Abstract: This invention provides compounds having the structural formula: wherein: \( R_1 \) is an acyl or sulfonyl group, \( - R_2 \) is an acyl group selected from the group consisting of acyl groups derived from cycloaliphatic, aromatic or heterocyclic monocarboxylic acids, imidazolycarbonyl and triazolylcarbonyl, and \( - R_3 \) is hydrogen or an amino-protecting group, a stereoisomer thereof, a solvate thereof, or a salt thereof, being useful as anti-inflammatory agents.
SYNEPHRINE DERIVATIVES USEFUL AS ANTI-INFLAMMATORY AGENTS

Field of the invention

The present invention relates to novel synephrine derivatives being useful for treating or preventing inflammatory diseases or disorders. The present invention also relates to a method for preparing such compounds, as well as to pharmaceutical compositions comprising a therapeutically effective amount of such compounds.

Background of the invention

Synthetic glucocorticoids remain among the most effective agents for the treatment of chronic inflammatory diseases. However, major side effects severely limit their therapeutic use. Physiologic and therapeutic activities of glucocorticoids are mediated by a nuclear receptor belonging to a family of ligand-inducible transcription factors that, in addition to directly regulating their cognate gene programs, can also interfere with other signalling pathways, such as those using NF-κB.

NF-κB is an inducible transcription factor complex which regulates the expression of various genes involved in inflammatory and immune responses. It is activated upon exposure of cells to, among others, pro-inflammatory cytokines (such as TNF or IL-1), oxidants (such as hydrogen peroxide, ozone, superoxide anions), bacterial compounds, viral products, PKC activators (such as phorbol esters and platelet activating factor) and UV- or gamma-irradiation. NF-κB is therefore a promising target for anti-inflammatory and immuno-suppressive therapies. Inhibition of NF-κB activity by glucocorticoids has been well documented, although gene stimulatory effects by glucocorticoids have also been observed. Although glucocorticoids remain among the most potent immuno-suppressive and anti-inflammatory drugs currently available, and are especially effective in the treatment of chronic asthma or rheumatoid arthritis, side effects such as hypothalamic-pituitary-adrenal axis insufficiency, diabetes, altered lipid metabolism, steroid myopathy, osteoporosis, and infectious or neuro-psychiatric complications significantly limit the therapeutic use of classical glucocorticoid agonists in a significant number of patients,
especially patients having a predisposition to one or more of the above-stated disorders.

WO 01/45693 discloses 2-(4-acetoxyphenyl)-2-chloro-N-methylethylammonium chloride as an anti-inflammatory agent.

Therefore there is a regular need in the art for novel compounds having significant and specific anti-inflammatory properties without having the side-effects of known effective anti-inflammatory agents such as glucocorticoids. There is a regular need in the art for effective anti-inflammatory agents having improved metabolism and/or pharmacokinetic behaviour and which therefore can be more easily formulated into effective dosage forms. There is also a need in the art for such novel compounds which can be easily produced in good yield and purity from commercially available materials through a limited number of fully reproducible synthetic process steps.

Summary of the invention

The present invention relates to the unexpected finding that certain synephrine derivatives having a specific substitution pattern are able to display specific anti-inflammatory activity. In accordance with some embodiments of the present invention this anti-inflammatory activity can be similar in extent as glucocorticoids. An advantage of embodiments of the present invention is that this anti-inflammatory activity can be without having the significant side effects of glucocorticoids and other known anti-inflammatory agents. These derivatives can be easily produced in good yield and purity from synephrine through a limited number of fully reproducible synthetic process steps.

The present invention therefore also relates to pharmaceutical compositions comprising a therapeutic effective amount of such synephrine derivatives, and optionally one or more pharmaceutically acceptable carriers. The present invention also relates to the use of such synephrine derivatives for making a medicament for treating or preventing anti-inflammatory disorders (in particular chronic inflammatory diseases). The present invention also includes a method of reduction or prevention or treatment of anti-inflammatory disorders (in particular chronic inflammatory diseases) by the
administration of synephrine derivatives to a patient in need thereof, optionally in combination with one or more other drugs such as, but not limited to, other anti-inflammatory agents. In particular, this invention relates to such combinations having synergistic activity.

5 Brief description of the drawings

Figures 1A and 1B show the performance of a representative compound of the present invention in an anti-inflammatory assay with comparison to reference compounds known in the art. Figure 1A shows the anti-inflammatory activity of dexamethasone and of compound A. Figure 1B shows the anti-inflammatory effect of 1-[(4-(benzoyloxy)phenyl)-2-[(terf-butoxycarbonyl)-methylamino]ethyl-1 H-imidazole-1-carboxylate.

Figure 2 shows, according to an embodiment of the invention, the anti-inflammatory activity of 1-[(4-(naphthoyloxy)phenyl)-2-[(terf-butoxycarbonyl)-methylamino]ethyl-1 H-imidazole-1-carboxylate.

Figure 3 shows, according to an embodiment of the invention, the anti-inflammatory activity of 1-[(4-(isobutanoyloxy)phenyl)-2-[(terf-butoxycarbonyl)-methylamino]ethyl-1 H-imidazole-1-carboxylate.

Definitions

As used herein, and unless otherwise stated, the term "C_{i-7} alkyl" means straight and branched chain saturated acyclic hydrocarbon monovalent groups having from 1 to 7 carbon atoms such as, for example, methyl, ethyl, propyl, n-butyl, 1-methylethyl (isopropyl), 2-methylpropyl (isobutyl), 1,1-dimethylethyl (ter-butyl), 2-methylbutyl, n-pentyl, dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, n-heptyl and the like; said C_{i-7} alkyl group may further optionally include one or more suitable substituents independently selected from the group consisting of amino, halogen, hydroxy, sulphydryl, trifluoromethyl, methoxy and the like.

As used herein, and unless otherwise stated, the term "C-2-io alkyl" means straight and branched chain saturated acyclic hydrocarbon monovalent groups having from 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, such as but not limited to ethyl, propyl, n-butyl, 1-methylethyl (isopropyl), 2-methylpropyl
(isobutyl), 1,1-dimethylethyl (ferf-butyl), 2-methylbutyl, n-pentyl, dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl and the like; said C_2-i_0 alkyl group may further optionally include one or more suitable substituents independently selected from the group consisting of amino, halogen, hydroxy, sulfhydryl, trifluoromethyl, methoxy and the like.

As used herein, and unless otherwise stated, the terms "cycloaliphatic" and "C_3-i_0 cycloalkyl" refer to a mono- or polycyclic saturated hydrocarbon monovalent group having from 3 to 10 carbon atoms, such as for instance cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like, or a C_7-i_0 polycyclic saturated hydrocarbon monovalent group having from 7 to 10 carbon atoms such as, for instance, norbornyl, fenchyl, trimethyltricycloheptyl or adamantyl.

As used herein, the term "C_3-i_0 cycloalkyl-alkyl" refers to an aliphatic saturated hydrocarbon monovalent group (preferably a C_i_7 alkyl such as defined above) to which a C_3-i_0 cycloalkyl (such as defined above) is already linked such as, but not limited to, cyclohexylmethyl, cyclopentylmethyl and the like.

As used herein, and unless otherwise stated, the terms "aromatic" and "aryl" designate any mono- or polycyclic aromatic monovalent hydrocarbon group having from 6 up to 30 carbon atoms such as but not limited to phenyl, naphthyl, anthracenyl, phenantracyl, fluorantheryl, chryseryl, pyrenyl, biphenyl, terphenyl, picenyl, indenyl, biphenyl, indacenyl, benzocyclobuteryl, benzocyclooctenyl and the like, including fused benzoC_4,8 cycloalkyl groups (the latter being as defined above) such as, for instance, indanyl, tetrahydronaphthyl, fluorenyl and the like, all of the said groups being optionally substituted with one or more substituents independently selected from the group consisting of halogen, amino, trifluoromethyl, hydroxyl, sulfhydryl and nitro, such as for instance 4-fluorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-cyanophenyl, 2,6-dichlorophenyl, 2-fluorophenyl, 3-chlorophenyl, 3,5-dichlorophenyl and the like.

