ABSTRACT

A method of treating Parkinson’s disease in warm-blooded animals comprising administering to warm-blooded animals in need thereof an amount of a compound of the formula

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\text{(1)}
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in racemic, enantiomeric form or any combination of these forms, wherein the substituents are as defined in the specification.
DERIVATIVES OF HETEROCYCLES WITH 5 MEMBERS, THEIR PREPARATION AND THEIR USE AS MEDICAMENTS

[0001] The present invention relates to the use of compounds of general formula (I) for preparing a medicament intended to inhibit monoamine oxidases (MAO) and/or lipidic peroxidation and/or to act as modulators of the sodium channels. A subject of the invention is also, as medicaments, the compounds of general formula (II) defined hereafter. Moreover it relates to new compounds of general formula (III).

[0002] The compounds mentioned above often present 2 or 3 of the activities mentioned above, which confer advantageous pharmacological properties on them.

[0003] In fact, taking into account the potential role of the MAO's and ROS's ("reactive oxygen species", at the origin of lipidic peroxidation) in physiopathology, the new described derivatives corresponding to general formula (I) can produce beneficial or favorable effects in the treatment of pathologies where these enzymes and/or these radical species are involved. In particular:

[0004] disorders of the central or peripheral nervous system such as for example neurological diseases where Parkinson’s disease, cerebral or spinal cord traumatisms, cerebral infarction, sub arachnoid hemorrhage, epilepsy, ageing, senile dementia, Alzheimer’s disease, Huntington’s chorea, amyotrophic lateral sclerosis, peripheral neuropathies, pain can in particular be mentioned;

[0005] schizophrenia, depressions, psychoses;

[0006] disorders of the memory and the humour;

[0007] pathologies such as for example migraine;

[0008] behavioural disorders, bulimia and anorexia;

[0009] auto-immune and viral diseases such as for example lupus, AIDS, parasitic and viral infections, diabetes and its complications, multiple sclerosis.

[0010] addiction to toxic substances;

[0011] proliferative and inflammatory pathologies;

[0012] and more generally all the pathologies characterised by an excessive production of ROS’s and/or participation of MAO’s.

[0013] In all of these pathologies, experimental evidence exists which demonstrates the involvement of ROS’s (Free Radic. Biol. Med. (1996) 20, 675-705; Antioxid. Health Dis. (1997) 4 (Handbook of Synthetic Antioxidants), 1-52) as well as the involvement of MAO’s (Goodman & Gilman’s: The pharmacological basis of therapeutics, 9th ed., 1995, 431-519).

[0014] The advantage of a combination of the inhibitory activities of MAO and inhibition of lipidic peroxidation is for example well illustrated in Parkinson’s disease. This pathology is characterized by a loss of dopaminergic neurons of the nigrostriatal route the cause of which would in part be linked to an oxidizing stress due to ROS’s. The exogenic dopamine from L Dopa is used in therapeutics in order to maintain sufficient levels of dopamine. MAO inhibitors are also used with L Dopa to avoid its metabolic degradation but do not act on the ROS’s. Compounds which act both on MAO’s and ROS’s will therefore have a certain advantage.

[0015] Moreover, the character of the modulator of the sodium channels is very useful for therapeutic indications such as:

[0016] the treatment or prevention of pain, and in particular;

[0017] post-operative pain,

[0018] migraine,

[0019] neuropathic pain such as trigeminal neuralgia, post-herpetic pain, diabetic neuropathies, glossopharyngeal neuralgias, secondary radiculopathies and neuropathies associated with metastatic infiltrations, adiposis dolorosa and pain associated with burns,

[0020] central pain as a result of vascular cerebral accidents, thalamic lesions and multiple sclerosis, and

[0021] chronic inflammatory pain or pain linked to a cancer;

[0022] the treatment of epilepsy;

[0023] the treatment of disorders linked to neurodegeneration, and in particular:

[0024] vascular cerebral accidents,

[0025] cerebral traumatisms, and

[0026] neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis;

[0027] the treatment of bipolar disorders and irritable colon syndrome.

[0028] The concrete advantages of the presence in a compound of at least one of these activities is therefore clearly apparent from the above.

[0029] The European Patent Application EP 432 740 describes derivatives of hydroxyphenylthiazoles, which can be used in the treatment of inflammatory diseases, in particular rheumatic diseases. These derivatives of hydroxyphenylthiazoles show properties of trapping free radicals and inhibitors of the metabolism of arachidonic acid (they inhibit lipoxigenase and cyclooxygenase).

[0030] Other derivatives of hydroxyphenylthiazoles or hydroxyphenoloxazoles are described in the PCT Patent Application WO 99/09829. These have analgesic properties.

[0031] A certain number of derivatives of imidazoles with close or identical structures to those of the compounds corresponding to general formula (I) according to the invention have moreover been described by the Applicant in the PCT Patent Application WO 99/64401 as agonists or antagonists of somatostatin. However, said derivatives of imidazoles have therapeutic properties in fields different from those indicated above (suppression of the growth hormone and the treatment of acromegalia, treatment of the recurrence of stenosis, inhibition of the secretion of gastric acid and prevention of gastro-intestinal bleeding in particular).
Moreover, the compounds of general formula (A1) in which:

R1 represents one of the aryl, heteroaryl, aralkyl or cycloalkyl radicals optionally substituted by one to three substituents chosen independently from a halogen atom, the CF3, CN, OH, alkyl or alkoxy radical, SO2R9 with R9 representing NH2 or NHCH3,

X represents NR2, R2 representing H or alkyl;
Y represents N or CR3;
Z represents CR3 or N;

on the condition however that Y and Z are not both CR3 or N at the same time;

R3 represents H, alkyl, halogen, hydroxyalkyl or phenyl optionally substituted by 1 to 3 substituents chosen from H, CF3, CN, SO2NH2, OH, alkyl or alkoxy;
m represents 0, 1 or 2;
R4 represents H or alkyl;

when Z represents CR3, then R3 and R4 can also represent together —(CH2)n1— with n1 an integer from 2 to 4 or R2 and R4 can also represent together —(CH2)n2— with n2 an integer from 2 to 4;

R5 and R6 represent independently H, alkyl, alkoxy, aryl or aralkyl;

NR5R6 can also represent together (in particular):

[0033] the optionally substituted 2-(1,9,3,4-tetrahydroquinolyl) radical,

[0034] a

radical in which R7 represents one of the phenyl, benzyl or phenethyl radicals in which the phenyl ring can be substituted;

[0035] a

radical in which p is an integer from 1 to 3,

W is N and R8 represents H, CF3, one of the phenyl, pyridyl or pyrimidinyl radicals optionally substituted once to twice by radicals chosen from halogen, OH, alkyl or alkoxy, or

W is CH and R8 represents phenyl optionally substituted or aralkyl optionally substituted on the aryl group;

have been described in the PCT Patent Application WO 96/16040 as partial agonists or antagonists of the dopamine sub-receptors of the brain or as prodrug forms of such partial agonists or antagonists. Therefore these compounds would have useful properties in the diagnosis and treatment of affective disorders such as schizophrenia and depression as well as certain disorders of movement such as Parkinson’s disease.

It has also been described in the PCT Patent Application WO 98/27108 that certain amides of general formula (A2) in which:

R1 represents in particular an alkyl, optionally substituted phenyl or optionally substituted heterocyclic aryl radical;
R2 represents H or phenylethyl;
R4 represents H, quinolyl, 3,4-methylenedioxyphenoxypenyl or one of the phenyl or pyridyl radicals optionally substituted, by a radical or radicals chosen in particular from alkyl, alkoxy, alkylthio, optionally protected hydroxy, amino, alkylaminoo, dialkylamino;
R5 represents H or an imidazolyl, phenyl, nitrophenyl, phenylalkyl radical, or also a —CO—N(R7)(R8) radical, in which R7 and R8 represent independently H, phenyl, phenylethyl, alkyl or alkoxy;
or R4 and R5 in combination form a group of formula —CH═CH—CH═CH--;

Y is a phenylene radical substituted by a phenyl, phenoxy or phenylalkoxy radical, or a group of formula —CH(R3)--; in which R3 represents H or a radical of formula —(CH2)n— R6, in which R6 represents an optionally protected hydroxy, acyl, carboxy, acylamino, alkoxy, phenylalkoxy, alkylthio, optionally substituted phenyl, optionally substituted pyridyl, pyrazinyl, pyrimidinyl, furyl, imidazolyl, naphthyl, N-alkylindolyl or 3,4-methylenedioxyphenyl radical and n is an integer from 0 to 3;

R2 and R3 taken together with the carbon atoms which carry them can form a phenyl group;

X represents S or NR9;
R9 representing H, an alkyl or cycloalkyl radical, or also a benzyl radical optionally substituted once on its phenyl part by H, alkyl or alkoxy;

are inhibitors of the NO synthases and can be used to treat diseases which include in particular cardiovascular or cerebral ischemia, cerebral hemorrhage, disorders of the central nervous system, Alzheimer’s disease, multiple sclerosis, diabetes, hepatitis, migraine, rheumatoid arthritis and osteoporosis.
In a different field, the Applicant has itself previously described in the PCT Patent Application WO 98/58934 derivatives of amidines having the ability to inhibit NO synthases and/or lipidic peroxidation.

The Applicant has now unexpectedly discovered that certain intermediates of the first stages of synthesis of the amidines described in the PCT Patent Application WO 98/58934, and more generally certain derivatives of heterocycles with five members, namely the products of general formula (I) defined hereafter, have at least one of the three properties chosen from the following properties (and often even two of these three properties even sometimes all three at the same time):

- MAO inhibition properties;
- lipidic peroxidation inhibition properties; and
- properties of modulating the sodium channels.

These advantageous properties offer the advantage of opening up numerous uses for such compounds, in particular in the treatment of neurodegenerative diseases, and in particular those indicated previously, of pain or of epilepsy.

According to the invention, the compounds corresponding to general formula (I)

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\begin{align*}
\text{in racemic, enantiomeric form or any combination of these forms, in which Het is a heterocycle with 5 members comprising 2 heteroatoms and such that general formula (I) corresponds exclusively to one of the following sub-formulae:}
\end{align*}
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- \( R^4, R^5, R^6, R^7 \) and \( R^8 \) represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro or \( NR^{10}R^{11} \) radical, \( R^{12} \) and \( R^{13} \) representing, independently, a hydrogen atom, an alkyl radical or a —COR\(^{15}\) group, or \( R^{16} \) and \( R^{17} \) forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, \( R^{12} \) representing a hydrogen atom or an alkyl, alkoxy or \( NR^{10}R^{11} \) radical, \( R^{12} \) and \( R^{13} \) representing, independently, a hydrogen atom or an alkyl radical, or \( R^{13} \) and \( R^{14} \) forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, \( R^{19} \) represents a hydrogen atom, an alkyl radical or a —COR\(^{15}\) group,
- \( R^{15} \) representing a hydrogen atom or an alkyl, alkoxy or \( NR^{10}R^{11} \) radical,
- \( R^{16} \) and \( R^{17} \) representing, independently, a hydrogen atom or an alkyl radical, or \( R^{16} \) and \( R^{17} \) forming together with the nitrogen atom an optionally substituted heterocycle contain-
ing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, and W doesn’t exist, or represents a bond, or —NR', —S— or —NR', in which R' represents a hydrogen atom or an alkyl radical, either a 

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radical in which Q represents H, —OR', —SR', —NR'R', —NR'R'R, a phenyl radical optionally substituted by one or more substituents chosen independently from a halogen atom, an OH, cyano, nitro, alkyl, alkoxy or —NR'R radical and a group with two substituents representing together a methylenedioxy or ethylenedioxy radical, or also Q represents a —COPh, —SO2Ph or —CH3Ph radical, said —COPh, —SO2Ph or —CH3Ph radical being optionally substituted on its aromatic part by one or more of the substituents chosen independently from an alkyl or alkoxy radical and a halogen atom, 

R10 and R11 representing, independently, a hydrogen atom, an alkyl radical or a —COR12 group, or R10 and R11 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, R12 representing a hydrogen atom, an alkyl or alkoxy or NR'R' radical, 

R13 and R14 representing, independently, a hydrogen atom or an alkyl radical, or R13 and R14 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, 

R15 representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alky, OH, halogen, nitro and alkoxy radicals, 

R15 and R16 representing, independently, a hydrogen atom, an alkyl radical or a —CO—R16 radical, 

R25 representing an alkyl radical, 

and R19, R20 and R21 represent, independently, a hydrogen, a halogen, the OH or SR21 group, or an alkyl, cycloalkyl, alkoxyl, alkoxy, cyano, nitro, —SO2NR16 or —CONR15, —S(O)2R16, —NH(CO)R17, —CF3, —OCF3 or NR27—R28 radical, 

R25 representing a hydrogen atom or an alkyl radical, 

R27 and R28 representing, independently, a hydrogen atom, an alkyl radical or a —COR18 group, or R27 and R28 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, 

R49 and R55 representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy carbonyl radical, q representing an integer from 0 to 2, 

R56 and R77 representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical, 

R29 representing a hydrogen atom, an alkyl, alkoxy or —NR'R radical, 

R30 and R33 representing, independently, a hydrogen atom or an alkyl radical, or R30 and R33 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, or a 

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radical in which R52 represents a hydrogen atom or an alkyl radical, and T represents a —(CH2)m— radical with m=1 or 2, 

or finally a 

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radical in which R53 represents a hydrogen atom or an alkyl radical, 

[0044] Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms, —R34 and R35 representing, independently, a hydrogen atom or an alkyl radical, 

R36 and R37 representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substi-
tuted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or NR'R'' radicals,

R' and R'' representing, independently, a hydrogen atom, an alkyl radical or a —COR15 group, or R' and R'' forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrroldine, piperidine, piperazine, morpholine or thiomorpholine,

R'12 representing a hydrogen atom or an alkyl, alkoxy or NR'14 radical,

R'13 and R'14 representing, independently, a hydrogen atom or an alkyl radical, or R'13 and R'14 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrroldine, piperidine, piperazine, morpholine or thiomorpholine, and T represents a —(CH2)m — radical with m = 1 or 2,

or also A represents an alkyl, cycloalkyl or alkycycloalkyl radical,

X represents S or NR38,

R38 representing a hydrogen atom or an alkyl, cyanoalkyl, aralkyl, alkoxyalkyl or aralkyloxalkyl radical,

Y represents O or S;

R1 represents a hydrogen atom, an alkyl, amionoalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl, alkenyl, allenylalkyl, alkenyl, cyanoalkyl, (CH2)n — Z — R50, —(CH2)m — COR51, —(CH2)n — COOR51, —(CH2)n — CONHR51 or —SO,R51 radical, or also a radical chosen from the aryl, aralkyl, aryloxyalkyl, aralkyloxalkyl, aryloxalkyl, aralkyloxalkyl, heteroaryl and in particular pyridinyl, pyridinylalkyl or pyridinylalkyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, aryloxyalkyl, aralkyloxalkyl, aryloxalkyl, aralkyloxalkyl, heteroaryl, pyridinylalkyl or pyridinylalkyl radicals being optionally substituted by one or more substituents chosen independently from the halogen, alkyl, alkoxy, hydroxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, dialkylamino, —(CH2)n — Z — R59 or —(CHF)m — COR59 radicals,

Z1 and Z2 representing a bond, —O —, —NR41 or —S —, R59 and R61 representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl or cyanoalkyl radical,

R60 representing, independently each time that it occurs, a hydrogen atom or an alkyl, alkenyl, allenylalkyl, alkenyl, cyanoalkyl, alkoxy or NR54 radical,

R62 and R63 representing, independently each time that they occur, a hydrogen atom or an alkyl, allenylalkyl, alkenyl, alkenyl, or cyanoalkyl radical,

and R62 represents a hydrogen atom, an alkyl amionoalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl or —(CH2)n — NHCOR52 radical, or also one of the alkylalkyl or heteroaryalkyl radicals optionally substituted on the aryl or heteroaryl group by one or more of the groups chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrroldine, piperidine, piperazine, morpholine or thiomorpholine,

R70 and R71 representing independently an alkyl or alkoxy radical;

or R1 and R2, taken together with the carbon atom which carries them, form a carbocycle with 3 to 7 members;

B represents a hydrogen atom, an alkyl radical, a —(CH2)n — Z — R44 radical or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical,

Z representing a bond, —O —, —NR45 or —S —, R44 and R45 representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, alkoxy, allenyl, allenylalkyl or cyanoalkyl radical;

Ω represents one of the NR46OR57 or OR48 radicals, in which:

R46 and R47 represent, independently, a hydrogen atom or an alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkyl, allenylalkyl, alkenyl, cyanoalkyl, (CH2)n — Z — R50, —(CH2)m — COR51, —(CH2)n — COOR51, —(CH2)n — CONHR51 or —SO,R51 radical, or also a radical chosen from the aryl, aralkyl, aryloxyalkyl, aralkyloxalkyl, aryloxalkyl, aralkyloxalkyl, heteroaryl and in particular pyridinyl, pyridinylalkyl or pyridinylalkyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, aryloxyalkyl, aralkyloxalkyl, aryloxalkyl, aralkyloxalkyl, heteroaryl, pyridinylalkyl or pyridinylalkyl radicals being optionally substituted by one or more substituents chosen independently from the halogen, alkyl, alkoxy, hydroxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, dialkylamino, —(CH2)n — Z — R59 or —(CHF)m — COR59 radicals,

Z1 and Z2 representing a bond, —O —, —NR52 or —S —, R52 and R54 representing independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R55 and R56 representing, independently each time that they occur, a hydrogen atom, one of the cycloalkyl or cycloalkylalkyl radicals in which the cycloalkyl radical has 3 to 7 carbon atoms, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl, alkynyl, allenyl, allenylalkyl, alkenyl, cyanoalkyl or NR58R59 radical, or also an aryl or aralkyl radical, said aryl or aralkyl radical being able to be substituted by one or more of the substituents chosen independently from the halogen atom and an alkyl or alkoxy radical,

R58 and R59 representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,
R\(^5\) and R\(^6\) representing, independently, a hydrogen atom or a \(-(\text{CH})_k-Z'\text{R'}\) or \(-(\text{CH})_k-\text{COR}\) radical, Z' representing a bond, \(-\text{O}--\), \(-\text{NR}^7--\) or \(-\text{S}--\),

[0053] R\(^5\) and R\(^6\) representing, independently, a hydrogen atom or an alkyl, alkenyl, allenylalkyl, alkynyl, cyanoalkyl, aryl, aralkyl, arylcarboxyl, aralkykarboxyl, pyridinyl, pyridinylalkyl or pyridinylcarboxyl radical, the aryl or pyridinyl group of the aryl, aralkyl, arylcarboxyl, aralkykarboxyl, pyridinyl, pyridinylalkyl or pyridinylcarboxyl radicals being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, nitro, alkoxy, cyano, cyanoalkyl, \(-(\text{CH})_2-Z'\text{R}^6\) and \(-(\text{CH})_k-\text{COR}^4\) radicals,

R\(^6\) representing a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or NR\(^5\)R\(^6\) radical,

R\(^5\) and R\(^6\) representing, independently, a hydrogen atom or an alkyl, alkenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

Z\(^8\) representing a bond, \(-\text{O}--\), \(-\text{NR}^7--\) or \(-\text{S}--\),

R\(^5\) and R\(^6\) representing, independently, a hydrogen atom, an alkyl, alkenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

R\(^4\) representing a hydrogen atom, an alkyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or NR\(^5\)R\(^6\) radical,

R\(^8\) and R\(^9\) representing, independently, a hydrogen atom or an alkyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R\(^4\) represents a hydrogen atom or an alkyl, alkynyl or cyanoalkyl radical;

g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6;

it being understood that when Het is such that the compound of general formula (I) corresponds to general sub-formula (I)\(_4\), then:

A represents the 4-hydroxy-2,3-di-tert-butoxy-phenyl radical;

B, R\(^1\) and R\(^2\) all represent H; and finally

\(\Omega\) represents OH;

or pharmaceutically acceptable salts of the compounds of general formula (I);

can be used for preparing a medicament intended to have at least one of the following three activities:

[0054] to inhibit the monoamine oxydases, in particular monoamine oxidase B,

[0055] to inhibit lipidic peroxidation,

[0056] to have a modulating activity vis-à-vis the sodium channels.

[0057] According to preferred variants of the invention, these compounds have at least two of the activities mentioned above. In particular, they inhibit both the MAO's and trap the ROS's or they will have both an antagonist activity vis-à-vis the sodium channels and a trapping activity on the ROS's. In certain cases, the compounds of general formula (I) even combine the three activities.

[0058] This allows the compounds of general formula (I) to be of use in the treatment of the diseases mentioned previously such as being linked to MAO's, to lipid peroxidation and to the sodium channels.

[0059] By alkyl, unless otherwise specified, is meant a linear or branched alkyl radical containing 1 to 6 carbon atoms. By cycloalkyl, when no further detail is given, is meant a monocyclic carbon system containing 3 to 7 carbon atoms. By alkenyl, when no further detail is given, is meant a linear or branched alkyl radical containing 1 to 6 carbon atoms and having at least one unsaturation (double bond). By alkynyl, when no further detail is given, is meant a linear or branched alkyl radical containing 1 to 6 carbon atoms and having at least one double unsaturation (triple bond). By allenyl, is meant the \(-\text{CH}==\text{C}==\text{CH}_2\) radical. By carboxyclic or heterocyclic aryl, is meant a carboxyclic system (in particular, the phenyl radical which can be noted Ph in an abbreviated fashion) or heterocyclic system comprising at least one aromatic ring, a system being called heterocyclic when at least one of the rings which comprises it contains a heteroatom (O, N or S). By heterocycle, is meant a mono- or polycyclic system, said system comprising at least one heteroatom chosen from O, N and S and being saturated, partially or totally unsaturated or aromatic. By heteroaryl, is meant a heterocycle as defined previously in which at least one of the rings which comprises it is aromatic. By halalkyl, is meant an alkyl radical at least one of hydrogen atoms of which (and optionally all) is replaced by a halogen atom.

[0060] Moreover, by an optionally substituted radical is meant unless otherwise specified a radical comprising one or more substituents chosen independently from the group composed of a halogen atom and the alkyl and alkoxy radicals.

[0061] By alkylthio, alkoxy, haloalkyl, alkoxyalkyl, trifluoromethylalkyl, cycloalkylalkyl, haloalkoxy, aminooalkyl, alkenyl, alkynyl, allenylalkyl, cyanoalkyl and aralkyl radicals, is meant respectively the alklythio, alkoxy, haloalkyl, alkoxyalkyl, trifluoromethylalkyl, cycloalkylalkyl, haloalkoxy, aminooalkyl, alkenyl, alkynyl, allenylalkyl, cyanoalkyl and aralkyl radicals the alkyl radical (the alkyl radicals) of which have the meaning(s) indicated previously.

[0062] By heterocycle, is meant in particular the thiophene, piperidine, piperazine, quinoline, indoline and indole radicals. By linear or branched alkyl having 1 to 6 carbon atoms, is meant in particular the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, pentyl, neopentyl, isopentyl, hexyl, isohexyl radicals. Finally, by halogen, is meant the fluorine, chlorine, bromine or iodine atoms.
Preferably, the compounds according to the invention are such that they correspond to general formula (I):

\[
\text{Het}
\]

in racemic, enantiomeric form or any combination of these forms, in which Het is a heterocycle with 5 members comprising 2 heteroatoms and such that general formula (I) corresponds exclusively to one of the following subformulae:

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\begin{align*}
\text{(I)}_1 & \quad \text{radical in which } R^5, R^6, R^7 \text{ and } R^8 \text{ represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro or } NR^{19}R^{17} \text{ radical;} \\
\text{(I)}_2 & \quad \text{R}^9 \text{ represents a hydrogen atom or an alkyl radical, and } W \text{ doesn't exist, or represents a bond, or } -O- , -S- \text{ or } -NR^{18}-, \text{ in which } R^{18} \text{ represents a hydrogen atom or an alkyl radical;} \\
\text{(I)}_3 & \quad \text{radical in which } Q \text{ represents } H, -OR^{22}, -SR^{22}, -NR^{23}R^{24}, \text{ a phenyl radical optionally substituted by one or more substituents chosen independently from a halogen atom, an } OH, \text{ cyano, nitro, alkoxy or } NR^{19}R^{17} \text{ radical and a group with two substituents representing together a methylenedioxy or ethylenedioxy radical, or also } Q \text{ represents a } -COPh, -OPh, -SPh, -SO_2Ph \text{ or } -CH_2Ph \text{ radical, said } -COPh, -OPh, -SPh, -SO_2Ph \text{ or } -CH_2Ph \text{ radical being optionally substituted on its aromatic part by one or more of the substituents chosen independently from an alkyl or alkoxy radical and a halogen atom, } R^{10} \text{ and } R^{11} \text{ representing, independently, a hydrogen atom or an alkyl radical, or } R^{10} \text{ and } R^{11} \text{ forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the } O, N \text{ and } S \text{ atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,} \\
\text{(I)}_4 & \quad R^{22} \text{ representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, } OH, \text{ halogen, nitro and alkoxy radicals,} \\
\text{radical in which } R^3 \text{ represents a hydrogen atom, the } OH \text{ group or an alkoxy or alkyl radical,}
\end{align*}
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in which

A represents

either a

\[
\begin{align*}
\text{(I)}_5 & \quad \text{radical in which } R^1 \text{ represents a hydrogen atom, the } OH \text{ group or an alkoxy or alkyl radical,}
\end{align*}
\]
R\(^{25}\) representing an alkyl radical, and R\(^{19}\), R\(^{20}\) and R\(^{21}\) represent, independently, a hydrogen, a halogen, the OH or SR\(^{26}\) group, or an alkyl, cycloalkyl, alkenyl, alkoxy, cyano, nitro, —SO\(_2\)NH\(_1\)R\(^{49}\), —CONHR\(^{55}\), —SO\(_2\)NH\(^{1}\)R\(^{56}\), —NH(CO)R\(^{37}\), —CF\(_3\), —OCF\(_3\) or NR\(^{27}\)R\(^{28}\) radical, R\(^{26}\) representing a hydrogen atom or an alkyl radical, R\(^{27}\) and R\(^{28}\) representing, independently, a hydrogen atom, an alkyl radical or a —COR\(^{29}\) group, or R\(^{27}\) and R\(^{28}\) forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, R\(^{49}\) and R\(^{55}\) representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical, q representing an integer from 0 to 2, R\(^{56}\) and R\(^{57}\) representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical, R\(^{59}\) representing a hydrogen atom, an alkyl, alkoxy or —NR\(^{51}\) radical, R\(^{30}\) and R\(^{31}\) representing, independently, a hydrogen atom or an alkyl radical, or R\(^{31}\) and R\(^{31}\) forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, or a radical in which R\(^{32}\) represents a hydrogen atom or an alkyl radical, and T represents a —(CH\(_2\))\(_m\)— radical with m=1 or 2, or finally a radical in which R\(^{33}\) represents a hydrogen atom or an alkyl, —Σ-NR\(^{34}\)R\(^{35}\) or —Σ-CHR\(^{36}\)R\(^{37}\) radical, Σ representing a linear or branched alkylenic radical containing 1 to 6 carbon atoms, R\(^{34}\) and R\(^{35}\) representing, independently, a hydrogen atom or an alkyl radical, R\(^{36}\) and R\(^{37}\) representing, independently, a hydrogen atom or a carbo cyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or NR\(^{1}\)R\(^{41}\) radicals, R\(^{10}\) and R\(^{31}\) representing, independently, a hydrogen atom, an alkyl radical, or R\(^{10}\) and R\(^{31}\) forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, and T represents a —(CH\(_2\))\(_m\)— radical with m=1 or 2, or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical, X represents S or NR\(^{48}\), R\(^{39}\) representing a hydrogen atom or an alkyl, cyanoalkyl, aralkyl, alky carbonyl or aralky carbonyl radical, Y represents O or S; R\(^{1}\) represents a hydrogen atom, an alkyl, aminoalkyl, alkoxyalkyl, cycloalkyl, cycloalky alky l, trifluoromethylalkyl, alkenyl, allenyl, allenylalkyl, alkenyl, cyanoalkyl, —(CH\(_{—}\))\(_{p}\)-Z\(^{39}\), —(CH\(_{—}\))\(_{k}\)-COR\(^{40}\), —(CH\(_{—}\))\(_{k}\)-NH-COR\(^{70}\) aryl, aralkyl, aryl carbonyl, heteroarylalkyl or aralky carbonyl radical, the aryl group of the aryl, aralkyl, aryl carbonyl, heteroarylalkyl or aralky carbonyl radicals itself being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, alkoxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, —(CH\(_{—}\))\(_{k}\)-Z\(^{39}\)-COR\(^{40}\) radicals, Z\(^{1}\) and Z\(^{2}\) representing a bond, —O—, —NR\(^{41}\)— or —S—, R\(^{39}\) and R\(^{41}\) representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alky nyl or cyanoalkyl radical, R\(^{40}\) representing, independently each time that it occurs, a hydrogen atom or an alkyl, allenyl, allenylenealkyl, alkenyl, alkenyl, cyanoalkyl, alkoxy or NR\(^{42}\)R\(^{43}\) radical, R\(^{42}\) and R\(^{43}\) representing, independently each time that they occur, a hydrogen atom or an alkyl, allenyl, allenylenealkyl, alkenyl, alkenyl, cyanoalkyl radical, and R\(^{2}\) represents a hydrogen atom, an alkyl, aminoalkyl, alkoxyalkyl, cycloalkyl, cycloalky alky l, trifluoromethylalkyl or —(CH\(_{—}\))\(_{m}\)-NiICOR\(^{71}\) radical, or also one of the arylalkyl or heteroarylalkyl radicals optionally substituted on the aryl or heteroaryl group by one or more of the groups chosen independently from the group composed of a halogen atom and an alkyl, alkoxy, hydroxy, cyano, nitro, amino, alkylamino or dialkylamino radical, R\(^{70}\) and R\(^{7}\) representing independently an alkyl or alkoxy radical;
or R¹ and R², taken together with the carbon atom which carries them, form a carbocycle with 3 to 7 members;

B represents a hydrogen atom, an alkyl radical, a -(CH₂)₃⁻Z⁻R⁺⁻ radical or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, a linear or branched alkylox radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical,

Z⁵ representing a bond, —O—, —NR⁴⁵— or —S—,
R⁴⁴ and R⁴⁵ representing, independently, an hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenlyalkyl or cyanoolkyl radical;
Ω represents one of the NR⁴⁶R⁴⁷ or OR⁴⁸ radicals, in which:
R⁴⁶ and R⁴⁷ represent, independently, a hydrogen atom or an alkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, allenyl, allenlyalkynyl, cyanoolkyl, -(CH₂)₃⁻Z⁻R⁺⁻, -(CH₂)₃⁻COR⁻³¹, -(CH₂)₃⁻CONR⁻³¹ or —SO⁻R⁻ radical, or also a radical chosen from the aryl, aralkyl, arylalkyl, arylalkynyl, aromatic, non-aromatic heterocycle with 4 to 8 members, the elements of the group being chosen from a group composed of —CH(R⁵³)—, —NR⁵⁴—, —O—, —S— and —CO—, said heterocycle being able to be for example an azetidin, a piperazine, a homopiperazine, a 3,5-dioxopiperazine, a piperidine, a pyrrolidine, a morpholine or a thiomorpholine,
R⁵⁰ and R⁵¹ representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, alkoxy, allenyl, allenlyalkynyl or cyanoolkyl radical,
R⁵² representing, independently each time that they occur, a hydrogen atom, one of the cycloalkyl or cycloalkylalkyl radicals in which the cycloalkyl radical has 3 to 7 carbon atoms, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkyl, alkenyl, allenyl, allenlyalkynyl, cyanoolkyl, alkoxyalkyl or -NR⁵⁶R⁵⁷ radical, or an aryl or alkylalkyl radical, said aryl or alkylalkyl radical being able to be substituted by one or more of the substituents chosen independently from a halogen atom, an alkyl or alkoxy radical,
R⁵⁸ and R⁵⁹ representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenlyalkyl or cyanoolkyl radical,
R⁶⁰ and R⁶¹ representing, independently, a hydrogen atom or an alkyl, alkenyl, allenyl, allenlyalkyl, alkynyl, cyanoolkyl, aryl, alkenyl, arylalkyl, alkenylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylalkynyl radical, the aryl or pyridinyl group of the aryl, aralkyl, aralkylcarbonyl, aralkylalkynyl, pyridinyl, pyridinylalkyl or pyridinylalkynyl radicals being optionally substituted by one or more substituents chosen independently from the group composed of the aryl, halogen, nitro, alkoxy, cyanooalkyl, -(CH₂)₃⁻Z⁻R⁺⁻ and -(CH₂)₃⁻COR⁻⁶¹ radicals,
R⁶² representing a hydrogen atom, an alkyl, allenlyalkyl, alkynyl, cyaanoolkyl, alkoxy or NR⁶⁵R⁶⁶ radical,
R⁶⁵ and R⁶⁶ representing, independently, a hydrogen atom or an alkyl, allenlyalkyl, alkenyl, alkynyl or cyanoolkyl radical,
Ω represents one of the NR⁶⁷R⁶⁸ or OR⁶⁹ radicals, in which:
R⁶⁷ and R⁶⁸ represent, independently, a hydrogen atom, an alkyl, allenlyalkyl, alkenyl, alkynyl or cyanoolkyl radical;
Ω represents one of the NR⁶⁹R⁷⁰ or OR⁷¹ radicals, in which:
Ω represents one of the NR⁷²R⁷³ or OR⁷⁴ radicals, in which:
g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6;
and R⁷⁵ represents a hydrogen atom or an alkyl alkoxy or cyanoolkyl radical;
it being understood that when Het is such that the compound of general formula (I) corresponds to general sub-formula (II), then:
A exclusively represents the 4-hydroxy-2,3-di-tetrahydrobiphenyl-phenyl radical;
B represents H;
R¹ and R² both represent H; and finally
Ω represents OH;
or salts of said compounds

