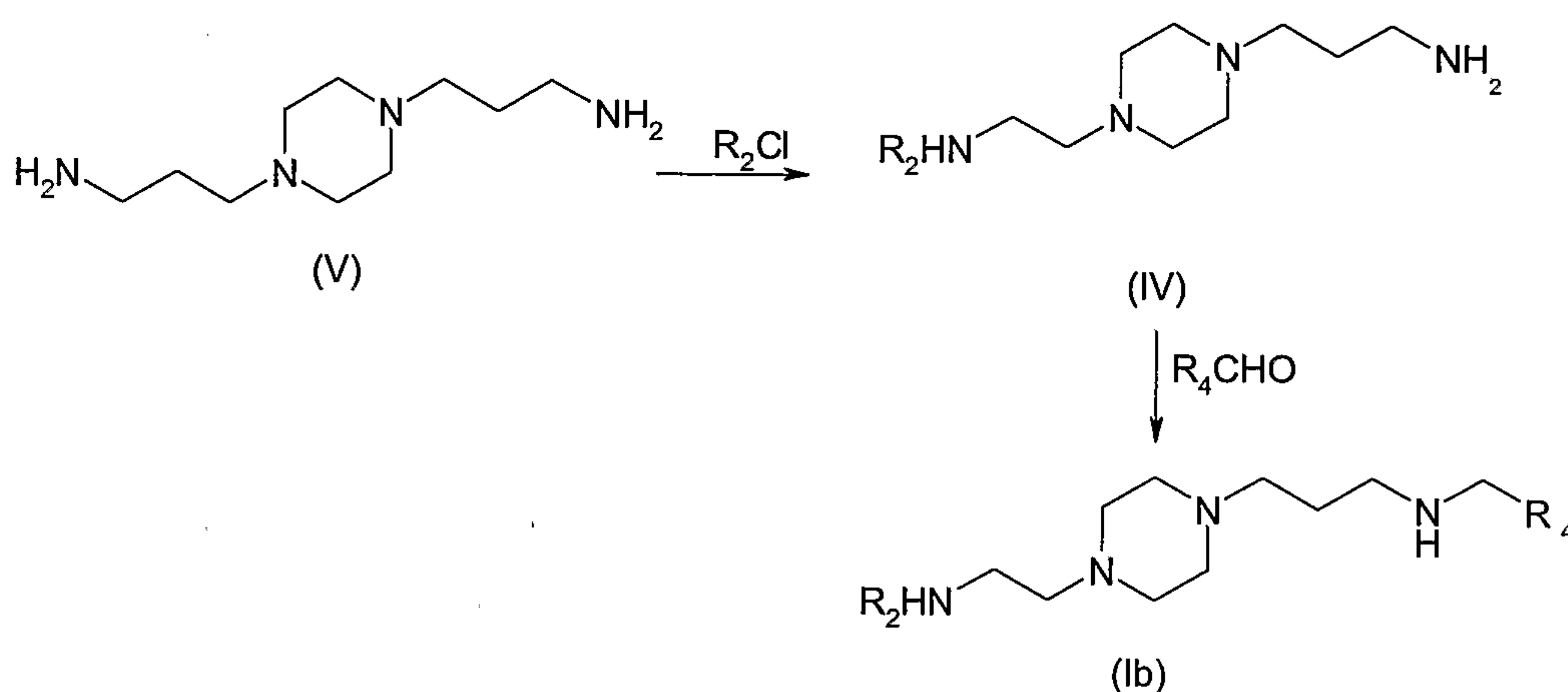
Other compounds of formula (Ia) can be obtained by reductive amination of a derivative of formula (V), namely 1,4-bis(3-aminopropyl)piperazine with an aldehyde of

formula $R_2'CHO$, in the presence of sodium borohydride, in a solvent methanol, for example at a temperature ranging between 0 and 40°C, to obtain a compound of formula (Ia) (B. Bonnet *et al*, Bioorganic & Medicinal Chemistry 8 (2000) 95-103).

5 The compound of general formula (Ib) can be prepared according to scheme 2 below.

Scheme 2

((Ib); $R_1 = R_3 = H$, $R_2 \neq R_4$)



10

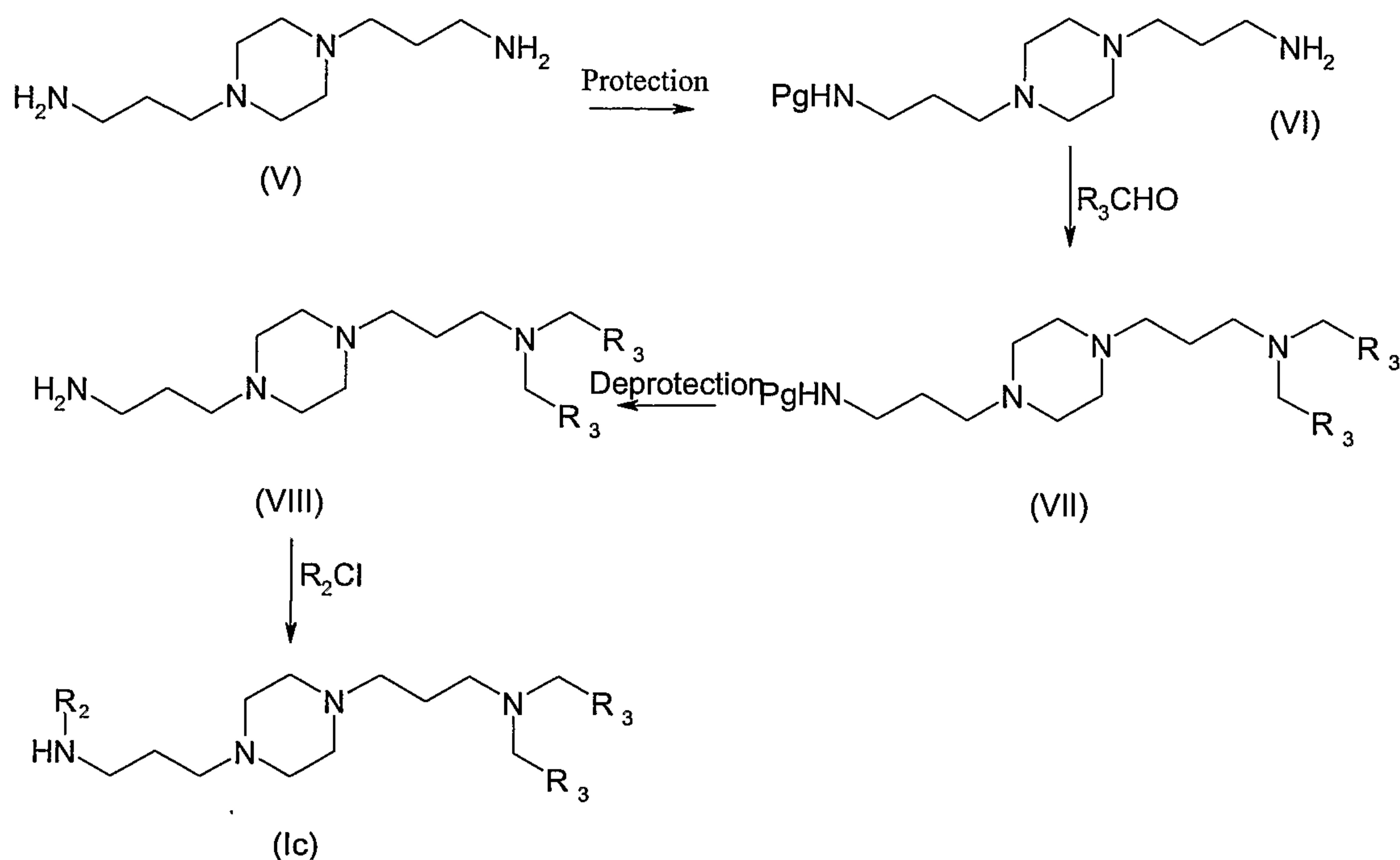
According to this process, a derivative of formula (V), namely 1,4-bis(3-aminopropyl)piperazine is reacted with a compound of formula R_2Cl , for example in a solvent pentanol, for example at a temperature ranging between 80° and 160°C, to obtain the compound of formula (IV). Compounds of formula (Ib) are obtained by reductive amination of a derivative of formula (IV), with an aldehyde of formula R_4CHO , in the presence of sodium borohydride, in a solvent methanol, for example at a temperature ranging between 0 and 40°C, to obtain a compound of formula (Ib) (A. Ryckebusch *et al*, J. Med. Chem. (2003), 46, 542-557).

20 The compound of general formula (Ic) can be prepared according to scheme 3 below.

Scheme 3

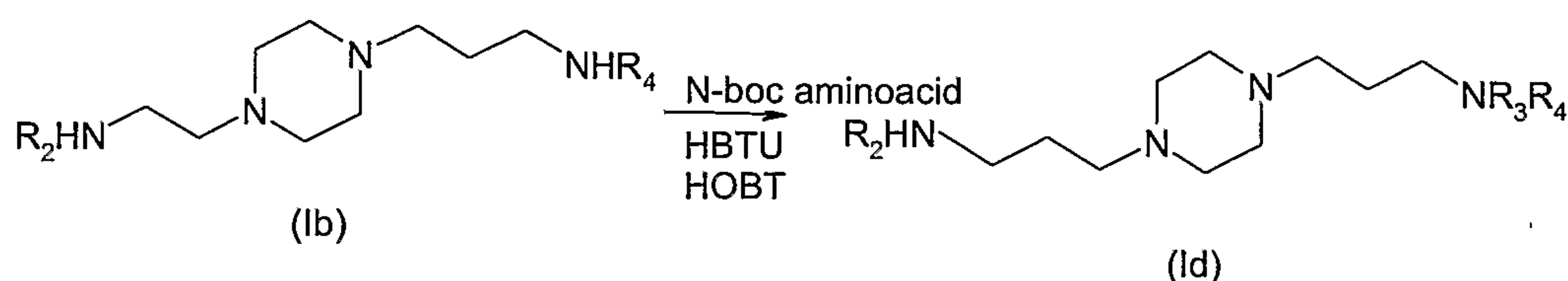
((Ic); $R_1 = H$, $R_2 \neq H$, $R_3 = R_4 \neq H$)

25



According to this process, a derivative of formula (V), namely 1,4-bis(3-aminopropyl)piperazine can be reacted with di-*tert*-dicarbonate, for example in the presence of sodium hydroxyde, for example in a solvent dioxane, for example at a temperature ranging between 0° and 25°C, to obtain the compound of formula (VI). Compounds of formula (VII) can be obtained by reductive amination of a derivative of formula (VI), with an aldehyde of formula $R_3\text{CHO}$, in the presence of sodium acetoxyborohydride, in a solvent methylene chloride, for example at a temperature ranging between 0 and 40°C. Compounds of formula (VIII) can be obtained by deprotection of a derivative of formula (VII), with an trifluoroacetic acid, in a solvent methylene chloride, for example at a temperature ranging between 0 and 40°C. Compounds of formula (Ic) can be obtained by reaction of a compound of formula $R_2\text{Cl}$, with compound of formula (VIII), in a solvent pentanol, for example at a temperature ranging between 80° and 160°C, to obtain a compound of formula (Ic).

The compound of general formula (Id) can be prepared according to scheme 4 below.

Scheme 4((Id); $R_1 = H, R_2 \neq R_3 \neq R_4 \neq H$)

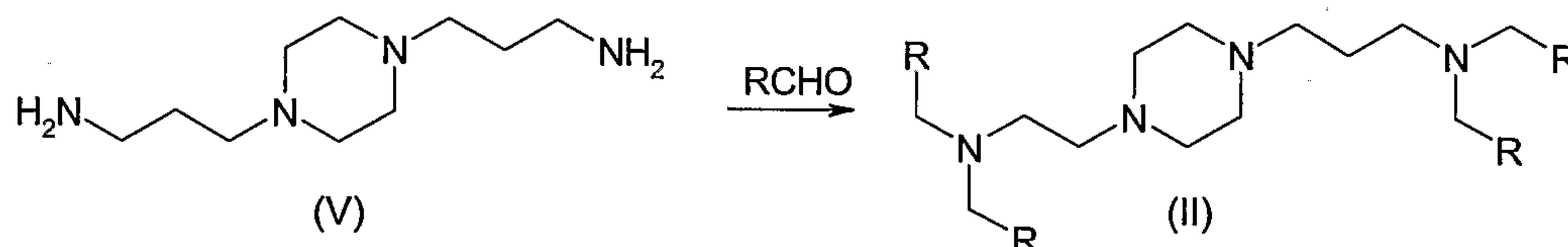
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In the scheme HOBT refers to hydroxybenzotriazole and HBTU refers to 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

According to this process, a derivative of formula (Ib), can be reacted with N-Boc-aminoacid, for example in the presence of HOBT, HBTU and N,N-diisopropylethylamine, for example in a solvent methylene chloride, for example at a temperature ranging between 0° and 40°C, to obtain a compound of formula (Id).

The compound of general formula (II) can be prepared according to scheme 5 below.

15

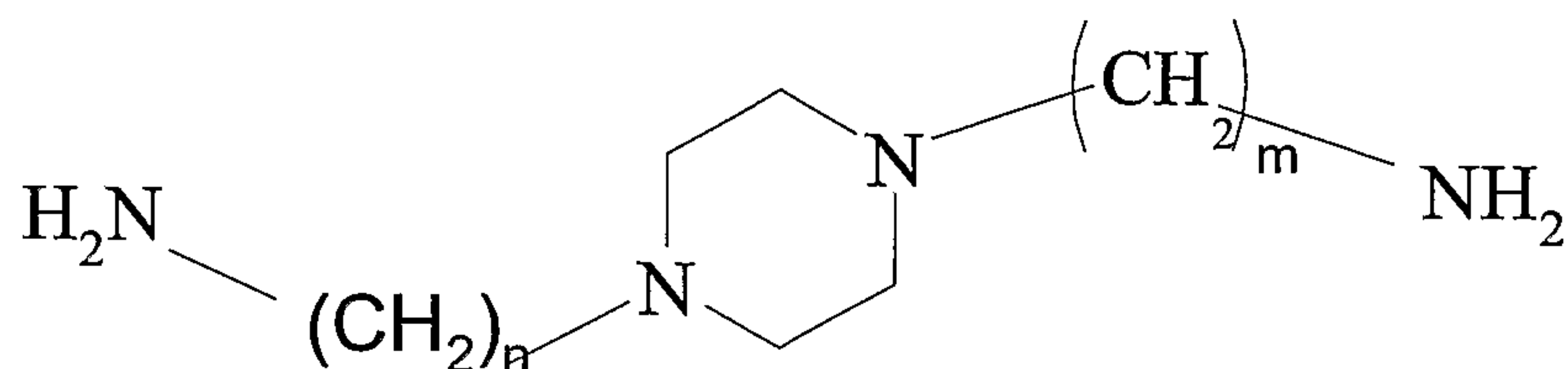
Scheme 5((II); $R_1 = R_2 = R_3 = R_4 \neq H$)

According to this process, a derivative of formula (V), namely 1,4-bis(3-aminopropyl)piperazine can be reacted with an aldehyde of formula RCHO, for example in the presence of sodium acetoxyborohydride, for example in a solvent methylene chloride, for example at a temperature ranging between 0° and 40°C, to obtain a compound of formula (II).

The starting compounds are commercially available or can be prepared according to methods known to the person skilled in the art.

For example, the compound of formula (V) is commercially available.

The corresponding starting compounds of formula (IX)

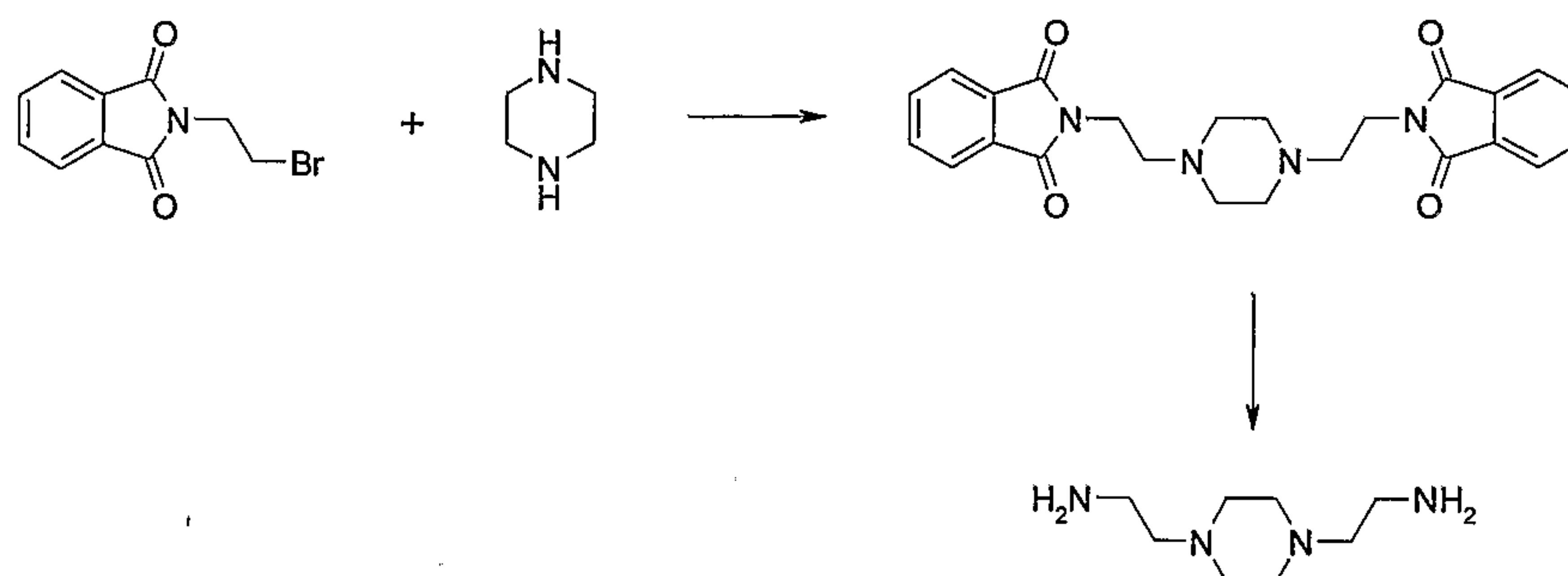


where n and m are different from 3, are not commercially available.

Synthesis of said starting compound of formula (IX) where n and m are
 5 simultaneously equal to 2 may be performed by anyone of the two chemical routes
 summarized hereinafter in schemes 6 and 7:

Scheme 6

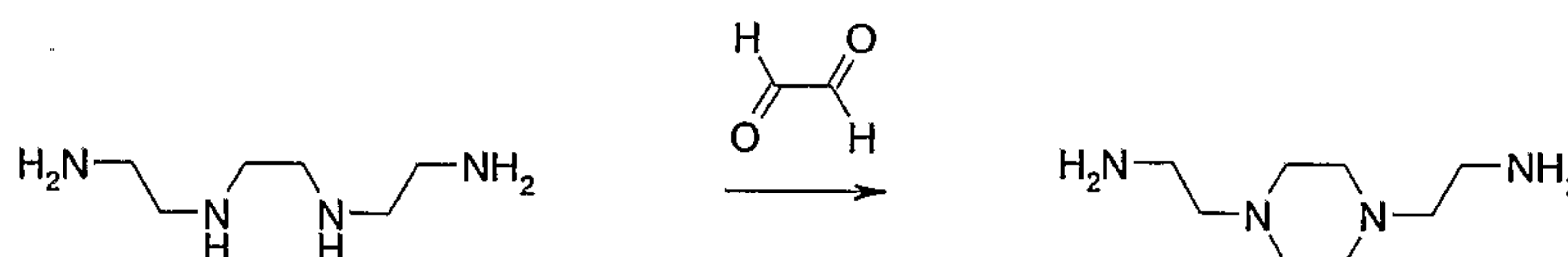
(Von Braun, Goll, Metz *Chem. Ber.* **1926**, 59, 2423 – Kermack, Smith *J. Chem. Soc.* **1931**,
 10 3096 – Ganin *et al. J. Org. Chem. USSR* (Engl. Transl.) **1987**, 23, 330)



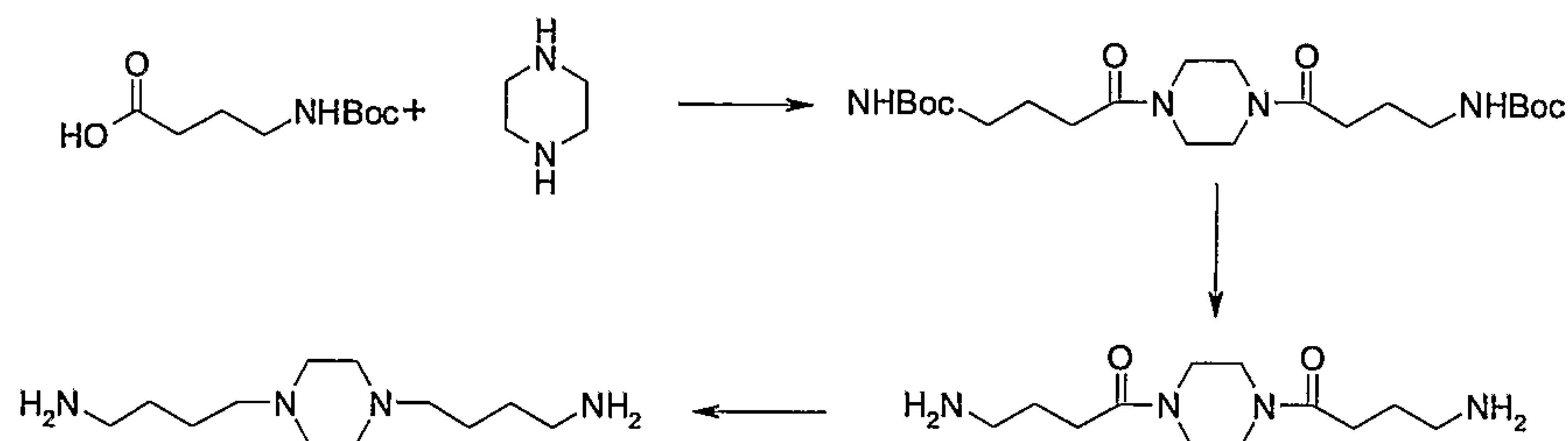
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Scheme 7

(Chuburu *et al. Eur. J. Org. Chem.* **2003**, 6, 1050)



The starting compound of formula (IX) where n and m are simultaneously
 20 equal to 4 may be prepared according to the following scheme 8:

Scheme 8(Zhou *et al. J. Med. Chem.* **1995**, 38, 4891)

5

The synthesis of compounds of formula (IX) where n and m are different may be carried out by solid-phase synthesis, for example by the method described in J. Renault *et al. Tetrahedron Letters* 42 (**2001**) 6655-6658.

The following Examples illustrate in detail the preparation of some compounds according to the invention, and more particularly compounds chosen among compounds (1) to (13) and of formula (II). The structures of the products obtained have been confirmed by NMR spectra.

Example 1**1,4-bis{3-[N-(7-chloroquinolin-4-yl)amino]propyl}piperazine**

A solution of 4,7-dichloroquinoline (1.58 g, 8.0 mmol) and 1,4-bis(3-aminopropyl)piperazine (0.33 mL, 1.6 mmol) in DMF (5mL) is refluxed (160°C) for 18h in the presence of K₂CO₃ (1.77 g, 12.8 mmol). After evaporation, the media is diluted with HCl 1M, and washed with ethyl acetate. Aqueous layer is alcalinised with NaHCO₃, extracted with CH₂Cl₂, and dried over MgSO₄. Crude compound is purified by precipitation in ethyl acetate.

m/z (MALDI) = 523.2

Example 2**1,4-bis{3-[N-(pyrid-3-ylmethyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.51 mL, 2.5 mmol) and 3-pyridinecarboxaldehyde (561 mg, 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 12h, NaBH₄ (1.9 g, 249.92 mmol) was added portionwise and the mixture was stirred for 12h at room

25

temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by flash chromatography on neutral aluminium oxide (CH₂Cl₂/MeOH).

m/z (MALDI) = 383.3

Example 3

10 **1,4-bis{3-[N-(3,4-dimethoxybenzyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.51 mL, 2.5 mmol) and 3,4-dimethoxybenzaldehyde (871 mg, 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 12h, NaBH₄ (1.9 g, 49.92 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by flash chromatography on neutral aluminium oxide (CH₂Cl₂/MeOH).

m/z (MALDI) = 501.4

Example 4

25 **1,4-bis{3-[4-chlorobenzyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.51 mL, 2.5 mmol) and 4-chlorobenzaldehyde (737 mg, 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 12h, NaBH₄ (1.9 g, 49.92 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined

organic layers were dried over MgSO_4 . Crude compound is purified by flash chromatography on neutral aluminium oxide ($\text{CH}_2\text{Cl}_2/\text{MeOH}$).

m/z (MALDI) = 449.3

5 Example 5 (compound No.1)

1,4-bis{3-[N-(quinol-4-ylmethyl)amino]propyl}piperazine

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.51 mL, 2.5 mmol) and 4-quinolinecarboxaldehyde (824 mg, 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 12h, NaBH_4 (1.9 g, 249.92 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH_2Cl_2 (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH_2Cl_2 . Combined organic layers were dried over MgSO_4 . Crude compound is purified by flash chromatography on neutral aluminium oxide ($\text{CH}_2\text{Cl}_2/\text{MeOH}$).

m/z (MALDI) = 483.4

Example 6 (compound No.2)

20 **1,4-bis{3-[N-(4-methoxybenzyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.51 mL, 2.5 mmol) and p-anisaldehyde (636 μL , 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 12h, NaBH_4 (1.9 g, 49.92 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH_2Cl_2 (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH_2Cl_2 . Combined organic layers were dried over MgSO_4 . Crude compound is purified by flash chromatography on neutral aluminium oxide ($\text{CH}_2\text{Cl}_2/\text{MeOH}$).

30 m/z (MALDI) = 441.3

Example 7**1,4-bis{3-[N-(cyclopropylmethyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.51 mL, 2.5 mmol) and cyclopropanecarboxaldehyde (6392 μ L, 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 12h, NaBH₄ (1.9 g, 49.92 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by flash chromatography on neutral aluminium oxide (CH₂Cl₂/MeOH).

m/z (MALDI) = 309.3

15 Example 8 (compound No.3)**1,4-bis{3-[N-(isobutyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.51 mL, 2.5 mmol) and isobutyraldehyde (476 μ L, 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 12h, NaBH₄ (1.9 g, 49.92 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by flash chromatography on neutral aluminium oxide (CH₂Cl₂/MeOH).

m/z (MALDI) = 313.3

Example 9 (compound No.4)30 **1,4-bis{3-[N-(2-ethylbutyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.51 mL, 2.5 mmol) and 2-ethylbutyraldehyde (645 μ L, 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular

sieves are added. After stirring the mixture at room temperature for 12h, NaBH₄ (1.9 g, 49.92 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by flash chromatography on neutral aluminium oxide (CH₂Cl₂/MeOH).

m/z (MALDI) = 369.4

Example 10 (compound No.5)

1,4-bis{3-[N-(*n*-heptyl)amino]propyl}piperazine

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.51 mL, 2.5 mmol) and heptanal (732 µL, 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 12h, NaBH₄ (1.9 g, 49.92 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by flash chromatography on neutral aluminium oxide (CH₂Cl₂/MeOH).

m/z (MALDI) = 397.4

Example 11 (compound No.6)

1,4-bis{3-[N-(4-fluorobenzyl)amino]propyl}piperazine

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.51 mL, 2.5 mmol) and 4-fluorobenzaldehyde (0.59 mL, 5.5 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 5h, NaBH₄ (0.47 g, 12.5 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with

CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified thick-layer chromatography (acetone/NH₄OH:90/10).