As used herein, and unless otherwise stated, the term "heterocyclic" means a mono- or polycyclic, saturated or mono-unsaturated or polycyclic aliphatic or alkenic group as defined above, the latter being as defined above, to which one or more substituents independently selected from the group consisting of amino, halogen, hydroxy, sulfhydryl, trifluoromethyl, methoxy and the like are optionally attached.
unsaturated monovalent hydrocarbon group having from 2 up to 15 carbon atoms and including one or more heteroatoms in one or more rings, each of said rings having from 3 to 10 atoms (and optionally further including one or more heteroatoms attached to one or more carbon atoms of said ring, for instance in the form of a carbonyl or thiocarbonyl or selenocarbonyl group, and/or to one or more heteroatoms of said ring, for instance in the form of a sulfone, sulfoxide, N-oxide, phosphate, phosphonate or selenium oxide group), each of said heteroatoms being independently selected from the group consisting of nitrogen, oxygen, sulfur, selenium and phosphorus, also including groups wherein a heterocyclic ring is fused to one or more aromatic hydrocarbon rings for instance in the form of benzo-fused, dibenzo-fused or naphto-fused heterocyclic groups; within this definition are included heterocyclic groups such as, but not limited to, diazepinyl, oxadiazinyl, thiadiazinyl, dithiazinyl, triazolonyl, diazepinonyl, triazepinyl, triazepinonyl, tetrazepinonyl, benzoquinolinyl, benzothiazinyl, benzothiazinonyl, benzoaxathiinyl, benzodioxinyl, benzodithiinyl, benzoazepinyl, benzothiazepinyl, benzodiaxepinyl, benzodioxepinyl, benzodithiepinyl, benzoxazocinyl, benzodiazocinyl, benzoxathiocinyl, benzo-dioxocinyl, benzotrioxepinyl, benzoaxathiazepinyl, benzoaxadiazepinyl, benzothiadiazepinyl, benzthiazepinyl, benzothiazepinonyl, benzoxathiepinyl, benzoxathiazepinyl, benzoxazolinonyl, azetidinonyl, azaspiroundecyl, dithiaspirodecyl, selenazinyl, selenazolyl, selenophenyl, hypoxanthinyl, azahypoxanthinyl, bipyrazinyl, bipyridinyl, oxazolidinyl, diselenopyrimidinyl, benzodioxocinyl, benzopyrenyl, benzopyranononyl, benzophenazinyl, benzoquinoliziny, dibenzocarbazolyl, dibenzoacridinyl, dibenzophenazinyl, dibenzotheipinyl, dibenzooxepinyl, dibenzopyranononyl, dibenzoquinoxalinyl, dibenzoazepinyl, dibenzoisoquinolinyl, tetraazaadamantyl, thiatetraazaadamantyl, oxauracil, oxazinyl, dibenzotheophenyl, dibenzofuranyl, oxazoliny, oxazolonyl, azaindolyl, azolonyl, thiazoliny, thiazolidinyl, thiazanyl, pyrimidinyl, thiopyrimidinyl, thiamorpholinyl, azlactonyl, naphtindazolyl, naphtindolyl, naphtothiazolyl, naphtothioxolyl, naphtoxindolyl, naphtotriazolyl, naphtopyranyl, oxabicycloheptyl, azabenzimidazolyl, azacycloheptyl, azacyclooctyl, azacyclononyl, azabicyclononyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydro-
pyronyl, tetrahydroquinoleinyl, tetrahydrothienyl and dioxide thereof, dihydrothienyl dioxide, dioxindolyl, dioxinyl, dioxazinyl, thioxanly, thiokolyl, thiourazolyl, thiotriazolyl, thiopyranyl, thiopyronyl, coumarinyl, quinoleinyl, oxyquinoleinyl, quinuclidinyl, xanthinyl, dihydropyranyl, benzodihydrofuryl, benzothiopyronyl, benzothiopyranyl, benzoxazinyl, benzoazolyl, benzodioxolyl, benzodioxanyl, benzothiadiazolyl, benzotriazinyl, benzothiazolyl, benzoxazolyl, phenothiazinyl, phenothienyl (benzothiofuranyl), phenopyronyl, phenoxazolyl, pyridinyl, dihydropyridinyl, tetrahydropyridinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl, benzotriazolyl, tetrathiazolyl, imidazolyl, pyrazolyl, thiazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrrolol, furyl, dihydrofuryl, furoyl, hydantoinyl, dioxolanyl, dioxolyl, dithianyl, dithienyl, dithiinyl, thienyl, indolyl, indazolyl, benzofuryl, quinolyl, quinoxalinyl, quinazolinyl, quinolizinyl, carbazolyl, phenoxazinyl, phenothiazinyl, xanthenyl, purinyl, benzothienyl, naphtothienyl, thianthrenyl, pyranyl, pyrrolon, benzopyronyl, isobenzofuranyl, chromenyl, phenoathienyl, indoliziny, quinolizinyl, isoquinolyl, phthalazinyl, naphthiridinyl, cinnolinyl, pteridinyl, carbolinyl, acridinyl, perimidinyl, phenanthenol, phenazinyl, phenothiazinyl, imidazolinyl, benzimidazolyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, piperazinyl, uradinyl, thymidinyl, cytidinyl, azirinyl, aziridinyl, diazirinyl, diazirinyl, oxiranyl, oxaziridinyl, dioxyranyl, thiiranyl, azetyl, dihydroazetyl, azetidinyl, oxetyl, oxetanyl, oxetanony, homopiperazinyl, homopiperidinyl, thietyl, thietanyl, diazacyclooctyl, diazetyl, diaziridinon, diaziridinethionyl, chromanony, chromanony, thiochromanony, thiochromanony, benzofuranyl, benzothiazolyl, benzofurocarbazolyl, benzochromony, benzisothiazolyl, benzocoumarinyl, thiocoumarinyl, phenometoxazinyl, phenoperoxazinyl, phentriazinyl, thiodiazolyl, thiodyazolyl, indoxyl, thiodioxyl, benzodiaxinyl (eg. phtalazinyl), phtalidyl, phtalimidinyl, phtalazonyl, alloxazinyl, dibenzopyronyl (i.e. xanthonyl), xanthionyl, isatyl, isopyrazolyl, isopyrazolony, urazolyl, urazinyl, uretninyl, uretidinyl, succinyl, succinimido, benzylsultimyl, benzylsultamyl and the like, including all possible isomeric forms thereof, wherein each carbon atom of said heterocyclic ring may be independently substituted with a substituent selected from the group
consisting of halogen, nitro, C$_{1-7}$ alkyl (such as above defined, in particular methyl), C$_{3-7}$ alkenyl, trifluoromethyl, C$_{3-10}$ cycloalkyl, aryl, arylalkyl, alkylaryl, hydroxyl, sulphydryl, C$_{1-7}$ alkoxy (such as above defined, in particular methoxy), arloxy, arylalkyloxy, thio C$_{1-7}$ alkyl, thio C$_{3-10}$ cycloalkyl, thioaryl, arylalkythio, cyano, carboxylic acid or esters thereof; depending upon the number of unsaturations in each of said rings, heterocyclic groups may be sub-divided into heteroaromatic (or "heteroaryl") groups and non-aromatic heterocyclic groups; when a heteroatom of the said non-aromatic heterocyclic group is nitrogen, the latter may be substituted with a substituent selected from the group consisting of C$_{1-7}$ alkyl, C$_{3-10}$ cycloalkyl, aryl, arylalkyl and alkylaryl (each of said groups being as defined herein).

As used herein, and unless otherwise stated, the terms " C$_{1-7}$ alkoxy ", " C$_{3-10}$ cycloalkoxy ", " arloxy ", " arylalkyloxy ", "thio C$_{1-7}$ alkyl", " thio C$_{3-10}$ cycloalkyl ", " arylthio " and " arylalkylthio " refer to substituents wherein respectively a C$_{1-7}$ alkyl, a C$_{3-10}$ cycloalkyl, aryl, arylalkyl or heterocyclic group (each of them such as defined herein), are attached to an oxygen atom or a divalent sulfur atom through a single bond, such as but not limited to methoxy, ethoxy, propoxy, butoxy, pentoxy, isopropoxy, sec-butoxy, tert-butoxy, isopentxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, thiomethyl, thioethyl, thiopropyl, thiosbutyl, thiopentyl, thiocyclopropyl, thiocyclobutanyl, thiocyclopentyl, thiophenyl, phenyloxy, benzylx, mercaptobenzyl, cresoxy, and the like.

As used herein, and unless otherwise stated, the term " halogen " means any atom selected from the group consisting of fluoro, chloro, bromo and iodo.

As used herein, and unless otherwise stated, the term " C$_{2-7}$ alkenyl " designates a straight or branched acyclic hydrocarbon monovalent group having one or more ethylenic unsaturations and having from 2 to 7 carbon atoms such as, for example, vinyl, 1-propenyl, 2-propenyl (allyl), 1-buteryl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-hexenyl, 2-hexenyl, 2-heptenyl, 1,3-butadienyl, pentadienyl, hexadienyl, heptadienyl, heptatrienyl and the like.
As used herein, and unless otherwise stated, the terms "arylalkyl," "arylalkenyl" and "heterocyclic-substituted alkyl" refer to an aliphatic saturated or ethylenically unsaturated hydrocarbon monovalent group (preferably a C₁₋₇ alkyl or C₂₋₇ alkenyl such as defined above) onto which an aryl or heterocyclic group (such as defined above) is attached, and wherein the said aliphatic, aryl or heterocyclic group may be optionally substituted with one or more substituents independently selected from the group consisting of halogen, amino, hydroxyl, sulphydryl, C₁₋₇ alkyl, trifluoromethyl and nitro, such as but not limited to benzyl, 4-chlorobenzyl, 4-fluorobenzyl, 2-fluorobenzyl, 3,4-dichlorobenzyl, 2,6-dichlorobenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-tert-butylbenzyl, phenylpropyl, 1-naphthylmethyl, phenylethyl, 1-amino-2-phenylethyl, 1-amino-2-[4-hydroxy-phenyl]ethyl, 1-amino-2-[indol-2-yl]ethyl, styryl, pyridylmethyl (including all isomers thereof), pyridylethyl, 2-(2-pyridyl)isopropyl, oxazolylbutyl, 2-thienylmethyl, pyrrolylethyl, morpholinylethyl, imidazol-1-yl-ethyl, benzodioxolylmethyl and 2-furylmethyl.

As used herein, and unless otherwise stated, the term "alkylaryl" and "alkyl-substituted heterocyclic" refer to an aryl or heterocyclic radical (such as defined above) onto which are bonded one or more aliphatic saturated or unsaturated hydrocarbon monovalent groups, preferably one or more C₁₋₇ alkyl, C₂₋₇ alkenyl or C₃₋₁₀ cycloalkyl groups as defined above such as, but not limited to, o-toluyl, m-toluyl, p-toluyl, 2,3-xylyl, 2,4-xylyl, 3,4-xylyl, o-cumeyl, m-cumeyl, p-cumeyl, o-cymenyl, m-cymenyl, p-cymenyl, mesityl, tert-butylphenyl, lutidinyl (i.e. dimethylpyridyl), 2-methylaziridinyl, methylbenzimidazolyl, methylbenzofuranyl, methylbenzothiazolyl, methylbenzotriazolyl, methylbenzoxazolyl and methylbenzsenelenazolyl.

As used herein, and unless otherwise stated, the term "acyl" refers to a substituent derived from an acid such as an organic monocarboxylic acid, a carboxylic acid, a carbamic acid (resulting into a carbamoyl substituent) or the thioacid or imidic acid (resulting into a carbamidoxylic substituent) corresponding to said acids, and the term "sulfonyl" refers to a substituent derived from an organic sulfonic acid, wherein said acids comprise an aliphatic, aromatic or heterocyclic group in the molecule. A more specific kind of "acyl" group within the scope of the above definition refers to a carbonyl (oxo) group...
adjacent to a C_i-7 alkyl, a C_3-10 cycloalkyl, an aryl, an arylalkyl or a heterocyclic
group, all of them being such as herein defined. Suitable examples of acyl
groups are to be found below.

Acyl and sulfonyl groups originating from aliphatic or cycloaliphatic
monocarboxylic acids are designated herein as aliphatic or cycloaliphatic acyl
and sulfonyl groups and include, but are not limited to, the following:
- alkanoyl (for example formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl,
  isovaleryl, pivaloyl and the like);
- cycloalkanoyl (for example cyclobutanecarbonyl, cyclopentanecarbonyl,
cyclohexanecarbonyl, 1-adamantanecarbonyl and the like);
- cycloalkyl-alkanoyl (for example cyclohexylacetyl, cyclopentylacetyl and
  the like);
- alkenoyl (for example acryloyl, methacryloyl, crotonoyl and the like);
- alkylthioalkanoyl (for example methylthioacetyl, ethylthioacetyl and the
  like);
- alkanesulfonyl (for example mesyl, ethanesulfonyl, propanesulfonyl and
  the like);
- alkoxy carbonyl (for example methoxycarbonyl, ethoxycarbonyl,
  propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl
  and the like);
- alkylcarbamoyl (for example methylcarbamoyl and the like);
- (N-alkyl)-thiocarbamoyl (for example (N-methyl)-thiocarbamoyl and the
  like);
- alkyl carbamidoyl (for example methyl carbamidoyl and the like); and
  alkoxalyl (for example methoxalyl, ethoxalyl, propoxalyl and the like);

Acyl and sulfonyl groups may also originate from aromatic monocarboxylic
acids and include, but are not limited to, the following:
- aroyl (for example benzooyl, toluoyl, xylooyl, 1-naphthoyl, 2-naphthoyl and
  the like);
- aralkanoyl (for example phenylacetyl and the like);
- aralkenoyl (for example cinnamoyl and the like);
- aryloxalkanoyl (for example phenoxyacetyl and the like);
- arylothioalkanoyl (for example phenylthioacetyl and the like);
- arylaminoalkanoyl (for example N-phenylglycyl, and the like);
- arylsulfonyl (for example benzenesulfonyl, toluenesulfonyl, naphthalene sulfonyl and the like);
- aryloxycarbonyl (for example phenoxy carbonyl, naphthyloxycarbonyl and the like);
- aralkoxycarbonyl (for example benzyloxycarbonyl and the like);
- arylcarbamoyl (for example phenylcarbamoyl, naphthylcarbamoyl and the like);
- arylglyoxyloyl (for example phenylglyoxyloyl and the like);
- arylthiocarbamoyl (for example phenylthiocarbamoyl and the like);
- arylcarbamidoyl (for example phenylcarbamidoyl and the like).