[0064] According to the invention, there will Generally be preferred the compounds of general formula (I) in which at least one of the following radicals is found:

[0065] A representing:

[0066] either the

[0067] radical in which R² represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,
or the

![Chemical Structure Image]

 radical in which \( R^4, R^5, R^6, R^7 \) and \( R^8 \) represent, independently, a hydrogen atom, the \( \text{OH} \) group or an alkyl or alkoxy radical,

\[ \text{[0070]} \]

\( R^9 \) represents a hydrogen atom or an alkyl radical,

\[ \text{[0071]} \]

and \( W \) does not exist, or represents a bond, \(-\text{O}-, -\text{S}-\) or \(-\text{NR}^\text{R'}\), \( R^\text{R'} \) representing a hydrogen atom or an alkyl radical;

\[ \text{[0072]} \]

or the

![Chemical Structure Image]

 radical in which \( Q \) represents \( H, \text{OR}^\text{R'}, \text{SR}^\text{R'} \) or a phenyl radical optionally substituted by one substituent or substituents chosen independently from a halogen atom, an \( \text{OH} \), cyano, nitro, alkyl, alkoxy or \(-\text{NR}^\text{R'}\) radical and a group of two substituents together representing a methylenedioxy or ethylenedioxy radical, or also \( Q \) represents an \(-\text{OPh}, -\text{SPh}, -\text{SO}_{2}\text{Ph} \) or \(-\text{CH}_{2}\text{Ph} \) radical, said \(-\text{OPh}, -\text{SPh}, -\text{SO}_{2}\text{Ph} \) or \(-\text{CH}_{2}\text{Ph} \) radical being optionally substituted on its aromatic part by a substituent or substituents chosen from an alkyl or alkoxy radical and a halogen atom,

\[ \text{[0073]} \]

\( R^{10} \) and \( R^{11} \) representing, independently, a hydrogen atom or an alkyl radical;

\[ \text{[0074]} \]

\( R^{22} \) representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, \( \text{OH}, \text{halogen, nitro and alkoxy radicals,} \)

\[ \text{[0075]} \]

and \( R^{19}, R^{20} \) and \( R^{21} \) represent, independently, a hydrogen, a halogen, the \( \text{OH} \) or \( \text{SR}^{25} \) group, or an alkyl, cycloalkyl, alkenyl, alkoxy, cyano, nitro, \(-\text{SO}_{2}\text{NHR}^{25}, -\text{CONHR}^{25}, -\text{S(O)R}^{25}, -\text{N(CO)R}^{27}, -\text{CF}_{3}, -\text{OCF}_{3} \) or \( \text{NR}^{27}\text{R}^{28} \) radical,

\[ \text{[0076]} \]

\( R^{25} \) representing a hydrogen atom or an alkyl radical,

\[ \text{[0077]} \]

\( R^{27} \) and \( R^{28} \) representing, independently, a hydrogen atom, an alkyl radical or a \(-\text{COR}^{29} \) group, or also \( R^{27} \) and \( R^{28} \) forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from \(-\text{CH}_{2}, -\text{NH}, -\text{N}, -\text{O} \),

\[ \text{[0078]} \]

\( R^{30} \) and \( R^{31} \) representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

\[ \text{[0079]} \]

\( q \) representing an integer from 0 to 2,

\[ \text{[0080]} \]

\( R^{30} \) and \( R^{31} \) representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

\[ \text{[0081]} \]

\( R^{30} \) representing a hydrogen atom, an alkyl, alkoxy or \(-\text{NR}^{25}\text{R}^{25} \) radical,

\[ \text{[0082]} \]

\( R^{30} \) and \( R^{31} \) representing, independently, a hydrogen atom or an alkyl radical,

\[ \text{[0083]} \]

or the

![Chemical Structure Image]

 radical in which \( R^{32} \) represents a hydrogen atom or an alkyl radical, and \( T \) represents the \(-\text{(CH}_{2}^{2})_{2}-\) radical

\[ \text{[0085]} \]

radical in which \( R^{33} \) represents a hydrogen atom or an alkyl, \(-\Sigma\text{-NR}^{25}\text{R}^{25} \) or \(-\Sigma\text{-CHR}^{25}\text{R}^{25} \) radical,

\[ \text{[0087]} \]

\( \Sigma \) representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,

\[ \text{[0088]} \]

\( R^{34} \) and \( R^{35} \) representing, independently, a hydrogen atom or an alkyl radical,

\[ \text{[0089]} \]

\( R^{36} \) and \( R^{37} \) representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, \( \text{OH}, \text{halogen, nitro, alkoxy or } \text{NR}^{25}\text{R}^{25} \) radicals,

\[ \text{[0090]} \]

\( R^{36} \) and \( R^{37} \) representing, independently, a hydrogen atom, an alkyl radical or a \(-\text{COR}^{25} \) group, or \( R^{36} \) and \( R^{31} \) forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the \( O, \text{N and S} \) atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,
[0092] R^12 representing a hydrogen atom or an alkyl, alkoxyl or NR^1^R^2^ radical,

[0093] R^1^3 and R^1^4 representing, independently, a hydrogen atom or an alkyl radical, or R^1^3 and R^1^4 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, such as for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

[0094] and T represents the —(CH_2)— radical;

[0095] \( \Omega \) representing:

[0096] either the NR^1^R^2^ radical in which R^1^ and R^2^ represent, independently, a hydrogen atom or an alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, —(CH_2)_k—COR^3^, —COOR^3^ or —SO_2—R^3^ radical or also a radical chosen from the aryl, aralkyl, aryloxalkyl, aryalkyl, arylcarboxyl, arylamino, aralkylcarboxyl, heteroaryl radicals and in particular pyridinyl, pyridinylalkyl or pyridinylcarboxyl, the aryl or heteroaryl group of said aryl, aralkyl, aryloxalkyl, aryalkyl, arylcarboxyl, arylamino, aralkylcarboxyl, heteroaryl, pyridinylalkyl or pyridinylcarboxyl radicals being optionally substituted by a substituent or substituents chosen independently from halogen, alkyl, alkoxy, hydroxy, nitro, cyano, cyanoalkyl, amino, alkyamine, dialkylamin, —(CH_2)_k—Z^R^3^ and —(CH_2)_k—COR^3^;

[0097] R^5^ representing a hydrogen atom or an alkyl, alkenyl, alkynyl or alkoxycarboxyl radical

[0098] or the OH radical;

[0099] Moreover, when A represents the radical, the Q radical is preferably found in para position with respect to the heterocycle Het.

[0100] Generally, all the preferences relating to subgroups of compounds of general formula (I) presented below remain applicable with respect to the use of compounds of general formula (I) as defined previously for the preparation of medicaments intended to inhibit monoamine oxidases, in particular monoamine oxidase B, to inhibit lipid peroxidation, to have a modulatory activity on the sodium channels or to have two of the three activities or the three activities mentioned previously.

[0101] According to a particular variant of the invention, the compounds of general formula (I) or their salts are more especially intended to have an inhibitory activity on MAO’s and/or ROS’s and they will therefore be preferably such that:

A represents

[0102] either a

radical in which R^3^ represents a hydrogen atom, the OH group or an alkyl or alkyl radical,

or a

radical in which R^5^, R^6^, R^7^ and R^8^ represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy or NR^1^R^2^ radical,

R^10^ and R^1^ representing, independently, a hydrogen atom or an alkyl radical, or R^10^ and R^1^ forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

R^9^ represents a hydrogen atom or an alkyl radical,

and W doesn’t exist, or represents a bond, or —O—, —S— or —NR^1^—, in which R^1^ represents a hydrogen atom or an alkyl radical,

or a

radical in which Q represents —OR^2^, —SR^2^, —NR^2^R^3^, a phenyl radical optionally substituted by one or more of the substituents chosen independently from a halogen atom and an OH, cyano, nitro, alkyl, alkoxy or NR^1^R^2^ radical,

R^10^ and R^1^ representing, independently, a hydrogen atom or an alkyl radical, or R^10^ and R^1^ forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by


the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine.

R\textsuperscript{32} representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,

R\textsuperscript{33} and R\textsuperscript{28} representing, independently, a hydrogen atom or an alkyl radical,

and R\textsuperscript{19}, R\textsuperscript{20} and R\textsuperscript{21} represent, independently, a hydrogen, a halogen, the OH or SR\textsuperscript{26} group, or an alkyl, alkenyl, alkoxy or NR\textsuperscript{27}R\textsuperscript{28} radical,

R\textsuperscript{26} representing a hydrogen atom or an alkyl radical,

R\textsuperscript{27} and R\textsuperscript{28} representing, independently, a hydrogen atom or an alkyl radical, or R\textsuperscript{27} and R\textsuperscript{28} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms; said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

or a

\[
\begin{align*}
R^{22}O & \quad \text{CH} \\
& \quad \text{CH}_3 \\
& \quad \text{CH}_3 \\
& \quad \text{H}_C \\
& \quad \text{O} \\
\end{align*}
\]

radical in which R\textsuperscript{22} represents a hydrogen atom or an alkyl radical,

and T represents a \( -(\text{CH}_2)_m - \) radical with \( m=1 \) or 2,

or finally a

\[
\begin{align*}
& \quad \text{R}^{21} \\
\end{align*}
\]

radical in which R\textsuperscript{21} represents a hydrogen atom or an alkyl radical,

\( \sum - \text{NR}^{24}R^{39} \) or \( \Sigma - \text{CHR}^{39}R^{37} \) radical,

\( \Sigma \) representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,

R\textsuperscript{34} and R\textsuperscript{35} representing, independently, a hydrogen atom or an alkyl radical,

R\textsuperscript{36} and R\textsuperscript{37} representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or NR\textsuperscript{30}R\textsuperscript{11} radicals,

R\textsuperscript{13} and R\textsuperscript{14} representing, independently, a hydrogen atom or an alkyl radical, or R\textsuperscript{13} and R\textsuperscript{14} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, and T represents a \( -(\text{CH}_2)_n - \) radical with \( n=1 \) or 2,

X represents S or NR\textsuperscript{38},

R\textsuperscript{38} representing a hydrogen atom or an alkyl or cyanoalkyl radical,

Y represents O or S;

R\textsuperscript{1} represents a hydrogen atom, an alkyl, cycloalkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, \( -(\text{CH}_2)_m - \text{Z}^{39} \) or \( -(\text{CH}_2)_m - \text{COR}^{39} \) ary1, aralkyl, arylicarbonyl, or aralkylcarbonyl radical, the ary1 group of the aryl, aralkyl, arylicarbonyl, or aralkylcarbonyl radicals being itself optionally substituted by a substituent or substituents chosen from the group constituted by the alkyl, haloxy, nitro, cyano, cyanoalkyl, \( -(\text{CH}_2)_m - \text{Z}^{39} \) or \( -(\text{CH}_2)_m - \text{COR}^{39} \) radicals,

Z\textsuperscript{1} and Z\textsuperscript{2} representing a bond, \( -O- \), \( -\text{NR}^{41} - \) or \( -S- \),

R\textsuperscript{39} and R\textsuperscript{40} representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkylnyl, alkoxy or cyanoalkyl radical,

R\textsuperscript{40} representing, independently each time that it occurs, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, alkoxyl, OR\textsuperscript{40}R\textsuperscript{43} radical,

R\textsuperscript{41} and R\textsuperscript{42} representing, independently each time that they occur, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkynyl, alkylnyl or cyanoalkyl radical,

and R\textsuperscript{2} represents a hydrogen atom or an alkyl radical

B represents a hydrogen atom or a \( -(\text{CH}_2)_m - \text{Z}^{44} \) radical,

Z\textsuperscript{3} representing a bond, \( -O- \), \( -\text{NR}^{45} - \) or \( -S- \),

R\textsuperscript{44} and R\textsuperscript{45} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkylnyl, allenylalkyl or cyanoalkyl radical;

\( \Omega \) represents one of the NR\textsuperscript{46}R\textsuperscript{37} or OR\textsuperscript{46} radicals, in which:

R\textsuperscript{46} and R\textsuperscript{47} represent, independently, a hydrogen atom or an alkyl, cycloalkyl, alkenyl, alkylnyl, allenylalkyl, cyanoalkyl, \( -(\text{CH}_2)_m - \text{Z}^{50} \) or \( -(\text{CH}_2)_m - \text{COR}^{53} \) radical, or also a radical chosen from the aryl, aralkyl, arylicarbonyl, arylicarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, arylicarbonyl, arylicarbonyl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more of the substituents chosen independently from halogen, alkyl, haloxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, \( -(\text{CH}_2)_m - \text{Z}^{53} \), \( -(\text{CH}_2)_m - \text{COR}^{53} \) and \( -(\text{CH}_2)_m - \text{COOR}^{54} \),

Z\textsuperscript{4} and Z\textsuperscript{5} representing a bond, \( -O- \), \( -\text{NR}^{50} - \) or \( -S- \),

or R\textsuperscript{46} and R\textsuperscript{47} taken together form with the nitrogen atom a non aromatic heterocycle with 4 to 8 members, the elements of the chain being chosen from a group composed of \( -\text{CH}R^{53} - \), \( -\text{NR}^{54} - \), \( -\text{O}- \), \( -\text{S}- \) and \( -\text{CO}- \),

or
said heterocycle being able to be for example an azetidine, a piperazine, a homopiperazine, a 3,5-dioxopiperazine, a piperidine, a pyrrolidine, a morpholine or a thiomorpholine,

R$^{50}$ and R$^{57}$, representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R$^{51}$ representing, independently each time that they occur, a hydrogen atom, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl or NR$^{56}$R$^{59}$ radical,

R$^{58}$ and R$^{59}$ representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, alkoxy, allenylalkyl or cyanoalkyl radical,

R$^{62}$ and R$^{63}$ representing, independently, a hydrogen atom or a radical in which R$^3$ represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

A radical in which R$^4$, R$^5$, R$^6$, R$^7$ and R$^8$ represent, independently, a hydrogen atom, or an alkyl or alkoxy radical,

and R$^{48}$ represents a hydrogen atom or an alkyl, alkenyl or cyanoalkyl radical;

and R$^{48}$ represents a hydrogen atom or an alkyl, alkenyl or cyanoalkyl radical;

g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6.

[0103] More preferentially, the compounds of general formula (I) (or their salts), when they are intended to have an inhibitory activity on MAO’s and/or ROS’s, will be such that:
radical in which \( R^2 \) represents a hydrogen atom or an alkyl radical,

and \( T \) represents a \(-\text{(CH}_2\text{)}_m-\) radical with \( m=1 \) or 2,

or finally a \(-\text{(CH}_2\text{)}_m-\text{N}^+\text{R'R'}\) radical in which \( R' \) represents a hydrogen atom or an alkyl radical,

\[ \Sigma \text{ representing a linear or branched alkyne radical containing 1 to 6 carbon atoms,} \]

\( R^{14} \) and \( R^{15} \) representing, independently, a hydrogen atom or an alkyl radical,

\( R^{16} \) and \( R^{17} \) representing, independently, a hydrogen atom or a carboxyl or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro or alkoxy radicals,

and \( T \) represents a \(-\text{(CH}_2\text{)}_m-\) radical with \( m=1 \) or 2,

\( X \) represents \( S \) or \( NR^2 \),

\( R^{38} \) representing a hydrogen atom or an alkyl or cyanocarbonyl radical,

\( Y \) represents \( O \) or \( S \),

\( R^1 \) represents a hydrogen atom, an alkyl, cycloalkyl, alkenyl, allenyl, allenylalkyl, alkenyl, cyanoalkyl, \(-\text{(CH}_2\text{)}_m-\text{Z}^R\text{Z}^2\text{R}^2\), \(-\text{(CH}_2\text{)}_m-\text{COR}^R\text{Z}^R\text{Z}^2\text{R}^2\), \(-\text{ary, aralkyl, arylecarbonyl, or aralkylecarbonyl radical, the aryl group of the aryl, aralkyl, arylecarbonyl, or aralkylecarbonyl radicals being itself optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, alkoxy, nitro, cyano, cyanoalkyl, \(-\text{(CH}_2\text{)}_m-\text{Z}^R\text{Z}^2\text{R}^2\) or \(-\text{(CH}_2\text{)}_m-\text{COR}^R\text{Z}^R\text{Z}^2\text{R}^2\) radicals,} \]

\( Z^1 \) and \( Z^2 \) representing a bond, \(-\text{O}^2\text{R}^{41} \) or \(-\text{S}^2\text{R}^{41} \),

\( R^{39} \) and \( R^{41} \) representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl or cyanoalkyl radical,

\( R^{40} \) representing, independently each time that it occurs, a hydrogen atom or an alkyl, allene, allenealkyl, alkenyl, alkynyl, cyanocarbonyl, alkoxy or \( NR^2 \text{R}^{39} \) radical,

\( R^{42} \) and \( R^{43} \) representing, independently each time that they occur, a hydrogen atom or an alkyl, allene, allenealkyl, alkenyl, alkynyl or cyanoalkyl radical,

and \( R^2 \) represents a hydrogen atom or an alkyl radical.

\( B \) represents a hydrogen atom or a \(-\text{(CH}_2\text{)}_m-\text{Z}^R\text{Z}^2\text{R}^4\) radical,

\( Z^3 \) representing a bond, \(-\text{O}^3\text{R}^{45} \) or \(-\text{S}^3\text{R}^{45} \),

\( R^{44} \) and \( R^{45} \) representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenealkyl or cyanoalkyl radical;

\( \Omega \) represents one of the \( NR^2 \text{R}^{47} \) or \( OR^2 \text{R}^{48} \) radicals, in which: \( R^{46} \) and \( R^{47} \) represent, independently, a hydrogen atom or an alkyl, cycloalkyl, alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, \(-\text{(CH}_2\text{)}_m-\text{Z}^R\text{Z}^2\text{R}^2\text{R}^{46} \) or \(-\text{(CH}_2\text{)}_m-\text{COR}^R\text{Z}^R\text{Z}^2\text{R}^2\text{R}^{46} \) radical or also a radical chosen from the aryl, aralkyl, arylecarbonyl, aralkylecarbonyl, pyridinyl, pyridinylalkyl or pyridinylecarbonyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, arylecarbonyl, aralkylecarbonyl, pyridinylalkyl or pyridinylecarbonyl radicals being optionally substituted by one or more of the substituents chosen independently from halogen, alkyl, alkoxy, nitro, cyano, cyanoalkyl, amino, alkenylamino, dialkylamino, \(-\text{(CH}_2\text{)}_m-\text{Z}^R\text{Z}^2\text{R}^{40} \), \(-\text{(CH}_2\text{)}_m-\text{COR}^R\text{Z}^R\text{Z}^2\text{R}^{40} \) and \(-\text{(CH}_2\text{)}_m-\text{COOR}^R\text{Z}^R\text{Z}^2\text{R}^{40} \),

\( Z^4 \) and \( Z^5 \) representing a bond, \(-\text{O}^5\text{R}^{42} \) or \(-\text{S}^5\text{R}^{42} \),

or \( R^{46} \) and \( R^{47} \) taken together form with the nitrogen atom a non-aromatic heterocycle with 4 to 8 members, the elements of the chain being chosen from a group comprising \(-\text{CH}^R(\text{C}^2\text{)} \), \(-\text{NR}^{44} \), \(-\text{O}^{44} \), \(-\text{S}^{44} \) and \(-\text{CO}^{44} \), said heterocycle being able to be for example an azetidine, a piperazine, a homopiperazine, a 3,5-dioxopiperazine, a piperidine, a pyrrolidine, a morpholine or a thiomorpholine.

\( R^{50} \) and \( R^{52} \) representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

\( R^{51} \) representing, independently each time that they occur, a hydrogen atom, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkyl, alkenyl, allenylalkyl, cyanoalkyl or \( NR^2 \text{R}^{55} \) radical,

\( R^{58} \) and \( R^{59} \) representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenylalkyl or cyanoalkyl radical,

\( R^{53} \) and \( R^{54} \) representing, independently, a hydrogen atom or a \(-\text{(CH}_2\text{)}_m-\text{Z}^R\text{Z}^2\text{R}^{50} \) or \(-\text{(CH}_2\text{)}_m-\text{COR}^R\text{Z}^R\text{Z}^2\text{R}^{50} \) radical,

\( Z^6 \) representing a bond, \(-\text{O}^6\text{R}^{42} \) or \(-\text{S}^6\text{R}^{42} \),

\( R^{60} \) and \( R^{62} \) representing, independently, a hydrogen atom or an alkyl, alkenyl, allenylalkyl, alkenyl, cyanoalkyl, aryl, aralkyl, arylecarbonyl, pyridinyl, pyridinylalkyl or pyridinylecarbonyl radical, the aryl or pyridinyl group of the aryl, aralkyl, arylecarbonyl, allenyl, allenylalkyl, cyanoalkyl, pyridinyl, pyridinylalkyl or pyridinylecarbonyl radicals being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, nitro, alkoxy, cyano, cyanocarbonyl, \(-\text{(CH}_2\text{)}_m-\text{Z}^R\text{Z}^2\text{R}^{65} \) and \(-\text{(CH}_2\text{)}_m-\text{COR}^R\text{Z}^R\text{Z}^2\text{R}^{65} \) radicals,

\( R^{61} \) representing a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or \( NR^2 \text{R}^{58} \) radical,

\( R^{65} \) and \( R^{66} \) representing, independently, a hydrogen atom or an alkyl, alkenyl, allenylalkyl, alkynyl, cyanoalkyl radical,

\( Z^8 \) representing a bond, \(-\text{O}^8\text{R}^{47} \) or \(-\text{S}^8\text{R}^{47} \),

\( R^{63} \) and \( R^{67} \) representing, independently, a hydrogen atom, an alkyl, allenylalkyl, alkynyl, alkynyl, cyanoalkyl, alkoxy or \( NR^2 \text{R}^{58} \) radical,
R^{58} and R^{59} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkylnyl or cyanoalkyl radical,

and R^{48} represents a hydrogen atom or an alkyl, alkylnyl or cyanoalkyl radical;

g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6.

As regards the compounds of general formula (I) (or their salts) more especially intended to have an inhibitory activity on MAO's and the ROS's, the said compounds having at least one of the following characteristics will generally be preferred:

the compound corresponds to general sub-formula (I), or (I), in which X represents S, the compounds corresponds to general formula (I), in which Y represents O or the compound corresponds to general sub-formula (Ia),

A represents the radical

either the

radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, or an alkyl or alkoxy radical,

R^9 represents a hydrogen atom,

and W doesn’t exist, or represents a bond, —O— or —S—,

or the

radical in which Q represents OH, two of the R^{19}, R^{20} and R^{21} radicals’ represent the radicals chosen independently from the alkyl, alkoxy, alkylthio, amino, alkylamino or dialkylamino radicals and the third represents a radical chosen from a hydrogen atom and the alkyl, alkoxy, alkylthio, amino, alkylamino or dialkylamino radicals, or in which Q represents a phenyl radical substituted by an OH radical and a radical or radicals chosen independently from a halogen atom and an OH, alkoxy or —NR^{10}R^{11} radical in which R^{10} and R^{11} represent independently a hydrogen atom or an alkyl radical,

or also the

radical in which T represents —CH_2— and R^7 represents a hydrogen atom, an aminoalkyl, alkylaminoalkyl or dialkylaminoalkyl radical;

B represents H;

n represents 0 or 1;

R^1 and R^2 both represent H;

Ω represents

preferably: an NR^{46}R^{47} radical such that NR^4 R^{47} represents the N-piperazinyl radical or the N-piperazinyl radical optionally N-substituted by an alkyl radical or in which one of R^{46} and R^{47} represents H or a hydroxyalkyl, alkylamino or cyanoalkyl radical and the other represents H or an alkyl radical.

or the OR^{48} radical in which R^{48} represents a hydrogen atom or an alkyl, alkylamino or cyanoalkyl radical.

As regards the compounds of general formula (I) (or their salts) more especially intended to have an inhibitory activity on MAO's and the ROS's, the said compounds having at least one of the following characteristics will be quite particularly preferred:

the compound corresponds to general sub-formula (I), or (I), in which X represents S or the compound corresponds to general formula (I), in which Y represents O;

A represents the
radical in which Q represents OH, two of the R⁻¹⁹, R⁻²⁰ and R⁻²¹ radicals represent an alkyl radical and the third represents H;

or in which Q represents a phenyl radical substituted by an OH radical and one or more radicals chosen independently from the alkyl radicals;

B represents H;

n represents 0 or 1;

R¹ and R² both represent H;

Ω represents:

preferably: an NR⁴⁶R⁴⁷ radical such that NR⁻⁴⁶R⁴⁷ represents an N-piperazinyl radical or in which one of R⁴⁶ and R⁴⁷ represents H or a hydroxyalkyl, alkenyl or cyanoalkyl radical and the other represents H or an alkyl radical,

or the OH radical.

In particular, the compounds of Examples 1 to 30, 210, 291, 316, 319 to 323, 329 to 336 and 346 to 349 (sometimes described in the form of salts) or their pharmaceutically acceptable salts are preferred when an inhibitory activity on MAO’s and/or the ROS’s is sought in the first place. Even more preferentially, the compounds of Examples 1, 3, 6, 22, 24, 26 to 29, 323 and 332 (sometimes described in the form of salts), or their pharmaceutically acceptable salts, are preferred when an inhibitory activity on MAO’s and/or the ROS’s is sought in the first place.

According to another variant of the invention, the compounds of general formula (I) or their pharmaceutically acceptable salts are more especially intended to have a modulating activity on the sodium channels and they are then preferably such that they correspond to general subformulae (I), and (I)₂ and that:

A represents

either a

radical in which Q represents H, —OR²², SR²² or a phenyl radical optionally substituted by one or more of the substituents chosen independently from a halogen atom, an alkyl or alkoxy radical, and a group of two substituents together representing a methylenedioxy or ethylenedioxy radical, or Q represents —CO₂Ph, —OPh, —SPh, —SO₂Ph or —CH₂Ph radical, said —CO₂Ph, —OPh, —SPh, —SO₂Ph or —CH₂Ph radical being optionally substituted on its aromatic part by one or more of the substituents chosen independently from an alkyl or alkoxy radical and a halogen atom,

R²⁷ representing a hydrogen atom or an alkyl radical, and R⁻¹⁹, R⁻²⁰ and R⁻²¹ represent, independently, a hydrogen, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro,
cycloalkyl, —SO₂NHR³⁹, —CONHR⁵⁵, —S(O)₂R⁵⁶, —NH(CO)R⁵⁷, —CF₃, —OCF₃ or NR²⁷R⁵⁸ radical,

R²⁷ and R⁵⁸ representing, independently, a hydrogen atom or an alkyl radical or R²⁷ and R⁵⁸ forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from —CH₂—, —NH— and —O—,

R⁴⁹ and R⁵⁵ representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxyalkyl radical, and W does not exist, or represents a bond, or —O—, —S— or —NR¹⁸—, in which R¹⁸ represents a hydrogen atom or an alkyl radical;

or a

radical in which R⁴, R⁵, R⁶, R⁷ and R⁸ represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy or NR¹⁰R¹¹ radical,

R¹⁰ and R¹¹ representing, independently, a hydrogen atom or an alkyl radical, or R¹⁰ and R¹¹ forming together with the nitrogen atom an optionally substituted heterocycle comprising 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example aminazine, pyrrolidine, piperidine, pyrazine, morpholine or thiomorpholine,

R⁹ represents a hydrogen atom or an alkyl radical,

and W does not exist, or represents a bond, or —O—, —S— or —NR¹⁸—, in which R¹⁸ represents a hydrogen atom or an alkyl radical;

or a

radical in which R³² represents a hydrogen atom or an alkyl radical, and T represents a —(CH₃)ₙ— radical with n=1 or 2,

or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical;
B represents a hydrogen atom, a linear or branched alkyl radical containing 1 to 6 carbon atoms or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, an alkyl or alkoxy radical, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical;

X represents NR\(^{38}\) or S,

R\(^{38}\) representing a hydrogen atom or an alkyl, aralkyl, alkylcarbonyl or aralkylcarbonyl radical,

R\(^1\) and R\(^2\) represent, independently, a hydrogen atom, an alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aminoolkyl, —(CH\(_2\))\(_n\) NH —CO —R\(^{70}\) radical or an aralkyl or heteroarylalkyl radical optionally substituted on the aryl or heteroaryl group by one or more groups chosen from the group composed of a halogen atom, an alkyl or alkoxy radical, a hydroxy, cyano or nitro radical and an amino, alkylamino or dialkylamino radical,

R\(^{70}\) representing, independently each time that it occurs, an alkyl or alkoxy radical;

R\(^1\) and R\(^2\) taken together can optionally form with the carbon atom which carries them a carbocycle with 3 to 7 members;

Ω represents OH or an NR\(^{64}\)R\(^{47}\) radical, in which:

R\(^{46}\) and R\(^{57}\) represent, independently, a hydrogen atom or an alkyl, cycloalkyl or cycloalkylalkyl, —CO —NH —R\(^{51}\), —CO —O —R\(^{52}\) or —SO\(_2\) —R\(^{72}\) radical or one of the heteroaryl, aralkyl, aryloxyalkyl or arylamino radicals optionally substituted on the heteroaryl or aryl group by one or more groups chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical,

R\(^{51}\) representing a hydrogen atom, one of the cycloalkyl or cycloalkylalkyl radicals in which the cycloalkyl radical contains 3 to 7 carbon atoms, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkoxyalkyl radical or also an aryl or aralkyl radical, said aryl or aralkyl radical being able to be substituted by one or more of the substituents chosen independently from a halogen atom and an alkyl or alkoxy radical, and R\(^{72}\) representing an alkyl radical, or one of the phenyl or aralkyl radicals optionally substituted on the aromatic ring by one or more of the radicals chosen from a halogen atom, an alkyl or alkoxy radical;

g represents an integer from 1 to 6; and finally

n represents an integer from 0 to 6.

[0138] More preferentially, the compounds of general formula (I) (or their pharmaceutically acceptable salts) intended to have a modulating activity on the sodium channels corresponding to general sub-formulae (I), and (I)\(_2\) and will be such that:

A represents the radical in which Q represents H, —OR\(^{22}\), —SR\(^{22}\), or a phenyl radical optionally substituted by one or more of the substituents chosen independently from a halogen atom and an alkyl or alkoxy radical, or also Q represents a —COPh, —OPh, —SPh, —SO\(_2\)Ph or —CH\(_2\)Ph radical, said —COPh, —OPh, —SPh, —SO\(_2\)Ph or —CH\(_2\)Ph radical being optionally substituted on its aromatic part by one or more of the substituents chosen from an alkyl or alkoxy radical and a halogen atom,

R\(^{22}\) representing a hydrogen atom or an alkyl radical, and R\(^{55}\), R\(^{20}\) and R\(^{21}\) represent, independently, a hydrogen, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro, cycloalkyl, —SO\(_2\)NH —R\(^{49}\), —CONH —R\(^{55}\), —Si(O),R\(^{56}\) —NH —(CO)R\(^{57}\), —OCF\(_3\) or NR\(^{38}\)R\(^{28}\) radical,

R\(^{27}\) and R\(^{28}\) representing, independently, a hydrogen atom or an alkyl radical or R\(^{27}\) and R\(^{28}\) forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from —CH\(_2\) —, —NH — and —O —,

R\(^{49}\) and R\(^{55}\) representing, individually each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical, q representing an integer from 0 to 2,

R\(^{56}\) and R\(^{77}\) representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical, or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical,

B represents a hydrogen atom, a linear or branched alkyl radical containing 1 to 6 carbon atoms or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, an alkyl or alkoxy radical, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical;

X represents NR\(^{38}\) or S,

R\(^{38}\) representing a hydrogen atom or an alkyl, aralkyl, alkylcarbonyl or aralkylcarbonyl radical,

R\(^1\) and R\(^2\) represent, independently, a hydrogen atom, an alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aminoolkyl, —(CH\(_2\))\(_n\) NH —CO —R\(^{70}\) radical or an aralkyl or heteroarylalkyl radical optionally substituted on the aryl or heteroaryl group by one or more groups chosen from the group composed of a halogen atom, an alkyl or alkoxy radical, a hydroxy, cyano or nitro radical and an amino, alkylamino or dialkylamino radical,

R\(^{70}\) representing, independently each time that it occurs, an alkyl or alkoxy radical;
R¹ and R² taken together can optionally form with the carbon atom which carries them a carbocycle with 3 to 7 members;

Ω represents the NR⁴⁶R⁴⁷ radical, in which:

R⁴⁶ and R⁴⁷ represent, independently, a hydrogen atom or an alkyl, cycloalkyl or cycloalkylalkyl, —CO—NH—R¹, —CO—O—R or —SO₂—R² radical or one of the heteroaryl, aralkyl, arylalkoxyalkyl or arylamino radicals optionally substituted on the heteroaryl or aryl group by one or more groups chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkyaminino or dialkylamino radical,

R²¹ representing a hydrogen atom, one of the cycloalkyl or cycloalkylalkyl radicals in which the cycloalkyl radical contains 3 to 7 carbon atoms, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkoyalkyl radical or also an aryl or aralkyl radical, said aryl or aralkyl radical being able to be substituted by one or more of the substituents chosen independently from a halogen atom and an alkyl or alkoxy radical, and R²⁷ representing an alkyl radical, or one of the phenyl or aralkyl radicals optionally substituted on the aromatic ring by one or more of the radicals chosen from a halogen atom, an alkyl or alkoxy radical and finally;

n represents an integer from 0 to 6.

