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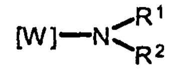
(54) Title: NON-IMIDAZOLE ALKYLAMINES AS HISTAMINE H_3-RECEPTOR LIGANDS AND THEIR THERAPEUTIC APPLICATIONS

(57) Abstract



$$[W]-N{<}^{R^1}_{R^2}$$

(A)

Use of a compound of formula (A), wherein: W is a residue which imparts antagonistic and/or agonistic activity at histamine H_3-receptors when attached to an imidazole ring in 4(5) position; R^1 and R^2 may be identical or different and represent each independently a lower alkyl or cycloalkyl, or taken together with the nitrogen atom to which they are attached, a saturated nitrogen-containing ring (i) as defined, a non-aromatic unsaturated nitrogen-containing ring (ii) as defined, a morpholino group, or a N-substituted piperazino group as defined for preparing medicaments acting as antagonists and/or agonists at the H_3-receptors of histamine.

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NON-IMIDAZOLE ALKYLAMINES AS HISTAMINE H_3-RECEPTOR LIGANDs AND THEIR THERAPEUTIC APPLICATIONS.

The present invention relates to alkylamines of formula (A) as defined hereafter, to their preparation and to their therapeutic applications.

Antagonists of histamine H_3-receptor are known especially to increase synthesis and release of cerebral histamine. Through this mechanism, they induce an extended wakefullness, an improvement in cognitive processes, a reduction in food intake and a normalization of vestibular reflexes (Schwartz et al., Physiol. Rev., 1991, 71: 1-51).

Whence these agents are potentially useful in several central nervous system disorders such as Alzheimer disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, obesity, vertigo and motion sickness.

Histamine H_3-receptor agonists are known to inhibit the release of several neurotransmitters including histamine, monoamines and neuropeptides and thereby exert sedative and sleep-promoting effects in brain. In peripheral tissues, H_3-receptor agonists exert namely anti-inflammatory, anti-nociceptive, gastro-intestinal, antisecretory smooth muscle decontracting activities.

All the H_3 receptor antagonist or agonist compounds known so far resemble histamine in possessing an imidazole ring generally monosubstituted in 4(5)-position (Ganellin et al., Ars Pharmaceutica, 1995, 36:3, 455-468; Stark et al., Drug of the Future, 1996, 21(5), 507-520).

Numerous patents and patent applications are directed to antagonist and/or agonist compounds having such structure, in particular EP 197 840, EP 494 010, WO 93/14070, WO 96/29315, WO 92/15 567, WO 93/20061, WO 93/20062, WO 95/11894, US 5 486 526, WO 93/12107, WO 93/12108, WO 95/14007, WO 95/06037, WO 97/29092, EP 680 960, WO 96/38141, WO 96/38142, WO 96/40126.

In the litterature, Plazzi et al., Eur. J. Med. Chem. 1995, 30, 881, Clitherow et al., Bioorg. & Med. Chem. Lett. 6 (7), 833-838 (1996) Wolin et al., Bioorg. & Med. Chem. Lett; 8, 2157 (1998) can be cited also in this respect.

Nevertheless, such imidazole derivatives may show drawbacks such as poor blood-brain barrier penetration, interaction with cytochrome P-450 proteins and/or some hepatic and ocular toxicities.

Non-imidazole known neuro-active compounds such as betahistine (J-M. Arrang et al., Eur. J. Pharmacol. 1985, 111: 72-84), phencyclidine (J-M. Arrang et al., Eur. J. Pharmacol. 1988, 157: 31-35), dimaprit (J-C Schwartz et al., Agents Actions 1990, 30: 13-23), clozapine (M. Kathmann et al., Psychopharmacology 1994, 116: 464-468), and sesquiterpenes (M. Takigawa et al., JP 06 345 642 (20 Dec 1994)) were suggested to display H_3-receptor antagonism but all these compounds have only very low potency.

These compounds were previously known as therapeutic agent before the discovery and characterization of the histamine H_3-receptor, in particular as neuro-active agents for example as neuroleptic (clozapine) or psychotomimetic (Phencyclidine) agent.

When tested at the H_3-receptor, these compounds were shown to display much lower potency than the imidazole-containing compounds described in patent applications quoted above.

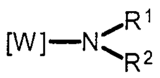
Attempts at replacing the imidazole ring was generally not successful and no potent H_3-receptor ligands not containing such ring was reported in the literature up to now.

These investigations showed the importance of the 4(5)-imidazole moiety.

The objective of the invention is to provide new potent H_3-receptor ligands which may reduce the above-mentioned drawbacks.

The present invention provides new compounds, the structure of which does not contain an imidazole moiety, which are useful as histamine H_3-receptor ligands.

The compounds of the invention have the following general formula (A):



$$[W]-N\begin{matrix} R^1 \\ R^2 \end{matrix}$$

(A)

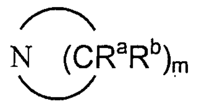
in which:

- W is a residue which imparts antagonistic and/or agonistic activity at histamine H_3-receptors when attached to an imidazole ring in 4(5)-position;
- R^1 and R^2 may be identical or different and represent each independently
    - a lower alkyl or cycloalkyl,

or taken together with the nitrogen atom to which they are attached,

- a saturated nitrogen-containing ring

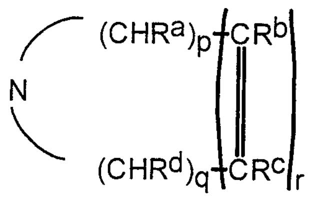
i)



with m ranging from 2 to 8, or

- a non-aromatic unsaturated nitrogen-containing ring

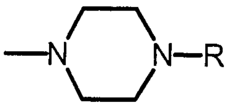
ii)



with p and q being from 0 to 3 independently and r being from 0 to 4, provided that p and q are not simulteously 0 and $2 \leq p + q + r \leq 8$,

R^{a-d} being independently a hydrogen atom or a lower alkyl, cycloalkyl, or carboalkoxy group, or

- a morpholino group, or
- a N-substituted piperazino group:



with R being a lower alkyl, cycloalkyl, carboalkoxy, aryl, arylalkyl, an alkanoyl or aroyl group.

The inventors have found, surprisingly, that antagonist and/or agonist compounds can be obtained by substituting a di(alkyl) or (cycloalkyl)amine, or a non-aromatic nitrogen-containing ring $-NR^1R^2$ as above-defined for the imidazole ring, in known antagonist and/or agonist imidazole derivatives.

It is also believed that antagonist and/or agonist activity can be foreseen, by equivalence, for compounds according to formula (A) having a W residue of imidazole derivatives which were suggested in the prior art as H_3 antagonists or agonists, and further for those W residues which would belong to future imidazole derivatives having substantial H_3 antagonist and/or agonist activity.

Moreover, the inventors have observed that such non-imidazole analogues can provide potent antagonist and/or agonist activity.

In this regards, they have prepared novel non-imidazole alkylamines analogues of formula (A) corresponding to known imidazole derivatives in particular from the above-mentioned prior art.

The invention also relates to the addition salts which the compounds form with pharmaceutically acceptable acids. The pharmaceutically acceptable salts comprise the nontoxic salt of inorganic or organic acids. Examples of these salts include the hydrochloride, the hydrobromide or the hydrogen maleate or hydrogen oxalate.

The present invention also encompasses the hydrates of the compounds, the hydrated salts of these compounds and the polymorphic crystalline structures.

When the compounds can exist in one or a number of isomeric forms according to the number of asymmetric centres in the molecule, the invention relates both to all the optical isomers and to their racemic modifications and the corresponding diastereoisomers. The separation of the diastereoisomers and/or of the optical isomers can be carried out according to methods known per se.

The present invention also encompasses all the possible tautomeric forms of the compounds, whether these tautomers occur in isolated form or in the form of mixtures.

According to the invention, lower alkyl or cycloalkyl is intended to mean a linear or branched alkyl group containing from 1 to 6 carbon atoms, or a saturated carbocycle containing 3 to 6 carbon atoms.

Typically examples of lower alkyl are methyl, ethyl, propyl, isopropyl and butyl groups.

A preferred group of compounds according to the invention comprises those with R^1 and R^2 representing independently a lower alkyl group, especially an ethyl group.

Preferred compounds are also those of formula (A) in which R^1 and R^2 taken together with the nitrogen atom to which they are attached, form a saturated nitrogen-containing ring:

i)

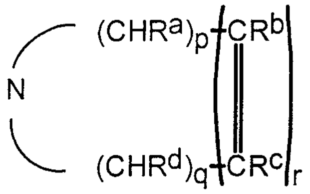
especially with m being 4, 5 or 6, optionally substituted with an alkyl group (R^a), preferably a methyl group.

The groups R^a and R^b are identical or different for each (CR^aR^b) moiety.

Piperidyl and pyrrolidinyl moieties are especially preferred.

Another preferred group of compounds comprises compounds (A) in which R^1 and R^2 taken together with the nitrogen atom to which they are attached, form a non-aromatic unsaturated nitrogen-containing ring:

ii)



especially with p, q, and r being independently 1 or 2.

In this group, more preferred compounds are those with p being 2 and q and r each being 1.

A sub-class in this group comprises compounds with R^{a-d} being each a hydrogen atom.

When NR^1R^2 is a nitrogen-containing ring i) or ii) as above-defined, the latter is preferably substituted with one or two lower alkyl group(s), especially a methyl group.

The position for substitution is preferably selected according the following order:

meta>para>ortho.

In this group, for nitrogen-containing ring bearing only one substituent, this latter is preferably in meta position with respect to the nitrogen-atom.

For nitrogen-containing ring bearing two substituents, meta-meta substitution is preferred, especially when these two substituents are in trans-relation.

According to the invention, piperidyl or pyrrolidinyl moiety substituted in meta or meta-meta position, especially with a methyl group, give particularly preferred compounds.

When NR^1R^2 represents a N-substituted piperazino group, R may be a lower alkyl e.g. methyl.

Typical examples of group R being an aryl or arylalkyl moiety are phenyl and benzyl.

R may be also an alkanoyl or aroyl group e.g. acetyl or benzoyl.

In all the possible groups for R, the alkyl moiety refers to a linear or branched chain containing from 1 to 6 carbon atoms.

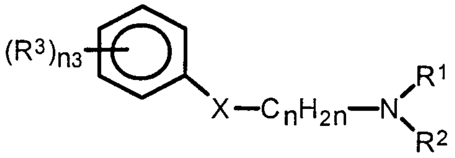
The cycloalkyl group refers to a saturated carbocycle containing 3 to 7 carbon atoms.

When R represents an aryl or arylalkyl group, the aryl moiety is especially a phenyl group optionally substituted with one or more substituents selected from halogen atoms, advantageously selected from fluorine, chlorine and bromine, or a lower alkyl or cycloalkyl, a trifluoromethyl, aryl, alkoxy, aryloxy, nitro, formyl, alkanoyl, aroyl, arylalkanoyl, amino, carboxamido, cyano, alkyloximino, aryloximino, α-hydroxyalkyl, alkenyl, alkynyl, sulphamido, sulfamoyl, carboxamide, carboalkoxy, arylalkyl or oxime group.

R may be also an optionally substituted benzoyl, the substituent being as defined above with reference to the phenyl group.

Typical example of $-NR^1R^2$ representing a N-substituted piperazino group is N-acetylpiperazino.

According to one aspect, the compounds of the invention have the following general formula (I):


(I)

in which:

- C_nH_2n is a linear or branched hydrocarbon chain with n ranging from 2 to 8;
- X is an oxygen or sulfur atom;
- n_3 is an integer from 0 to 5;
- R^3 represents each independently
  - a halogen atom,
  - a lower alkyl or cycloalkyl, a trifluoromethyl, aryl, alkoxy, α-alkyloxyalkyl, aryloxy, nitro, formyl, alkanoyl, aroyl, arylalkanoyl, amino, carboxamido, cyano, alkyloximino, alkylalkoximino, aryloximino, α-hydroxyalkyl, alkenyl, alkynyl, sulphamido, sulfamoyl, sulphonamido, carboxamide, carbonylcycloalkyl, alkylcarbonylalkyl, carboalkoxy, arylalkyl or oxime group,
  - or taken together with the carbon atoms of the phenyl ring to which it is fused, a 5- or 6-membered saturated or unsaturated ring or a benzene ring.
- R^1 and R^2 are as above-defined in formula (A).

A preferred group of compounds according to the invention is the group composed of compounds of formula (I) in which X is an oxygen atom.

Another preferred group of compounds comprises compounds (I) in which $-C_nH_{2n}-$ is a linear chain $-(CH_2)_n-$ with n being as previously defined.

Preferred compounds are also those with n varying from 3 to 5, and with n being more preferably 3.

A sub-class of compounds according to the invention comprises the compounds of formula (I) with n_3 being zero that is those having an unsubstituted phenyl moiety.

Another group of compounds according to the invention is composed of compounds containing one or more substituents R^3 which may be identical or different. In this group, the compounds having a mono- or di-substituted (n_3 = 1 or 2) phenyl moiety are preferred and those mono-substituted with one group R^3 as defined above in para-position are particularly preferred.

Among these compounds, (n_3 being 1) R^3 is preferably a halogen atom or a cyano, nitro, alkanoyl, alkyloximino or α-hydroxyalkyl group.

Still more preferred compounds are those with R^3 being CN, NO_2, $COCH_3$, COC_2H_5, H_3C-C=N-OH, H_3C-CH-OH and cycloalkyl-CO like cyclopropyl-CO.

R^3 being a halogen atom may be advantageously selected from fluorine, chlorine and bromine.

R^3 being an aryl group, may be especially a phenyl group.

In the other substituents R^3, the aryl moiety is advantageously a phenyl moiety.

R^3 being an aryloxy group may be especially a phenoxy group.

According to the invention, alkanoyl is intended to mean a group containing an alkyl moiety as defined above.

Typical examples of R^3 being an alkanoyl, aroyl or arylalkanoyl group are acetyl, butyryl and propionyl groups, benzoyl group or phenylacetyl group.

Typical examples of R^3 forming together with the carbon atoms of the phenyl ring to which it is fused, a saturated ring leads to 5,6,7,8-tetrahydronaphthyl or forming a benzene ring leads to a naphthyl moiety.

According to the invention, alkenyl or alkynyl group may contain advantageously from 1 to 8 carbon atoms, in particular from 1 to 6 carbon atoms and preferably 1 to 4 carbon atoms.

In carboalkoxy, carboxyamido, carbonylcycloalkyl, alkylcarbonylalkyl, or carboxamide groups, the hydrocarbon chain is saturated, linear or branched and contains an alkyl moiety as defined above.

In alkoxy, alkylalkoximino, alkyloximino, α-alkyloxyalkyl, arylalkyl or α-hydroxyalkyl group, the alkyl moiety is as previously defined also.

Particularly preferred compounds are:

1-(5-phenoxypentyl)-piperidine
1-(5-phenoxypentyl)-pyrrolidine
N-methyl-N-(5-phenoxypentyl)-ethylamine
1-(5-phenoxypentyl)-morpholine
N-(5-phenoxypentyl)-hexamethyleneimine
N-ethyl-N-(5-phenoxypentyl)-propylamine
1-(5-phenoxypentyl)-2-methyl-piperidine
1-(5-phenoxypentyl)-4-propyl-piperidine
1-(5-phenoxypentyl)-4-methyl-piperidine
1-(5-phenoxypentyl)-3-methyl-piperidine
1-acetyl-4-(5-phenoxypentyl)-piperazine
1-(5-phenoxypentyl)-3,5-trans-dimethyl-piperidine
1-(5-phenoxypentyl)-3,5-cis-dimethyl-piperidine
1-(5-phenoxypentyl)-2,6-cis-dimethyl-piperidine
4-carboethoxy-1-(5-phenoxypentyl)-piperidine
3-carboethoxy-1-(5-phenoxypentyl)-piperidine
1-[3-(4-cyclopropylcarbonylphenoxy) propyl]-piperidine
1-[3-(4-acetylphenoxy)-2-R-methylpropyl] piperidine
1-[3-(4-cyanophenoxy)propyl]-4-methylpiperidine
1-[3-(4-cyanophenoxy)propyl]-3-methylpiperidine
1-[3-(4-acetylphenoxy)-2-S-methylpropyl] piperidine
1-{3-[4-(3-oxobutyl)phenoxy] propyl}piperidine
1-[3-(4-cyano-3-fluorophenoxy)propyl] piperidine
1-[3-(4-nitrophenoxy)propyl]-3-methylpiperidine
1-[3-(4-cyanophenoxy)propyl]-2-methylpiperidine
1-[3-(4-nitrophenoxy)propyl]-2-methylpiperidine
1-[3-(4-nitrophenoxy)propyl]-4-methylpiperidine
1-[3-(4-cyanophenoxy)propyl]-2,6-dimethylpiperidine
1-[3-(4-propionylphenoxy)propyl]-3-methylpiperidine

1-[3-(4-cyclobutylcarbonylphenoxy)propyl] piperidine
1-[3-(4-cyclopentylcarbonylphenoxy) propyl]piperidine
1-[3-(4-cyanophenoxy)propyl]-cis-2-methyl-5-ethylpiperidine
1-[3-(4-cyanophenoxy)propyl]-trans-2-methyl-5-ethylpiperidine
1-[3-(4-cyanophenoxy)propyl]-cis-3,5-dimethylpiperidine
1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine
1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine
1-{3-[4-(1-hydroxypropyl)phenoxy]propyl}-3-methylpiperidine
1-{3-[4-(1-hydroxypropyl)phenoxy]propyl}-4-methylpiperidine
1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine
1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine methoxime
1-[3-(4-cyanophenoxy)propyl]-trans-3,5-dimethylpiperidine
1-[3-(4-cyclopropyl carbonyl phenoxy) propyl] -trans-3,5 -dimethylpiperidine
1-[3-(4-cyclopropyl carbonyl phenoxy) propyl] -cis-3,5 -dimethylpiperidine
1-[3-(4-carbomethoxyphenoxy)propyl] piperidine
1-[3-(4-propenylphenoxy)propyl]-2-methyl piperidine
1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine
1-{3-[4-(1-ethoxypropyl)phenoxy]propyl}-2-methyl piperidine
1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine
1-[3-(4-bromophenoxy)propyl]piperidine
1-[3-(4-nitrophenoxy)propyl]piperidine
1-[3-(4-N,N-dimethylsulfonamidophenoxy) propyl]piperidine
1-[3-(4-isopropylphenoxy)propyl]piperidine
1-[3-(4-sec-butylphenoxy)propyl]piperidine
1-[3-(4-propylphenoxy)propyl]piperidine
1-[3-(4-ethylphenoxy)propyl]piperidine
1-(5-phenoxypentyl)-1,2,3,6-tetrahydropyridine
1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-methoxyphenoxy)-pentyl]-pyrrolidine

1-[5-(4-methylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-pyrrolidine
1-[5-(2-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(1-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(3-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenylphenoxy)-pentyl]-pyrrolidine
1-{5-[2-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-[5-(3-phenylphenoxy)-pentyl]-pyrrolidine
1-(5-phenoxypentyl)-2,5-dihydropyrrole
1-{5-[1-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-(4-phenoxybutyl)-pyrrolidine
1-(6-phenoxyhexyl)-pyrrolidine
1-(5-phenylthiopentyl)-pyrrolidine
1-(4-phenylthiobutyl)-pyrrolidine
1-(3-phenoxypropyl)-pyrrolidine
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1-[5-(4-acetylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-aminophenoxy)-pentyl]-pyrrolidine
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N-[3-(4-nitrophenoxy)-propyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-diethylamine
1-[5-(4-benzoylphenoxy)-pentyl]-pyrrolidine
1-{5-[4-(phenylacetyl)-phenoxy]-pentyl}-pyrrolidine
N-[3-(4-acetylphenoxy)-propyl]-diethylamine
1-[5-(4-acetamidophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-N-benzamidophenoxy)-pentyl]-pyrrolidine
1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-diethylamine
1-[5-(4-cyanophenoxy)-pentyl]-piperidine

N-[5-(4-cyanophenoxy)-pentyl]-dimethylamine
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N-[4-(4-cyanophenoxy)-butyl]-diethylamine
N-[5-(4-cyanophenoxy)-pentyl]-dipropylamine
1-[3-(4-cyanophenoxy)-propyl]-pyrrolidine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-[6-(4-cyanophenoxy)-hexyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dipropylamine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-trans-dimethyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-cis-dimethyl-piperidine
1-[3-(4-formylphenoxy)-propyl]-piperidine
1-[3-(4-isobutyrylphenoxy)-propyl]-piperidine
N-[3-(4-propionylphenoxy)-propyl]-diethylamine
1-[3-(4-butyrylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-1,2,3,6-tetrahydropyridine

More preferred compounds are:

1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
N-[3-(4-cyanophenoxy)-propyl]-diethylamine
N-[3-(4-acetylphenoxy)-propyl]-diethylamine
1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine
N-[4-(4-cyanophenoxy)-butyl]-diethylamine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine

4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine

Compounds of formula (I) in which:

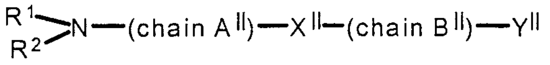
- $-NR^1R^2$ is a pyrrolidinyl group, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and n_3 is zero, X being an oxygen atom with n ranging from 3 to 5, or X being a sulfur atom with n being 4 or 5;
- $-NR^1R^2$ is a piperidinyl group, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and X is an oxygen atom, n_3 being zero with n being 2, 5 or 8 or n_3 being 1 with R^3 being 4-CN and n being 5;
- $-NR^1R^2$ is a diethylamine group, X is an oxygen atom, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and n_3 is 1, R^3 being $4\text{-}NO_2$ or $4\text{-}COCH_3$ with n being 3 or R^3 being 4-CN with n being 2 to 4;
- $-NR^1R^2$ is a dimethylamine group, X is an oxygen atom, C_nH_{2n} is a linear chain $-(CH_2)_n-$ and n^3 is 1, R^3 being 4-CN with n being 3,

are known in the art.

A subject of the invention is thus the use of these compounds as ligands of the histamine H_3-receptors in particular as H_3-antagonists, agonists and/or partial agonists, in particular to prepare medicaments acting as ligands for the histamine H_3-receptors in particular as H_3-antagonists and/or agonists, intended for the treatments detailed below.

According to a second aspect, the object of the present invention is non-imidazole compounds analogous to the compounds disclosed in WO 96/29315 and WO 93/14070.

Thus, a first sub-class of the compounds (A) of the invention is defined by the compounds having the following general formula (IIa) and (IIb):



$$\begin{matrix}R^1\\R^2\end{matrix}\!>\!N-(\text{chain }A^{II})-X^{II}-(\text{chain }B^{II})-Y^{II}$$

(IIa)

or

$$\begin{matrix}R^1\\R^2\end{matrix}\!>\!N-(\text{chain }A^{II})-X^{II}-Y^{II}$$

(IIb)

in which

- R^1 and R^2 are as defined with reference to general formula (A);

- the chain A^{II} represents a saturated or unsaturated, straight or branched hydrocarbon chain containing 1 to 6 carbon atoms, it being possible for the saturated hydrocarbon chain to be interrupted by a hetero atom such as a sulphur atom;

- X^{II} represents an oxygen or sulphur atom, -NH-, -NHCO-, -N(alkyl)CO-, -NHCONH-, -NH-CS-NH-, -NHCS-, -O-CO-, -CO-O-, -OCONH-, -OCON(alkyl)-, -OCON(alkene),-OCONH-CO-, -CONH-, -CON(alkyl)-, -SO-, -CO-, -CHOH-, -N(saturated or unsaturated alkyl), -S-C(=NY")-NH-Y"- with the Y" identical or different and as defined previously, or $-NR_{II}-C(=NR''_{II})-NR'_{II}-$, R_{II} and R'_{II} denoting a hydrogen atom or a lower alkyl radical and R''_{II} a hydrogen atom or another powerful electronegative group, such as a cyano or COY_1^{II} group, Y_1^{II} denoting an alkoxy group;

- the chain B^{II} represents an aryl, arylalkyl or arylalkanoyl group, a straight alkylene chain $-(CH_2)_{nII}-$, n being an integer which can vary between 1 and 5 or a branched alkylene chain containing from 2 to 8 carbon atoms, the alkylene chain being optionally interrupted by one or a number of oxygen or sulphur atoms, or a group $-(CH_2)_{nII}-O-$ or $-(CH_2)_{nII}-S-$ where n_{II} is an integer equal to 1 or 2;

Y^{II} represents a straight or branched alkyl group containing 1 to 8 carbon atoms; a cycloalkyl containing 3 to 6 carbon atoms; a bicycloalkyl group; a cycloalkenyl group; an aryl group such as an optionally substituted phenyl group; a 5- or 6-membered heterocyclic radical containing one or two heteroatoms chosen from nitrogen and sulphur atoms, the said heterocyclic radical optionally being substituted; or also a bicyclic radical resulting from the fusion of a benzene ring to a heterocycle as defined above.

The chain A can be a straight alkylene chain $-(CH_2)_{nII}-$, n_{II} representing an integer between 1 and 6 carbon atoms, preferably between 1 and 4 carbon atoms, or a branched alkylene chain, preferably a chain substituted by one or a number of methyl or ethyl radicals.

The chain A^{II} can also be a straight or branched unsaturated alkylene chain, and can be, for example, the allyl group.

When Y^{II} represents a cycloalkyl group, the latter can be, for example, cyclopentyl, cyclohexyl or a bicycloalkyl group.

When Y^{II} represents a substituted phenyl group, the phenyl group can be mono- or polysubstituted, for example, by a halogen, by a lower alkyl, for example CH_3, by CF_3, CN, $COCH_3$, $COOR^{II}_1$ or OR^{II}_1, R^{II}_1 representing a lower alkyl, for example $COOCH_3$, the NO_2 group or the group $NR^{II}_2R^{II}_3$, R^{II}_2 and R^{II}_3 representing a hydrogen atom and/or a lower alkyl radical ("lower alkyl" means an alkyl radical containing at most 6 carbon atoms).

When Y^{II} represents a heterocyclic radical, the latter can be, for example, the pyridyl radical, the pyridyl N-oxide radical or the pyrazinyl radical, optionally mono- or polysubstituted by NO_2, CF_3, CH_3, NH_2, a halogen such as Cl, the $COOCH_3$ group or also the thiazolyl radical.

When Y^{II} represents a polycyclic radical resulting from condensed aromatic or heteroaromatic moieties the radical can be, for example, the benzothiazolyl, quinolinyl, isoquinolinyl radical or related moieties.

A second sub-class of the compounds (A) according to the invention comprises the compounds having the above-formulae (IIa) and (IIb) in which:

– R^1R^2 are as defined with reference to general formula (A);

– the chain A" represents an unbranched, branched or unsaturated alkyl group $-(CH_2)_{nII}-$ where n_{II} is an integer which can vary between 1 and 8 and preferably between 1 and 4; an unbranched or branched alkene group comprising from 1 to 8 carbon atoms and preferably 1 to 4 carbon atoms; an unbranched or branched alkyne group comprising from 1 to 4 carbon atoms;

– the group X^{II} represents -OCONH-; -OCON(alkyl)-; -OCON(alkene)-; -OCO-; -OCSNH-; $-CH_2-$; -O-; $-OCH_2CO-$; -S-; -CO-; -CS-; amine; saturated or unsaturated alkyl;

– the chain B^{II} represents an unbranched, branched or unsaturated lower alkyl comprising from 1 to 8 carbon atoms and preferably 1 to

5 carbon atoms; -$(CH_2)_{nII}$(hetero atom)- where the hetero atom is preferably a sulphur or oxygen atom; n_{II} being an integer which can vary between 1 and 5, preferably between 1 and 4;

– the group Y^{II} represents a phenyl group, unsubstituted or mono- or polysubstituted with one or more identical or different substituents selected from halogen atoms, OCF_3, CHO, CF_3, $SO_2N(alkyl)_2$ such as $SO_2N(CH_3)_2$, NO_2, S(alkyl), S(aryl), SCH_2(phenyl), an unbranched or branched alkene, an unbranched or branched alkyne optionally substituted with a trialkylsilyl radical, -O(alkyl), -O(aryl), -CH_2CN, a ketone, an aldehyde, a sulphone, an acetal, an alcohol, a lower alkyl, -CH=CH-CHO, -C(alkyl)=N-OH, -C(alkyl)=N-O(alkyl) and other keto derivatives, -CH=NOH, -CH=NO(alkyl), and other aldehyde derivatives, -C(alkyl)=NH-NH-$CONH_2$, an O-phenyl or -OCH_2(phenyl) group, -C(cycloalkyl)=NOH, -C(cycloalkyl)=N-O(alkyl), an optionally substituted heterocycle; a heterocycle comprising a sulphur hetero atom; a cycloalkyl; a bicyclic group and preferably a norbornyl group; a phenyl ring fused to a heterocycle comprising a nitrogen hetero atom or to a carbocycle or a heterocycle bearing a keto function; an unbranched or branched lower alkyl comprising from 1 to 8 carbon atoms; an unbranched or branched alkyne comprising from 1 to 8 carbon atoms and preferably 1 to 5 carbon atoms; a linear or branched alkyl mono- or polysubstituted with phenyl groups which are either unsubstituted or mono- or polysubstituted; a phenyl alkyl ketone in which the alkyl group is branched or unbranched or cyclic; a substituted or unsubstituted benzophenone; a substituted or unsubstituted, unbranched or branched or cyclic phenyl alcohol; an unbranched or branched alkene; a piperidyl group; a phenylcycloalkyl group; a polycyclic group, in particular a fluorenyl group, a naphthyl or polyhydronaphthyl group or an indanyl group; a phenol group; a ketone or keto derivative; a diphenyl group; a phenoxyphenyl group; a benzyloxyphenyl group.

According to the invention, group X^{II} representing an amine is understood to mean a secondary or tertiary amine.

The alkyl, alkene, alkyne, keto, aldehyde, cycloalkyl, S-alkyl, O-alkyl, phenyl alcohol and phenyl-cycloalkyl groups mentioned above as well as in the remainder of the description and the claims of the present patent comprise from 1 to 8 carbon atoms, and preferably 1 to 5.

Likewise, keto derivatives are understood to mean any oxime, alkyloxime, hydrazone, acetal, aminal, ketal, thione, carbazone or semicarbazone group and the thio analogues of these derivatives.

Likewise, by mono- or polysubstituted phenyl and/or benzophenone groups, it is understood to mean that these groups are substituted with one or more identical or different substituents selected from halogen atoms, OCF_3, CHO, CF_3, $SO_2N(alkyl)_2$, $SO_2N(CH_3)_2$, NO_2, S(alkyl), S(aryl), SCH_2(phenyl), an unbranched or branched alkene, an unbranched or branched alkyne optionally substituted with a trialkylsilyl radical, -O(alkyl), -O(aryl), $-CH_2CN$, a ketone, an aldehyde, a sulphone, an acetal, an alcohol, a lower alkyl, -CH=CH-CHO, -C(alkyl)=N-OH, -C(alkyl)=N-O(alkyl) an other keto derivatives, -CH=NOH, -CH=NO(alkyl), and other aldehyde derivatives, $-C(alkyl)=NH-NH-CONH_2$, an O-phenyl or $-OCH_2$(phenyl) group, -C(cycloalkyl)=NOH, -C(cycloalkyl)=N-O(alkyl), an optionally substituted heterocycle.

The keto substituent is preferably selected from a linear- or branched-chain aliphatic ketone, it being possible for the said chain to comprise from 1 to 8 carbon atoms and optionally to bear a hydroxyl group, a cycloalkyl ketone, an aryl alkyl ketone or aryl alkenyl ketone in which the aryl group is unsubstituted or mono- or polysubstituted, or a heteroaryl ketone in which the heteroaryl unit is preferably monocyclic.

The acetal substituent preferably consists of an aliphatic acetal comprising from 1 to 8 carbon atoms and optionally bearing a hydroxyl radical.

Group Y^{II} representing a ketone is understood to mean, in particular, a ketone substituted with an alkyl or aryl group, it being possible for these groups to be substituted or unsubstituted.

As regards the heterocycles, these comprise from 1 to 3 hetero atoms, preferably sulphur, oxygen or nitrogen atoms.

The heterocycle substituent is preferably selected from an oxadiazole or an imidazole.

Preferred compounds (IIa) and (IIb) are those in which X^{II} is selected from -O-, -NH-, $-CH_2-$, -OCONH-, -NHCO-, -NHCONH-. X^{II} represents more preferably an oxygen atom.

Preferred compounds (IIa) and (IIb) are also those in which Y^{II} is selected from a linear or branched alkyl group as above defined; a cycloalkyl group as above-defined, in particular cyclopentyl or cyclohexyl group; a phenyl group unsubstituted or mono-substituted, preferred substituent being halogen atom, in particular chorine; a heterocyclic radical, in particular pyridyl N-oxide or pyrazinyl radicals; a bicyclic radical such as a benzothiazolyl radical.

Y^{II} is preferably a phenyl group at least mono-substituted with -CHO, a ketone, an aldehyde, -CH=CH-CHO, -C(alkyl)=N-OH, -C(alkyl)=N-O(alkyl) and other keto derivatives, -CH=N-OH, -CH=NO(alkyl) and other aldehyde derivatives, -C(cycloalkyl)=NOH, -C(cycloalkyl)=N-O(alkyl).

According to the invention, Y^{II} represents especially a phenyl group at least mono-substituted with a keto-substituent or an oxime-substituent, or an halogen atom.

Particularly preferred keto-substituent is cycloalkylketone.

Other preferred compounds are those wherein Y^{II} represents a phenyl group fused to a carbocycle bearing a keto-function.

Yet other preferred Y^{II} are phenylalkyl ketone in which the alkyl group is branched or unbranched or cyclic; an optionally substituted benzophenone, a ketone.

Particularly preferred group Y^{II} are a phenyl group unsubstituted or mono-substituted as above-defined.

The chain A^{II} is preferably a chain $-(CH_2)_n{}^{II}-$ with n_{II} varying from 1 to 6, preferably from 1 to 4. The chain A^{II} represents especially $-(CH_2)_3-$.

Preferred chain B^{II} is $-(CH_2)_2-$ or $-(CH_2)_3-$.

Among compounds (IIa) and (IIb), particularly preferred compounds are those in which X^{II} is an oxygen atom, the chain A^{II} represents $-(CH_2)_3-$ and, for compounds of formula (IIa), the chain B^{II} represents $-(CH_2)_3-$ also.

In this group, Y^{II} is preferably an aryl group.

Preferred group R^1 and R^2 are as above-defined with reference to formula (A).

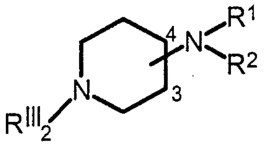
Examples of compounds (IIa) and (IIb) are:

- 3,3-Dimethylbutyl 3-piperidinopropyl ether
- 3-Phenylpropyl 3-piperidinopropyl ether
- 3-(4-Chlorophenyl)propyl 3-piperidinopropyl ether
- 2-Benzothiazolyl 3-piperidinopropyl ether
- 3-Phenylpropyl 3-(4-methylpiperidino)propyl ether
- 3-Phenylpropyl 3-(3,5-cis-dimethylpiperidino)propyl ether
- 3-Phenylpropyl 3-(3,5-trans-dimethylpiperidino)propyl ether
- 3-Phenylpropyl 3-(3-methylpiperidino)propyl ether
- 3-Phenylpropyl 3-pyrrolidinopropyl ether
- 3-(4-Chlorophenyl)propyl 3-(4-methylpiperidino)propyl ether
- 3-(4-Chloro phenyl) propyl 3-(3,5-cis –dimethyl piperidino) propyl ether
- 3-(4-Chloro phenyl) propyl 3-(3,5-trans-dimethyl piperidino) propyl ether
- 3-Phenylpropyl 3-(N,N-diethylamino)propyl ether
- N-Phenyl-3-piperidinopropyl carbamate
- N-Pentyl-3-piperidinopropyl carbamate
- (S)-(+)-N-[2-(3,3-Dimethyl)butyl]-3-piperidinopropyl carbamate
- 3-Cyclopentyl-N-(3-(1-pyrrolidinyl)propyl)propanamide
- N-Cyclohexyl-N'-(1-pyrrolidinyl-3-propyl)urea
- 2-((2-Piperidinoethyl)amino)benzothiazole
- 5-Piperidinopentylamine
- 2-Nitro-5-(6-piperidinohexyl)pyridine
- 3-Nitro-2-(6-piperidinohexylamino)pyridine

- 2-(6-Piperidinohexylamino)pyrimidine
- N-(6-Phenylhexyl)piperidine
- N-(3-(N,N-Diethylamino)propyl)N'-phenylurea
- N-Cyclohexylmethyl-N'-(3-piperidinopropyl)guanidine

According to a third aspect, the object of the present invention is non-imidazole compounds analogous to the compounds disclosed in EP 197 840.

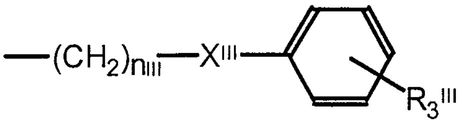
Thus, a sub-class of compounds (A) according to the invention comprises compounds having the following formula (III)



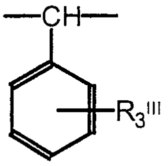
(III)

in which:

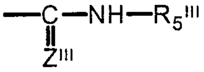
- NR^1R^2 is either in 3-position or in 4-position on the piperidyl moiety, R^1 and R^2 being as defined with reference to formula (A);
- R_2^{III} denotes a linear or branched alkyl group having 1 to 6 carbon atoms; a piperonyl group, a 3-(1-benzimidazolonyl)propyl group; a group of formula



in which n_{III} is 0, 1, 2 or 3, X^{III} is a single bond or alternatively -O-, -S-, -NH-, -CO-, -CH=CH- or

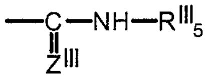


and R_3^{III} is H, CH_3, halogen, CN, CF_3 or an acyl group $-COR_4^{III}$, R_4^{III} being a linear or branched alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms or a phenyl group which can bear a CH_3 or F substituent; or alternatively a group of formula



$$-\underset{\underset{Z^{III}}{\|}}{C}-NH-R_5^{III}$$

in which Z^{III} denotes an O or S atom or a divalent group NH, N-CH_3 or N-CN and R_5^{III} denotes a linear or branched alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms which can bear a phenyl substituent, a (C_3-C_6 cycloalkyl) (linear or branched, C_1-C_3 alkyl) group, a phenyl group which can bear a CH_3, halogen or CF_3 substituent, a phenyl(linear or branched, C_1-C_3 alkyl) group or a naphthyl, adamantyl or p-toluenesulphonyl group.

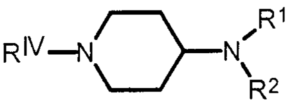
Preferred compounds (III) are those with R^{III} representing the group  $-\underset{\underset{Z^{III}}{\|}}{C}-NH-R^{III}_5$, Z^{III} and R^{III}_5 being as above-defined and Z^{III} is especially O, S or NH.

Preferred group R^{III}_5 is a (C_3-C_6)cycloalkyl group.

Preferred R^1 and R^2 groups are as above-described in formula (A).

An example of such compound (III) is N'-Cyclohexylthiocarbamoyl-N-1,4'-bipiperidine (compound 123).

According to a fourth aspect, a sub-class of compounds (A) includes the compounds which have the following formula (IV), analogous to compounds disclosed in EP 494 010:



(IV)

in which

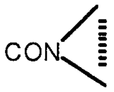
- R^1 and R^2 are as defined with reference to general formula (A);
- R^{IV} represents a hydrogen atom or a group COR_3^{IV}, in which R_3^{IV} represents

(a) a linear or branched aliphatic group containing 1 to 11, and in particular 1 to 9, carbon atoms;

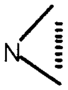
(b) a cyclane ring-system such as cyclopropane, phenylcyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, norbornane, adamantane, noradamantane, chlorooxonorbornane, chloroethylenedioxynorbornane, bromoethylenedioxynorbornane and the anhydride group of hydroxycarboxy-1,2,2-trimethylcyclopentanecarboxylic acid;

(c) a benzene ring, unsubstituted or substituted at the para-position with a linear or branched aliphatic group containing 3 to 5 carbon atoms, as well as with a halogen;

(d) a group $(CH_2)_{mIV}R_4^{IV}$ in which m_{IV} is a number between 1 and 10, and R_4^{IV} represents a cyclane ring system such as cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cycloheptane, norbornane, noradamantane, adamantane and 6,6-dimethylbicyclo[3.1.1] heptene; a benzene ring, unsubstituted or monosubstituted with a fluorine atom, a chlorine atom, a methyl group or a methoxy group; a thiophene ring grafted via its ring-position 2 or its ring-position 3; a carboxylic acid ester group $COOR_5^{IV}$, in which R_5^{IV} is a cyclane ring-system such as cyclopropane, cyclobutane, cyclopentane, cyclohexane or norbornane; a carboxylic acid amide group of structure $CONHR_6^{IV}$, in which R_6^{IV} represents a cyclane ring-system such as cyclopropane, cyclobutane, cyclopentane, cyclohexane or norbornane; a carboxylic acid amide group of structure



in which the group

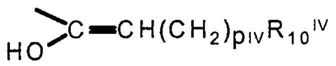


represents pyrrolidine, piperidine or 2,6-dimethylmorpholine; or an ether group –O-R_7^{IV}, it being possible for R_7^{IV} to be a benzene ring, unsubstituted or monosubstituted with a chlorine or fluorine atom or disubstituted with a chlorine atom and with a methyl group;

(e) a group -CH=CHR_8^{IV}, in which R_8^{IV} represents a cyclane ring-system such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, norbomane or norbornene;

(f) a secondary amine group $-NH(CH_2)_{nIV}R_9^{IV}$, in which n_{IV} is a number between 1 and 5 and R_9^{IV} constitutes a cyclane ring-system such as cyclopropane, cyclobutane, cyclopentane, cyclohexane or norbornane, or a benzene ring, unsubstituted, mono-substituted with a fluorine or chlorine atom or with a methoxy group or trisubstituted with methoxy groups;

R^{IV} also represents a hydroxyalkenyl group



$$\mathrm{HO}{>}C{=}CH(CH_2)_{p_{IV}}R_{10}^{IV}$$

in which p_{IV} is a number between 2 and 9 and R_{10}^{IV}, represents a benzene ring or a phenoxy group; as well as a group

$$CSNH(CH_3)_{nIV}R_9^{IV}$$

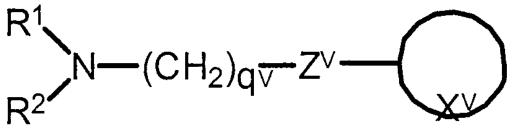
– in which n_{IV} is a number between 1 and 5 and R_9^{IV} has the meaning stated above.

Preferred compounds (IV) are those in which R^{IV} represents the group COR_3^{IV}, R_3^{IV} representing especially an aliphatic group a).

An example of compound (IV) is N-Heptanoyl-1,4'-bipiperidine or 1-(5-Cyclohexylpentanoyl)-1,4-bipiperidine.

According to a fifth aspect, the invention is relative to non-imidazole compounds analogous to those disclosed by Plazzi et al. (Eur. J. Med. Chem. 1995, 30, 881).

Thus, another sub-class of compounds (A) comprises compounds having the following formula (V):

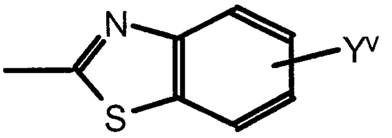


(V)

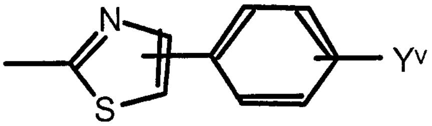
in which

- R^1 and R^2 are as defined with reference to formula (A) in claim 1;
- q^V is 2 to 5
- Z^V represents NH, O or S
- X_V represents a heterocycle, optionally condensed, containing one or more heteroatoms like nitrogen, oxygen or sulfur, unsubstituted or substituted by one or more groups like aryl, lower alkyl and halogen.

Preferred compounds are those with X^V being an heterocycle like :

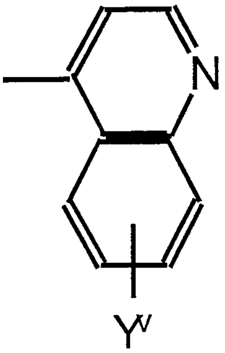


(Va)



(Vb)

or



(Vc)

with Y^V representing an hydrogen atom, an halogen or a lower alkyl.

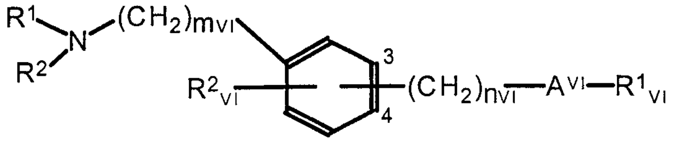
Examples of compounds (V) are :

2-((2-Piperidinoethyl)amino)benzothiazole

2-(6-Piperidinohexylamino)benzothiazole
4-(6-Piperidinohexylamino)quinoline
2-Methyl 4-(3-piperidinopropylamino)quinoline
2-Methyl 4-(6-piperidinohexylamino)quinoline
7-Chloro-4-(3-piperidinopropylamino)quinoline
7-Chloro-4-(4-piperidinobutylamino)quinoline
7-Chloro-4-(8-piperidinooctylamino)quinoline
7-Chloro-4-(10-piperidinodecylamino)quinoline
7-Chloro-4-(12-piperidinododecylamino)quinoline
7-Chloro-4-(4-(3-piperidinopropoxy)phenylamino)quinoline
7-Chloro-4-(2-(4-(3-piperidinopropoxy) phenyl) ethylamino) quinoline

According to a sixth aspect, the present invention concerns non-imidazole compounds which are analogous to those disclosed in WO 95/14007.

Thus, another subclass of compounds (A) includes the compounds having the following formula (VI):



(VI)

wherein:

– A^{VI} is selected from -O-CO-NR^1_{VI}-, -O-CO-, -NR^1_{VI}-CO-, -NR^1_{VI}-, -NR^1_{VI}-CO-, -NR^1_{VI}-, -O-, -CO-NR^1_{VI}-, -CO-O-, and -C(=NR^1_{VI})-NR^1_{VI}-;

– the groups R^1_{VI}, which may be the same or different when there are two or three such groups in the molecule of formula VI, are selected from hydrogen, and lower alkyl, aryl, cycloalkyl, heterocyclic and heterocyclyl-alkyl groups, and groups of the formula -$(CH_2)_{yVI}$-G^{VI}, where G^{VI} is selected from $CO_2R^3_{VI}$, COR^3_{VI}, $CONR^3_{VI}R^4_{VI}$, OR^3_{VI}, SR^3_{VI}, $NR^3_{VI}R^4_{VI}$, heteroaryl and phenyl, which phenyl is optionally substituted by halogen, lower alkoxy or polyhaloloweralkyl, and y_{VI} is an integer from 1 to 3;

- R^2_{VI} is selected from hydrogen and halogen atoms, and alkyl, alkenyl, alkynyl and trifluoromethyl groups, and groups of the formula OR^3_{VI}, SR^3_{VI} and $NR^3_{VI}R^4_{VI}$;
- R^3_{VI} and R^4_{VI} are independently selected from hydrogen, and lower alkyl and cycloalkyl groups, or R^3_{VI} and R^4_{VI} together with the intervening nitrogen atom can form a saturated ring containing 4 to 6 carbon atoms that can be substituted with one or two lower alkyl groups;
- the group $-(CH_2)_{nVI}-A^{VI}-R^1_{VI}$ is at the 3- or 4-position, and the group R^2_{VI} is at any free position;
- m_{VI} is an integer from 1 to 3;
- and n_{VI} is 0 or an integer from 1 to 3.

When used herein, the following terms have the given meanings:

lower alkyl (including the alkyl portions of lower alkoxy) – represents a straight or branched, saturated hydrocarbon chain having from 1 to 6 carbon atoms, preferably from 1 to 4;

lower alkenyl (in R^2_{VI}) – represents a straight or branched aliphatic hydrocarbon radical having at least one carbon-to-carbon double bond (preferably in conjugation with the benzene ring that the group R^2 substitutes) and having from 2 to 6 carbon atoms;

lower alkynyl (in R^2_{VI}) – represents a straight or branched aliphatic hydrocarbon radical having at least one carbon-to-carbon triple bond (preferably in conjugation with the benzene ring that the group R^2 substitutes) and having from 2 to 6 carbon atoms;

aryl – represents a carbocyclic group having from 6 to 14 carbon atoms and having at least one benzenoid ring, with all available substitutable aromatic carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally substituted with 1 to 3 Y_{VI} groups, each independently selected from halo, alkyl, hydroxy, loweralkyoxy, phenoxy, amino, loweralkylamino, diloweralkylamino, and polyhaloloweralkyl. Preferred aryl groups include 1-naphthyl, 2-naphthyl and indanyl, and especially phenyl and substituted phenyl;

cycloalkyl – represents a saturated carbocyclic ring having from 3 to 8 carbon atoms, preferably 5 or 6;

halogen – represents fluorine, chlorine, bromine and iodine;

heterocyclic – represents, in addition to the heteroaryl groups defined below, saturated and unsaturated cyclic organic groups having at least one O, S and/or N atom interrupting a carbocyclic ring structure that consists of one ring or two fused rings, wherein each ring is 5-, 6- or 7-membered and may or may not have double bonds that lack delocalized pi electrons, which ring structure has from 2 to 8, preferably from 3 to 6 carbon atoms; e.g., 2- or 3-piperidinyl, 2- or 3-piperazinyl, 2- or 3-morpholinyl, or 2- or 3-thiomorpholinyl;

heteroaryl – represents a cyclic organic group having at least one O, S and/or N atom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic group having from 2 to 14, preferably 4 or 5 carbon atoms, e.g., 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2- or

2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, or 3- or 4-pyridazinyl, etc.

