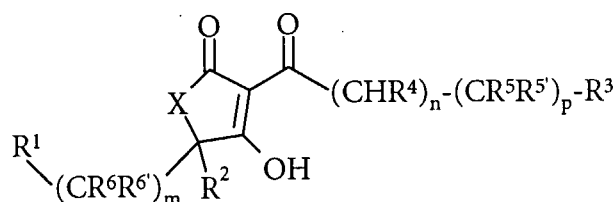


TETRONIC AND TETRAMIC ACIDS AS INHIBITORS OF BETA-SECREASE

This invention relates to new tetronic and tetramic acid derivatives with beta-secretase inhibitory activity, processes for their preparation, compositions containing said tetronic and tetramic acid derivatives and their use in the treatment and prevention of diseases.

5 One object of the present invention is a compound of the formula I



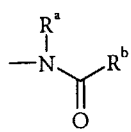
wherein

X is O or NH;

10 R¹ is lower alkyl, cycloalkyl, heterocycloalkyl or aryl, wherein the aryl ring is unsubstituted or substituted by benzyloxy;

R² is H, lower alkyl or aryl;

R³ is lower alkyl, -SCH₃, acetyl,



, wherein R^a is H or lower alkyl, R^b is lower alkyl, heteroaryl, -OC(CH₃)₃ or aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl,

15 cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by lower alkyl or aryl,

heterocycloalkyl, wherein the heterocycloalkyl ring is unsubstituted or substituted by -COOC(CH₃)₃;

20 (CH=CR⁷)₆-aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl, alkoxy, hydroxyl, benzyloxy, halogen, acetyl, -(CH₂)₂NHSO₂Ph,

-NHCO(CH₂)₂NHCOOC(CH₃)₃, -(CH₂)₂NHCOC₆H₃OCH₃Cl, or for the non aromatic part of fused ring system also by oxo,

o is 0 or 1;

R' is H or lower alkyl,

5 aryloxy, wherein the aryl ring is unsubstituted or substituted by lower alkyl or alkoxy, or

(CH=CH)_q-heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by lower alkyl, acetyl, alkoxy, halogen, -COOC(CH₃)₃ or by halogen substituted benzyl; or for the non aromatic part of fused ring system also by oxo;

10 q is 0 or 1;

R⁴ is H, lower alkyl, -(CH₂)₂SCH₃, -NHCOCH₃, -NHSO₂p-Cl-Ph, amino, -NHCOOC(CH₃)₃, hydroxyl, aryl, benzyl or halogen substituted benzyl;

R⁵, R^{5'} are independently from each other H, lower alkyl or aryl;

R⁶, R^{6'} are independently from each other H, lower alkyl or -SCH₃;

15 m is 1, 2 or 3;

n is 0 or 1; and

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts thereof,

with the exception that the compound is not 3-acetyl-4-hydroxy-5-isobutyl-1,5-dihydro-pyrrol-2-one or 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-5H-furan-2-one.
20

Compounds of 3-acetyl-4-hydroxy-5-isobutyl-1,5-dihydro-pyrrol-2-one and 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-5H-furan-2-one are disclosed in EP 0841063 A1. The said compounds are claimed in said European Patent Application to be effective in preventing and treating cytopenia caused by cancer chemotherapy, radiation therapy,
25 and the like.

Unless otherwise stated, the following terms used in this Application have the definitions given below. It must be noted that, as used in the description and the claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise.

“Alkyl” means the monovalent linear or branched saturated hydrocarbon moiety, consisting solely of carbon and hydrogen atoms, having from one to twelve carbon atoms. “Lower alkyl” refers to an alkyl group of one to six carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl, octyl, dodecyl, and the like or those which are specifically exemplified herein.

“Alkoxy” means a moiety of the formula $-OR^z$, wherein R^z is an alkyl moiety as defined herein. Examples of alkoxy moieties include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like or those which are specifically exemplified herein.

10 “Aryl” means a mono-, bi- or tricyclic aromatic radical consisting of one or more fused rings, in which at least one ring is aromatic in nature. The aryl group can optionally be substituted with one, two, three or four substituents, wherein each substituent is independently hydroxy, cyano, alkyl, alkoxy, thiol, thioalkyl, halo, haloalkyl, nitro, amino, monoalkylamino, phenyloxy, benzyloxy, acetyl, $(CH_2)_2NHSO_2Ph$,
15 $-NHCO(CH_2)_2NHCOOC(CH_3)_3$, $-(CH_2)_2NHCOC_6H_3OCH_3Cl$ or for the non aromatic part fused ring system also by oxo, unless otherwise specifically indicated. Examples of aryl moieties include, but are not limited to, optionally substituted phenyl, optionally substituted naphthyl, optionally substituted 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5yl, optionally substituted 9H-fluoren-9-yl, optionally substituted indan-1-yl and the like
20 or those which are specifically exemplified herein.

“Aryloxy” means a moiety of the formula $-OR^y$, wherein R^y is an aryl moiety as defined herein. Examples of aryloxy moieties include, but are not limited to, optionally substituted phenoxy and optionally substituted naphthoxy.

“Cycloalkyl” means a monovalent or divalent saturated carbocyclic moiety
25 consisting of mono- or bicyclic rings. Cycloalkyl can optionally be substituted with one, two, three or four substituents, wherein each substituent is independently hydroxy, alkyl, alkoxy, halogen, amino, unless otherwise specifically indicated. Examples of cycloalkyl moieties include, but are not limited to, optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted
30 cyclopentenyl, optionally substituted cyclohexyl, optionally substituted cyclohexylen, optionally substituted cycloheptyl, and the like or those which are specifically exemplified herein.

“Halogen” refers to a substituent fluoro, chloro, bromo, or iodo.

“Heteroaryl” means a monocyclic, bicyclic or tricyclic radical of 5 to 12 ring atoms
35 having at least one aromatic ring and furthermore containing one, two, or three ring

heteroatoms selected from N, O, or S, the remaining ring atoms being C. Heteroaryl can optionally be substituted with one, two, three or four substituents, wherein each substituent is independently hydroxy, cyano, alkyl, alkoxy, thioalkyl, halo, haloalkyl, hydroxyalkyl, alkoxycarbonyl, amino, acetyl, -NHCOOC(CH₃)₃ or halogen substituted benzyl, or for the non aromatic part of cyclic ring also by oxo, unless otherwise specifically indicated. Examples of heteroaryl moieties include, but are not limited to, optionally substituted imidazolyl, optionally substituted oxazolyl, optionally substituted thiazolyl, optionally substituted pyrazinyl, optionally substituted pyrrolyl, optionally substituted pyrazinyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted indonyl, optionally substituted isoquinolinyl, optionally substituted carbazol-9-yl, optionally substituted furanyl, optionally substituted benzofuranyl, optionally substituted benzo[1,2,3]thiadiazolyl, optionally substituted benzo[b]thiophenyl, optionally substituted 9H-thioxanthenyl, optionally substituted thieno[2,3-c]pyridinyl and the like or those which are specifically exemplified herein.

“Heterocycloalkyl” means a monovalent saturated moiety, consisting of one, two or three rings, incorporating one, two, or three heteroatoms (chosen from nitrogen, oxygen or sulfur). Heterocycloalkyl can optionally be substituted with one, two, three or four substituents, wherein each substituent is independently hydroxy, alkyl, alkoxy, thioalkyl, halo, haloalkyl, hydroxyalkyl, alkoxycarbonyl, amino, alkylamino, dialkylamino, aminocarbonyl, or carbonylamino, unless otherwise specifically indicated. Examples of heterocyclic moieties include, but are not limited to, optionally substituted tetrahydro-furanyl, optionally substituted piperidinyl, optionally substituted pyrrolidinyl, optionally substituted morpholinyl, optionally substituted piperazinyl, and the like or those which are specifically exemplified herein.

“Pharmaceutically acceptable salts” of a compound means salts that are pharmaceutically acceptable, as defined herein, and that possess the desired pharmacological activity of the parent compound. Such salts include:

salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic or inorganic base. Acceptable organic bases include diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide; or

addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid,

ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphthoic acid, 2-hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, 2-naphthalenesulfonic acid, propionic acid, salicylic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, and the like.

“LDA” means lithiumdiisopropylamide.

“DCC” means dicyclohexyl carbodiimide.

“EDC” means N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride.

“DMAP” means 4-dimethylamino pyridine.

10 “BOC” means t-butyloxycarbonyl.

It has been found that the compounds of general formula I are β -secretase inhibitors and the related compounds may be useful in the treatment of Alzheimer's disease.

Alzheimer's disease (AD) is the most common cause of dementia in later life.

15 Pathologically AD is characterized by the deposition in the brain of amyloid in extracellular plaques and intracellular neurofibrillary tangles. The amyloid plaques are mainly composed of amyloid peptides (A β peptides) which originate from the β -Amyloid Precursor Protein (APP) by a series of proteolytic cleavage steps. Several forms of APP have been identified of which the most abundant are proteins of 695, 751 and 770

20 amino acids length. They all arise from a single gene through differential splicing. The A β peptides are derived from the same domain of the APP but differ at their N- and C-termini, the main species are of 40 and 42 amino-acid length.

A β peptides are produced from APP through the sequential action of 2 proteolytic enzymes termed β - and γ -secretase. β -Secretase cleaves first in the

25 extracellular domain of APP just outside of the trans-membrane domain (TM) to produce a C-terminal fragment of APP containing the TM- and cytoplasmatic domain (CTF β). CTF β is the substrate for γ -secretase which cleaves at several adjacent positions within the TM to produce the A β peptides and the cytoplasmic fragment. The β -Secretase is a typical aspartyl protease.

30 It is hypothesized that inhibiting the production of A-beta will prevent and reduce neurological degeneration, by controlling the formation of amyloid plaques, reducing neurotoxicity and, generally, mediating the pathology associated with A-beta production.

Compounds that inhibit beta- or gamma-secretase activity, either directly or indirectly, could control the production of A-beta.

Thus, the compounds of this invention will be useful in treating AD by blocking the activity of β -secretase and reducing or preventing the formation of the A-beta

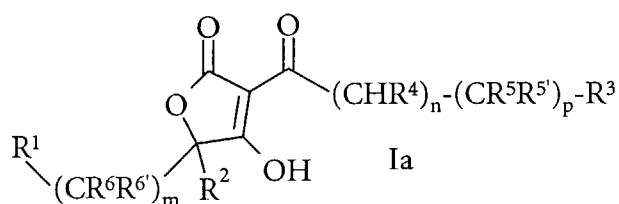
5 peptides.

Objects of the present invention are the compounds of formula I per se, the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases, relating to the β -secretase inhibition, their manufacture, medicaments based on a compound in accordance with the invention and
10 their production as well as the use of compounds of formula I in the control or prevention of Alzheimer's disease.

A further object of the invention are all forms of enantiomers, racemates or diastereomeric mixtures of compounds of formula I.

In one embodiment the invention provides the compounds of the general formula

15 Ia



wherein

R¹ is lower alkyl, cycloalkyl, heterocycloalkyl or aryl, wherein the aryl ring is unsubstituted or substituted by benzyloxy;

20 R² is H, lower alkyl or aryl;

R³ is lower alkyl, -SCH₃, acetyl,

, wherein R^a is H or lower alkyl, R^b is lower alkyl, heteroaryl, -OC(CH₃)₃ or aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl,

cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by lower alkyl
25 or aryl,

heterocycloalkyl, wherein the heterocycloalkyl ring is unsubstituted or substituted by $-\text{COOC}(\text{CH}_3)_3$;

- ($\text{CH}=\text{CR}'$)_o-aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl, alkoxy, hydroxyl, benzyloxy, halogen, acetyl, $-(\text{CH}_2)_2\text{NHSO}_2\text{Ph}$,
 5 $-\text{NHCO}(\text{CH}_2)_2\text{NHCOOC}(\text{CH}_3)_3$, $-(\text{CH}_2)_2\text{NHCOC}_6\text{H}_3\text{OCH}_3\text{Cl}$, or for the non aromatic part of fused ring system also by oxo,
 o is 0 or 1;
 R' is H or lower alkyl,

- aryloxy, wherein the aryl ring is unsubstituted substituted by lower alkyl or alkoxy,
 10 or

- ($\text{CH}=\text{CH}$)_q-heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by lower alkyl, acetyl, alkoxy, halogen, $-\text{COOC}(\text{CH}_3)_3$ or by halogen substituted benzyl; or for the non aromatic part of fused ring system also by oxo;
 q is 0 or 1;

- 15 R⁴ is H, lower alkyl, $-(\text{CH}_2)_2\text{SCH}_3$, $-\text{NHCOCH}_3$, $-\text{NHSO}_2\text{p-Cl-Ph}$, amino, $-\text{NHCOOC}(\text{CH}_3)_3$, hydroxyl, aryl, benzyl or halogen substituted benzyl;

R⁵, R^{5'} are independently from each other H, lower alkyl or aryl;

R⁶, R^{6'} are independently from each other H, lower alkyl or $-\text{SCH}_3$;

m is 1, 2 or 3;

- 20 n is 0 or 1; and

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts thereof,

with the exception that the compound is not 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-5H-furan-2-one.

- 25 In another embodiment the present invention provides the compound of formula Ia, wherein

R¹ is lower alkyl, cycloalkyl, heterocycloalkyl, or aryl, wherein the aryl ring is unsubstituted or substituted by benzyloxy;

R² is H, lower alkyl or aryl;

- R^3 is lower alkyl, $-SCH_3$, acetyl,
cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by lower alkyl or aryl,
heterocycloalkyl,
- 5 $(CH=CR')_o$ -aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl, alkoxy, hydroxyl, benzyloxy, halogen, acetyl, $-(CH_2)_2NHSO_2Ph$, $-NHCO(CH_2)_2NHCOOC(CH_3)_3$ or $-(CH_2)_2NHCOC_6H_5OCH_3Cl$,
 o is 0 or 1;
 R' is H or lower alkyl,
- 10 aryloxy, wherein the aryl ring is unsubstituted or substituted by lower alkyl or alkoxy, or
 $(CH=CH)_q$ -heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by lower alkyl, acetyl, alkoxy, halogen, or by halogen substituted benzyl;
 q is 0 or 1;
- 15 R^4 is H, lower alkyl, $-(CH_2)_2SCH_3$, $-NHSO_2p-Cl-Ph$, amino, $-NHCOOC(CH_3)_3$, hydroxyl, aryl, benzyl or halogen substituted benzyl;
 $R^5, R^{5'}$ are independently from each other H, lower alkyl or aryl;
 $R^6, R^{6'}$ are independently from each other H, lower alkyl or $-SCH_3$;
- m is 1, 2 or 3;
- 20 n is 0 or 1; and
 p is 0, 1, 2 or 3;
- and pharmaceutically acceptable salts thereof,
with the exception that the compound is not 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-5H-furan-2-one.
- 25 In still another embodiment the present invention provides the compound of formula Ia, wherein
 R^1 is methyl, cyclohexyl, phenyl, morpholin-4-yl or 4-benzyloxy-phenyl;
 R^2 is H, methyl or phenyl;

- R^3 is methyl, $-SCH_3$, acetyl,
cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by methyl,
tert-butyl or phenyl,
tetrahydro-furan-2-yl, pyrrolidine-2-yl, 1-tert-butyloxycarbonylpyrrolidine-2-yl,
5 piperidine-2-yl, 1-tert-butyloxycarbonyl piperidine-2-yl,
 $(CH=CR')_o$ -aryl, wherein the aryl ring is unsubstituted or substituted by methyl,
tert-butyl, methoxy, hydroxyl, benzyloxy, chloro, fluoro, acetyl, $-(CH_2)_2NHSO_2Ph$,
 $-NHCO(CH_2)_2NHCOOC(CH_3)_3$, or $-(CH_2)_2NHCO$ -3-chloro-2-methoxybenzene,
o is 0 or 1;
10 R' is H or methyl,
aryloxy, wherein the aryl ring is unsubstituted or substituted by methyl or
methoxy, or
 $(CH=CH)_q$ -heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted
by methyl, acetyl, methoxy, chloro, or by chloro or fluoro substituted benzyl;
15 q is 0 or 1;
 R^4 is H, methyl, ethyl, $-(CH_2)_2SCH_3$, $-NHSO_2p$ -Cl-Phenyl, amino, $-NHCOOC(CH_3)_3$,
hydroxyl, phenyl, benzyl or chloro substituted benzyl;
 $R^5, R^{5'}$ are independently from each other H, methyl or phenyl;
 $R^6, R^{6'}$ are independently from each other H, methyl or $-SCH_3$;
20 m is 1, 2 or 3;
n is 0 or 1; and
p is 0, 1, 2 or 3;
and pharmaceutically acceptable salts thereof,
with the exception that the compound is not 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-
25 5H-furan-2-one.