As regards the compounds of general formula (I) (or their salts) more especially intended to have a modulating activity on the sodium channels, said compounds of general sub-formula (I), or (I)₂ will generally be preferred having at least one of the following characteristics:

A represents:

[0143] and R¹⁹, R²⁰ and R²¹ represent, independently, a hydrogen atom, a halogen atom, the OH group, an alkoxyl, alkylthio or phenyl radical optionally substituted by one or more radicals chosen from a halogen atom and an alkyl radical,

[0144] R²⁷ and R²⁸ representing, independently, a hydrogen atom or an alkyl radical or R²⁷ and R²⁹ forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from —CH₂—, —NH— and —O—,

[0145] R⁴⁹ and R⁵⁵ representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,
[0160] and $R^{19}$, $R^{20}$ and $R^{21}$ represent, independently, a hydrogen atom, a halogen atom or an alkyl, alkoxy, cyano, cycloalkyl, —CF$_3$ or NR$^{27}$R$^{28}$ radical,

[0161] $R^{27}$ and $R^{28}$ representing, independently, a hydrogen atom or an alkyl radical or $R^{27}$ and $R^{28}$ forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from $-$CH$_2$— and $-$NH—;

[0162] or a cycloalkyl radical;

[0163] $R$ represents H;

[0164] $n$ represents 0 or 1;

[0165] $R^1$ represents H, an alkyl, cycloalkyl and in particular a cyclohexyl radical, and $R^2$ represents H;

[0166] $\Omega$ represents an NR$^{46}$R$^{47}$ radical in which $R^{46}$ represents a cycloalkylalkyl radical, a cycloalkyl radical and in particular a cyclohexyl or cyclohexyl, an alkoxyalkyl radical, a (cycloalkyl)oxyalkyl radical, a cycloalkylalkoxyalkyl radical or also a benzylic radical optionally substituted by an alkoxy radical, and $R^{47}$ represents H;

[0167] $X$ represents the NH radical.

[0168] Furthermore, still for the compounds more particularly intended to have a modulatory activity on sodium channels, when $n$ represents 1, $R^1$ and $R^2$ will preferably represent hydrogen atoms.

[0169] In particular, the compounds of Examples 1, 3, 6, 7, 9 to 11, 13, 15 to 17, 20, 24, 26, 28 to 31, 32, 34 to 33 and 33 to 345 (sometimes described in the form of salts), or their pharmaceutically acceptable salts, are preferred when a modulating activity on the sodium channels is sought in the first place.

[0170] More preferably, the compounds of Examples 1, 6, 7, 11, 13, 15, 17, 20, 24, 31 to 38, 42, 43, 46 to 48, 53, 56, 57, 59 to 61, 64 to 80, 82 to 88, 9 to 95, 97, 105, 106, 108, 110, 113, 117, 118, 121 to 123, 125, 128, 130 to 139, 142 to 145, 149, 151, 152, 154, 162 to 166, 168 to 178, 181, 183 to 186, 188, 190 to 196, 198 to 206, 208 to 210, 212 to 218, 220 to 231, 233 to 250, 252 to 259, 261 to 281, 283 to 288, 293 to 313, 324 and 338 to 340 (sometimes described in the form of salts), or their pharmaceutically acceptable salts, are preferred when a modulating activity on the sodium channels is sought in the first place.

[0171] According to a more particular variant of the invention, the compounds of the invention of general formula (I) as defined previously in which:

Het is such that the compounds of general formula (I) correspond to one of the general sub-formulae (I), and (I), in which $X$ represents NII or S or general sub-formula (I)$_3$ in which $Y$ represents O;

[0172] $A$ represents a radical in which $Q$ represents OH, two of the radicals $R^{19}$, $R^{20}$ and $R^{21}$ radicals represent an alkyl radical and the third represents a hydrogen atom,

or in which $Q$ represents a phenyl radical substituted by an OH radical and one or more radicals chosen independently from alkyl radicals;

$B$ represents a hydrogen atom;

$n$ represents 0 or 1;

$R^1$ and $R^2$ both represent a hydrogen atom;

and $\Omega$ represents an NR$^{46}$R$^{47}$ radical in which $R^{46}$ represents a hydrogen atom or an alkyl, alkynyl, hydroxyalkyl or cyanoalkyl radical and $R^{47}$ represents a hydrogen atom or an alkyl radical or also $R^{46}$ and $R^{47}$ form together with the nitrogen atom which carries them a non-aromatic heterocycle with 5 to 7 members, the additional members being chosen from $-$CH$_2$— and $-$NH—;

A can be used to prepare a medicament intended both to inhibit MAO's and lipid peroxidation and to modulate the sodium channels.

[0173] More preferentially, the compounds of general formula (I) which can be used to prepare a medicament intended both to inhibit MAO's and lipid peroxidation and to modulate the sodium channels will be such that:

Het is such that the compounds of general formula (I) correspond to general sub-formula (I)$_3$ in which $X$ represents S or to general sub-formula (I)$_3$ in which $Y$ represents O;

[0174] $A$ represents a radical in which $Q$ represents OH, two of the radicals $R^{19}$, $R^{20}$ and $R^{21}$ represent an alkyl radical and the third represents a hydrogen atom,

$B$ represents a hydrogen atom;

$n$ represents 0 or 1;

$R^1$ and $R^2$ both represent a hydrogen atom;

and $\Omega$ represents an NR$^{46}$R$^{47}$ radical in which $R^{46}$ represents a hydrogen atom or an alkyl, hydroxyalkyl or cyanoalkyl radical and $R^{47}$ represents a hydrogen atom or an alkyl radical.
radical or also R' and R" form together with the nitrogen atom which carries them an N-piperazinyl radical.

[0175] Still for the compounds of general formula (I) which can be used to prepare a medicament intended both to inhibit the MAO's and lipidic peroxidation and to modulate the sodium channels, n will preferably represent 0 when Het is such that the compounds of general formula (I) correspond to general sub-formula (I), in which X represents S and preferably 1 when Het is such that the compounds of general formula (I) correspond to general sub-formula (I), in which Y represents O.

[0176] In particular, the compounds of Examples 1, 3, 6, 24, 26, 28 and 29 (sometimes described in the form of salts) or their pharmaceutically acceptable salts will be preferred if one wishes to prepare a medicament intended both to inhibit MAO's and lipidic peroxidation and to modulate the sodium channels.

[0177] The invention also offers, as medicaments, the compounds of general formula (II)

\[
A\begin{array}{c}
\text{Het} \\
\end{array} \\
R^1 \quad R^2 \quad \Omega
\]

in racemic, enantiomeric form or any combinations of these forms, in which Het is a heterocycle with 5 members comprising 2 heteroatoms and such that general formula (II) correspond exclusively to one of the following sub-formulae:

\[
\begin{align*}
& (\text{II}) \\
& \begin{array}{c}
A \quad \text{Het} \\
R^1 \quad R^2 \quad \Omega
\end{array}
\end{align*}
\]

\[
\begin{align*}
& (\text{II})_1 \\
& \begin{array}{c}
A \quad \text{Het} \\
R^1 \quad R^2 \quad \Omega
\end{array}
\end{align*}
\]

\[
\begin{align*}
& (\text{II})_2 \\
& \begin{array}{c}
A \quad \text{Het} \\
R^1 \quad R^2 \quad \Omega
\end{array}
\end{align*}
\]

\[
\begin{align*}
& (\text{II})_3 \\
& \begin{array}{c}
A \quad \text{Het} \\
R^1 \quad R^2 \quad \Omega
\end{array}
\end{align*}
\]

\[
\begin{align*}
& (\text{II})_4 \\
& \begin{array}{c}
A \quad \text{Het} \\
R^1 \quad R^2 \quad \Omega
\end{array}
\end{align*}
\]

in which

A represents either a

\[
\begin{align*}
& \begin{array}{c}
R^1 \\
\end{array}
\end{align*}
\]

radical in which R' represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

or a

\[
\begin{align*}
& \begin{array}{c}
R^4 \\
\end{array}
\end{align*}
\]

radical in which R", R", R", R" and R" represent, independently, a hydrogen atom, a halogen, the OH group or an alkoxy, cyano, nitro or NR' radical,

R" and R" representing, independently, a hydrogen atom, an alkyl radical or a —COR' group, or R" and R" forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R" representing a hydrogen atom, an alkyl radical or a —COR' group,

R" representing a hydrogen atom or an alkyl, alkoxy or NR' radical,

R" and R" representing, independently, a hydrogen atom or an alkyl radical, or R" and R" forming together with the nitrogen atom an optionally substituted heteroatom with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

and W doesn’t exist, or represents a bond, or —O—, —S— or —NR'—, in which R" represents a hydrogen atom or an alkyl radical;
or a

radical in which Q represents H, —OR, —SR, —NR'R'' radical in which R represents H, —OR, —SR, —NR'R'' radical and a group with two substituents together representing a methylidenedioxy or ethylenedioxy radical, or also Q represents a —COPh, —SO,Ph or —CH,Ph radical, said —COPh, —SO,Ph or —CH,Ph radical being optionally substituted on its aromatic part by one or more of the substituents chosen independently from an alkyl or alkyloxy radical and a halogen atom,

R and R representing, independently, a hydrogen atom, an alkyl radical or a —OR group, or R and R forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R representing a hydrogen atom, an alkyl or alkyloxy radical,

R and R representing, independently, a hydrogen atom or an alkyl radical, or R and R forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,

R and R representing, independently, a hydrogen atom, an alkyl radical or a —CO—R radical,

R representing an alkyl radical,

and R, R and R representing, independently, a hydrogen, a halogen, the OH or SR group, or an alkyl, cycloalkyl, alkenyl, alkoxy, nitro, —SO,NHR or —CONHR radicals, —S(O),R, —NH(CO)R, —CF or —CF radicals,

R representing a hydrogen atom or an alkyl radical,

R and R representing, independently, a hydrogen atom, an alkyl radical or a —COR group, or R and R forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R and R representing, independently each time that they occur, a hydrogen atom or an alkyl or alkyloxy radical, a hydrogen atom or an alkyl or alkyloxy radical,

R representing a hydrogen atom, an alkyl, alkoxy or —NR'R'' radical,

R and R representing, independently, a hydrogen atom or an alkyl radical, or R and R forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

or a

radical in which R represents a hydrogen atom or an alkyl radical,

and T represents a —(CH,). radical with m=1 or 2, or finally a

radical in which R represents a hydrogen atom or an alkyl, —NR'R'' or —CHR'R'' radical,

 representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,

R and R representing, independently, a hydrogen atom or an alkyl radical,

R and R representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or NR radicals,

R representing a hydrogen atom, an alkyl radical or a —COR group, or R and R forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R representing a hydrogen atom or an alkyl, alkoxy or NR radical,
R^13 and R^14 representing, independently, a hydrogen atom or an alkyl radical, or R^13 and R^14 forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

and T represents a —(CH_2)_m— radical with m=1 or 2, or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical;

X represents S or NR^38,

R^38 representing a hydrogen atom or an alkyl, cyanoalkyl, aralkyl, alkenylcarbonyl or aralkylcarbonyl radical,

Y represents O or S;

R^1 represents a hydrogen atom, an alkyl, aminomethyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trihydroxymethylalkyl, alkynyl, allenyl, allenylnylalkyl, cyanoalkyl, —(CH_2)_k—Z^R^39, —(CH_2)_k—COR^40, —(CH_2)_k—NH-COR^40, aroyl, aralkyl, arylenylalkyl, heteroaryalkyl or aralkylcarbonyl radical, the aryl group of the aroyl, aralkyl, arylenylalkyl, heteroaryalkyl or aralkylcarbonyl radicals being itself optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, alkoxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, —(CH_2)_h—Z^R^39 or —(CH_2)_k—COR^40 radicals,

Z^1 and Z^2 representing a bond, —O—, —NR^41— or —S—,

R^39 and R^41 representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl or cyanoalkyl radical,

R^40 representing, independently each time that it occurs, a hydrogen atom or an alkyl, alkenyl, allenylnylalkyl, alkenyl, cyanoalkyl, alkoxy or NR^40 R^43 radical,

R^42 and R^43 representing, independently each time that they occur, a hydrogen atom or an alkyl, allenylalkyl, alkenyl, alkenyl or cyanoalkyl radical,

and R^2 represents a hydrogen atom, an alkyl, alkoxyalkyl, alkoxyalkylalkyl, cycloalkyl, cycloalkylalkyl, trihydroxymethylalkyl or —(CH_2)_k—NH-COR^72 radical, or also one of the aralkyl or heteroaryalkyl radicals optionally substituted on the aroyl or heteroaryl group by one or more of the groups chosen independently from the group composed of a halogen atom and an alkyl, alkenylnylalkyl, alkenylnylalkyl, cyanoalkyl, alkoxyalkyl or NR^40 R^43 radical, or also one of the aralkyl or heteroaryalkyl radicals optionally substituted on the aroyl or heteroaryl group by one or more of the groups chosen independently from the group composed of a halogen atom and an alkyl, alkenylnylalkyl, alkenylnylalkyl, cyanoalkyl, alkoxyalkyl or NR^40 R^43 radical, or also one of the aralkyl or heteroaryalkyl radicals optionally substituted on the aroyl or heteroaryl group by one or more of the groups chosen independently from the group composed of a halogen atom and an alkyl, alkenylnylalkyl, alkenylnylalkyl, cyanoalkyl, alkoxyalkyl or NR^40 R^43 radical,

R^70 and R^71 representing independently an alkyl or alkoxy radical;

or R^1 and R^2, taken together with the carbon atom which carries them, form a carbocycle with 3 to 7 members;

B represents a hydrogen atom, an alkyl radical, a —(CH_2)_k—Z^R^44 radical or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical,

Z^3 representing a bond, —O—, —NR^45— or —S—,
Z represents a bond, \(-O-, \text{NR}^7-\) or \(-S-,\)

R^3 and R^7 representing, independently, a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical.

R^4 representing a hydrogen atom, an alkyl, allenylalkyl, alkenyl, alkynyl, cycloalkyl, alkoxy or NR^6R^9 radical,

R^8 and R^9 representing, independently, a hydrogen atom or an alkyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R^10 represents a hydrogen atom or an alkyl, alkynyl or cyanoalkyl radical;

g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6;

it being understood that when Het is such that the compound of general formula (II) corresponds to general sub-formula (IIa), then:

A represents the 4-hydroxy-2,3-di-tertiobutyl-phenyl radical;

B, R^1 and R^2 all represent H; and finally

\(\Omega\) represents OH;

it also being understood that at least one of the following characteristics must be present:

Hetz is a thiazole, oxazole or isoxazoline ring, and

A represents a radical in which R^3 represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

or A represents a radical in which R represents a hydrogen atom or an alkyl radical,

and W doesn’t exist, or represents a bond, or \(-O-, \text{S}−\) or \(-\text{NR}^7-,\) in which R^10 represents a hydrogen atom or an alkyl radical,

or A represents a radical in which Q represents OH or Q represents a phenyl radical substituted by an OH radical and one or more of the radicals chosen independently from a halogen atom and an OH, alkyl, alkoxy or NR^6R^9 radical in which R^10 and R^11 represent independently a hydrogen atom or an alkyl radical,

or also A represents a radical in which R^32 represents a hydrogen atom or an alkyl radical and T represents a \(-(\text{CH}_2)_m-\) radical with m=1 or 2,

or finally A represents a radical in which the R^33 radical represents a hydrogen atom or an alkyl, \(\Sigma-\text{NR}^3\text{R}^3-\) or \(\Sigma-\text{R}^3\text{R}^3-\) radical, \(\Sigma\) representing a linear or branched alkyene radical containing 1 to 6 carbon atoms, R^34 and R^35 representing, independently, a hydrogen atom or an alkyl radical, R^36 and R^37 representing, independently, a hydrogen atom or a carbocyclic or heterocyclic ary radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or NR^38R^39 radicals, R^10 and R^11 representing, independently, a hydrogen atom, an alkyl radical, or R^10 and R^11 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,
said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

and T represents a \(-\left(\text{CH}_2\right)_{m}\) radical with \(m=1\) or 2;

Het is an imidazole ring,

A represents a

radical in which \(Q\) represents OH,

\(\Omega\) represents NR\(^{46}\)R\(^{47}\) in which R\(^{46}\) or R\(^{47}\) represents an aminophenyl, nitrophenyl, aminophenylcarbonyl, nitrophenylcarbonyl, aminophenylalkyl or nitrophenylalkyl radical;

A represents a

radical B represents a carbocyclic aryl radical optionally substituted 1 to 3 times by radicals chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical, and one of R\(^2\) and R\(^2\) represents one of the optionally substituted arylalkyl or heteroarylalkyl radicals;

A represents a cycloalkyl or cycloalkylalkyl radical;

\(\Omega\) represents NR\(^{46}\)R\(^{47}\) and one of R\(^{46}\) and R\(^{47}\) represents an alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl or hydroxalkyl radical;

one of R\(^1\) and R\(^2\) represents a cycloalkyl or cycloalkylalkyl radical;

none of R\(^1\) and R\(^2\) represents H;

n=1 and A represents a biphenyl, phenoxypbenyl, phenylthiophenyl, phenylcarbonylphenyl or phenylsulphonylphenyl radical;

when Het is a thiazole ring and \(\Omega\) represents the OR\(^{48}\) radical in which R\(^{48}\) is a cyanoalkyl radical, then the cyano group is not attached to the carbon atom immediately adjacent to the oxygen atom;

the pharmaceutically acceptable salts of the compounds of general formula (II).

Generally, the medicaments of General formula (II) having one of the following additional characteristics are preferred:

i. \(n=0\),

Het is an oxazole, thiazole or isoxazoline ring

A represents a

radical in which R\(^5\) represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

or A represents a

radical in which R\(^4\), R\(^5\), R\(^6\), R\(^7\), R\(^8\) and R\(^9\) represent hydrogen atoms and W doesn’t exist, or represents a bond, or \(-\text{O}\) — S — or \(-\text{NR}^{18}\) in which R\(^{18}\) represents a hydrogen atom or an alkyl radical,

or A represents a

radical in which R\(^4\), R\(^5\), R\(^6\), R\(^7\), R\(^8\) and R\(^9\) represent hydrogen atoms and W doesn’t exist, or represents a bond, or \(-\text{O}\) — S — or \(-\text{NR}^{18}\) in which R\(^{18}\) represents a hydrogen atom or an alkyl radical,

or also A represents a
radical in which $R'_{22}$ represents a hydrogen atom or an alkyl radical and $T$ represents $-\text{CH}_2-$. 

or finally $A$ represents a radical in which $T$ represents the $-\text{CH}_2-$ radical and the $R'_{33}$ radical represents a hydrogen atom or a $-\Sigma-NR'_{34}R'_{35}$ radical, $\Sigma$ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms, and $R'_{44}$ and $R'_{55}$ representing, independently, a hydrogen atom or an alkyl radical.

$B$ represents $H$.

$R'_{1}$ and $R'_{2}$ represent, independently, a hydrogen atom or an alkyl radical,

and $\Omega$ represents an $NR'_{46}R'_{57}$ radical in which one of $R'_{46}$ and $R'_{57}$ represents an alkyl, alkenyl, allenyl, allenyalkyl, alkynyl, cyanoalkyl or hydroxyalkyl radical and the other represents a hydrogen atom or an alkyl radical; or

ii. $n=0$,

$A$ represents a radical in which $Q$ represents a hydrogen atom or an $-\text{OR}'_{19}$ or $-\text{SR}'_{19}$ radical in which $R'_{20}$ represents an alkyl radical or an ary1 radical optionally substituted by one or more substituents chosen from the alkyl, alkoxy, cyano, nitro, aroyl, alkenyl, alkoxy, alkyl, cycloalkyl, alkenyl, alkyl, cyano, nitro, $-\text{SO}_2\text{NHR}^{40}$, $-\text{CONHR}^{45}$, $-\text{S(O)}_2R'_{56}$, $-\text{NH(CO)}R'_{57}$, $-\text{CF}_3$, $-\text{OCF}_3$ or $-\text{NR'}_{22}R'_{23}$ radical,

$R'_{22}$ representing an alkyl radical,

$R'_{23}$ and $R'_{28}$ representing, independently, a hydrogen atom or an alkyl radical or $R'_{27}$ and $R'_{28}$ forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from $-\text{CH}_2-$, $-\text{NH}-$ and $-\text{O}-$,

$R'_{24}$ and $R'_{25}$ representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,

$q$ representing an integer from 0 to 2,
The invention also relates, as new industrial products, to the compounds of general formula (III) in racemic, enantiomeric form or any combinations of these forms, in which Het is a heterocycle with 5 members comprising 2 heteroatoms and such that general formula (III) corresponds exclusively to one of the following subformulae:

\[
\text{(III)}_1
\]

\[
\text{(III)}_2
\]

\[
\text{(III)}_3
\]

\[
\text{(III)}_4
\]

in which

A represents either a

radical in which \( R^1 \) represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

radical in which \( Q \) represents \( H, -OR^{22}, -SR^{22}, -NR^{23}R^{24} \), a phenyl radical optionally substituted by one

radical in which \( R^6, R^7, R^8 \) represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro or NR\(^{10}\)R\(^{11}\) radical,

\( R^{10} \) and \( R^{11} \) representing, independently, a hydrogen atom, an alkyl radical or a \(-\text{COR}^{13} \) group, or \( R^{10} \) and \( R^{11} \) forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

\( R^{12} \) representing a hydrogen atom or an alkyl, alkoxy or NR\(^{10}\)R\(^{11}\) radical,

\( R^{13} \) and \( R^{14} \) represent, independently, a hydrogen atom or an alkyl radical, or \( R^{13} \) and \( R^{14} \) forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

\( R^9 \) represents a hydrogen atom, an alkyl radical or a \(-\text{COR}^{13} \) group.

\( R^{15} \) representing a hydrogen atom or an alkyl, alkoxy or NR\(^{10}\)R\(^{11}\) radical,

\( R^{16} \) and \( R^{17} \) representing, independently, a hydrogen atom or an alkyl radical, or \( R^{16} \) and \( R^{17} \) forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

and \( W \) doesn’t exist, or represents a bond, or \(-\text{O}-, -\text{S}-\) or \(-\text{NR}^{18}-\), in which \( R^8 \) represents a hydrogen atom or an alkyl radical;
or more of the substituents chosen independently from a halogen atom, an OH, cyano, alkyl, alkoxy or —NR_R1 radical and a group of two substituents together representing a methylenedioxy or ethylenedioxy radical, or also Q represents a —COPh, —SO2Ph or —CH2Ph radical, said —COPh, —SO2Ph or —CH2Ph radical being optionally substituted on its aromatic part by one or more of the substituents chosen independently from an alkyl or alkoxy radical and a halogen atom,

R^10 and R^13 representing, independently, a hydrogen atom, an alkyl radical or a COR^12 group, or R^10 and R^11 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^12 representing a hydrogen atom, an alkyl or alkoxy or NR_R14 radical,

R^13 and R^14 representing, independently, a hydrogen atom or an alkyl radical, or R^13 and R^14 forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^12 representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,

R^13 and R^14 representing, independently, a hydrogen atom, an alkyl radical or a —CO—R^12 radical,

R^14 representing an alkyl radical,

and R^19, R^20 and R^21 represent, independently, a hydrogen, a halogen, the OH or SR^20 group, or an alkyl, cycloalkyl, alkenyl, alkylcyano, nitro, —SO2NHROH, —CONHROH, S(O)R^20, —NH(CO)R^20, —CF3, —OCH3 or NR^22R^23 radical,

R^20 representing a hydrogen atom or an alkyl radical,

R^21 representing, independently, a hydrogen atom, an alkyl radical or a —COR^22 group, or R^21 and R^22 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^23 representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxycarbonyl radical, q representing an integer from 0 to 2,

R^24 and R^25 representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

R^26 representing a hydrogen atom, an alkyl, alkoxy or —NR_R31 radical,

R^27 and R^28 representing, independently, a hydrogen atom, an alkyl radical or a —COR^27 group, or R^27 and R^28 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^29 representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

R^30 and R^31 representing, independently, a hydrogen atom or an alkyl radical, or R^30 and R^31 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

or a

radical in which R^32 represents a hydrogen atom or an alkyl radical, and T represents a —(CH2)m— radical with m=1 or 2,

or finally a

radical in which R^33 represents a hydrogen atom or an alkyl, —NR^18R^19 or —CHR^18R^19 radical,

Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,

R^34 and R^35 representing, independently, a hydrogen atom or an alkyl radical,

R^36 and R^37 representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or NR^10R^11 radicals,

R^10 and R^11 representing, independently, a hydrogen atom, an alkyl radical or a —COR^27 group, or R^10 and R^11 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^12 representing a hydrogen atom or an alkyl, alkoxy or NR^18, R^18 radical,

R^13 and R^14 representing, independently, a hydrogen atom or an alkyl radical, or R^13 and R^14 forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

and T represents a —(CH2)m— radical with m=1 or 2,

or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical;

X represents S or NR^18.
R\textsuperscript{28} representing a hydrogen atom or an alkyl, cyanoalkyl, aralkyl, alkenyloaryl or aralkenyloaryl radical,

Y represents O or S;

R\textsubscript{1} represents a hydrogen atom, an alkyl, aminooalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl, alkenyl, allyl, allylenylalkyl, alkynyl, cyanoalkyl, —(CH\textsubscript{2})\textsubscript{3}—Z\textsuperscript{R\textsubscript{39}}, —(CH\textsubscript{2})\textsubscript{3}—COR\textsuperscript{83},

—(CH\textsubscript{2})\textsubscript{3}—NH—COR\textsuperscript{57}, ary1, aralkyl, ary1acyl, heteroaryloalkyl or aralkenyloaryl radical, the aryl group of the aryl, aralkyl, aryloaryl, heteroaryloalkyl or aralkenyloaryl radicals being itself optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, alkoxy, nitro, cyano, cyanoalkyl, amino, alkylamino, diarylamino, —(CH\textsubscript{2})\textsubscript{3}—Z\textsuperscript{R\textsubscript{39}} or —(CH\textsubscript{2})\textsubscript{3}—COR\textsuperscript{84} radicals.

Z\textsuperscript{1} and Z\textsuperscript{2} representing a bond, —O—, —NR\textsuperscript{41}— or —S—,

R\textsuperscript{39} and R\textsuperscript{41} representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl or cyanoalkyl radical.

R\textsuperscript{40} representing, independently each time that it occurs, a hydrogen atom or an alkyl, alkenyl, allylalkynyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or NR\textsuperscript{42}—R\textsuperscript{43} radical,

R\textsuperscript{42} and R\textsuperscript{43} representing, independently each time that they occur, a hydrogen atom or an alkyl, allyl, allylenylalkyl, alkenyl, alkynyl or cyanoalkyl radical, and

R\textsuperscript{2} represents a hydrogen atom, an alkyl, aminooalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl or —(CH\textsubscript{2})\textsubscript{3}—NH—COR\textsuperscript{57} radical, or also one of the arylalkyl or heteroaryloalkyl radicals optionally substituted on the aryl or heteroaryl group by one or more of the groups chosen independently from the group constituted by the aryl atom and an alkyl, alkoxy, hydroxy, cyano, nitro, amino, alkylamino or diarylamino radical,

R\textsuperscript{40} and R\textsuperscript{41} representing independently each alkyl or aralkyl radical; or

R\textsuperscript{1} and R\textsuperscript{2} taken together with the carbon atom which carries them, form a carbocycle with 3 to 7 members;

B represents a hydrogen atom, an alkyl radical, a —(CH\textsubscript{2})\textsubscript{3}—Z\textsuperscript{R\textsubscript{39}} radical or a carbocyclic aryl radical optionally substituted 1 to 3 times by the groups chosen from the group constituted of a halogen atom, a linear or branched alkyl or aralkyl radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or diarylamino radical and a carbocyclic aryl radical,

Z\textsuperscript{3} representing a bond, —O—, —NR\textsuperscript{45}— or —S—,

R\textsuperscript{45} and R\textsuperscript{45} representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, allyl, allylenylalkyl or cyanoalkyl radical;

Ω represents one of the NR\textsuperscript{46}—R\textsuperscript{47} or OR\textsuperscript{48} radicals, in which:

R\textsuperscript{28} and R\textsuperscript{29} represent, independently, a hydrogen atom or an alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, allyl, alkenyl, allylenylalkyl, cyanoalkyl, —(CH\textsubscript{2})\textsubscript{3}—Z\textsuperscript{R\textsubscript{39}}, —(CH\textsubscript{2})\textsubscript{3}—COR\textsuperscript{83},

—(CH\textsubscript{2})\textsubscript{3}—CO—OR\textsuperscript{84}, —(CH\textsubscript{2})\textsubscript{3}—CONH—R\textsuperscript{53} or —SOR\textsuperscript{54} radical, or also a radical chosen from the aryl, aralkyl, aryloxyalkyl, aryloxyaryl, arylamino, aralkylamino, heteroaryl and in particular pyridinyl, pyridylalkyl or pyridylalkylcarbonyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, aryloxyalkyl, aryloxyaryl, arylamino, aralkylamino, heteroaryl and in particular pyridinyl, pyridylalkyl or pyridylalkylcarbonyl radicals being optionally substituted by one or more of the substituents chosen independently from halogen, alkyl, alkoxy, hydroxy, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, —(CH\textsubscript{2})\textsubscript{3}—Z\textsuperscript{R\textsubscript{39}}, —(CH\textsubscript{2})\textsubscript{3}—COR\textsuperscript{83} and —(CH\textsubscript{2})\textsubscript{3}—COOR\textsuperscript{84} radicals.
and R⁴⁸ represents a hydrogen atom or an alkyl, alkenyl or cyanoalkyl radical;
g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6;
it being understood that when Het is such that the compound of general formula (III) corresponds to general sub-formula (III₄), then:
A represents the 4-hydroxy-2,3-di-tertiobutyl-phenyl radical;
B, R¹ and R² all represent H; and finally
Ω represents OH;
it being also understood that at least one of the following characteristics must be present:
[0238] when A represents a

[0238] radical in which Q represents OH,
[0240] Ω does not represent an NR'R'' radical in which R' or R'' is chosen from a hydrogen atom and a alkyl radical or an alkenyl radical in which R represents an aminophenyl, nitrophenyl, aminophenylcarbonyl, nitrophenylcarbonyl, aminophenylalkyl or nitrophenylalkyl radical;

[0241] A represents a

[0241] radical in which Q represents OH,
[0240] Ω does not represent an NR'R'' radical in which R' or R'' is chosen from a hydrogen atom and an alkyl radical or an alkenyl radical in which R represents an aminophenyl, nitrophenyl, aminophenylcarbonyl, nitrophenylcarbonyl, aminophenylalkyl or nitrophenylalkyl radical;

[0242] radical B represents a carbo cyclic aryl radical optionally substituted 1 to 3 times by radicals chosen from the group composed of a halogen atom, a linear or branched alkyl or alkenyl radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbo cyclic aryl radical, and one of R¹ and R² represents one of the optionally substituted arylalkyl or heteroarylalkyl radicals;

[0243] A represents a cycloalkyl or cycloalkylalkyl radical;

[0244] Ω represents NR⁴⁶R⁴⁷ and one of R⁴⁶ and R⁴⁷ represents an alkanyl, allenyl, allenyllalkyl, alkynyl, cyanoalkyl or hydroxyalkyl radical;

[0245] one of R¹ and R² represents a cycloalkyl or cycloalkylalkyl radical;

[0246] none of R¹ and R² represent H;
[0247] n=1 and A represents a biphenyl, phenoxyphe nyl, phenylthiophenyl, phenylcarbonylphenyl or phenylsulphonylphenyl radical;

[0248] when Het is a thiazole ring and Ω represents the OR⁴⁸ radical in which R⁴⁸ is a cyanoalkyl radical, then the cyano group is not attached to the carbon atom immediately adjacent to the oxygen atom;
or the salts of the compounds of general formula (III).

[0249] According to one of the preferred variants of the invention, the compounds of general formula (III) will be both ROS and MAO inhibitors and have at least one of the following characteristics:

[0250] A representing the:

[0251] radical in which Q represents OH, two of the R¹, R² and R³ radicals represent radicals chosen independently from the alkyl, alkoxy, alkylthio, amino, alkylamino or dialkylamino radicals and the third represents a radical chosen from a hydrogen atom and the alkyl, alkoxy, alkylthio, amino, alkylamino or dialkylamino radicals;

[0252] n representing 0 or 1;

[0253] R¹ and R² both representing H;

[0254] Ω representing OH or the NR⁴⁶R⁴⁷ radical in which one of R⁴⁶ and R⁴⁷ represents a cyanoalkyl radical and the other represents H or alkyl or also in which R⁴⁶ and R⁴⁷ taken together form with the nitrogen atom a non aromatic heterocycle with 4 to 8 members, the elements of the chain being chosen from a group composed of—CH(R⁵²)—, —NR⁵⁴—, —O—, —S—, —CO—, R⁵³ and R⁵⁴ being as defined in general formula (III).