Preferred heteroaryl groups are 2-, 3- and 4-pyridyl;

heterocyclyl-alkyl – represents a heterocyclic group defined above substituting an alkyl group; e.g., 2-(3-piperidinyl)-ethyl, (2-piperazinyl)-methyl, 3-(2-morpholinyl)-propyl, (3-thiomorpholinyl)-methyl, 2-(4-pyridyl)-ethyl, (3-pyridyl)-methyl, or (2-thienyl)-methyl.

Preferably, A^{VI} is $-CH_2-NR^1{}_{VI}-$ or especially $-C(=NH)-NR^1{}_{VI}-$ preferred compounds include those wherein m_{VI} is 1 or 2, and n_{VI} is 0, 1 or 2.

Other preferred values of A include $-O-CO-NR^1{}_{VI}-$, -O-, and -CO-O-. In all these compounds, the groups $R^1{}_{VI}$ are as defined above, and the side chain is preferably at the 4-position. In compounds of formula VI, one group $R^1{}_{VI}$ is preferably selected from hydrogen, 2-phenylethyl, 4-chlorophenylmethyl, 4-methoxyphenylmethyl, 4-trifluoromethylphenylmethyl and 4-pyridylmethyl, but is especially 4-chlorophenylmethyl; any other group $R^1{}_{VI}$ that is present is preferably a hydrogen atom or a methyl group.

Particularly preferred compounds are those wherein n_{VI} and m_{VI} are each 1, and A^{VI} represents an oxygen atom.

$R^1{}_{VI}$ is preferably an aryl or $-(CH_2)_{yVI}-G^{VI}$ with G^{VI} being a phenyl.

R^1 and R^2 are preferably selected as specified with reference to formula (A).

Another sub-class of compounds (A) comprises compounds of formula (VI) wherein $R^1{}_{VI}$ represents an aryl group, especially a phenyl optionally substituted with a keto substituent, $R^2{}_{VI}$, n_{VI}, m_{VI} and A^{VI} having the above-meaning.

The keto substituent is as above-defined in Y^{II} with reference to compounds (IIa) and (IIb).

Preferred compounds are those with n_{VI} and m_{VI} being each 1 and A^{VI} being an oxygen atom.

Examples of compounds VI are :

α-(Acetylphenoxy)-α'-piperidino p-xylol

α-(4-Acetylphenoxy)-α'-(1-pyrrolidinyl)p-xylol

α-(3-Phenylpropoxy)-α'-piperidino p-xylol

α-(4-Acetylphenoxy)-α'-(4-methylpiperidino)p-xylol

α-(4-Acetylphenoxy)-α'-(3,5-*cis*-dimethylpiperidino)p-xylol

α-(4-Acetylphenoxy)-α'-(3,5-*trans*-dimethylpiperidino)p-xylol

α-(4-Acetylphenoxy)-α'-(2-methylpyrrolidino)p-xylol

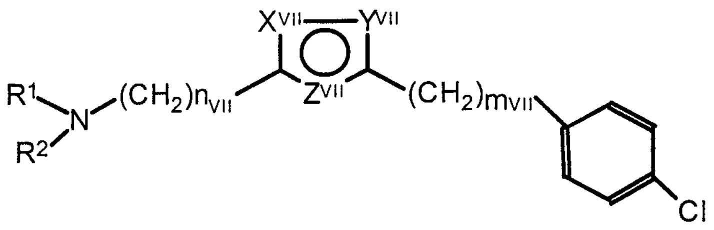
α-(4-Cyclopropylcarbonylphenoxy)-α'-piperidino-p-xylol

α-(4-Cyclopropylcarbonylphenoxy)-α'-(4-methylpiperidino)p-xylol

α-(4-Cyclopropylcarbonylphenoxy)-α'-pyrrolidino-p-xylol

N-(4-Chlorobenzyl)-2-(4-piperidino methyl) phenyl) ethan-amidine

According to a seventh aspect, the present invention is directed to another sub-class of compounds (A) including non-imidazole compounds having the following formula (VII) which are analogous to compounds disclosed in Clitherow et al. (Bioorg. & Med. Chem. Lett., 6 (7), 833, 1996) :



(VII)

in which

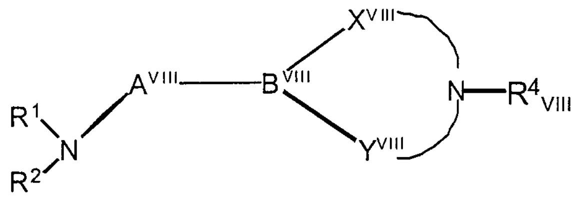
- R^1 and R^2 are as defined in reference to formula (A);
- X^{VII}, Y^{VII} and Z^{VII} are identical or different and represent O, N or S;
- n_{VII} is varying from 1 to 3;
- m_{VII} is 1 or 2.

n_{VII} is preferably 2 or 3, especially 2 and m_{VI} is preferably 1.

Preferred compounds are those with X^{VII} being 0 and Y^{VII} and Z^{VII} each being N to represent a 1, 2, 4-oxadiazolyl group.

An illustrative compound is given in example 130.

According to a eighth aspect, the present invention is directed to another sub-class of compounds (A) including the non-imidazole compounds having the following formula (VIII), which are analogous to those disclosed in WO 95/06037:

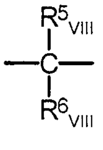


(VIII)

wherein R^1 and R^2 are as defined with reference to formula (A) and wherein

A^{VIII} is

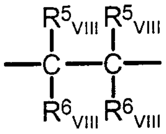
1) a group of the formula $(CH_2)_{mVIII}$, wherein m_{VIII} = 0-9; or
2) a group of the formula:



$$-C(R^5_{VIII})(R^6_{VIII})-$$

wherein R^5_{VIII} represents hydrogen, $(C_1\text{-}C_3)$alkyl-, aryl$(C_1\text{-}C_3)$alkyl-, aryl-, wherein aryl may optionally be substituted, hydroxyl-, $(C_1\text{-}C_3)$alkoxy-, halogen, amino-, cyano- or nitro; and R^6_{VIII} represents hydrogen, $(C_1\text{-}C_3)$alkyl-, aryl$(C_1\text{-}C_3)$alkyl-, or aryl-, wherein aryl may optionally be substituted; or

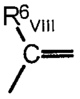
3) a group of the formula:



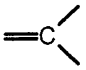
$$-\overset{R^5_{VIII}}{\underset{R^6_{VIII}}{C}}-\overset{R^5_{VIII}}{\underset{R^6_{VIII}}{C}}-$$

wherein R^5_{VIII} and R^6_{VIII} are as defined above; or

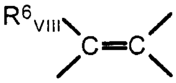
4) a group of the formula:



if B^{VIII} is a group of the formula:

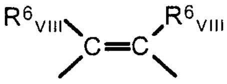


such that A^{VIII} and B^{VIII} together form a group of the formula:



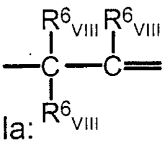
wherein R^6_{VIII} is as defined above; or

5) a group of the formula:



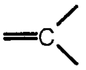
wherein R^6_{VIII} is as defined above; or

6) a group of the formula:

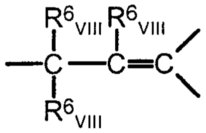


$$-\overset{R^6_{VIII}}{\underset{R^6_{VIII}}{C}}-\overset{R^6_{VIII}}{C}=$$

if B^{VIII} is a group of the formula:



such that A^{VIII} and B^{VIII} together form a group of the formula:



wherein R^6_{VIII} is as defined above; or

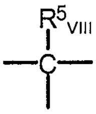
7) a group of the formula:

$$-(CH_2)_{x_{VIII}}-S-(CH_2)_{y_{VIII}}-$$

wherein $x_{VIII} + y_{VIII} = m_{VIII}-1$;

B^{VIII} is

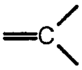
1) a group of the formula:



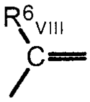
$$-\overset{R^5_{VIII}}{\underset{|}{\overset{|}{C}}}-$$

wherein R^5_{VIII} is as defined above; or

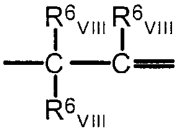
2) a group of the formula:



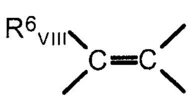
if A is a group of one of the formulas:



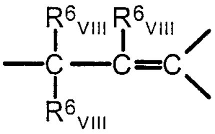
or



such that A and B together form a group of one of the formulas:

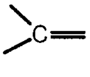


or

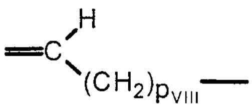


wherein R^6_{VIII} is as defined above; or

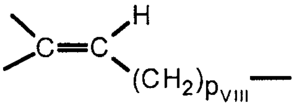
3) a group of the formula:



if X^{VIII} is a group of the formula:



such that B^{VIII} and X^{VIII} together form a group of the formula

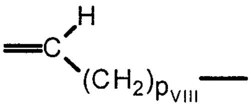


wherein p_{VIII} = 1-3; or

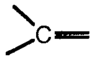
X^{VIII} is

1) a group of the formula $(CH_2)_{nVIII}$ wherein n_{VIII} = 2-4; or

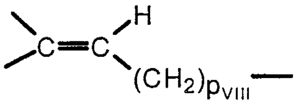
2) a group of the formula:



if B^{VIII} is a group of the formula:



such that X^{VIII} and B^{VIII} together form a group of the formula:



wherein p_{VIII} = 1-3; or

3) two hydrogens (one on the carbon and one on the nitrogen); or

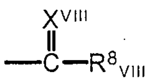
4) one hydrogen on the carbon atom and one R^7_{VIII} group on the nitrogen atom,

wherein R^7_{VIII} represents hydrogen, $(C_1$-$C_{10})$alkyl-, aryl $(C_1$-$C_{10})$alkyl-, or aryl, wherein aryl may optionally be substituted;

Y^{VIII} is a group of the formula $(CH_2)_{kVIII}$, wherein k_{VIII} = 0-2;

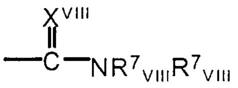
R^4_{VIII} represents hydrogen, $(C_1$-$C_{10})$alkyl-, $(C_1$-$C_3)$alkyl-sulfonamide-, aryl$(C_1$-$C_{10})$alkyl-, aryl, wherein aryl may optionally be substituted;

or a group of the formula:



$$-\overset{X^{VIII}}{\overset{\|}{C}}-R^8_{VIII}$$

or a group of the formula:



$$-\overset{X^{VIII}}{\overset{\|}{C}}-NR^7_{VIII}R^7_{VIII}$$

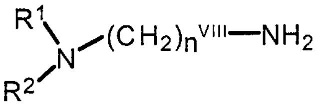
wherein X^{VIII} represents O, S, or NH,

R^7_{VIII} is as defined as above;

R^8_{VIII} represents (C_1-C_{10})alkyl-, aryl(C_1-C_{10})alkyl- or aryl, wherein aryl may optionally be substituted and wherein aryl is phenyl, substituted phenyl, naphtyl, substituted naphtyl, pyridyl.

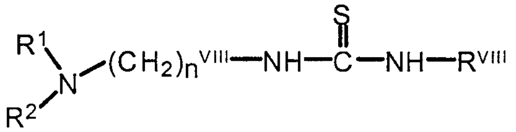
The present invention comprises both linear and ringstructured compounds.

The linear compounds have for example one of the formulas



(VIIIa)

or

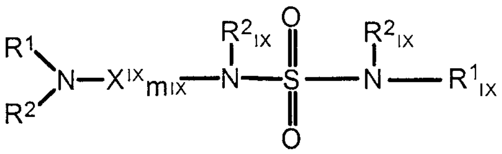


(VIIIb)

Preferred R^1 and R^2 groups are as defined with reference to formula (A).

A compound (VIII) is described in examples 132 and 169.

According to a ninth aspect, the invention is relative to a sub-class of compounds (A) consisting of compounds having the following formula (IX) which are analogous to those described in WO 97/29092:



(IX)

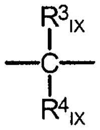
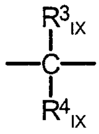
wherein:

R^1 and R^2 are as defined with reference to formula (A)

R^1_{IX} is C_4 to C_{20} hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen, and up to four carbon atoms [and especially from 0 to 3 carbon atoms] may be replaced by oxygen, nitrogen or sulphur atoms, provided that R^1_{IX} does not contain an -O-O-group),

R^2_{IX} identical or different, are H or C_1 to C_{15} hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen, and up to three carbon atoms may be replaced by oxygen, nitrogen or sulphur atoms, provided that R^2_{IX} does not contain an -O-O-group),

m_{IX} is from 1 to 15 (preferably 1 to 10, more preferably 3 to 10, eg. 4 to 9)

each X^{IX} group is independently  $-\overset{R^3_{IX}}{\underset{R^4_{IX}}{C}}-$, or one X^{IX} group is -N(R^4_{IX})-, -O- or -S- (provided that this X^{IX} group is not adjacent the -NR^2_{IX}- group) and the remaining X^{IX} groups are independently  $-\overset{R^3_{IX}}{\underset{R^4_{IX}}{C}}-$, wherein

R^3_{IX} is H, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, -$CO_2R^5_{IX}$, -$CON(R^5_{IX})_2$, -$CR^5_{IX2}OR^6_{IX}$ or -OR^5_{IX} (in which R^5_{IX} and R^6_{IX} are H or C_1 to C_3 alkyl), and R^4_{IX} is H or C_1 to C_6 alkyl.

The term "hydrocarbyl", as used herein, refers to monovalent groups consisting of carbon and hydrogen. Hydrocarbyl groups thus include alkyl, alkenyl, and alkynyl groups (in both straight and branched chain forms), cycloalkyl (including polycycloalkyl), cycloalkenyl, and aryl groups, and combinations of the foregoing, such as alkylaryl, alkenylaryl, alkynylaryl, cycloalkylaryl, and cycloalkenylaryl groups.

A "carbocyclic" group, as the term is used herein, comprises one or more closed chains or rings, which consist entirely of carbon atoms. Included in such groups are alicyclic groups (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl), groups containing both alkyl and cycloalkyl moieties (such as adamantanemethyl), and aromatic groups (such as phenyl, naphthyl, indanyl, fluorenyl, (1,2,3,4)-tetrahydronaphthyl, indenyl and isoindenyl).

The term "aryl" is used herein to refer to aromatic carbocyclic groups, including those mentioned above.

When reference is made herein to a substituted carbocyclic group (such as substituted phenyl), or a substituted heterocyclic group, the substituents are preferably from 1 to 3 in number and selected from C_1 to C_6

alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylthio, carboxy, C_1 to C_6 carboalkoxy, nitro, trihalomethyl, hydroxy, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, aryl, C_1 to C_6 alkylaryl, halo, sulphamoyl and cyano.

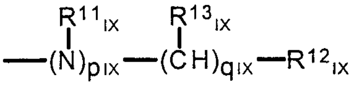
The term "halogen", as used herein, refers to any of fluorine, chlorine, bromine and iodine.

Preferably, R^2_{IX} is selected from H, C_1 to C_6 alkyl, C_1 to C_6 cycloalkyl, C_1 to C_6 hydroxyalkyl, C_1 to C_6 alkylhydroxyalkyl, aryl C_1 to C_6 alkyl and substituted aryl C_1 to C_6 alkyl. For example, R^2_{IX} may be H or C_1 to C_3 alkyl.

In certain embodiments, $-X^{IX}{}_{mIX}-$ is a C_1 to C_8 alkylene group, e.g. a butylene group.

Included in the definition of R^1_{IX} are aryl-containing groups (such as phenyl, substituted phenyl, naphthyl and substituted naphthyl), and (cycloalkyl)alkyl groups (such as cyclohexylpropyl and adamantylpropyl).

Preferably, R^1_{IX} is a group of the formula



$$-(\overset{R^{11}_{IX}}{\overset{|}{N}})_{pIX}-(\overset{R^{13}_{IX}}{\overset{|}{C}}H)_{qIX}-R^{12}_{IX}$$

wherein

p_{IX} is 0 or 1,

R^{11}_{IX} is H or C_1 to C_3 alkyl,

q_{IX} is from 0 to 4,

R^{12}_{IX} is a carboxyclic, substituted carbocyclic, heterocyclic or substituted heterocyclic group, and

R^{13}_{IX} is independently selected from H, C_1 to C_6 alkyl, C_1 to C_6 cycloalkyl, C_1 to C_6 hydroxyalkyl, C_1 to C_6 alkylhydroxyalkyl, aryl C_1 to C_6 alkyl and substituted aryl C_1 to C_6 alkyl.

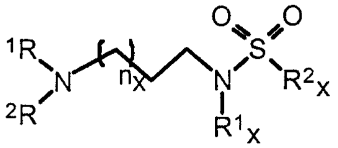
Preferably, R^{13}_{IX} is hydrogen.

Compounds (IX) wherein R^1_{IX} is a group $-NH-CH_2-Ph$ where Ph represents an optionally substituted phenyl, are preferred.

Preferred groups R^1 and R^2 are as specified with reference to formula (A).

An illustrative example is compound 173.

According to a tenth aspect, the present invention is relative to another sub-class of compounds (A) comprising compounds having the following formula (X), which are analogous to compounds disclosed by Wolin et al. (Bioorg. & Med. Chem. Lett., 8, 2157 (1998)):



(X)

wherein:

- R^1 and R^2 are as defined with reference to formula (A);
- R^1_x is H or CH_3;
- R^2_x is selected from a phenyl optionally substituted with a halogen atom, preferably chlorine, a $(C_1$-$C_4)$alkyl, a $(C_1$-$C_4)$alkoxy, CF_3, OCF_3, NO_2, NH_2; or a CH_2-phenyl optionally substituted as above-specified;
- n_x is from 0 to 3.

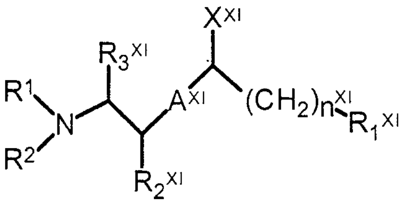
n_x is preferably 1. R^2 is preferably a phenyl group, especially a mono-substituted phenyl group.

Preferred R^1 and R^2 are as above-specified for formula (A).

Compound 174 is illustrative of compounds (X).

According to a eleventh aspect, the invention is directed to non-imidazole compounds which are analogous to those disclosed in WO 96/38142.

Thus, another sub-class of compounds (A) of the invention is directed to compounds having the following formula (XI):



(XI)

where R^1 and R^2 are as defined with reference to formula (A);

where A^{XI} is -NHCO-, -N(CH_3)-CO-, -NHCH_2-, -N(CH_3)-CH_2-, -CH=CH-, -COCH_2-, CH_2CH_2-, -CH(OH)CH_2-, or –C≡C– ;

X^{XI} is H, CH_3, NH_2, NH(CH_3), N(CH_3)$_2$, OH, OCH_3, or SH;

R_2^{XI} is hydrogen or a methyl or ethyl group;

R_3^{XI} is hydrogen or a methyl or ethyl group;

n^{XI} is 0, 1, 2, 3, 4, 5 or 6; and

R_1^{XI} is selected from the group consisting of C_3 to C_8 cycloalkyl; phenyl or substituted phenyl; decahydronaphthalene and octahydroindene; or

R_1^{XI} and X^{XI} may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X^{XI} is NH, O, S, or SO_2.

Preferably for compounds of formula (XI):

A^{XI} is -NHCO-, -N(CH_3)-CO-, -NHCH_2-, -N(CH_3)-CH_2-, -CH=CH-, -COCH_2-, -CH_2CH_2-, -CH(OH)CH_2-, or -C≡C-;

X^{XI} is H, CH_3, NH_2, NH(CH_3), N(CH_3)$_2$, OH, OCH_3, or SH;

R_2^{XI} is hydrogen or a methyl or ethyl group;

R_3^{XI} is hydrogen or a methyl or ethyl gorup;

n^{XI} is 0, 1, 2, 3, 4, 5, or 6; and

R_1^{XI} is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic (e) decahydronaphthalene and (f) octahydroindene; or

R_1^{XI} and X^{XI} may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X^{XI} can be NH, O, or S.

More preferably, the present invention provides compounds

where A^{XI} is -NHCH_2-, -N(CH_3)-CH_2-, -CH=CH-, -COCH_2-, -CH_2CH_2, -CH(OH)CH_2-, or -C≡C-;

X^{XI} is H, CH_3, NH_2, NH(CH_3), N(CH_3)$_2$, OH, OCH_3, or SH;

$R^{XI}{}_2$ is hydrogen or a methyl or ethyl group;

$R^{XI}{}_3$ is hydrogen or a methyl or ethyl group;

n^{XI} is 0, 1, 2, 3, 4, 5, or 6; and

$R^{XI}{}_1$ is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic; (e) decahydronaphthalene and (f) octahydroindene; or

R^{XI}_1 and X^{XI} may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X^{XI} can be NH, O, or S.

Most preferably, the present invention provides compounds where A^{XI} is –CH=CH or –C≡C-;

X^{XI} is H, CH_3 or NH_2;

R_2^{XI} and R_3^{XI} are H;

n^{XI} is 1, 2, or 3;

R_1^{XI} is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl or substituted phenyl; (d) heterocyclic; (e) decahydronaphthalene and (f) octahydroindene; or

R_1^{XI} and X^{XI} may be taken together to denote a 5,6 or 6,6 saturated bicyclic ring structure when X^{XI} is NH, O, or S.

The term "substituted phenyl" as used herein refers to a phenyl group substituted by one or more groups such as alkyl, halogen, amino, methoxy and cyano groups.

The term "alkyl" refers to straight or branched chain radicals. Representative examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl and the like.

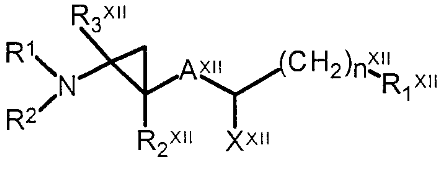
Compounds (XI) where A^{XI} is -CH=CH- or –C≡C-, X^{XI}, R_2^{XI} and R_3^{XI} are each H, n_{XI} is 1 and R_1^{XI} is a C_3-C_8 cycloalkyl, are especially preferred.

R^1 and R^2 are preferably selected as above-indicated in reference to formula (A).

Representative particularly preferred compounds are compounds 177, 178 or 179.

According to a twelfth aspect, the invention concerns non-imidazole compounds which are analogous to those disclosed in WO 96/38141.

Thus, the invention is relative to compounds having the following formula (XII):



(XII)

where R^1 and R^2 are as defined in reference to formula (A),
where R_2^{XII} is a hydrogen or a methyl or ethyl group;
R_3^{XII} is a hydrogen or a methyl or ethyl group;
n^{XII} is 0, 1, 2, 3, 4, 5, or 6; and
R_1^{XII} is selected from the group consisting of (a) C_3 to C_8 cycloalkyl; (b) phenyl substituted or not by one or more groups such as a halogen atom, a lower alkyl or cycloalkyl, a trifluoromethyl, aryl, alkoxy, α-alkyloxyalkyl, aryloxy, nitro, formyl, alkanoyl, aroyl, arylalkanoyl, amino, carboxamido, cyano, alkyloximino, alkylalkoximino, aryloximino, α-hydroxyalkyl, alkenyl, alkynyl, sulphamido, sulfamoyl, sulphonamido, carboxamide, carbonylcycloalkyl, alkylcarbonylalkyl, carboalkoxy, arylalkyl or oxime group, or two substituants taken together with the carbon atoms of the phenyl ring to which it is fused form 5- or 6-membered saturated or unsaturated ring or a benzene ring ; (c) alkyl; (d) heterocyclic; (e) decahydronaphthalene; and (f) octahydroindene;
with the provisos that
when X^{XII} is H, A^{XII} can be $-CH_2CH_2-$, $-COCH_2-$, -CONH-, $-CON(CH_3)-$, -CH=CH-, -C≡C-, $-CH_2-NH-$, $-CH_2-N(CH_3)-$, $-CH(OH)CH_2-$, $-NH-CH_2-$, $-N(CH_3)-CH_2-$, $-CH_2O-$, $-CH_2S-$, or –NHCOO-;
when X^{XII} is NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH, OCH_3, CH_3, SH or SCH_3; A^{XII} can be -NHCO-, $-N(CH_3)-CO-$, $-NHCH_2-$, $-N(CH_3)-CH_2-$, -CH=CH-, $-COCH_2-$, $-CH_2CH_2-$, $-CH(OH)CH_2-$, or -C≡C- ; and
when R_1^{XII} and X^{XII} taken together denote a 5,6 or 6,6 saturated bicyclic ring structure X^{XII} can be NH, O, or S.

The term "alkyl" as used herein refers to straight or branched chain radicals derived from saturated hydrocarbons by the removal of one hydrogen atom. Representative examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, and the like.

The term "substituted phenyl" as used herein refers to a phenyl group substituted by one or more groups such as alkyl, halogen, amino, methoxy, and cyano groups.

The term "bicyclic alkyl" as used herein refers to an organic compound having two ring structures connected to an alkyl group. They may or may not be the same type of ring and the rings may be substituted by one or more groups. Representative bicyclic alkyl groups include adamanthyl, decahydronaphthalene and norbornane.

The cyclopropane attached to the NR^1R^2 moiety is preferably in trans configuration.

More preferably, the present invention provides compounds of the general formula (XII) :

where A^{XII} is -CONH, -CH=CH-, -NHCOO-, or -C≡C-;

X^{XII} is H or NH_2;

R_2^{XII} and R_3^{XII} are H;

n^{XII} is 0, 1, 2 or 3;

R_1^{XII} is cyclohexyl, phenyl or substituted phenyl.

In compounds (XII), A^{XII} is especially -CH=CH- or -C≡C-;

R_2^{XII}, R_3^{XII} and X^{XII} are each especially a hydrogen atom;

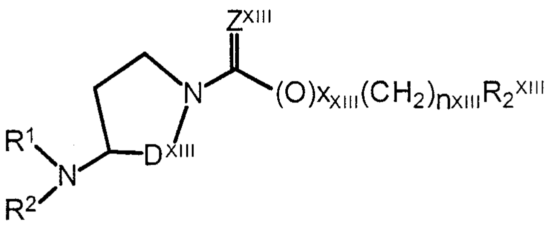
n_{XII} is preferably 1 and R_1^{XII} is especially an alkyl group.

R^1 and R^2 are preferably selected as above-indicated with reference to formula (A).

Representative example of compounds (XII) is compound 180.

According to a thirteenth aspect, the invention is directed to non-imidazole compounds analogous to those disclosed in WO 95/11894.

Thus, the present invention is relative to a sub-class of compounds (A) comprising compounds having the following formula (XIII):



(XIII)

wherein R^1 and R^2 are as defined with reference to formula (A)
wherein D^{XIII} is CH_2 or CH_2-CH_2, Z^{XIII} represents sulfur (S) or oxygen (O), preferably O, X_{XIII} is 0 or 1, n_{XIII} is an integer from 0 to 6,
and R_2^{XIII} represents a substituted or unsubstituted linear chain or branched chain alkyl group of up to about 20 carbon atoms, a substituted or unsubstituted carbocyclic group of up to about 20 carbon atoms including mono and bicyclic moieties, and a substituted or an unsubstituted aryl group of up to about 20 carbon atoms, or any combination of above-mentioned groups, or salts thereof and with the substituants being represented by one or more groups such as a halogen atom, a lower alkyl or cycloalkyl, a trifluoromethyl, aryl, alkoxy, α-alkyloxyalkyl, aryloxy, nitro, formyl, alkanoyl, aroyl, arylalkanoyl, amino, carboxamido, cyano, alkyloximino, alkylalkoximino, aryloximino, α-hydroxyalkyl, alkenyl, alkynyl, sulphamido, sulfamoyl, sulphonamido, carboxamide, carbonylcycloalkyl, alkylcarbonylalkyl, carboalkoxy, arylalkyl or oxime group, or two substituants taken together with the carbon atoms of the phenyl ring to which it is fused form 5- or 6-membered saturated or unsaturated ring or a benzene ring.

In a specific embodiment, R_2^{XIII} can represents a disubstituted methyl, such as but not limited to dicyclohexyl methyl ($-CH(C_6H_{11})_2$), diphenyl methyl ($-CH(C_6H_5)_2$), and the like. If R_2^{XIII} is tert-butyl, cyclohexyl, or dicyclohexylmethyl, X_{XIII} or n_{XIII} must not be 0. If R_2^{XIII} is adamantane, the sum of x_{XIII} and n_{XIII} must be greater than 1.

In a preferred embodiment, D^{XIII} is CH_2-CH_2, resulting in a piperidine ring structure. However, it is contemplated that D^{XIII} can be CH_2, yielding a pyrrolidine ring structure. In yet another embodiment, D^{XIII} can be $(CH_2)_3$, yielding a cycloheptimide (seven membered heterocycle with one nitrogen).

In a specific embodiment, a tetramethylene bound to the amide or carbamate group is used. Preferably a cyclic alkyl or aryl group is linked to the amide or carbamate via the straight chain alkyl group. In a specific embodiment, tetramethylene cyclohexane (cyclohexylbutyl) is bound to an amide. Although specific hydrophobic alkyl and aryl groups have been mentioned, one of ordinary skill in the art will recognize that there are many possible hydrophobic groups for use in the compounds of the invention. These fall within the scope of the instant invention.

Thus, R_2^{XIII} can be one or more bulky substituent groups. As stated above, in a preferred aspect of the invention, the bulky substituents are removed from the amide or carbamate group on the piperidyl, by increasing n_{XIII}. In one embodiment, R_2^{XIII} is $CHR_3^{XIII}R_4^{XIII}$, in which n_{XIII} is 3 or 4 and R_3^{XIII} and R_4^{XIII} are cyclohexyl, phenyl, or the like. R_3^{XIII} and R_4^{XIII} can be the same group or different groups. In another embodiment, R_2^{XIII} is decalin or adamantane or the like. If R_2^{XIII} is adamantane, preferably n_{XIII} is greater than 1, but the sum of x_{XIII} and n_{XIII} must be greater than 1.

As used herein, the phrase linear chain or branched chained alkyl groups of up to about 20 carbon atoms means any substituted or unsubstituted acyclic carbon-containing compounds, including alkanes, alkenes and alkynes. Examples of alkyl groups include lower alkyl, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl; upper alkyl, for example, octyl, nonyl, decyl, and the like; and lower alkylene, for example, ethylene, propylene, propyldiene, butylene, butyldiene, and the like. The ordinary skilled artisan is familiar with numerous linear and branched alkyl groups, which are with the scope of the present invention.

In addition, such alkyl group may also contain various substituents in which one or more hydrogen atoms has been replaced by a functional group. Functional groups include but are not limited to hydroxyl, amino, carboxyl, amide, ester, ether, and halogen (fluorine, chlorine, bromine and iodine), to mention but a few.

As used herein, substituted and unsubstituted carbocyclic groups of up to about 20 carbon atoms means cyclic carbon-containing compounds, including but not limited to cyclopentyl, cyclohexyl, cycloheptyl, admantyl, and the like. Such cyclic groups may also contain various substituents in which one or more hydrogen atoms has been replaced by a functional group. Such functional groups include those described above, and lower alkyl groups as describe above. The cyclic groups of the invention may further comprise a heteroatom. For example, in a specific embodiment, R_2^{XIII} is cyclohexanol.

As used herein, substituted and unsubstituted aryl groups means a hydrocarbon ring bearing a system of conjugated double bonds, usually comprising six or more even number of π (pi) electons. Examples of aryl groups include, by are not limited to, phenyl, naphthyl, anisyl, toluyl, xylenyl and the like. According to the present invention, aryl also includes heteroaryl groupss, e.g., pyrimidine or thiophene. These aryl groups may also be substituted with any number of a variety of functional groups. In addition to the functional groups described above in connection with substituted alkyl groups and carbocyclic groups, functional groups on the aryl groups can be nitro groups.

As mentioned above, R_2^{XIII} can also represents any combination of alkyl, carbocyclic or aryl groups, for example, 1-cyclohexylpropyl, benzyl cyclohexylmethyl, 2-cyclohexylpropyl, 2,2-methylcyclohexylpropyl, 2,2-methylphenylpropyl, 2,2-methylphenylbutyl.

In a specific embodiment, R_2 represents cyclohexane, and n_{XIII}=4 (cyclohexylvaleroyl). In another specific embodiment, R_2^{XIII} represents cinnamoyl.

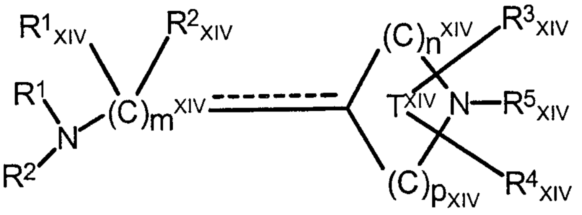
Particularly preferred are compounds (XIII) wherein Z^{XIII} is an oxygen atom and wherein x_{XIII} is 0 or 1, n_{XIII} is an integer from 0 to 6, more preferably n_{XIII} = 3-6, and most preferably n_{XIII}=4, and R_2^{XIII} is as defined above. Examples of preferred alkyl groups for R_2^{XIII} include but are not limited to cyclopentyl, cyclohexyl, admantane methylene, dicyclohexyl methyl, decanyl and t-butyryl and the like. Examples of preferred aryl and substituted aryl groups include but are not limited to phenyl, aryl cyclohexyl methyl and the like.

Preferred R^1 and R^2 are selected as indicated with reference to formula (A).

Representative examples are compounds 123 and 176.

According to a fourteenth aspect, the present invention is directed to compounds analogous to those disclosed in WO 93/12107.

Thus, a sub-class of compounds (A) of the invention concerns compounds having the following formula (XIV)



(XIV)

wherein R^1 and R^2 are as defined in reference of formula (A);

(A) m_{XIV} is an integer selected from the group consisting of: 1 and 2;

(B) n_{XIV} and p_{XIV} are intergers and are each independently selected from the group consisting of: 0, 1, 2, 3, and 4 such that the sum of n_{XIV} and p_{XIV} is 4 and T^{XIV} is a 6-membered ring;

(C) R^3_{XIV} and R^4_{XIV} are each independently bound to the same or different carbon atom of ring T^{XIV} such that there is only one R^3_{XIV} group and one R^4_{XIV} group in ring T^{XIV}, and each R^1_{XIV}, R^2_{XIV}, R^3_{XIV} and R^4_{XIV} is independently selected from the group consisting of:

(1) H;

(2) C_1 to C_6 akyl; and

(3) $-(CH_2)_{qXIV}-R^6_{XIV}$ wherein q_{XIV} is an integer of: 1 to 7, and R^6_{XIV} is selected from the group consisting of: phenyl, substituted phenyl, $-OR^7_{XIV}$, $-C(O)OR^7_{XIV}$, $-C(O)R^7_{XIV}$, $-OC(O)R^7_{XIV}$, $-C(O)NR^7_{XIV}R^8_{XIV}$, CN and $-SR^7_{XIV}$ wherein R^7_{XIV} and R^8_{XIV} are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C_1 to C_6)alkyl, halogen, C_1 to C_6 alkyl, $-CF_3$, -CN, and $-NO_2$, and wherein said substituted phenyl contains from 1 to 3 substituents;

(D) R^5_{XIV} is selected from the group consisting of:

(1) H;

(2) C_1 to C_{20} alkyl;

(3) C_3 to C_6 cycloalkyl;

(4) -C(O)OR$^{7'}_{XIV}$; wherein R$^{7'}_{XIV}$ is the same as R$^{7}_{XIV}$ defined below except that R$^{7'}_{XIV}$ is not H;

(5) -C(O)R$^{7'}_{XIV}$;

(6) -C(O)NR$^{7'}_{XIV}$R$^{8}_{XIV}$;

(7) allyl;

(8) propargyl; and

(9) -$(CH_2)_q$-R$^{6}_{XIV}$ wherein q_{XIV} and R$^{6}_{XIV}$ are as defined above, and when q_{XIV} is equal to 1, then R$^{6}_{XIV}$ is not OH or SH;

(E) R$^{7}_{XIV}$ and R$^{8}_{XIV}$ are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and C_3 to C_6 cycloalkyl;

(F) the dotted line (--------) represents a double bond that is optionally present when m_{XIV} is 1, and n_{XIV} is not 0, and p is not 0 (i.e., the nitrogen in the ring is not bound directly to the carbon atom bearing the double bond), and when said double bond is present then R$^{2}_{XIV}$ is absent; and

(G) when m_{XIV} is 2, each R$^{1}_{XIV}$ is the same or different substituent for each m_{XIV}, and each R$^{2}_{XIV}$ is the same or different substituent for each m_{XIV}, and at least two of the substituents R$^{1}_{XIV}$ and/or R$^{2}_{XIV}$ are H.

Those skilled in the art will appreciate that the total number of substituents on each of the -$(C)_n{}^{XIV}$- and -$(C)_p{}^{XIV}$- groups is two, and that such substituents are independently selected from the group consisting of hydrogen, R$^{3}_{XIV}$ and R$^{4}_{XIV}$ such that there is a total of only one R$^{3}_{XIV}$ and one R$^{4}_{XIV}$ substituent in ring T^{XIV}.

As used herein the following terms have the following meanings unless indicated otherwise:

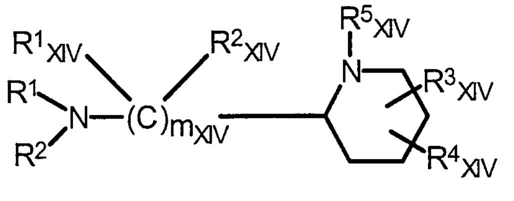
alkyl – represents a straight or branched, saturated hydrocarbon chain having from 1 to 20 carbon atoms;

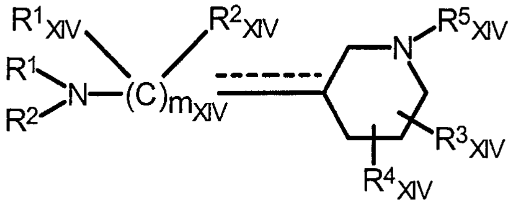
cycloalkyl – represents a saturated carbocyclic ring having from 3 to 6 carbon atoms;

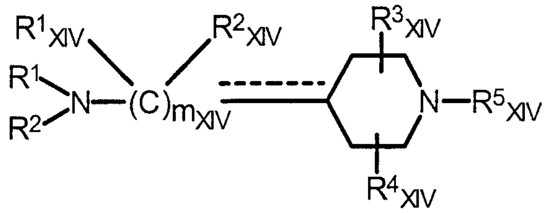
halogen (halo) – represents fluoro, chloro, bromo or iodo.

Preferably, for compounds of formula (XIV) m is 1; R^5_{XIV} is selected from the group consisting of H and C_1 to C_{15} alkyl; and R^1_{XIV} to R^4_{XIV} are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and $-(CH_2)_{qXIV}-R^6_{XIV}$ wherein R^6_{XIV} is phenyl. Most preferably, R^5_{XIV} is selected from the group consisting of H and C_1 to C_6 alkyl with H and methyl being even more preferable; and R^3_{XIV} and R^4_{XIV} are each independently selected from the group consisting of: H and methyl.

Representative compounds of this invention include compounds of the formula:


; (XIVa)


; and (XIVb)


(XIVc)

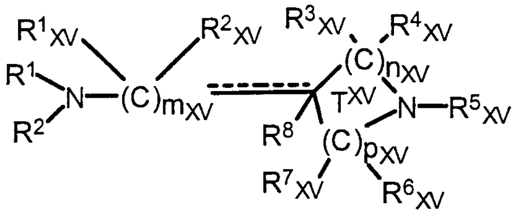
.

For formula (XIVa), (XIVb) or (XIVc), R^5_{XIV} is preferably H or CH_3; R^3_{XIV} and R^4_{XIV} are preferably each an hydrogen atom.

Preferred R^1 and R^2 are as specified for formula (A).

According to a fifteenth aspect, the invention is directed to compounds analogous to those disclosed in WO 93/12108.

Thus, the invention concerns compounds having the following formula (XV):


(XV)

wherein R^1 and R^2 are as defined in reference to formula (A)

(A) m_{XV} is an integer selected from the group consisting of: 0,1, and 2;

(B) n_{XV} and p_{XV} are integers and are each independently selected from the group consisting of: 0, 1, 2, and 3 such that the sum of n_{XV} and p_{XV} is 2 or 3 such that when the sum of n_{XV} and p_{XV} is 2, T^{XV} is a 4-membered ring and when the sum of n_{XV} and p_{XV} is 3, T^{XV} is a 5-membered ring;

(C) each R^1_{XV}, R^2_{XV}, R^3_{XV}, R^4_{XV}, R^6_{XV}, R^7_{XV} and R^8_{XV} is independently selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl;

(3) C_3 to C_6 cycloalkyl; and

(4) $-(CH_2)_q{}^{XV}-R^9{}_{XV}$ wherein q_{XV} is an integer of: 1 to 7, and $R^9{}_{XV}$ is selected from the group consisting of: phenyl, substituted phenyl, $-OR^{10}{}_{XV}$, $-C(O)OR^{10}{}_{XV}$, $-C(O)R^{10}{}_{XV}$, $-OC(O)R^{10}{}_{XV}$, $-C(O)NR^{10}{}_{XV}R^{11}{}_{XV}$, CN and $-SR^{10}{}_{XV}$ wherein $R^{10}{}_{XV}$ and $R^{11}{}_{XV}$ are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C_1 to C_6) alkyl, halogen, C_1 to C_6 alkyl, $-CF_3$, -CN, and $-NO_2$, and wherein said substituted phenyl contains from 1 to 3 substituents; examples of $-(CH_2)_{qXV}-R^9{}_{XV}$ include benzyl, substituted benzyl and the like, wherein the substitutents on the substituted benzyl are as defined above for said substituted phenyl;

(D) $R^5{}_{XV}$ is selected from the group consisting of:

(1) H;

(2) C_1 to C_{20} alkyl;

(3) C_3 to C_6 cycloalkyl;

(4) $-C(O)OR^{10'}{}_{XV}$; wherein $R^{10'}{}_{XV}$ is the same as $R^{10}{}_{XV}$ defined below except that $R^{10'}{}_{XV}$ is not H;

(5) $-C(O)R^{10}{}_{XV}$;

(6) $-C(O)NR^{10}{}_{XV}R^{11}{}_{XV}$;

(7) allyl;

(8) propargyl; and

(9) $-(CH_2)_q{}^{XV}-R^9{}_{XV}$, wherein q_{XV} and $R^9{}_{XV}$ are as defined above with the proviso that when q_{XV} is 1 then $R^9{}_{XV}$ is not -OH or -SH;

(E) $R^{10}{}_{XV}$ and $R^{11}{}_{XV}$ are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and C_3 to C_6 cycloalkyl; and, for the substituent $-C(O)NR^{10}{}_{XV}R_{XV}{}^{11}$, $R^{10}{}_{XV}$ and $R^{11}{}_{XV}$, together with the nitrogen to which they are bound, can form a ring having 5, 6, or 7 atoms;

(F) the dotted line (-----) represents a double bond that is optionally present when m_{XV} is 1, and T^{XV} is a 5-membered ring, and n_{XV} is not 0, and p_{XV} is not 0 (i.e., the nitrogen in the ring is not bound directly to the carbon atom bearing the double bond), and when said double bond is present then $R^2{}_{XV}$ and $R^8{}_{XV}$ are absent;

(G) when m_{XV} is 2, each $R^1{}_{XV}$ is the same or different substituent for each m_{XV}, and each $R^2{}_{XV}$ is the same or different substituent for each m_{XV};

(H) when n_{XV} is 2 or 3, each $R^3{}_{XV}$ is the same or different substituent for each n_{XV}, and each $R^4{}_{XV}$ is the same or different substituent for each n_{XV}; and

(I) when p_{XV} is 2 or 3, each $R^6{}_{XV}$ is the same or different substituent for each p, and each $R^7{}_{XV}$ is the same or different substituent for each p_{XV}.

As used herein the following terms have the following meanings unless indicated otherwise:

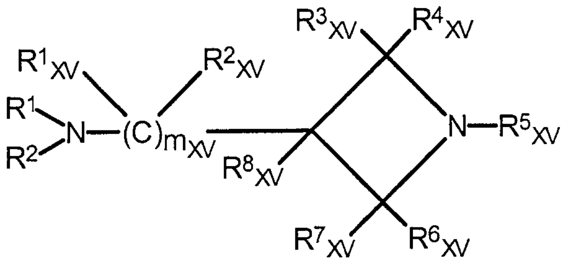
alkyl – represents a straight or branched, saturated hydrocarbon chain having from 1 to 20 carbon atoms;

cycloalkyl – represents a saturated carbocyclic ring having from 3 to 6 carbon atoms; and

halogen (halo) –represents fluoro, chloro, bromo or iodo.

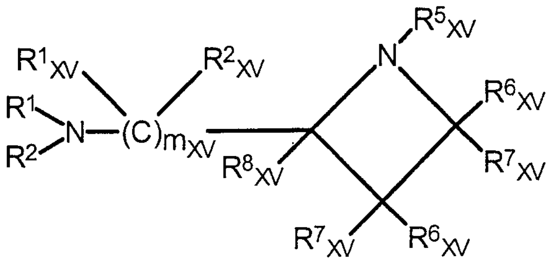
Preferably, for compounds of formula (XV) m_{XV} is 0 or 1; R^5_{XV} is selected from the group consisting of H and C_1 to C_{20} alkyl; and R^1_{XV} to R^4_{XV} and R^6_{XV} to R^8_{XV} are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and $-(CH_2)_{qXV}-R^9_{XV}$ wherein R^9_{XV} is phenyl. Most preferably, R^5_{XV} is selected from the group consisting of H and methyl; and R^1_{XV}, R^2_{XV}, R^3_{XV}, R^4_{XV}, R^6_{XV}, R^7_{XV}, and R^8_{XV} are each independently selected from the group consisting of: H, methyl, ethyl, pentyl, benzyl, and 2-phenylethyl.

Representative compounds of this invention include compounds of the formula:



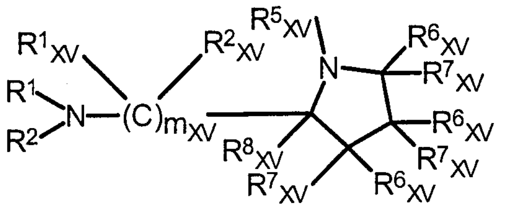
(XVa)

;



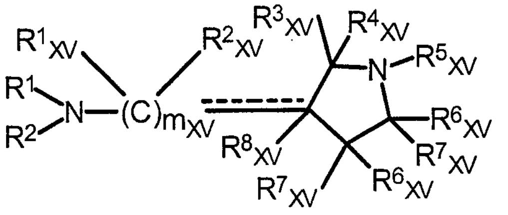
(XVb)

;



(XVc)

; and



(XVd)

.

wherein m_{XV} and R^1_{XV} to R^8_{XV} are as defined for formula (XV)

Compounds (XVc) or (XVd) are preferred.

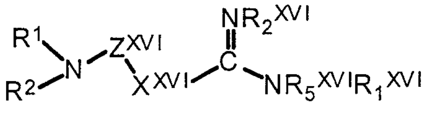
Representative compounds (XVa) to (XVd) are those wherein R^5_{XV} is H or CH_3.

Preferably, only one or two of substituents R^3_{XV}, R^4_{XV}, R^6_{XV}, R^7_{XV}, R^8_{XV} is different from H and represents especially CH_3.

R^1 and R^2 are preferably selected as indicated in reference to formula (A).

According to a sixteenth aspect, the invention is directed to compounds analogous to those disclosed in WO 92/15567.

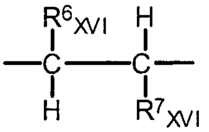
Thus, the invention is relative to a sub-class of compounds (A) consisting of compounds having the following formula (XVI)



(XVI)

wherein R^1 and R^2 are as defined in reference to formula (A)

Z^{XVI} is a group of the formula $(CH_2)_{mXVI}$ wherein m_{XVI} = 1-5 or a group of the formula:



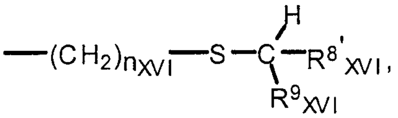
$$-\overset{R^6_{XVI}}{\underset{H}{C}}-\overset{H}{\underset{R^7_{XVI}}{C}}-$$

, wherein $R^6_{XVI} = (C_1\text{-}C_3)$alkyl
$R^7_{XVI} = (C_1\text{-}C_3)$alkyl ;

wherein Z^{XVI} may optionally comprise other substituents selected such that the activity of the derivative is not negatively affected,

X^{XVI} represents S, NH or CH_2

R^1_{XVI} represents hydrogen, $(C_1\text{-}C_3)$alkyl-, aryl$(C_1\text{-}C_{10})$alkyl, wherein aryl may optionally be substituted, aryl, $(C_5\text{-}C_7)$cycloalkyl$(C_1\text{-}C_{10})$alkyl-, or a group of the formula:



$$-(CH_2)_{n_{XVI}}-S-\overset{H}{\underset{R^9_{XVI}}{C}}-R^{8'}_{XVI},$$

wherein n_{XVI} = 1-4, R^8_{XVI} is aryl, aryl$(C_1\text{-}C_{10})$alkyl-, $(C_5\text{-}C_7)$cycloalkyl- or $(C_5\text{-}C_7)$ cycloalkyl$(C_1\text{-}C_{10})$alkyl-, and R^9_{XVI} is hydrogen, $(C_1\text{-}C_{10})$alkyl- or aryl; R_2^{XVI} and R_5^{XVI} represent hydrogen, $(C_1\text{-}C_3)$alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted; wherein aryl is phenyl, substituted phenyl, naphthyl, substituted napththyl, pyridyl or substituted pyridyl;

R_2^{XVI} and R_5^{XVI} are preferably a hydrogen atom.

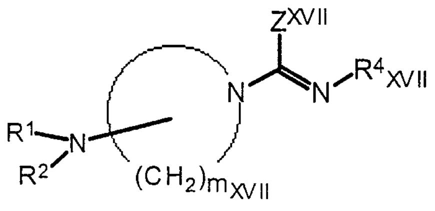
m_{XVI} is preferably 2 or 3

X^{XVI} is preferably S or NH

R_1^{XVI} is preferably selected from H or an optionally substituted aryl.

