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Ksander

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[54] **BIARYL SUBSTITUTED 4-AMINO-BUTYRIC ACID AMIDES**

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[51] **Int. Cl.**[5] **C07C 229/34**; A61K 31/235

[52] **U.S. Cl.** **514/533**; 514/563; 546/335; 549/452; 558/267; 558/275; 560/41; 562/450

[58] **Field of Search** 560/41, 39; 562/450; 549/77, 452, 496; 546/335; 558/267, 275; 514/533, 563

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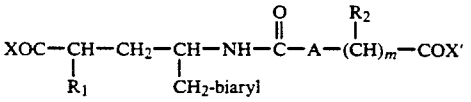
[57] **ABSTRACT**

The invention relates to biaryl substituted 4-amino-butyric acid derivatives of formula I



(I)

wherein COX and COX′ independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; R_1 represents hydrogen, lower alkyl, C_3–C_7-cycloalkyl-lower alkyl, aryl-lower alkyl, biaryl-lower alkyl, lower alkoxy, aryl-lower alkoxy, aryloxy, N-lower alkylamino, N,N-di-lower alkylamino, N-aryl-lower alkylamino, N,N-di-aryl-lower alkylamino, N-arylamino, N,N-diarylamino, lower alkanoylamino, aryl-lower alkanoylamino or aroylamino; R_2 represents hydrogen, hydroxy, lower alkoxy, lower alkyl, aryl-lower alkyl, C_3–C_7-cycloalkyl-lower alkyl, amino-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkylthio-lower alkyl or aryl-lower alkoxy-lower alkyl; biaryl represents phenyl substituted by carbocyclic or heterocyclic aryl; A represents a direct bond, lower alkylene, phenylene or cyclohexylene; m represents 1 or zero, provided that m represents 1 when A is a direct bond; or pharmaceutically acceptable salts thereof; pharmaceutical compositions comprising said compounds; methods for the preparation of said compounds and for the preparation of intermediates; and methods of treating disorders in mammals which are responsive to the inhibition of neutral endopeptidases by administration of said compounds to mammals in need of such treatment.

11 Claims, No Drawings

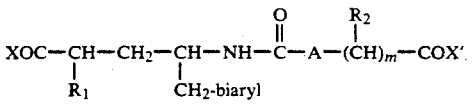
BIARYL SUBSTITUTED 4-AMINO-BUTYRIC ACID AMIDES

SUMMARY OF THE INVENTION

Endogenous atrial natriuretic peptides (ANP), also called atrial natriuretic factors (ANF) have diuretic, natriuretic and vasorelaxant functions in mammals. The natural ANF peptides are metabolically inactivated, in particular by a degrading enzyme which has been recognized to correspond to the enzyme neutral endopeptidase (NEP) EC 3.4. 24.11, also responsible for e.g. the metabolic inactivation of enkephalins.

The aim of the present invention is to provide novel biaryl substituted 4-amino-butyric acid amide derivatives described below which are useful as neutral endopeptidase (NEP) inhibitors, e.g. as inhibitors of the ANF-degrading enzyme in mammals, so as to prolong and potentiate the diuretic, natriuretic and vasodilator properties of ANF in mammals, by inhibiting the degradation thereof to less active metabolites. The compounds of the invention are thus particularly useful for the treatment of conditions and disorders responsive to the inhibition of neutral endopeptidase EC 3.4. 24.11, particularly cardiovascular disorders, such as hypertension, renal insufficiency including edema and salt retention, pulmonary edema and congestive heart failure. By virtue of their inhibition of neutral endopeptidase, the compounds of the invention may also be useful for the treatment of pain, depression and certain psychotic conditions. Other potential indications include the treatment of angina, premenstrual syndrome, Meniere's disease, hyperaldosteronism, hypercalciuria, ascites, glaucoma, asthma, inflammations and gastrointestinal disorders such as diarrhea, irritable bowel syndrome and gastric hyperacidity.