[0255] According to another preferred variant of the invention, the compounds of general formula (III) will be modulators of the sodium channels and preferably have one of the following two characteristics:

[0256] n=0;

[0257] A represents a

[0258] radical in which Q represents a hydrogen atom or an —OR²² or —SR²² radical in which R²² represents
an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals, \( R^{55}, R^{60} \) and \( R^{21} \) represent, independently, a hydrogen, a halogen, an \( SR \) radical, or an alkyl, cycloalkyl, alkyl, haloxy, cyano, nitro, \(-SO_2NH\) or \(-CONHR)\), \(-Si(OR))\), \(-NHCO(R))\), \(-CF_3\), \(-OCF_3\) or \( NR^{2}R^{25} \) radical, \( R \) representing an alkyl radical,

\[ R^{27} \text{ and } R^{28} \text{ representing, independently, a hydrogen atom or an alkyl radical or } R^{27} \text{ and } R^{28} \text{ forming together with the nitrogen atom which carries then a heterocycle with } 5 \text{ to } 6 \text{ members chosen from } C_2H_4, \text{ and } -OH, \]

\[ R^{66} \text{ and } R^{67} \text{ representing, independently each time that they occur, a hydrogen atom or an alkyl or alkycarboxyl radical, } \]

\[ q \text{ representing an integer from } 0 \text{ to } 2, \]

\[ R^{66} \text{ and } R^{67} \text{ representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarboxyl radical, } \]

\[ n = 1, \]

\[ A \text{ represents a biphenyl or cyclohexylphenyl radical, } \]

\[ B \text{ represents a hydrogen atom, } \]

\[ R^{1} \text{ and } R^{2} \text{ each represent a hydrogen atom, } \]

\[ \Omega \text{ represents a } NR^{46}R^{47} \text{ radical in which } R \text{ represents a } COOR^{46} \text{ radical, } R^{47} \text{ representing an alkyl, cycloalkyl, cycloalkylalkyl or alkoxyalkyl radical and } R^{47} \text{ representing a hydrogen atom. } \]

\[ \text{More preferentially, the compounds of general formula (III)} \]

\[ \text{which are modulators of the sodium channels are such that } Het \text{ represents an imidazole ring (i.e. that they correspond to one of general formulae (III) or (III)}) \]

\[ \text{in which } X \text{ represents an } NR^{46} \text{ radical in which } R^{46} \text{ is as defined previously). } \]

\[ \text{Generally, the compounds of general formula (III) will be preferably chosen from the compounds described (sometimes in the form of salts) in Examples 1 to 7, 9, 10, 24, 26 to 35, 52, 57, 61, 80, 82, 83, 85 to 87, 90, 94, 113, 115, 123, 127, 130, 132, 134, 138, 139, 147, 152, 154, 161, 164, 169, 171 to 173, 176 to 180, 203, 237 to 239, 243 to 247, 249, 251, 255, 258 to 262, 264 to 271, 273 to 275, 277 to 333 and 335 to 349, or the salts of these compounds. } \]

\[ \text{More preferentially, the compounds of general formula (III) will be chosen from the compounds described (sometimes in the form of salts) in Examples 1, 3, 6, 7, 24, 26 to 35, 57, 61, 82, 83, 85 to 87, 94, 113, 123, 130, 132, 134, 138, 139, 152, 154, 164, 169, 171 to 173, 176 to 178, 203, 237 to 239, 243 to 247, 249, 255, 258, 259, 261, 262, 264 to 271, 273 to 275, 277 to 281, 283 to 288, 293 to 313, 321, 323, 324, 332 and 338 to 340, or the salts of these compounds. } \]

\[ \text{The same preferences as those indicated for the compounds of general formula (I) and (II) are moreover applicable by analogy to the compounds of general formula (III). } \]

\[ \text{In certain cases, the compounds according to the present invention (i.e. the compounds of general formula (I), (II) or (III)) can contain asymmetrical carbon atoms. As a result, the compounds according to the present invention have two possible enantiomeric forms, i.e. the "R" and "S" configurations. The present invention includes the two enantiomeric forms and all combinations of these forms, including the racemic "RS" mixtures. For the sake of simplicity, when no specific configuration is indicated in the structural formula, it should be understood that the two enantiomeric forms and their mixtures are represented. } \]

\[ \text{The invention also relates to the pharmaceutical compositions containing, as active ingredient, a compound of general formula (II) or a pharmaceutically acceptable salt of a compound of general formula (II), as well as the use of the compounds of general formula (II) for preparing a medicament intended to inhibit the monoamine oxidases, in particular monoamine oxidase B, to inhibit lipide peroxidation, to have a modulatory activity on the sodium channels or to have two of the three or all three of the aforementioned activities. } \]

\[ \text{The invention relates moreover, as medicaments, to the compounds of general formula (III) or their pharmaceutically acceptable salts. Similarly it relates to the pharmaceutical compositions containing, as active ingredient, a compound of general formula (III) or a pharmaceutically acceptable salt of a compound of general formula (III), as well as the use of the compounds of general formula (III) for preparing a medicament intended to inhibit monoamine oxidases, in particular monoamine oxidase B, to inhibit lipide peroxidation, to have a modulatory activity on the sodium channels or to have two of the three or all three of the aforementioned activities. } \]

\[ \text{In particular, the compounds of general formula (I), (II) or (III) can be used for preparing a medicament intended to treat one of the following disorders or one of the following diseases: Parkinson's disease, senile dementia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, schizophrenia, depressions, psychoses, migraine or pains and in particular neuropathic pains. } \]

\[ \text{By pharmaceutically acceptable salt, is meant in particular the addition salts with inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, diphosphate and nitrate or with organic acids such as acetate, maleate, fumarate, tartrate, succinate, citrate, lactate, methanesulphonate, p-toluensulphonate, pamoate and stearate. Also included in the field of the present invention, when they can be used, are the salts formed from bases such as sodium or potassium hydroxide. For other examples of pharmaceutically acceptable salts, reference can be made to "Salt selection for basic drugs", Int. J. Pharm. (1986), 33, 201-217. } \]

\[ \text{The pharmaceutical composition can be in the form of a solid, for example powders, granules, tablets, gelatin capsules, liposomes or suppositories. Appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, talc, sugars, luctose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone and wax.}\]

\[ \text{The pharmaceutical compositions containing a compound of the invention can also be presented in liquid form, for example, solutions, emulsions, suspensions or syrups. Appropriate liquid supports can be, for example, } \]
water, organic solvents such as glycerol or glycols, similarly their mixtures, in varying proportions, in water.

[0280] The administration of a medicament according to the invention can be done by topical, oral, parenteral route, by intramuscular injection, etc.

[0281] The administration dose envisaged for a medicament according to the invention is comprised between 0.1 mg to 10 g according to the type of active compound used.

[0282] In accordance with the invention, the compounds of general formula (I) can be prepared by the procedures described below.

PREPARATION OF THE COMPOUNDS OF THE INVENTION

Generalities

[0283] The preparations of the compounds of the invention which correspond to general formulae (I), (II) or (III) in which \( \Omega \) represents OH are carried out in a similar fashion to those described in the PCT Patent Application WO 99/09829 and the European Patent Application EP 432 740.

[0284] As regards the compounds of the invention which correspond to general formulae (I), (II) and (III) and in which Het is an imidazole ring, a person skilled in the art can also usefully consult the PCT Patent Application WO 99/64401.

[0285] The preparations of the other compounds of the invention which correspond to general formulae (I), (II) and (III) are carried out in a similar fashion to those described in the PCT Patent Application WO 98/58934 (cf. in particular on pages 39 to 45 of this document the elaboration of intermediates of general formulae (XXV) and (XXVIII)) or according to the procedures described hereafter.

Preparation of the Compounds of General Formula (I)

[0286] The compounds of general formula (I) can be prepared by the 8 synthesis routes illustrated below (Diagram 1) starting from the intermediates of general formula (IV), (V), (VI), (VII), (VIII), (IX), (X) and (I) in which A, B, Q, R1, R2, Het and n are as defined above. L is a parting group such as for example a halogen, Alk is an alkyl radical, Gp is a protective group for an amine function, for example a 2-(trimethylsilyl)ethoxymethyl (SEM) group, and Gp' a protective group for an alcohol function, for example a group of benzyl, acetate or also silyl type such as tert-butylimidemethylsilyl, and finally A represents a bond or a \(-\text{CH}_2\text{CH}_2\text{CH}_3\), \(-\text{CO}-\text{CH}_2\text{CH}_2\text{CH}_3\), \(-\text{CH}_2\text{CH}_2\text{O}-\) or \(-\text{C}(\equiv \text{NH})-\) radical. Of course, a person skilled in the art can choose to use protective groups other than Gp and Gp' from those which are known, and in particular those mentioned in: Protective groups in organic synthesis, 2nd ed., (John Wiley & Sons Inc., 1991).

Diagram 1
Route 1: Het is Imidazole and K is NR\textsuperscript{46}\textsuperscript{47} but Not a Radical of Carbamate Type

[0287] The amines and carboxamides of general formula (I), Diagram 2, in which A, B, R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{46}, R\textsuperscript{47}, Het and n are as defined above, are prepared by deprotection for example, in the case where Gp represents SEM, with tert-butylammonium fluoride (TBAF) in THF, of the amine of general formula (IV) in order to release the amine of the heterocycle of the compound of general formula (I). The protected amines of general formula (IV) are accessible by a general synthesis route described in Biorg. and Med. Chem. Lett., 1993, 3, 915 and Tetrahedron Lett., 1993, 34, 1901 and more particularly in the PCT Patent Application WO 98/58934.

Diagram 2

Route 2: Het is Imidazole, Oxazole or Thiazole and Ω is NR\textsuperscript{46}\textsuperscript{47}

[0288] The amines and carboxamides of general formula (I), Diagram 3, in which A, B, R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{46}, Het, g, k and n are as defined above, Δ represents an alkyl, cycloalkylalkyl, aryalkyl, aryl, alkenyl, alkylalkyl, alkenyl, alkynyl, cyanoalkyl or hydroxyalkyl radical and Ω represents an alkyl, cycloalkylalkyl, aryalkyl or aryl radical when g or k do not represent 0, or Ω represents an alkyl, cycloalkylalkyl, aryalkyl radical or an aryl radical preferably deactivated (i.e. an aryl radical substituted by an electron attractor group such as for example a nitro or cyano group) when g or k represents 0, are prepared by condensation of the amines of general formula (V) with carboxylic acids (or the corresponding acid chlorides) of general formula (XIII) under standard conditions of peptide synthesis, with the aldehydes of general formula (XII) in the presence of a reducing agent such as sodium triacetoxoborohydride or sodium borohydride in a lower aliphatic alcohol such as methanol and optionally in the presence of molecular sieves, or with halogenated derivatives (Hal=halogen atom) of general formula (XI). In particular, when Ω represents an alkenyl, alkylalkyl, alkenyl, alkynyl, cyanoalkyl or hydroxyalkyl radical, the compounds of general formula (V) are converted to the corresponding compounds of general formula (I) by reaction with the halogenated derivatives of general formula (XI) in a solvent such as acetonitrile, dichloromethane or acetone and in the presence of a base such as for example triethylamine or potassium carbonate at a temperature comprised between ambient temperature and the reflux temperature of the solvent.

Diagram 3

[0289] The derivatives of general formula (V) are in particular accessible by a general synthesis route described in Biorg. and Med. Chem. Lett., 1993, 3, 915 and Tetrahedron Lett., 1993, 34, 1901, and more particularly in the Patent Application WO 98/58934. When R\textsuperscript{47}=H, the compounds of general formula (V) can be prepared, for example, according to a protocol described in the Patent Application WO 98/58934 (using the appropriate amino acid in place of N—Boc-sarcosinamide).

Diagram 3a

[0290] In the particular case where R\textsuperscript{47} represents a cycloalkyl radical, the amines of general formula (I), Diagram 3a, in which A, B, R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{46}, Het and n are as defined above and k represents an integer from 0 to 4 are prepared by condensation of the amines of general formula (V) with the cycloalkylketones of general formula (XIV) in the presence of a reducing agent such as sodium triacetoxoborohydride or sodium borohydride in a lower aliphatic alcohol such as methanol and optionally in the presence of molecular sieves at ambient temperature.

Diagram 3b

[0291] The sulphonamides of general formula (I), Diagram 3b, in which A, B, R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{46}, Het and n are as defined above, R\textsuperscript{47} represents an —SO\textsubscript{2} radical and Δ represents
an alkyl, cycloalkyl, cycloalkylalkyl or arylalkyl radical, are prepared by condensation of the amines of general formula (V) with the sulphonylchlorides of general formula (XV) under standard conditions, for example in a solvent such as dimethylformamide at ambient temperature.

Route 3: Het is Oxazole or Thiazole, R¹ and R² are both H and Ω is OH.

[0293] The alcholic derivatives of general formula (I), Diagram 4, in which A, B, Het and n are as defined above and R¹ and R² are hydrogen atoms are obtained by reduction of the acids or esters of general formula (VI) (accessible by a general synthesis route described in J. Med. Chem., 1996, 39, 237-245 and the PCT Patent Application WO 99/09829). This reduction can, for example, be carried out by the action of boron hydride or lithium aluminium hydride or also dibobutylaluminium hydride in an aprotic polar solvent such as tetrahydrofuran.

Route 5: Het is Imidazole and Ω is a Radical of Carbamate Type

[0295] When Ω is a radical of carbamate type, the acids of general formula (VIII) can be cyclized in the form of derivatives of imidazoles of general formula (I), Diagram 6, by the addition of caesium carbonate followed by a condensation with an α-halogenoalkene of formula A-CO—CH(B)—[Br, CI] followed by the addition of a large excess of ammonium acetate (for example 15 or 20-equivalents per equivalent of acid of general formula (VIII)). This reaction is preferably carried out in a mixture of xylenes and white
heating (one can also, if appropriate, simultaneously eliminate the water formed during the reaction).

Diagram 6

Route 6: Het is Imidazole, Oxazole or Thiazole and \( \Omega \) is NR\(^4\)R\(^5\)

[0296] When \( \Omega \) is an NR\(^4\)R\(^5\) radical in which R\(^4\) is a radical comprising a termination of aminophenylene, alkylaminophenylene or dialkylaminophenylene type, the compounds of general formula (I), in which A, B, Het, n, R\(^1\), R\(^2\), and R\(^6\) are as defined above and \( \Lambda \) represents a bond or a \(-\text{CH}_2\)\(^x\)\(\cdots\) radical, \( x \) and \( y \) being integers from 0 to 6, can be obtained, Diagram 7, by reduction of the compound of general formula (IX), for example by the action of hydrogen in the presence of a catalyst of palladium on carbon type in a solvent such as for example methanol, ethanol, dichloromethane or tetrahydrofuran. Reduction of the nitro function can also be carried out, for example, by heating the product in an appropriate solvent such as ethyl acetate with a little ethanol in the presence of SnCl\(_2\) (J. Heterocyclic Chem. (1987), 24, 927-930; Tetrahedron Letters (1984), 25 (8), 839-842) or in the presence of SnCl\(_2\)/Zn (Synthesis, (1996), 9, 1076-1078), using NaBH\(_4\)—BiCl\(_3\) (Synth. Com. (1995) 25 (23), 3799-3803) in a solvent such as ethanol, or then by using Raney Ni with hydrazine hydrate added to it (Monatshefte für Chemie, (1995), 126, 725-732), or also using indium in a mixture of ethanol and ammonium chloride under reflux (Synlett (1998) 9, 1028).

[0297] When R\(^7\) is a radical of aminophenylene, alkylaminophenylene or dialkylaminophenylene type (Alk and Alk' are identical or different alkyl radicals), the compound of general formula (IX) is reduced in order to produce the aniline derivative of general formula (I) and optionally mono- or di-alkylated according to standard reactions known to a person skilled in the art. The mono-alkylation is carried out by reducing amination with an aldehyde or by a nucleophilic substitution by reaction with an equivalent of halogenoalkyl Alk-Hal. A second alkylation can then be carried out if appropriate using a halogenoalkyl Alk'-Hal.
In the particular case where $\text{Alk}=$ and where $A$ does not represent $-\text{CH}=\text{CH}_2$, the nitro derivative of general formula (IX) will be treated with suitable quantities of paraformaldehyde under a flow of hydrogen in a solvent such as ethanol and in the presence of a catalyst of palladium on carbon type (Diagram 7a).

Route 7: Het is Imidazole, Oxazole or Thiazole and $\Omega$ is OH

This route can be used when $\Omega$ is OH. Contrary to route 3, $R^1$ and $R^2$ cannot be hydrogen atoms. In this case, the compounds of general formula (I) can be obtained, Diagram 8, by deprotection of the protected alcohol of general formula (X).

Route 8: Het is Imidazole, Oxazole or Thiazole and $\Omega$ is OR with $R^{48}$H

The compounds of general formula (I) in which $\Omega$ is an OR radical with $R^{48}$ H are obtained, for example, from alcohols of general formula (Ia) which are compounds of general formula (I) as defined previously in which $Q$ represents OR) by reacting the latter with a halide of general formula $R^{48}$Hal (Hal=Br, Cl or I) in a solvent such as dichloromethane, acetonitrile, anhydrous tetrahydrofuran or anhydrous ether and in the presence of a base such as potassium or sodium carbonate, sodium hydride or triethylamine.

In the case where the A, B, $R^1$, and $R^2$ radicals contain alcohol, amine or amine, functions, it may be necessary to add protection/deprotection stage for these functions according to standard methods known to a person skilled in the art (stages not represented in Diagram 9).

Preparation of the Synthesis Intermediates

Preparation of the Imidazoles and Thiazoles of General Formula (V)

General Outline

The non-commercial ketonic derivative of general formula (V.i) or (V.i), in which A and B are as defined in
general formula (I) is converted, Diagram 3.1, to the corresponding α-bromo-ketone of general formula (V.ii) or (V.iii), by reaction with a bromination agent such as CuBr₂ (J. Org. Chem. (1964), 29, 3459), bromine (J. Het. Chem. (1988), 25, 337), N-bromosuccinimide (J. Amer. Chem. Soc. (1980), 102, 2838) in the presence of acetic acid in a solvent such as ethyl acetate or dichloromethane, HBr or Br₂ in ether, ethanol or acetic acid (Biorg. Med. Chem. Lett. (1996), 6(3), 253-258; J. Med. Chem. (1988), 31(10), 1910-1918 J. Am. Chem. Soc. (1999), 121, 24) or also using a bromination resin (J. Macromol. Sci. Chem. (1977), A11, (3) 507-514). Alternatively to the synthesis shown in Diagram 3.1, a person skilled in the art can, if appropriate, use an α-chloro-ketone in place of an α-bromo-ketone.

Hydrogenation in the presence of palladium on carbon when the protective group is a benzyl carbamate.

Diagram 3.2

Diagram 3.1

[0304] Alternatively to the synthesis shown in Diagram 3.1, a person skilled in the art can, if appropriate, use an α-chloro-ketone in place of an α-bromo-ketone.

Obtaining the Imidazoles of General Formula (V)

The acid of general formula (V.iii), in which Gp represents a protective group for an amine function, for example a protective group of carbamate type, is treated, Diagram 3.2, with Cs₂CO₃ in a solvent such as methanol or ethanol. The α-halogeno-ketone of general formula (V.ii) in an inert solvent such as dimethylformamide is added to the caesium salt recovered. The intermediate ketoester is cyclized by heating to reflux in xylene (mixture of isomers) in the presence of a large excess of ammonium acetate (15 or 20 equivalents for example) in order to produce the imidazole derivative of general formula (V.iv) (the water formed being optionally eliminated during the reaction).

In the case where R₃₈ is not H, the amine function of the imidazole ring of the compound of general formula (V.iv) is substituted by reaction with the halogenated derivative R₃₈-Hal (Hal=halogen atom); the protected amine function is then deprotected under standard conditions (for example: trifluoroacetic acid or HCl in an organic solvent when it is a protective group of carbamate type, or also hydrogenation in the presence of palladium on carbon when the protective group is a benzyl carbamate).

Diagram 3.2

Obtaining the Thiazoles of General Formula (V) Intended for the Preparation of Compounds of General Formulae (I₁) or (I₂):
[0307] The thiocarboxamide of general formula (V.v), in which Gp represents a protective group for an amine function, for example a protective group of carbamate type, is obtained for example by reaction of the corresponding carboxamide with Lawesson reagent or with \((P,S)_2\), is reacted, Diagram 3.3, with the \(\alpha\)-bromo-ketone of general formula (V.ii) or (V.ii), according to an experimental protocol described in the literature (J. Org. Chem., 1995, 60, 5638-5642). The protected amine function is then deprotected under standard conditions in a strong acid medium (for example: trifluoroacetic acid or HCl in an organic solvent when it is a protective group of carbamate type), releasing the amine of general formula (V).

![Diagram 3.3]

Obtaining the Thiazoles (V) Intended for the Preparation of Compounds of General Formula (I):

[0308] These compounds are obtained according to a method summarized in Diagram 3.4 below. The carboxamide of general formula (VII.ii) is reacted with the halogenated derivative of general formula (V.vii). The protected amine of general formula (V.ii) thus obtained is then deprotected under standard conditions for a person skilled in the art in order to produce the compound of general formula (V) (for example: trifluoroacetic acid or HCl in an organic solvent when Gp is a protective group of carbamate type).

![Diagram 3.4]

Obtaining the Oxazoles of General Formula (V) Intended for the Preparation of Compounds of General Formula (I):

[0309] These compounds are obtained according to a method summarized in Diagram 3.5 below. The carboxamide of general formula (VII.ii) is reacted with the halogenated derivative of general formula (V.vii). The protected amine of general formula (V.ii) thus obtained is then deprotected under standard conditions for a person skilled in the art in order to produce the compound of general formula (V) (for example: trifluoroacetic acid or HCl in an organic solvent when Gp is a protective group of carbamate type).
Preparation of the Ketonic Derivatives of General Formula (V.i) and of Certain α-Bromoketonic Derivatives of General Formula (V.ii), (V.ii) or (V.ii)

[0310] The non-commercial ketonic derivatives of general formula (V.i) or their α-bromoketonic homologues are accessible from methods in the literature or similar methods adapted by a person skilled in the art. In particular:

[0311] when A represents an indoliny1 or tetrahydroquinolyl radical, the compounds of general formula (V.i) are accessible from methods in the literature such as for example J. Med. Chem. (1986), 29, (6), 1009-1015 or J. Chem. Soc., Perkin Trans. 1 (1992), 24, 13401-3406;

[0312] Alternatively, the compounds of general formula (V.ii) in which A represents an indoliny1 or tetrahydroquinolyl radical in which R3 does not represent H can be synthesized according to a protocol which is slightly modified compared to that described in J. Chem. Soc., Perkin Trans. 1 (1992), 24, 3401-3406. This protocol is summarized in Diagram 3.6 below.

Diagram 3.6

[0313] The indolene or tetrahydroquinoline (T represents —CH2— or —(CH2)n—) is protected using chloroacetyl chloride in order to produce the compound of general formula (XVII) which is subjected to a Friedel-Crafts reaction (substituted chloroacetyl chloride of general formula (XVIII), in which B has the meaning, indicated previously, in a solvent such as carbon disulphide and in the presence of aluminium chloride) in order to produce the compound of general formula (XIX). Then the compound of general formula (XIX) is hydrolyzed in the presence of acid, for example an acetic acid/HCl mixture, in order to produce the compounds of general formula (V.ii) in the form of a mixture of meta and para isomers. These isomers can be separated by fractional crystallization from a solvent such as glacial acetic acid.

[0314] A person skilled in the art will know how to adapt the syntheses described previously to the case where A represents an indoliny1 or tetrahydroquinolyl radical in which R3 does not represent H. For example, when R3 represents an alkyl or aralkyl radical, the protection and deprotection stages will be unnecessary.

when A represents a radical of 4-(4-hydroxyphenyl)-phenyl type, the compounds of general formula (V.i) are accessible from methods in the literature such as for example J. Org. Chem., (1994), 59(16), 4482-4489.

[0315] Alternatively, the compounds of general formula (V.i) and (V.ii) in which A represents a radical of 4-(4-hydroxyphenyl)-phenyl type are accessible for example by the method illustrated in Diagram 3.7 below.

Diagram 3.7
The compounds of general formula (V.i) or (V.ii), in which S₁, S₂, S₃, and S₄ are chosen independently from a hydrogen atom and OH, cyano, nitro, alkyl, alkoxy or —NR R¹¹ as defined in general formula (I), are prepared, Diagram 3.7, from the esters of general formula (XX) (cf. in particular Chem. Lett. (1998), 9, 931-932 and Synthesis (1993), 8, 788-790). Of course, the phenol or aniline functions resulting from the nature of the R¹⁰, R¹⁰, R¹¹, S₁, S₂, S₃ and S₄ substituents can lead a person skilled in the art to add to the stages represented in Diagram 3.7 protection stages (and, subsequently in the synthesis of the compounds of general formula (I), deprotection stages) of these functions so that they do not interfere with the remainder of the chemical synthesis. The esters of general formula (XX) are hydrolyzed in order to produce the acids of general formula (XXI). The latter are then subjected to coupling with N,O-dimethylhydroxylamine (Syn. Commun. (1995), 25(8), 1255; Tetrahedron Lett. (1999), 40(3), 411-414) in a solvent such as dimethylformamide or dichloromethane, in the presence of a base such as triethylamine with dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and hydroxybenzotriazole, in order to produce the intermediates of general formula (XXII). The compounds of general formula (V.i) are prepared from the compounds of general formula (XXII) by a substitution reaction with MeLi (J. Med. Chem. (1992), 35(13), 2392).

The bromoacetophenones of general formula (V.ii) are now accessible from the acetophenone of general formula (V.i) under the conditions described previously.

when A represents a carbazoyl radical, the compounds of general formula (V.i) are accessible from methods in the literature such as for example J. Org. Chem., (1951), 16, 1198 or Tetrahedron (1980), 36, 3017.

Alternatively, the compounds of general formula (V.ii) in which A represents a carbazoyl radical in which R9 represents H can be synthesized according to a protocol which is slightly modified with respect to that described for A=carbazoyl in Tetrahedron (1980), 36, 3017. This method is summarized in Diagram 3.8 hereafter:

The carbazole of general formula (XXIII) is protected using acetic anhydride in order to produce the compound of general formula (XXIV), which is subjected to a Friedel-Crafts reaction (substituted chloroacetyl chloride of general formula (XVIII) as defined previously in a solvent
such as carbon disulphide and in the presence of aluminium chloride) in order to produce the compound of general formula (XXV).

[0319] Then the acyl group protecting the amine function is hydrolyzed in the presence of acid, for example an AcOH/HCl mixture, in order to produce the compound of general formula (V.ii). When A represents a carboazolyl radical in which R⁵ represents alkyl or a —COR¹⁵ group (case not shown in Diagram 3.8), the initial acylation stage is unnecessary and the last two stages of Diagram 3.8 allow the compounds of general formula (V.ii) to be obtained. Of course, the phenol or aniline functions resulting from the nature of the R⁴, R⁵, R⁶, R⁷ and R⁸ substituents can lead a person skilled in the art to add to the stages represented in Diagram 3.8 protection stages (and, subsequently in the synthesis of the compounds of general formula (I), deprotection stages) of these functions so that they do not interfere with the remainder of the chemical synthesis.

when A represents a phenothiazinyl radical, the intermediates of general formula (V.i) and (V.ii) are accessible from methods in the literature; J. Heterocyclic Chem. (1978), 15, 175-176 and Arzneimittel Forschung (1962), 12, 48.

[0320] Alternatively, the intermediates of general formula (V.ii) in which A represents a phenothiazinyl radical can be prepared according to a protocol which is slightly modified with respect to that described for the phenothiazinyl radical in Arzneimittel Forschung (1962), 12, 48, which is summarized in Diagram 3.9 hereafter (see also the examples). The phenothiazine of general formula (XXVI) is protected using chloroacetyl chloride in order to produce the compound of general formula (XXVII), which is then subjected to a Friedel-Crafts reaction (compound of general formula (XVIII) in a solvent such as carbon disulphide in the presence of aluminium chloride) in order to produce the compound of general formula (XXVIII). During the last stage of the process, hydrolysis with HCl/acetic acid is accompanied by a halogen exchange and allows the chloroketone of general formula (V.ii) to be obtained. Of course, the phenol or aniline functions resulting from the nature of the R⁴, R⁵, R⁶, R⁷ and R⁸ substituents can lead a person skilled in the art to add to the stages shown in Diagram 3.9 protection stages (and, subsequently in the synthesis of the compounds of general formula (I), deprotection stages) of these functions so that they do not interfere with the remainder of the chemical synthesis.

when A represents a phenylaminophenyl radical, the compounds of general formula (V.i) are accessible from methods in the literature such as for example Chem. Commun., (1998), 15, (6) 1509-1510 or Chem Ber., (1986), 119, 3165-3197, or similar methods which a person skilled in the art will have adapted.

[0321] For example, the intermediates of general formula (V.ii) in which A represents a phenylaminophenyl radical (which correspond to the corresponding compounds of general formula (V.i) and (V.ii) the aniline function of which has been acetylated), can be prepared according to a protocol which is slightly modified with respect to that described for the phenylaminophenyl radical in Chem Ber., (1986), 119, 3165-3197. This protocol is summarized in Diagram 3.10 hereafter.
[0322] In the case (shown in Diagram 3.10) where the R<sup>5</sup> radical of the compound of general formula (I) to be synthesized is a hydrogen atom or an acetyl group, the diphenylamine of general formula (XXIX) formed after the coupling reaction in the presence of CuI is protected by acetylation using, for example, acetic anhydride in order to produce the compound of general formula (V.i)a. In the case (not shown in Diagram 3.10) where the R<sup>9</sup> radical of the compound of general formula (I) to be synthesized is not a hydrogen atom or an acetyl radical, the acetylation stage is replaced by a substitution stage of the aniline according to standard methods known to a person skilled in the art in order to produce the corresponding compound of general formula (V.i). The compound of general formula (V.i)a (or (V.i), in the case not shown in Diagram 3.10) is then subjected to a bromination reaction using a bromination resin, PVP/H resin (Poly(VinylPyridinium Hydrobromide Perbromide), described in J. Macromol. Sci. Chem. (1977), A11, (3), 507-514, in order to produce the compound of general formula (V.ii)a or (V.ii), in the case not shown in Diagram 3.10). Of course, the phenol or aniline functions resulting from the nature of the R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> substituents can lead a person skilled in the art to add to the stages shown in Diagram 3.10 protection stages (and, subsequently in the synthesis of the compounds of general formula (I), deprotection stages) of these functions so that they do not interfere with the remainder of the chemical synthesis. The deprotection of the acetylated aniline function will be carried out in principle during the latter stage of the synthesis of the compounds of general formula (I).

when A represents a benzopyran or benzofuran radical as defined in general formula (I) with R<sup>52</sup> representing a hydrogen atom, the intermediates of general formula (V.ii)

[0323] The compounds of general formulæ (V.i) and (V.ii), according to Diagram 3.11, in which T is as defined above and Gp=protective group, are prepared from the acids of general formula (XXX). The acids of general formula (XXX) are subjected to coupling with N,O-dimethylhydroxylamine (Syn. Commun. (1995), 25, (8), 1255; Tetrahedron Lett. (1999), 40, (3), 411-414) in a solvent such as dimethylformamide or dichloromethane, in the presence of a base such as triethylamine with dicyclohexylcarbodimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride and hydroxybenzotriazol, in order to produce the intermediates of general formula (XXXI). The protection of the phenol function in the form of a benzylated or tert-butylmethyldimethylsilylated derivative or by other protective groups (Gp) known to a person skilled in the art is then carried out in order to produce the compounds of general formula (XXXII). The compounds of general formula (V.i)
are prepared from the compounds of general formula (XXXII) by a substitution reaction with a Grignard reagent, MeMgCl (J. Het. Chem. (1990), 27, 1709-1712) or with MeLi (J. Med. Chem. (1992), 35, 13). The bromoacetophenones of general formula (V.ii) are now accessible from the acetophenone of general formula (V.i) under previously described conditions.

[0324] Alternatively, the compound of general formula (V.ii) in which R² represents a hydrogen atom or an alkyl radical can be prepared according to a process in only 3 stages (cf. Diagram 3.12—see also the examples). In this process, the bromination in the last stage of the compound of general formula (V.i) in order to produce the compound of general formula (V.ii) will preferably be carried out according to J. Am. Chem. Soc. (1999), 121, 24.

[Diagram 3.12]

Diagram 3.12

[Diagram 3.13]

Diagram 3.13

[0325] When A represents a substituted phenol radical, it can be necessary to use intermediates of general formula (V.ii) as defined previously the phenol function of which has been acetylated (hereafter designated as compounds of general formula (V.ii)b). In particular:

[0326] when A represents a 4-hydroxy-3,5-diisopropylphenyl radical, the homologous α-bromoketonic derivatives of the compound of formula (V.ii) the phenol function of which is protected by an acetyl radical can be prepared as summarized in Diagram 3.13 hereafter.

[0327] 2,6-diisopropylphenol is acetylated according to methods known to a person skilled in the art, for example by reacting it with acetic acid in the presence of trifluoroacetic acid anhydride or with acetyl chloride in the presence of a base such as for example K₂CO₃. The acetylated homologue of 2,6-diisopropylphenol is then subjected to a Fries rearrangement in the presence of aluminium chloride in a solvent such as nitrobenzene in order to produce the compound of formula (V.i). Then the compound of formula (V.i) is acetylated in order to produce the compound of formula (V.ii)b. The protection stage to release the phenol function will occur subsequently in the synthesis of the compounds of general formula (I) (at the time considered most appropriate by a person skilled in the art).

[0328] when A represents a radical of dimethoxyphenol type, the compounds of general formula (V.ii)b can be prepared in a similar fashion to the synthesis described for the compound of formula (V.ii)b derived from 2,6-diisopropylphenol, optionally with a few minor modifications within the scope of a person skilled in the art. For example, when A represents the 3,5-dimethoxy-
4-hydroxyphenyl radical, the corresponding α-bromoketonic derivative of formula (V.ii)b can be prepared, for example, as indicated in Diagram 3.13 from the commercial compound of formula (XXXV):

\[ \text{Diagram 3.13} \]

The compounds of general formula (V.ii) in which A and B are as defined previously can be prepared according to the method summarized in Diagram 3.15 hereafter.

\[ \text{Diagram 3.15} \]

Moreover, the non-commercial (X-halogenoketonic derivatives of general formula (V.vii) are accessible from methods in the literature. In particular, they can be obtained according to a procedure summarized in Diagram 3.16.

\[ \text{Diagram 3.16} \]

The protected amino acids of general formula (XXXVIII) are obtained by protection of the corresponding amino acids by a group of carbamate type according to methods known to a person skilled in the art. The acids of general formula (XXXVIII) are then subjected to coupling with N,O-dimethylhydroxylamine (Syn. Commun. (1995), 25, (8), 1255; Tetrahedron Lett. (1999), 40, (3), 411-414) in a solvent such as dimethylformamide or dichloromethane, in the presence of a base such as triethylamine with dicyclohexylcarbodiimide or 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride and hydroxybenzotriazol, in order to produce the intermediates of general formula (XXXVII). The compounds of general formula (V.ii) can now be accessed from the ketones of general formula (V.ii) under the conditions previously described.
a solvent such as dimethylformamide or dichloromethane, in the presence of a base such as triethylamine with dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and hydroxybenzotriazole, in order to produce the intermediates of general formula (XXXIX). The compounds of general formula (XLI) are prepared from the compounds of general formula (XXXIX) by a substitution reaction with lithium compound or magnesium compound derivatives of general formula (XL) (in which Hal=I, Br or Cl) in solvents such as ether or anhydrous tetrahydrofuran. The benzo or chloroacetophenones of general formula (V.vi) are now accessible from the acetophenone of general formula (XL) under the conditions previously described.


