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New derivatives of 2-(iminomethyl)amino-phenyl,
their preparation, their use as medicaments
and the pharmaceutical compositions containing them

A subject of the present invention is new derivatives of 2-(iminomethyl)amino-phenyl which
5 have an inhibitory activity on NO-synthase enzymes producing nitrogen monoxide NO and/or
an activity which traps the reactive oxygen species (ROS). The invention relates to the
derivatives corresponding to general formula (I) defined below, their preparation methods, the
pharmaceutical preparations containing them and their use for therapeutic purposes, in
10 particular their use as NO-synthase inhibitors and selective or non selective traps for reactive
oxygen species.

Given the potential role of NO and the ROS's in physiopathology, the new derivatives
described corresponding to general formula (I) may produce beneficial or favourable effects
in the treatment of pathologies where these chemical species are involved. In particular:

- 15 • cardio-vascular and cerebro-vascular disorders including for example atherosclerosis,
migraine, arterial hypertension, septic shock, ischemic or hemorrhagic cardiac or cerebral
infarctions, ischemias and thromboses.
- 20 • disorders of the central or peripheral nervous system such as for example
neurodegenerative diseases where there can in particular be mentioned cerebral infarctions,
sub-arachnoid haemorrhaging, ageing, senile dementias including Alzheimer's disease,
Huntington's chorea, Parkinson's disease, Creutzfeld Jacob disease and prion diseases,
amyotrophic lateral sclerosis but also pain, cerebral and bone marrow traumas, addiction to
opiates, alcohol and addictive substances, erectile and reproductive disorders, cognitive
disorders, encephalopathies, encephalopathies of viral or toxic origin.
- 25 • disorders of the skeletal muscle and neuromuscular joints (myopathy, myosis) as well as
cutaneous diseases.
- 30 • proliferative and inflammatory diseases such as for example atherosclerosis, pulmonary
hypertension, respiratory distress, glomerulonephritis, portal hypertension, psoriasis,
arthrosis and rheumatoid arthritis, fibroses, amyloidoses, inflammations of the gastro-
intestinal system (colitis, Crohn's disease) or of the pulmonary system and airways
(asthma, sinusitis, rhinitis).
- organ transplants.

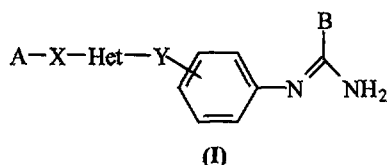
- auto-immune and viral diseases such as for example lupus, AIDS, parasitic and viral infections, diabetes, multiple sclerosis.
- cancer.
- neurological diseases associated with intoxications (Cadmium poisoning, inhalation of n-hexane, pesticides, herbicides), associated with treatments (radiotherapy) or disorders of genetic origin (Wilson's disease).
- all the pathologies characterized by an excessive production or dysfunction of NO and/or ROS's.

In all these pathologies, there is experimental evidence demonstrating the involvement of NO or ROS's (*J. Med. Chem.* (1995) **38**, 4343-4362; *Free Radic. Biol. Med.* (1996) **20**, 675-705; *The Neuroscientist* (1997) **3**, 327-333).

Furthermore, the inventors have already described NO Synthase inhibitors and their use in previous Patents (US Patent 5,081,148; US Patent 5,360,925) and more recently the combination of these inhibitors with products having antioxidant or antiradicular properties (an unpublished Patent Application).

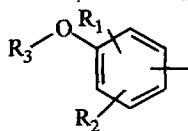
A subject of the present invention is new derivatives of 2-(iminomethyl)amino-phenyl, their preparation and their therapeutic use.

The compounds of the invention correspond to general formula (I):



in which:

A is a hydrogen atom or preferably an aromatic corresponding to structures:

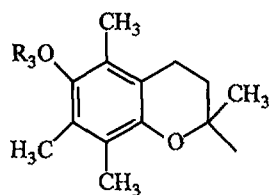


in which:

R₁ and R₂ represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms

R₃ represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a -COR₄ radical, R₄ representing an alkyl radical having from 1 to 6 carbon atoms,

or



B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl radical having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-\text{CO}-\text{N}(\text{R}_3)-\text{X}'-$, $-\text{NH}-\text{CO}-\text{X}'-$, $-\text{CH}=\text{}$, $-\text{CO}-$ or a bond,

X' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

Y represents $-\text{Y}'-$, $-\text{CO}-\text{NH}-\text{Y}'-$, $-\text{Y}'-\text{NH}-\text{CO}-$, $-\text{CO}-\text{Y}'-$, $-\text{Y}'-\text{CO}-$, $-\text{N}(\text{R}_3)-\text{Y}'-$, $-\text{Y}'-\text{N}(\text{R}_3)-$, $\text{Y}'-\text{CH}_2-\text{N}(\text{R}_3)-\text{CO}-$, $-\text{O}-\text{Y}'-$, $-\text{Y}'-\text{O}-$, $-\text{S}-\text{Y}'-$, $-\text{Y}'-\text{S}-$, $-\text{Y}'-\text{O}-\text{Y}'-$, $-\text{Y}'-\text{N}(\text{R}_3)-\text{Y}'-$ or a bond, Y' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $\text{X}'-\text{OR}_3$, $\text{X}'-\text{NR}_3$, $\text{X}'-\text{SR}_3$ and such as for example:

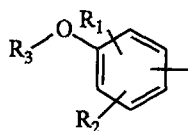
oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

it being understood that when A represents a hydrogen atom, Het does not represent a piperidine, pyrrolidine or morpholine radical.

The compounds of general formula (I) containing one or more asymmetrical centres having isomer forms. The racemics and enantiomers of these compounds are also part of this invention. Similarly, the compounds of the invention can also exist in the state of bases or addition salts with acids.

More particularly the invention relates to the compounds of general formula (I) in which:

A is a hydrogen atom or preferably an aromatic corresponding to the structure:



in which:

R_1 and R_2 represent, independently a linear or branched alkyl radical having 1 to 6 carbon atoms or a linear or branched alkoxy radical having from 1 to 6 carbon atoms,

R_3 represents a hydrogen atom or a linear or branched alkyl radical having from 1 to 6 carbon atoms;

B represents a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-NH-CO-X'-$, $-CH=$, $-CO-$ or a bond,

X' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

Y represents $-Y'-$, $-Y'-NH-CO-$, $-Y'-CO-$, $-Y'-O-$, $-Y'-O-Y'-$, $-Y'-N(R_3)-Y'-$ or a bond, Y' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

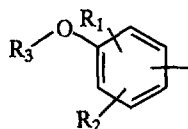
Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-OR_3$, $X'-NR_3$, $X'-S-R_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

it being understood that when A represents a hydrogen atom, Het does not represent a piperidine, pyrrolidine or morpholine radical.

Quite particularly the invention relates to the compounds of general formula (I) in which:

A is a hydrogen atom or an aromatic corresponding to the structure:



in which:

R_1 and R_2 represent, independently a linear or branched alkyl radical having from 1 to 6 carbon atoms or a linear or branched alkoxy radical having from 1 to 6 carbon atoms,

5 R_3 represents a hydrogen atom or a linear or branched alkyl radical having from 1 to 6 carbon atoms;

B represents a thiophene ring, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

10 X represents $-NH-CO-X'-$, $-CH=$, $-CO-$ or a bond,
 X' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

Y represents $-Y'-$, $-Y'-NH-CO-$, $-Y'-CO-$, $-Y'-O-$, $-Y'-O-Y'-$, $-Y'-N(R_3)-Y'-$ or a bond, Y' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

15 Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-OR_3$, $X'-NR_3$, $X'-S-R_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, 20 thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

25 it being understood that when A represents a hydrogen atom, Het does not represent a piperidine, pyrrolidine or morpholine radical.

The invention preferably relates to the following compounds:

- N-[4-(1H-imidazol-1-yl)phenyl]-2-thiophenecarboximidamide hydroiodide;
- N-[4-(3-thiazolidinylmethyl)phenyl]-2-thiophenecarboximidamide;
- N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate;

- N-[4-(1H-imidazol-1-yl methyl)phenyl]-2-thiophenecarboximidamide hydrochloride;
- N-[4-{2-(3-thiazolidinyl)ethyl}phenyl]-2-thiophenecarboximidamide;
- N-{4-[2-(1H-imidazol-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide hydroiodide;
- N-{4-[2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide
5 fumarate
- N-[4-(3-thiazolidinylcarbonylmethyl)phenyl]-2-thiophenecarboximidamide;
- N-(4-{[2-thiazolidinyl]carbonylaminomethyl}phenyl)-2-thiophenecarboximidamide fumarate;
- N-(3,5-di-t-butyl-4-hydroxyphenyl)-5-[4-{imino(2-thienyl)-methylamino}phenyl]-2-furan
10 carboxamide hydroiodide;
- 3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-[4-{imino(2-thienyl)-methylamino}phenyl]-2,5-imidazolidinedione hydrochloride;
- 2-(3,5-di-t-butyl-4-hydroxyphenyl)-3-[4-{imino(2-thienyl)-methylamino}phenyl]-4-thiazolidinone hydrochloride;
- 15 - 5-[(3,5-di-t-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-[4-{imino(2-thienyl)methylamino}phenyl]-2,4-imidazolidinedione fumarate;
- 2-(S)-4-(S)-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)-phenyl]-4-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-prolinamide hydrochloride;
- 5,6-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1-(2H)-pyridine carboxamide
20 hydrochloride;
- N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-2-(R,S)-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-(R)-thiazolidine carboxamide fumarate;
- N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-thiazolecarboxamide hydroiodide
- 25 - N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine-2-(R)-carboxamide dihydrochloride
- methyl 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2-H-[1]-benzopyran-2-yl)carbonyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]-phenoxy}-pyrrolidine-2-(S)- carboxylate hydrochloride

- 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine hydrochloride
- 3-{[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)-carbonyl]amino}-1-{4-[(imino(2-thienyl)methyl)amino]phenyl}pyrrolidine
- 5 - 4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]benzoyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride
- N-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1H-pyrrole-2-carboxamide hydroiodide
- 10 - 1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-3-{4-[(imino(2-thienyl)methyl)amino]phenyl}carbonyl}-2-imidazolidinone hydroiodide
- 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-5-isoxazoleacetamide hydroiodide
- 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-2-thiazolemethanamine hydrochloride
- 15 - 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride
- 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-{2-{4-[(imino(2-thienyl)methyl)amino]phenoxy}ethyl}isoxazole
- 20 - 1-{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]amino}-carbonyl}-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride
- 1-(2-hydroxy-5-methoxybenzoyl)-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride
- 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-4-[4-[(imino(2-thienyl)methyl)amino]phenoxy]-piperidine hydrochloride
- 25 - 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride

or their salts or enantiomers.

The invention particularly relates to the following compounds:

- N-[4-(1H-imidazol-1-yl)phenyl]-2-thiophenecarboximidamide hydroiodide;

- N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate;
- N-{4-[2-(1H-imidazol-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide hydroiodide;
- N-{4-[2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide fumarate;
- 5 - N-[4-(3-thiazolidinylcarbonylmethyl)phenyl]-2-thiophenecarboximidamide;
- 3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-[4-{imino(2-thienyl)-methylamino}phenyl]-2,5-imidazolidinedione hydrochloride;
- 2-(3,5-di-t-butyl-4-hydroxyphenyl)-3-[4-{imino(2-thienyl)-methylamino}phenyl]-4-thiazolidinone hydrochloride;
- 10 - 5-[(3,5-di-t-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-[4-{imino(2-thienyl)methylamino}phenyl]-2,4-imidazolidinedione fumarate;
- 2-(S)-4-(S)-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)-phenyl]-4-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-prolinamide hydrochloride;
- 5,6-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1-(2H)-pyridine carboxamide hydrochloride;
- 15 - N-[4-hydroxy-3,5-bis-(1,1-dimethyl)ethyl -phenyl]-2-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-thiazole carboxamide hydrochloride;

or their salts or enantiomers.

20 Finally, the invention quite particularly relates to N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate or its salts.

A subject of the invention is also, as medicaments, the compounds of general formula (I) described previously or their pharmaceutically acceptable salts. It also relates to pharmaceutical compositions containing these compounds or their pharmaceutically acceptable salts, and the use of these compounds or of their pharmaceutically acceptable salts
25 for producing medicaments intended to inhibit NO synthase, to inhibit lipidic peroxidation or to provide the double function of NO synthase inhibition and lipidic peroxidation inhibition.

By pharmaceutically acceptable salt is meant in particular addition salts of inorganic acids such as hydrochloride, sulphate, phosphate, diphosphate, hydrobromide, hydroiodide and nitrate, or of organic acids, such as acetate, maleate, fumarate, tartrate, succinate, citrate,
30 lactate, methane sulphonate, p-toluenesulphonate, pamoate, oxalate and stearate. The salts

formed from bases such as sodium or potassium hydroxide also fall within the scope of the present invention, when they can be used. For other examples of pharmaceutically acceptable salts, reference can be made to "Pharmaceutical salts", *J. Pharm. Sci.* **66**:1 (1977).

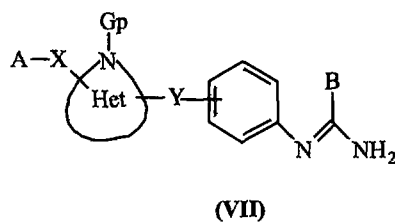
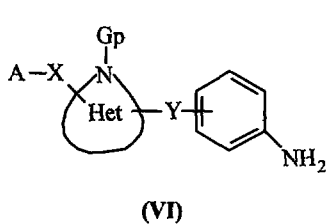
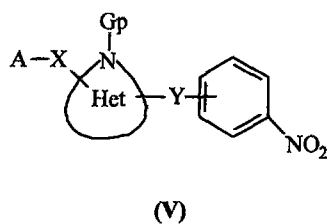
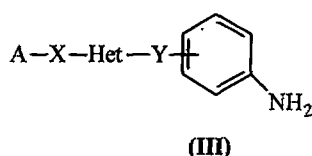
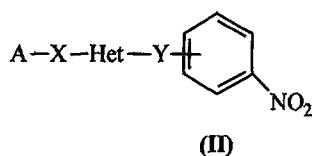
5 The pharmaceutical composition can be in the form of a solid, for example powders, granules, tablets, capsules, liposomes or suppositories. Appropriate solid supports can be for example calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose,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

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

A medicament according to the invention can be administered by topical, oral or parenteral route, by intramuscular injection, etc.

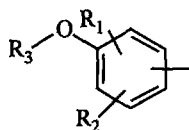
The envisaged administration dose for the medicament according to the invention is
15 comprised between 0.1 mg and 10 g according to the type of active compound used.

The invention also offers, as new industrial products, the synthetic intermediates of the products of general formula (I), namely the products of general formula (II), (III), (V), (VI) and (VII)



in which

A is an aromatic corresponding to structures:

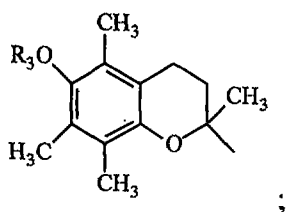


in which:

- 5 R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,

R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-COR_4$ radical, R_4 representing an alkyl radical having 1 to 6 carbon atoms,

or



- 10 B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

- 15 X represents $-CO-N(R_3)-X'$ -, $-NH-CO-X'$ -, $-CH=$, $-CO-$ or a bond,
 X' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

Y represents $-Y'$ -, $-CO-NH-Y'$ -, $-Y'-NH-CO-$, $-CO-Y'$ -, $-Y'-CO-$, $-N(R_3)-Y'$ -, $-Y'-N(R_3)-$, $Y'-CH_2-N(R_3)-CO-$, $-O-Y'$ -, $-Y'-O-$, $-S-Y'$ -, $-Y'-S-$, $-Y'-O-Y'$ -, $-Y'-N(R_3)-Y'$ - or a bond, Y' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

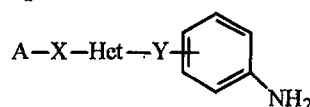
- 20 Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-OR_3$, $X'-NR_3$, $X'-S-R_3$ and such as for example:

- oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulfolane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione,
 25 oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine,

with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

G_p represents a protective group of the amine function preferably cleavable in an anhydrous acid medium, such as for example the carbamates of t-butyl, trichloroethyl or trimethylsilylethyl or also the trityl group.

Finally, the invention offers preparation processes for the compounds of general formula (I) as defined above and consisting of, for example, the reaction in a lower alcohol, such as methanol, ethanol, isopropyl alcohol or t-butanol, preferably in isopropyl alcohol, at a temperature between 20 and 90°C, for example at 50 °C, and for one to 48 hours, preferably for 15 to 24 hours, optionally in the presence of DMF, of a compound of general formula (III)



(III)

with a compound of general formula (IV)



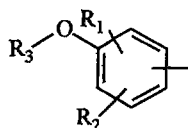
(IV)

said compound of general formula (IV) optionally being able to be salified by a mineral acid G, B having the meaning indicated above and L representing a parting group and in particular an alkoxy, thioalkyl, sulphonic acid, halide, aryl alcohol or tosyl radical (other parting groups well-known to a person skilled in the art and being optionally able to be used for the invention are described in the following work: Advanced Organic Chemistry, J. March, 3rd Edition (1985), Mc Graw-Hill, p. 315). Preferably, G represents HCl, HBr or HI.

Other production processes can be envisaged and are accessible from the literature (for example: The Chemistry of amidines and imidates, Vol. 2, Saul PATAI and Zvi RAPPOPORT, John Wiley & Sons, 1991).

For the above processes, the compounds of general formula (I), (III), (IV), (VI) and (VII) are such that:

A is a hydrogen atom or an aromatic corresponding to the structures:

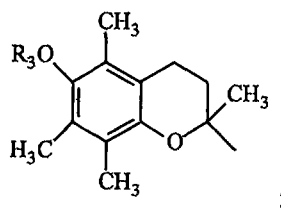


in which:

R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,

- 5 R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-COR_4$ radical, R_4 representing an alkyl radical having from 1 to 6 carbon atoms,

or



- 10 B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-CO-N(R_3)-X'$, $-NH-CO-X'$, $-CH=$, $-CO-$ or a bond,

- 15 X' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

Y represents $-Y'$, $-CO-NH-Y'$, $-Y'-NH-CO-$, $-CO-Y'$, $-Y'-CO-$, $-N(R_3)-Y'$, $-Y'-N(R_3)-$, $Y'-CH_2-N(R_3)-CO-$, $-O-Y'$, $-Y'-O-$, $-S-Y'$, $-Y'-S-$, $-Y'-O-Y'$, $-Y'-N(R_3)-Y'$ or a bond, Y' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

- 20 Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-OR_3$, $X'-NR_3$, $X'-S-R_3$ and such as for example:

- oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, 25 thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

- 30 G_p represents a protective group of the amine function preferably cleavable in an anhydrous acid medium, such as for example the carbamates of t-butyl, trichloroethyl or trimethylsilylethyl or also the trityl group.

In accordance with the invention, the compounds of general formula (I) can be prepared by the process below.

Preparation of the compounds of general formula (I):

- 5 The compounds of general formula (I) can be prepared starting from intermediates of general formula (II), (III) or (V) according to Diagram 1.

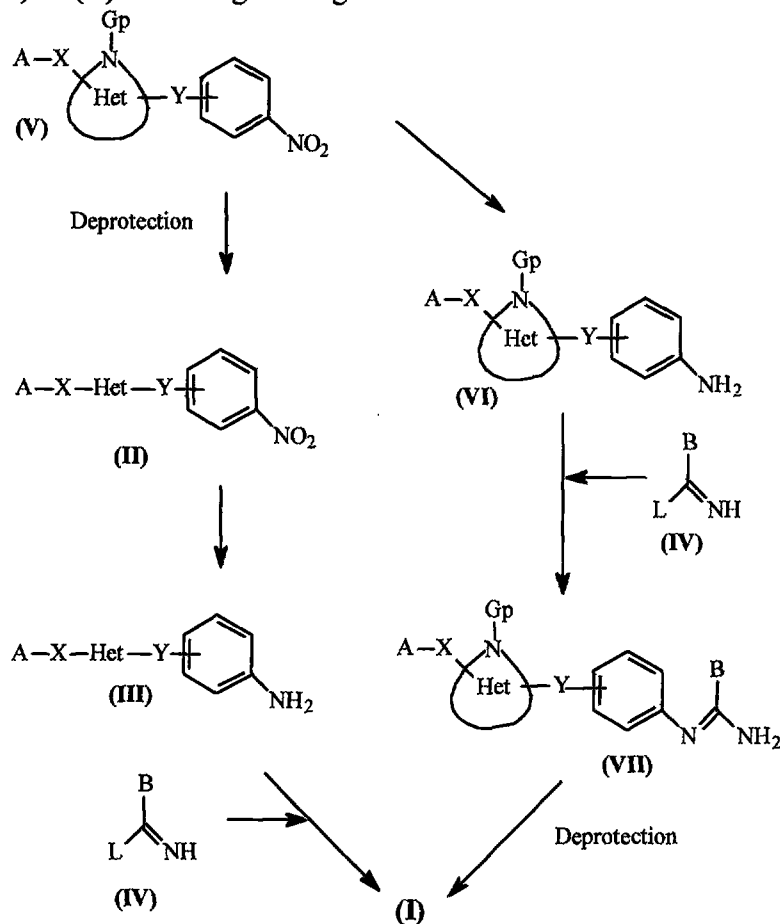


Diagram 1

- The reduction of the nitro function of the intermediates of general formula (II) is generally carried out by catalytic hydrogenation in ethanol, in the presence of Pd/C, except when the molecules contain an unsaturation or a sulphur atom, this being a poison to the Pd/C. In this case, the nitro group is selectively reduced, for example, by heating the product in solution in 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 by using Raney Ni with hydrazine hydrate added to it (*Monatshefte für Chemie*, (1995), **126**, 725-732).

The aniline derivatives of general formula (III) thus obtained can be condensed with derivatives of general formula (IV), for example derivatives of O-alkyl thioimide or S-alkyl thioimide type, in order to produce final compounds of general formula (I) (cf. Diagram 1).

For example, for B = thiophene, the derivatives of general formula (III) can be condensed with S-methylethiophene thiocarboxamide hydriodide, prepared according to a method in the literature (*Ann. Chim.* (1962), 7, 303-337). Condensation can be carried out by heating in an alcohol (for example in methanol or isopropanol), optionally in the presence of DMF at a temperature comprised between 50 and 100°C for a duration generally comprised between a few hours and overnight.

The final molecules of general formula (I) are also accessible through another synthetic route passing through the intermediates of general formula (V) which carry a heterocyclic amine function protected by a protective group "Gp", for example a 2-(trimethylsilyl)ethoxymethyl group (SEM) or by another protective group mentioned in: *Protective groups in organic synthesis*, 2d ed., (John Wiley & Sons Inc., 1991). The reduction and condensation stages which lead to intermediates (VI) and (VII) respectively are carried out under the same conditions as those described previously. The last stage of the synthesis consists in regenerating, for example in an acid medium or in the presence of a fluoride ion, the protected heterocyclic amine function.

Alternatively, the intermediates of general formula (V) can be converted directly into the intermediate of general formula (II) by release of the heterocyclic amine by treatment, for example, in an acid medium or in the presence of a fluoride ion.

20 **Preparation of the compounds of general formula (II), (III) and (V):**

The intermediates of general formula (II), (III) and (V) can be prepared by the different synthetic routes illustrated below.

When: Het = Imidazole, tetrahydropyridine, thiazolidine, dihydroimidazole-2-one
and Y = -Y'-.

25 The amines of general formula (II), Diagram 2, in which A, X, Y and Het are as defined above, can be obtained by nucleophilic substitution of commercial halogenated derivatives of general formula (IX) by a heterocyclic amine of general formula (VIII). The reaction is carried out in acetonitrile, THF or DMF in the presence of a base such as K₂CO₃ at a temperature varying from 20 to 110°C. The synthesis of heterocyclic derivatives of general
30 formula (VIII), which are not commercially-available, is described below.

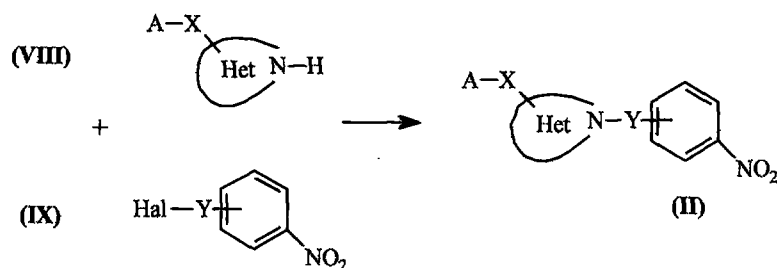


Diagram 2

When: Het = imidazole, thiazolidine, tetrahydropyridine
and Y = -Y'-.

- 5 The heterocyclic amines of general formula (III), Diagram 3, in which A, X, Y and Het are as defined above, are prepared in two stages starting from the amines of general formula (VIII) (see below). The mixture of a brominated derivative of general formula (X), the synthesis of which is explained in detail below, with an amine of general formula (VIII) in a solvent such as acetonitrile or DMF in the presence of a base leads to intermediates of general formula
- 10 (XI). The deprotection of the amine function, in an organic acid medium, allows the compounds of general formula (III) to be obtained.

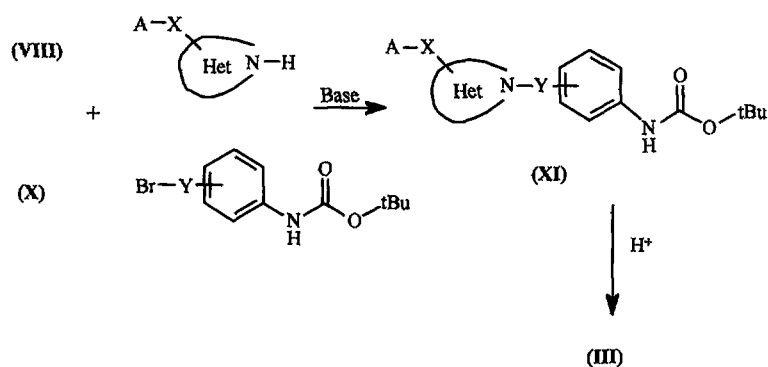


Diagram 3

When: Het = thiazolidine
and Y = -CO-Y'-.

15

- The carboxamides of general formula (III), Diagram 4, in which A, X, Y and Het are as defined above, are prepared by condensation of the amines of general formula (VIII), described previously, with the carboxylic acids of general formula (X.2). The carboxamide bonds are formed under standard conditions of peptide synthesis (M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, 145 (Springer-Verlag, 1984)) in THF, dichloromethane or DMF in the presence of a coupling reagent such as dicyclohexylcarbodiimide (DCC), 1,1'-carbonyldiimidazole (CDI) (*J. Med. Chem.* (1992), **35** (23), 4464-4472) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC or
- 20

WSCI) (John Jones, The chemical synthesis of peptides, 54 (Clarendon Press, Oxford, 1991)). The synthesis of the carboxylic acids of general formula (X.2) is described below. The intermediates of general formula (XII) are then deprotected in an acid medium using, for example, trifluoroacetic acid or an organic solution of HCl.

5

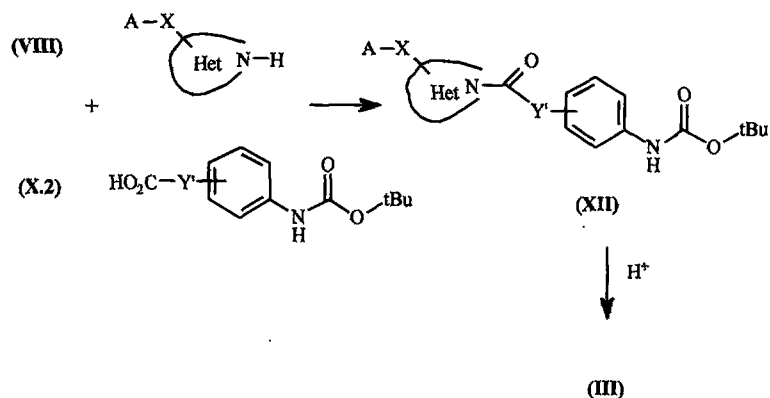


Diagram 4

When: Het = thiazolidine
and Y = -CO-NH-Y'-.

10 The carboxamides of general formula (V), Diagram 5, in which A, X, Y and Het are as defined above, are prepared by condensation of carboxylic acids of general formula (XIII) with the commercial amines of general formula (XIV) under standard conditions for peptide synthesis. The synthesis of the carboxylic acids of general formula (XIII) is described below.

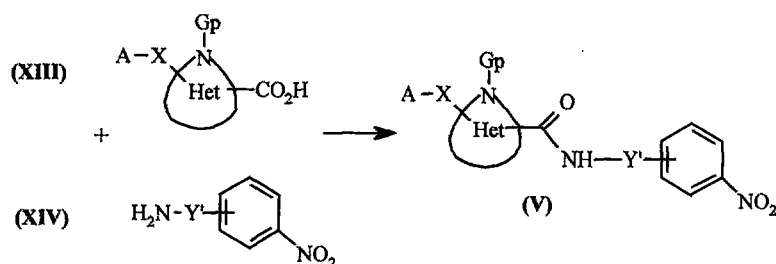


Diagram 5

15 When: Het = thiazole, furan, pyrrole, tetrahydropyridine, pyrrolidine
and X = -NH-CO-X'-.

20 The carboxamides of general formula (II), Diagram 6, in which A, X, Y and Het are as defined above, are prepared by condensation of anilines of general formula (XV) with the carboxylic acids of general formula (XVI) under standard conditions for peptide condensation. The anilines of general formula (XV) are obtained by hydrogenation, in the presence of a catalytic quantity of Pd/C, of corresponding nitrobenzene derivatives, themselves synthesized according to a method described in the literature (*J. Org. Chem.*

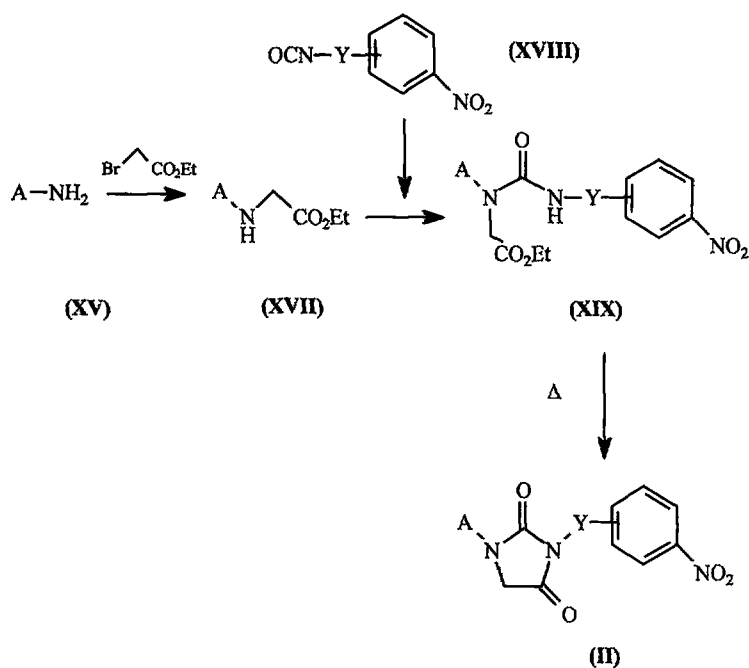


Diagram 7

When: Het = thiazolidinone
and Y = -Y'-.

The thiazolidinones of general formula (II), Diagram 8, in which A, X, Y and Het are as defined above, are prepared starting from commercial amines of general formula (XIV) and aldehydes of general formula (XX) in the presence of mercaptoacetic acid according to an experimental protocol described in the literature (*J. Med. Chem.*, (1992), **35**, 2910-2912).

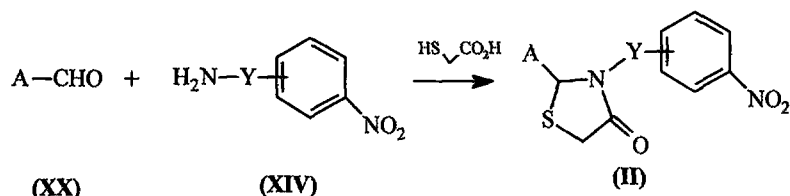


Diagram 8

When: Het = hydantoin
X = -CH= and Y = -Y'-.

The hydantoines of general formula (II), Diagram 9, in which A, X, Y and Het are as defined above, are prepared in 2 stages starting from the isocyanates of general formula (XVIII) described previously. The reaction of the ethyl ester of sarcosine with the isocyanates of general formula (XVIII), is carried out according to an experimental protocol described in the literature (*J. Heterocyclic Chem.*, (1979), **16**, 607-608), leads to the formation of the heterocycle of the compounds of general formula (XXI). The substitution of the hydantoin is carried out in the presence of a weak base, β -alanine, and an aldehyde of general formula (XX) according to the experimental conditions described in *J. Med. Chem.*, (1994), **37**, 322-328.

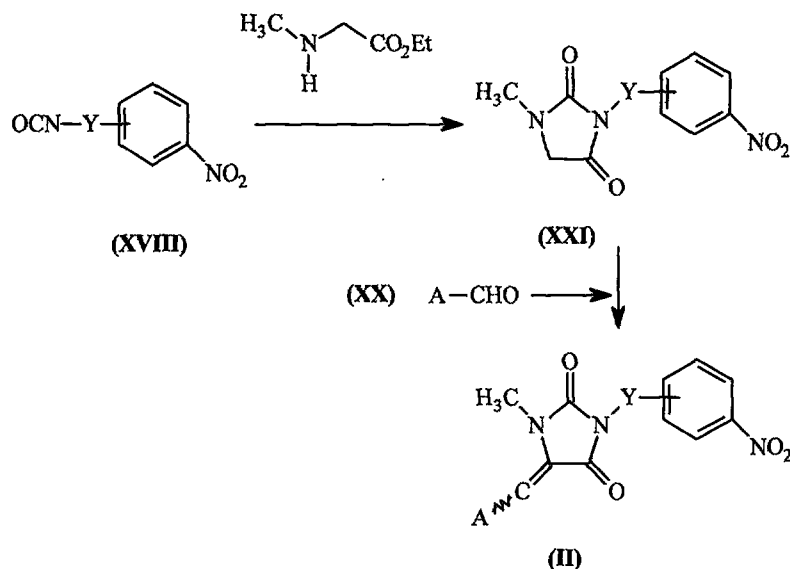


Diagram 9

- 5 When: Het = pyrrolidine, thiazolidine
 $X = -\text{NH-CO-X}'-$ and $Y = -\text{O-Y}'-$ or $-\text{Y}'-$.

The carboxamides of general formula (V), Diagram 10, in which A, X, Y and Het are as defined above, are prepared by condensation of the anilines of general formula (XV), described previously, with the acids of general formula (XXII) under standard conditions for peptide synthesis. The syntheses of carboxylic acids (XXII), which are not commercially available, are described below.

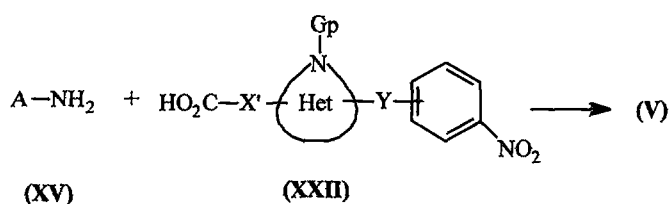


Diagram 10

- 15 When: Het = tetrahydropyridine
and $Y = -\text{CO-NH-Y}'-$.