The present invention relates to biaryl substituted 4-amino-butyric acid derivatives of formula I



wherein COX and COX' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester or amide; R_1 represents hydrogen, lower alkyl, C_3–C_7-cycloalkyl-lower alkyl, aryl-lower alkyl, biaryl-lower alkyl, lower alkoxy, aryl-lower alkoxy, aryloxy, N-lower alkylamino, N,N-di-lower alkylamino, N-aryl-lower alkylamino, N,N-di-aryl-lower alkylamino, N-arylamino, N,N-diarylamino, lower alkanoylamino, aryl-lower alkanoylamino or aroylamino; R_2 represents hydrogen, hydroxy, lower alkoxy, lower alkyl, aryl-lower alkyl, C_3–C_7-cycloalkyl-lower alkyl, amino-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkoxy-lower alkyl, aryl-lower alkylthio-lower alkyl or aryl-lower alkoxy-lower alkyl; biaryl represents phenyl substituted by carbocyclic or heterocyclic aryl; A represents a direct bond, lower alkylene, phenylene or cyclohexylene; m represents 1 or zero, provided that m represents 1 when A is a direct bond; or a pharmaceutically acceptable salt thereof.

Pharmaceutically acceptable ester and amide derivatives are preferably prodrug derivatives, such being convertible by solvolysis or under physiological conditions to the free carboxylic acids of formula I wherein COX and/or COX' represent carboxyl.

Compounds of formula I and derivatives thereof, depending on the nature of substituents, possess one or more asymmetric carbon atoms. The resulting diastereoisomers and optical antipodes are encompassed by the instant invention.

DETAILED DESCRIPTION OF THE INVENTION

The definitions used herein, unless denoted otherwise, have the following meanings within the scope of the present invention.

The term biaryl represents phenyl substituted by carbocyclic aryl or heterocyclic aryl as defined herein, ortho, meta or para to the point of attachment of the phenyl ring, advantageously para; biaryl is also represented as the $—C_6H_4—R_3$ substituent in formulae herein.

Carbocyclic aryl preferably represents preferably monocyclic carbocyclic aryl or optionally substituted naphthyl.

Monocyclic carbocyclic aryl represents optionally substituted phenyl, being preferably phenyl or phenyl substituted by one to three substituents, such being advantageously lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, halogen, cyano, trifluoromethyl, lower alkanoylamino or lower alkoxycarbonyl. Monocyclic carbocyclic aryl particularly preferably represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, hydroxy, halogen, cyano or trifluoromethyl.

Optionally substituted naphthyl represents 1- or 2-naphthyl or 1- or 2-naphthyl preferably substituted by lower alkyl, lower alkoxy or halogen.

Heterocyclic aryl represents preferably monocyclic heterocyclic aryl such as optionally substituted thienyl, indolyl, imidazolyl, furanyl, pyridyl, pyrrolyl or N-lower alkylpyrrolyl.

Optionally substituted furanyl represents 2- or 3-furanyl or 2- or 3-furanyl preferably substituted by lower alkyl.

Optionally substituted pyridyl represents 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl preferably substituted by lower alkyl, halogen or cyano.

Optionally substituted thienyl represents 2- or 3-thienyl or 2- or 3-thienyl preferably substituted by lower alkyl.

Optionally substituted indolyl represents preferably 2- or 3-indolyl or 2- or 3-indolyl preferably substituted by lower alkyl, lower alkoxy or halogen.

Optionally substituted imidazolyl is preferably 1- or 2-imidazolyl or 1- or 2-imidazolyl preferably substituted by lower alkyl.

Aryl as in aryl-lower alkyl, aryl-lower alkoxy, aryloxy, N-arylamino, N,N-diarylamino, aryl-lower alkoxycarbonyl or aryl-lower alkanoylamino is preferably phenyl or phenyl substituted by one or two of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen, trifluoromethyl, cyano, lower alkanoylamino or lower alkoxycarbonyl.