Preferred R^1 and R^2 are selected as specified for formula A.

According to a seventeenth aspect, a sub-class of compounds (A) of the invention comprises compounds having the following formula (XVII), which can be considered as analogous to those disclosed in EP 680 960:



XVII

Wherein m_{XVII} represents an integer of from 4 to 6.

R^4_{XVII} represents a hydrogen atom, a linear or branched alkyl group, a cycloalkyl group, a cycloalkylalkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group; and Z^{XVII} represents R^5_{XVII} or A^{XVII}-R^6_{XVII}, wherein A^{XVII} represents S or O, R_5^{XVII} represents a hydrogen atom, a lower alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, and R_6^{XVII} represents a lower alkyl group, a lower alkenyl group, a lower alkynyl group or a substituted or unsubstituted aralkyl group;

The lower alkyl groups are preferably linear or branched alkyl groups having 1 to 6 carbon atoms. Specific examples thereof include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl groups.

The linear or branched alkyl groups are preferably those having 1 to 8 carbon atoms. Specific examples thereof include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl and 1,2,2-trimethylpropyl groups.

The cycloalkyl groups are preferably those having 3 to 10 carbon atoms. The cycloalkyl groups include not only monocycloalkyl groups (for example, cyclopentyl, cyclohexyl and cycloheptyl) but also polycycloalkyl groups (for example, bicycloalkyl and tricycloalkyl). Examples of the bicycloalkyl groups include norbornyl (for example, exo-2-norbornyl and endo-2-norbornyl), 3-pinanyl and bicyclo[2.2.2]oct-2-yl groups, while examples of the tricycloalkyl groups include adamantyl groups (for example, 1-adamantyl and 2-adamantyl). Such a cycloalkyl group may be substituted by alkyl group(s), etc.

The cycloalkylalkyl groups are preferably those composed of a cycloalkyl group having 3 to 10 carbon atoms with a linear or branched alkyl group having 1 to 3 carbon atoms. Specific examples thereof include 1-cyclohexylethyl and 1-cyclopropylethyl groups.

The lower alkenyl groups are preferably linear or branched alkenyl groups having 3 to 6 carbon atoms. Specific examples thereof include allyl, 1-

methyl-2-propenyl, 2-methyl-2-propenyl, cis-2-butenyl, trans-2-butenyl and 3-methyl-2-butenyl groups.

The lower alkynyl groups are preferably those having 3 to 6 carbon atoms. A specific example thereof includes a 2-propynyl group.

The substituted aryl groups are preferably phenyl and naphthyl groups which may be substituted by halogen atoms and trifluoromethyl, lower alkyl, lower alkoxy, lower alkylthio, cyano and nitro groups.

Specific examples thereof include phenyl, 1-naphthyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 3-fluorophenyl, 4-fluorophenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-tolyl and 3-tolyl groups.

The aralkyl groups are preferably benzyl, diarylmethyl and trityl groups.

The substituted aralkyl groups are preferably arylalkyl groups composed of a phenyl or naphthyl group, which may be substituted by halogen atoms and trifluoromethyl, lower alkyl, lower alkoxy, lower alkylthio, cyano and nitro groups, and a linear or branched alkyl group having 1 to 4 carbon atoms.

Specific examples thereof include benzyl, α-methylbenzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 4-chlorobenzyl, 4-fluorobenzyl, 4-methoxybenzyl, 4-chloro-α-methylbenzyl, 4-fluoro-αmethylbenzyl and 4-methoxy-α-methylbenzyl groups.

Among the compounds represented by the general formula (XVII) preferable examples include those wherein:

m_{XVII} is from 4 to 6;

R^4_{XVII} is a hydrogen atom; a linear or branched alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 10 carbon atoms, a cycloalkylalkyl group composed of a cycloalkyl moiety having 3 to 10 carbon atoms and an alkyl moiety having 1 to 3 carbon atoms, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group carrying an alkyl moiety having 1 to 4 carbon atoms;

R^5_{XVII} is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group carrying an alkyl moiety having 1 to 4 carbon atoms; and

R^6_{XVII} is an alkyl group having 1 to 6 carbon atoms, an alkenyl group having 3 to 6 carbon atoms, an alkynyl group having 3 to 6 carbon atoms or a substituted or unsubstituted aryl group.

Preferable examples of the compounds represented by the general formula (XVII) are those satisfying the following requirements:

(1) A compound wherein m^{XVII} is 5 and R^1, R^2 and R^3 are each a hydrogen atom.

(2) A compound wherein R^4_{XVII} is a cycloalkyl group, such as monocycloalkyl, bicycloalkyl and tricycloalkyl groups. A preferable example of the monocycloalkyl group is a cyclohexyl group. A preferable example of the bicycloalkyl group is a norbornyl group, more preferably a 2-exo-norbornyl group. A preferable example of the tricycloalkyl group is an adamantyl group, more preferably a 1-adamantyl group.

(3) A compound wherein R^4_{XVII} is a substituted or unsubstituted phenyl group or a substituted or unsubstituted phenylalkyl group.

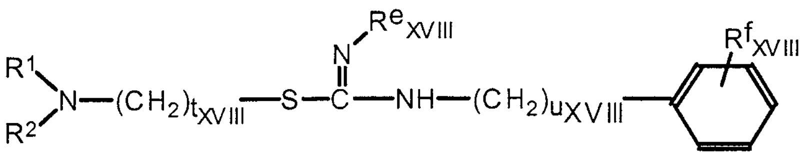
(4) A compound wherein R^5_{XVII} is a hydrogen atom.

(5) A compound wherein A^{XVII} is S and R^6_{XVII} is a lower alkyl group.

(6) A compound wherein a lower alkyl group is a methyl group.

R^1 and R^2 are preferably selected as specified for the formula (A).

According to a eighteenth aspect, the invention is directed to non imidazole compounds having the following formula (XVIII), analogous to those disclosed in Van der Goot et al. (Eur. J. Med. Chem. (1992) 27, 511-517):



(XVIII)

in which:

- R^1 and R^2 are as defined with reference to formula (A);
- R^e_{XVIII} is H, alkyl or cycloalkyl;
- R^f_{XVIII} is H or halogen, in particular Cl, F, Br, or an alkyl;
- t_{XVIII} is 1 to 3;
- u_{XVIII} is 1 to 4.

Preferred groups R^1 and R^2 are as defined with reference to formula (A).

Representative example is compound 122 and 167.

According to the invention, the W residue as defined in formula (A) and in particular as illustrated by formulae (I) to (XVIII), preferably contains no imidazole moiety attached in 4(5)-position and more preferably W contains no imidazole moiety.

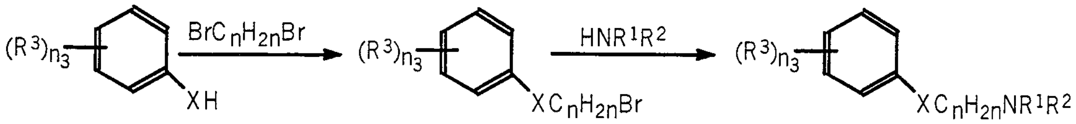
The compounds according to the invention may be prepared according to one of the following schemes:

More specifically, compounds of formula (I) can be obtained by the schemes 1 to 5:

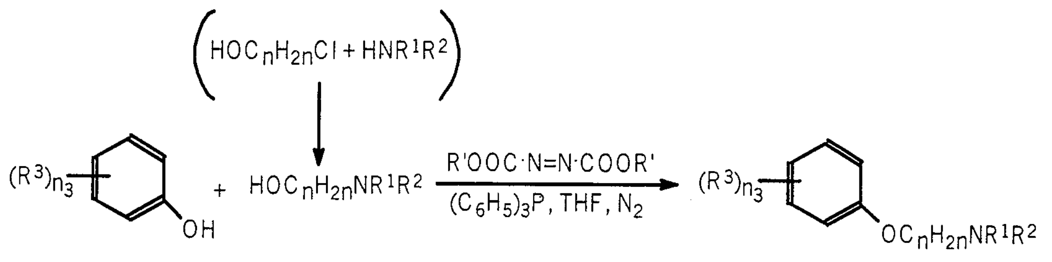
In these schemes, R^1, R^2, R^3, X and n are as defined in general formula (I).

Me and Et are intended to mean methyl and ethyl.

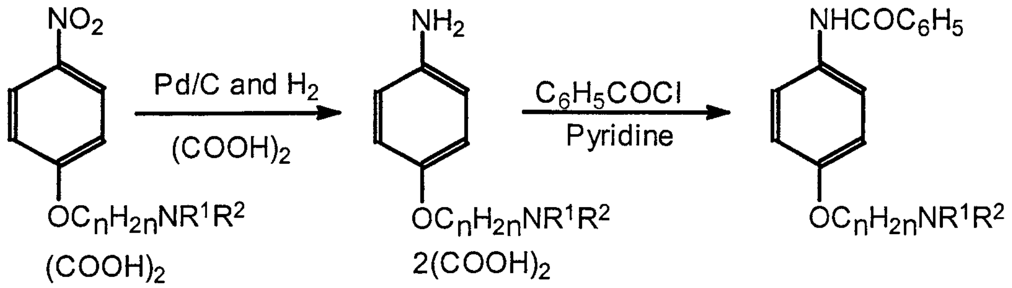
SCHEME 1 (methods A, B, C, D, H and K):



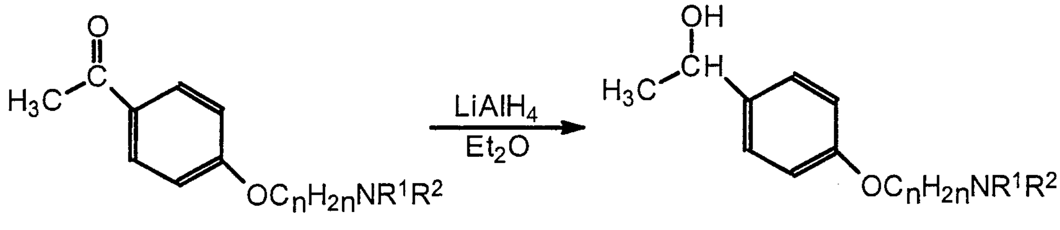
SCHEME 2 (methods F and L):



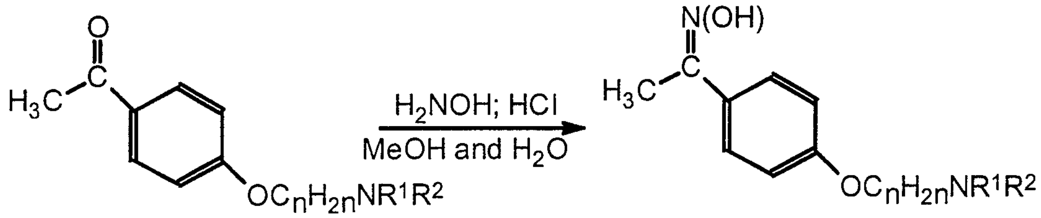
SCHEME 3 (method E):



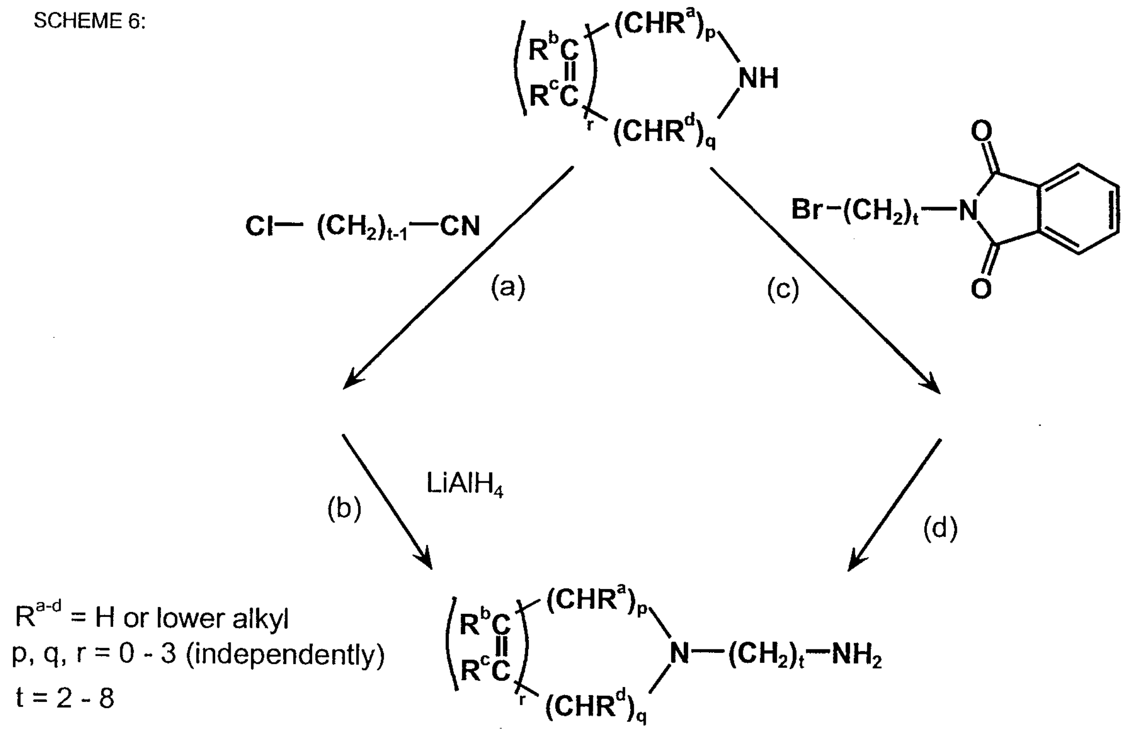
SCHEME 4 (method G):



SCHEME 5 (method J):



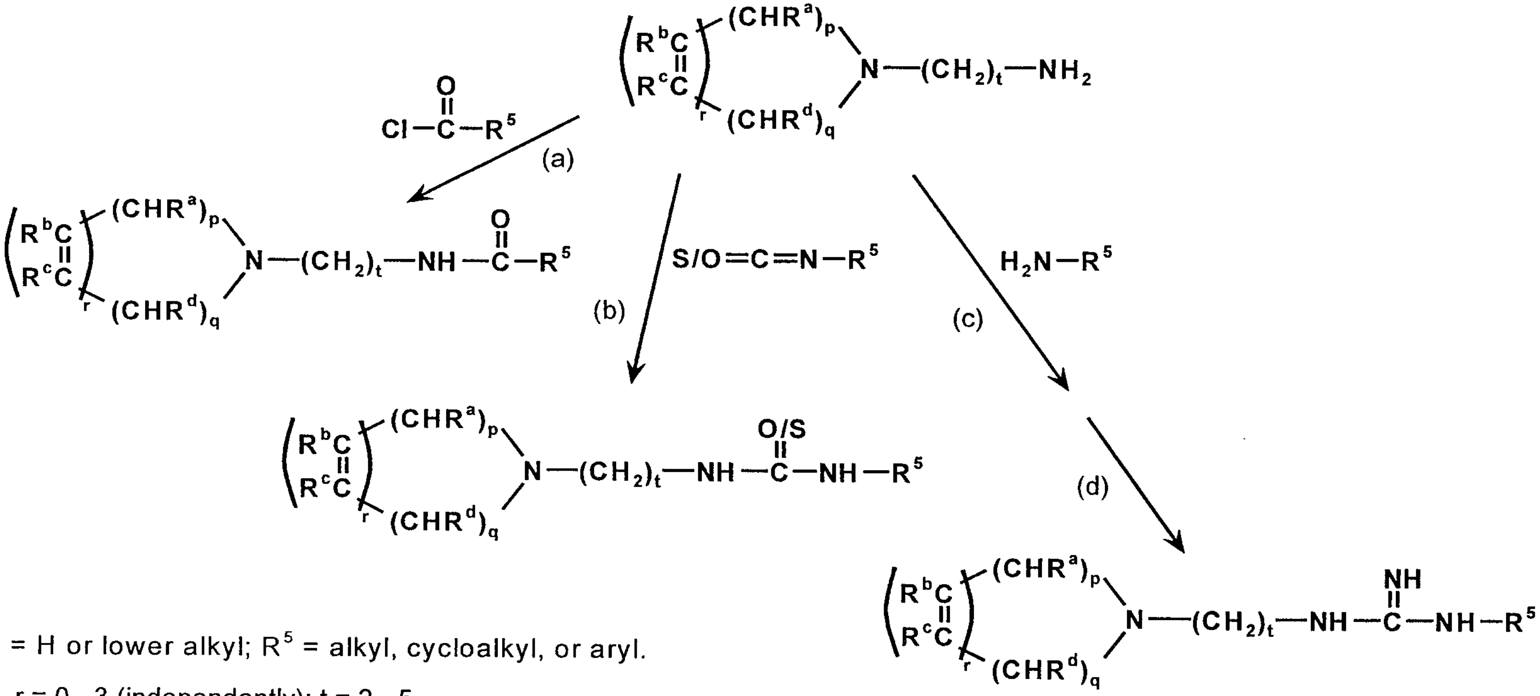
SCHEME 6:



R^{a-d} = H or lower alkyl
p, q, r = 0 - 3 (independently)
t = 2 - 8

For example: (a) KI, K_2CO_3, EtOH, 6 h, reflux; (b) THF, 3 h, reflux.
(c) KI, K_2CO_3, EtOH, 3 h, 60 °C; (d) 6N HCl, 2 h, 100 °C.

SCHEME 7:

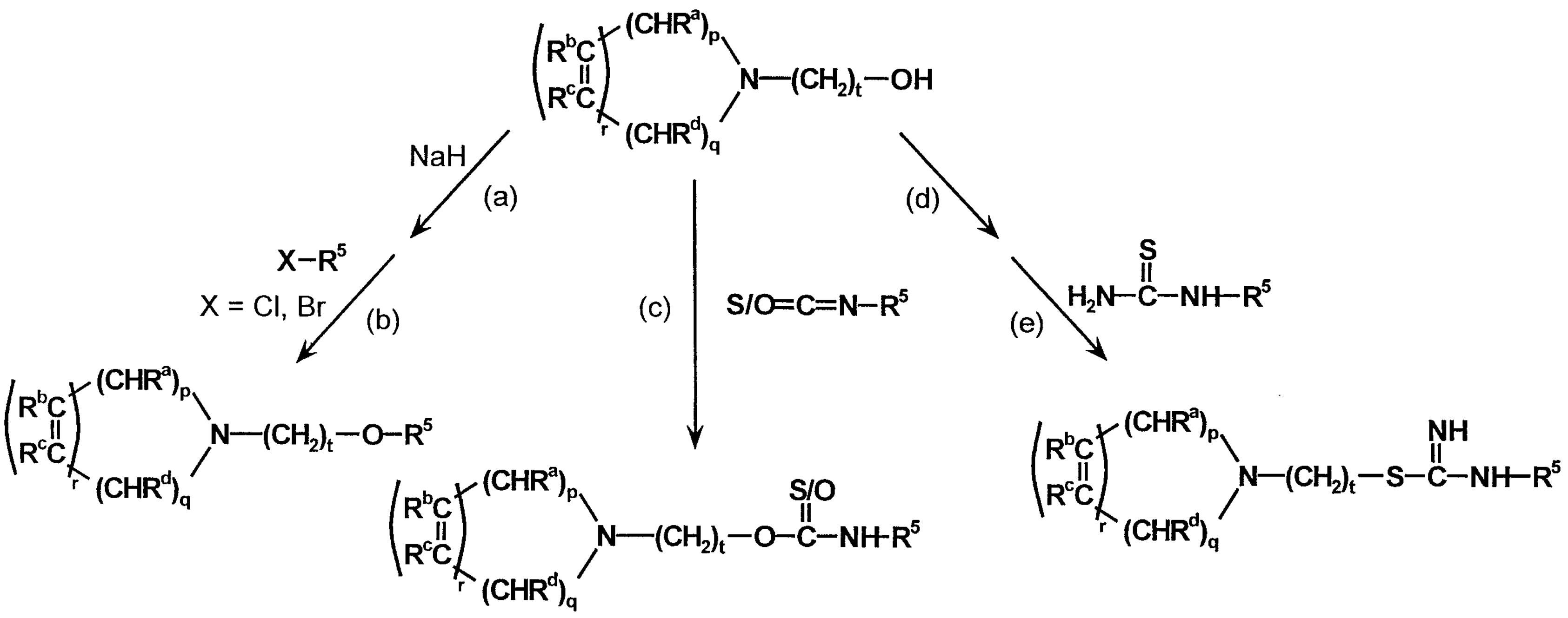


R^{a-d} = H or lower alkyl; R^5 = alkyl, cycloalkyl, or aryl.

p, q, r = 0 - 3 (independently); t = 2 - 5.

For example: (a) dioxane/H_2O (1+1), 4 h, 0 °C; (b) acetonitrile, 5min, r.t.; (c) *N*-Boc-diphenylimido carbonate, 10 h, reflux; (d) 1N HCl, 0.5 h, reflux.

SCHEME 8:

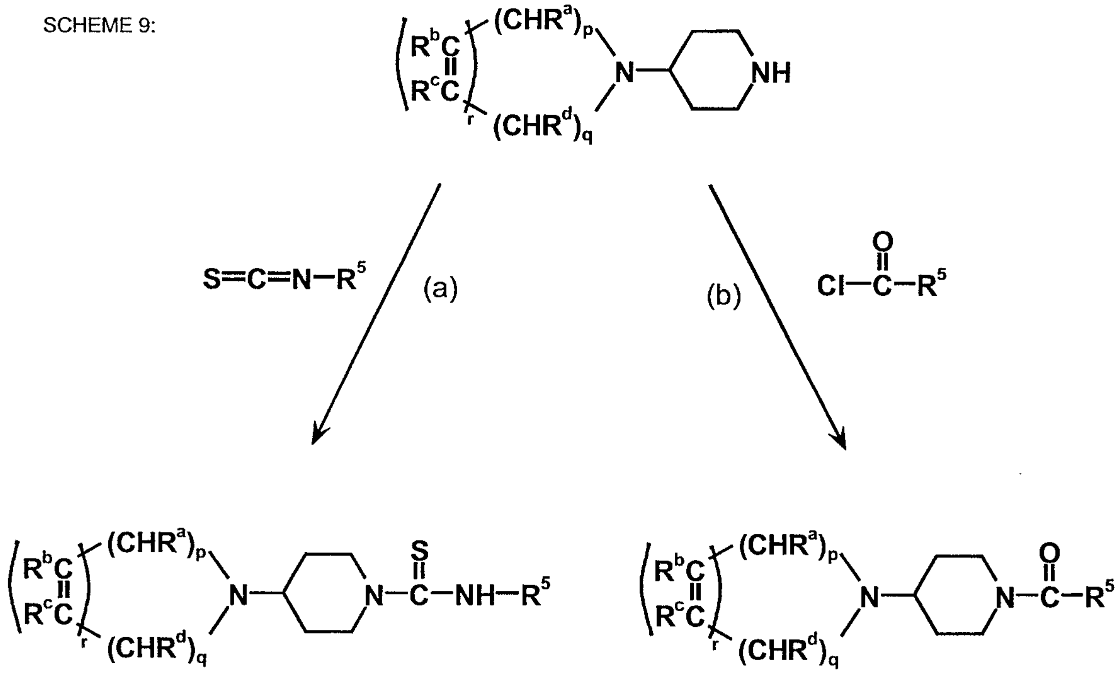


$R^{a\text{-}d}$ = H or lower alkyl; R^5 = alkyl, cycloalkyl, or aryl.

p, q, r = 0 - 3 (independently); t = 2 - 5.

For example: (a) toluene, 12 h, r.t.; (b) toluene, tetrabutylammonium iodide, 15-crown-5, 12 h, 80 °C; (c) acetonitrile, 4 (d) thionyl chloride, THF, 12 h, 50 °C; (e) K_2CO_3, H_2O, EtOH, 2 days, reflux.

SCHEME 9:

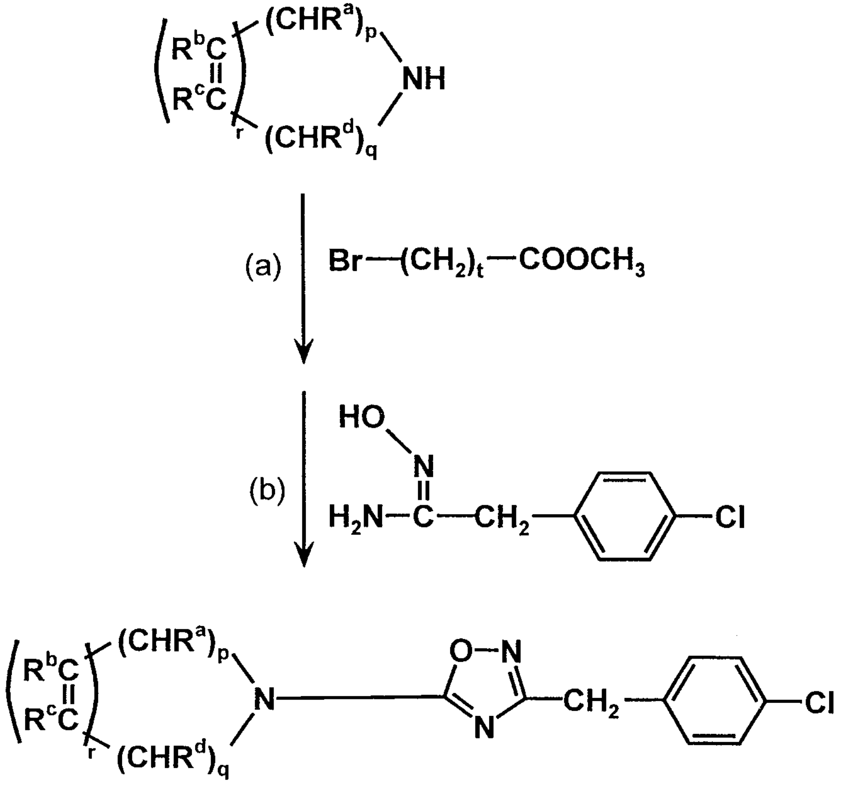


R^{a-d} = H or lower alkyl; R^5 = alkyl, cycloalkyl, or aryl.

p, q, r = 0 - 3 (independently).

For example: (a) diethyl ether, 2 h, r.t.; (b) dioxane/H_2O (1+1), 4 h, 0 °C.

SCHEME 10:

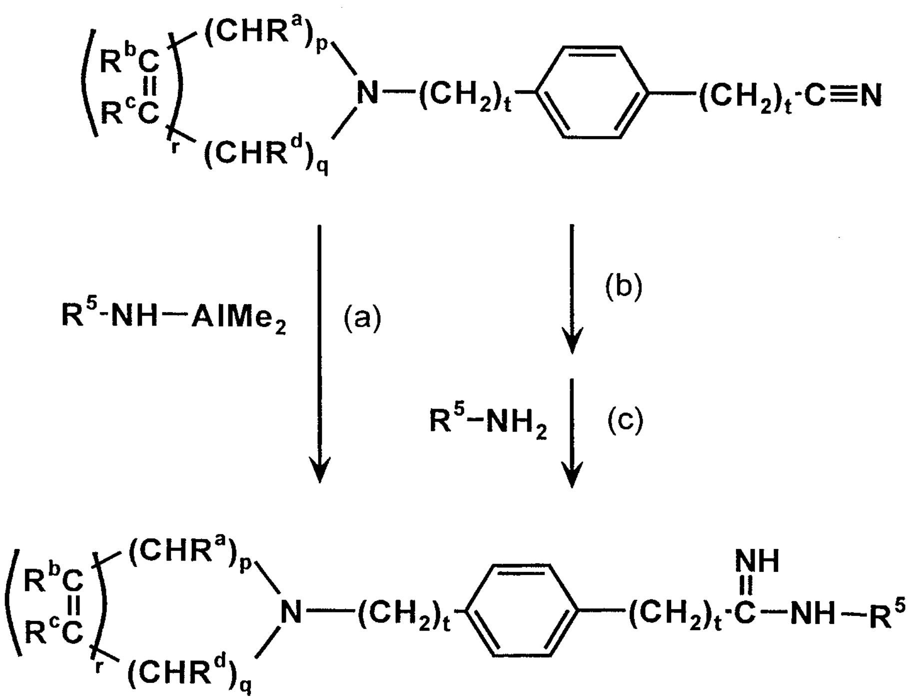


R^{a-d} = H or lower alkyl.

p, q, r = 0 - 3 (independently); t = 2 - 5.

For example: (a) acetone, triethylamine, 8 h, 50 °C; (b) NaH, MeOH, DMF, 6 h, 80 °C.

SCHEME 11:

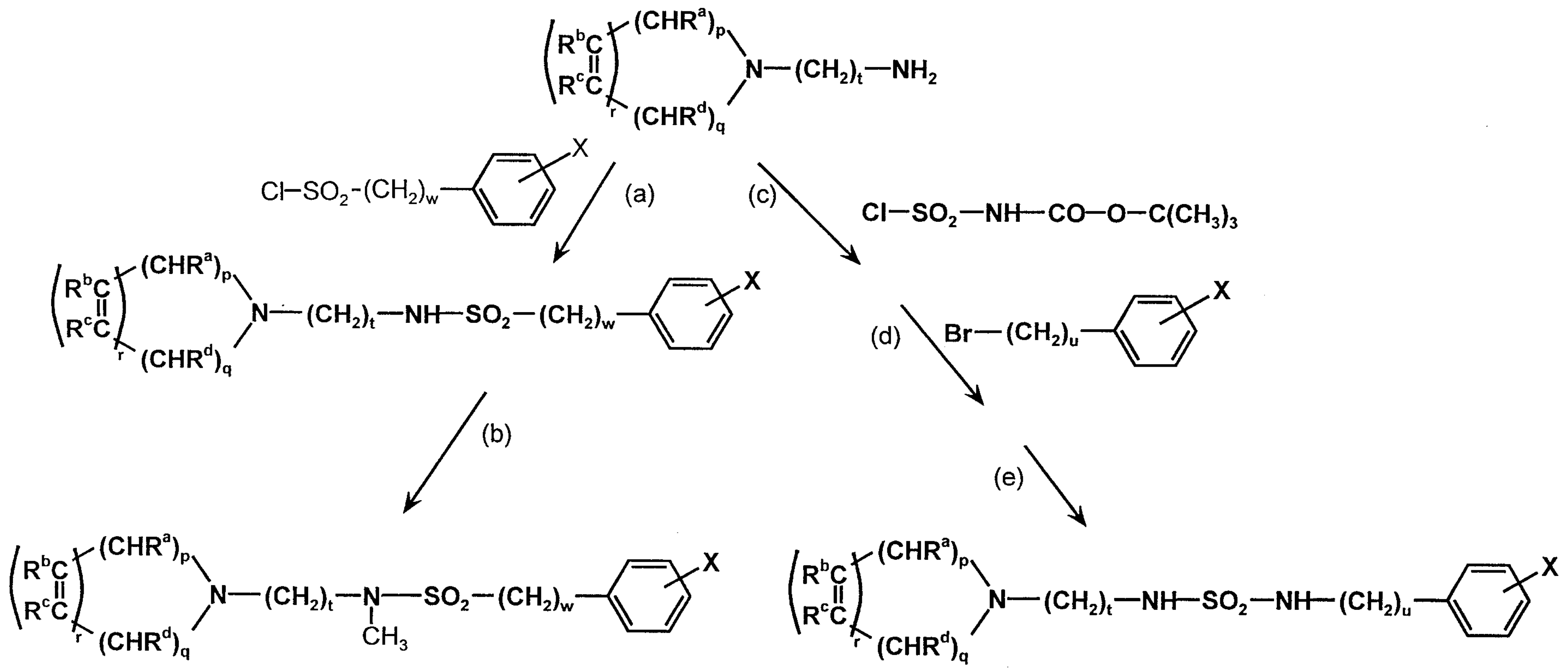


R^{a-d} = H or lower alkyl; R^5 = alkyl, cycloalkyl, or aryl.

p, q, r = 0 - 3 (independently); t = 0 - 2 (independently).

For example: (a) toluene, 100 °C, nitrogen atmosphere, 12 h; (b) MeOH, SOCl$_2$; (c) triethylamine, MeOH.

SCHEME 12

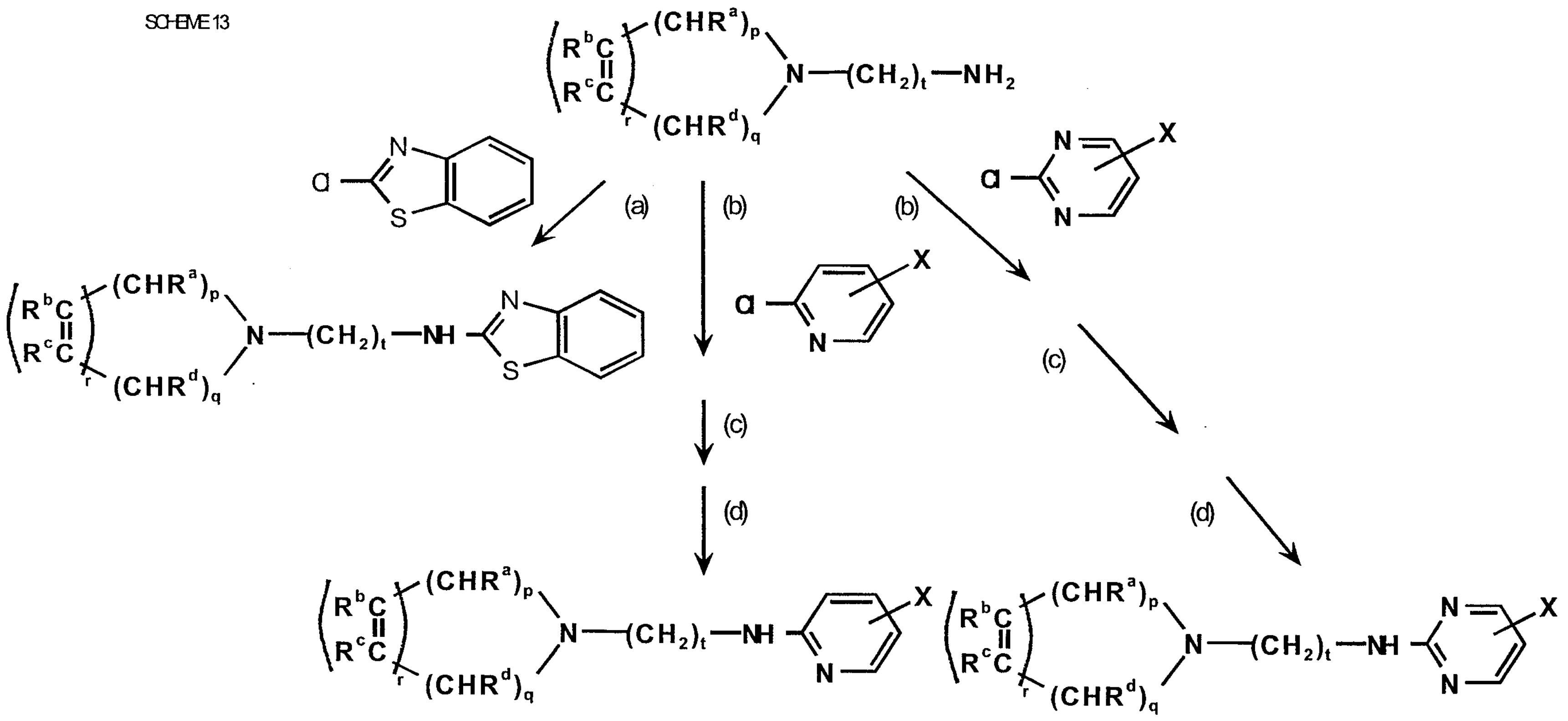


$R^{a\text{-}d}$ = H or lower alkyl; X = Cl, Br, etc.

p, q, r = 0 - 3 (independently); t = 2 - 5; u = 1 - 5; w = 0 - 2.

For example: (a) triethylamine, CH_2Cl_2, 24 h, r.t; (b) N,N,N′,N′-tetramethylazodicarboxamide, tributylphosphine, MeOH, benzene, 24 h, r.t.; (c) triethylamine, CH_2Cl_2, argon atmosphere, 0 °C, 18 h; (d) NaH, DMF, argon atmosphere, -15 °C; (e) 1N HCl, MeOH, 18 h, reflux.

SCHEME 13

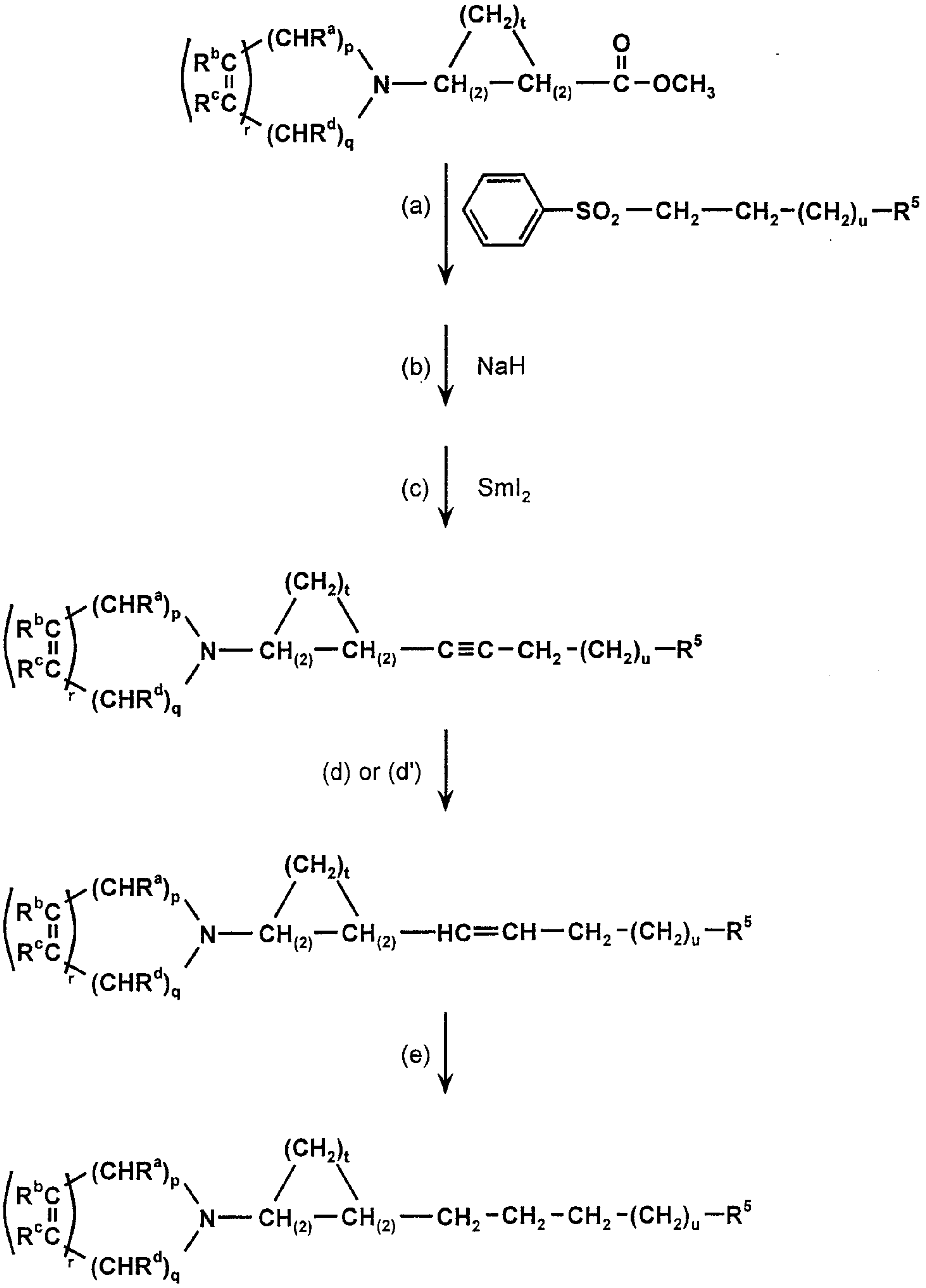


R^{a-d} = H or lower alkyl; X = NO_2, NH_2, OCH_3, etc.

p, q, r = 0-3 (independently); t = 2-6

For example: (a) triethylamine, CH_2Cl_2, 24 h, 50 °C; (b) triethylamine, KI, EtOH, 6 h, reflux; (c) thionyl chloride, THF, 2 h, 0 °C; (d) K_2CO_3, KI, EtOH, 6 h, reflux.

SCHEME 14:



$R^{a\text{-}d}$ = H or lower alkyl; R^5 = alkyl, cycloalkyl, or aryl.

p, q, r = 0 - 3 (independently); t, u = 0 - 3.

For example: (a) n-BuLi, -78 °C; (b) THF, $ClP(O)OEt_2$; (c) THF, 4 mole% HMPA; (d) H_2, quinoline, ethyl acetate (cis); (d') Na/NH_3 (trans); (e) H_2, Pd (black), MeOH.

Detailed synthesis procedures are given in the examples.

The compounds of formula (A) according to the invention have antagonistic and/or agonistic properties at the histamine H_3-receptors. They affect the synthesis and release of histamine monoamines or neuropeptides in brain and peripheral tissues.

This property makes the compounds of the invention useful derivatives in human or veterinary medicine.

Their therapeutical applications are those known for H_3-antagonist and/or agonist compounds and especially relate to the central nervous system disorders.

Regarding antagonistic activity, the compounds according to the invention can be used in the treatment of Alzheimer disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, obesity, vertigo and motion sickness.

Regarding agonistic activity, the compounds according to the invention can be used in the treatment of various allergic and inflammatory diseases and as a sedative agent.

Therefore, the compounds of formula (A) according to the invention are advantageously used as active ingredient of medicaments which act as ligand for H_3-receptors of histamine and in particular as an antagonist and/or agonist of H_3-receptors of histamine.

The present invention is also directed to the use of at least one following compounds

1-(5-phenoxypentyl)-piperidine
1-(5-phenoxypentyl)-pyrrolidine
N-methyl-N-(5-phenoxypentyl)-ethylamine
1-(5-phenoxypentyl)-morpholine
N-(5-phenoxypentyl)-hexamethyleneimine
N-ethyl-N-(5-phenoxypentyl)-propylamine
1-(5-phenoxypentyl)-2-methyl-piperidine
1-(5-phenoxypentyl)-4-propyl-piperidine
1-(5-phenoxypentyl)-4-methyl-piperidine
1-(5-phenoxypentyl)-3-methyl-piperidine
1-acetyl-4-(5-phenoxypentyl)-piperazine

1-(5-phenoxypentyl)-3,5-trans-dimethyl-piperidine

1-(5-phenoxypentyl)-3,5-cis-dimethyl-piperidine

1-(5-phenoxypentyl)-2,6-cis-dimethyl-piperidine

4-carboethoxy-1-(5-phenoxypentyl)-piperidine

3-carboethoxy-1-(5-phenoxypentyl)-piperidine

1-[3-(4-cyclopropylcarbonylphenoxy) propyl]-piperidine

1-[3-(4-acetylphenoxy)-2-R-methylpropyl] piperidine

1-[3-(4-cyanophenoxy)propyl]-4-methylpiperidine

1-[3-(4-cyanophenoxy)propyl]-3-methylpiperidine

1-[3-(4-acetylphenoxy)-2-S-methylpropyl] piperidine

1-{3-[4-(3-oxobutyl)phenoxy] propyl}piperidine

1-[3-(4-cyano-3-fluorophenoxy)propyl] piperidine

1-[3-(4-nitrophenoxy)propyl]-3-methylpiperidine

1-[3-(4-cyanophenoxy)propyl]-2-methylpiperidine

1-[3-(4-nitrophenoxy)propyl]-2-methylpiperidine

1-[3-(4-nitrophenoxy)propyl]-4-methylpiperidine

1-[3-(4-cyanophenoxy)propyl]-2,6-dimethylpiperidine

1-[3-(4-propionylphenoxy)propyl]-3-methylpiperidine

1-[3-(4-cyclobutylcarbonylphenoxy)propyl] piperidine

1-[3-(4-cyclopentylcarbonylphenoxy) propyl]piperidine

1-[3-(4-cyanophenoxy)propyl]-cis-2-methyl-5-ethylpiperidine

1-[3-(4-cyanophenoxy)propyl]-trans-2-methyl-5-ethylpiperidine

1-[3-(4-cyanophenoxy)propyl]-cis-3,5-dimethylpiperidine

1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine

1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine

1-{3-[4-(1-hydroxypropyl)phenoxy]propyl}-3-methylpiperidine

1-{3-[4-(1-hydroxypropyl)phenoxy]propyl}-4-methylpiperidine

1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine

1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine methoxime

1-[3-(4-cyanophenoxy)propyl]-trans-3,5-dimethylpiperidine

1-[3-(4-cyclopropylcarbonylphenoxy) propyl] -trans-3,5 –dimethyl piperidine

1-[3-(4-cyclopropylcarbonylphenoxy) propyl] -cis-3,5 –dimethyl piperidine

1-[3-(4-carbomethoxyphenoxy)propyl] piperidine
1-[3-(4-propenylphenoxy)propyl]-2-methyl piperidine
1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine
1-{3-[4-(1-ethoxypropyl)phenoxy]propyl}-2-methyl piperidine
1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine
1-[3-(4-bromophenoxy)propyl]piperidine
1-[3-(4-nitrophenoxy)propyl]piperidine
1-[3-(4-N,N-dimethylsulfonamidophenoxy) propyl]piperidine
1-[3-(4-isopropylphenoxy)propyl]piperidine
1-[3-(4-sec-butylphenoxy)propyl]piperidine
1-[3-(4-propylphenoxy)propyl]piperidine
1-[3-(4-ethylphenoxy)propyl]piperidine
1-(5-phenoxypentyl)-1,2,3,6-tetrahydropyridine
1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-methoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-methylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-pyrrolidine
1-[5-(2-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(1-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(3-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenylphenoxy)-pentyl]-pyrrolidine
1-{5-[2-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-[5-(3-phenylphenoxy)-pentyl]-pyrrolidine
1-(5-phenoxypentyl)-2,5-dihydropyrrole
1-{5-[1-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-(4-phenoxybutyl)-pyrrolidine
1-(6-phenoxyhexyl)-pyrrolidine
1-(5-phenylthiopentyl)-pyrrolidine
1-(4-phenylthiobutyl)-pyrrolidine
1-(3-phenoxypropyl)-pyrrolidine
1-[5-(3-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-fluorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-nitrophenoxy)-pentyl]-3-methyl-piperidine

1-[5-(4-acetylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-aminophenoxy)-pentyl]-pyrrolidine
1-[5-(3-cyanophenoxy)-pentyl]-pyrrolidine
N-[3-(4-nitrophenoxy)-propyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-diethylamine
1-[5-(4-benzoylphenoxy)-pentyl]-pyrrolidine
1-{5-[4-(phenylacetyl)-phenoxy]-pentyl}-pyrrolidine
N-[3-(4-acetylphenoxy)-propyl]-diethylamine
1-[5-(4-acetamidophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-N-benzamidophenoxy)-pentyl]-pyrrolidine
1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-diethylamine
1-[5-(4-cyanophenoxy)-pentyl]-piperidine
N-[5-(4-cyanophenoxy)-pentyl]-dimethylamine
N-[2-(4-cyanophenoxy)-ethyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dimethylamine
N-[4-(4-cyanophenoxy)-butyl]-diethylamine
N-[5-(4-cyanophenoxy)-pentyl]-dipropylamine
1-[3-(4-cyanophenoxy)-propyl]-pyrrolidine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-[6-(4-cyanophenoxy)-hexyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dipropylamine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-trans-dimethyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-cis-dimethyl-piperidine
1-[3-(4-formylphenoxy)-propyl]-piperidine
1-[3-(4-isobutyrylphenoxy)-propyl]-piperidine

N-[3-(4-propionylphenoxy)-propyl]-diethylamine
1-[3-(4-butyrylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-1,2,3,6-tetrahydropyridine
α-(4-Acetylphenoxy)-α′-(4-methylpiperidino)p-xylol
α-(4-Acetylphenoxy)-α′-(3,5-*cis*-dimethylpiperidino)p-xylol
α-(4-Acetylphenoxy)-α′-(3,5-*trans*-dimethylpiperidino)p-xylol
α-(4-Acetylphenoxy)-α′-(2-methylpyrrolidino)p-xylol
α-(4-Cyclopropylcarbonylphenoxy)-α′-piperidino-p-xylol
α-(4-Cyclopropylcarbonylphenoxy)-α′-(4-methylpiperidino)p-xylol
α-(4-Cyclopropylcarbonylphenoxy)-α′-pyrrolidino-p-xylol
3-Phenylpropyl 3-(4-methylpiperidino)propyl ether
3-Phenylpropyl 3-(3,5-*cis*-dimethylpiperidino)propyl ether
3-Phenylpropyl 3-(3,5-*trans*-dimethylpiperidino)propyl ether
3-Phenylpropyl 3-(3-methylpiperidino)propyl ether
3-Phenylpropyl 3-pyrrolidinopropyl ether
3-(4-Chlorophenyl)propyl 3-(4-methylpiperidino)propyl ether
3-(4-Chlorophenyl)propyl 3-(3,5-*cis*-dimethylpiperidino)propyl ether
3-(4-Chlorophenyl)propyl3-(3,5–*trans*-dimethylpiperidino)propyl ether
4-(6-Piperidinohexylamino)quinoline
2-Methyl 4-(3-piperidinopropylamino)quinoline
2-Methyl 4-(6-piperidinohexylamino)quinoline
7-Chloro-4-(3-piperidinopropylamino)quinoline
7-Chloro-4-(4-piperidinobutylamino)quinoline
7-Chloro-4-(8-piperidinooctylamino)quinoline
7-Chloro-4-(10-piperidinodecylamino)quinoline
7-Chloro-4-(12-piperidinododecylamino)quinoline
7-Chloro-4-(4-(3-piperidinopropoxy)phenylamino)quinoline
7-Chloro-4-(2-(4-(3-piperidinopropoxy)phenyl)ethylamino)quinoline
4-(6-Piperidinohexanoyl)phenyl 3-piperidinopropyl ether
5-Nitro-2-(5-piperidinopentylamino)pyridine
3-Nitro-2-(6-piperidinopentylamino)pyridine
5-Amino-2-(6-piperidinopentylamino)pyridine
2-(6-Piperidinohexylamino)quinoline

N-(4-Chlorobenzyl)-*N'*-cyclohexyl-3-piperidinopropyl isothiourea
2-(6-Piperidinohexylamino)benzothiazole
10-Piperidinodecylamine
3-Phenylpropyl 3-(*N,N*-diethylamino)propyl ether
N-(3-(N,N-Diethylamino)propyl)N'-phenylurea
N-Cyclohexylmethyl-N'-(3-piperidinopropyl)guanidine
N-(4-Bromobenzyl)-N'-(4-piperidinobutyl)sulphamide
3-Chloro-N-(4-piperidinobutyl)-N-methyl-benzene sulphonamide
N-(4-Chlorobenzyl)-2-(4-piperidinomethyl) phenyl) ethan amidine
1-(5-Cyclohexylpentanoyl)-1,4-bipiperidine
cis-1-(6-Cyclohexyl-3-hexen-1-yl)piperidine
trans-1-(6-Cyclohexyl-3-hexen-1-yl)piperidine
1-(2-(5,5-Dimethyl-1-hexin-1-yl)cyclopropyl)piperidine

for the preparation of a medicament acting as a ligand for the histamine H_3-receptor and in particular as an antagonist and/or agonist of the histamine H_3-receptors.