Acyl groups may also originate from an heterocyclic monocarboxylic acids and include, but are not limited to, the following:

- heterocyclic-carbonyl, in which said heterocyclic group is as defined herein, preferably an aromatic or non-aromatic 5- to 7-membered heterocyclic ring with one or more heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur in said ring (for example thiophenoyl, furoyl, pyrrole carbonyl, nicotinoyl and the like);
- heterocyclic-alkanoyl in which said heterocyclic group is as defined herein, preferably an aromatic or non-aromatic 5- to 7-membered heterocyclic ring with one or more heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur in said ring (for example thiopheneneacetyl, furylacetyl, imidazolylpropionyl, tetrazolylacetyl, 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetyl and the like).

As used herein and unless otherwise stated, the term " stereoisomer " refers to all possible different isomeric as well as conformational forms which the compounds of this invention may possess, in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers and/or conformers of the basic molecular structure.

As used herein and unless otherwise stated, the term " enantiomer " means each individual optically active form of a compound of this invention, having an optical purity or enantiomeric excess (as may be determined by methods standard in the art) of at least 80% (i.e. at least 90% of one
enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

As used herein and unless otherwise stated, the term " solvate " includes any combination which may be formed by a derivative of this invention with a suitable inorganic solvent (e.g. hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters and the like.

**Detailed description of the invention**

In a first aspect, the present invention relates to a family of compounds represented by the structural formula (I):

![Structural formula](image)

wherein:

- $R_i$ is an acyl or sulfonyle group, in particular $R_i$ is $C(=O)-R_4$ or $S(=O)_2-R_4$;
- $R_4$ is selected from the group consisting of $R_5$, $OR_5$, $NHR_5$ and $SR_5$;
- $R_5$ is selected from the group consisting of hydrogen; straight chain or branched chain, aliphatic or cycloaliphatic or aromatic groups such as $C_{2-10}$ alkyl, $02-10$ alkenyl, $C_{2-10}$ cycloalkyl, $C_{2-10}$ alkynyl, aryl, arylalkyl, and saturated, partly unsaturated or aromatic heterocyclic groups,
- $R_2$ is an acyl group selected from the group consisting of acyl groups derived from cycloaliphatic, aromatic or heterocyclic monocarboxylic acids, imidazolycarbonyl or triazolylcarbonyl, in particular $R_2$ is $C(=O)-R_6$;
- $R_6$ is selected from the group consisting of aliphatic or cycloaliphatic or aromatic groups such as $C_{2-10}$ alkyl, $03.10$ cycloalkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl, aryl, arylalkyl and saturated, partly unsaturated or aromatic heterocyclic groups,
- $R_3$ is hydrogen or an amino-protecting group, in particular $R_3$ is hydrogen, $C(=O)-R_7$, $C(=O)-OR_7$ or aryl-$C_i$-$alkyl$; and
- $R_7$ is $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, aryl, or aryl-$C_i$-$alkyl$, wherein each of said alkyl, alkenyl or aryl may be substituted with one or more substituents
independently selected from the group consisting of halogen, alkyl, alkoxy, nitro, cyano and hydroxy,
As well as stereoisomers thereof, solvates thereof, or salts thereof.

Within this broad acceptance of the invention, each generic term such as, but not limited to, "acyl ", " sulfonyl ", " heterocyclic ", " cycloaliphatic ", and " aromatic " may, independently from each other, be understood according to any of the particular meanings thereof indicated in the above definitions.

A first embodiment of this aspect of the invention relates to compounds wherein Ri is an acyl group derived from an aliphatic, cycloaliphatic, aromatic or heterocyclic monocarboxylic acid. Ri may be different from R₂, especially when Ri is an aliphatic acyl group. Alternatively, according to a second embodiment of this aspect of the invention, when Ri is an acyl group derived from a cycloaliphatic, aromatic or heterocyclic monocarboxylic acid, Ri may be the same as R₂.

In view of the commercial availability of the starting materials, a preferred embodiment of this aspect of the invention relates to compounds wherein Ri is selected from the group consisting of benzoyl, p-toluoyl, 1-naphthalenecarbonyl, 2-naphthalenecarbonyl, 4-morpholinocarbonyl, 1-piperidinocarbonyl, 1-imidazolidinocarbonyl, 1-pyrrolidinocarbonyl, 2-thiazolecarbonyl, 1-methyl-1H-pyrrole-2-carbonyl, 2-furanecarbonyl, 3-furanecarbonyl, 3-pyridinecarbonyl, 4-pyridinecarbonyl, 2-thiophencarbonyl, cyclobutancarbonyl, cyclopentancarbonyl, cyclohexancarbonyl, 1-adamantancarbonyl, pipecolinyl and 2-norbornanecarbonyl.

Another embodiment of this aspect of the invention relates to compounds wherein Ri is selected from the group consisting of acetyl, formyl, propanoyl, butanoyl and pentanoyl.

Another embodiment of this aspect of the invention relates to compounds wherein R₃ is the same as R₂.

Suitable amino-protecting groups such as required for R₃ are well known in the art and are preferably selected from the group consisting of arylcarbonyl, alkyloxy carbonyl and arylalkyloxy carbonyl. A few non-limiting examples of suitable amino-protecting groups include benzyloxy carbonyl
(which may be introduced by reaction with benzylchloroformate under alkaline conditions, e.g. making use of sodium hydroxide or hydrogenocarbonate) and 9-fluorenylmethoxycarbonyl (which may be introduced by reaction with 9-fluorenylmethyl chloroformate). Another example of an amino-protecting group is a ferf-butoxycarbonyl group which may be introduced by reaction with di-tert-butyl dicarbonate under alcaline conditions. Other suitable amino-protecting groups for R₃ include, but are not limited to aralkyl type protecting groups comprising benzyl, p-methoxybenzyl, p-nitrobenzyl, p-bromobenzyl and triphenylmethyl (trityl); alternative acyl type protecting groups comprising formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, o-nitrophenoxyacetyl, sec-butryrl, pivaloyl- (also known as tert-butryrl), cyclopropanoyl, benzoyl, o-nitrobenzoyl, and alpha-chlorobutyryl; or other urethane type protecting groups comprising benzylloxycarbonyl, p-chlorobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, tert-butyloxycarbonyl, te/t-amyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, allyloxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl and cyclohexyloxycarbonyl.

Still another embodiment of the present invention relates to compounds represented by the structural formula (I), wherein when R₄ is R₅ and Ri is -C(=O)-R₄ then a heterocyclic group R₅ (i.e. R₄) may be attached through one of its heteroatoms to the carbon atom of the carbonyl group of Ri.

Still another embodiment of the present invention relates to compounds represented by the structural formula (I), wherein a heterocyclic group R₆ may be attached through one of its heteroatoms to the carbon atom of the carbonyl group of R₂.

For pharmaceutical use, especially for the formulation of suitably bioavailable drug formulations, it may be particularly preferred that the compound of the invention is present in the form of a non-toxic acid addition salt, more preferably a pharmaceutically acceptable acid addition salt, of a compound defined according to the above structural formula and wherein R₃ is hydrogen.
The latter form includes any therapeutically active non-toxic addition salt which the compounds of this invention are able to form with a (preferably pharmaceutically acceptable) salt-forming agent. Such addition salts may conveniently be obtained by treating the compounds of the invention with an effective amount (preferably an at least stoechiometric amount) of an appropriate salt-forming acid, while using reaction conditions (such as, but not limited to, temperature, pressure, time and the like) conventional in the art for such treatment. For instance, compounds having basic properties such as the amino compounds of the present invention, may conveniently be converted into the corresponding therapeutically active, non-toxic acid addition salt form by treating the free base form with a suitable amount of an appropriate acid following conventional procedures. Examples of such appropriate salt-forming acids include, for instance, inorganic acids resulting in forming salts such as, but not limited to, hydrohalides (e.g. hydrochloride and hydrobromide), sulfate, nitrate, phosphate, diphosphate, carbonate, bicarbonate, and the like; and organic monocarboxylic or dicarboxylic acids resulting in forming salts such as, but not limited to, acetate, propanoate, hydroxyacetate, 2-hydroxypropanoate, 2-oxopropanoate, lactate, pyruvate, oxalate, malonate, succinate, maleate, fumarate, malate, tartrate, citrate, methanesulfonate, ethanesulfonate, benzoate, 2-hydroxybenzoate, 4-amino-2-hydroxybenzoate, benzene-sulfonate, p-toluenesulfonate, salicylate, p-aminosalicylate, pamoate, bitartrate, camphorsulfonate, edetate, 1,2-ethanedisulfonate, fumarate, glucoheptonate, gluconate, glutamate, hexylrescorinate, hydroxynaphtoate, hydroxyethanesulfonate, mandelate, methylsulfate, pantotenate, stearate, as well as salts derived from ethanedioic, propanedioic, butanedioic (Z)-2-butenedioic, (E)2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, cyclohexanesulfamic acids and the like.

An advantage of the present invention is that compounds defined according to the above structural formula are easily accessible in good yield and purity through a synthetic scheme involving a limited number of process steps and starting from commercially available materials. An exemplary but
non-limiting method for preparing the compounds of this invention comprises the steps of:

(a) reacting synephrine with an amino-protecting reagent to form an amino-protected synephrine,

(b) reacting said amino-protected synephrine with a chloride selected from the group consisting of carboxylic acid chlorides, carbamic acid chlorides, chloroformates, thiocarboxylic acid chlorides, imidic acid chlorides and sulfonic acid chlorides to produce a 4-[2-(N-protected-methylamino)-1-hydroxyethyl] phenyl ester, in particular 4-[2-(N-protected-methylamino)-1-hydroxyethyl] phenyl benzoate, and

(c) reacting said 4-[2-(N-protected-methylamino)-1-hydroxyethyl]phenyl ester, in particular said 4-[2-(N-protected-methylamino)-1-hydroxyethyl]phenyl benzoate, with an activated carbonyl compound selected from the group consisting of carboxylic acid chlorides, carbamic acid chlorides, chloroformates, thiocarboxylic acid chlorides, imidic acid chlorides, 1,1'-carbonyldiimidazole and 1,1'-carbonylditriazole.