Preparations of the Compounds of General Formula (V.vi)

[0334] The acid derivatives of general formula (V.vi) can be obtained, Diagram 3.17, directly by reaction of the commercial amino acid of general formula (V.vi) with the compounds of (ar)alkylchlorofromate or di(ar)alkylcarbonate type (A represents an alkyl or benzyl radical) under standard conditions known to a person skilled in the art.

Preparation of the Acid Derivatives of General Formula (V.vi)

[0335] The thiocarboxamides of general formula (V.v) can be obtained in three stages starting from the compounds of general formula (V.vi) as indicated in the Diagram 3.18 below. The amine function of the amino acid of general formula (V.vi) is firstly protected under standard conditions with tBz-O—CO—Cl or tBz-O—CO₂OT (or other protective groups known to a person skilled in the art), then the intermediate obtained is converted to its corresponding amide by methods described in the literature (cf. for example, J. Chem. Soc. Perkin Trans. 1, (1998), 20, 3479-3484 or the PCT Patent Application WO 99/09829). Finally, the carboxamide is converted to the thiocarboxamide of general formula (V.v), for example by reaction with Lawesson reagent in a solvent such as dioxane or tetrahydrofuran at a temperature preferably comprised between ambient temperature and the reflux temperature of the mixture, or also using (P₂S₅)₂ under standard conditions for a person skilled in the art.

Preparation of the Acids of General Formula (VI)

[0336] Alternatively, the thiocarboxamides of general formula (V.v) can also be obtained, Diagram 3.19, by the addition of H₂S on the corresponding cyanide derivatives of general formula (V.x) under standard conditions known to a person skilled in the art.

Preparation of the Acid Derivatives of Thiazoles of General Formula (VI)

[0337] The acids of general formula (VI) derived from thiazoles can be prepared according to the procedures represented in Diagram 4.1 below.
The carboxamides of general formula (VII.ii) are treated under standard conditions in order to produce the thiocarboxamide of general formula (VII.iii), for example by Lawesson reagent or also using (P₂S₃)₂ under standard conditions for a person skilled in the art. Alternatively the acid of general formula (VII.i) is activated by the action of 1,1'-carbonyldimidazole then treated with methylamine in an aprotic polar solvent such as for example tetrahydrofuran. The carboxamide intermediate obtained is converted to the thiocarboxamide of general formula (VI.i) under standard conditions, for example using Lawesson reagent or also using (P₂S₃)₂ under standard conditions for a person skilled in the art. The thiocarboxamide of general formula (VII.iii) or (VI.i) is then reacted with the compound of general formula (VI.ii), for example while heating at reflux in a solvent such as benzene, dioxane or dimethylformamide. The ester of general formula (VI.iii) obtained can then be saponified by the action of a base such as for example potassium in alcoholic medium or LiOH in tetrahydrofuran in order to produce the acid of general formula (VI).

Preparation of the Acid Derivatives of oxazoles of General Formula (VI)

The acids of general formula (VI) derived from oxazoles can be prepared according to a procedure represented in Diagram 4.2 below.

The carboxamides of general formula (VII.ii) are reacted with the compound of general formula (VI.ii) while heating, for example at reflux, in the absence or in the
presence of a solvent such as dimethylformamide. The ester of general formula \((VI.iv)\) obtained can then be saponified by the action of a base such as for example potash in alcoholic medium or LiOH in tetrahydrofuran in order to produce the acid of general formula \((VI)\).

Preparation of the Acid Derivatives of Isoxazolines of General Formula \((VI)\)

[0342] The acid derivatives of isoxazolines of general formula \((VI)\), used in the preparation of compounds of general formula \((I)\), can be prepared according to a procedure represented in Diagram 4.3 below.

![Diagram 4.3](attachment:Diagram4.3.png)

\[
\text{Diagram 4.3}
\]

\[(VI.v) \xrightarrow{\text{NH}_2\text{OH}} (VI.vi) \xrightarrow{\text{Cl}} (VI.vii)
\]

The acids of general formula \((VI)\) derived from isoxazolines can be prepared as follows: the commercial aldehydes of general formula \((VI.v)\) are reacted with hydroxylamine hydrochloride. The oxime of general formula \((VI.vi)\) thus obtained is activated in the form of oxime chloride, of general formula \((VI.vii)\), by reaction with N-chlorosuccinimide in DMF before reacting with the esters of general formula \((VI.viii)\) (in which Alk represents an alkyl radical) in order to produce the isoxazoline derivatives according to an experimental protocol described in the literature (Tetrahedron Lett., 1996, 37 (26), 4455; J. Med. Chem., 1997, 40, 50-60 and 2064-2084). Saponification of the isoxazolines of general formula \((VI.ix)\) is then carried out in a standard fashion (for example by the action of KOH in an alcoholic solvent or LiOH in a solvent such as tetrahydrofuran) in order to produce the acid derivative of general formula \((VI)\).


Preparation of the Thiazoles and Oxazoles of General Formula \((VII)\)

General Outline

[0345] The acids of general formula \((VII.i)\), Diagram 5.1, are converted to the corresponding carboxamides of general formula \((VII.ii)\) by methods described in the literature (cf. for example, J. Chem. Soc., Perkin Trans. 1, (1998), 20, 3479-3484 or the PCT Patent Application WO 99/09829). The compounds of general formula \((VII)\) can then be obtained in a standard fashion according to the procedures represented in Diagrams 5.2 and 5.3 (thiazoles) and Diagram 5.4 (oxazoles) hereafter.

[0346] This synthesis route is useful for then preparing the compounds corresponding to general sub-formulæ \((I)_{1}\) and \((I)_{3}\).

![Diagram 5.1](attachment:Diagram5.1.png)

Obtaining the Thiazoles of General Formula \((VII)\)

[0347] When \(R^{1}\) and \(R^{2}\) both represent H, the thiazoles of general formula \((VII)\) intended for the preparation of compounds of general formula \((I)\) can be prepared according to the method summarized in Diagram 5.2. The carboxamide of general formula \((VII.ii)\) is converted to the corresponding thio carboxamide of general formula \((VII.iii)\) in the presence of Lawesson reagent in a solvent such as dioxane or benzene at a temperature preferably comprised between ambient temperature and that of reflux of the mixture. The thio carboxamide of general formula \((VII.iii)\) is then treated with the \(\alpha\)-halogenoketoester of general formula \((VII.iv)\) in which Alk represents an alkyl radical (for example methyl, ethyl or tert-butyl), in order to produce the ester of general formula \((VII.v)\), which is reduced to the corresponding alcohol of general formula \((VII.vi)\), for example by the action of lithium aluminium hydride or disobutylaluminium hydride in a solvent such as tetrahydrofuran. This latter can then be converted to a halogenated derivative of general formula \((VII)\) according to the methods known to a person skilled in the art, for example, in the case of a brominated derivative \((L=Br)\), by reaction with \(\text{CBr}_3\) in the presence of triphenylphosphine in dichloromethane at ambient temperature.
The thiazoles of general formula (VII) intended for the preparation of compounds of general formula (I) can be prepared according to the method summarized in Diagram 5.3. The cyano derivative of general formula (VII.vii) in which Gp' is a protective group for an alcohol function (for example a benzyl or —CO-σ group in which σ represents alkyl, for example methyl or tert-butyl) is converted to the corresponding thiocarboxamide of general formula (VII.viii) by the action of H₂S in a solvent such as ethanol in the presence of triethanolamine at a temperature preferably comprised between ambient temperature and that of reflux of the mixture. The thiocarboxamide of general formula (VII.viii) is then treated with the α-halogenoketone of general formula (VII.ix) in order to produce the compound of general formula (VII.x), which is deprotected in order to produce the corresponding alcohol of general formula (VII.xi) according to methods known to a person skilled in the art (for example when Gp' is a protective group of acetate type, this is removed in situ by the action of an aqueous solution of sodium carbonate). This latter can then be converted to a halogenated derivative of general formula (VII) according to the methods known to a person skilled in the art, for example, in the case of a brominated derivative (L=Br), by reaction with CBr₃ in the presence of triphenylphosphine in dichloromethane at ambient temperature.
Obtaining the Oxazoles of General Formula (VII)

When R¹ and R² both represent H, the oxazoles of general formula (VII) intended for the preparation of compounds of general formula (I), can be prepared according to the method summarized in Diagram 5.4. The carboxyamide of general formula (VII.i) is treated with the α-halogenoketoester of general formula (VII.iv) in which Alk represents an alkyl radical (for example methyl, ethyl or tert-butyl), in order to produce the ester/acid of general formula (VII.xii). This latter is reduced to the corresponding alcohol of general formula (VII.xiii), for example by the action of lithium and aluminium hydride or diisobutylaluminium hydride in a solvent such as tetrahydrofuran when one starts from the ester or by the action of diboran in tetrahydrofuran when one starts from the acid. This latter can then be converted to a halogenated derivative of general formula (VII) according to methods known to a person skilled in the art, for example, in the case of a brominated derivative (L=Br), by reaction with CBr₃ in the presence of triphenylphosphine in dichloromethane at ambient temperature.

When A represents an indolyl radical, the acids of general formula (VII.i) are accessible from methods in the literature such as for example J. Het. Chem. (1993), 30, 1133-1136 or Tetrahedron (1967), 23, 3823;

When A represents a phenylaminophenyl radical, the acids of general formula (VII.i) are accessible from methods in the literature such as for example J. Amer. Chem. Soc. (1940), 62, 3208; Zh. Obsch. Khim. (1953), 23, 121-122 or J. Org. Chem. (1974), 1239-1243;


When A represents a radical of 4(4-hydroxyphenyl)-phenyl type, reference will be made for example to the following publication: Synthesis (1993) 788-790.

Preparation of the Compounds of General Formula (VIII)

When R¹ and R² both represent H, the protected amino acids of general formula (VIII) are either commercial, or obtained by protection of commercial amino acids by a group of carbamate type according to the methods known to a person skilled in the art.

When at least one of R¹ and R² is not H, and n=0, the protected amino acids of general formula (VIII) are obtained in one stage, Diagram 6.1, by alkylation, in a solvent such as tetrahydrofuran and at low temperature, of commercial compound of general formula (VIII.i) using 3 equivalents of butyllithium and approximately one equivalent of the halogenated derivative of general formula (VIII.i) in which R¹ represents a radical of alkyl, cycloalkyl, cycloalkylalkyl or arylalkyl type and Hal a halogen atom. Depending on the case, a second alkylation (not represented in Diagram 6.1) can be carried out in a similar fashion, thus allowing the compounds of general formula (VIII) to be obtained in which neither R¹ nor R² represents H.

Preparation of the Imidazoles, Thiazoles and Oxazoles of General Formula (IX)

The preparation of the intermediates of general formula (IX) is described in the Patent Application WO 98/58934 (cf. in particular pages 10 to 50 and the examples of this document) or carried out by analogy from commercial starting products.

Preparation of the Protected Alcohols of General Formula (X)

The acid of general formula (X.i) is successively treated, Diagram 8.1, with Cs₂CO₃, the compound of gen-
eral formula (Vii) and with NH₄OAc, in order to produce the compound of general formula (X). The reaction conditions are similar to those described above for this type of synthesis.

Preparation of the Compounds of General Formula (X) Derived from Thiocarboxylic Acids

[0361] The cyano derivative of general formula (X.ii) is treated, Diagram 8.2, with H₂S in order to produce the thioester of general formula (X.iii), which, condensed with the compound of general formula (V.ii), allows the compound of general formula (X) to be obtained. The reaction conditions are similar to those described above (Diagram 5.3) for this type of synthesis.

Preparation of the Acids of General Formula (XXXVI)

[0362] The non-commercial acids of general formula (XXXVI) are accessible from methods in the literature or similar methods adapted by a person skilled in the art. In particular:


[0364] when A represents a diphenylamine radical, the acids of general formula (XXXVI) can be accessed from methods in the literature: Chem. Ber., (1986), 119, 3165-3197; J. Heterocyclic. Chem. (1982), 15, 1557-1559; Chem. Abstr., (1968), 68, 68730c; or by adaptation of these methods by a person skilled in the art;

[0365] when A represents a radical of 4-(4-hydroxyphenyl)-phenyl type, the acids of general formula (XXXVI) can be accessed from methods in the literature such as for example Tetrahedron Lett. (1968), 4739 or J. Chem. Soc. (1961), 2898.

[0366] when A represents a carboxyl radical, the acids of general formula (XXXVI) can be accessed from methods in the literature such as for example J. Amer. Chem., (1946), 68, 2104 or J. Het. Chem (1975), 12, 547-549.


[0369] Of course, the phenol, amine or aniline functions resulting from the nature of the substituents on the A radical of the compounds of general formula (XXXVI) can lead a person skilled in the art to add protection/deprotection stages of these functions to the stages described so that they do not interfere with the rest of the chemical synthesis.

[0370] Unless defined otherwise, all the technical and scientific terms used here have the same meaning as that usually understood by an ordinary specialist in the field to which this invention belongs. Likewise, all publications, patent applications, all patents and all other references mentioned here are incorporated by way of reference.

[0371] The following examples are presented to illustrate the above procedures and must in no case be considered as limiting the scope of the invention.
EXAMPLES

Example 1

4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-2-thiazolemethanamine

[0372] This product is obtained according to the procedure described in the PCT Patent Application WO 98/58934. Alternatively, it can also be prepared according to the method described below.

1.1) N—Boc-sarcosinamide

[0373] 15.0 g (0.120 mmol) of sarcosinamide hydrochloride (N-Me-Gly-NH₂.HCl) is dissolved in dichloromethane containing 46.2 ml (0.265 mmol) of disopropylethylamine. The mixture is cooled down to 0°C. Then Boc—O—Boc (28.8 g; 0.132 mmol) is added in fractions and the mixture is stirred overnight at ambient temperature. The reaction medium is then poured into ice-cooled water followed by extraction with dichloromethane. The organic phase is washed successively with a 10% aqueous solution of sodium bicarbonate and with water, then finally with a saturated solution of sodium chloride. The organic phase is then dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from diisopropyl ether in order to produce a white solid with a yield of 72%. Melting point: 103°C.

1.2) 2-{{[(1,1-dimethylethoxy)carbonyl]methyl}amino-ethanethioamide

[0374] 16.0 g (0.085 mmol) of intermediate 1.1 is dissolved in dimethoxyethane (500 ml) and the solution obtained is cooled down to 5°C. Sodium bicarbonate (28.5 g; 0.34 mmol) is added in small portions, (PS₂)₅ (38.76 g; 0.17 mmol) are added. The reaction medium is allowed to return to ambient temperature under stirring over 24 hours. After evaporation of the solvents under vacuum, a 10% aqueous solution of sodium bicarbonate is added to the residue and the solution is extracted using ethyl acetate. The organic phase is washed successively with a 10% aqueous solution of sodium bicarbonate and with water, then finally with a saturated solution of sodium chloride. The organic phase is then dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from ether in order to produce a white solid with a yield of 65%. Melting point: 150-151°C.

1.3) 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{{(1,1-dimethylethoxy)carbonyl}methyl}-2-thiazolemethanamine

[0375] Intermediate 1.2 (4.3 g; 2.11 mmol) and bromo-1-(3,5-dinitro-butyryl-4-hydroxyphenyl)ethane (6.9 g; 2.11 mmol) are dissolved in benzene (75 ml) under an argon atmosphere, then the mixture is stirred at ambient temperature for 12 hours. The reaction medium is heated under reflux for 4 hours. After evaporation of the solvents, the residue is diluted with dichloromethane and washed with a saturated solution of NaCl. The organic phase is separated, dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 20% ethyl acetate in heptane) in the form of an oil which crystallizes very slowly in a refrigerator with a yield of 28%. Melting point: 126.5-127.3°C.

1.4) 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-2-thiazolemethanamine

[0376] 2.3 ml (29 mmol) of trifluoroacetic acid is added dropwise, at 0°C, to a solution of 2.5 g (5.8 mmol) of intermediate 1.3 and 2 ml (1.6 mmol) of triethylsilane in 50 ml of dichloromethane. After stirring for one hour, the reaction mixture is concentrated under vacuum and the residue is diluted in 100 ml of ethyl acetate and 50 ml of a saturated solution of NaHCO₃. After stirring and decantation, the organic phase is dried over magnesium sulphate, filtered and concentrated under vacuum. The residue is taken up in heptane in order to produce, after drying, a white solid with a yield of 73%. Melting point: 136°C.

1.5 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-2-thiazolemethanamine hydrochloride

[0377] 2.0 g (0.602 mmol) of intermediate 1.4 is dissolved in anhydrous ether. The solution is cooled down to 0°C. Then 18 ml (1.81 mmol) of a 1N solution of HCl in ether is added dropwise. The mixture is allowed to return to ambient temperature under stirring. After filtering and drying under vacuum, a white solid is obtained with a yield of 92%. Melting point: 185.3-186.0°C.

Example 2

2,6-di[tert-butyl]-4-[[2-[[methyl(2-propynyl)amino]methyl]-1,3-thiazol-4-yl]phenol

[0378] 0.52 ml (3.7 mmol) of triethyamine and an excess of 0.56 g (7.5 mmol) of chloropropargyl are added dropwise at 0°C, to a solution of 0.5 g (1.5 mmol) of the compound of Example 1 in 15 ml of acetonitrile. After stirring overnight, the reaction mixture is concentrated under vacuum and the residue is diluted with dichloromethane and 50 ml of a saturated solution of NaCl. After stirring and decantation, the organic phase is separated and dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 20% ethyl acetate in heptane). After evaporation, the pure fractions produce a white solid with a yield of 20%. Melting point: 210-215°C.


Example 3

2-[[4-[3,5-di[tert-butyl]-4-hydroxyphenyl]-1,3-thiazol-2-yl]methyl]methyl]aminoacetonitrile

[0380] The experimental protocol used is identical to that described for Example 2, chloroacetonitrile being used as starting product in place of the chloropropargyl. A beige solid is obtained with a yield of 54%. Melting point: 150-156°C.


Example 4

5-[[4-[3,5-di[tert-butyl]-4-hydroxyphenyl]-1,3-thiazol-2-yl]methyl]aminopentanenitrile

[0382] The experimental protocol used is identical to that described for Example 2, bromovaleronitrile being used as
starting product in place of the chloropropargyl. A yellow oil is obtained with a yield of 24%.

Example 5

6-[(4-[3,5-di(tet-butyl)-4-hydroxyphenyl]-1,3-thiazol-2-yl)ethyl]methyl]amino]hexanenitrile

The experimental protocol used is identical to that described for Example 2, bromohexanenitrile being used as starting product in place of the chloropropargyl. A red oil is obtained with a yield of 35%.

Example 6

2,6-di(tet-butyl)-4-((2-((2-hydroxyethyl)(methyl)amino)methyl)-1,3-thiazol-4-yl)phenol

The experimental protocol used is identical to that described for Example 2, 2-bromoethanol is used as starting product in place of the chloropropargyl. A yellow oil is obtained with a yield of 57%.

Example 7

4-((2-((benzyl(methyl)amino)methyl)-1,3-thiazol-4-yl)-2,6-di(tet-butyl)phenol

The experimental protocol used is identical to that described for Example 2, benzyl chloride being used as starting product in place of the chloropropargyl. A white solid is obtained with a yield of 52%. Melting point: 165-170°C.

Example 8

2,6-di(tet-butyl)-4-([4(phenyl-4-nitroanilino)meth-1-yl]-1,3-thiazol-4-yl)phenol

This product is obtained according to the procedure described in the PCT Patent Application WO 98/58934.

Example 9

2,6-di(tet-butyl)-4-((2-(4(dimethylamino)methyl-1-namino)methyl)-1,3-thiazol-4-yl)phenol

0.8 ml of paraformaldehyde and 0.10 g of 20% palladium on carbon is added to a solution of 0.5 g (1.1 mmol) of Example 8 in 20 ml of ethanol. The medium is placed under hydrogen for 4 hours. The catalyst is filtered out and the solvent evaporated to dryness. The expected product is obtained after chromatography on a silica column (eluent: 3% ethanol in dichloromethane). The expected compound is obtained in the form of a brown oil with a yield of 54%.

Example 10

benzyl[4-[3,5-di(tet-butyl)-4-hydroxyphenyl]-1,3-thiazol-2-yl]methylcarbamate

The compound is produced according to an experimental protocol described in the Patent Application WO 98/58934 (see preparation of intermediates 26.1 and 26.2), using Z-Gly-NH₂ in place of the N—BOC sarcosinamide. The expected compound is obtained in the form of a pale yellow oil with a yield of 99%.

Example 11

4-[2-(aminomethyl)-1,3-thiazol-4-yl]-2,6-di(tet-butyl)phenol

0.1 ml of a 40% solution of potassium hydroxide is added dropwise to a solution of 0.106 g (1.1 mmol) of the compound of Example 10 in 10 ml of methanol. After overnight stirring under reflux, the reaction mixture is concentrated under vacuum and the residue is diluted with dichloromethane and washed with a 1N solution of HCl then with 50 ml of a saturated solution of NaCl. The organic phase is separated and dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 5% ethanol in dichloromethane) in the form of a brown foam with a yield of 76%.

Example 12

2,6-di(tet-butyl)-4-([4(methyl)4-nitrobenzyl]-1-namino)methyl)-1,3-thiazol-4-yl)phenol

The experimental protocol used is identical to that described for Example 2, 4-nitro-benzyl bromide being used as starting product in place of the chloropropargyl. A yellow solid is obtained with a yield of 63%. Melting point: 114.4-111.7°C.

Example 13

4-((2-((4-aminobenzyl)(methyl)amino)methyl)-1,3-thiazol-4-yl)-2,6-di(tet-butyl)phenol

0.059 g (0.26 mmol) of SnCl₄·2H₂O and 0.017 g (0.26 mmol) of Zn are added successively to a solution of 0.05 g (0.107 mmol) of the compound of Example 12 in a mixture of 0.55 ml of glacial acetic acid and 0.07 ml of a 12N solution of HCl. The mixture is stirred for 18 hours at 20°C. The reaction mixture is then made basic by adding a 30% aqueous solution of NaOH. The product is then extracted using two times 50 ml of CH₂Cl₂. The organic solution is washed with 50 ml of saturated solution of MgSO₄, filtered and concentrated under vacuum. The residue is purified on a silica column (eluent: 5% ethanol in dichloromethane). A yellow gum is obtained with a yield of 52%.

Example 14

2,6-di(tet-butyl)-4-((2-[4(phenyl-4-nitroanilino)methyl]-1-namino)methyl)-1,3-thiazol-4-yl)phenol

0.5 g (1.57 mmol) of the compound of Example 9, 0.237 g (1.57 mmol) of 4-nitrobenzaldehyde and 1 g of previously activated pulverulent 4 Å molecular sieve are
added successively to a flask containing 30 ml of anhydrous MeOH, under an inert atmosphere. The reaction mixture is vigorously stirred for 18 hours before the addition, by portions, of 0.06 g (1.57 mmol) of NaBH₄. Stirring is maintained for another 4 hours before the addition of 5 ml of water. After a quarter of hour, the sieve is filtered out and the reaction mixture is extracted with two times 100 ml of CH₂Cl₂. The organic phase is washed successively with 50 ml of water then with 50 ml of salt water, dried over sodium sulphate, filtered and concentrated under vacuum. The residue is purified on a silica column (eluent: 50% ethyl acetate in heptane). A yellow oil is obtained with a yield of 55%.

Example 15

4-(2-[[4-amino(phenyl)amino]methyl]-1,3-thiazol-4-yl)-2,6-di(tert-butyl)phenol

Example 16

4-[3,5-bis(1,1-dimethylthethyl)-4-hydroxyphenyl]-N-methyl-N-(4-amino(phenyl))-1H-imidazole-2-methanamine

Example 17

4-[3,5-bis(1,1-dimethylthethyl)-4-hydroxyphenyl]-N-methyl-1H-imidazole-2-methanamine

Example 21

4-[3,5-bis-(1,1-dimethylthethyl)-4-hydroxyphenyl]-N-methyl-N-(4-amino(phenyl))-1H-imidazole-2-methanamine

is intermediate 22.7 of the PCT Application WO 98/58934

Example 22

3-[3,5-bis(1,1-dimethylthethyl)-4-hydroxyphenyl]-4,5-dihydro-5-isoxazoleethanolenol

is intermediate 28.1 of the PCT Application WO 98/58934

Example 23

2-[3,5-bis(1,1-dimethylthethyl)-4-hydroxyphenyl]-4-oxazoleethanol

is intermediate 1.6 of the PCT Application WO 99/09829; alternatively, this compound can also be obtained according to the procedure described in J. Med. Chem. (1996), 39, 237-245.

Example 24

4-[[4-(3,5-ditert-butyl-1,3-thiazol-2-yl)methyl]amino]butanenitrile

Example 25

2,6-ditert-butyl-4-[[3-nitrobenzyl]amino]methy1]-1,3-thiazol-4-yl]phenol

Example 26

2,6-ditert-butyl-4-[[2-[methyl(2-propynyl)amino]ethyl]-1,3-oxazol-2-yl]phenol

Example 27

The compound of Example 23 is converted to brominated derivative, intermediate 3, according to the procedure indicated in Diagram 1(c) of the PCT Application WO 99/09829. Then the brominated derivative (0.5 g; 1.31 mmol) is added to a solution of N-methylpropargylamine 0.34 ml (3.94 mmol) and potassium carbonate (1.11 g) in dimethylformamide (20 ml). After overnight stirring at 80°C, the reaction mixture is concentrated under vacuum and the residue is diluted with dichloromethane and 50 ml of a saturated solution of NaCl. After stirring and decantation, the organic phase is separated and dried over magnesium sulphate, filtered and concentrated under vacuum. The
expected product is obtained after chromatography on a silica column (eluent: 50% ethyl acetate in heptane). After evaporation, the pure fractions produce a yellow oil with a yield of 24%.

Example 27

\[
\text{[(2-[2-(3,5-ditert-butyl-4-hydroxyphenyl)-1,3-oxazol-4-yl]ethyl]methylamino} \text{acetoni} \text{trile}
\]

The experimental protocol used is identical to that described for Example 26, methylaminacetoni trile being used as starting product in place of the N-methylpropargylamine. A white solid is obtained with a yield of 56%. Melting point: 165-167.8° C.

Example 28

3\{[2-[2-(3,5-ditert-butyl-4-hydroxyphenyl)-1,3-oxazol-4-yl]ethyl]methylamino}propanenitrile

The experimental protocol used is identical to that described for Example 26, N-methyl-β-alaninetrile being used as starting product in place of the N-methylpropargylamine. A white solid is obtained with a yield of 56%. Melting point: 104-104.8° C.

Example 29

2,6-ditert-butyl-4-[4-[2-(1-piperazinyl)ethyl]-1,3-oxazol-2-yl]phenol hydrochloride

29.1 tert-butyl 4-[[2-[2-(3,5-ditert-butyl-4-hydroxyphenyl)-1,3-oxazol-4-yl]ethyl]-1-piperazinecarboxylate

The experimental protocol used is identical to that described for Example 26, tert-butyl piperazinecarboxylate being used as starting product in place of the N-methylpropargylamine. A brown oil is obtained with a yield of 72%.

Example 30

\[
\text{N-methyl[4-(10H-phenothiazin-2-yl)-1,3-thiazol-2-yl]methanamine hydrochloride}
\]

A stream of HCl gas is passed bubblewise into a solution at 0° C. of intermediate 29.1 (0.450 g; 9.27 mmol) in ethyl acetate (30 ml). The mixture is left to return to ambient temperature overnight. A stream of argon is passed through the reaction mass, then the powder obtained is filtered and washed with ethyl acetate then with ether in order to produce a white solid with a yield of 70%. Melting point: >200° C.

Example 31

butyl 2-[4-[1,1'-biphenyl]-4-yl]-1H-imidazol-2-yl)ethylcarbamate

31.1 N-(butoxycarbonyl)-β-alanine

A solution containing β-alanine (8.9 g; 0.1 mol) and 100 ml of a 1N solution of sodium hydroxide is cooled down to 10° C. n-butyl chloroformate (13.66 g; 0.1 mol) and 50 ml of a 2N solution of sodium hydroxide are added simultaneously. After stirring for 16 hours at 23° C., approximately 10 ml of a solution of concentrated hydrochloric acid (approximately 11 N) is added in order to adjust the pH to 4-5. The oil obtained is extracted with ethyl acetate (2×50 ml), washed with water then dried over magnesium sulphate. The product crystallizes from isopentane in the form of a white powder (yield of 68%). Melting point: 50.5° C.

Example 32

butyl 2-[4-[1,1'-biphenyl]-4-yl]-1H-imidazol-2-yl)ethylcarbamate

32.1 Mixture of N-(butoxycarbonyl)-β-alanine (prepared in Stage 31.1; 5.67 g; 0.03 mol) and caesium carbonate (4.89 g; 0.015 mol) in 100 ml of ethanol is stirred at 23° C. for 1 hour. The ethanol is eliminated by evaporation under
reduced pressure in a rotary evaporator. The mixture obtained is dissolved in 100 ml of dimethylformamide then 4-phenyl-bromocacetophenone (8.26 g; 0.03 mol) is added. After stirring for 16 hours, the solvent is evaporated off under reduced pressure. The mixture obtained is taken up in ethyl acetate then the caesium bromide is filtered. The ethyl acetate of the filtrate is evaporated and the reaction oil is taken up in a mixture of xylene (100 ml) and ammonium acetate (46.2 g; 0.6 mol). The reaction medium is heated at reflux for approximately one hour and 30 minutes then, after cooling down, a mixture of ice-cooled water and ethyl acetate is poured into the reaction medium. After decantation, the organic phase is washed with a saturated solution of sodium bicarbonate, dried over magnesium sulphate then evaporated under vacuum. The solid obtained is filtered then washed with ether in order to produce a light beige-coloured powder (yield of 50%). Melting point: 136.7°C.

Example 32

N-[2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethyl] pentanamide

32.1) tert-butyl 2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethylcarbamate

[0427] This compound is obtained according to an operating method similar to that of Stage 3.1.2 of Example 31, N-(tert-butoxycarbonyl)-l-alanine acid replacing the l-alanine. A yellow-coloured powder is obtained with a yield of 37%.

Example 33

N-[2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethyl]-1-butanesulphonamide

[0433] A mixture containing 2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethylamine (obtained in Stage 32.2 of Example 32; 660 mg; 0.0025 mol) and p-butyisulphoxide (390 mg; 0.0025 mol) in 20 ml of DMSO is stirred for two hours at 23°C. Potassium carbonate (345 mg; 0.0025 mol.) is then added, then stirring is continued for two hours. The solvent is evaporated off and the reaction mixture is taken up in water and dichloromethane. The organic phase is then washed with a saturated solution of sodium chloride then dried. The solvent is evaporated off and the residue obtained is purified on a silica column (eluent: CH₂Cl₂-MeOH/93-07). A light beige-coloured powder is obtained with a yield of 19%. Melting point: 168.5°C.

Example 34

4-[2-(2-[butylamino]carbonyl]amino)ethyl]-1H-imidazol-4-yl-1,1'-biphenyl

[0435] A mixture containing 2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethylamine (obtained in Stage 32.2 of Example 32; 660 mg; 0.0025 mol) and p-butyisulphoxide (341 mg; 0.0025 mol) in 20 ml of 1,2-dichloroethane is stirred for fifteen minutes at 60°C. The suspension is stirred for sixteen hours at 23°C. The mixture obtained is washed with 1,2-dichloroethane and then ether. A white-coloured powder is obtained with a yield of 66%. Melting point: 178°C.

Example 35

N-{[(S)-cyclohexyl][4-(4-fluorophenyl)-1H-imidazol-2-yl]methyl}cyclobutanamine

35.1 tert-butyl (S)-cyclohexyl[4-(4-fluorophenyl)-1H-imidazol-2-yl]methylcarbamate

[0437] This compound is obtained according to an operating method similar to the preparation of the compound of Stage 3.2.1 of Example 31 using Boc-aminocyclohexylglycine (9.4 g; 0.036 mol) in place of the N-(butoxycarbonyl)-l-alanine and parafluorobromocacetophenone (7.9 g; 0.036 mol) in place of the 4-phenyl-bromocacetophenone. A white-coloured powder is obtained with a yield of 53%.

Example 36

N-[2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethyl]pentanamide

[0431] A mixture containing valeric acid (0.24 ml; 0.002 mol), dicyclohexylcarbodiimide (2.2 ml; 1M solution in methylene chloride) and 1-hydroxybenzotriazole hydrate (336 mg; 0.0022 mol) in 15 ml of dimethylformamide (DMF) is stirred at 23°C. For thirty minutes. The 2-[4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl]ethylamine prepared previously is added then the mixture is stirred for 48 hours at 23°C. The dicyclohexylurea formed is filtered then the DMF is evaporated off under reduced pressure. The residue obtained is taken up in ethyl acetate then the residual dicyclohexylurea is filtered again. The filtrate is washed with water and then the solvent is evaporated off. The residue obtained is washed with ether. A white-coloured powder is obtained with a yield of 13%. Melting point: 166-167°C.