In yet another embodiment the present invention provides the compound of
formula Ia, wherein

R^1 is methyl, cyclohexyl, phenyl, morpholin-4-yl or 4-benzyloxy-phenyl;

R² is H, methyl or phenyl;

R³ is methyl, -SCH₃, acetyl, cyclopropanyl, 2,2,3,3-tetramethyl-cyclopropanyl, 2-phenyl-cyclopropanyl, cyclopent-2-enyl, cyclohexanyl, 4-tert-butyl-cyclohexanyl, tetrahydro-furan-2-yl, pyrrolidine-2-yl, 1-tert-butyloxycarbonylpyrrolidine-2-yl
 5 piperidine-2-yl, 1-tert-butyloxycarbonylpiperidine-2-yl,

phenyl, 2-toluenyl, 3-toluenyl, 4-tert-butyl-phenyl, 4-fluoro-phenyl, 4-chloro-phenyl, 4-hydroxy-phenyl, 4-benzyloxy-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, -CH=C-phenyl, 2,4-dimethoxy-phenyl, 2,5-dimethoxy-phenyl, 3,4-dimethoxy-phenyl, 3,5-dimethoxy-phenyl, 4,5-dimethoxy-phenyl, 4-methoxy-2-methyl-phenyl, 4-methoxy-3-methyl-phenyl, -phenyl-4-
 10 (CH₂)₂NHSO₂Ph, -phenyl-4-NHCO(CH₂)₂NHCOOC(CH₃)₃, -phenyl-4-(CH₂)₂NHCO-3-chloro-2-methoxybenzene, naphthalen-2-yl, 6-methoxy-naphthalen-2-yl, 2-acetyl-naphthalen-1-yl, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl, 9H-fluoren-9-yl,
 15

phenoxy, 3-dimethyl-phenoxy, 2,3-dimethyl-phenoxy, 2-methoxy-phenoxy, 3-methoxy-phenoxy, naphthalene-1-yloxy,

-CH=CH-pyridin-3-yl, indol-1-yl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 4-fluoro-benzyl-1H-indol-3-yl, 1-(4-chloro-benzyl)-5-methoxy-2-methyl-1H-indol-
 20 3-yl, 1-(4-chloro-benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl, 2-acetyl-1,2-dihydro-isoquinolin-1-yl, 1,2,3,4-tetrahydro-isoquinoline-2-yl, (3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester)-3-yl, 2-methyl-benzofuran-3-yl, 5-chloro-benzofuran-3-yl, benzo[b]thiophen-3-yl, or 9H-thioxanthen-9-yl,

R⁴ is H, methyl, ethyl, -(CH₂)₂SCH₃, -NHSO₂p-Cl-Phenyl, amino, -NHCOOC(CH₃)₃,
 25 hydroxyl, phenyl, benzyl or chloro substituted benzyl;

R⁵, R^{5'} are independently from each other H, methyl or phenyl;

R⁶, R^{6'} are independently from each other H, methyl or -SCH₃;

m is 1, 2 or 3;

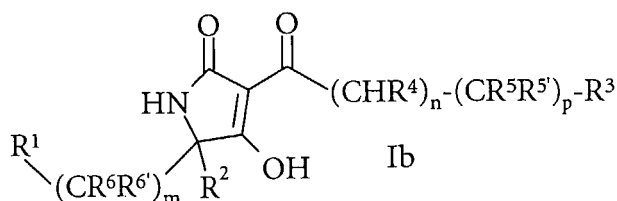
n is 0 or 1; and

30 p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts thereof,

with the exception that the compound is not 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-5H-furan-2-one

Still in another embodiment the present invention provides the compound of general formula Ib

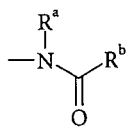


wherein

R¹ is lower alkyl, cycloalkyl, heterocycloalkyl or aryl, wherein the aryl ring is unsubstituted or substituted by benzyloxy;

R^2 is H, lower alkyl or aryl;

10 R³ is lower alkyl, -SCH₃, acetyl,



or aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl,

cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by lower alkyl or aryl,

15 heterocycloalkyl, wherein the heterocycloalkyl ring is unsubstituted or substituted by $-\text{COOC}(\text{CH}_3)_3$;

(CH=CR')_o-aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl, alkoxy, hydroxyl, benzyloxy, halogen, acetyl, -(CH₂)₂NHSO₂Ph, -NHCO(CH₂)₂NHCOOC(CH₃)₃, or -(CH₂)₂NHCOC₆H₄OCH₃Cl, or for the non aromatic part of fused ring system also by oxo,

o is 0 or 1;

R' is H or lower alkyl,

aryloxy, wherein the aryl ring is unsubstituted or substituted by lower alkyl or alkoxy, or

(CH=CH)_q-heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by lower alkyl, acetyl, alkoxy, halogen, -COOC(CH₃)₃ or by halogen substituted benzyl; or for the non aromatic part of fused ring system also by oxo, q is 0 or 1;

- 5 R⁴ is H, lower alkyl, -(CH₂)₂SCH₃, -NHCOCH₃, -NHSO₂p-Cl-Ph, amino, -NHCOOC(CH₃)₃, hydroxyl, aryl, benzyl or halogen substituted benzyl;

R⁵, R^{5'} are independently from each other H, lower alkyl or aryl;

R⁶, R^{6'} are independently from each other H, lower alkyl or -SCH₃;

m is 1, 2 or 3;

- 10 n is 0 or 1; and

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts thereof,

with the exception that the compound is not 3-acetyl-4-hydroxy-5-isobutyl-1,5-dihydro-pyrrol-2-one.

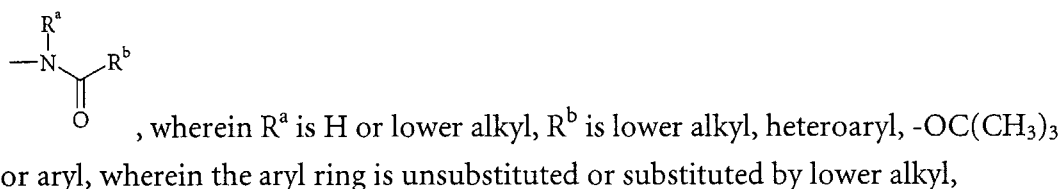
- 15 Still yet in another embodiment the present invention provides the compound of formula Ib,

wherein

R¹ is aryl;

R² is H;

- 20 R³ is -SCH₃,



cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by lower alkyl,

- 25 heterocycloalkyl, wherein the heterocycloalkyl ring is unsubstituted or substituted by -COOC(CH₃)₃;

aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl, alkoxy, benzyloxy or for the non aromatic part of fused ring system also by oxo,,

aryloxy, wherein the aryl ring is unsubstituted or substituted by alkoxy, or

heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by lower alkyl, $-\text{COOC}(\text{CH}_3)_3$ or by halogen substituted benzyl, or for the non aromatic part of fused ring system also by oxo;

R^4 is H, lower alkyl, $-\text{NHCOCH}_3$, amino, $-\text{NHCOOC}(\text{CH}_3)_3$, aryl or benzyl;

R^5, R^5 are H;

R^6, R^6 are H;

m is 2;

n is 0 or 1; and

p is 0, 1, 2 or 3;

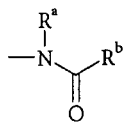
and pharmaceutically acceptable salts thereof.

Yet in another embodiment the present invention provides the compound of formula Ib wherein

R^1 is phenyl;

R^2 is H;

R^3 is $-\text{SCH}_3$,



, wherein R^a is H or methyl, R^b is methyl, 1H-pyrrol-3-yl, $-\text{OC}(\text{CH}_3)_3$ or aryl, wherein the aryl ring is unsubstituted or substituted by methyl,

cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by methyl,

heterocycloalkyl, wherein the heterocycloalkyl ring is unsubstituted or substituted by $-\text{COOC}(\text{CH}_3)_3$;

aryl, wherein the aryl ring is unsubstituted or substituted by methyl, tert-butyl, methoxy, benzyloxy or for the non aromatic part of fused ring system also by oxo,

aryloxy, wherein the aryl ring is substituted by methoxy, or

heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by methy, -COOC(CH₃)₃ or by 4-fluoro-benzyl-1-yl, or for the non aromatic part of fused ring system also by oxo;

5 R⁴ is H, methyl, -NHCOCH₃, amino, -NHCOOC(CH₃)₃, phenyl or benzyl;

R⁵, R⁵ are H;

R⁶, R⁶ are H;

m is 2;

n is 0 or 1; and

10 p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts thereof.

Still yet in another embodiment the present invention provides the compound of formula Ib, wherein

R¹ is phenyl;

15 R² is H;

R³ is -SCH₃, -NHCOCH₃, -NHCO-phenyl, -NHCO-(4-methyl-phenyl), -NHCO-(2,5-dihydro-1H-pyrrol-3-yl), NHCOOC(CH₃)₃,

cyclopropanyl, 1-methyl-cyclopropanyl, cyclohexanyl,

20 1-tert-butyloxycarbonylpyrrolidine-2-yl, 1-tert-butyloxycarbonylpiperidine-2-yl, tetrahydro-furan-2-yl,

phenyl, toluenyl, 4-tert-butyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-benzoxo-phenyl, 3,4-dimethoxy-phenyl, naphthalene-2-yl, 6-methoxy-naphthalen-2-yl, 3-oxo-indan-1-yl,

2-methyl-phenoxy,

25 1,2,5-trimethyl-1H-pyrrole-3-yl, 5-methyl-pyrazine-2-yl, 5-methyl-2,4-dioxo-1H-pyrimidine-1-yl, 3-methyl-furan-2-yl, indol-1-yl, 1H-indol-3-yl, (4-fluoro-benzyl)-1H-indol-3-yl, isoquinoline-3-yl, 3,4-dihydro-1H-isoquinoline-2-carboxylic acid

ter-butyl ester, thieno[2,3-c]pyridine-7-yl, benzo[1,2,3]thiadiazole-5-yl, 2,3-dihydro-benzofuran-7-yl, 2-benzo[b]thiophen-3-yl, or carbazol-9-yl,

R^4 is H, methyl, $-NHCOCH_3$, amino, $-NHCOOC(CH_3)_3$, phenyl or benzyl;

R^5, R^5 are H;

5 R^6, R^6 are H;

m is 2;

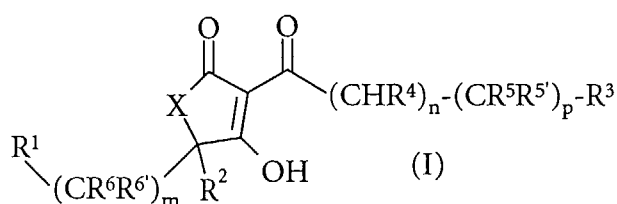
n is 0 or 1; and

p is 0, 1, 2 or 3;

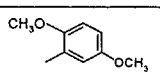
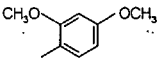
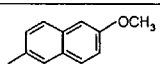
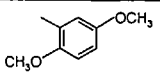
and pharmaceutically acceptable salts thereof.

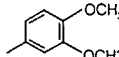
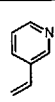
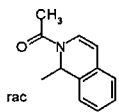
10 Representative compounds of formula I in accordance with the present invention are shown in Table 1 below..

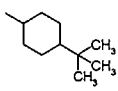
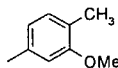
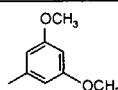
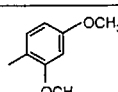
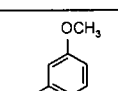
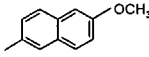
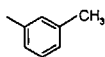
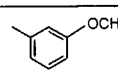
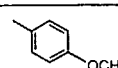
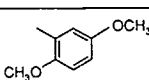
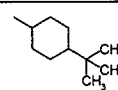
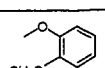
Table 1

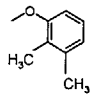
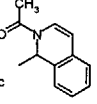
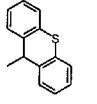
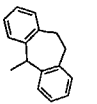


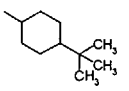
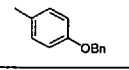
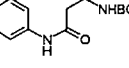
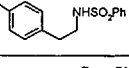
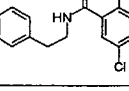
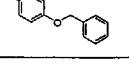
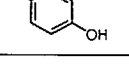
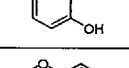
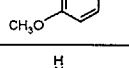
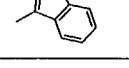
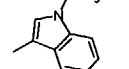
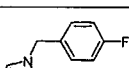
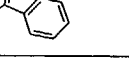
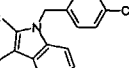
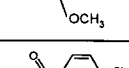
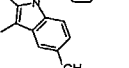
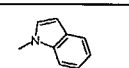
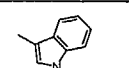
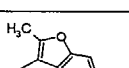
Ex	X	R^1	$-(CR^6R^6')_m-$	R^2	$-(CHR^4)_n(CR^5R^5')_p-$	R^3
A1	O	CH ₃	$-\text{CH}(\text{CH}_3)\text{CH}_2-$	H	$-\text{CH}_2\text{CH}(\text{CH}_3)-$	CH ₃
A2	O	CH ₃	$-\text{CH}(\text{CH}_3)\text{CH}_2-$	H	$-\text{CH}_2\text{CH}_2-$	SCH ₃
A3	O	CH ₃	$-\text{CH}(\text{CH}_3)\text{CH}_2-$	H	$-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)-$	CH ₃
A4	O	CH ₃	$-\text{CH}(\text{CH}_3)\text{CH}_2-$	H	$-\text{CH}(\text{CH}_3)\text{CH}_2-$	$-\text{COCH}_3$
A5	O	CH ₃	$-\text{CH}(\text{CH}_3)\text{CH}_2-$	H	-	
A6	O	CH ₃	$-\text{CH}(\text{CH}_3)\text{CH}_2-$	H	-	
A7	O	CH ₃	$-\text{CH}(\text{CH}_3)\text{CH}_2-$	H	-	
A8	O	CH ₃	$-\text{CH}(\text{CH}_3)\text{CH}_2-$	H	-	
A9	O	CH ₃	$-\text{CH}(\text{CH}_3)\text{CH}_2-$	H	-	