The ureas of general formula (II), Diagram 11, in which A, X, Y and Het are as defined above, are prepared by condensation of the heterocyclic amines of general formula (VIII), described previously, with the isocyanates of general formula (XVIII) (cf. above) in a solvent such as dichloromethane, at 20°C, in the presence of a tertiary amine (e.g. diisopropylthylamine).

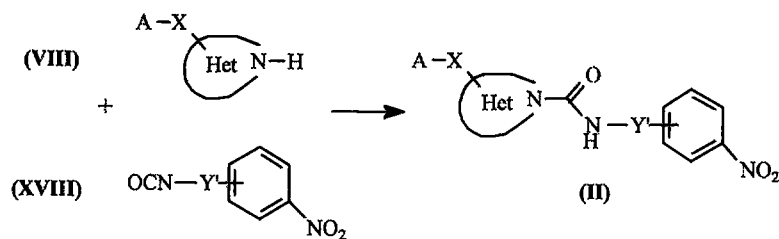


Diagram 11

When: Het = pyrrolidine, thiazole, thiadiazole
and X = -CO-NH-X'-.

- 5 The carboxamides of general formula (II), Diagram 12, in which A, X, Y and Het are as defined above, are prepared by condensation of commercial carboxylic acids of general formula (XXIII) with the amines of general formula (XXIV) under standard conditions for peptide synthesis. The syntheses of the amines of general formula (XXIV), which are not commercially available, are described below.

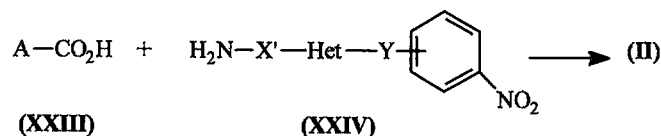


Diagram 12

When: Het = imidazole, oxazole and thiazole
and Y = -CH(R₃)-N(R₃)-CO-Y'-.

- 15 The carboxamides of general formula (V), Diagram 13, in which A, X, Y and Het are as defined above, are prepared by condensation of the amines of general formula (XXV) with commercial carboxylic acids (or the corresponding acid chlorides) of general formula (XXVI) under standard conditions for peptide synthesis. The synthesis of the imidazole derivatives of general formula (XXV) is described below.

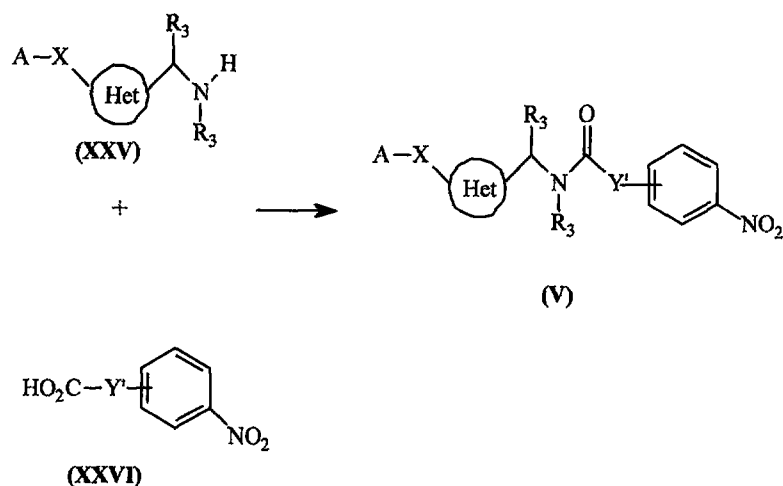


Diagram 13

When: Het = imidazole
and Y = -CH₂-N(R₃)-Y'-.

- 5 The amines of general formula (V), Diagram 14, in which A, X, Y and Het are as defined above, are prepared by condensation of the amines of general formula (XXV) (see below) with the commercial halogenated derivatives of general formula (IX) under the conditions described previously.

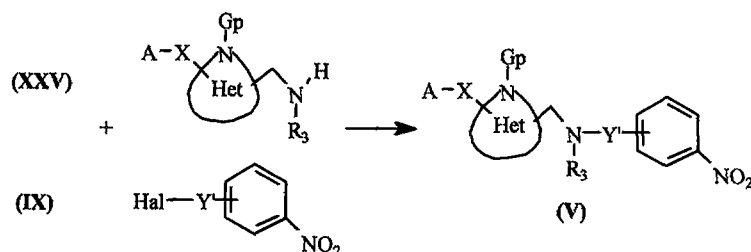


Diagram 14

When: Het = dihydroimidazole-2-one
and Y = -CO-Y'.

- 15 The amines of general formula (II), Diagram 15, in which A, X, Y and Het are as defined above, are prepared by condensation of the amines of general formula (VIII) (see below) with the commercial halogenated derivatives of general formula (XXVII), for example in an acetonitrile and THF mixture and in the presence of a base such as K₂CO₃.

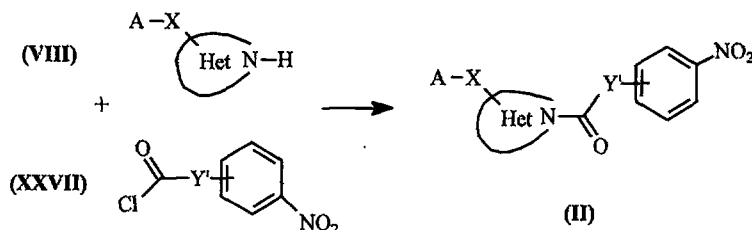


Diagram 15

When: Het = oxazolidinone
and Y = -Y'-O-

- 5 The oxazolidinones of general formula (II), Diagram 16, are prepared starting from the diols of general formula (XXVII) the synthesis of which is described in the literature (Daumas, M., *Tetrahedron*, 1992, **48**(12), 2373). The formation of carbonates of general formula (XXVIII) is obtained, for example, in the presence of carbonyl di-imidazole (Kutney, J.P., *Synth. Commun.*, 1975, **5**(1), 47) or in the presence of triphosgene at low temperature as described in
- 10 *Synth. Commun.*, 1994, **24**(3), 305. The formation of oxazolidinone occurs during heating of the amines of general formula (XV) with the carbonates of general formula (XXVIII) in the presence of an acid catalyst, such as ZnCl_2 , at xylene reflux in order to eliminate the water formed during the reaction (Laas, H., *Synthesis*, 1981, 958).

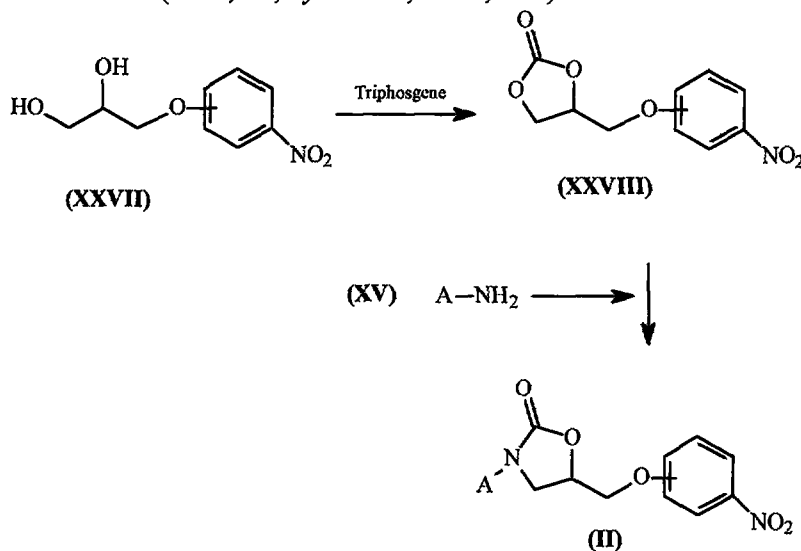


Diagram 16

When: Het = isoxazoline, isoxazole, oxazole, thiazole
and Y = -Y'-CO-NH-Y'-

The carboxamides of general formula (II), Diagram 17, in which A, X, Y and Het are as defined above, can be prepared starting from the commercial amines of general formula (XIV)

and the carboxylic acids of general formula (XXVIII) by condensation in the presence of isobutyl chloroformate (*Org. Prep. Proced. Int.*, (1975), 7, 215).

The preparation of the oxazoles of general formula (XXVIII) is carried out according to an experimental protocol described in *Tetrahedron Lett.*, 1994, 35 (13), 2039. Similarly for the synthesis of the thiazoles of general formula (XXVIII): *J. Med. Chem.*, 1983, 26, 884. The preparation of the isoxazolines is described below.

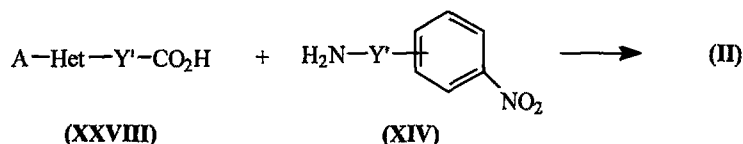


Diagram 17

When: Het = pyrrolidine, piperidine

X = -CO-NH-

and Y = -O-Y'-.

The carboxamides of general formula (II), Diagram 18, in which A, X, Y and Het are as defined above, can be prepared by condensation of the commercial carboxylic acids of general formula (XXIII) with the amines of general formula (XXIX) under standard conditions for peptide synthesis. The syntheses of amines of general formula (XXIX) are described below.

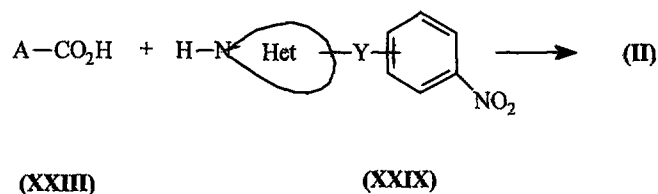


Diagram 18

When: Het = isoxazoline, oxazole, thiazole, imidazole

and Y = -Y'-O-Y'- or -Y'-N(R₃)-Y'-.

The etheroxides of general formula (II), Diagram 19, in which A, X, Y and Het are as defined above, can be prepared starting from the esters of general formula (XXVIII.4), Diagram 17.1, by reaction with hydrides, for example LiAlH₄, in a solvent such as, for example, anhydrous THF. The primary alcohols thus obtained are then condensed on halogenated derivatives of general formula (IX) using a base such as for example KOH in an organic medium and in the presence of a phase transfer catalyst such as for example Aliquat 336.

The primary alcohols (XXXI) can also be activated in the form of sulphonate derivatives, by tosyl chloride in the presence of pyridine, in order to produce intermediates of general formula (XXXII). The condensation of alcohols of general formula (XXII.2) is then carried out in the presence of a strong base, such as, for example, NaH, in an aprotic solvent (THF or DMF) at

a temperature comprised between 20°C and 80°C, in order to obtain the etheroxides of general formula (II).

Similarly, the amines of general formula (II), Diagram 19, are obtained by substitution of the tosylate function of the intermediates of general formula (XXXII), obtained in a standard fashion starting from the alcohols of general formula (XXXI) and tosyl chlosride in the presence of pyridine, by the commercial amines of general formula (XXX) by reaction in a solvent such as, for example, acetonitrile or DMF, in the presence of a base (K_2CO_3) at a temperature comprised between 20 and 85°C.

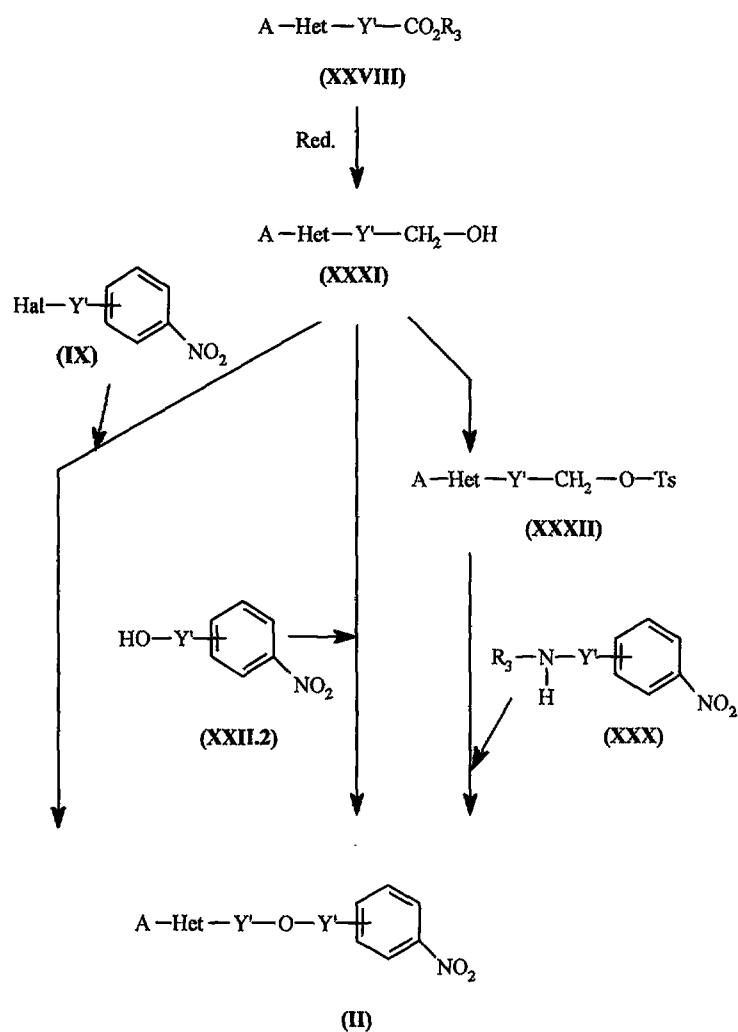
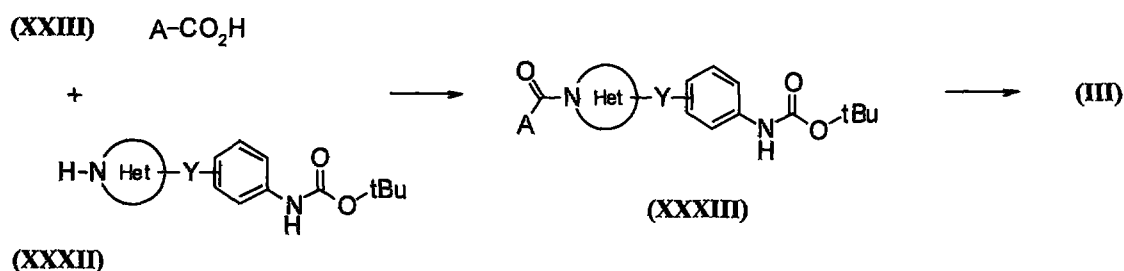


Diagram 19

When: Het = azetidine
X = -CO-NH-
and Y = -O-Y'-.

The carboxamides of general formula (III), Diagram 20, in which A, X, Y and Het are as defined above, can be prepared by condensation of commercial carboxylic acids of general formula (XXIII) with the amines of general formula (XXXII) under standard conditions for

peptide synthesis. The synthesis of amines of general formula (XXXII) is described below. The deprotection of the aniline is carried out by a strong acid such as, for example, trifluoroacetic acid optionally in the presence of triethylsilane.



5

Diagram 20

When: Het = azetidine
 X = -NH-CO-X'-
 and Y = -O-Y'-.

The ureas of general formula (III), Diagram 21, in which A, X, Y and Het are as defined above, can be prepared by the addition of the amines of general formula (XXXII) on the isocyanates (XXXIV) obtained from the reaction of the amines of general formula (XV) with triphosgene in the presence of a tertiary amine such as for example diisopropylthylamine in a neutral solvent such as dichloromethane (*J. Org. Chem.* (1994), **59** (7), 1937-1938). The ureas of general formula (XXXV) thus obtained are deprotected by treatment in a strong acid medium as described previously. The synthesis of the amines of general formula (XXXII) is described below.

15

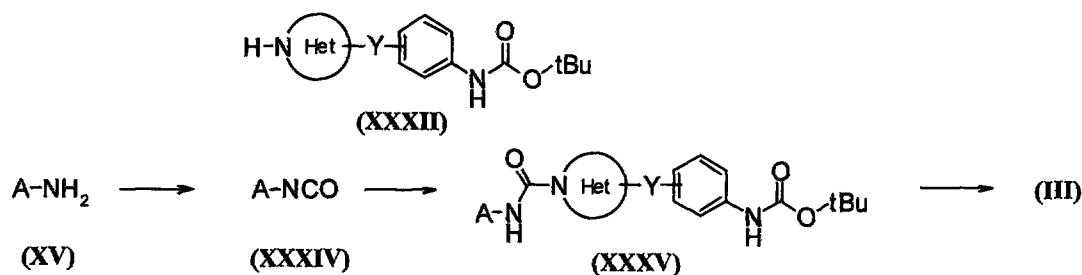


Diagram 21

When: Het = thiazole
 and Y = -CH₂-N(R₃)-Y'-.

20

The amines of general formula (II), Diagram 22, in which A, X, Y and Het are as defined above, are prepared by condensation of the amines of general formula (XXV) (see below) with the commercial halogenated derivatives of general formula (IX) under the conditions described previously.

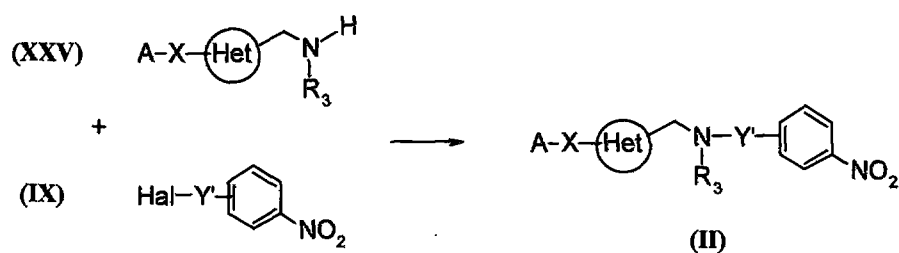


Diagram 22

Preparation of different synthesis intermediates:

Synthesis of Intermediates (VIII):

- 5 The syntheses of the intermediates of general formula (VIII) are illustrated in Diagrams 2.1 and 2.2.

The intermediates of general formula (VIII), Diagram 2.1, can be prepared, for example, in 3 stages starting from 4-imidazole carboxylic acid. The protection of the nitrogen of the heterocycle is carried out using (Boc)₂O in the presence of a base such as K₂CO₃ in DMF. The condensation with the amines of general formula (XV) (see above) is carried out in a standard fashion under the conditions for peptide synthesis in order to produce the intermediates of general formula (VIII.3). The amine of the heterocycle is regenerated by treatment in an acid medium and in particular with trifluoroacetic acid in order to produce the intermediates of general formula (VIII).

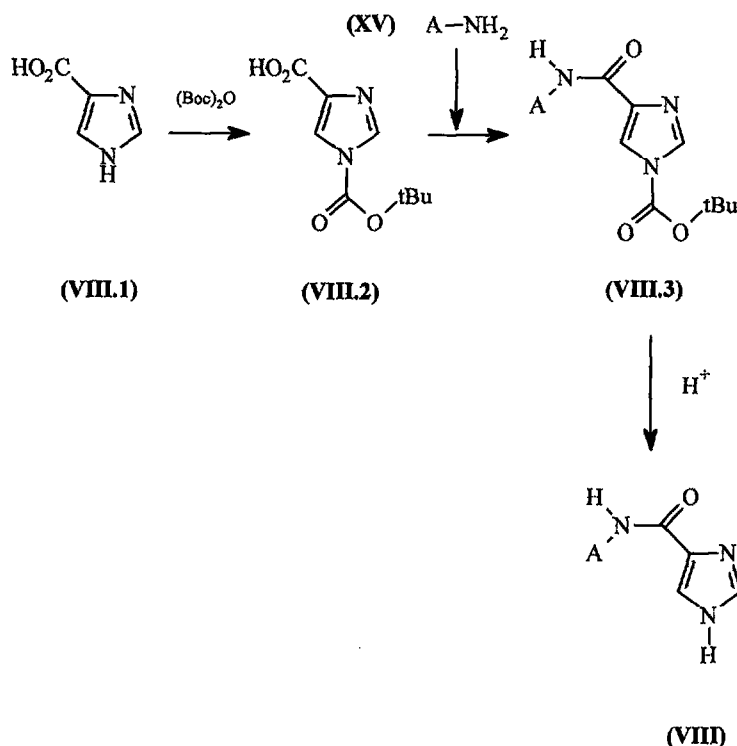


Diagram 2.1

The dihydroimidazole-2-ones of general formula (VIII), Diagram 2.2, can be prepared, for example, in 2 stages starting from the anilines of general formula (XV) (see above) which are condensed with 2-chloroethyl isocyanate in DMF at 20° C in order to produce the ureas of general formula (VIII.4). The cyclization to produce (VIII) is then carried out by treatment in a basic medium using, for example, tBuOK in DMF.

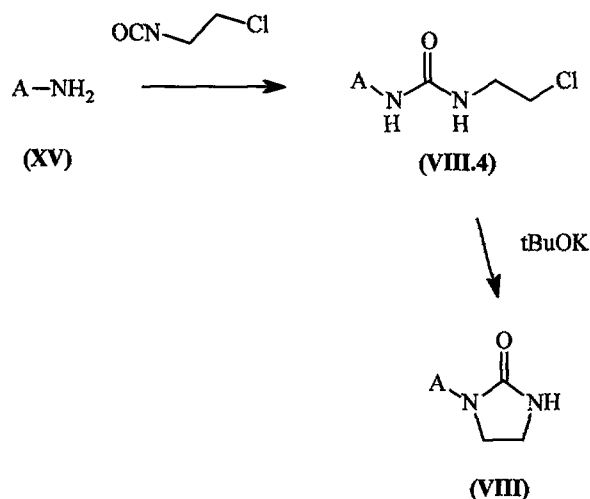


Diagram 2.2

Synthesis of Intermediates (X):

- 10 The intermediates of general formula (X), Diagram 3.1, can be prepared starting from commercial carboxylic acids of general formula (X.1). Protection of the amine function in the form of a carbamate is followed by the selective reduction of the carboxylic acid function by lithium and aluminium hydride in a solvent such as THF, at 20°C. Intermediate (X.3) is then brominated in the presence of carbon tetrabromide and triphenylphosphine in a solvent such
- 15 as dichloromethane.

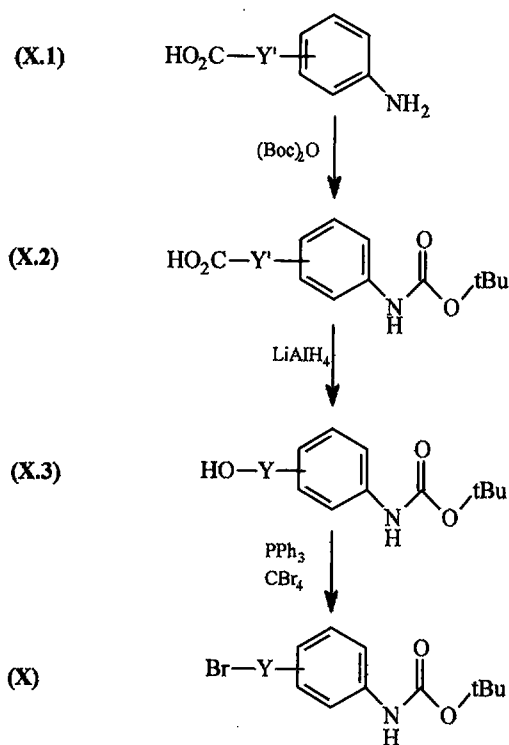


Diagram 3.1

Synthesis of Intermediates (XIII):

The intermediates of general formula (XIII), Diagram 5.1, can be prepared starting from (R or S) derivatives of thiazolidine carboxylic acids in the presence of $(\text{Boc})_2\text{O}$ under standard conditions.

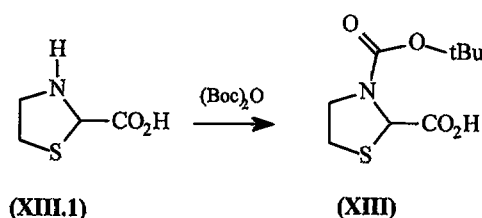


Diagram 5.1

Synthesis of Intermediates (XVI):

The intermediates of general formula (XVI), Diagram 6.1, can be prepared starting from commercial carboxamide derivatives of general formula (XVI.1). These carboxamides are treated by a Lawesson reagent in a solvent such as 1,4-dioxane for 2 to 3 hours at a temperature which varies from 25°C to the reflux temperature of the mixture. The thiocarboxamides of general formula (XVI.2) are then treated by ethyl bromopyruvate, at 20°C in DMF according to an experimental protocol described in *J. Med. Chem.*, (1983), **26**, 884-891, in order to produce the thiazoles of general formula (XVI.3). The saponification of the ester is carried out over 15 hours by aqueous potash in solution in acetone.

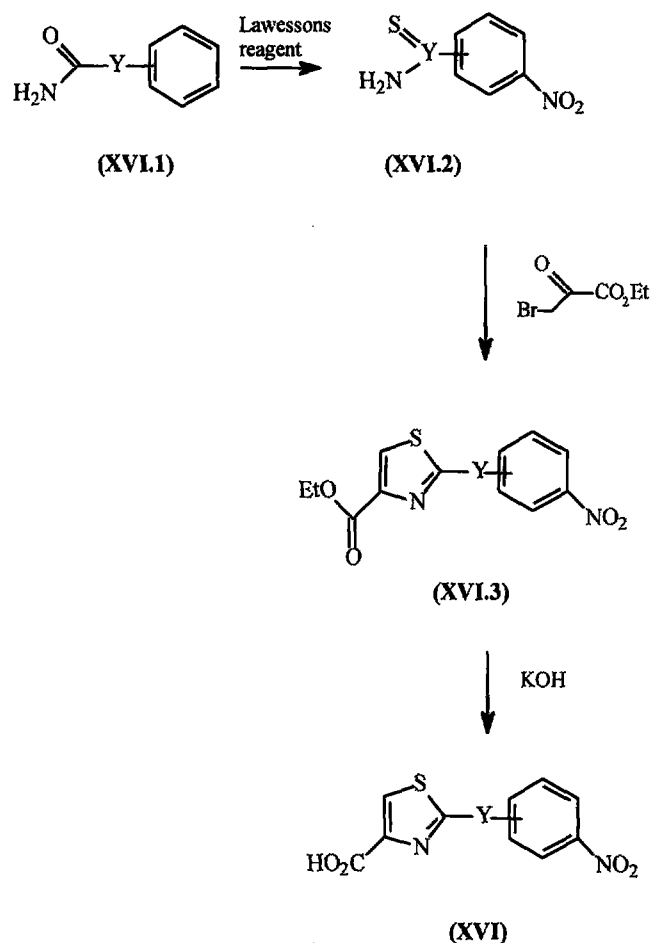


Diagram 6.1

The tetrahydropyridines of general formula (XVI), Diagram 6.2, can be prepared starting from commercial tetrahydro-4-pyridine carboxylic acid. Esterification is carried out in a standard fashion in the presence of para-toluene sulphonic acid, in methanol, in order to produce the intermediate (XVI.4) which is then condensed with a halogenated derivative of general formula (IX) under the conditions described previously. The acid of general formula (XVI) is obtained by saponification in the presence of, for example, LiOH or KOH.

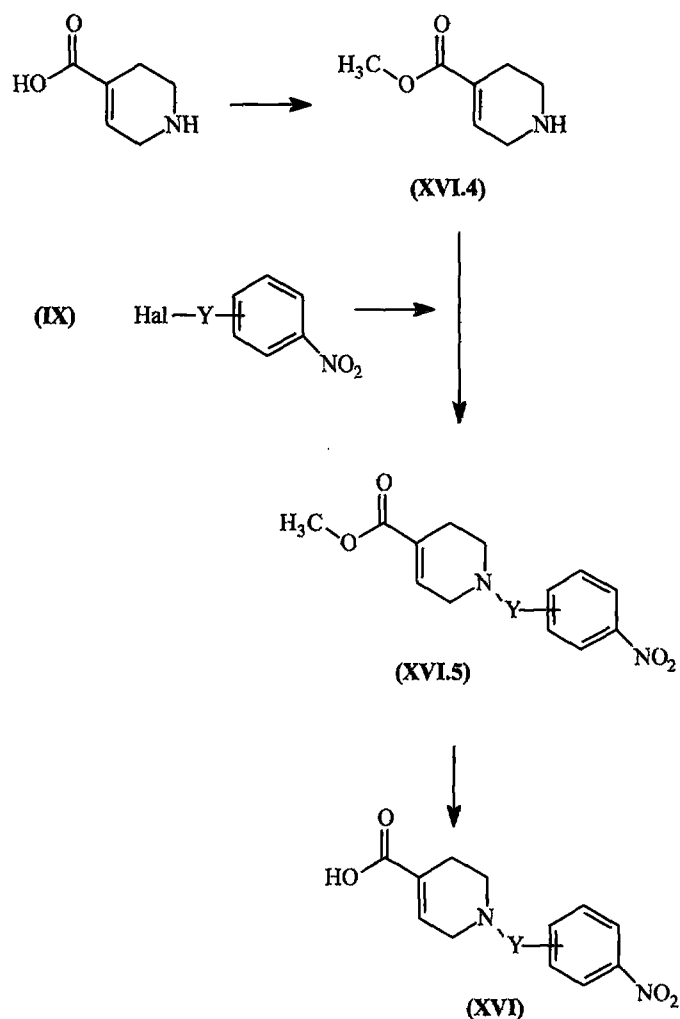


Diagram 6.2

Synthesis of Intermediates (XXII):

5 The syntheses of intermediates of general formula (XXII) are described in Diagrams 10.1 and 10.2.

10 The tosylate function of the (L or D) proline derivatives of general formula (XXII.1) (Tetrahedron Lett., (1983), 24 (33), 3517-3520), Diagram 10.1, is substituted by the alcoholate of the derivatives of general formula (XXII.2), generated *in situ* by a base such as NaH. The substitution is carried out at 20°C in a solvent such as N-methylpyrrolidinone which produces the appropriate inversion of the configuration of the carbon seat of the reaction (Tetrahedron Lett., (1983), 24 (33), 3517-3520). The intermediates of general formula (XXII.3) thus obtained are then saponified in a standard fashion by alcoholic potash.

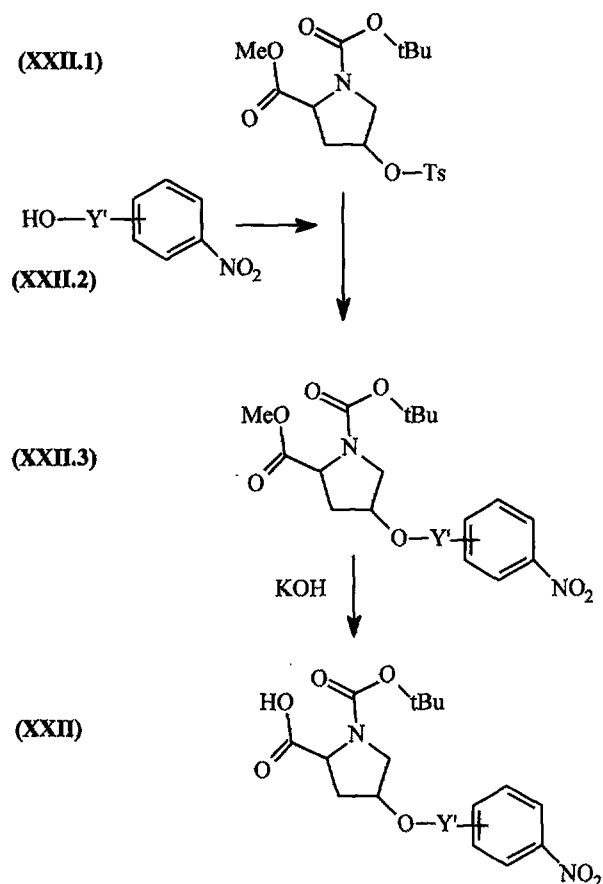


Diagram 10.1

The intermediates of general formula (XXII) can also be prepared (Diagram 10.2) starting from the condensation of cysteine (L or D) with an aldehyde of general formula (XXII.5) according to an experimental protocol described in the literature (*J. Org. Chem.*, (1957), **22**, 943-946). The amine of the heterocycle is then protected in the form of a carbamate in order to produce intermediates of general formula (XXII). The aldehydes of general formula (XXII.5), which are not commercially available, can be prepared according to *J. Chem. Soc., Perkin Trans. I*, 1973, 1, 35.

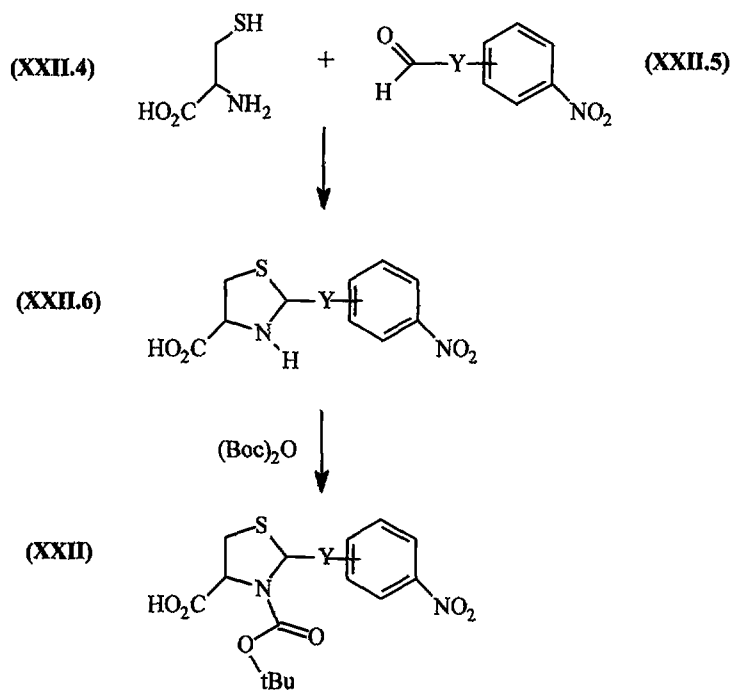


Diagram 10.2

Synthesis of Intermediates (XXIV):

The synthesis of intermediates of general formula (XXIV) is described in Diagram 12.1.

- 5 The condensation of the amines (R or S) of general formula (XXIV.1), Diagram 12.1, with the halogenated derivatives of general formula (IX) is carried out in the presence of a base such as potassium carbonate in a solvent such as DMF. The condensation product (XXIV.2) is then deprotected in an acid medium in order to produce intermediates of general formula (XXIV).

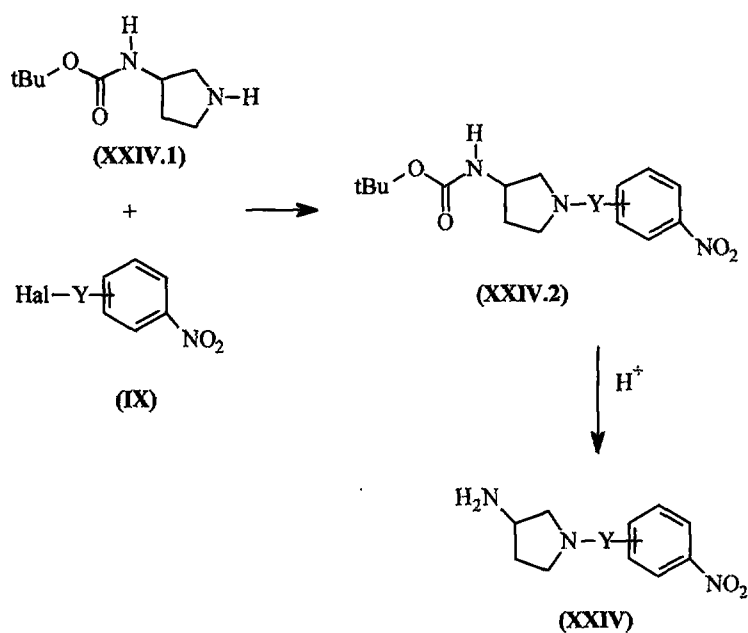


Diagram 12.1

Synthesis of Intermediates (XXV):

The syntheses of intermediates of general formula (XXV) are described in Diagrams 13.1, 13.2, 13.3 and 13.4.