5 m/z (MALDI) = 417.3

Example 12

N⁴-[3-(4-{3-[(cyclopropylmethyl)amino]propyl}piperazino)propyl]-7-chloroquinolin-4-amine

10 a) *N⁴-3-[4(3-aminopropyl)piperazine]propyl-7-chloroquinolin-4-amine*
(Intermediate)

A solution of 4,7-dichloroquinoline (1.0g, 5.05 mmol) and 1,4-bis(3-aminopropyl)piperazine (3.1 mL, 15.1 mmol) in 1-pentanol (5.5 mL) is refluxed (160°C) for 18h. After cooling, the media is diluted with 50mL CH₂Cl₂ washed with NaOH 10% (3
15 x 50 mL), dried over MgSO₄. Crude compound is purified by flash chromatography (CH₂Cl₂/MeOH/NH₄OH:80/20/0.9).

m/z (MALDI) = 360.5

b) *N⁴-[3-(4-{3-[(cyclopropylmethyl)amino]propyl}piperazino)propyl]-7-chloroquinolin-4-amine*
20

To a solution of the compound obtain in the preceeding step (150 mg, 0.41 mmol) in CH₂Cl₂ (4mL) cyclopropane-1-carboxaldehyde (51 µL, 0.46 mmol), triethylamine (26 µL, 0.16 mmol) and 3 Å molecular sieves are added. The reaction media is stirred for 3h and cooled before NaBH₄ (78 mg, 2.05 mmol) is added portionwise over
25 30 min. Stirring is left for 1.5h, water (10 mL) is added and the media is filtered. Compound is extracted with CH₂Cl₂ (3 x 20 mL). Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH:80/20/1.8).

m/z (TOF) = 416.2

30

Example 13**N⁴-[3-(4-{3-(isobutylamino)propyl}piperazino)propyl]-7-chloroquinolin-4-amine**

To a solution of N⁴-3-[4(3-aminopropyl)piperazine]propyl-7-chloroquinolin-4-amine (Intermediate of example 12) (150 mg, 0.41 mmol) in CH₂Cl₂ (4mL) isobutyraldehyde (62 µL, 0.46 mmol), triethylamine (26 µL, 0.16 mmol) and 3 Å molecular sieves are added. The reaction media is stirred for 3h and cooled before NaBH₄ (78 mg, 2.05 mmol) is added portionwise over 30 min. Stirring is left for 1.5h, water (10 mL) is added and the media is filtered. Compound is extracted with CH₂Cl₂ (3 x 20 mL). Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH:90/10/1.4).

$$m/z \text{ (TOF)} = 418.3$$

Example 14**N⁴-[3-(4-{3-(tert-pentylamino)propyl}piperazino)propyl]-7-chloroquinolin-4-amine**

To a solution of N⁴-3-[4(3-aminopropyl)piperazine]propyl-7-chloroquinolin-4-amine (Intermediate of example 12) (150 mg, 0.41 mmol) in CH₂Cl₂ (4mL) trimethylacetaldehyde (40 mg, 0.46 mmol), triethylamine (26 µL, 0.16 mmol) and 3 Å molecular sieves are added. The reaction media is stirred for 3h and cooled before NaBH₄ (78 mg, 2.05 mmol) is added portionwise over 30 min. Stirring is left for 1.5h, water (10 mL) is added and the media is filtered. Compound is extracted with CH₂Cl₂ (3 x 20 mL). Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH:90/10/1).

$$m/z \text{ (TOF)} = 432.4$$

Example 15**N⁴-[3-(4-{3-(cyclohexylmethylamino)propyl}piperazino)propyl]-7-chloroquinolin-4-amine**

To a solution of N⁴-3-[4(3-aminopropyl)piperazine]propyl-7-chloroquinolin-4-amine (Intermediate of example 12) (150 mg, 0.41 mmol) in CH₂Cl₂ (4mL) cyclohexane-1-carboxaldehyde (83 µL, 0.46 mmol), triethylamine (26 µL, 0.16 mmol) and 3 Å

molecular sieves are added. The reaction media is stirred for 3h and cooled before NaBH₄ (78 mg, 2.05 mmol) is added portionwise over 30 min. Stirring is left for 1.5h, water (10 mL) is added and the media is filtered. Compound is extracted with CH₂Cl₂ (3 x 20 mL). Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH:90/10/1.4).

$$m/z \text{ (TOF)} = 458.4$$

Example 16

N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-benzimidazol-2-amine

a) N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-amine

(Intermediate synthesised in 3 steps)

Step 1 : Synthesis of N-(3-{4-[3-(tert-butylcarbobenzyloxyamino)propyl]piperizano}propyl)amine

To a solution of 1,4-bis(3-aminopropyl)piperazine (5.0 g, 24.9 mmol) in dry dioxane (25 mL) NaOH 0.5M (60 mL) then Boc₂O (150 mg, 0.41 mmol) in dry dioxane (25 mL) are added dropwise. The reaction media is stirred for 48h, evaporated and solubilized in CH₂Cl₂. NaOH 1M is added. Organic layer is separated and aqueous layer is washed with CH₂Cl₂. Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 80/20/0.9).

$$m/z \text{ (MALDI)} = 301.3$$

Step 2: Synthesis of N,N-diisobutyl-N-(3-{4[3-(-(tert-butylcarbobenzyloxyamino)propyl]piperizano}propyl)amine

To a solution of N-(3-{4-[3-(tert-butylcarbobenzyloxyamino)propyl]piperizano}propyl)amine (2.86g, 9.52 mmol) in dry CH₂Cl₂ (25 mL) isobutyraldehyde (2.6 mL, 28.6 mmol) and NaHB(OAc)₃ (6.05g, 28.6 mmol) in dry CH₂Cl₂ (25 mL) are added dropwise. The reaction media is stirred for 18h and NaOH 1M (5mL) is added. Organic layer is separated and aqueous layer is washed with CH₂Cl₂. Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/0.9).

$$m/z \text{ (MALDI)} = 413.3$$

Step 3: Synthesis of the intermediate

A solution of N,N-diisobutyl-N-(3-{4-[3-(tert-butylcarbobenzyloxyamino)propyl]piperizano}propyl)amine (0.701 g, 1.70 mmol) in TFA/ CH₂Cl₂: 1/1 (20 mL) is stirred overnight. After evaporation triethylamine is added until neutralisation. After evaporation to dryness, the residue is solubilized in CH₂Cl₂, washed with NaOH 2.5M and dried over MgSO₄.

m/z (MALDI) = 313.2

10 b) 1-{3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-3-(2-nitro-phenyl)-thiourea

To a solution of N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-amine (372 mg, 1.19 mmol) in THF (10 mL), 2-nitrophenyl isothiocyanate (244 mg, 1.31 mmol) was added portionwise and the reaction media has been stirred for 24h at room temperature. After evaporation, crude compound is purified by flash chromatography (CH₂Cl₂/MeOH: 90/10).

m/z (MALDI) = 493.5

20 c) {3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-(1H-benzimidazol-2-yl)-amine

To a solution of thiourea (282 mg, 0.57 mmol) in absolute ethanol (13 mL), SnCl₂ (217 mg, 1.14 mmol) is added. After stirring the mixture at reflux for 24h, the solvent was removed under reduced pressure. NaOH 1M (20 mL) was added and the aqueous layer was extracted several times with CH₂Cl₂. Combined organic layers were washed with brine and dried over MgSO₄. Crude compound is purified by flash chromatography (CH₂Cl₂/MeOH/NH₄OH : 90/10/0.2).

m/z (MALDI) = 429.3

Compound is used as its oxalate salt

30 Example 17 (compound No.7)

N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-pyrimidin-2-amine

A solution of intermediate of Example 16 (175 mg, 0.56 mmol), triethylamine (0.39 mL, 2.80 mmol) and 2-chloropyrimidin (193 mg, 1.68 mmol) in 2-pentanol (3.mL) is refluxed for 48h. After cooling to room temperature, the medium is diluted with CH₂Cl₂ (40 mL), organic layer washed with NaOH 2.5M and dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/0.9).

m/z (MALDI) = 391.30

Example 18

N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-pyrazin-2-amine

A solution of intermediate of Example 16 (190 mg, 0.61 mmol), triethylamine (0.43 mL, 3.04 mmol) and 2-chloropyrazine (0.163 mL, 1.83 mmol) in 2-pentanol (4.mL) is refluxed for 48h. After cooling to room temperature, the medium is diluted with CH₂Cl₂ (40 mL), organic layer washed with NaOH 2.5M and dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/1.8).

m/z (MALDI) = 391.25

Example 19

N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-purine-6-amine

A solution of intermediate of Example 16 (220 mg, 0.71 mmol), triethylamine (0.49 mL, 3.52 mmol), diisopropylethylamine (0.123 mL, 0.705 mmol) and 6-chloropurine (327 mg, 2.11 mmol) in 2-pentanol (4 mL) is refluxed for 3h. After cooling to room temperature, the medium is diluted with CH₂Cl₂ (40 mL), organic layer washed with NaOH 2.5M and dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/0.9).

m/z (MALDI) = 431.25

Example 20

N⁴-[3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-7-chloroquinolin-4-amine

To a solution of N⁴-3-[4(3-aminopropyl)piperazine]propyl-7-chloroquinolin-4-amine (Intermediate of example 12) (150 mg, 0.41 mmol) in dry CH₂Cl₂ (1.5 mL) isobutyraldehyde (169 µL, 1.24 mmol) and NaHB(OAc)₃ (263 mg, 1.23 mmol) in dry

CH₂Cl₂ (1.5 mL) are added dropwise. The reaction media is stirred for 4h and NaOH 1M (5mL) is added. Organic layer is separated and aqueous layer is washed with CH₂Cl₂. Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/0.9).

5 m/z (MALDI) = 474.2

Example 21

N⁴-[3-(4-{3-[di(cyclopropylmethyl)amino]propyl}piperizano)propyl]-7-chloroquinolin-4-amine

10 To a solution of N⁴-3-[4(3-aminopropyl)piperazine]propyl-7-chloroquinolin-4-amine (Intermediate of example 12) (150 mg, 0.41 mmol) in dry CH₂Cl₂ (3 mL) cyclopropane-1-carboxaldehyde (139 µL, 1.24 mmol) and NaHB(OAc)₃ (263 mg, 1.23 mmol) are added. The reaction media is stirred for 4h and NaOH 1M (5mL) is added. Organic layer is separated and aqueous layer is washed with CH₂Cl₂. Combined organic
15 layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/0.9).

m/z (MALDI) = 470.4

Example 22 (compound No.8)

N⁴-[3-(4-{3-[di(cyclopropylmethyl)amino]propyl}piperizano)propyl]-6-chloro-2-methoxyacridin-9-amine

a) N⁴-3-[4-(3-aminopropyl)piperazine]propyl-6-chloro-2-methoxyacridin-9-amine (Intermediate)

25 A solution of 6,9-dichloro-2-methoxyacridin (1.0 g, 3.6 mmol) and 1,4-bis(3-aminopropyl)piperazine (2.2 mL, 10.8 mmol) in 1-pentanol (18 mL) is refluxed (160°C) for 4h. After cooling, the media is diluted with 50 mL CH₂Cl₂, washed with NaOH 10% (3 x 50 mL), dried over MgSO₄. Crude compound is purified by flash chromatography (CH₂Cl₂/MeOH/NH₄OH: 80/20/0.9).

b) N⁴-[3-(4-{3-[di(cyclopropylmethyl)amino]propyl}piperizano)propyl]-6-chloro-2-methoxyacridin-9-amine

To a solution of the intermediate obtained in the preceding step (238 mg, 0.54 mmol) in dry CH₂Cl₂ (1.5 mL) cyclopropane-1-carboxaldehyde (160 µL, 2.15 mmol) and

NaHB(OAc)₃ (456 mg, 2.15 mmol) are added. The reaction media is stirred for 4h and NaOH 1M (5mL) is added. Organic layer is separated and aqueous layer is washed with CH₂Cl₂. Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/0.9).

5 m/z (MALDI) = 550.16

Example 23

N⁴-[3-(4-{3-[diisobutylamino]propyl}piperizano)propyl]-4- benzyloxyamine

To a solution of the intermediate obtained in example 16 (150 mg, 0.48 mmol) in dry methanol (3 mL) para-anisaldehyde (64 µL, 0.53 mmol), triethylamine (27 µL, 0.19 mmol) and 3 Å molecular sieves are added. The reaction media is stirred for 3h, cooled to 0°C. NaBH₄ (109 mg, 2.89 mmol) is added portionwise for 30 min. After 1.5h stirring, the reaction is hydrolysed with water (10 mL), filtered and washed with CH₂Cl₂ (3 x 20 mL). Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 80/20/0.9).

m/z (MALDI) = 433.27

Compound is used as its oxalate salt

Example 24

N⁴-[3-(4-{3-[diisobutylamino]propyl}piperizano)propyl]-4-pyridinylmethanamine

To a solution of the intermediate obtained in example 16 tetrahydrochlorhydrate (150 mg, 0.48 mmol) in dry methanol (3 mL) 4-pyridinecarboxaldehyde (35 µL, 0.33 mmol) and 3 Å molecular sieves are added. The reaction media is stirred for 3h, cooled to 0°C. NaBH₄ (75 mg, 1.97 mmol) is added portionwise for 30 min. After 1.5h stirring, the reaction is hydrolysed with water (10 mL), filtered and washed with CH₂Cl₂ (3 x 20 mL). Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/1.8).

30 m/z (MALDI) = 404.2

Example 25 (compound No.9)**N⁴-[3-(4-{3-[diisobutylamino]propyl}piperizano)propyl]-4-fluorobenzylamine**

To a solution of the intermediate obtained in example 16 (150 mg, 0.48 mmol) in dry ethanol (6 mL) 4-fluorobenzaldehyde (57 μ L, 0.53 mmol) and 3 Å molecular sieves are added. The reaction media is stirred for 5h, cooled to 0°C. NaBH₄ (46 mg, 1.2 mmol) is added portionwise. After 12 h stirring, the reaction was quenched by dropwise addition of water (10 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂. Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/1).

m/z (MALDI) = 421.4

15 Example 26**N⁴-[3-(4-{3-diisobutylamino]propyl}piperizano)propyl]-4-chlorobenzylamine**

To a solution of the intermediate obtained in example 16 (150 mg, 0.48 mmol) in dry ethanol (6 mL) 4-chlorobenzaldehyde (74 mg, 0.53 mmol) and 3 Å molecular sieves are added. The reaction media is stirred for 5h, cooled to 0°C. NaBH₄ (46 mg, 1.2 mmol) is added portionwise. After 12 h stirring, the reaction was quenched by dropwise addition of water (10 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂. Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by thick-layer chromatography (ethyl acetate/MeOH/NH₄OH: 90/10/2).

m/z (MALDI) = 437.4

Example 27 (compound No.10)30 **N⁴-[3-(4-{3-[diisobutylamino]propyl}piperizano)propyl]-2-thiazolylmethylaniline**

To a solution of the intermediate obtained in example 16 (150 mg, 0.48 mmol) in dry ethanol (6 mL) 2-thiazolecarboxaldehyde (47 μ L, 0.53 mmol) and 3 Å molecular sieves are added. The reaction media is stirred for 5h, cooled to 0°C. NaBH₄ (46 mg, 1.2 mmol) is added portionwise. After 12 h stirring, the reaction was quenched by dropwise addition of water (10 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂. Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by thick-layer chromatography (ethyl acetate/MeOH/NH₄OH: 90/10/2).

m/z (MALDI) = 410.4

Example 28

N¹-[3-(4-3-[(7-chloro-4-quinolyl)amino]propylpiperizano)propyl]-N¹-cyclopropyl-methylcyclopropane-1-carboxamide

To a solution of compound of example 12 (150 mg, 0.36 mmol) in dry CH₂Cl₂ (4 mL), cyclopropanecarboxylic acid (50 μ L, 0.54 mmol), HBTU (314 mg, 0.82 mmol), HOBT (112 mg, 0.82 mmol) and N,N-diisopropylethylamine (361 μ L, 2.05 mmol) are added. The reaction media is stirred for 4h, diluted with CH₂Cl₂ (15 mL) and washed with NaHCO₃ 1M (2 x 25 mL). Organic layer is dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/0.9).

m/z (MALDI) = 484.4

Example 29

Tert-butyl-N-3-[[3-(4-3-[(7-chloro-4-quinolyl)amino]propylpiperazino)propyl](cyclopropylmethyl)amino]-3-oxopropylcarbamate

To a solution of compound of example 12 (150 mg, 0.36 mmol) in dry CH₂Cl₂ (4 mL), Boc- β -alanine (102 mg, 0.54 mmol), HBTU (314 mg, 0.82 mmol), HOBT (112 mg, 0.82 mmol) and N,N-diisopropylethylamine (361 μ L, 2.05 mmol) are added. The reaction media is stirred for 4h, diluted with CH₂Cl₂ (15 mL) and washed with NaHCO₃ 1M (2 x 25 mL). Organic layer is dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/0.9).

m/z (MALDI) = 587.2

Example 30**5-{[3-(4-[3-(7-chloro-4-quinolyl)amino]propylpiperazino)propyl](cyclopropylmethyl)amino}pentanenitrile**

5 A solution of compound of example 12 (150 mg, 0.36 mmol), 1-ethylpiperidine (247 μ L, 1.8 mmol) and 5-chlorovaleronitrile (58 μ L, 0.72 mmol) in acetonitrile (4mL) was stirred at 40°C for 6H. After evaporation, crude residue is solubilised in CH₂Cl₂ and washed with NaOH 1M. Organic layer is dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/0.9).

10 m/z = 497.5

Example 31**Tert-butyl-N-3-{[3-(4-[3-(7-chloro-4-quinolyl)amino]propylpiperazino)propyl](cyclopropylmethyl)amino}propylcarbamate**

15 a) *N-Boc-aminopropanal (Intermediate synthesised in 2 steps)*

Step 1: Synthesis of N-Boc-aminopropan-3-ol

A solution of aminopropanol (1.02 mL, 13.3 mmol), Boc₂O (3.2 g, 14.6 mmol) in dioxane/NaOH 0.5 M: 1/1 (48.8 mL) was stirred overnight. After evaporation, crude residue is solubilised in ethyl acetate and washed with citric acid. Organic layer is dried
20 over MgSO₄ and evaporated to yield expected compound.

Step 2: Synthesis of the intermediate

A solution of N-Boc-aminopropan-3-ol (0.5 g, 2.83 mmol) and PCC (pyridinium chlorochromate) (0.91 g, 4.24 mmol) in dry CH₂Cl₂ (15 mL) was stirred for
25 4h. After evaporation, crude residue is purified by flash chromatography (cyclohexane/AcOEt : 1/1) to yield expected compound as white powder.

b) Tert-butyl-N-3-{[3-(4-[3-(7-chloro-4-quinolyl)amino]propylpiperazino)propyl](cyclopropylmethyl)amino}propylcarbamate

30 To a solution of N-Boc-aminopropanal (94 g, 0.54mmol) and compound of example 12 (150 mg, 0.36 mmol) in dry CH₂Cl₂ (4 mL), NaHB(OAc)₃ (229 mg, 1.08 mmol) is added. The reaction media was stirred for 4h and NaOH 1M (5mL) is added.

Organic layer is washed with NaOH 1M and dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH: 80/20/0.9).

m/z (TOF)= 573.3

5 Example 32 (compound No.11)

1,4-bis(3-[diisobutylamino]propyl)piperazine

To a solution of 1,4-bis(3-aminopropyl)piperazine (200 mg, 1.0 mmol) in dry CH₂Cl₂ (15 mL) isobutyraldehyde (818 µL, 6.0 mmol) and NaHB(OAc)₃ (1.27 g, 6.0 mmol) are added. The reaction media is stirred for 4h and NaOH 1M (25 mL) is added.

10 Organic layer is separated and aqueous layer is washed with CH₂Cl₂. Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH : 90/10/0.9).

m/z (MALDI) = 425.4

15 Example 33 (compound No.12)

1,4-bis(3-[dicyclopropylmethylamino]propyl)piperazine

To a solution of 1,4-bis(3-aminopropyl)piperazine (400 µL, 1.94 mmol) in dry CH₂Cl₂ (30 mL) cyclopropanecarboxaldehyde (871 µL, 11.6 mmol) and NaHB(OAc)₃ (2.47 g, 11.6 mmol) are added. The reaction media is stirred for 4h and NaOH 1M (75 mL)

20 is added. Organic layer is separated and aqueous layer is washed with CH₂Cl₂. Combined organic layers are dried over MgSO₄. Crude compound is purified by flash chromatography (CH₂Cl₂/MeOH/NH₄OH: 90/10/1).

m/z (MALDI) = 417.4

25 Example 34 (compound No.13)

1,4-bis{2-[4-chlorobenzyl]amino}ethyl}piperazine

To a solution of 1,4-bis(2-aminoethyl)piperazine (0.43g, 2.5 mmol) and 4-chlorobenzaldehyde (737 mg, 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 12h, NaBH₄ (1.9 g, 49.92 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with

CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH: 80/20).

5 m/z (MALDI) = 421.4

Example 35 (compound No.14)

1,4-bis{2-[4-fluorobenzyl]amino}ethyl}piperazine

To a solution of 1,4-bis(2-aminoethyl)piperazine (0.43 g, 2.5 mmol) and 4-fluorobenzaldehyde (0.59 mL, 5.5 mmol) in absolute ethanol (20 mL), 3 Å molecular
10 sieves are added. After stirring the mixture at room temperature for 5h, NaBH₄ (0.47 g, 12.5 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with
15 CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH : 80/20).

m/z (MALDI) = 389.5

20

Example 36 (compound No.15)

1,4-bis{4-[4-chlorobenzyl]amino}butyl}piperazine

To a solution of 1,4-bis(4-aminobutyl)piperazine (0.57 g, 2.5 mmol) and 4-chlorobenzaldehyde (737 mg, 5.24 mmol) in absolute ethanol (20 mL), 3 Å molecular
25 sieves are added. After stirring the mixture at room temperature for 12h, NaBH₄ (1.9 g, 49.92 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with
30 CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH : 80/20/0.9).

m/z (MALDI) = 477.3

Example 37 (compound No.16)**1,4-bis{4-[4-fluorobenzyl)amino]butyl}piperazine**

To a solution of 1,4-bis(4-aminobutyl)piperazine (0.57 g, 2.5 mmol) and 4-fluorobenzaldehyde (0.59 mL, 5.5 mmol) in absolute ethanol (20 mL), 3 Å molecular sieves are added. After stirring the mixture at room temperature for 5h, NaBH₄ (0.47 g, 12.5 mmol) was added portionwise and the mixture was stirred for 12h at room temperature. The reaction was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL). Combined organic layers were extracted with HCl 1M. The combined aqueous layers were neutralized with NaOH 1M and extracted with CH₂Cl₂. Combined organic layers were dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH : 80/20/0.9).

m/z (MALDI) = 445.6

Example 38***N*-(7-chloro-quinolin-4-yl)-*N*-3-[4-(3-pyrrolidin-1-yl-propyl)piperazin-1-yl]propylamine**

To a solution of 1,4-bis{3-[*N*-(7-chloroquinolin-4-yl)amino] propyl} piperazine described in example 1 (0.15 g, 0.41 mmol), 1,4-dibromobutane (0.06 mL, 0.5 mmol) in DMF (5 mL), K₂CO₃ (287 mg, 2.07 mmol) is added. After stirring the mixture at room temperature for 48h, the solvent was removed under reduced pressure. The residue was solubilized in CH₂Cl₂, washed with NaHCO₃ 1M and dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH : 80/20/2.7).

m/z (MALDI) = 416.2

Example 39***N*-(7-chloro-quinolin-4-yl)-*N*-3-[4-(3-piperidin-1-yl-propyl)piperazin-1-yl]propylamine**

To a solution of 1,4-bis{3-[*N*-(7-chloroquinolin-4-yl)amino] propyl} piperazine described in example 1 (0.15 g, 0.41 mmol), 1,5-dibromopentane (0.068 mL, 0.5 mmol) in DMF (5 mL), K₂CO₃ (287 mg, 2.07 mmol) is added. After stirring the

mixture at room temperature for 48h, the solvent was removed under reduced pressure. The residue was solubilized in CH₂Cl₂, washed with NaHCO₃ 1M and dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH : 80/20/2.7).

5 m/z (MALDI) = 430.2

Example 40

***N*-3-[4-(3-azepan-1-ylpropyl)piperazin-1-yl]propyl-*N*-(7-chloro-4-quinolyl)-amine**

10 To a solution of 1,4-bis{3-[*N*-(7-chloroquinolin-4-yl)amino] propyl} piperazine described in example 1 (0.15 g, 0.41 mmol), 1,6-dibromohexane (0.077 mL, 0.5 mmol) in DMF (5 mL), K₂CO₃ (287 mg, 2.07 mmol) is added. After stirring the mixture at room temperature for 48h, the solvent was removed under reduced pressure. The residue was solubilized in CH₂Cl₂, washed with NaHCO₃ 1M and dried over MgSO₄. Crude
15 compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH : 80/20/2.7).
m/z (MALDI) = 444.1

Example 41 (compound No.17)

***3*-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-(6-methyl-1*H*-benzimidazol-2-yl)-amine**

a) 1-{3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-3-(4-methyl-2-nitro-phenyl)-thiourea (intermediate)

A solution of N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-amine
25 (intermediate of example 16) (103 mg, 0.33 mmol) and 4-methyl-2-nitrophenyl isothiocyanate (128 mg, 0.66 mmol) in CH₂Cl₂ (10 mL) has been stirred for 4h at room temperature. NaOH 1M is added until alkaline pH. Organic layer was washed with NaOH 0.5M and dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH: 90/10).

30 m/z (MALDI) = 507.3

*b) {3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-(6-methyl-1*H*-benzimidazol-2-yl)-amine*

To a solution of thiourea (289 mg, 0.57 mmol) in absolute ethanol (13 mL), SnCl₂ (217 mg, 1.14 mmol) is added. After stirring the mixture at reflux for 24h, the solvent was removed under reduced pressure. NaOH 1M (20 mL) was added and the aqueous layer was extracted several times with CH₂Cl₂. Combined organic layers were
 5 washed with brine and dried over MgSO₄. Crude compound is purified by flash chromatography (CH₂Cl₂/MeOH/NH₄OH : 90/10/0.2).

m/z (MALDI) = 443.4

Example 42 (compound No.18)

10 **{3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-(6-methoxy-1H-benzimidazol-2-yl)-amine**

a) 1-{3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-3-(4-methoxy-2-nitro-phenyl)-thiourea (intermediate)

15 A solution of N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-amine (intermediate of exemple 16) (103 mg, 0.33 mmol) and 4-methoxy-2-nitrophenyl isothiocyanate (139 mg, 0.66 mmol) in CH₂Cl₂ (10 mL) has been stirred for 4h at room temperature. NaOH 1M is added until alkaline pH. Organic layer was washed with NaOH 0.5M and dried over MgSO₄. Crude compound is purified by thick-layer chromatography
 20 (CH₂Cl₂/MeOH: 90/10).

m/z (MALDI) = 523.3

b) {3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-(6-methoxy-1H-benzimidazol-2-yl)-amine

To a solution of thiourea (298 mg, 0.57 mmol) in absolute ethanol (13 mL),
 25 SnCl₂ (217 mg, 1.14 mmol) is added. After stirring the mixture at reflux for 24h, the solvent was removed under reduced pressure. NaOH 1M (20 mL) was added and the aqueous layer was extracted several times with CH₂Cl₂. Combined organic layers were washed with brine and dried over MgSO₄. Crude compound is purified by flash chromatography (CH₂Cl₂/MeOH/NH₄OH : 90/10/0.2).