Example 37

N-[2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethyl]-1-butanesulphonamide

[0432] MIH+=348.2.

Example 38

35.2 (S)-cyclohexyl[4-(4-fluorophenyl)-1H-imidazol-2-yl]methanamine

[0439] This compound is prepared according to an operating method similar to that of Stage 3.2.2 of Example 32 using tert-butyl-(S)-cyclohexyl[4-(4-fluorophenyl)-1H-imidazol-2-yl]methylcarbamate (7.5 g; 0.02 mol) as starting compound. A white-coloured powder is obtained with a yield of 92%.

Example 39

MIH+=274.2.
35.3) **N-[(S)-cyclohexyl-[4-(4-fluorophenyl)-1H-imidazol-2-yl]methyl]cyclobutanamine**

**[0441]** A mixture containing (S)-cyclohexyl-[4-(4-fluorophenyl)-1H-imidazol-2-yl]methanamine (prepared in Stage 5.2; 519 mg; 0.0015 mol), triethylamine (0.4 ml; 0.003 mol) and butanone (140 mg; 0.002 mol) in 10 ml of methanol is stirred for thirty minutes at 23° C. Sodium triacetoxyborohydride (630 mg; 0.003 mol) is then added. The reaction mixture is stirred for sixteen hours then poured into water. After extraction with ethyl acetate, the organic phase is washed with a saturated solution of sodium chloride then dried over magnesium sulphate. The solvent is evaporated off and the residue is purified on a silica column (eluent: CH₂Cl₂-MeOH mixture/95:05). A white-coloured powder is obtained with a yield of 12%. Melting point: 170-172° C.

**[0442]** MH⁺=328.2.

**Example 36**

N-[1-(4-cyclohexyl-1H-imidazol-2-yl)heptyl]cyclohexanamine

36.1) 2-bromo-1-cyclohexylethanone

**[0443]** Cyclohexylacetone (5.4 ml, 0.039 mol) and bromine (2 ml; 0.039 mol) are stirred at 23° C in 100 ml of methanol. After decolorization, 100 ml of water are gently added. The mixture obtained is neutralized with 5 g of sodium bicarbonate. Extraction is carried out with ether followed by washing the organic phase with 100 ml of water. After drying over magnesium sulphate, the mixture is concentrated with a rotary evaporator. An oil is obtained with a yield of 97% c.

**[0444]** NMR ¹H (δ ppm, DMSO): 1.21-1.27 (m, 5H); 1.59-1.83 (m, 5H); 2.59-2.64 (m, 1H); 4.42 (s, 2H).

36.2) 2-[(tert-butoxycarbonyl)amino]octanoic acid

**[0445]** A mixture of 2-amino-octanoic acid (25.25 g; 0.156 mol) and di-tert-butyl dicarbonate (37.8 g; 0.173 mol) in 425 ml of dioxane is stirred at reflux for three hours. After returning to 23° C, the mixture is again stirred for twenty four hours then the insoluble part is filtered out. The filtrate is evaporated. An oil is obtained with a yield of 99%. NMR ¹H (δ ppm, DMSO): 0.85 (t, 3H); 1.11-1.27 (m, 8H); 1.37 (s, 9H); 1.51-1.65 (m, 2H); 3.81-3.87 (m, 1H); 6.96-6.97 (m, 1H); 12.3 (s, 1H).

**[0446]** IR (cm⁻¹): 3500; 2860; 1721 (νC=O (acid)); 1680 (νC=O (carbamate)); 1513 (νC=NH (carbamate)).

36.3) tert-butyl 1-(4-cyclohexyl-1H-imidazol-2-yl)heptylcarbamate

**[0447]** This compound is obtained according to an operating method similar to that of Stage 31.2 of Example 31, using 2-[(tert-butoxycarbonyl)amino]octanoic acid (8.1 g; 0.0314 mol) in place of the N-(butoxycarbonyl)-β-alanine and 2-bromo-1-cyclohexylethanone (6.4 g; 0.0314 mol) in place of the 4-phenyl-bromoacectophenone. An oil is obtained which is sufficiently pure to be used in the following reaction (yield of 88%).

36.4) 1-(4-cyclohexyl-1H-imidazol-2-yl)-1-heptanamine

**[0448]** This compound is obtained according to an operating method similar to that of Stage 32.2 of Example 32 using as starting compound tert-butyl 1-(4-cyclohexyl-1H-imidazol-2-yl)heptylcarbamate (prepared in Stage 6.3; 10 g; 0.0275 mol). A yellow solid is obtained in the form of a paste (yield of 37%).

**[0449]** MH⁺=264.2

36.5) **N-[1-(4-cyclohexyl-1H-imidazol-2-yl)heptyl]cyclohexanamine**

**[0450]** This compound is obtained according to an operating method similar to that of Stage 35.3 of Example 35 using as starting amine 1-(4-cyclohexyl-1H-imidazol-2-yl)-1-heptanamine (obtained in Stage 6.4; 2.5 g; 0.074 mol) and as ketone, cyclohexanone (1 ml; 0.0097 mol). After purification on a silica column (eluent: ethyl acetate—heptane/7:3 with CH₂Cl₂-MeOH/95:05), a white-coloured powder is obtained with a yield of 12%. Melting point: 172-174° C.

**[0451]** MH⁺=346.3.

**Example 37**

N-[1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methylthiethyl] -N-cyclohexylamine

37.1) 2-[(tert-butoxycarbonylamino]-6-methylheptanoic acid

**[0452]** A solution of diisopropylamine (13.2 ml; 0.094 mol) in 130 ml of tetrahydrofuran (THF) is cooled down to -40° C. n-butyllithium (37 ml of a 2.5 M solution in hexane; 0.094 mol) is added dropwise. The temperature is allowed to rise to 0° C. At this temperature, Boc-glycine (5 g; 0.028 mol) in solution in 30 ml of THF is introduced into the mixture. The reaction medium is left for ten minutes at this temperature then 1-bromo-4-methylpentane (7.9 ml; 0.056 mol) in solution in 20 ml of THF is added rapidly. The temperature is allowed to return to 23° C and the mixture is stirred at this temperature for one hour. After hydrolysis with 100 ml of water then acidification with 150 ml of a saturated solution of potassium hydrogen sulphate, the mixture obtained is extracted twice with 50 ml of ethyl acetate. The organic phase is washed with 100 ml of water then with 100 ml of a saturated solution of sodium chloride. After drying over magnesium sulphate and evaporating the solvent, the residue obtained is purified on a silica column (eluent: ethyl acetate—heptane/6:4) in order to produce a white-coloured powder with a yield of 50%.

**[0453]** MH⁺=260.3.

37.2) tert-butyl 1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methylhexylcarbamate

**[0454]** This compound is obtained according to an operating method similar to that of Stage 31.2 of Example 31 using 2-[(tert-butoxycarbonyl)amino]-6-methylheptanoic acid (3.5 g; 0.0135 mol) in place of the N-(butoxycarbonyl)-β-alanine and 3-bromophenacyl bromide (3.75 g; 0.0135 mol) in place of the 4-phenyl-bromoacectophenone. A white powder is obtained with a yield of 63%. Melting point: 134-136° C.

**[0455]** MH⁺=436.2.

37.3) 1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methyl-1-hexanamine

**[0456]** This compound is obtained according to an operating method similar to that of Stage 32.2 of Example 32.
using as starting compound tert-butyl 1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methylhexylcarbamate (obtained in Stage 37.2; 3.5 g; 0.008 mol). A white-coloured powder is obtained with a yield of 97%. Melting point: 200-202°C.

[0457] MIH+ = 336.2.

37.4 N-[1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methylhexyl]-N-cyclohexylamine

[0458] This compound is obtained according to an operating method similar to that of Stage 35.3 of Example 35 using as starting amine, 1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methyl-1-hexanamine (obtained in Stage 7.3; 0.8 g; 0.0019 mol) and as ketone, cyclohexanone (0.32 ml; 0.0023 mol). A white-coloured powder is obtained with a yield of 38%. Melting point: 236-238°C.

[0459] MIH+ = 418.2.

Example 38

N-[1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]heptyl]cyclohexylamine

38.1) tert-buty1 1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]heptylcarbamate

[0460] This compound is obtained according to an operating method similar to that of Stage 31.2 of Example 31 using 2-[tert-butoxycarbonyl]amino]octanoic acid (6.2 g; 0.024 mol) in place of the N-(butoxycarbonyl)-β-alanine and 2-bromo-4-fluorocacetophenone (5.2 g; 0.024 mol) in place of the 4-phenyl-bromoacetophenone. A white powder is obtained (yield: 58%) which is sufficiently pure to be used as it is for the following stage.

38.2) 1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-1-heptanamine

[0461] This compound is obtained according to an operating method similar to that of Stage 32.2 of Example 32 using as starting compound tert-buty1 1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]heptylcarbamate (5.2 g; 0.014 mol). After purification on a silica column (elucent: CH₂Cl₂-MeOH—NMeOH/H₂O/98910-1), a grey-coloured powder is obtained (yield of 72%). Melting point: 148-150°C.

[0462] MIH+ = 276.2.

38.3) N-[1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]heptyl]cyclohexylamine

[0463] This compound is obtained according to an operating method similar to that of Stage 35.3 of Example 35 using as starting amine, 1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-1-heptanamine (0.5 g; 0.0014 mol) and as ketone, cyclohexanone (0.17 ml; 0.0014 mol). A white-coloured powder is obtained with a yield of 15%.

[0464] Melting point: 190-192°C.

[0465] MIH+ = 358.2.

Example 39

(1R)—N-benzyl-1-(1-benzyl-4-tert-butyl-1H-imidazol-2-yl)-2-(1H-indol-3-yl)ethanamine

[0466] Triethylamine (0.83 ml; 0.006 mol) is added at 23°C. to a solution containing (1R)-1-(1-benzyl-4-tert-butyl-1H-imidazol-2-yl)-2-(1H-indol-3-yl)ethanamine (0.7 g; 0.002 mol; prepared under experimental conditions similar to those previously and using suitable starting reagents and reaction products) in 15 ml of acetonitrile. The mixture is stirred for one hour at 23°C. then benzyl chloride (0.23 ml; 0.002 mol) is added. Stirring is maintained for 16 hours. The reaction mixture is concentrated using a rotary evaporator and the oil obtained is taken up in ethyl acetate and water. The aqueous phase is extracted with ethyl acetate and washed with water then with a saturated solution of sodium chloride. The solvents are evaporated off under vacuum. After purification on a silica column (elucent: Al₂-heptane/7-3), a deep beige-coloured solid is obtained in the form of a paste (yield of 5% c). Free base. Melting point: 60-62°C.

[0467] MIH+ = 463.3.

Example 40

(R,S)—N-benzyl-1-[1-benzyl-4-phenyl-1H-imidazol-2-yl]-1-heptanamine

[0468] (R,S)-1-[4-(phenyl-1H-imidazol-2-yl)heptylamine (1 g; 0.003 mol; prepared under experimental conditions similar to those previously and using suitable starting reagents and reaction products) is diluted in 20 ml of dimethylformamide. Potassium carbonate (2.2 g; 0.016 mol) is added at 23°C. then benzyl bromide (1.2 ml; 0.010 mol) is added fairly slowly. The mixture is stirred for 72 hours at 23°C. before being poured into ice-cooled water. The mixture is extracted with ethyl acetate. The organic phase is washed with water then with a saturated solution of sodium chloride. After drying over magnesium sulphate, the solvents are concentrated using a rotary evaporator. After purification on a silica column (elucent: ethyl acetate-heptane/10-90), a white-coloured powder is obtained (yield of 31%). Free base. Melting point: 94-96°C.

[0469] MIH+ = 438.3.

Example 41

N-benzyl-N-[4-[1,1′-biphenyl]-4-yl-1H-imidazol-2-yl]methyl]-1-hexanamine

[0470] N-benzyl[4-[1,1′-biphenyl]-4-yl-1H-imidazol-2-yl]methanamine (1 g; 0.0024 mol; prepared under experimental conditions similar to those previously and using suitable starting reagents and reaction products) is diluted in 15 ml of dimethylformamide. Potassium carbonate (1 g; 0.0073 mol) is added at 23°C. then hexane bromide (0.34 ml; 0.0024 mol) is added fairly slowly. The reaction mixture is brought to about 70°C. for 3 hours before being poured into ice-cooled water. The mixture is extracted with ethyl acetate and the organic phase is washed with water. After drying over magnesium sulphate, the solvents are concentrated using a rotary evaporator. After purification on a silica column (elucent: ethyl acetate-heptane/7-3), a light yellow-coloured solid is obtained in the form of a paste (yield of 13%). Free base. Melting point: 120-122°C.

[0471] MIH+ = 424.3.

Example 42

N-benzyl[4-[1,1′-biphenyl]-4-yl-1H-imidazol-2-yl]-N-methylmethanamine

[0472] (4-[1,1′-biphenyl]-4-yl-1H-imidazol-2-yl]-N-methylmethanamine (1 g; 0.003 mol; prepared under experi-
mental conditions similar to those previously and using suitable starting reagents and reaction products) is diluted in 20 ml of dimethylformamide. Potassium carbonate (1.23 g; 0.009 mol) is added at 23°C then benzyl bromide (0.34 ml; 0.003 mol) is added dropwise. The reaction mixture is stirred at this temperature for 48 hours then poured into ice-cooled water. The mixture is extracted with ethyl acetate and the organic phase washed with water. After drying over magnesium sulphate, the solvents are concentrated using a rotary evaporator. After purification on a silica column (eluent: ethyl acetate-heptane-8:2), a white-coloured solid is obtained in the form of a paste (yield of 16%). Free base. Melting point: 106-108°C.

Example 43

(RS)-N,N-diethyl-1-(4-phenyl-1H-imidazol-2-yl)-1-heptanamine

Example 44

N-[1R)-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]2-pyrimidinamine

Example 45

(1-benzyl-4-phenyl-1H-imidazol-2-yl)-N,N-dimethylmethanamine

Example 46

(1R)-N-benzyl-2-(1H-indol-3-yl)-N-methyl-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

The compounds of Examples 47 to 318 are obtained, according to procedures similar to those described for Examples 31 to 46 or above iii the part entitled “Preparation of the compounds of general formula (I)”.

Example 47

(1R)-2-(1H-indol-3-yl)-N-(2-phenylethyl)-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

Free base. The melting point could not be measured (paste).

Example 48

(1R)—N-benzyl-2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

Free base. Melting point: 228-230°C.

Example 49

N-benzyl(4-phenyl-1H-imidazol-2-yl)methanamine

Free base. The melting point could not be measured (paste).
Example 50

tert-butyl(1R)-1-(4-tert-butyl-1H-imidazol-2-yl)-2-(1H-indol-3-yl)-ethylcarbamate

Example 51:
(4-phenyl-1H-imidazol-2-yl) methanamine

Example 52

1-methyl-1-(4-phenyl-1H-imidazol-2-yl) ethylamine

Example 53

N-(1S)-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-1-hexanamine

Example 54

tert-butyl(R,S)-1-(4-phenyl-1H-imidazol-2-yl) heptylcarbamate

Example 55

(4-[1,1'-biphenyl]-4-yl-1-methyl-1H-imidazol-2-yl) methanamine

Example 56

(1S)-3-methyl-1-(4-phenyl-1H-imidazol-2-yl)-1-butanimine

Example 57

butyl 2-[4-(4-phenoxycarbonyl)-1H-imidazol-2-yl] ethylcarbamate

Example 58

(R,S)—N-[2-(1-methyl-1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-1-butanimine

Example 59

(R,S)-4-(2-[1-{(tert-butoxycarbonyl) amino}pentyl]-1H-imidazol-4-yl]-1,1’-biphenyl

Example 60

(R,S)—N-benzyl-1-(4-{1,1’-biphenyl}-4-yl-1H-imidazol-2-yl)-1-pentanamine

Example 61

N-[2-(4-{1,1’-biphenyl}-4-yl]-1H-imidazol-2-yl-ethyl]-3,3-dimethyl-butanamide

Example 62

(1R)—N-benzyl-1-{4,5-dimethyl-1,3-oxazol-2-yl}-2-(1H-indol-3-yl)ethanamine

Example 63

tert-butyl(R,S)-1-(4-phenyl-1H-imidazol-2-yl)hexylcarbamate

Example 64

(R,S)—N-hexyl-1-(4-phenyl-1H-imidazol-2-yl)-1-heptanamine

Example 65

(R,S)-1-(4-phenyl-1H-imidazol-2-yl) hexylamine

Example 66

(R,S)—N-benzyl-1-[4-(4-methoxyphenyl)-1H-imidazol-2-yl]-1-heptanamine

Example 67

(R,S)—N-(2,6-dichlorobenzyl)-1-(4-phenyl-1H-imidazol-2-yl)-1-heptanamine

Example 68

(R,S)—N-(4-chlorobenzyl)-1-(4-phenyl-1H-imidazol-2-yl)-1-heptanamine

Example 69

(R,S)-1-[4-(3-methoxyphenyl)-1H-imidazol-2-yl] heptylamine

Example 70

Hydrochloride. Melting point: 110-112° C.
Example 70

(R,S)—N-(2-chlorobenzyl)-1-(4-phenyl-1H-imidazol-2-yl)-1-heptanamine

Free base. The melting point could not be measured (paste).

Example 71

(R,S)—N-(2-fluorobenzyl)-1-(4-phenyl-1H-imidazol-2-yl)-1-heptanamine

Free base. The melting point could not be measured (paste).

Example 72

(R,S)—N-butyl-1-(4-phenyl-1H-imidazol-2-yl)-1-heptanamine

Free base. The melting point could not be measured (paste).

Example 73

(R,S)—N-isopentyl-N-[1-(4-phenyl-1H-imidazol-2-yl)heptyl]amine

Free base. The melting point could not be measured (paste).

Example 74

(R,S)—1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-N-hexyl-1-heptanamine

Free base. The melting point could not be measured (paste).

Example 75

(R,S)—N-pentyl-1-(4-phenyl-1H-imidazol-2-yl)-1-heptanamine

Free base. Melting point: 118-120° C.

Example 76

(R,S)—N-[1-(4-phenyl-1H-imidazol-2-yl)heptyl]cyclohexanocarboxamide

Free base. Melting point: 68-70° C.

Example 77

(R,S)—N-benzyl-1-[4-(3,4-dichlorophenyl)-1H-imidazol-2-yl]-1-heptanamine

Free base. Melting point: 192-194° C.

Example 78

butyl(4-[1,1′-biphenyl]-4-yl-1H-imidazol-2-yl)methylcarbamate

Free base. Melting point: 130-132° C.

Example 79

(R,S)—N-[1-(4-phenyl-1H-imidazol-2-yl)heptyl]cycloheptanamine

Free base. The melting point could not be measured (paste).

Example 80

(S)-cyclohexyl(4-phenyl-1H-imidazol-2-yl)methylamine

Hydrochloride. Melting point: 208-210° C.

Example 81

(R,S)—N-[1-(4-phenyl-1H-imidazol-2-yl)heptyl]-cyclohexanamine

Hydrochloride. Melting point: 155-157° C.

Example 82

N—[(S)-cyclohexyl(4-cyclohexyl-1H-imidazol-2-yl)methyl]-cyclohexanamine

Hydrochloride. Melting point: 180-182° C.

Example 83

N—[(S)-cyclohexyl(4-phenyl-1H-imidazol-2-yl)methyl]-cyclobutanamine

Hydrochloride. Melting point: 210-212° C.

Example 84

(R,S)—N-[1-(4-phenyl-1H-imidazol-2-yl)heptyl]-cyclobutanamine

Hydrochloride. Melting point: 144-146° C.

Example 85

N—[(S)-cyclohexyl(4-(3-fluoro-4-methoxyphenyl)-1H-imidazol-2-yl)methyl]-cyclobutanamine

Free base. Melting point: from 95° C.

Example 86

N—((S)-cyclohexyl(4-(4-trifluoromethyl)phenyl)-1H-imidazol-2-yl)methyl)cyclobutanamine

Free base. Foam.

Example 87

N—[(S)-cyclohexyl(4-(3-fluorophenyl)-1H-imidazol-2-yl)methyl]-cyclobutanamine

Free base. Melting point: 172-176° C.

Example 88

(1R)—N-benzyl-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

Free base. Melting point: 100-102° C.
Example 89
(R,S)-2-(1H-indol-3-yl)-1-(5-methyl-4-phenyl-1H-imidazol-2-yl)ethanamine


Example 90
(1R)-1-(4,5-diphenyl-1H-imidazol-2-yl)-2-(1H-imidol-3-yl)ethanamine

[0526] Hydrochloride. Melting point: >260°C.

Example 91
(R,S)-2-phenyl-1-(4-phenyl-1H-imidazol-2-yl)ethanamine


Example 92
(R,S)-2-(1-methyl-1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethylamine

[0528] Hydrochloride. Melting point: 110-114°C.

Example 93
(1S)—N-benzyl-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

[0529] Free base. Melting point: 118-120°C.

Example 94
(1R)—N-benzyl-1-(4,5-diphenyl-1H-imidazol-2-yl)-2-(1H-indol-3-yl)ethanamine


Example 95
(1R)—N-benzyl-2-(1H-indol-3-yl)-1-(5-methyl-4-phenyl-1H-imidazol-2-yl)ethanamine

[0531] Free base. Melting point: 120-122°C.

Example 96
tert-butyl(1R)-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethylcarbamate


Example 97
(1R)-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

[0533] Hydrochloride. The melting point could not be measured (paste).

Example 98
N-[(1R)-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]benzamide


Example 99
benzyl(1R)-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethylcarbamate


Example 100
(1R)—N-benzyl-2-(1H-indol-3-yl)-1-(4-phenyl-1,3-thiazol-2-yl)ethanamine


Example 101
N-[(1R)-2-(1H-indol-3-yl)-1-(4-phenyl-1,3-thiazol-2-yl)-ethyl]benzamide


Example 102
tert-butyl(1R)-2-(1H-indol-3-yl)-1-[4-(4-nitrophenyl)-1H-imidazol-2-yl]ethylcarbamate


Example 103
tert-butyl(4-phenyl-1H-imidazol-2-yl)methylcarbamate


Example 104
tert-butyl(1-benzyl-4-phenyl-1H-imidazol-2-yl)methylcarbamate

[0540] Free base. Melting point: 140-142°C.

Example 105
(R,S)—N-benzyl-2-(3-furo-1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

[0541] Free base. Melting point: 98-100°C.

Example 106
(1R)-2-(1H-indol-3-yl)-1-[4-(4-nitrophenyl)-1H-imidazol-2-yl]ethanamine

[0542] Hydrochloride. Melting point: becomes pasty at about 220°C.

Example 107
(1-benzyl-4-phenyl-1H-imidazol-2-yl)methylamine


Example 108
(1R)-2-(1H-indol-3-yl)-N-(2-pheoxyethyl)-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

Example 109

(1R)-1-(4-tert-butyl-1H-imidazol-2-yl)-2-(1H-indol-3-yl)ethylamine

Hydrochloride. Melting point: 230-232° C.

Example 110

N-benzyl(1-benzyl-4-phenyl-1H-imidazol-2-yl) methanamine

Free base. Melting point: 60-62° C.

Example 111

(1R)-2-(1-benzothen-3-yl)-N-benzyl-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

Free base. Melting point: 152-154° C.

Example 112

(1R)-2-(1H-indol-3-yl)-N-(2-phenoxyethyl)-1-(4-phenyl-1,3-thiazol-2-yl)ethanamine

Free base. Melting point: 124-126° C.

Example 113

tert-butyl 1-(4-phenyl-1H-imidazol-2-yl)cyclohexylcarbamate

Free base. Melting point: 170-172° C.

Example 114

tert-butyl(RS)-2-(6-chloro-1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethylcarbamate

Free base. Melting point: 208-210° C.

Example 115

1-(4-phenyl-1H-imidazol-2-yl)cyclohexanamine

Hydrochloride. Melting point: 202-204° C.

Example 116

N-[(1R)-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]N'-phenylurea


Example 117

N-[(1R)-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]benzene-carboximidamide


Example 118

(1R)—N-(cyclohexylmethyl)-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethanamine


Example 119

(R,S)—N1-benzyl-1-(4-phenyl-1H-imidazol-2-yl)-1,5-pentanediadamine


Example 120

tert-butyl(RS)-5-(benzylamino)-5-(4-phenyl-1H-imidazol-2-yl)pentylcarbamate


Example 121

N-[(1R)-2-(1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]-4-methoxybenzene-carboximidade


Example 122

(R,S)-2-(6-chloro-1H-indol-3-yl)-1-(4-phenyl-1H-imidazol-2-yl)ethylamine

Hydrochloride. Melting point: 210-212° C.

Example 123

N-benzyl-1-(4-phenyl-1H-imidazol-2-yl)cyclohexanamine

Free base. Melting point: 114-116° C.

Example 124

tert-butyl(1R)-3-methyl-1-(4-phenyl-1H-imidazol-2-yl)butylcarbamate

Free base. Melting point: 88-90° C.

Example 125

(1R)—N-benzyl-3-methyl-1-(4-phenyl-1H-imidazol-2-yl)-1-butanamine

Free base. Melting point: 134-135° C.

Example 126

tert-butyl(RS)-phenyl(4-phenyl-1H-imidazol-2-yl)methylcarbamate

Free base. Melting point: 134-136° C.

Example 127

tert-butyl 1-methyl-1-(4-phenyl-1H-imidazol-2-yl)ethylcarbamate

Free base. Melting point: 130-132° C.

Example 128

(R,S)-phenyl(4-phenyl-1H-imidazol-2-yl)methylamine

Hydrochloride. The melting point could not be measured (paste).
Example 129
tert-butyl[(1R)-3-phenyl-1-(4-phenyl-1H-imidazol-2-yl)propylcarbamate

[0565] Free base. Melting point: 72-74° C.

Example 130
tert-butyl[(1R)-2-cyclohexyl-1-(4-phenyl-1H-imidazol-2-yl)ethylcarbamate


Example 131
(1R)-3-phenyl-1-(4-phenyl-1H-imidazol-2-yl)-1-propanamine


Example 132
(1R)-2-cyclohexyl-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

[0568] Hydrochloride. Melting point: 196-198° C.

Example 133
(R,S)—N-benzyl(phenyl)(4-phenyl-1H-imidazol-2-yl)methanamine

[0569] Free base. Melting point: 144-146° C.

Example 134
(1R)—N-benzyl-2-cyclohexyl-1-(4-phenyl-1H-imidazol-2-yl)ethanamine

[0570] Free base. Melting point: 52-54° C.

Example 135
(1R)—N-benzyl-3-phenyl-1-(4-phenyl-1H-imidazol-2-yl)-1-propanamine

[0571] Free base. Melting point: 142-144° C.

Example 136
(R,S)—N-[5,5,5-trifluoro-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]pentyl]cyclohexanamine


Example 137
4-(2-[[[tert-butoxycarbonylamino]methyl]-1-methyl-1H-imidazol-4-yl]-1,1'-biphenyl

[0573] Free base. Melting point: 100-102° C.

Example 138
N-[S-cyclohexyl][4-(4-methylsulphonylphenyl)-1H-imidazol-2-yl]methyl]cyclohexanamine


Example 139
N-benzyl-2-(4-phenyl-1H-imidazol-2-yl)-2-propanamine


Example 140
4-(1-benzyl-2-[[[tert-butoxycarbonylamino]methyl]-1H-imidazol-4-yl]-1,1'-biphenyl


Example 141
(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)methanamine


Example 142
(R,S) 1-(4-phenyl-1H-imidazol-2-yl)heptylamine

[0578] Hydrochloride. Melting point: 131-134° C.

Example 143
(1-benzyl-4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)methanamine


Example 144
N,N-dibenzyl(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)methanamine

[0580] Free base. Melting point: 70-74° C.

Example 145
(R,S)—N-benzyl-1-(4-phenyl-1H-imidazol-2-yl)-1-heptanamine


Example 146
4-(2-[[[tert-butoxycarbonylamino]methyl]-1-methyl-1H-imidazol-4-yl]-1,1'-biphenyl


Example 147
tert-butyl(1S)-1-(4,5-diphenyl-1H-imidazol-2-yl)-2-(1H-indol-3-yl)ethylcarbamate

[0583] Free base. Melting point: 142-143° C.

Example 148
tert-butyl(1R)-2-(1H-indol-3-yl)-1-(1-methyl-4-phenyl-1H-imidazol-2-yl)ethylcarbamate

[0584] Free base. Melting point: 96-100° C.
Example 149
4-(2-[(tert-butoxycarbonyl)(methyl)amino]methyl)-1H-imidazol-4-yl)-1,1'-biphenyl free base. Melting point: 72-74°C.

Example 150
4-(2-{(1R)1-[tert-butoxycarbonyl]amino}-2-cyclohexylethyl)-1H-imidazol-4-yl)-1,1'-biphenyl
Free base. Melting point: 112-114°C.

Example 151
(1R)-2-(1H-indol-3-yl)-1-(1-methyl-4-phenyl-1H-imidazol-2-yl)ethanamine
Hydrochloride. Melting point: 206-210°C.

Example 152
4-(2-[(tert-butoxycarbonyl)amino]ethyl)-1H-imidazol-4-yl)-1,1'-biphenyl
Free base. Melting point: 140-142°C.

Example 153
tert-butyl methyl[(5-methyl-4-phenyl-1H-imidazol-2-yl)methyl]carbamate
Free base. Melting point: 70-72°C.

Example 154
(1R)-1-(4-{1,1'-biphenyl}-4-yl-1H-imidazol-2-yl)-2-cyclohexylethanamine
Hydrochloride. Melting point: 178-180°C.

Example 155
(4-{1,1'-biphenyl}-4-yl-1H-imidazol-2-yl)-N-methylmethanamine
Hydrochloride. Melting point: 218-220°C.

Example 156
tert-butyl(4,5-diphenyl-1H-imidazol-2-yl)methyl (methyl)carbamate
Free base. Melting point: 170-172°C.

Example 157
tert-butyl(4,5-diphenyl-1H-imidazol-2-yl)methyl carbamate
Free base. Melting point: 144-146°C.

Example 158
N-methyl(5-methyl-4-phenyl-1H-imidazol-2-yl)methanamine
Hydrochloride. Melting point: 218-220°C.

Example 159
(RS)—N,N-dibenzy1-1-[(1-benzyl-4-phenyl-1H-imidazol-2-yl)-1-heptanamine
Hydrochloride. Melting point: 130-132°C.

Example 160
(4,5-diphenyl-1H-imidazol-2-yl)methanamine
Hydrochloride. Melting point: 210-212°C.

Example 161
2-(4-{1,1'-biphenyl}-4-yl-1H-imidazol-2-yl)ethanamine
Hydrochloride. Melting point: 228-230°C.

Example 162
(4,5-diphenyl-1H-imidazol-2-yl)-N-methylmethanamine
Hydrochloride. Melting point: 198-200°C.

Example 163
N-benzyl(4,5-diphenyl-1H-imidazol-2-yl)methanamine
Free base. Melting point: 160-162°C.

Example 164
N-benzyl-2-(4-{1,1'-biphenyl}-4-yl-1-imidazol-2-yl)ethanamine
Free base. Melting point: 174-176°C.

Example 165
4-(2-[(benzyl)(tert-butoxycarbonyl)amino]methyl)-1H-imidazol-4-yl)-1,1'-biphenyl
Free base. Melting point: 130-132°C.

Example 166
(1R)-1-(4-{1,1'-biphenyl}-4-yl-1H-imidazol-2-yl)3-phenyl-1-propanamine
Hydrochloride. Melting point: 215-218°C.

Example 167
4-(2-{(1R)-1-[tert-butoxycarbonyl]amino}-3-phenylpropyl)-1H-imidazol-4-yl)-1,1'-biphenyl
Free base. Melting point: 154-156°C.

Example 168
N-benzyl(4-{1,1'-biphenyl}-4-yl-1H-imidazol-2-yl)methanamine
Hydrochloride. Melting point: >250°C.
Example 169

(1R)—N-benzyl-1-[(4-1,1'-biphenyl)-4-yl-1H-imidazol-2-yl]-2-cyclohexylethanamine

Free base. Melting point: 233-238° C.

Example 170

(1R)—N-benzyl-1-[(4-1,1'-biphenyl)-4-yl-1H-imidazol-2-yl]-3-phenyl-1-propanamine

Free base. Melting point: 210-213° C.

Example 171

4-(2-[[tert-butoxycarbonyl]amino]propyl]-1H-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 145-146° C.

Example 172

4-[2-[[tert-butoxycarbonyl]amino]carboxthiyl]-1H-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 98-99° C.

Example 173

tert-butyl

6-(4-phenyl-1H-imidazol-2-yl)hexylcarbamate

Free base. The melting point could not be measured (paste).

Example 174

tert-butyl(R,S)-1-[(4-phenyl-1H-imidazol-2-yl)pentylcarbamate

Free base. Melting point: 126° C.

Example 175

(R,S)-1-[(4,1,1'-biphenyl)-4-yl-1H-imidazol-2-yl]-1-pentanamine

Hydrochloride. Melting point: 197-200° C.

Example 176

N-[2-(4,1,1'-biphenyl)-4-yl-1H-imidazol-2-yl]ethyl]-1-hexanamine

Free base. Melting point: 152-154° C.

Example 177

4-[2-[[tert-butoxycarbonyl]amino]carboxthiyl]amino]ethyl]-1H-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 195-196° C.

Example 178

N-benzyl-3-(4,1,1'-biphenyl)-4-yl-1H-imidazol-2-yl]-1-propanamine

Free base. Melting point: 254-256° C.

Example 179

3-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)-1-propanamine

Hydrochloride. Melting point: >260° C.

Example 180

6-(4-phenyl-1H-imidazol-2-yl)hexylamine

Hydrochloride. Melting point: 244-246° C.

Example 181

(R,S)-1-[4-phenyl-1H-imidazol-2-yl]pentylamine

Hydrochloride. Melting point: 178-180° C.