5 The imidazoles of general formula (XXV), Diagram 13.1, can be prepared in 4 stages starting from the commercial compounds (XXV.1) and (XXV.2). The condensation between the bromoacetophenones of general formula (XXV.1) and the carboxylic acids of general formula (XXV.2) is carried out in the presence of Caesium carbonate in DMF. The ketoester obtained (XXV.3) is cyclized in the presence of 15 equivalents of ammonium acetate by heating in a mixture of xylenes and simultaneous elimination of the water formed during the reaction in
10 order to produce the imidazoles of general formula (XXV.4). The nitrogen of the heterocycle is then protected, for example using 2-(Trimethylsilyl)ethoxymethyl (SEM) or by another protective group mentioned in: *Protective groups in organic synthesis*, 2nd ed., (John Wiley & Sons Inc., 1991), in order to produce intermediates of general formula (XXV.5). The release of the amine from the chain can be carried out by hydrogenolysis in the presence of
15 Pd/C.

Alternatively, the intermediates of general formula (XXV.4) can be alkylated in the presence of a base such as, for example, K_2CO_3 , and a reagent such as R_3-X in a solvent such as DMF or acetonitrile in order to produce the imidazoles of general formula (XXV.6). Deprotection of the side chain, as described previously, allows the intermediates of general formula (XXV) to
20 be accessed.

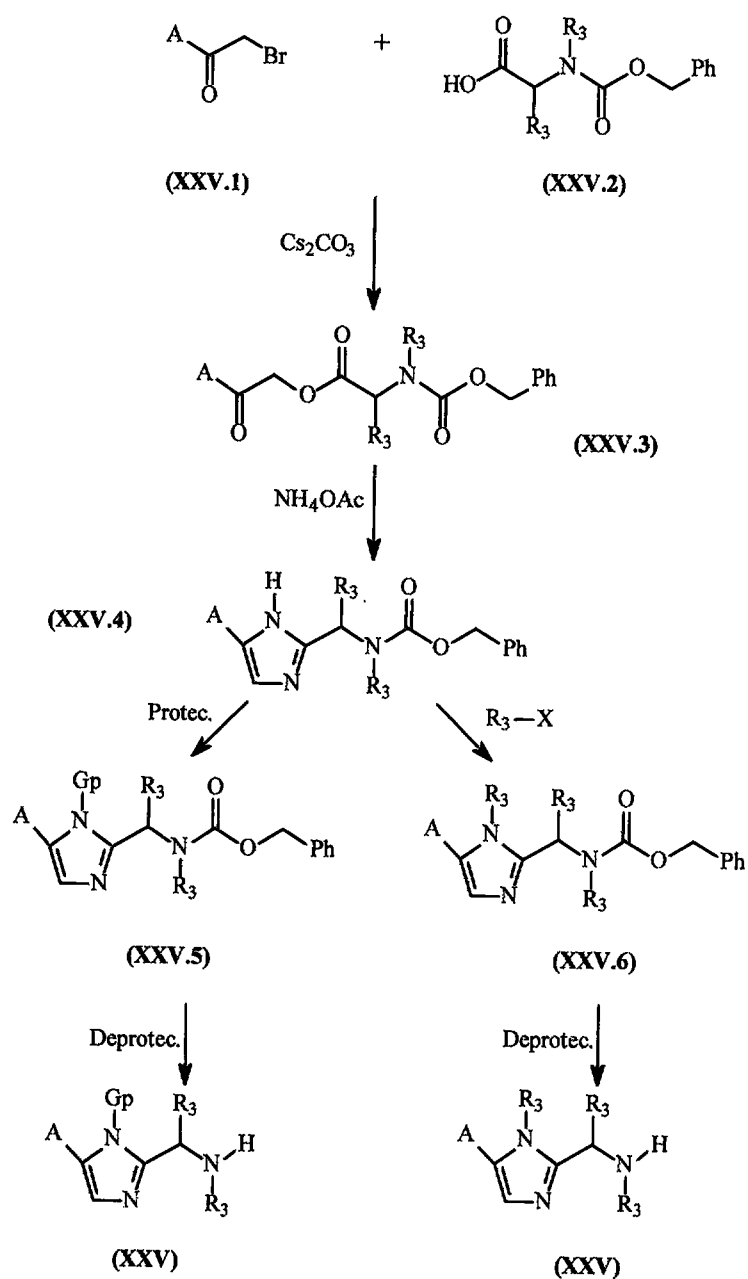


Diagram 13.1

The intermediates of general formula (XXV) containing an oxazole, thiazole or an imidazole are also accessible via other synthetic routes such as that described in *Bioorg. and Med. Chem. Lett.*, 1993, **3**, 915 or *Tetrahedron Lett.*, 1993, **34**, 1901. The intermediates of general formula (XXV.7) thus obtained can be modified, Diagram 13.2, by saponification followed by decarboxylation, for example thermic, in order to produce disubstituted heterocycles of general formula (XXV.9). Release of the amine from the side chain, as described previously, allows the intermediates of general formula (XXV) to be accessed.

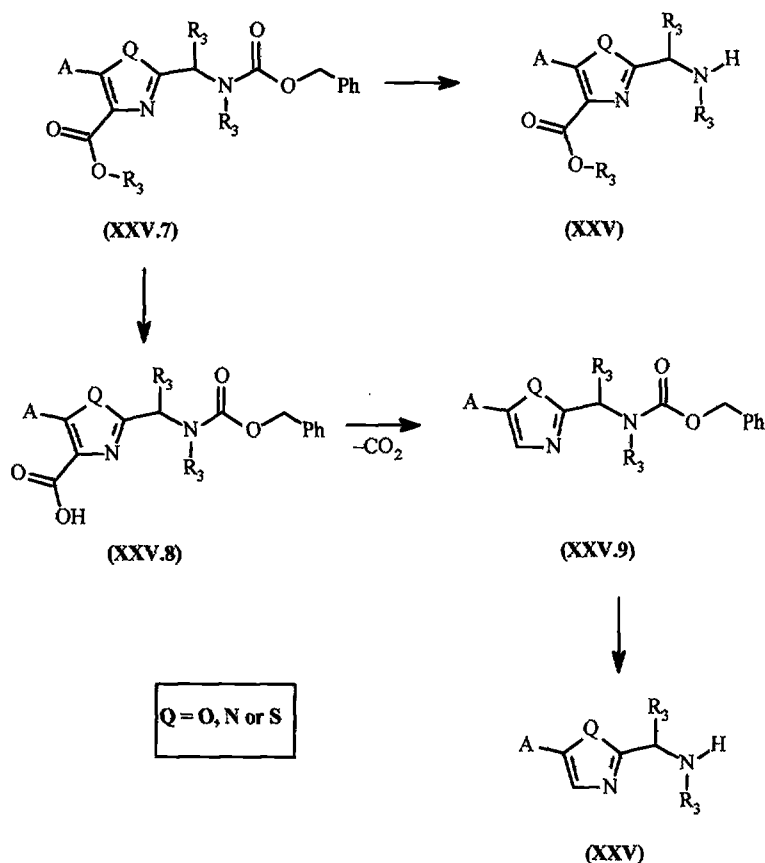


Diagram 13.2

Alternatively, the carboxylic function of the heterocycles of general formula (XXV.7), can be reduced, for example by NaBH₄, in order to produce alcoholic derivatives of general formula (XXV.10), Diagram 13.3, which can be alkylated in the presence of R₃-X and a base such as K₂CO₃ in a solvent such as acetonitrile or DMF. Release of the amine from the side chain, as described previously, allows the intermediates of general formula (XXV) to be accessed.

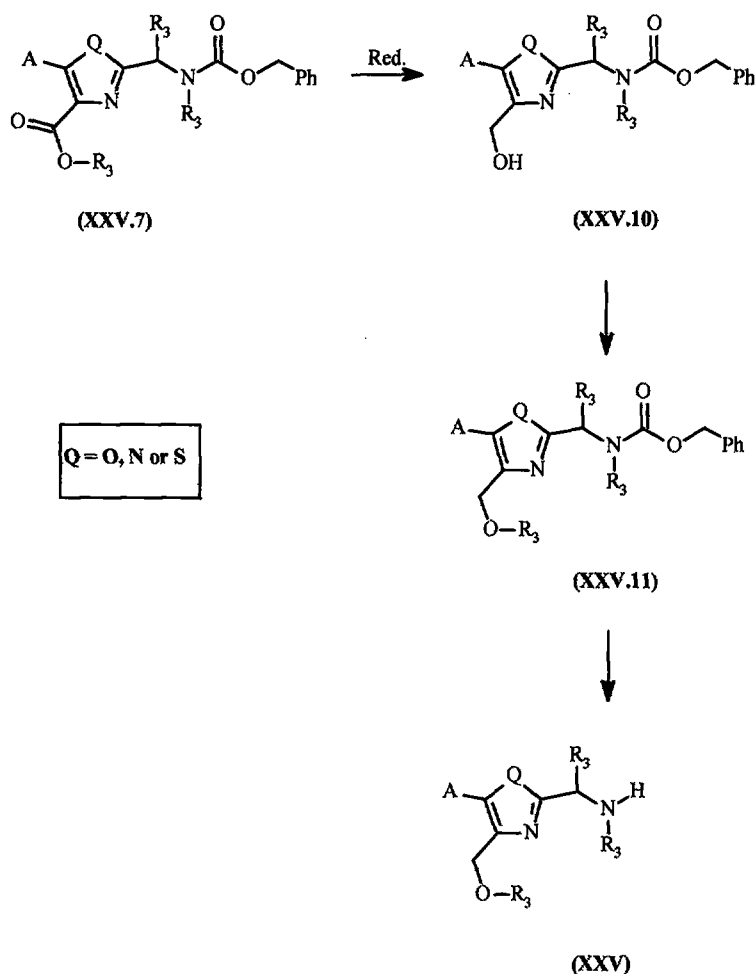


Diagram 13.3

The thiazoles of general formula (XXV), Diagram 13.4, can also be prepared in 4 stages starting from commercial sarcosine hydrochloride. The amine is first protected in a standard fashion in the form of tBu carbamate and the carboxamide function is converted to thiocarboxamide in the presence of Lawesson reagent. The formation of the thiazole ring is carried out by the reaction of thiocarboxamide with the intermediate of general formula (XXV.1) according to an experimental protocol described in the literature (*J. Org. Chem.*, (1995), **60**, 5638-5642). The amine function is regenerated by treatment with the intermediate of general formula (XXV.12) in a strong acid medium such as, for example, trifluoroacetic acid.

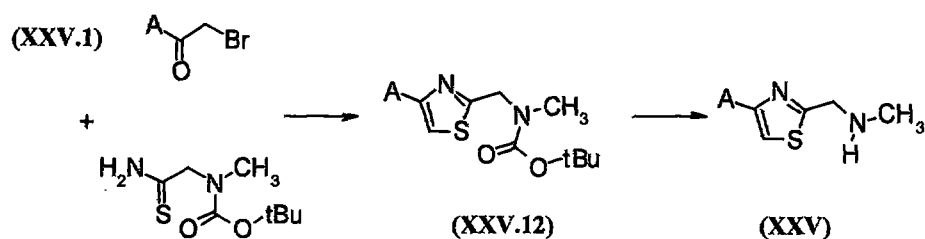


Diagram 13.4

Synthesis of Intermediates (XXVIII):

The isoxazolines and isoxazoles of general formula (XXVIII), Diagram 17.1, are prepared by reaction of commercial aldehydes of general formula (XX) with hydroxylamine hydrochloride. The oxime of general formula (XXVIII.1) thus obtained is activated in the form of the oxime chloride, of general formula (XXVIII.2), by reaction with N-chlorosuccinimide in DMF before reacting with the esters of general formula (XXVIII.3) in order to produce isoxazoline derivatives or with the esters of general formula (XXVIII.4) in order to produce isoxazole 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 or isoxazoles of general formula (XXVIII.5) is then carried out in a standard fashion under the conditions described previously.

The unsaturated esters of general formula (XXVIII.3) and (XXVIII.4), which are not commercially available, can be prepared according to methods described in the literature (*J. Med. Chem.*, 1987, 30, 193; *J. Org. Chem.*, 1980, 45, 5017).

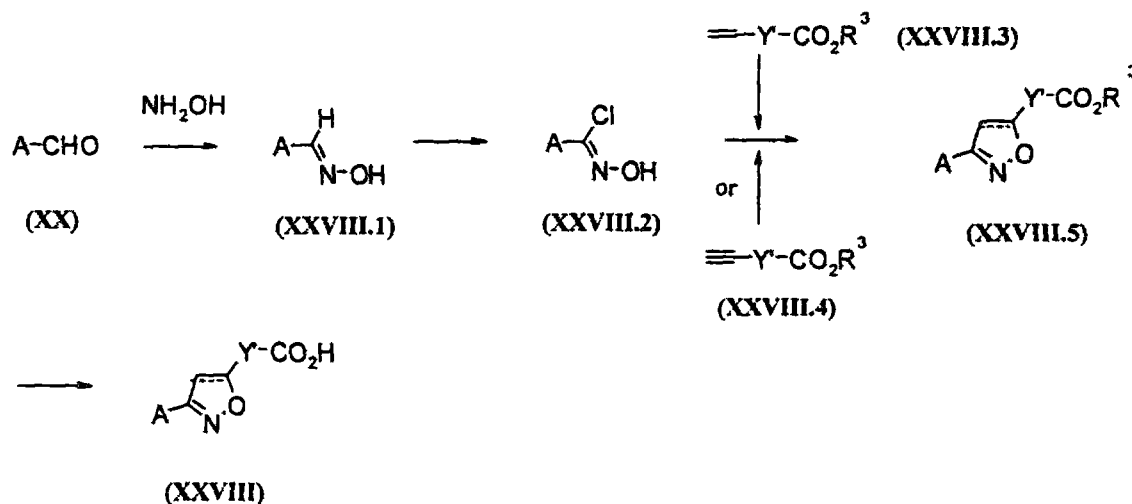


Diagram 17.1

Synthesis of Intermediates (XXIX):

The syntheses of intermediates of general formula (XXIX) are described in Diagrams 18.1, 18.2, 18.3 and 18.4

The intermediates of general formula (XXIX) can be prepared, Diagram 18.1, starting from the intermediates of general formula (XXII.3), described previously, by treatment in a strong acid medium to regenerate the heterocyclic amine function. The selective reduction of the carboxylic function in the presence of, for example, sodium borohydride in a solvent such as, for example, anhydrous THF, allows the intermediate of general formula (XXIX) carrying a primary alcohol function to be obtained without touching the nitro group (Rao, A. V. R., *J. Chem. Soc. Chem. Commun.*, 1992, 11, 859).

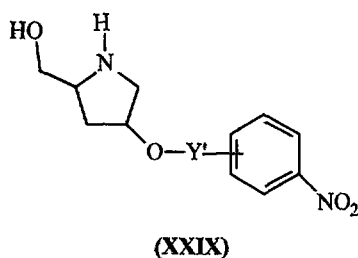
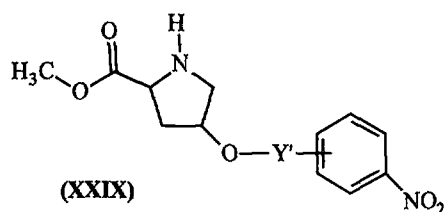
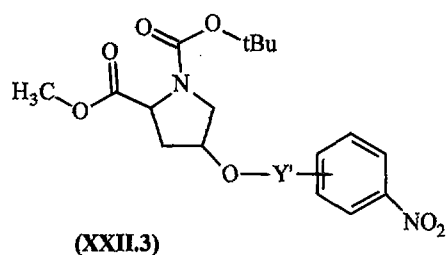


Diagram 18.1

The intermediates of general formula (XXIX) can also be prepared, Diagram 18.2, starting from intermediates of general formula (XXIX.1) (R or S) the preparation of which is similar to that of the compounds of general formula (XXII.1). Condensation of the alcoholic derivatives of general formula (XXII.2) with the intermediates of general formula (XXIX.1) is also described above. Release of the heterocyclic amine is carried out in the presence of an organic solution of a strong acid, for example, trifluoroacetic acid.

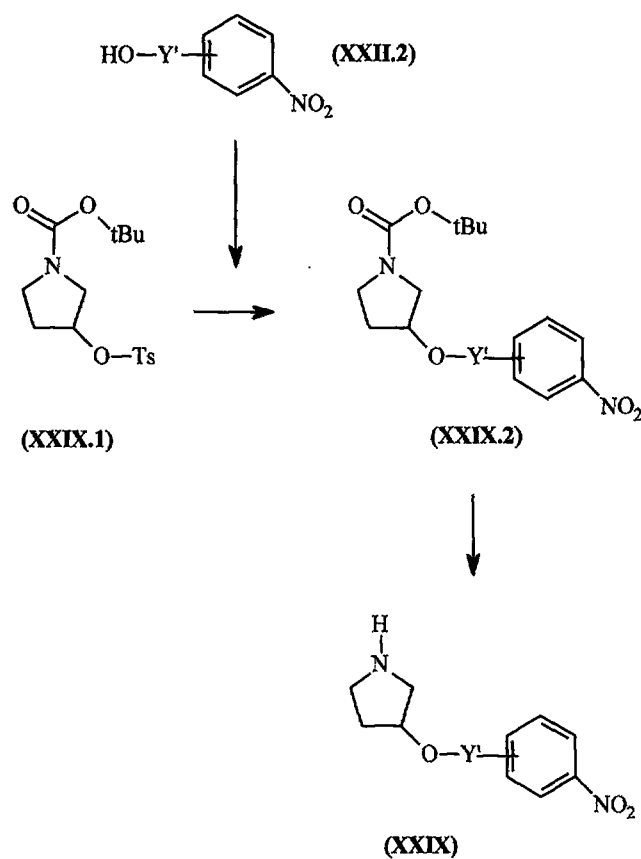


Diagram 18.2

The amines of general formula (XXIX), Diagram 18.3, are also accessible starting from the substitution of tosylated derivatives of general formula (XXIX.1) by the commercial amines of general formula (XXX). Detachment of the carbamate function from the intermediates of general formula (XXIX.3) is carried out as described previously.

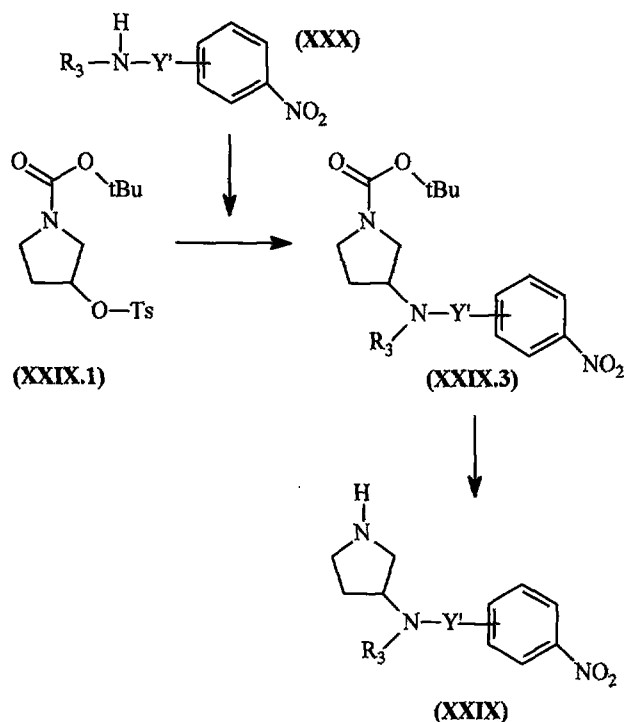


Diagram 18.3

The intermediates of general formula (XXIX) can also be prepared, Diagram 18.4, by reaction of the halogenated derivatives of general formula (IX) with an alcohol of general formula (XXIX.4) in the presence of a base such as for example tBuO^-K^+ in an anhydrous solvent such as THF. The intermediate of general formula (XXIX.5) thus obtained is then deprotected in a strong acid medium (HCl or TFA).

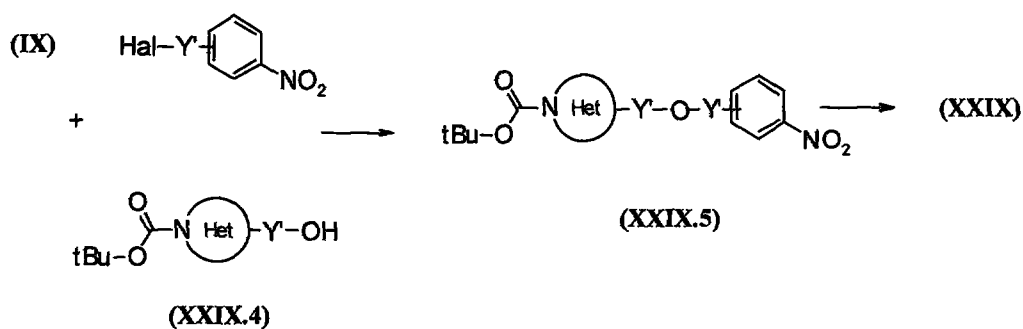


Diagram 18.4

Synthesis of intermediates (XXXII):

The intermediates of general formula (XXXII) can be prepared, Diagram 20.1, by reaction of the halogenated derivatives of general formula (IX) with commercial 1-(diphenylmethyl)-3-hydroxyazetidine (XXXII.1) in the presence of a base such as for example NaH in an anhydrous solvent such as THF. In this case, the nitro group of the intermediate of general formula (XXXII.2) is reduced in the presence of SnCl₂, as described previously, in order to produce the intermediate of general formula (XXXII.3) the amine of which is then protected in the form of a tButyl carbamate. The detachment of the diphenylmethyl protective group is then carried out in a standard fashion by hydrogenolysis in the presence of Pd(OH)₂ in order to produce the intermediate of general formula (XXXII).

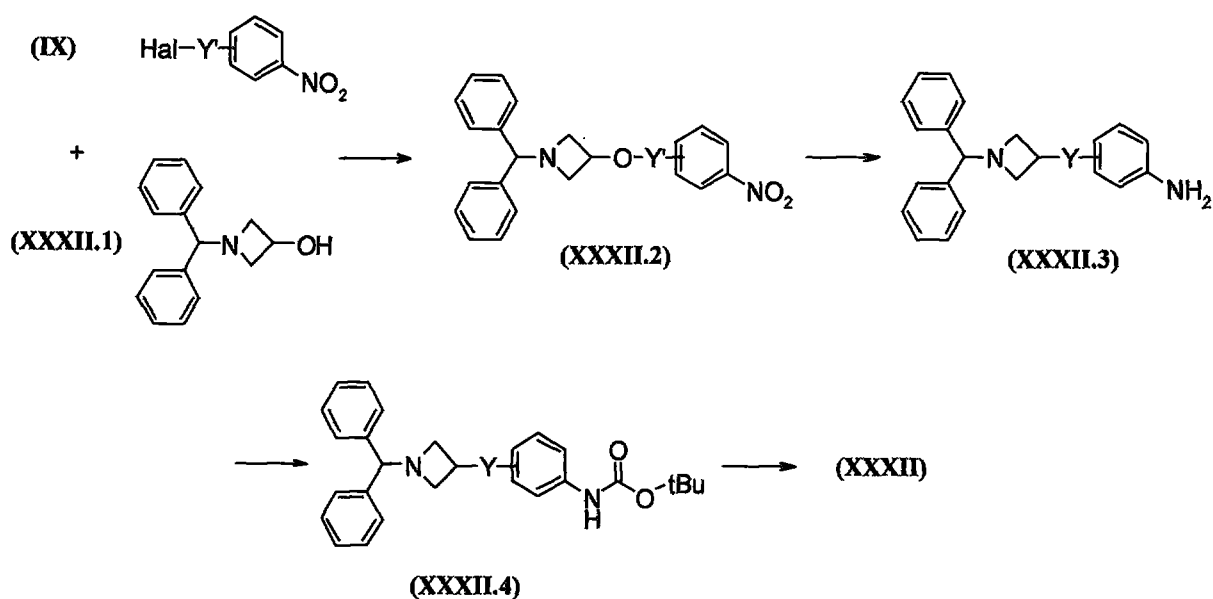


Diagram 20.1

Unless they are defined differently, 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 the invention belongs. Similarly, all publications, Patent Applications, Patents and other references mentioned here are incorporated by way of reference.

The following examples are presented to illustrate the above procedures and should in no way be considered as limiting the scope of the invention.

EXAMPLES:

Example 1: N-[4-(1H-imidazol-1-yl)phenyl]-2-thiophenecarboximidamide hydroiodide (1):

1.1 1-(4-nitrophenyl)-1H-imidazole:

5 9 g (64.5 mmoles) of potassium carbonate and 5 g (3.75 ml; 35.2 mmoles) of 1-fluoro-4-nitrobenzene are added to a solution of 2 g of imidazole (29.4 mmoles) in 14 ml of DMF. The reaction mixture is agitated for 1.5 hours at 110° C. Ethyl acetate (50 ml) is added to the medium which is washed 3 times with 50 ml of water. The organic phases are dried over magnesium sulphate and concentrated under vacuum. 4.4 g of product are thus obtained (yield = 80%) in the form of a clear oil and used without further purification in the following stages.

NMR ¹H (CDCl₃, 100 MHz, δ): 6.92 (t, 1H, Arom. H imidazole), 7.16 (s, 1H, Arom. H imidazole), 7.24-7.32-8.18-8.27 (4s, 4H, Arom. H), 7.59 (s, 1H, arom. H imidazole).

1.2 1-(4-aminophenyl)-1H-imidazole:

15 1-(4-nitrophenyl)-1H-imidazole (4.4 g; 23.5 mmoles) is put in solution in anhydrous methanol (140 ml) and palladium on carbon (0.44 g) is added to the medium. The reaction medium is placed under hydrogen for 4 hours. The catalyst is filtered off and the solvent is evaporated to dryness. The expected product is obtained in a virtually pure state with a yield of 89 % (3.3 g).

NMR ¹H (CDCl₃, 100 MHz, δ): 6.61-6.69-6.95-7.05 (4s, 4H, Arom. H), 6.88 (t, 1H, Arom. H imidazole), 7.07 (s, 1H, Arom. H imidazole), 7.52 (s, 1H, arom. H imidazole).

20 1.3 N-[4-(1H-imidazol-1-yl)phenyl]-2-thiophenecarboximidamide hydroiodide (1):

1-(4-aminophenyl)-1H-imidazole (0.3 g; 1.7 mmoles) and S-methyl-2-thiophenethiocarboximide hydroiodide (0.5 g; 1.75 mmoles) are put into solution in 1 ml isopropanol and 1 ml of DMF and the reaction mixture is agitated for 18 hours at 25°C. The precipitate formed is filtered and washed with 15 ml of dichloromethane and 15 ml of ethanol. The expected product is thus obtained (0.48 g; 73 %) in salified form (hydroiodide). Melting point: 252-253° C (decomposition).

NMR ¹H (DMSO, 400 MHz, δ): 7.24 (s, 1H, arom. H). 7.38 (t, 1H, arom. H). 7.55-7.57-7.85-7.87 (4s, 4H, arom. H), 7.89 (s, 1H, arom. H), 8.10 (m. 2H, arom. H), 8.50 (s, 1H, arom. H).

IR: ν_{C=N} (amidine): 1585 cm⁻¹.

Example 2: N-[4-(3-thiazolidinylmethyl)phenyl]-2-thiophenecarboximidamide (2):

2.1 *1-bromomethyl-4-nitrobenzene*:

4-nitrobenzyl alcohol (6 g, 39 mmol) is put into solution in dichloromethane (100 ml) and carbon tetrabromide (14.9 g, 45 mmol) is added. Triphenylphosphine (11.8 g, 45 mmol) is added in portions to the medium at 0°C. Then the mixture is agitated for 2 hours at ambient temperature. The solvent is evaporated off and the product obtained is purified on silica gel in an ethyl acetate/heptane mixture (1/2). It is obtained in the form of white needle-shaped crystals (7.2 g; 85 %). Melting point: 97-98°C.

NMR ¹H (CDCl₃, 100 MHz, δ): 4.53 (s, 2H, CH₂). 7.53-7.61-8.18-8.27 (4 s, 4H, arom. H).

2.2 *3-(4-nitrobenzyl)-thiazolidine*:

A mixture of thiazolidine (0.9 g, 10 mmol) and potassium carbonate (2.5 g, 18 mmol) in acetonitrile (10 ml) is heated to 70°C. 1-bromomethyl-4-nitrobenzene (2 g, 9.2 mmol) in solution in acetonitrile (25 ml) is added dropwise and the reaction is maintained under reflux for 2 hours.

The precipitate formed is filtered, the mother liquors are evaporated and the residue is taken up in 50 ml of dichloromethane and washed 3 times with 50 ml of water. The organic phases are dried, evaporated and purified over silica gel in an ethyl acetate/heptane mixture (1/2). The expected product is obtained in the form of a colourless oil (1.5 g, 72 %).

NMR ¹H (CDCl₃, 100 MHz, δ): 3.05 (m, 4H, 2CH₂), 3.68 (s, 2H, CH₂-S), 4.04 (s, 2H, CH₂), 7.53-7.62-8.17-8.26 (4s, 4H, arom. H).

2.3 *3-(4-aminobenzyl)-thiazolidine*:

3-(4-nitrobenzyl)-thiazolidine (1.1 g, 5 mmol) is put into solution in 10 ml concentrated hydrochloric acid at 0°C. Dihydrated tin chloride (7.7 g, 34 mmol) is added in portions. The mixture is heated for 2 hours under reflux and the acid is evaporated off under reduced pressure. The residue is then taken up in 20 ml of water and neutralized with a 2N soda solution (approximately 100 ml). 100 ml of dichloromethane is added to the medium and the whole is filtered on celite in order to eliminate the salts in suspension. The organic phase is extracted, washed 3 times with 50 ml of water, dried, filtered and evaporated to dryness under reduced pressure. The expected product is purified on silica gel in a dichloromethane/methanol (98/2) mixture and is obtained in the form of a beige powder (0.6 g, 63 %). Melting point: 73-74°C.

NMR ^1H (CDCl_3 , 100 MHz, δ): 3.02 (m, 4H, 2CH_2). 3.44 (s, 2H, CH_2). 3.66 (wide s, 2H, NH_2), 4.07 (s, 2H, CH_2), 6.62-6.71-7.10-7.27 (4 s, 4H, arom. H).

2.4 [4-(3-thiazolidinylmethyl)phenyl]-2-thiophenecarboximidamide (2):

3-(4-aminobenzyl)-thiazolidine (0.6 g, 3 mmol) and S-methyl-2-thiophenethiocarboximide hydroiodide (1.14 g, 4 mmol) are put into solution in 7 ml of an isopropanol/DMF mixture (2/5). The reaction medium is agitated for 18 hours at ambient temperature. Then 10 ml of ethyl acetate is added to the medium and the reaction product is extracted 3 times with 10 ml of water. The aqueous phase is collected and basified with a saturated solution of sodium hydrogen carbonate, then the product is extracted 3 times with 10 ml of ethyl acetate. It is purified on silica gel in a dichloromethane/methanol mixture (95/5) and is obtained in the form of a white powder (0.6 g, 65 %). Melting point: 161.5-163.5° C.

NMR ^1H (CDCl_3 , 400 MHz, δ): 2.98 (t, 2H, CH_2). 3.14 (t, 2H, CH_2), 3.54 (s, 2H, CH_2), 4.10 (s, 2H, CH_2), 4.85 (wide s, 2H, NH_2), 6.98 (s, 1H, arom. H), 7.00 (s, 1H, arom. H), 7.10 (t, 1H, thiophene), 7.34 (s, 1H, arom. H), 7.36 (s, 1H, arom. H), 7.42 (t, 1H, thiophene), 7.45 (m, 1H, thiophene).

IR: $\nu_{\text{C=N}}$ (amidine): 1593 cm^{-1} .

Example 3: N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate (3):

3.1 1-(4-nitrophenyl)-1,2,3,6-tetrahydropyridine:

The experimental protocol used is the same as that described for intermediate 1.1, 1,2,3,6-tetrahydropyridine replacing imidazole. Colourless oil.

NMR ^1H (CDCl_3 , 100 MHz, δ): 2.33 (m, 2H, CH_2), 3.59 (t, 2H, CH_2), 3.90 (m, 2H, CH_2), 5.90 (m, 2H, CH=CH), 6.75-6.82-8.07-8.18 (m, 4H, arom. H).

3.2 1-(4-aminophenyl)-1,2,3,6-tetrahydropyridine:

The experimental protocol used is the same as that described for intermediate 2.3, 1-(4-nitrophenyl)-1,2,3,6-tetrahydropyridine replacing 3-(4-nitrobenzyl)-thiazolidine. Colourless oil.

NMR ^1H (CDCl_3 , 100 MHz, δ): 2.31 (m, 2H, CH_2), 3.21 (t, 2H, CH_2), 3.43 (m, 2H, NH_2), 3.56 (m, 2H, CH_2), 5.84 (m, 2H, CH=CH), 6.75 (m, 4H, arom. H).

3.3 N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate (3):

The experimental protocol used is the same as that described for intermediate 1.3, 1-(4-aminophenyl)-1,2,3,6-tetrahydropyridine replacing 1-(4-aminophenyl)-1H-imidazole. Beige powder. Melting point: 193-194° C.

NMR ¹H (DMSO, 400 MHz, δ): 2.23 (m, 2H, CH₂), 3.29 (m, 2H, CH₂), 3.61 (m, 2H, CH₂),
5 5.84 (m, 2H, CH=CH), 6.56 (s, 1H, fumaric acid), 6.89 (m, 4H, arom. H), 7.13 (m, 1H, arom. H), 7.67 (m, 1H, arom. H), 7.77 (m, 1H, arom. H).

IR: ν_{C=N} (amidine): 1560 cm⁻¹.

Example 4: N-[4-(1H-imidazol-1-yl methyl)phenyl]-2-thiophenecarboximidamide hydrochloride (4):

10 4.1 1-(4-nitrobenzyl)-1H-imidazole:

The experimental protocol used is the same as that described for intermediate 1.1, 1-bromomethyl-4-nitrobenzene replacing 1-fluoro-4-nitrobenzene. Colourless oil.

NMR ¹H (CDCl₃, 100 MHz, δ): 5.26 (s, 2H, CH₂), 6.92 (m, 1H, H imidazole), 7.16 (m, 1H, H imidazole), 7.59 (m, 1H, H imidazole), 7.24-7.32-8.18-8.27 (4s, 4H, arom. H).

15 4.2 1-(4-aminobenzyl)-1H-imidazole:

The experimental protocol used is the same as that described for intermediate 1.2, 1-(4-nitrobenzyl)-1H-imidazole replacing 1-(4-aminophenyl)-1H-imidazole. Pale yellow powder. Melting point: 121-122°C.

NMR ¹H (CDCl₃, 100 MHz, δ): 2.87 (wide s, 2H, NH₂), 4.98 (s, 2H, CH₂), 6.88 (m, 1H, H imidazole), 7.06 (m, 1H, H imidazole), 7.52 (m, 1H, H imidazole), 6.60-6.69-6.95-7.05 (4s, 4H, arom. H).