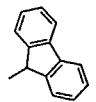
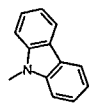
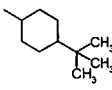
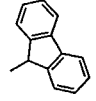
A10	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A11	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
A12	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-	
A13	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A14	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A15	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A16	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A17	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A18	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A19	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A20	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH(CH ₃)-	
A21	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH(CH ₂ CH ₃)-	
A22	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH(CH ₃)-	
A23	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
A24	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
A25	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
A26	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
A27	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
A28	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH(CH ₃)CH ₂ -	
A29	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH(CH ₃)CH ₂ -	
A30	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ CH(CH ₃)-	
A31	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-	
A32	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	

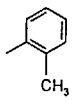
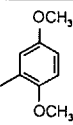
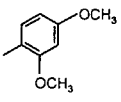
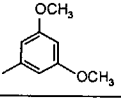
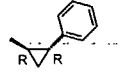
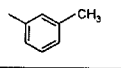
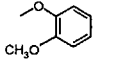
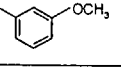
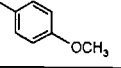
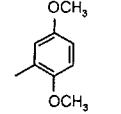
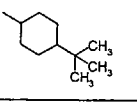
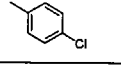
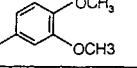
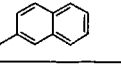
A33	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A34	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH(CH ₃)-	
A35	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
A36	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
A37	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH(CH ₃)CH ₂ -	
A38	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH(CH ₃)CH ₂ -	
A39	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A40	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
A41	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A42	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A43	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH(C ₆ H ₅)-	
A44	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH(C ₆ H ₅)CH ₂ -	
A45	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
A46	O	CH ₃	-CH(CH ₃)CH ₂ -	H	-CH ₂ -	
B1	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	-SCH ₃
B2	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-	
B3	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-	
B4	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-	
B5	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-	

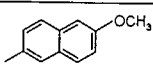
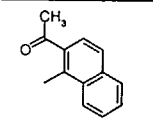
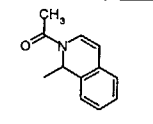
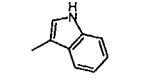
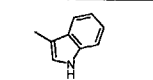
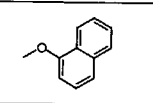
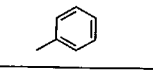
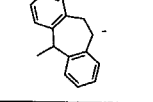
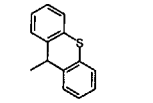
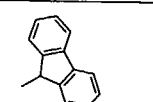
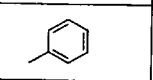
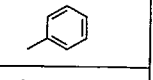
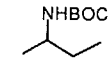
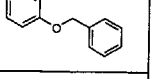
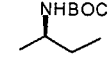
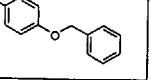
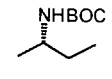
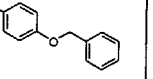
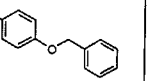
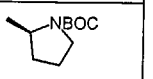
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IB7	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B8	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
B9	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B10	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B11	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B12	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B13	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B14	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B15	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH(CH ₃)-	
B16	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH(CH ₂ CH ₃)-	
B17	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH(CH ₃)-	
IB18	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
B19	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
B20	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
B21	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
B22	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
B23	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH(CH ₃)CH ₂ -	
B24	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH(CH ₃)-	
B25	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-	
B26	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	

B27	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B28	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH(CH ₃)-	
B29	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH(CH ₂ CH ₃)-	
B30	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B31	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
B32	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
B33	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B34	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH ₂ -	
B35	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B36	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH(C ₆ H ₅)-	
B37	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ CH(C ₆ H ₅)-	
B38	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
B39	O	CH ₃	-CH(SCH ₃)CH ₂ -	H	-CH ₂ -	
C1	O	cyclohexyl	-CH ₂ -	H	-	
C2	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C3	O	cyclohexyl	-CH ₂ -	H	-CH ₂ CH ₂ -	
C4	O	cyclohexyl	-CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
C5	O	cyclohexyl	-CH ₂ -	H	-CH(NHSO ₂ -4-Cl-Phenyl)CH ₂ CH ₂ -	
C6	O	cyclohexyl	-CH ₂ -	H	-CH ₂ CH ₂ CH ₂ CH ₂ -	
C7	O	cyclohexyl	-CH ₂ -	H	-CH(CH ₃)CH ₂ -	

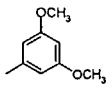
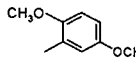
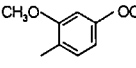
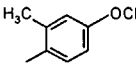
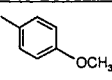
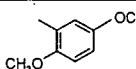
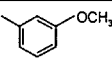
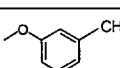
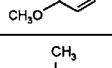
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C9	O	cyclohexyl	-CH ₂ -	H	-CH(CH ₃)CH ₂ -	
C10	O	cyclohexyl	-CH ₂ -	H	-CH(CH ₃)CH ₂ -	
C11	O	cyclohexyl	-CH ₂ -	H	-CH(CH ₃)CH ₂ -	
C12	O	cyclohexyl	-CH ₂ -	H	-CH(CH ₃)CH ₂ -	
C13	O	cyclohexyl	-CH ₂ -	H	-CHNHBOCCH ₂ -	
C14	O	cyclohexyl	-CH ₂ -	H	-CHNHCOCH ₂ -	
C15	O	cyclohexyl	-CH ₂ -	H	-CH(NH ₂)CH ₂ -	
C16	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C17	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C18	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C19	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C20	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C21	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C22	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C23	O	cyclohexyl	-CH ₂ -	H	-CH ₂ CH ₂ -	
C24	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C25	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C26	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	

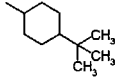
C27	O	cyclohexyl	-CH ₂ -	H	-CH ₂ CH(C ₆ H ₅)-	-C ₆ H ₅
C28	O	cyclohexyl	-CH ₂ -	H	-CH(C ₆ H ₅)CH ₂ -	-C ₆ H ₅
C29	O	cyclohexyl	-CH ₂ -	H	-CH(C ₆ H ₅)CH ₂ -	
C30	O	cyclohexyl	-CH ₂ -	H	-CH(CH ₂ C ₆ H ₅)CH ₂ -	-C ₆ H ₅
C31	O	cyclohexyl	-CH ₂ -	H	-CH(CH ₂ C ₆ H ₅ -4-Cl)CH ₂ -	
C32	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
C33	O	cyclohexyl	-CH ₂ -	H	-CH ₂ -	
D1	O	C ₆ H ₅ -	-CH ₂ -	H	-	
D2	O	C ₆ H ₅ -	-CH ₂ -	H	-CH(CH ₃)CH ₂ -	
D3	O	C ₆ H ₅ -	-CH ₂ -	H	-CH ₂ -	
D4	O	C ₆ H ₅ -	-CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
D5	O	C ₆ H ₅ -	-CH ₂ -	H	-CH ₂ -	
D6	O	C ₆ H ₅ -	-CH ₂ -	H	-CH(C ₆ H ₅)CH ₂ -	
D7	O	C ₆ H ₅ -	-CH ₂ -	H	-CH ₂ -	
E1	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	-SCH ₃
E2	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₃)-CH ₂ CH(CH ₃)-	-CH ₃
E3	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₃)-CH ₂ CH ₂ CH ₂ -	-CH ₃
E4	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
E5	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
E6	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E7	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
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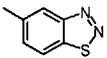
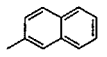
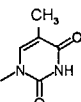
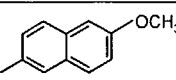
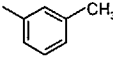
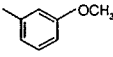
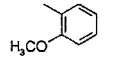
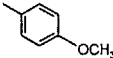
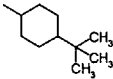
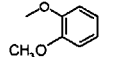
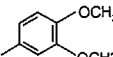
E9	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E10	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₃)-	
E11	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₂ CH ₃)-	
E12	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E13	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E14	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E15	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
E16	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
E17	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH(CH ₃)-	
E18	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(OH)CH ₂ -	
E19	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
E20	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E21	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
E22	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
E23	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
E24	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₃)CH ₂ -	
E25	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₃)CH ₂ -	
E26	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
E27	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
E28	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	

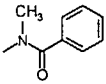
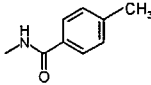
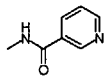
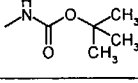
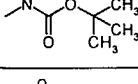
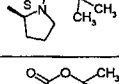
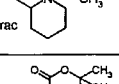
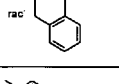
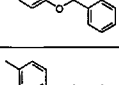
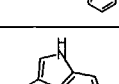
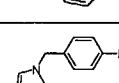
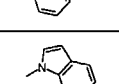
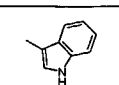
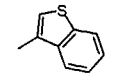
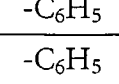
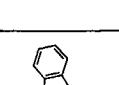
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E30	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E31	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E32	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E33	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
E34	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E35	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH(C ₆ H ₅)-	
E36	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E37	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E38	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
E39	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(NHBOC)-	CH ₃
E40	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(NH ₂)-	CH ₃
E41	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(NHBOC)CH ₂ -	
E42	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(NH ₂)CH ₂	
E43	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H		
E44	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H		
E45	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H		
E46	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(NH ₂)CH ₂ -	
E47	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	

E48	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
E49	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
E50	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
E51	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
E52	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
F1	O	C ₆ H ₅ -	-CH ₂ CH ₂ CH ₂ -	H	-	
F2	O	C ₆ H ₅ -	-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
F3	O	C ₆ H ₅ -	-CH ₂ CH ₂ CH ₂ -	H	-CH(CH ₃)CH ₂ -	
F4	O	C ₆ H ₅ -	-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
F5	O	C ₆ H ₅ -	-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
F6	O	C ₆ H ₅ -	-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH(C ₆ H ₅)-	
F7	O	C ₆ H ₅ -	-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G1	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	-SCH ₃
G2	O		-CH ₂ CH ₂ CH ₂ -	H	-	
G3	O		-CH ₂ CH ₂ CH ₂ -	H	-	
G4	O		-CH ₂ CH ₂ CH ₂ -	H	-	
G5	O		-CH ₂ CH ₂ CH ₂ -	H	-	
G6	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G7	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
G8	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G9	O		-CH ₂ CH ₂ CH ₂ -	H	-CH(CH ₃)-	

G10	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G11	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G12	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G13	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G14	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
G15	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH(CH ₃)-	
G16	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
G17	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
G18	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
G19	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G20	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G21	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G22	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G23	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
G24	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G25	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G26	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G27	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
G28	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	
G29	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ CH(C ₆ H ₅)-	
G30	O		-CH ₂ CH ₂ CH ₂ -	H	-CH ₂ -	

H1	O	4-benzyl- oxyphenyl	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
I1	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	CH ₃	-	
I2	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	CH ₃	-CH ₂ CH ₂ CH ₂ -	
I3	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	CH ₃	-CH(CH ₃)CH ₂ -	
I4	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	CH ₃	-CH ₂ -	
I5	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	CH ₃	-CH ₂ -	
I6	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	CH ₃	-CH ₂ CH(C ₆ H ₅)-	
I7	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	CH ₃	-CH ₂ -	
J1	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	C ₆ H ₅	-	
J2	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	C ₆ H ₅	-CH ₂ -	
J3	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	C ₆ H ₅	-CH ₂ -	
J4	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	C ₆ H ₅	-CH ₂ CH(C ₆ H ₅)-	
J5	O	C ₆ H ₅ -	-CH ₂ CH ₂ -	C ₆ H ₅	-CH ₂ -	
K1	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	-SCH ₃
K2	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K3	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K4	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K5	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
K6	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K7	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	

K8	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K9	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K10	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K11	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K12	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K13	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K14	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K15	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K16	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K17	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₃)-	
K18	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₃)-	
K19	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
K20	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
K21	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
K22	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
K23	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₃)CH ₂ -	
K24	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K25	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
K26	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ CH ₂ -	
K27	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	-NHCOCH ₃
K28	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CHNHCOCH ₃ -CH ₂ CH ₂ -	-SCH ₃

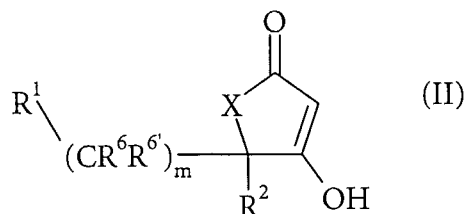
K29	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K30	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K31	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K32	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₃)-	
K33	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(CH ₂ C ₆ H ₅)-	
K34	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K35	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K36	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-	
K37	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(NHBOC)CH ₂ -	
K38	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(NH ₂)CH ₂ -	
K39	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K40	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K41	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K42	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH ₂ -	
K43	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	
K44	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ CH(C ₆ H ₅)-	-C ₆ H ₅
K45	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH(C ₆ H ₅)CH ₂ -	-C ₆ H ₅
K46	NH	C ₆ H ₅ -	-CH ₂ CH ₂ -	H	-CH ₂ -	

Still yet in another embodiment the present invention provides the compound of formula I, which is

- Rac-4-hydroxy-5-isobutyl-3-[(9H-thioxanthen-9-yl)-acetyl]-5H-furan-2-one;
- 3-[3-(4-tert-Butyl-phenyl)-2(R,S)-methyl-propionyl]-5(R,S)-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 5-Chloro-N-(2-{4-[3-(5(R,S)-cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-2(R,S)-methyl-3-oxo-propyl]-phenyl}-ethyl)-2-methoxy-benzamide;
- Rac-5-cyclohexylmethyl-4-hydroxy-3-[(1H-indol-3-yl)-acetyl]-5H-furan-2-one;
- Rac-5-cyclohexylmethyl-3-{[1-(4-fluoro-benzyl)-1H-indol-3-yl]-acetyl}-4-hydroxy-5H-furan-2-one;
- Rac-5-cyclohexylmethyl-3-[(9H-fluoren-9-yl)-acetyl]-4-hydroxy-5H-furan-2-one;
- 10 Rac-3-(carbazol-9-yl-acetyl)-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 5(R,S)-Benzyl-3-[3-(4-tert-butyl-phenyl)-2(R,S)-methyl-propionyl]-4-hydroxy-5H-furan-2-one;
- Rac-4-hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5-phenethyl-5H-furan-2-one;
- Rac-4-hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-phenethyl-5H-furan-2-one;
- 15 Rac-3-(3,3-diphenyl-propionyl)-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-4-hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-(3-phenyl-propyl)-5H-furan-2-one;
- Rac-3-[(9H-fluoren-9-yl)-acetyl]-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one;
- 4-Hydroxy-3(R,S)-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-5(R,S)-phenethyl-1,5-dihydro-pyrrol-2-one;
- 20 [1-(4-Benzyloxy-benzyl)-2-(4-hydroxy-2-oxo-5(R,S)-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2(R,S)-oxo-ethyl]-carbamic acid tert-butyl ester;
- Rac-4-hydroxy-3-(indol-1-yl-acetyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one; or
- Rac-3-(carbazol-9-yl-acetyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one.