The term "lower" referred to herein in connection with organic radicals or compounds respectively defines such with up to and including 7, preferably up and including 4 and advantageously one or two carbon atoms. Such may be straight chain or branched.

A lower alkyl group preferably contains 1–4 carbon atoms and represents e.g. ethyl, n- or iso-propyl, n-, iso-, sec.- or tert.-butyl or advantageously methyl.

A lower alkoxy group preferably contains 1–4 carbon atoms and represents for example methoxy, n-propoxy, isopropoxy, n-, iso-, sec.- or tert.-butoxy or advantageously ethoxy.

Aryl-lower alkyl is advantageously benzyl or phenethyl optionally substituted by one or two of lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen or trifluoromethyl.

Aryl-lower alkoxy represents advantageously e.g. benzyloxy, benzyloxy substituted by lower alkyl, lower alkoxy, lower alkanoyloxy, halogen or trifluoromethyl, or pyridylmethoxy.

Aryloxy preferably represents phenoxy or phenoxy substituted by lower alkyl, lower alkoxy, lower alkanoyloxy, halogen or trifluoromethyl.

N-arylamino and N,N-diarylamino represent advantageously N-phenylamino or N,N-diphenylamino optionally substituted in the phenyl moiety or phenyl moieties by lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen or trifluoromethyl.

The term C_3–C_7-cycloalkyl represents a saturated cyclic hydrocarbon radical which contains 3 to 7 and preferably 5 to 7 ring carbon and is, most preferably, cyclopentyl or cyclohexyl.

The term cycloalkyl-lower alkyl represents preferably 1- or 2-(cyclopentyl or cyclohexyl)ethyl, 1-, 2- or 3-(cyclopentyl or cyclohexyl)propyl, or 1-, 2-, 3- or 4-(cyclopentyl or cyclohexyl)-butyl.

Amino-lower alkyl represents preferably amino-(ethyl, propyl or butyl), particularly omega-amino-(ethyl, propyl or butyl).

A N-lower alkylamino group preferably contains 1–4 carbon atoms in the lower alkyl portion and represents, for example, N-n-propyl-amino, N-iso-propylamino, N-n-butylamino, N-tert.-butylamino and advantageously N-methylamino or N-ethylamino.

A N,N-di-lower alkylamino group preferably contains 1–4 carbon atoms in each lower alkyl portion and represents, for example, N,N-dimethylamino, N-methyl-N-ethylamino and advantageously N,N-diethylamino.

Hydroxy-lower alkyl is for example 2-hydroxyethyl and preferably hydroxymethyl.

Lower alkylthio as in lower alkylthio-lower alkyl represents advantageously C_1–C_4-alkylthio and preferably methylthio or ethylthio.

Lower alkylene represents branched or straight chain alkylene of 1 to 7 carbon atoms, advantageously straight chain (or linear) alkylene, such as methylene, ethylene, propylene, butylene, pentylene or hexylene and most preferably straight chain C_1–C_4-alkylene.

Phenylene represents preferably 1,3 or 1,4-phenylene, advantageously 1,4-phenylene.

Cyclohexylene represents preferably 1,4-cyclohexylene.

Halogen (halo) preferably represents fluoro or chloro, but may also be bromo or iodo.

Lower alkanoyloxy advantageously contains 2 to 5 carbon atoms and is preferably acetoxy, pivaloyloxy or propionyloxy.

Lower alkanoylamino advantageously contains 2 to 5 carbon atoms and is preferably acetylamino or propionylamino.

A lower alkoxycarbonyl group preferably contains 1 to 4 carbon atoms in the alkoxy portion and represents, for example, methoxycarbonyl, n-propoxycarbonyl, iso-propoxycarbonyl or advantageously ethoxycarbonyl.

Aroylamino is preferably benzoylamino or benzoylamino substituted on the benzene ring by lower alkyl, lower alkoxy, halogen or trifluoromethyl.