4.3 N-[4-(1H-imidazol-1-yl methyl)phenyl]-2-thiophenecarboximidamide hydrochloride (4):

The experimental protocol used is the same as that described for intermediate 2.4, 1-(4-aminobenzyl)-1H-imidazole replacing 3-(4-aminobenzyl)-thiazolidine. After salification
25 by a molar solution of HCl in anhydrous diethyl ether, a beige powder is obtained. Melting point: 261-263°C.

NMR ¹H (DMSO, 400 MHz, δ): 5.12 (s, 2H, CH₂), 6.46 (wide s, 2H, NH₂), 6.83-6.85-7.22-7.24 (4s, 4H, arom. H), 6.90 (s, 1H, arom. H), 7.09 (t, 1H, arom. H), 7.20 (s, 1H, arom. H), 7.60 (d, 1H, arom. H), 7.74 (s, 2H, arom. H).

30 IR: ν_{C=N} (amidine): 1599 cm⁻¹.

Example 5: N-[4-{2-(3-thiazolidinyl)ethyl}phenyl]-2-thiophenecarboximidamide (5):

5.1 4-(*t*-butoxycarbonylamino)-benzeneacetic acid:

Para-aminophenylacetic acid (3 g, 20 mmol) is dissolved in 60 ml of a THF /H₂O mixture (2/1). 11 ml of 10% soda is added. Then 6 g of di-*t*-butyl-dicarbonate (28 mmol) in solution in 50 ml of a THF/H₂O mixture (2/1). Agitation is carried out for 18 hours at ambient temperature. Then the THF is evaporated off under reduced pressure. The medium is then acidified (pH = 2) with a 10% solution of potassium acid sulphate (approximately 45 ml) and the reaction product is extracted with 3 washings with ethyl acetate (3 times 50 ml). The organic phases are dried and evaporated in order to produce 4.32 g (87 %) of pure 4-(*t*-butoxycarbonylamino)-benzeneacetic acid in the form of a beige powder. Melting point: 149-150° C.

NMR ¹H (CDCl₃, 100 MHz, δ): 1.52 (s, 9H, *t*Bu), 3.60 (s, 2H, CH₂), 4.12 (wide s, 1H, COOH), 6.55 (s, 1H, NH), 7.21 (m, 4H, arom. H).

5.2 (*t*-butoxycarbonylamino)-benzene ethanol:

4-(*t*-butoxycarbonylamino)-benzeneacetic acid (2.9 g, 11.4 mmol) is dissolved in 10 ml of anhydrous THF at 0°C and added to a suspension of LiAlH₄ (0.52 g, 13.6 mmol) in 30 ml of THF. The reaction mixture is agitated at ambient temperature for 1.5 hours. 50 ml of ethyl acetate then 20 ml of 2N soda are added to the medium. The expected product is extracted from the organic phase, which is then washed with 3 times 15 ml of water. The organic phase is dried and the solvent evaporated off under reduced pressure, then the reaction product is purified on silica gel in a dichloromethane/methanol mixture (95/5). 1.1 g (40%) is thus obtained in the form of a colourless oil.

NMR ¹H (CDCl₃, 100 MHz, δ): 1.53 (s, 9H, *t*Bu), 2.82 (t, 2H, CH₂), 3.83 (q, 2H, CH₂-OH), 6.47 (s, 1H, NH), 7.23 (m, 4H, arom. H).

5.3 (2-bromoethyl-4-*t*-butoxycarbonylamino)benzene:

4-(*t*-butoxycarbonylamino)-benzene ethanol (0.75 g, 3.1 mmol) and carbon tetrabromide (1.2 g, 3.6 mmol) are dissolved in 20 ml of dichloromethane at 0° C. Triphenylphosphine (0.94 g, 3.6 mmol) is added in portions and the whole is agitated for 1 hour at ambient temperature. The solvent is evaporated off under reduced pressure and the product obtained is purified on silica gel in an ethyl acetate/heptane mixture (1/2), 1-(2-bromoethyl-4-*t*-butoxycarbonylamino)benzene is obtained in the form of a white powder (0.8 g, 84%). Melting point: 129-130° C.

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.52 (s, 9H, tBu), 3.11 (t, 2H, CH_2), 3.54 (t, 2H, CH_2Br), 6.45 (s, 1H, NH), 7.22 (m, 4H, arom. H).

5.4 3-{2-[4-(*t*-butoxycarbonylamino)phenyl]ethyl}thiazolidine:

The experimental protocol used is the same as that described for intermediate 2.2, (2-bromoethyl-4-*t*-butoxycarbonylamino)benzene replacing 1-bromomethyl-4-nitrobenzene. Colourless oil.

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.52 (s, 9H, tBu), 2.90 (m, 8H, 4CH_2), 4.10 (s, 2H, N- CH_2 -S), 6.46 (s, 1H, NH), 7.25 (m, 4H, arom. H).

5.5 3-{2-[4-aminophenyl]ethyl}thiazolidine:

2.3 g (20 mmoles) of trifluoroacetic acid is added to a 100 ml flask containing a solution of 616 mg (2 mmoles) of intermediate 5.4 in 10 ml of dichloromethane. After agitation for one hour at 20°C. the reaction mixture is concentrated to dryness under vacuum. The residue is diluted with a mixture of 20 ml of dichloromethane and 20 ml of 4N soda. After decantation, the organic phase is washed successively with 3 x 20 ml of water followed by 20 ml of salt water. The organic solution is dried over sodium sulphate, filtered and the solvent is evaporated off under reduced pressure in order to obtain a colourless oil with a yield of 72 %.

NMR ^1H (CDCl_3 , 100 MHz, δ): 2.85 (m, 8H, 4CH_2), 4.15 (s, 2H, N- CH_2 -S), 7.25 (m, 4H, arom. H).

5.6 [4-{2-(3-thiazolidinyl)ethyl}phenyl]-2-thiophenecarboximidamide (5):

The experimental protocol used is the same as that described for intermediate 2.4, 3-{2-[4-aminophenyl]ethyl}thiazolidine replacing 3-(4-aminobenzyl)-thiazolidine. Beige powder. Melting point: 60.5-61.5°C.

NMR ^1H (DMSO, 400 MHz, δ): 2.65 (t, 2H, CH_2), 2.82 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.13 (t, 2H CH_2), 4.13 (s, 2H, N- CH_2 -S), 6.93-6.95-7.19-7.21 (4s, 4H, arom. H), 7.09 (t, 1H, H thiophene), 7.44 (m, 2H, H thiophene).

IR: $\nu_{\text{C=N}}$ (amidine): 1591 cm^{-1} .

Example 6: N-{4-[2-(1H-imidazol-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide hydroiodide (6):

6.1 1-{2-[4-(*t*-butoxycarbonylamino)phenyl]ethyl}-1H-imidazole:

- 2.5 g (18 mmoles) of K_2CO_3 is mixed together in a 100 ml flask with 680 mg (10 mmoles) of imidazole diluted in 10 ml of acetonitrile. The reaction mixture is heated at 70°C before the dropwise addition of a solution of 2 g (9.2 mmoles) of 1-bromomethyl-4-nitrobenzene in solution in 25 ml of acetonitrile. After agitation for 2 hours at this temperature, the reaction mixture is cooled down and filtered in order to eliminate the insoluble part. The filtrate is concentrated under vacuum and the residue is diluted in 50 ml of dichloromethane. The organic solution is successively washed with 3 x 50 ml of water and 50 ml of salt water. After drying over Na_2SO_4 , filtration, the organic phase is concentrated under vacuum and the residue purified on a silica column (eluant: dichloromethane/methanol: 95/5). Brown oil.
- 10 NMR 1H ($CDCl_3$, 100 MHz, δ): 1.50 (s, 9H, tBu), 2.90 (t, 2H, CH_2), 4.10 (t, 2H, CH_2), 6.50 (s, 1H, NH), 7.05 (m, 4H, arom. H), 6.85 (m, 1H, H imidazole.), 7.03 (s, 1H, H imidazole.), 7.32 (m, 1H, H imidazole).

6.2 1-[2-(4-aminophenyl)ethyl]-1H-imidazole:

- The experimental protocol used is the same as that described for intermediate 5.5, 1-{2-[4-(t-butoxycarbonylamino)phenyl]ethyl}-1H-imidazole replacing 3-{2-[4-(t-butoxycarbonylamino)phenyl]ethyl}thiazolidine. Colourless oil.

NMR 1H ($CDCl_3$, 100 MHz, δ): 2.90 (t, 2H, CH_2), 3.35 (wide s, 2H, NH_2), 4.10 (t, 2H, CH_2), 6.70 (m, 4H, arom. H), 6.85 (m, 1H, H imidazole.), 7.03 (s, 1H, H imidazole.), 7.32 (m, 1H, H imidazole).

- 20 6.3 N-{4-[2-(1H-imidazol-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide hydroiodide (6):

The experimental protocol used is the same as that described for intermediate 1.3, 1-[2-(4-aminophenyl)ethyl]-1H-imidazole replacing 1-(4-aminophenyl)-1H-imidazole. Beige powder. Melting point: 214-215°C.

- NMR 1H (DMSO, 400 MHz, δ): 3.11 (t, 2H, CH_2), 4.33 (t, 2H, CH_2), 7.29 (m, 6H, arom. H), 7.99 (m, 1H, arom. H), 8.70 (wide s, 2H, NH_2).
- 25 IR: $\square_{C=N}$ (amidine): 1597 cm^{-1} .

Example 7: N-{4-[2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide fumarate (7):

7.1 1-{2-[4-(t-butoxycarbonylamino)phenyl]ethyl}-1,2,3,6-tetrahydropyridine:

- 30 The experimental protocol used is the same as that described for intermediate 6.1, 1,2,3,6-tetrahydropyridine replacing thiazolidine. Colourless oil.

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.57 (s, 9H, tBu), 2.10 (m, 2H, CH_2), 2.70 (m, 6H, 3 CH_2), 3.00 (m, 2H, CH_2), 5.72 (m, 2H, $\text{CH}=\text{CH}$), 6.48 (s, 1H, NH), 7.10 (m, 4H, arom. H).

7.2 1-[2-(4-aminophenyl)ethyl]-1,2,3,6-tetrahydropyridine:

The experimental protocol used is the same as that described for intermediate 5.5, 1-{2-[4-(t-butoxycarbonylamino)phenyl]ethyl}-1,2,3,6-tetrahydropyridine replacing 3-{2-[4-aminophenyl]ethyl}thiazolidine. Colourless oil.

NMR ^1H (CDCl_3 , 100 MHz, δ): 3.20 (m, 2H, CH_2), 3.80 (m, 6H, 3 CH_2), 4.10 (m, 2H, CH_2), 4.57 (wide s, 2H, NH_2), 6.90 (m, 2H, $\text{CH}=\text{CH}$), 8.00 (m, 4H, arom. H).

7.3 N-{4-[2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide fumarate (7):

The experimental protocol used is same as that described for intermediate 1.3, 1-[2-(4-aminophenyl)ethyl]-1,2,3,6-tetrahydropyridine replacing 1-(4-aminophenyl)-1H-imidazole. White powder. Melting point: 128-129° C.

NMR ^1H (DMSO , 400 MHz, δ): 2.19 (m, 2H, CH_2), 2.83 (m, 6H, 3 CH_2), 3.25 (m, 2H, CH_2), 5.72 (m, 2H, $\text{CH}=\text{CH}$), 6.58 (s, 3H, fumaric acid), 6.81-6.83-7.18-7.20 (4s, 4H, arom. H), 7.10 (t, 1H, H thiophene), 7.63 (m, 1H, H thiophene), 7.75 (m, 1H, H thiophene).

IR: $\square_{\text{C}=\text{N}}$ (amidine): 1620 cm^{-1} .

Example 8: N-[4-(3-thiazolidinylcarbonylmethyl)phenyl]-2-thiophenecarboximidamide (8):

8.1 3-[[4-(t-butoxycarbonylamino)phenyl]methylcarbonyl]thiazolidine:

4-(t-butoxycarbonylamino)-benzeneacetic acid (1.4 g, 5.6 mmol), intermediate 5.1, and carbonyldiimidazole (0.9 g, 5.6 mmol) are dissolved in 15 ml of THF. The reaction is maintained at ambient temperature for 1 hour, then thiazolidine (0.5 g, 5.6 mmol), in solution in THF (5 ml), is added to the medium. The whole is agitated again for 2 hours at ambient temperature. The solvents are evaporated off under reduced pressure, then the residue is taken up in 25 ml of dichloromethane and washed 3 times with 15 ml of water. The organic phase is dried and concentrated under reduced pressure. 3-[[4-(t-butoxycarbonylamino)phenyl]methylcarbonyl]thiazolidine is obtained in the form of a white powder (1.43 g, 79 %) and will be used without further purification in the following stages. Melting point: 223-224°C.

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.51 (s, 9H, tBu), 3.00 (m, 2H, $\text{CH}_2\text{-S}$), 3.67 (s, 2H, $\text{N-CH}_2\text{-S}$), 3.88 (m, 2H, $\text{CH}_2\text{-N}$), 4.52 (d, $J = 16$ Hz, 2H, $\text{CH}_2\text{-CO}$), 6.52 (wide s, 1H, NH), 7.26 (m, 4H, arom. H).

8.2 3-[(4-aminophenyl)methylcarbonyl]thiazolidine:

- 5 3-[(4-aminophenyl)methylcarbonyl]thiazolidine is obtained in the form of a colourless oil with a yield of 44 % by following the operating method described for intermediate 5.5.

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.62 (wide s, 2H, NH_2), 2.98 (m, 2H, $\text{CH}_2\text{-S}$), 3.61 (s, 2H, $\text{N-CH}_2\text{-S}$), 3.80 (m, 2H, $\text{CH}_2\text{-N}$), 4.52 (d, $J = 16$ Hz, 2H, $\text{CH}_2\text{-CO}$), 6.61-6.69-7.01-7.09 (4 s, 4H, arom. H).

- 10 8.3 [4-(3-thiazolidinylcarbonylmethyl)phenyl]-2-thiophenecarboximidamide (8):

The operating method used is the same as that described for intermediate 2.4, 3-[(4-aminophenyl)methylcarbonyl]thiazolidine replacing 3-(4-aminobenzyl)-thiazolidine. The free base is obtained with a yield of 64 %. Melting point: 163.0-163.5° C.

- 15 NMR ^1H (CDCl_3 , 400 MHz, δ): 3.01 (m, 2H, $\text{CH}_2\text{-S}$), 3.69 (d, $J = 6$ Hz, 2H, $\text{N-CH}_2\text{-S}$), 3.75-3.88 (2 t, 2H, $\text{CH}_2\text{-N}$), 4.55 (d, 2H, $\text{CH}_2\text{-CO}$), 4.87 (s, 2H, NH_2), 6.95-6.97-7.22-7.24 (4 s, 4H, arom. H), 7.08 (t, 1H, thiophene), 7.43 (m, 2H, thiophene).

IR: $\nu_{\text{C=O}}$ (amide): 1630 cm^{-1} ; $\nu_{\text{C=N}}$ (amidine): 1577 cm^{-1} .

Example 9: N-(4-{[2-thiazolidinyl]carbonylaminomethyl}phenyl)-2-thiophenecarboximidamide fumarate (9):

- 20 9.1 3-(*t*-butoxycarbonyl)thiazolidine-2-carboxylic acid:

Thiazolidine-2-carboxylic acid (2 g, 15 mmols) is agitated in the presence of di-*t*-butyl dicarbonate according to the operating method described for intermediate 5.1. 3-(*t*-butoxycarbonyl)thiazolidine-2-carboxylic acid is obtained in the form of a pale yellow oil with a yield of 97 % (3.4 g) and will be used as is in the following stages.

- 25 NMR ^1H (CDCl_3 , 100 MHz, δ): 1.46 (s, 9H, tBu), 3.10 (m, 3H, $\text{CH}_2\text{-S}$, CH-S), 3.85 (m, 2H, $\text{CH}_2\text{-N}$).

9.2 (4-nitrobenzyl)-3-(*t*-butoxycarbonyl)thiazolidine-2-carboxamide:

- 30 3-(*t*-butoxycarbonyl)thiazolidine-2-carboxylic acid (1 g, 4.3 mmols) and carbonyldiimidazole (0.7 g, 4.3 mmols) are dissolved in THF (10 ml). the mixture is agitated for 1 hour at ambient temperature. The hydrochloride of 4-nitrobenzylamine (0.81 g, 4.3

mmoles) and triethylamine (0.6 ml, 0.43 g, 4.3 mmoles) in suspension in 10 ml of a THF and DMF mixture (1/1) are added to the preceding solution and the whole is heated under reflux for 5 hours. The solvents are then evaporated off under reduced pressure. The residue is taken up in 25 ml of ethyl acetate and washed 3 times with 15 ml of water. The organic phase is dried and the solvent is evaporated off under reduced pressure. The product obtained is purified on silica gel in a dichloromethane/methanol mixture (95/5). N-(4-nitrobenzyl)-3-(t-butoxycarbonyl)thiazolidine-2-carboxamide is obtained in the form of a pale yellow oil with a yield of 80 % (1.25 g).

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.45 (s, 9H, tBu), 3.09 (m, 3H, $\text{CH}_2\text{-S}$, CH-S), 3.86 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-N}$), 4.57 (m, 2H, $\text{CH}_2\text{-NH}$), 6.60 (wide s, 1H, NH), 7.41-7.50-8.14-8.23 (4s, 4H, arom. H).

9.3 (4-aminobenzyl)-3-(t-butoxycarbonyl)thiazolidine-2-carboxamide:

A spatula tip's worth of Raney Nickel is added to a solution of 1.25 g (3.4 mmoles) of N-(4-nitrobenzyl)-3-(t-butoxycarbonyl)thiazolidine-2-carboxamide in 2.5 ml of methanol. The whole is taken to reflux and hydrazine hydrate (1.75 ml) is added dropwise to the medium. The reaction is maintained for 1 hour under reflux, then returned to ambient temperature. The catalyst is filtered off and rinsed abundantly with methanol. The solvent is evaporated off under reduced pressure, then the residue is taken up in dichloromethane (20 ml) and washed 3 times with 15 ml of water. The organic phase is dried and the solvent is evaporated off under reduced pressure. N-(4-aminobenzyl)-3-(t-butoxycarbonyl)thiazolidine-2-carboxamide is obtained in the form of an inert yellow solid (0.815 g, 71 %); it will be used in following stages without further purification.

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.43 (s, 9H, tBu), 3.08 (m, 2H, $\text{CH}_2\text{-S}$), 3.67 (m, 3H, $\text{CH}_2\text{-CH}_2\text{-N}$, CH-S), 4.36 (m, 2H, $\text{CH}_2\text{-NH}$), 6.05 (wide s, 1H, NH), 6.60-6.69-7.04-7.12 (4 s, 4H, arom. H).

9.4 [4-{[3-(t-butoxycarbonyl)-2-thiazolidinyl]carbonylaminomethyl}phenyl]-2-thiophenecarboximidamide:

The experimental protocol used is the same as that described for intermediate 2.4, N-(4-aminobenzyl)-3-(t-butoxycarbonyl)thiazolidine-2-carboxamide replacing 3-(4-aminobenzyl)-thiazolidine. The expected compound is obtained with a yield of 77 %.

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.45 (s, 9H, tBu), 3.14 (m, 3H, $\text{CH}_2\text{-S}$, CH-S), 3.84 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-N}$), 4.46 (m, 2H, $\text{CH}_2\text{-NH}$), 4.83 (wide s, 2H, NH_2), 6.27 (wide s, 1H, NH), 7.22 (m, 7H, arom. H).

9.5 *N*-(4-{[2-thiazolidinyl]carbonylaminomethyl}phenyl)-2-thiophenecarboximidamide fumarate (9):

The experimental protocol used is the same as that described for intermediate 5.5, [4-{[3-(*t*-butoxycarbonyl)-2-thiazolidinyl]carbonylaminomethyl}phenyl]-2-thiophene-carboximidamide replacing 3-{2-[4-aminophenyl]ethyl}thiazolidine. The expected compound is obtained in the form of the free base with a yield of 34 %. It is salified with an equivalent of fumaric acid in ethanol under reflux. Melting point: 167-168° C.

NMR ¹H (DMSO, 400 MHz, δ): 2.78 (t, 2H, CH₂-S), 3.06 (m, 2H, CH₂-CH₂-N), 3.28 (wide s, 1H, CH-S), 4.26 (m, 2H, CH₂-NH), 4.86 (wide s, 1H, NH), 6.45 (wide s, 2H, NH₂), 6.81-6.83-7.19-7.21 (4 s, 4H, arom. H), 7.10 (t, 1H, thiophene), 7.61 (d. 1H, thiophene), 7.74 (m, 1H, thiophene), 8.53 (t, 1H, NH-CO).

IR: ν_{C=O} (amide): 1624 cm⁻¹; ν_{C=N} (amidine): 1584 cm⁻¹.

Example 10: *N*-(3,5-di-*t*-butyl-4-hydroxyphenyl)-5-[4-{imino(2-thienyl)-methylamino}phenyl]-2-furan carboxamide hydroiodide (10):

10.1 2,6-di-*t*-butyl-4-nitrophenol:

2,6-di-*t*-butylphenol (8 g, 39 mmoles) is dissolved in 25 ml of cyclohexane at 10°C. A (1/1) mixture of nitric acid/acetic acid (5 ml) is added dropwise to the reaction medium maintained at this temperature. Agitation is then carried out for 15 minutes at ambient temperature then the precipitate formed is filtered off, rinsed with water and pentane. The 2,6-di-*t*-butyl-4-nitrophenol obtained (6.34 g, 65 %) is dried in an oven and will be used without further purification in the following stages. Pale yellow powder. Melting point: 167-168°C.

NMR ¹H (CDCl₃, 100 MHz, δ): 1.48 (s, 18H, 2*t*Bu), 5.93 (s, 1H, OH), 8.13 (s, 2H, arom. H).

10.2 2,6-di-*t*-butyl-4-aminophenol:

2,6-di-*t*-butyl-4-nitrophenol (6.3 g, 25 mmoles) is dissolved in methanol (100 ml). 0.6 g of palladium on carbon (10 %) is added and the reaction medium is placed under a hydrogen atmosphere under 2 bars of pressure. The catalyst is filtered out and the solvent is evaporated off under reduced pressure. The residue is taken up in heptane and filtered. In this way 2,6-di-*t*-butyl-4-aminophenol (2.7 g, 48 %) is obtained which will be used without further purification in the following stages. Pink powder. Melting point: 123-124°C.

NMR ¹H (CDCl₃, 100 MHz, δ): 6.60 (s, 2H, Ph); 4.65 (wide s, 1H, OH); 3.15 (wide s, 2H, NH₂); 1.42 (s, 18H, 2 *t*Bu).

10.3 *N*-(3,5-di-*t*-butyl-4-hydroxyphenyl)-5-(4-nitrophenyl)-2-furan carboxamide:

The experimental protocol used is the same as that described for intermediate 8.1, 2,6-di-*t*-butyl-4-aminophenol and 5-(4-nitrophenyl)-2-furan carboxylic acid replacing thiazolidine and 4-(*t*-butoxycarbonylamino)-benzeneacetic acid respectively. The expected compound is obtained in the form of a colourless oil with a yield of 56 %.

- 5 NMR ^1H (DMSO, 100 MHz, δ): 1.41 (s, 18H, 2*t*Bu), 6.91 (s, 1H, OH), 7.42 (m, 4H, arom. H), 7.54 (s, 2H, arom. H), 8.30 (m, 4H, arom. H), 10.11 (s, 1H, NH).

10.4 *N*-(3,5-di-*t*-butyl-4-hydroxyphenyl)-5-(4-aminophenyl)-2-furan carboxamide:

- 10 The experimental protocol used is the same as that described for intermediate 1.2, *N*-(3,5-di-*t*-butyl-4-hydroxyphenyl)-5-(4-nitrophenyl)-2-furan carboxamide replacing 1-(4-nitrophenyl)-1H-imidazole. The expected compound is obtained in the form of a colourless oil with a yield of 59 %.

NMR ^1H (DMSO, 100 MHz, δ): 1.41 (s, 18H, 2 *t*Bu), 4.70 (wide s, 2H, NH₂), 6.91 (s, 1H, OH), 7.50 (m, 4H, arom. H), 7.54 (s, 2H, arom. H), 8.20 (m, 4H, arom. H).

- 15 10.5 *N*-(3,5-di-*t*-butyl-4-hydroxyphenyl)-5-[4-{imino(2-thienyl)-methylamino}phenyl]-2-furan carboxamide hydroiodide (**10**):

The experimental protocol used is the same as that described for intermediate 1.3, *N*-(3,5-di-*t*-butyl-4-hydroxyphenyl)-5-(4-aminophenyl)-2-furan carboxamide replacing 1-(4-aminophenyl)-1H-imidazole. The expected product is obtained in salified form with a yield of 27 %. Melting point: 273-274° C.

- 20 NMR ^1H (DMSO, 400 MHz, δ): 1.40 (s, 18H, 2*t*Bu), 6.90 (s, 1H, OH), 7.45 (m, 5H, arom. H), 7.54 (s, 2H, arom. H), 8.15 (m, 4H, arom. H), 9.05-9.90 (wide 2s's, 2H, NH₂), 10.01 (s, 1H, NH-CO), 11.57 (s, 1H, HI).

IR: ν_{OH} : 3423-3242 cm^{-1} ; $\nu_{\text{C=O}}$ (amide): 1646 cm^{-1} ; $\nu_{\text{C=N}}$ (amidine): 1554 cm^{-1} .

- 25 **Example 11:** 3-(3,5-di-*t*-butyl-4-hydroxyphenyl)-1-[4-{imino(2-thienyl)-methylamino}phenyl]-2,5-imidazolidinedione hydrochloride (**11**):

11.1 *Ethyl* (3,5-di-*t*-butyl-4-hydroxyphenyl)amino acetate:

- 30 1 g (4.5 mmoles) of 2,6-di-*t*-butyl-4-aminophenol (intermediate 10.2) and 0.65 g of sodium acetate (7.9 mmoles) are put into suspension in 1 ml of ethanol. Then bromoethyl acetate (0.94 g, 5.65 mmoles) is added to the medium and the reaction medium is heated at 65°C for 2 hours. The reaction mixture is poured into 20 ml of ice-cooled water and the reaction product is extracted with dichloromethane (3 times 15 ml). The organic phases are dried and the solvent is evaporated off under reduced pressure. The residue is passed over silica gel in

dichloromethane. A colourless oil is obtained constituted by a mixture of 2 compounds: the product of mono- and di- substitution. The mixture of these 2 compounds is used without further purification in the following stage.

11.2 *Ethyl (3,5-di-t-butyl-4-hydroxyphenyl)-(4-nitrophenylcarbamoyl)amino acetate:*

- 5 1.13 g (4.2 mmoles) of intermediate 11.1 and 0.69 g (4.23 mmoles) of 4-nitrophenylisocyanate are dissolved in 9 ml of dichloromethane. The reaction mixture is agitated for 2.5 hours at ambient temperature. The solvent is evaporated off under reduced pressure and the residue is passed over silica gel in dichloromethane. In this way 0.66 g of pure ethyl (3,5-di-t-butyl-4-hydroxyphenyl)-(4-nitrophenylcarbamoyl)amino acetate is isolated
10 in the form of a colourless oil. (Yield over 2 stages: 31 %).

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.30 (t, 3H, CH_3), 1.46 (s, 18H, 2tBu), 4.23 (q, 2H, $\text{CH}_2\text{-CH}_3$), 4.38 (s, 2H, $\text{CH}_2\text{-CO}$), 5.50 (s, 1H, OH), 6.75 (wide s, 1H, NH), 7.28 (s, 2H, arom. H), 7.40-7.50-8.10-8.20 (4s, 4H, arom. H).

11.3 *(3,5-di-t-butyl-4-hydroxyphenyl)-1-(4-nitrophenyl)-2,5-imidazolidinedione:*

- 15 0.66 g (1.4 mmole) of intermediate 11.2 is dissolved in 10 ml of ethanol at 50°C and the whole is heated at this temperature for 2 hours. The precipitate formed is filtered off and washed with cold ethanol. The compound obtained is used directly in the following stage without additional purification.

20 NMR ^1H (CDCl_3 , 100 MHz, δ): 1.47 (s, 18H, 2tBu), 4.51 (s, 2H, N- $\text{CH}_2\text{-CO}$), 5.27 (s, 1H, OH), 7.33 (s, 2H, arom. H), 7.77-7.86-8.32-8.41 (4s, 4H, arom. H).

11.4 *(3,5-di-t-butyl-4-hydroxyphenyl)-1-(4-aminophenyl)-2,5-imidazolidinedione:*

- The experimental protocol used is the same as that described for intermediate 1.2, 3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-(4-nitrophenyl)-2,5-imidazolidinedione replacing 1-(4-nitrophenyl)-1H-imidazole. The expected compound is obtained in the form of a white
25 precipitate with a yield of 87 %. It is used without additional purification in the following stage.

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.47 (s, 18H, 2tBu), 4.45 (s, 2H, N- $\text{CH}_2\text{-CO}$), 5.18 (s, 1H, OH), 6.70-6.80-7.16-7.23 (4s, 4H, arom. H), 7.39 (s, 2H, arom. H).

- 30 11.5 *3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-[4-{imino(2-thienyl)-methylamino}phenyl]-2,5-imidazolidinedione hydrochloride (11):*

The experimental protocol used is the same as that described for intermediate 2.4, 3-(3,5-di-*t*-butyl-4-hydroxyphenyl)-1-(4-aminophenyl)-2,5-imidazolidinedione replacing 3-(4-aminobenzyl)-thiazolidine. The free base is salified by treatment with a 1N solution of hydrochloric ether. The hydrochloride is obtained with a yield of 53 %. Melting point: 258-265°C.

NMR ^1H (DMSO, 400 MHz, δ): 1.40 (s, 18H, 2 *t*Bu), 4.65 (s, 2H, CH_2), 7.08 (s, 1H, OH), 7.40 (m, 3H, arom. H), 7.61 (s, 4H, arom. H), 8.21 (m, 2H, arom. H), 9.20-9.95 (wide 2s's, 2H, NH_2), 11.75 (s, 1H, HCl).

IR: ν_{OH} : 3637-3437 cm^{-1} ; $\nu_{\text{C=O}}$ (imidazolidinedione): 1712 cm^{-1} ; $\nu_{\text{C=O}}$ (amidine): 1598 cm^{-1} .

Example 12: 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-[4-{imino(2-thienyl)-methylamino}phenyl]-4-thiazolidinone hydrochloride (**12**):

12.1 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-(4-nitrophenyl)-4-thiazolidinone:

5 g of 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (21 mmoles) and 2.95 g of para-nitroaniline (21 mmoles) are dissolved in 50 ml of anhydrous toluene. 0.5 ml of glacial acetic acid is added and the whole is taken to reflux for 24 hours. Then 1.96 g of mercaptoacetic acid (21 mmoles) is added to the medium and reflux is continued for another 24 hours. After the reaction mixture has returned to ambient temperature, it is washed with water (3 times 30 ml), after decantation. the organic phase is dried over sodium sulphate and the solvent is evaporated off under reduced pressure. The residue is purified on silica gel in an ethyl acetate/heptane mixture (1/4) and 1.33 g of pure 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-(4-nitrophenyl)-4-thiazolidinone is obtained in the form of a colourless oil (15 %).

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.36 (s, 18H, 2*t*Bu), 3.91 (s, 2H, CH-S), 5.28 (s, 1H, CH-S), 6.20 (s, 1H, OH), 7.03 (s, 2H, arom. H), 7.38-7.48-8.11-8.20 (4 s, 4H, arom. H).

12.2 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-(4-aminophenyl)-4-thiazolidinone:

1.3 g of 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-(4-nitrophenyl)-4-thiazolidinone (3 mmoles) and 3.4 g (15 mmoles) of dihydrated tin chloride are dissolved in 25 ml of ethyl acetate. The reaction is maintained for 2 hours at 70°C. After the mixture has returned to ambient temperature, it is poured into a saturated solution of sodium hydrogen carbonate. The expected product is then extracted from the organic phase then it is washed 3 times with 10 ml of water. The 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-(4-aminophenyl)-4-thiazolidinone is purified on silica gel in an ethyl acetate/heptane mixture (1/1) and is obtained in the form of a beige oil with a yield of 69 % (0.82 g).

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.37 (s, 18H, 2tBu), 3.64 (wide s, 2H, NH_2), 3.89 (s, 2H, $\text{CH}_2\text{-S}$), 5.22 (s, 1H, CH-S), 5.91 (s, 1H, OH), 6.51-6.59-6.78-6.86 (4 s, 4H, arom. H), 7.04 (s, 2H, arom. H).

5 12.3 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-[4-{imino(2-thienyl)-methylamino}phenyl]-4-thiazolidinone hydrochloride (12):

The experimental protocol used is the same as that described for intermediate 2.4, 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-(4-aminophenyl)-4-thiazolidinone replacing 3-(4-aminobenzyl)-thiazolidine. The expected compound is obtained in salified form (hydrochloride) by treatment of the free base with a 1N solution of hydrochloric ether with a yield of 43 %.

10 Melting point: 58-61°C.

NMR ^1H (DMSO, 400 MHz, δ): 1.32 (s, 18H, 2tBu), 3.93 (m, 2H, CH-S), 6.57 (s, 1H, CH-S), 7.08 (s, 2H, arom. H), 7.41 (m, 5H, arom. H), 8.15 (m, 2H, arom. H), 9.10-9.90 (wide 2s's, 2H, NH_2), 11.45 (wide s, 1H, HCl).

IR: ν_{OH} : 3624-3423 cm^{-1} ; $\nu_{\text{C=O}}$ (thiazolidinone): 1679-1658 cm^{-1} ; $\nu_{\text{C=N}}$ (amidine):

15 1568 cm^{-1} .

Example 13: 5-[(3,5-di-*t*-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-[4-{imino(2-thienyl)methylamino}phenyl]-2,4-imidazolidinedione fumarate (13):

13.1 1-Methyl-3-(4-nitrophenyl)-2,4-imidazolidinedione:

0.47 g of the ethyl ester of sarcosine, HCl (3 mmoles) is dissolved in 5 ml of dichloromethane and 0.42 ml (3 mmoles) of triethylamine is added. 0.5 g of 4-nitrophenylisocyanate (3 mmoles) in solution in 5 ml of dichloromethane is added dropwise to the preceding mixture and the reaction mixture is maintained for 30 minutes at ambient temperature. The organic solution is then washed with water (3 times 10 ml) then dried and the solvent is evaporated off under reduced pressure.

25 The residue is taken up in 10 ml of ethanol and the reaction medium is heated under reflux for 2 hours, After the reaction medium has returned to ambient temperature, the precipitate formed is filtered. In this way 1-methyl-3-(4-nitrophenyl)-2,4-imidazolidinedione is obtained with a yield of 72% (0.5 g) and will be used without further purification in the following stage.

30 NMR ^1H (CDCl_3 , 100 MHz, δ): 3.11 (s, 3H, CH_3), 4.09 (s, 2H, CH_2), 7.70-7.79-8.27-8.37 (4 s, 4H, arom. H).

13.2 *5-[(3,5-di-*t*-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-(4-nitrophenyl)-2,4-imidazolidinedione:*

Intermediate 13.1 (0.5 g, 2.13 mmol), 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (0.5 g, 2.13 mmol) and β -alanine (0.123 g, 1.4 mmol) are dissolved in acetic acid (10 ml). The reaction is maintained under reflux for 24 hours. After the reaction medium has returned to ambient temperature, 40 ml of water is added to the medium and the whole is agitated for 1 hour. The precipitate formed is filtered and washed with water. The filtrate is concentrated under vacuum and the evaporation residue is purified on silica gel (eluant: heptane/ethyl acetate: 4/1). The pure fractions are collected and concentrated to dryness in order to produce the expected product with a yield of 32% (0.3 g).