Carboxylic acid chlorides suitable for use in the synthesis of the compounds of the present invention include benzyol chlorides such as, but not limited to, benzyol chloride, p-anisoyl-chloride, 2-bromobenzoyl chloride, 4-bromobenzoyl chloride, 3-chlorobenzoyl chloride, pentafluorobenzoyl chloride, 2-chlorobenzoyl chloride, p-toluoyl chloride, 4-chlorobenzoyl chloride, 2,4-dichlorobenzoyl chloride, 3,4-dichlorobenzoyl chloride, 4-nitrobenzoyl chloride, 4-fluorobenzoyl chloride, 2-fluoro-benzoyl chloride, o-toluoyl chloride, m-toluoyl chloride, 4-cyanobenzoyl chloride, 3-nitrobenzoyl chloride, 4-tert-butylbenzoyl chloride, 4-biphenylcarbonyl chloride, 3,5-dimethoxybenzoyl chloride, 3-fluorobenzoyl chloride, 2,6-dichlorobenzoyl chloride, 4-butylobenzoyl chloride, 4-heptyloxybenzoyl chloride, 4-hexylbenzoyl chloride, 4-hexyloxybenzoyl chloride, 4-pentylbenzoyl chloride, m-anisoyl chloride, 2,6-difluoro-benzoyl chloride, 2-nitrobenzoyl chloride, 4-chloro-3-nitro-benzoyl chloride, 3,4-difluorobenzoyl chloride, 2-iodobenzoyl chloride, 1-naphthoyl chloride, o-anisoyl chloride, 2,4-difluorobenzoyl chloride, 4-(trifluoromethyl)benzoyl chloride, m-anisoyl chloride, 2,6-difluorobenzoyl chloride, 2-nitrobenzoyl chloride, 4-chloro-3-nitrobenzoyl chloride, 3,4-difluorobenzoyl chloride, 2-iodobenzoyl chloride,
chloride, 1-naphthoyl chloride, o-anisoyl chloride, 2,4-difluorobenzoyl chloride, 4-(trifluoromethyl)benzoyl chloride, 3-(chloro-methyl)-benzoyl chloride, A-(chloromethyl)-benzoyl chloride, 3-(dichloromethyl)-benzoyl chloride, 2,3,4,5-tetrafluorobenzoyl chloride, 2,4,6-trichlorobenzoyl chloride, 2,3,4-trifluorobenzoyl chloride, 2,4,6-trifluorobenzoyl chloride, 4-bromo-2-fluorobenzoyl chloride, 2,3,5,6-tetrafluorobenzoyl chloride, 3,5-dinitrobenzoyl chloride, 4-heptylbenzoyl chloride, 4-iodobenzoyl chloride, 4-octylbenzoyl chloride, 4-pentyl-oxybenzoyl chloride, 4-phenylazobenzoyl chloride, A-propylbenzoyl chloride, methyl 4-chloro-carbonylbenzoate, 3,5-dichlorobenzoyl chloride, 3-fluoro-4-trifluoromethyl-benzoyl chloride, 2,6-dimethoxybenzoyl chloride, piperonyloyl chloride, 2,4-dimethoxybenzoyl chloride, 3,4-dihydro-2H-1,5-benzodioxepine-6-carbonyl chloride, 2,3-dihydro-1,4-benzodioxine-6-carbonyl chloride, 2,3-dihydro-1,4-benzodioxine-5-carbonyl chloride, 1-benzofuran-5-carbonyl chloride, 2,1,3-benzothiadiazole-4-carbonyl chloride, 2,1,3-benzothiadiazole-5-carbonyl chloride, 1,2,3-benzothia-diazole-5-carbonyl chloride, 2,1,3-benzoxadiazole-5-carbonyl chloride, 6-quinoxaline-carbonyl chloride, 4-(2-thienyl)-benzoyl chloride, A-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-carbonyl chloride, 4-(1,2,3-thiadiazol-4-yl)benzoyl chloride, 4-(1 H-pyrazol-1-yl)benzoyl chloride, 1-methyl-1H-1,2,3-benzotriazole-5-carbonyl chloride, i-benzo thiophene-5-carbonyl chloride, 2,2-dimethyl-2,3-dihydro-1-benzofuran-7-carbonyl chloride, A-[(dipropyl-amino)sulfonyl] benzene-1-carbonyl chloride, 4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzoyl chloride, 2-bromo-5-methoxybenzene-1-carbonyl chloride, 5-bromo-2,3,4-trimethylbenzoyl chloride, 2-chloro-6-fluorobenzene-1-carbonyl chloride, 2,3-dimethylbenzene-1-carbonyl chloride, 3,4-dimethylbenzene-1-carbonyl chloride, 2-chloro-4-fluorobenzoyl chloride, 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalene-carbonyl chloride, 2-(4-methoxyphenoxy)-5-nitrobenzene-1-carbonyl chloride, 2,3-difluorobenzoyl chloride, 2-fluoro-5-(trifluoromethyl)benzoyl chloride, 2,3,6-trifluoro-benzoyl chloride, 1-isopropyl-1H-1,2,3-benzotriazole-5-carbonyl chloride, 1-isopropyl-1H-1,2,3-benzotriazole-5-carbonyl chloride, 3-fluoro-4-methylbenzoyl chloride, 3-(cyclo-pentyloxy)-4-methoxybenzoyl chloride, 4-fluoro-3-(trifluoromethyl)benzoyl chloride, 2,3-dihydro-i-benzofuran-7-carbonyl
chloride, 3-(2-methyl-thiazol-4-yl)-benzoyl chloride, 1-isopropyl-2-(trifluoromethyl)-i H-benzimida-zole-5-carbonyl chloride, 5-bromo-2,3-di-hydrobenzo[b]furan-7-carbonyl chloride, 2,4,6-trimethylbenzoyl chloride, 2-(2-thienyl)-benzoyl chloride, 3-cyanobenzoyl chloride, acetylsalicyloyl chloride, 3-(5-methyl-1,2,4-oxadiazol-3-yl)-benzoyl chloride, and 4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzoyl chloride.

Numerous other carboxylic acid chlorides are known to the person skilled in the art and commercially available for use as acylating reagent for use in the above reaction step. Particular carbonyl chlorides for use in the method of the invention include, but are not limited to, cinnamoyl chloride, hydrocinnamoyl chloride, 2-phenylbutyryl chloride, phenylacetyl chloride and 4-fluorophenylacetyl chloride.

Phenylsulfonyl chlorides (represented by the structural formula V-B) suitable for use in the synthesis of the compounds of the present invention include, but are not limited to, 4-fluorobenzenesulfonfyl chloride, 2-mesitylenesulfonfyl chloride, 4-methoxybenzene-sulfonfyl chloride, p-toluencesulfonfyl chloride, pentafluorobenzenesulfonfyl chloride, benzenesulfonfyl chloride, 4-bromobenzenesulfonfyl chloride, N-acetylsulfanilyl chloride, 2,4,6-triisopropyl-benzenesulfonfyl chloride 2-naphthalenesulfonfyl chloride, 4-chloro-benzenesulfonfyl chloride 3,5-dichloro-2-hydroxy-benzenesulfonfyl chloride, 2,5-dichloro-benzenesulfonfyl chloride, pipsyl chloride, 1-naphthalenesulfonfylchloride, methyl 2-(chlorosulfonfyl)benzoate, 4-tert-butylbenzene-sulfonfyl chloride, 3-(trifluoromethyl)benzenesulfonfyl chloride, 2-bromobenzenesulfonfyl chloride, 4-acetylbenezene-sulfonfyl chloride, 2-(trifluoromethyl)-benzenesulfonfyl chloride, 3,4-dichlorobenzene-sulfonfyl chloride, 3,4-dimethoxybenzenesulfonfyl chloride, 3-chlorobenzenesulfonfyl chloride, 2-chloro-4-fluorobenzenesulfonfyl chloride, 3,5-dichlorobenzenesulfonfyl chloride, 3-chloro-4-fluorobenzenesulfonfyl chloride, 2,4-dichlorobenzenesulfonfyl chloride, 2,5-dimethoxybenzenesulfonfyl chloride, 3-bromo-benzenesulfonfyl chloride, 2,3-dichlorobenzenesulfonfyl chloride, 5-fluoro-2-methylbenzenesulfonfyl chloride, 3-fluorobenzenesulfonfyl chloride, 2,3,5,6-tetramethyl-benzenesulfonfyl chloride, 2,5-dibromo-3,6-difluoro-benzenesulfonfyl chloride.
chloride, 2,6-difluorobenzenesulfonyl chloride, 2-chloro-benzenesulfonyl chloride, 5-bromo-2-methoxybenzenesulfonyl chloride, 5-chloro-2-methoxybenzenesulfonyl chloride, 2,4-difluorobenzenesulfonyl chloride, 2-cyano-benzenesulfonyl chloride, 2-chloro-5-(trifluoromethyl)-benzenesulfonyl chloride, 4-bromomethylbenzenesulfonyl chloride, 2,4-dimethoxybenzenesulfonyl chloride, 4-chloro-3-nitrobenzenesulfonyl chloride, 4-(chlorosulfonyl)-benzoic acid, 3-nitro-benzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 2-(methylsulfanyl)-benzenesulfonyl chloride, 4-(methylsulfonyl)-benzene-sulfonyl chloride, 3-(chloro-sulfonyl)-benzoic acid, 2,4-dichloro-5-methylbenzene-sulfonyl chloride, 4-(trifluoro-methoxy)-benzenesulfonyl chloride, 2-methoxy-4-nitrobenzenesulfonyl chloride, 4-bromo-2-chlorobenzenesulfonyl chloride, 2,3-dihydro-1-benzofuran-5-sulfonyl chloride, 2,3-dihydro-1,4-benzodioxine-6-sulfonyl chloride, 1,3-benzothiazole-6-sulfonyl chloride, 2,1,3-benzothiadiazole-4sulfonyl chloride, 2,1,3-benzothiadiazole-5-sulfonyl chloride, 2,1,3-benzoxadiazole-4-sulfonyl chloride, 3,4-dihydro-2H-1,5-benzodioxepine-7-sulfonyl chloride, 4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-sulfonyl chloride, 4-(1,3-oxazol-5-yl)benzenesulfonyl chloride, 4-(1,2,3-thiadiazol-4-yl)benzenesulfonyl chloride, 4-(1 H-pyrazol-1-yl)benzenesulfonyl chloride, 4-(3-chloro-2-cyanophenoxyl)benzene-1-sulfonyl chloride, 5-chlorosulfonyl^a^-hydroxy-benzoic acid, 4-bromo-2,5-difluorobenzene-1-sulfonyl chloride, 4-(acetylamino)-3-chloro-benzene-1-sulfonyl chloride, 3,5-di-(trifluoromethyl)-benzene-1-sulfonyl chloride, 2-fluorobenzenesulfonyl chloride, 4-methyl-3-nitrobenzene-1-sulfonyl chloride, 5-chloro-2,1,3-benzoxadiazole-4-sulfonyl chloride, 3-(5-methyl-1,3,4-oxadiazol-2-yl) benzenesulfonyl chloride, methyl 3-(chlorosulfonyl)-4-methoxybenzoate, 4-bromo-2-(trifluoromethyl)-benzenesulfonyl chloride, 2,2-dimethyl-6-chromanesulfonyl chloride, 4-(morpholine-4-sulfonyl)benzenesulfonyl chloride, 4-(pyrrolidine-1-sulfonyl)-benzene-sulfonyl chloride, 3-(2-methyl-4-pyrimidinyl)benzenesulfonyl chloride, 2-cyano-5-methylbenzenesulfonyl chloride, 2,5-dimethylbenzenesulfonyl chloride, 4-chloro-3-(trifluoromethyl)-benzene-sulfonyl chloride, 4-bromo-2-methylbenzenene-1-sulfonyl chloride, 2-chloro-4-(trifluoro-methyl)-benzene-1-sulfonyl chloride, 2-chloro-4-cyano-benzenesulfonic acid, 2,6-dichloro-
4-(trifluoromethyl)-benzene-1-sulfonyl chloride, 3,4-difluorobenzene-1-sulfonyl chloride, 2-iodobenzene-1-sulfonyl chloride, 4-methyl-1-naphthalenesulfonyl chloride, 4-(trifluoromethyl)benzene-1-sulfonyl chloride, 2,6-dichlorobenzene-1-sulfonyl chloride, 2-(trifluoromethoxy)benzene-1-sulfonyl chloride, 4-cyanobenzene-1-sulfonyl chloride, 4-butoxybenzene-1-sulfonyl chloride, 2,6-dichlorobenzene-1-sulfonyl chloride, 2-(trifluoromethoxy)benzene-1-sulfonyl chloride, 3-cyanobenzene-1-sulfonyl chloride, 4-bromo-2-ethyl-benzene-1-sulfonyl chloride, 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthalene-sulfonyl chloride, 4-(2-chloro-6-nitrophenoxy)benzene-1-sulfonyl chloride, 3,5-dichloro-4-(2-chloro-4-nitrophenoxy) benzene-1-sulfonyl chloride, 4-pentylbenzene-1-sulfonyl chloride, 4-ethylbenzene-1-sulfonyl chloride, 4-propylbenzene-1-sulfonyl chloride, 4-butylbenzene-1-sulfonyl chloride, 3-toluenesulfonyl chloride, 4-isopropyl-benzenesulfonyl chloride, 4-(2-oxo-1-pyrrolidinyl)benzene sulfonyl chloride, 4-(2-methoxyphenoxy)benzenesulfonyl chloride, 4-(2-chloro-phenoxy)benzenesulfonyl chloride, 4-(2-chloro-phenoxy)benzenesulfonyl chloride, 4-(2-methoxyphenoxy)benzenesulfonyl chloride, 4-(2-chloro-phenoxy)benzenesulfonyl chloride, 4-(2-methoxyphenoxy)benzenesulfonyl chloride, 4,1'-biphenyl)-4-sulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 4-phenoxybenzenesulfonyl chloride, 4'-methyl-(1,1'-biphenyl)-4-sulfonyl chloride, 5-bromo-2,3-dihydrobenzo[b]furan-7-sulphonyl chloride, 3,4,5-trifluorobenzenesulfonyl chloride, 3-(5-methyl-1,2,4-oxadiazol-3-yl)benzenesulfonyl chloride, 4-(2-methyl-1,3-thiazol-4-yl)benzenesulfonyl chloride, 1-acetyl-5-indolesulfonyl chloride, 3-(2-methyl-1,3-thiazol-4-yl)benzene-sulfonyl chloride and 1,3-benzodioxole-5-sulfonyl chloride.