The present compounds of formula I and their pharmaceutically acceptable salts
 25 can be prepared by methods known in the art, for example, by the process described below, which process comprises

acylation of a compound of formula II



wherein

X is O or NH;

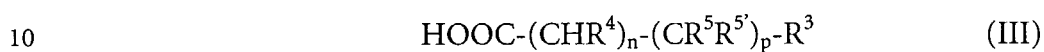
R¹ is lower alkyl, cycloalkyl, heterocycloalkyl or aryl, wherein the aryl ring is
5 unsubstituted or substituted by benzyloxy;

R² is H, lower alkyl or aryl;

R⁶, R^{6'} are independently from each other H, lower alkyl or -SCH₃;

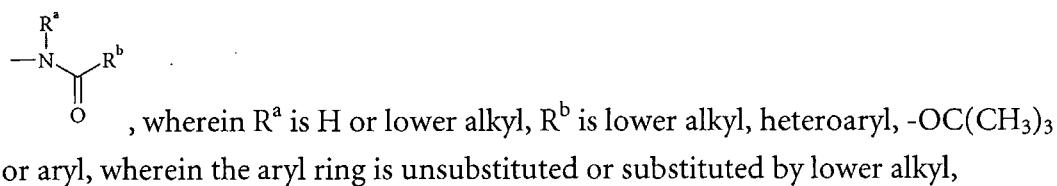
m is 1, 2 or 3;

with a carboxylic acid of formula III



wherein

R³ is lower alkyl, -SCH₃, acetyl,



15 cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by lower alkyl or aryl,

heterocycloalkyl, wherein the heterocycloalkyl ring is unsubstituted or substituted by -COOC(CH₃)₃;

(CH=CR')_o-aryl, wherein the aryl ring is unsubstituted or substituted by lower
20 alkyl, alkoxy, hydroxyl, benzyloxy, halogen, acetyl, -(CH₂)₂NHSO₂Ph, -NHCO(CH₂)₂NHCOOC(CH₃)₃, -(CH₂)₂NHCOC₆H₃OCH₃Cl, or for the non aromatic part of fused ring system also by oxo,

o is 0 or 1;

R' is H or lower alkyl,

aryloxy, wherein the aryl ring is unsubstituted or substituted by lower alkyl or alkoxy, or

(CH=CH)_q-heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by lower alkyl, acetyl, alkoxy, halogen, -COOC(CH₃)₃ or by halogen substituted benzyl; or for the non aromatic part of fused ring system also by oxo;
 5 q is 0 or 1;

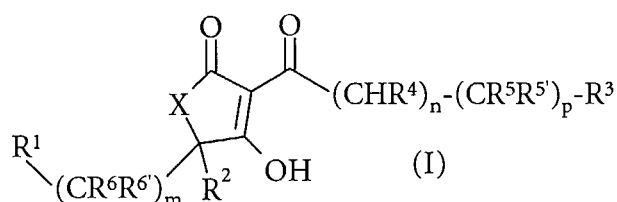
R⁴ is H, lower alkyl, -(CH₂)₂SCH₃, -NHCOCH₃, -NHSO₂p-Cl-Ph, amino, -NHCOOC(CH₃)₃, hydroxyl, aryl, benzyl or halogen substituted benzyl;

R⁵, R^{5'} are independently from each other H, lower alkyl or aryl;

10 n is 0 or 1; and

p is 0, 1, 2 or 3;

to produce a compound of formula I

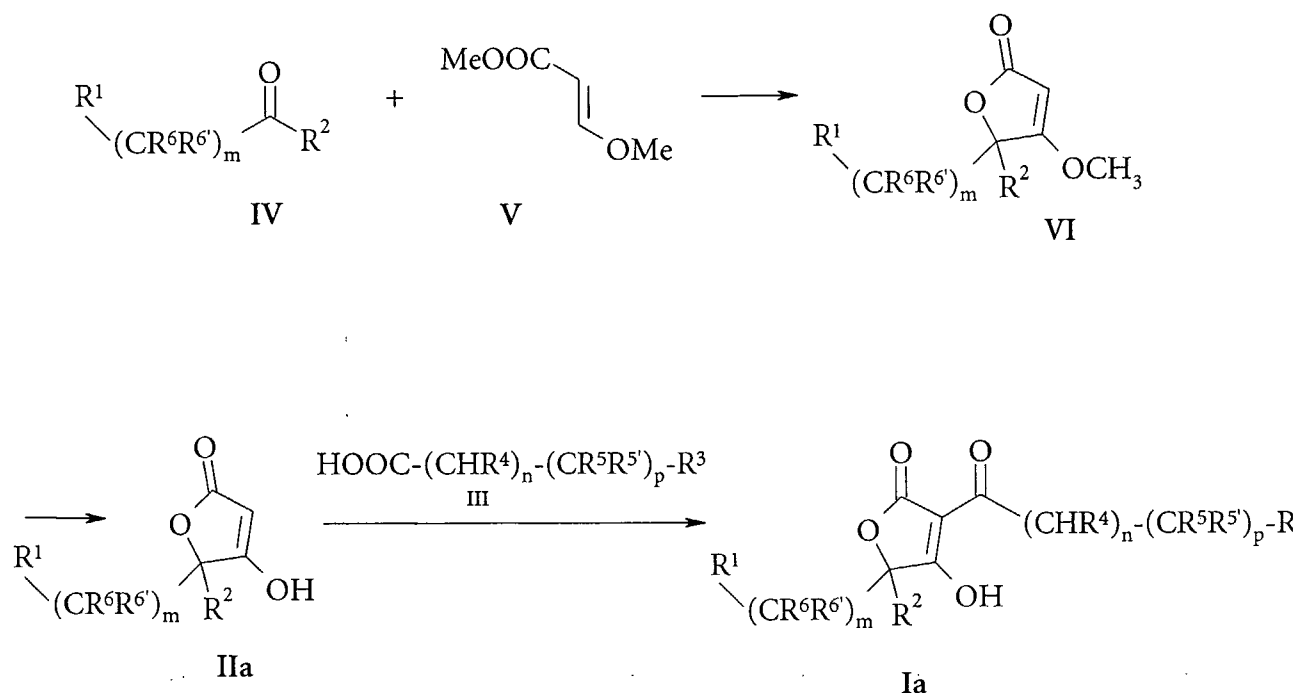


wherein X, R¹, R², R³, R⁴, R⁵, R^{5'}, R⁶, R^{6'}, m, n and p, are as defined above, and

15 if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The compounds of formula Ia may be prepared in accordance with the following scheme 1:

Scheme 1



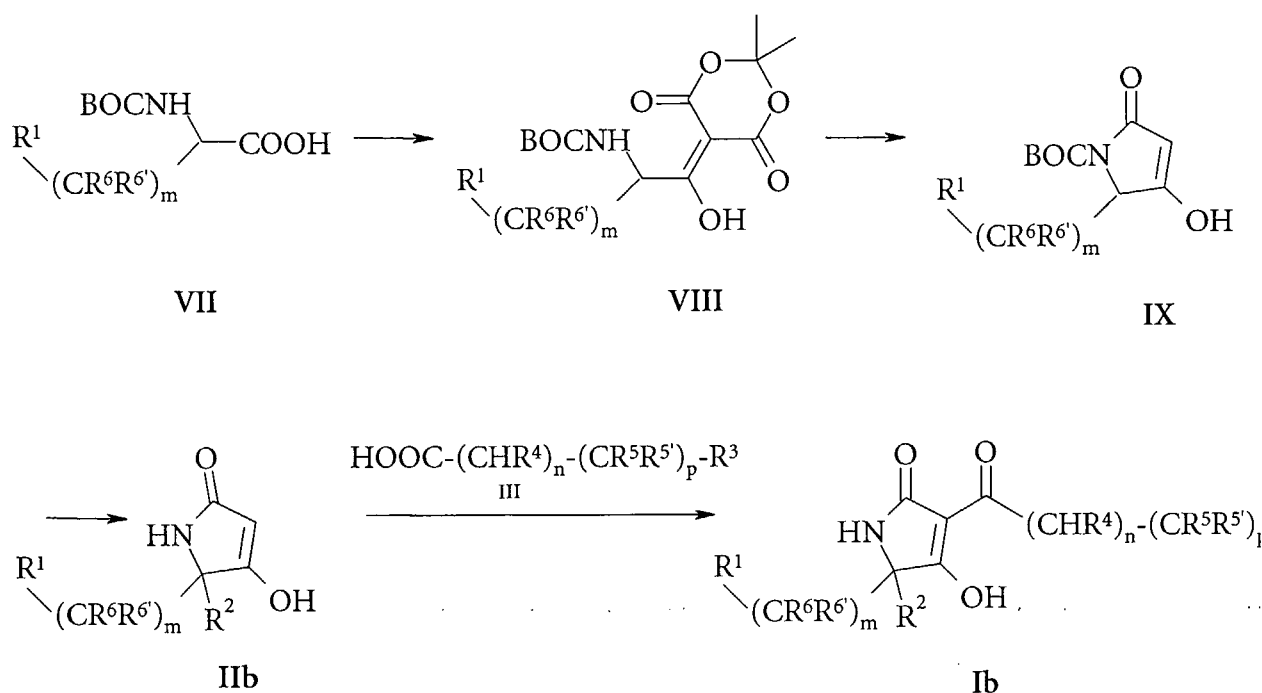
Aldehydes or ketones IV may be reacted with 3(E)-methoxy-acrylic acid methyl ester V (Miyata, Okiko; Schmidt, Richard R.; Angewandte Chemie (1982), 94(8), 651-2) in
5 solvents like diethyl ether or THF in the presence of a base like
lithiumdiisopropylamide(LDA) at a temperature in the range of -100°C to -50°C , or at
 -80°C to give the tetronic acid derivatives VI.

Cleavage of the methoxy group in VI may be accomplished with a strong mineral acid such as HI, HBr or HCl preferably HBr in water and acetic acid at a temperature in the range of 20°C to 100°C, or at 40°C to give the tetronic acid IIa.

Acylation of IIa followed by Fries rearrangement (Nomura, Keiichi; Hori, Kozo; Arai, Mikio; Yoshii, Eiichi; Chem. Pharm. Bull. (1986), 34(12), 5188-90) may be effected with a carboxylic acid and a dehydrating agent such as dicyclohexyl carbodiimide(DCC) or N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride(EDC), preferably
15 EDC and a base like an alkylamine, preferably NEt_3 in a solvent like CH_2Cl_2 or THF, preferably THF in the presence of 10 to 50 mole%, preferably 30 mole% of 4-dimethylamino pyridine(DMAP) at a temperature in the range of 0°C to 35°C , preferably at 25°C to give the acylated tetronic acid Ia.

The compounds of formula Ib may be prepared in accordance with the following
20 scheme 2:

Scheme 2



The tetramic acid **IIb** may be prepared according to the method described by Jouin, P;

5 Castro, B; J. Chem. Soc. Perkin Trans. I, 1987, 1177.

Acylation of **IIb** followed by Fries rearrangement (Nomura, Keiichi; Hori, Kozo; Arai, Mikio; Yoshii, Eiichi; Chem. Pharm. Bull. (1986), 34(12), 5188-90) may be effected with a carboxylic acid and a dehydrating agent such as DCC or EDC, preferably EDC and a base like an alkylamine, preferable NEt_3 in a solvent like CH_2Cl_2 or THF, preferably

10 THF in the presence of 10 to 50 mole%, preferably 30 mole% of DMAP at temperatures between 0°C to 35°C , preferably 25°C to give the acylated tetramic acid **Ib**.

A more detailed description for preparing a compound of formula I can be found in Examples A1-A46, B1-B39, C1-C33, D1-D7, E1-E52, F1-F7, G1-G30, H1, I1-I7, J1-J5 and K1-K46.

15 The compounds of formula I and their pharmaceutically acceptable salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention inhibit the β -secretase.

Cellular screening methods for inhibitors of A-beta production, testing methods for the *in vivo* suppression of A-beta production, and assays with membranes or cellular

extracts for the detection of secretase activity are known in the art and have been disclosed in numerous publications, including WO 98/22493, US 5,703,129, US 5,593,846 and GB 2,395,124; all hereby incorporated by reference. β -Secretase has been described in several publications including EP 855,444, WO 00/17,369, WO 00/58,479, 5 WO 00/47,618, WO 01/00,663 and WO 01/00,665.

For example, inhibition of β -secretase of the pharmaceutical compounds may be demonstrated by their ability, e.g., to inhibit the cleavage of a fluorescent peptide substrate (e.g. in an assay like e.g. the FRET Assay as described *inter alia* by Grueninger-Leitch et al.) or to displace, e.g., a peptidic β -secretase inhibitor at the active binding site 10 of β -secretase, e.g. as demonstrated in accordance with the following test method.

Competitive Radioligand Binding Assay (RLBA)

96 well microplates (Optiplate Packard) are coated with purified BACE protein (see e.g. GB 2,385,124: Examples 1 and 2) using a concentration of 1 μ g/ml in 30 mM sodium citrate buffer adjusted to pH 5.5. The coating is achieved by incubation of 100 μ l/well for 15 1-3 days at 4 °C. The plate is then washed with 2 x 300 μ l/well of 10 mM citrate pH 4.1. To each well 100 μ l binding buffer (30 mM citrate, 100 mM NaCl, 0.1% BSA, pH 4.1) is dispensed. The test compound is added in 5 μ l from a DMSO stock solution or appropriate dilutions. To this the tracer (tritiated Compound A, see e.g. GB 2,385,124: Example 4) is added in 10 μ l/well from a 10 μ Ci/ml stock solution in binding buffer. 20 After incubation for 1.5-2 hours in a humid chamber at ambient temperature the plate is washed with 2 x 300 μ l/well water and flipped on a dry towel. Following the addition of 50 μ l/well MicroScint20 (Packard) the plate is sealed and vibrated for 5 seconds. The bound radioactivity is counted on a Topcount (Packard). Total binding is typically between 2000 and 10000 cpm/well depending mainly on the purity and concentration of 25 the BACE protein. Non-specific binding as assessed by competition with >1 μ M peptidic inhibitor (Bachem # H-4848) is typically between 30 and 300 cpm/well. The IC-50 values are calculated by Microsoft Excel FIT.

Some exemplary IC50 inhibition data for the β -secretase inhibition are given in Table 2 below:

30 Table 2

Example No.	IC ₅₀ in vitro (μ M)	Example No.	IC ₅₀ in vitro (μ M)
C12	12	G29	85
C9	13	C33	11

C19	15	I7	31
D2	33	J4	41
E7	57	K38	16
F5	14	K46	36

In another embodiment, the present invention provides the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to the β -secretase inhibition. In still another embodiment the present invention provides the use of compounds of formula I and their pharmaceutically acceptable salts in the manufacture of medicaments for the prevention or treatment of CNS disease. In yet another embodiment the present invention provides the use of compounds of formula I and their pharmaceutically acceptable salts in the manufacture of medicaments for the prevention or treatment of Alzheimer's disease.

The compounds of formula I and the pharmaceutically acceptable salts of the compound of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compound of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if
 5 desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention compounds of formula I as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses based on the inhibition of the β -secretase, such as of Alzheimer's disease.

10 The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and,
 15 in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

<u>Item</u>	<u>Ingredients</u>	<u>mg/tablet</u>			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
20 2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

25 Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

30 Capsule Formulation

<u>Item</u>	<u>Ingredients</u>	<u>mg/capsule</u>			
		5 mg	25 mg	100 mg	500 mg

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1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5	5. Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
- 10 3. Fill into a suitable capsule.

Example A1

(RS)-4-Hydroxy-5-isobutyl-3-(3-methyl-butyryl)-5H-furan-2-one

a) 5-Isobutyl-4-methoxy-5H-furan-2-one

To a solution of 20 ml of LDA (2M in THF) and 130 ml of THF was added at -95°C to
5 -100°C a solution of 5.47 g of 3(E)-methoxy-acrylic acid methyl ester in 4.5 ml of THF
within 1 min, stirring was continued at the same temperature for 5 min, which was
followed by the addition of a pre-cooled (-78°C) solution of 33 mmole of the 3-methyl
butyraldehyde in 4.5 ml of THF within 2 min and stirring was continued at -100°C for 30
min and at -78°C for 1 h. The cold solution was poured onto 130 ml of ice-water, the pH
10 was adjusted to 4 with 6.5 ml of aqueous HCl (37%) and the layers were separated. The
aqueous layer was extracted twice with dichloromethane, the organic layers were washed
with brine, dried and evaporated. The residue was chromatographed on silica
(n-heptane/AcOEt, various ratios) to give the 5-isobutyl-4-methoxy-5H-furan-2-one in
30-40% yield.