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.49 (s, 18H, 2*t*Bu), 3.35 (s, 3H, CH_3), 5.59 (s, 1H, OH), 6.40 (s, 1H, $\text{CH}=\text{C}$), 7.75-7.84-8.31-8.40 (4 s, 4H, arom. H), 7.92 (s, 2H, arom. H).

13.3 *5-[(3,5-di-*t*-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-(4-aminophenyl)-2,4-imidazolidinedione:*

The experimental protocol used is the same as that described for intermediate 12.2, 5-[(3,5-di-*t*-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-(4-nitrophenyl)-2,4-imidazolidinedione replacing 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-(4-nitrophenyl)-4-thiazolidinone. The expected compound is obtained with a yield of 45%.

NMR ^1H (CDCl_3 , 100 MHz, δ): 1.47 (s, 18H, 2*t*Bu), 3.30 (s, 3H, CH_3), 5.51 (s, 1H, OH), 6.28 (s, 1H, $\text{CH}=\text{C}$), 6.69-6.78-7.12-7.21 (4 s, 4H, arom. H), 7.91 (s, 2H, arom. H).

13.4 *5-[(3,5-di-*t*-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-[4-{imino(2-thienyl)methylamino}phenyl]-2,4-imidazolidinedione fumarate (13):*

The experimental protocol used is the same as that described for intermediate 2.4, 5-[(3,5-di-*t*-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-(4-aminophenyl)-2,4-imidazolidinedione replacing 3-(4-aminobenzyl)-thiazolidine. The expected compound is obtained in salified form (fumarate) by treatment of the free base with an equivalent of fumaric acid in ethanol while warm with a yield of 35%. Melting point: 54.5-57.5°C.

NMR ^1H (DMSO, 400 MHz, δ): 1.40 (s, 18H, 2*t*Bu), 3.22 (s, 3H, CH_3), 6.59 (s, 1H, $\text{CH}=\text{C}$), 6.61 (s, fumaric acid), 6.97-6.99-7.30-7.32 (4 s, 4H, arom. H), 7.11 (t, 1H, thiophene), 7.64 (d, 1H, thiophene), 7.79 (m, 1H, thiophene), 7.96 (s, 2H, arom. H).

IR: ν_{OH} : 3618-3433 cm^{-1} ; $\nu_{\text{C}=\text{O}}$ (imidazolidinedione): 1711 cm^{-1} ; $\nu_{\text{C}=\text{N}}$ (amidine): 1585 cm^{-1} .

Example 14: 2-(S)-4-(S)-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)-phenyl]-4-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-prolinamide hydrochloride (**14**):

14.1 *Methyl ester of 2-(S)-4-(S)-1-[(1,1-dimethylethoxy)carbonyl]-4-(4-nitrophenoxy)-proline:*

5 A solution of 4.37 g (30.7 mmol) of 4-nitrophenol in 30 ml of anhydrous N-methyl-2-pyrrolidinone is added slowly to a suspension, cooled down to 0°C, of 1.23 g (30.7 mmol) of NaH at 60 % in suspension in 30 ml of anhydrous N-methyl-2-pyrrolidinone, under an inert atmosphere. After agitation for one hour at 0°C, the proline derivative (6g, 15 mmol) is added in one go. The reaction mixture is agitated at 20°C for 15 hours followed by heating at
10 80°C for 2 hours in order to complete the reaction. After the reaction mixture has returned to 20°C, 200 ml of ethyl acetate and 100 ml of 1N soda are added to the medium. After decantation, the organic phase is washed successively with dilute solutions of 1N soda until complete extraction of the unreacted phenolic derivative, 2 x 100 ml of water and 100 ml of salt water. The organic solution is dried over sodium sulphate, filtered and concentrated to
15 dryness under reduced pressure, in order to produce a light yellow oil which crystallizes spontaneously in air. The crystals are collected and washed with 3 x 50 ml of ethyl ether. After drying, colourless crystals are obtained with a yield of 63%. Melting point: 155-157°C.

NMR ¹H (DMSO, 400 MHz, δ): 1.34-1.40 (2s, 9H, tBu); 2.45 (m, 2H, CH₂); 3.60 (m, 2H, CH₂-N); 3.58-3.63 (2s, 3H, O-CH₃); 4.40 (m, 1H, CH-CO₂); 5.22 (m, 1H, HC-O); 7.63 (m,
20 4H, Ph).

14.2 2-(S)-4-(S)-1-[(1,1-dimethylethoxy)carbonyl]-4-(4-nitrophenoxy)-proline:

730 mg (approximately 16 mmol) of potash diluted in 5 ml of water is added at 20°C to a 100 ml flask containing 2.87 g (7.84 mmol) of compound 14.1 in 40 ml of ethanol. After agitation for 15 hours, the reaction mixture is diluted with 100 ml of ethyl acetate, acidified at
25 0°C with a 12N solution of HCl and decanted. The organic phase is washed with 50 ml of water followed by 50 ml of salt water. After drying over sodium sulphate, the organic solution is filtered and concentrated to dryness under vacuum. 2.67 g of a white powder is obtained which is used directly in the following stage without additional purification.

NMR ¹H (CDCl₃, 100 MHz, δ): 1.50 (s, 9H, tBu); 2.60 (m, 2H, CH₂); 3.80 (m, 2H, CH₂-N);
30 4.60 (m, 1H, CH-CO₂); 5.07 (m, 1H, HC-O); 7.58 (m, 4H, Ph); 8.95 (wide s, 1H, CO₂H).

14.3 2-(S)-4-(S)-1-[(1,1-dimethylethoxy)carbonyl]-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-4-(4-nitrophenoxy)-prolinamide:

1.28 g (6.20 mmoles) of dicyclohexylcarbodiimide is added at 0°C to a solution of 1.99 g (5.64 mmoles) of intermediate 14.2, 1.25 g (5.64 mmoles) of intermediate 10.2 and 845 mg (6.20 mmoles) of hydroxybenzotriazole in 25 ml of DMF. After agitation for 24 hours at 20°C, the reaction mixture is filtered and the precipitate is washed with ethyl acetate. The filtrate is diluted with 100 ml of ethyl acetate and washed successively with 2 x 40 ml of 1N soda, 2 x 40 ml of water and 40 ml of salt water. After drying over sodium sulphate, the organic solution is filtered and concentrated to dryness under vacuum in order to produce a brown oil which is purified on a silica column (eluant heptane/ethyl acetate: 1/1). The pure fractions are collected and after concentration under vacuum, 1.35 g (43%) of a beige powder is obtained. Melting point: 117-120°C.

NMR ¹H (CDCl₃, 100 MHz, δ): 1.20-1.70 (m, 27 H, 3 x tBu); 2.68 (m, 2H, CH₂); 3.80 (m, 2H, CH₂-N); 4.58 (m, 1H, CH-CO₂); 5.10 (m, 2H, OH, HC-O); 7.25-7.28 (2s, 2H, Ph-OH); 7.51 (m, 4H, Ph-NO₂); 8.00 (wide s, 1H, NHCO).

14.4 2-(S)-4-(S)-1-[(1,1-dimethylethoxy)carbonyl]-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-4-(4-aminophenoxy)-prolinamide:

1.35 g (2.4 mmoles) of intermediate 14.3 is dissolved in 30 ml of ethanol in an autoclave equipped with a magnetic stirrer in the presence of 1/2 a spatula's worth of Pd/C at 10%. The reaction mixture is agitated under 1.5 bar of hydrogen for 3 hours. After filtration on celite, the filtrate is concentrated under vacuum. The residue is taken up in a 1/1 ethyl ether/heptane mixture and after crystallization, it is filtered and rinsed using heptane. A beige powder is obtained with a yield of 60%. Melting point: 112-113°C.

NMR ¹H (CDCl₃, 100 MHz, δ): 1.20-1.70 (m, 27 H, 3 x tBu); 2.55 (m, 2H, CH₂); 3.50 (wide s, 2H, NH₂); 3.75 (m, 2H, CH₂-N); 4.48 (m, 1H, CH-CO₂); 4.80 (m, 1H, HC-O); 5.10 (s, 1H, OH); 6.65 (m, 4H, Ph-NH₂); 7.28 (m, 2H, Ph-OH); 8.00 (wide s, 1H, NHCO).

14.5 2-(S)-4-(S)-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-4-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-prolinamide hydrochloride (14):

A mixture of 694 mg (1.32 mmole) of intermediate 14.4 is heated at 50°C for 48 hours in the presence of 376 mg (1.32 mmole) of S-methyl-2-thiophenethiocarboximide hydroiodide in solution in 15 ml of isopropanol. The reaction mixture is then concentrated to dryness under vacuum and the evaporation residue is suspended in 50 ml of ethyl acetate. After the addition of 50 ml of a saturated solution of Na₂CO₃ the organic phase is decanted and successively washed with 25 ml of a saturated solution of Na₂CO₃, 50 ml of water and 50 ml of salt water. After drying over sodium sulphate, the organic solution is filtered and concentrated to dryness under vacuum in order to produce a yellow powder which is purified on a silica column (eluant: ethyl acetate). The pure fractions are collected and after concentration under vacuum.

686 mg (82 %) of a beige powder is obtained which is immediately dissolved in 5 ml of a 4M solution of HCl in 1,4-dioxan. After agitation for 15 hours at 20°C, 20 ml of dry ethyl ether is added to the reaction mixture. The precipitate which appears is then filtered off, rinsed with 2 x 25 ml of dry ethyl ether and dried in an oven in order to produce 270 mg of a beige powder.

5 Melting point: 233.5-235°C.

NMR ¹H (DMSO, 400 MHz, δ): 1.37 (s, 18H, 2 x tBu); 2.61 (m, 2H, CH₂); 3.60 (m, 2H, CH₂-N); 4.56 (m, 1H, CH-CO₂); 5.25 (m, 1H, HC-O); 6.92 (s, 1H, OH); 7.21 (m, 4H, Ph-N); 7.38 (m, 1H, thiophene); 7.45 (s, 2H, Ph-OH); 8.18 (m, 2H, thiophene); 8.78 (wide s, 1H, NH⁺); 9.09 (wide s, 1H, NH⁺); 9.80 (wide s, 1H, NH⁺); 10.68 (c. 1H, CONH); 11.42 (wide s, 1H, NH⁺).

10 IR: ν_{OH}: 3624-3420 cm⁻¹; ν_{C=O} (amide): 1653 cm⁻¹; ν_{C=N} (amidine): 1610 cm⁻¹.

Example 15: 5,6-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1-(2H)-pyridine carboxamide hydrochloride (15):

15.1 5,6-dihydro-N-(4-nitrophenyl)-1-(2H)-pyridine carboxamide:

15 900 mg (5 mmoles) of 4-nitrophenylisocyanate is dissolved, under an argon atmosphere, in a 100 ml three-necked flask in 17 ml of dry DMF. 0.45 ml (5 mmoles) of 1,2,3,6-tetrahydropyridine is added to this solution in one go, and agitation is maintained for 15 hours. The reaction mixture is then concentrated to dryness under vacuum and the evaporation residue placed on a silica gel column. After elution with a heptane/ethyl acetate mixture: 4/6, 20 the pure fractions are collected and concentrated under reduced pressure in order to produce 860 mg (70 %) of a bright yellow powder. Melting point: 169-170° C.

NMR ¹H (DMSO, 100 MHz, δ): 2.29 (m, 2H, =CH-CH₂); 3.69 (m, 2H, CH₂-N); 4.10 (m, 2H, =CH-CH₂-N); 5.91 (m, 2H, CH=CH); 8.09 (m, 4H, Ph); 9.32 (wide s, 1H, NHCO).

15.2 N-(4-aminophenyl)-5,6-dihydro-1-(2H)-pyridine carboxamide:

25 The experimental protocol used is the same as that described for intermediate 12.2, 5,6-dihydro-N-(4-nitrophenyl)-1-(2H)-pyridine carboxamide replacing 2-(3,5-di-t-butyl-4-hydroxyphenyl)-3-(4-nitrophenyl)-4-thiazolidinone. A brown oil is obtained with a yield of 36 %.

NMR ¹H (CDCl₃ + D₂O, 400 MHz, δ): 2.20 (m, 2H, =CH-CH₂); 3.59 (m, 2H, CH₂-N); 3.95 (m, 2H, =CH-CH₂-N); 5.84 (m, 2H, CH=CH); 6.90 (m, 4H, Ph); 9.32 (wide s, 1H, NHCO).

30 15.3 5,6-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1-(2H)-pyridine carboxamide hydrochloride (15):

The experimental protocol used is the same as that described for intermediate 14.5, N-(4-aminophenyl)-5,6-dihydro-1-(2H)-pyridine carboxamide replacing 2-(S)-4-(S)-1-[(1,1-dimethylethoxy)carbonyl]-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-4-(4-aminophenoxy)-prolinamide. After salification and using a solution of 1M HCl in ethyl ether, a pale yellow powder is obtained with a yield of 55%. Melting point: 230-231°C.

NMR ^1H (DMSO, 400 MHz, δ): 2.16 (m, 2H, =CH-CH₂); 3.59 (m, 2H, CH₂-N); 3.98 (m, 2H, =CH-CH₂-N); 5.80 (m, 2H, CH=CH); 7.52 (m, 4H, Ph); 7.38 (s, 1H, thiophene); 8.16 (m, 2H, thiophene); 8.78 (wide s, 1H, NH⁺); 8.81 (s, 1H, CONH); 9.73 (wide s, 1H, NH⁺); 11.41 (wide s, 1H, NH⁺).
 IR: $\nu_{\text{C=O}}$ (urea): 1637 cm⁻¹; $\nu_{\text{C=N}}$ (amidine): 1583 cm⁻¹.

Example 16: N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-2-(R,S)-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-(R)-thiazolidine carboxamide fumarate(16):

16.1 2-(R,S)-(4-nitrophenyl)-4-(R)-thiazolidine carboxylic acid:

3 g (17.08 mmoles) of L-Cysteine hydrochloride and 2.18 g (22.2 mmoles) of sodium acetate are dissolved in 75 ml of water. The solution is agitated vigorously during the addition, in one portion, of 3.10 g (20.5 mmoles) of 4-nitrobenzaldehyde in solution in 80 ml of 95% ethanol. A white precipitate rapidly appears in this pale yellow solution which forms abundantly. Agitation is maintained for one hour, the reaction mixture is then cooled down to 0°C and filtered. The precipitate is successively rinsed with 200 ml of water, 100 ml of cold ethanol and 100 ml of ethyl ether. After drying, a white powder is obtained with a yield of 87%. Melting point: 120-121°C.

NMR ^1H (Acetone D₆, 100 MHz, δ): 3.50 (m, 2H, CH₂-S); 4.25 (m, 1H, CH-CO); 4.75 (hump, 2H, CO₂H + NH); 5.86 (s, 1H, N-CH-S); 8.20 (m, 4H, Ph).

16.2 3-[(1,1-dimethylethoxy)carbonyl]-2-(R,S)-(4-nitrophenyl)-4-(R)-thiazolidine carboxylic acid:

The experimental protocol used is the same as that described for intermediate 5.1, 2-(R,S)-(4-nitrophenyl)-4-(R)-thiazolidine carboxylic acid replacing 4-(t-butoxy-carbonylamino)-benzeneacetic acid. A pale yellow powder is obtained with a yield of 59%. Melting point: 145-146°C.

NMR ^1H (CDCl₃, 100 MHz, δ): 1.35 (m, 9H, tBu); 3.40 (m, 2H, CH₂-S); 4.95 (m, 1H, CH-CO); 6.10 (m, 1H, N-CH-S); 8.00 (m, 4H, Ph); 10.00 (wide s, 1H, CO₂H).

16.3 3-[(1,1-dimethylethoxy)carbonyl]-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-2-(R,S)-(4-nitrophenyl)-4-(R)-thiazolidine carboxamide:

The experimental protocol used is the same as that described for intermediate 14.3, 3-[(1,1-dimethylethoxy)carbonyl]-2-(R,S)-(4-nitrophenyl)-4-(R)-thiazolidine carboxylic acid replacing
5 2-(S)-4-(S)-1-[(1,1-dimethylethoxy)carbonyl]-4-(4-nitrophenoxy)-proline. A white powder is obtained with a yield of 41%. Melting point: 226-227°C.

NMR ¹H (CDCl₃, 100 MHz, δ): 1.45 (m, 27H, 3 x tBu); 3.52 (m, 2H, CH₂-S); 5.00 (m, 1H, CH-CO); 5.15 (s, 1H, OH); 6.10 (wide s, 1H, N-CH-S); 7.30 (s, 2H, Ph-OH); 7.92 (m, 4H, Ph-NO₂); 8.60 (wide s, 1H, CONH).

10 16.4 3-[(1,1-dimethylethoxy)carbonyl]-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-2-(R,S)-(4-aminophenyl)-4-(R)-thiazolidine carboxamide:

The experimental protocol used is the same as that described for intermediate 12.2, 3-[(1,1-dimethylethoxy)carbonyl]-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-2-(R,S)-(4-nitrophenyl)-4-(R)-thiazolidine carboxamide replacing 2-(3,5-di-t-butyl-4-hydroxyphenyl)-3-
15 (4-nitrophenyl)-4-thiazolidinone. The expected product is obtained in the form of a pale yellow powder with a yield of 21%. Melting point: 196-198°C.

NMR ¹H (CDCl₃, 100 MHz, δ): 1.40 (m, 27H, 3 x tBu); 3.50 (m, 4H, CH₂-S + NH₂); 5.00 (m, 1H, CH-CO); 5.10 (s, 1H, OH); 6.01 (wide s, 1H, N-CH-S); 6.98 (m, 4H, Ph-NH₂); 7.25 (s, 2H, Ph-OH); 8.50 (wide s, 1H, CONH).

20 16.5 N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-2-(R,S)-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-(R)-thiazolidine carboxamide fumarate (16):

The experimental protocol used is the same as that described for intermediate 14.5, intermediate 16.4 replacing 2-(S)-4-(S)-1-[(1,1-dimethylethoxy)carbonyl]-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-4-(4-aminophenoxy)-prolinamide. Compound 16.5 obtained in
25 the form of the free base is then salified in the presence of fumaric acid under reflux of ethanol for 30 minutes. A yellow powder is obtained with an overall yield of 30%. Melting point: 201-204°C.

NMR ¹H (DMSO, 400 MHz, δ): 1.37 (s, 18H, 2 x tBu); 3.17 (m, 2H, CH₂-S); 3.29 (wide s, 1H, NH thiazolidine); 3.91 (m, _H, CH-CO); 4.31 (m, _H, CH-CO); 5.59 (s, _H, N-CH-S);
30 5.67 (s, _H, N-CH-S); 6.61 (s, 2H, fum.); 6.74 (m, 2H, NH₂ amidine); 7.11 (m, 1H, thiophene); 7.19 (m, 4H, Ph-N); 7.42 (s, 2H, Ph-OH); 7.62 (m, 1H, thiophene); 7.73 (wide s, 1H, thiophene); 9.69 (s, _H, CONH); 9.95 (s, _H, CONH).

IR: ν_{OH}: 3625-3421 cm⁻¹; ν_{C=O} (amide): 1652 cm⁻¹; ν_{C=N} (amidine): 1604 cm⁻¹.

Example 17: N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-thiazolecarboxamide hydroiodide (17):

17.1 *4-nitrobenzene-carbothioamide*:

6.06 g (15 mmoles) of Lawesson reagent is added to a solution of 4.15 g (25 mmoles) of 4-nitrobenzamide in 100 ml of 1,4-dioxan. The reaction mixture is heated under reflux for two hours. After the solution has returned to ambient temperature, it is poured into 150 ml of water and extracted with 5 times 100 ml of ethyl acetate. The organic solution is dried over magnesium sulphate, filtered and concentrated under vacuum in order to produce a yellow oil which is purified on a silica gel column (eluant: heptane/ethyl acetate 1/1). The pure fractions are collected and concentrated under vacuum. 3.26 g of a yellow powder is obtained with a yield of 72%. Melting point: 165-167°C.

17.2 *Ethyl 2-(4-nitrophenyl)-4-thiazolecarboxylate*:

3.26 g (17.9 mmoles) of intermediate 17.1 and 2.26 ml (18 mmoles) of ethyl bromopyruvate are introduced successively into a flask containing 100 ml of DMF. After agitating the reaction mixture at 23°C, for 1 hour, the solution is concentrated under vacuum. The evaporation residue is dissolved in 150 ml of dichloromethane and washed successively with 100 ml of water and 100 ml of salt water. After drying over magnesium sulphate and filtration, the organic solution is concentrated under vacuum. The powder obtained is then agitated in the presence of 100 ml of a (3/1) mixture of toluene and ethanol, filtered and rinsed with 25 ml of the same mixture of solvents. 3.2 g (60%) of a beige powder is obtained. Melting point: 156-158°C.

17.3 *2-(4-nitrophenyl)-4-thiazolecarboxylic acid*:

A solution of 0.82 g (14.5 mmoles) of KOH in 5 ml of water is added dropwise at 23°C to a solution of intermediate 17.2 (2.15g, 7.25 mmoles) in 100 ml of acetone. After agitation overnight, the precipitate formed is filtered off and rinsed with 10 ml of acetone. This precipitate is taken up in a mixture of 100 ml of ethyl acetate and 100 ml of a 1M solution of HCl. After decantation, the aqueous phase is reextracted with 25 ml of ethyl acetate. The organic phases are collected and washed successively with 25 ml of water and 50 ml of salt water. The organic solution is dried over sodium sulphate, filtered and concentrated under vacuum in order to produce a yellow powder with a yield of 93%. Melting point: 250-252°C.

17.4 *N*-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-(4-nitrophenyl)-4-thiazolecarboxamide:

The experimental protocol used is the same as that described for intermediate 14.3, intermediate 17.3 replacing intermediate 14.2. The expected compound is obtained in the form of a yellow powder with a yield of 51%. Melting point: 262-264°C. NMR ¹H (acetone d₆, 100 MHz, δ): 1.60 (s, 18H, 2 tBu), 6.12 (s, 1H, OH), 8.21 (m, 2H, arom. H), 8.50 (s, 4H, arom. H), 8.60 (s, 1H, thiazole), 9.93 (wide s, 1H, CO-NH).

17.5 *N*-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-(4-aminophenyl)-4-thiazolecarboxamide:

3.59 g (16 mmoles) of SnCl₂·2H₂O is introduced into a solution of intermediate 17.4 (1.50g, 3.18 mmoles) in 50 ml of an ethyl acetate/ethanol/acetone mixture (2/1/2). The reaction mixture is heated under reflux for 5 hours and finally after cooling down, concentration to one half is carried out under vacuum. The evaporation residue is then poured into 50 ml of cold water, the precipitate which forms is diluted with 100 ml of ethyl acetate and 25 ml of a saturated solution of NaHCO₃. The cloudy mixture is filtered on celite and the filtrate is decanted. The organic phase is washed successively with 50 ml of water and 50 ml of salt water. After drying over magnesium sulphate and filtration, the organic solution is concentrated under vacuum in order to produce a bright yellow powder which is purified by washing with an Et₂O/Heptane mixture (90/10). The expected compound is obtained in the form of a pale yellow powder with a yield of 55%. Melting point: 267-268°C. NMR ¹H (CDCl₃, 100 MHz, δ): 1.49 (s, 18H, 2 tBu), 4.00 (wide s, 2H, NH₂), 5.11 (s, 1H, OH), 6.72 (m, 2H, arom. H), 7.60 (s, 2H, arom. H), 7.81 (m, 2H, arom. H), 8.05 (s, 1H, thiazole), 9.10 (wide s, 1H, CO-NH).

17.6 *N*-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-thiazolecarboxamide hydroiodide (17):

The experimental protocol used is the same as that described for intermediate 1.3, intermediate 17.5 replacing intermediate 1.2. A yellow powder is obtained with a yield of 27%. Melting point: 270-272°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 6.89 (s, 1H, OH), 7.41 (m, 1H, arom. H), 7.63 (m, 4H, arom. H), 8.11 (m, 1H, arom. H), 8.20 (m, 1H, arom. H), 8.36 (m, 2H, arom. H), 8.48 (s, 1H, arom. H), 9.19 (wide s, 1H, NH⁺), 9.90 (wide s, 1H, NH⁺), 10.02 (s, 1H, CO-NH), 11.50 (s, 1H, NH⁺). IR: ν_{C=O} (amide): 1660 cm⁻¹; ν_{C=N} (amidine): 1646 cm⁻¹.

Example 18: N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine-2-(R)-carboxamide dihydrochloride (18):

5 18.1 *1-(1,1-dimethylethyl) and 2-methyl 4-(S)-(4-nitrophenoxy)-1,2-(R)-pyrrolidinedicarboxylate:*

4.38 g (31.5 mmoles) of 4-nitrophenol in solution in 40 ml of anhydrous N-methyl-2-pyrrolidinone is added dropwise to a suspension of 1.26 g (31.5 mmoles) of NaH at 60% in 60 ml of anhydrous N-methyl-2-pyrrolidinone in a three-necked flask cooled down to 0°C. under an inert atmosphere. The reaction is accompanied by a significant release of hydrogen. After
10 agitation for one hour at 0°C, 6 g (15 mmoles) of 1-(1,1-dimethylethyl) and 2-methyl 4-(R)-{[(4-methylphenyl)sulphonyl]oxy}-1,2-(R)-pyrrolidinedicarboxylate is added in one go, agitation is maintained for another 15 hours at 23°C and the reaction is completed by 5 hours of reflux. After the reaction mixture is returned to 23°C, it is diluted with 150 ml of ethyl acetate and 100 ml of a 1M solution of soda. After decantation, the aqueous phase is
15 reextracted twice with 50 ml of ethyl acetate. The organic phases are collected and washed successively with 1N soda (until the excess of 4-nitrophenol of the organic phase disappears), with water until neutrality is achieved and finally with 100 ml of salt water. After drying over magnesium sulphate and filtration, the organic solution is concentrated under vacuum in order to produce an oily brown residue which is purified on a silica column (eluant: heptane/ethyl acetate: 8/2). The pure fractions are collected and concentrated under vacuum in order to
20 produce a pale yellow oil with a yield of 83%. NMR ¹H (CDCl₃, 100 MHz, δ): 1.41 (s, 9H, tBu), 2.40 (m, 2H, CH₂), 3.80 (s, 5H, CH₃ + CH₂), 4.50 (m, 1H, CH-N), 5.03 (m, 1H, CH-O), 6.95 (m, 2H, arom. H), 8.22 (m, 2H, arom. H).

18.2 *1,1-dimethylethyl 2-(R)-carboxy-4-(S)-(4-nitrophenoxy)-1-pyrrolidinecarboxylate:*

25 A solution of 2.14 g (38 mmoles) of KOH in 15 ml of water is added dropwise at 0°C to a solution of 7 g (19 mmoles) of intermediate 18.1 in 100 ml of methanol. The reaction mixture is agitated at 23°C for 15 hours and finally concentrated to one half under vacuum. After dilution with 50 ml of ethyl acetate and 50 ml of 1N soda, the mixture is decanted. The organic phase is eliminated and the aqueous phase is acidified cold with 1M HCl. The product
30 is then extracted with 100 ml of ethyl acetate. The organic solution is then washed with 50 ml of water and 50 ml of salt water. After drying over magnesium sulphate and filtration, the solution is concentrated under vacuum. A pale yellow oil is obtained with a yield of 66%. NMR ¹H (CDCl₃, 100 MHz, δ): 1.45 (s, 9H, tBu), 2.52 (m, 2H, CH₂), 3.80 (m, 2H, CH₂), 4.48 (m, 1H, CH-N), 5.03 (m, 1H, CH-O), 5.92 (wide s, CO₂H), 6.92 (m, 2H, arom. H), 8.20 (m,
35 2H, arom. H).

18.3 *1,1-dimethylethyl 2-(R)-{[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]amino]carbonyl}-4-(S)-(4-nitrophenoxy)-pyrrolidine-1-carboxylate:*

The experimental protocol used is the same as that described for intermediate 14.3, intermediate 18.2 replacing intermediate 14.2. A beige powder is obtained with a yield of 43%. Melting point: 140-142°C. NMR ¹H (CDCl₃, 100 MHz, δ): 1.45 (s, 18H, 2 tBu), 1.50 (s, 9H, tBu), 2.30 (m, 1H, 1/2 CH₂), 2.95 (m, 1H, 1/2 CH₂), 3.75 (m, 2H, CH₂), 4.65 (m, 1H, CH-N), 5.10 (m, 2H, CH-O + OH), 6.98 (m, 2H, arom. H), 7.31 (s, 2H, arom. H), 8.22 (m, 2H, arom. H), 9.10 (wide s, 1H, CO-NH).

18.4 *1,1-dimethylethyl 2-(R)-{[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]amino]carbonyl}-4-(S)-(4-aminophenoxy)-pyrrolidine-1-carboxylate:*

The experimental protocol used is the same as that described for intermediate 14.4, intermediate 18.3 replacing intermediate 14.3. After purification on a silica column (eluant: heptane/ethyl acetate: 1/1) and concentration of the pure fractions, the expected compound is obtained in the form of a beige powder with a yield of 70%. Melting point: 104-106°C. NMR ¹H (CDCl₃, 100 MHz, δ): 1.45 (s, 18H, 2 tBu), 1.50 (s, 9H, tBu), 1.60 (s, 2H, NH₂), 2.10 (m, 1H, 1/2 CH₂), 2.80 (m, 1H, 1/2 CH₂), 3.60 (m, 2H, CH₂), 4.60 (m, 1H, CH-N), 4.85 (m, 1H, CH-O), 5.04 (s, 1H, OH), 6.70 (m, 4H, arom. H), 7.34 (s, 2H, arom. H), 9.10 (wide s, 1H, CO-NH).

18.5 *N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine-2-(R)-carboxamide dihydrochloride (18):*

The experimental protocol used is the same as that described for intermediate 2.4, intermediate 18.4 replacing 3-(4-aminobenzyl)-thiazolidine. The free base, obtained in the form of a light yellow powder, is directly deprotected in the presence of 10 equivalents of a 4M solution of anhydrous HCl in 1,4-dioxan. After agitation for 15 hours, the precipitate formed is filtered, the crystals are washed with acetone followed by ethyl ether. The expected product is obtained in the form of a pale yellow powder with a yield of 53%. Melting point: 245-247°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.36 (s, 18H, 2 tBu), 2.29 (m, 1H, 1/2 CH₂), 2.71 (m, 1H, 1/2 CH₂), 3.42 (m, 1H, 1/2 CH₂), 3.77 (m, 1H, 1/2 CH₂), 4.57 (m, 1H, CH-N), 5.26 (m, 1H, CH-O), 6.93 (s, 1H, OH), 7.17 (m, 2H, arom. H), 7.37 (m, 1H, arom. H), 7.42 (m, 2H, arom. H), 7.48 (s, 2H, arom. H), 8.17 (m, 2H, arom. H), 8.81 (wide s, 1H, NH⁺), 9.03 (wide s, 1H, NH⁺), 9.78 (wide s, 1H, NH⁺), 10.70 (s, 1H, CO-NH), 10.84 (wide s, 1H, NH⁺), 11.50 (wide s, 1H, NH⁺). IR: ν_{C=O} (amide): 1681 cm⁻¹; ν_{C=N} (amidine): 1652 cm⁻¹.

Example 19: Methyl 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2-H-[1]-benzopyran-2-yl)carbonyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]-phenoxy}-pyrrolidine-2-(S)- carboxylate hydrochloride (19):

5 19.1 *1-(1,1-dimethylethyl) and 2-methyl 4-(S)-(4-nitrophenoxy)-1,2-(S)-pyrrolidinedicarboxylate*

The experimental protocol used is the same as that described for intermediate 18.1, the 1-(1,1-dimethylethyl) and 2-methyl 4-(S)-{[(4-methylphenyl)sulphonyl]oxy}-1,2-(R)-pyrrolidinedicarboxylate derivative being used instead of the 1-(1,1-dimethylethyl) and 2-methyl 4-(R)-{[(4-methylphenyl)sulphonyl]oxy}-1,2-(R)-pyrrolidinedicarboxylate derivative.

10 The expected product is obtained in the form of a white powder with a yield of 63%. Melting point: 155-157°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.37 (2 s, 9H, tBu), 2.22 (m, 1H, 1/2 CH₂), 2.62 (m, 1H, 1/2 CH₂), 3.45 (m, 1H, 1/2 CH₂), 3.62 (2 s, 3H, OCH₃), 3.78 (m, 1H, 1/2 CH₂), 4.42 (m, 1H, CH-N), 5.20 (m, 1H, CH-O), 7.07 (m, 2H, arom. H), 8.20 (m, 2H, arom. H).

15 19.2 *Methyl 4-(S)-(4-nitrophenoxy)-pyrrolidine-2-(S)-carboxylate:*

10 ml (94 mmoles) of trifluoroacetic acid diluted with 10 ml of dichloromethane is added at 0°C to a solution of 3.45 g (9.4 mmoles) of intermediate 19.1 in 15 ml of dichloromethane. The reaction mixture is then agitated for 2 hours at 23°C and finally it is concentrated under vacuum. The evaporation residue is diluted with 100 ml of dichloromethane and the organic solution is washed successively 3 times with 20 ml of a saturated solution of Na₂CO₃, twice with 20 ml of water and finally with 20 ml of salt water. After drying over magnesium sulphate and filtration, the organic solution is concentrated under vacuum in order to produce a pale yellow oil with a yield of 78%.

25 19.3 *Methyl 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2-H-[1]-benzopyran-2-yl)carbonyl]-4-(S)-(4-nitrophenoxy)-pyrrolidine-2-(S)-carboxylate:*

1.3 g (8.06 mmoles) of 1,1'-carbonyldiimidazole is added to a solution of 1.83 g (7.33 mmoles) of Trolox in 20 ml of dry THF. After agitation for one hour at 23°C, a solution of 1.95 g (7.33 mmoles) of intermediate 19.2 diluted in 10 ml of dry THF is added dropwise.

30 The reaction mixture is agitated at 23°C for 15 hours and finally concentrated to dryness under vacuum. The residue is diluted with 100 ml of ethyl acetate and the organic solution is washed twice with 50 ml of water and 50 ml of salt water. After drying over magnesium sulphate and filtration, the organic solution is concentrated under vacuum. The evaporation residue is purified on a silica gel column (eluant: heptane/ethyl acetate: 6/4). The pure

fractions are collected and evaporated under vacuum in order to produce a yellow powder with a yield of 61%. Melting point: 103-105°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.55-2.50 (m, 16H, Trolox), 2.63 (m, 2H, CH₂), 3.60-3.71 (2 s, 3H, OCH₃), 3.85 (m, 2H, CH₂), 4.70-4.88 (2 m, 1H, CH-N), 5.02 (m, 1H, CH-O), 6.82 (m, 2H, arom. H), 8.20 (m, 2H, arom. H).

- 5 19.4 *Methyl 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2-H-[1]-benzopyran-2-yl)carbonyl]-4-(S)-(4-aminophenoxy)-pyrrolidine-2-(S)-carboxylate:*

The protocol used is the same as that described for intermediate 14.4, intermediate 19.3 replacing intermediate 14.3. The expected product is obtained in the form of a white powder with a yield of 95%. Melting point: 110-112°C.