The antagonists are advantageously used as active ingredient in particular, of medicaments having psychotropic effects, promoting wakefullness, attention, memory and improving mood, in treatment of pathologies such as Alzheimer disease and other cognitive disorders in aged persons, depressive or simply asthenic states.

Their nootropic effects can be useful to stimulate attention and memorization capacity in healthy humans.

In addition, these agents can be useful in treatment of obesity, vertigo and motion sickness.

It can also be useful to associate the compounds of the invention with other psychiatric agents such as neuroleptics to increase their efficiency and reduce their side effects.

Application in certain form of epilepsy is also foreseen.

Their therapeutic applications involve also peripheral organs mainly a stimulant of secretions or gastro-intestinal motricity.

The compounds of the invention are particularly useful for the treatment of CNS disorders of aged persons.

The said compounds may also be used as an agonist or partial agonist action on the said histamine receptors.

H_3 receptor agonists and partial agonists, through their cerebral effects, mainly exert sedative, tranquillizing, antistress and analgesic activity, indicating their use as mild sedative psychotropics, in particular in various psychosomatic disorders.

H_3 agonists and partial agonists are also indicated in the treatment of migraine states and other headaches.

Through their peripheral effects, H_3 receptor agonists and partial agonists will be mainly indicated in the treatment of respiratoy, allergic or inflammatory conditions (asthma, bronchitis, rhinitis, tracheitis, and the like), cardiac conditions (myocardial dysfunction and infarction), gastrointestinal conditions as a result of their antisecretory and anti-inflammatory actions (gastric and duodenal ulcers, ulcerative colitis, Crohn's disease, irritable bowel, faecal incontinence, and the like), conditions of the urogenital system (cystitis, metritis, premenstrual syndrome, prostatic inflammations, urinary incontinence, genital disorders) and conditions of the cutaneous system (urticaria, itching). The anti-inflammatory and analgesic effect may usefully be turned to good account in the treatment of arthritis and other rheumatic conditions, conjunctivitis and other ocular inflammations, and sialorrhoea.

Compounds which are histamine H_3 receptor agonists or partial agonists are advantageously used as active principle of medicinal products, in particular having mild sedative, antisecretory, anti-inflammatory, steep-regulating and anticonvulsant effects, regulatory effects on hypothalamohypophyseal secretion, anti-depressant effects, modulatory effects on cerebral circulation, modulatory effects on the immune system, and anti-allergic and antimigraine effects.

Hence the present invention also relates to pharmaceutical compositions which contain as active principle a therapeutically effective amount of one of the agonist or partial agonist compounds of formule (A).

The present invention also relates to medicaments having the above-mentioned effects comprising as active ingredient, a therapeutically effective amount of a compound of formula (A).

The present invention relates more particularly to such medicaments containing a compound of formula (I) to (XVIII).

The present invention also relates to pharmaceutical compositions containing as active ingredient, a therapeutically effective amount of a compound (A) together with a pharmaceutically acceptable vehicle or excipient.

The invention is directed to such pharmaceutical compositions containing as active-ingredient, a compound of formula (I) to (XVIII).

The medicaments or pharmaceutical compositions according to the invention can be administered via oral, parenteral or topical routes, the active ingredient being combined with a therapeutically suitable excipient or vehicle.

According to the invention, oral administration is advantageously used.

Another subject of the present invention is the use of the compounds of formula (A) for the preparation of H_3-antagonist and/or agonist medicaments according to the above-mentioned forms.

The invention further relates to the use of the compounds of formula (A) for preparing medicaments having the pre-cited effects.

The invention also concerns the use of a compound of formula (I) to (XVIII).

Still another subject of the invention is a method for the treatment of precited ailments comprising administering a therapeutically effective dose of a compound (I), optionally in combination with a therapeutically acceptable vehicle or excipient.

The invention is also directed to such a method comprising administering a therapeutically effective dose of a compound of formula (I) to (XVIII).

For each of the above-indications, the amount of the active ingredient will depend upon the condition of the patient.

However, a suitable effective dose will be in general in the range of from 10 to 500 mg per day and of from 1 to 10 mg/day for particularly active compounds.

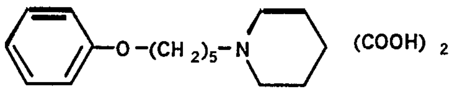
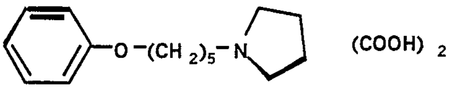
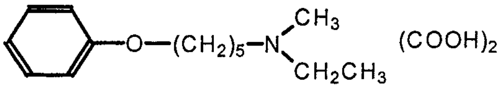
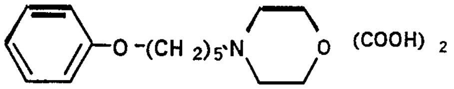
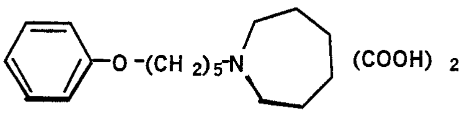
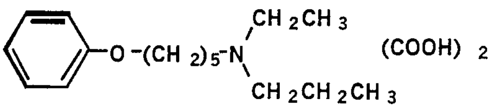
These doses are given on the basis of the compound and should be adapted for the salts, hydrates or hydrated salts thereof.

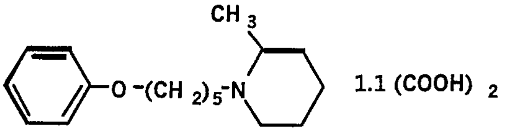
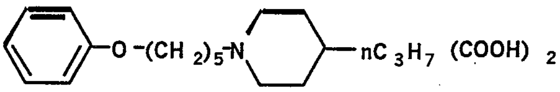
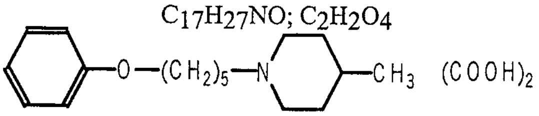
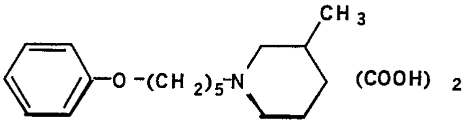
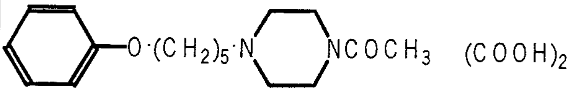
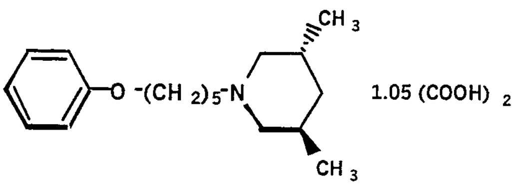
The invention is now illustrated by the following examples.

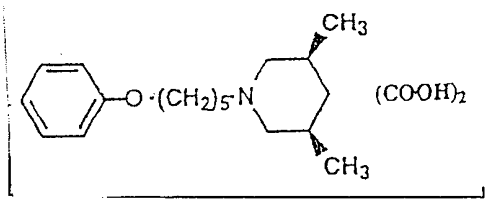
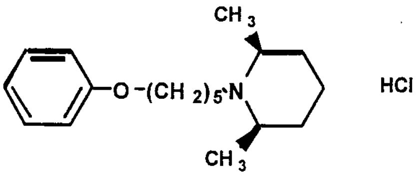
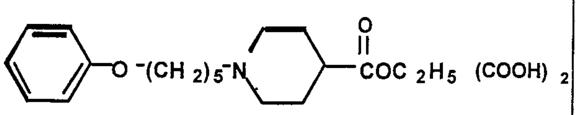
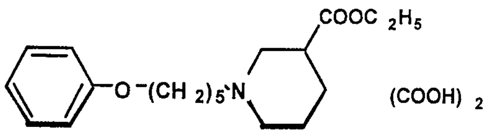
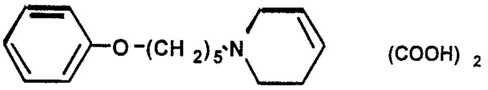
EXAMPLES

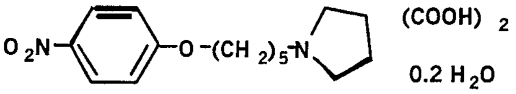
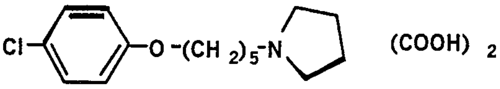
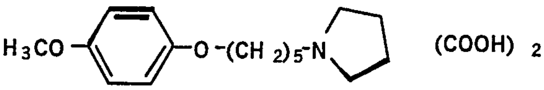
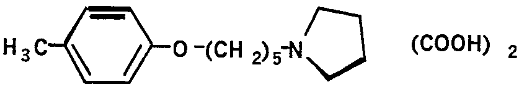
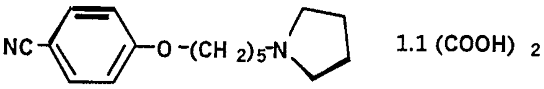
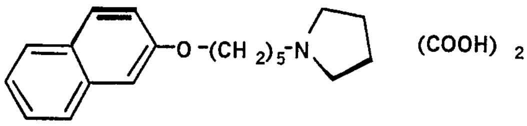
The structure of the synthesized compounds and their method of preparation as well as their melting point, recrystalisation solvant and elemental analysis are summarized in the following Table I:

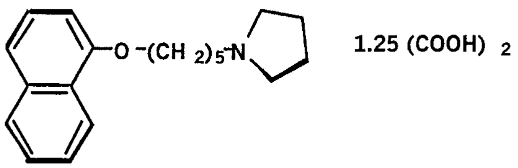
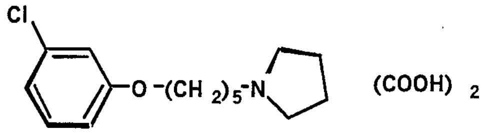
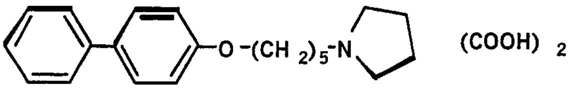
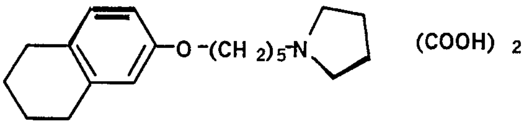
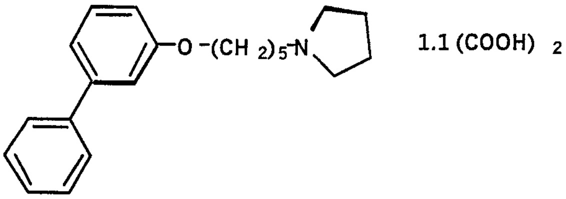
TABLE 1:

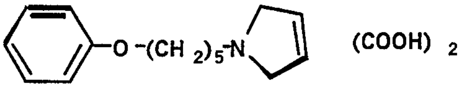
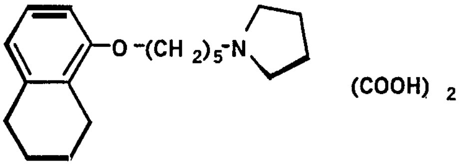
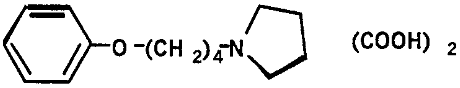
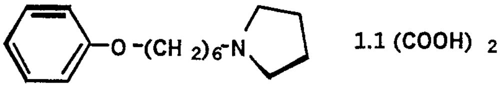
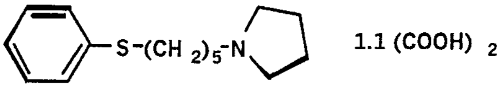
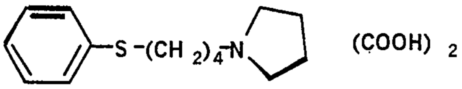
N	FORMULA STRUCTURE NAME	mp (recryst. solv)	analysis (calc.)	method
1	$C_{16}H_{25}NO; C_2H_2O_4$  1-(5-phenoxypentyl)-piperidine hydrogen oxalate	143-145°C (absolute ethanol)	C: 64.06 (64.07) H: 8.09 (8.16) N: 4.14 (4.15)	A
2	$C_{15}H_{23}NO; C_2H_2O_4$  1-(5-phenoxypentyl)-pyrrolidine hydrogen oxalate	153-155°C (absolute ethanol)	C: 63.06 (63.14) H: 7.78 (7.79) N: 4.42 (4.33)	A
3	$C_{14}H_{23}NO; C_2H_2O_4$  N-methyl-N-(5-phenoxypentyl)-ethylamine hydrogen oxalate	122-124°C (absolute ethanol)	C: 61.74 (61.72) H: 8.24 (8.09) N: 4.52 (4.50)	A
4	$C_{15}H_{23}NO_2; C_2H_2O_4$  1-(5-phenoxypentyl)-morpholine hydrogen oxalate	166-168°C (absolute ethanol)	C: 60.10 (60.16) H: 7.45 (7.31) N: 4.08 (4.13)	A
5	$C_{17}H_{27}NO; C_2H_2O_4$  N-(5-phenoxypentyl)-hexamethyleneimine hydrogen oxalate	132-134°C (absolute ethanol)	C: 64.70 (64.93) H: 8.34 (8.32) N: 3.85 (3.99)	A
6	$C_{16}H_{27}NO; C_2H_2O_4$  N-ethyl-N-(5-phenoxypentyl)-propylamine hydrogen oxalate	90-91°C (isopropyl alcohol)	C: 63.60 (63.69) H: 8.81 (8.61) N: 3.97 (4.13)	B

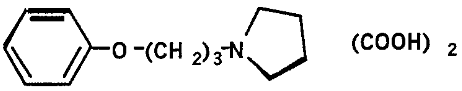
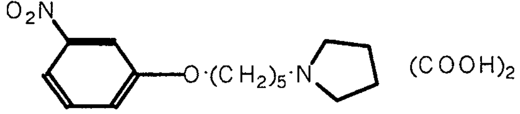
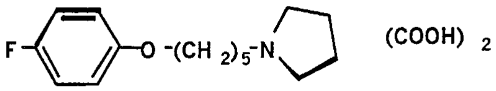
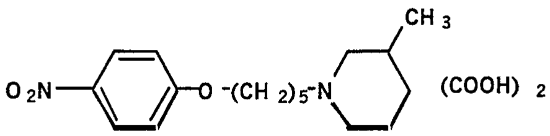
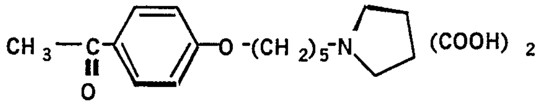
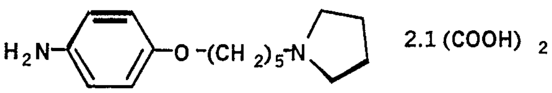
7	$C_{17}H_{27}NO$; 1.1 $C_2H_2O_4$  1-(5-phenoxypentyl)-2-methyl-piperidine hydrogen oxalate	80-83°C (isopropyl alcohol)	C: 64.15 (63.98) H: 8.42 (8.17) N: 3.97 (3.89)	B
8	$C_{19}H_{31}NO$; $C_2H_2O_4$  1-(5-phenoxypentyl)-4-propyl-piperidine hydrogen oxalate	165-166°C (absolute ethanol)	C: 66.27 (66.46) H: 8.94 (8.76) N: 3.72 (3.69)	B
9	$C_{17}H_{27}NO$; $C_2H_2O_4$  1-(5-phenoxypentyl)-4-methyl-piperidine hydrogen oxalate	151-152°C (absolute ethanol)	C: 64.87 (64.93) H: 8.41 (8.32) N: 4.01 (3.99)	B
10	$C_{17}H_{27}NO$; $C_2H_2O_4$  1-(5-phenoxypentyl)-3-methyl-piperidine hydrogen oxalate	140-141°C (isopropyl alcohol)	C: 65.35 (64.93) H: 8.49 (8.32) N: 4.00 (3.99)	B
11	$C_{17}H_{26}N_2O_2$; $C_2H_2O_4$  1-acetyl-4-(5-phenoxypentyl)-piperazine hydrogen oxalate	186-188°C (absolute ethanol)	C: 59.78 (59.99) H: 7.47 (7.42) N: 7.35 (7.36)	B
12	$C_{18}H_{29}NO$; 1.05 $C_2H_2O_4$  1-(5-phenoxypentyl)-3,5-trans-dimethyl-piperidine hydrogen oxalate	154-155°C (absolute ethanol)	C: 65.16 (65.25) H: 8.61 (8.47) N: 3.66 (3.79)	B

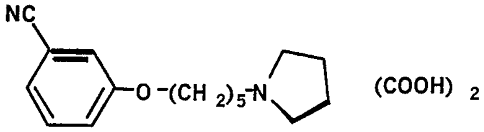
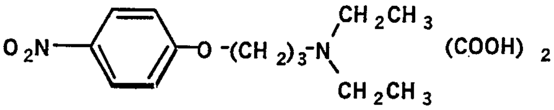
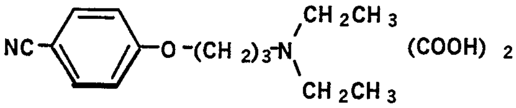
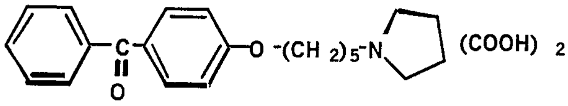
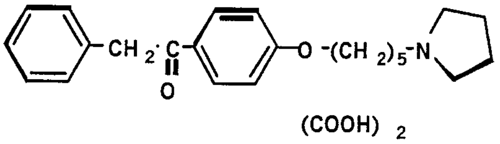
13	$C_{18}H_{29}NO$; $C_2H_2O_4$  1-(5-phenoxypentyl)-3,5-cis-dimethyl-piperidine hydrogen oxalate	154-155°C (isopropyl alcohol)	C: 65.62 (65.73) H: 8.64 (8.55) N: 3.63 (3.83)	B
14	$C_{18}H_{29}NO$; HCl  1-(5-phenoxypentyl)-2,6-cis-dimethyl-piperidine hydrochloride	135-136°C (acetone)	C: 69.18 (69.32) H: 9.79 (9.70) N: 4.28 (4.49)	B
15	$C_{19}H_{29}NO_3$; $C_2H_2O_4$  4-carboethoxy-1-(5-phenoxypentyl)-piperidine hydrogen oxalate	149-150°C (absolute ethanol)	C: 61.16 (61.60) H: 7.76 (7.63) N: 3.40 (3.42)	B
16	$C_{19}H_{29}NO_3$; $C_2H_2O_4$  3-carboethoxy-1-(5-phenoxypentyl)-piperidine hydrogen oxalate	117-118°C (isopropyl alcohol)	C: 61.54 (61.60) H: 7.87 (7.63) N: 3.29 (3.42)	B
17	$C_{16}H_{23}NO$; $C_2H_2O_4$  1-(5-phenoxypentyl)-1,2,3,6-tetrahydropyridine hydrogen oxalate	177-179°C (methanol)	C: 64.19 (64.46) H: 7.49 (7.51) N: 4.25 (4.18)	B

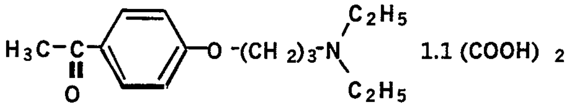
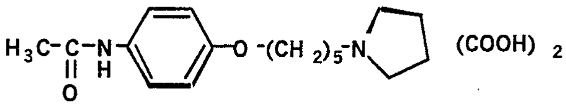
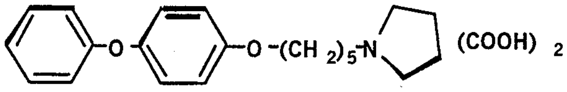
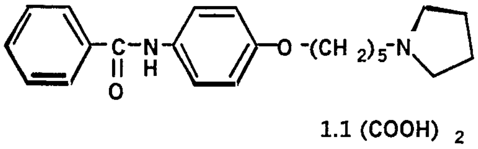
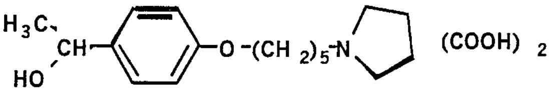
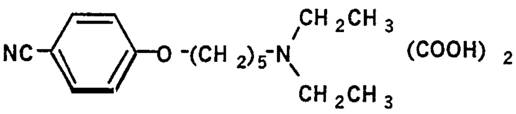
18	$C_{15}H_{22}N_2O_3$; $C_2H_2O_4$; 0.2 H_2O  1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	145-147°C (absolute ethanol)	C: 54.89 (54.89) H: 6.68 (6.61) N: 7.41 (7.53)	C
19	$C_{15}H_{22}ClNO$; $C_2H_2O_4$  1-[5-(4-chlorophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	139-141°C (absolute ethanol)	C: 57.00 (57.06) H: 6.63 (6.76) N: 3.79 (3.91) Cl: 10.24 (9.91)	C
20	$C_{16}H_{25}NO_2$; $C_2H_2O_4$  1-[5-(4-methoxyphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	115-116°C (absolute ethanol)	C: 61.22 (61.17) H: 7.72 (7.70) N: 4.03 (3.96)	C
21	$C_{16}H_{25}NO$; $C_2H_2O_4$  1-[5-(4-methylphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	138-140°C (absolute ethanol)	C: 64.05 (64.07) H: 8.00 (8.07) N: 4.10 (4.15)	C
22	$C_{16}H_{22}N_2O$; 1.1 $C_2H_2O_4$  1-[5-(4-cyanophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	129-130°C (absolute ethanol)	C: 61.24 (61.16) H: 6.81 (6.82) N: 7.95 (7.84)	C
23	$C_{19}H_{25}NO$; $C_2H_2O_4$  1-[5-(2-naphthyloxy)-pentyl]-pyrrolidine hydrogen oxalate	166-167°C (methanol)	C: 67.42 (67.54) H: 7.26 (7.29) N: 3.66 (3.75)	C

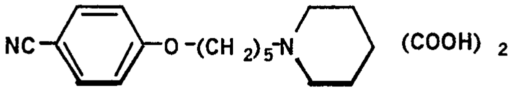
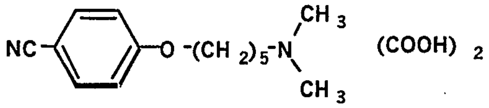
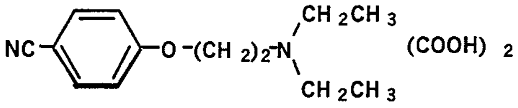
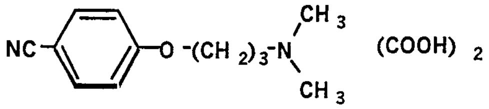
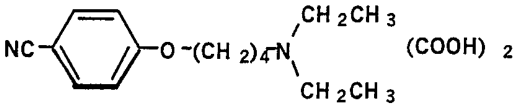
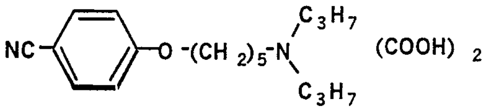
24	$C_{19}H_{25}NO$; 1.25 $C_2H_2O_4$  1-[5-(1-naphthyloxy)-pentyl]-pyrrolidine hydrogen oxalate	160-163°C (methanol)	C: 65.12 (65.22) H: 7.17 (7.00) N: 3.52 (3.54)	C
25	$C_{15}H_{22}ClNO$; $C_2H_2O_4$  1-[5-(3-chlorophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	131-132°C (absolute ethanol)	C: 56.94 (57.06) H: 6.67 (6.76) N: 3.74 (3.91) Cl: 9.64 (9.91)	C
26	$C_{21}H_{27}NO$; $C_2H_2O_4$  1-[5-(4-phenylphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	189-190°C (methanol)	C: 69.16 (69.15) H: 7.39 (7.32) N: 3.39 (3.51)	C
27	$C_{19}H_{29}NO$; $C_2H_2O_4$  1-{5-[2-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine hydrogen oxalate	131-132°C (absolute ethanol)	C: 66.73 (66.82) H: 8.37 (8.28) N: 3.68 (3.71)	C
28	$C_{21}H_{27}NO$; 1.1 $C_2H_2O_4$  1-[5-(3-phenylphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	155-157°C (absolute ethanol)	C: 68.40 (68.22) H: 7.04 (7.21) N: 3.45 (3.43)	C

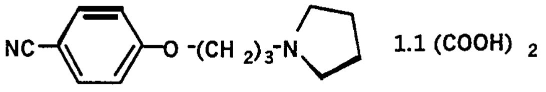
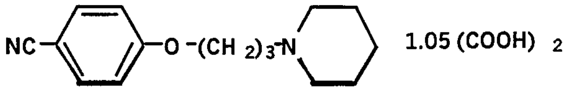
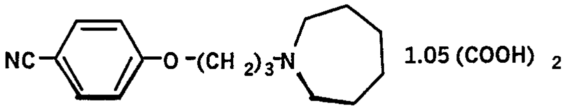
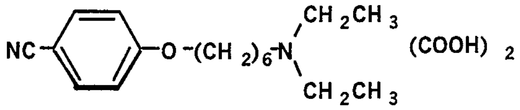
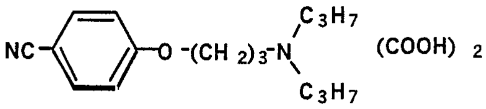
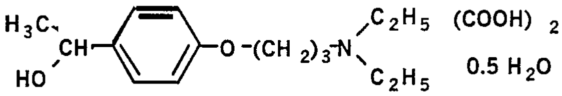
29	$C_{15}H_{21}NO; C_2H_2O_4$  1-(5-phenoxypentyl)-2,5-dihydropyrrole hydrogen oxalate	140-141°C (absolute ethanol)	C: 63.45 (63.54) H: 7.26 (7.21) N: 4.26 (4.36)	B
30	$C_{19}H_{29}NO; C_2H_2O_4$  1-{5-[1-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine hydrogen oxalate	148-149°C (absolute ethanol)	C: 66.99 (66.82) H: 8.47 (8.28) N: 3.72 (3.71)	C
31	$C_{14}H_{21}NO; C_2H_2O_4$  1-(4-phenoxybutyl)-pyrrolidine hydrogen oxalate	143-144°C (absolute ethanol)	C: 62.25 (62.12) H: 7.46 (7.49) N: 4.49 (4.53)	C
32	$C_{16}H_{25}NO; 1.1\ C_2H_2O_4$  1-(6-phenoxyhexyl)-pyrrolidine hydrogen oxalate	146-147°C (absolute ethanol)	C: 63.06 (63.10) H: 8.03 (7.91) N: 4.32 (4.04)	C
33	$C_{15}H_{23}NS; 1.1\ C_2H_2O_4$  1-(5-phenylthiopentyl)-pyrrolidine hydrogen oxalate	150-152°C (absolute ethanol)	C: 59.52 (59.29) H: 7.44 (7.29) N: 4.06 (4.02)	C
34	$C_{14}H_{21}NS; C_2H_2O_4$  1-(4-phenylthiobutyl)-pyrrolidine hydrogen oxalate	114-116°C (absolute ethanol)	C: 59.24 (59.05) H: 7.16 (7.12) N: 4.16 (4.30) S: 9.79 (9.85)	C

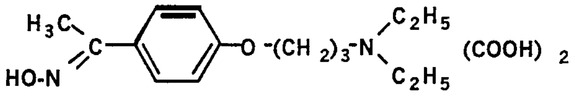
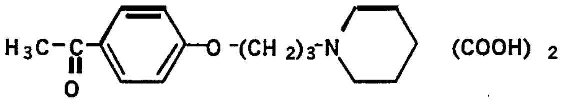
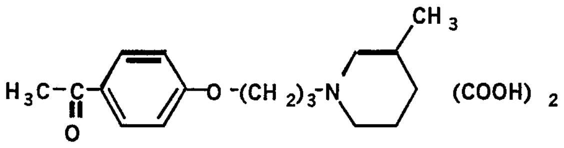
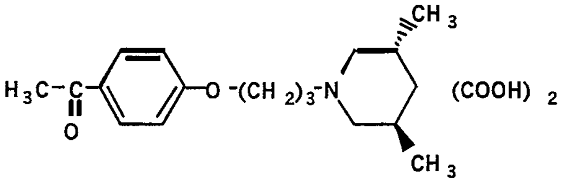
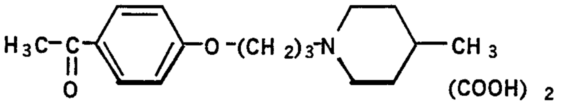
35	$C_{13}H_{19}NO; C_2H_2O_4$  1-(3-phenoxypropyl)-pyrrolidine hydrogen oxalate	169-170°C (absolute ethanol)	C: 60.98 (61.00) H: 7.14 (7.17) N: 4.64 (4.74)	C
36	$C_{15}H_{22}N_2O_3; C_2H_2O_4$  1-[5-(3-nitrophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	130-131°C (absolute ethanol)	C: 55.30 (55.43) H: 6.55 (6.57) N: 7.49 (7.60)	C
37	$C_{15}H_{22}FNO; C_2H_2O_4$  1-[5-(4-fluorophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	149-150°C (absolute ethanol)	C: 59.52 (59.81) H: 7.12 (7.09) N: 4.05 (4.10)	C
38	$C_{17}H_{26}N_2O_3; C_2H_2O_4$  1-[5-(4-nitrophenoxy)-pentyl]-3-methyl-piperidine hydrogen oxalate	148-149°C (absolute ethanol)	C: 57.32 (57.55) H: 7.19 (7.12) N: 6.89 (7.07)	C
39	$C_{17}H_{25}NO_2; C_2H_2O_4$  1-[5-(4-acetylphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	130-134°C (absolute ethanol)	C: 62.43 (62.45) H: 7.41 (7.45) N: 3.75 (3.83)	D
40	$C_{15}H_{24}N_2O; 2.1\ C_2H_2O_4$  1-[5-(4-aminophenoxy)-pentyl]-pyrrolidine di-(hydrogen oxalate)	120-122°C (absolute ethanol)	C: 52.49 (52.72) H: 6.74 (6.50) N: 6.32 (6.40)	E_1

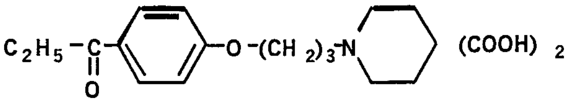
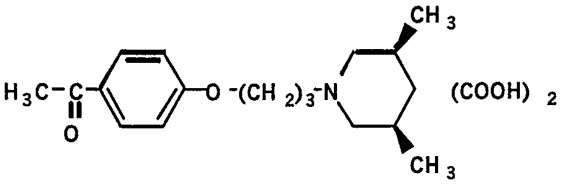
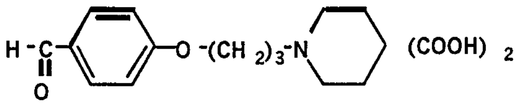
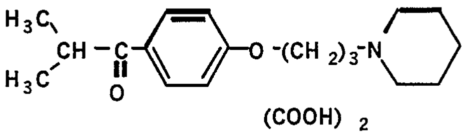
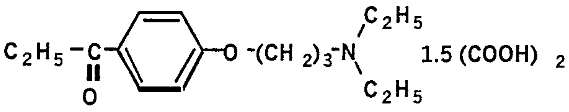
41	$C_{16}H_{22}N_2O; C_2H_2O_4$  1-[5-(3-cyanophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	119-120°C (absolute ethanol)	C: 61.95 (62.05) H: 6.88 (6.94) N: 8.00 (8.04)	C
42	$C_{13}H_{20}N_2O_3; C_2H_2O_4$  N-[3-(4-nitrophenoxy)-propyl]-diethylamine hydrogen oxalate	160-161°C (absolute ethanol/ methanol 1:1)	C: 52.46 (52.63) H: 6.49 (6.48) N: 8.10 (8.12)	F
43	$C_{14}H_{20}N_2O; C_2H_2O_4$  N-[3-(4-cyanophenoxy)-propyl]-diethylamine hydrogen oxalate	148-150°C (absolute ethanol)	C: 59.40 (59.62) H: 6.82 (6.88) N: 8.60 (8.69)	F
44	$C_{22}H_{27}NO_2; C_2H_2O_4$  1-[5-(4-benzoylphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	141-142°C (absolute ethanol)	C: 67.17 (67.43) H: 6.80 (6.84) N: 3.18 (3.28)	D
45	$C_{23}H_{29}NO_2; C_2H_2O_4$  1-{5-[4-(phenylacetyl)-phenoxy]-pentyl}-pyrrolidine hydrogen oxalate	177-178°C (absolute ethanol)	C: 67.77 (68.01) H: 7.09 (7.08) N: 3.26 (3.17)	D

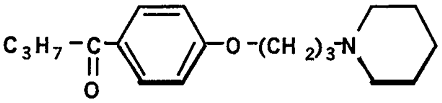
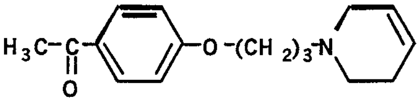
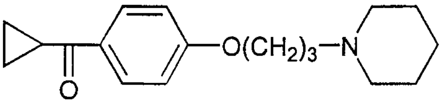
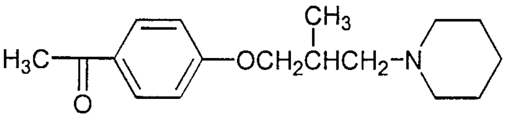
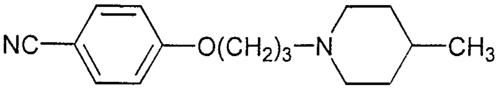
46	$C_{15}H_{23}NO_2$; 1.1 $C_2H_2O_4$  N-[3-(4-acetylphenoxy)-propyl]-diethylamine hydrogen oxalate	108-110°C (absolute ethanol)	C: 59.30 (59.30) H: 7.47 (7.29) N: 4.18 (4.02)	F
47	$C_{17}H_{26}N_2O_2$; $C_2H_2O_4$  1-[5-(4-acetamidophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	142-144°C (absolute ethanol)	C: 59.67 (59.99) H: 7.55 (7.42) N: 7.25 (7.36)	C
48	$C_{21}H_{27}NO_2$; $C_2H_2O_4$  1-[5-(4-phenoxyphenoxy)-pentyl]-pyrrolidine hydrogen oxalate	135-136°C (absolute ethanol)	C: 66.49 (66.49) H: 7.05 (7.04) N: 3.24 (3.37)	D
49	$C_{22}H_{28}N_2O_2$; 1.1 $C_2H_2O_4$  1-[5-(4-N-benzamidophenoxy)-pentyl]-pyrrolidine hydrogen oxalate	176-178°C (absolute ethanol)	C: 64.56 (64.38) H: 6.89 (6.74) N: 6.26 (6.20)	E2
50	$C_{17}H_{27}NO_2$; $C_2H_2O_4$  1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine hydrogen oxalate	102-104°C (absolute ethanol)	C: 61.89 (62.11) H: 7.94 (7.96) N: 3.77 (3.81)	G
51	$C_{16}H_{24}N_2O$; $C_2H_2O_4$  N-[5-(4-cyanophenoxy)-pentyl]-diethylamine hydrogen oxalate	120-122°C (absolute ethanol)	C: 61.56 (61.70) H: 7.54 (7.48) N: 7.87 (7.99)	H

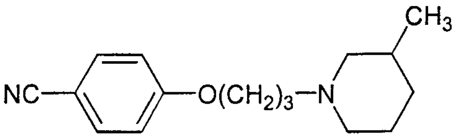
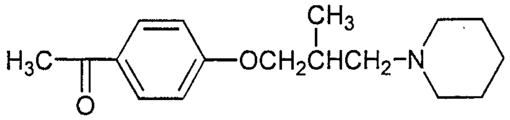
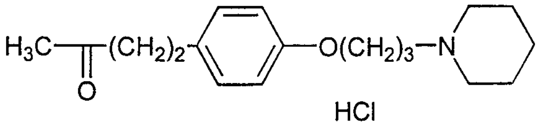
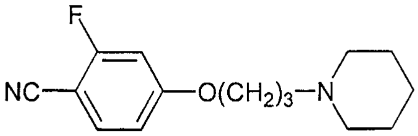
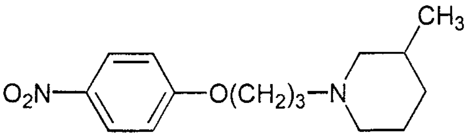
52	$C_{17}H_{24}N_2O; C_2H_2O_4$  1-[5-(4-cyanophenoxy)-pentyl]-piperidine hydrogen oxalate	115-116°C (absolute ethanol)	C: 62.62 (62.97) H: 7.20 (7.23) N: 7.76 (7.73)	H
53	$C_{14}H_{20}N_2O; C_2H_2O_4$  N-[5-(4-cyanophenoxy)-pentyl]-dimethylamine hydrogen oxalate	148-149°C (absolute ethanol)	C: 59.68 (59.62) H: 6.76 (6.88) N: 8.57 (8.69)	H
54	$C_{13}H_{18}N_2O; C_2H_2O_4$  N-[2-(4-cyanophenoxy)-ethyl]-diethylamine hydrogen oxalate	124-125°C (absolute ethanol)	C: 58.15 (58.43) H: 6.30 (6.54) N: 8.95 (9.09)	H
55	$C_{12}H_{16}N_2O; C_2H_2O_4$  N-[3-(4-cyanophenoxy)-propyl]-dimethylamine hydrogen oxalate	166-167°C (absolute ethanol/ methanol 1:1)	C: 57.01 (57.14) H: 6.02 (6.16) N: 9.46 (9.52)	H
56	$C_{15}H_{22}N_2O; C_2H_2O_4$  N-[4-(4-cyanophenoxy)-butyl]-diethylamine hydrogen oxalate	143-145°C (absolute ethanol)	C: 60.80 (60.70) H: 7.11 (7.19) N: 8.22 (8.33)	H
57	$C_{18}H_{28}N_2O; C_2H_2O_4$  N-[5-(4-cyanophenoxy)-pentyl]-dipropylamine hydrogen oxalate	134-136°C (absolute ethanol)	C: 63.38 (63.47) H: 8.11 (7.99) N: 7.29 (7.40)	H

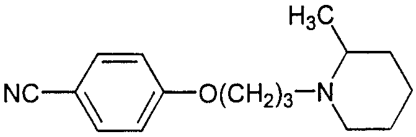
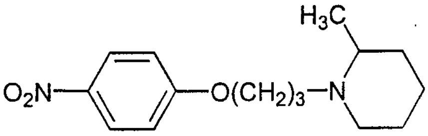
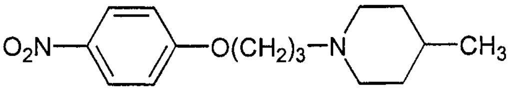
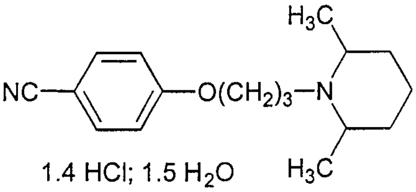
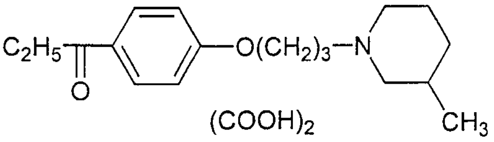
58	$C_{14}H_{18}N_2O$; 1.1 $C_2H_2O_4$  1-[3-(4-cyanophenoxy)-propyl]-pyrrolidine hydrogen oxalate	163-165°C (absolute ethanol)	C: 58.95 (59.08) H: 6.23 (6.18) N: 8.43 (8.51)	H
59	$C_{15}H_{20}N_2O$; 1.05 $C_2H_2O_4$  1-[3-(4-cyanophenoxy)-propyl]-piperidine hydrogen oxalate	151-153°C (absolute ethanol)	C: 60.62 (60.61) H: 6.66 (6.57) N: 8.25 (8.27)	H
60	$C_{16}H_{22}N_2O$; 1.05 $C_2H_2O_4$  N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine hydrogen oxalate	124-125°C (absolute ethanol)	C: 61.62 (61.60) H: 6.94 (6.88) N: 7.87 (7.94)	H
61	$C_{17}H_{26}N_2O$; $C_2H_2O_4$  N-[6-(4-cyanophenoxy)-hexyl]-diethylamine hydrogen oxalate	110-112°C (absolute ethanol)	C: 62.90 (62.62) H: 7.76 (7.74) N: 7.61 (7.69)	H
62	$C_{16}H_{24}N_2O$; $C_2H_2O_4$  N-[3-(4-cyanophenoxy)-propyl]-dipropylamine hydrogen oxalate	127-128°C (absolute ethanol)	C: 61.57 (61.70) H: 7.57 (7.48) N: 7.91 (7.99)	H
63	$C_{15}H_{25}NO_2$; $C_2H_2O_4$; 0.5 H_2O  N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine hydrogen oxalate hemihydrate	33-36°C (isopropyl alcohol)	C: 58.15 (58.27) H: 8.15 (8.05) N: 4.21 (4.00)	G

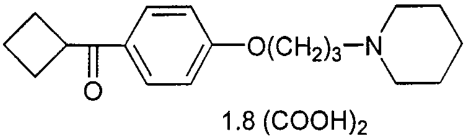
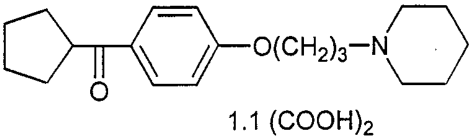
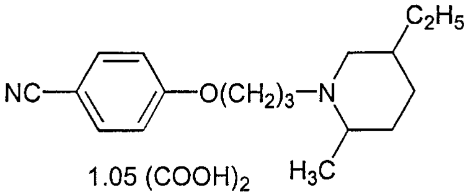
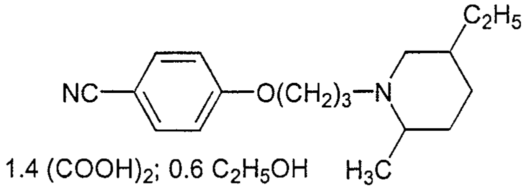
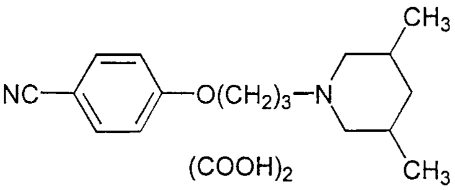
64	$C_{15}H_{24}N_2O_2$; $C_2H_2O_4$  4'-(3-diethylaminopropoxy)-acetophenone-oxime hydrogen oxalate	99-100°C (absolute ethanol)	C: 57.26 (57.61) H: 7.47 (7.39) N: 7.72 (7.90)	J
65	$C_{16}H_{23}NO_2$; $C_2H_2O_4$  1-[3-(4-acetylphenoxy)-propyl]-piperidine hydrogen oxalate	159-160°C (absolute ethanol)	C: 61.18 (61.52) H: 7.11 (7.17) N: 3.96 (3.99)	K
66	$C_{17}H_{25}NO_2$; $C_2H_2O_4$  1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine hydrogen oxalate	143-144°C (absolute ethanol)	C: 62.11 (62.45) H: 7.41 (7.45) N: 3.79 (3.83)	K
67	$C_{18}H_{27}NO_2$; $C_2H_2O_4$  1-[3-(4-acetylphenoxy)-propyl]-3,5-trans-dimethyl-piperidine hydrogen oxalate	171-172°C (absolute ethanol)	C: 63.06 (63.31) H: 7.44 (7.70) N: 3.64 (3.69)	K
68	$C_{17}H_{25}NO_2$; $C_2H_2O_4$  1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine hydrogen oxalate	160-161°C (absolute ethanol)	C: 62.47 (62.45) H: 7.46 (7.45) N: 3.77 (3.83)	K

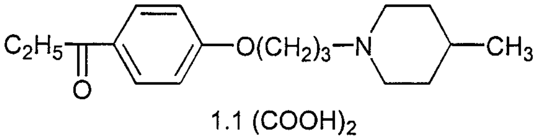
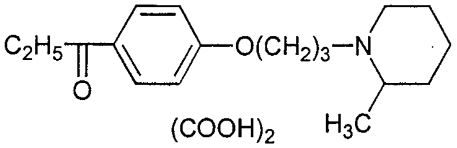
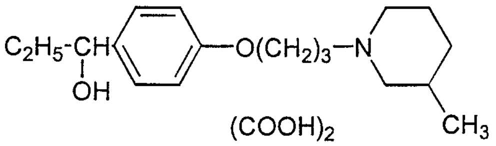
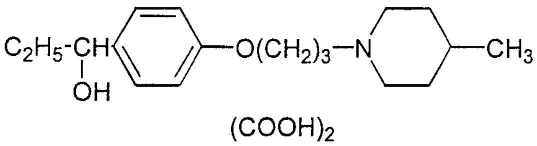
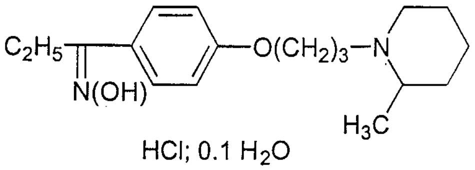
69	$C_{17}H_{25}NO_2$; $C_2H_2O_4$  1-[3-(4-propionylphenoxy)-propyl]-piperidine hydrogen oxalate	148-149°C (absolute ethanol)	C: 62.54 (62.45) H: 7.51 (7.45) N: 3.79 (3.83)	L
70	$C_{18}H_{27}NO_2$; $C_2H_2O_4$  1-[3-(4-acetylphenoxy)-propyl]-3,5-cis-dimethyl-piperidine hydrogen oxalate	174-175°C (absolute ethanol)	C: 63.22 (63.31) H: 7.60 (7.70) N: 3.64 (3.69)	K
71	$C_{15}H_{21}NO_2$; $C_2H_2O_4$  1-[3-(4-formylphenoxy)-propyl]-piperidine hydrogen oxalate	152-153°C (absolute ethanol)	C: 60.23 (60.52) H: 6.81 (6.87) N: 4.15 (4.15)	L
72	$C_{18}H_{27}NO_2$; $C_2H_2O_4$  1-[3-(4-isobutyrylphenoxy)-propyl]-piperidine hydrogen oxalate	121-122°C (absolute ethanol)	C: 63.02 (63.31) H: 7.73 (7.70) N: 3.66 (3.69)	L
73	$C_{16}H_{25}NO_2$; 1.5 $C_2H_2O_4$  N-[3-(4-propionylphenoxy)-propyl]-diethylamine hydrogen oxalate	118-120°C (absolute ethanol)	C: 57.27 (57.28) H: 7.00 (7.08) N: 3.47 (3.52)	L

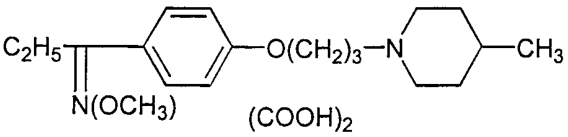
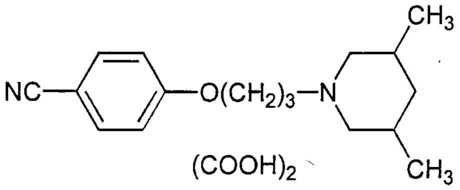
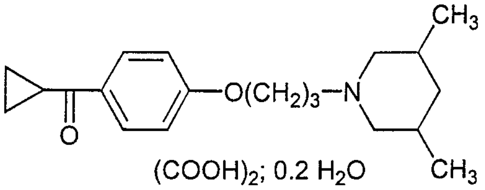
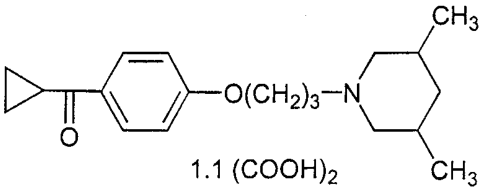
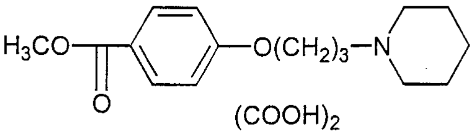
74	$C_{18}H_{27}NO_2$; $C_2H_2O_4$  $(COOH)_2$ 1-[3-(4-butyrylphenoxy)-propyl]-piperidine hydrogen oxalate	138-139°C (absolute ethanol)	C: 63.09 (63.31) H: 7.78 (7.70) N: 3.75 (3.69)	L
75	$C_{16}H_{21}NO_2$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-[3-(4-acetylphenoxy)-propyl]-1,2,3,6-tetrahydropyridine hydrogen oxalate	143-144°C (absolute ethanol)	C: 61.21 (61.00) H: 6.25 (6.52) N: 4.00 (3.91)	K
76	$C_{18}H_{25}NO_2$; 1.05 $C_2H_2O_4$  1.05 $(COOH)_2$ 1-[3-(4-cyclopropanecarbonylphenoxy) propyl]-piperidine hydrogen oxalate	177-179°C (absolute ethanol)	C: 63.10 (63.21) H: 7.28 (7.15) N: 3.61 (3.67)	L
77	$C_{17}H_{25}NO_2$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-[3-(4-acetylphenoxy)-2-R-methylpropyl] piperidine hydrogen oxalate	149-151°C (absolute ethanol)	C: 61.72 (61.59) H: 7.59 (7.32) N: 3.74 (3.74)	M
78	$C_{16}H_{22}N_2O$; HCl; 0.1 H_2O  HCl; 0.1 H_2O 1-[3-(4-cyanophenoxy)propyl]-4-methylpiperidine hydrochloride	200-202°C (absolute ethanol/diethyl ether 1:1)	C: 64.57 (64.79) H: 8.02 (7.88) N: 9.30 (9.44)	N