15 MS: 171.2 (M+H)⁺

b) 4-Hydroxy-5-isobutyl-5H-furan-2-one

A mixture of the 5-isobutyl-4-methoxy-5H-furan-2-one (10 mmole) and 15 ml of
aqueous HCl (37%) was stirred at 40°C until completion of the reaction. The suspension
was filtered and the residue washed with ice-cold water and dried. An oily reaction
20 mixture was extracted with dichloromethane, the organic layers were washed with brine,
dried and evaporated. The residue was either triturated with AcOEt/hexane or
chromatographed with dichloromethane/MeOH (various ratios) to give the 4-hydroxy-
5-isobutyl-5H-furan-2-one in 60- 90% yield.

MS: 100.1 (M-C₄H₈)⁺

25 c) (RS)-4-Hydroxy-5-isobutyl-3-(3-methyl-butyryl)-5H-furan-2-one

To a suspension of the 4-hydroxy-5-isobutyl-5H-furan-2-one (0.2 mmole), NEt₃ (0.68
mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was added at
 22°C 3-methyl-butyric acid (0.22 mmole) (commercially available) and stirring was
continued until completion of the reaction. The pH of the reaction mixture was adjusted
30 to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic
layer was separated, washed with brine dried and evaporated. The residue was purified on
preparative HPLC (RP-18, CH₃CN/H₂O, gradient) to give the (RS)-4-hydroxy-5-
isobutyl-3-(3-methyl-butyryl)-5H-furan-2-one in 10-60% yield.

MS m/e (%): 239.2 (M-H)⁻

Example A2

4-Hydroxy-5-isobutyl-3-(3-methylsulfanyl-propionyl)-5H-furan-2-one

- 5 The title compound was obtained in comparable yields according to the procedures described for example A1 using 3-methylsulfanyl-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 256.9 (M-H)⁻

Example A3

4-Hydroxy-5-isobutyl-3-(4-methyl-pentanoyl)-5H-furan-2-one

- 10 The title compound was obtained in comparable yields according to the procedures described for example A1 using 4-methyl-pentanoic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 253.2 (M-H)⁻

Example A4

- 15 1-(4-Hydroxy-5-isobutyl-2-oxo-2,5-dihydro-furan-3-yl)-2-methyl-pentane-1,4-dione

The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-methyl-4oxo-pentanoic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 268.3 (M-H)⁻

20

Example A5

4-Hydroxy-5-isobutyl-3-(2,2,3,3-tetramethyl-cyclopropanecarbonyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 2,2,3,3-tetramethyl-cyclopropanecarboxylic acid (commercially available) instead of 3-methyl-butyric acid in step c).

- 25 MS: 279.0 (M-H)⁻

Example A6

4-Hydroxy-5-isobutyl-3-(tetrahydro-furan-2-carbonyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using tetrahydro-furan-2-carboxylic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 252.9 (M-H)⁻

5

Example A7

3-Cyclohexanecarbonyl-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using cyclohexanecarboxylic acid (commercially available) instead of 3-methyl-butyric acid in step c).

10 MS: 265.2 (M-H)⁻

Example A8

3-(4-tert-Butyl-cyclohexanecarbonyl)-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 4-tert-butyl-cyclohexanecarboxylic acid (commercially available) instead of 3-methyl-butyric acid in step c).

15

MS: 321.1 (M-H)⁻

Example A9

3-(Cyclopent-2-enyl-acetyl)-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using cyclopent-2-enecarboxylic acid (prepared according to Palaty, Jan; Abbott, Frank S.; Journal of Medicinal Chemistry (1995), 38(17), 3398-406) instead of 3-methyl-butyric acid in step c).

20

MS: 263.1 (M-H)⁻

Example A10

3-(2-Cyclohexyl-acetyl)-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using cyclohexyl-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

25

MS: 281.1 (M+H)⁺

Example A11

3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-isobutyl-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example A1 using cyclohexyl-butyric acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 307.0 (M-H)⁻

Example A12

4-Hydroxy-5-isobutyl-3-(2-phenoxy-benzoyl)-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-phenoxy-benzoic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 351.2 (M-H)⁻

Example A13

- 15 4-Hydroxy-5-isobutyl-3-phenylacetyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using phenyl-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 275.1 (M+H)⁺

- 20 Example A14

4-Hydroxy-5-isobutyl-3-o-tolylacetyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using o-tolyl-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

- 25 MS: 287.2 (M-H)⁻

Example A15

3-[(4-Chloro-phenyl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using (4-chloro-phenyl)-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 307.2 (M-H)⁻

5

Example A16

4-Hydroxy-5-isobutyl-3-[2-(4-methoxy-3-methyl-phenyl)-acetyl]-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using (4-methoxy-3-methyl-phenyl)-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

10 MS: 317.1 (M-H)⁻

Example A17

3-[2-(3,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using (3,5-dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

15

MS: 352.3 (M+NH₄)⁺

Example A18

3-[2-(2,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using (2,5-dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

20

MS: 335.2 (M+H)⁺

Example A19

3-[2-(2,4-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one

25 The title compound was obtained in comparable yields according to the procedures described for example A1 using (3,4-dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 335.2 (M+H)⁺

Example A20

3-(2-phenyl-propionyl-4-hydroxy-5-isobutyl-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-phenyl-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 287.0 (M-H)⁻

Example A21

4-Hydroxy-5-isobutyl-3-(2-phenyl-butyryl)-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-phenyl-butyric acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 303.2 (M+H)⁺

Example A22

- 4-Hydroxy-5-isobutyl-3-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-(6-methoxy-naphthalen-2-yl)-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 369.2 (M+H)⁺

- Example A23

4-Hydroxy-5-isobutyl-3-(3-phenyl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 3-phenyl-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

- MS: 287.0 (M+H)⁻

Example A24

4-Hydroxy-5-isobutyl-3-(3-m-tolyl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 3-m-tolyl-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 320.4 (M+NH₄)⁺

5

Example A25

4-Hydroxy-5-isobutyl-3-[3-(3-methoxy-phenyl)-propionyl]-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 3-(3-methoxy-phenyl)-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

10 MS: 336.2 (M+NH₄)⁺

Example A26

4-Hydroxy-5-isobutyl-3-[3-(4-methoxy-phenyl)-propionyl]-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 3-(4-methoxy-phenyl)-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

15

MS: 336.2 (M+NH₄)⁺

Example A27

3-[3-(2,5-Dimethoxy-phenyl)-propionyl]-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 3-(2,5-dimethoxy-phenyl)-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

20

MS: 349.4 (M+H)⁺

Example A28

3-[3-(4-Chloro-phenyl)-2-methyl-propionyl]-4-hydroxy-5-isobutyl-5H-furan-2-one

25 The title compound was obtained in comparable yields according to the procedures described for example A1 using 3-(4-chloro-phenyl)-2-methyl-propionic acid (prepared according to Ferorelli, S.; Loiodice, F.; Tortorella, V.; Amoroso, R.; Bettoni, G.; Conte-

Camerino, D.; De Luca, A.; Farmaco (1997), 52(6-7), 367-374.) instead of 3-methyl-butyric acid in step c).

MS: 354.3 (M+NH₄)⁺

Example A29

5 3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 3-(4-tert-Butyl-phenyl)-2-methyl-propionic acid (prepared according to Kuchar, Miroslav; Rejholec, Vaclav; Roubal, Zdenek; Nemecek, Oldrich; Collect. Czech. Chem. Commun. (1979), 44(1), 183-93) instead of 3-methyl-
10 butyric acid in step c).

MS: 376.5 (M+NH₄)⁺

Example A30

4-Hydroxy-5-isobutyl-3-(3-phenyl-butyryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures
15 described for example A1 using 3-phenyl-butyric acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 320.4 (M+NH₄)⁺

Example A31

4-Hydroxy-5-isobutyl-3-((R)-(R)-2-phenyl-cyclopropanecarbonyl)-5H-furan-2-one

20 The title compound was obtained in comparable yields according to the procedures described for example A1 using (R)-(R)-2-phenyl-cyclopropanecarboxylic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 318.3 (M+NH₄)⁺

Example A32

25 4-Hydroxy-5-isobutyl-3-[2-(2-methoxy-phenoxy)-acetyl]-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-(2-methoxy-phenoxy)-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 319.1 (M-H)⁻

Example A33

4-Hydroxy-5-isobutyl-3-[2-(naphthalen-1-yloxy)-acetyl]-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-(naphthalen-1-yloxy)-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 339.0 (M-H)⁻

Example A34

4-Hydroxy-5-isobutyl-3-(2-phenoxy-propionyl)-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-phenoxy-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 322.4 (M+NH₄)⁺

Example A35

- 15 4-Hydroxy-5-isobutyl-3-(4-phenyl-butyryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 4-phenyl-butyric acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 301.2 (M-H)⁻

20

Example A36

3-[4-(3,4-Dimethoxy-phenyl)-butyryl]-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 4-(3,4-dimethoxy-phenyl)-butyric acid (commercially available) instead of 3-methyl-butyric acid in step c).

- 25 MS: 380.3 (M+NH₄)⁺

Example A37

4-Hydroxy-5-isobutyl-3-((Z)-2-methyl-5-pyridin-3-yl-pent-4-enoyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using (Z)-2-methyl-5-pyridin-3-yl-pent-4-enoic acid (prepared according to Ziegler, Frederick E.; Sobolov, Susan B. Journal of the American Chemical Society (1990), 112(7), 2749-58) instead of 3-methyl-butyric acid in step c).

5 MS: 328.1 (M-H)⁻

Example A38

4-Hydroxy-5-isobutyl-3-((Z)-2-methyl-5-phenyl-hex-4-enoyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using (Z)-2-methyl-5-phenyl-hex-4-enoic acid (prepared
10 according to Ziegler, Frederick E.; Sobolov, Susan B. Journal of the American Chemical Society (1990), 112(7), 2749-58) instead of 3-methyl-butyric acid in step c).

MS: 341.1 (M-H)⁻

Example A39

4-Hydroxy-3-(2-1H-indol-3-yl-acetyl)-5-isobutyl-5H-furan-2-one

15 The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-1H-indol-3-yl-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 314.2 (M+H)⁺

Example A40

20 4-Hydroxy-3-(3-1H-indol-3-yl-propionyl)-5-isobutyl-5H-furan-2-one

The title was obtained in comparable yields according to the procedures described for example A1 using 3-1H-indol-3-yl-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 345.3 (M+NH₄)⁺

25 Example A41

4-Hydroxy-5-isobutyl-3-(2-naphthalen-2-yl-acetyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-naphthalen-2-yl-acetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 342.2 (M+NH₄)⁺

5

Example A42

3-[2-(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using 2-(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetic acid
10 (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 368.0 (M-H)⁻

Example A43

3-Diphenylacetyl-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures
15 described for example A1 using diphenylacetic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 368.3 (M+NH₄)⁺

Example A44

3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-isobutyl-5H-furan-2-one

20 The title compound was obtained in comparable yields according to the procedures described for example A1 using 3,3-Diphenyl-propionic acid (commercially available) instead of 3-methyl-butyric acid in step c).

MS: 363.1 (M-H)⁻

Example A45

25 4-Hydroxy-5-isobutyl-3-[(9H-thioxanthen-9-yl)-acetyl]-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using (9H-thioxanthen-9-yl)-acetic acid (prepared according to Jilek, Jiri O.; Holubek, Jiri; Svatek, Emil; Ryska, Miroslav; Pomykacek, Josef; Protiva,

Miroslav. Collection of Czechoslovak Chemical Communications (1979), 44(7), 2124-38) instead of 3-methyl-butyric acid in step c).

MS: 312.4 (M+NH₄)⁺

Example A46

5 3-[(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example A1 using (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (prepared according to Tucker, Thomas J.; Lumma, William C.; Lewis, S. Dale; 10 Gardell, Stephen J.; Lucas, Bobby J.; Sisko, Jack T.; Lynch, Joseph J.; Lyle, Elizabeth A.; Baskin, Elizabeth P.; Woltmann, Richard F.; Appleby, Sandra D.; Chen, I-Wu; Dancheck, Kimberley B.; Naylor-Olsen, Adel M.; Krueger, Julie A.; Cooper, Carolyn M.; Vacca, Joseph P. Journal of Medicinal Chemistry (1997), 40(22), 3687-3693) instead of 3-methyl-butyric acid in step c).

15 MS: 308.4 (M+NH₄)⁺

Example B1

4-Hydroxy-3-(3-methylsulfanyl-propionyl)-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

a) 4-Methoxy-5-(2-methyl-sulfanyl-propyl)-5H-furan-2-one

20 To a solution of 20 ml of LDA (2M in THF) and 130 ml of THF was added at -95°C to -100°C a solution of 5.47 g of 3(E)-methoxy-acrylic acid methyl ester in 4.5 ml of THF within 1 min, stirring was continued at the same temperature for 5 min, which was followed by the addition of a pre-cooled (-78°C) solution of 33 mmole of the 3-methylsulfanyl-butyraldehyde in 4.5 ml of THF within 2 min and stirring was continued 25 at -100°C for 30 min and at -78°C for 1 h. The cold solution was poured onto 130 ml of ice-water, the pH was adjusted to 4 with 6.5 ml of aqueous HCl (37%) and the layers were separated. The aqueous layer was extracted twice with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was chromatographed on silica (n-heptane/AcOEt, various ratios) to give the 4-methoxy-5-(2-methyl-sulfanyl-propyl)-5H-furan-2-one in 30-40% yield. 30

MS: 202.3 (M)⁺

b) 4-Hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

A mixture of the 4-methoxy-5-(2-methyl-sulfanyl-propyl)-5H-furan-2-one (10 mmole) and 15 ml of aqueous HCl (37%) was stirred at 40°C until completion of the reaction. The suspension was filtered and the residue washed with ice-cold water and dried. An oily reaction mixture was extracted with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was either triturated with AcOEt/hexane or chromatographed with dichloromethane/MeOH (various ratios) to give the 4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one in 60- 90% yield.

MS: 188.0 (M)⁺

10 c) 4-Hydroxy-3-(3-methylsulfanyl-propionyl)-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

To a suspension of the 4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one (0.2 mmole), NEt₃ (0.68 mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was added at 22°C 3-methylsulfanyl-propionic acid (0.22 mmole) (commercially available) and stirring was continued until completion of the reaction. The pH of the reaction mixture was adjusted to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic layer was separated, washed with brine dried and evaporated. The residue was purified on preparative HPLC (RP-18, CH₃CN/H₂O, gradient) to give the 4-hydroxy-3-(3-methylsulfanyl-propionyl)-5-(2-methylsulfanyl-propyl)-5H-furan-2-one in 10-60% yield.