Phenylacetyl chlorides also suitable for use in the synthesis of the compounds of the present invention include, but are not limited to, phenylacetyl chloride, 4-methoxyphenylacetyl chloride, 2-(2-naphthyl)acetyl chloride, 2-(3,5-difluorophenyl)ethanoyl chloride, 2-(1-naphthyl)ethanoyl chloride, 4-chloropheny lacetyl chloride, 3-methoxyphenylacetyl chloride, and 4-fluorophenylacetyl chloride.

The above method is able to provide compounds defined according to the above structural formula and wherein R₃ is an amino-protecting group such as
referred herein above or, in the presence of an additional final step, wherein R₃ is hydrogen.

Suitable experimental conditions for performing protection step (a) are well known in the art. An exemplary but non-limiting embodiment of the method of the invention includes a step (a) comprising reacting synephrine with an amino-protected thiazolidine-2-thione. Preferably, the amino-protected thiazolidine-2-thione or other amino-protecting reagent may be dissolved in an organic solvent such as an ether for use in said step (a), and is preferably used in a molar ratio of at least 1:1, more preferably from 1:1 to about 2:1, with respect to synephrine. Preferably the reaction of step (a) is performed in a solvent system which may comprise water, a lower alcohol (such as, but not limited to, methanol), and optionally in the presence of a further organic solvent (such as the solvent used for introducing the amino-protected thiazolidine-2-thione or other amino-protecting reagent).

When the amino-protected thiazolidine-2-thione used in step (a) is tert-butoxycarbonyl-thiazolidine-2-thione, step (a) results into a tert-butoxy-carbonyl-protected synephrine as an intermediate readily available, optionally without further purification, for the subsequent step (b).

In step (b), said N-protected synephrine is reacted with a suitable chloride for introducing the relevant substituent R₁. Suitable experimental conditions for performing acylation or sulfonation step (b), especially the molar ratio between the selected acylating or sulfonating agent and the N-protected synephrine are well known in the art and, depending upon the selected acylating or sulfonating agent, and the number of hydroxyl groups to be acylated or sulfonated, may be tailored at will without undue experimentation.

In step (c), said N-protected and acylated or sulfonated synephrine is reacted with a suitable activated carbonyl compound for introducing the relevant substituent R₂. Suitable experimental conditions for performing said step (c) are well known in the art and, depending upon the selected activated carbonyl compound, may be tailored at will without undue experimentation. It should be realized, however, that when R₂ is imidazolylcarbonyl or triazolylcarbonyl, a limited number of activated carbonyl compounds are available for efficiently introducing the substituent R₂. In the latter situation, the
activated carbonyl compound should preferably be carbonyldiimidazole or, respectively, carbonylditriazole, both being well known for their selective activation capacity.

When compounds defined according to the above structural formula and wherein \( R_3 \) is hydrogen are desired, the above-referred general synthetic method preferably further comprises a step (d) for selectively deprotecting the amino group of the compound resulting from step (c), without affecting any of groups \( R_1 \) and \( R_2 \) being present in said compound. For instance the amino-protecting group may be removed by deprotection methods conventional in the art, such as:

- when the amino-protecting group is a phenylmethoxycarbonyl group, cleavage of the benzylic ether function by hydrogenolysis, e.g. using \( \text{H}_2, \text{Pd-C} \) at about 25°C, or under strongly acidic conditions (e.g. making use of bromhydric acid), or

- when the amino-protecting group is a tert-butoxycarbonyl group, by treatment with an acid, e.g. using aqueous hydrochloric acid or trifluoroacetic acid, under conditions mild enough to avoid further cleavage of the molecule, or

- when the amino-protecting group is a 9-fluorenylethoxycarbonyl group, by treatment with a base such as piperidine.

As is well known in the art, the method of said step (d) may be capable of simultaneously achieving selective deprotection of the amino group and the formation of a non-toxic acid addition salt such as, but not limited to, a hydrochloride, a hydrobromide or a trifluoroacetate, of the compounds of the invention wherein \( R_3 \) is hydrogen. This particular aspect of the invention may be useful when the said compound is intended for formulation into a medicament since the water-solubility of the said salt is expected to be significantly higher than that of the corresponding free base form of said compound.

In another aspect, based on the fact that the above-defined novel synephrine derivatives exhibit biologically-active properties, the present invention relates to a pharmaceutical composition comprising a therapeutic effective amount of a compound defined by the above structural formula (with
any of the available individual meanings for each of R₁, R₂ and R₃), and optionally one or more pharmaceutically acceptable carriers or excipients. Said pharmaceutical composition may comprise a novel synephrine derivative of the invention as the single bio-active ingredient, or as a bio-active ingredient in combination with one or more other drugs in a combined preparation for a so-called combination therapy.

The term "pharmaceutically acceptable carrier or excipient" as used herein in relation to pharmaceutical compositions and combined preparations means any material or substance with which the bio-active principle(s), i.e. the synephrine derivative and the said one or more other drugs, may be formulated in order to facilitate application or dissemination to the locus to be treated, for instance by dissolving, dispersing or diffusing the said composition, and/or to facilitate its storage, transport or handling without impairing its effectiveness. The pharmaceutically acceptable carrier may be a solid or a liquid or a gas which has been compressed to form a liquid, i.e. the compositions of this invention can suitably be used in the form of concentrates, emulsions, solutions, granulates, dusts, sprays, aerosols, pellets or powders, but are not limited thereto.

Suitable pharmaceutical carriers or excipients for use in the said pharmaceutical compositions and their formulation are well known to those skilled in the art. There is no particular restriction to their selection within the present invention although, in case of a low or very low water-solubility of the synephrine derivative of this invention, special attention must be paid to the selection of suitable carrier combinations that can assist in a proper formulation in view of the expected time release profile. Suitable pharmaceutical carriers or excipients include additives such as, but not limited to, wetting agents, dispersing agents, stickers, adhesives, emulsifying or surface-active agents, thickening agents, complexing agents, gelling agents, solvents, coatings, antibacterial and antifungal agents (for example phenol, sorbic acid, chlorobutanol), isotonic agents (such as sugars or sodium chloride) and the like, provided that the same are consistent with standard pharmaceutical practice, i.e. carriers and additives which do not create severe and/or permanent damage to the mammal, in particular the human being, to
be treated with said medicament. The pharmaceutical compositions of the present invention may be prepared by any method well known in the art, for instance by homogeneously mixing, dissolving, spray-drying, coating and/or grinding the bio-active ingredient(s), in a one-step or a multi-steps procedure, with the selected carrier material(s) and, where appropriate, the other additives such as surface-active agents. The pharmaceutical compositions of the present invention may also be prepared by micronisation, for instance in view to obtain them in the form of microspheres usually having a diameter of about 1 to about 10 µm, namely for the manufacture of microcapsules for controlled or sustained release of the said biologically-active ingredient(s).

Suitable surface-active agents useful as a pharmaceutically acceptable carrier or excipient in the pharmaceutical compositions of the present invention include non-ionic, cationic and/or anionic surfactants having good emulsifying, dispersing and/or wetting properties. Suitable anionic surfactants include both water-soluble soaps and water-soluble synthetic surface-active agents. Suitable soaps are alkaline or alkaline-earth metal salts, non-substituted or substituted ammonium salts of higher fatty acids (C10-C22), e.g. the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures obtainable form coconut oil or tallow oil. Synthetic surfactants include sodium or calcium salts of polyacrylic acids; fatty sulphonates and sulphates; sulphonated benzoimidazole derivatives and alkylaryl sulphonates. Fatty sulphonates or sulphates are usually in the form of alkaline or alkaline-earth metal salts, non-substituted ammonium salts or ammonium salts substituted with an alkyl or acyl radical having from 8 to 22 carbon atoms, e.g. the sodium or calcium salt of lignosulphonic acid or dodecylsulphonic acid or a mixture of fatty alcohol sulphates obtained from natural fatty acids, alkaline or alkaline-earth metal salts of sulphuric or sulphonic acid esters (such as sodium lauryl sulphate) and sulphonic acids of fatty alcohol/ethylene oxide adducts. Suitable sulphonated benzoimidazole derivatives preferably contain 8 to 22 carbon atoms. Examples of alkylaryl sulphonates are the sodium, calcium or alcanolamine salts of dodecylbenzene sulphonic acid or dibutyl-naphtalenesulphonic acid or a naphtalene-sulphonic acid/formaldehyde condensation product. Also suitable are the corresponding phosphates, e.g.
salts of phosphoric acid ester and an adduct of p-nonylphenol with ethylene and/or propylene oxide, or phospholipids. Suitable phospholipids for this purpose are the natural (originating from animal or plant cells) or synthetic phospholipids of the cephalin or lecithin type such as e.g. phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, lysolceithin, cardiolipin, dioctanoylphosphatidylcholine, dipalmitoylphosphatidylcholine and their mixtures.