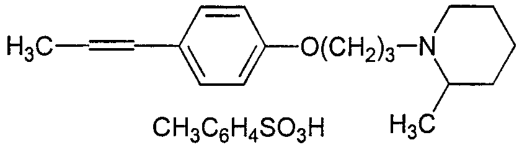
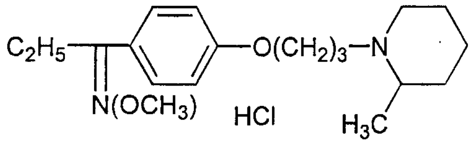
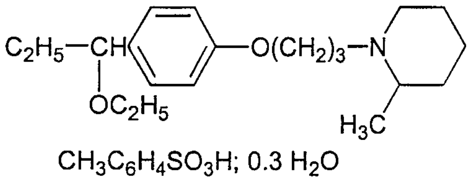
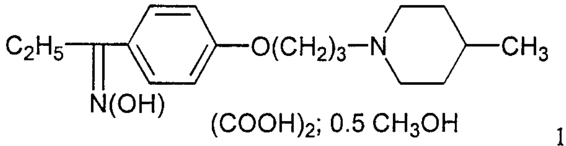
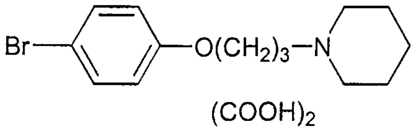
79	$C_{16}H_{22}N_2O$; HCl  HCl 1-[3-(4-cyanophenoxy)propyl]-3-methylpiperidine hydrochloride	171-173°C (absolute ethanol/diethyl ether 1:1)	C: 64.87 (65.18) H: 8.01 (7.86) N: 9.40 (9.50)	N
80	$C_{17}H_{25}NO_2$; $C_2H_2O_4$  $(COOH)_2$ 1-[3-(4-acetylphenoxy)-2-S-methylpropyl] piperidine hydrogen oxalate	148-150°C (absolute ethanol)	C: 62.20 (62.45) H: 7.46 (7.45) N: 3.73 (3.83)	M
81	$C_{18}H_{27}NO_2$; HCl  HCl 1-{3-[4-(3-oxobutyl)phenoxy] propyl}piperidine hydrochloride	148-150°C (acetone)	C: 66.10 (66.34) H: 8.92 (8.66) N: 4.16 (4.30)	O
82	$C_{15}H_{19}FN_2O$; HCl; 0.25 H_2O  HCl; 0.25 H_2O 1-[3-(4-cyano-3-fluorophenoxy)propyl] piperidine hydrochloride	157-159°C (absolute ethanol/diethyl ether 1:4)	C: 59.13 (59.40) H: 6.60 (6.81) N: 8.94 (9.24)	L
83	$C_{15}H_{22}N_2O_3$; $C_2H_2O_4$  $(COOH)_2$ 1-[3-(4-nitrophenoxy)propyl]-3-methylpiperidine hydrogen oxalate	172-174°C (absolute ethanol)	C: 55.45 (55.43) H: 6.53 (6.57) N: 7.58 (7.60)	N

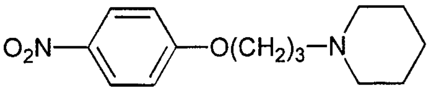
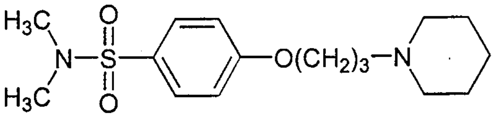
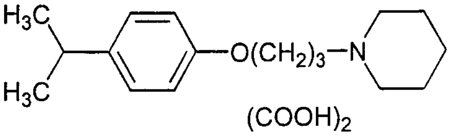
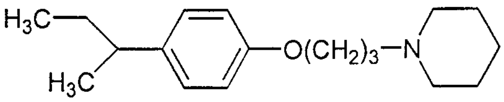
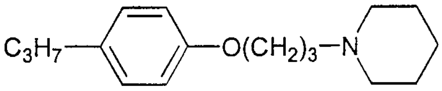
84	$C_{16}H_{22}N_2O$; HCl  HCl 1-[3-(4-cyanophenoxy)propyl]-2-methylpiperidine hydrochloride	177-180°C (absolute ethanol/diethyl ether 1:5)	C: 64.96 (65.18) H: 7.79 (7.86) N: 9.44 (9.50)	N
85	$C_{15}H_{22}N_2O_3$; $C_2H_2O_4$  $(COOH)_2$ 1-[3-(4-nitrophenoxy)propyl]-2-methylpiperidine hydrogen oxalate	151-153°C (absolute ethanol)	C: 55.38 (55.43) H: 6.57 (6.57) N: 7.40 (7.60)	N
86	$C_{15}H_{22}N_2O_3$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-[3-(4-nitrophenoxy)propyl]-4-methylpiperidine hydrogen oxalate	119-121°C (absolute ethanol)	C: 54.52 (54.74) H: 6.55 (6.46) N: 7.19 (7.42)	N
87	$C_{16}H_{22}N_2O$; 1.4 HCl; 1.5 H_2O  1.4 HCl; 1.5 H_2O 1-[3-(4-cyanophenoxy)propyl]-2,6-dimethylpiperidine hydrochloride	180-1825°C (absolute ethanol/diethyl ether 1:5)	C: 58.52 (58.26) H: 8.20 (8.17) N: 7.90 (7.99)	N
88	$C_{18}H_{27}NO_2$; $C_2H_2O_4$  $(COOH)_2$ 1-[3-(4-propionylphenoxy)propyl]-3-methylpiperidine hydrogen oxalate	135-136°C (methanol/ absolute ethanol 1:1)	C: 63.34 (63.31) H: 7.63 (7.70) N: 3.65 (3.69)	N

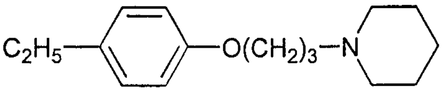
89	$C_{19}H_{27}NO_2$; 1.8 $C_2H_2O_4$  1-[3-(4-cyclobutanecarbonylphenoxy)propyl] piperidine hydrogen oxalate	80-82°C (absolute ethanol)	C: 58.54 (58.57) H: 6.57 (6.65) N: 2.97 (3.02)	L
90	$C_{20}H_{29}NO_2$; 1.1 $C_2H_2O_4$  1-[3-(4-cyclopentanecarbonylphenoxy) propyl]piperidine hydrogen oxalate	143-145°C (absolute ethanol/diethyl ether 1:1)	C: 64.39 (64.33) H: 7.78 (7.59) N: 3.36 (3.38)	L
91	$C_{18}H_{26}N_2O$; 1.05 $C_2H_2O_4$  1-[3-(4-cyanophenoxy)propyl]-cis-2-methyl-5-ethylpiperidine hydrogen oxalate	158-159°C (absolute ethanol)	C: 63.38 (63.37) H: 7.19 (7.43) N: 7.22 (7.35)	N
92	$C_{18}H_{26}N_2O$; 1.4 $C_2H_2O_4$; 0.6 C_2H_5OH  1-[3-(4-cyanophenoxy)propyl]-trans-2-methyl-5-ethylpiperidine hydrogen oxalate	sticky oil (after removal of absolute ethanol)	C: 59.89 (60.04) H: 7.39 (7.42) N: 6.31 (6.37)	N
93	$C_{17}H_{24}N_2O$; $C_2H_2O_4$  1-[3-(4-cyanophenoxy)propyl]-cis-3,5-dimethylpiperidine hydrogen oxalate	161-163°C (absolute ethanol)	C: 62.73 (62.97) H: 7.28 (7.23) N: 7.64 (7.73)	N

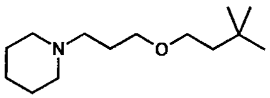
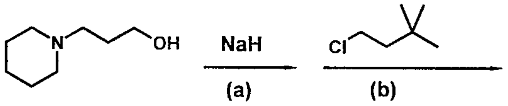
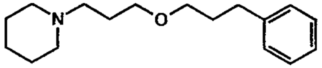
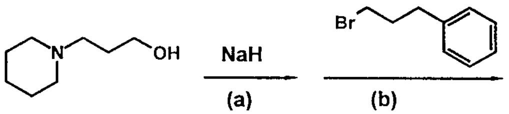
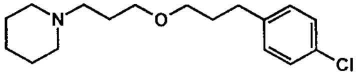
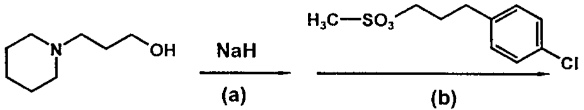
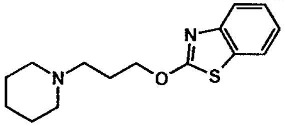
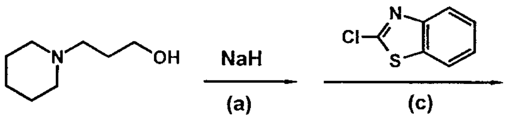
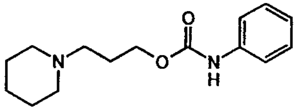
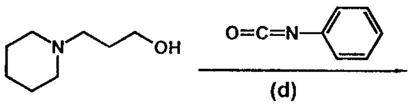
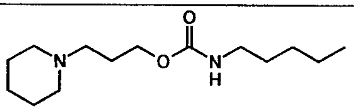
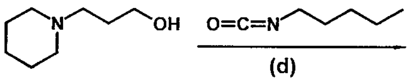
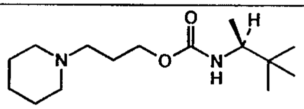
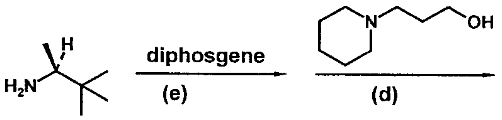
94	$C_{18}H_{27}NO_2$; 1.1 $C_2H_2O_4$  1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine hydrogen oxalate	163-165°C (methanol/ absolute ethanol 1:1)	C: 62.43 (62.46) H: 7.67 (7.58) N: 3.53 (3.61)	N
95	$C_{18}H_{27}NO_2$; $C_2H_2O_4$  1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine hydrogen oxalate	92-94°C (methanol/ absolute ethanol 1:1)	C: 63.01 (63.31) H: 7.79 (7.70) N: 3.61 (3.69)	N
96	$C_{18}H_{29}NO_2$; $C_2H_2O_4$  1-{3-[4-(1-hydroxypropyl)phenoxy]propyl}-3-methylpiperidine hydrogen oxalate	144-145°C (methanol/ absolute ethanol 1:1)	C: 62.95 (62.97) H: 8.13 (8.19) N: 3.54 (3.67)	P
97	$C_{18}H_{29}NO_2$; $C_2H_2O_4$  1-{3-[4-(1-hydroxypropyl)phenoxy]propyl}-4-methylpiperidine hydrogen oxalate	182-183°C (methanol/ absolute ethanol 1:1)	C: 62.64 (62.97) H: 8.31 (8.19) N: 3.62 (3.67)	P
98	$C_{18}H_{28}N_2O_2$; HCl; 0.1 H_2O  1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine oxime hydrochloride	151-153°C (absolute ethanol/diethyl ether 1:1)	C: 62.91 (63.09) H: 8.64 (8.59) N: 8.28 (8.17)	J

99	$C_{19}H_{30}N_2O_2$; $C_2H_2O_4$  1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine methoxime hydrogen oxalate	179-181°C (methanol/ absolute ethanol 1:1)	C: 61.86 (61.75) H: 7.81 (7.90) N: 6.82 (6.86)	Q
100	$C_{17}H_{24}N_2O$; $C_2H_2O_4$  1-[3-(4-cyanophenoxy)propyl]-trans-3,5-dimethylpiperidine hydrogen oxalate	163-165°C (absolute ethanol)	C: 63.04 (62.97) H: 7.10 (7.23) N: 7.53 (7.73)	N
101	$C_{20}H_{29}NO_2$; $C_2H_2O_4$; 0.2 H_2O  1-[3-(4-cyclopropylcarbonylphenoxy)propyl] -trans-3,5-dimethylpiperidine hydrogen oxalate	136-138°C (absolute ethanol/diethyl ether 1:1)	C: 64.54 (64.59) H: 7.70 (7.74) N: 3.44 (3.42)	N
102	$C_{20}H_{29}NO_2$; 1.1 $C_2H_2O_4$  1-[3-(4-cyclopropylcarbonylphenoxy)propyl] -cis-3,5-dimethylpiperidine hydrogen oxalate	130-132°C (absolute ethanol/diethyl ether 1:1)	C: 64.50 (64.33) H: 7.82 (7.59) N: 3.33 (3.38)	N
103	$C_{16}H_{23}NO_3$; $C_2H_2O_4$  1-[3-(4-carbomethoxyphenoxy)propyl] piperidine hydrogen oxalate	156-158°C (methanol)	C: 59.03 (58.85) H: 6.76 (6.86) N: 3.77 (3.81)	L

104	$C_{18}H_{27}NO; C_7H_8SO_3$  1-[3-(4-propenylphenoxy)propyl]-2-methyl piperidine hydrogen p-toluene sulfonate	118-120°C (absolute ethanol/diethyl ether 1:3)	C: 67.26 (67.38) H: 7.83 (7.92) N: 3.08 (3.14)	R
105	$C_{19}H_{30}N_2O_2; HCl$  1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine methoxime hydrochloride	185-187°C (absolute ethanol/diethyl ether 1:3)	C: 64.28 (64.30) H: 8.77 (8.80) N: 7.80 (7.89)	Q
106	$C_{20}H_{33}NO_2; C_7H_8SO_3; 0.3\ H_2O$  1-{3-[4-(1-ethoxypropyl)phenoxy]propyl} -2-methyl piperidine hydrogen p-toluene sulfonate	105-107°C (absolute ethanol/diethyl ether 1:3)	C: 65.25 (65.24) H: 8.44 (8.44) N: 2.80 (2.82)	S
107	$C_{18}H_{28}N_2O_2; C_2H_2O_4; 0.5\ CH_3OH$  1 -[3-(4-propionylphenoxy)propyl]-4-methylpiperidine oxime hydrogen oxalate	157-160°C (methanol)	C: 59.92 (59.98) H: 8.00 (7.86) N: 6.74 (6.82)	J
108	$C_{14}H_{20}BrNO; C_2H_2O_4$  1-[3-(4-bromophenoxy)propyl]piperidine hydrogen oxalate	175-177°C (absolute ethanol)	C: 49.52 (49.50) H: 5.62 (5.71) N: 3.50 (3.61)	L

109	$C_{14}H_{20}N_2O_3$; $C_2H_2O_4$  $(COOH)_2$ 1-[3-(4-nitrophenoxy)propyl]piperidine hydrogen oxalate	148-151°C (absolute ethanol)	C: 54.14 (54.23) H: 6.26 (6.26) N: 7.88 (7.91)	L
110	$C_{16}H_{26}SN_2O_3$; $C_2H_2O_4$  $(COOH)_2$ 1-[3-(4-N,N-dimethylsulfonamidophenoxy) propyl]piperidine hydrogen oxalate	149-153°C (absolute ethanol)	C: 51.58 (51.91) H: 6.80 (6.78) N: 6.84 (6.73)	L
111	$C_{17}H_{27}NO$; $C_2H_2O_4$  $(COOH)_2$ 1-[3-(4-isopropylphenoxy)propyl]piperidine hydrogen oxalate	131-134°C (absolute ethanol)	C: 64.68 (64.93) H: 8.50 (8.32) N: 3.96 (3.99)	L
112	$C_{18}H_{29}NO$; 1.1 $C_2H_2O_4$  1.1 $(COOH)_2$ 1-[3-(4-sec-butylphenoxy)propyl]piperidine hydrogen oxalate	133-136°C (absolute ethanol)	C: 64.67 (64.79) H: 8.47 (8.40) N: 3.76 (3.74)	L
113	$C_{17}H_{27}NO$; $C_2H_2O_4$; 0.5 H_2O  $(COOH)_2$; 0.5 H_2O 1-[3-(4-propylphenoxy)propyl]piperidine hydrogen oxalate	121-124°C (absolute ethanol)	C: 63.46 (63.31) H: 8.36 (8.39) N: 3.92 (3.89)	L

114	$C_{16}H_{25}NO$; $C_2H_2O_4$; 0.5 H_2O  $(COOH)_2$; 0.5 H_2O 1-[3-(4-ethylphenoxy)propyl]piperidine hydrogen oxalate	148-151°C (absolute ethanol)	C: 62.65 (62.41) H: 7.88 (8.15) N: 4.42 (4.04)	L

No	Structure	Synthesis
115		
116		
117		
118		
119		
120		
121		

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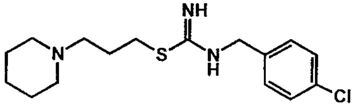
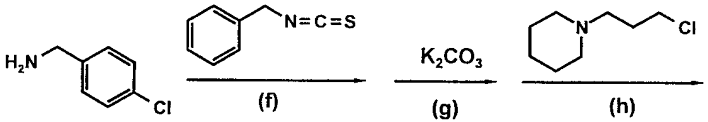
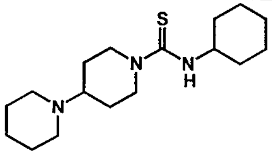
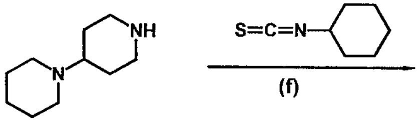
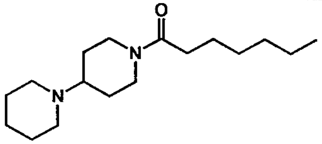
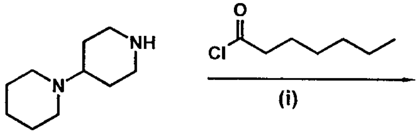
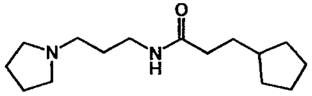
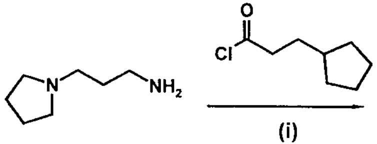
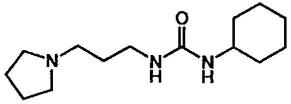
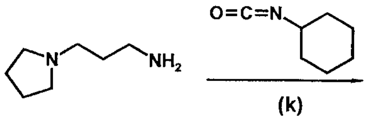
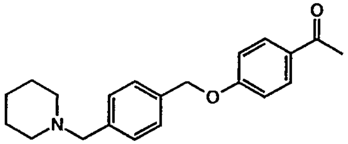
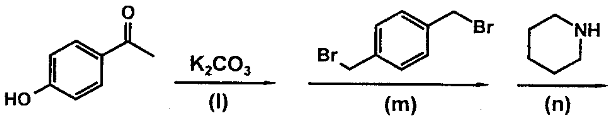
122		
123		
124		
125		
126		
127		

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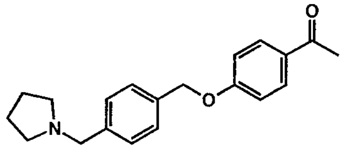
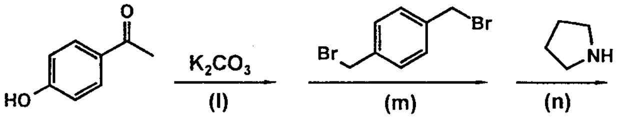
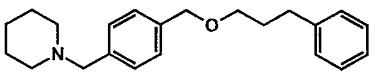
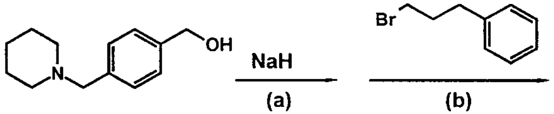
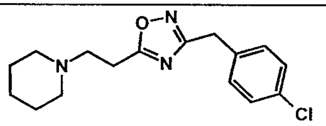
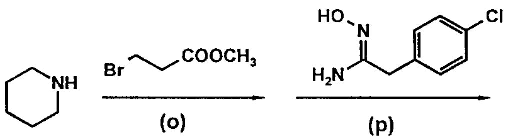
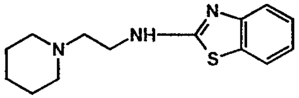
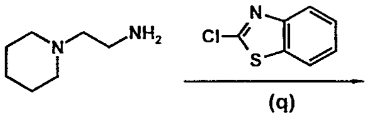
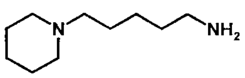
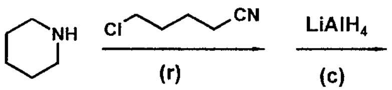
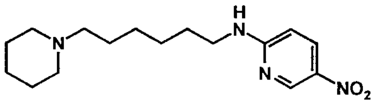
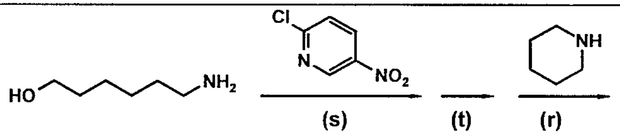
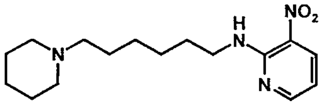
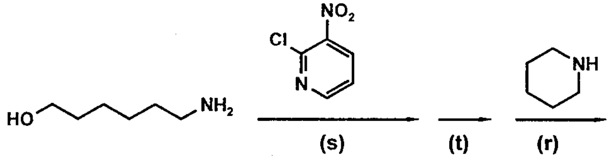
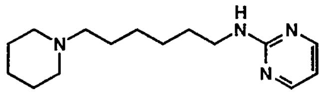
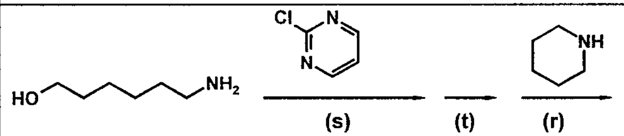
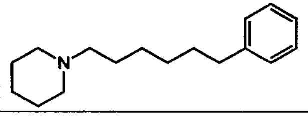
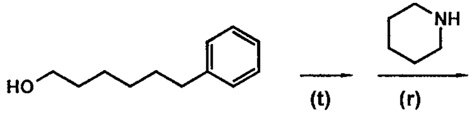
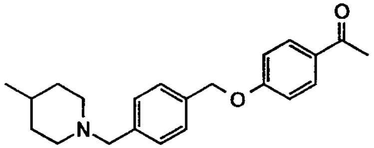
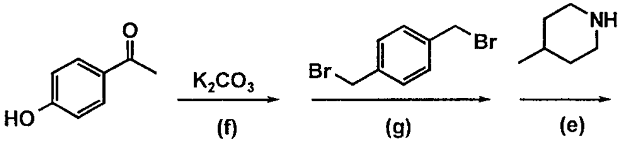
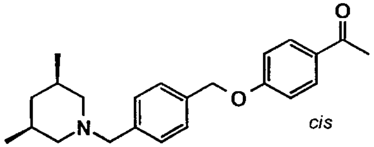
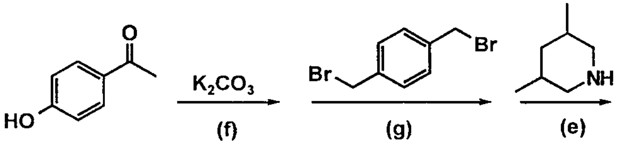
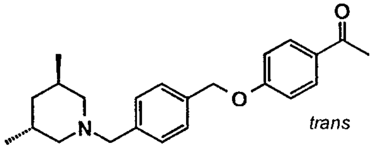
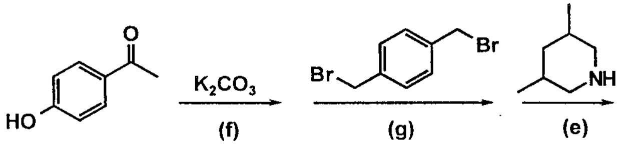
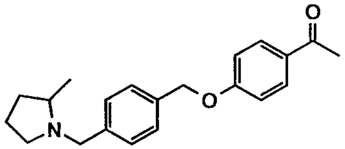
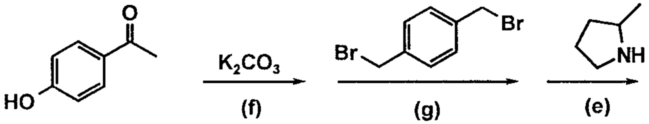
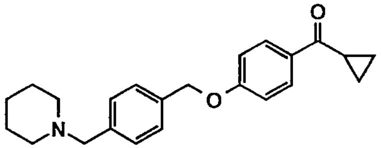
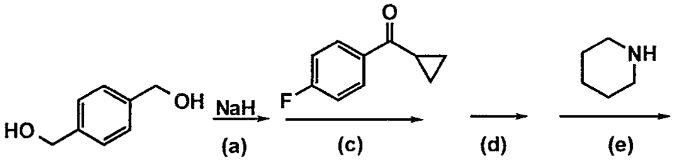
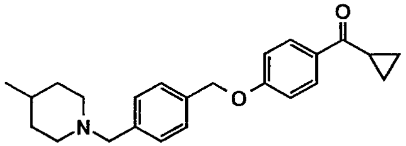
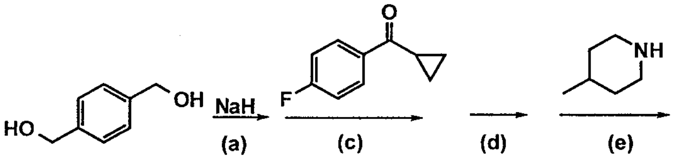
128		
129		
130		
131		
132		
133		
134		

No	Structure	Synthesis
135		
136		

(a) toluene, 12 h, r.t.
(b) toluene, tetrabutylammonium iodide, 15-crown-5, 12 h, 80 °C.
(c) THF, 12 h, reflux.
(d) acetonitrile, 4 h, 80 °C.
(e) ethyl acetate, 3 h, 60 °C.
(f) diethyl ether, 2 h, r.t.
(g) H_2O/EtOH, 2 h, reflux.
(h) KI, EtOH, 2 d, reflux.
(i) dioxane/H_2O (1+1), 4 h, 0 °C.
(k) acetonitrile, 5 min, r.t.
(l) acetone/DMF (10:1), 10 min, r.t.
(m) 12 h, r.t.
(n) 1 h, reflux.
(o) triethylamine, acetone, 8 h, 50 °C.
(p) Na, MeOH, DMF, 6 h, 80 °C.
(q) triethylamine, MeOH, 24 h, 50 °C.
(r) K_2CO_3, KI, EtOH, 6 h, reflux.
(s) triethylamine, KI, EtOH, 12 h, reflux.
(t) thionyl chloride, THF, 2 h, 0 °C.

No	Structure	Synthesis
137		
138		
139		
140		
141		
142		

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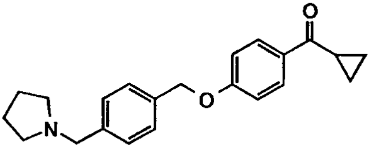
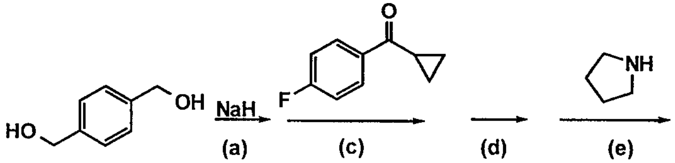
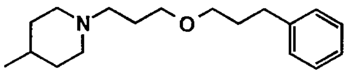
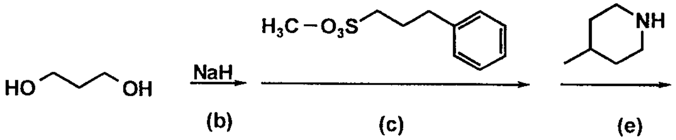
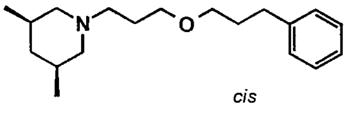
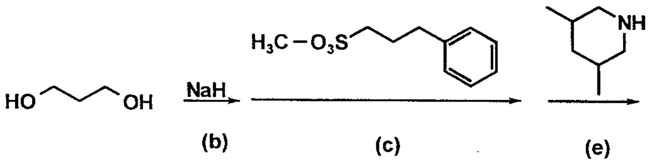
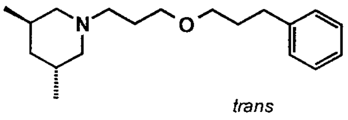
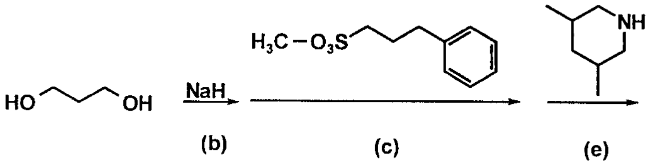
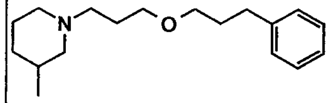
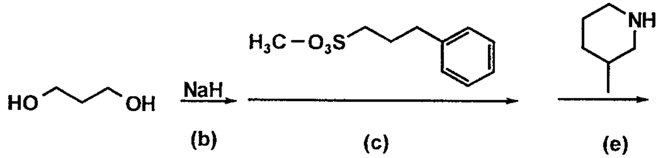
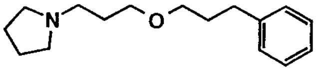
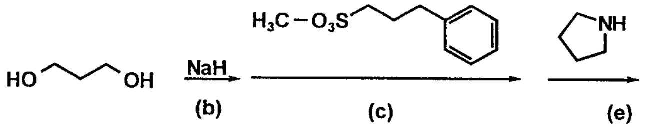
143		
144		
145	 cis	
146	 trans	
147		
148		

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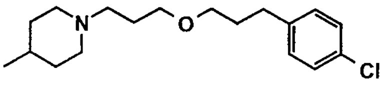
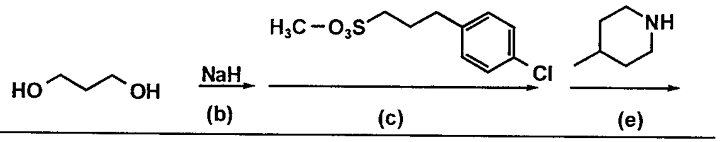
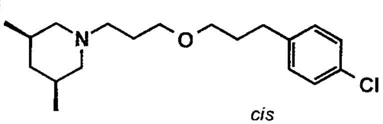
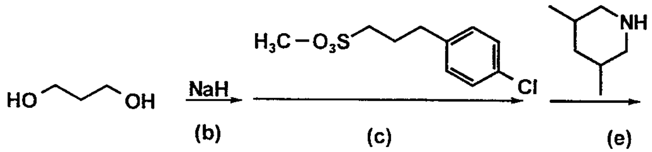
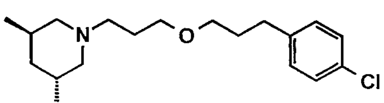
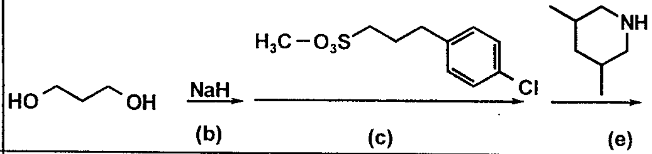
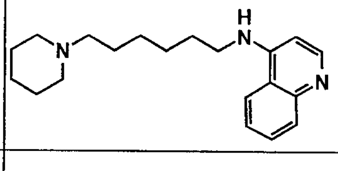
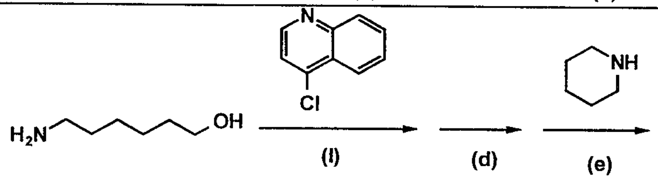
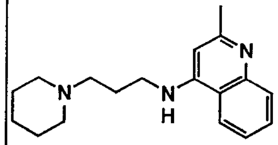
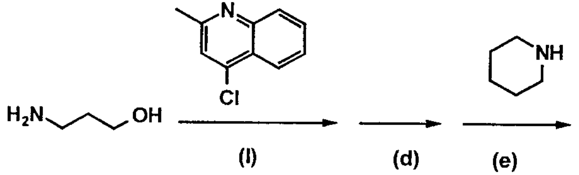
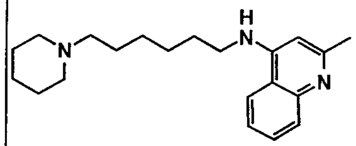
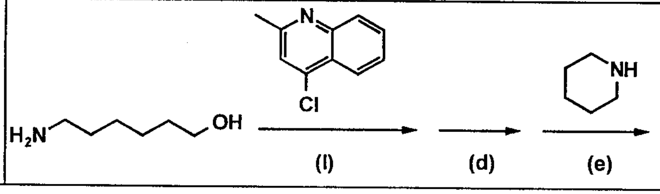
149		
150	 cis	
151	 trans	
152		
153		
154		

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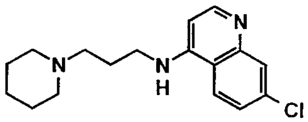
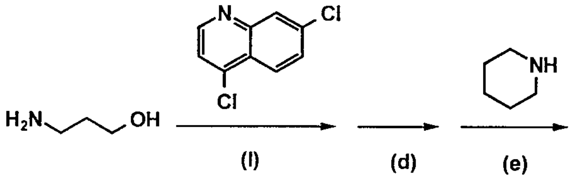
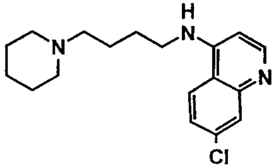
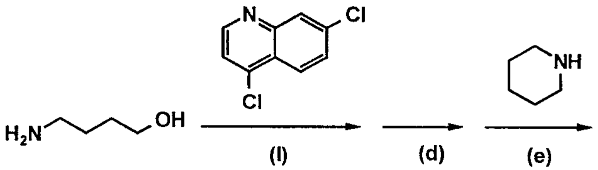
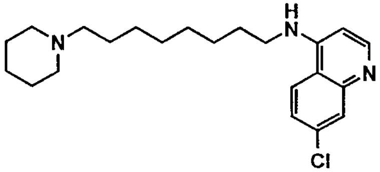
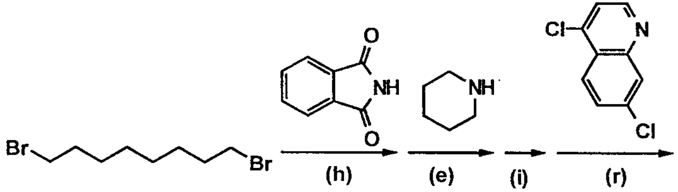
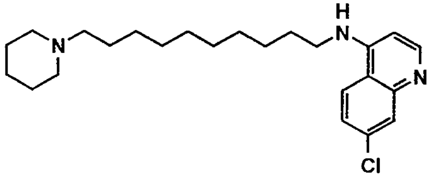
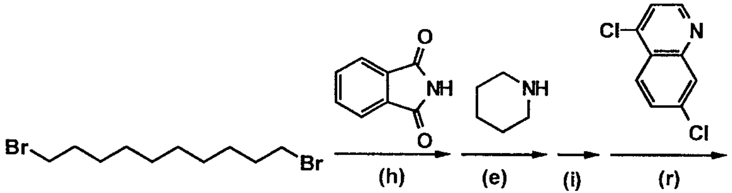
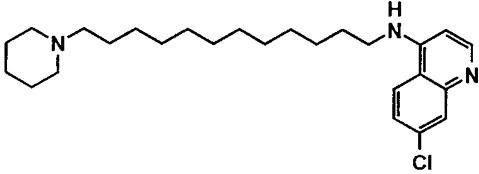
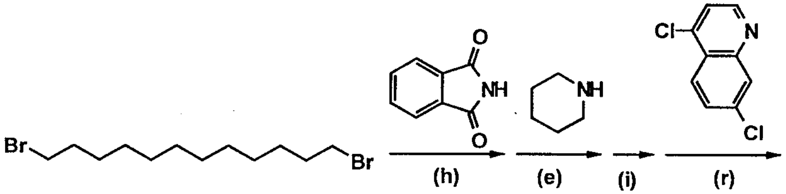
155		
156		
157		
158		
159		

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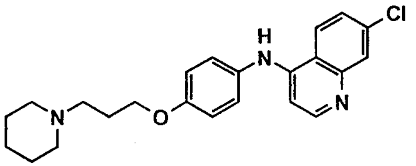
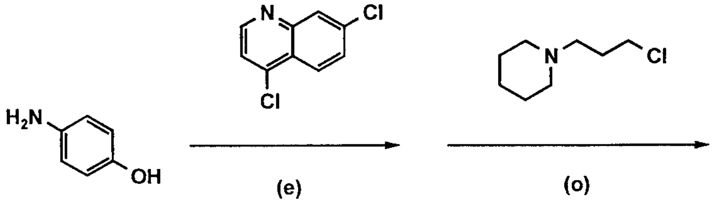
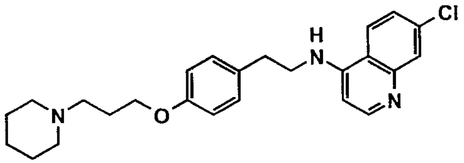
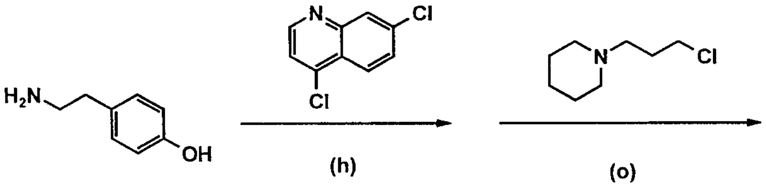
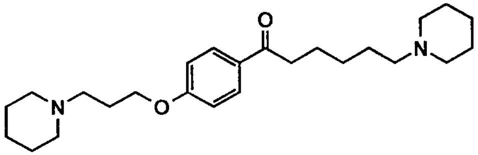
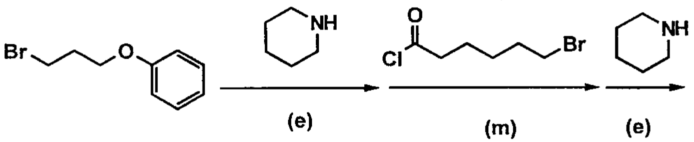
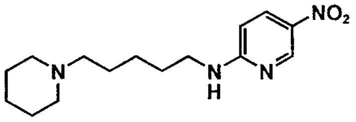
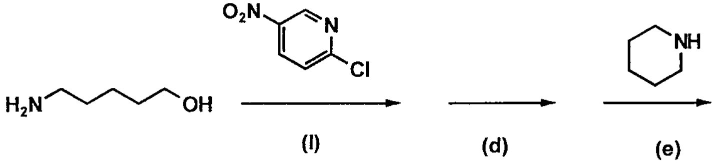
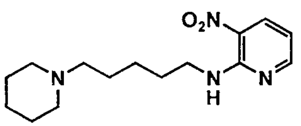
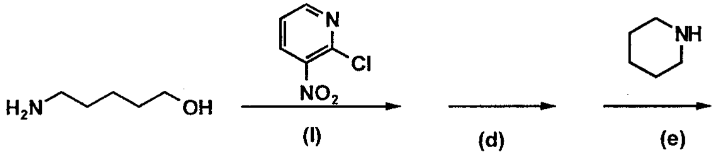
160		
161		
162		
163		
164		

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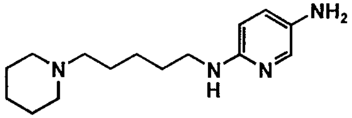
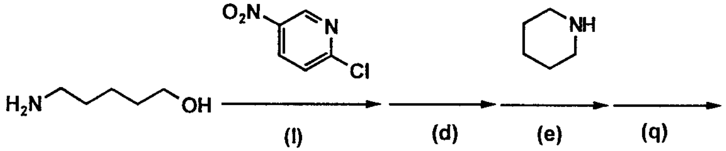
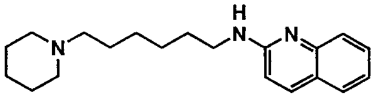
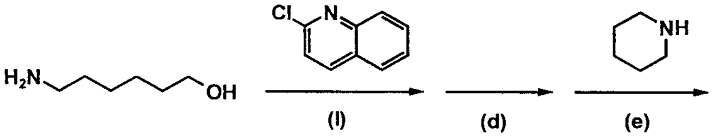
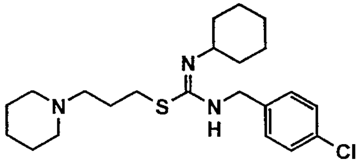
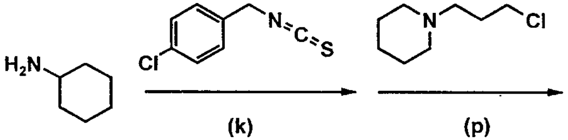
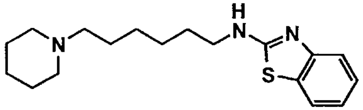
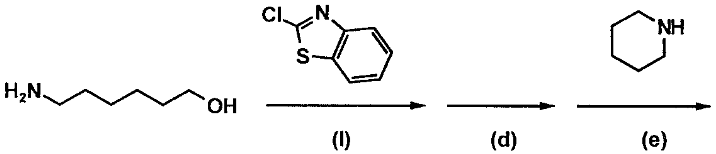
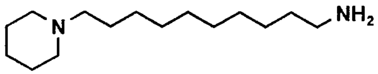
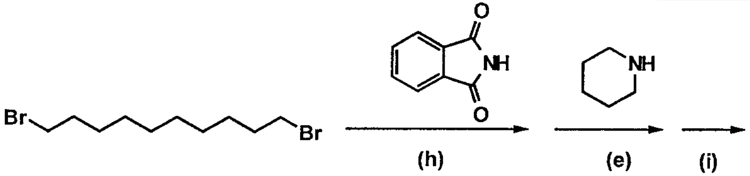
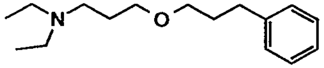
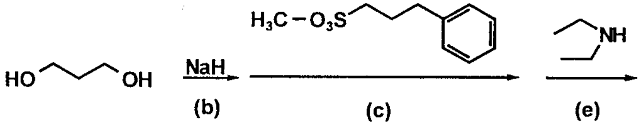
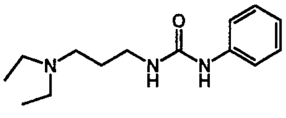
165		
166		
167		
168		
169		
170		

a) THF, 10 h, r.t.
b) THF, 10 h, reflux
c) THF, tetrabutylammonium iodide, 15-crown-5, 24 h, reflux
d) thionyl chloride, 3h, 0 °C - 70 °C
e) acetone, KI, 12 h, reflux
f) acetone, 10 min., r.t.
g) acetone, 12 h, reflux
h) acetone, KI, 3 d, reflux
i) 6N HCl, 12 h, reflux

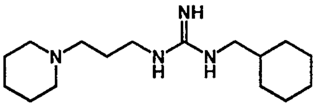
k) ether, 2 h, r.t.
l) ethanol, KI, triethylamine, 12 h, reflux
m) nitrobenzol, $AlCl_3$, 3 d, r.t.
n) DMF, KI, K_2CO_3, 22 h, reflux
o) acetone, KI, K_2CO_3, 22 h, reflux
p) ethanol, KI, 6 d, reflux
q) THF, Pd/C, 1 bar, 12 h
r) phenol, KI, 12 h, 150 °C

The following compounds can be prepared according to the synthesis schemes:

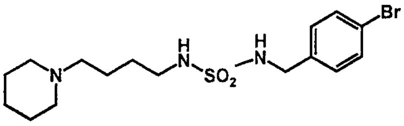
No. Structure Synthesis

171  scheme 7

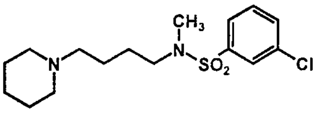
N-(3-(N,N-Diethylamino)propyl)N'-phenylurea

172  scheme 7

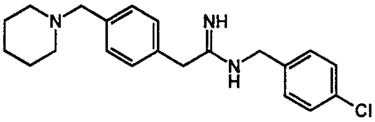
N-Cyclohexylmethyl-N'-(3-piperidinopropyl)guanidine

173  scheme 12

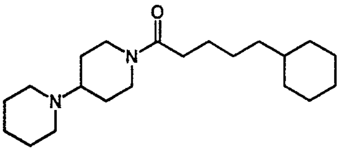
N-(4-Bromobenzyl)-N'-(4-piperidinobutyl)sulphamide

174  scheme 12

3-Chloro-N-(4-piperidinobutyl)-N-methyl-benzene sulphonamide

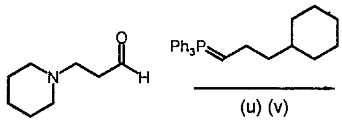
175  scheme 11

N-(4-Chlorobenzyl)-2-(4-piperidinomethyl)phenyl) ethan amidine

176  scheme 9

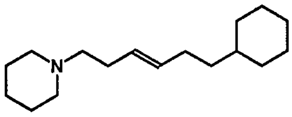
1-(5-Cyclohexylpentanoyl)-1,4-bipiperidine

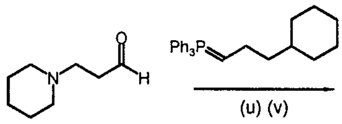
177



cis-1-(6-Cyclohexyl-3-hexen-1-yl)piperidine

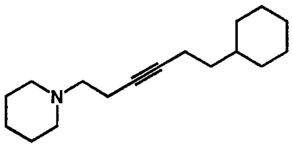
178

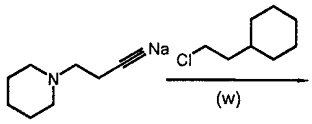




trans-1-(6-Cyclohexyl-3-hexen-1-yl)piperidine

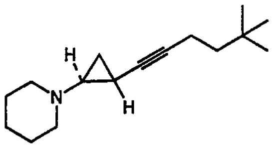
179





1-(6-Cyclohexyl-3-hexin-1-yl)piperidine

180



scheme 14

1-(2-(5,5-Dimethyl-1-hexin-1-yl)cyclopropyl)piperidine

(u) potassium tert. butanolate, THF, 24h, 0 - 50 °C; (v) chromatographic separation; (w) NH_3 (fl.), MeOH, -78 - 0 °C.

Compounds 1 to 114 are prepared according to the following procedures:

METHOD A:

A solution of 1-bromo-5-phenoxypentane (1.4 to 3.5 mmol) in ten equivalents of the suitable secondary amine was heated to reflux temperature with stirring for 48 hours (compds. 1, 3 and 4), 24 hours (compd. 2) or 4 hours (compd. 5). After cooling, the excess base was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. The precipitate formed was washed with diethyl ether and recrystallised from absolute ethanol.

METHOD B:

A solution of 1-bromo-5-phenoxypentane (0.9 to 1.7 mmol) and an excess of the suitable secondary amine (2.3 to 10 equivalents) in 10 ml absolute ethanol was heated to reflux temperature with stirring for 48 hours (compd. 6) or 24 hours (compds. 7, 8, 9, 10, 11, 12&13, 14, 15, 16, 17 and 29). After cooling, the solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The cis and trans isomers 12 and 13 were separated by column chromatography on silica gel eluting with a solvent mixture of petroleum spirit (bp 60-80°C), diethyl ether and triethylamine in the ratio 66:33:1, and the eluent was removed under reduced pressure to leave an oil. Compounds 14 and 16 were purified by column chromatography on silica gel eluting with diethyl ether and triethylamine in the ratio 99:1, and the eluent was removed under reduced pressure to leave an oil. The oil was converted to oxalate salt (compds. 6, 7, 8, 9, 11, 12, 13, 15, 16, 17 and 29) by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents of oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from isopropyl alcohol (compds. 6, 7, 10, 13 and 16), absolute ethanol (compds. 8, 9, 11, 12, 15 and 29) or methanol (compd. 17). The oil was converted to hydrochloride salt (compd. 14) by adding 2N HCl. The precipitate was formed in a mixture of chloroform and diethyl ether (1:1) and recrystallised from acetone.

METHOD C:

A solution of the suitable α-bromo-ω-aryloxy alkane (0.4 to 1.4 mmol) or ω-bromoalkyl phenyl sulphide (1 mmol, compds. 33 and 34) and an excess of pyrrolidine (10 to 15 equivalents) or 3-methylpiperidine (10 equivalents, compd. 38) in 10 ml absolute ethanol was heated to reflux temperature with stirring for 24 hours or 16 hours (compd. 47). After cooling, the solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol.

METHOD D:

A solution of the suitable 4'-(5-bromopentoxy)phenyl ketone (0.7 to 1 mmol, compds. 39, 44 and 45) or 1-bromo, 5-(4-phenoxyphenoxy)pentane (0.6 mmol, compd. 48) and an excess of pyrrolidine (10 to 15 equivalents) in 10 ml absolute ethanol was heated to reflux temperature with stirring for 16 hours (compds. 39, 44 and 48) or 24 hours (compd. 45). After cooling, the solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with chloroform (compds. 39, 45 and 48) or dichloromethane (compd. 44), the organic extracts dried over magnesium sulphate, filtered and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. The precipitate was washed with diethyl ether and recrystallised from absolute ethanol (recrystallised twice from absolute ethanol in the case of compd. 39).