MS: 289.0 (M-H)⁻

Example B2

3-Cyclopropanecarbonyl-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using cyclopropanecarboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 255.0 (M-H)⁻

Example B3

4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2,2,3,3-tetramethyl-cyclopropanecarbonyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2,2,3,3-tetramethyl-cyclopropanecarboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 311.0 (M-H)⁻

5

Example B4

4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(tetrahydro-furan-2-carbonyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using tetrahydro-furan-2-carboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

10

MS: 285.0 (M-H)⁻

Example B5

3-Cyclohexanecarbonyl-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using cyclohexanecarboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

15

MS: 297.2 (M-H)⁻

Example B6

3-(4-tert-Butyl-cyclohexanecarbonyl)-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

20

The title compound was obtained in comparable yields according to the procedures described for example B1 using 4-tert-butyl-cyclohexanecarboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 353.2 (M-H)⁻

25

Example B7

3-(2-Cyclohexyl-acetyl)-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-cyclohexyl-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 311.0 (M-H)⁻

5

Example B8

3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 4-Cyclohexyl-butyric acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

10 MS: 339.1 (M-H)⁻

Example B9

4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-phenylacetyl-5H-furan-2-one

15 The title compound was obtained in comparable yields according to the procedures described for example B1 using phenylacetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 305.0 (M-H)⁻

Example B10

4-Hydroxy-3-[2-(4-methoxy-3-methyl-phenyl)-acetyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

20 The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-(4-methoxy-3-methyl-phenyl)-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 349.2 (M-H)⁻

Example B11

25 3-[2-(3,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-(3,5-dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 365.1 (M-H)⁻

5

Example B12

3-[2-(2,4-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-(2,4-dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

10

MS: 365.1 (M-H)⁻

Example B13

3-[2-(2,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2,5-Dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

15

MS: 365.1 (M-H)⁻

Example B14

4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-naphthalen-2-yl-acetyl)-5H-furan-2-one

20

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2,2,3,3-tetramethyl-cyclopropanecarboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 355.1 (M-H)⁻

25

Example B15

4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-phenyl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-phenyl-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 319.1 (M-H)⁻

5

Example B16

4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-phenyl-butyryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-phenyl-butyric acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

10 MS: 333.0 (M-H)⁻

Example B17

4-Hydroxy-3-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

15 The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-(6-methoxy-naphthalen-2-yl)-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 399.2 (M-H)⁻

Example B18

4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(3-phenyl-propionyl)-5H-furan-2-one

20 The title compound was obtained in comparable yields according to the procedures described for example B1 using 3-phenyl-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 319.1 (M-H)⁻

Example B19

25 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(3-m-tolyl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 3-m-tolyl-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 333.1 (M-H)⁻

Example B20

4-Hydroxy-3-[3-(3-methoxy-phenyl)-propionyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

- 5 The title compound was obtained in comparable yields according to the procedures described for example B1 using 3-(3-methoxy-phenyl)-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 349.2 (M-H)⁻

Example B21

- 10 4-Hydroxy-3-[3-(4-methoxy-phenyl)-propionyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 3-(4-methoxy-phenyl)-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

- 15 MS: 349.2 (M-H)⁻

Example B22

3-[3-(2,5-Dimethoxy-phenyl)-propionyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

- 20 The title compound was obtained in comparable yields according to the procedures described for example B1 using 2,5-dimethoxy-phenic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 379.1 (M-H)⁻

Example B23

- 25 3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 3-(4-tert-Butyl-phenyl)-2-methyl-propionic acid (prepared according to Kuchar, Miroslav; Rejholec, Vaclav; Roubal, Zdenek; Nemecek,

Oldrich; Collect. Czech. Chem. Commun. (1979), 44(1), 183-93) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 389.2 (M-H)⁻

Example B24

5 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(3-phenyl-butyryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 3-phenyl-butyric acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 333.0 (M-H)⁻

10

Example B25

4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-((R)-(R)-2-phenyl-cyclopropanecarbonyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-((R)-(R)-2-phenyl-cyclopropanecarboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

15

MS: 331.0 (M-H)⁻

Example B26

4-Hydroxy-3-[2-(2-methoxy-phenoxy)-acetyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

20 The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-(2-methoxy-phenoxy)-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 351.1 (M-H)⁻

Example B27

25 3-[2-(2,3-Dimethyl-phenoxy)-acetyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-(2,3-dimethyl-phenoxy)-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 349.2 (M-H)⁺

Example B28

4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-phenoxy-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-phenoxy-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

10 MS: 335.0 (M-H)⁻

Example B29

4-Hydroxy-5-(2-methylsulfonyl-propyl)-3-(2-phenoxy-buteryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-phenoxy-butyric acid (commercially available) instead
15 of 3-methylsulfonyl-propionic acid in step c).

MS: 349.2 (M-H)⁻

Example B30

4-Hydroxy-5-(2-methylsulfonyl-propyl)-3-[2-(naphthalen-1-yloxy)-acetyl]-5H-furan-2-one

20 The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-(naphthalen-1-yloxy)-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 371.1 (M-H)⁻

Example B31

25 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(4-phenyl-butyryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 4-phenyl-butyric acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 333.1 (M-H)⁻

Example B32

3-[4-(3,4-Dimethoxy-phenyl)-butyryl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

- 5 The title compound was obtained in comparable yields according to the procedures described for example B1 using 4-(3,4-dimethoxy-phenyl)-butyric acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 393.0 (M-H)⁻

Example B33

- 10 4-Hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using (1H-indol-3-yl)-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 344.0 (M-H)⁻

- 15

Example B34

4-Hydroxy-3-(3-1H-indol-3-yl-propionyl)-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 3-1H-indol-3-yl-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

- 20 MS: 358.0 (M-H)⁻

Example B35

3-[2-(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

- 25 The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-(2-acetyl-1,2-dihydro-isoquinolin-1-yl)-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 400.2 (M-H)⁻

Example B36

3-Diphenylacetyl-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using diphenylacetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 341.1 (M-H)⁻

Example B37

3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 3,3-diphenyl-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 394.9 (M-H)⁻

Example B38

4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-9H-thioxanthen-9-yl-acetyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-9H-thioxanthen-9-yl-acetic acid (prepared according to Jilek, Jiri O.; Holubek, Jiri; Svatek, Emil; Ryska, Miroslav; Pomykacek, Josef; Protiva, Miroslav. Collection of Czechoslovak Chemical Communications (1979), 44(7), 2124-2138) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 425.2 (M-H)⁻

Example B39

3-(2-10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl-acetyl)-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example B1 using 2-10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl-acetic acid (prepared according to Tucker, Thomas J.; Lumma, William C.; Lewis, S. Dale; Gardell, Stephen J.; Lucas, Bobby J.; Sisko, Jack T.; Lynch, Joseph J.; Lyle, Elizabeth A.; Baskin, Elizabeth P.; Woltmann, Richard F.; Appleby, Sandra D.; Chen, I-Wu;

Dancheck, Kimberley B.; Naylor-Olsen, Adel M.; Krueger, Julie A.; Cooper, Carolyn M.; Vacca, Joseph P. Journal of Medicinal Chemistry (1997), 40(22), 3687-3693) instead of 3-methylsulfanyl-propionic acid in step c).

MS: 421.2 (M-H)⁻

5 Example C1

3-Cyclohexanecarbonyl-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

a) 5-Cyclohexylmethyl-4-methoxy-5H-furan-2-one

To a solution of 20 ml of LDA (2M in THF) and 130 ml of THF was added at -95°C to -100°C a solution of 5.47 g of 3(E)-methoxy-acrylic acid methyl ester in 4.5 ml of THF
10 within 1 min, stirring was continued at the same temperature for 5 min, which was followed by the addition of a pre-cooled (-78°C) solution of 33 mmole of the cyclohexyl-acetaldehyde in 4.5 ml of THF within 2 min and stirring was continued at -100°C for 30 min and at -78°C for 1 h. The cold solution was poured onto 130 ml of ice-water, the pH was adjusted to 4 with 6.5 ml of aqueous HCl (37%) and the layers were separated. The
15 aqueous layer was extracted twice with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was chromatographed on silica (n-heptane/AcOEt, various ratios) to give the 5-cyclohexylmethyl-4-methoxy-5H-furan-2-one in 30-40% yield.

MS: 114.0 (M-C₇H₁₂)⁺

20 b) 5-Cyclohexylmethyl-4-hydroxy-5H-furan-2-one

A mixture of the 5-cyclohexylmethyl-4-methoxy-5H-furan-2-one (10 mmole) and 15 ml of aqueous HCl (37%) was stirred at 40°C until completion of the reaction. The suspension was filtered and the residue washed with ice-cold water and dried. An oily reaction mixture was extracted with dichloromethane, the organic layers were washed
25 with brine, dried and evaporated. The residue was either triturated with AcOEt/hexane or chromatographed with dichloromethane/MeOH (various ratios) to give 5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one in 60-90% yield.

MS: 197.2 (M+H)⁺

c) 3-Cyclohexanecarbonyl-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

30 To a suspension of the 5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one (0.2 mmole), NEt₃ (0.68 mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was

added at 22°C cyclohexanecarboxylic acid (0.22 mmole) (commercially available) and stirring was continued until completion of the reaction. The pH of the reaction mixture was adjusted to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic layer was separated, washed with brine dried and evaporated. The residue was purified on preparative HPLC (RP-18, CH₃CN/H₂O, gradient) to give the 3-cyclohexanecarbonyl-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one in 10-60% yield.

MS: 305.1 (M-H)⁻

Example C2

3-Cyclohexylacetyl-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using cyclohexylacetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 319.2 (M-H)⁻

Example C3

5-Cyclohexylmethyl-3-(3-cyclohexyl-propionyl)-4-hydroxy-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using 3-cyclohexyl-propionic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 333.3 (M-H)⁻

Example C4

3-(4-Cyclohexyl-butyryl)-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

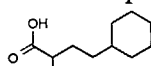
The title compound was obtained in comparable yields according to the procedures described for example C1 using 4-cyclohexyl-butyric acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 347.3 (M-H)⁻

Example C5

4-Chloro-N-[3-cyclohexyl-1-(5-cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-carbonyl)-propyl]-benzenesulfonamide

The title compound was obtained in comparable yields according to the procedures



described for example C1 using (Prepared from the commercially available amine and the corresponding sulfochloride) instead of cyclohexanecarboxylic acid in step c).

5 MS: 536.3 (M-H)⁻

Example C6

5-Cyclohexylmethyl-3-(5-cyclohexyl-pentanoyl)-4-hydroxy-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using 5-cyclohexyl-pentanoic acid (commercially available)

10 instead of cyclohexanecarboxylic acid in step c).

MS: 361.3 (M-H)⁻

Example C7

5-Cyclohexylmethyl-4-hydroxy-3-(2-methyl-3-phenyl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures

15 described for example C1 using 2-methyl-3-phenyl-propionic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 341.1 (M-H)⁻

Example C8

3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using (4-tert-butyl-phenyl)-2-methyl-propionic acid (prepared according to Kuchar, Miroslav; Rejholec, Vaclav; Roubal, Zdenek; Nemecek, Oldrich; Collect. Czech. Chem. Commun. (1979), 44(1), 183-93) instead of

25 cyclohexanecarboxylic acid in step c).

MS: 397.2 (M-H)⁻

Example C9

3-[3-(4-Benzyloxy-phenyl)-2-methyl-propionyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

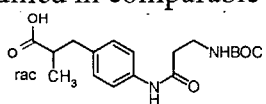
The title compound was obtained in comparable yields according to the procedures described for example C1 using 3-(4-benzyloxy-phenyl)-2-methyl-propionic acid
 5 (prepared according to Hitchcock, Janice M.; Sorenson, Stephen M.; Dudley, Mark W.; Peet, Norton P; WO 9419349 A1 (1994)) instead of cyclohexanecarboxylic acid in step c).

MS: 447.2 (M-H)⁻

Example C10

10 (2-{4-[3-(5-Cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-2-methyl-3-oxo-propyl]-phenylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester

The title compound was prepared from the corresponding BOC-protected precursor by deprotection using CF₃COOH and was obtained in comparable yields according to the

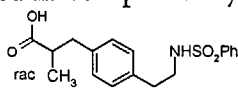
procedures described for example C1 using
 15  (prepared from the aniline (Biagi, Giuliana; Dell'omodarme, Giuliana; Giorgi, Irene; Livi, Oreste; Scartoni, Valerio; Farmaco (1992), 47(1), 91-8) and the corresponding acid) instead of cyclohexanecarboxylic acid in step c).

MS: 527.3 (M-H)⁻

Example C11

20 N-(2-{4-[3-(5-Cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-2-methyl-3-oxo-propyl]-phenyl}-ethyl)-benzenesulfonamide

The title compound was obtained in comparable yields according to the procedures

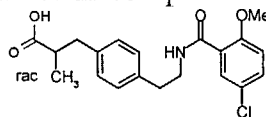
described for example C1 using
 25  (prepared from the amine (Bosies, Elmar; Heerdt, Ruth; Kuhnle, Hans Frieder; Schmidt, Felix H.; Stach, Kurt; U.S. 4,113,871 (1980), 13 pp) and the corresponding sulfochloride)) instead of cyclohexanecarboxylic acid in step c).

MS: 524.2 (M-H)⁻

Example C12

5-Chloro-N-(2-{4-[3-(5-cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-2-methyl-3-oxo-propyl]-phenyl}-ethyl)-2-methoxy-benzamide

The title compound was prepared from the corresponding BOC-protected precursor by deprotection using CF_3COOH and was obtained in comparable yields according to the



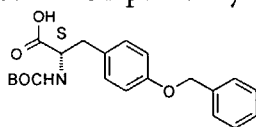
- 5 procedures described for example C1 using Bosies, Elmar; Heerdt, Ruth; Kuhnle, Hans Frieder; Schmidt, Felix H.; Stach, Kurt; U.S. 4,113,871 (1980), 13 pp.) instead of cyclohexanecarboxylic acid in step c).

MS: 552.1 (M-H)⁻

Example C13

- 10 [1-(4-Benzoyloxy-benzyl)-2-(5-cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures



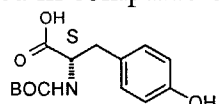
described for example C1 using (commercially available) instead of cyclohexanecarboxylic acid in step c).

- 15 MS: 567.6 (M+NH₄)⁺

Example C14

[2-(5-Cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures



- 20 described for example C1 using (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 458.4 (M-H)⁻

Example C15

- 3-[2-Amino-3-(4-hydroxy-phenyl)-propionyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one; compound with trifluoro-acetic acid
- 25

The title compound was prepared from the corresponding BOC-protected precursor (Example C14) by deprotection using CF_3COOH .

MS: 360.2 (M+H)⁺

Example C16

5 5-Cyclohexylmethyl-4-hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using (2-methoxy-phenoxy)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 359.0 (M-H)⁻

10 Example C17

5-Cyclohexylmethyl-4-hydroxy-3-[(1H-indol-3-yl)-acetyl]-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using (1H-indol-3-yl)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

15 MS: 352.2 (M-H)⁻

Example C18

5-Cyclohexylmethyl-4-hydroxy-3-[(1-methyl-1H-indol-3-yl)-acetyl]-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using (1-methyl-1H-indol-3-yl)-acetic acid (commercially
20 available) instead of cyclohexanecarboxylic acid in step c).

MS: 366.0 (M-H)⁻

Example C19

5-Cyclohexylmethyl-3-[[1-(4-fluoro-benzyl)-1H-indol-3-yl]-acetyl]-4-hydroxy-5H-furan-2-one

25 The title compound was obtained in comparable yields according to the procedures described for example C1 using 1-(4-fluoro-benzyl)-1H-indol-3-yl]-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 462.3 (M-H)⁻

Example C20

3-{{1-(4-Chloro-benzyl)-5-methoxy-2-methyl-1H-indol-3-yl}-acetyl}-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

- 5 The title compound was obtained in comparable yields according to the procedures described for example C1 using 1-(4-Chloro-benzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-acetic acid (prepared by alkylation of the indole with the corresponding p-chlorophenyl methyl bromide) instead of cyclohexanecarboxylic acid in step c).

MS: 520.3 (M-H)⁻

10

Example C21

3-{{1-(4-Chloro-benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl}-acetyl}-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example C1 using 1-(4-Chloro-benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-acetic acid (prepared by acylation of the indole with the corresponding acid chloride)
15 instead of cyclohexanecarboxylic acid in step c).