30 m/z (MALDI) = 459.4

Example 43 (compound No.19)

(1H-Benzimidazol-2-yl)-{3-[4-(3-pyrrolidin-1-yl-propyl)-piperazin-1-yl]-propyl}-amine

5 *a){3-[4-(3-Amino-propyl)-piperazin-1-yl]-propyl}-(1H-benzimidazol-2-yl)-amine (Intermediate synthesised in 3 steps)*

Step 1 : Synthesis of [3-(4-{3-[3-(2-Nitro-phenyl)-thioureido]-propyl}-piperazin-1-yl)-propyl]-carbamic acid tert-butyl ester

10 N-(3-{4-[3-(tert-butylcarbobenzyloxyamino)propyl]piperizano}propyl)amine (synthesized for example 16) (0.5g , 1.17mmol) was dissolved in freshly distilled CH₂Cl₂ (30 mL) . 2-nitrophenylisothiocyanate (0.6 g, 3.33 mmol) was added by small portions. The resulting yellow solution was stirred for 4h at room temperature. Then a sodium hydroxide solution 1,0M was added until pH 12-13. The organic layer was washed three
15 times with a hydroxide sodium solution 0,5M (3 x 20mL). It was then dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (AcOEt/MeOH : 85/15).

m/z (MALDI) = 481.4

20 *Step 2: Synthesis of (3-{4-[3-(1H-Benzimidazol-2-ylamino)-propyl]-piperazin-1-yl}-propyl)-carbamic acid tert-butyl ester*

[3-(4-[3-[3-(2-Nitro-phenyl)-thioureido]-propyl]-propyl)-carbamic acid tert-butyl ester (0.45 g , 0.93 mmol) was dissolved in absolute ethanol (50 mL) then anhydrous tin chloride (0.35 g, 1.87 mmol) was added. The solution was heated to reflux. After 48h,
25 the resulting mixture was cooled to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL), adjusted until pH 8-9 with NaOH 1M and the organic layer was washed with water (3 x 25mL). It was then dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH₂Cl₂/MeOH/NH₄OH 9/1/0,1).

30 m/z (MALDI) = 417.4

Step 3: Synthesis of the intermediate

(3-[4-[3-(1H-Benzimidazol-2-ylamino)-propyl]-piperazin-1-yl]-propyl)-carbamic acid tert-butyl ester (0.2 g, 0.5 mmol) was dissolved in CH₂Cl₂ (20 mL). Trifluoroacetic acid (0.38 mL, 5 mmol) was then added and the reaction mixture was stirred overnight at room temperature. The solvent and excess TFA were removed under reduced pressure and the resulting solid was triturated in hexane and filtrated.

m/z (MALDI) = 317.3

10 *b) (1H-Benzimidazol-2-yl)-{3-[4-(3-pyrrolidin-1-yl-propyl)-piperazin-1-yl]-propyl}-amine*

[3-[4-(3-Amino-propyl)-piperazin-1-yl]-propyl]-(1H-benzimidazol-2-yl)-amine (intermediate) (65 mg, 0.021 mmol) was dissolved in anhydrous DMF (20 mL) in the presence of potassium carbonate (142 mg, 1.0 mmol). 1,4-dibromobutane (0.03 mL, 0.25 mmol) was added. The resulting mixture was stirred for 48h at room temperature. The solution was filtered and the solvent was removed under reduced pressure.

m/z (MALDI) = 371.3

Example 44 (compound No.20)

20 **(1H-Benzimidazol-2-yl)-{3-[4-(3-isobutylamino-propyl)-piperazin-1-yl]-propyl}-amine**

To a solution of [3-[4-(3-Amino-propyl)-piperazin-1-yl]-propyl]-(1H-benzimidazol-2-yl)-amine (Intermediate of example 44) (130 mg, 0.41 mmol) in CH₂Cl₂ (4 mL) isobutyraldehyde (62 µL, 0.46 mmol), triethylamine (26 µL, 0.16 mmol) and 3 Å molecular sieves are added. The reaction media is stirred for 3h and cooled before NaBH₄ (78 mg, 2.05 mmol) is added portionwise over 30 min. Stirring is left for 1.5h, water (10 mL) is added and the media is filtered. Compound is extracted with CH₂Cl₂ (3 x 20 mL). Combined organic layers are dried over MgSO₄. Crude compound is purified by thick-layer chromatography (CH₂Cl₂/MeOH/NH₄OH : 90/10/1.2).

m/z (TOF) = 433.3

30

Example 45 (compound No.21)

1,4-bis{3-[N-(1H-Benzimidazol-2-yl)amino]propyl}piperazine

a) *1,4-bis{3-[4-methoxy-2-nitro-phenyl]-thiourea}propyl}piperazine (intermediate)*

1,4-bis (3-aminopropyl)-piperazine (1.0 g, 5 mmol) was dissolved in freshly distilled CH₂Cl₂ (50 mL) . 2-nitrophenylisothiocyanate (3.6 g, 20 mmol) was added by small portions. The resulting yellow solution was stirred for 4h at room temperature. A sodium hydroxide solution 1M was added until pH 12-13. The organic layer was washed with a hydroxide sodium solution 0,5M (3 x 50ml). It was then dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH₂Cl₂/MeOH : 9/1).

10 m/z (MALDI) = 561.3

b) *1,4-bis{3-[N-(1H-Benzimidazol-2-yl)amino]propyl}piperazine*

To a solution of bis-thiourea (0.5 g, 0.9 mmol) in absolute ethanol (50 mL), SnCl₂ (0.68 g, 3.6 mmol) is added. After 48h, the resulting mixture was cooled to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL), adjusted until pH 8-9 with NaOH 1M and the organic layer was washed with water (3 x 25 mL). It was then dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH₂Cl₂/MeOH/NH₄OH : 9/1/0,1).

m/z (MALDI) = 433.3

20

Example 46

1,4-bis{3-[N-(anthr-9-ylmethyl)amino]propyl}piperazine

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.513 mL, 2.49 mmol) and 9-anthracenaldehyde (1.080 g, 5.24 mmol) in absolute ethanol (20 mL) was added 3Å molecular sieves (5g). After stirring the mixture for 12h at room temperature, sodium borohydride (1.9g, 49.9 mmol) was added and the mixture was stirred for 12h at room temperature. Then the reaction mixture was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were extracted with HCl 1N (2 x 50 mL). The combined aqueous layers were neutralized with NaOH 1N (50 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄,

30

evaporated to dryness and the oily residue purified by flash chromatography (neutral aluminium oxide, CH₂Cl₂/MeOH : 90/10).

m/z (MALDI) = 581.36

5 Example 47

1,4-bis{3-[N-(Benzyl)amino]propyl}piperazine

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.513 mL, 2.49 mmol) and benzaldehyde (0.532 mL, 5.24 mmol) in absolute ethanol (20 mL) was added 3Å molecular sieves (5g). After stirring the mixture for 12h at room temperature, sodium
10 borohydride (1.9g, 49.9 mmol) was added and the mixture was stirred for 12h at room temperature. Then the reaction mixture was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were extracted with HCl 1N (2 x 50 mL). The combined aqueous layers were neutralized with NaOH 1N (50 mL) and
15 extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, evaporated to dryness and the oily residue purified by flash chromatography (neutral aluminium oxide, CH₂Cl₂/MeOH : 90/10).

m/z (MALDI) = 381.3

20 Example 48

1,4-bis{3-[N-(4-nitrobenzyl)amino]propyl}piperazine

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.513 mL, 2.49 mmol) and 4-nitrobenzaldehyde (792 mg, 5.24 mmol) in absolute ethanol (20 mL) was added 3Å molecular sieves (5g). After stirring the mixture for 12h at room temperature, sodium
25 borohydride (1.9g, 49.9 mmol) was added and the mixture was stirred for 12h under reflux. Then the reaction mixture was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were extracted with HCl 1N (2 x 50 mL). The combined aqueous layers were neutralized with NaOH 1N (50 mL) and extracted
30 with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, evaporated to dryness and the oily residue purified by flash chromatography (neutral aluminium oxide, CH₂Cl₂/MeOH : 90/10).

m/z (MALDI) = 471.3

Example 49**1,4-bis{3-[N-(naph-2-ylmethyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.513 mL, 2.49 mmol) and
5 2-naphthaldehyde (818 mg, 5.24 mmol) in absolute ethanol (20 mL) was added 3Å
molecular sieves (5g). After stirring the mixture for 12h at room temperature, sodium
borohydride (1.9g, 49.9 mmol) was added and the mixture was stirred for 12h at room
temperature. Then the reaction mixture was quenched by dropwise addition of water (20
mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted
10 with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were extracted with HCl 1N (2
x 50 mL). The combined aqueous layers were neutralized with NaOH 1N (50 mL) and
extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄,
evaporated to dryness and the oily residue purified by flash chromatography (neutral
aluminium oxide, CH₂Cl₂/MeOH : 90/10).

15 m/z (MALDI) = 481.3

Example 50**1,4-bis{3-[N-(4-phenylbenzyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.513 mL, 2.49 mmol) and
20 4-phenylbenzaldehyde (955 mg, 5.24 mmol) in absolute ethanol (20 mL) was added 3Å
molecular sieves (5g). After stirring the mixture for 12h at room temperature, sodium
borohydride (1.9g, 49.9 mmol) was added and the mixture was stirred for 12h at room
temperature. Then the reaction mixture was quenched by dropwise addition of water (20
mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted
25 with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were extracted with HCl 1N (2
x 50 mL). The combined aqueous layers were neutralized with NaOH 1N (50 mL) and
extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄,
evaporated to dryness and the oily residue purified by flash chromatography (neutral
aluminium oxide, CH₂Cl₂/MeOH : 90/10).

30 m/z (MALDI) = 533.4

Example 51**1,4-bis{3-[N-(3,4-dibenzyloxybenzyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.513 mL, 2.49 mmol) and 3,4-dibenzyloxybenzaldehyde (1.668 g, 5.24 mmol) in absolute ethanol (20 mL) was added
5 3Å molecular sieves (5g). After stirring the mixture for 12h at room temperature, sodium borohydride (1.9g, 49.9 mmol) was added and the mixture was stirred for 12h at room temperature. Then the reaction mixture was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were extracted with HCl 1N (2
10 x 50 mL). The combined aqueous layers were neutralized with NaOH 1N (50 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, evaporated to dryness and the oily residue purified by flash chromatography (neutral aluminium oxide, CH₂Cl₂/MeOH : 90/10).

m/z (MALDI) = 805.5

15

Example 52**1,4-bis{3-[N-(fluoren-2-ylmethyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.513 mL, 2.49 mmol) and 2-fluorene-carboxaldehyde (1.018 g, 5.24 mmol) in absolute ethanol (20 mL) was added 3Å
20 molecular sieves (5g). After stirring the mixture for 12h at room temperature, sodium borohydride (1.9g, 49.9 mmol) was added and the mixture was stirred for 12h at room temperature. Then the reaction mixture was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were extracted with HCl 1N (2
25 x 50 mL). The combined aqueous layers were neutralized with NaOH 1N (50 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, evaporated to dryness and the oily residue purified by flash chromatography (neutral aluminium oxide, CH₂Cl₂/MeOH : 90/10).

m/z (MALDI) = 557.36

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Example 53**1,4-bis{3-[N-(benzofur-2-ylmethyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.513 mL, 2.49 mmol) and benzo[b]furan-2-carboxaldehyde (565 mg, 5.24 mmol) in absolute ethanol (20 mL) was added 3Å molecular sieves (5g). After stirring the mixture for 12h at room temperature, sodium borohydride (1.9g, 49.9 mmol) was added and the mixture was stirred for 12h at room temperature. Then the reaction mixture was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were extracted with HCl 1N (2 x 50 mL). The combined aqueous layers were neutralized with NaOH 1N (50 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, evaporated to dryness and the oily residue purified by flash chromatography (neutral aluminium oxide, CH₂Cl₂/MeOH : 90/10).

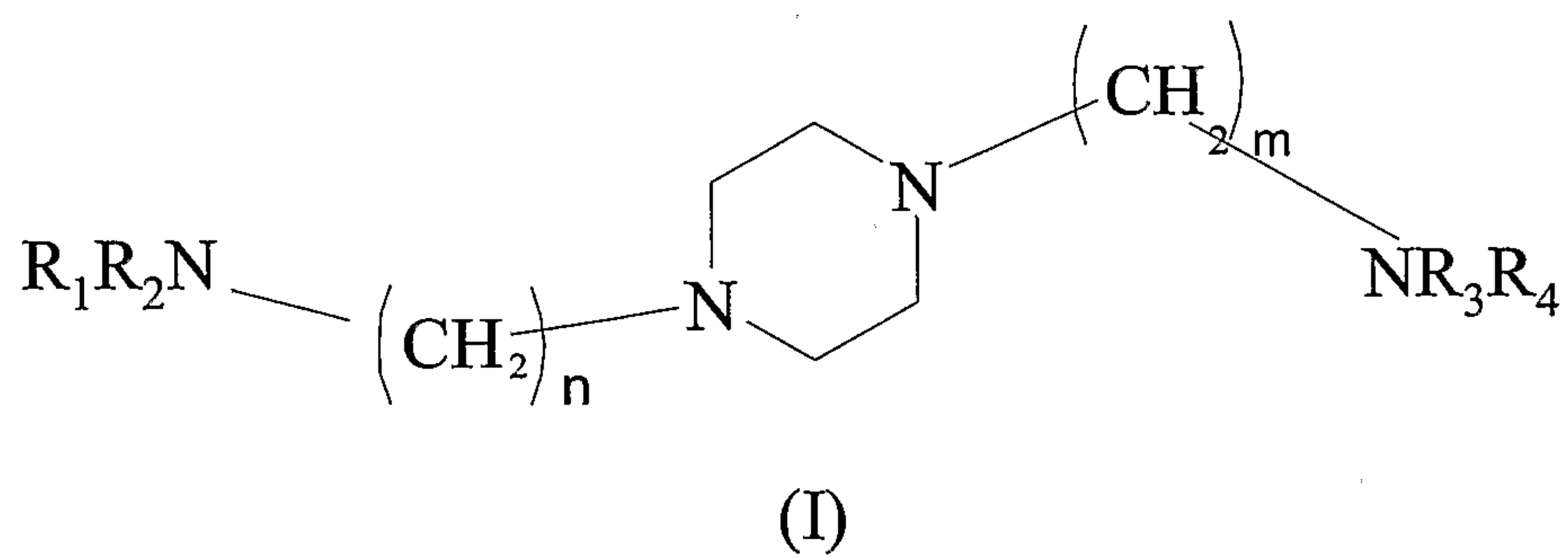
m/z (MALDI) = 461.3

Example 54**1,4-bis{3-[N-(quinol-2-ylmethyl)amino]propyl}piperazine**

To a solution of 1,4-bis(3-aminopropyl)piperazine (0.513 mL, 2.49 mmol) and 2-quinolinecarbaldehyde (823 mg, 5.24 mmol) in absolute ethanol (20 mL) was added 3Å molecular sieves (5g). After stirring the mixture for 12h at room temperature, sodium borohydride (1.9g, 49.9 mmol) was added and the mixture was stirred for 12h at room temperature. Then the reaction mixture was quenched by dropwise addition of water (20 mL) and ethanol was removed under reduced pressure. The aqueous residue was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were extracted with HCl 1N (2 x 50 mL). The combined aqueous layers were neutralized with NaOH 1N (50 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, evaporated to dryness and the oily residue purified by flash chromatography (neutral aluminium oxide, CH₂Cl₂/MeOH : 90/10).