Carboxyl esterified in form of a pharmaceutically acceptable ester, represents advantageously a prodrug ester that may be convertible by solvolysis or under physiological conditions to the free carboxylic acid, such being preferably C_1–C_{20}-alkoxycarbonyl, advantageously lower alkoxycarbonyl; (amino, acylamino, mono-or di-lower alkylamino)-lower alkoxycarbonyl; carboxy-lower alkoxycarbonyl, e.g. alpha-carboxy-lower alkoxycarbonyl; lower alkoxycarbonyl-lower alkoxycarbonyl, e.g. alpha-lower alkoxycarbonyl-lower alkoxycarbonyl; α-(di-lower alkylamino, amino, mono-lower alkylamino, morpholino, piperidino, pyrrolidino, 1-lower alkylpiperazino)-carbonyl-lower alkoxycarbonyl; aryl-lower alkoxycarbonyl, preferably optionally (halo, lower alkyl or lower alkoxy)-substituted benzyloxycarbonyl, or pyridylmethoxycarbonyl; 1-(hydroxy, lower alkanoyloxy or lower alkoxy)-lower alkoxycarbonyl, e.g. pivaloyloxymethoxycarbonyl; (hydroxy, lower alkanoyloxy or lower alkoxy)-lower alkoxymethoxycarbonyl; bicycloalkoxycarbonyl-lower alkoxycarbonyl, e.g. bicyclo[2,2,1]-heptyloxycarbonyl-lower alkoxycarbonyl, especially bicyclo-[2,2,1]-heptyloxycarbonylmethoxycarbonyl such as bornyloxycarbonylmethoxycarbonyl; 1-(lower alkoxycarbonyloxy)-lower alkoxycarbonyl; 5-indanyloxycarbonyl; 3-phthalidoxycarbonyl and (lower alkyl, lower alkoxy or halo)-substituted 3-phthalidoxycarbonyl; polyhydroxy-lower alkoxycarbonyl or protected polyhydroxy-lower alkoxycarbonyl in which polyhydroxy-lower alkoxy and protected polyhydroxy-lower alkoxy represent preferably dihydroxypropyloxy or trihydroxybutyloxy wherein hydroxy groups are free or one or more, as appropriate, are protected in form of esters, e.g. a lower alkanoyl or a benzoyl ester, in form of ethers, e.g. a lower alkyl or benzyl ether, or, in case two vicinal hydroxy groups are involved, in the form of acetals or ketals, e.g. a lower alkylidene, a benzylidene or a 5- or 6-membered cycloalkylidene derivative.

Protected polyhydroxy-lower alkoxycarbonyl advantageously represents (2,2-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl.

Acyl as in acyloxy or acylamino represents preferably lower alkanoyl, carbocyclic aryl-lower alkanoyl, aroyl, lower alkoxycarbonyl or aryl-lower alkoxycarbonyl, advantageously lower alkanoyl. Lower alkoxycarbonyl for acyl is preferably t-butoxycarbonyl (abbreviated t-BOC). Aryl-lower alkoxycarbonyl for acyl is preferably benzyloxycarbonyl (abbreviated CBZ).

Carboxy-lower alkoxycarbonyl represents advantageously e.g. 1-carboxyethoxycarbonyl.

Lower alkoxycarbonyl-lower alkoxycarbonyl represents advantageously e.g. 1-(ethoxycarbonyl)ethoxycarbonyl.

Amino-lower alkoxycarbonyl, mono-lower alkylamino-lower alkoxycarbonyl, di-(lower)alkylamino-lower alkoxycarbonyl advantageously represent e.g. aminoethoxycarbonyl, ethylaminoethoxycarbonyl, diethylaminoethoxycarbonyl.

Lower alkylidene is preferably isopropylidene.

Cycloalkylidene is preferably cyclohexylidene.

Carboxyl esterified in form of a pharmaceutically acceptable prodrug ester represents most advantageously C_1–C_4-alkoxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl,

pivaloyloxymethoxycarbonyl, 1-(C_2–C_4-alkanoyloxy)-ethoxycarbonyl, (2,2-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl, 5-indanyloxycarbonyl, 3-phthalidoxycarbonyl, bornyloxycarbonylmethoxycarbonyl, 1-(C_1–C_4-alkoxycarbonyloxy)-ethoxycarbonyl or 3-pyridylmethoxycarbonyl.