- 10 19.5 *Methyl 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2-H-[1]-benzopyran-2-yl)carbonyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine-2-(S)-carboxylate hydrochloride (19):*

The protocol used is the same as that described for intermediate 2.4, intermediate 19.4 replacing intermediate 2.3. The condensation reaction is carried out in 2-propanol only. After salification, the expected product is obtained in the form of a pale yellow powder with a yield of 75%. Melting point: 203-206°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.55-2.50 (m, 16H, Trolox), 2.45 (m, 2H, CH₂), 3.45-3.60 (2 s, 3H, OCH₃), 3.70 (m, 2H, CH₂), 4.51 (m, 1H, CH-N), 5.02 (m, 1H, CH-O), 7.00 (m, 2H, arom. H), 7.39 (m, 3H, arom. H), 8.16 (m, 2H, arom. H), 8.80 (wide s, 1H, NH⁺), 9.75 (wide s, 1H, NH⁺), 11.36 (wide s, 1H, NH⁺).

- 20 IR: ν_{C=O} (amide): 1650 cm⁻¹; ν_{C=N} (amidine): 1611 cm⁻¹.

Example 20: 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine hydrochloride (20):

20.1 *1,1-dimethylethy 3-(R)-{[(4-methylphenyl)sulphonyl]oxy}-1-pyrrolidinecarboxylate:*

- 25 21.6 g (114 mmoles) of p-toluenesulphonyl chloride is added to a solution of 10 g (57 mmoles) of (R)-N-Boc-3-pyrrolidinol (prepared in a standard fashion starting from commercial (R)-3-pyrrolidinol) and of 13.7 ml (171 mmoles) of pyridine in 150 ml of dichloromethane. After agitation for 24 hours at 23°C, the reaction mixture is washed with 3 times 50 ml of a 1M solution of HCl. After decantation, the organic phase is washed with 50
30 ml of water followed by 50 ml of salt water and finally dried over magnesium sulphate, filtered and concentrated under vacuum. The evaporation residue is purified rapidly on a silica

column (eluant: heptane/ethyl acetate: 8/2) in order to produce a pale yellow oil with a yield of 67%.

20.2 *1,1-dimethylethyl 3-(S)-(4-nitrophenoxy)-1-pyrrolidine-carboxylate:*

5 The experimental protocol used is the same as that described for intermediate 18.1, intermediate 20.1 replacing the 1-(1,1-dimethylethyl) and 2-methyl 4-(R)-{[(4-methylphenyl)sulphonyl]oxy}-1,2-(R)-pyrrolidinedicarboxylate derivative. The expected product is obtained in the form of a light yellow powder with a yield of 77%. Melting point: 112-114°C. NMR ¹H (CDCl₃, 100 MHz, δ): 1.45 (s, 9H, tBu), 2.20 (m, 2H, CH₂), 3.60 (m, 4H, CH₂-CH₂), 5.00 (m, 1H, CH-O), 6.94 (m, 2H, arom. H), 8.20 (m, 2H, arom. H).

10 20.3 *3-(S)-(4-nitrophenoxy)pyrrolidine:*

The experimental protocol used is the same as that described for intermediate 19.2, intermediate 20.2 replacing intermediate 19.1. A brown oil is obtained with a quantitative yield.

15 20.4 *1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-(S)-(4-nitrophenoxy)pyrrolidine:*

20 The experimental protocol used is the same as that described for intermediate 19.3, intermediate 20.3 replacing intermediate 19.2, the expected product is obtained after chromatography on a silica column (eluant: heptane/ethyl acetate: 7/3). The pure fractions, after evaporation, produce a beige powder with a yield of 23%. Melting point: 176-178°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.52-2.60 (m, 16H, Trolox), 2.62 (m, 2H, CH₂), 3.50-4.40 (m, 4H, CH₂-CH₂), 4.80 (m, 1H, CH-O), 6.89 (m, 2H, arom. H), 8.20 (m, 2H, arom. H).

20.5 *1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-(S)-(4-aminophenoxy)pyrrolidine:*

25 The experimental protocol used is the same as that described for intermediate 14.4, intermediate 20.4 replacing intermediate 14.3. A white powder is obtained with a yield of 78%. Melting point: 98-100°C.

20.6 *1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}pyrrolidine hydrochloride (20):*

The protocol used is the same as that described for intermediate 2.4, intermediate 20.5 replacing intermediate 2.3. The condensation reaction is carried out in 2-propanol only. After salification, the expected product is obtained in the form of a pale yellow powder with a yield of 85%. Melting point: 195-197°C. NMR ¹H (pyridine d₅, 400 MHz, δ): 1.52-2.48 (m, 16H, Trolox), 2.60-3.05 (m, 2H, CH₂), 3.58-4.42 (m, 4H, CH₂-CH₂), 4.59-4.90 (m, 1H, CH-O), 6.65 (m, 1H, arom. H), 6.89 (m, 2H, arom. H), 7.01 (m, 1H, arom. H), 7.15 (m, 1H, arom. H), 7.30 (m, 1H, NH⁺), 7.41 (m, 1H, NH⁺), 7.74 (m, 2H, arom. H), 8.95 (m, 1H, NH⁺). IR: ν_{C=O} (amide): 1650 cm⁻¹; ν_{C=N} (amidine): 1610 cm⁻¹

Example 21: 3-{[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)-carbonyl]amino}-1-{4-[(imino(2-thienyl)methyl)amino] phenyl}pyrrolidine (21):

21.1 3-{[(1,1-dimethylethoxy)carbonyl]amino}-1-(4-nitrophenyl)pyrrolidine:

The experimental protocol used is the same as that described for intermediate 1.1, 3-(tert-butoxycarbonylamino)pyrrolidine replacing imidazole.

NMR ¹H (CDCl₃, 100 MHz, δ): 1.45 (s, 9H, tBu), 2.20 (m, 2H, CH₂), 3.50 (m, 4H, 2 x CH₂-N), 4.35 (m, 1H, CH-N), 4.75 (m, 1H, NH), 6.45 (m, 2H, arom. H), 8.10 (m, 2H, arom. H).

21.2 3-amino-1-(4-nitrophenyl)pyrrolidine:

The experimental protocol used is the same as that described for intermediate 19.2, intermediate 21.1 replacing intermediate 19.1. NMR ¹H (CDCl₃, 100 MHz, δ): 1.50 (wide s, 2H, NH₂), 2.10 (m, 2H, CH₂), 3.10 (m, 1H, CH), 3.50 (m, 4H, 2 x CH₂), 6.40 (m, 2H, arom. H), 8.10 (m, 2H, arom. H).

21.3 3-{[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]amino}-1-(4-nitrophenyl)pyrrolidine:

The experimental protocol used is the same as that described for intermediate 19.3, intermediate 21.2 replacing intermediate 19.2. A yellow solid is obtained which is used directly in the following stages without further purification.

NMR ¹H (CDCl₃, 100 MHz, δ): 1.50-2.20 (m, 18H, Trolox + CH₂), 3.45 (m, 4H, 2 x CH₂), 4.40 (m, 1H, CH), 4.50 (wide s, 1H, NH), 8.15 (m, 2H, arom. H), 8.35 (m, 2H, arom. H).

21.4 3-{[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]amino}-1-(4-aminophenyl)pyrrolidine:

The experimental protocol used is the same as that described for intermediate 14.4, intermediate 21.3 replacing intermediate 14.3. NMR ^1H (CDCl_3 , 100 MHz, δ): 1.50-2.50 (m, 18H, Trolox + CH_2), 3.15 (m, 4H, 2 x CH_2), 4.50 (m, 2H, CH + NH), 6.40 (m, 4H, arom. H).

21.5 3- $\{[(3,4\text{-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]amino\}$ -1- $\{4-[(\text{imino}(2\text{-thienyl)methyl)amino}]phenyl\}$ pyrrolidine (**21**):

The experimental protocol used is the same as that described for intermediate 2.4, intermediate 21.4 replacing intermediate 2.3. The expected product is obtained in the form of a yellow powder (free base) with a yield of 81%. Melting point: 135-138°C. NMR ^1H (DMSO d_6 , 400 MHz, δ): 1.39-2.50 (m, 18H, Trolox + CH_2), 2.85-3.43 (m, 4H, 2 x CH_2), 4.37 (m, 1H, CH), 6.23 (wide s, 2H, NH_2), 6.46 (m, 2H, arom. H), 6.73 (m, 2H, arom. H), 7.07 (m, 1H, arom. H), 7.17 (d, 1/2H, 1/2 CONH. $J = 7.6$ Hz), 7.34 (d, 1/2H, 1/2 CONH. $J = 7.6$ Hz), 7.56 (m, 1H, arom. H), 7.68 (m, 1H, arom. H).

IR: $\nu_{\text{C=O}}$ (amide): 1657 cm^{-1} ; $\nu_{\text{C=N}}$ (amidine): 1626 cm^{-1} .

Example 22: 4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]benzoyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride (**22**):

22.1 $\{[3,5\text{-bis-(1,1-dimethylethyl)-4-hydroxyphenyl}]carbonyl\}methyl$ N-methyl-N-[(phenylmethoxy)carbonyl] glycinate :

This intermediate is obtained in a standard fashion starting from Cbz-Sarcosine and 1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-bromo-ethanone in the presence of caesium carbonate in DMF. NMR ^1H (CDCl_3 , 100 MHz, δ): 1.46 (s, 18H, 2 tBu), 3.00 (s, 3H, N- CH_3), 4.20 (m, 2H, O- CH_2 -Ph), 5.10-5.40 (m, 4H, $\text{CH}_2\text{-N}(\text{CH}_3) + \text{CO-CH}_2\text{-O-CO}$), 5.80 (s, 1H, OH), 7.30 (m, 5H, arom. H), 7.70 (s, 2H, arom. H).

22.2 4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-[(phenylmethoxy)-carbonyl]-1H-imidazole-2-methanamine:

This intermediate is obtained, starting from intermediate 22.1, using the same experimental protocol as that described in *Tetrahedron Lett.*, 1993, **34**, 1901. A pale green powder is obtained with a yield of 81%. Melting point: 200-207°C. NMR ^1H (CDCl_3 , 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 3.00 (s, 3H, N- CH_3), 4.50 (m, 2H, O- CH_2 -Ph), 5.10 (s, 2H, $\text{CH}_2\text{-N-COO}$), 5.20 (s, 1H, OH), 7.00 (s, 1H, imidazole), 7.20-7.50 (m, 7H, arom. H), 9.90 (s, 1H, NH).

22.3 4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-[(phenylmethoxy)-carbonyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-2-methanamine:

7.1 g (51.2 mmol) of potassium carbonate is added by portions to a mixture of 9.96 ml (56.3 mmol) of 2-(trimethylsilyl)ethoxymethyl chloride and 23 g (51.2 ml) of intermediate 22.2 in 200 ml of DMF. When the addition is finished, the reaction mixture is agitated for 3 hours at 50°C. The solvent is then eliminated under vacuum and the residue is diluted with 200 ml of ethyl acetate. The organic solution is washed twice with 100 ml of salt water, dried over magnesium sulphate, filtered and concentrated under vacuum. The evaporation residue is purified on a silica gel column (eluant heptane/ethyl acetate: 1/1). The pure fractions are evaporated in order to produce a green oil with a yield of 53%. NMR ¹H (CDCl₃, 400 MHz, δ): 0.0 (s, 9H, Si(CH₃)₃), 0.9 (m, 2H, CH₂-Si), 1.50 (s, 18H, 2 tBu), 3.00 (s, 3H, N-CH₃), 3.30-3.50 (m, 2H, O-CH₂-CH₂-Si), 4.70 (s, 2H, CH₂-N-COO), 5.10 (s, 2H, O-CH₂-Ph), 5.20 (s, 2H, imidazole-CH₂-OSEM), 5.30 (s, 1H, OH), 7.20 (s, 1H, imidazole), 7.35 (m, 5H, arom. H), 7.60 (s, 2H, arom. H).

22.4 4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-1-{[2-(trimethylsilyl)ethoxy]-methyl}-1H-imidazole-2-methanamine:

The experimental protocol used is the same as that described for intermediate 14.4, intermediate 22.3 replacing intermediate 14.3. A brown oil is obtained with a yield of 98%. NMR ¹H (CDCl₃, 100 MHz, □): 0.0 (s, 9H, Si(CH₃)₃), 0.9 (m, 2H, CH₂-Si), 1.50 (s, 18H, 2 tBu), 2.50 (s, 3H, N-CH₃), 3.50 (m, 2H, O-CH₂-CH₂-Si), 4.00 (s, 2H, N-CH₂-imidazole), 5.20 (s, 1H, OH), 5.40 (s, 2H, imidazole-CH₂-OSEM), 7.10 (s, 1H, imidazole), 7.50 (s, 2H, arom. H).

22.5 4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-nitrobenzoyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-2-methanamine:

A solution of 2.67 g (14.4 mmol) of 4-nitrobenzoic acid chloride in 50 ml of dry THF is added dropwise to a solution of 5.34 g (11.9 mmol) of intermediate 22.4 and 2 ml (14.4 mmol) of triethylamine in 50 ml of dichloromethane. After agitation for 2 hours at 23°C, the mixture is diluted with 100 ml of dichloromethane and the organic solution is washed twice with 100 ml of salt water. After drying over magnesium sulphate, the organic phase is filtered and concentrated under vacuum in order to produce a yellow oil which is used as it is in the following stage. NMR ¹H (CDCl₃, 400 MHz, δ): 0.0 (s, 9H, Si(CH₃)₃), 0.9 (m, 2H, CH₂-Si), 1.50 (s, 18H, 2 tBu), 3.15 (s, 3H, N-CH₃), 3.50 (m, 2H, O-CH₂-CH₂-Si), 4.80 (s, 2H, N-CH₂-imidazole), 5.20 (s, 2H, imidazole-CH₂-OSEM), 5.30 (s, 1H, OH), 6.90 (m, 2H, arom. H), 7.15 (s, 1H, imidazole), 7.60 (s, 2H, arom. H), 8.10 (m, 2H, arom. H).

22.6 *4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-nitrobenzoyl)-1H-imidazole-2-methanamine:*

Intermediate 22.5 (7.42 g, 12.5 mmol) is dissolved in 62.4 ml (62.4 mmol) of a 1M solution of tetrabutylammonium fluoride in the presence of 1.12g (18.7 mmol) of ethylenediamine. The reaction mixture is heated under reflux for 5 hours and finally poured directly into 200 ml of salt water and diluted with 200 ml of ethyl acetate. The organic phase is decanted, washed with 100 ml of salt water and finally dried over magnesium sulphate, filtered and concentrated under vacuum. The evaporation residue is purified on a silica column (eluant: dichloromethane + 5% of ethanol). The expected product is obtained in the form of a red foam with a yield of 37%. NMR ¹H (CDCl₃, 400 MHz, δ): 1.50 (s, 18H, 2 tBu), 3.00 (s, 3H, N-CH₃), 4.70 (s, 2H, N-CH₂-imidazole), 5.20 (s, 1H, OH), 7.10 (s, 1H, imidazole), 7.40-7.60 (m, 4H, arom. H), 8.30 (m, 2H, arom. H), 10.10 (wide s, 1H, NH).

22.7 *4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-aminobenzoyl)-1H-imidazole-2-methanamine:*

The experimental protocol used is the same as that described for intermediate 14.4, intermediate 22.6 replacing intermediate 14.3. An orange solid is obtained with a yield of 52%. Melting point: 129-131°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.50 (s, 18H, 2 tBu), 3.10 (s, 3H, N-CH₃), 3.90 (s, 2H, N-CH₂-imidazole), 4.70 (s, 2H, NH₂), 5.20 (s, 1H, OH), 6.60 (m, 2H, arom. H), 7.10 (s, 1H, Imidazole), 7.30-7.60 (m, 4H, arom. H), 10.30 (wide s, 1H, NH).

22.8 *4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]benzoyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride (22):*

The experimental protocol used is the same as that described for intermediate 4.3, intermediate 22.7 replacing intermediate 4.2. A light beige solid is obtained with a yield of 54%. Melting point: 250-260°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.50 (s, 18H, 2 tBu), 3.20 (s, 3H, N-CH₃), 5.00 (s, 2H, N-CH₂-imidazole), 7.30 (s, 1H, OH), 7.35 (m, 1H, thiophene), 7.50 (m, 4H, arom. H), 7.70 (s, 2H, a. H), 8.00 (s, 1H, Imidazole), 8.20 (m, 2H, thiophene), 9.20 (s, 1H, NH⁺), 10.00 (s, 1H, NH⁺), 11.8 (s, 1H, NH⁺), 14.8 (s, 1H, NH⁺), 15.2 (s, 1H, NH⁺).

IR: ν_{C=O} (amide): 1635 cm⁻¹; ν_{C=N} (amidine): 1601 cm⁻¹.

Example 23: N-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1H-pyrrole-2-carboxamide hydroiodide (**23**):

23.1 *Ethyl 1-(4-nitrophenyl)-1H-pyrrole-2-carboxylate:*

0.9 g (7.2 mmol) of the methyl ester of pyrrole-2-carboxylic acid (prepared in a standard fashion by the esterification of commercial pyrrole-2-carboxylic acid) diluted with 10 ml of dry DMF is added dropwise at 0°C, under an inert atmosphere, to a suspension of 0.3 g (7.4 mmol) of NaH at 60% in 15 ml of dry DMF. After agitation for one hour at 23°C, a solution of 1.01 g (7.2 mmol) of 4-fluoronitrobenzene in 10 ml of dry DMF is added dropwise. The reaction mixture is then heated for 3 hours at 80°C. After the reaction medium has returned to 23°C, it is poured into 100 ml of an ice + water mixture and finally diluted with 200 ml of ethyl acetate. After decantation, the organic phase is washed with 3 times 100 ml of water followed by 100 ml of salt water. The organic solution is dried over magnesium sulphate, filtered and concentrated under vacuum. The evaporation residue is purified on a silica column (eluant: heptane/ethyl acetate: 9/1). The pure fractions are collected and evaporated under vacuum in order to produce a pale yellow powder with a yield of 49%.

23.2 *1-(4-nitrophenyl)-1H-pyrrole-2-carboxylic acid:*

A solution of 0.5 g (7.1 mmol) of KOH in 5 ml of water is added to a flask containing a solution of 0.87 g (3.5 mmol) of intermediate 23.1 in 20 ml of THF cooled down to 0°C. The reaction mixture is agitated for 24 hours at 23°C and finally diluted with 100 ml of ethyl acetate. After decantation, the organic phase is eliminated and the aqueous phase is cooled down using an ice bath before acidification with a solution of concentrated HCl. The precipitate formed is then filtered and washed twice with 20 ml of water. After drying, the expected product is obtained with a yield of 66%.

23.3 *N-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-(4-nitrophenyl)-1H-pyrrole-2-carboxamide:*

The experimental protocol used is the same as that described for intermediate 14.3, intermediate 23.2 replacing intermediate 14.2. The expected compound is obtained in the form of a greenish powder with a crude yield of 25%. The product is used as it is in the following stage.

23.4 *N-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-(4-aminophenyl)-1H-pyrrole-2-carboxamide*

The experimental protocol used is similar to that described for intermediate 14.4, intermediate 23.3 replacing intermediate 14.3. The reaction is carried out in a dichloromethane/ethanol mixture (1/1). A white powder is obtained with a yield of 61%. Melting point: 218-219°C.

23.5 *N*-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1*H*-pyrrole-2-carboxamide hydroiodide (**23**):

The experimental protocol used is similar to that described for intermediate 1.3, intermediate 23.4 replacing intermediate 1.2. A pale yellow powder is obtained with a yield of 73%. Melting point: 271-272°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.35 (s, 18H, 2 tBu), 6.36 (s, 1H, OH), 6.78 (s, 1H, arom. H), 7.01 (s, 1H, arom. H), 7.16 (s, 1H, arom. H), 7.45 (m, 7H, arom. H), 8.10 (m, 1H, arom. H), 8.19 (m, 1H, arom. H), 9.16 (wide s, 1H, NH⁺), 9.89 (wide s, 2H, CONH + NH⁺), 11.39 (wide s, 1H, NH⁺). IR: ν_{C=O} (amide): 1633 cm⁻¹; ν_{C=N} (amidine): 1609 cm⁻¹.

Example 24: 1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-3-{[4-[[imino(2-thienyl)methyl]amino]phenyl]carbonyl}-2-imidazolidinone hydroiodide (**24**):

24.1 *N*-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-*N'*-(2-chloroethyl)urea:

0.17 ml (2 mmoles) of chloroethylisocyanate is added to a flask containing a solution of 0.5 g (2 mmoles) of intermediate 10.2 in 5 ml of DMF. The reaction mixture is agitated for 2 hours at 23°C and finally diluted with 100 ml of ethyl acetate and 25 ml of water. After decantation, the organic solution is washed with 25 ml of water, twice with 25 ml of salt water and finally dried over magnesium sulphate. After filtration and evaporation, the residue is taken up in isopentane in order to finally produce the expected product, in the form of a pink solid, with a yield of 83%. Melting point: 169-171°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.30 (s, 18H, 2 tBu), 3.35 (t, 2H, CH₂-NH, J = 6.0 Hz), 3.60 (t, 2H, CH₂-Cl, J = 6.0 Hz), 6.20 (t, 1H, NH-CH₂, J = 5.6 Hz), 6.60 (s, 1H, OH), 7.10 (s, 2H, arom. H), 8.30 (s, 1H, NH-Ph).

24.2 1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-imidazolidinone:

A solution of 0.22 g (1.93 mmole) of tBuOK⁺ in 2 ml of dry DMF is added to a solution of 0.56 g (1.93 mmole) of intermediate 24.1 in 10 ml of dry DMF. After agitation for 3 hours at 23°C, the reaction mixture is diluted with 50 ml of water and 100 ml of ethyl acetate. The organic phase is decanted, washed successively with 50 ml of water and 50 ml of salt water, dried over magnesium sulphate, filtered and finally concentrated under vacuum. The brown oil thus obtained is taken up in isopropyl ether in order to produce a white powder with a yield of 51%. Melting point: 205-207°C. NMR ¹H (DMSO d₆, 100 MHz, δ): 1.40 (s, 18H, 2 tBu),

4.60 (m, 2H, CH₂), 4.90 (m, 2H, CH₂), 4.90 (wide s, 1H, NH), 5.00 (s, 1H, OH), 7.15 (s, 2H, arom. H).

24.3 *1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-3-[(4-nitrophenyl)carbonyl]-2-imidazolidinone:*

5 1.28 g (6.9 mmol) of 4-nitrobenzoic acid chloride is added by portions to a solution of 1.0 g (3.45 mmol) of intermediate 24.2 in a mixture of 20 ml of acetonitrile and 10 ml of THF, followed by 0.71 g (5.15 mmol) of potassium carbonate. After agitation for 3 hours at 23°C, the reaction mixture is diluted with 100 ml of dichloromethane and 50 ml of salt water. The organic phase, after decantation, is washed with 50 ml of salt water and dried over magnesium sulphate. After filtration and concentration under vacuum, the evaporation residue is taken up in isopropyl ether in order to produce a yellow solid with a yield of 83% after drying. Melting point > 260°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 3.95-4.20 (m, 4H, 2 CH₂), 5.20 (s, 1H, OH), 7.20 (s, 2H, arom. H), 7.80 (m, 2H, arom. H), 8.25 (m, 2H, arom. H).

15 24.4 *1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-3-[(4-aminophenyl)carbonyl]-2-imidazolidinone:*

The experimental protocol used is similar to that described for intermediate 14.4, intermediate 24.3 replacing intermediate 14.3. The expected product is obtained in the form of a white powder with a yield of 45%. Melting point > 260°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 3.90-4.00 (m, 4H, 2 CH₂), 5.15 (s, 1H, OH), 6.60 (m, 2H, arom. H), 7.13 (s, 2H, arom. H), 7.60 (m, 2H, arom. H).

24.5 *1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-3-{[4-[[imino(2-thienyl)methyl]amino]phenyl]carbonyl}-2-imidazolidinone hydroiodide (24):*

The experimental protocol used is identical to that described for intermediate 1.3, intermediate 24.4 replacing intermediate 1.2. The expected product is obtained in the form of a light beige solid with a yield of 79%. Melting point: 220-260°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.30 (s, 18H, 2 tBu), 4.00 (m, 4H, 2 CH₂), 6.95 (s, 1H, OH), 7.20 (s, 2H, arom. H), 7.40 (m, 1H thiophene), 7.50 (m, 2H, arom. H), 7.70 (m, 2H, arom. H), 8.20 (m, 2H, thiophene), 9.20 (wide s, 1H, NH⁺), 9.90 (wide s, 1H, NH⁺), 11.60 (wide s, 1H, NH⁺). IR: ν_{C=O} (urea): 1735 cm⁻¹; ν_{C=O} (amide): 1649 cm⁻¹; ν_{C=N} (amidine): 1595 cm⁻¹.

30 **Example 25:** *3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-N-{4-[[imino(2-thienyl)methyl]amino]phenyl}-5-isoxazoleacetamide hydroiodide (25):*

25.1 3,5-bis-(1,1-dimethylethyl)-N,4-dihydroxy-benzene carboxime:

This intermediate is prepared according to an experimental protocol described in *J. Med. Chem.*, 1997, **40**, 50-60, starting from commercial 3,5-di-tert-butyl-4-hydroxybenzaldehyde. A red foam is obtained with a quantitative yield.

5 25.2 3,5-bis-(1,1-dimethylethyl)-N,4-dihydroxy-benzene carboximidoyl chloride:

The experimental protocol used is the same as that described in *Tetrahedron Lett.*, 1996, **37** (26), 4455 starting from intermediate 25.1. A beige solid is obtained with a crude yield of 77%. The product is used directly in the following stage without additional purification.

10 25.3 Methyl 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-isoxazoleacetate:

The reaction of intermediate 25.2 with the methyl ester of 3-butenic acid is carried out under the same conditions as those described in *Tetrahedron Lett.* 1996, **37** (26), 4455. The expected compound is obtained in the form of a brown oil with a yield of 49%. NMR ¹H (CDCl₃, 400 MHz, δ): 1.50 (s, 18H, 2 tBu), 2.60 (dd, 1H, 1/2 CH₂-C=N, J = 16.0 Hz and J = 7.8 Hz), 2.90 (dd, 1H, 1/2 CH₂-C=N, J = 16.0 Hz and J = 5.8 Hz), 3.10 (dd, 1H, 1/2 CH₂-C=O, J = 16.6 Hz and J = 6.9 Hz), 3.60 (dd, 1H, 1/2 CH₂-C=O, J = 16.6 Hz and J = 10.2 Hz), 5.10 (m, 1H, CH), 5.50 (s, 1H, OH), 7.50 (s, 2H, arom. H).

25.4 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-isoxazoleacetic acid:

This intermediate is obtained by the saponification of intermediate 25.3 according to an experimental protocol described in *J. Med. Chem.* 1997, **40**, 50-60. A white solid is obtained with a yield of 74%. Melting point: 229-231°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.50 (s, 18H, 2 tBu), 2.70 (dd, 1H, 1/2 CH₂-C=N, J = 16.3 Hz and J = 7.5 Hz), 2.90 (dd, 1H, 1/2 CH₂-C=N, J = 16.3 Hz and J = 6.0 Hz), 3.10 (dd, 1H, 1/2 CH₂-C=O, J = 16.6 Hz and J = 6.9 Hz), 3.50 (dd, 1H, 1/2 CH₂-C=O, J = 16.6 Hz and J = 10.2 Hz), 5.05 (m, 1H, CH), 5.50 (s, 1H, OH), 7.45 (s, 2H, arom. H).

25.5 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-N-(4-nitrophenyl)-5-isoxazoleacetamide:

The experimental protocol used is the same as that described in *Org. Prep. Proced. Int.* (1975), **7**, 215 starting from intermediate 25.4 and 4-nitroaniline. A white solid is obtained with a yield of 45%. Melting point: 149-151°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.50 (s, 18H,

2 tBu), 2.70 (m, 1H, 1/2 CH₂-C=N), 2.85 (dd, 1H, 1/2 CH₂-C=N, J = 15.1 Hz and J = 7.5 Hz), 3.20 (dd, 1H, 1/2 CH₂-C=O, J = 16.7 Hz and J = 7.0 Hz), 3.70 (dd, 1H, 1/2 CH₂-C=O, J = 16.7 Hz and J = 10.1 Hz), 5.05 (m, 1H, CH), 5.50 (s, 1H, OH), 7.45 (s, 2H, arom. H), 7.70 (m, 2H, arom. H), 8.20 (m, 2H, arom. H), 8.50 (s, 1H, NH-CO).

5 25.6 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-N-(4-aminophenyl)-5-isoxazoleacetamide:

The experimental protocol used is the same as that described for intermediate 17.5, intermediate 25.5 replacing intermediate 17.4. A colourless oil is obtained with a yield of 80%. NMR ¹H (CDCl₃, 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 2.60 (dd, 1H, 1/2 CH₂-C=N, J = 15.0 Hz and J = 5.7 Hz), 2.80 (dd, 1H, 1/2 CH₂-C=N, J = 15.0 Hz and J = 6.7 Hz), 3.15 (dd, 1H, 1/2 CH₂-C=O, J = 16.7 Hz and J = 7.2 Hz), 3.50 (dd, 1H, 1/2 CH₂-C=O, J = 16.7 Hz and J = 10.1 Hz), 3.70 (2H, NH₂), 5.10 (m, 1H, CH), 5.60 (s, 1H, OH), 6.60 (m, 2H, arom. H), 7.20 (m, 2H, arom. H), 7.50 (s, 2H, arom. H), 8.10 (s, 1H, NH-CO).

15 25.7 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-5-isoxazoleacetamide hydroiodide (25):

The experimental protocol used is identical to that described for intermediate 1.3, intermediate 25.6 replacing intermediate 1.2. The expected product is obtained in the form of a pale yellow powder with a yield of 72%. Melting point > 260°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 2.70 (m, 2H, CH₂-C=N), 3.20 (dd, 1H, 1/2 CH₂-C=O, J = 16.8 Hz and J = 6.8 Hz), 3.60 (dd, 1H, 1/2 CH₂-C=O, J = 16.8 Hz and J = 10.2 Hz), 5.00 (m, 1H, CH), 7.35 (m, 6H, arom. H + OH), 7.80 (m, 2H, arom. H), 8.20 (m, 2H, thiophene), 8.70 (wide s, 1H, NH⁺), 9.70 (wide s, 1H, NH⁺), 10.30 (s, 1H, NH-CO), 11.20 (wide s, 1H, NH⁺). IR: ν_{C=O} (amide): 1650 cm⁻¹; ν_{C=N} (amidine): 1603 cm⁻¹.

25 **Example 26:** 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-2-thiazolemethanamine hydrochloride (26):

26.1 2-{[(1,1-dimethylethoxy)carbonyl]methyl}amino-ethanethioamide:

The experimental protocol used is identical to that described for intermediate 17.1, N-Boc sarcosinamide (obtained in a standard fashion starting from commercial sarcosinamide and BocOBoc) is used as starting product in place of 4-nitrobenzamide. A white paste is obtained which is used directly in the following stage.

26.2 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-[(1,1-dimethylethoxy)carbonyl]-N-methyl-2-thiazolemethanamine:

The experimental protocol used is the same as that described in *J. Org. Chem.* (1995), **60**, 5638-5642, starting from intermediate 26.1 and 1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-bromo-ethanone. A brown oil is obtained. NMR ¹H (CDCl₃, 400 MHz, δ): 1.50 (m, 27H, 3 tBu), 3.00 (s, 3H, N-CH₃), 4.70 (s, 2H, CH₂), 5.30 (s, 1H, OH), 7.25 (s, 1H, thiazole), 7.70 (s, 2H, arom. H).

26.3 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-2-thiazolemethanamine:

2.3 ml (29 mmoles) of TFA is added dropwise at 0°C to a solution of 2.5 g (5.8 mmoles) of intermediate 26.2 and 2 ml (1.6 mmole) of triethylsilane in 50 ml of dichloromethane. After agitation for one hour, the reaction mixture is concentrated under vacuum and the residue is diluted with 100 ml of ethyl acetate and 50 ml of a saturated solution of NaHCO₃. After agitation 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 a white solid, after drying, with a yield of 73%. Melting point: 136°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.50 (s, 18H, 2 tBu), 2.60 (s, 3H, N-CH₃), 4.20 (s, 2H, CH₂), 5.30 (s, 1H, OH), 7.20 (s, 1H, thiazole), 7.70 (s, 2H, arom. H).

26.4 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-nitrophenyl)-2-thiazolemethanamine:

The experimental protocol used is the same as that described for intermediate 1.1, intermediate 26.3 replacing imidazole. A yellow solid is obtained with a yield of 23%. Melting point: 199-201°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 3.25 (s, 3H, N-CH₃), 5.10 (s, 2H, CH₂), 6.95 (m, 2H, arom. H), 7.10 (s, 1H, OH), 7.60 (s, 2H, arom. H), 7.80 (s, 1H, thiazole), 8.05 (m, 2H, arom. H).

26.5 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-aminophenyl)-2-thiazolemethanamine:

The experimental protocol used is the same as that described for intermediate 17.5, intermediate 26.4 replacing intermediate 17.4. The expected product is obtained in the form of a beige foam with a yield of 71%. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 2.90 (s, 3H, N-CH₃), 4.50 (wide s, 2H, NH₂), 4.60 (s, 2H, CH₂), 6.50 (m, 2H, arom. H), 6.60 (m, 2H, arom. H), 7.10 (s, 1H, OH), 7.60 (s, 2H, arom. H), 7.70 (s, 1H, thiazole).

26.6 *4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-2-thiazolemethanamine hydrochloride (26):*

The experimental protocol used is the same as that described for intermediate 4.3, intermediate 26.5 replacing intermediate 4.2. A white powder is obtained with a yield of 67%.

- 5 Melting point: 157-160°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.50 (s, 18H, 2 tBu), 3.15 (s, 3H, N-CH₃), 5.00 (s, 2H, CH₂), 6.95 (m, 2H, arom. H), 7.15 (s, 1H, OH), 7.20 (m, 2H, arom. H), 7.40 (m, 1H, thiophene), 7.65 (s, 2H, arom. H), 7.75 (s, 1H, thiazole), 8.15 (m, 2H, thiophene), 8.70 (wide s, 1H, NH⁺), 9.70 (wide s, 1H, NH⁺), 11.30 (wide s, 1H, NH⁺). IR: ν_{C=O} (amide): 1648 cm⁻¹; ν_{C=N} (amidine): 1611 cm⁻¹.

- 10 **Example 27:** *4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride (27):*

27.1 *4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-nitrophenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-imidazole-2-methanamine:*

- 15 The experimental protocol used is the same as that described for intermediate 1.1, intermediate 22.4 replacing imidazole. A yellow solid is obtained with a yield of 53%. Melting point: 149-151°C. NMR ¹H (CDCl₃, 400 MHz, δ): 0.0 (s, 9H, Si(CH₃)₃), 0.9 (t, 2H, CH₂-Si, J = 8.4 Hz), 1.50 (s, 18H, 2 tBu), 3.15 (s, 3H, N-CH₃), 3.50 (t, 2H, O-CH₂-CH₂-Si, J = 8.4 Hz), 4.80 (s, 2H, N-CH₂-imidazole), 5.20 (s, 2H, imidazole-CH₂-OSEM), 5.25 (s, 1H, OH), 6.90 (m, 2H, arom. H), 7.10 (s, 1H, imidazole), 7.60 (s, 2H, arom. H), 8.15 (m, 2H, arom. H).
- 20

27.2 *4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-nitrophenyl)-1H-imidazole-2-methanamine:*

- The experimental protocol used is the same as that described for intermediate 22.6, intermediate 27.1 replacing intermediate 22.5. A yellow solid is obtained with a yield of 44%. Melting point: 209-211°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 3.20 (s, 3H, N-CH₃), 4.70 (s, 2H, CH₂), 6.80-7.10 (m, 3H, arom. H), 7.20-7.60 (m, 3H, arom. H + OH), 8.10 (m, 2H, arom. H), 12.00 (s, 1H, NH).
- 25

- 27.3 *4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-aminophenyl)-1H-imidazole-2-methanamine:*
- 30

The experimental protocol used is the same as that described for intermediate 14.4, intermediate 27.2 replacing intermediate 14.3. A beige foam is obtained with a yield of 67%. NMR ¹H (CDCl₃, 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 2.80 (s, 3H, N-CH₃), 4.20 (s, 2H, CH₂), 4.30-4.70 (m, 3H, NH₂ + NH imidazole), 5.00 (s, 1H, OH), 6.50 (m, 2H, arom. H), 6.70 (m, 2H, arom. H), 6.80 (s, 1H, imidazole), 7.40 (s, 2H, arom. H).