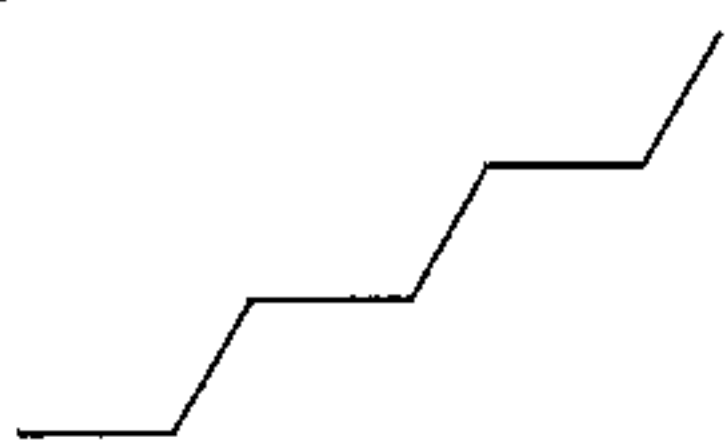
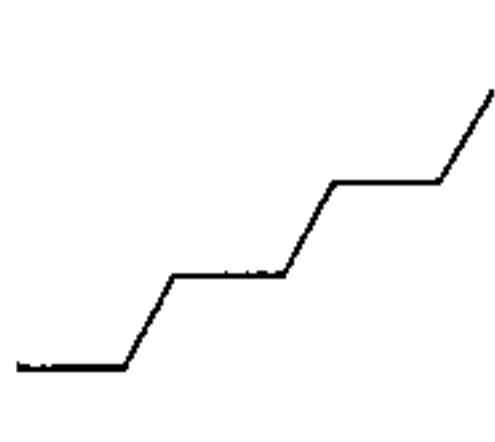
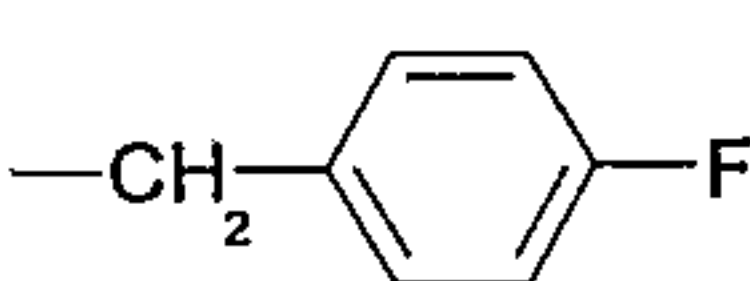
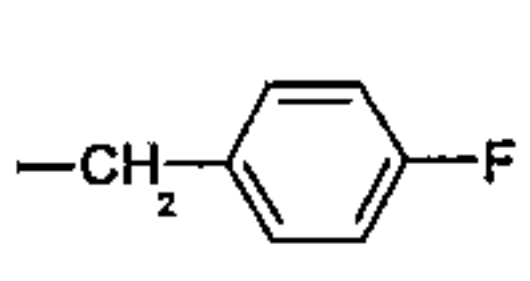
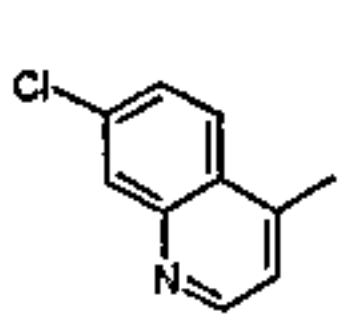
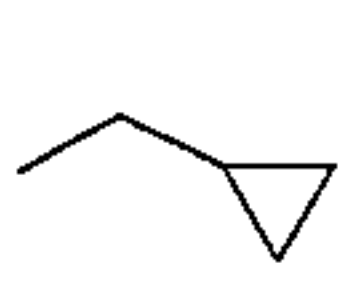
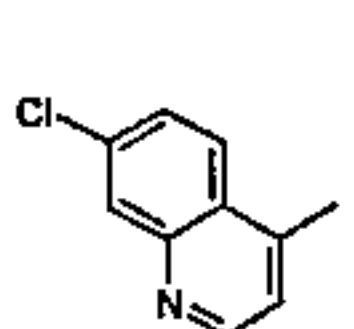
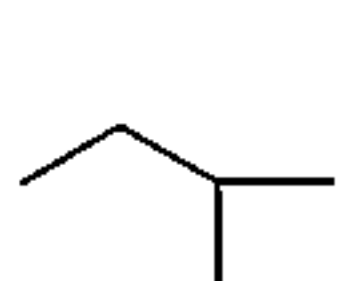
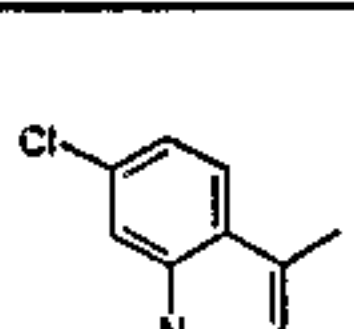
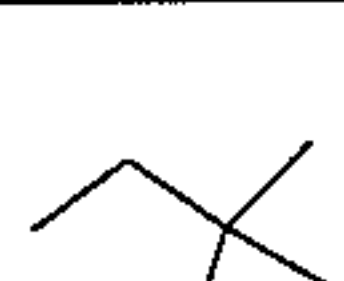
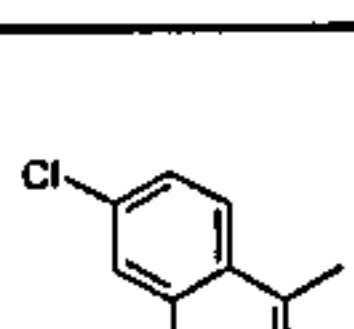
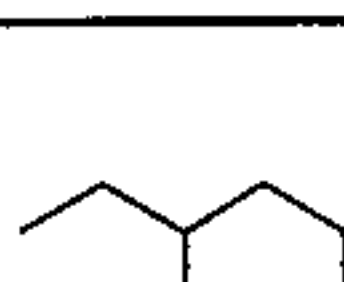
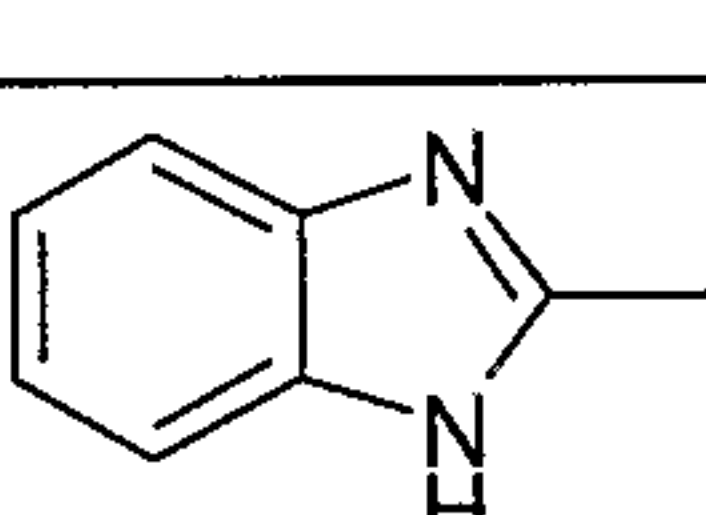
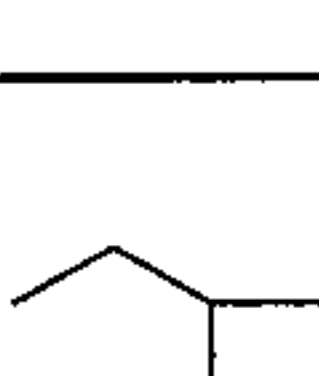
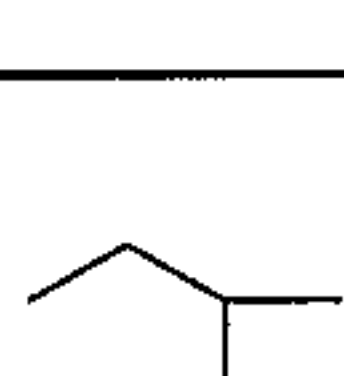
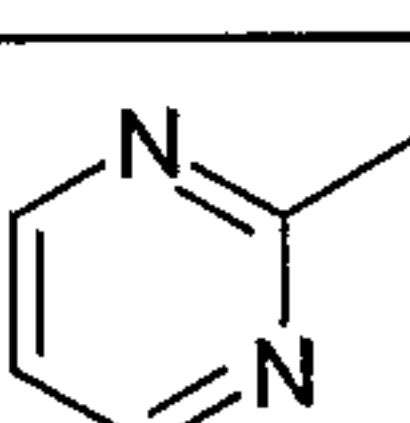
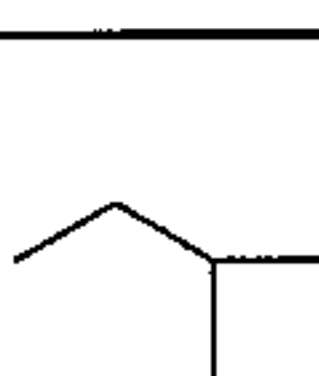
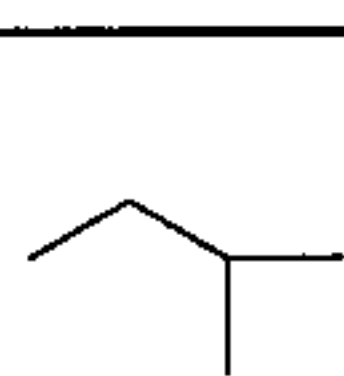
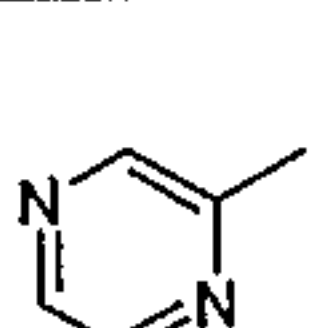
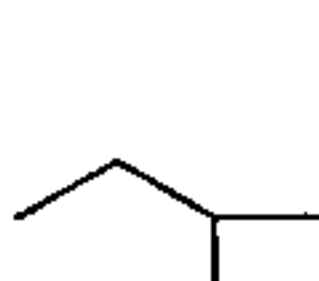
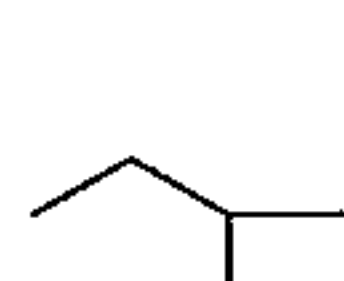
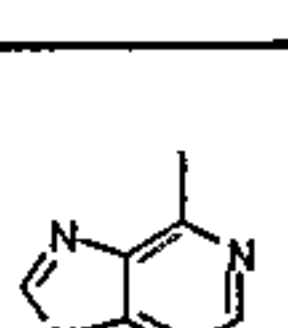
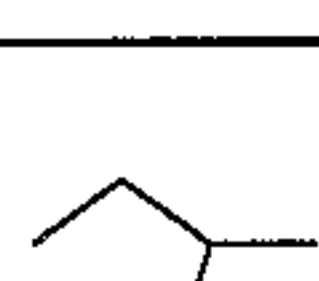
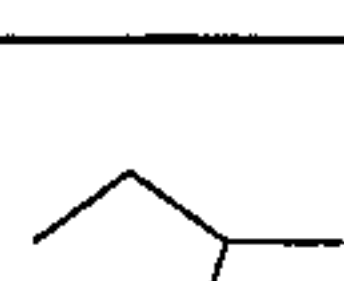
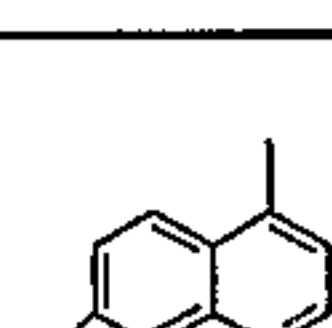
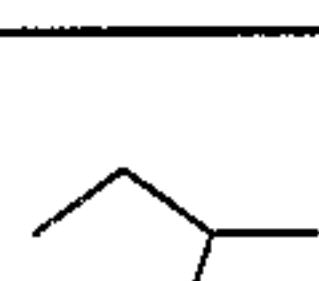
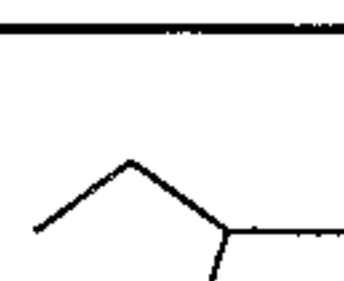
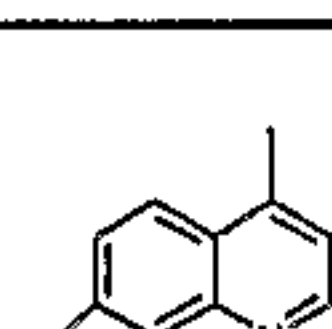
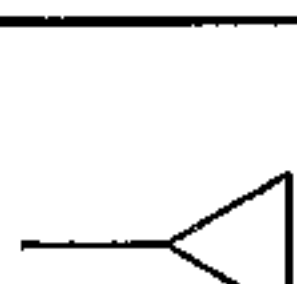
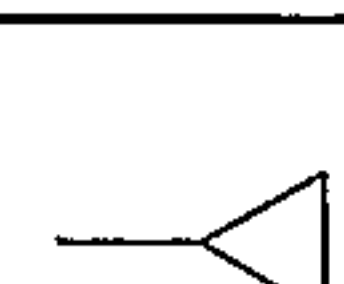
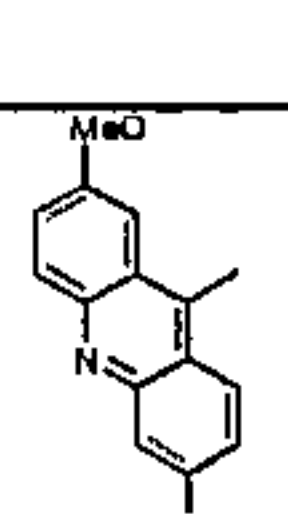
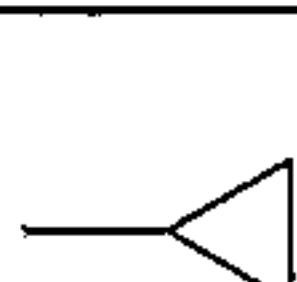
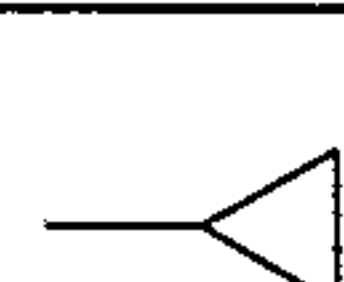
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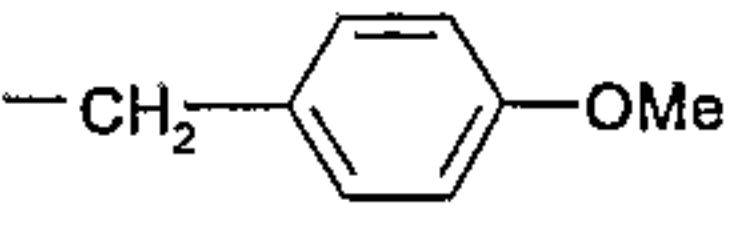
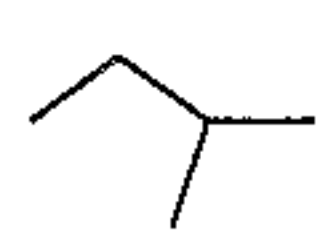
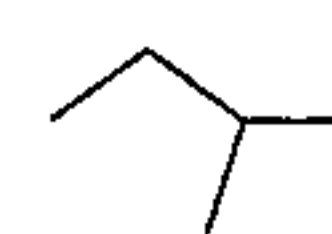
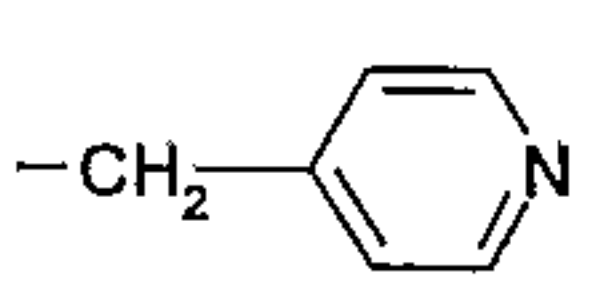
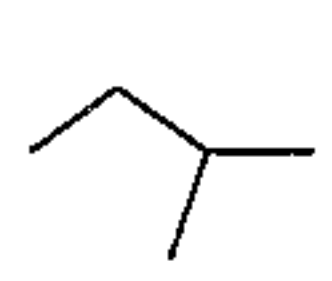
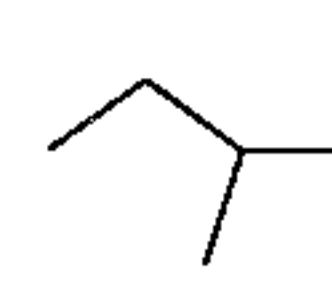
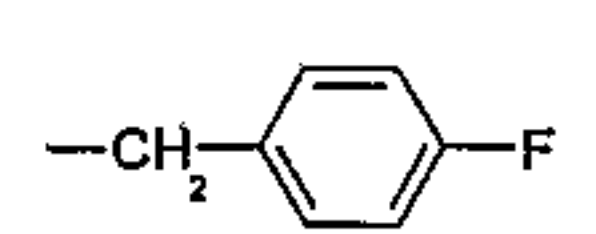
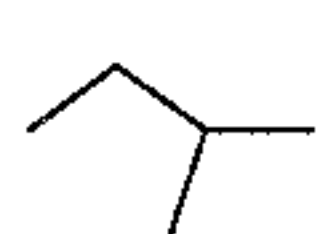
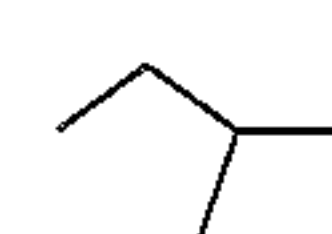
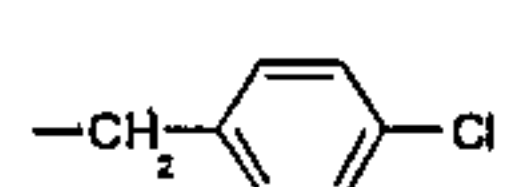
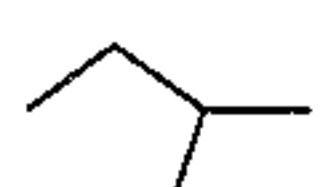
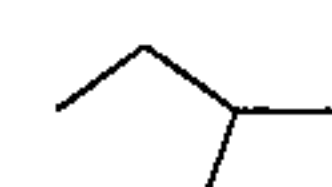
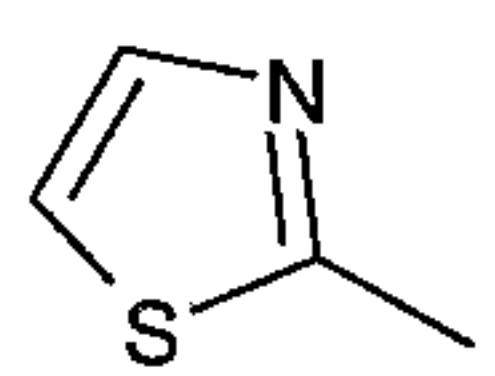
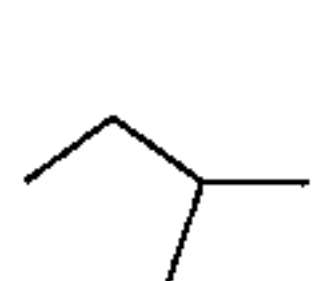
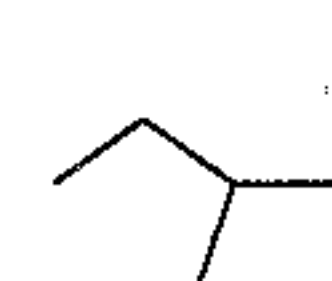
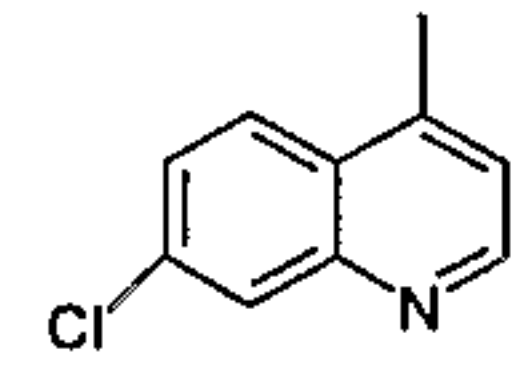
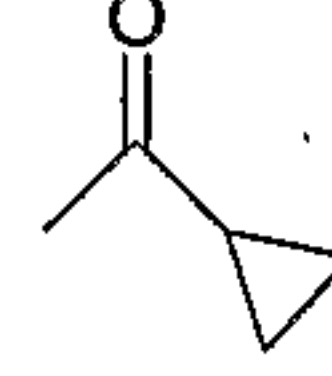
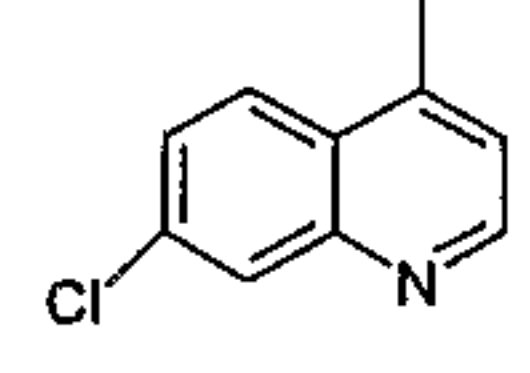
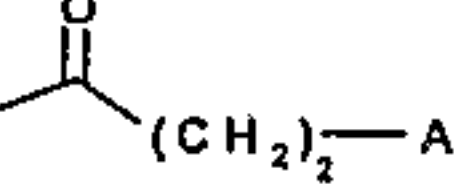
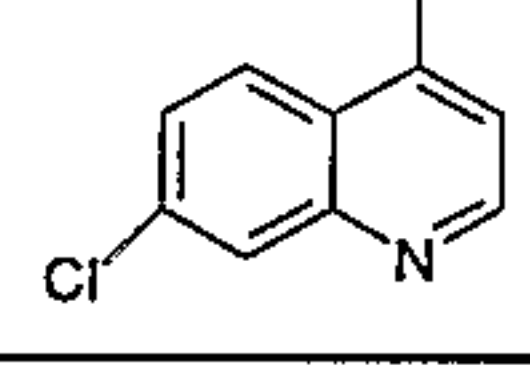
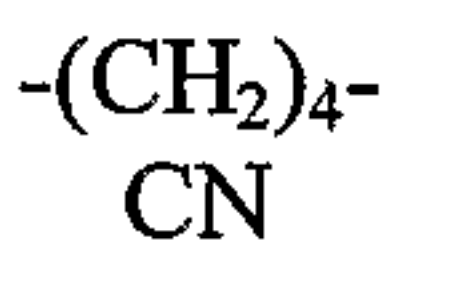
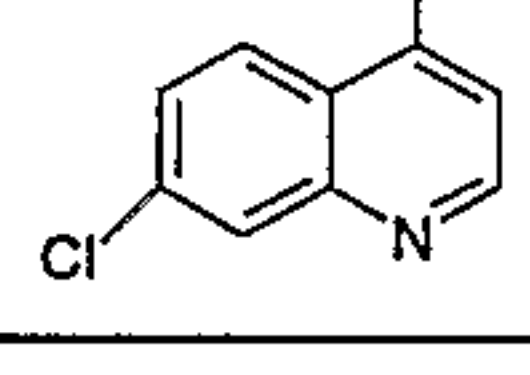
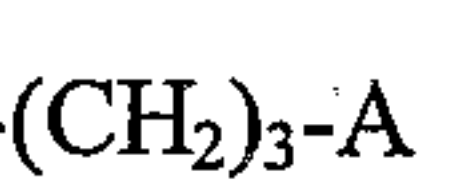
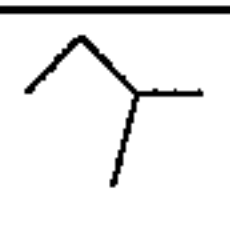
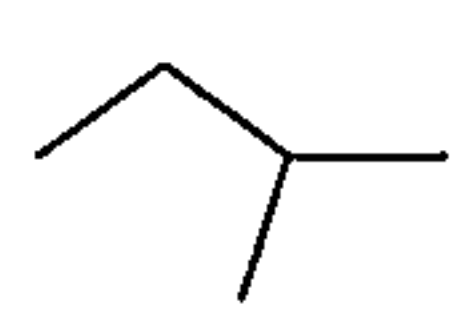
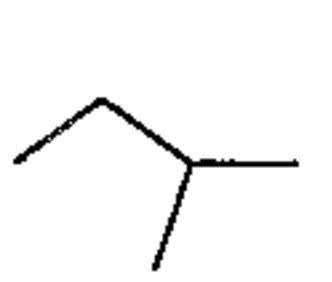
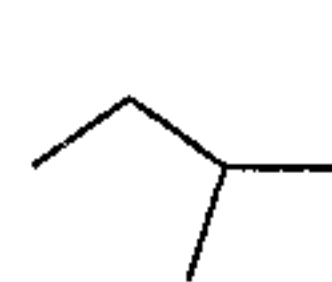
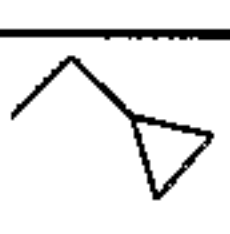
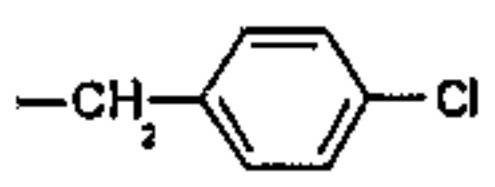
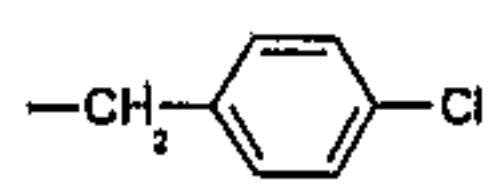
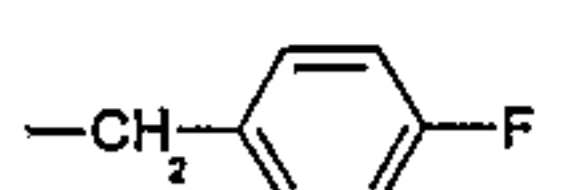
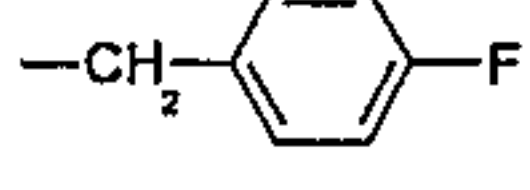
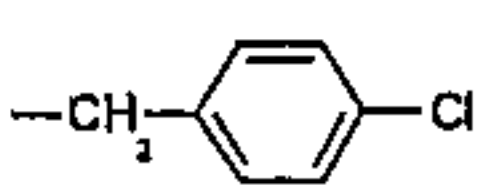
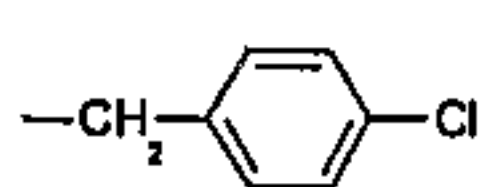
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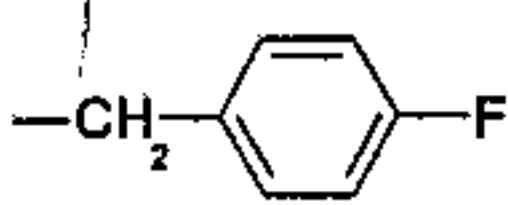
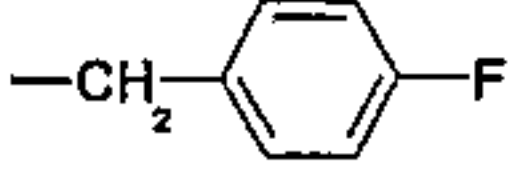
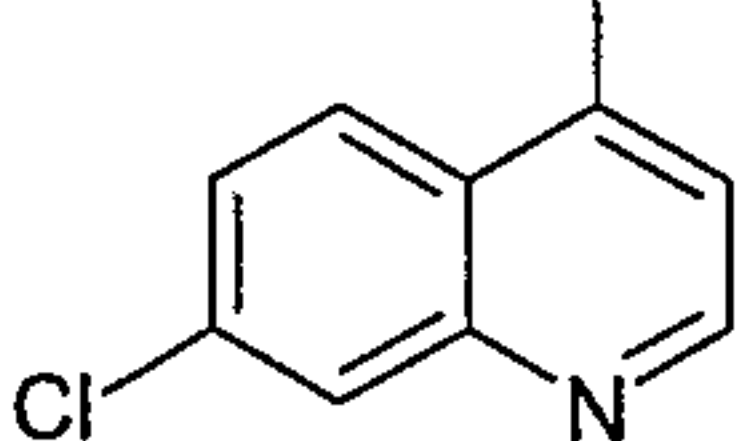
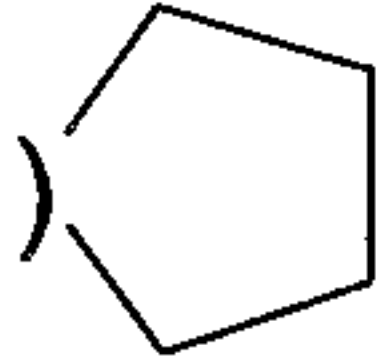
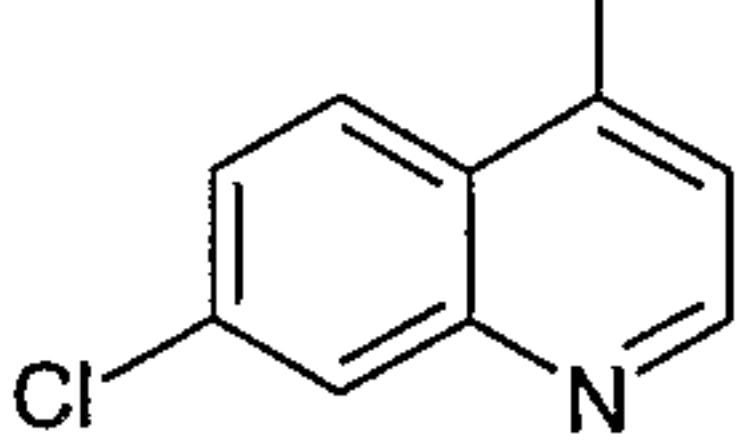
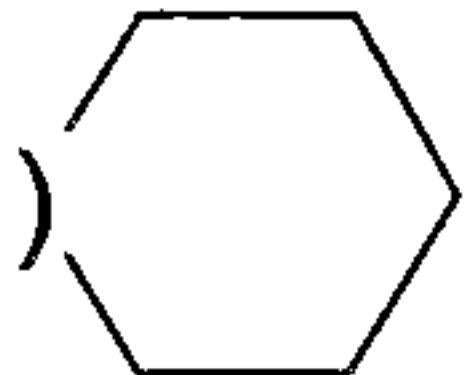
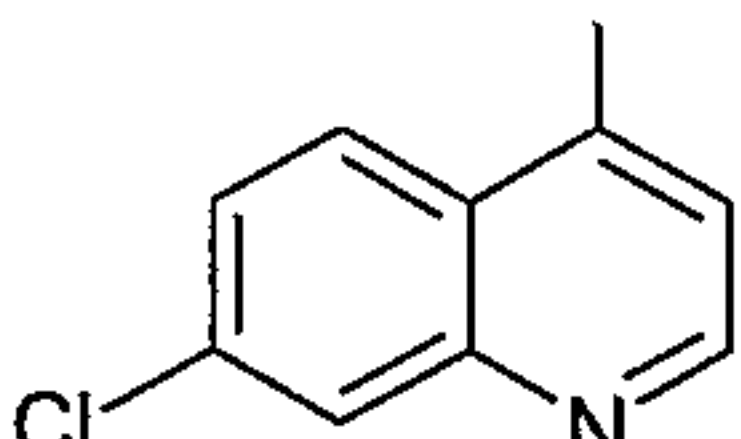
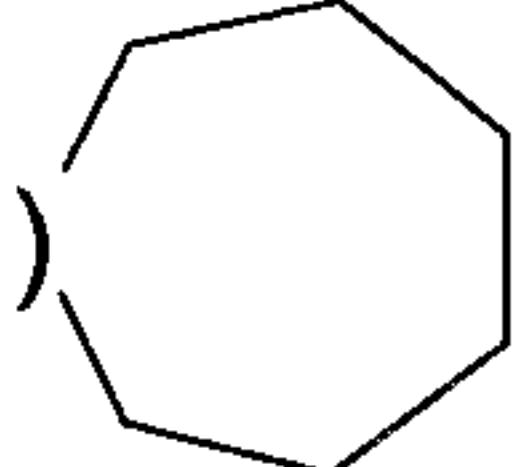
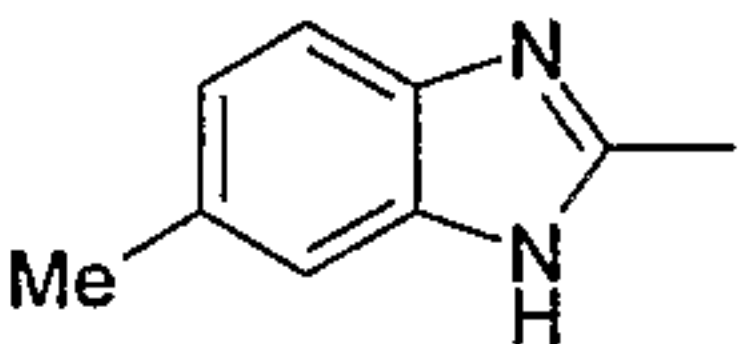
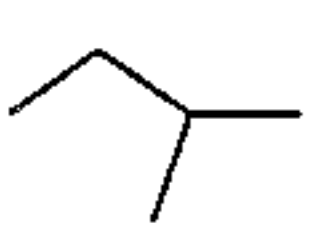
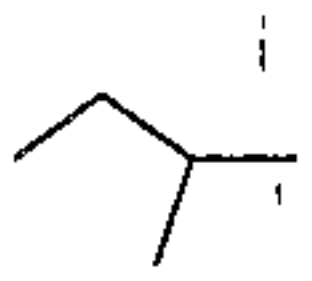
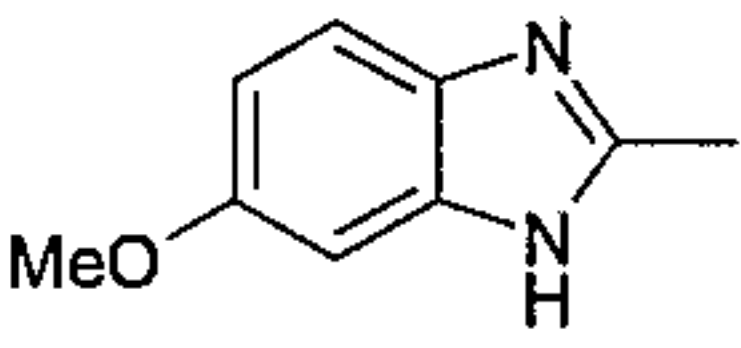
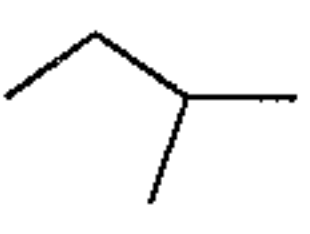
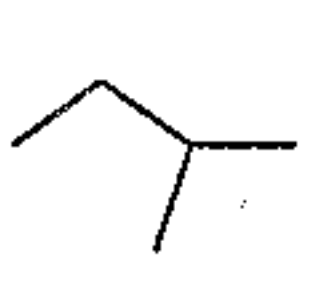
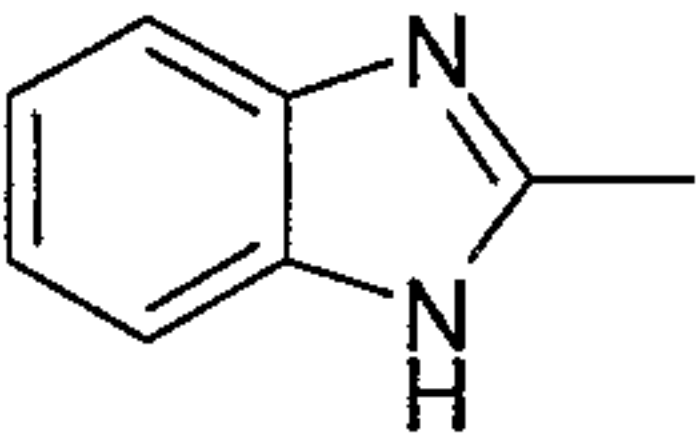
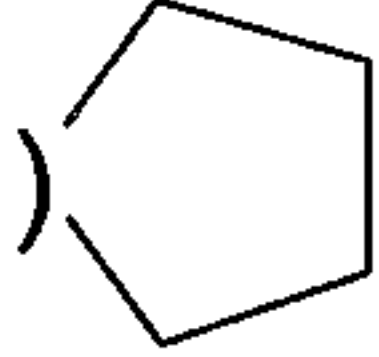
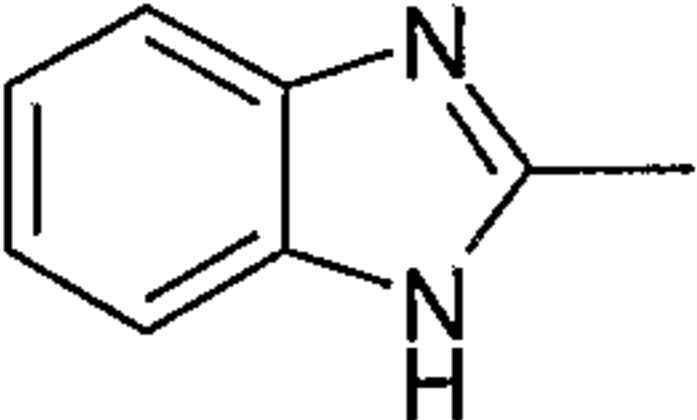
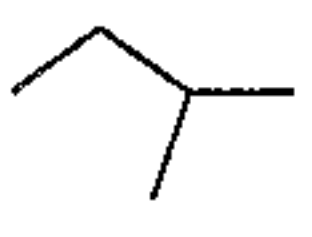
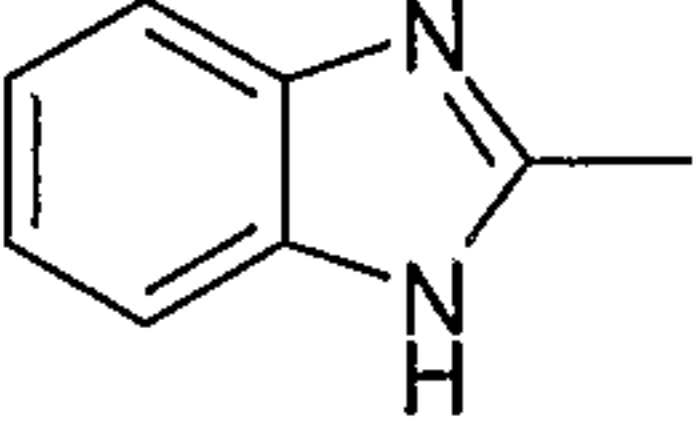
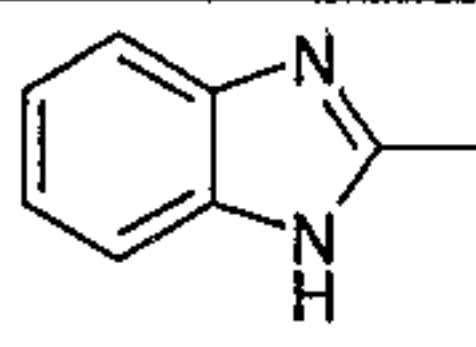
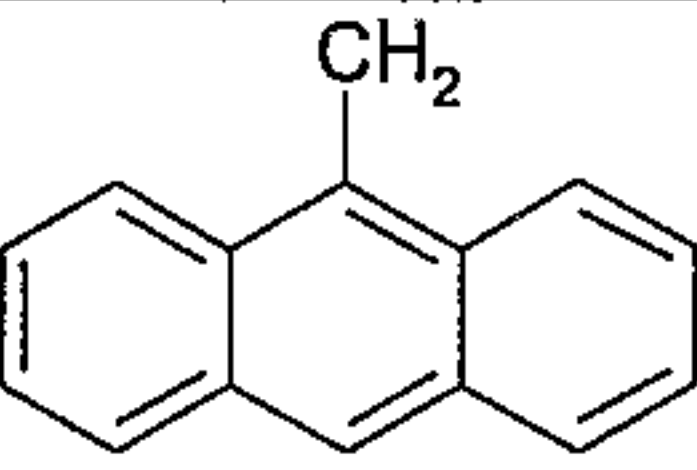
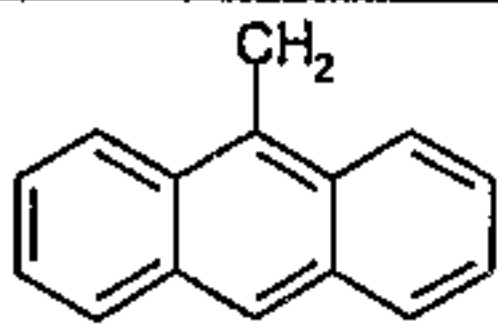
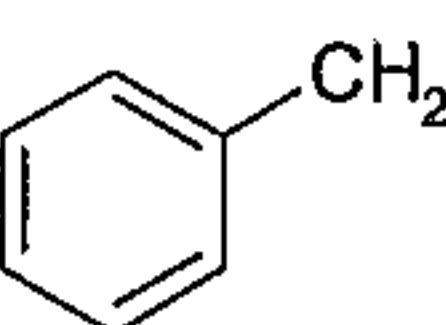
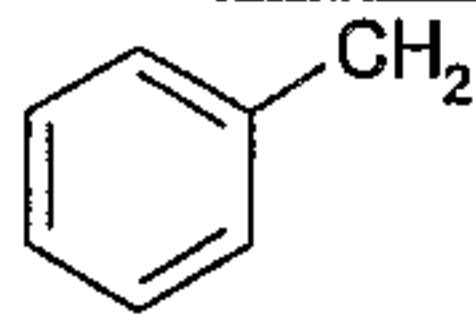
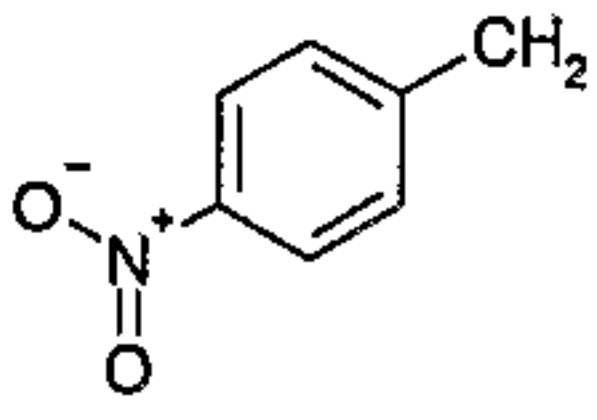
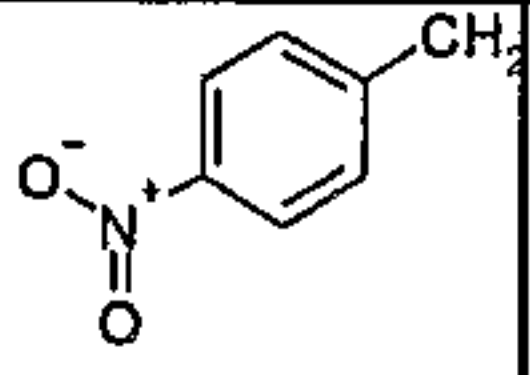
Table I