Carboxyl derivatized in the form of a pharmaceutically acceptable amide represents preferably carbamoyl or N-substituted carbamoyl, advantageously [lower alkylamino, arylamino, di-lower alkylamino, morpholino, N-lower alkylpiperazino, pyrrolidino, piperidino, perhydroazepino, (amino or acylamino)-lower alkylamino or aryl-lower alkylamino]-carbonyl.

Pharmaceutically acceptable salts are either pharmaceutically acceptable acid addition salts for any basic compounds of the invention or salts derived from pharmaceutically acceptable bases for any acidic compounds of the invention.

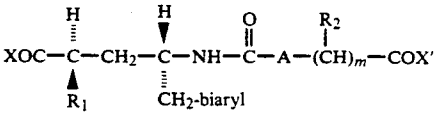
Pharmaceutically acceptable salts of basic compounds of the invention are acid addition salts, which are preferably such of therapeutically acceptable inorganic or organic acids, such as strong mineral acids, for example hydrohalic, e.g. hydrochloric or hydro-bromic acid, sulfuric, phosphoric or nitric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g. formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, gluconic, citric, maleic, fumaric, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, pamoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, 1,2-ethanedisulfonic acid, benzenesulfonic, p-toluenesulfonic, naphthalenesulfonic, sulfanilic, cyclohexylsulfamic acid, or ascorbic acid.

Pharmaceutically acceptable salts of the acidic compounds of the invention, e.g. those having a free carboxyl group are salts formed with pharmaceutically acceptable bases, e.g. alkali metal salts (e.g. sodium, potassium salts), alkaline earth metal salts (e.g. magnesium, calcium salts), ammonium salts, mono-, di- or tri-lower (alkyl or hydroxyalkyl)-ammonium salts (e.g. ethanolammonium, diethanolammonium, triethanolammonium, tromethamine salts).

The compounds of the invention, of formula I and derivatives thereof may contain several asymmetric carbon atoms, depending on the nature of the substituents. Thus the compounds of the invention exist in the form of geometric isomers, racemates, diastereoisomers, pure enantiomers or mixtures thereof, all of which are within the scope of the invention.

For example, the compounds of formula I exist in isomeric forms, e.g. wherein the asymmetric carbon atom on the butyryl chain bearing the R_1 and/or biarylmethyl groups may either exist in the S or R configuration. The compounds of the invention, e.g. those of formula I having said two asymmetric centers exist as two different racemic diastereoisomeric forms which may be called erythro and threo depending on the relative orientation of the R_1 and biarylmethyl substituents of the chain. Each of the two racemates consists of the optically active enantiomers (or antipodes) having (S,S), (R,R), (R,S) or (S,R) configurations, respectively.

Preferred is the threo racemic form and particularly the enantiomeric form depicted in formula I'

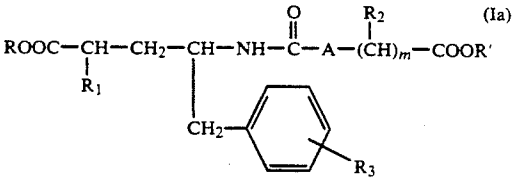


(I')

wherein COX, COX', R_1, R_2, A, biaryl and m have the meanings as defined herein above for compounds of formula I. The compounds of formulae Ia, Ib, Ic, Id, Ie and If given below are present as well, preferably in the enantiomeric form depicted in formula I'.

Illustrative thereof, in the above compounds of formula I wherein R_1 is lower alkyl, the carbon atom carrying said substituent is assigned the (R)-configuration; and the carbon atom carrying the biarylmethyl substituent is assigned the (S)-configuration.