MS: 534.2 (M-H)⁻

Example C22

5-Cyclohexylmethyl-4-hydroxy-3-(indol-1-yl-acetyl)-5H-furan-2-one

- 20 The title compound was obtained in comparable yields according to the procedures described for example C1 using indol-1-yl-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 352.2 (M-H)⁻

Example C23

- 25 5-Cyclohexylmethyl-4-hydroxy-3-(3-1H-indol-3-yl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using 3-1H-indol-3-yl-propionic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 366.1 (M-H)⁻

Example C24

5-Cyclohexylmethyl-4-hydroxy-3-[(2-methyl-benzofuran-3-yl)-acetyl]-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example C1 using 2-methyl-benzofuran-3-yl)-acetic acid (prepared according to Wu, Jing et al.; WO 9828268(1998), 889 pp.) instead of cyclohexanecarboxylic acid in step c).

MS: 367.2 (M-H)⁻

Example C25

- 10 3-[(5-Chloro-benzofuran-3-yl)-acetyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using 5-Chloro-benzofuran-3-yl)-acetic acid (prepared according to Aeggi, Knut A.; Renner, Ulrich; CH504429 (1971), 7 pp.) instead of cyclohexanecarboxylic acid in step c).

- 15 MS: 387.2 (M-H)⁻

Example C26

3-(Benzo[b]thiophen-3-yl-acetyl)-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example C1 using Benzo[b]thiophen-3-yl-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 369.1 (M-H)⁻

Example C27

5-Cyclohexylmethyl-3-(3,3-diphenyl-propionyl)-4-hydroxy-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example C1 using 3,3-diphenyl-propionic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 403.3 (M-H)⁻

Example C28

5-Cyclohexylmethyl-3-(2,3-diphenyl-propionyl)-4-hydroxy-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example C1 using 2,3-diphenyl-propionic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 403.3 (M-H)⁻

Example C29

5-Cyclohexylmethyl-3-[3-(4-fluoro-phenyl)-2-phenyl-propionyl]-4-hydroxy-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example C1 using 3-(4-fluoro-phenyl)-2-phenyl-propionic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 421.1 (M-H)⁻

Example C30

- 3-(2-Benzyl-3-phenyl-propionyl)-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using 2-benzyl-3-phenyl-propionic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 417.2 (M-H)⁻

20

Example C31

3-[2-(4-Chloro-benzyl)-3-(4-chloro-phenyl)-propionyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example C1 using 2-(4-chloro-benzyl)-3-(4-chloro-phenyl)-propionic acid (prepared according to Iizuka, Kinji; Kamiyo, Tetsuhide; Kubota, Tetsuhiro; Akahane, Kenji; Umeyama, Hideaki; Kiso, Yoshiaki. EP252727 A1 (1988), 21 pp.) instead of cyclohexanecarboxylic acid in step c).

MS: 485.2 (M-H)⁻

Example C32

5-Cyclohexylmethyl-3-[(9H-fluoren-9-yl)-acetyl]-4-hydroxy-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using (9H-fluoren-9-yl)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 401.4 (M-H)⁻

Example C33

3-(Carbazol-9-yl-acetyl)-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example C1 using Carbazol-9-yl-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 402.3 (M-H)⁻

¹H-NMR (300 MHz, internal standard TMS, *J* values in Hz, d₆-DMSO): 8.13 (d, *J* = 7.1, 2H), 7.26 (s, br. 4H), 7.20-7.10 (m, 2H), 5.49 (s, br. 2H), 4.33 (dd, *J* = 9.8 and 2.8, 1H), 3.0 (s, br., 1H), 1.90-0.80 (m, 13H)

Example D1

5-Benzyl-3-cyclohexanecarbonyl-4-hydroxy-5H-furan-2-one

a) 5-Benzyl-4-methoxy-5H-furan-2-one

To a solution of 20 ml of LDA (2M in THF) and 130 ml of THF was added at -95°C to -100°C a solution of 5.47 g of 3(E)-methoxy-acrylic acid methyl ester in 4.5 ml of THF within 1 min, stirring was continued at the same temperature for 5 min, which was followed by the addition of a pre-cooled (-78°C) solution of 33 mmole of the phenyl-acetaldehyde in 4.5 ml of THF within 2 min and stirring was continued at -100°C for 30 min and at -78°C for 1 h. The cold solution was poured onto 130 ml of ice-water, the pH was adjusted to 4 with 6.5 ml of aqueous HCl (37%) and the layers were separated. The aqueous layer was extracted twice with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was chromatographed on silica (n-heptane/AcOEt, various ratios) to give the 5-benzyl-4-methoxy-5H-furan-2-one in 30-40% yield.

MS: 205.2 (M+H)⁺

b) 5-Benzyl-4-hydroxy-5H-furan-2-one

A mixture of the 5-benzyl-4-methoxy-5H-furan-2-one (10 mmole) and 15 ml of aqueous HCl (37%) was stirred at 40°C until completion of the reaction. The suspension was filtered and the residue washed with ice-cold water and dried. An oily reaction mixture was extracted with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was either triturated with AcOEt/hexane or chromatographed with dichloromethane/MeOH (various ratios) to give 5-benzyl-4-hydroxy-5H-furan-2-one in 60- 90% yield.

MS: 190.1 (M)⁺

10 5-Benzyl-3-cyclohexanecarbonyl-4-hydroxy-5H-furan-2-one

To a suspension of the 5-benzyl-4-hydroxy-5H-furan-2-one (0.2 mmole), NEt₃ (0.68 mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was added at 22°C cyclohexanecarboxylic acid (0.22 mmole) (commercially available) and stirring was continued until completion of the reaction. The pH of the reaction mixture was adjusted to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic layer was separated, washed with brine, dried and evaporated. The residue was purified on preparative HPLC (RP-18, CH₃CN/H₂O, gradient) to give the 5-Benzyl-3-cyclohexanecarbonyl-4-hydroxy-5H-furan-2-one in 10-60% yield.

MS: 299.2 (M-H)⁻

20

Example D2**5-Benzyl-3-[3-(4-tert-butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5H-furan-2-one**

The title compound was obtained in comparable yields according to the procedures described for example D1 using 3-(4-tert-butyl-phenyl)-2-methyl-propionic acid (prepared according to Kuchar, Miroslav; Rejholec, Vaclav; Roubal, Zdenek; Nemecek, Oldrich; Collect. Czech. Chem. Commun. (1979), 44(1), 183-93) instead of cyclohexanecarboxylic acid in step c).

MS: 391.1 (M-H)⁻

Example D3**5-Benzyl-4-hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5H-furan-2-one**

The title compound was obtained in comparable yields according to the procedures described for example D1 using (2-methoxy-phenoxy)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 353.1 (M-H)⁻

5

Example D4

5-Benzyl-3-(4-cyclohexyl-butyryl)-4-hydroxy-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example D1 using 4-cyclohexyl-butyric acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

10 MS: 341.1 (M-H)⁻

Example D5

5-Benzyl-4-hydroxy-3-[(1H-indol-3-yl)-acetyl]-5H-furan-2-one

The title compound compound was obtained in comparable yields according to the procedures described for example D1 using (1H-indol-3-yl)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

15

MS: 346.1 (M-H)⁻

Example D6

5-Benzyl-3-(3,3-diphenyl-propionyl)-4-hydroxy-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example D1 using 3,3-diphenyl-propionic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

20

MS: 397.2 (M-H)⁻

Example D7

5-Benzyl-3-[(9H-fluoren-9-yl)-acetyl]-4-hydroxy-5H-furan-2-one

25 The title compound was obtained in comparable yields according to the procedures described for example D1 using (9H-fluoren-9-yl)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 395.1 (M-H)⁻

Example E1

Rac-4-Hydroxy-3-(3-methyl-sulfanyl-propionyl)-5-phenethyl-5H-furan-2-one

a) 4-Hydroxy-5-phenethyl-5H-furan-2-one

- 5 To as solution of 20 ml of LDA (2M in THF) and 130 ml of THF was added at -95°C to -100°C a solution of 5.47 g of 3(E)-methoxy-acrylic acid methyl ester in 4.5 ml of THF within 1 min, stirring was continued at the same temperature for 5 min, which was followed by the addition of a pre-cooled (-78°C) solution of 33 mmole of the 3-phenyl-propionaldehyde in 4.5 ml of THF within 2 min and stirring was continued at -100°C for
10 30 min and at -78°C for 1 h. The cold solution was poured onto 130 ml of ice-water, the pH was adjusted to 4 with 6.5 ml of aqueous HCl (37%) and the layers were separated. The aqueous layer was extracted twice with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was chromatographed on silica (n-heptane/AcOEt, various ratios) to give the 4-hydroxy-5-phenethyl-5H-furan-2-one in
15 30-40% yield.

MS: 218.0 (M)⁺

b) 4-Hydroxy-5-phenethyl-5H-furan-2-one

- A mixture of the 4-hydroxy-5-phenethyl-5H-furan-2-one (10 mmole) and 15 ml of aqueous HCl (37%) was stirred at 40°C until completion of the reaction. The suspension
20 was filtered and the residue washed with ice-cold water and dried. An oily reaction mixture was extracted with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was either triturated with AcOEt/hexane or chromatographed with dichloromethane/MeOH (various ratios) to give 4-hydroxy-5-phenethyl-5H-furan-2-one in 60- 90% yield.

- 25 MS: 202.9 (M-H)⁻

c) Rac-4-Hydroxy-3-(3-methyl-sulfanyl-propionyl)-5-phenethyl-5H-furan-2-one

- To as suspension of the 4-hydroxy-5-phenethyl-5H-furan-2-one (0.2 mmole), NEt₃ (0.68 mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was added at 22°C 3-methyl-sulfanyl-propionic acid (0.22 mmole) (commercially available) and
30 stirring was continued until completion of the reaction. The pH of the reaction mixture was adjusted to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic layer was separated, washed with brine dried and evaporated. The

residue was purified on preparative HPLC (RP-18, CH₃CN/H₂O, gradient) to give the Rac-4-hydroxy-3-(3-methyl-sulfanyl-propionyl)-5-phenethyl-5H-furan-2-one in 10-60% yield.

MS: 305.0 (M-H)⁻

5

Example E2

Rac-3-(2(R,S),4-dimethyl-pentanoyl)-4-hydroxy-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2(R,S),4-dimethyl-pentanoic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

10 MS: 315.2 (M-H)⁻

Example E3

Rac-4-hydroxy-3-(2(R,S)-methyl-hexanoyl)-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2(R,S),4-dimethyl-pentanoic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

15

MS: 315.2(M-H)⁻

Example E4

Rac-3-cyclopropane-carbonyl-4-hydroxy-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 3-cyclopropane-carboxylic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

20

MS: 271.2 (M-H)⁻

Example E5

Rac-3-cyclohexane-carbonyl-4-hydroxy-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using cyclohexane-carboxylic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

25

MS: 210.1 ($M-C_8H_8$)⁺

Example E6

Rac-3-(2-cyclohexyl-acetyl)-4-hydroxy-5-phenethyl-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-cyclohexyl-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 327.2 ($M-H$)⁻

Example E7

Rac-3-(4-cyclohexyl-butyryl)-4-hydroxy-5-phenethyl-5H-furan-2-one

- 10 The title compound was obtained in comparable yields according to the procedures described for example E1 using 4-cyclohexyl-butyric acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 355.2 ($M-H$)⁻

Example E8

- 15 **Rac-4-hydroxy-5-phenethyl-3-phenylacetyl-5H-furan-2-one**

The title compound was obtained in comparable yields according to the procedures described for example E1 using phenylacetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 321.1 ($M-H$)⁻

20

Example E9

Rac-4-hydroxy-5-phenethyl-3-(2-o-tolyl-acetyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-o-tolyl-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

- 25 MS: 335.1 ($M-H$)⁻

Example E10

Rac-4-hydroxy-5-phenethyl-3-(2(R,S)-phenyl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2(R,S)-phenyl-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 335.0 (M-H)⁻

5

Example E11

Rac-4-hydroxy-5-phenethyl-3-(2(R,S)-phenyl-butyryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2(R,S)-phenyl-butyric acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

10 MS: 349.2 (M-H)⁻

Example E12

Rac-3-[2-(2,5-dimethoxy-phenyl)-acetyl]-4-hydroxy-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-(2,5-dimethoxy-phenic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

15

MS: 381.2 (M-H)⁻

Example E13

Rac-3-[2-(2,4-dimethoxy-phenyl)-acetyl]-4-hydroxy-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-(2,4-dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

20

MS: 381.1 (M-H)⁻

Example E14

Rac-3-[2-(3,5-dimethoxy-phenyl)-acetyl]-4-hydroxy-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-(3,5-dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

25

MS: 381.1 (M-H)⁻

Example E15

Rac-4-hydroxy-5-phenethyl-3-(3-phenyl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 3-phenyl-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 335.1 (M-H)⁻

Example E16

4-Hydroxy-5-phenethyl-3-((R)-(R)-2-phenyl-cyclopropanecarbonyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using (R)-(R)-2-phenyl-cyclopropanecarboxylic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 347.2 (M-H)⁻

Example E17

Rac-4-hydroxy-5-phenethyl-3-(3(R,S)-phenyl-butyryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 3(R,S)-phenyl-butyric acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 349.2 (M-H)⁻

Example E18

Rac-4-hydroxy-3-(2(R,S)-hydroxy-3-phenyl-propionyl)-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2(R,S)-hydroxy-3-phenyl-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 351.1 (M-H)⁻

Example E19

Rac-4-hydroxy-5-phenethyl-3-(3-m-tolyl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 3-m-tolyl-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 349.3 (M-H)⁻

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Example E20

Rac-4-hydroxy-3-[2-(2-methoxy-phenoxy)-acetyl]-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-(2-methoxy-phenoxy)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

10 MS: 369.2 (M+H)⁺

Example E21

Rac-4-hydroxy-3-[3-(3-methoxy-phenyl)-propionyl]-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 3-(3-methoxy-phenyl)-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

15

MS: 365.1 (M-H)⁻

Example E22

Rac-4-hydroxy-3-[3-(4-methoxy-phenyl)-propionyl]-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 3-(4-methoxy-phenyl)-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

20

MS: 365.0 (M-H)⁻

Example E23

Rac-3-[3-(2,5-dimethoxy-phenyl)-propionyl]-4-hydroxy-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 3-(2,5-dimethoxy-phenyl)-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

25

MS: 395.2 (M-H)⁻

Example E24

Rac-3-[3-(4-tert-butyl-phenyl)-2(R,S)-methyl-propionyl]-4-hydroxy-5-phenethyl-5H-furan-2-one

- 5 The title compound was obtained in comparable yields according to the procedures described for example E1 using 3-(4-tert-butyl-phenyl)-2(R,S)-methyl-propionic acid (prepared according to Kuchar, Miroslav; Rejholec, Vaclav; Roubal, Zdenek; Nemecek, Oldrich; Collect. Czech. Chem. Commun. (1979), 44(1), 183-93) instead of 3-methyl-sulfanyl-propionic acid in step c).