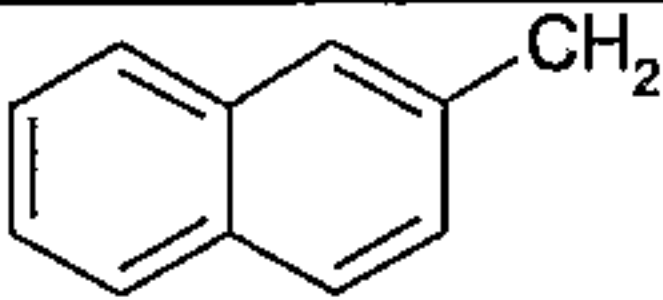
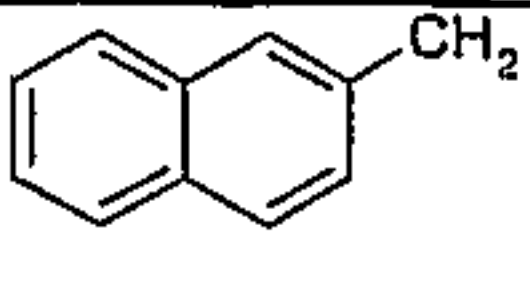
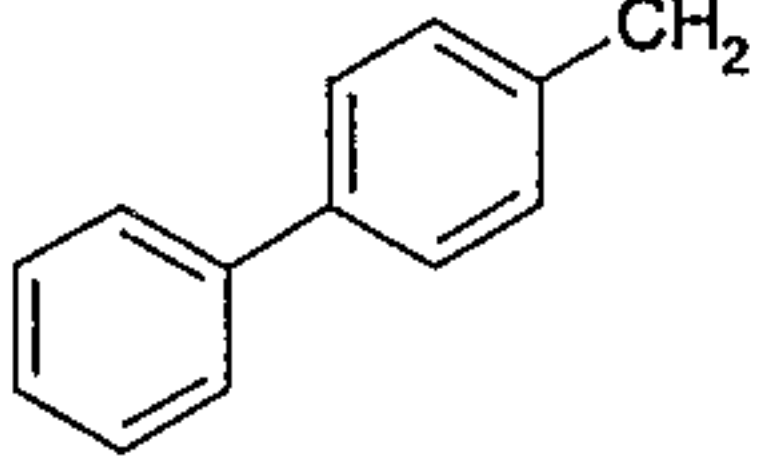
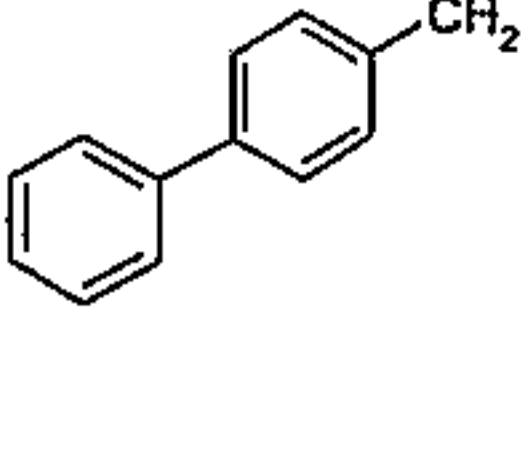
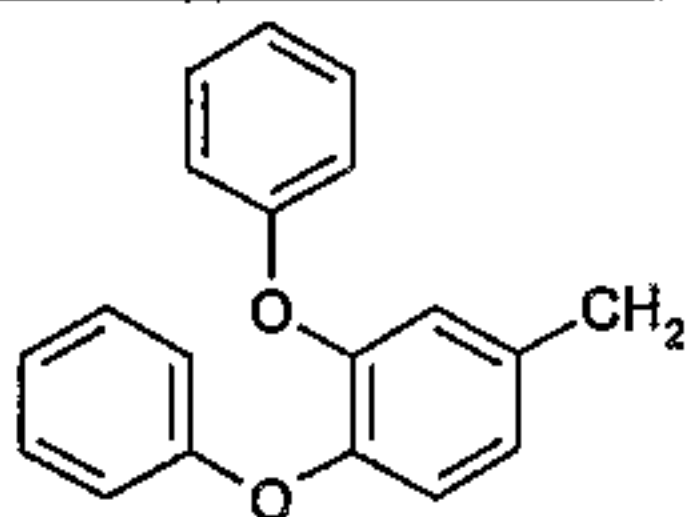
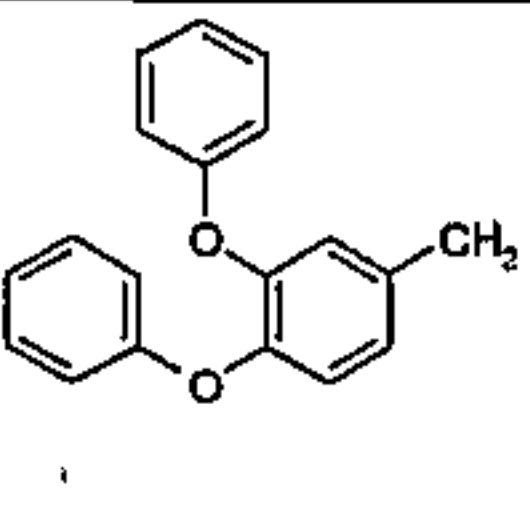
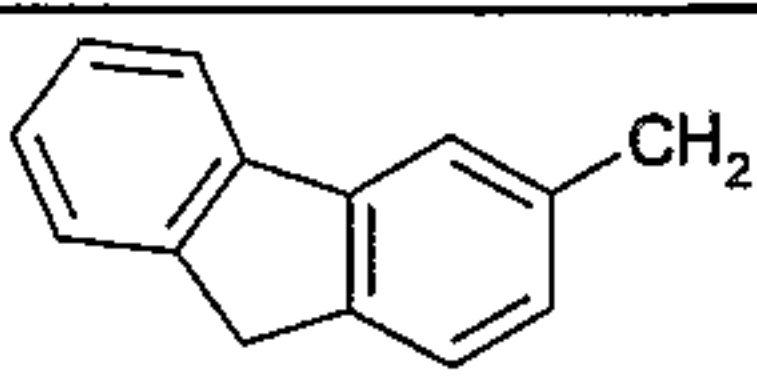
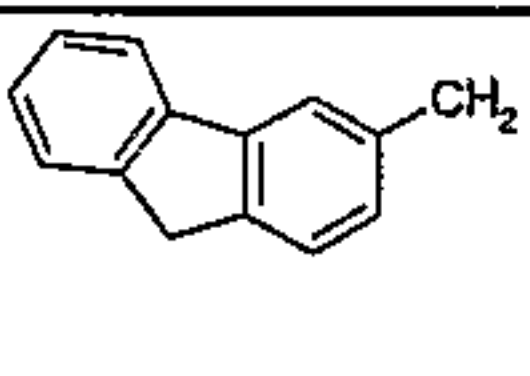
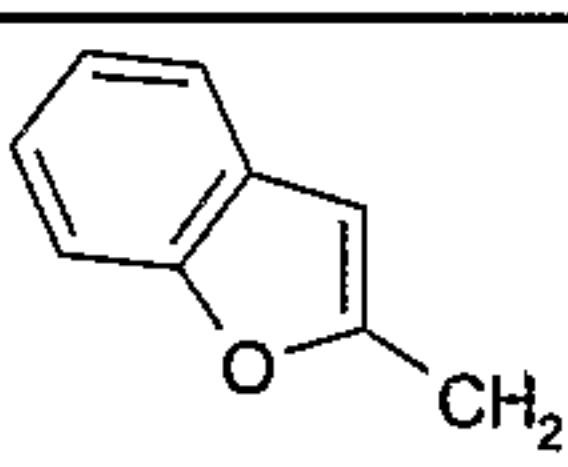
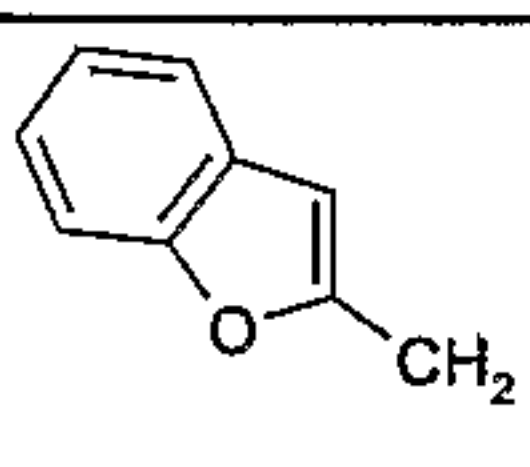
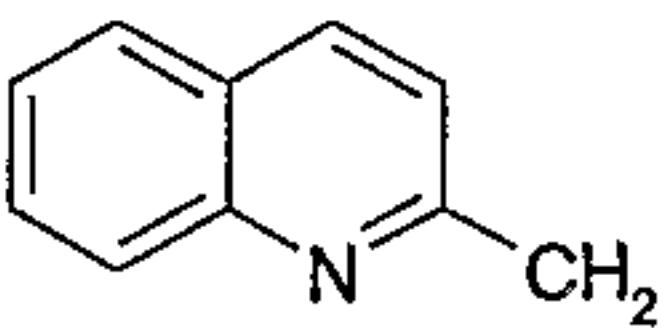
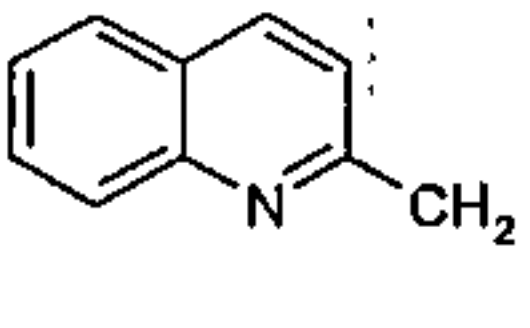
5

Example	n	m	R ₁	R ₂	R ₃	R ₄	Salt	MWT
1	3	3	H		H		—	522.21
2	3	3	H		H		4 HCl	526.19
3	3	3	H		H		4 HCl	644.24
4	3	3	H		H		4 HCl	592.12
5 (compound No. 1)	3	3	H		H		6 HCl	698.18
6 (compound No. 2)	3	3	H		H		4 HCl	584.22
7	3	3	H		H		4 HCl	452.20
8 (compound No. 3)	3	3	H		H		4 HCl	456.23
9 (compound No. 4)	3	3	H		H		4 HCl	512.29

Example	n	m	R ₁	R ₂	R ₃	R ₄	Salt	MWT
10 (compound No. 5)	3	3	H		H		4 HCl	540.33
11 (compound No. 6)	3	3	H		H			416.27
12	3	3	H		H		—	415.25
13	3	3	H		H		—	417.27
14	3	3	H		H		—	431.28
15	3	3	H		H		—	457.30
16	3	3	H				2 COOH- COOH	608.35
17 (compound No. 7)	3	3	H				—	390.35
18	3	3	H				—	390.35
19	3	3	H				—	430.35
20	3	3	H				—	473.33
21	3	3	H				—	469.30
22 (compound No. 8)	3	3	H				—	549.32

Example	n	m	R ₁	R ₂	R ₃	R ₄	Salt	MWT
23	3	3	H				2 COOH-COOH	612.37
24	3	3	H				—	403.37
25 (compound No. 9)	3	3	H				—	420.36
26	3	3	H				—	436.33
27 (compound No. 10)	3	3	H				—	409.32
28	3	3	H				—	483.28
29	3	3	H				—	586.34
30	3	3	H				—	496.31
31	3	3	H				—	572.36
32 (compound No. 11)	3	3					—	424.45
33 (compound No. 12)	3	3					—	416.39
34 (compound No. 13)	2	2	H		H		4 HCl	564.09
35 (compound No. 14)	2	2	H		H		4 HCl	532.15
36 (compound No. 15)	4	4	H		H		4 HCl	620.15

Example	n	m	R ₁	R ₂	R ₃	R ₄	Salt	MWT
37 (compound No. 16)	4	4	H		H		4 HCl	588.22
38	3	3	H				—	424.32
39	3	3	H				—	429.26
40	3	3	H				—	443.28
41 (compound No. 17)	3	3	H				—	442.38
42 (compound No. 18)	3	3	H				—	458.37
43 (compound No. 19)	3	3	H				—	370.28
44 (compound No. 20)	3	3	H		H		—	372.30
45 (compound No. 21)	3	3	H		H		—	432.27
46	3	3	H		H		4 HCl	724.26
47	3	3	H		H		4 COOH-COOH	740.28
48	3	3	H		H		4 COOH-COOH	830.25

Example	n	m	R ₁	R ₂	R ₃	R ₄	Salt	MWT
49	3	3	H		H		-	480.33
50	3	3	H		H		4 HCl	676.26
51	3	3	H		H		4 HCl	948.37
52	3	3	H		H		4 HCl	700.26
53	3	3	H		H		4 HCl	604.19
54	3	3	H		H		4 HCl	626.22

In this table:

- "-" represents a compound in free form,
- Me represents a methyl group,
- OMe represents a methoxy group,
- A represents NHBoc with Boc being a tert-butoxycarbonyl group.
- HCl represents a compound in a chlorhydrate form.

10

Example 34: Pharmacological test

The compounds of the invention have been the subject of pharmacological tests which have demonstrated their relevance as active substances in therapy and in particular in the treatment of neurodegenerative diseases.

15

MATERIAL AND METHODS

The cell line for drug screening

Cell culture of neuroblastoma SKNSH-SY5Y and stable transfection

The human neuroblastoma cell line SH-SY5Y were cultured in Dulbecco's modified Eagle medium supplemented with 10% fetal calf serum, 2 mM L-glutamine, 1 mM non-essential amino-acids, penicillin/streptomycin (Invitrogen SARL, Cergy Pontoise, France) and 200 µg/ml G418 (to select for APP expression) in a 5% CO₂ humidified incubator at 37°C. APP751 cDNA with the Swedish mutation (APP^{Sw}) was subcloned into stably eukaryotic expression vector pcDNA3 (Invitrogen), allowing for a G418 (Invitrogen) selection of stable clones. This APP cDNA was stably transfected into SH-SY5Y cells using the ethyleneimine polymer ExGen 500 (Euromedex) according to the manufacturer's instructions.

Drug treatment of the transfected cell line

Cells were plated into 6-well plates 24 h before drug exposure. Preceding the addition of drugs, cultures were washed once with warm phosphate-buffered saline (37°C) and then exposed for 4, 8 or 24h with drugs to be tested. After treatment, the medium was collected for the dosage of Aβ₁₋₄₂. Cells were washed with phosphate-buffered saline and scraped with a policeman rubber in 70µl of Laemmli sample buffer with protease inhibitors (Complete Mini, Roche Molecular Biochemicals, Meylan, France), sonicated and heat-treated for 5 min at 100°C. Protein concentration was established using the PlusOne™ 2-D Quant Kit (Amersham Biosciences, Orsay, France) and samples were kept at -80°C until used.

Antibodies for the quantification of APP-CTFs by western blots

The APPCter-C₁₇ antibody is raised against the last 17 amino acids of the human APP sequence (Sergeant, N., David, J. P., Champain, D., Ghestem, A., Wattez, A., and Delacourte, A. (2002) *J Neurochem* 81, 663-672). This polyclonal antibody detects all APP-CTFs fragments. The tubulin signal was used as a loading control and to normalize the APP-CTFs content. Anti-mouse or anti-rabbit secondary antibodies coupled with horseradish peroxidase were purchased at SIGMA Immunochemicals (Saint Quentin Fallavier, France).

Western blotting

The same quantity of total proteins (20 µg/lane) was loaded on a 16.5% Tris-tricine polyacrylamide gel. Tris-tricine SDS-polyacrylamide gel electrophoresis (PAGE) was performed following the procedure of Schagger and Von Jagow (1987) (Schagger, H., and von Jagow, G. (1987) *Anal Biochem* 166, 368-379) with a protean II Xi Cell (Bio-Rad, Marnes la coquette, France). Proteins were transferred to nitrocellulose membrane at 2.5 mA/cm² per gel using the SemiDry Novablot Transfer system (Amersham Biosciences, Orsay, France), according to the manufacturer's instructions. Proteins were reversibly stained with Ponceau Red to check the quality of the transfer. 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°C with appropriate dilutions of the primary antibodies, and incubated for 1h at room temperature with secondary antibody. The immunoreactive complexes were revealed using the ECLTM Western Blotting kit (Amersham Biosciences) and Hyperfilms (Amersham Pharmacia Biotech).

Western blot films were digitized using an UMax scanner calibrated for optical densities (Amersham Biosciences). The Image-MASTER 1D ELITE Software (Amersham Biosciences) was used to quantify the signal, and data were collected using Excel Software (Microsoft, LesUlis, France).

Quantification of secreted Aβ

The collected medium was spun at 200g to eliminate the cell debris and Aβ₁₋₄₂ concentration was determined using the Innostest[®] β-Amyloid₁₋₄₂ (Innogenetics, Ghent, Belgium) according to the manufacturer's instructions.

RESULTS

Impact of drugs on the levels of APP-CTFs α, β, γ stubs and on the resulting Aβ peptide.

SKNSH SY5Y transfected cells were grown in the presence of drugs at different concentrations, for example at 1µM or 5µM, then cells were harvested and analyzed for their APP-CTF content, using the western-blot approach, while Aβ 1-42 of the cell supernatant was quantified by ELISA, as described in material and methods. For

each compound, normal levels have the arbitrary value of 1. For example, if one APP-CTF is increased 10 times, the value is reported as 10. For A β peptide, if decreased of 60%, the value is reported as 0,4 (40% remaining).

Figure 1 shows the results obtained for both compounds of the invention, the compound of example 4 and compound (5) of example 10. These results show that both compounds, compared to the control (i.e. without compound according to the invention), are efficient to decrease A β peptide levels at low concentration (1 μ M) at 6 hours and that this efficiency is confirmed for a greater concentration (5 μ M) at 24 hours. Furthermore, the compound of example 4 exhibits a particularly high efficiency for α and γ -APP-CTFs stubs (next table) as well for A β peptide (figure 1).

For the most active compounds, values for γ stubs were superior to 1 and in particular in the range 1 to 20; values for α stubs were superior to 1 and in particular in the range from 1 to 16 while the values for β stubs were inferior to 1 and in particular in the range from 0,4 to 1 and the values for A β peptide were inferior to 1 and in particular in the range from 0,1 to 1.

The table here-after submits data obtained for the compound of example 4 at two concentrations 1 μ M and 5 μ M, the values having been measured at 6 hours and 24 hours for each concentration.

	6h		24h	
	1 μ M	5 μ M	1 μ M	1 μ M
β	0.8	1.2	0.8	5
α	14	11	3.5	7
γ	9.6	5.7	5.1	14.4
CTFs	6	5	3.5	65
A β	0.2	0	1	0.1

Screening of the molecules through the Blood-Brain Barrier

The ability of some compounds to cross the Blood-Brain Barrier (BBB) has been evaluated, using an *in vitro* model (Cecchelli, R., et al., *In vitro model for evaluating drug transport across the blood-brain barrier*. Adv Drug Deliv Rev, 1999. 36(2-3): p. 165-178). The described model consists in brain capillary endothelial cells co-cultured with

glial cells, thereby closely mimicking the *in vivo* conditions (Lundquist, S. and M. Renftel, *The use of in vitro cell culture models for mechanistic studies and as permeability screens for the blood-brain barrier in the pharmaceutical industry-background and current status in the drug discovery process*. Vascul Pharmacol, 2002. 38(6): p. 355-64) and developed by
5 CELLIAL Technologies SA.

For instance, examples 16 and 23 were soluble, able to diffuse across the filter membrane coated with collagen and without cells, and were not toxic on the endothelial cell monolayer at a concentration of 10 μ M. The transport of drug was good for example
10 16 and moderate for example 23. Indeed, the permeability coefficients obtained for example 16 (2.26×10^{-3} cm/min) and example 23 (1.81×10^{-3} cm/min) indicate that these compounds cross the BBB and are good candidates as CNS drugs.

It is reminded here that from the literature, a good anti-Alzheimer compound should increase the levels of γ stubs that have a potential physiological role for the
15 transcription of genes (Cao, X. and T.C. Sudhof, A transcriptively active complex of APP with Fe65 and histone acetyltransferase tip60. Science, 2001. 293(5527): p. 115-20 ; Pardossi-Piquard, R., et al., Presenilin-dependent transcriptional control of the Abeta-degrading enzyme neprilysin by intracellular domains of betaAPP and APLP. Neuron, 2005. 46(4): p. 541-54). Increased levels of α stubs are also expected, because the
20 cleavage is in competition with the β cleavage involved in the generation of A β species (Lichtenthaler S. F. and Haass C. (2004) Amyloid at the cutting edge: activation of α -secretase prevents amyloidogenesis in an Alzheimer disease mouse model. J Clin Invest 113, 1384-1387). The β cleavage that generates the β stub should be either normal or decreased. A β peptide, which is a potential neurotoxic, should be decreased. Together, a
25 good anti-Alzheimer compound should in priority increased the levels of α and γ stubs and simultaneously decreased the A β peptide.

Therefore, the result of the tests carried out on the compounds disclosed in the present invention show that, *in vitro*, they exhibit the property to rectify the Amyloid Protein Precursor metabolism.

30 For this purpose an effective amount of a said compound may be administered to a subject suffering from a neurodegenerative disease or more generally to a subject suffering from a pathology linked to a metabolic defect of the APP protein. Among said

neurodegenerative disease, Alzheimer's disease, Down syndrome, amyloid angiopathies, dementia with Lewy bodies and Parkinson's disease may be cited. The results also suggest that the compounds can be used for the treatment of cancer. Said compounds may also be used for diagnostic purposes.

5 More particularly, compounds of formula (I) containing a radiolabelled fluorine atom may be used as a medical imaging agent in particular or a metabolic marker, for example in the usual technics in the medical field such as Position Emission Tomography (PET).

10 Among said compounds containing a fluorine atom, compounds Nos. 11 and 25 of the table may be cited, which necessitate a radiolabelling step in their synthesis.

Therefore the present invention is also related to the use of a compound of formula (I) including a marker system, for instance a radiolabelled fluorine atom, for the manufacture of a medical imaging agent intended for the diagnostic in the human being of a pathological or non pathological status, linked with a modification of the metabolism of
15 Amyloid Protein Precursor (APP) or APP-like proteins, and in particular to neurodegenerative troubles.

The present invention also encompasses compositions for medical diagnostic containing a compound of formula (I) characterized in that said compound of formula (I) including a marker system, for instance a radiolabelled fluorine atom.

20 A further object of the invention relates to a compound of formula (II) according to the invention or anyone of the individual compounds (1) to (21) listed above for use as a medicament.

According to another of its aspects, the present invention relates to pharmaceutical compositions containing an active ingredient, chosen among a compound
25 of formula (II) according to the invention and anyone of the individual compounds (1) to (21) listed above, their salts with pharmaceutically acceptable acids and mixture thereof.

Thus, these pharmaceutical compositions contain an effective amount of said compound, and one or more pharmaceutical excipients.

The aforementioned excipients are selected according to the dosage form and
30 the desired mode of administration.