More particularly, the present invention is concerned with and has for its object the compounds of formula Ia



(Ia)

wherein COOR and COOR' independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 represents hydrogen, lower alkyl, lower alkoxy, N-lower alkylamino, lower alkanoylamino, aryl-lower alkyl, aryl-lower alkoxy, aryloxy, N-arylamino or aroylamino wherein aryl in each case represents phenyl optionally substituted by lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl, or aryl represents thienyl or furanyl optionally substituted by lower alkyl; R_2 represents hydrogen, hydroxy, lower alkyl or aryl-lower alkyl wherein aryl independently has the meaning given above under R_1; R_3 represents phenyl, or phenyl substituted by lower alkyl, lower alkoxy, halogen, cyano, acyloxy or trifluoromethyl; or R_3 represents thienyl or furanyl optionally substituted by lower alkyl; A represents a direct bond, lower alkylene, 1,4-phenylene or 1,4-cyclohexylene; m represents 1 or zero provided that m represents 1 when A is a direct bond; or a pharmaceutically acceptable salt thereof.

Advantageously, R_3 is located in the para position.

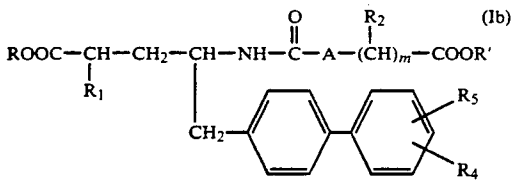
Particularly preferred embodiments of the invention as described above relate to:

a) compounds wherein R_3 is phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen, cyano, acyloxy or trifluoromethyl;

b) compounds wherein A is lower alkylene, m represents 1 or zero, and R_2 represents hydrogen, lower alkyl, hydroxy or lower alkoxy.

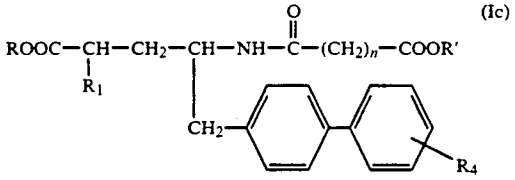
c) compounds wherein R_1 represents hydrogen, lower alkyl, lower alkoxy or aryl-lower alkyl wherein aryl represents phenyl optionally substituted by one or two of lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl; most preferably compounds wherein R_1 represents lower alkoxy or lower alkyl.

A particular embodiment of the invention relates to compounds of formula Ib



wherein COOR and COOR′ independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 is hydrogen, lower alkyl, lower alkoxy or aryl-lower alkyl wherein aryl represents phenyl optionally substituted by lower alkyl, lower alkoxy, halogen, hydroxy, cyano, acyloxy or trifluoromethyl; R_2 represents hydrogen, hydroxy or lower alkoxy; R_4 and R_5 independently represent hydrogen, lower alkyl, hydroxy, lower alkoxy, halogen, cyano or trifluoromethyl; A represents lower alkylene; m represents 1 or zero; or a pharmaceutical acceptable salt thereof.

Particularly preferred are compounds of formula Ic

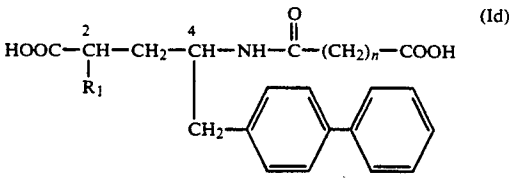


wherein COOR and COOR′ independently represent carboxyl or carboxyl derivatized in form of a pharmaceutically acceptable ester; R_1 is lower alkyl or lower alkoxy; R_4 represents hydrogen, lower alkyl, lower alkoxy, halogen, or trifluoromethyl; n represents an integer 1 through 6; or a pharmaceutical acceptable salt thereof.