Example 182

tert-butyl(R,S)-1-[4-(4-methylphenyl)-1H-imidazol-2-yl]heptylcarbamate

Free base. Melting point: 77-80° C.

Example 183

tert-butyl(R,S)-1-[4-(2-methoxyphenyl)-1H-imidazol-2-yl]heptylcarbamate

Free base. Melting point: 64-65° C.

Example 184

(R,S)-1-[4-(4-methylphenyl)-1H-imidazol-2-yl]-1-heptanamine

Hydrochloride. Melting point: 157-160° C.

Example 185

(R,S)-1-[4-(2-methoxyphenyl)-1H-imidazol-2-yl]

Hydrochloride. Melting point: 238-240° C.

Example 186

(R,S)—N-benzyl-1-(4-phenyl-1H-imidazol-2-yl)-1-pentanamine

Free base. Melting point: 200-202° C.

Example 187

tert-butyl(R,S)-1-[4-(4-methoxyphenyl)-1H-imidazol-2-yl]heptylcarbamate

Free base. Melting point: 125-127° C.

Example 188

(R,S)-1-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)-1-heptanamine

Hydrochloride. Melting point: 182-184° C.
Example 189
tert-butyl(R.S)-1-[4-(3-bromophenyl)-1H-imidazol-2-yl]heptylcarbamate

Example 190
(R.S)-1-[4-(4-methoxyphenyl)-1H-imidazol-2-yl]heptylamine

Example 191
(R.S)-1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-1-heptanamine

Example 192
(R,S)-4-[2-[(t)ert-butoxycarbonyl]amino]heptyl]-1H-imidazol-4-yl)-1,1′-biphenyl

Example 193
(R,S)—N-benzyl-1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-1-heptanamine

Example 194
4-[(1S)-1-{(t)ert-butoxycarbonyl}amino]propyl]-1H-imidazol-4-yl)-1,1′-biphenyl

Example 195
(R,S)—N-benzyl-1-(4-[1,1′-biphenyl]-4-yl-1H-imidazol-2-yl]-1-heptanamine

Example 196
(1S)-1-[4-[1,1′-biphenyl]-4-yl-1H-imidazol-2-yl]-1-propanamine

Example 197
tert-butyl(1S)-1-(4,5-diphenyl-1H-imidazol-2-yl)propylcarbamate

Example 198
(1S)—N-benzyl-1-(4-[1,1′-biphenyl]-4-yl-1H-imidazol-2-yl)-1-propanamine

Example 199
(1S)-1-[4,5-diphenyl-1H-imidazol-2-yl]-1-propanamine

Example 200
(R.S)—N-benzyl-1-[4-(4-methylphenyl)-1H-imidazol-2-yl]-1-heptanamine

Example 201
(R.S)—N-benzyl-1-[4-(2-methoxyphenyl)-1H-imidazol-2-yl]-1-heptanamine

Example 202
(R,S)—N-benzyl-1-[4-(2-methoxyphenyl)-1H-imidazol-2-yl]-1-hexanamine

Example 203
(R,S)—N-benzyl-1-[4-(4-phenyl-1H-imidazol-2-yl)-1-hexanamine

Example 204
4-[(2-[(n)ecapentylxycarbonyl]amino]ethyl]-1H-imidazol-4-yl)-1,1′-biphenyl

Example 205
(R,S)-4-[(2-{(1)arninoheptyl})-1H-imidazol-4-yl]benzonitrile

Example 206
(1S)—N-benzyl-1-(4,5-diphenyl-1H-imidazol-2-yl)-1-propanamine

Example 207
tert-butyl(1R)-1-[4-phenyl-1H-imidazol-2-yl]butylcarbamate

Example 208
(1S)—N-benzyl-1-[4-[1,1′-biphenyl]-4-yl-1H-imidazol-2-yl]-1-propanamine

Example 209
4-[(2-{(1)arninoheptyl})-1H-imidazol-4-yl]-1,1′-biphenyl

Example 210
Free base. Melting point: 220-222°C.

Example 211
Free base. Melting point: 155-157°C.

Example 212
Free base. Melting point: 192-194°C.

Example 213
Free base. Melting point: 162-164°C.

Example 214
Free base. Melting point: 182-184°C.

Example 215
Free base. Melting point: 218-220°C.

Example 216
Free base. Melting point: from 126°C C.

Example 217
Free base. Melting point: 156-158°C.

Example 218
Free base. Melting point: 145.6°C.
Example 209

(1R)-1-[4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl]-1-butanamine Hydrochloride. Melting point: 155.4°C.

Example 210

(R.S)-4-[2-(1-aminooctyl)-1H-imidazol-4-yl]-2,6-di(tert-butyl)-phenol

Example 211

(1R)-1-(4-phenyl-1H-imidazol-2-yl)-1-butanamine Hydrochloride. Melting point: 204-206°C.

Example 212

(R.S)—N-benzyl-1-[4-[4-bromophenyl]-1H-imidazol-2-yl]-1-heptanamine

Example 213

(1R)—N-benzyl-1-[4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl]-1-butanamine Free base. Melting point: becomes pasty from 130°C.

Example 214

(1R)—N-benzyl-1-[4-phenyl-1H-imidazol-2-yl]-1-butanamine Free base. Melting point: 78.6°C.

Example 215

(R.S)—N-(3-chlorobenzyl)-1-[4-phenyl-1H-imidazol-2-yl]-1-heptanamine Free base. The melting point could not be measured (paste).

Example 216

(R.S)—N-benzyl-1-[4-[3-methoxyphenyl]-1H-imidazol-2-yl]-1-heptanamine Free base. Melting point: 141-142°C.

Example 217

(R.S)-4-[2-[1-(benzylamino)heptyl]-1H-imidazol-4-yl]benzonitrile Free base. Melting point: 188-189°C.

Example 218

(R.S)-4-[2-(1-aminoheptyl)-1H-imidazol-4-yl]-N,N-diyethylanthaniline Hydrochloride. Melting point: 192°C.

Example 219

(1R)-1-(4-phenyl-1H-imidazol-2-yl)ethanamine Hydrochloride. Melting point: 178-181°C.

Example 220

(R,S)-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-1-heptanamine

Example 221

(R,S)-1-[4-(2-chlorophenyl)-1H-imidazol-2-yl]-1-heptanamine Hydrochloride. Melting point: 138-140°C.

Example 222

N-[1(S)-1-1-[4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl]propyl]-1-butanamine Free base. The melting point could not be measured (paste).

Example 223

(1R)—N-benzyl-1-[4-phenyl-1H-imidazol-2-yl]-1-heptanamine Free base. The melting point could not be measured (paste).

Example 224

(R,S)—N-[1-(4-phenyl-1H-imidazol-2-yl)heptyl]-N-propylamine Free base. Melting point: 94-98°C.

Example 225

(R,S)—N-benzyl-1-[4-(3-methoxyphenyl)-1H-imidazol-2-yl]-1-heptanamine

Example 226

(R,S)-4-[2-[1-(benzylamino)heptyl]-1H-imidazol-4-yl]benzonitrile Hydrochloride. Melting point: from 120°C.

Example 227

(R,S)—N-(4-methoxybenzyl)-1-(4-phenyl-1H-imidazol-2-yl)-1-heptanamine Hydrochloride. Melting point: from 185°C.

Example 228

(R,S)—N-benzyl-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-1-heptanamine Free base. Melting point: 126-128°C.

Example 229

(R,S)—N-benzyl-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-1-heptanamine Hydrochloride. Melting point: from 110°C.
Example 229
(R.S)—N-benzyl-1-[4-(2-chlorophenyl)-1H-imidazol-2-yl]-1-heptanamine

Example 230
(R.S)—N-benzyl-N-(1-[4-[4-(diethylamino)phenyl]-1H-imidazol-2-yl]heptyl)amine

Example 231
(R.S)—N-benzyl-N-(1-[4-(3,4-dichlorophenyl)-1H-imidazol-2-yl]-1-heptanamine)

Example 232
tert-butyl(R.S)-1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methylhexylcarbamate

Example 233
(R.S)—N-isobutyl-1-[4-(4-phenyl-1H-imidazol-2-yl]-1-heptanamine

Example 234
(R.S)—N-benzyl-1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methyl-1-hexanamine

Example 235
(R.S)—N-isobutyl-1-[4-(4-phenyl-1H-imidazol-2-yl]-1-heptanamine

Example 236
4-(2-[2-(isobutoxy carbonyl)amino]ethyl)-1H-imidazol-4-yl)-1,1′-biphenyl

Example 237
4-(2-[2-(benzyloxy)carbonylamino]ethyl)-1H-imidazol-4-yl)-1,1′-biphenyl

Example 238
4-(2-[1-[butoxy carbonyl]amino]-1-methylethyl]-1H-imidazol-4-yl)-1,1′-biphenyl

Example 239
4-(2-[2-[isobutoxy carbonyl]amino]ethyl)-1H-imidazol-4-yl)-1,1′-biphenyl

Example 240
(R.S)—N-[1-(4-phenyl-1H-imidazol-2-yl)heptyl]cyclobutanamine

Example 241
4-(2-[1s]-1-[butoxy carbonyl]amino]ethyl]-1H-imidazol-4-yl)-1,1′-biphenyl

Example 242
4-(2-[1R]-1-[butoxy carbonyl]amino]ethyl]-1H-imidazol-4-yl)-1,1′-biphenyl

Example 243
N—[(S)-cyclobexyl][4-phenyl-1H-imidazol-2-yl]methyl]-cyclohexanamine

Example 244
4-(2-[2-[methoxy carbonyl]amino]ethyl]-1H-imidazol-4-yl)-1,1′-biphenyl

Example 245
4-(2-[2-[propoxycarbonyl]amino]ethyl]-1H-imidazol-4-yl)-1,1′-biphenyl

Example 246
4-(2-[2-[ethoxycarbonyl]amino]ethyl]-1H-imidazol-4-yl)-1,1′-biphenyl

Example 247
4-(2-[1-[benzyloxy] carbonyl]amino]-1-methylethyl]-1H-imidazol-4-yl]-1,1′-biphenyl

Example 248
(R.S)—N-isopropyl-N-[1-(4-phenyl-1H-imidazol-2-yl)heptyl]amine

Example 249
Free base. Melting point: 134-135° C.

Example 250
Free base. Melting point: 148-150° C.

Example 251
Free base. Melting point: 118-122° C.

Example 252
Free base. Melting point: 114-116° C.

Example 253
Free base. Melting point: 240-242° C.

Example 254
Free base. Melting point: 177.2° C.

Example 255
Free base. Melting point: 141.2° C.

Example 256
Free base. Melting point: 132.5° C.
Example 249
N-[2-[4-[1,1'-biphenyl]-4-yl]-1H-imidazol-2-yl]ethylcyclohexanamine

Example 250
(R,S)—N-[1-{4-[3,4-dichlorophenyl]-1H-imidazol-2-yl}ethyl]-cyclohexanamine

Example 251
butyl 2-{4-(4-fluorophenyl)-1H-imidazol-2-yl}ethylcarbamate

Example 252
(R,S)—N-[1-{4-[1,1'-biphenyl]-4-yl}-1H-imidazol-2-yl}ethyl]-cyclohexanamine

Example 253
(R,S) 2-(5-fluoro-1H-indol-3-yl)-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]ethylyamine

Example 254
N-[4-(3-bromophenyl)-1H-imidazol-2-yl]methyl]-cyclohexanamine

Example 255
hexyl 2-{4-[1,1'-biphenyl]-4-yl}-1H-imidazol-2-yljethylcarbamate

Example 256
(R,S)—N-[2-(5-fluoro-1H-indol-3-yl)-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl}ethyl]-cyclobutanamine

Example 257
(R,S)—N-[1-[4-(4-fluorophenyl)-1H-imidazol-2-y]-4-methylpentyl]-cyclohexanamine

Example 258
(S)-cyclohexyl[4-(3,4-difluorophenyl)-1H-imidazol-2-yl]-methanamine

Example 259
(S)-cyclohexyl[4-(3-fluoro-4-methoxyphenyl)-1H-imidazol-2-yl]-methanamine

Example 260
(R,S)-cyclopropyl[4-(4-fluorophenyl)-1H-imidazol-2-yl]-methanamine

Example 261
N-[(S)-cyclohexyl][4-(4-fluorophenyl)-1H-imidazol-2-yl]methyl]-2-propanamine

Example 262
N-[(S)-cyclohexyl][4-(3,4-difluorophenyl)-1H-imidazol-2-yl]methyl]-cyclobutanamine

Example 263
(R,S)N-(cyclohexylmethyl)-1-[4-(phenyl-1H-imidazol-2-yl)-1-heptanamine

Example 264
N-[(S)-cyclohexyl][4-(4-fluorophenyl)-1H-imidazol-2-yl]methyl]-cyclobutanamine

Example 265
(S)-cyclohexyl-N-(cyclohexylmethyl)[4-phenyl-1H-imidazol-2-yl]methanamine

Example 266
(R,S)—N-[cyclopropyl][4-(4-fluorophenyl)-1H-imidazol-2-yl]methyl]-cyclobutanamine

Example 267
(S)-cyclohexyl-N-(cyclopropylmethyl)[4-phenyl-1H-imidazol-2-yl]methanamine

Example 268
butyl 2-{4-(cyclohexylphenyl)-1H-imidazol-2-yl}ethylcarbamate

Example 269
Free base. Melting point: 207-210° C.

Example 270
Hydrochloride. Melting point: 225-227° C.

Example 271
Hydrochloride. Melting point: 230-232° C.

Example 272
Free base. Melting point: 210-212° C.

Example 273
Hydrochloride. Melting point: 142-144° C.

Example 274
Hydrochloride. Melting point: >250° C.

Example 275
Hydrochloride. Melting point: 180-182° C.

Example 276
Hydrochloride. The melting point could not be measured (pale).

Example 277
Hydrochloride. Melting point: 151-152° C.

Example 278
Free base. Melting point: 138.4° C.
Example 269

4-[2-(2-[[cyclohexyloxycarbonyl]amino]ethyl]-1H-imidazol-4-yl]-1',1'-biphenyl

[0704] Free base. Melting point: 150° C.

Example 270

N-[(S)-cyclohexyl][4-(trifluoromethoxy)phenyl]-1H-imidazol-2-yl]methyl)cyclobutanamine


Example 271

4-[2-(2-[[cyclopentyloxycarbonyl]amino]ethyl]-1H-imidazol-4-yl]-1',1'-biphenyl

[0706] Free base. Melting point: 140.5° C.

Example 272

(RS)-N-[[1-[4-(3-bromophenyl)-1]-imidazol-2-yl]-5-methylhexyl]cyclohexanamine

[0707] Hydrochloride. Melting point: 216.7° C.

Example 273

(S)-cyclohexyl-N-(cyclopropylmethyl)[4-(4-fluorophenyl)-IIH-imidazol-2-yl]-methanamine

[0708] Hydrochloride. Melting point: 221.4° C.

Example 274

(RS)-N-[[cyclopentyl][4-(4-fluorophenyl)-1H-imidazol-2-yl]methyl)cyclobutanamine


Example 275

N-[(S)-cyclohexyl][4-(4-cyclohexylphenyl)-1H-imidazol-2-yl]methyl)cyclobutanamine

[0710] Hydrochloride. Melting point: 190-192° C.

Example 276

N-[[1R]-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-2-methylpropyl]cyclohexanamine


Example 277

N-[[S)-cyclohexyl][4-(4-trifluoromethyl)phenyl]-1H-imidazol-2-ylmethyl)cyclobutanamine

[0712] Acetate. Melting point: from 130° C.

Example 278

butyl 2-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1H-imidazol-2-yl]ethylcarbamate


Example 279

N-[(S)-cyclohexyl][4-(4-fluorophenyl)-1-methyl-1H-imidazol-2-yl]methyl)cyclohexanamine

[0714] Hydrochloride. Melting point: 190-194° C.

Example 280

cyclohexylmethyl 2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethylcarbamate


Example 281

4-bromo-4'-[2-[[butoxycarbonyl]amino]ethyl]-1H-imidazol-4-yl]-1,1'-biphenyl

[0716] Free base. Melting point: 166° C.

Example 282

N-[[S)-cyclohexyl][4-methyl[thiophenyl]-1H-imidazol-2-yl]methyl)cyclohexanamine


Example 283

N-[(S)-cyclohexyl][4-(4-fluorophenyl)-1H-imidazol-2-yl]methyl)cyclohexanamine


Example 284

N-[[S)--[4-[3,5-bis(trifluoromethyl)phenyl]-1H-imidazol-2-yl][cyclohexyl)methyl)cyclohexanamine


Example 285

cyclobutylmethyl 2-[4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl]ethylcarbamate


Example 286

cyclobutylmethyl 2-[4-(4-fluorophenyl)-1H-imidazol-2-yl]ethylcarbamate

[0721] Free base. Melting point: 149-150° C.

Example 287

N-[[S)-cyclohexyl][4-(4-difluorophenyl)-1H-imidazol-2-yl]methyl)cyclohexanamine

[0722] Free base. Melting point: 182.3° C.

Example 288

4-[2-(2-[[2-methoxyethoxy]carbonyl]amino]ethyl]-1H-imidazol-4-yl]-1,1'-biphenyl

[0723] Free base. Melting point: 123.3° C.
Example 289
(S)-1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-1-cyclohexyl-N-cyclohexymethyl)methanamine

[0724] Free base. Melting point: 134.3° C.

Example 290
4-(2-[(S)-cyclohexyl(cyclohexymethyl)amino]methyl)-1H-imidazol-4-yl)-N,N-diethylaniline

[0725] Hydrochloride. Melting point: 204-206° C.

Example 291
2,6-dinitro-butyral-[4-2-[(S)-cyclohexyl(cyclohexymethyl)amino]-methyl]-1H-imidazol-4-yl]phenol

[0726] Hydrochloride. Melting point: 254.6° C.

Example 292
4-[2-[(S)-cyclohexyl(cyclohexylamino)methyl]-1H-imidazol-2-yl]-N,N-diethylaniline

[0727] Hydrochloride. Melting point: 204-210° C.

Example 293
(S)-1-cyclohexyl-N-cyclohexymethyl)-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]methanamine

[0728] Free base. Melting point: 184.8° C.

Example 294
butyl 2-[4-(4-tet-butyphenyl)-1H-imidazol-2-yl] ethylcarbamate


Example 295
(S)-1-cyclohexyl-N-cyclohexymethyl)-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]methanamine

[0730] Hydrochloride. Melting point: 190-192° C.

Example 296
N-[(S)-cyclohexyl][4-[4-(3-trifluoromethyl)phenyl]-1H-imidazol-2-yl]methyl)cyclohexanamine


Example 297
N-[(S)-4-(3-bromophenyl)-1H-imidazol-2-yl]cyclohexylnethyl)cyclohexanamine

[0732] Hydrochloride. Melting point: 230.4° C.

Example 298
N-[(S)-cyclohexyl][4-[4-(3-trifluoromethyl)phenyl]-1H-imidazol-2-yl]methyl)cyclohexanamine


Example 299
butyl 2-[4-(4-bromophenyl)-1H-imidazol-2-yl]ethylcarbamate

[0734] Free base. Melting point: 99-100° C.

Example 300
butyl 2-[4-[4-(trifluoromethyl)phenyl]-1H-imidazol-2-yl] ethylcarbamate


Example 301
N-[(S)-cyclohexyl][4-(4-fluorophenyl)-1H-imidazol-2-yl]methyl)cycloheptanamine

[0736] Free base. Melting point: 140-142° C.

Example 302
cyclohexymethyl 2-[4-(4-tet-butyphenyl)-1H-imidazol-2-yl]ethylcarbamate


Example 303
cyclohexymethyl 2-[4-(4-tet-butyphenyl)-1H-imidazol-2-yl]ethylcarbamate


Example 304
N-[(S)-cyclohexyl][4-[3-(3-trifluoromethyl)phenyl]-1H-imidazol-2-yl]methyl)cyclohexanamine


Example 305
(S)-1-cyclohexyl-N-(cyclohexymethyl)-1-[4-[3-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]methanamine

[0740] Free base. Melting point: 143.9° C.

Example 306
(S)-1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-1-cyclohexyl-N-(cyclohexymethyl)methanamine

[0741] Hydrochloride. Melting point: 206.3° C.

Example 307
(S)-1-cyclohexyl-N-(cyclohexymethyl)-1-[4-[3-(trifluoromethyl)phenyl]-1H-imidazol-2-yl]methanamine

[0742] Hydrochloride. Melting point: 198-200° C.

Example 308
(1-R)-2-cyclohexyl-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]ethanamine

Example 309
N-[(1R)-2-cyclohexyl-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]ethyl]cyclohexanamine


Example 310
4-[2-[(S)-amino(cyclohexyl)methyl]-1H-imidazol-4-yl]-N,N-diethylamine


Example 311
(S)-1-cyclohexyl-1-[4-(3-fluorophenyl)-1H-imidazol-2-yl]methanamine


Example 312
(S)-1-cyclohexyl-N-(cyclohexylmethyl)-1-[4-(3-fluorophenyl)-1H-imidazol-2-yl]methanamine

[0747] Hydrochloride. Melting point: 180-186°C.

Example 313
butyl 2-[4-(4-pyrrolidin-1-ylphenyl)-1H-imidazol-2-yl]ethyl carbamate

[0748] Free base. Melting point: 125°C.

Example 314
N-[(S)-cyclohexyl][4-(3-fluorophenyl)-1H-imidazol-2-yl]methyl]cyclohexanamine

[0749] Hydrochloride. Melting point: 213.9°C.

Example 315
N-[(1R)-2-cyclohexyl-1-[4-(4-fluorophenyl)]-1H-imidazol-2-yl]ethyl]cyclohexanamine

[0750] Hydrochloride. Melting point: decomposes from 250°C.

Example 316
4-2-[(S)-amino(cyclohexyl)methyl]-1H-imidazol-4-yl]-2,6-dietert-butylphenol

[0751] Hydrochloride. Melting point: 222-228°C.

Example 317
butyl 2-[4-(4-pyrrolidin-1-ylphenyl)-1H-imidazol-2-yl]ethyl carbamate

[0752] Hydrochloride. Melting point: 165-166°C.

Example 318
(R)-1-cyclohexyl-N-(cyclohexylmethyl)-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]methanamine

[0753] Hydrochloride. Melting point: 188.2°C.

Example 319
2,6-dietert-butyl-4-[4-(hydroxymethyl)-1,3-thiazol-2-yl]phenol

[0754] The compound of Example 319 can be obtained according to a protocol analogous to that described for the compound of Example 38, Stage E of PCT Patent Application WO 99/09829, except that ethyl bromopropionate replaces the 3-chloroacetoacetate in Stage 38.C and that disobutylnitrium hydride replaces the lithium aluminium hydride in Stage 38.E.


Example 320
meta-[4-(2,3-dihydro-1H-indol-6-yl)-1,3-thiazol-2-yl]-N-methylmethanamine hydrochloride

320.1 Mixture of meta-2-chloro-1-[1-(chloroacetyl)-2,3-dihydro-1H-indol-6-yl]ethane and para-2-chloro-1-[1-(chloroacetyl)-2,3-dihydro-1H-indol-6-yl]ethane

[0756] 1-(chloroacetyl)-2,3-dihydro-1H-indole (3.9 g; 20 mmol) is dissolved in carbon disulphide (40 ml). ACl (6.15 g; 46 mmol) is added slowly then chloroacetyl chloride (1.835 ml; 22 mmol) is added dropwise to the mixture which is then heated under reflux for 18 hours. After the reaction medium is cooled down, the CsH in decanted and ice-cooled water containing concentrated HCl is added. After extraction with dichloromethane, the organic phase is separated and dried over magnesium sulphate before being filtered and concentrated under vacuum. The expected product (a 50/50 mixture of the meta and para isomers) is obtained by purification by crystallization from glacial acetic acid. White-coloured solid (1.6 g; yield of 30%).

[0757] MH+ = 271.

320.2 meta-2-chloro-1-(2,3-dihydro-1H-indol-6-yl)ethane hydrochloride

[0758] Intermediate 320.1 (mixture of isomers; 1.6 g; 6.0 mmol) is dissolved hot in a mixture of acetic acid (10 ml) and 20% HCl (2 ml). The reaction medium is heated under reflux for 24 hours. After evaporation the purification by crystallization of the hydrochloride from glacial acetic acid in order to separate the mixture of isomers, the meta isomer crystallizes in the form of a brown solid (the para isomer remains in the mother liquor) with a yield of 47%. Melting point: decomposition from 158°C.

[0759] MH+ = 196.

[0760] The meta structure of the compound was established by NMR/NOESY.

320.3 meta-[4-(2,3-dihydro-1H-indol-6-yl)-1,3-thiazol-2-yl]-N-methylmethanamine hydrochloride

[0761] The experimental protocol used is identical to that described for compound 30.2 of Example 30, intermediate 320.2 being used as the starting product instead of intermediate 30.1, tetrahydrofuran replacing the toluene in the
presence of one equivalent of triethylamine in order to release the base of the salt. A brown-coloured solid is obtained with a yield of 9%. Melting point: decomposition from 235°C.

Example 321

2,5,7,8-tetramethyl-2-[2-][(methylamino)methyl]-1,3-thiazol-4-yl]-6-chromanol hydrochloride

321.1) 6-hydroxy-N-methoxy-N,2,5,7,8-pentamethyl-2-chromane carboxamide

2.2 g (22.0 mmol) of ON-dimethylhydroxylamine hydrochloride, triethylamine (6.2 ml), 3.0 g (22.0 mmol) of hydroxybenzotriazole and 4.2 g (22.0 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride are added successively to a solution of 5.0 g (20.0 mmol) of (R,S)-6-hydroxy-2,5,7,8-tetramethyl-2-chromane carboxylic acid (Trolox®) in 175 ml of DMF. After the reaction mixture is stirred overnight at 25°C, the mixture is diluted with ice-cooled water and stirring is maintained for 30 more minutes. The product is extracted using 3 times 100 ml of ethyl acetate. The organic solution is washed successively with a 10% aqueous solution of sodium bicarbonate, with water, with a 10% aqueous solution of citric acid and finally with a saturated solution of sodium chloride. The organic phase is then dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from ether in order to produce a white-coloured solid with a yield of 63%. Melting point: 139-140°C.

Example 322

N-[4-((9H-carbazol-2-yl)-1,3-thiazol-2-yl)methyl]-N-methylamine hydrochloride

322.1) 9-acetyl-9H-carbazole

This compound is obtained according to Tetrahe dron (1980), 36, 3017-3019. The carbazole (10 g, 60 mmol) is suspended in 150 ml of acetic anhydride. 70% perchloric acid (0.5 ml) is added. After stirring for 30 minutes at ambient temperature, the mixture is poured into ice and the precipitate formed is filtered. After drying under vacuum, redissolving in dichloromethane and treatment with charcoal, the suspension is filtered on celite, the solvents are evaporated off and the product recrystallized from heptane. 12 g of brown crystals (yield of 90%) is obtained in this way. Melting point: 70-71°C (literature: 72-74°C.).

322.2) 1-(9-acetyl-9H-carbazol-2-yl)-2-chloroethane none

This compound is obtained according to a protocol analogous to that of Stage 320.1 of Example 320, using 5 g (24 mmol) of intermediate 322.1. 5.4 g of the expected compound is obtained (yield of 79%). White solid. Melting point: 175-176°C.

322.3) 1-(9H-carbazol-2-yl)-2-chloroethanone

Intermediate 322.2 (2.85 g; 1 mmol) is suspended in a mixture of acetic acid (50 ml) and concentrated HCl (5 ml). The reaction medium is heated under reflux for 2 hours before being left to return to ambient temperature. The new precipitate formed is filtered. After drying under vacuum, 1.9 g of a greenish solid is obtained (yield of 78%). Melting point: 203-204°C.

322.4) N-[4-((9H-carbazol-2-yl)-1,3-thiazol-2-yl)methyl]-N-methylamine hydrochloride

This compound is obtained according to a protocol analogous to that of Stage 30.2 from 487 mg (2 mmol) of intermediate 322.3 and 406 mg (2 mmol) of tert-butyl 2-amino-2-thioxoethyl(methyl)carbamate. 300 mg of the expected product is obtained (yield of 43%). White solid. Melting point: >250°C.

Example 323

3,5-ditert-butyl-4′-[2-][(methylamino)methyl]-1,3-thiazol-4-yl]-1′,1′-biphenyl-4-ol hydrochloride

323.1) 3,5-ditert-butyl-4′-hydroxy-1,1′-biphenyl-4-carboxylic acid

5.0 g (1.41 mmol) of ethyl 3,5-ditert-butyl-4′-hydroxy-1,1′-biphenyl-4-carboxylate (Chem. Lett. (1998), 9,
(1R)-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-2-phenylethanamine

Hydrochloride. Melting point: 173-180°C.

Example 325
cyclohexylmethyl 2-{4-[4-(diethylamino)phenyl]-1H-imidazol-2-yl}ethylcarbamate

Hydrochloride. Melting point: decomposes from 168°C.

Example 326
cyclohexylmethyl 2-{4-[4-(pyrrolidin-1-ylphenyl)-1H-imidazol-2-yl}ethylcarbamate

Free base. Melting point: 128.5°C.

Example 327
N-[(1R)-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-2-phenylethyl]cyclohexanamine

Hydrochloride. Melting point: 210-213°C.

Example 328
(1R)-N-cyclohexylmethyl-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-2-phenylethylcarbamate

Hydrochloride. Melting point: from 140°C.

Example 329
cyclohexylmethyl 2-[4-(3,5-dinitro-5-hydroxyphenyl)-1H-imidazol-2-yl]ethylcarbamate

Hydrochloride. Melting point: 111.5°C.

Example 330
butyl 2-[4-(3,5-dinitro-4-hydroxyphenyl)-1H-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 180.9°C.

Example 331
2,6-dimethoxy-4-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}phenol hydrochloride

331.1) 4-acetyl-2,6-dimethoxyphenyl acetate

3.0 g (15.3 mmol) of 3,5-dimethoxy-4-hydroxyacetophenone is dissolved in dichloromethane (30 ml) and 2.53 g (18.3 mmol) of K₂CO₃ is added. Triethylamine (2.6 ml) is then added dropwise. The reaction medium is cooled down to 0°C and acetyl chloride (1.31 ml; 18.3 mmol) is added. The mixture is stirred for 24 hours at ambient temperature and then poured into ice-cooled water. After extraction with dichloromethane, the organic phase is washed with sodium chloride in a saturated aqueous solution before being dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from ether in order to produce a white solid with a yield of 99%. Melting point: 145°C.
331.2) 4-(bromoacetyl)-2,6-dimethoxyphen-1 acetate

[0790] Intermediate 331.1 (0.850 g; 3.57 mmol) is solubilized in ethyl acetate then 1.35 g (6.07 mmol) of previously dried CuBr₂ is added. The mixture is heated under reflux for 2.5 hours before being left to return to ambient temperature. Ground charcoal is added and the mixture is stirred for 10 minutes. After filtering and evaporating to dryness, the solid obtained is taken up in diisopropyl ether. After filtering, a grey solid is obtained with a yield of 75%. Melting point: 124.2-126.3°C.

331.3) 4-(2-[[[(tert-butoxycarbonyl)(methyl)amino]-1,3-thiazol-4-yl]-2,6-dimethoxyphenyl acetate

[0791] Intermediate 331.3 is prepared according to an experimental protocol described in Example 1, Stage 1.3, using intermediate 331.2 instead of bromo-1-(3,5-dinitrobutyl-4-hydroxyphenyl)ethanone. The expected compound is obtained in the form of a white solid with a yield of 55%. Melting point: 135.2-137.4°C.

331.4) tert-butyl[4-(4-hydroxy-3,5-dimethoxyphenyl)-1,3-thiazol-2-yl]methyl[methyl]carbamate

[0792] 0.530 g (1.25 mmol) of intermediate 331.3 is dissolved in methanol (20 mL). The solution is cooled down using an ice bath then a 1N solution of NaOH is added dropwise. The mixture is left to return to ambient temperature under stirring. After evaporation to dryness and dilution of the residue with water, the solution is neutralised using citric acid followed by extraction with dichloromethane. The organic phase is washed with sodium chloride in a saturated aqueous solution before being dried over magnesium sulphate, filtered and concentrated under vacuum. The product is obtained in the form of a yellow oil with a yield of 96%.

[0793] M1H+=381.20.

331.5) 2,6-dimethoxy-4-[[[(methylamino)methyl]-1,3-thiazol-4-yl]phenol hydrochloride

[0794] The experimental protocol used is identical to that described for intermediate 323.6, intermediate 331.4 replacing intermediate 323.5. A light beige solid is obtained with a yield of 97%. Melting point: 229.8-232.0°C.

Example 332

2,6-diisopropyl-4-[[((methylamino)methyl)-1,3-thiazol-4-yl]phenol hydrochloride

332.1) 2,6-diisopropylphenyl acetate

[0795] 3.45 g (16.4 mmol) of trifluoroacetic anhydride is added to 0.83 mL (14.6 mmol) of acetic acid at 0°C while leaving the mixture to return to ambient temperature over 2 hours. The mixture is then cooled down to 0°C and 1.95 g (11.0 mmol) of 2,6-diisopropophenol is added dropwise. The reaction medium is maintained under stirring for 12 hours before being poured into ice-cooled water. After extraction with dichloromethane, the organic phase is washed with sodium chloride in a saturated aqueous solution before being dried over magnesium sulphate, filtered and concentrated under vacuum. A colourless oil is obtained with a yield of 86%. This product is sufficiently pure to be used directly in the following stage.