In this context they can be present in any pharmaceutical form which is suitable for enteral or parenteral administration, in association with appropriate excipients,

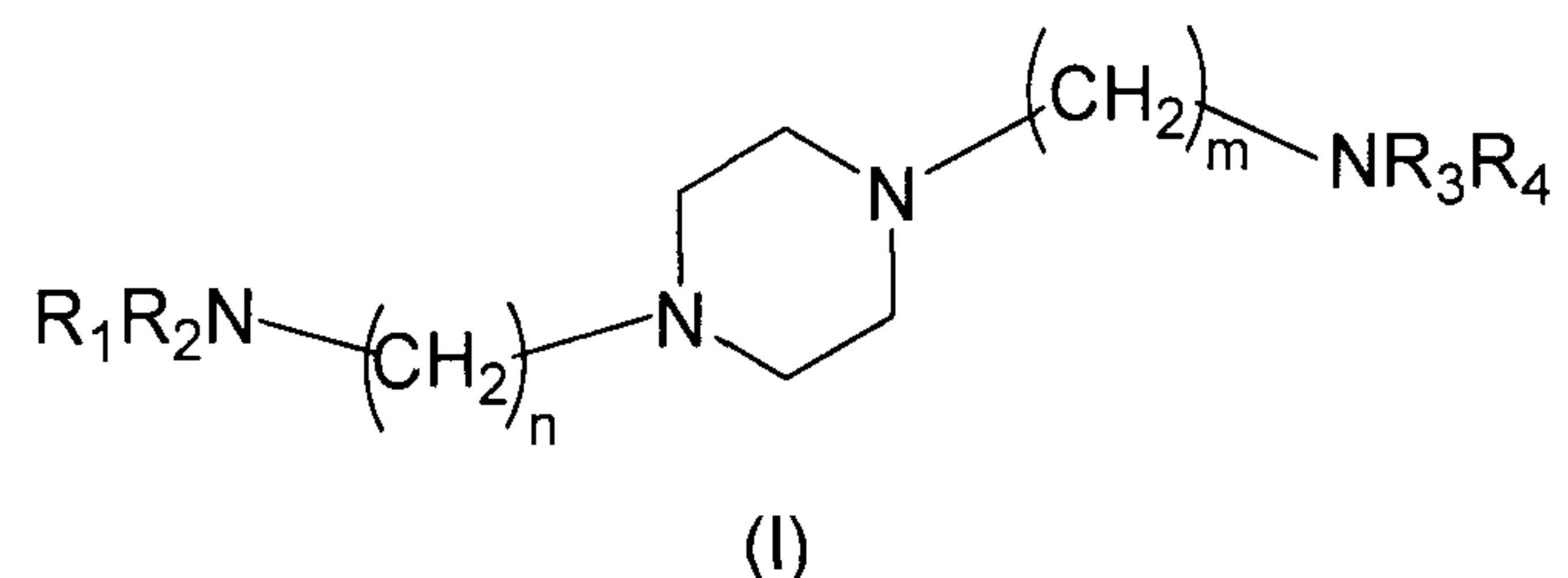
for example in the form of plain or coated tablets, hard gelatin and other capsules, suppositories, or drinkable or injectable solutions or suspensions, in doses which enable the daily administration of from 0.1 to 1000 mg of active substance.

- 5 The present invention according to another of its aspects, also relates to a method of treatment of pathologies above indicated which comprises administering to a subject an effective amount of a compound according to formulae (I) or (II) or anyone of the individual compound (1) to (21) according to the invention or one of its pharmaceutically acceptable salts.

10

CLAIMS

1. Use of a compound of formula (I)



in which n and m are identical or different and independently represent an integer of greater than or equal to 2, the resulting hydrocarbon chain optionally comprising one or more heteroatoms selected among oxygen, nitrogen and sulphur, and,

in which R₁, R₂, R₃ and R₄, independently, represent

- a hydrogen atom,
- a (C₁-C₇)alkyl group, straight or branched, saturated or unsaturated,
- a (C₁-C₇)alkylcarbonyl group,
- an aryl group,
- an aralkyl group, where the aryl group is attached to a (C₁-C₇)alkylene bridging moiety,
- a heteroaryl group,

where each (C₁-C₇)alkyl group is optionally substituted by one or more identical or different groups selected from the group consisting of a halogen, the cyano group, the hydroxy group, the nitro group, the amino group, a (C₁-C₇)alkylamino group, a (C₁-C₄)alkoxy group, a tertbutoxycarbonylamino group, a HO-(C₁-C₈)alkyl- group, a H₂N-(C₁-C₈)alkyl- group, a HO-(C=O)- group, a (C₁-C₈)alkyl-O-(C=O)- group, a (C₁-

C₈)alkyl-(C=O)- group, a (C₁-C₈)alkyl-(C=O)-(C₁-C₈)alkyl- group, a HSO₃(C₁-C₈)alkyl- group, a H₂N-(C=O)- group and a H₂N-(C=O)-(C₁-C₈)alkyl- group,

where the aryl group is selected from the group consisting of groups benzyl, phenyl, biphenyl, anthryl, phenylbenzyl, fluorenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl and indanyl,

where the heteroaryl group is an aromatic monocycle, an aromatic bicycle, an aromatic tricycle or a bicycle or a tricycle of which one or two of the cycles is aromatic and the other cycle(s) is or are partially hydrogenated, from C₅ to C₁₄ comprising within the cyclic system one, two or three heteroatoms, identical or different, selected from the group consisting of oxygen, nitrogen and sulphur, and

where each one of these aryl or heteroaryl groups comprises optionally one or more substitutions, identical or different, selected from the group consisting of a halogen, the hydroxy group, a (C₁-C₇)alkyl group, a (C₁-C₇)alkoxy group, a (C₇-C₁₃)arylalkoxy group, the cyano group, the nitro group, the amino group, a (C₁-C₇)alkylamino group, a HO-(C₁-C₈)alkyl- group, a H₂N-(C₁-C₈)alkyl- group, a HO-(C=O)- group, a (C₁-C₈)alkyl-O-(C=O)- group, a (C₁-C₈)alkyl-(C=O)- group, a (C₁-C₈)alkyl-(C=O)-(C₁-C₈)alkyl- group, a HSO₃(C₁-C₈)alkyl- group, a H₂N-(C=O)- group and a H₂N-(C=O)-(C₁-C₈)alkyl- group,

where (R₁ and R₂) and/or (R₃ and R₄), independently, optionally form an aromatic or partially or totally hydrogenated C₄ to C₁₄ monocycle, optionally comprising within the cyclic system one, two or three heteroatoms, identical or different, selected from the group consisting of oxygen, nitrogen and sulphur,

provided that at most two of the radicals selected from the group consisting of R₁, R₂, R₃ and R₄ simultaneously represent a hydrogen atom and that (R₁ and R₂) or (R₃ and R₄) do not simultaneously represent a hydrogen atom,

or their salts with pharmaceutically acceptable acids,

for the manufacture of a pharmaceutical composition for the treatment of pathologies related to amyloidopathies, tauopathies and synucleopathies.

2. Use according to claim 1, characterized in that n is ranging from 2 to 8.
3. Use according to claim 1 or 2, characterized in that n and m are identical.
4. Use according to claim 3, characterized in that n and m are equal to 2, 3 or 4.
5. Use according to any one of claims 1 to 4, characterized in that the pathology related to amyloidopathies, tauopathies and synucleopathies is Alzheimer's disease, Down Syndrome, amyloid angiopathies, dementia with Lewy bodies or Parkinson's disease.
6. Use according to any one of claims 1 to 5, characterized in that the pathology related to amyloidopathies, tauopathies and synucleopathies is Alzheimer's disease.
7. Use according to any one of claims 1 to 6, characterized in that the compound of formula (I) is such that R_1 and R_3 are hydrogen atoms and R_2 and R_4 are identical and different from a hydrogen atom.
8. Use according to claim 7, characterized in that R_2 and R_4 are selected from the group consisting of
 - a chloroquinoliny group,
 - a pyridinylmethyl group,
 - a benzyl group optionally substituted once or twice on the phenyl group by a group selected from the group consisting of an atom of halogen and a methoxy group,
 - a quinolinylmethyl group, and,
 - a (C₁-C₇)alkyl group.

9. Use according to any one of claims 1 to 6, characterized in that the compound of formula (I) is such that R_1 and R_3 are hydrogen atoms and R_2 and R_4 are different and do not represent a hydrogen atom.

10. Use according to claim 9, characterized in that R_2 is a heteroaryl group and the R_4 group is a (C₁-C₇)alkyl group.

11. Use according to any one of claims 1 to 6, characterized in that the compound of formula (I) is such that R_1 is a hydrogen atom, R_2 is different from a hydrogen atom and R_3 and R_4 are identical and different from a hydrogen atom.

12. Use according to claim 11, characterized in that R_3 and R_4 represent a (C₁-C₇)alkyl group or R_3 and R_4 form with the nitrogen atom a saturated or unsaturated heterocycle, and R_2 represents a group selected from the group consisting of:

- a benzimidazol group,
- a pyrimidin group,
- a pyrazinyl group,
- a purin group,
- a quinolinyl group,
- a chloroquinolinyl group,
- an acridin group,
- a benzyl group optionally substituted one or several times on the phenyl group by a group selected from the group consisting of an atom of halogen and a methoxy group,
- a pyridinylmethyl group and,

- a thiazolylmethyl group.

13. Use according to claim 11, characterized in that R_3 and R_4 represent an isobutyl group or a cyclopropylmethyl group, and R_2 represents a group selected from the group consisting of:

- a benzimidazol group,
- a pyrimidin group,
- a pyrazinyl group,
- a purin group,
- a quinolinyl group,
- a chloroquinolinyl group,
- an acridin group,

- a benzyl group optionally substituted one or several times on the phenyl group by a group selected from the group consisting of an atom of halogen and a methoxy group,

- a pyridinylmethyl group and,
- a thiazolylmethyl group.

14. Use according to any one of claims 1 to 6, characterized in that the compound of formula (I) is such that R_1 is a hydrogen atom and R_2 , R_3 and R_4 are different and do not represent a hydrogen atom.

15. Use according to any one of claims 1 to 6, characterized in that the compound of formula (I) is such that R_1 , R_2 , R_3 and R_4 are identical.

16. Use according to any one of claims 1 to 6 characterized in that said compound is selected from the group consisting of:

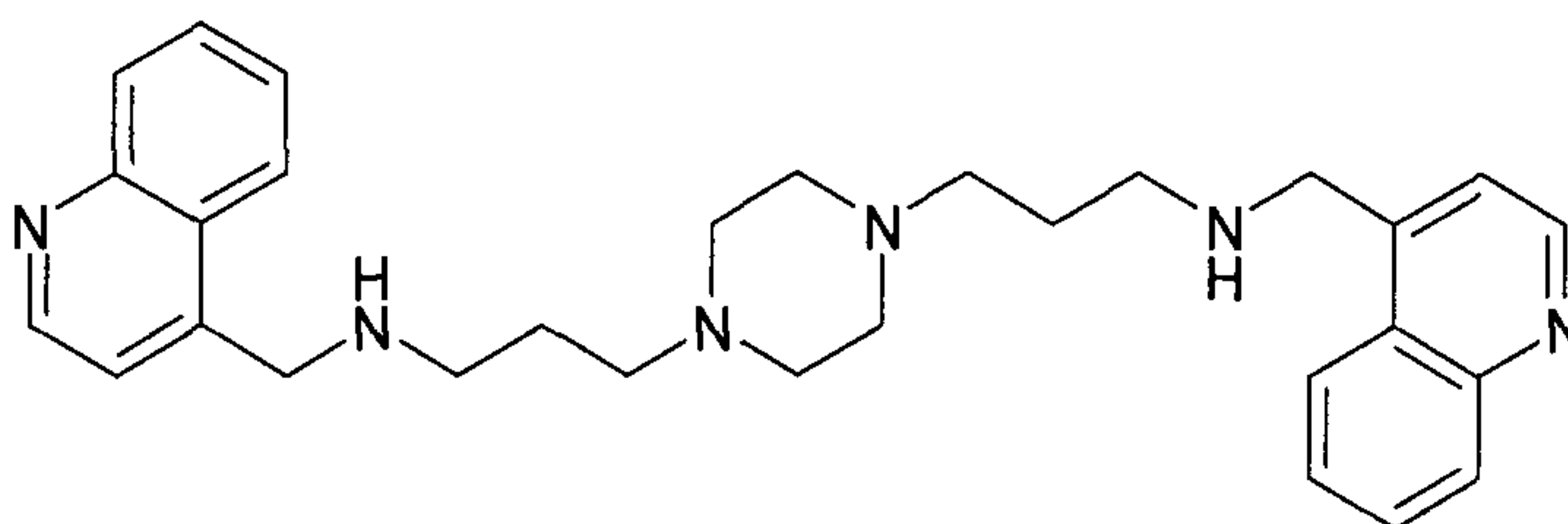
- 1,4-bis{3-[N-(7-chloroquinolin-4-yl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(pyrid-3-ylmethyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(3,4-dimethoxybenzyl)amino]propyl}piperazine,
- 1,4-bis{3-[4-chlorobenzyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(quinol-4-ylmethyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(4-methoxybenzyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(cyclopropylmethyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(isobutyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(2-ethylbutyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(n-heptyl)amino]propyl}piperazine,
- 1,4-bis{3-[N-(4-fluorobenzyl)amino]propyl}piperazine,
- N⁴-[3-(4-{3-[(cyclopropylmethyl)amino]propyl}piperazino)propyl]-7-chloroquinolin-4-amine,
- N⁴-[3-(4-{3-(isobutylamino)propyl}piperazino)propyl]-7-chloroquinolin-4-amine,
- N⁴-[3-(4-{3-(*tert*-pentylamino)propyl}piperazino)propyl]-7-chloroquinolin-4-amine,
- N⁴-[3-(4-{3-(cyclohexylmethylamino)propyl}piperazino)propyl]-7-chloroquinolin-4-amine,

- N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-benzimidazol-2-amine,
- N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-pyrimidin-2-amine,
- N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-pyrazin-2-amine,
- N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-purine-6-amine,
- N⁴-(3-{4-[3-(diisobutylamino)propyl]piperizano}propyl)-7-chloroquinolin-4-amine,
- N⁴-(3-(4-{3-[di(cyclopropylmethyl)amino]propyl}piperizano)propyl)-7-chloroquinolin-4-amine,
- N⁴-(3-(4-{3-[di(cyclopropylmethyl)amino]propyl}piperizano)propyl)-6-chloro-2-methoxyacridin-9-amine,
- N⁴-(3-(4-{3-[diisobutylamino]propyl}piperizano)propyl)-4-benzyloxyamine,
- N⁴-(3-(4-{3-[diisobutylamino]propyl}piperizano)propyl)-4-pyridinylmethylamine,
- N⁴-(3-(4-{3-[diisobutylamino]propyl}piperizano)propyl)-4-fluorobenzylamine,
- N⁴-(3-(4-{3-diisobutylamino]propyl}piperizano)propyl)-4-chlorobenzylamine,
- N⁴-(3-(4-{3-[diisobutylamino]propyl}piperizano)propyl)-2-thiazolylmethylamine,
- N¹-(3-(4-3-[(7-chloro-4-quinolyl)amino]propylpiperizano)propyl)-N1-cyclopropyl-methylcyclopropane-1-carboxamide,

- *Tert*-butyl-*N*-3-[[3-(4-3-[(7-chloro-4-quinolyl)amino]propylpiperazino)propyl](cyclopropylmethyl)amino]-3-oxopropylcarbamate,
- 5-[[3-(4-[3-(7-chloro-4-quinolyl)amino]propyl piperazino)propyl](cyclopropylmethyl)amino}pentanenitrile,
- *Tert*-butyl-*N*-3-[[3-(4-[3-(7-chloro-4-quinolyl)amino]propyl piperazino)propyl](cyclopropylmethyl)amino}propylcarbamate,
- 1,4-bis(3-[diisobutylamino]propyl)piperazine,
- 1,4-bis(3-[dicyclopropylmethylamino]propyl)piperazine,
- 1,4-bis{2-[4-chlorobenzyl)amino]ethyl}piperazine,
- 1,4-bis{2-[4-fluorobenzyl)amino]ethyl}piperazine,
- 1,4-bis{4-[4-chlorobenzyl)amino]butyl}piperazine,
- 1,4-bis{4-[4-fluorobenzyl)amino]butyl}piperazine,
- *N*-(7-chloro-quinolin-4-yl)-*N*-3-[4-(3-pyrrolidin-1-yl-propyl)piperazin-1-yl]propylamine,
- *N*-(7-chloro-quinolin-4-yl)-*N*-3-[4-(3-piperidin-1-yl-propyl)piperazin-1-yl]propylamine,
- *N*-3-[4-(3-azepan-1-ylpropyl)piperazin-1-yl]propyl-*N*-(7-chloro-4-quinolyl)-amine,
- {3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-(6-methyl-1*H*-benzimidazol-2-yl)-amine,

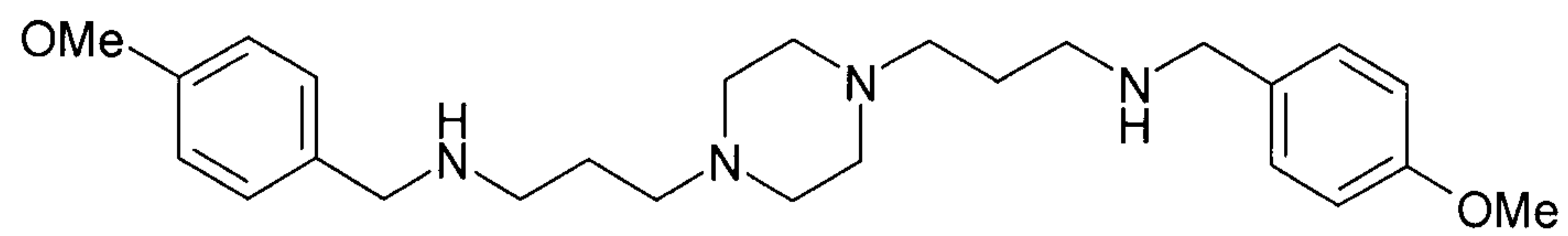
- {3-[4-(3-Diisobutylamino-propyl)-piperazin-1-yl]-propyl}-(6-methoxy-1*H*-benzimidazol-2-yl)-amine,
- (1*H*-Benzimidazol-2-yl)-{3-[4-(3-pyrrolidin-1-yl-propyl)-piperazin-1-yl]-propyl}-amine,
- (1*H*-Benzimidazol-2-yl)-{3-[4-(3-isobutylamino-propyl)-piperazin-1-yl]-propyl}-amine,
- 1,4-bis{3-[*N*-(1*H*-Benzimidazol-2-yl)amino]propyl}piperazine,
- 1,4-bis{3-[*N*-(anthr-9-ylmethyl)amino]propyl}piperazine,
- 1,4-bis{3-[*N*-(Benzyl)amino]propyl}piperazine,
- 1,4-bis{3-[*N*-(4-nitrobenzyl)amino]propyl}piperazine,
- 1,4-bis{3-[*N*-(napht-2-ylmethyl)amino]propyl}piperazine,
- 1,4-bis{3-[*N*-(4-phenylbenzyl)amino]propyl}piperazine,
- 1,4-bis{3-[*N*-(3,4-dibenzyloxybenzyl)amino]propyl}piperazine,
- 1,4-bis{3-[*N*-(fluoren-2-ylmethyl)amino]propyl}piperazine,
- 1,4-bis{3-[*N*-(benzofur-2-ylmethyl)amino]propyl}piperazine and
- 1,4-bis{3-[*N*-(quinol-2-ylmethyl)amino]propyl}piperazine.

17. Compound selected from the group consisting of

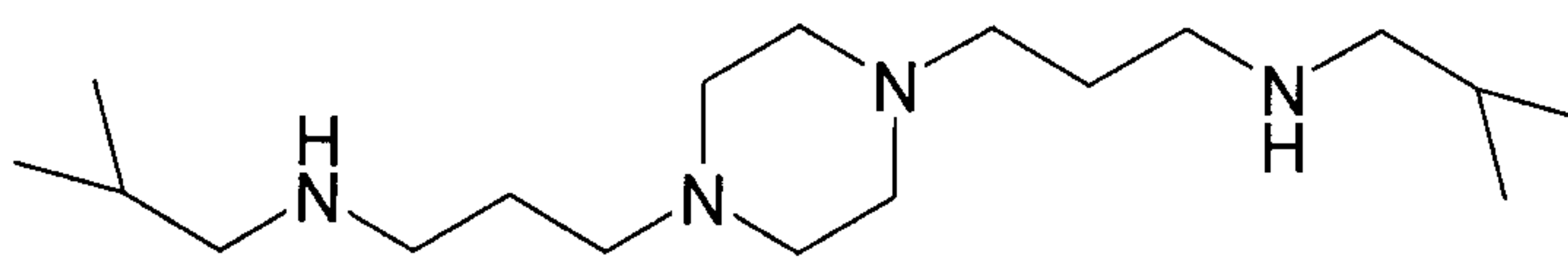


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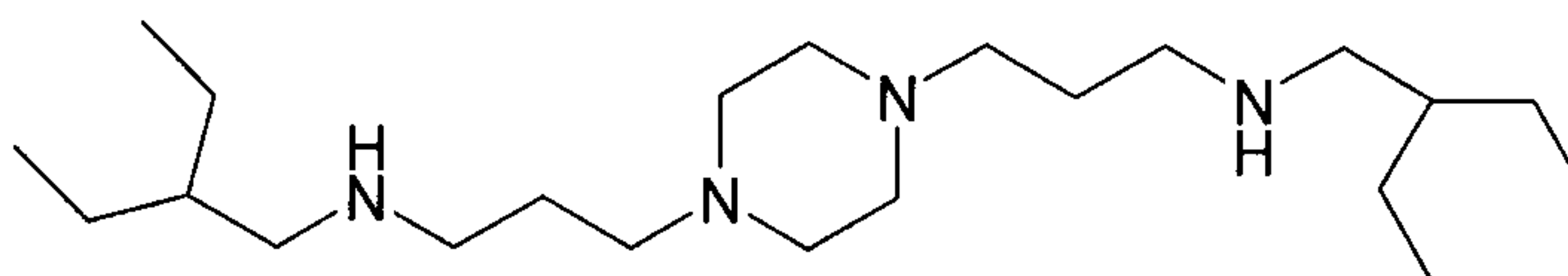
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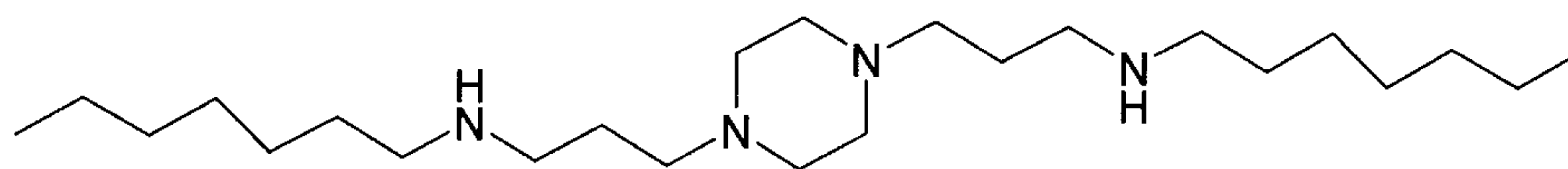
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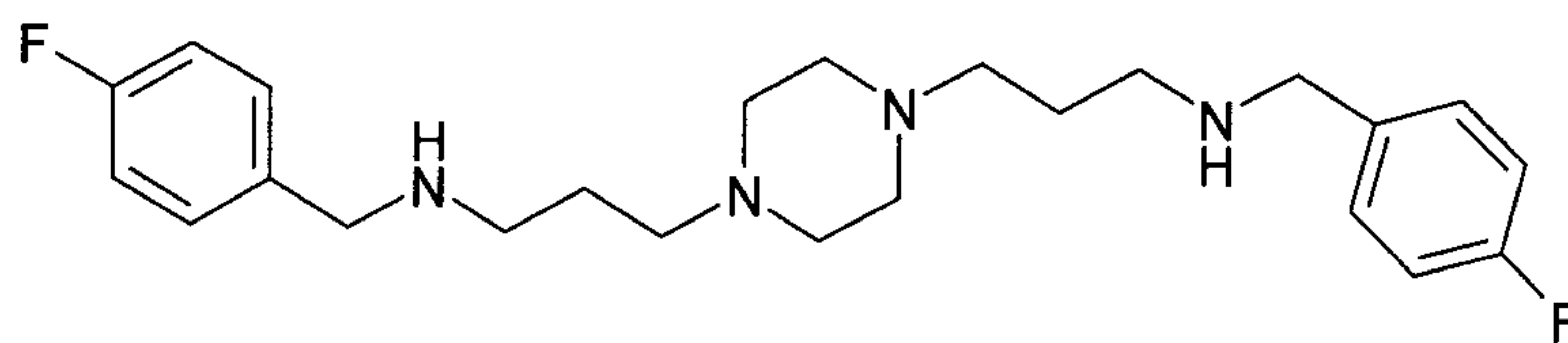
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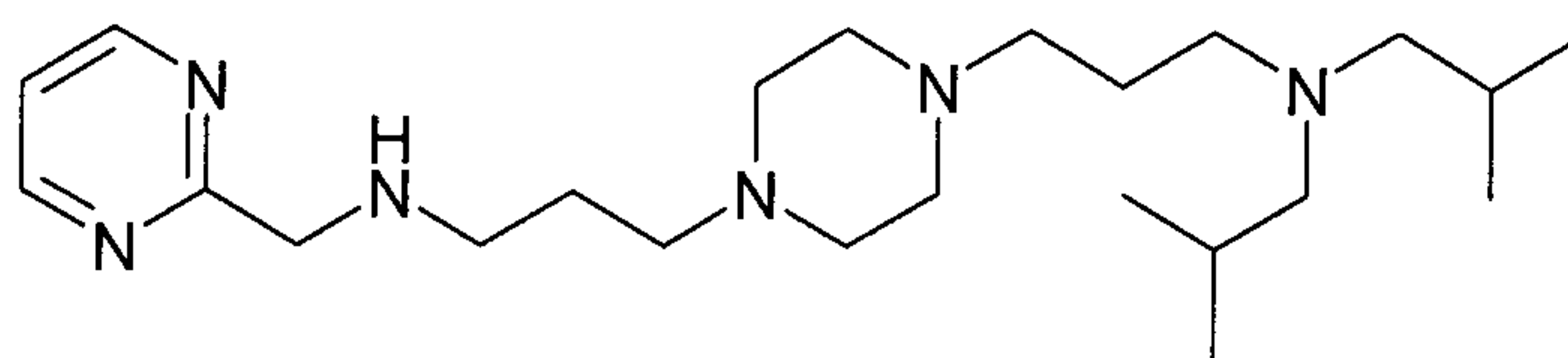


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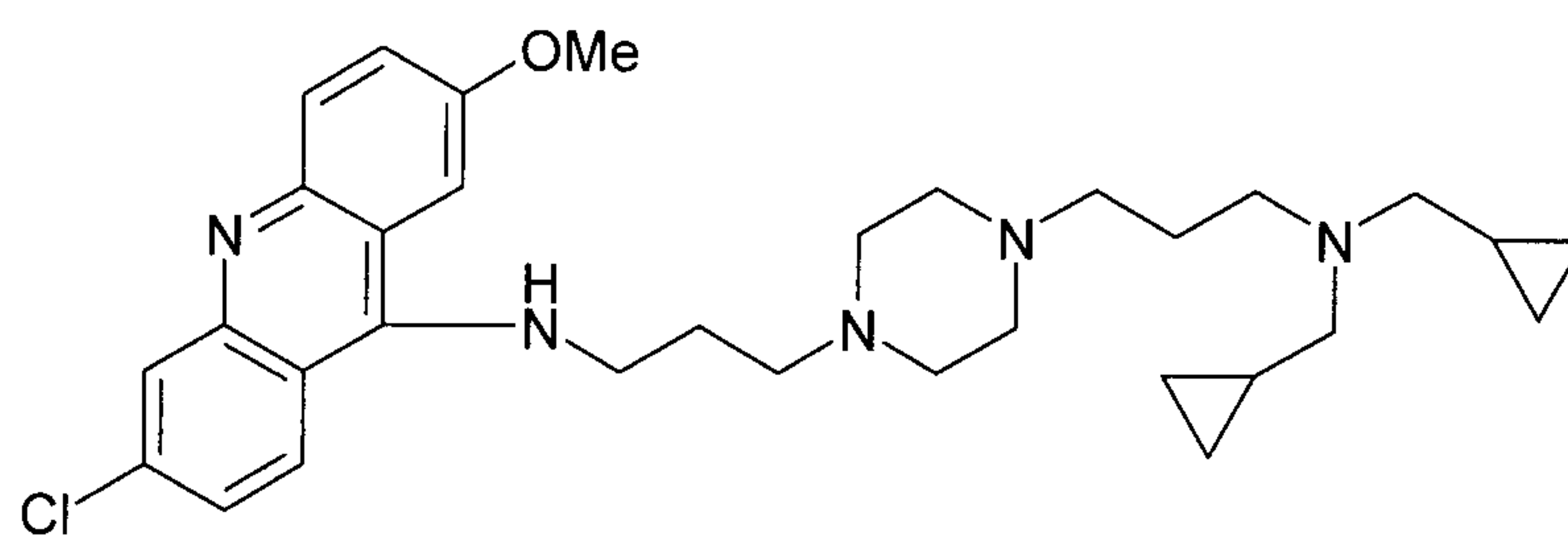