27.4 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride (27):

The experimental protocol used is the same as that described for intermediate 4.3, intermediate 27.3 replacing intermediate 4.2. A yellow powder is obtained with a yield of 86%. Melting point: 195-200°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.50 (s, 18H, 2 tBu), 3.20 (s, 3H, N-CH₃), 5.00 (s, 2H, CH₂), 7.00 (m, 2H, arom. H), 7.20 (m, 2H, arom. H), 7.40 (m, 2H, thiophene + OH), 7.60 (s, 2H, arom. H), 7.90 (s, 1H, imidazole), 8.20 (m, 2H, thiophene), 8.70 (wide s, 1H, NH⁺), 9.70 (wide s, 1H, NH⁺), 11.40 (wide s, 1H, NH⁺), 14.60 (wide s, 1H, NH⁺), 15.60 (wide s, 1H, NH⁺). IR: ν_{C=O} (amide): 1646 cm⁻¹; ν_{C=N} (amidine): 1612 cm⁻¹.

Example 28: 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-{2-{4-[(imino(2-thienyl)methyl)amino]phenoxy}ethyl}isoxazole (28):

28.1 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-isoxazoleethanol:

0.09 g (2.4 mmoles) of LiAlH₄ is added in small portions to a solution of 0.69 g (2.1 mmoles) of intermediate 25.3 in 15 ml of dry THF, cooled down to 0°C. After agitation for one hour at 23°C, the reaction mixture is cooled down using an ice bath and the excess hydride is destroyed by the addition of water (5 ml). The product is extracted using twice 25 ml of ethyl ether. The organic phase is washed twice with 10 ml of salt water, dried over magnesium sulphate, filtered and concentrated under vacuum. The residue is purified on silica (eluant: heptane/ethyl acetate: 1/1). A white foam is obtained with a yield of 58%. NMR ¹H (DMSO d₆, 100 MHz, δ): 1.40 (s, 18H, 2 tBu), 1.60-1.80 (m, 2H, CH₂-CH₂-O), 3.05 (m, 1H, 1/2 CH₂ isoxazoline), 3.40 (m, 1H, 1/2 CH₂ isoxazoline), 3.50 (m, 2H, CH₂-CH₂-O), 4.60 (s, 1H, OH), 4.70 (m, 1H, CH isoxazoline), 7.40 (wide s, 3H, arom. H + OH).

28.2 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-[2-(4-nitrophenoxy)ethyl]isoxazole:

A mixture composed of 0.37 g (1.58 mmole) of intermediate 28.1, 0.5 ml of Aliquat 336, 0.18 g (1.27 mmole) of 4-fluoronitrobenzene and 0.071 g (1.27 mmole) of KOH in 2 ml of toluene is heated at 80°C for 2 hours. After the reaction mixture has returned to 23°C, it is divided between 50 ml of dichloromethane and 20 ml of water. After decantation, the organic phase is washed with 20 ml of water followed by 20 ml of salt water. The organic solution is then dried over magnesium sulphate, filtered and concentrated under vacuum. The evaporation residue is purified on a silica column (eluant: heptane/ethyl acetate: gradient 10/0 up to 0/10). A white powder is obtained with a yield of 60%. Melting point: 151-153°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.50 (s, 18H, 2 tBu), 2.15 (m, 2H, CH₂-CH₂-O), 3.10 (dd, 1H, 1/2 CH₂ isoxazoline, J = 16.3 Hz and J = 6.65 Hz), 3.50 (dd, 1H, 1/2 CH₂ isoxazoline, J = 16.3 Hz and J = 10.4 Hz), 4.10-4.30 (m, 2H, CH₂-CH₂-O), 5.00 (m, 1H, CH isoxazoline), 5.50 (s, 1H, OH), 6.90 (m, 2H, arom. H), 7.50 (s, 2H, arom. H), 8.20 (m, 2H, arom. H).

28.3 *3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-[2-(4-aminophenoxy)ethyl]isoxazole:*

The experimental protocol used is the same as that described for intermediate 17.5, intermediate 28.2 replacing intermediate 17.4. A white powder is obtained with a yield of 60%. Melting point: 129-131°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.35 (s, 18H, 2 tBu), 2.00 (m, 2H, CH₂-CH₂-O), 3.15 (dd, 1H, 1/2 CH₂ isoxazoline, J = 16.7 Hz and J = 7.5 Hz), 3.40 (dd, 1H, 1/2 CH₂ isoxazoline, J = 16.7 Hz and J = 10.5 Hz), 3.90 (m, 2H, CH₂-CH₂-O), 4.60 (s, 2H, NH₂), 4.70 (m, 1H, CH isoxazoline), 6.50 (m, 2H, arom. H), 6.70 (m, 2H, arom. H), 7.40 (s, 3H, arom. H + OH).

28.4 *3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-{2-[4-[(imino(2-thienyl)methyl)amino]phenoxy}ethyl}isoxazole (28):*

The experimental protocol used is the same as that described for intermediate 4.3, intermediate 28.3 replacing intermediate 4.2. A white solid is obtained with a yield of 32%. Melting point: 240-245°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.40 (s, 18H, 2 tBu), 2.15 (m, 2H, CH₂-CH₂-O), 3.20 (dd, 1H, 1/2 CH₂ isoxazoline, J = 16.65 Hz and J = 7.35 Hz), 3.50 (dd, 1H, 1/2 CH₂ isoxazoline, J = 16.65 Hz and J = 10.3 Hz), 4.20 (wide s, 2H, CH₂-CH₂-O), 4.90 (m, 1H, CH isoxazoline), 7.20 (m, 2H, arom. H), 7.40 (m, 6H, arom. H + OH), 8.20 (m, 2H, thiophene), 8.80 (wide s, 1H, NH⁺), 9.80 (wide s, 1H, NH⁺), 11.40 (wide s, 1H, NH⁺). IR: ν_{C=O} (amide): 1655 cm⁻¹; ν_{C=N} (amidine): 1618 cm⁻¹.

Example 29: 1-{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]amino}-carbonyl}-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride (29):

29.1 *1-(diphenylmethyl)-3-(4-nitrophenoxy)azetidine:*

0.5 g (2 mmoles) of 1-(diphenylmethyl)-3-hydroxyazetidine is added under an argon atmosphere to a suspension of 0.06 g (2.3 mmoles) of NaH in 20 ml of dry THF. After agitation for one hour at 23°C, a solution of 0.29 g (2.1 mmoles) of 4-fluoronitrobenzene in 5 ml of dry THF is added dropwise to the reaction mixture. Agitation is maintained for another 2 hours at 23°C and the whole is finally poured into 25 ml of water. The product is extracted twice with 25 ml of ethyl acetate, the organic phase is then washed twice with 25 ml of salt water, dried over magnesium sulphate, filtered and concentrated under vacuum. The product is purified on a silica column (eluant: 12% of ethyl acetate in heptane). The pure fractions are evaporated in order to produce a colourless oil with a yield of 40%. NMR ¹H (CDCl₃, 400 MHz, δ): 3.20 (m, 2H, azetidine), 4.50 (s, 1H, CH-(Ph)₂), 4.80 (m, 2H, azetidine), 4.90 (m, 1H, CH-O), 6.80 (m, 2H, arom. H), 7.20-7.50 (m, 10H, arom. H), 8.20 (m, 2H, arom. H).

29.2 *1-(diphenylmethyl)-3-(4-aminophenoxy)azetidine:*

The experimental protocol used is the same as that described for intermediate 17.5, intermediate 29.1 replacing intermediate 17.4. A colourless oil is obtained with a yield of 75%. NMR ¹H (CDCl₃, 400 MHz, δ): 3.10 (m, 2H, azetidine), 3.40 (wide s, 2H, NH₂), 4.40 (s, 1H, CH-(Ph)₂), 4.70 (m, 2H, azetidine), 4.75 (m, 1H, CH-O), 6.60 (s, 4H, arom. H), 7.10-7.40 (m, 10H, arom. H).

29.3 *1-(diphenylmethyl)-3-{4-[(1,1-dimethylethoxy)carbonyl]aminophenoxy}azetidine:*

Protection of the amine is carried out in a standard fashion with BocOBoc in the presence of triethylamine in dichloromethane. A white solid is obtained with a yield of 77%. Melting point: 149-151°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.40 (s, 9H, tBu), 2.90 (wide s, 2H, azetidine), 3.60 (wide s, 2H, azetidine), 4.50 (s, 1H, CH-(Ph)₂), 4.70 (m, 1H, CH-O), 6.70 (m, 2H, arom. H), 7.10-7.60 (m, 12H, arom. H), 9.10 (s, 1H, NH).

29.4 *3-{4-[(1,1-dimethylethoxy)carbonyl]aminophenoxy}azetidine:*

The experimental protocol used is the same as that described for intermediate 14.4 except for the hydrogenation catalyst which is replaced by Pd(OH)₂. A white solid is obtained with a yield of 78%. Melting point 184-186°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.50 (s, 9H, tBu), 3.50 (m, 2H, azetidine), 3.70 (m, 2H, azetidine), 4.90 (m, 1H, CH-O), 6.70 (m, 2H, arom. H), 7.30 (m, 2H, arom. H), 9.10 (s, 1H, NH).

29.5 1-*{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]amino}carbonyl*}-3-*{4-[(1,1-dimethylethoxy)carbonyl]aminophenoxy}azetidine*:

A solution of 0.6 g (2.7 mmol) of intermediate 10.2 in 10 ml of dichloromethane is added dropwise, over one hour, to a solution of 0.27 g (0.9 mmol) of triphosgene in 6 ml of dichloromethane. After agitation for 5 minutes at 23°C, a solution of 0.72 g (2.7 mmol) of intermediate 29.4 and 0.52 ml (3 mmol) of diisopropylethylamine in 6 ml of dichloromethane is added in one go. The reaction mixture is agitated for 2 hours at 23°C and finally evaporated to dryness under vacuum. The residue is diluted in 50 ml of ethyl acetate and this organic solution is washed twice with 25 ml of water followed by 25 ml of salt water. After drying over magnesium sulphate and filtration, the organic solution is concentrated under vacuum. The residue is purified on a silica column (eluant: heptane/ethyl acetate: 7/3). A white solid is obtained with a yield of 61%. Melting point: 224-226°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.35 (s, 18H, 2 tBu), 1.45 (s, 9H, tBu), 3.80 (m, 2H, azetidine), 4.30 (m, 2H, azetidine), 4.90 (m, 1H, CH-O), 6.60 (s, 1H, OH), 6.70 (m, 2H, arom. H), 7.20 (s, 2H, arom. H), 7.35 (m, 2H, arom. H), 8.20 (s, 1H, NH urea), 9.10 (s, 1H, NH).

29.6 1-*{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]amino}carbonyl*}-3-*(4-aminophenoxy)azetidine*:

The experimental protocol used is the same as that described for intermediate 26.3, intermediate 29.5 replacing intermediate 26.2. A white solid is obtained with a yield of 93%. Melting point: 225-227°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.30 (s, 18H, 2 tBu), 3.80 (m, 2H, azetidine), 4.30 (m, 2H, azetidine), 4.70 (wide s, 2H, NH₂), 4.85 (m, 1H, CH-O), 6.40-6.70 (m, 5H, arom. H + OH), 7.25 (s, 2H, arom. H), 8.20 (s, 1H, NH urea).

29.7 1-*{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]amino}carbonyl*}-3-*{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride (29)*:

The experimental protocol used is the same as that described for intermediate 4.3, intermediate 29.6 replacing intermediate 4.2. A white solid is obtained with a yield of 16%. Melting point: 235-240°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.30 (s, 18H, 2 tBu), 3.90 (m, 2H, azetidine), 4.40 (m, 2H, azetidine), 5.10 (m, 1H, CH-O), 6.60 (s, 1H, OH), 6.90-7.50 (m, 7H, arom. H), 8.20 (m, 2H, thiophene), 8.30 (s, 1H, NH urea), 8.80 (s, 1H, NH⁺), 9.80 (s, 1H, NH⁺), 11.50 (s, 1H, NH⁺). IR: ν_{C=O} (urea): 1660 cm⁻¹; ν_{C=N} (amidine): 1640 cm⁻¹.

Example 30: 1-*(2-hydroxy-5-methoxybenzoyl)*-3-*{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride (30)*:

30.1 *1-(2-hydroxy-5-methoxybenzoyl)-3-{4-[(1,1-dimethylethoxy)carbonyl]-aminophenoxy}azetidine:*

Condensation of 2-hydroxy 5-methoxybenzoic acid and intermediate 29.4 is carried out under the same experimental conditions as those described for intermediate 8.1. A white solid is obtained with a yield of 62%. Melting point: 152-153°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.50 (s, 9H, tBu), 3.70 (s, 3H, OCH₃), 4.00-4.80 (m, 4H, azetidine), 5.00 (m, 1H, CH-O), 6.70-6.90 (m, 5H, arom. H), 7.30 (m, 2H, arom. H), 9.1 (s, 1H, OH), 10.65 (s, 1H, NH).

30.2 *1-(2-hydroxy-5-methoxybenzoyl)-3-aminophenoxy-azetidine:*

The experimental protocol used is the same as that described for intermediate 26.3, intermediate 30.1 replacing intermediate 26.2. A yellow oil is obtained with a yield of 90%. NMR ¹H (DMSO d₆, 400 MHz, δ): 3.25 (wide s, 2H, NH₂), 3.80 (s, 3H, OCH₃), 4.20-4.90 (m, 4H, azetidine), 4.95 (m, 1H, CH-O), 6.60-7.00 (m, 7H, arom. H), 11.35 (wide s, 1H, OH).

30.3 *1-(2-hydroxy-5-methoxybenzoyl)-3-{4-[(imino(2-thienyl)methyl)-amino]phenoxy}azetidine hydrochloride (30):*

The experimental protocol used is the same as that described for intermediate 4.3, intermediate 30.2 replacing intermediate 4.2. A white powder is obtained with a yield of 44%. Melting point: 165-166°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 3.70 (s, 3H, OCH₃), 4.00-4.80 (m, 4H, azetidine), 5.15 (m, 1H, CH-O), 6.80-7.10 (m, 5H, arom. H), 7.40 (m, 3H, arom. H), 8.20 (m, 2H, thiophene), 8.75 (wide s, 1H, NH⁺), 9.80 (wide s, 1H, NH⁺), 10.60 (s, 1H, OH), 11.50 (wide s, 1H, NH⁺). IR: ν_{C=O} (amide): 1655 cm⁻¹; ν_{C=N} (amidine): 1612 cm⁻¹.

Example 31: 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-4-[4-[(imino(2-thienyl)methyl)amino]phenoxy]-piperidine hydrochloride (31):

31.1 *1,1-dimethylethyl 4-(4-nitrophenoxy)-1-piperidinecarboxylate:*

A solution of 2.01 g (10 mmoles) of N-Boc-4-hydroxypiperidine (prepared in a standard fashion starting from commercial 4-hydroxypiperidine) in 10 ml of dry THF is added dropwise to a solution of 1.23 g (11 mmoles) of tBuOK⁺ in 10 ml of dry THF in a three necked flask, under an inert atmosphere, cooled by an ice bath. After agitation for 30 minutes at 0°C, a solution of 1.06 ml (10 mmoles) of 4-fluoronitrobenzene in 10 ml of dry THF is added dropwise. The reaction mixture is agitated for 5 hours at 23°C and finally poured into 25 ml of a water + ice mixture. The product is extracted using 50 ml of ethyl acetate. After

decantation, the organic phase is washed twice with 25 ml of water and 25 ml of salt water. The organic solution is dried over magnesium sulphate, followed by filtration and concentration of the filtrate under vacuum to produce a residue which is purified on a silica column (eluant: heptane/ethyl acetate: 8/2). The pure fractions are collected and evaporated under vacuum. The expected product is obtained in the form of a pale yellow powder with a yield of 47%. Melting point: 97-98°C.

31.2 4-(4-nitrophenoxy)piperidine:

The experimental protocol used is the same as that described for intermediate 19.2, intermediate 31.1 replacing intermediate 19.1. A yellow oil is obtained with a yield of 87%.
10 NMR ¹H (CDCl₃, 100 MHz, δ): 1.58 (s, 1H, NH), 1.59-2.19 (m, 4H, CH₂-CH₂), 2.65-3.30 (m, 4H, CH₂-CH₂), 4.51 (m, 1H, CH-O), 6.98 (m, 2H, arom. H), 8.21 (m, 2H, arom. H).

31.3 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-4-(4-nitrophenyl)piperidine:

The experimental protocol used is the same as that described for intermediate 19.3, intermediate 31.2 replacing intermediate 19.2. A pale yellow powder is obtained with a crude yield of 83%. The product is sufficiently pure to be used directly in the following stage.

31.4 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-4-(4-aminophenyl)piperidine:

The experimental protocol used is similar to that described for intermediate 14.4, intermediate 31.3 replacing intermediate 14.3. The reaction is carried out in a dichloromethane/ethanol mixture (1/1). A white powder is obtained with a yield of 77%. Melting point: 153-154°C.
20 NMR ¹H (CDCl₃ + D₂O, 400 MHz, δ): 1.60-2.18 (m, 18H, CH₂ + Trolox), 2.52-2.81 (m, 2H, CH₂), 3.41-4.28 (m, 5H, 2 x CH₂ + CH-O), 6.63 (m, 2H, arom. H), 6.74 (m, 2H, arom. H).

31.5 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-4-[4-[(imino(2-thienyl)methyl)amino]phenoxy]piperidine hydrochloride (31):

The protocol used is the same as that described for intermediate 2.4, intermediate 31.4 replacing intermediate 2.3. The condensation reaction is carried out in 2-propanol only. After salification, the expected product is obtained in the form of a yellow powder with a yield of 25%. Melting point: decomposition from 170°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.50-2.10 (m, 18H, CH₂ + Trolox), 2.40-2.65 (m, 2H, CH₂), 3.13-4.37 (m, 4H, 2 x CH₂), 4.64 (m,
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1H, CH-O), 7.11 (m, 2H, arom. H), 7.35 (m, 2H, arom. H), 7.57 (s, 1H, arom. H), 8.17 (m, 2H, arom. H), 8.74 (wide s, 1H, NH⁺), 9.76 (wide s, 1H, NH⁺), 11.42 (wide s, 1H, NH⁺). IR: $\nu_{C=N}$ (amidine): 1611 cm⁻¹.

Example 32: 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-{4-[(imino(2-thienyl)methyl)amino]-phenoxy}azetidine hydrochloride (32):

32.1 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-{4-[(1,1-dimethylethoxy)carbonyl]aminophenoxy}azetidine:

The condensation of Trolox and intermediate 29.4 is carried out under the same experimental conditions as those described for intermediate 8.1. A white solid is obtained with a yield of 98%. Melting point: 182-183°C. NMR ¹H (CDCl₃, 400 MHz, δ): 1.50 (s, 9H, tBu), 1.60-2.60 (m, 16H, Trolox), 3.90-4.90 (m, 5H, azetidine), 6.40 (s, 1H, OH), 6.65 (m, 2H, arom. H), 7.20-7.30 (m, 3H, arom. H + NH).

32.2 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-aminophenoxy-azetidine:

The experimental protocol used is the same as that described for intermediate 26.3, intermediate 32.1 replacing intermediate 26.2. A white foam is obtained with a yield of 43%. NMR ¹H (CDCl₃, 400 MHz, δ): 1.60-2.60 (m, 16H, Trolox), 3.50 (wide s, 2H, NH₂), 3.90-4.90 (m, 5H, azetidine), 6.50-6.70 (m, 4H, arom. H).

32.3 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride (32):

The experimental protocol used is the same as that described for intermediate 4.3, intermediate 32.2 replacing intermediate 4.2. A white powder is obtained with a yield of 56%. Melting point: 190-195°C. NMR ¹H (DMSO d₆, 400 MHz, δ): 1.60-2.50 (m, 16H, Trolox), 3.60-5.00 (m, 5H, azetidine), 6.90 (m, 2H, arom. H), 7.30 (m, 3H, arom. H), 8.15 (m, 2H, thiophene), 8.80 (wide s, 1H, NH⁺), 9.80 (wide s, 1H, NH⁺), 11.50 (wide s, 1H, NH⁺). IR: $\nu_{C=O}$ (amide): 1647 cm⁻¹; $\nu_{C=N}$ (amidine): 1611 cm⁻¹.

Pharmacological study of the products of the invention

Study of the effects on neuronal constitutive NO synthase of a rat's cerebellum

The inhibitory activity of the products of the invention is determined by measuring their effects on the conversion by the NO synthase of the [³H]L-arginine to [³H]L-citrulline according to the modified method of Bredt and Snyder (*Proc. Natl. Acad. Sci. USA*, (1990) 87: 682-685). The cerebellums of Sprague-Dawley rats (300g - Charles River) are rapidly removed, dissected at 4°C and homogenized in a volume of extraction buffer (HEPES 50 mM, EDTA 1 mM, pH 7.4, pepstatin A 10 mg/ml, leupeptin 10 mg/ml). The homogenates are then centrifuged at 21000 g for 15 min at 4°C. Dosage is carried out in glass test tubes in which 100 µl of incubation buffer containing 100 mM of HEPES (pH 7.4), 2 mM of EDTA, 2.5 mM of CaCl₂, 2 mM of dithiotreitol, 2 mM of reduced NADPH and 10 µg/ml of calmodulin are distributed. 25 µl of a solution containing 100 nM of [³H]L-arginine (Specific activity: 56.4 Ci/mmol, Amersham) and 40 µM of non-radioactive L-arginine is added. The reaction is initiated by adding 50 µl of homogenate, the final volume being 200 µl (the missing 25 µl are either water or the tested product). After 15 min, the reaction is stopped with 2 ml of stopping buffer (20 mM of HEPES, pH 5.5, 2 mM of EDTA). After passing the samples through a 1 ml column of DOWEX resin, the radioactivity is quantified by a liquid scintillation spectrometer. The compounds of Examples 1, 6, 7 and 8 described above show an IC₅₀ lower than 3.5 µM. As for the compound of Example 3, it shows an IC₅₀ lower than 5 µM.

Study of the effects on lipidic peroxidation of the cerebral cortex of a rat

The inhibitory activity of the products of the invention is determined by measuring their effects on the degree of lipidic peroxidation, determined by the concentration of malondialdehyde (MDA). The MDA produced by peroxidation of unsaturated fatty acids is a good indication of lipidic peroxidation (H Esterbauer and KH Cheeseman, *Meth. Enzymol.* (1990) 186: 407-421). Male Sprague Dawley rats of 200 to 250 g (Charles River) were sacrificed 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 was centrifuged twice at 50000 g for 10 minutes at 4°C. The pellet is maintained at -80°C. On the day of the experiment, the pellet is replaced in suspension 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 lipidic 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 solvent (10 µl). The lipidic peroxidation reaction is initiated by adding 50 µl of FeCl₂ at 1 mM, EDTA at 1 mM and ascorbic acid at 4 mM. After 30 minutes of incubation at 37°C, the reaction is stopped by adding 50 µl of a solution of hydroxylated di-tertio-butyl 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 µl 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. (Caldwell et al. *European J. Pharmacol.* (1995) **285**, 203-206). The compounds of Examples 3, 11, 12, 13, 14 and 15 described above all show an IC₅₀ lower than 30 µM.

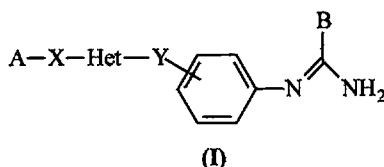
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CLAIMS

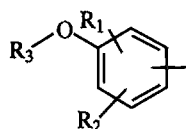


1. Product characterized in that it corresponds to general formula (I)



in which:

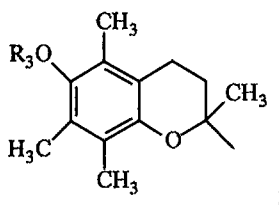
5 A is an aromatic corresponding to the structures:



in which R₁ and R₂ represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,

10 R₃ represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a -COR₄ radical, R₄ representing an alkyl radical having from 1 to 6 carbon atoms,

or



15 B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl radical having from 1 to 6 carbon atoms; an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

20 X represents -CO-N(R₃)-X'-, -NH-CO-X'-, -CH=, -CO- or a bond,
X' representing -(CH₂)_n- with n an integer from 0 to 6;

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Y represents $-Y'$ -, $-\text{CO}-\text{NH}-Y'$ -, $-Y'-\text{NH}-\text{CO}-$, $-\text{CO}-Y'$ -, $-Y'-\text{CO}-$, $-\text{N}(\text{R}_3)-Y'$ -, $-Y'-\text{N}(\text{R}_3)-$, $Y'-\text{CH}_2-\text{N}(\text{R}_3)-\text{CO}-$, $-\text{O}-Y'$ -, $-Y'-\text{O}-$, $-\text{S}-Y'$ -, $-Y'-\text{S}-$, $-Y'-\text{O}-Y'$ -, $-Y'-\text{N}(\text{R}_3)-Y'$ - or a bond, Y' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

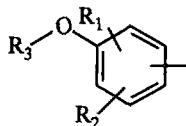
Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-\text{OR}_3$, $X'-\text{NR}_3$, $X'-\text{S}-\text{R}_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxole-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

it being understood that when A represents a hydrogen atom, Het does not represent a piperidine, pyrrolidine or morpholine radical.

2. Product according to claim 1, characterized in that:

A is an aromatic corresponding to the structure:



in which:

R_1 and R_2 represent, independently a linear or branched alkyl radical having from 1 to 6 carbon atoms or a linear or branched alkoxy radical having from 1 to 6 carbon atoms, R_3 represents a hydrogen atom or a linear or branched alkyl radical having from 1 to 6 carbon atoms;

B represents a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-\text{NH}-\text{CO}-X'$ -, $-\text{CH}=$, $-\text{CO}-$ or a bond,

X' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

Y represents $-Y'$ -, $-Y'-\text{NH}-\text{CO}-$, $-Y'-\text{CO}-$, $-Y'-\text{O}-$, $-Y'-\text{O}-Y'$ -, $-Y'-\text{N}(\text{R}_3)-Y'$ - or a bond, Y' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

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Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-OR_3$, $X'-NR_3$, $X'-S-R_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

it being understood that when A represents a hydrogen atom, Het does not represent a piperidine, pyrrolidine or morpholine radical.

3. Product according to claim 2. characterized in that B represents a thiophene ring, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen.

4. Product according to one of claims 1 to 3, characterized in that it is one of the following compounds:

- N-[4-(1H-imidazol-1-yl)phenyl]-2-thiophenecarboximidamide hydroiodide;
- 20 - N-[4-(3-thiazolidinylmethyl)phenyl]-2-thiophenecarboximidamide;
- N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate;
- N-[4-(1H-imidazol-1-yl methyl)phenyl]-2-thiophenecarboximidamide hydrochloride;
- N-[4-{2-(3-thiazolidinyl)ethyl}phenyl]-2-thiophenecarboximidamide;
- N-{4-[2-(1H-imidazol-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide hydroiodide;
- 25 - N-{4-[2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide fumarate;
- N-[4-(3-thiazolidinylcarbonylmethyl)phenyl]-2-thiophenecarboximidamide;
- N-(4-{[2-thiazolidinyl]carbonylaminomethyl}phenyl)-2-thiophenecarboximidamide fumarate;
- 30 - N-(3,5-di-t-butyl-4-hydroxyphenyl)-5-[4-{imino(2-thienyl)-methylamino}phenyl]-2-furan carboxamide hydroiodide;

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- 3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-[4-{imino(2-thienyl)-methylamino}phenyl]-2,5-imidazolidinedione hydrochloride;
- 2-(3,5-di-t-butyl-4-hydroxyphenyl)-3-[4-{imino(2-thienyl)-methylamino}phenyl]-4-thiazolidinone hydrochloride;
- 5 - 5-[(3,5-di-t-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-[4-{imino(2-thienyl)methylamino}phenyl]-2,4-imidazolidinedione fumarate;
- 2-(S)-4-(S)-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)-phenyl]-4-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-prolinamide hydrochloride;
- 5,6-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1-(2H)-pyridine carboxamide hydrochloride;
- 10 - N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-2-(R,S)-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-(R)-thiazolidine carboxamide fumarate;
- N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-thiazolecarboxamide hydroiodide
- 15 - N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine-2-(R)-carboxamide dihydrochloride
- methyl 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]-phenoxy}-pyrrolidine-2-(S)- carboxylate hydrochloride
- 20 - 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine hydrochloride
- 3-{[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)-carbonyl]amino}-1-{4-[(imino(2-thienyl)methyl)amino]phenyl}pyrrolidine
- 4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]- N-{4-[(imino(2-thienyl)methyl)amino]benzoyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride
- 25 - N-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1H-pyrrole-2-carboxamide hydroiodide
- 1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-3-{[4-[(imino(2-thienyl)methyl)amino]phenyl]carbonyl}-2-imidazolidinone hydroiodide

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- 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-5-isoxazoleacetamide hydroiodide
- 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-2-thiazolemethanamine hydrochloride
- 5 - 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride
- 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-{2-[4-[(imino(2-thienyl)methyl)amino]phenoxy]ethyl}isoxazole
- 1-{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]amino}-carbonyl}-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride
- 10 - 1-(2-hydroxy-5-methoxybenzoyl)-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride
- 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-4-[4-[(imino(2-thienyl)methyl)amino]phenoxy]-piperidine hydrochloride
- 15 - 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride

or their salts or enantiomers.

5. Product according to any one of claims 1 to 4, characterized in that it is one of the following compounds::

- 20 - N-[4-(1H-imidazol-1-yl)phenyl]-2-thiophenecarboximidamide hydroiodide;
- N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate;
- N-{4-[2-(1H-imidazol-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide hydroiodide;
- N-{4-[2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide fumarate;
- 25 - N-[4-(3-thiazolidinylcarbonylmethyl)phenyl]-2-thiophenecarboximidamide;
- 3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-[4-{imino(2-thienyl)-methylamino}phenyl]-2,5-imidazolidinedione hydrochloride;

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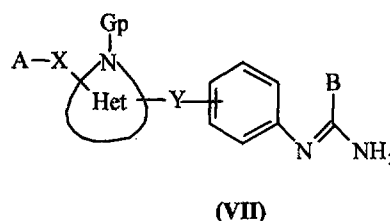
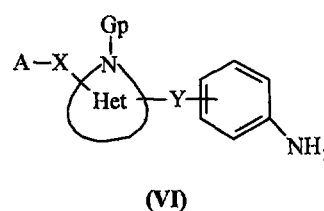
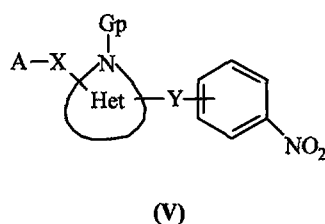
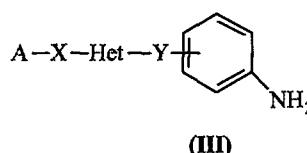
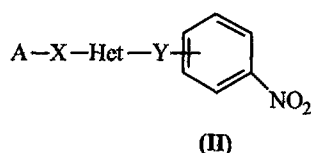


- 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-[4-{imino(2-thienyl)-methylamino}phenyl]-4-thiazolidinone hydrochloride;
- 5-[(3,5-di-*t*-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-[4-{imino(2-thienyl)methylamino}phenyl]-2,4-imidazolidinedione fumarate;
- 5 - 2-(*S*)-4-(*S*)-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)-phenyl]-4-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-prolinamide hydrochloride;
- 5,6-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1-(2H)-pyridine carboxamide hydrochloride;
- N-[4-hydroxy-3,5-bis-(1,1-dimethyl)ethyl -phenyl]-2-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-thiazole carboxamide hydrochloride;

or their salts or enantiomers.

6. Product according to any one of claims 1 to 5, characterized in that it is N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate or one of its salts.

7. As new industrial products, the compounds of general formula (II), (III), (V), (VI) and (VII)



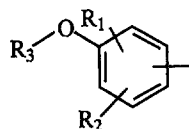
in which

A is an aromatic corresponding to structures :

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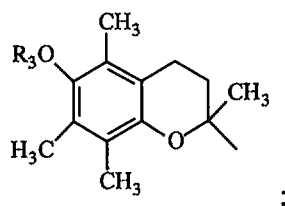
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in which:

- R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,
- R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-COR_4$ radical, R_4 representing an alkyl radical having from 1 to 6 carbon atoms,

or



- B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

- X represents $-CO-N(R_3)-X'-$, $-NH-CO-X'-$, $-CH=$, $-CO-$ or a bond,
 X' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

Y represents $-Y'-$, $-CO-NH-Y'-$, $-Y'-NH-CO-$, $-CO-Y'-$, $-Y'-CO$, $-N(R_3)-Y'-$, $-Y'-N(R_3)-$, $Y'-CH_2-N(R_3)-CO-$, $-O-Y'-$, $-Y'-O-$, $-S-Y'-$, $-Y'-S-$, $-Y'-O-Y'-$, $-Y'-N(R_3)-Y'-$ or a bond, Y' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

- Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-OR_3$, $X'-NR_3$, $X'-S-R_3$ and such as for example:

- oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

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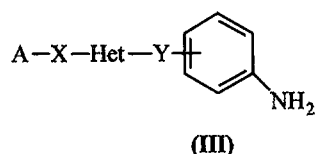
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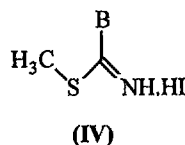


G_p represents a protective group of the amine function preferably cleavable in an anhydrous acid medium, such as for example the carbamates of t-butyl, trichloroethyl or trimethylsilylethyl or also the trityl group.