METHOD E:

1. The oxalate 18 was prepared according to method C. A solution of compound 18 (0.57 mmol) in 10 ml methanol and 10 ml absolute ethanol was placed with 100 mg of palladium (5%) on carbon catalyst in a two-neck round-bottom flask fitted with a balloon filled with hydrogen. The mixture was stirred vigorously at room temperature and the flask was purged of air and filled with hydrogen. After 3 hours, the catalyst was filtered off on celite and the solvent removed under reduced pressure. The residual solid was converted to oxalate salt by dissolving in methanol and adding a solution of oxalic acid (2 equivalents) in absolute ethanol. Diethyl ether was added to form a precipitate. The product was recrystallised from absolute ethanol.

2. To a solution of compound 40 (0.35 mmol) in pyridine vigorously stirred at 0°C was added dropwise a slight excess of benzoyl chloride (0.4 mmol). The stirring was allowed to continue 20 minutes after the end of the addition after which the mixture was placed in the refrigerator overnight (16 hours). The solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with chloroform, the organic extracts dried over magnesium sulphate, filtered and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. The precipitate was dissolved in methanol, filtered, and concentrated under reduced pressure. the solid was recrystallised from absolute ethanol

METHOD F:

In a three-neck flask kept under nitrogen was placed a solution of the suitable phenol (1.6 mmol), 3-(diethylamino)propanol (1.5 mmol), and triphenyl phosphine (1.9 mmol) in 10 ml freshly distilled tetrahydrofuran. The mixture was stirred and cooled to 0°C with an ice and salt bath. A solution of diisopropyl azodicarboxylate (2 mmol) in 10 ml tetrahydrofuran was added very slowly (typically over 40 minutes) and the mixture was allowed to warm to room temperature after which it was stirred overnight at room temperature (16 hours). The solvent was then removed under reduced pressure, the residue dissolved in ethyl acetate (20 ml) and the product extracted with 2N HCl (2x10 ml). The aqueous solution was neutralised with sodium hydroxide and the product extracted with dichloromethane. After drying over magnesium sulphate and filtration, the solvent was removed under reduced pressure. The residue was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol (compds. 43 and 46) or from a 1:1 mixture of methanol and absolute ethanol (compd. 42).

METHOD G:

A solution of the free base of compound 39 (0.6 mmol) or compound 46 (0.8 mmol) in 20 ml dry diethyl ether was added dropwise to a stirred suspension of lithium aluminium hydride (0.6 or 0.8 mmol) in 20 ml dry diethyl ether kept under nitrogen. The mixture was stirred at room temperature under nitrogen for two hours. Ice-cold water was carefully added and the organic layer decanted. The aqueous phase was extracted with diethyl ether. The combined organic solutions were dried over magnesium sulphate, filtered and concentrated under reduced pressure to leave a yellow oil. The oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. The precipitate was washed with diethyl ether and recrystallised from absolute ethanol (compd 50) or from isopropyl alcohol, giving a very hygroscopic solid (compd. 63).

METHOD H:

A solution of the suitable α-bromo-ω-(4-cyanophenoxy) alkane (0.5 to 0.7 mmol) and an excess of the suitable secondary amine (8 to 12 equivalents) in 10 ml absolute ethanol was heated to reflux temperature with stirring for 24 hours (compds. 54, 55, 57 and 60), 20 hours (compd. 52), 16 hours (compds. 56, 58, 59 and 61) or 8 hours (compd. 51) or was stirred at room temperature for 48 hours (compd. 53) or 24 hours (compd. 60). After cooling, the solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. Compound 62 was purified by column chromatography on silica gel eluting with ethyl acetate, and concentrated under reduced pressure. For all the compounds of method H, the remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol (two recrystallisations were required for compds. 58 and 59) or from a 1:1 mixture of methanol and absolute ethanol (compd. 55).

METHOD J:

A solution of compound 46 (1 mmol) in 10 ml methanol was stirred at room temperature and a solution of hydroxylamine hydrochloride (2 equivalents) in 2 ml water was added. The mixture was stirred at 50-70°C in a water bath for 20 minutes. Methanol was removed under reduced pressure. The residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. Compound 64 was purified by column chromatography on silica gel eluting with ethyl acetate, and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. Diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol.

For example 98, the product was converted to the hydrochloride salt by addition of 2N HCl. The salt was recrystallised from absolute ethanol/diethyl ether (1:1).

METHOD K:

A solution of 4'-(3-bromopropoxy)acetophenone (0.8 to 1.9 mmol) and an excess of the suitable piperidine (3 to 10 equivalents) in 10 ml absolute ethanol was heated to reflux temperature with stirring for 16 hours. After cooling, the solvent was removed under reduced pressure and the residue diluted with aqueous sodium hydroxide. The product was extracted with diethyl ether, the organic extracts washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The cis and trans isomers 67 and 70 were separated by column chromatography on silica gel eluting with a solvent mixture of diethyl ether, petroleum spirits (bp 60-80°C) and triethylamine in the ratio 66:33:1, and the eluent was removed under reduced pressure to leave an oil. Compound 75 was purified by column chromatography on silica gel eluting with chloroform and methanol (1:1), and concentrated under reduced pressure. The remaining oil was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents of oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol.

METHOD L:

In a three-neck flask kept under nitrogen was placed a solution of the suitable 4'-hydroxyphenyl ketone (0.9 to 3 mmol), 3-(1-piperidinyl)propanol (0.9 to 3 mmol), and triphenyl phosphine (1 to 3.5 mmol) in 10 ml freshly distilled tetrahydrofuran. The mixture was stirred and cooled to 0°C with an ice and salt bath. A solution of diethyl azodicarboxylate (1 to 3.6 mmol) in 10 ml tetrahydrofuran was added very slowly (typically over 40 minutes) and the mixture was allowed to warm to room temperature after which it was stirred overnight at room temperature (16 hours). The solvent was then removed under reduced pressure, the residue dissolved in ethyl acetate (20 ml) and the product extracted with 2N HCl (2x10 ml). The aqueous solution was neutralised with sodium hydroxide and the product extracted with dichloromethane. After drying over magnesium sulphate and filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with diethyl ether containing 1% triethylamine, and concentrated under reduced pressure. The residue was converted to oxalate salt by dissolving in a small amount of absolute ethanol and adding a solution of two equivalents oxalic acid in absolute ethanol. If no precipitate appeared, diethyl ether was added to form a precipitate. The solid was washed with diethyl ether and recrystallised from absolute ethanol.

For example 82, the amine was converted to the hydrochloride salt by addition of 2N HCl. The salt was recrystallised from absolute ethanol/diethyl ether (1:14).

Method M:

A solution of 3-(4-acetylphenoxy)-2-(R or S)-methylpropyl *para*-toluene sulfonate (0.55 to 0.66 mmol) and piperidine (5 to 6 mmol) in 10 ml absolute ethanol was stirred and heated under reflux for 2 hours. After cooling, the solvent was removed under reduced pressure, the residue diluted with aqueous NaOH (10 ml) and the oil was extracted with diethyl ether (3 x 10 ml). The combined extracts were dried over magnesium sulfate, and the solvent removed under reduced pressure. The yellow oil was purified by column chromatography on silica gel eluting with a 1:1 mixture of chloroform and absolute ethanol (example 80). After concentration, the oil was dissolved in about 2 ml absolute ethanol and a solution of oxalic acid (1 to 1.1 mmol) in 2 ml absolute ethanol was added. The precipitate was recrystallised from absolute ethanol.

Method N:

A solution of 1-bromo-3-(4-substitutedphenoxy)propane (0.4 to 2 mmol) and the suitably substituted piperidine (2.5 to 8 mmol) in 10 ml absolute ethanol was stirred and heated under reflux for 6 to 24 hours. After cooling, the solvent was removed under reduced pressure, the residue diluted with aqueous NaOH (10 ml) and the oil was extracted with diethyl ether (3 x 10 ml). The combined extracts were dried over magnesium sulfate, and the solvent removed under reduced pressure. The residual oil was dissolved in about 5 ml diethyl ether and a solution of HCl in 10 ml diethyl ether was added. The precipitate was recrystallised from a 1:1 or 1:5 mixture of absolute ethanol and diethyl ether (examples 78, 79, 84, 87). The oil was purified by column chromatography on silica gel eluting with a mixture of 33% petroleum ether (60-80°C), 66% diethyl ether and 1% triethylamine (examples 101 and 102) or with 99% diethyl ether and 1% triethylamine (examples 88, 94 and 95) and concentrated. The residual oil was dissolved in about 5 ml absolute ethanol and a solution of oxalic acid (1 to 1.6 mmol) in 5 ml absolute ethanol was added. The precipitate was recrystallised from absolute ethanol or from a 1:1 mixture of methanol and absolute ethanol (examples 83, 85, 86, 91, 93, 100, 101 and 102). The product was obtained as a sticky oil after removal of absolute ethanol (example 92).

Method O:

A mixture of 4-(4-hydroxyphenyl)-2-butanone (200 mg, 1.2 mmol), 3-chloropropyl piperidine hydrochloride (200 mg, 1 mmol) and potassium carbonate (830 mg, 6 mmol) in 10 ml absolute ethanol was stirred and heated under reflux for 8 hours. After cooling, the reaction mixture was filtered and concentrated under reduced pressure. The residue was diluted with aqueous sodium hydroxide and extracted with diethyl ether (3 x 10 ml). The combined extracts were dried over magnesium sulfate, and the solvent removed under reduced pressure. The free base was dissolved in diethyl ether and a solution of HCl in diethyl ether was added. The precipitate was recrystallised from acetone.

Method P:

A solution of the ketone (0.4 mmol) in 10 ml methanol was stirred at 0°C in an ice-bath. To this solution was added portionwise $NaBH_4$ (1 mmol). The mixture was left to stir at room temperature for 16 hours. The solvent was removed, water (10 ml) was added to the residue and the product was extracted with chloroform (4 x 10 ml). The combined extracts were dried over magnesium sulfate, and the solvent removed under reduced pressure. The free base was dissolved in absolute ethanol (5 ml) and a solution of oxalic acid (1 mmol) in 5 ml absolute ethanol was added. The precipitate was recrystallised from absolute ethanol.

Method Q:

Similar to method J using methoxylamine in place of hydroxylamine. For example 105, the product was converted to the hydrochloride salt by addition of 2N HCl. The salt was recrystallised from absolute ethanol/diethyl ether (1:3).

Method R:

Similar to method P. The reduced product was converted to the hydrochloride salt by addition of 2N HCl. Then, the product was converted to the free base by addition of 10% aqueous NaOH. Then, the product was converted to the para-toluene sulfonate by addition of a solution of para-toluene sulfonic acid (1 mmol) in 5 ml absolute ethanol. The precipitate was recrystallised from absolute ethanol/diethyl ether (1:3).

Method S:

Similar to method P. The reduced product was converted to the para-toluene sulfonate by addition of a solution of para-toluene sulfonic acid (1 mmol) in 5 ml absolute ethanol. The precipitate was recrystallised from absolute ethanol/diethyl ether (1:3).

Intermediates:

(4-hydroxyphenyl)cyclopropyl ketone, intermediate for examples 76, 101 and 102.

S. N. Rastogi et al. *J. Med. Chem.* 15, 286-291 (1972)

4'-(3-hydroxy-2-(R)-methylpropoxy)acetophenone and 4'-(3-hydroxy-2-(S)-methylpropoxy) acetophenone, intermediates for examples 77 and 80.

A mixture of 4'-hydroxyacetophenone (1.3 to 2.8 mmol), 3-bromo-2-(R or S)-methyl-1-propanol (1.3 to 2.6 mmol) and potassium carbonate (1.7 to 3.6 mmol) in acetone (20 ml) was stirred and heated under reflux for 24 hours. The suspension was filtered hot and the solvent removed under reduced pressure to leave an oil that was purified by column chromatography on silica gel eluting with a mixture of diethyl ether and petroleum ether (60-80 °C). After concentration, a colourless oil was obtained.

NMR: 7.91 (m, 2H); 6.92 (m, 2H); 4.01 (m, 2H); 3.71 (br, 2H); 2.54 (s, 3H); 2.21 (m, 1H); 2.10 (br, 1H); 1.06 (d, 3H)

NMR: 7.91 (m, 2H); 6.93 (m, 2H); 4.01 (m, 2H); 3.71 (br, 2H); 2.55 (s, 3H); 2.23 (m, 1H); 2.09 (br, 1H); 1.06 (d, 3H)

3-(4-acetylphenoxy)-2-(S)-methylpropyl *para*-toluene sulfonate and 3-(4-acetylphenoxy)-2-(R)-methylpropyl *para*-toluene sulfonate, intermediates for examples 77 and 80.

A solution of 4'-(3-hydroxy-2-(R or S)-methylpropoxy)acetophenone (0.7 to 1.2 mmol) in pyridine (5 ml) was stirred at 0 °C and *para*-toluene sulfonyl chloride (1 to 1.6 mmol) was added portionwise. The mixture was subsequently placed in the refrigerator overnight. The solvent was then removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with a mixture of 50% diethyl ether and 50% petroleum ether 60-80 °C. After concentration, a colourless oil was obtained. In the case of the R-isomer, the oil formed a white solid that was recrystallised from absolute ethanol.

NMR: 7.91 (m, 2H); 7.74 (m, 2H); 7.23 (m, 2H); 6.79 (m, 2H); 4.11 (m, 2H); 3.87 (m, 2H); 2.57 (s, 3H); 2.38 (s, 3H); 2.33 (m, 1H); 1.07 (d, 3H)

NMR: 7.88 (m, 2H); 7.71 (m, 2H); 7.21 (m, 2H); 6.75 (m, 2H); 4.07 (m, 2H); 3.83 (m, 2H); 2.53 (s, 3H); 2.34 (s, 3H); 2.30 (m, 1H); 1.04 (d, 3H)

1-bromo-3-(4-nitrophenoxy)propane, intermediate for examples 83, 85 and 86.

J. N. Ashley et al. *J. Chem. Soc.* 3298-3304 (1958)

1-bromo-3-(4-propionylphenoxy)propane, intermediate for examples 88, 94 and 95.

To a stirred and heated mixture of 1,3-dibromopropane (80 mmol) and potassium carbonate (50 mmol) in acetone (200 ml) was added dropwise a solution of the hydroxy ketone (40 mmol) in acetone (80 ml). The reaction was allowed to continue overnight. The mixture was filtered hot and the solvent removed under reduced pressure to leave an oil that was dissolved in ethyl acetate. Addition of petroleum spirit (60-80°C) formed a precipitate. The solid was filtered and dried under reduced pressure.

NMR: 7.96 (m, 2H); 6.93 (m, 2H); 4.18 (t, 2H); 3.62 (t, 2H); 2.96 (q, 2H); 2.34 (m, 2H); 1.22 (t, 3H)

(4-hydroxyphenyl)cyclobutyl ketone and (4-hydroxyphenyl)cyclopentyl ketone, intermediates for examples 89 and 90.

A mixture of cyclobutylcarbonyl chloride (5 mmol) or cyclopentylcarbonyl chloride (7 mmol) and aluminium chloride (15 mmol) in dry dichloromethane (40 ml) was stirred at 0 °C and a solution of phenol (8 mmol) in dry dichloromethane (20 ml) was added dropwise. the mixture was then stirred and heated under reflux for 3 hours. After cooling to 0 °C, water was added with vigorous stirring. The organic layer was decanted off, dried over magnesium sulfate and concentrated. The crude product was purified by column chromatography on silica gel eluting with petroleum ether/diethyl ether (2:1).

NMR: 7.72 (m, 2H); 6.80 (m, 2H); 3.95 (m, 1H); 2.45 (m, 2H); 2.15 (m, 4H)

NMR: 7.92 (m, 2H); 7.25 (s, 1H); 6.92 (m, 2H); 3.70 (m, 1H); 2.00 (m, 4H); 1.75 (m, 4H)

1-bromo-3-(4-cyclopropanecarbonylphenoxy)propane, intermediate for examples 101 and 102.

To a stirred and heated mixture of 1,3-dibromopropane (5 mmol) and potassium carbonate (3.4 mmol) in acetone (40 ml) was added dropwise a solution of 4-cyclopropanecarbonylphenol (5 mmol) in acetone (20 ml). The reaction was allowed to continue overnight. The mixture was filtered hot and the solvent removed under reduced pressure to leave an oil. The oil was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (15:1).

4-(N,N-dimethylsulfonamido)phenol, intermediate for example 110.
N. Eliel *J. Org. Chem.* 20, 1657-1660 (1955)

Compounds 115 to 170 are prepared according to the following procedures :

Example 115

3,3-Dimethylbutyl 3-piperidinopropyl ether

Sodium 3-piperidinopropanolate (5 mmol), 5 mmol of 3,3-dimethylbutyl chloride, a catalytic amount of tetrabutylammonium iodide, and 0.5 mmol of 15-crown-5 in 10 ml of dry dimethyl sulfoxide were refluxed for 12 hours. Water was added, and it was extracted with diethyl ether. The organic layer was purified by column chromatography on silica gel (eluent: methylene chloride/methanol (90/10), ammonia atmosphere). The solvent was removed under reduced pressure and the residue crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{14}H_{29}NO \times 1.1\ C_2H_2O_4$ (326.4) mp: 143 °C

CHN analysis	calculated:	C	59.6	H	9.63	N	4.29
	found:	C	59.7	H	9.61	N	4.30

Example 116

3-Phenylpropyl 3-piperidinopropyl ether

Sodium 3-piperidinopropanolate (20 mmol), 20 mmol of 3-phenylpropyl bromide, and 0.5 mmol of 15-crown-5 in 30 ml of dry toluene were refluxed for 4 hours. The solvent was evaporated and the residue purified by column chromatography on silica gel (eluent: methylene chloride/methanol/aqueous ammonia (90/10/0.5)). After removing the solvent under reduced pressure the residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{17}H_{27}NO \times C_2H_2O_4$ (351.4) mp: 125 °C

CHN analysis	calculated:	C	64.9	H	8.32	N	3.99
	found:	C	64.9	H	8.13	N	4.02

Example 117

3-(4-Chlorophenyl)propyl 3-piperidinopropyl ether

Sodium 3-piperidinopropanolate (20 mmol), 7 mmol of 3-(4-chlorophenyl)propyl-mesylate, and 0.5 mmol of 15-crown-5 in 30 ml of dry toluene were refluxed for 4 hours. The solvent was evaporated and the residue purified by column chromatography on silica gel (eluent: methylene chloride/methanol (90/10)). After removing the solvent under reduced pressure the residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{17}H_{26}NOCl \times C_2H_2O_4$ (385.9) mp: 147 °C

CHN analysis	calculated:	C	59.1	H	7.31	N	3.63
	found:	C	59.0	H	7.34	N	3.60

Example 118

2-Benzothiazolyl 3-piperidinopropyl ether

Sodium 3-piperidinopropanolate (5 mmol) and 5 mmol of 2-chlorobenzothiazole in

20 ml of dry tetrahydrofurane were refluxed for 12 hours. The suspension was filtered and the solvent evaporated under reduced pressure. The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{15}H_{20}N_2OS \times C_2H_2O_4$ (366.4) mp: 178.2-178.8 °C

CHN analysis	calculated:	C	55.7	H	6.05	N	7.64
	found:	C	55.6	H	6.03	N	7.51

Example 119

N-Phenyl-3-piperidinopropyl carbamate

3-Piperidinopropanol hydrochloride (10 mmol) and 10 mmol of phenyl isocyanate in 40 ml of dry acetonitrile were refluxed for 3 hours. The solvent was evaporated, and then the residue was recrystallized in dry ethanol.

SF: $C_{15}H_{22}N_2O_2 \times HCl \times 0.1\ H_2O$ (300.6) mp: 169-170 °C

CHN analysis	calculated:	C	59.9	H	7.78	N	9.32
	found:	C	59.9	H	7.64	N	9.05

Example 120

N-Pentyl-3-piperidinopropyl carbamate

3-Piperidinopropanol hydrochloride (4 mmol) and 4 mmol of pentyl isocyanate in 20 ml of dry acetonitrile were refluxed for 3 hours. The solvent was evaporated and the residue purified by column chromatography on silica gel (eluent: methylene chloride/methanol/aqueous ammonia (90/10/0.5)). After removing the solvent under reduced pressure the residue was crystallized with hydrochloric acid in 2-propanol.

SF: $C_{14}H_{28}N_2O_2 \times HCl \times 0.5\ H_2O$ (301.9) mp: 88-89 °C

CHN analysis	calculated:	C	55.7	H	10.0	N	9.28
	found:	C	55.7	H	9.84	N	9.18

Example 121

(*S*)-(+)-*N*-[2-(3,3-Dimethyl)butyl]-3-piperidinopropyl carbamate

3-Piperidinopropanol hydrochloride (5 mmol) and 5 mmol of (*S*)-2-(3,3-dimethyl)butyl isocyanate in 10 ml of dry acetonitrile were refluxed for 12 hours. The solvent was evaporated and the residue purified by column chromatography on silica gel (eluent: methylene chloride/methanol (90/10), ammonia atmosphere). The solvent was removed and the residue crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{15}H_{30}N_2O_2 \times C_2H_2O_4 \times 0.25\ H_2O$ (365.0) mp: 148 °C

$[\alpha]_D^{23}$ = +10.4° (c = 0.495, Methanol)

CHN analysis	calculated:	C	56.0	H	8.98	N	7.68
	found:	C	56.0	H	9.01	N	7.64

Example 122

N-(4-Chlorobenzyl)-S-(3-piperidinopropyl) isothiourea

4-Chlorobenzylamine (10 mmol) was added dropwise to 10 mmol of benzoylisothiocyanate dissolved in 20 ml of dry ether followed by stirring for 2 hours. The precipitated product was filtered off and crystallized from ethyl acetate (Yield: 60%). Potassium carbonate (10 mmol) in 30 ml of water was added dropwise to 5 mmol of the product in 20 ml of ethanol and refluxed for 2 hours. The precipitated product was filtered off and crystallized from ethyl acetate/petroleum ether (Yield: 65%). 3-Piperidinopropyl chloride hydrochloride (3 mmol), 3 mmol of the product, and a catalytic amount of potassium iodide were refluxed in 20 ml of ethanol for 2 days. Subsequently the ethanol was evaporated and the residue purified by column chromatography using methanol/ethyl acetate (2/8) as eluent. After evaporation of the solvent, the product was crystallized with hydrochloric acid from diethyl ether/ethanol.

SF: $C_{16}H_{24}ClN_3S$ x 2 HCl x H_2O (416.8) mp: 104-107.5 °C

CHN analysis	calculated:	C	46.1	H	6.77	N	10.1
	found:	C	45.9	H	6.87	N	9.69

Example 123

N'-Cyclohexylthiocarbamoyl-N-1,4′-bipiperidine

1,4′-Bipiperidine (5 mmol) in 10 ml of dry ether was added dropwise to 5 mmol of cyclohexyl isothiocyanate in 30 ml of dry ether followed by stirring for 2 hours. Filtration gave a residue, which was dissolved in ethanol and crystallized with oxalic acid. Recrystallization resulted in the pure product.

SF: $C_{17}H_{31}N_3S$ x $H_2C_2O_4$ x 0.25 H_2O (404.1) mp: 225-226 °C

CHN analysis	calculated:	C	56.5	H	8.35	N	10.39
	found:	C	56.2	H	8.25	N	10.33

Example 124

N-Heptanoyl-1,4′-bipiperidine

1,4′-Bipiperidine (10 mmol) in 5 ml of water was added dropwise to a solution of 5 mmol of n-heptanoyl chloride in 20 ml of dioxane. After stirring for 15 minutes the solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica gel (eluent: methylene chloride/methanol/aqueous ammonia (90/10/0.5)). The solvent was removed under reduced pressure, and the residue was crystallized with oxalic acid.

SF: $C_{17}H_{32}N_2O$ x $H_2C_2O_4$ (370.5) mp: 131-132 °C

CHN analysis	calculated:	C	61.6	H	9.25	N	7.56
	found:	C	61.6	H	9.36	N	7.50

Example 125

3-Cyclopentyl-*N*-(3-(1-pyrrolidinyl)propyl)propanamide

3-Cyclopentyl propionylchloride (5 mmol) in 10 ml of dioxane was added dropwise to a solution of 10 mmol of 1-(3-aminopropyl)pyrrolidine in water. After stirring for 4 hours the solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica gel (eluent: methylene chloride/

methanol/aqueous ammonia (90/10/1)). The solvent was removed under reduced pressure and the residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{17}H_{28}N_2O$ x $H_2C_2O_4$ x 0.5 H_2O (351.2) mp: 89.5 °C

CHN analysis	calculated:	C	58.1	H	8.83	N	7.97
	found:	C	58.1	H	8.76	N	7.87

Example 126

N-Cyclohexyl-*N*′-(1-pyrrolidinyl-3-propyl)urea

In an argon atmosphere 10 mmol of cyclohexylisocyanate was added slowly to 10 mmol of 1-(3-aminopropyl)pyrrolidine in 10 ml of acetonitrile. The product preci-pitated instantly as a pure white solid. The solvent was removed under reduced pressure and the product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{14}H_{27}N_3O$ x $C_2H_2O_4$ x 0.25 H_2O (347.7) Yield: 83% mp: 113.3 °C

CHN analysis	calculated:	C	56.0	H	8.45	N	12.2
	found:	C	55.6	H	8.27	N	12.0

Example 127

α-(4-Acetylphenoxy)-α′-piperidino p-xylol

Hydroxyacetophenone (2 mmol) and 5 mmol of K_2CO_3 were stirred in 20 ml of acetone with 2 ml of DMF for 10 minutes. After addition of 3.5 mmol of α,α′-dibromoxylol the reaction was stirred at ambient temperature for 12 hours and after addition of 7 mmol of piperidine for 1 hour under reflux. The solvent was evaporated under reduced pressure. The residue was suspended in water, extracted with methylene chloride. The combined organic extracts were crystallized with oxalic acid. Recrystallization resulted in the pure product.

SF: $C_{21}H_{25}NO_2 \times C_2H_2O_4$ (413.5) mp: 136-137 °C

CHN analysis	calculated:	C	66.8	H	6.58	N	3.39
	found:	C	66.7	H	6.70	N	3.40

Example 128

α-(4-Acetylphenoxy)-α′-(1-pyrrolidinyl) p-xylol

Hydroxyacetophenone (2 mmol) and 5 mmol of K_2CO_3 were stirred in 20 ml of acetone with 2 ml of DMF for 10 minutes. After addition of 3.5 mmol of α,α′-dibromoxylol the reaction was stirred at ambient temperature for 12 hours and after addition of 7 mmol of pyrrolidine for 1 hour under reflux. The solvent was evaporated under reduced pressure. The residue was suspended in water, extracted with methylene chloride. The combined organic extracts were crystallized with oxalic acid. Recrystallization resulted in the pure product.

SF: $C_{20}H_{23}NO_2 \times C_2H_2O_4 \times 0.25\ H_2O$ (404.0) mp: 136-137 °C

CHN analysis	calculated:	C	65.4	H	6.36	N	3.47
	found:	C	65.6	H	6.29	N	3.47

Example 129

α-(3-Phenylpropoxy)-α′-piperidino p-xylol

4-(Piperidinomethyl)benzoic acid methyl ester (22 mmol) in dry tetrahydrofurane was added dropwise to a suspension of 44 mmol of lithium aluminium hydride in 30 ml of dry tetrahydrofurane at 0 °C. After refluxing for 2 hours a saturated solution of ammonium chloride in water was added dropwise. After stirring for 12 hours at ambient temperature the organic layer was isolated and the aqueous layer extracted with methylene chloride. The organic extracts were combined and the solvent was evaporated under reduced pressure. The residue was crystallized with maleic acid from diethyl ether/2-propanol (Yield: 91%). Sodium 4-(piperidinomethyl)benzyl alcoholate (5 mmol) and 6 mmol of 3-phenylpropyl bromide in 10 ml of dry toluene were refluxed for 6 hours. The solvent was evaporated under reduced pressure. The residue was purified by rotatory chromatography on silica gel using methylene chloride/ammonia atmosphere as eluent. The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{22}H_{29}NO \times C_2H_2O_4 \times 0.5\ H_2O$ (422.5) mp: 104-105 °C

CHN analysis	calculated:	C	68.2	H	7.63	N	3.32
	found:	C	68.3	H	7.26	N	3.36

Example 130

3-(4-Chlorobenzyl)-5-(2-piperidinoethyl)-1,2,4-oxadiazole

Hydroxylamine hydrochloride (20 mmol) was added dropwise to a solution of 20 mmol of sodium in 50 ml of methanol at 0 °C. After stirring for 30 minutes at ambient temperature 10 mmol of 4-chlorobenzyl cyanide was added dropwise at

0 °C. After refluxing for 6 hours the suspension was filtered and the solvent evaporated under reduced pressure. The residue was crystallized from diethyl ether (Yield: 41%). To a solution of 4 mmol of the product and 6 mmol of 3-piperidinopropionic acid methyl ester in 15 ml of dry methanol 5 mmol of sodium

in 20 ml of methanol was added dropwise at 0 °C. After stirring for 1 hour under argon atmosphere followed by refluxing for 18 hours the solvent was evaporated under reduced pressure. The residue was suspended in DMF and stirred for 6 hours at 80 °C. The solvent was evaporated under reduced pressure. The residue was suspended in water and extracted with methylene chloride. The residue of the organic layer was purified by rotatory chromatography on silica gel using methylene chloride/ammonia atmosphere as eluent. The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{16}H_{20}ClN_3O \times C_2H_2O_4$ (395.8) mp: 152-154 °C

CHN analysis	calculated:	C	54.6	H	5.60	N	10.6
	found:	C	54.3	H	5.60	N	10.5

Example 131

2-((2-Piperidinoethyl)amino)benzothiazole

2-Chlorobenzothiazole (10 mmol), 10 mmol of 2-piperidinoethanamine, and 30 mmol of triethylamine in 50 ml of dry ethanol were refluxed for 6 hours. The product was crystallized with hydrochloric acid in 2-propanol and recrystallized in methanol.

SF: $C_{14}H_{19}N_3S \times 2\ HCl \times 0.25\ H_2O$ (338.8) Yield: 95% mp: 225 °C

CHN analysis	calculated:	C	49.6	H	6.40	N	12.4
	found:	C	49.5	H	6.49	N	12.3

Example 132

5-Piperidinopentylamine

5-Chlorovaleronitrile (10 mmol), 20 mmol of piperidine, 20 mmol of potassium carbonate and a catalytic amount of potassium iodide in 50 ml of ethanol were refluxed for 6 hours. The solvent was removed under reduced pressure, the residue suspended in water and extracted with methylene chloride. The organic layer was purified by column chromatography on silica gel using methylene chloride/methanol/aqueous ammonia (90/10/1) as eluent (Yield: 59%). The product was added dropwise to a suspension of 25 mmol of lithium aluminium hydride in 25 ml of dry tetrahydrofurane at 0 °C. After refluxing for 1 hour 10 ml of a saturated solution of sodium/potassium tartrate in water was added dropwise. The residue was filtered off and the filtrate purified by column chromatography on silica gel using methylene chloride/methanol/aqueous ammonia (90/10/1) as eluent. The residue was crystallized with hydrochloric acid from diethyl ether/2-propanol.

SF: $C_{10}H_{22}N_2$ x 2 HCl x 0.5 H_2O (252.2) mp: 187 °C

CHN analysis	calculated:	C	47.6	H	9.99	N	11.1
	found:	C	47.8	H	9.70	N	11.0

Example 133

5-Nitro-2-(6-piperidinohexyl)pyridine

6-Aminohexanol (15 mmol), 15 mmol of 2-chloro-5-nitropyridine, 5 ml of triethylamine, and a catalytic amount of potassium iodide were refluxed in 30 ml of ethanol for 12 hours. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (eluent : methylene chloride/methanol (95/5), ammonia atmosphere). The solvent was removed under reduced pressure (Yield: 66%). The product (5 mmol) was dissolved in tetrahydrofurane, stirred at 0 °C and 10 mmol of thionyl chloride was added dropwise. After 1 hour at ambient temperature the mixture was warmed to 60 °C for 2 hours. The solvent and the excess of thionyl chloride were evaporated. The oily residue was crystallized with hydrochloric acid from diethyl ether/ethanol (Yield: 95%). The product (5 mmol), 10 mmol of piperidine, 15 mmol of potassium carbonate, and a catalytic amount of potassium iodide were refluxed in 30 ml of ethanol for 12 hours. The solvent was evaporated and the residue purified by column chromatography (eluent: methylene chloride/methanol (95/5), ammonia atmosphere). The solvent was removed under reduced pressure, and the residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{16}H_{26}N_4O_2 \times C_2H_2O_4$ (396.4)				mp: 118.6-119.7 °C			
CHN analysis	calculated:	C	54.5	H	7.12	N	14.1
	found:	C	54.4	H	7.18	N	14.2

Example 134

3-Nitro-2-(6-piperidinohexylamino)pyridine

6-Aminohexanol (15 mmol), 15 mmol of 2-chloro-3-nitropyridine, 5 ml of triethylamine and a catalytic amount of potassium iodide were refluxed in 30 ml of ethanol for 12 hours. The solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: methylene chloride/methanol (98/2), ammonia atmosphere). The solvent was removed under reduced pressure (Yield: 55%). The product (5 mmol) was dissolved in tetrahydrofurane, stirred at 0 °C and 10 mmol of thionyl chloride was added dropwise. After 1 hour at ambient temperature the mixture was warmed to 60 °C for 2 hours. The solvent and the excess of thionyl chloride were evaporated. The oily residue was crystallized with hydrochloric acid from diethyl ether/ethanol (Yield: 95%). The product (5 mmol), 10 mmol of piperidine, 15 mmol of potassium carbonate, and a catalytic amount of potassium iodide were refluxed in 30 ml of ethanol for 12 hours. The solvent was evaporated and the residue purified by column chromatography (eluent: methylene chloride/methanol (95/5), ammonia atmosphere). The solvent was removed under reduced pressure, and the residue was crystallized with oxalic acid from diethyl ether/ethanol

SF: $C_{16}H_{26}N_4O_2 \times C_2H_2O_4$ (396.4)				mp: 130.3-130.7 °C			
CHN analysis	calculated:	C	54.5	H	7.12	N	14.1
	found:	C	54.3	H	7.14	N	13.9

Example 135

2-(6-Piperidinohexylamino)pyrimidine

6-Aminohexanol (15 mmol), 15 mmol of 2-chloropyrimidine, 5 ml of triethylamine, and a catalytic amount of potassium iodide were refluxed in 30 ml of ethanol for 12 hours. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (eluent: methylene chloride/methanol (98/2), ammonia atmosphere). The solvent was removed under reduced pressure (Yield: 40%). The product (5 mmol) was dissolved in tetrahydrofurane, stirred at 0 °C and 10 mmol of thionyl chloride was added dropwise. After 1 hour at ambient temperature the mixture was warmed to 60 °C for 2 hours. The solvent and the excess of thionyl chloride were evaporated. The oily residue was crystallized with hydrochloric acid from diethyl ether/ethanol (Yield: 95%). The product (5 mmol), 10 mmol of piperidine, 15 mmol of potassium carbonate, and a catalytic amount of potassium iodide were refluxed in 30 ml of ethanol for 12 hours. The solvent was evaporated and the residue purified by column chromatography (eluent: methylene chloride/methanol (95/5), ammonia atmosphere). The solvent was removed under reduced pressure, and the residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{15}H_{26}N_4 \times C_2H_2O_4$ (352.4) mp: 150.3-150.9 °C

CHN analysis	calculated:	C	57.9	H	8.00	N	15.9
	found:	C	58.0	H	8.14	N	15.8

Example 136

N-(6-Phenylhexyl)piperidine

6-Phenylhexanol (5 mmol) was stirred at 0 °C, and thionyl chloride (10 mmol) was added dropwise. After 1 hour at ambient temp. the mixture was warmed to 60 °C for 2 hours. The excess of thionyl chloride was evaporated. The oily residue was purified by column chromatography on silica gel (eluent: methylene chloride) (Yield: 98%). The product was dissolved in 50 ml of ethanol, and 10 mmol of K_2CO_3, 1 mmol of KI, and 10 mmol of piperidine were added. After refluxing for 6 hours the solvent was evaporated under reduced pressure. The residue was suspended in water and extracted with methylene chloride. The organic extracts were combined, dried with $MgSO_4$ and the residue purified by column chromatography on silica gel (eluent: methylene chloride/methanol/aqueous ammonia (90/10/1)). The residue was crystallized with oxalic acid from diethyl ether/methanol.

SF: $C_{17}H_{27}N$ x $C_2H_2O_4$ (335.5) mp: 152 °C

CHN analysis	calculated:	C	68.0	H	8.71	N	4.18
	found:	C	68.0	H	8.67	N	4.05

Example 137

α-(4-Acetylphenoxy)-α′-(4-methylpiperidino)p-xylol

α,α′-Dibromo-para-xylene (30 mmol), 4-hydroxyacetophenone (20 mmol), and potassium carbonate (50 mmol) were refluxed in 50 ml of acetone for 12 hours. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (eluent: methylene chloride/petroleum ether/methanol (60/38/2)).

The product (2 mmol), 4-methylpiperidine (6 mmol), potassium carbonate (8 mmol), and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. The solvent was evaporated. The residue was washed with water and extracted with ethyl acetate. The solvent was removed under reduced pressure. The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{22}H_{27}NO_2$ x $C_2H_2O_4$ x 0.75 H_2O (440.7) mp: 145 °C

CHN analysis	calculated:	C	65.41	H	6.92	N	3.18
	found:	C	65.12	H	6.69	N	3.17

Example 138

α-(4-Acetylphenoxy)-α´-(3,5-*cis*-dimethylpiperidino)p-xylol

Following the procedure described in example 137, the ether obtained (2 mmol), 3,5-dimethylpiperidine (mixture of cis and trans, 8 mmol), potassium carbonate (8 mmol), and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel and thereby separated from the corresponding diastereomer (eluent: diethyl ether/petroleum ether/triethylamine (66/33/1)). The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{23}H_{29}NO_2$ x $C_2H_2O_4$ x 0.5 H_2O (450.2) mp: 148 °C

CHN analysis	calculated:	C	66.69	H	7.11	N	3.11
	found:	C	66.95	H	7.30	N	3.20

Example 139

α-(4-Acetylphenoxy)-α´-(3,5-*trans*-dimethylpiperidino)p-xylol

Following the procedure described in example 137, the ether obtained (2 mmol), 3,5-dimethylpiperidine (mixture of cis and trans, 8 mmol), potassium carbonate (8 mmol), and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel and thereby separated from the corresponding diastereomer (eluent: diethyl ether/petroleum ether/triethylamine (66/33/1)). The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{23}H_{29}NO_2$ x $C_2H_2O_4$ x 0.5 H_2O (450.2) mp: 141 °C

CHN analysis	calculated:	C	66.69	H	7.11	N	3.11
	found:	C	66.94	H	7.17	N	3.19

Example 140

α-(4-Acetylphenoxy)-α′-(2-methylpyrrolidino)p-xylol

Following the procedure described in example 137, the ether obtained (2 mmol), 2-methylpyrrolidine (6 mmol), potassium carbonate (8 mmol) and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. The solvent was evaporated. The residue was washed with water and extracted with ethyl acetate. The solvent was removed under reduced pressure. The product was crystallized with hydrochloric acid from diethyl ether/ethanol. Recrystallization resulted in the pure product.

SF: $C_{21}H_{25}NO_2$ x HCl x 0.25 H_2O (361.1) mp: 324 °C

CHN analysis	calculated:	C	69.26	H	7.00	N	3.85
	found:	C	69.52	H	7.12	N	3.85

Example 141

α-(4-Cyclopropylcarbonylphenoxy)-α′-piperidino-p-xylol

A solution containing 1,4-benzenedimethanol (30 mmol), sodium hydride (25 mmol), catalytic amounts of tetrabutylammonium iodide, and 15-crown-5 (0.5 mmol) in tetrahyrofuran was stirred for 10 minutes. Cyclopropyl-4-fluorophenylketone (20 mmol) was added dropwise, and the solution was refluxed for 24 hours. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: methylene chloride/methanol (98/2)).

At 0 °C the product (4 mmol) was added to thionyl chloride (8 mmol). The temperature was raised to 70 °C for three hours. Excess thionyl chloride was evaporated and the residue purified by column chromatography on silica gel (eluent: methylene chloride/methanol (95/5)). The product (2 mmol), piperidine (4 mmol), catalytic amounts of potassium iodide, and potassium carbonate (6 mmol) dissolved in acetone were refluxed for 12 hours. The solvent was evaporated. The crude product was washed with water and extracted with ethyl acetate. The organic layer was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{23}H_{27}NO_2 \times C_2H_2O_4$ (439.2) mp: 194 °C

CHN analysis	calculated:	C	68.33	H	6.61	N	3.19
	found:	C	68.38	H	6.78	N	3.29

Example 142

α-(4-Cyclopropylcarbonylphenoxy)-α′-(4-methylpiperidino)p-xylol

Following the procedure described in example 141, the chloride obtained (2 mmol), 4-methylpiperidine (4 mmol), potassium carbonate (6 mmol), and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. The solvent was evaporated. The crude product was washed with water and extracted with ethyl acetate. The organic layer was removed under reduced pressure, and the residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{24}H_{29}NO_2 \times C_2H_2O_4 \times 0.75\ H_2O$ (466.7) mp: 169-170 °C

CHN analysis	calculated:	C	66.91	H	6.96	N	2.99
	found:	C	66.85	H	6.83	N	2.96

Example 143

α-(4-Cyclopropylcarbonylphenoxy)-α′-pyrrolidino-p-xylol

Following the procedure described in example 141, the chloride obtained (2 mmol), pyrrolidine (4 mmol), catalytic amounts of potassium iodide, and potassium carbonate (6 mmol) were refluxed in acetone for 12 hours. The solvent was evaporated. The crude product was washed with water and extracted with ethyl acetate. The organic layer was removed under reduced pressure, and the residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{22}H_{25}NO_2 \times C_2H_2O_4 \times 0.5\ H_2O$ (434.2) mp: 179 °C

CHN analysis	calculated:	C	66.38	H	6.45	N	3.22
	found:	C	66.61	H	6.45	N	3.22

Example 144

3-Phenylpropyl 3-(4-methylpiperidino)propyl ether

3-Phenylpropylmesilate (18 mmol), catalytic amounts of tetrabutylammonium iodide, and 15-crown-5 (0.5 mmol) were added under argon atmosphere to a solution of 1,3-propanediol (25 mmol) and sodium hydride (25 mmol) in tetrahydrofuran which had been stirred over night. The mixture was refluxed for 24 hours. The solvent was evaporated and the oily residue purified by column chromatography (eluent: methylene chloride/methanol (95/5)). At 0 °C the product (8 mmol) was added to thionyl chloride (16 mmol). The temperature was raised to 70 °C for three hours. Excess thionyl chloride was evaporated. The residue was purified by column chromatography on silica gel (eluent: methylene chloride), and the solvent was evaporated under reduced pressure. The chloride obtained (5 mmol), 4-methylpiperidine (10 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were dissolved in acetone and refluxed for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel (eluent: diethyl ether/petroleum ether/triethylamine (66/33/1)) and crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{18}H_{29}NO \times C_2H_2O_4$ (365.4) mp: 119-120 °C

CHN analysis	calculated:	C	65.73	H	8.55	N	3.83
	found:	C	65.44	H	8.83	N	3.79

Example 145

3-Phenylpropyl 3-(3,5-*cis*-dimethylpiperidino)propyl ether

Following the procedure described in example 144 the chloride obtained (5 mmol), 3,5-dimethylpiperidine (mixture of *cis* and *trans*, 10 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were dissolved in acetone and refluxed for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel and thereby separated from the corresponding diastereomer (eluent: diethyl ether/petroleum ether/triethylamine (66/33/1)). The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{19}H_{31}NO \times C_2H_2O_4$ (379.5) mp: 107-108 °C

CHN analysis calculated: C 66.46 H 8.76 N 3.69

found: C 66.42 H 8.54 N 3.67

Example 146

3-Phenylpropyl 3-(3,5-*trans*-dimethylpiperidino)propyl ether

Following the procedure described in example 143 the chloride obtained (5 mmol), 3,5-dimethylpiperidine (mixture of *cis* and *trans*, 10 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were dissolved in acetone and refluxed for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel and thereby separated from the corresponding diastereomer (eluent: diethyl ether/petroleum ether/triethylamine (66/33/1)). The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{19}H_{31}NO \times C_2H_2O_4$ 379.5) mp: 123.5 °C

CHN analysis calculated: C 66.46 H 8.76 N 3.69

found: C 66.35 H 8.72 N 3.75

Example 147

3-Phenylpropyl 3-(3-methylpiperidino)propyl ether

Following the procedure described in example 143 the chloride obtained (5 mmol), 3-methylpiperidine (10 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were dissolved in acetone and refluxed for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel (eluent: diethyl ether/petroleum ether/triethylamine

(66/33/1)). The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{18}H_{29}NO \times C_2H_2O_4$ (365.4) mp: 123 °C

CHN analysis	calculated:	C	65.73	H	8.55	N	3.83
	found:	C	65.39	H	8.72	N	3.79

Example 148

3-Phenylpropyl 3-pyrrolidinopropyl ether

Following the procedure described in example 143 the chloride obtained (5 mmol), pyrrolidine (10 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were dissolved in acetone and refluxed for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel (eluent: diethyl ether/petroleum ether/triethylamine (66/33/1)). The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: C15H25NO x C2H2O4 (337.4) mp: 105.5 °C

CHN analysis	calculated:	C	64.07	H	8.07	N	4.15
	found:	C	63.85	H	7.84	N	4.13

Example 149

3-(4-Chlorophenyl)propyl 3-(4-methylpiperidino)propyl ether

3-(4-Chlorophenyl)propylmesilate (18 mmol), catalytic amounts of tetrabutylammonium iodide, and 15-crown-5 (0.5 mmol) were added under argon atmosphere to a solution of 1,3-propanediol (25 mmol) and sodium hydride (25 mmol) in tetrahydrofuran which had been stirred over night. The mixture was refluxed for 24 hours. The solvent was evaporated and the oily residue purified by column chromatography (eluent: methylene chloride/methanol (95/5)). At 0 °C the product (8 mmol) was added to thionyl chloride (16 mmol). The temperature was raised to 70 °C for three hours. Excess thionyl chloride was evaporated. The residue was purified by column chromatography on silica gel (eluent: methylene chloride) and the solvent was evaporated under reduced pressure. The chloride obtained (5 mmol), 4-methylpiperidine (10 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were dissolved in acetone and refluxed for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel (eluent: diethyl ether/petroleum ether/triethylamine (66/33/1)) and crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{18}H_{28}NOCl$ x $C_2H_2O_4$ (399.9) mp: 116 °C

CHN analysis	calculated:	C	60.08	H	7.56	N	3.50
	found:	C	59.78	H	7.33	N	3.49

Example 150

3-(4-Chlorophenyl)propyl 3-(3,5-*cis*-dimethylpiperidino)propyl ether

Following the procedure described in example 149 the chloride obtained (5 mmol), 3,5-dimethylpiperidine (mixture of *cis* and *trans*, 10 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were dissolved in acetone and refluxed for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel and thereby separated from the corresponding diastereomer (eluent: diethyl ether/petroleum ether/triethylamine (66/33/1)). The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{19}H_{30}NOCl$ x $C_2H_2O_4$ x 0.25 H_2O (418.5) mp: 117.5 °C

CHN analysis	calculated:	C	66.46	H	8.76	N	3.69
	found:	C	66.42	H	8.54	N	3.67

Example 151

3-(4-Chlorophenyl)propyl 3-(3,5-*trans*-dimethylpiperidino)propyl ether

Following the procedure described in example 149 the chloride obtained (5 mmol), 3,5-dimethylpiperidine (mixture of *cis* and *trans*, 10 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were dissolved in acetone and refluxed for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel and thereby separated from the corresponding diastereomer (eluent: diethyl ether/petroleum ether/triethylamine (66/33/1)). The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{19}H_{30}NOCl \times C_2H_2O_4$ (413.4) mp: 150 °C

CHN analysis	calculated:	C	60.93	H	7.79	N	3.38
	found:	C	60.95	H	7.39	N	3.34

Example 152

4-(6-Piperidinohexylamino)quinoline

6-Aminohexanol (15 mmol), 4-chloroquinoline (15 mmol), 5 ml of triethylamine and catalytic amounts of potassium iodide were refluxed in ethanol for 12 hours. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (eluent: methylene chloride/methanol (98/2), ammonia atmosphere). The solvent was removed under reduced pressure. At 0 °C the product (5 mmol) was added to thionyl chloride (10 mmol). The temperature was raised to 70 °C for three hours. Excess thionyl chloride was evaporated. The residue was recrystallized from diethyl ether/ethanol. The product (5 mmol), piperidine (10 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. The solvent was evaporated and the residue purified by flash chromatography (eluent: ethyl acetate/methanol/triethylamine (95/5/2)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{20}H_{29}N_3 \times 2\ C_2H_2O_4 \times 0.5\ H_20$ (500.6) mp: 167.3-168.1 °C

CHN analysis	calculated:	C	57.6	H	6.85	N	8.39
	found:	C	57.7	H	6.55	N	8.42

Example 153

2-Methyl 4-(3-piperidinopropylamino)quinoline

Synthesis and purification were performed according to the procedure stated in example 152 using reagents 3-aminopropanol (15 mmol), 4-chloro-2-methylquinoline (15 mmol), 5 ml of triethylamine, and catalytic amounts of potassium iodide in the first step. The final product was purified by flash chromatography (eluent: ethyl acetate/triethylamine (95/5)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{18}H_{25}N_3$ x 2 $C_2H_2O_4$ (463.5) mp: 185.5-186.3 °C