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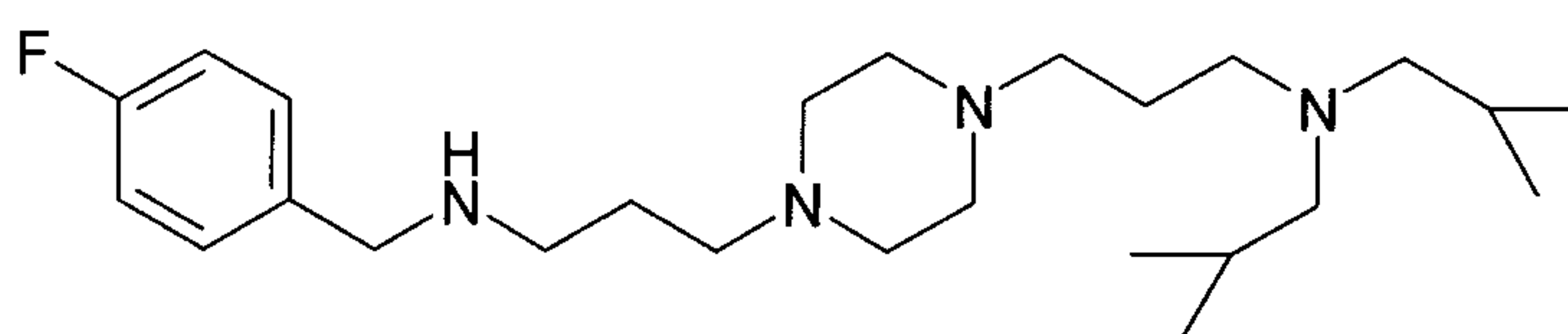
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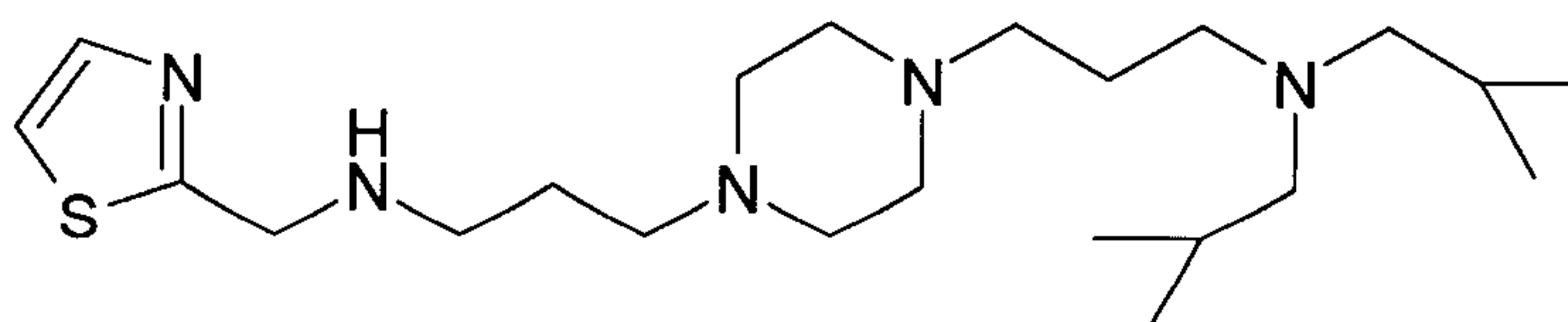
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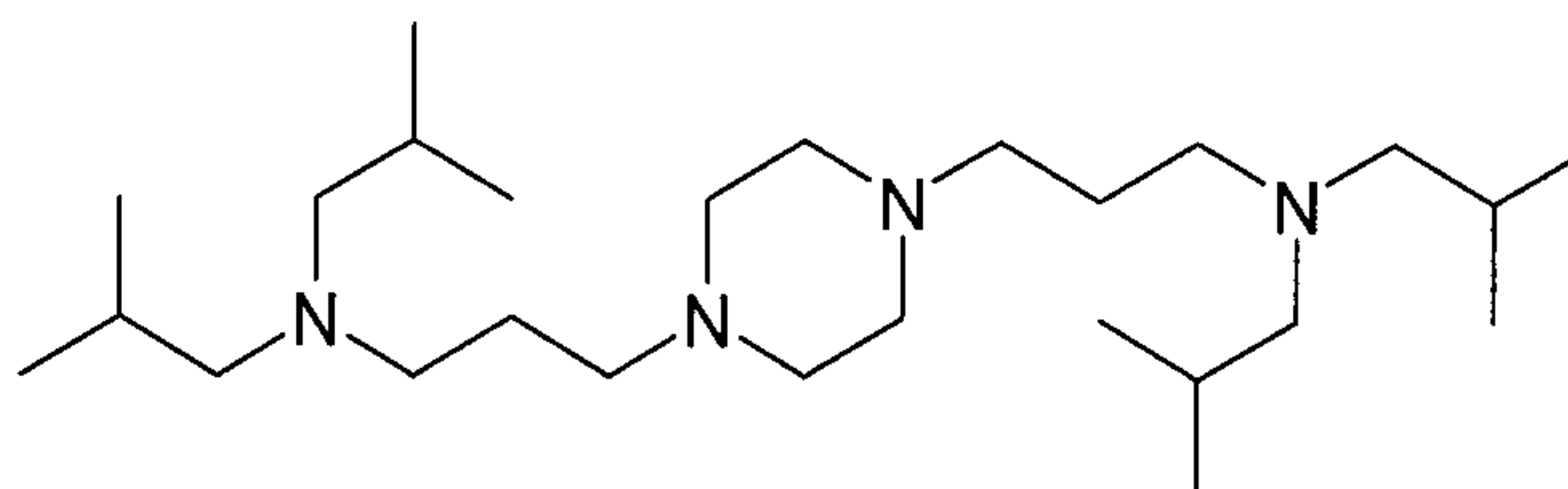
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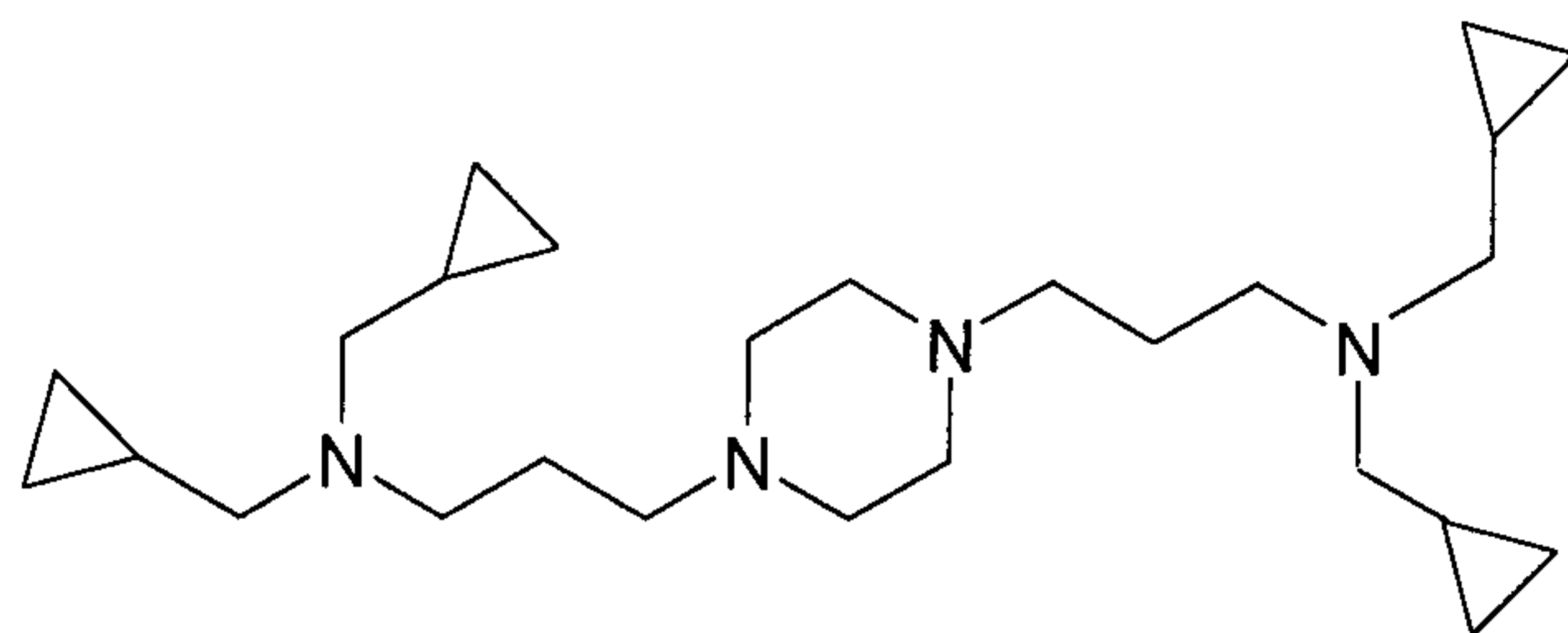


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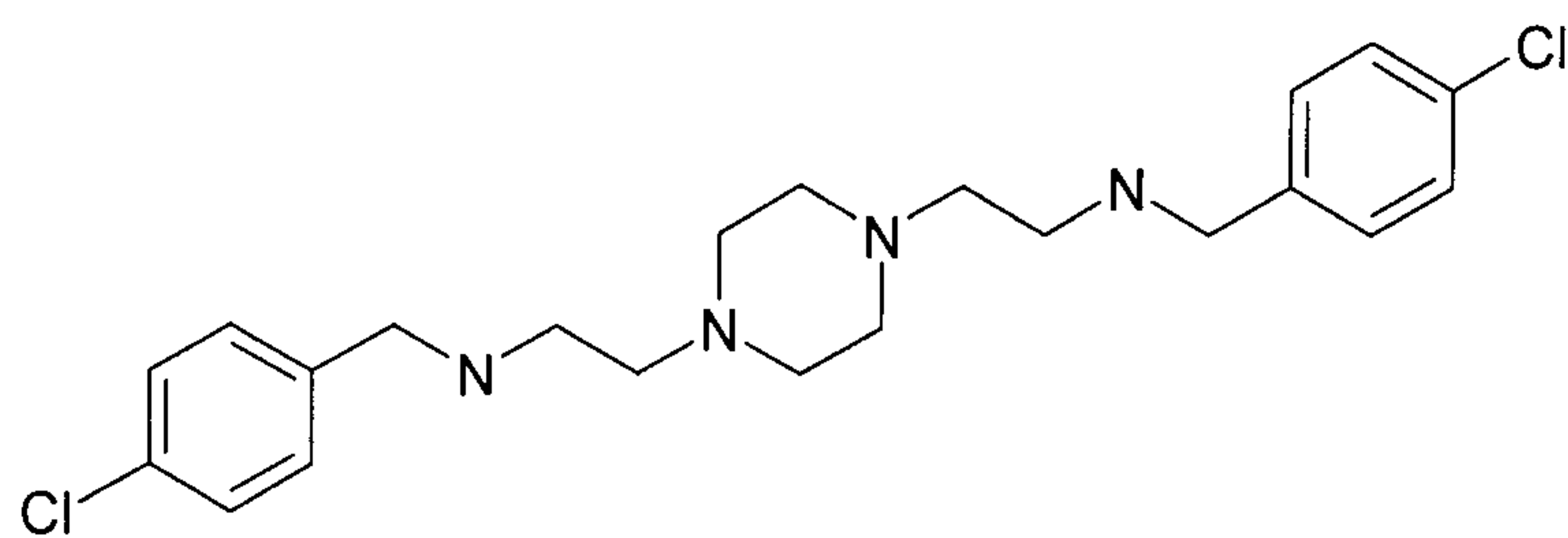


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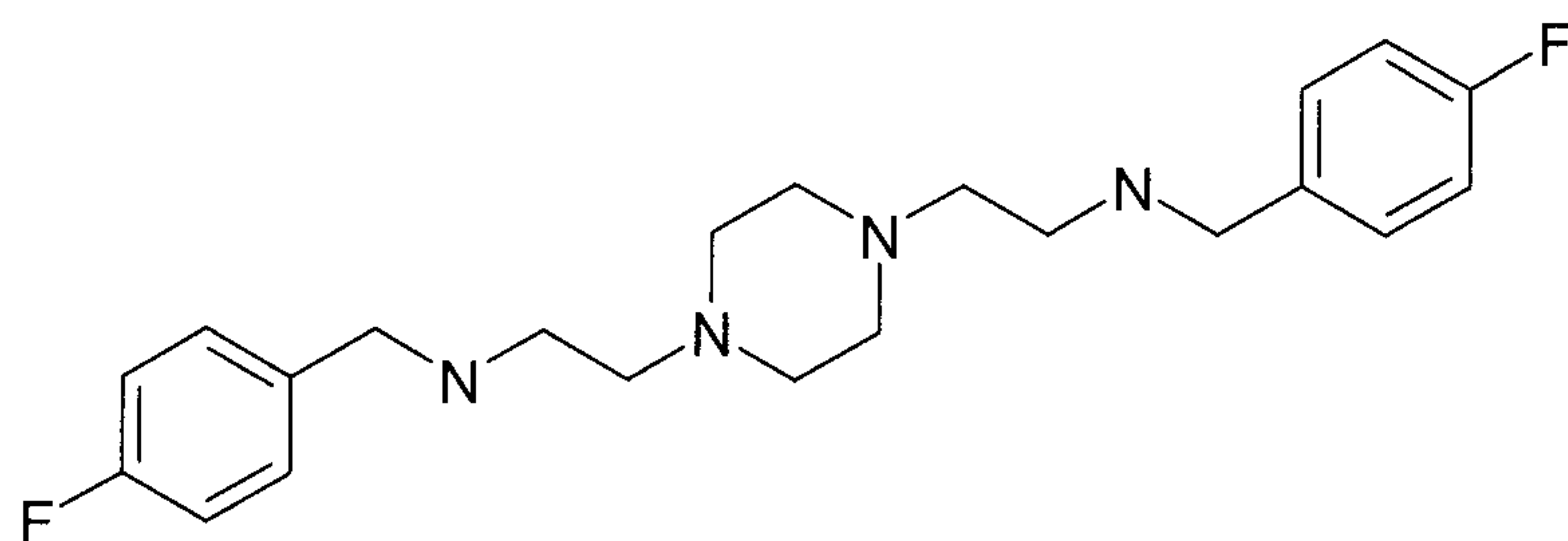
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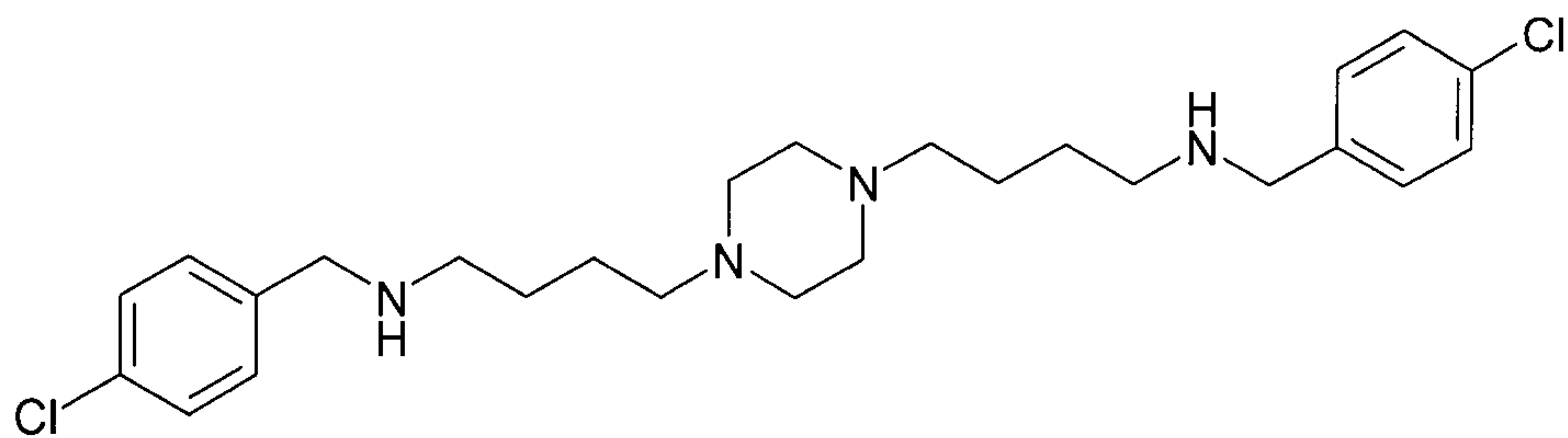
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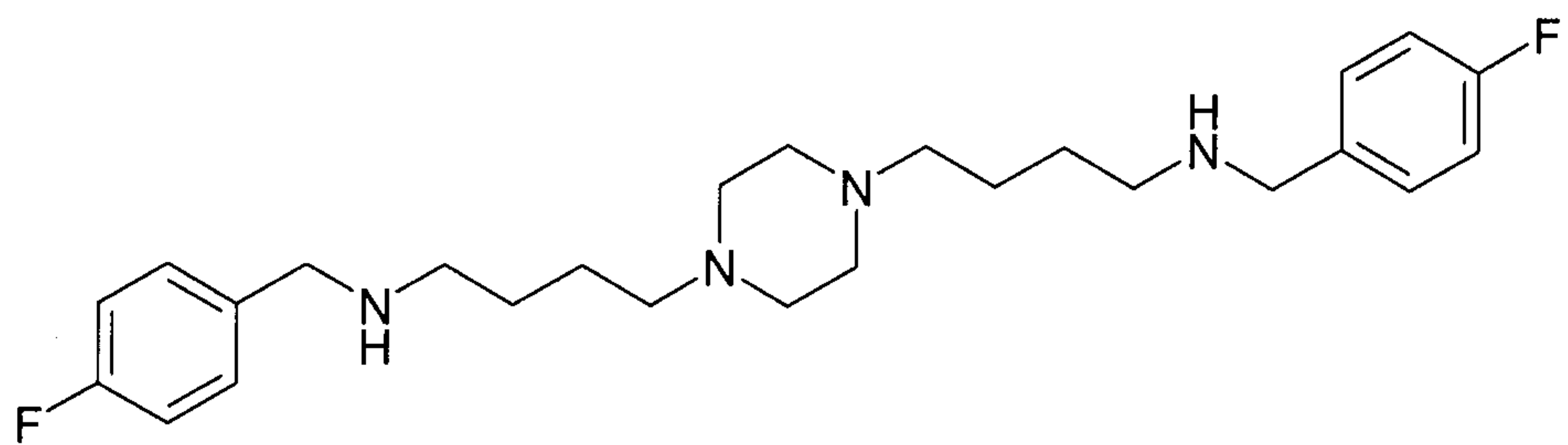


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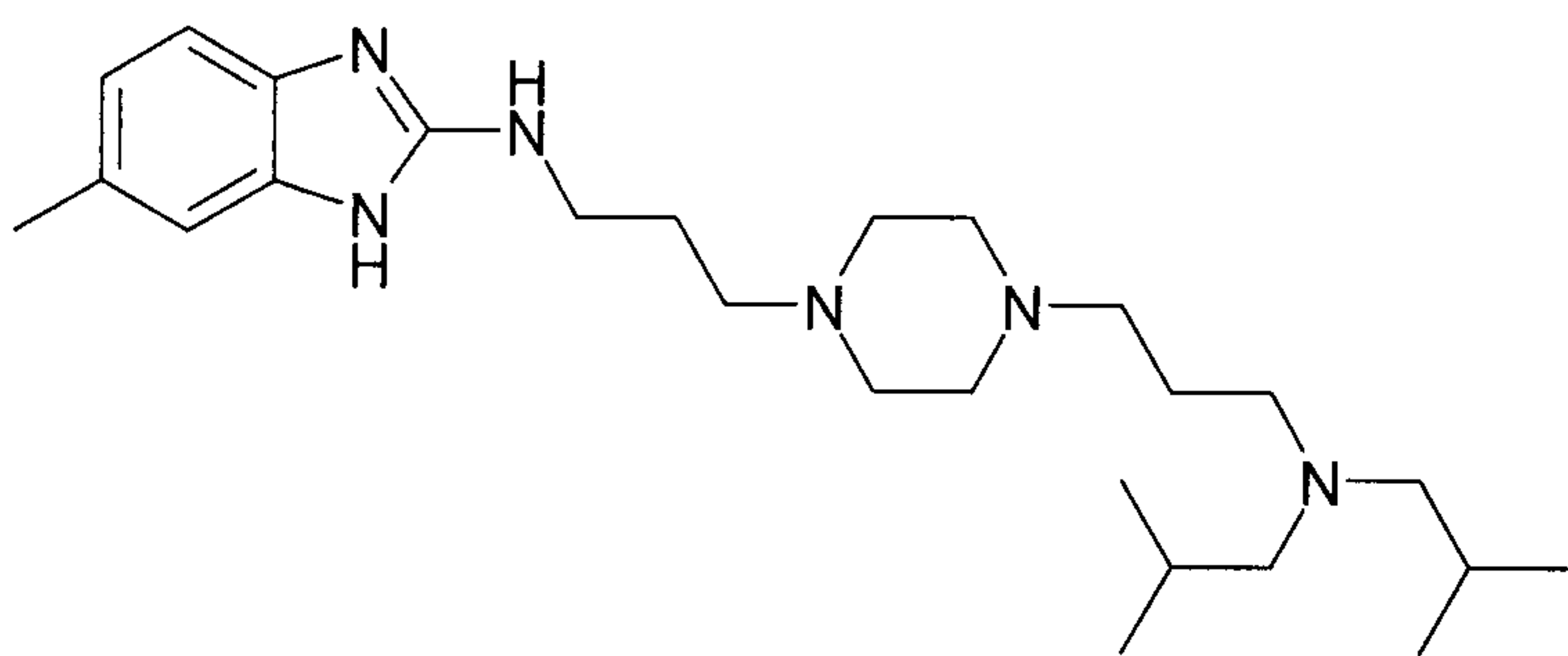


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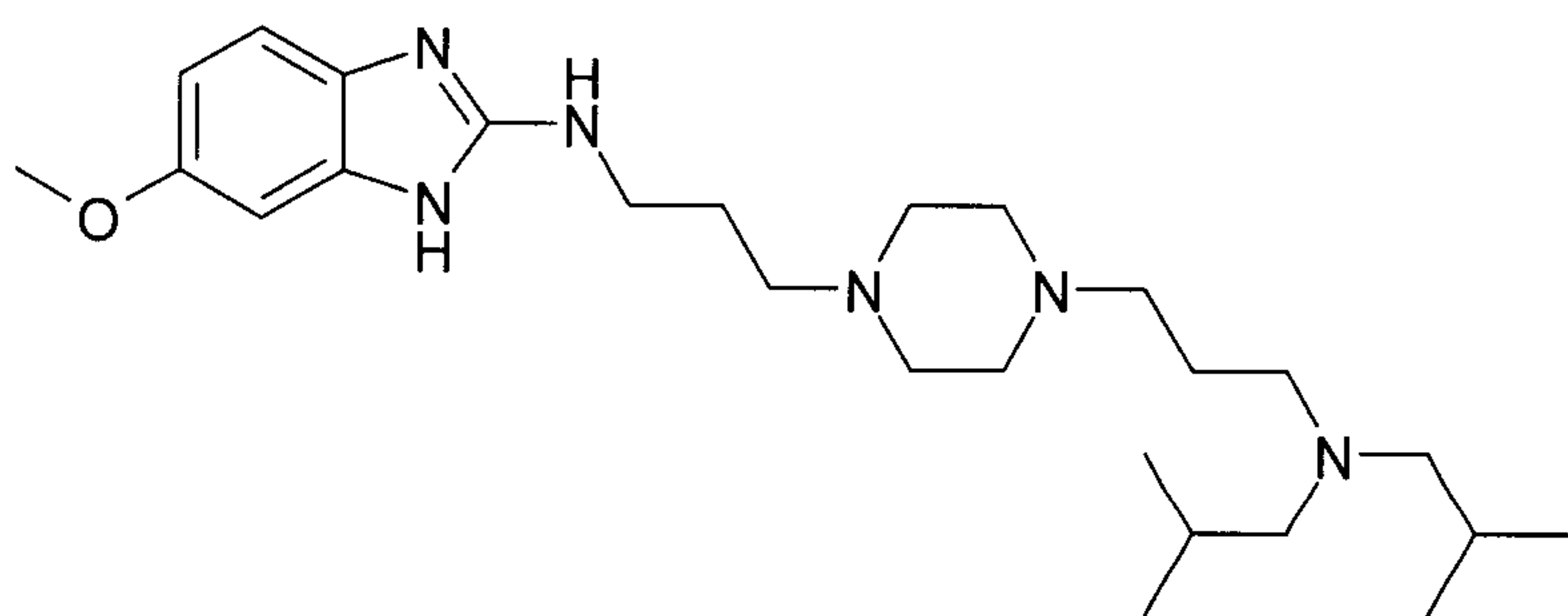
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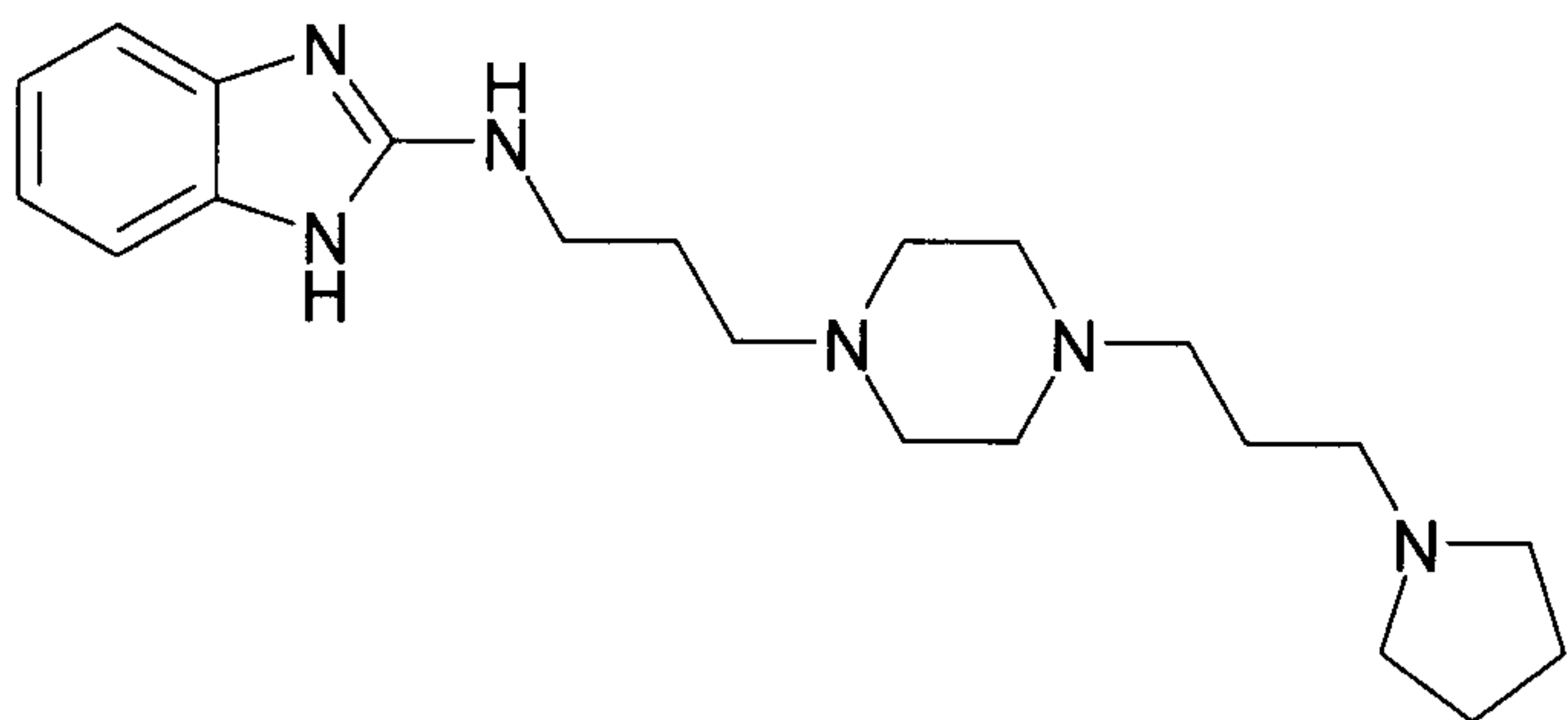
(16) ,