Suitable non-ionic surfactants useful as pharmaceutically acceptable carriers or excipients in the pharmaceutical compositions of the present invention include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylarenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100 propyleneglycol ether groups. Such compounds usually contain from 1 to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol-polyethoxyethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethyleneglycol and octylphenoxypolyethoxyethanol. Fatty acid esters of polyethylene sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and pentaerythritol are also suitable non-ionic surfactants.

Suitable cationic surfactants useful as pharmaceutically acceptable carriers or excipients in the pharmaceutical compositions of the present invention include quaternary ammonium salts, preferably halides, having 4 hydrocarbon radicals optionally substituted with halo, phenyl, substituted phenyl or hydroxy; for instance quaternary ammonium salts containing as N-
substituent at least one Cβ-C-22 alkyl radical (e.g. cetyl, lauryl, palmityl, myristyl, oleyl and the like) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl radicals.

tetraacetic acid; flavoring agents such as natural vanillin; buffers such as citric acid and acetic acid; extenders or bulking agents such as silicates, diatomaceous earth, magnesium oxide or aluminum oxide; densification agents such as magnesium salts; and mixtures thereof.

Additional carriers or excipients may be included in order to control the duration of action of the biologically-active ingredient(s) in the compositions and combined preparations of the invention. Control release compositions may thus be achieved by selecting appropriate polymer carriers such as for example polyesters, polyamino-acids, polyvinylpyrrolidone, ethylene-vinyl acetate copolymers, methylcellulose, carboxymethylcellulose, protamine sulfate and the like. The rate of drug release and duration of action may also be controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxymethyl-cellulose, polymethyl methacrylate and the other above-described polymers. Such methods include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition or combined preparation of the invention may also require protective coatings.

Pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers or excipients for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol, complexing agents such as, but not limited to, cyclodextrins, maltodextrins and the like, and mixtures thereof.

In another embodiment, this invention provides combinations, preferably synergistic combinations, of one or more synephrine derivatives represented by the above structural formula with one or more biologically-active drugs being preferably selected from the group consisting of anti-inflammatory drugs. As is conventional in the art, the evaluation of a synergistic effect in a drug combination may be made by analyzing the quantification of the interactions between individual drugs, using the median effect principle described by Chou et al. in Adv. Enzyme Reg. (1984) 22:27. Briefly, this
principle states that interactions (synergism, additivity, antagonism) between two drugs can be quantified using the combination index (hereinafter referred as CI) defined by the following equation:

$$CI_x = \frac{ED_L}{ED_{x1}} + \frac{ED^{2c}}{ED^{2r}}$$

wherein $ED_x$ is the dose of the first or respectively second drug used alone (1a, 2a), or in combination with the second or respectively first drug (1c, 2c), which is needed to produce a given effect. The said first and second drug have synergistic or additive or antagonistic effects depending upon CI < 1, CI = 1, or CI > 1, respectively. As will be explained in more detail herein-below, this principle may be applied to a number of desirable effects such as, but not limited to, an activity against inflammation. For instance the present invention relates to a pharmaceutical composition or combined preparation having synergistic effects against inflammation.

In yet another embodiment, this invention provides the use of a synephrine derivative represented by the above structural formula (with any of the available individual meanings for each of $R_i$, $R_2$ and $R_3$) for the manufacture of a medicament for preventing or treating an inflammatory disease or disorder. The compounds of the present invention have anti-inflammatory, analgesic and antipyretic activities comparable with glucocorticoids, but without side effects thereof, and are therefore safely useful in methods of treating or preventing diseases or conditions in which NF-κB and/or its target genes such as but not limited to IL-6, IL-8 and E-selectin are implicated. Such diseases and conditions include, but are not limited to, those in which inflammation or tissue injury is involved such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and the like, as well as other rheumatologic or pain indications. Other diseases in which inflammation is involved and for which the novel compounds of the present invention are therapeutically useful include, but are not limited to, asthma, psoriasis, septic shock and inflammatory bowel disease. Since NF-κB may also be involved in apoptosis, the compounds of the present invention are also useful to limit tissue and/or cell damage and for ischaemic disease, neural injury or myocardial infarction. The compounds of
the invention are also useful in the treatment or prevention of Alzheimer's disease by delaying the onset or slowing the progression of said disease.

In view of the above methods of treatment or prevention, the aforementioned compounds of the invention (with any of the available individual meanings for each of R1, R2 and R3) or pharmaceutical compositions (formulations) thereof may be administered by any conventional method including oral and parenteral (e.g. subcutaneous, intraperitoneal, intravascular or intramuscular) injection. The treatment may consist of a single dose or a plurality of doses of the bio-active ingredient over a predetermined period of time.

Thus, the present invention involves a method of treating a patient having inflammation or an inflammation-related disorder by the administration of a therapeutically effective amount of a novel synephrine compound of the present invention. The invention is therefore useful for, but not limited to, the treatment of inflammation in a patient, and for treatment of other inflammation-associated disorders such as pain, headache or fever. The compounds of the present invention are also useful to treat arthritis, including but not limited to rheumatoid arthritis, spondylarthritis, gouty arthritis, osteoarthritis, systemic lupus erythematosus, and juvenile arthritis. The compounds of the present invention are also useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, and skin-related conditions such as psoriasis, eczema, acne, burns and dermatitis. Moreover, the compounds of the present invention are useful for the treatment of gastrointestinal inflammatory conditions such as, but not limited to, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. The compounds of the present invention are also useful in the treatment or prevention of inflammatory effects of cancer, such as colorectal cancer, breast cancer, prostate cancer or leukemia. The compounds of the present invention are further useful in treating inflammation in diseases such as vascular diseases, migraine, headache, periarteritis nodosa, thyroiditis, plastic anemia, Hodgkin's disease, chronic lymphocytic leukemia, scleroderma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, myocardial
ischemia and the like. In addition, the compounds of the present invention are useful in the treatment of inflammatory effects of ophthalmic diseases such as retinitis, retinopathy, conjunctivitis, uveitis, ocular photophobia, and acute injury to the eye tissue. The compounds of the present invention are also useful in the treatment of pulmonary inflammation, such as one associated with viral infection or cystic fibrosis. The compounds of the present invention are further useful for the treatment of certain central nervous system disorders such as, but not limited to, cortical dementia, Alzheimer's disease, and multiple sclerosis. The compounds of the present invention are also useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis and central nervous system damage resulting from stroke, ischemia or trauma. Besides being useful for human treatment, the compounds of the present invention are also useful for the treatment of higher mammals, including pets and cattle such as, but not limited to, horses, dogs, cats, sheep and pigs.

The term "therapeutically-effective" as used herein refers to an amount of the bio-active agent for use in anti-inflammation therapy which achieves improvement in inflammation severity, as may be determined by any practical or reproducible method. For oral administration, the pharmaceutical composition of this invention may be in the form of a dosage unit containing a predetermined amount of the bio-active ingredient. Examples of such dosage units are tablets or capsules.

The therapeutically active amount of compound that can be administered and the dosage regimen for treating an inflammatory disease condition with a compound and/or pharmaceutical composition of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the patient, the severity of the disease, the route and frequency of administration, and the particular compound used, and thus may vary in accordance with said factors.

The pharmaceutical composition may contain the bio-active ingredient of this invention in a range from about 0.1 to about 2000 mg, preferably about 0.5 to 500 mg and more preferably about 1 to 100 mg per dosage unit. A daily dose of about 0.01 to 100 mg/kg body weight, preferably about 0.1 to 20
mg/kg body weight and more preferably about 0.1 to 10 mg/kg body weight, may be appropriate for administration to a human being. The daily dose may suitably be administered in one to four sub-doses per day. In the case of psoriasis and other skin inflammatory conditions, it may be preferred to apply a topical preparation of the compound of this invention to the affected area two to four times per day.

The following examples are provided for illustration of the invention without limiting its scope in any way, and will be explained with reference to the general scheme 1 below.

**Scheme 1**

**EXAMPLE 1 - preparation of a N-protected synephrine**

The following refers to the preparation of N-protected synephrines according to scheme 1, step a.

Synephrine (referred as 13 in the above scheme 1) (1.65 g, 9.87 mmol) was dissolved in a boiling mixture of water (25 ml) and methanol (12 ml). This hot solution was stirred vigorously, and then a yellow solution of a N-acyl...
thiazolidine-2-thione (referred to as 14 in the above scheme 1; for the purpose of the present example N-acetyl-thiazolidine-2-thione (14a) was used) (1.592 g, 9.87 mmol) in THF (10 ml) was added portion-wise. Disappearance of the yellow color was nearly instantaneous, however in order to ensure complete reaction, triethyl amine (202 mg, 2 mmol) was added, and after 10 minutes the resulting colorless solution was cooled to 40°C and concentrated under reduced pressure onto a rotary evaporator. The crude product was purified by column chromatography using 200 g of silica gel and eluting with 300 ml of a 98:2 (volume ratio) CH₂Cl₂-methanol mixture, followed by a 94:6 (volume ratio) CH₂Cl₂-methanol mixture. The desired product (1.40 g, yield 72%) may be re-crystallized from ethyl acetate.

EXAMPLE 2 - preparation of N-Boc-syneprine: tert-butyl [2-hydroxy-2-(4-hydroxyphenvDethyllmethylcarbamate

Synthesis of N-Boc Syneprine was carried out as described in example 1 but using N-te/?-butyloxycarbonyl thiazolidine-2-thione (N-Boc-thiazolidine-2-thione) as the N-acyl thiazolidine-2-thione. N-Boc-thiazolidine-2-thione may be easily obtained by reacting di-terf-butyl dicarbonate with 1,3-thiazolidine-2-thione preferably in the presence of an organic base such as triethylamine.

One molar equivalent of N-Boc thiazolidine-2-thione was added to a boiling solution of synephrine in methanol and water followed by one molar equivalent of triethyl amine. The solution was maintained at 70°C. The crude resulting product was purified by column chromatography using a mixture of CH₂Cl₂ and MeOH in a volume to volume ratio of 98:2, to yield 85% of the pure crystalline material.

EXAMPLE 3 - preparation of N-protected-di-O-acyl-syneprines

The following refers to the preparation of N-protected-di-O-acyl-syneprines according to scheme 1, step b.