CHN analysis calculated: C 57.0 H 6.31 N 9.07

found: C 56.9 H 6.19 N 8.98

Example 154

2-Methyl 4-(6-piperidinohexylamino)quinoline

Synthesis and purification were performed according to the procedure stated in example 152 using reagents 6-aminohexanol (15 mmol), 4-chloro-2-methylquinoline (15 mmol), 5 ml of triethylamine, and catalytic amounts of potassium iodide in the first step. The final product was purified by column chromatography (eluent: ethyl acetate/triethylamine (95/5)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{21}H_{31}N_3$ x 2 $C_2H_2O_4$ x 0.75 H_{20} (519.1) mp: 193.6-194.0 °C

CHN analysis calculated: C 57.9 H 7.09 N 8.10

found: C 57.8 H 7.08 N 7.85

Example 155

7-Chloro-4-(3-piperidinopropylamino)quinoline

Synthesis and purification were performed according to the procedure stated in example 152 using reagents 3-aminohexanol (15 mmol), 4,7-dichloroquinoline (15 mmol), 5 ml of triethylamine, and catalytic amounts of potassium iodide in the first step. The final product was purified by column chromatography (eluent: ethyl acetate/triethylamine (90/10)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol

SF: $C_{17}H_{22}ClN_3$ x 2 $C_2H_2O_4$ (483.9) mp: 202.9-204.0 °C

CHN analysis	calculated:	C	52.1	H	5.42	N	8.68
	found:	C	51.9	H	5.25	N	8.65

Example 156

7-Chloro-4-(4-piperidinobutylamino)quinoline

Synthesis and purification were performed according to the procedure stated in example 152 using reagents 3-aminobutanol (15 mmol), 4,7-dichloroquinoline (15 mmol), 5 ml of triethylamine, and catalytic amounts of potassium iodide in the first step. The final product was purified by column chromatography (eluent: ethyl acetate/triethylamine (90/10)).The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{18}H_{24}ClN_3$ x 2 $C_2H_2O_4$ x 0.5 H_20 (506.9) mp: 162.6-163.5 °C

CHN analysis	calculated:	C	52.1	H	5.76	N	8.28
	found:	C	52.2	H	5.64	N	8.15

Example 157

7-Chloro-4-(8-piperidinooctylamino)quinoline

1,8-Dibromooctane (30 mmol), potassium phthalimide (15 mmol), and catalytic amounts of potassium iodide were refluxed in acetone for 3 days. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (eluent: methylene chloride/petroleum ether (60/40)). The solvent was removed under reduced pressure. The product (12,5 mmol), piperidine (50 mmol), and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. Solvent and piperidine were evaporated. The residue was treated with hydrochloric acid (2N), with potassium carbonate solution and was then extracted with methylene chloride. The solvent was removed under reduced pressure, and the residue was refluxed in hydrochloric acid (6N) for 12 hours. The solution was neutralized with potassium carbonate solution and extracted with methylene chloride. The organic layer was evaporated and the product was purified by flash chromatography on silica gel (eluent: methylene chloride/triethylamine/ methanol (90/10/2)). The product (5 mmol), 4,7-dichloroquinoline (5 mmol), and catalytic amounts of potassium iodide were melted with 10 g of phenole for 12 hours. The residue was purified by flash chromatography (eluent: ethyl acetate/triethylamine (95/5)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{22}H_{32}ClN_3$ x 2 $C_2H_2O_4$ (554.0) mp: 150.7-150.9 °C

CHN analysis	calculated:	C	56.4	H	6.55	N	7.58
	found:	C	56.2	H	6.48	N	7.42

Example 158

7-Chloro-4-(10-piperidinodecylamino)quinoline

Synthesis and purification were performed according to the procedure described in example 157 using reagents 1,10-dibromodecane (30 mmol), potassium phthalimide (15 mmol), and catalytic amounts of potassium iodide in the first step. The final product was purified by column chromatography (eluent: ethyl acetate/triethylamine 95/5). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{24}H_{36}ClN_3$ x 2 $C_2H_2O_4$ (582.1) mp: 151.2-151.5 °C

CHN analysis	calculated:	C	57.8	H	6.93	N	7.22
	found:	C	57.4	H	6.81	N	7.07

Example 159

7-Chloro-4-(12-piperidinododecylamino)quinoline

Synthesis and purification were performed according to the procedure described in example 157 using regents 1,12-dibromododecane (30 mmol), potassium phthalimide (15 mmol), and catalytic amounts of potassium iodide in the first step. The residue was purified by flash chromatography (eluent: ethyl acetate/triethylamine (95/5)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{26}H_{40}ClN_3$ x 2 $C_2H_2O_4$ (610.2) mp: 141.6-142.9 °C

CHN analysis	calculated:	C	59.1	H	7.27	N	6.89
	found :	C	58.7	H	7.30	N	6.78

Example 160

7-Chloro-4-(4-(3-piperidinopropoxy)phenylamino)quinoline

4-Hydroxyaniline (11 mmol), 4,7-dichloroquinoline (10 mmol), 1 ml of 2N hydrochloric acid, and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. The product was filtered. The product (5 mmol), 3-piperidinopropylchloride hydrochloride (5 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were refluxed in acetone for 22 hours. The product was filtered and purified by flash chromatography (eluent: methylene chloride/petroleum ether/triethylamine (95/25/5)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{23}H_{26}ClN_{3}O \times 2\ C_2H_2O_4 \times 0.25\ H_20$ (580.5) mp: 189.8-190.3 °C

CHN analysis	calculated:	C	55.9	H	5.29	N	7.23
	found:	C	55.7	H	5.43	N	7.14

Example 161

7-Chloro-4-(2-(4-(3-piperidinopropoxy)phenyl)ethylamino)quinoline

Tyramine (10 mmol), 4,7-dichloroquinoline, and catalytic amounts of potassium iodide were melted in 10 g of phenol at 150 °C for 12 hours. The residue was crystallized with hydrochloric acid from ethyl acetate/water. The product (5 mmol), 3-piperidinopropylchloride hydrochloride (5 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were refluxed in *N,N*-dimethylformamide for 22 hours. The solvent was evaporated and the residue purified by flash chromatography (eluent: ethyl acetate/petroleum ether/triethylamine (95/50/5)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{25}H_{30}ClN_{3}O \times 2\ C_2H_2O_4 \times H_20$ (622.1) mp: 149.8-150.2 °C

CHN analysis	calculated:	C	56.0	H	5.83	N	6.75
	found:	C	55.7	H	5.77	N	6.46

Example 162

4-(6-Piperidinohexanoyl)phenyl 3-piperidinopropyl ether

3-Phenoxypropylbromide (10 mmol), piperidine (20 mmol), and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. The solvent was evaporated. The residue was treated with ethyl acetate. The solvent was removed under reduced pressure, and the product was crystallized with hydrochloric acid from isopropanol/diethyl ether. The product (5 mmol) was added to a solution of 6-bromohexanoylchloride (7.5 mmol) and aluminiumtrichloride (22.5 mmol) in 10 ml of nitrobenzol. The mixture was stirred at room temperature for 3 days. Ethyl acetate was added, and the mixture was extracted with hydrochloric acid (6N). The solution was neutralized with potassium carbonate solution and extracted with methylene chloride. The solvent was removed under reduced pressure. The product (2.5 mmol), piperidine (5 mmol), potassium carbonate (7.5 mmol), and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. The solvent was evaporated, and the residue was purified by flash chromatography (eluent: methylene chloride/petroleum ether/methanol (96/3/3)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{25}H_{40}N_2O_2$ x 2 $C_2H_2O_4$ (580.7) mp: 149.1-149.5 °C

CHN analysis	calculated:	C	60.0	H	7.64	N	4.82
	found:	C	59.9	H	7.59	N	4.81

Example 163

5-Nitro-2-(5-piperidinopentylamino)pyridine

Synthesis and purification were performed according to the procedure stated in example 152 using reagents 5-aminopentanol (15 mmol), 2-chloro-5-nitropyridine (15 mmol), 5 ml of triethylamine, and catalytic amounts of potassium iodide in the first step. The final product was purified by column chromatography (eluent: ethyl acetate/triethylamine (90/10)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{15}H_{24}N_4O_2$ x $C_2H_2O_4$ (382.4) mp: 95.7-96.0 °C

CHN analysis	calculated:	C	53.4	H	6.85	N	14.65
	found:	C	53.6	H	7.00	N	14.55

Example 164

3-Nitro-2-(6-piperidinopentylamino)pyridine

Synthesis and purification were performed according to the procedure stated in example 152 using reagents 5-aminopentanol (15 mmol), 2-chloro-3-nitropyridine (15 mmol), 5 ml of triethylamine, and catalytic amounts of potassium iodide in the first step. The final product was purified by column chromatography (eluent: ethyl acetate/triethylamine (95/5), ammonia atmosphere). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{15}H_{24}N_4O_2$ x $C_2H_2O_4$ x 0.25 H_20 (386.9) mp: 148.5-149.2 °C

CHN analysis	calculated:	C	52.8	H	6.90	N	14.48
	found:	C	52.8	H	6.80	N	14.51

Example 165

5-Amino-2-(6-piperidinopentylamino)pyridine

Synthesis and purification were performed according to the procedure stated in example 152 using reagents 5-aminopentanol (15 mmol), 2-chloro-5-nitropyridine (15 mmol), 5 ml of triethylamine, and catalytic amounts of potassium iodide in the first step. The product was purified by column chromatography on silica gel (eluent: methylene chloride/methanol (95/5), ammonia atmosphere) and dissolved in 20 ml of tetrahydrofuran. 100 mg of palladium/active charcoal (10%) was added, and the mixture was hydrogenated at 1 bar H2 for 12 hours. The solvent was removed under reduced pressure, and the residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{15}H_{26}N_4$ x 2 $C_2H_2O_4$ (442.5) mp: 85.7-87.3 °C

CHN analysis	calculated:	C	51.6	H	6.83	N	12.66
	found:	C	51.4	H	6.81	N	12.83

Example 166

2-(6-Piperidinohexylamino)quinoline

Synthesis and purification were performed according to the procedure stated in example 152 using reagents 6-aminohexanol (15 mmol), 2-chloroquinolin (15 mmol), 5 ml of triethylamine, and catalytic amounts of potassium iodide in the first step. The final product was purified by flash chromatography (eluent: ethyl acetate/triethylamine (95/5)). The solvent was removed under reduced pressure, and the residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{20}H_{29}N_3$ x 2 $C_2H_2O_4$ x 0.75 H20 (505.1) mp: 90.7-91.5 °C

CHN analysis	calculated:	C	57.1	H	6.88	N	8.32
	found:	C	57.1	H	6.54	N	8.17

Example 167

N-(4-Chlorobenzyl)-*N'*-cyclohexyl-3-piperidinopropyl isothiourea

Cyclohexylamine (10 mmol) was added dropwise to 4-chlorobenzylisothiocyanate (10 mmol) dissolved in 20 ml of dry ether . The solution was stirred for 2 hours at room temperature. The precipitated product was filtered off and crystallized from ethyl acetate. 3-Piperidinopropyl chloride hydrochloride (3 mmol), the product (3 mmol), and ca-talytic amounts of potassium iodide were refluxed in ethanol for 6 days. Sub-sequently, ethanol was evaporated, and the residue was purified by column chromato-graphy (eluent: methylene chloride/methanol (95/5)). After evaporation of the solvent the product was crystallized with hydrochloric acid from diethyl ether/ethanol.

SF: $C_{22}H_{34}ClN_3S$ x 2 HCl x H_2O (499.0) mp: 103.0-107.0 °C

CHN analysis	calculated:	C	53.0	H	7.68	N	8.42
	found:	C	52.6	H	7.88	N	8.24

Example 168

2-(6-Piperidinohexylamino)benzothiazole

Synthesis and purification were performed according to the procedure stated in example 152 using reagents 6-aminohexanol (15 mmol), 2-chlorobenzothiazole (15 mmol), 5 ml of triethylamine, and catalytic amounts of potassium iodide in the first step. The final product was purified by flash chromatography (eluent: methylene chloride/methanol (95/5), ammonia atmosphere). The solvent was removed under reduced pressure, and the residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{18}H_{27}N_3S$ x 1.9 $C_2H_2O_4$ (488.6) mp: 98.5-101.8 °C

CHN analysis calculated: C 53.6 H 6.35 N 8.60

found: C 54.0 H 6.43 N 8.33

Example 169

10-Piperidinodecylamine

The synthesis was performed according to the procedure described in example 157 using reagents 1,10-dibromodecane (30 mmol), potassium phthalimide (15 mmol), and catalytic amounts of potassium iodide in the first step. The product (12.5 mmol), piperidine (50 mmol) and catalytic amounts of potassium iodide were refluxed in acetone for 12 hours. Solvent and piperidine were evaporated. The residue was treated with hydrochloric acid (2N), with potassium carbonate solution and then extracted with methylene chloride. The solvent was removed under reduced pressure, and the residue was refluxed in hydrochloric acid (6N) for 12 hours. The solution was neutralized with potassium carbonate solution and extracted with methylene chloride. The organic layer was evaporated, and the final product purified by flash chromatography (eluent: methylene chloride/triethylamine/methanol (90/10/2)). The solvent was removed under reduced pressure. The residue was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{15}H_{32}N_2$ x 2 $C_2H_2O_4$ x 0.75 H_20 (434.0) mp: 116.1-117.2 °C

CHN analysis calculated: C 52.6 H 8.71 N 6.45
found: C 52.5 H 8.70 N 6.35

Example 170

3-Phenylpropyl 3-(*N,N*-diethylamino)propyl ether

Following the procedure described in example 144 the chloride obtained (5mmol), diethylamine (10 mmol), potassium carbonate (15 mmol), and catalytic amounts of potassium iodide were dissolved in acetone and refluxed for 12 hours. After evaporating the solvent the product was purified by column chromatography on silica gel (eluent: diethyl ether/petroleum ether/triethylamine (66/33/1)). The product was crystallized with oxalic acid from diethyl ether/ethanol.

SF: $C_{16}H_{27}NO$ x $C_2H_2O_4$ (340.3) mp: 80 °C
CHN analysis calculated: C 63.69 H 8.61 N 4.13
found: C 63.52 H 8.40 N 4.06

Pharmacological study

Interaction of compounds with the H_3 receptor are evidenced *in vitro* by the measurement of the release of neosynthesized tritiated histamine from rat cerebral cortex synaptosomes preincubated with tritiated histidine (Garbarg et al., J. Pharmacol. Exp. Ther., 1992, 263 : 304-310). The H_3 potency of agonists is measured by the inhibition of tritiated histamine release and that of antagonists by the progressive reversal of release inhibition by the selective H_3 agonist (R)α-methylhistamine (Arrang et al., Nature, 1987, 327: 117-123).

Interaction of compounds with the H_3 receptor are evidenced in vitro on guinea-pig ileum by the procedure described by Ligneau et al., J. Pharmacol. Exp. Ther. 271, 452-459 (1994).

Briefly, longitudinal muscle strips from guinea-pig small intestine were dissected out and incubated in a gassed O_2/CO_2 (95 %/5 %) modified Krebs-Ringer's bicarbonate medium at +37°C in presence of 1 µM mepyramine to block the H_1 receptor. After equilibration, contractile activity under stimulation (rectangular pulses of 15 V, 0,5 msec, 0,1 Hz) was recorded.

Concentration-response curves of the effect of (R)α-Methylhistamine alone or together with the antagonist were established.

The effects of agonists and antagonists were estimated *in vivo* by the measurement of the tele-methylhistamine level variations in the brain of mice (Garbarg et al., J. Neurochem., 1989, 53: 1724-1730). At various time after p.o. administration of the compounds, the effect of agonists and antagonists are evidenced by the decrease and increase respectively in telemethylhistamine level induced.

The changes are compared to those induced by reference compounds given in high dosage and this allows the calculation of the ED_{50} value for each compound which correspond to the dose responsible for an half maximal effect.

The results are listed here-below or reported in the following tables II and III:

- example 59 : 1-[3-(4-cyanophenoxy)propyl]piperidine, ED_{50}=0.02 mg/kg
- example 74 : 1-[3-(4-buyrylphenoxy)propyl]piperidine, ED_{50}=0.21 mg/kg
- example 76 : 1-[3-(4-cyclopropanecarbonylphenoxy)propyl]piperidine, ED_{50}=0.18 mg/kg
- example 88 : 1-[3-(4-propionylphenoxy)propyl]-3-methylpiperidine, ED_{50}=0.14 mg/kg
- example 101 : 1-[3-(4-cyclopropane carbonyl phenoxy) propyl]-*trans*-3,5 dimethylpiperidine, ED_{50}=0.17 mg/kg

TABLE II:

Ex No.	X	n	R^1R^2	R^3 (n_3 = 1)	Ki (nM)	ED_{50} (mg/kg/p.o.)
18	O	5	$-(CH_2)_4-$	p-NO_2	39 ± 11	1.1
43	O	3	Et, Et	p-CN	95 ± 28	0.50
46	O	3	Et, Et	p-CH_3CO	20 ± 7	0.44
50	O	5	$-(CH_2)_4-$	p-$CH_3CH(OH)$	28 ± 7	1.0
56	O	4	Et, Et	p-CN	62 ± 15	1.1
59	O	3	$-(CH_2)_5-$	p-CN	11 ± 2	0.20
60	O	3	$-(CH_2)_6-$	p-CN	8.7 ± 2.1	0.64
63	O	3	Et, Et	p-$CH_3CH(OH)$	60 ± 18	0.45
64	O	3	Et, Et	p-$CH_3C{=}N(OH)$	2.7 ± 0.9	0.8
66	O	3	-(3-Me)-$(CH_2)_5-$	p-CH_3CO	3.7 ± 0.5	0.3
68	O	3	-(4-Me)-$(CH_2)_5-$	p-CH_3CO	4.6 ± 2.0	0.5
69	O	3	$-(CH_2)_5-$	p-C_2H_5CO	4.7 ± 0.8	0.6

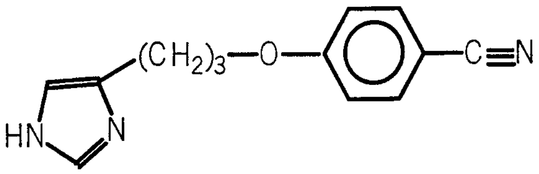
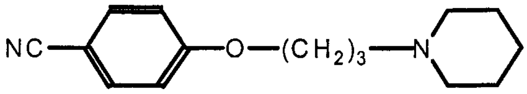
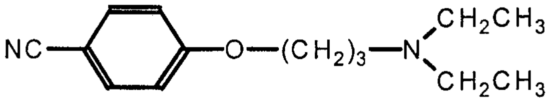
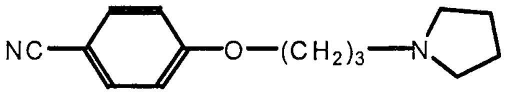
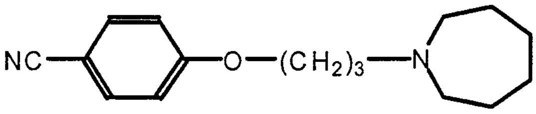
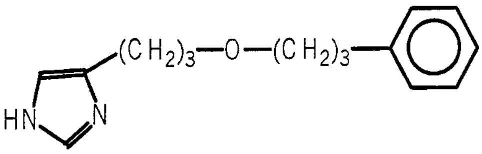
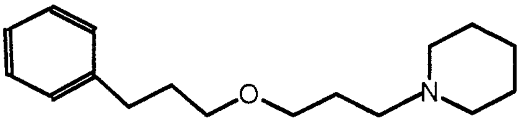
TABLE III:

Example No.	H_3-receptor antagonist activity pA_2 (guinea-pig ileum)
120	6.3
124	6.4
130	7.2
131	6.6
136	6.5

All the above compounds were find to be H_3-antagonists.

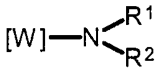
Comparative data concerning the activity of imidazole derivatives and of the non-imidazole analogues according to the invention, are reported below in Table IV:

TABLE IV:

Imidazole derivative	Non-imidazole analogue according to the invention
 Ki = 12 nM ED_{50} = 0.54 mg/kg	ex 59:  Ki = 11 nM ED_{50} = 0,20 mg/kg ex 43:  Ki = 95 nM ED_{50} = 0.50 mg/kg ex 58:  Ki = 20 nM ex 60:  Ki = 9 nM
 Ki = 17 nM	ex 116:  Ki = 15 nM

CLAIMS

1. Use of a compound having the general formula (A):



$$[W]-N(R^1)(R^2)$$

(A)

in which:

- W is a residue which imparts antagonistic and/or agonistic activity at histamine H_3-receptors when attached to an imidazole ring in 4(5)-position;
- R^1 and R^2 may be identical or different and represent each independently
  - a lower alkyl or cycloalkyl,

or taken together with the nitrogen atom to which they are attached,

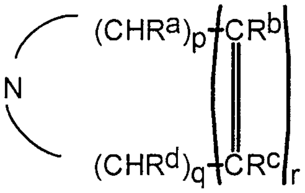
- a saturated nitrogen-containing ring

i)

with m ranging from 2 to 8, or

- a non-aromatic unsaturated nitrogen-containing ring

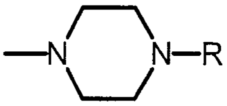
ii)



with p and q being from 0 to 3 independently and r being from 0 to 4, provided that p and q are not simulteously 0 and $2 \leq p + q + r \leq 8$,

R^{a-d} being independently a hydrogen atom or a lower alkyl, cycloalkyl, or carboalkoxy group, or

- a morpholino group, or
- a N-substituted piperazino group:



with R being a lower alkyl, cycloalkyl, carboalkoxy, aryl, arylalkyl, an alkanoyl or aroyl group,

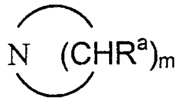
as well as their pharmaceutically acceptable salts, their hydrates, their hydrated salts, the polymorphic crystalline structures of these compounds and their optical isomers, racemates, diastereoisomers and enantiomers, for the preparation of a medicament acting as a ligand of the histamine H_3-receptors.

2. Use according to claim 1, in which R^1 and R^2 are independently a lower alkyl group.

3. Use according to claim 2, in which R^1 and R^2 are each an ethyl group.

4. Use according to claim 1, in which $-NR^1R^2$ is a saturated nitrogen-containing ring:

i)



m being as defined in claim 1.

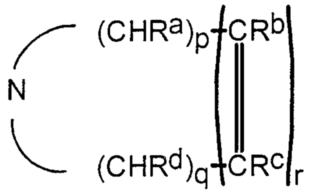
5. Use according to claim 4, characterized in that m is 4, 5 or 6.

6. Use according to claim 5, characterized in that $-NR^1R^2$ represents a piperidyl group.

7. Use according to claim 5, characterized in that $-NR^1R^2$ represents a pyrrolidinyl group.

8. Use according to claim 1, characterized in that $-NR^1R^2$ is a non-aromatic unsaturated nitrogen-containing ring:

ii)



R^{a-d} and p, q and r being as defined in claim 1.

9. Use according to claim 8, characterized in that p, q and r are 1 or 2, more preferably p is 2 and q and r are 1.

10. Use according to anyone of claims 4 to 9, characterized in that R^{a-d} represents each an hydrogen atom.

11. Use according to anyone of claim 4 to 9, characterized in that the nitrogen-containing ring i) or ii) is substituted, preferably mono- or di-substituted, more preferably mono-substituted, with an alkyl group.

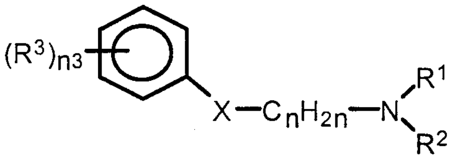
12. Use according to claim 11, characterized in that the nitrogen-containing ring is mono-substituted with a methyl group.

13. Use according to anyone of claims 11 and 12, characterized in that the substituent(s) is(are) in meta-position with respect to the nitrogen atom.

14. Use according to claim 1, characterized in that $-NR^1R^2$ is a morpholino group.

15. Use according to claim 1, characterized in that $-NR^1R^2$ is a N-substituted piperazino group, preferably N-acetylpiperazino.

16. Use according to anyone of claims 1 to 15, of general formula (I):



(I)

in which:

- C_nH_2n is a linear or branched hydrocarbon chain with n ranging from 2 to 8;
- X is an oxygen or sulfur atom;
- R^1 and R^2 are as defined in claim 1;
- n_3 is an integer from 0 to 5 ; and
- R^3 represents each independently
  - a halogen atom,
  - a lower alkyl or cycloalkyl, a trifluoromethyl, aryl, alkoxy, α-alkyloxyalkyl, aryloxy, nitro, formyl, alkanoyl, aroyl, arylalkanoyl, amino, carboxamido, cyano, alkyloximino, aryloximino, alkylalkoximino, α-hydroxyalkyl, alkenyl, alkynyl, sulphamido, sulfamoyl, sulphonamido, carboxamide, carbonylcycloalkyl, alkylcarbonylalkyl, carboalkoxy, arylalkyl or oxime group,
  - or taken together with the carbon atoms of the phenyl ring to which it is fused, a 5- or 6-membered saturated or unsaturated ring or a benzene ring.

17. Use according to claim 16, characterized in that n_3 is zero.

18. Use according to anyone of claims 16 and 17, characterized in that n_3 is 1 with R^3 being as defined in claim 1 and preferably in para-position.

19. Use according to anyone of claims 16 and 18, characterized in that R^3 is a lower alkyl, preferably a C_1-C_4 alkyl.

20. Use according to anyone of claims 16 and 18, characterized in that R^3 is a halogen atom, a cyano, nitro, alkanoyl, alkyloximino or hydroxyalkyl, preferably CN, NO_2, $COCH_3$, COC_2H_5, H_3C-C=N-OH or H_3C-CHOH or cycloalkyl-CO.

21. Use according to claim 16, characterized in that R^3 taken together with the carbon atoms of the phenyl group to which it is fused, form a 5- or 6- membered saturated or unsaturated ring, in particular a 5,6,7,8-tetrahydronaphthyl group.

22. Use according to claim 16, characterized in that R^3 taken together with the phenyl group to which it is fused, form a naphthyl group.

23. Use according to anyone of claims 16 to 22, characterized in that $-C_nH_{2n}-$ is a linear hydrocarbon chain $-(CH_2)_n-$, n being as defined in claim 16.

24. Use according to anyone of claims 16 to 23, characterized in that X is an oxygen atom.

25. Use according to anyone of claims 16 to 23, characterized in that X is a sulfur atom.

26. Use according to anyone of claims 16 to 25, characterized in that n is varying from 3 to 5 and is preferably 3.

27. Use according to anyone of claims 16 to 26, characterized in that it is one of the following compounds:

1-(5-phenoxypentyl)-piperidine
1-(5-phenoxypentyl)-pyrrolidine
N-methyl-N-(5-phenoxypentyl)-ethylamine
1-(5-phenoxypentyl)-morpholine
N-(5-phenoxypentyl)-hexamethyleneimine
N-ethyl-N-(5-phenoxypentyl)-propylamine
1-(5-phenoxypentyl)-2-methyl-piperidine
1-[3-(4-cyclopropanecarbonylphenoxy) propyl]-piperidine

1-[3-(4-acetylphenoxy)-2-R-methylpropyl] piperidine
1-[3-(4-cyanophenoxy)propyl]-4-methylpiperidine
1-[3-(4-cyanophenoxy)propyl]-3-methylpiperidine
1-[3-(4-acetylphenoxy)-2-S-methylpropyl] piperidine
1-{3-[4-(3-oxobutyl)phenoxy] propyl}piperidine
1-[3-(4-cyano-3-fluorophenoxy)propyl] piperidine
1-[3-(4-nitrophenoxy)propyl]-3-methylpiperidine
1-[3-(4-cyanophenoxy)propyl]-2-methylpiperidine
1-[3-(4-nitrophenoxy)propyl]-2-methylpiperidine
1-[3-(4-nitrophenoxy)propyl]-4-methylpiperidine
1-[3-(4-cyanophenoxy)propyl]-2,6-dimethylpiperidine
1-[3-(4-propionylphenoxy)propyl]-3-methylpiperidine
1-[3-(4-cyclobutanecarbonylphenoxy)propyl] piperidine
1-[3-(4-cyclopentanecarbonylphenoxy) propyl]piperidine
1-[3-(4-cyanophenoxy)propyl]-cis-2-methyl-5-ethylpiperidine
1-[3-(4-cyanophenoxy)propyl]-trans-2-methyl-5-ethylpiperidine
1-[3-(4-cyanophenoxy)propyl]-cis-3,5-dimethylpiperidine
1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine
1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine
1-{3-[4-(1-hydroxypropyl)phenoxy]propyl}-3-methylpiperidine
1-{3-[4-(1-hydroxypropyl)phenoxy]propyl}-4-methylpiperidine
1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine
1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine methoxime
1-[3-(4-cyanophenoxy)propyl]-trans-3,5-dimethylpiperidine
1-[3-(4-cyclopropyl carbonyl phenoxy) propyl] -trans-3,5 -dimethylpiperidine
1-[3-(4-cyclopropyl carbonyl phenoxy) propyl] -cis-3,5 -dimethylpiperidine
1-[3-(4-carbomethoxyphenoxy)propyl] piperidine
1-[3-(4-propenylphenoxy)propyl]-2-methyl piperidine
1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine
1-{3-[4-(1-ethoxypropyl)phenoxy]propyl}-2-methyl piperidine
1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine

1-[3-(4-bromophenoxy)propyl]piperidine
1-[3-(4-nitrophenoxy)propyl]piperidine
1-[3-(4-N,N-dimethylsulfonamidophenoxy) propyl]piperidine
1-[3-(4-isopropylphenoxy)propyl]piperidine
1-[3-(4-sec-butylphenoxy)propyl]piperidine
1-[3-(4-propylphenoxy)propyl]piperidine
1-[3-(4-ethylphenoxy)propyl]piperidine
1-(5-phenoxypentyl)-4-propyl-piperidine
1-(5-phenoxypentyl)-4-methyl-piperidine
1-(5-phenoxypentyl)-3-methyl-piperidine
1-acetyl-4-(5-phenoxypentyl)-piperazine
1-(5-phenoxypentyl)-3,5-trans-dimethyl-piperidine
1-(5-phenoxypentyl)-3,5-cis-dimethyl-piperidine
1-(5-phenoxypentyl)-2,6-cis-dimethyl-piperidine
4-carboethoxy-1-(5-phenoxypentyl)-piperidine
3-carboethoxy-1-(5-phenoxypentyl)-piperidine
1-(5-phenoxypentyl)-1,2,3,6-tetrahydropyridine
1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-methoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-methylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-pyrrolidine
1-[5-(2-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(1-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(3-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenylphenoxy)-pentyl]-pyrrolidine
1-{5-[2-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-[5-(3-phenylphenoxy)-pentyl]-pyrrolidine
1-(5-phenoxypentyl)-2,5-dihydropyrrole
1-{5-[1-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-(4-phenoxybutyl)-pyrrolidine
1-(6-phenoxyhexyl)-pyrrolidine
1-(5-phenylthiopentyl)-pyrrolidine

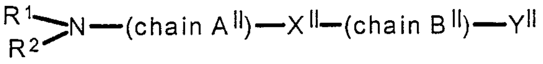
1-(4-phenylthiobutyl)-pyrrolidine
1-(3-phenoxypropyl)-pyrrolidine
1-[5-(3-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-fluorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-nitrophenoxy)-pentyl]-3-methyl-piperidine
1-[5-(4-acetylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-aminophenoxy)-pentyl]-pyrrolidine
1-[5-(3-cyanophenoxy)-pentyl]-pyrrolidine
N-[3-(4-nitrophenoxy)-propyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-diethylamine
1-[5-(4-benzoylphenoxy)-pentyl]-pyrrolidine
1-{5-[4-(phenylacetyl)-phenoxy]-pentyl}-pyrrolidine
N-[3-(4-acetylphenoxy)-propyl]-diethylamine
1-[5-(4-acetamidophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-N-benzamidophenoxy)-pentyl]-pyrrolidine
1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-diethylamine
1-[5-(4-cyanophenoxy)-pentyl]-piperidine
N-[5-(4-cyanophenoxy)-pentyl]-dimethylamine
N-[2-(4-cyanophenoxy)-ethyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dimethylamine
N-[4-(4-cyanophenoxy)-butyl]-diethylamine
N-[5-(4-cyanophenoxy)-pentyl]-dipropylamine
1-[3-(4-cyanophenoxy)-propyl]-pyrrolidine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-[6-(4-cyanophenoxy)-hexyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dipropylamine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine

1-[3-(4-acetylphenoxy)-propyl]-3,5-trans-dimethyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-cis-dimethyl-piperidine
1-[3-(4-formylphenoxy)-propyl]-piperidine
1-[3-(4-isobutyrylphenoxy)-propyl]-piperidine
N-[3-(4-propionylphenoxy)-propyl]-diethylamine
1-[3-(4-butyrylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-1,2,3,6-tetrahydropyridine.

28. Use according to anyone of claims 16 to 27, characterized in that it is one of the following compounds :

1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-diethylamine
N-[3-(4-acetylphenoxy)-propyl]-diethylamine
N-[4-(4-cyanophenoxy)-butyl]-diethylamine

29. Use according to anyone of claims 1 to 15, having the following general formula (IIa) and (IIb):



$$\begin{matrix} R^1 \\ R^2 \end{matrix}\!>\!N\text{—(chain }A^{II}\text{)—}X^{II}\text{—(chain }B^{II}\text{)—}Y^{II} \qquad \text{(IIa)}$$

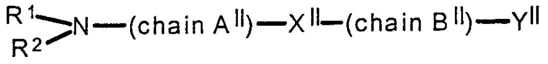
or

$$\begin{matrix}R^1\\R^2\end{matrix}\!\!>\!N\text{—(chain }A^{II}\text{)—}X^{II}\text{—}Y^{II} \qquad \text{(IIb)}$$

in which

- R^1 and R^2 are as defined with reference to general formula (A) in claim 1;
- the chain A^{II} represents a saturated or unsaturated, straight or branched hydrocarbon chain containing 1 to 6 carbon atoms, it being possible for the saturated hydrocarbon chain to be interrupted by a hetero atom such as a sulphur atom;
- X^{II} represents an oxygen or sulphur atom, -NH-, -NHCO-, -N(alkyl)CO-, -NHCONH-, -NH-CS-NH-, -NHCS-, -O-CO-, -CO-O-, -OCONH-, -OCON(alkyl)-, -OCON(alkene), -OCONH-CO-, -CONH-, -CON(alkyl)-, -SO-, -CO-, -CHOH-, -N(saturated or unsaturated alkyl), -S-C(=NY")-NH-Y"- with the Y" identical or different, as defined previsouly, or –NR_{II}-C(=NR''_{II})-NR'_{II}-, R_{II} and R'_{II} denoting a hydrogen atom or a lower alkyl radical and R''_{II} a hydrogen atom or another powerful electronegative group, such as a cyano or COY_1^{II} group, Y_1^{II} denoting an alkoxy group;
- the chain B^{II} represents an aryl, arylalkyl or arylalkanoyl group, a straight alkylene chain -$(CH_2)_{nII}$-, n being an integer which can vary between 1 and 5 or a branched alkylene chain containing from 2 to 8 carbon atoms, the alkylene chain being optionally interrupted by one or a number of oxygen or sulphur atoms, or a group -$(CH_2)_{nII}$-O- or -$(CH_2)_{nII}$-S- where n_{II} is an integer equal to 1 or 2;
- Y^{II} represents a straight or branched alkyl group containing 1 to 8 carbon atoms; a cycloalkyl containing 3 to 6 carbon atoms; a bicycloalkyl group; a cycloalkenyl group; an aryl group such as an optionally substituted phenyl group; a 5- or 6-membered heterocyclic radical containing one or two heteroatoms chosen from nitrogen and sulphur atoms, the said heterocyclic radical optionally being substituted; or also a bicyclic radical resulting from the fusion of a benzene ring to a heterocycle as defined above.

30. Use according to anyone of claims 1 to 15, having the following formula (IIa) and (IIb):



$$\begin{matrix}R^1\\R^2\end{matrix}\!\!>\!N—(\text{chain }A^{II})—X^{II}—(\text{chain }B^{II})—Y^{II}$$

(IIa)

or

$$\begin{matrix}R^1\\R^2\end{matrix}\!\!>\!N—(\text{chain }A^{II})—X^{II}—Y^{II}$$

(IIb)

in which:

– R^1 and R^2 are as defined with reference to general formula (A) in claim 1;

– the chain A" represents an unbranched, branched or unsaturated alkyl group $-(CH_2)_{nII}-$ where n_{II} is an integer which can vary between 1 and 8 and preferably between 1 and 4; an unbranched or branched alkene group comprising from 1 to 8 carbon atoms and preferably 1 to 4 carbon atoms; an unbranched or branched alkyne group comprising from 1 to 4 carbon atoms;

– the group X^{II} represents -OCONH-; -OCON(alkyl)-; -OCON(alkene)-; -OCO-; -OCSNH-; $-CH_2-$; -O-; $-OCH_2CO-$; -S-; -CO-; -CS-; amine; saturated or unsaturated alkyl;

– the chain B^{II} represents an unbranched, branched or unsaturated lower alkyl comprising from 1 to 8 carbon atoms and preferably 1 to 5 carbon atoms; $-(CH_2)_{nII}$(hetero atom)- where the hetero atom is preferably a sulphur or oxygen atom; n_{II} being an integer which can vary between 1 and 5, preferably between 1 and 4;

– the group Y^{II} represents a phenyl group, unsubstituted or mono- or polysubstituted with one or more identical or different substituents selected from halogen atoms, OCF_3, CHO, CF_3, $SO_2N(alkyl)_2$ such as $SO_2N(CH_3)_2$, NO_2, S(alkyl), S(aryl), SCH_2(phenyl), an unbranched or branched alkene, an unbranched or branched alkyne optionally substituted with a trialkylsilyl radical, -O(alkyl), -O(aryl), $-CH_2CN$, a ketone, an aldehyde, a sulphone, an acetal, an alcohol, a lower alkyl, -CH=CH-CHO, -C(alkyl)=N-OH, -C(alkyl)=N-O(alkyl) and other keto derivatives, -CH=NOH, -CH=NO(alkyl), and other aldehyde derivatives, $-C(alkyl)=NH-NH-CONH_2$, an O-phenyl or $-OCH_2$(phenyl) group, -C(cycloalkyl)=NOH, -C(cycloalkyl)=N-O(alkyl), an optionally substituted heterocycle; a heterocycle comprising a sulphur hetero atom; a cycloalkyl; a bicyclic group and preferably a norbornyl group; a phenyl ring fused to a heterocycle comprising a nitrogen hetero atom or to a carbocycle or a heterocycle bearing a keto function; an unbranched or branched lower alkyl comprising from 1 to 8 carbon atoms; an unbranched or branched alkyne comprising from 1 to 8 carbon atoms and preferably 1 to 5 carbon atoms; a linear or branched alkyl mono- or polysubstituted with phenyl groups which are either unsubstituted or mono- or polysubstituted; a phenyl alkyl ketone in which the alkyl group is branched or unbranched or cyclic; a substituted or unsubstituted benzophenone; a substituted or unsubstituted, unbranched or branched or cyclic phenyl alcohol; an unbranched or branched alkene; a piperidyl group; a phenylcycloalkyl group; a polycyclic group, in particular a fluorenyl group, a naphthyl or polyhydronaphthyl group or an indanyl group; a phenol group; a ketone or keto derivative; a diphenyl group; a phenoxyphenyl group; a benzyloxyphenyl group.

31. Use according to claim 29 or 30, characterized in that X^{II} is selected from -O-, -NH-, $-CH_2-$, -OCONH-, -NHCO-, -NHCONH- and represents more preferably an oxygen atom.

32. Use according to anyone of claims 29 to 31, characterized in that Y^{II} is selected from a linear or branched alkyl group; a cycloalkyl group, in particular cyclopentyl or cyclohexyl group; a phenyl group unsubstituted or mono-substituted, preferred substituent being halogen atom, in particular chorine; a heterocyclic radical, in particular pyridyl N-oxide or pyrazinyl radicals; a bicyclic radical such as a benzothiazolyl radical, Y^{II} being more preferably a phenyl group unsubstituted or mono-substituted as above-defined.

33. Use according to anyone of claims 29 to 31, characterized in that Y^{II} represents a phenyl group at least mono-substituted with a keto-substituent, in particular a linear or branched chain aliphatic ketone comprising from 1 to 8 carbon atoms and optionnally bearing a hydroxyl group, a cycloalkylketone, an aryl alkyl ketone or arylalkenylketone in which the aryl group is optionally substituted, or a heteroaryl ketone, preferably a cycloalkylketone; an oxime-substituent or an halogen atom.

34. Use according to anyone of claims 29 to 31, characterized in that Y^{II} is a phenyl group at least mono-substituted with -CHO, a ketone, an

aldehyde, -CH=CH-CHO, -C(alkyl)=N-OH, -C(alkyl)=N-O(alkyl) and other keto derivatives, -CH=N-OH, -CH=NO(alkyl) and other aldehyde derivatives, -C(cycloalkyl)=NOH, -C(cycloalkyl)=N-O(alkyl).

35. Use according to anyone of claims 29 to 34, characterized in that chain A^{II} is a chain $-(CH_2)_{nII}-$ with n varying from 1 to 6, preferably from 1 to 4, the chain A^{II} representing especially $-(CH_2)_3-$.

36. Use according to anyone of claims 29 to 35, characterized in that the chain B^{II} is $-(CH_2)_2-$ or $-(CH_2)_3-$.

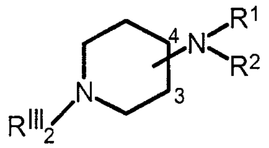
37. Use according to anyone of claims 29 to 36, characterized in that X is an oxygen atom, the chain A represents $-(CH_2)_3-$ and, for compounds of formula (IIa), the chain B represents $-(CH_2)_3-$ also.

38. Use according to anyone of claims 29 to 37, characterized in that it is one of the following compounds:

- 3,3-Dimethylbutyl 3-piperidinopropyl ether
- 3-Phenylpropyl 3-piperidinopropyl ether
- 3-(4-Chlorophenyl)propyl 3-piperidinopropyl ether
- 2-Benzothiazolyl 3-piperidinopropyl ether
- 3-Phenylpropyl 3-(4-methylpiperidino)propyl ether
- 3-Phenylpropyl 3-(3,5-cis-dimethylpiperidino)propyl ether
- 3-Phenylpropyl 3-(3,5-trans-dimethylpiperidino)propyl ether
- 3-Phenylpropyl 3-(3-methylpiperidino)propyl ether
- 3-Phenylpropyl 3-pyrrolidinopropyl ether
- 3-(4-Chlorophenyl)propyl 3-(4-methylpiperidino)propyl ether
- 3-(4-Chlorophenyl) propyl 3-(3,5-cis–dimethyl piperidino) propyl ether
- 3-(4-Chlorophenyl) propyl 3-(3,5-trans-dimethyl piperidino) propyl ether
- 3-Phenylpropyl 3-(N,N-diethylamino)propyl ether
- N-Phenyl-3-piperidinopropyl carbamate
- N-Pentyl-3-piperidinopropyl carbamate

- (S)-(+)-N-[2-(3,3-Dimethyl)butyl]-3-piperidinopropyl carbamate
- 3-Cyclopentyl-N-(3-(1-pyrrolidinyl)propyl)propanamide
- N-Cyclohexyl-N'-(1-pyrrolidinyl-3-propyl)urea
- 2-((2-Piperidinoethyl)amino)benzothiazole
- 5-Piperidinopentylamine
- 2-Nitro-5-(6-piperidinohexyl)pyridine
- 3-Nitro-2-(6-piperidinohexylamino)pyridine
- 2-(6-Piperidinohexylamino)pyrimidine
- N-(6-Phenylhexyl)piperidine
- N-phenyl-N'-(diethylamino-3-propyl)urea
- N-benzyl-N'-(3-piperidinopropyl)guanidine
- N-(3-(N,N-Diethylamino)propyl)N'-phenylurea
- N-Cyclohexylmethyl-N'-(3-piperidinopropyl)guanidine

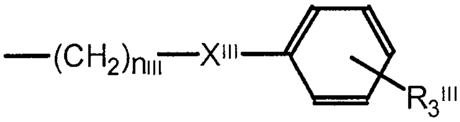
39. Use according to anyone of claims 1 to 15, having the following formula (III)



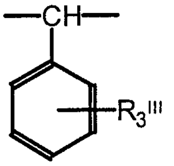
(III)

in which:

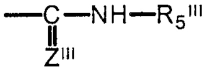
- NR^1R^2 is either in 3-position or in 4-position on the piperidyl moiety, R^1 and R^2 being as defined with reference to formula (A) in claim 1;
- R_2^{III} denotes a linear or branched alkyl group having 1 to 6 carbon atoms; a piperonyl group, a 3-(1-benzimidazolonyl)propyl group; a group of formula



in which n_{III} is 0, 1, 2 or 3, X^{III} is a single bond or alternatively -O-, -S-, -NH-, -CO-, -CH=CH- or

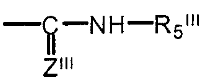


and R_3^{III} is H, CH_3, halogen, CN, CF_3 or an acyl group $-COR_4^{III}$, R_4^{III} being a linear or branched alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms or a phenyl group which can bear a CH_3 or F substituent; or alternatively a group of formula



$$-\underset{\underset{Z^{III}}{\parallel}}{C}-NH-R_5^{III}$$

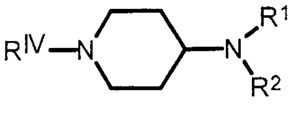
in which Z^{III} denotes an O or S atom or a divalent group NH, $N-CH_3$ or N-CN and R_5^{III} denotes a linear or branched alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms which can bear a phenyl substituent, a (C_3-C_6 cycloalkyl) (linear or branched, C_1-C_3 alkyl) group, a phenyl group which can bear a CH_3, halogen or CF_3 substituent, a phenyl(linear or branched, C_1-C_3 alkyl) group or a naphthyl, adamantyl or p-toluenesulphonyl group.

40. Use according to claim 39, characterized in that R^{III} represents the group  $-\underset{\underset{Z^{III}}{\parallel}}{C}-NH-R_5^{III}$, Z^{III} and R^{III}_5 being as defined in claim 39, Z^{III} being especially O, S or NH.

41. Use according to claim 40, characterized in that R^{III}_5 is a (C_3-C_6)cycloalkyl group.

42. Use according to anyone of claims 39 to 41, which is N'-Cyclohexylthiocarbamoyl-N-1,4'-bipiperidine.

43. Use according to anyone of claims 1 to 15, which have the following formula (IV):



(IV)

in which

– R^1 and R^2 are as defined with reference to general formula (A) in claim 1;

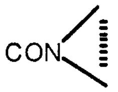
– R^{IV} represents a hydrogen atom or a group COR_3^{IV}, in which R_3^{IV} represents

(a) a linear or branched aliphatic group containing 1 to 11, and in particular 1 to 9, carbon atoms;

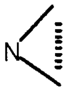
(b) a cyclane ring-system such as cyclopropane, phenylcyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, norbornane, adamantane, noradamantane, chlorooxonorbornane, chloroethylenedioxynorbornane, bromoethylenedioxynorbornane and the anhydride group of hydroxycarboxy-1,2,2-trimethylcyclopentanecarboxylic acid;

(c) a benzene ring, unsubstituted or substituted at the para-position with a linear or branched aliphatic group containing 3 to 5 carbon atoms, as well as with a halogen;

(d) a group $(CH_2)_{m_{IV}}R_4^{IV}$ in which m_{IV} is a number between 1 and 10, and R_4^{IV} represents a cyclane ring system such as cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cycloheptane, norbornane, noradamantane, adamantane and 6,6-dimethylbicyclo[3.1.1] heptene; a benzene ring, unsubstituted or monosubstituted with a fluorine atom, a chlorine atom, a methyl group or a methoxy group; a thiophene ring grafted via its ring-position 2 or its ring-position 3; a carboxylic acid ester group $COOR_5^{IV}$, in which R_5^{IV} is a cyclane ring-system such as cyclopropane, cyclobutane, cyclopentane, cyclohexane or norbornane; a carboxylic acid amide group of structure $CONHR_6^{IV}$, in which R_6^{IV} represents a cyclane ring-system such as cyclopropane, cyclobutane, cyclopentane, cyclohexane or norbornane; a carboxylic acid amide group of structure



in which the group

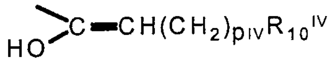


represents pyrrolidine, piperidine or 2,6-dimethylmorpholine; or an ether group $-O-R_7^{IV}$, it being possible for R_7^{IV} to be a benzene ring, unsubstituted or monosubstituted with a chlorine or fluorine atom or disubstituted with a chlorine atom and with a methyl group;

(e) a group $-CH{=}CHR_8^{IV}$, in which R_8^{IV} represents a cyclane ring-system such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, norbomane or norbornene;

(f) a secondary amine group $-NH(CH_2)_{n_{IV}}R_9^{IV}$, in which n_{IV} is a number between 1 and 5 and R_9^{IV} constitutes a cyclane ring-system such as cyclopropane, cyclobutane, cyclopentane, cyclohexane or norbornane, or a benzene ring, unsubstituted, mono-substituted with a fluorine or chlorine atom or with a methoxy group or trisubstituted with methoxy groups;

R^{IV} also represents a hydroxyalkenyl group



$$\mathrm{HO}{-}C{=}CH(CH_2)_{p_{IV}}R_{10}^{IV}$$

in which p_{IV} is a number between 2 and 9 and R_{10}^{IV}, represents a benzene ring or a phenoxy group; as well as a group

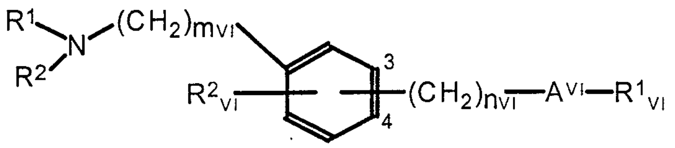
$$CSNH(CH_3)_{n_{IV}}R_9^{IV}$$

in which n_{IV} is a number between 1 and 5 and R_9^{IV} has the meaning stated above.