(17) ,

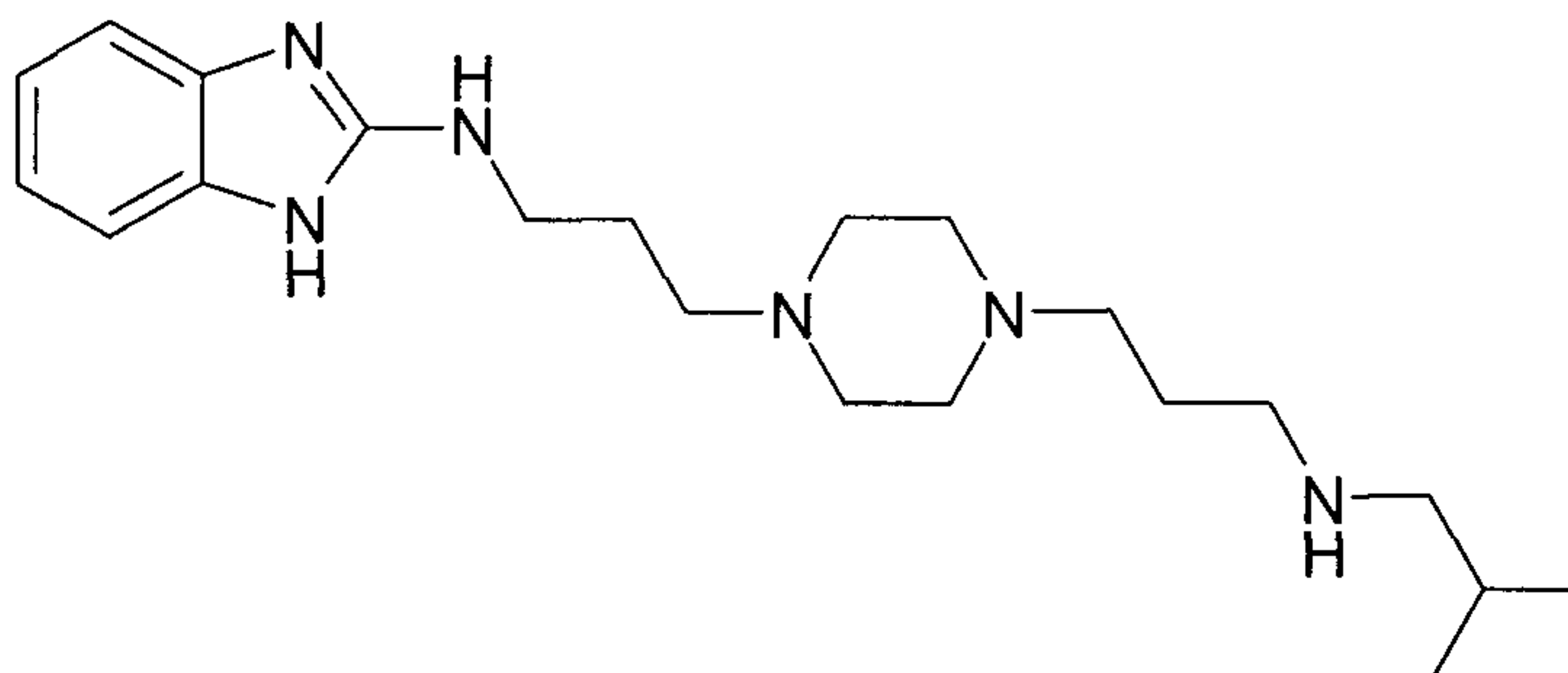


(18) ,

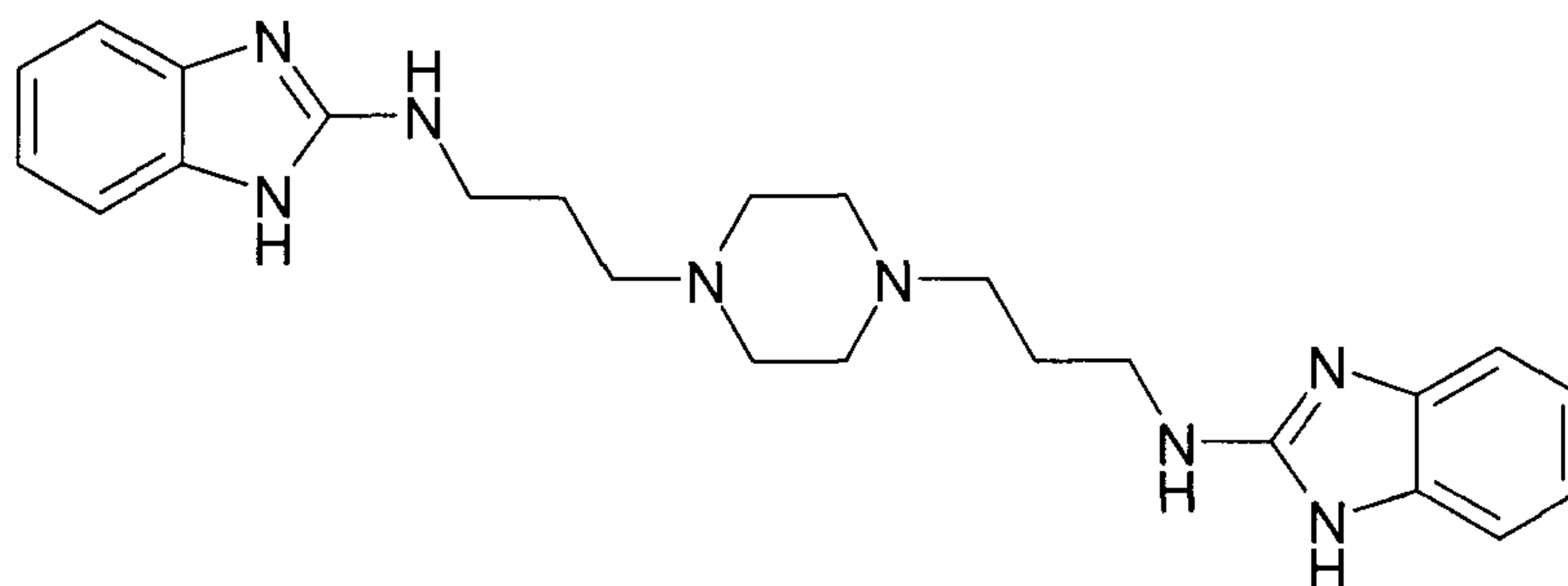


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(19) ,



(20) ,

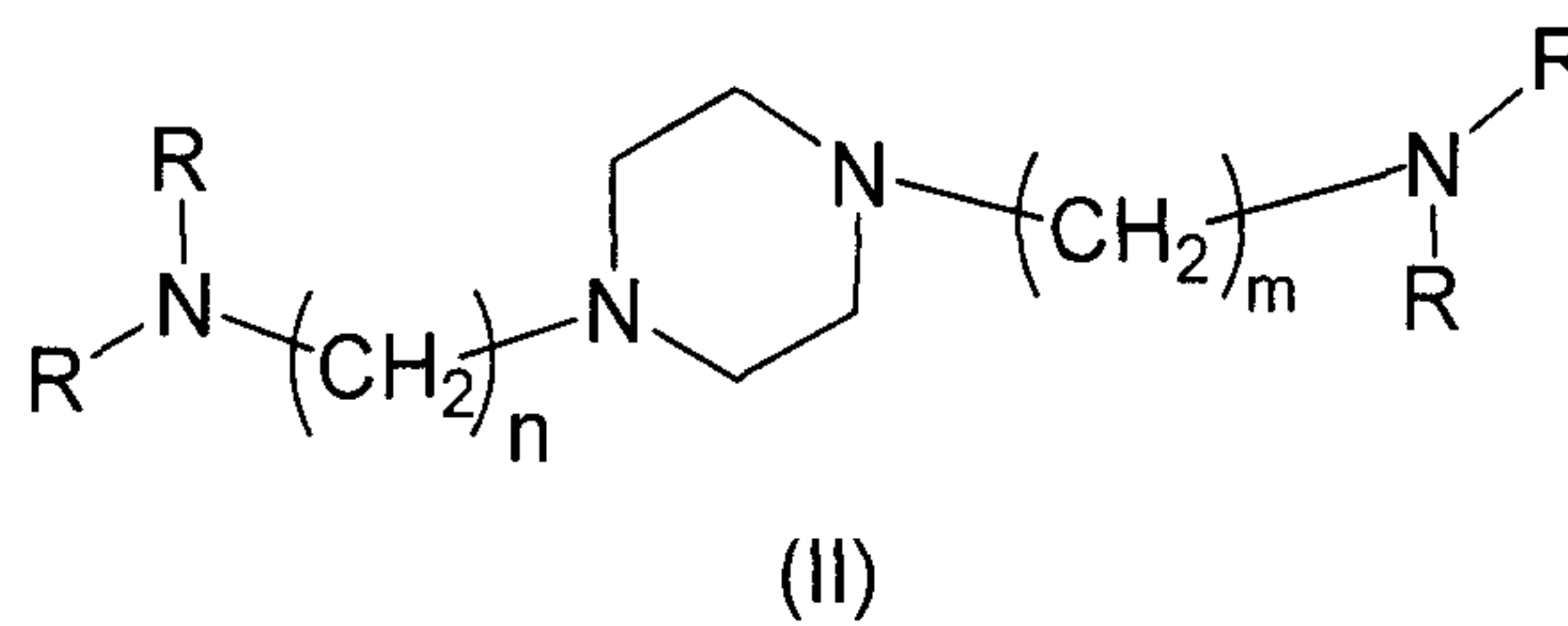


(21)

and their salts with pharmaceutically acceptable acids.

18. Compound according to claim 17 for use for the treatment of pathologies related to amyloidopathies, tauopathies and synucleopathies.

19. Compound of general formula (II)



in which n and m are identical or different and independently represent an integer of greater than or equal to 2, the resulting hydrocarbon chain optionally comprising one or more heteroatoms selected among oxygen, nitrogen and sulphur, and,

in which R is selected from the group consisting of:

- a (C₃-C₈)alkyl group, straight or branched, saturated or unsaturated,
- an aralkyl group,
- an aryl group and,
- a heteroaryl group,

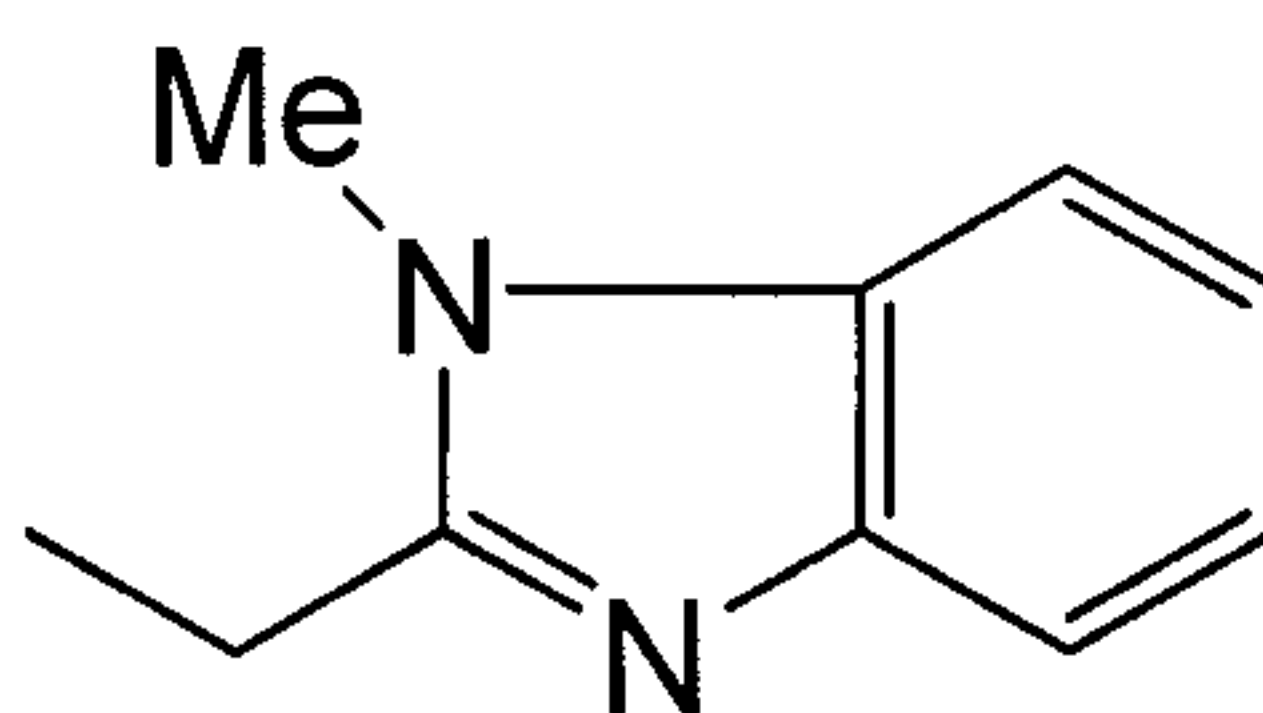
where the group (C₃-C₈)alkyl is optionally substituted by one or more identical or different groups selected from the group consisting of a halogen, the cyano group, the hydroxy group, the nitro group, the amino group, a group (C₁-C₇)alkylamino, a group (C₁-C₇)alkoxy, a tertbutoxycarbonylamino group, a HO-(C₁-C₈)alkyl- group, a H₂N-(C₁-C₈)alkyl- group, a HO-(C=O)- group, a (C₁-C₈)alkyl-O-(C=O)- group, a (C₁-C₈)alkyl-(C=O)- group, a (C₁-C₈)alkyl-(C=O)-(C₁-C₈)alkyl- group, a HSO₃(C₁-C₈)alkyl- group, a H₂N-(C=O)- group and a H₂N-(C=O)-(C₁-C₈)alkyl- group,

where the aryl group is selected from the group consisting of benzyl, phenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl and indanyl,

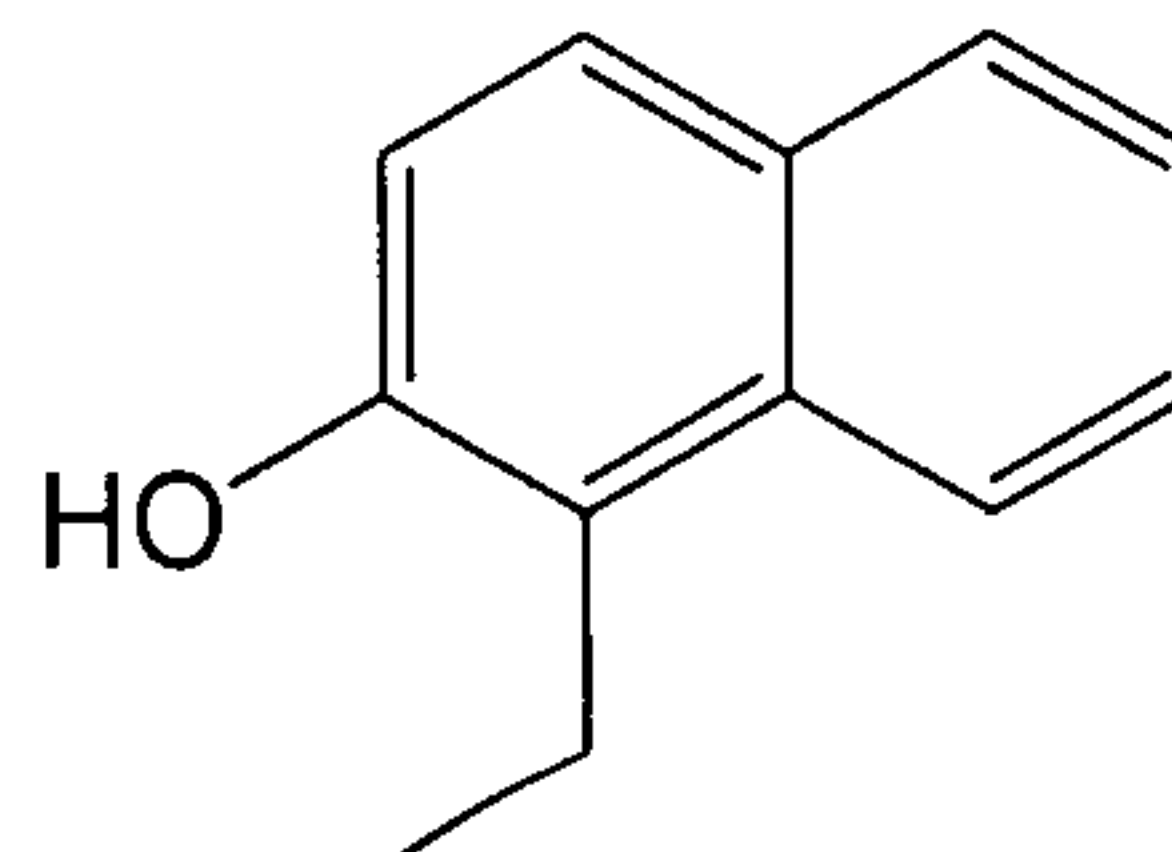
where the heteroaryl group is an aromatic monocycle, an aromatic bicycle, or a bicycle of which one of the cycles is aromatic and the other cycle is partially hydrogenated, having from 5 to 12 links, comprising within the cyclic system one, two or three heteroatoms, identical or different, selected among oxygen, nitrogen and sulphur and,

where each one of these groups aryl or heteroaryl comprises optionally one or more substitutions, identical or different, selected from the group consisting of a halogen, the hydroxy group, a (C₁-C₇)alkyl group, a (C₁-C₇)alkoxy group, the cyano group, the nitro group, the amino group and a (C₁-C₇)alkylamino group, a HO-(C₁-C₈)alkyl- group, a H₂N-(C₁-C₈)alkyl- group, a HO-(C=O)- group, a (C₁-C₈)alkyl-O-(C=O)- group, a (C₁-C₈)alkyl-(C=O)- group, a (C₁-C₈)alkyl-(C=O)-(C₁-C₈)alkyl- group, a HSO₃(C₁-C₈)alkyl- group, a H₂N-(C=O)- group and a H₂N-(C=O)-(C₁-C₈)alkyl-group,

provided that compounds for which R represents a n-hexyl group or R represents a



group are excluded,



provided that compound for which R is

and n=2

and dichloride salt of compound for which R is phenyl and n=3 are excluded, and provided that the compound wherein n and m are equal to 2 and R is a -CH₂-CH=CH₂ group is excluded,

and their salts with pharmaceutically acceptable acids.

20. Compound according to claim 19 for use for the treatment of pathologies related to amyloidopathies, tauopathies and synucleopathies.

21. Pharmaceutical composition comprising in association with a pharmaceutically acceptable carrier a compound of formula (II) as defined in claim 19, any one of compounds (1) to (21) defined in claim 17, a salt thereof with a pharmaceutically acceptable acid or a mixture thereof.

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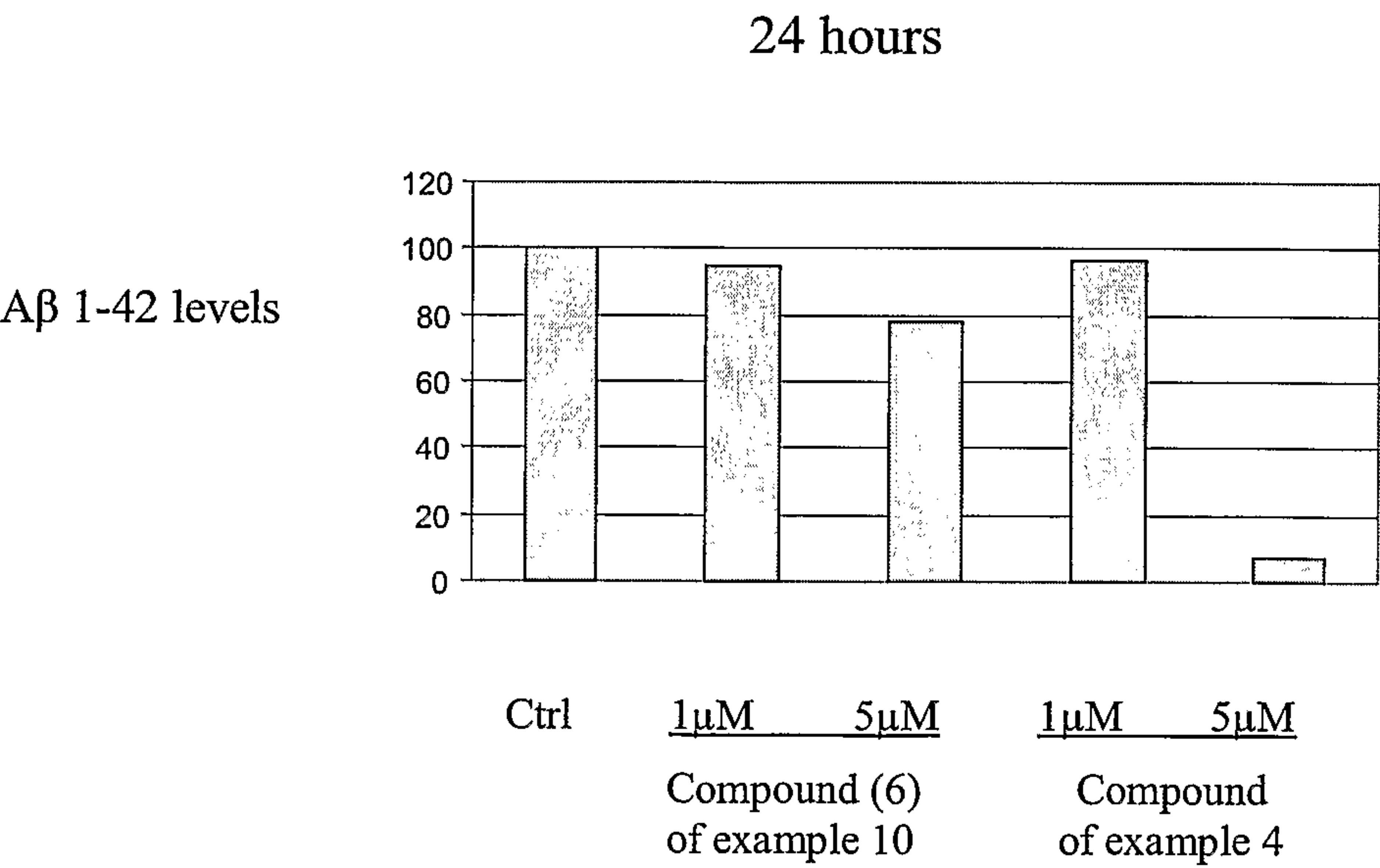
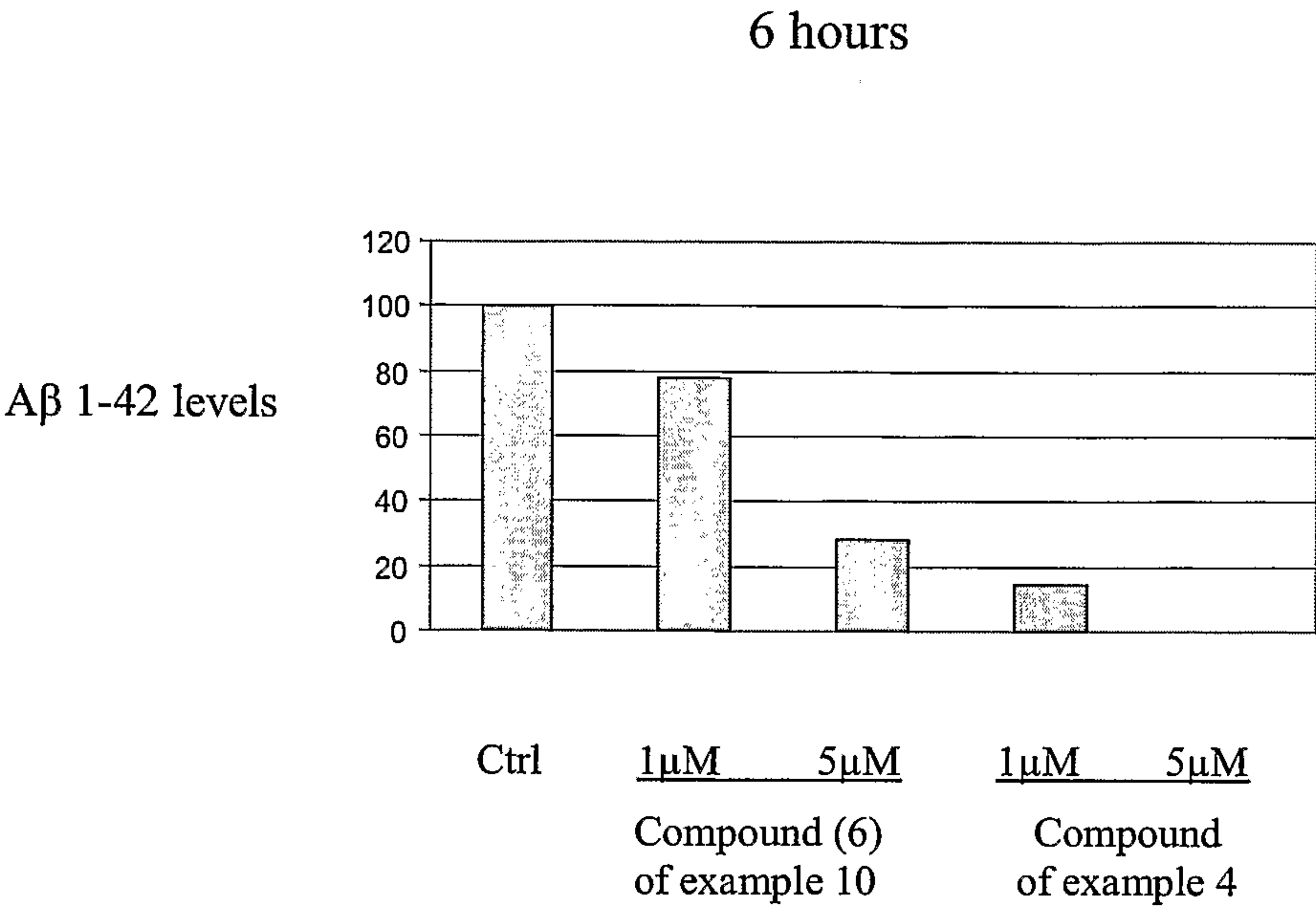


Figure 1