Dry methylene chloride (17 ml) and triethylamine (346 mg, 3.42 mmol) were added to a 50 ml round bottom flask containing the N-protected
synephrine obtained in example 1 (1.71 mmol). This mixture was stirred at room temperature until a slightly turbid solution was obtained. The flask was placed under nitrogen pressure and immersed into an ice bath. An acyl chloride (3.42 mmol) was then added drop-wise within four minutes to the chilled solution. The ice bath was removed two minutes after addition was completed, and the reaction solution was stirred at room temperature for 43 hours. The reaction flask was chilled in an ice bath, and addition of 0.25 equivalent of triethylamine followed by drop-wise addition of 0.25 equivalent of the same acyl chloride was carried out. After one hour, thin layer chromatography (TLC) analysis (performed with a 98:2 (volume ratio) CHbCVmethanol mixture) indicated that reaction was complete. The reaction solution was diluted with methylene chloride and extracted with a half-saturated NaHCO₃ solution. The organic layer was dried over anhydrous MgSO₄, filtered and concentrated into an oil. The crude material obtained was purified by column chromatography (100 g silica gel, 98:2 (volume ratio) CH₂Cl₂/methanol mixture) to afford the desired product with a yield of about 70%.

**EXAMPLE 4 - preparation of 4-(2-(ferf-butoxycarbonvD(methyl)arninol-1-hydroxyethyl)phenyl benzoate and related derivatives**

The following refers in general to the preparation of N-protected synephrine derivatives according to scheme 1, step c.

To a N-protected synephrine, in particular for the purpose of the present example N-BOC synephrine as obtained in example 2 (1.75 mmole) dissolved in 6 ml methanol was added solid potassium hydroxide (85 mg, 1.516 mmole). The mixture was stirred until full KOH dissolution, then methanol was removed under reduced pressure. The resulting residue was dried under vacuum, placed under a nitrogen atmosphere and then stirred in 3 ml of dry DMF. Once dissolution was effected, an acyl chloride such as benzoyl chloride (1.516 mmole) was added drop-wise so that only slight warming was observed. TLC analysis with a 96:4 (volume ratio) CH₂Cb-methanol mixture showed that reaction was completed within 15 minutes.
Eventually, the reaction mixture was diluted with methylene chloride and extracted with water. The organic layer was dried over anhydrous MgSO₄, filtered, concentrated and, in order to ensure full DMF removal, dried under high vacuum. The resulting crystalline crude material was purified by column chromatography (90 g silica gel, elution with 200 ml of a ChkCVmethanol mixture (volume ratio progressively ranging from 99:1 to 96:4). The desired product (409 mg) was obtained with a 73% yield.


A flask containing a stirring bar was purged with nitrogen and charged with N-Boc synephrine (obtained in example 2). The flask was fitted with a rubber septum and placed under nitrogen pressure. Dry methylene chloride (10 ml) and triethyl amine (1.05 molar equivalents) were added. Once dissolution was complete, the flask containing the slightly turbid solution was immersed in an ice bath. After sufficient cooling, the appropriate acyl chloride (1 molar equivalent; for the purpose of the example respectively isobutyril chloride, hexanoyl chloride and 1-naphthoyl chloride) was added dropwise to the stirred solution. Once addition was complete, the ice bath was removed after several minutes, and the clear solution was stirred at room temperature. The progress of the reaction was monitored by TLC on silica using a mixture of CH₂Cl₂ and MeOH at 98/2 (v/v). After completion of the reaction was noted, the reaction solution was diluted with methylene chloride, and the resulting solution was extracted first with water and then saturated NaCl. The organic phase was dried over MgSO₄, filtered and concentrated on the rotary evaporator. The crude material was purified by silica gel column chromatography eluting the final compound with 98/2, CH₂Cl₂/MeOH (v/v). In this way the following compounds were obtained:

- 4-{2-[(tert-butoxycarbonyl)(methyl)amino]-1-hydroxyethyl}phenyl isobutyrate (example 5) in 92% yield;
- 4-{2-[(tert-butoxycarbonyl)(methyl)amino]-1-hydroxyethyl}phenyl hexanoate (example 6) in 82% yield; and
- 4-{2-[(tert-butoxycarbonyl)(methyl)amino]-1-hydroxyethyl}phenyl 1-naphthoate (example 7) in 89% yield.

Example 8 - synthesis of 1-r4-(benzoyloxy)phenyll-2-[(ter/t-butoxycarbonyl)-methylamino]ethyl-1H-imidazole-1-carboxylate

The following refers in general to the preparation of N-protected synephrine derivatives according to scheme 1, step d.

2-[4-(benzoyloxy)phenyl]-2-hydroxy-1-[N-(tert-butoxycarbonyl)]methylamino]ethyl (50 mg, 0.135 mmol) was weighed into a flask equipped with a stirring bar, and the system was purged with nitrogen. Dry methylene chloride (1 ml) was added, and the mixture was stirred until a solution was obtained. To this solution, at room temperature, was added 1,1'-carbonyldiimidazole (hereinafter referred as CDI, 23 mg, 0.142 mmol). Reaction progress was monitored by TLC analysis. Additional portions of CDI were introduced after stirring for 3 hours (6.5 mg, 0.04 mmol), 4.5 hours (6 mg, 0.037 mmol) and 6.5 hours (3.5 mg, 0.022 mmol). After 7.5 hours, the reaction solution was diluted with methylene chloride, and the resulting solution was extracted two times with water. The organic layer was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure, and the residue was dried in vacuo. The desired product was obtained quantitatively (yield: 100%).

EXAMPLES 9 to 11 - preparation of 1-f4-(isobutanoyloxy)phenyll-2-[(ter/-butoxycarbonyl)-methylamino]ethyl-1H-imidazole-1-carboxylate.

1-r4-(hexanoyloxy)phenyl1-2-f(te/t-butoxycarbonyl)-methylaminoethyl-1 H-imidazole-1-carboxylate and 1-f4-(naphthoyloxy)phenyll-2-(te/t-butoxy-carbonyl)-methylaminoethyl-1 H-imidazole-1-carboxylate

The synthesis of 1-[4-(isobutanoyloxy)phenyl]-2-[(ter/butoxycarbonyl)-methylamino]ethyl-1 H-imidazole-1-carboxylate (example 9),
1-[4-(hexanoyloxy)phenyl]-2-[(te/t-butoxycarbonyl)-methylamino]ethyl-1 H-imidazole-1-carboxylate (example 10) and 1-[4-(naphthoyloxy)phenyl]-2-[(te/t-butoxycarbonyl)-methylamino]ethyl-1 H-imidazole-1-carboxylate (example 11) was carried out as described in example 8, starting from the compounds of examples 5 to 7 respectively. The title products were all obtained in quantitative yield (higher than 98%).

EXAMPLE 12 - preparation of 4-M-(acetyloxy)-2-(methylamino)ethylphenyl acetate hydrochloride

The following refers to the preparation of di-O-acylsynephrine salts according to scheme 1, step f. A compound obtained according to example 2 (0.246 mmol) was dissolved in 1 ml of 4M HCl in dioxane, and the resulting solution was stirred at room temperature for 1 hour. TLC analysis (performed with a 98:2 (volume ratio) ChbCVmethanol mixture) after one hour indicated complete disappearance of the starting material. The solution was then diluted with ethyl ether, and the resulting cloudy solution was purged with N₂ in order to remove HCl. Upon standing 1 hour at room temperature the reaction solution became clear and product white beads deposited. Ether washing was repeated four times. The resulting desired product was dried under vacuum and obtained (60 mg) in a 85% yield.

EXAMPLE 13 - biological evaluation with pE-selectine-Luc transfected cells.

L929sA cells were cultured in DMEM supplemented with 5 % new-born calf serum and 5 % fetal calf serum, 100 units/ml penicillin and 0.1 mg/ml streptomycin. L929sA mouse fibroblast cells were stably transfected with pE-selectine-Luc (also referred to as pELAM-luc) by the calcium phosphate precipitation procedure described by De Bosscher et al. in *Proc. Natl. Acad. Sci. USA* (1997) 94:13504-13509. The co-transfected plasmid pPGKβGeobpA, conferring resistance to G418 and expressing constitutive β-galactosidase enzymatic activity, was used as an internal control. L929sA cells were transiently transfected by the DEAE-dextran transfection method described by De Bosscher et al. (cited supra).
Recombinant murine tumor necrosis factor (TNF) was produced according to a method standard in the art. Dexamethasone (hereinafter abbreviated as DEX) commercially available from Sigma, and 2-(4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium chloride (hereinafter abbreviated as compound A) was synthesized according to Louw et al. in Biochemical Pharmacology (1997) 53:189-197. A stock solution was prepared in ethanol (for DEX) or DMSO (for both comparative compound A and for the compound of example 6 according to this invention, i.e. 1-[4-(benzoyloxy)phenyl]-2-[(tert-butoxy-carbonyl)-methylamino]ethyl-1 H-imidazole-1-carboxylate), aliquoted and stored at -70°C. Control experiments verified that the final concentration of organic solvent did not interfere with any of the assays.

Induction was performed in triplicate for each independent experiment, which was carried out at least twice. Induction with DEX, compound A, and for the compound of example 6 according to this invention at 1 µM, 10 µM or respectively any other indicated concentration were performed at -2 hours for a total of 8 hours, while TNF (2000 IU/ml) was added at time point zero and left on the cells for 6 hours. After induction, cells were lysed with a lysis buffer (commercially available from Tropix, Bedford, Massachussets) and samples were assayed according to the manufacturer's instructions (Promega Biotech).

Promoter activities are expressed as a ratio of luciferase over β-galactosidase, multiplied by 100.

In order to investigate whether the inhibitory effect of compound A or the compound of example 6 according to this invention is directed at the transcriptional level of NF-κB-driven genes, the NF-κB-dependent physiological promoter construct, pE-selectin-Luc stably integrated into L929sA cells, was tested. Inhibition of TNF-induced gene expression by the mediation of the compound of example 6 according to this invention was observed in a dose-responsive manner, as shown in figure 1B. DEX-mediated and A-mediated inhibition of TNF-induced gene expression were used as controls (figure 1A). In the appended figures, NI stands for non-induced (either in presence of solvent controls like ethanol or DMSO).
EXAMPLE 14 - biological evaluation with p(IL6-kB)\textsubscript{3}-50hu.II_6P-luc+
transfected cells

L929sA mouse fibroblast cells were cultured in DMEM supplemented with 5% newborn calf serum and 5% FCS, 100 units/ml penicillin and 0.1 mg/ml streptomycin. The L929sA mouse fibroblast cells were stably transfected with plasmid p(IL6-kB)\textsubscript{3}-50hu.II_6P-luc+ by a calcium phosphate precipitation procedure well known in the art. The co-transfected plasmid pPGKβGeobpA, conferring resistance to G418 and expressing constitutive β-galactosidase enzymatic activity, was used as an internal control.

TNF, Dexamethasone, and compound A were obtained and handled as described for example 13.

Inductions were performed in triplicate for each independent experiment, which was carried out at least twice. Inductions with DEX, compound A or synephrine derivatives of the present invention at 1mM, 10mM or at the indicated concentrations respectively, were performed at -2 hours for a total of 8 hours, while TNF (20001 U/ml) was added at time point zero and left on the cells for 6 hours. Synephrine derivatives tested according to this protocol included 1-[4-(isobutanoyloxy)phenyl]-2-[(fer Nbutoxycarbonyl)-methyl-amino]ethyl-1 H-imidazole-1-carboxylate, and 1-[4-(naphthoyloxy)phenyl]-2-[(fer/t-butoxycarbonyl)-methylamino]ethyl-1 H-imidazole-1-carboxylate.