8. Preparation process for the compounds of general formula (I) according to claim 1,
5 characterized in that it consists of the condensation, preferably in a mixture of isopropanol and DMF and at ambient temperature, of the aniline derivatives of general formula (III)



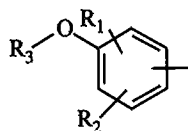
with the S-alkyl thioimide derivatives of general formula (IV)



- 10 in order to produce the final compounds of general formula (I),

the compounds of general formula (I), (III) and (IV) such that

A is an aromatic corresponding to structures :

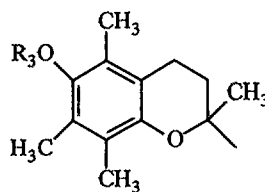


in which:

- 15 R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,
 R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-\text{COR}_4$ radical, R_4 representing an alkyl radical having from 1 to 6 carbon atoms,

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or



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B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-\text{CO}-\text{N}(\text{R}_3)-\text{X}'-$, $-\text{NH}-\text{CO}-\text{X}'-$, $-\text{CH}=\text{}$, $-\text{CO}-$ or a bond,
X' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

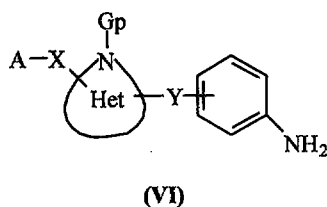
Y represents $-\text{Y}'-$, $-\text{CO}-\text{NH}-\text{Y}'$, $-\text{Y}'-\text{NH}-\text{CO}-$, $-\text{CO}-\text{Y}'-$, $-\text{Y}'-\text{CO}-$, $-\text{N}(\text{R}_3)-\text{Y}'-$, $-\text{Y}'-\text{N}(\text{R}_3)-$, $\text{Y}'-\text{CH}_2-\text{N}(\text{R}_3)-\text{CO}-$, $-\text{O}-\text{Y}'-$, $-\text{Y}'-\text{O}-$, $-\text{S}-\text{Y}'-$, $-\text{Y}'-\text{S}-$, $-\text{Y}'-\text{O}-\text{Y}'-$, $-\text{Y}'-\text{N}(\text{R}_3)-\text{Y}'-$ or a bond, Y' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $\text{X}'-\text{OR}_3$, $\text{X}'-\text{NR}_3$, $\text{X}'-\text{S}-\text{R}_3$ and such as for example:

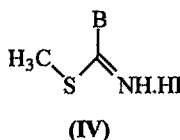
oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulfolane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

9. Preparation process for the compounds of general formula (I) according to claim 1 heterocycle Het of which contains at least one nitrogen atom, characterized in that it includes the following two stages:

- the condensation, preferably in an isopropanol and DMF mixture and at ambient temperature, of a compound of general formula (VI)



with a compound of general formula (IV)



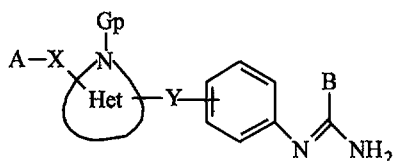
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in order to produce a compound of general formula (VII)

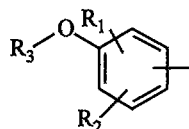


(VII)

- the cleavage of the protective group G_p of the compound of general formula (VII) defined above in order to obtain the compound of general formula (I),

5 the compounds of general formula (I), (IV), (VI) and (VII) being such that

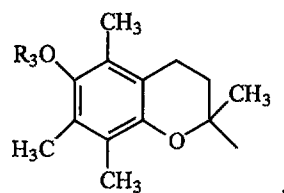
A is an aromatic corresponding to structures :



in which :

R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or
10 branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,
 R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-COR_4$ radical R_4 representing an alkyl radical having 1 to 6 carbon atoms,

or



15

B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are
20 optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-\text{CO}-\text{N}(\text{R}_3)-\text{X}'-$, $-\text{NH}-\text{CO}-\text{X}'-$, $-\text{CH}=\text{}$, $-\text{CO}-$ or a bond,
 X' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

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Y represents $-Y'-$, $-\text{CO}-\text{NH}-Y'-Y'-\text{NH}-\text{CO}-$, $-\text{CO}-Y'-$, $-Y'-\text{CO}-$, $-\text{N}(\text{R}_3)-Y'-$, $-Y'-\text{N}(\text{R}_3)-$, $Y'-\text{CH}_2-\text{N}(\text{R}_3)-\text{CO}-$, $-\text{O}-Y'-$, $-Y'-\text{O}-$, $-\text{S}-Y'-$, $-Y'-\text{S}-$, $-Y'-\text{O}-Y'-$, $-Y'-\text{N}(\text{R}_3)-Y'-$ or a bond, Y' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

5 Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-\text{OR}_3$, $X'-\text{NR}_3$, $X'-\text{S}-\text{R}_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, 10 thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

G_p represents a protective group of the amine function preferably cleavable in an anhydrous 15 acid medium, such as for example the carbamates of *t*-butyl, trichloroethyl or trimethylsilylthyl or also the trityl group.

10. As a medicament, a product of general formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt of this product.

20 11. Pharmaceutical composition containing as active ingredient at least one product according to claim 10.

12. Use of a product of general formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt of this product, to manufacture a medicament intended to inhibit NO synthase.

25 13. Use of a product of general formula (I) according to any one of claims 1 to 6, or or a pharmaceutically acceptable salt of this product, to manufacture a medicament intended to inhibit lipidic peroxidation.

14. Use of a product of general formula (I) according to any one of claims 1 to 6, or or a pharmaceutically acceptable salt of this product, to manufacture a medicament having both an activity on the inhibition of NO synthase and the inhibition of lipidic peroxidation.

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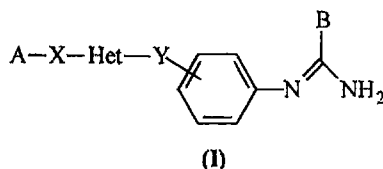
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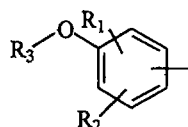
CLAIMS

1. Product characterized in that it corresponds to general formula (I)



in which:

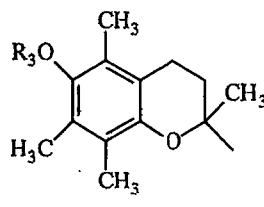
5 A is a an aromatic corresponding to the structures:



in which R₁ and R₂ represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,

10 R₃ represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a -COR₄ radical, R₄ representing an alkyl radical having from 1 to 6 carbon atoms,

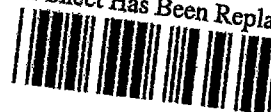
or



15 B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl radical having from 1 to 6 carbon atoms; an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

20 X represents -CO-N(R₃)-X'-, -NH-CO-X'-, -CH=, -CO- or a bond,
X' representing -(CH₂)_n- with n an integer from 0 to 6;

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Y represents $-Y'$ -, $-CO-NH-Y'$ -, $-Y'-NH-CO-$ -, $-CO-Y'$ -, $-Y'-CO-$ -, $-N(R_3)-Y'$ -, $-Y'-N(R_3)-$ -, $Y'-CH_2-N(R_3)-CO-$ -, $-O-Y'$ -, $-Y'-O-$ -, $-S-Y'$ -, $-Y'-S-$ -, $-Y'-O-Y'$ -, $-Y'-N(R_3)-Y'$ - or a bond, Y' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

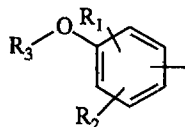
5 Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-OR_3$, $X'-NR_3$, $X'-S-R_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, 10 thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxole-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

15 it being understood that when A represents a hydrogen atom, Het does not represent a piperidine, pyrrolidine or morpholine radical.

2. Product according to claim 1, characterized in that:

A is an aromatic corresponding to the structure:



in which:

20 R_1 and R_2 represent, independently a linear or branched alkyl radical having from 1 to 6 carbon atoms or a linear or branched alkoxy radical having from 1 to 6 carbon atoms, R_3 represents a hydrogen atom or a linear or branched alkyl radical having from 1 to 6 carbon atoms;

25 B represents a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-NH-CO-X'$ -, $-CH=$ -, $-CO-$ or a bond,

X' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

30 Y represents $-Y'$ -, $-Y'-NH-CO-$ -, $-Y'-CO-$ -, $-Y'-O-$ -, $-Y'-O-Y'$ -, $-Y'-N(R_3)-Y'$ - or a bond, Y' representing $-(CH_2)_n-$ with n an integer from 0 to 6.

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Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-OR_3$, $X'-NR_3$, $X'-S-R_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene,
 5 sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione,
 oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline,
 thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-
 dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine,
 with the exception of the following heterocycles: piperazines, homopiperazines, 4-
 10 aminopiperidine;
 it being understood that when A represents a hydrogen atom, Het does not represent a
 piperidine, pyrrolidine or morpholine radical.

3. Product according to claim 2. characterized in that B represents a thiophene ring, the
 carbons of which are optionally substituted by one or more groups chosen from a linear or
 15 branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon
 atoms or a halogen.

4. Product according to one of claims 1 to 3, characterized in that it is one of the following
 compounds:

- N-[4-(1H-imidazol-1-yl)phenyl]-2-thiophenecarboximidamide hydroiodide;
- 20 - N-[4-(3-thiazolidinylmethyl)phenyl]-2-thiophenecarboximidamide;
- N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate;
- N-[4-(1H-imidazol-1-yl methyl)phenyl]-2-thiophenecarboximidamide hydrochloride;
- N-[4-{2-(3-thiazolidinyl)ethyl}phenyl]-2-thiophenecarboximidamide;
- N-{4-[2-(1H-imidazol-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide hydroiodide;
- 25 - N-{4-[2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide
 fumarate;
- N-[4-(3-thiazolidinylcarbonylmethyl)phenyl]-2-thiophenecarboximidamide;
- N-(4-{[2-thiazolidinyl]carbonylaminomethyl}phenyl)-2-thiophenecarboximidamide
 fumarate;
- 30 - N-(3,5-di-t-butyl-4-hydroxyphenyl)-5-[4-{imino(2-thienyl)-methylamino}phenyl]-2-furan
 carboxamide hydroiodide;

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- 3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-[4-{imino(2-thienyl)-methylamino}phenyl]-2,5-imidazolidinedione hydrochloride;
- 2-(3,5-di-t-butyl-4-hydroxyphenyl)-3-[4-{imino(2-thienyl)-methylamino}phenyl]-4-thiazolidinone hydrochloride;
- 5 - 5-[(3,5-di-t-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-[4-{imino(2-thienyl)methylamino}phenyl]-2,4-imidazolidinedione fumarate;
- 2-(S)-4-(S)-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)-phenyl]-4-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-prolinamide hydrochloride;
- 5,6-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1-(2H)-pyridine carboxamide hydrochloride;
- 10 - N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-2-(R,S)-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-(R)-thiazolidine carboxamide fumarate;
- N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-thiazolecarboxamide hydroiodide
- 15 - N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine-2-(R)-carboxamide dihydrochloride
- methyl 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2-H-[1]-benzopyran-2-yl)carbonyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]-phenoxy}-pyrrolidine-2-(S)- carboxylate hydrochloride
- 20 - 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine hydrochloride
- 3-{[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)-carbonyl]amino}-1-{4-[(imino(2-thienyl)methyl)amino]phenyl}pyrrolidine
- 4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]- N-{4-[(imino(2-thienyl)methyl)amino]benzoyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride
- 25 - N-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1H-pyrrole-2-carboxamide hydroiodide
- 1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-3-{[4-[(imino(2-thienyl)methyl)amino]phenyl]carbonyl}-2-imidazolidinone hydroiodide

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- 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-5-isoxazoleacetamide hydroiodide
- 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-2-thiazolemethanamine hydrochloride
- 5 - 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride
- 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-{2-{4-[(imino(2-thienyl)methyl)amino]phenoxy}ethyl}isoxazole
- 1-{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]amino}-carbonyl}-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride
- 10 - 1-(2-hydroxy-5-methoxybenzoyl)-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride
- 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-4-[4-[(imino(2-thienyl)methyl)amino]phenoxy]-piperidine hydrochloride
- 15 - 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride

or their salts or enantiomers.

5. Product according to any one of claims 1 to 4, characterized in that it is one of the following compounds::

- 20 - N-[4-(1H-imidazol-1-yl)phenyl]-2-thiophenecarboximidamide hydroiodide;
- N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate;
- N-{4-[2-(1H-imidazol-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide hydroiodide;
- N-{4-[2-(1,2,3,6-tetrahydropyridin-1-yl)ethyl]phenyl}-2-thiophenecarboximidamide fumarate;
- 25 - N-[4-(3-thiazolidinylcarbonylmethyl)phenyl]-2-thiophenecarboximidamide;
- 3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-[4-{imino(2-thienyl)-methylamino}phenyl]-2,5-imidazolidinedione hydrochloride;

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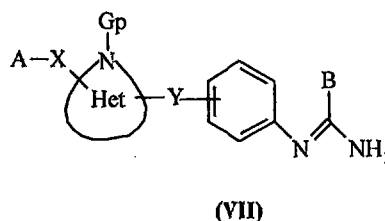
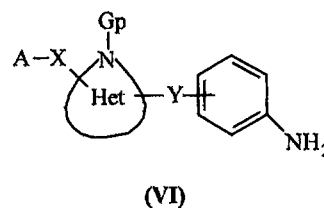
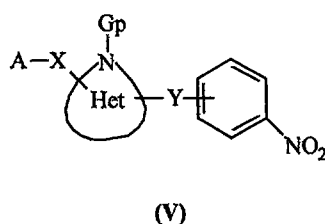
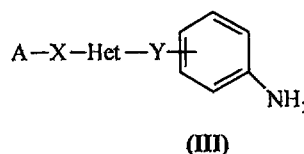
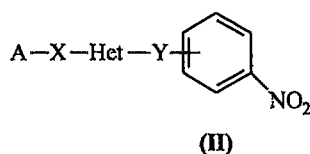


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- 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-[4-{imino(2-thienyl)-methylamino}phenyl]-4-thiazolidinone hydrochloride;
 - 5-[(3,5-di-*t*-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-[4-{imino(2-thienyl)methylamino}phenyl]-2,4-imidazolidinedione fumarate;
 - 5 - 2-(*S*)-4-(*S*)-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)-phenyl]-4-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-prolinamide hydrochloride;
 - 5,6-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1-(2H)-pyridine carboxamide hydrochloride;
 - N-[4-hydroxy-3,5-bis-(1,1-dimethyl)ethyl -phenyl]-2-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-thiazole carboxamide hydrochloride;
- 10 or their salts or enantiomers.
6. Product according to any one of claims 1 to 5, characterized in that it is N-[4-(1,2,3,6-tetrahydropyridin-1-yl)phenyl]-2-thiophenecarboximidamide fumarate or one of its salts.
7. As new industrial products, the compounds of general formula (II), (III), (V), (VI) and (VII)
- 15



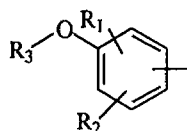
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in which

A is an aromatic corresponding to structures :

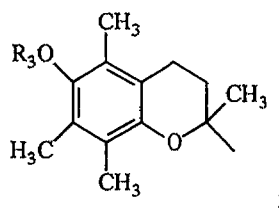
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in which:

- R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,
- 5 R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-COR_4$ radical, R_4 representing an alkyl radical having from 1 to 6 carbon atoms,

or



- 10 B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

- 15 X represents $-\text{CO}-\text{N}(\text{R}_3)-\text{X}'-$, $-\text{NH}-\text{CO}-\text{X}'-$, $-\text{CH}=\text{}$, $-\text{CO}-$ or a bond,
 X' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

Y represents $-\text{Y}'-$, $-\text{CO}-\text{NH}-\text{Y}'$, $-\text{Y}'-\text{NH}-\text{CO}-$, $-\text{CO}-\text{Y}'$, $-\text{Y}'-\text{CO}-$, $-\text{N}(\text{R}_3)-\text{Y}'$, $-\text{Y}'-\text{N}(\text{R}_3)-$, $\text{Y}'-\text{CH}_2-\text{N}(\text{R}_3)-\text{CO}-$, $-\text{O}-\text{Y}'$, $-\text{Y}'-\text{O}-$, $-\text{S}-\text{Y}'$, $-\text{Y}'-\text{S}-$, $-\text{Y}'-\text{O}-\text{Y}'$, $-\text{Y}'-\text{N}(\text{R}_3)-\text{Y}'$ or a bond, Y' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

- 20 Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $\text{X}'\text{-OR}_3$, $\text{X}'\text{-NR}_3$, $\text{X}'\text{-SR}_3$ and such as for example:

- oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione,
- 25 oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

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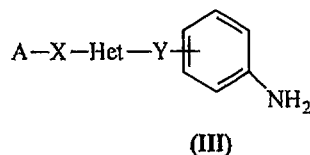


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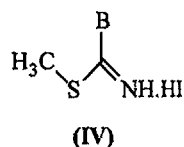


G_p represents a protective group of the amine function preferably cleavable in an anhydrous acid medium, such as for example the carbamates of t-butyl, trichloroethyl or trimethylsilylethyl or also the trityl group.

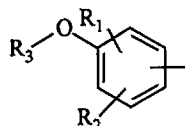
8. Preparation process for the compounds of general formula (I) according to claim 1, characterized in that it consists of the condensation, preferably in a mixture of isopropanol and DMF and at ambient temperature, of the aniline derivatives of general formula (III)



with the S-alkyl thioimide derivatives of general formula (IV)



- 10 in order to produce the final compounds of general formula (I), the compounds of general formula (I), (III) and (IV) such that A is an aromatic corresponding to structures :

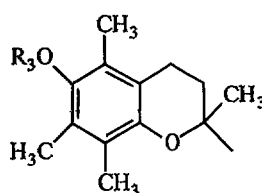


in which:

- 15 R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms, R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-\text{COR}_4$ radical, R_4 representing an alkyl radical having from 1 to 6 carbon atoms,

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or



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B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-\text{CO}-\text{N}(\text{R}_3)-\text{X}'-$, $-\text{NH}-\text{CO}-\text{X}'-$, $-\text{CH}=\text{}$, $-\text{CO}-$ or a bond,

X' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

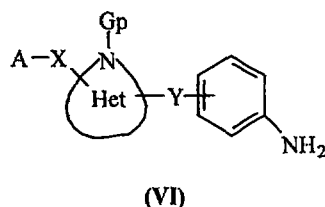
Y represents $-\text{Y}'-$, $-\text{CO}-\text{NH}-\text{Y}'$, $-\text{Y}'-\text{NH}-\text{CO}-$, $-\text{CO}-\text{Y}'-$, $-\text{Y}'-\text{CO}-$, $-\text{N}(\text{R}_3)-\text{Y}'-$, $-\text{Y}'-\text{N}(\text{R}_3)-$, $\text{Y}'-\text{CH}_2-\text{N}(\text{R}_3)-\text{CO}-$, $-\text{O}-\text{Y}'-$, $-\text{Y}'-\text{O}-$, $-\text{S}-\text{Y}'-$, $-\text{Y}'-\text{S}-$, $-\text{Y}'-\text{O}-\text{Y}'-$, $-\text{Y}'-\text{N}(\text{R}_3)-\text{Y}'-$ or a bond, Y' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $\text{X}'\text{-OR}_3$, $\text{X}'\text{-NR}_3$, $\text{X}'\text{-S-R}_3$ and such as for example:

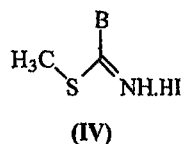
oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

9. Preparation process for the compounds of general formula (I) according to claim 1 heterocycle Het of which contains at least one nitrogen atom, characterized in that it includes the following two stages:

- the condensation, preferably in an isopropanol and DMF mixture and at ambient temperature, of a compound of general formula (VI)



with a compound of general formula (IV)



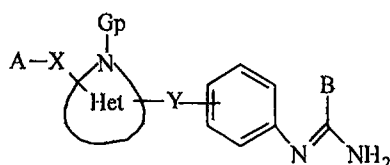
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in order to produce a compound of general formula (VII)

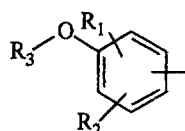


(VII)

- the cleavage of the protective group G_p of the compound of general formula (VII) defined above in order to obtain the compound of general formula (I),

5 the compounds of general formula (I), (IV), (VI) and (VII) being such that

A is an aromatic corresponding to structures :

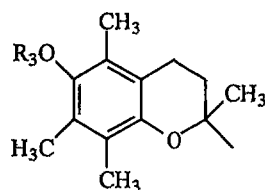


in which :

R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or
10 branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,

R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-COR_4$ radical R_4 representing an alkyl radical having 1 to 6 carbon atoms,

or



15

B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having
20 from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-\text{CO}-\text{N}(\text{R}_3)-\text{X}'-$, $-\text{NH}-\text{CO}-\text{X}'-$, $-\text{CH}=\text{}$, $-\text{CO}-$ or a bond,

X' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

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Y represents $-Y'-$, $-CO-NH-Y'$, $-Y'-NH-CO-$, $-CO-Y'-$, $-Y'-CO-$, $-N(R_3)-Y'-$, $-Y'-N(R_3)-$, $Y'-CH_2-N(R_3)-CO-$, $-O-Y'-$, $-Y'-O-$, $-S-Y'-$, $-Y'-S-$, $-Y'-O-Y'-$, $-Y'-N(R_3)-Y'-$ or a bond, Y' representing $-(CH_2)_n-$ with n an integer from 0 to 6;

5 Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-OR_3$, $X'-NR_3$, $X'-S-R_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, 10 thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

G_p represents a protective group of the amine function preferably cleavable in an anhydrous 15 acid medium, such as for example the carbamates of t-butyl, trichloroethyl or trimethylsilylthyl or also the trityl group.

10. As a medicament, a product of general formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt of this product.

11. Pharmaceutical composition containing as active ingredient at least one product according 20 to claim 10.

12. Use of a product of general formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt of this product, to manufacture a medicament intended to inhibit NO synthase.

13. Use of a product of general formula (I) according to any one of claims 1 to 6, or or a 25 pharmaceutically acceptable salt of this product, to manufacture a medicament intended to inhibit lipidic peroxidation.

14. Use of a product of general formula (I) according to any one of claims 1 to 6, or or a pharmaceutically acceptable salt of this product, to manufacture a medicament having both an activity on the inhibition of NO synthase and the inhibition of lipidic peroxidation.

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Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-OR_3$, $X'-NR_3$, $X'-S-R_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

it being understood that when A represents a hydrogen atom, Het does not represent a piperidine, pyrrolidine or morpholine radical.

3. Product according to claim 2. characterized in that B represents a thiophene ring, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen.

4. Product according to one of claims 1 to 3, characterized in that it is one of the following compounds:

- N-(3,5-di-*t*-butyl-4-hydroxyphenyl)-5-[4-{imino(2-thienyl)-methylamino}phenyl]-2-furan carboxamide hydroiodide;
- 3-(3,5-di-*t*-butyl-4-hydroxyphenyl)-1-[4-{imino(2-thienyl)-methylamino}phenyl]-2,5-imidazolidinedione hydrochloride;
- 2-(3,5-di-*t*-butyl-4-hydroxyphenyl)-3-[4-{imino(2-thienyl)-methylamino}phenyl]-4-thiazolidinone hydrochloride;
- 5-[(3,5-di-*t*-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-[4-{imino(2-thienyl)methylamino}phenyl]-2,4-imidazolidinedione fumarate;
- 2-(*S*)-4-(*S*)-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)-phenyl]-4-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-prolinamide hydrochloride;
- N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)phenyl]-2-(*R,S*)-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-(*R*)-thiazolidine carboxamide fumarate;
- N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-thiazolecarboxamide hydroiodide;
- N-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4-(*S*)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine-2-(*R*)-carboxamide dihydrochloride

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- methyl 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2-H-[1]-benzopyran-2-yl)carbonyl]-4-(S)-{4-[(imino(2-thienyl)methyl)amino]-phenoxy}-pyrrolidine-2-(S)-carboxylate hydrochloride;
- 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-(S)-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-pyrrolidine hydrochloride;
- 3-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)-carbonyl]amino}-1-{4-[(imino(2-thienyl)methyl)amino]phenyl}pyrrolidine;
- 4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]benzoyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride;
- N-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-1-{4-[(imino(2-thienyl)methyl)amino]phenyl}-1H-pyrrole-2-carboxamide hydroiodide;
- 1-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-3-{[4-[(imino(2-thienyl)methyl)amino]phenyl]carbonyl}-2-imidazolidinone hydroiodide;
- 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-5-isoxazoleacetamide hydroiodide;
- 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-2-thiazolemethanamine hydrochloride;
- 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-{4-[(imino(2-thienyl)methyl)amino]phenyl}-N-methyl-1H-imidazole-2-methanamine hydrochloride;
- 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-{2-[4-[(imino(2-thienyl)methyl)amino]phenoxy]ethyl}isoxazole;
- 1-{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]amino}-carbonyl}-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride;
- 1-(2-hydroxy-5-methoxybenzoyl)-3-{4-[(imino(2-thienyl)methyl)amino]phenoxy}azetidine hydrochloride;
- 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-4-[4-[(imino(2-thienyl)methyl)amino]phenoxy]-piperidine hydrochloride;
- 1-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-[1]-benzopyran-2-yl)carbonyl]-3-{4-[(imino(2-thienyl)methyl)amino]-phenoxy}azetidine hydrochloride;

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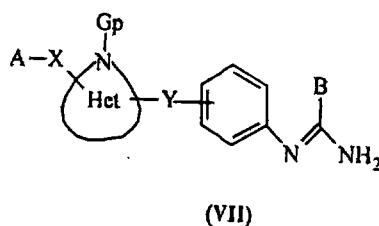
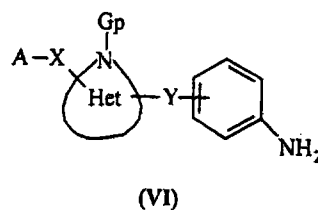
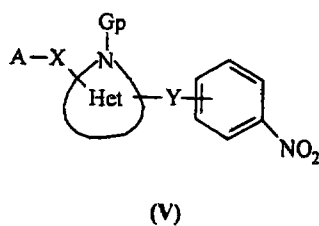
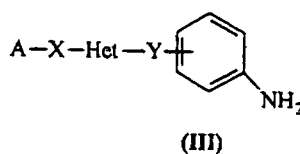
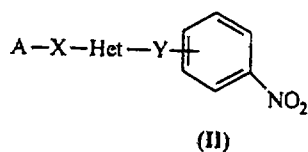
or their salts or enantiomers.

5. Product according to any one of claims 1 to 4, characterized in that it is one of the following compounds::

- 3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-[4-{imino(2-thienyl)-methylamino}phenyl]-2,5-imidazolidinedione hydrochloride;
- 2-(3,5-di-t-butyl-4-hydroxyphenyl)-3-[4-{imino(2-thienyl)-methylamino}phenyl]-4-thiazolidinone hydrochloride;
- 5-[(3,5-di-t-butyl-4-hydroxyphenyl)methylene]-1-methyl-3-[4-{imino(2-thienyl)methylamino}phenyl]-2,4-imidazolidinedione fumarate;
- 2-(*S*)-4-(*S*)-N-[4-hydroxy-3,5-bis-(1,1-dimethylethyl)-phenyl]-4-{4-[(imino(2-thienyl)methyl)amino]phenoxy}-prolinamide hydrochloride;
- N-[4-hydroxy-3,5-bis-(1,1-dimethyl)ethyl -phenyl]-2-{4-[(imino(2-thienyl)methyl)amino]phenyl}-4-thiazole carboxamide hydrochloride;

or their salts or enantiomers.

6. As new industrial products, the compounds of general formula (II), (III), (V), (VI) and (VII)

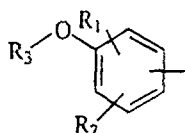


in which

A is an aromatic corresponding to structures :

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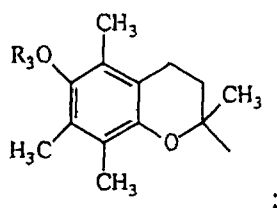


in which:

R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,

R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-COR_4$ radical, R_4 representing an alkyl radical having from 1 to 6 carbon atoms,

or



B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-\text{CO}-\text{N}(\text{R}_3)-\text{X}'-$, $-\text{NH}-\text{CO}-\text{X}'-$, $-\text{CH}=\text{}$, $-\text{CO}-$ or a bond,

X' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

Y represents $-\text{Y}'-$, $-\text{CO}-\text{NH}-\text{Y}'-$, $-\text{Y}'-\text{NH}-\text{CO}-$, $-\text{CO}-\text{Y}'-$, $-\text{Y}'-\text{CO}-$, $-\text{N}(\text{R}_3)-\text{Y}'-$, $-\text{Y}'-\text{N}(\text{R}_3)-$, $\text{Y}'-\text{CH}_2-\text{N}(\text{R}_3)-\text{CO}-$, $-\text{O}-\text{Y}'-$, $-\text{Y}'-\text{O}-$, $-\text{S}-\text{Y}'-$, $-\text{Y}'-\text{S}-$, $-\text{Y}'-\text{O}-\text{Y}'-$, $-\text{Y}'-\text{N}(\text{R}_3)-\text{Y}'-$ or a bond, Y' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $\text{X}'\text{-OR}_3$, $\text{X}'\text{-NR}_3$, $\text{X}'\text{-S-R}_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

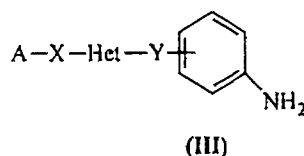
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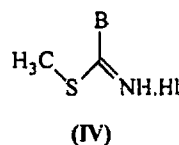


G_p represents a protective group of the amine function preferably cleavable in an anhydrous acid medium, such as for example the carbamates of t-butyl, trichloroethyl or trimethylsilylethyl or also the trityl group.

7. Preparation process for the compounds of general formula (I) according to claim 1, characterized in that it consists of the condensation, preferably in a mixture of isopropanol and DMF and at ambient temperature, of the aniline derivatives of general formula (III)



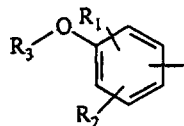
with the S-alkyl thioimide derivatives of general formula (IV)



in order to produce the final compounds of general formula (I),

the compounds of general formula (I), (III) and (IV) such that

A is an aromatic corresponding to structures :

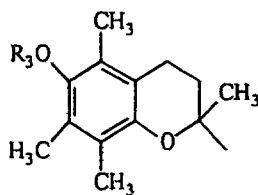


in which:

R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,

R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-\text{COR}_4$ radical, R_4 representing an alkyl radical having from 1 to 6 carbon atoms,

or



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B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-\text{CO}-\text{N}(\text{R}_3)-\text{X}'-$, $-\text{NH}-\text{CO}-\text{X}'-$, $-\text{CH}=\text{}$, $-\text{CO}-$ or a bond,

X' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

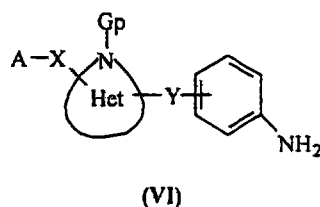
Y represents $-\text{Y}'-$, $-\text{CO}-\text{NH}-\text{Y}'$, $-\text{Y}'-\text{NH}-\text{CO}-$, $-\text{CO}-\text{Y}'-$, $-\text{Y}'-\text{CO}-$, $-\text{N}(\text{R}_3)-\text{Y}'-$, $-\text{Y}'-\text{N}(\text{R}_3)-$, $\text{Y}'-\text{CH}_2-\text{N}(\text{R}_3)-\text{CO}-$, $-\text{O}-\text{Y}'-$, $-\text{Y}'-\text{O}-$, $-\text{S}-\text{Y}'-$, $-\text{Y}'-\text{S}-$, $-\text{Y}'-\text{O}-\text{Y}'-$, $-\text{Y}'-\text{N}(\text{R}_3)-\text{Y}'-$ or a bond, Y' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $\text{X}'-\text{OR}_3$, $\text{X}'-\text{NR}_3$, $\text{X}'-\text{S}-\text{R}_3$ and such as for example:

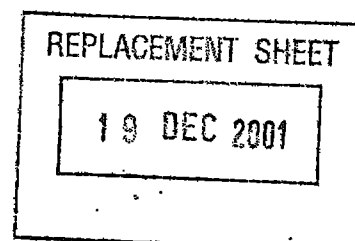
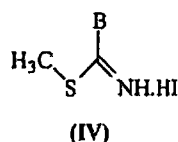
oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

8. Preparation process for the compounds of general formula (I) according to claim 1 heterocycle Het of which contains at least one nitrogen atom, characterized in that it includes the following two stages:

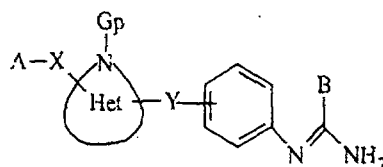
- the condensation, preferably in an isopropanol and DMF mixture and at ambient temperature, of a compound of general formula (VI)



with a compound of general formula (IV)



in order to produce a compound of general formula (VII)

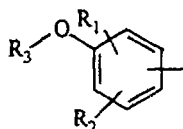


(VII)

- the cleavage of the protective group G_p of the compound of general formula (VII) defined above in order to obtain the compound of general formula (I),

the compounds of general formula (I), (IV), (VI) and (VII) being such that

A is an aromatic corresponding to structures :

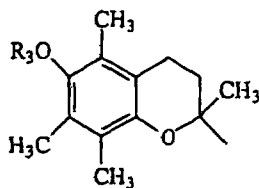


in which :

R_1 and R_2 represent, independently, a hydrogen atom, a halogen, the OH group, a linear or branched alkyl radical having from 1 to 6 carbon atoms, a linear or branched alkoxy radical having from 1 to 6 carbon atoms,

R_3 represents a hydrogen atom, a linear or branched alkyl radical having from 1 to 6 carbon atoms or a $-COR_4$ radical R_4 representing an alkyl radical having 1 to 6 carbon atoms,

or



B represents a linear or branched alkyl radical having from 1 to 6 carbon atoms, phenyl, pyridinyl or a heterocycle with 5 members containing from 1 to 4 heteroatoms chosen from O, S, N and more particularly: thiophene, furan, pyrrole or thiazole, the carbons of which are optionally substituted by one or more groups chosen from a linear or branched alkyl having from 1 to 6 carbon atoms, an alkoxy radical having from 1 to 6 carbon atoms or a halogen;

X represents $-\text{CO}-\text{N}(\text{R}_3)-\text{X}'-$, $-\text{NH}-\text{CO}-\text{X}'-$, $-\text{CH}=\text{}$, $-\text{CO}-$ or a bond,
 X' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

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Y represents $-Y'-$, $-\text{CO}-\text{NH}-Y'$, $-Y'-\text{NH}-\text{CO}-$, $-\text{CO}-Y'-$, $-Y'-\text{CO}-$, $-\text{N}(\text{R}_3)-Y'-$, $-Y'-\text{N}(\text{R}_3)-$, $Y'-\text{CH}_2-\text{N}(\text{R}_3)-\text{CO}-$, $-\text{O}-Y'-$, $-Y'-\text{O}-$, $-\text{S}-Y'-$, $-Y'-\text{S}-$, $-Y'-\text{O}-Y'-$, $-Y'-\text{N}(\text{R}_3)-Y'-$ or a bond. Y' representing $-(\text{CH}_2)_n-$ with n an integer from 0 to 6;

Het represents a heterocycle containing from 1 to 5 heteroatoms chosen from O, N, S which can be substituted by one or more substituents $X'-\text{OR}_3$, $X'-\text{NR}_3$, $X'-\text{S}-\text{R}_3$ and such as for example:

oxetane, pyrrole, pyrrolidine, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, sulpholane, imidazole, imidazoline, dihydroimidazole-2-one, dihydroimidazole-2-thione, oxazole, isoxazole, oxazoline, isoxazoline, oxazolidine, oxazolidinone, thiazole, thiazoline, thiazolidine, thiazolidinone, hydantoin, 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,1-dioxide-1,2,5-thiadiazolidine, 1,2,4-triazole-3-one, tetrazole, tetrahydropyridine, azetidine, with the exception of the following heterocycles: piperazines, homopiperazines, 4-aminopiperidine;

G_p represents a protective group of the amine function preferably cleavable in an anhydrous acid medium, such as for example the carbamates of *t*-butyl, trichloroethyl or trimethylsilylthyl or also the trityl group.

9. As a medicament, a product of general formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt of this product.

10. Pharmaceutical composition containing as active ingredient at least one product according to claim 10.

11. Use of a product of general formula (I) according to any one of claims 1 to 6, or a pharmaceutically acceptable salt of this product, to manufacture a medicament intended to inhibit NO synthase.

12. Use of a product of general formula (I) according to any one of claims 1 to 6, or or a pharmaceutically acceptable salt of this product, to manufacture a medicament intended to inhibit lipidic peroxidation.

13. Use of a product of general formula (I) according to any one of claims 1 to 6, or or a pharmaceutically acceptable salt of this product, to manufacture a medicament having both an activity on the inhibition of NO synthase and the inhibition of lipidic peroxidation.