44. Use according to claim 43, characterized in that R^{IV} represents the group COR_3^{IV}, R_3^{IV} representing especially an aliphatic group a).

45. Use according to anyone of claims 43 and 44, which is N-Heptanoyl-1,4'-bipiperidine or 1-(5-Cyclohexylpentanoyl)-1,4-bipiperidine

46. Use according to anyone of claims 1 to 15, having the following formula (VI):



(VI)

wherein:

– A^{VI} is selected from $-O-CO-NR^1_{VI}-$, $-O-CO-$, $-NR^1_{VI}-CO-NR^1_{VI}-$, $-NR^1_{VI}-CO-$, $-NR^1_{VI}-$, $-O-$, $-CO-NR^1_{VI}-$, $-CO-O-$, and $-C(=NR^1_{VI})-NR^1_{VI}-$;

– the groups R^1_{VI}, which may be the same or different when there are two or three such groups in the molecule of formula VI, are selected from hydrogen, and lower alkyl, aryl, cycloalkyl, heterocyclic and heterocyclyl-alkyl groups, and groups of the formula $-(CH_2)_{y_{VI}}-G^{VI}$, where G^{VI} is selected from $CO_2R^3_{VI}$, COR^3_{VI}, $CONR^3_{VI}R^4_{VI}$, OR^3_{VI}, SR^3_{VI}, $NR^3_{VI}R^4_{VI}$, heteroaryl and phenyl, which phenyl is optionally substituted by halogen, lower alkoxy or polyhaloloweralkyl, and y_{VI} is an integer from 1 to 3;

– R^2_{VI} is selected from hydrogen and halogen atoms, and alkyl, alkenyl, alkynyl and trifluoromethyl groups, and groups of the formula OR^3_{VI}, SR^3_{VI} and $NR^3_{VI}R^4_{VI}$;

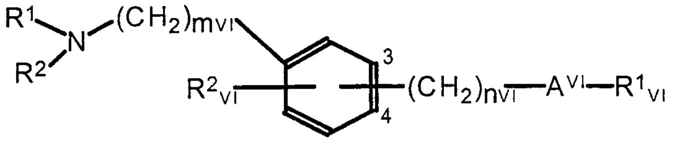
– R^3_{VI} and R^4_{VI} are independently selected from hydrogen, and lower alkyl and cycloalkyl groups, or R^3_{VI} and R^4_{VI} together with the intervening nitrogen atom can form a saturated ring containing 4 to 6 carbon atoms that can be substituted with one or two lower alkyl groups;

– the group $-(CH_2)_{n_{VI}}-A^{VI}-R^1_{VI}$ is at the 3- or 4-position, and the group R^2_{VI} is at any free position;

– m_{VI} is an integer from 1 to 3;

– and n_{VI} is 0 or an integer from 1 to 3.

47. Use according to anyone of claims 1 to 15, having the following formula (VI):



(VI)

wherein R^1_{VI} is an aryl group, preferably a phenyl group optionally substituted with a keto-substituent, in particular a linear or branched chain aliphatic ketone comprising from 1 to 8 carbon atoms and optionnally bearing a hydroxyl group, a cycloalkylketone, an aryl alkyl ketone or arylalkenylketone in which the aryl group is optionally substituted, or a heteroaryl ketone, preferably a cycloalkylketone, R^2_{VI}, n_{VI}, m_{VI} and A^{VI} being as defined in claim 46.

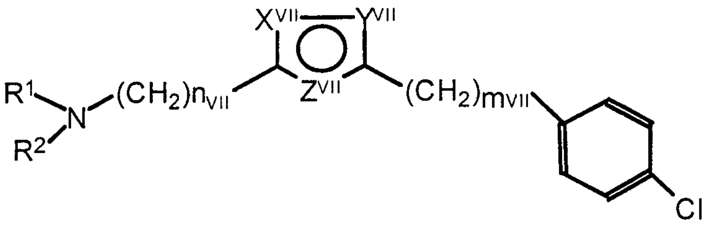
48. Use according to claim 46 or 47, characterized in that n_{VI} and m_{VI} are each 1, and A^{VI} represents an oxygen atom.

49. Use according to claim 46 or 48, characterized in that R^1_{VI} is an aryl or $-(CH_2)_{y_{VI}}-G^{VI}$ with G^{VI} being a phenyl.

50. Use according to anyone of claims 46 to 49, with one of the following compounds:

- α-(4-Acetylphenoxy)-α'-piperidino p-xylol
- α-(4-Acetylphenoxy)-α'-(1-pyrrolidinyl) p-xylol
- α-(3-Phenylpropoxy)-α'-piperidino p-xylol
- α-(4-Acetylphenoxy)-α'-(4-methylpiperidino)p-xylol
- α-(4-Acetylphenoxy)-α'-(3,5-cis-dimethylpiperidino)p-xylol
- α-(4-Acetylphenoxy)-α'-(3,5-trans-dimethylpiperidino)p-xylol
- α-(4-Acetylphenoxy)-α'-(2-methylpyrrolidino)p-xylol
- α-(4-Cyclopropylcarbonylphenoxy)-α'-piperidino-p-xylol
- α-(4-Cyclopropylcarbonylphenoxy)-α'-(4-methylpiperidino) p-xylol
- α-(4-Cyclopropylcarbonylphenoxy)-α'-pyrrolidino-p-xylol
- N-(4-Chlorobenzyl)-2-(4-piperidinomethyl)phenyl) ethan amidine

51. Use according to anyone of claims 1 to 15, having the following formula (VII):



(VII)

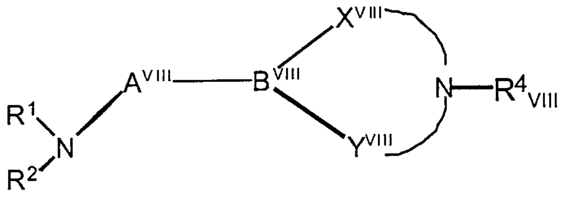
in which

- R^1 and R^2 are as defined in reference to formula (A) in claim 1;
- X^{VII}, Y^{VII} and Z^{VII} are identical or different and represent O, N or S;
- n_{VII} is varying from 1 to 3;
- m_{VII} is 1 or 2.

52. Use according to claim 51, characterized in that X^{VII} is 0 and Y^{VII} and Z^{VII} are each N to represent a 1, 2, 4-oxadiazolyl group.

53. Use according to claims 51 or 52 of a compound which is 3-(4-Chlorobenzyl)-5-(2-piperidinoethyl)-1,2,4-oxadiazole

54. Use according to anyone of claims 1 to 15 of a compound having the following formula (VIII):



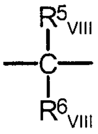
(VIII)

wherein R^1 and R^2 are as defined with reference to formula (A) in claim 1 and wherein

A^{VIII} is

1) a group of the formula $(CH_2)_{mVIII}$, wherein m_{VIII} = 0-9; or

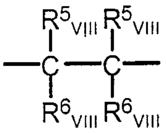
2) a group of the formula:



$$-\overset{R^5_{VIII}}{\underset{R^6_{VIII}}{C}}-$$

wherein R^5_{VIII} represents hydrogen, $(C_1\text{-}C_3)$alkyl-, aryl$(C_1\text{-}C_3)$alkyl-, aryl-, wherein aryl may optionally be substituted, hydroxyl-, $(C_1\text{-}C_3)$alkoxy-, halogen, amino-, cyano- or nitro; and R^6_{VIII} represents hydrogen, $(C_1\text{-}C_3)$alkyl-, aryl$(C_1\text{-}C_3)$alkyl-, or aryl-, wherein aryl may optionally be substituted; or

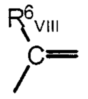
3) a group of the formula:



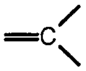
$$-\overset{R^5_{VIII}}{\underset{R^6_{VIII}}{C}}-\overset{R^5_{VIII}}{\underset{R^6_{VIII}}{C}}-$$

wherein R^5_{VIII} and R^6_{VIII} are as defined above; or

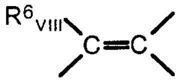
4) a group of the formula:



if B^{VIII} is a group of the formula:

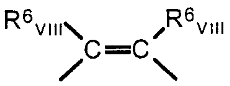


such that A^{VIII} and B^{VIII} together form a group of the formula:



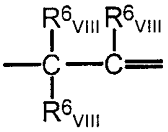
wherein $R^6{}_{VIII}$ is as defined above; or

5) a group of the formula:



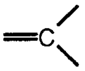
wherein $R^6{}_{VIII}$ is as defined above; or

6) a group of the formula:

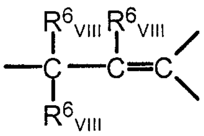


$$-\overset{R^6{}_{VIII}}{\underset{R^6{}_{VIII}}{C}}-\overset{R^6{}_{VIII}}{C}=$$

if B^{VIII} is a group of the formula:



such that A^{VIII} and B^{VIII} together form a group of the formula:



wherein $R^6{}_{VIII}$ is as defined above; or

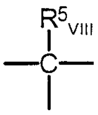
7) a group of the formula:

$$-(CH_2)x_{VIII}-S-(CH_2)y_{VIII}-$$

wherein $x_{VIII} + y_{VIII} = m_{VIII}-1$;

B^{VIII} is

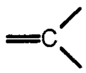
1) a group of the formula:



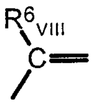
$$-\overset{R^5{}_{VIII}}{\underset{|}{C}}-$$

wherein R^5_{VIII} is as defined above; or

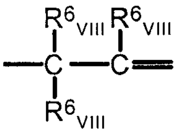
2) a group of the formula:



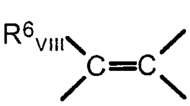
if A is a group of one of the formulas:



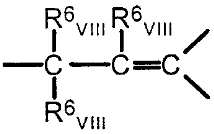
or



such that A and B together form a group of one of the formulas:

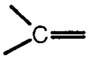


or

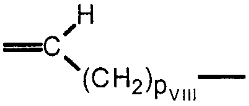


wherein R^6_{VIII} is as defined above; or

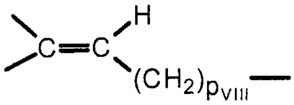
3) a group of the formula:



if X^{VIII} is a group of the formula:



such that B^{VIII} and X^{VIII} together form a group of the formula

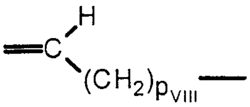


wherein p_{VIII} = 1-3; or

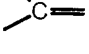
X^{VIII} is

1) a group of the formula $(CH_2)_{nVIII}$ wherein n_{VIII} = 2-4; or

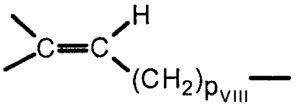
2) a group of the formula:



if B^{VIII} is a group of the formula:



such that X^{VIII} and B^{VIII} together form a group of the formula:



wherein $p_{VIII} = 1\text{-}3$; or

3) two hydrogens (one on the carbon and one on the nitrogen); or

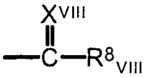
4) one hydrogen on the carbon atom and one R^7_{VIII} group on the nitrogen atom,

wherein R^7_{VIII} represents hydrogen, $(C_1\text{-}C_{10})$alkyl-, aryl $(C_1\text{-}C_{10})$alkyl-, or aryl, wherein aryl may optionally be substituted;

Y^{VIII} is a group of the formula $(CH_2)_{kVIII}$, wherein $k_{VIII} = 0\text{-}2$;

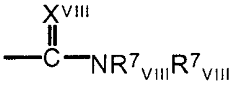
R^4_{VIII} represents hydrogen, $(C_1\text{-}C_{10})$alkyl-, $(C_1\text{-}C_3)$alkyl-sulfonamide-, aryl$(C_1\text{-}C_{10})$alkyl-, aryl, wherein aryl may optionally be substituted;

or a group of the formula:



$$-\overset{\displaystyle X^{VIII}}{\overset{\|}{C}}-R^8_{VIII}$$

or a group of the formula:



$$-\overset{\displaystyle X^{VIII}}{\overset{\|}{C}}-NR^7_{VIII}R^7_{VIII}$$

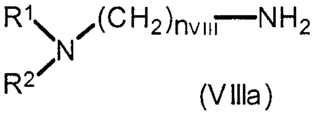
wherein X^{VIII} represents O, S, or NH,

R^7_{VIII} is as defined as above;

R^8_{VIII} represents $(C_1\text{-}C_{10})$alkyl-, aryl$(C_1\text{-}C_{10})$alkyl- or aryl,

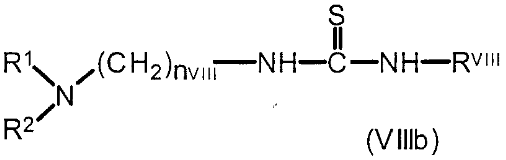
wherein aryl may optionally be substituted and wherein aryl is phenyl, substituted phenyl, naphtyl, substituted naphtyl, pyridyl;

55. Use according to claim 54 of a compound having the formula



(VIIIa)

or

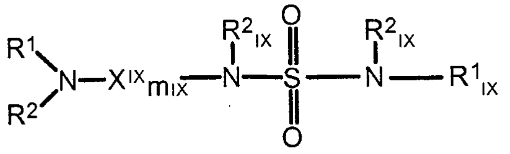


(VIIIb)

R^1 and R^2 having the meaning given in claim 1 and n_{VIII} and R^{VIII} having the meaning given in claim 54.

56. Use according to claim 54 or 55 of a compound which is 2-Nitro-5-(6-piperidinohexyl)pyridine or 10-piperidinodecylamine.

57. Use according to anyone of claims 1 to 15 of a compound having the following formula (IX):



$$R^1R^2N-(X^{IX})_{m_{IX}}-N(R^2_{IX})-S(=O)_2-N(R^2_{IX})-R^1_{IX}$$

(IX)

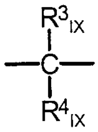
wherein:

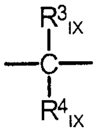
R^1 and R^2 are as defined with reference to formula (A) in claim 1.

R^1_{IX} is C_4 to C_{20} hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen, and up to four carbon atoms [and especially from 0 to 3 carbon atoms] may be replaced by oxygen, nitrogen or sulphur atoms, provided that R^1_{IX} does not contain an -O-O-group),

R^2_{IX} identical or different, are H or C_1 to C_{15} hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen, and up to three carbon atoms may be replaced by oxygen, nitrogen or sulphur atoms, provided that R^2_{IX} does not contain an -O-O-group.

m_{IX} is from 1 to 15 (preferably 1 to 10, more preferably 3 to 10, eg. 4 to 9)

each X^{IX} group is independently  $-C(R^3_{IX})(R^4_{IX})-$, or one X^{IX} group is



$$-C(R^3_{IX})(R^4_{IX})-$$

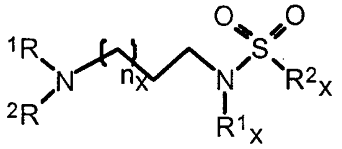
-N(R^4_{IX})-, -O- or -S- (provided that this X^{IX} group is not adjacent the -NR^2_{IX}-group) and the remaining X^{IX} groups are independently

, wherein R^3_{IX} is H, C_1 to C_6 alkyl, C_2 to C_6 alkenyl,

$-CO_2R^5_{IX}$, $-CON(R^5_{IX})_2$, $-CR^5_{IX2}OR^6_{IX}$ or $-OR^5_{IX}$ (in which R^5_{IX} and R^6_{IX} are H or C_1 to C_3 alkyl), and R^4_{IX} is H or C_1 to C_6 alkyl.

58. Use according to claim 57 of a compound which is N-(4-Bromobenzyl)-N'-(4-piperidinobutyl)sulphamide.

59. Use according to anyone of claims 1 to 15 of a compound having the following formula (X):



(X)

wherein:

– R^1 and R^2 are as defined with reference to formula (A) in claim 1;

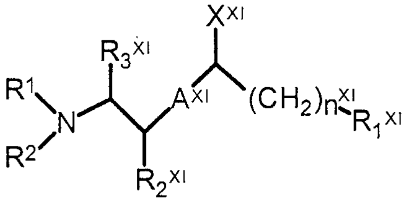
– R^1_x is H or CH_3;

– R^2x is selected from a phenyl optionally substituted with a halogen atom, preferably chlorine, a (C_1-C_4)alkyl, a (C_1-C_4)alkoxy, CF_3, OCF_3, NO_2, NH_2; or a CH_2-phenyl optionally substituted as above-specified;

– n_x is from 0 to 3.

60. Use according to claim 59, of a compound which is 3-Chloro-N-(4-piperidinobutyl)-N-methyl-benzene sulphonamide.

61. Use according to claims 1 to 15, having the following formula (XI):



(XI)

where R^1 and R^2 are as defined with reference to formula (A) in claim 1;

where A^{XI} is -NHCO-, $-N(CH_3)-CO-$, $-NHCH_2-$, $-N(CH_3)-CH_2-$, -CH=CH-, $-COCH_2-$, CH_2CH_2-, $-CH(OH)CH_2-$, or $-C\equiv C-$;

X^{XI} is H, CH_3, NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH, OCH_3, or SH;

R_2^{XI} is hydrogen or a methyl or ethyl group;

R_3^{XI} is hydrogen or a methyl or ethyl group;

n^{XI} is 0, 1, 2, 3, 4, 5 or 6; and

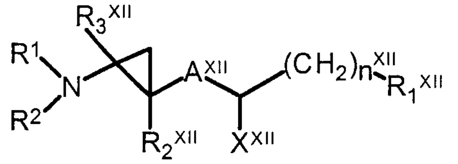
R_1^{XI} is selected from the group consisting of C_3 to C_8 cycloalkyl; phenyl or substituted phenyl; decahydronaphthalene and octahydroindene; or

R_1^{XI} and X^{XI} may be taken together to denote a 5,6- or 6,6-saturated bicyclic ring structure when X^{XI} is NH, O, S, or SO_2.

62. Use according to claim 61, characterized in that it is one of the following compounds :

- *cis*-1-(6-Cyclohexyl-3-hexen-1-yl)piperidine
- *trans*-1-(6-Cyclohexyl-3-hexen-1-yl)piperidine
- 1-(6-Cyclohexyl-3-hexin-1-yl)piperidine

63. Use according to claim 1 to 15, having the following formula (XII):



(XII)

where R^1 and R^2 are as defined in reference to formula (A) in claim 1;

where R_2^{XII} is a hydrogen or a methyl or ethyl group;

R_3^{XII} is a hydrogen or a methyl or ethyl group;

n^{XII} is 0, 1, 2, 3, 4, 5, or 6; and

R_1^{XII} is selected from the group consisting of C_3 to C_8 cycloalkyl; phenyl substituted or not by one or more groups such as a halogen atom, a lower alkyl or cycloalkyl, a trifluoromethyl, aryl, alkoxy, α-alkyloxyalkyl, aryloxy, nitro, formyl, alkanoyl, aroyl, arylalkanoyl, amino, carboxamido, cyano, alkyloximino, alkylalkoximino, aryloximino, α-hydroxyalkyl, alkenyl, alkynyl, sulphamido, sulfamoyl, sulphonamido, carboxamide, carbocycloalkyl, alkylcarbnyloalkyl, carbonylalkoxy, arylalkyl or oxime group, or two substituants taken together with the carbon atoms of the phenyl ring to which it is fused form 5- or 6-membered saturated or unsaturated ring or a benzene ring or alkyl; heterocyclic; decahydronaphthalene; and octahydroindene;

with the provisos that

when X^{XII} is H, A^{XII} can be $-CH_2CH_2-$, $-COCH_2-$, -CONH-, $-CON(CH_3)-$, -CH=CH-, -C≡C-, $-CH_2-NH-$, $-CH_2-N(CH_3)-$, $-CH(OH)CH_2-$, $-NH-CH_2-$, $-N(CH_3)-CH_2-$, $-CH_2O-$, $-CH_2S-$, or –NHCOO-;

when X^{XII} is NH_2, $NH(CH_3)$, $N(CH_3)_2$, OH, OCH_3, CH_3, SH or SCH_3; A^{XII} can be -NHCO-, $-N(CH_3)-CO-$, $-NHCH_2-$, $-N(CH_3)-CH_2-$, -CH=CH-, $-COCH_2-$, $-CH_2CH_2-$, $-CH(OH)CH_2-$, or –C≡C- ; and

when R_1^{XII} and X^{XII} taken together denote a 5,6 or 6,6 saturated bicyclic ring structure X^{XII} can be NH, O, or S.

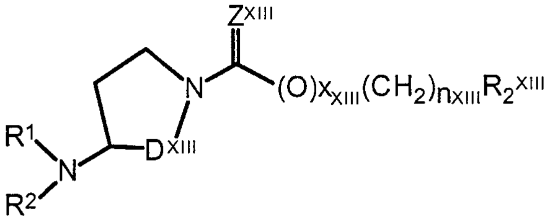
64. Use according to claim 63, characterized in that, A^{XII} is –CH=CH- or –C≡C-.

65. Use according to claims 63 to 64, characterized in that R_2^{XII}, R_3^{XII} are each hydrogen atom.

66. Use according to anyone of claims 63 to 65, characterized in that n_{XII} is an alkyl group.

67. Use according anyone of claims 63 to 66, of a compound which is 1-(2-(5,5-Dimethyl-1-hexin-1-yl)cyclopropyl)piperidine.

68. Use according to anyone of claims 1 to 15 having the following formula (XIII):



(XIII)

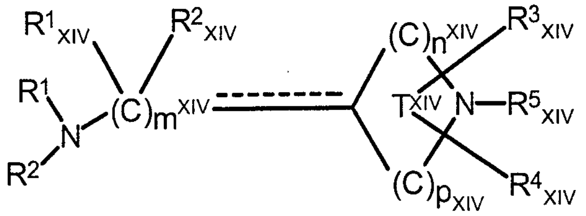
wherein R^1 and R^2 are as defined with reference to formula (A) in claim 1.

wherein D^{XIII} is CH_2 or CH_2-CH_2, Z^{XIII} represents sulfur (S) or oxygen (O), preferably O, X_{XIII} is 0 or 1, n_{XIII} is an integer from 0 to 6,

and R_2^{XIII} represents a substituted or unsubstituted linear chain or branched chain alkyl group of up to about 20 carbon atoms, a substituted or unsubstituted carbocyclic group of up to about 20 carbon atoms including mono and bicyclic moieties, and a substituted or an unsubstituted aryl group of up to about 20 carbon atoms, or any combination of above-mentioned groups, or salts thereof.

69. Use according to claim 68, of a compound which is *N* -heptanoyl-1,4'-bipiperidine or 1-(5-Cyclohexylpentanoyl)-1,4' -bipiperidine.

70. Use according to anyone of claims 1 to 15, having the following formula (XIV)



(XIV)

wherein R^1 and R^2 are as defined in reference of formula (A) in claim 1;

(A) m_{XIV} is an integer selected from the group consisting of: 1 and 2;

(B) n_{XIV} and p_{XIV} are intergers and are each independently selected from the group consisting of: 0, 1, 2, 3, and 4 such that the sum of n_{XIV} and p_{XIV} is 4 and T^{XIV} is a 6-membered ring;

(C) R^3_{XIV} and R^4_{XIV} are each independently bound to the same or different carbon atom of ring T^{XIV}, such that there is only one R^3_{XIV} group and one R^4_{XIV} group in ring T^{XIV}, and each R^1_{XIV}, R^2_{XIV}, R^3_{XIV} and R^4 is independently selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl; and

(3) $-(CH_2)_{qXIV}-R^6_{XIV}$ wherein q_{XIV} is an integer of: 1 to 7, and R^6_{XIV} is selected from the group consisting of: phenyl, substituted phenyl, $-OR^7_{XIV}$, $-C(O)OR^7_{XIV}$, $-C(O)R^7_{XIV}$, $-OC(O)R^7_{XIV}$, $-C(O)NR^7_{XIV}R^8_{XIV}$, CN and $-SR^7_{XIV}$ wherein R^7_{XIV} and R^8_{XIV} are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C_1 to C_6)alkyl, halogen, C_1 to C_6 alkyl, $-CF_3$, -CN, and $-NO_2$, and wherein said substituted phenyl contains from 1 to 3 substituents;

(D) R^5_{XIV} is selected from the group consisting of:

(1) H;

(2) C_1 to C_{20} alkyl;

(3) C_3 to C_6 cycloalkyl;

(4) $-C(O)OR^{7'}_{XIV}$; wherein $R^{7'}_{XIV}$ is the same as R^7_{XIV} defined below except that $R^{7'}_{XIV}$ is not H;

(5) $-C(O)R^7_{XIV}$;

(6) $-C(O)NR^7_{XIV}R^8_{XIV}$;

(7) allyl;

(8) propargyl; and

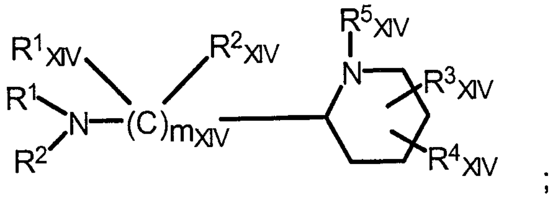
(9) $-(CH_2)_q-R^6_{XIV}$ wherein q_{XIV} and R^6_{XIV} are as defined above, and when q_{XIV} is equal to 1, then R^6_{XIV} is not OH or SH;

(E) R^7_{XIV} and R^8_{XIV} are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and C_3 to C_6 cycloalkyl;

(F) the dotted line (--------) represents a double bond that is optionally present when m_{XIV} is 1, and n_{XIV} is not 0, and p is not 0 (i.e., the nitrogen in the ring is not bound directly to the carbon atom bearing the double bond), and when said double bond is present then R^2_{XIV} is absent; and

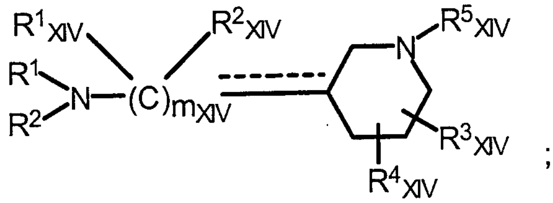
(G) when m_{XIV} is 2, each R^1_{XIV} is the same or different substituent for each m_{XIV}, and each R^2_{XIV} is the same or different substituent for each m_{XIV}, and at least two of the substituents R^1_{XIV} and/or R^2_{XIV} are H.

71. Use according to claim 70, of a compound which is selected from compounds having the following formula (XIVa), (XIVb) or (XIVc)



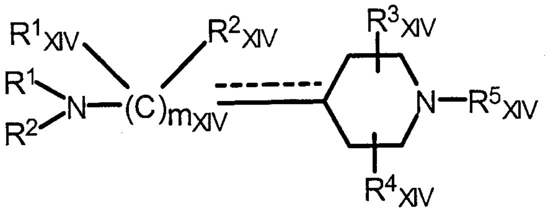
(XIVa)

;



(XIVb)

; and

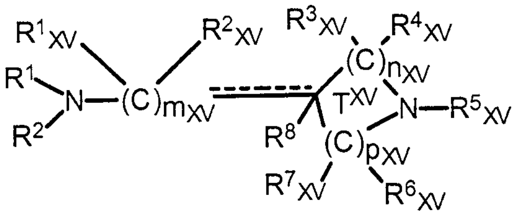


(XIVc)

.

in which R^5_{XIV} is preferably H or CH_3 and R^3_{XIV} and R^4_{XIV} are preferably each H.

72. Use according to anyone of claims 1 to 15, of a compound having the following formula (XV):



(XV)

where R^1 and R^2 are as defined in reference to formula (A) in claim 1;

(A) m_{XV} is an integer selected from the group consisting of: 0,1, and 2;

(B) n_{XV} and p_{XV} are intergers and are each independently selected from the group consisting of: 0, 1, 2, and 3 such that the sum of n_{XV} and p_{XV} is 2 or 3 such that when the sum of n_{XV} and p_{XV} is 2, T^{XV} is a 4-membered ring and when the sum of n and p_{XV} is 3, T^{XV} is a 5-membered ring;

(C) each R^1_{XV}, R^2_{XV}, R^3_{XV}, R^4_{XV}, R^6_{XV}, R^7_{XV} and R^8_{XV} is independently selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl;

(3) C_3 to C_6 cycloalkyl; and

(4) $-(CH_2)_{qXV}-R^9_{XV}$ wherein q_{XV} is an integer of: 1 to 7, and R^9_{XV} is selected from the group consisting of: phenyl, substituted phenyl, $-OR^{10}_{XV}$, $-C(O)OR^{10}_{XV}$, $-C(O)R^{10}_{XV}$, $-OC(O)R^{10}_{XV}$, $-C(O)NR^{10}_{XV}R^{11}_{XV}$, CN and $-SR^{10}_{XV}$ wherein R^{10}_{XV} and R^{11}_{XV} are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C_1 to C_6) alkyl, halogen, C_1 to C_6 alkyl, $-CF_3$, -CN, and $-NO_2$, and wherein said substituted phenyl contains from 1 to 3 substituents; examples of $-(CH_2)_{qXV}-R^9_{XV}$ include benzyl, substituted benzyl and the like, wherein the substitutents on the substituted benzyl are as defined above for said substituted phenyl;

(D) R^5_{XV} is selected from the group consisting of:

(1) H;

(2) C_1 to C_{20} alkyl;

(3) C_3 to C_6 cycloalkyl;

(4) $-C(O)OR^{10'}_{XV}$; wherein $R^{10'}_{XV}$ is the same as R^{10}_{XV} defined below except that $R^{10'}_{XV}$ is not H;

(5) $-C(O)R^{10}_{XV}$;

(6) $-C(O)NR^{10}_{XV}R^{11}_{XV}$;

(7) allyl;

(8) propargyl; and

(9) $-(CH_2)_{qXV}-R^9_{XV}$, wherein q_{XV} and R^9_{XV} are as defined above with the proviso that when q_{XV} is 1 then R^9_{XV} is not -OH or -SH;

(E) R^{10}_{XV} and R^{11}_{XV} are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and C_3 to C_6 cycloalkyl; and, for the substituent $-C(O)NR^{10}_{XV}R^{11}$, R^{10}_{XV} and R^{11}_{XV}, together with the nitrogen to which they are bound, can form a ring having 5, 6, or 7 atoms;

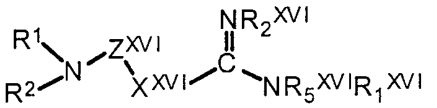
(F) the dotted line (-----) represents a double bond that is optionally present when m_{XV} is 1, and T^{XV} is a 5-membered ring, and n_{XV} is not 0, and p_{XV} is not 0 (i.e., the nitrogen in the ring is not bound directly to the carbon atom bearing the double bond), and when said double bond is present then R^2_{XV} and R^8_{XV} are absent;

(G) when m_{XV} is 2, each R^1_{XV} is the same or different substituent for each m_{XV}, and each R^2_{XV} is the same or different substituent for each m_{XV};

(H) when n_{XV} is 2 or 3, each R^3_{XV} is the same or different substituent for each n_{XV}, and each R^4_{XV} is the same or different substituent for each n_{XV}; and

(I) when p_{XV} is 2 or 3, each R^6_{XV} is the same or different substituent for each p, and each R^7_{XV} is the same or different substituent for each p_{XV}.

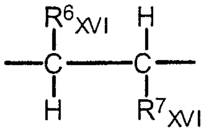
73. Use according to anyone of claims 1 to 15, of a compound having the following formula (XVI)



(XVI)

where R^1 and R^2 are as defined in reference to formula (A) in claim 1;

Z^{XVI} is a group of the formula $(CH_2)_{mXVI}$ wherein m_{XVI} = 1-5 or a group of the formula:



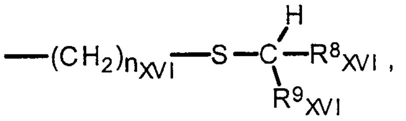
, wherein $R^6_{XVI} = (C_1\text{-}C_3)$alkyl

$R^7_{XVI} = (C_1\text{-}C_3)$alkyl ;

wherein Z^{XVI} may optionally comprise other substituents selected such that the activity of the derivative is not negatively affected,

X^{XVI} represents S, NH or CH_2

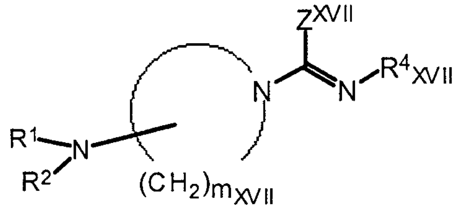
R^1_{XVI} represents hydrogen, $(C_1\text{-}C_3)$alkyl-, aryl$(C_1\text{-}C_{10})$alkyl, wherein aryl may optionally be substituted, aryl, $(C_5\text{-}C_7)$cycloalkyl$(C_1\text{-}C_{10})$alkyl-, or a group of the formula:



$$-(CH_2)_{n_{XVI}}-S-\overset{H}{\underset{R^9_{XVI}}{C}}-R^8_{XVI}\ ,$$

wherein n_{XVI} = 1-4, R^8_{XVI} is aryl, aryl$(C_1\text{-}C_{10})$alkyl-, $(C_5\text{-}C_7)$cycloalkyl- or $(C_5\text{-}C_7)$ cycloalkyl$(C_1\text{-}C_{10})$alkyl-, and R^9_{XVI} is hydrogen, $(C_1\text{-}C_{10})$alkyl-or aryl; R_2^{XVI} and R_5^{XVI} represent hydrogen, $(C_1\text{-}C_3)$alkyl-, aryl or arylalkyl-, wherein aryl may optionally be substituted; wherein aryl is phenyl, substituted phenyl, naphthyl, substituted napththyl, pyridyl or substituted pyridyl.

74. Use according to anyone of claims 1 to 15, of a compound having the following formula (XVII):

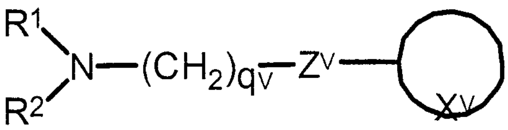


XVII

wherein m_{XVII} represents an integer of from 4 to 6.

R^4_{XVII} represents a hydrogen atom, a linear or branched alkyl group, a cycloalkyl group, a cycloalkylalkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group; and Z^{XVII} represents R^5_{XVII} or $A^{XVII}\text{-}R^6_{XVII}$, wherein A^{XVII} represents S or O, R_5^{XVII} represents a hydrogen atom, a lower alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, and R_6^{XVII} represents a lower alkyl group, a lower alkenyl group, a lower alkynyl group or a substituted or unsubstituted aralkyl group.

75. Use according to anyone of claims 1 to 15, of a compound having the following formula (V) :

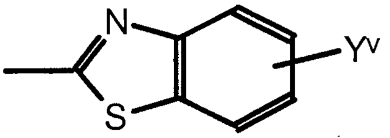


(V)

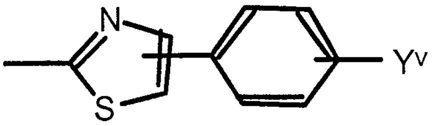
in which

- R^1 and R^2 are as defined with reference to formula (A) in claim 1;
- q^V is 2 to 5
- Z^V represents NH, O or S
- X_V represents a heterocycle, optionally condensed, containing one or more heteroatoms like nitrogen, oxygen or sulfur, unsubstituted or substituted by one or more groups like aryl or lower alkyl and halogen.

76. Use according to claim 75 wherein X^V means an heterocycle like :

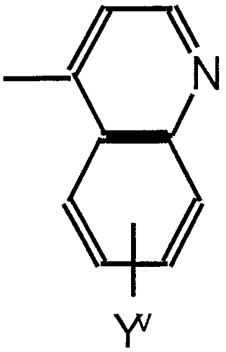


(Va)



(Vb)

or



(Vc)

with Y^V being an hydrogen atom, a halogen or a lower alkyl.

77. Use according to claims 75 or 76 with one of the following compounds :

2-((2-Piperidinoethyl)amino)benzothiazole
2-(6-Piperidinohexylamino)benzothiazole
4-(6-Piperidinohexylamino)quinoline
2-Methyl 4-(3-piperidinopropylamino)quinoline
2-Methyl 4-(6-piperidinohexylamino)quinoline
7-Chloro-4-(3-piperidinopropylamino)quinoline
7-Chloro-4-(4-piperidinobutylamino)quinoline
7-Chloro-4-(8-piperidinooctylamino)quinoline
7-Chloro-4-(10-piperidinodecylamino)quinoline
7-Chloro-4-(12-piperidinododecylamino)quinoline
7-Chloro-4-(4-(3-piperidinopropoxy)phenylamino)quinoline
7-Chloro-4-(2-(4-(3-piperidinopropoxy) phenyl) ethylamino) quinoline

78. Use according to claim 1 with at least one of the following compounds :

1-(5-phenoxypentyl)-piperidine
1-(5-phenoxypentyl)-pyrrolidine
N-methyl-N-(5-phenoxypentyl)-ethylamine
1-(5-phenoxypentyl)-morpholine
N-(5-phenoxypentyl)-hexamethyleneimine
N-ethyl-N-(5-phenoxypentyl)-propylamine
1-(5-phenoxypentyl)-2-methyl-piperidine
1-(5-phenoxypentyl)-4-propyl-piperidine
1-(5-phenoxypentyl)-4-methyl-piperidine
1-(5-phenoxypentyl)-3-methyl-piperidine
1-acetyl-4-(5-phenoxypentyl)-piperazine
1-(5-phenoxypentyl)-3,5-trans-dimethyl-piperidine
1-(5-phenoxypentyl)-3,5-cis-dimethyl-piperidine
1-(5-phenoxypentyl)-2,6-cis-dimethyl-piperidine
4-carboethoxy-1-(5-phenoxypentyl)-piperidine
3-carboethoxy-1-(5-phenoxypentyl)-piperidine
1-[3-(4-cyclopropylcarbonylphenoxy) propyl]-piperidine
1-[3-(4-acetylphenoxy)-2-R-methylpropyl] piperidine

1-[3-(4-cyanophenoxy)propyl]-4-methylpiperidine
1-[3-(4-cyanophenoxy)propyl]-3-methylpiperidine
1-[3-(4-acetylphenoxy)-2-S-methylpropyl] piperidine
1-{3-[4-(3-oxobutyl)phenoxy] propyl}piperidine
1-[3-(4-cyano-3-fluorophenoxy)propyl] piperidine
1-[3-(4-nitrophenoxy)propyl]-3-methylpiperidine
1-[3-(4-cyanophenoxy)propyl]-2-methylpiperidine
1-[3-(4-nitrophenoxy)propyl]-2-methylpiperidine
1-[3-(4-nitrophenoxy)propyl]-4-methylpiperidine
1-[3-(4-cyanophenoxy)propyl]-2,6-dimethylpiperidine
1-[3-(4-propionylphenoxy)propyl]-3-methylpiperidine
1-[3-(4-cyclobutylcarbonylphenoxy)propyl] piperidine
1-[3-(4-cyclopentylcarbonylphenoxy) propyl]piperidine
1-[3-(4-cyanophenoxy)propyl]-cis-2-methyl-5-ethylpiperidine
1-[3-(4-cyanophenoxy)propyl]-trans-2-methyl-5-ethylpiperidine
1-[3-(4-cyanophenoxy)propyl]-cis-3,5-dimethylpiperidine
1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine
1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine
1-{3-[4-(1-hydroxypropyl)phenoxy]propyl}-3-methylpiperidine
1-{3-[4-(1-hydroxypropyl)phenoxy]propyl}-4-methylpiperidine
1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine
1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine methoxime
1-[3-(4-cyanophenoxy)propyl]-trans-3,5-dimethylpiperidine
1-[3-(4-cyclopropylcarbonylphenoxy) propyl] -trans-3,5 –dimethyl piperidine
1-[3-(4-cyclopropylcarbonylphenoxy) propyl] -cis-3,5 –dimethyl piperidine
1-[3-(4-carbomethoxyphenoxy)propyl] piperidine
1-[3-(4-propenylphenoxy)propyl]-2-methyl piperidine
1-[3-(4-propionylphenoxy)propyl]-2-methylpiperidine
1-{3-[4-(1-ethoxypropyl)phenoxy]propyl}-2-methyl piperidine
1-[3-(4-propionylphenoxy)propyl]-4-methylpiperidine
1-[3-(4-bromophenoxy)propyl]piperidine

1-[3-(4-nitrophenoxy)propyl]piperidine
1-[3-(4-N,N-dimethylsulfonamidophenoxy) propyl]piperidine
1-[3-(4-isopropylphenoxy)propyl]piperidine
1-[3-(4-sec-butylphenoxy)propyl]piperidine
1-[3-(4-propylphenoxy)propyl]piperidine
1-[3-(4-ethylphenoxy)propyl]piperidine
1-(5-phenoxypentyl)-1,2,3,6-tetrahydropyridine
1-[5-(4-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-methoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-methylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-pyrrolidine
1-[5-(2-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(1-naphthyloxy)-pentyl]-pyrrolidine
1-[5-(3-chlorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenylphenoxy)-pentyl]-pyrrolidine
1-{5-[2-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-[5-(3-phenylphenoxy)-pentyl]-pyrrolidine
1-(5-phenoxypentyl)-2,5-dihydropyrrole
1-{5-[1-(5,6,7,8-tetrahydronaphthyl)-oxy]-pentyl}-pyrrolidine
1-(4-phenoxybutyl)-pyrrolidine
1-(6-phenoxyhexyl)-pyrrolidine
1-(5-phenylthiopentyl)-pyrrolidine
1-(4-phenylthiobutyl)-pyrrolidine
1-(3-phenoxypropyl)-pyrrolidine
1-[5-(3-nitrophenoxy)-pentyl]-pyrrolidine
1-[5-(4-fluorophenoxy)-pentyl]-pyrrolidine
1-[5-(4-nitrophenoxy)-pentyl]-3-methyl-piperidine
1-[5-(4-acetylphenoxy)-pentyl]-pyrrolidine
1-[5-(4-aminophenoxy)-pentyl]-pyrrolidine
1-[5-(3-cyanophenoxy)-pentyl]-pyrrolidine
N-[3-(4-nitrophenoxy)-propyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-diethylamine

1-[5-(4-benzoylphenoxy)-pentyl]-pyrrolidine
1-{5-[4-(phenylacetyl)-phenoxy]-pentyl}-pyrrolidine
N-[3-(4-acetylphenoxy)-propyl]-diethylamine
1-[5-(4-acetamidophenoxy)-pentyl]-pyrrolidine
1-[5-(4-phenoxyphenoxy)-pentyl]-pyrrolidine
1-[5-(4-N-benzamidophenoxy)-pentyl]-pyrrolidine
1-{5-[4-(1-hydroxyethyl)-phenoxy]-pentyl}-pyrrolidine
1-[5-(4-cyanophenoxy)-pentyl]-diethylamine
1-[5-(4-cyanophenoxy)-pentyl]-piperidine
N-[5-(4-cyanophenoxy)-pentyl]-dimethylamine
N-[2-(4-cyanophenoxy)-ethyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dimethylamine
N-[4-(4-cyanophenoxy)-butyl]-diethylamine
N-[5-(4-cyanophenoxy)-pentyl]-dipropylamine
1-[3-(4-cyanophenoxy)-propyl]-pyrrolidine
1-[3-(4-cyanophenoxy)-propyl]-piperidine
N-[3-(4-cyanophenoxy)-propyl]-hexamethyleneimine
N-[6-(4-cyanophenoxy)-hexyl]-diethylamine
N-[3-(4-cyanophenoxy)-propyl]-dipropylamine
N-3-[4-(1-hydroxyethyl)-phenoxy]-propyl-diethylamine
4-(3-diethylaminopropoxy)-acetophenone-oxime
1-[3-(4-acetylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3-methyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-trans-dimethyl-piperidine
1-[3-(4-acetylphenoxy)-propyl]-4-methyl-piperidine
1-[3-(4-propionylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-3,5-cis-dimethyl-piperidine
1-[3-(4-formylphenoxy)-propyl]-piperidine
1-[3-(4-isobutyrylphenoxy)-propyl]-piperidine
N-[3-(4-propionylphenoxy)-propyl]-diethylamine
1-[3-(4-butyrylphenoxy)-propyl]-piperidine
1-[3-(4-acetylphenoxy)-propyl]-1,2,3,6-tetrahydropyridine
α-(4-Acetylphenoxy)-α'-(4-methylpiperidino)p-xylol

α-(4-Acetylphenoxy)-α′-(3,5-*cis*-dimethylpiperidino)p-xylol
α-(4-Acetylphenoxy)-α′-(3,5-*trans*-dimethylpiperidino)p-xylol
α-(4-Acetylphenoxy)-α′-(2-methylpyrrolidino)p-xylol
α-(4-Cyclopropylcarbonylphenoxy)-α′-piperidino-p-xylol
α-(4-Cyclopropylcarbonylphenoxy)-α′-(4-methylpiperidino)p-xylol
α-(4-Cyclopropylcarbonylphenoxy)-α′-pyrrolidino-p-xylol
3-Phenylpropyl 3-(4-methylpiperidino)propyl ether
3-Phenylpropyl 3-(3,5-*cis*-dimethylpiperidino)propyl ether
3-Phenylpropyl 3-(3,5-*trans*-dimethylpiperidino)propyl ether
3-Phenylpropyl 3-(3-methylpiperidino)propyl ether
3-Phenylpropyl 3-pyrrolidinopropyl ether
3-(4-Chlorophenyl)propyl 3-(4-methylpiperidino)propyl ether
3-(4-Chlorophenyl)propyl 3-(3,5-*cis*-dimethylpiperidino)propyl ether
3-(4-Chlorophenyl)propyl3-(3,5–*trans*-dimethylpiperidino)propyl ether
4-(6-Piperidinohexylamino)quinoline
2-Methyl 4-(3-piperidinopropylamino)quinoline
2-Methyl 4-(6-piperidinohexylamino)quinoline
7-Chloro-4-(3-piperidinopropylamino)quinoline
7-Chloro-4-(4-piperidinobutylamino)quinoline
7-Chloro-4-(8-piperidinooctylamino)quinoline
7-Chloro-4-(10-piperidinodecylamino)quinoline
7-Chloro-4-(12-piperidinododecylamino)quinoline
7-Chloro-4-(4-(3-piperidinopropoxy)phenylamino)quinoline
7-Chloro-4-(2-(4-(3-piperidinopropoxy)phenyl)ethylamino)quinoline
4-(6-Piperidinohexanoyl)phenyl 3-piperidinopropyl ether
5-Nitro-2-(5-piperidinopentylamino)pyridine
3-Nitro-2-(6-piperidinopentylamino)pyridine
5-Amino-2-(6-piperidinopentylamino)pyridine
2-(6-Piperidinohexylamino)quinoline
N-(4-Chlorobenzyl)-*N*′-cyclohexyl-3-piperidinopropyl isothiourea
2-(6-Piperidinohexylamino)benzothiazole
10-Piperidinodecylamine

3-Phenylpropyl 3-(*N,N*-diethylamino)propyl ether
N-(3-(N,N-Diethylamino)propyl)N'-phenylurea
N-Cyclohexylmethyl-N'-(3-piperidinopropyl)guanidine
N-(4-Bromobenzyl)-N'-(4-piperidinobutyl)sulphamide
3-Chloro-N-(4-piperidinobutyl)-N-methyl-benzene sulphonamide
N-(4-Chlorobenzyl)-2-(4-piperidinomethyl) phenyl) ethan amidine
1-(5-Cyclohexylpentanoyl)-1,4-bipiperidine
cis-1-(6-Cyclohexyl-3-hexen-1-yl)piperidine
trans-1-(6-Cyclohexyl-3-hexen-1-yl)piperidine
1-(2-(5,5-Dimethyl-1-hexin-1-yl)cyclopropyl)piperidine

for the preparation of a medicament acting as a ligand of the histamine H_3-receptors.

79. Pharmaceutical composition characterized in that it comprises as active ingredient, a therapeutically effective amount of a compound according to anyone of claim 1 to 78 in combination with a pharmaceutically acceptable vehicle or excipient.

80. Medicament acting as an antagonist and/or agonist of the histamine H_3-receptors, characterized in that it comprises as active ingredient, an effective amount of a compound according to anyone of claims 1 to 78.

81. Medicament according to anyone of claims 1 to 78, for the treatment of central nervous system disorders, in particular Alzheimer disease, mood and attention alterations, cognitive deficits in psychiatric pathologies, obesity, vertigo and motion sickness.

82. Medicament according to anyone of claims 1 to 78, having psychotropic effects, promoting wakefulness, attention, memory and improving mood, intended to be used in particular in the treatment of Alzheimer disease and other cognitive disorders in aged persons, depressive or asthenic states.

83. Medicament according to anyone of claims 1 to 78, having nootropic effects, intended to be used in particular in treatment to stimulate attention and memorization capacity.

84. Medicament according to anyone of claims 1 to 78, for the treatment of obesity, vertigo and motion sickness.

85. Medicament according to anyone of claims 1 to 78, for the treatment of CNS disorders, in particular of aged persons.

86. Medicament, acting as an histamine H_3-receptor agonist or partial agonist characterized in that it comprises as active ingredient, an effective amount of a compound according to anyone of claims 1 to 78.

87. Medicament according to anyone of claims 1 to 78 for exerting sedative, tranquillizing, anti-stress, analgesic and antimigraine activity, and for treating psychosomatic disorders, respiratory, allergic and rheumatic conditions of inflammatory conditions of the eye, urogenital system, digestive tract, skin, respiratory system and bronchi.

88. Medicament according to anyone of claims 1 to 78 and 87 for the treatment of asthma, bronchitis, rhinitis, tracheitis, myocardial dysfunctions and infarctions, gastric or duodenal ulcers, ulcerative colitis, Crohn's disease, irritable bowel syndrome, cystitis, metritis, urinary and faecal incontinence, urticaria, itching, arthritis, conjunctivitis and premenstrual syndrome.