After induction with TNF, cells were lysed with a lysis buffer (commercially available from TROPIX, Bedford, Massachusetts) and samples were assayed for their protein or β-galactosidase content and luciferase activity according to the manufacturer's instructions (Promega Biotech). Promoter activities are calculated as ratios of luciferase over β-galactosidase and represented as 'induction fold ', whereby the promoter activity of the solvent-treated fraction was arbitrarily taken as 1.

In order to demonstrate that these synephrine derivatives are anti-inflammatory agents, and that their mechanism of action is directed at the transcriptional level of NF-kB-driven genes (with NF-kB being widely acknowledged as a key regulatory transcription factor driving inflammatory cytokine gene expression), we tested the recombinant NF-kB-driven promoter construct p(IL6-kB)\textsubscript{3}-50hu.II_6P-luc+, stably integrated into L929sA cells, and
observed for specific and selected synephrine derivatives an inhibition of the pro-inflammatory TNF-induced gene expression in a dose-responsive manner.

Figure 2 illustrates the anti-inflammatory effect of 1-[4-(naphthoyloxy)-phenyll^-Kt/butoxycarbonylJ-methylaminoethyl-1 H-imidazole-i-carboxylate (referred to in figure 2 as Naphth). Figure 3 illustrates the anti-inflammatory effect of 1-[4-(isobutanoyloxy)phenyl]-2-[(fe/t-butoxycarbonyl)-methylamino]ethyl-1 H-imidazole-1-carboxylate (referred to in figure 3 as Isobut). Dexamethasone and compound A (referred to in figure 2 and 3 as DEX and CpdA respectively) were used as positive control based on their known anti-inflammatory effect. As a negative control, solvent control (solvent Ctrl) was performed as well.

It was thus observed that the synephrine derivatives of this invention display a marked anti-inflammatory potential. The anti-inflammatory effectiveness of the active compounds are comparable to the effectiveness obtained by using known anti-inflammatory compounds such as dexamethasone or compound A.
1. A compound represented by the structural formula (I):

\[
\begin{align*}
\text{N} & \quad \text{CH}_3 \\
\text{O} & \quad \text{R}_1 \\
\text{O} & \quad \text{R}_2 \\
\text{C} & \quad \text{R}_3 \\
\end{align*}
\]

wherein:

- \( \text{R}_1 \) is \(-\text{C}(=\text{O})-\text{R}_4 \) or \(-\text{S}(=\text{O})_2-\text{R}_4 \),
- \( \text{R}_2 \) is \(-\text{C}(=\text{O})-\text{R}_6 \),
- \( \text{R}_3 \) is hydrogen, \(-\text{C}(=\text{O})-\text{R}_7 \) or \(-\text{C}(=\text{O})-\text{OR}_7 \) or aryl-\( \text{Ci}_7 \) alkyl;
- \( \text{R}_4 \) is selected from the group consisting of \( \text{R}_5-\text{OR}_5 \), \(-\text{NHR}_5 \), and \(-\text{SR}_5 \),
- \( \text{R}_5 \) is selected from the group consisting of hydrogen, \( \text{C}_{2.10} \) alkyl, \( \text{C}_{3.10} \) cycloalkyl, \( \text{C}_{2.10} \) alkenyl, \( \text{C}_{2.10} \) alkynyl, aryl, aryl-\( \text{Ci}_7 \) alkyl, arylalkyl, and aromatic heterocyclic groups,
- \( \text{R}_6 \) is selected from the group consisting of \( \text{C}_{2.10} \) alkyl, \( \text{C}_{3.10} \) cycloalkyl, \( \text{C}_{2.10} \) alkenyl, \( \text{C}_{2.10} \) alkynyl, aryl, arylalkyl, and aromatic heterocyclic groups,
- \( \text{R}_7 \) is selected from the group consisting of \( \text{C}_{1.10} \) alkyl, \( \text{C}_{2.10} \) alkenyl, aryl, and aryl-\( \text{C}_{1.10} \) alkyl, wherein each of said alkyl or aryl groups may be substituted with one or more substituents independently selected from the group consisting of halogen, alkyl, alkoxy, nitro, cyano and hydroxy, a stereoisomer thereof, a solvate thereof, or a salt thereof.

2. A compound according to claim 1, wherein \( \text{R}_1 \) is \(-\text{C}(=\text{O})-\text{R}_4 \), and \( \text{R}_4 \) is selected from \( \text{R}_5 \).

3. A compound according to claim 1 or claim 2, wherein \( \text{R}_1 \) is \(-\text{C}(=\text{O})-\text{R}_4 \), and \( \text{R}_4 \) is selected from \( \text{R}_5 \), and \( \text{R}_1 \) is the same as \( \text{R}_2 \).

4. A compound according to any of claims 1 to 3, wherein \( \text{R}_1 \) is selected from the group consisting of benzoyl, \( \text{p-toluoyl} \), \( 1\text{-naphthalenecarbonyl} \), 2-
naphthalenecarbonyl, 4-morpholinocarbonyl, 1-piperidinocarbonyl, 1-imidazolidinocarbonyl, 1-pyrrolidinocarbonyl, 2-thiazolecarbonyl, 1-methyl-1H-pyrrole-2-carbonyl, 2-furanecarbonyl, 3-furanecarbonyl, 3-pyridinecarbonyl, 4-pyridinecarbonyl, 2-thiophenecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, 1-adamantanecarbonyl, pipecolinyl and 2-norbornanecarbonyl.

5. A compound according to claim 1 or claim 2, wherein \( R_i \) is selected from the group consisting of acetyl, formyl, propanoyl, butanoyl and pentanoyl.

6. A compound according to any of claims 1 to 5, wherein \( R_3 \) is the same as \( R_2 \).

7. A compound according to any of claims 1 to 6, wherein \( R_3 \) is selected from the group consisting of arylcarbonyl, alkyloxy carbonyl and arylalkyloxy carbonyl.

8. A compound according to any of claims 1 to 7, wherein \( R_3 \) is tert-butoxycarbonyl.

9. A non-toxic acid addition salt of a compound according to any of claims 1 to 8 wherein \( R_3 \) is hydrogen.

10. A method for preparing a compound according to any of claims 1 to 9, comprising the steps of:

(a) reacting synephrine with an amino-protecting reagent to form an amino-protected synephrine,

(b) reacting said amino-protected synephrine with a chloride selected from the group consisting of carboxylic acid chlorides, carbamic acid chlorides, chloroformates, thiocarboxylic acid chlorides, imidic acid chlorides and sulfonic acid chlorides to produce a 4-[2-(N-protected-methylamino)-1-hydroxyethyl] phenyl ester, and
(c) reacting said 4-[2-(N-protected-methylamino)-1-hydroxyethyl]phenyl ester
with an activated carbonyl compound selected from the group consisting of
carboxylic acid chlorides, carboxylic acid chlorides, chloroformates,
imidic acid chlorides, 1,1'-carbonyldiimidazole and 1,1'-carbonylditriazole.

11. A method according to claim 10, wherein step (a) comprises reacting
synephrine with an amino-protected thiazolidine-2-thione.

12. A method according to claim 11, wherein the amino-protected thiazolidine-
2-thione used in step (a) is te/t-butoxycarbonyl-thiazolidine-2-thione and step
(a) results into a fe/t-butoxycarbonyl-protected synephrine.

13. A method according to any of claims 10 to 12, wherein said N-protected
synephrine is reacted in step (b) with a carboxylic acid chloride.

14. A method according to any of claims 10 to 13, further comprising the step
(d) of selectively de-protecting the amino group of the compound resulting
from step (c), without affecting any of groups R1 and R2.

15. A method according to claim 14, wherein said step (d) simultaneously
achieves the formation of a non-toxic acid addition salt.

16. A pharmaceutical composition comprising a therapeutic effective amount
of a compound according to any of claims 1 to 9, and optionally one or more
pharmaceutically acceptable carriers.

17. A pharmaceutical composition according to claim 16, further comprising a
therapeutic amount of one or more anti-inflammatory drugs.

18. Use of a compound according to any of claims 1 to 9 for the manufacture
of a medicament for preventing or treating an inflammatory disease or
disorder.
19. A method of ameliorating or preventing or treating an inflammatory disease or disorder, comprising administration of a synephrine derivative according to any of claims 1 to 9 or a synephrine derivative manufactured by a process according to any of claims 10 to 15 or a composition according to claim 16 or 17 to a patient in need thereof.

20. A compound according to claim 1, wherein when \( R_4 \) is \( R_5 \) and \( R_1 \) is \(-\text{C(=O)-}R_4\) then a heterocyclic group \( R_5 \) is attached through one of its heteroatoms to the carbon atom of the carbonyl group of \( R_1 \).

21. A compound according to claim 1, wherein a heterocyclic group \( R_6 \) is attached through one of its heteroatoms to the carbon atom of the carbonyl group of \( R_2 \).
Fig. 1A

E-selectine-Luc stably integrated in L929sA cells
13-07-05

Fig. 1B

II18 tests 13-07-05
Fig. 2
Fig. 3
**INTERNATIONAL SEARCH REPORT**

**International application No**
PCT/EP2006/012520

**A. CLASSIFICATION OF SUBJECT MATTER**

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

- C07C
- C07D
- A61K
- A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the International search (name of data base and, where practical search terms used)

- EPO-Internal
- WPI Data
- BEILSTEIN Data
- CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Category</th>
<th>Citation of document with indication where appropriate of the relevant passages</th>
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<td>A</td>
<td>WO 01/45693 A (vlaams interuniv inst biotech [BE]; bosscher karolien de [BE]; vanden) 28 June 2001 (2001-06-28) cited in the application claims</td>
<td>1, 9, 10, 16, 18, 19</td>
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</table>

Further documents are listed in the continuation of Box C. See patent family annex.

- Special categories of cited documents:
  - *A:* document defining the general state of the art which is not considered to be of particular relevance
  - *E:* earlier document but published on or after the international filing date
  - *L:* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - *O:* document referring to an oral disclosure use exhibition or other means
  - *P:* document published prior to the international filing date but later than the priority date claimed

- Further documents:
  - *IT:* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - *X:* document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  - *Y:* document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art
  - *A:* document member of the same patent family

**Date of the actual completion of the international search**

19 March 2007

**Date of mailing of the international search report**

29/03/2007

**Name and mailing address of the ISA/Authorized officer**

European Patent Office, P B 5818 Patentlaan 2 NL-2280 HV RUSWIJK Tel (+31-70) 340-8040, Tx 31 651 epo nl, Fax (+31-70) 340-3016

Zervas, Brigitte

Form PCT/ISA/210 (second sheet) (April 2006)
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<tr>
<td>A</td>
<td>EP 0 721 939 A1 (KOREA RES INST CHEM TECH [KR]) 17 July 1996 (1996-07-17) claims; examples</td>
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INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos. because they relate to subject matter not required to be searched by this Authority, namely.

Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos. because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically.

3. [ ] Claims Nos. because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows.

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.
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