Preferred are compounds of formula Ic wherein COOR and COOR′ independently represent carboxyl, C_1–C_{20}-alkoxycarbonyl, (carbocyclic or heterocyclic aryl)-lower alkoxycarbonyl, (di-lower alkylamino, N-lower alkylpiperazino, morpholino, pyrrolidino, piperidino or perhydrazepino)-C_2 to C_4-alkoxycarbonyl, dihydroxypropyloxycarbonyl protected in form of a ketal, 5-indanyloxycarbonyl, 3-phthalidoxycarbonyl, bicycloalkoxycarbonyl-lower alkoxycarbonyl, α-(lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkoxycarbonyl, 1-(lower alkoxycarbonyloxy)-lower alkoxycarbonyl or 1-(lower alkanoyloxy)-lower alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

Particularly preferred are said compounds of formula Ic wherein COOR and COOR′ independently represent carboxyl, C_1–C_4-alkoxycarbonyl, 3-pyridylmethoxycarbonyl, benzyloxycarbonyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, 5-indanyloxycarbonyl, 1-(C_2–C_5-alkanoyloxy)-ethoxycarbonyl, 3-phthalidoxycarbonyl, (2,2′-dimethyl-1,3-dioxolan-4-yl)-methoxycarbonyl, bornyloxycarbonylmethoxycarbonyl, 1-(C_1–C_4-alkoxycarbonyloxy)-ethoxycarbonyl; or a pharmaceutically acceptable salt thereof.

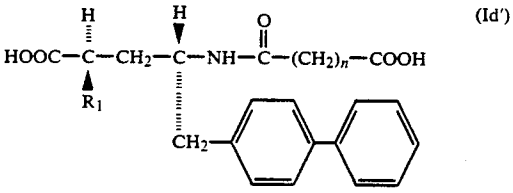
A preferred embodiment of the invention relates to compounds of formula Id



wherein R_1 is lower alkyl; n is an integer 1 through 4; or a pharmaceutically acceptable mono- or di-ester derivative thereof in which one or two of the acidic hydroxy groups of the carboxyl functional groups are esterified in form of a mono- or di-pharmaceutically acceptable ester; or a pharmaceutically acceptable salt thereof; or an optical antipode thereof.

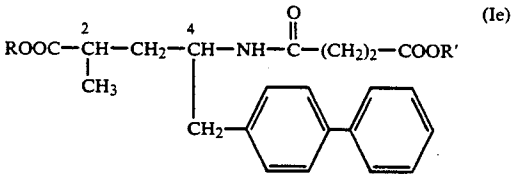
Preferred are said compounds of formula Id wherein R_1 is methyl and n is 2; and mono- or di-esters thereof.

As discussed before, the butyric acid compounds of e.g. formula Id exist in two distinct diastereomeric forms which may be called erythro and threo. Preferred are e.g. the compounds of formula Id as the threo diastereomer (racemate), more particularly as the enantiomeric form having the R-configuration at C-atom 2 and the S-configuration at C-atom 4 and wherein the butyryl portion is as depicted in formula Id′



wherein R_1 and n are as defined under formula Id; or a pharmaceutical acceptable mono-or diester derivative thereof; or a pharmaceutical acceptable salt thereof.

Particularly preferred are compounds of formula Ie



wherein COOR and COOR′ independently represent carboxyl or carboxyl esterified in form of a pharmaceutical acceptable prodrug ester; or a pharmaceutically acceptable salt thereof.

Particularly preferred embodiments of the invention as described above relate to:

(a) compounds of the above formula Ie wherein R and R′ independently represent hydrogen, C_1–C_4-alkyl, benzyl optionally substituted on phenyl by lower alkyl, lower alkoxy, halo or trifluoromethyl, pivaloyloxymethyl, 1-(C_2–C_4-alkanoyloxy)-ethyl, (2,2-dimethyl-1,3-dioxolan-4-yl)-methyl, 5-indanyl, 3-phthalidyl, bornyloxycarbonylmethyl, 1-(C_1–C_4-alkoxycarbonyloxy)-ethyl or 3-pyridylmethyl; or a pharmaceutically acceptable salt thereof;

(b) compounds of the above formula Ie wherein COOR′ is carboxyl; and COOR represents carboxyl or carboxyl derivatized in form of a pharma-

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