332.2) 1-(4-hydroxy-3,5-diisopropylphenyl)ethanone

[0796] 1.94 g (14.53 mmol) of AlCl₃ is dissolved in nitrobenzene (5 mL). At the same time, 2.0 g (9.08 mmol) of intermediate 332.1 is dissolved in nitrobenzene (1 mL). The solution of intermediate 332.1 is added dropwise to the solution of AlCl₃ at ambient temperature. The mixture is taken to 50°C for 48 hours before being left to return to ambient temperature. The reaction medium is then poured into ice-cooled water. A 1N solution of HCl (5 mL) and then a concentrated solution of HCl (2 mL) are added. The mixture is stirred at ambient temperature followed by extraction with dichloromethane. The organic phase is washed with sodium chloride in a saturated aqueous solution before being dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 13% of ethyl acetate in heptane). After evaporation, the pure fractions produce a grey-white solid with a yield of 25%. Melting point: 88-93°C.

332.3) 4-acetyl-2,6-diisopropylphenyl acetate

[0797] The experimental protocol used is identical to that described for intermediate 331.1, intermediate 332.2 replacing the 3,5-dimethoxy-4-hydroxyacetophenone. A sand-coloured solid is obtained with a yield of 95%. Melting point: 102-103°C.

332.4) 4-(bromoacetyl)-2,6-diisopropylphenyl acetate

[0798] The experimental protocol used is identical to that described for intermediate 331.2, intermediate 332.3 replacing intermediate 331.1. A yellow oil is obtained which crystallizes slowly with a yield of 88%. This product is sufficiently pure to be used directly in the following stage.

332.5) 4-[[((tert-butoxycarbonyl)(methyl)amino)methyl]-1,3-thiazol-4-yl]2,6-diisopropylphenyl acetate

[0799] Intermediate 332.5 is prepared according to a protocol identical to that described for Example 1, Stage 1.3, using intermediate 332.4 instead of the bromo-1-(3,5-dinitrobutyl-4-hydroxyphenyl)ethanone. The expected compound is obtained in the form of a pale yellow solid with a yield of 76%.


332.6) tert-butyl[4-(4-hydroxy-3,5-diisopropylphenyl)-1,3-thiazol-2-yl]methyl[methyl]carbamate

[0801] The experimental protocol used is identical to that described for intermediate 331.4, intermediate 332.5 replacing intermediate 331.3. An ochre oil is obtained with a yield of 91%. This product is sufficiently pure to be used directly in the following stage.

[0802] M1H+=405.20.
The experimental protocol used is identical to that described for intermediate 323.6, intermediate 332.6 replacing intermediate 332.5. A beige-pink solid is obtained with a yield of 69%. Melting point: loses its colour at 162°C and melts at 173-177°C.

Example 333
4-{2-[(methylamino)(methyl)-1,3-thiazol-4-yl]phenol hydrochloride

Example 332.7) 2,6-diisopropyl-4-[2-[(methylamino)(methyl)-1,3-thiazol-4-yl]phenol hydrochloride

Example 333.1) 2-bromo-4-(hydroxyphenyl)ethanone

The experimental protocol used is identical to that described for intermediate 331.2. 4-hydroxy-acetophenone replacing intermediate 331.1. A brown-pink solid is obtained with a yield of 60%. Melting point: 118°C.

Example 333.2) tert-butyl[4-(4-hydroxyphenyl)-1,3-thiazol-2-yl]methyl[methyl]carbamate

Intermediate 333.2 is prepared according to a protocol identical to that described for Example 1, Stage 1.3, using intermediate 333.1 instead of the bromo-1-(3,5-ditert-butyl-4-hydroxyphenyl)ethanone and toluene replacing the benzene. The expected compound is obtained in the form of a clear-yellow oil which very slowly crystallizes cold with a yield of 35%.

Example 334
2,6-ditert-butyl-4-[2-(hydroxymethyl)-1,3-thiazol-4-yl]phenol

Example 334.1) [4-(3,5-ditert-butyl-4-hydroxyphenyl)-1,3-thiazol-2-yl]methyl pivalate

Intermediate 334.1 is prepared according to a protocol identical to that described for Example 1, Stage 1.3, using 2-(tert-butylcarbonyloxy)thioacetamide instead of the 2-[[1.1-dimethyl ethoxy]carbonyl]methyl] amino-ethanethioamide and toluene replacing the benzene. The expected compound is obtained in the form of a white solid with a yield of 100%. Melting point: 114.6-116.0°C.

Example 335
N-[4-(4-aminophenyl)-1,3-thiazol-2-yl]methyl-N-methylamine hydrochloride

Example 335.1) 1-(4-aminophenyl)ethanone

4-amino-acetophenone (4.87 g; 36.0 mmol) is dissolved in dimethylformamide (75 ml). 15 g (0.108 mol) of potassium carbonate (previously dried at 170°C under an argon atmosphere), 7.236 g (36.0 mmol) of iodobenzene, 0.4 g of copper powder and a catalytic quantity of copper iodide are added. The reaction mixture is taken to reflux for 12 hours. After leaving the reaction medium to return to ambient temperature, the latter is filtered on celite and poured into ice-cooled water. After extraction with ethyl acetate, the organic phase is washed with water before being dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from heptane in order to produce a yellow solid with a yield of 53.4%. Melting point: 105°C.

Example 335.2) N-(4-acetylphenyl)-N-phenylacetamidine

N-[4-(bromoacetyl)phenyl]-N-phenylacetamidine

Example 335.3) N-[4-(4-acetylphenyl)anilino][phenyl]-1,3-thiazol-2-yl]methyl[methyl]carbamate

Intermediate 335.2 (0.633 g; 2.5 mmol) is dissolved in methanol (20 ml) and 1 g (2.0 mmol) of bromination resin PVPHP (J. Macromol. Sci. Chem. (1977), A11, (3), 507-514) is added. After stirring under an argon atmosphere for 4 hours, filtration is carried out and the resins are rinsed with methanol. After evaporation of the filtrate solvents and crystallization from methanol, a white solid is obtained with a yield of 59%. Melting point: 152-153°C.

Example 335.4) tert-butyl[4-(4-acetylphenyl)anilino][phenyl]-1,3-thiazol-2-yl]methyl[methyl]carbamate

Intermediate 335.4 is prepared according to a protocol identical to that described for Example 1, Stage 1.3, using intermediate 335.3 instead of the bromo-1-(3,5-ditert-butyl-4-hydroxyphenyl)ethanone and toluene replacing the benzene. The expected compound is obtained in the form of an oil with a yield of 73%.

Example 335.5) N-[4-(2-[methylamino][methyl]-1,3-thiazol-4-yl)]phenyl]-N-phenylacetamidine hydrochloride

Example 335.6) N-[4-(4-anilino-phenyl)-1,3-thiazol-2-yl]methyl]-N-methylamine hydrochloride

Example 335.8) N-[4-(4-anilino-phenyl)-1,3-thiazol-2-yl]methyl]-N-methylamine hydrochloride

Example 335.8) N-[4-(4-anilino-phenyl)-1,3-thiazol-2-yl]methyl]-N-methylamine hydrochloride
Example 336
2,6-ditert-butyl-4-[[2-[(dimethylamino)methyl]-1,3-thiazol-4-yl]phenol hydrochloride

336.1) 4-[2-(bromomethyl)-1,3-thiazol-4-yl]-2,6-ditert-butylphenol

[0817] 1.5 g (4.70 mmol) of intermediate 334.2, (2,6-ditert-butyl-4-[2-(hydroxymethyl)-1,3-thiazol-4-yl]phenol is dissolved in dichloromethane (30 mL). After adding CBr₄ (2.02 g; 6.10 mmol), the reaction medium is cooled down to 0°C. PPh₃ (1.48 g; 5.63 mmol) is added by fractions then the mixture is left to return to ambient temperature. The reaction medium is then poured into ice-cooled water before being extracted with dichloromethane. The organic phase is washed with salt water before being dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 30% of ethyl acetate in heptane), in order to produce a brown oil with a yield of 92%. This product is sufficiently pure to be used directly in the following stage.


336.2) 2,6-ditert-butyl-4-[[2-[(dimethylamino)methyl]-1,3-thiazol-4-yl]phenol hydrochloride

[0819] 0.8 ml (1.57 mmol) of dimethylamine and 0.4 ml (2.62 mmol) of triethylamine are dissolved in dimethylformamide (15 ml). 0.400 g (1.05 mmol) of intermediate 336.1 dissolved in dimethylformamide (5 ml) is added then the mixture is stirred at ambient temperature for 18 hours. The reaction medium is then poured into ice-cooled water followed by extraction with ethyl acetate. The organic phase is washed with salt water before being dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 50% of ethyl acetate in heptane), in order to produce an orange oil with a yield of 92%. The hydrochloride is then obtained by solubilizing the base in ether and adding 1.2 ml of a 1N solution of HCl in ether. After filtering and washing of the solid formed with ether then with isopentane, a beige-pink solid is obtained with a yield of 15.2%. Melting point: 166.8-169.0°C.

[0820] The compounds of Examples 337 to 345 are obtained according to procedures analogous to those described for Examples 31 to 46 or above in the part entitled “Preparation of compounds of general formula (I).”

Example 337
cyclobutylmethyl 2-[4-(4′-bromo-1,1′-biphenyl-4-yl)-1H-imidazol-2-yl]ethylcarbamate


Example 338
isobutyl 2-[4-(4′-bromo-1,1′-biphenyl-4-yl)-1H-imidazol-2-yl]ethylcarbamate

[0822] Free base. Melting point: 158.7°C.

Example 339
isobutyl 2-[4-(4-tert-butylphenyl)-1H-imidazol-2-yl]ethylcarbamate

[0823] Free base. Melting point: 110.6°C.

Example 340
cyclobutylmethyl 2-[4-(4-tert-butylphenyl)-1H-imidazol-2-yl]ethylcarbamate

[0824] Free base. Melting point: 103°C.

Example 341
cyclohexyl 2-[4-(4-bromo-1,1′-biphenyl-4-yl)-1H-imidazol-2-yl]ethylcarbamate


Example 342
cyclohexyl 2-[4-(4-tert-butylphenyl)-1H-imidazol-2-yl]ethylcarbamate


Example 343
3-[4-(4-fluorophenyl)-1H-imidazol-2-yl]propan-1-amine

[0827] Hydrochloride. Melting point: 245-246°C.

Example 344
4,4,4-trifluorobutyl 2-[4-(4′-bromo-1,1′-biphenyl-4-yl)-1H-imidazol-2-yl]ethylcarbamate

[0828] Free base. Melting point: 176.5°C.

Example 345
4,4,4-trifluorobutyl 2-[4-(1,1′-biphenyl-4-yl)-1H-imidazol-2-yl]ethylcarbamate


Example 346
2,6-ditert-butyl-4-[[methylamino)methyl]-1,3-thiazol-2-yl]phenol hydrochloride

346.1) 4-[2-(bromomethyl)-1,3-thiazol-2-yl]-2,6-ditert-butylphenol

[0830] The experimental protocol used is identical to that described for intermediate 336.1, the compound of Example 319 replacing intermediate 334.2, 1,2-dichloroethane replacing the dimethylformamide and the reaction medium being heated under reflux for 12 hours. A reddish oil is obtained with a yield of 77%. This product is used as it is directly in the following stage.

346.2) 2,6-ditert-butyl-4-[[methylamino)methyl]-1,3-thiazol-2-yl]phenol

[0831] The experimental protocol used is identical to that described for intermediate 336.2, intermediate 346.1 replac-
ing intermediate 336.1, a 2N solution of methylamine in tetrahydrofuran replacing the dimethylamine and acetoni-
trile replacing the dimethylformamide. The hydrochloride is
obtained by solubilizing the base in ether and adding a 1N
solution of HCl in ether. The solid formed is filtered and
purified by recrystallization from acetone in order to pro-
duce a white solid with a yield of 18%. Melting point:
184.0-185.0° C.

Example 347
2,6-ditert-butyryl-4-[2-(piperidin-1-ylmethyl)-1,3-thia-
 zol-4-yl]phenol hydrochloride

[0832] The experimental protocol used is identical to that
described for intermediate 336.2, piperidine replacing the
dimethylamine. A white solid is obtained with a yield of
56%. Melting point: >195° C.

Example 348
2,6-ditert-butyryl-4-[2-{4-(methyl)piperazin-1-ylm-
 ethyl]-1,3-thiazol-4-yl]phenol hydrochloride

[0833] The experimental protocol used is identical to that
described for intermediate 336.2, N-methylpiperazine
replacing the dimethylamine. A light brown solid is obtained
with a yield of 62%. Melting point: 234.6-235.2° C.

Example 349
2,6-ditert-butyryl-4-[2-(piperazin-1-ylmethyl)-1,3-
 thiazol-4-yl]phenol hydrochloride

349.1 tert-butyryl 4-[[4-(3,5-ditert-butyryl-4-hydroxy-
 phenyl)-1,3-thiazol-2-yl]methyl]piperazine-1-car-
boxylate

[0834] The experimental protocol used is identical to that
described for intermediate 336.2, N--Boc-piperazine
replacing the dimethylamine. A pale orange solid is obtained
with a yield of 64%. Melting point: 108-109° C.

349.2 2,6-ditert-butyryl-4-[2-(piperazin-1-ylmethyl)-
1,3-thiazol-4-yl]phenol hydrochloride

[0835] The experimental protocol used is identical to that
described for intermediate 323.6, intermediate 349.1 replacing
intermediate 323.5. A white solid is obtained with a yield
of 86%. Melting point: 255.4-257.7° C.

Pharmacological Study of the Products of the Invention
Study of the Effects on a Specific Ligand of MAO-B, [3H]Ro 19-6327

[0836] The inhibitory activity of the products of the inven-
tion is determined by measurement of their effects on the
bond of a specific ligand of MAO-B, [3H]Ro 19-6327.

a) Mitochondrial Preparation of the Cortex of Rats

[0837] The mitochondrial preparation of the cortex of rats is
carried out according to the method described in Cesura
48 (1987), 170-176. The rats are decapitated and their cortex is
removed, homogenized in 9 volumes of a 0.32 M sucrose buffer,
buffered to pH 7.4 with 5 mM of HEPES, then centrifuged at 800 g for 20 minutes. The supernatants are
recovered and the pellets are washed twice with the 0.32 M
sucrose buffer as previously. The collected supernatants are
centrifuged at 10000 g for 20 minutes. The pellets obtained
are suspended in a Tris buffer (50 mM Tris, 130 mM NaCl,
5 mM KCl, 0.5 mM EDTA, 1 mM MgCl₂, pH 7.4) and
centrifuged at 10000 g for 20 minutes. This stage is repeated
twice, and the final pellet, corresponding to the mitochondrial
fraction, is stored at ~80° C, in the Tris buffer. The
proteic content of the preparation is determined by the
Lowry method.

b) Bond of [3H]Ro 19-6327

[0838] 100 μl of the mitochondrial preparation (2 mg
protein/ml) are incubated for 1 hour at 37° C. in an Eppen-
dorf tube, in the presence of 100 μl of [3H] Ro 19-6327 (33
nM, final concentration) and 100 μl of Tris buffer containing
or not containing the inhibitors. The reaction is stopped by
the addition of 1 ml of unlabelled Tris buffer into each tube,
then the samples are centrifuged for 2 minutes at 12000 g.
The supernatants are removed by suction and the pellets
washed with 1 ml of Tris buffer. The pellets are then
solubilized in 200 μl of sodium dodecyl sulphate (20%
weight/volume) for 2 hours at 70° C. The radioactivity is
determined by counting the samples using liquid scintilla-
tion.

c) Results

[0839] The compounds of Examples 1, 3, 6, 22, 24, 26 to
29, 323 and 332 described above show an IC₅₀ lower than
10 μM.

Study of the Effects on Lipid Peroxidation of the Cerebral Cortex of the Rat

[0840] The inhibitory activity of the products of the inven-
tion is determined by measuring their effects on the degree of
lipid peroxidation, determined by the concentration of
malondialdehyde (MDA). The MDA produced by peroxi-
dation of unsaturated fatty acids is a good indication of
lipid peroxidation (H Esterbauer and K H Cheeseman,
ley rats weighing 200 to 250 g (Charles River) were sacri-
ficed by decapitation. The cerebral cortex is removed, then
homogenized using a Thomas potter in a 20 mM Tris-HCl
buffer, pH=7.4. The homogenate is centrifuged twice at
5000 g for 10 minutes at 4° C. The pellet is stored at ~80°
C. On the day of the experiment, the pellet is resuspended at
a concentration of 1 g/15 ml and centrifuged at 515 g for 10
minutes at 4°C. The supernatant is used immediately to
determine the lipid peroxidation. The homogenate of rat’s
cerebral cortex (500 μl) is incubated at 37° C for 15 minutes
in the presence of the compounds to be tested or of the
solvent (10 μl). The lipid peroxidation reaction is initiated
by adding 50 μl of FeCl₃ at 1 mM, EDTA at 1 mM and
ascorbic acid at 4 mM. After incubation for 30 minutes at
37° C, the reaction is stopped by adding 50 μl of a solution of
hydroxylated di-tet-butyli toluene (BHT, 0.2%). The
MDA is quantified using a colorimetric test, by reacting a
chromogenic reagent (R), N-methyl-2-phenylindol (650 μl)
with 200 oil of the homogenate for 1 hour at 45° C. The
condensation of an MDA molecule with two molecules of
reagent R produces a stable chromophore the maximum
absorbance wavelength of which is equal to 586 nm. (Cal-
The compounds of Examples 1 to 3, 6 to 17, 20 to 30, 320,
321, 323, 331 and 332 described above show an IC₅₀ lower
than 10 μM.
Bond Test on the Cerebral Sodium Channels of the Cortex of the Rat

[0841] The test consists in measuring the interaction of the compounds vis-à-vis the bond of tritiated batrachotoxin on the voltage-dependent sodium channels according to the protocol described by Brown (J. Neurosci. (1986), 6, 2004-2070).

Preparation of Homogenates of Cerebral Cortices of the Rat

[0842] The cerebral cortices of Sprague-Dawley rats weighing 230-250 g (Charles River, France) are removed, weighed and homogenized using a Potter homogenizer provided with a teflon piston (10 strokes) in 10 volumes of isolation buffer the composition of which is as follows (sucrose 0.52 M; KHPO4 5 mM; pH 7.4). The homogenate is subjected to a first centrifugation at 1000 g for 10 minutes. The supernatant is removed and centrifuged at 20000 g for 15 minutes. The pellet is taken up in the isolation buffer and centrifuged at 20000 g for 15 minutes. The pellet obtained is resuspended in incubation buffer (HEPES 50 mM; KCl 5.4 mM; MgSO4 0.8 mM; glucose 5.5 mM; choline chloride 130 mM pH 7.4) then aliquoted and stored at -80°C until the day of assay. The final protein concentration is comprised between 4 and 8 mg/ml. The assay of proteins is carried out using a kit marketed by BioRad (France).

Measurement of the Bond of Tritiated Batrachotoxin

[0843] The bond reaction is carried out by incubating for 1 hour 30 minutes at 25°C. 100 μl of homogenate of rat cortex containing 75 μg of proteins with 100 μl of [3H] batrachotoxin-A 20-alpha benzoate (37.5 Ci/mmol, NEN) at 5 nM (final concentration), 200 μl of tetrodotoxin at 1 μM (final concentration) and scorpion venom at 40 μg/ml (final concentration) and 100 μl of incubation buffer alone or in the presence of the products to be tested at different concentrations. The non-specific bond is determined in the presence of 300 μM of veratridine and the value of this non-specific bond is subtracted from the other values. The samples are then filtered using a Brandel (Gaithersburg, MD, USA) using Unifilter GF/C plates pre-incubated with 0.1% of polyethylene imine (20 μl/well) and rinsed twice with 2 ml of filtration buffer (HEPES 5 mM; CaCl2 1.8 mM; MgSO4 0.8 mM; choline chloride 130 mM; BSA 0.01%; pH 7.4). After having added 20 μl of Microscint M, the radioactivity is counted using a liquid scintillation counter (Topecount, Packard). The measurement is carried out in duplicate. The results are expressed as % of the specific bond of tritiated batrachotoxin relative to the control.

Results

[0844] The compounds of Examples 1, 6, 7, 11, 13, 15, 17, 20, 24, 31 to 38, 42, 43, 46 to 48, 53, 56, 57, 59 to 61, 64 to 80, 82 to 88, 92 to 95, 97, 105, 106, 108, 110, 113, 117, 118, 121 to 125, 128, 130 to 139, 142 to 145, 149, 151, 152, 154, 162 to 166, 168 to 178, 181, 183 to 186, 188, 190 to 196, 198 to 206, 208 to 210, 212 to 218, 220 to 231, 233 to 250, 252 to 259, 261 to 281, 283 to 288, 293 to 313, 324 and 338 to 340 described above all show an IC50 lower than or equal to 1 μM. Moreover, the compounds of Examples 3, 9, 10, 26, 28 to 30 and 321 described above also show an IC50 lower than or equal to 3.5 μM.

1-21. (canceled)

22. A method of treating Parkinson’s disease in warm-blooded animals comprising administering to warm-blooded animals in need thereof an amount of a compound of the formula

![Chemical Structure](attachment:chemical_structure.png)

in racemic, enantiomeric form or any combination of these forms, in which A is

in which Q is selected from the group consisting of H, —OR23, —NR25R26, phenyl optionally substituted by at least one substituent independently selected from the group consisting of —OH, cyano, nitro, alkyl, alkoxy or —NR11 and a group with two substituents representing together a methylenedioxy or ethylenedioxy, or Q is selected from the group consisting of —COPh, —SO2Ph or —CH2Ph, said COPh, —SO2Ph or —CH2Ph optionally substituted on its aromatic parts by at least one independently alkyl or alkoxy or halogen. R11 and R11 are independently selected from the group consisting of hydrogen, alkyl and —COR12, or R11 and R11 form together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being independently selected from the group consisting of O, N and S, R11 is selected from the group consisting of hydrogen, alkyl, alkoxy and NR11R11, R13 and R14 are independently; hydrogen or alkyl, or R13 and R14 form together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group consisting of O, N and S, R13 is selected from the group consisting of hydrogen, alkyl and aryl optionally substituted by at least one substituent selected from the group consisting of alkyl, OH, halogen, nitro and alkoxy, R11 and R14 are independently selected from the group consisting of hydrogen, alkyl and —CO—R24, R24 is alkyl, and R11, R20 and R21 are independently selected from the group consisting of hydrogen, halogen, —OH, —SR26, alkyl, cycloalkyl, alkenyl, alkoxy, cyano, nitro, —SO2NH2R27, —CONHR28, —S(O)2R29, —NH(CO)R30, —CF3, —OCF3 and NR27R28, R27 and R28 are independently selected from the group consisting of hydrogen, alkyl and —COR29, or R27 and R28 form together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being independently selected from the group consisting of...
O, N and S, R<sup>49</sup> and R<sup>55</sup> are independently each time that they occur, hydrogen or alkyl or alkylcarbonyl, q is an integer from 0 to 2, R<sup>56</sup> and R<sup>77</sup> are each time that they occur, hydrogen or alkyl or alkoxo, R<sup>55</sup> is selected from the group consisting of hydrogen, alkyl, alkoxylalkyl, hydroxyalkyl, cycloalkylalkyl, trifluoromethyl, alkyl, alkenyl, alkenylalkyl, alkenyl, cyanooalkyl, —(CH<sub>2</sub>)<sub>q</sub>—Z<sup>R59</sup> and —(CH<sub>2</sub>)<sub>q</sub>—COR<sup>40</sup>, Z<sup>1</sup> and Z<sup>2</sup> are selected from the group consisting of a bond, —O—, —NR<sup>41</sup>— and —S—, R<sup>59</sup> and R<sup>41</sup> are each time that they occur, selected from the group consisting of hydrogen, alkyl, alkenyl, alkynylalkyl, R<sup>40</sup> is, independently each time that it occurs, selected from the group consisting of hydrogen, alkyl, alkenyl, alkynylalkyl, R<sup>41</sup> is selected from the group consisting of a bond, —O—, —NR<sup>42</sup>— and —S—, R<sup>42</sup> and R<sup>41</sup> are each time that they occur, selected from the group consisting of hydrogen, alkyl, alkenyl, allylalkyl, alkyl, cyanooalkyl, R<sup>40</sup> and R<sup>41</sup> are each time that they occur, independently each time that they occur, selected from the group consisting of hydrogen, alkyl, alkenyl, alkenylalkyl, R<sup>41</sup> is selected from the group consisting of a bond, —O—, —NR<sup>43</sup>— and —S—, R<sup>43</sup> and R<sup>41</sup> are each time that they occur, independently each time that they occur, selected from the group consisting of hydrogen, alkyl, alkenyl, alkenylalkyl, alkyl, cyanooalkyl, and R<sup>41</sup> is selected from the group consisting of cyanooalkyl, —(CH<sub>2</sub>)<sub>q</sub>—NR<sup>41</sup>, —(CH<sub>2</sub>)<sub>q</sub>—OR<sup>41</sup> and —(CH<sub>2</sub>)<sub>q</sub>—COR<sup>41</sup> optionally substituted on the aryl or heteroaryl by at least one member selected from the group consisting of halogen, alkyl, hydroxyl, cyano, nitro, amino, alkylaminooalkyl, dialkylaminooalkyl, alkylaminooalkyl, and hydroxycyano, cycloalkylalkyl, and carboxylic acid 1 to 3 members, carboxylic acid and a carbocyclic aryl or carboxylic acid optionally substituted by a member selected from the group consisting of halogen, alkyl and alkoxy of 1 to 6 carbon atoms, hydroxyl, cyano, nitro, amino, alkylaminooalkyl, dialkylaminooalkyl and a carbocyclic aryl Z<sup>7</sup> is selected from the group consisting of a bond, —O—, —NR<sup>45</sup>— and —S—, R<sup>45</sup> and R<sup>47</sup> are independently each time that they occur, selected from the group consisting of hydroxy, alkyl, alkynylalkyl, alkenyl, alkenylalkyl, alkyl, cyanooalkyl, —(CH<sub>2</sub>)<sub>q</sub>—Z<sup>R50</sup> and —(CH<sub>2</sub>)<sub>q</sub>—COR<sup>51</sup>, —(CH<sub>2</sub>)<sub>q</sub>—CONR<sup>31</sup>, —SO<sub>2</sub>R<sup>51</sup>, aryalkyl, aralkylalkyl, aryalkyl, aromaticalkyl, heteroaryl, pyridinylalkyl or pyridinylcarbonyl, the aryl or heteroaryl of said aryl, alkenyl, aryloxyalkyl, aryalkyl, aralkylalkyl, aryloxyalkyl, aralkylalkyl, heteroaryl, pyridinylalkyl or pyridinylcarbonyl being optionally substituted by at least one member independently selected from the group consisting of a bond, —O—, —NR<sup>52</sup>— and —S—, R<sup>52</sup> and R<sup>55</sup> are independently each time that they occur, selected from the group consisting of hydroxy, alkyl, alkenyl, alkenylalkyl and cyanooalkyl, Z<sup>7</sup> is, independently each time that they occur, selected from the group consisting of hydroxy or a salt thereof sufficient to treat Parkinson’s disease. 23. The method of claim 22 wherein A is

\[
\begin{align*}
&\text{O} \\
&\text{R}^{21} \quad \text{R}^{20}
\end{align*}
\]

in which Q is selected from the group consisting of —H, —OR<sup>22</sup>, —SR<sup>22</sup>, —NR<sup>23</sup>R<sup>24</sup>, phenyl optionally substituted.
by at least one member selected from the group consisting of halogen, —OH, cyano, nitro, alkyl, alkoxy and —NR'R'' and a group of two substituents together being methyleneedioxy or ethylenedioxy, or Q is selected from the group consisting of —COPh, —OPh, —SPh, —SO₂Ph or —CH₂Ph, said —COPh, —OPh, —SPh, —SO₂Ph or —CH₂Ph being optionally substituted on its aromatic part by at least one member selected from the group consisting of alkyl, alkoxy and halogen, R²⁶ and R²⁷ are independently selected from the group consisting of hydrogen, alkyl, alkoxy, alkylthio, amino, and Q is —OH, two of the R¹⁰, R¹⁵ and R²⁴ are, independently, hydrogen or alkyl, and R¹⁰, R²⁰ and R²¹ are independently selected from the group consisting of hydrogen, halogen, —OH, —SR²⁶, alkyl, alkoxy, alkylthio, amino, alkylaminolino and dialkylamino and the third is selected from the group consisting of hydrogen, alkyl, alkoxy, alkylthio, amino, alkylaminolino and dialkylamino, or Q is phenyl substituted by —OH and at least one member selected from the group consisting of hydrogen, halogen, —OH, alkyl and alkoxy, R²⁶ is hydrogen or alkyl, and R²⁰ and R²¹ are independently selected from the group consisting of hydrogen, alkyl, or R²⁷ and R²⁸ form together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 ring members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being independently selected from the group consisting of O, N and S, R²⁶ is selected from the group consisting of hydrogen, alkyl and aryloxy, R²⁷ and R²⁸ are, independently, hydrogen, or alkyl or —CO—R⁲⁹, R²⁵ is alkyl, and R¹⁰, R²⁰ and R²¹ are independently selected from the group consisting of hydrogen, halogen, OH, SR²⁶, alkyl, cycloalkyl, alkylthio, alkoxy, cyano, nitro, —SO₂NR'R'' or —CONH₂, —S(O)₂R²⁶, —NH(CO)R²⁷, —CF₃, —OCl, and NR²⁷R²⁸, R²⁶ is hydrogen or alkyl, R²⁷ and R²⁸ are independently selected from the group consisting of hydrogen, alkyl and —COR²⁹, R²⁴ and R²⁵ form together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 ring members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being independently selected from the group consisting of hydrogen, alkyl and alkoxy, R²⁶ is selected from the group consisting of hydrogen, alkyl, alkoxy and —NR⁰³R¹³, R²⁰ and R²¹ are independently selected from the group consisting of hydrogen, alkyl, or R²⁴ and R²⁵ form together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 ring members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being selected from the group consisting of O, N and S.

25. The method of claim 24 wherein A is

![Diagram]

in which Q is selected from the group consisting of —OR²², —SR²² and phenyl substituted by —OH and optionally by at least one member selected from the group consisting of hydrogen, —OH, alkyl and alkoxy, R²² is hydrogen or alkyl, and R¹⁰, R²⁰ and R²¹ are independently selected from the group consisting of hydrogen, halogen, —OH, alkyl and alkoxy, R²⁶ is hydrogen or alkyl, and R²⁰ and R²¹ are independently selected from the group consisting of hydrogen, halogen, —OH, SR²⁶, alkyl and alkoxy, R²⁶ is hydrogen or alkyl.

26. The method of claim 25 wherein the compound corresponds to formula (I), in which Y is O

![Diagram]

A is

in which Q is —OH, two of the R¹⁰, R²⁰ and R²¹ are selected from the group consisting of alkyl, alkoxy, alkylthio, amino, alkylaminolino and dialkylamino and the third is selected from the group consisting of hydrogen, alkyl, alkoxy, alkylthio, amino, alkylaminolino and dialkylamino, or Q is phenyl substituted by —OH and at least one member selected from the group consisting of hydrogen, halogen, —OH, alkyl, alkoxy and —NR⁰³R¹³, R¹⁰ and R¹¹ are independently hydrogen or alkyl.

27. The method of claim 26 wherein A is

![Diagram]

in which Q is —OH, two of the R¹⁰, R²⁰ and R²¹ are alkyl and the third is H, or Q is phenyl substituted by —OH and at least one alkyl.
28. The method of claim 22 wherein Y is O; A is

![Chemical structure](image)

in which Q is —OH, two of the R₁, R₂, and R³ are alkyl and the third is hydrogen, or in which Q is phenyl substituted by —OH and at least one alkyl; B is hydrogen; n is 0 or 1; R⁴ and R⁵ both are hydrogen, and Ω is NR⁶R⁷, R⁶ is selected from the group consisting of hydrogen, alkyl, alkenyl, hydroxylalkyl and cyanoalkyl and R⁷ is hydrogen or alkyl or R⁶ and R⁷ form together with the nitrogen atom which carries them a non-aromatic heterocycle with 5 to 7 ring members, the additional members are —CH₂— or —NH—.

29. The method of claim 28, wherein the compound is selected from the group consisting of

- 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-2-thiazolemethanamine;
- 2-[[4-[3,5-di(tert-butyl)-4-hydroxyphenyl]-1,3-thiazol-2-yl]methyl](methyl)amino)-acetonitrile;
- 2,6-di(tert-butyl)-4-[[2-hydroxyethyl](methyl)amino]-1,3-thiazol-4-yl]phenol;
- 4-[[4-(3,5-di(tert-butyl)-4-hydroxyphenyl)-1,3-thiazol-2-yl]methyl](methyl)amino)-butanenitrile;
- 2,6-di(tert-butyl)-4-[[2-methyl(2-propynyl)amino]-ethyl]-1,3-oxazol-2-yl]phenol;
- 3-[[2-[[2-(3,5-di(tert-butyl)-4-hydroxyphenyl)-1,3-oxazol-4-yl]ethyl](methyl)amino]-propanenitrile;
- 2,6-di(tert-butyl)-4-[[2-(1-piperazinyl)ethyl]-1,3-oxazol-2-yl]phenol; and the pharmaceutically acceptable salts of the latter.

30. The method of claim 22 wherein the compound is selected from the group consisting of 2-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4-oxazoleethanol, 2,6-di(tert-butyl)-4-[[2-(methyl)(2-propynyl)amino]-ethyl]-1,3-oxazol-2-yl]phenol, 2-[[2-[[2-(3,5-di(tert-butyl)-4-hydroxyphenyl)-1,3-oxazol-4-yl]ethyl](methyl)amino]-propanenitrile, 2,6-di(tert-butyl)-4-[[2-(1-piperazinyl)ethyl]-1,3-oxazol-2-yl]phenol hydrochloride, 2,6-di(tert-butyl)-4-[[4-hydroxypropyl]-1,3-thiazol-2-yl]phenol and 2,6-di(tert-butyl)-4-[[2-(methylamino)(methyl)amino]-1,3-thiazol-2-yl]phenol hydrochloride.

* * * *