10 MS: 405.4 (M-H)⁻

Example E25

Rac-3-[3-(4-chloro-phenyl)-2(R,S)-methyl-propionyl]-4-hydroxy-5-phenethyl-5H-furan-2-one

- 15 The title compound was obtained in comparable yields according to the procedures described for example E1 using 3-(4-chloro-phenyl)-2(R,S)-methyl-propionic acid (prepared according to Ferorelli, S.; Loiodice, F.; Tortorella, V.; Amoroso, R.; Bettoni, G.; Conte-Camerino, D.; De Luca, A.; Farmaco (1997), 52(6-7), 367-374) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 383.1 (M-H)⁻

20

Example E26

4-Hydroxy-5-phenethyl-3-(4-phenyl-butyryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 4-phenyl-butyric acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

25 MS: 349.3 (M-H)⁻

Example E27

3-[4-(3,4-Dimethoxy-phenyl)-butyryl]-4-hydroxy-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 4-(3,4-Dimethoxy-phenyl)-butyric acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 409.2 (M-H)⁻

5

Example E28

4-Hydroxy-3-(2-naphthalen-2-yl-acetyl)-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-naphthalen-2-yl-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

10 MS: 371.1 (M-H)⁻

Example E29

Rac-4-hydroxy-3-[2(R,S)-(6-methoxy-naphthalen-2-yl)-propionyl]-5-phenethyl-5H-furan-2-one

15 The title compound was obtained in comparable yields according to the procedures described for example E1 using 2(R,S)-(6-methoxy-naphthalen-2-yl)-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 415.2 (M-H)⁻

Example E30

3-[(2-Acetyl-naphthalen-1-yl)-acetyl]-4-hydroxy-5-phenethyl-5H-furan-2-one

20 The title compound was obtained in comparable yields according to the procedures described for example E1 using (2-Acetyl-naphthalen-1-yl)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 415.2 (M-H)⁻

Example E31

25 3-[2-(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetyl]-4-hydroxy-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 416.1 (M-H)⁻

5 Example E32

4-Hydroxy-3-(2-1H-indol-3-yl-acetyl)-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-1H-indol-3-yl-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

10 MS: 360.0 (M-H)⁻

Example E33

Rac-4-hydroxy-3-(3-1H-indol-3-yl-propionyl)-5-phenethyl-5H-furan-2-one.

The title compound was obtained in comparable yields according to the procedures described for example E1 using 3-1H-indol-3-yl-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 374.2 (M-H)⁻

Example E34

Rac-4-hydroxy-3-[2-(naphthalen-1-yloxy)-acetyl]-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures
20 described for example E1 using 2-(naphthalen-1-yloxy)-acetic acid (commercially
available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 387.1 (M-H)⁻

Example E35

Rac-3-(3,3-diphenyl-propionyl)-4-hydroxy-5-phenethyl-5H-furan-2-one

25 The title compound was obtained in comparable yields according to the procedures described for example E1 using 3,3-diphenyl-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 411.2 (M-H)⁺

Example E36

Rac-3-(2-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl-acetyl)-4-hydroxy-5-phenethyl-5H-furan-2-one

- 5 The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl-acetic acid (prepared according to Tucker, Thomas J.; Lumma, William C.; Lewis, S. Dale; Gardell, Stephen J.; Lucas, Bobby J.; Sisko, Jack T.; Lynch, Joseph J.; Lyle, Elizabeth A.; Baskin, Elizabeth P.; Woltmann, Richard F.; Appleby, Sandra D.; Chen, I-Wu; Dancheck,
- 10 Kimberley B.; Naylor-Olsen, Adel M.; Krueger, Julie A.; Cooper, Carolyn M.; Vacca, Joseph P. Journal of Medicinal Chemistry (1997), 40(22), 3687-3693) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 437.3 (M-H)⁺

Example E37

- 15 **Rac-4-hydroxy-5-phenethyl-3-(2-9H-thioxanthen-9-yl-acetyl)-5H-furan-2-one**

The title compound was obtained in comparable yields according to the procedures described for example E1 using 2-9H-thioxanthen-9-yl-acetic acid (prepared according to Jilek, Jiri O.; Holubek, Jiri; Svatek, Emil; Ryska, Miroslav; Pomykacek, Josef; Protiva, Miroslav. Collection of Czechoslovak Chemical Communications (1979), 44(7), 2124-

20 38) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 441.6 (M-H)⁺

Example E38

Rac-3-(2-9H-fluoren-9-yl-acetyl)-4-hydroxy-5-phenethyl-5H-furan-2-one

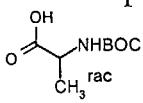
- The title compound was obtained in comparable yields according to the procedures
- 25 described for example E1 using 2-9H-fluoren-9-yl-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 409.2 (M-H)⁺

Example E39

Rac-[2-(4-hydroxy-2-oxo-5-phenethyl-2,5-dihydro-furan-3-yl)-1(R,S)-methyl-2-oxo-ethyl]-carbamic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures

described for example E1 using  (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 374.2 (M-H)⁻

Example E40

Rac-3-(2(R,S)-amino-propionyl)-4-hydroxy-5-phenethyl-5H-furan-2-one

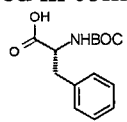
The title compound was prepared from the corresponding BOC-protected precursor (Example E40) by deprotection using CF₃COOH.

MS: 276.1(M+H)⁺

Example E41

[1(R)-Benzyl-2-(4-hydroxy-2-oxo-5(R,S)-phenethyl-2,5-di-hydro-furan-3-yl)-2-oxo-ethyl]-carbamic acid tert-butylester

The title compound was obtained in comparable yields according to the procedures

described for example E1 using  (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 450.1 (M-H)⁻

Example E42

3-(2(R)-Amino-3-phenyl-propionyl)-4-hydroxy-5(R,S)-phenethyl-5H-furan-2-one

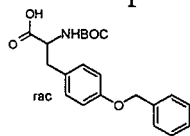
The title compound was prepared from the corresponding BOC-protected precursor (Example E42) by deprotection using CF₃COOH.

MS: 352.2 (M+H)⁺

Example E43

Rac-[1(R,S)-(4-benzyloxy-benzyl)-2-(4-hydroxy-2-oxo-5-phenethyl-2,5-dihydro-furan-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures



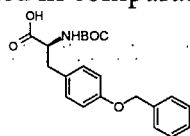
described for example E1 using (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 556.2 (M-H)⁻

Example E44

[1(S)-(4-Benzyloxy-benzyl)-2-(4-hydroxy-2-oxo-5(R,S)-phenethyl-2,5-dihydro-furan-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester

10 The title compound was obtained in comparable yields according to the procedures



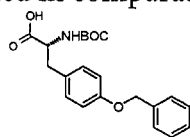
described for example E1 using (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 458.2 (M+H-C₅H₉O₂)⁺

Example E45

15 [1(R)-(4-Benzyloxy-benzyl)-2-(4-hydroxy-2-oxo-5(R,S)-phenethyl-2,5-dihydro-furan-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures



described for example E1 using (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

20 MS: 458.2 (M+H-C₅H₉O₂)⁺

Example E46

Rac-3-[2(R,S)-amino-3-(4-benzyloxy-phenyl)-propionyl]-4-hydroxy-5-phenethyl-5H-furan-2-one

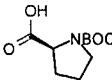
The title compound compound was prepared from the corresponding BOC-protected precursor (Example E44) by deprotection using CF_3COOH .

MS: 458.3 ($\text{M}+\text{H}$)⁺

Example E47

- 5 2-(4-Hydroxy-2-oxo-5(R,S)-phenethyl-2,5-dihydro-furan-3-carbonyl)-pyrrolidine-1(S)-carboxylic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures

described for example E1 using  (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

- 10 MS: 400.3 ($\text{M}-\text{H}$)⁻

Example E48

4-Hydroxy-5(R,S)-phenethyl-3-(pyrrolidine-2(S)-carbonyl)-5H-furan-2-one

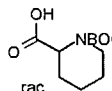
The title compound was prepared from the corresponding BOC-protected precursor (Example E48) by deprotection using CF_3COOH .

- 15 MS: 302.1 ($\text{M}+\text{H}$)⁺

Example E49

Rac-2(R,S)-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-furan-3-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures

- 20 described for example E1 using  (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 414.2 ($\text{M}-\text{H}$)⁻

Example E50

Rac-4-hydroxy-5-phenethyl-3(R,S)-(piperidine-2-carbonyl)-5H-furan-2-one

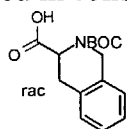
- 25 The title compound was prepared from the corresponding BOC-protected precursor (Example E50) by deprotection using CF_3COOH .

MS: 316.1 (M+H)⁺

Example E51

Rac-3(R,S)-(4-hydroxy-2-oxo-5-phenethyl-2,5-dihydro-furan-3-carbonyl)-3,4-dihydro-1H-iso-quinoline-2-carboxylic acid tert-butyl ester

- 5 The title compound was obtained in comparable yields according to the procedures



described for example E1 using (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 462.2 (M-H)⁻

Example E52

- 10 Rac-4-hydroxy-5-phenethyl-3(R,S)-(1,2,3,4-tetrahydro-isoquinoline-3-carbonyl)-5H-furan-2-one

The title compound was prepared from the corresponding BOC-protected precursor (Example E52) by deprotection using CF₃COOH.

MS: 364.1 (M+H)⁺

- 15 **Example F1**

3-4-Cyclohexanecarbonyl-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one

a) 4-Methoxy-5-(3-phenyl-propyl)-5H-furan-2-one

- To a solution of 20 ml of LDA (2M in THF) and 130 ml of THF was added at -95°C to -100°C a solution of 5.47 g of 3(E)-methoxy-acrylic acid methyl ester in 4.5 ml of THF within 1 min, stirring was continued at the same temperature for 5 min, which was followed by the addition of a pre-cooled (-78°C) solution of 33 mmole of the 4-phenyl-butyraldehyde in 4.5 ml of THF within 2 min and stirring was continued at -100°C for 30 min and at -78°C for 1 h. The cold solution was poured onto 130 ml of ice-water, the pH was adjusted to 4 with 6.5 ml of aqueous HCl (37%) and the layers were separated. The aqueous layer was extracted twice with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was chromatographed on silica (n-heptane/AcOEt, various ratios) to give the 4-methoxy-5-(3-phenyl-propyl)-5H-furan-2-one in 30-40% yield.

MS : 250.3 (M+NH₄)⁺

b) 4-Hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one

A mixture of the the 4-methoxy-5-(3-phenyl-propyl)-5H-furan-2-one (10 mmole) and 15 ml of aqueous HCl (37%) was stirred at 40°C until completion of the reaction. The suspension was filtered and the residue washed with ice-cold water and dried. An oily reaction mixture was extracted with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was either triturated with AcOEt/hexane or chromatographed with dichloromethane/MeOH (various ratios) to give 4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one in 60- 90% yield.

MS: 218.1 (M)⁺

c) 3-4-Cyclohexanecarbonyl-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one

To as suspension of the 4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one (0.2 mmole), NEt₃ (0.68 mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was added at 22°C cyclohexanecarboxylic acid (0.22 mmole) (commercially available) and stirring was continued until completion of the reaction. The pH of the reaction mixture was adjusted to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic layer was separated, washed with brine dried and evaporated. The residue was purified on preparative HPLC (RP-18, CH₃CN/H₂O, gradient) to give the 3-4-Cyclohexanecarbonyl-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one in 10-60% yield.

MS: 327.2 (M-H)⁻

Example F2

3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example F1 using 4-cyclohexyl-butyric acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 369.1 (M-H)⁻

Example F3

3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example F1 using 3-(4-tert-Butyl-phenyl)-2-methyl-propionic acid (prepared according to Kuchar, Miroslav; Rejholec, Vaclav; Roubal, Zdenek; Nemecek, Oldrich; Collect. Czech. Chem. Commun. (1979), 44(1), 183-93) instead of cyclohexanecarboxylic acid in step c).

MS: 419.1 (M-H)⁻

Example F4

4-Hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5-(3-phenyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example F1 using (2-methoxy-phenoxy)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 381.1(M-H)⁻

Example F5

4-Hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-(3-phenyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example F1 using (1H-indol-3-yl)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 374.2 (M-H)⁻

Example F6

3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example F1 using 3,3-Diphenyl-propionic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 425.2 (M-H)⁻

Example F7

3-[(9H-Fluoren-9-yl)-acetyl]-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example F1 using (9H-Fluoren-9-yl)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 423.2 (M-H)⁻

5

Example G1

4-Hydroxy-3-(3-methylsulfanyl-propionyl)-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

a) 4-Methoxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

To a solution of 20 ml of LDA (2M in THF) and 130 ml of THF was added at -95°C to -
10 100°C a solution of 5.47 g of 3(E)-methoxy-acrylic acid methyl ester in 4.5 ml of THF
within 1 min, stirring was continued at the same temperature for 5 min, which was
followed by the addition of a pre-cooled (-78°C) solution of 33 mmole of the 4-
morpholin-4-yl-butyraldehyde in 4.5 ml of THF within 2 min and stirring was continued
at -100°C for 30 min and at -78°C for 1 h. The cold solution was poured onto 130 ml of
15 ice-water, the pH was adjusted to 4 with 6.5 ml of aqueous HCl (37%) and the layers
were separated. The aqueous layer was extracted twice with dichloromethane, the organic
layers were washed with brine, dried and evaporated. The residue was chromatographed
on silica (n-heptane/AcOEt, various ratios) to give the 4-methoxy-5-(3-morpholin-4-yl-
propyl)-5H-furan-2-one in 30-40% yield.

20 MS: 242.3 (M+H)⁺

b) 4-Hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one

A mixture of the 4-methoxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one (10 mmole)
and 15 ml of aqueous HCl (37%) was stirred at 40°C until completion of the reaction.
The suspension was filtered and the residue washed with ice-cold water and dried. An
25 oily reaction mixture was extracted with dichloromethane, the organic layers were
washed with brine, dried and evaporated. The residue was either triturated with
AcOEt/hexane or chromatographed with dichloromethane/MeOH (various ratios) to
give 4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one in 60- 90% yield.

MS: 226.0 (M-H)⁻

30 c) 4-Hydroxy-3-(3-methylsulfanyl-propionyl)-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

- To a suspension of the 4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one (0.2 mmole), NEt₃ (0.68 mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was added at 22°C 3-methyl-sulfanyl-propionic acid (0.22 mmole) (commercially available) and stirring was continued until completion of the reaction. The pH of the reaction mixture was adjusted to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic layer was separated, washed with brine dried and evaporated. The residue was purified on preparative HPLC (RP-18, CH₃CN/H₂O, gradient) to give the 4-hydroxy-3-(3-methylsulfanyl-propionyl)-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one in 10-60% yield.
- 10 MS: 328.1 (M-H)⁻

Example G2

3-Cyclopropanecarbonyl-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example G1 using cyclopropanecarboxylic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).
- 15

MS: 294.2 (M-H)⁻

Example G3

4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(2,2,3,3-tetramethyl-cyclopropanecarbonyl)-5H-furan-2-one

- The title compound was obtained in comparable yields according to the procedures described for example G1 using 2,2,3,3-tetramethyl-cyclopropanecarboxylic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).
- 20

MS: 350.3 (M-H)⁻

Example G4

- 25 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(tetrahydro-furan-2-carbonyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using tetrahydro-furan-2-carboxylic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

- 30 MS: 324.1 (M-H)⁻

Example G5

3-Cyclohexanecarbonyl-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using cyclohexanecarboxylic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 338.2 (M+H)⁺

Example G6

3-(2-Cyclohexyl-acetyl)-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-cyclohexyl-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 350.3 (M-H)⁻

Example G7

3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 4-cyclohexyl-butyric acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 378.2 (M-H)⁻

Example G8

4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-phenylacetyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using phenylacetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 344.2 (M-H)⁻

25

Example G9

4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(2-phenyl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-phenyl-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 358.1 (M-H)⁻

5

Example G10

3-[2-(3,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-(3,5-Dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

10

MS: 404.4 (M-H)⁻

Example G11

3-[2-(2,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-(2,5-dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

15

MS: 404.3 (M-H)⁻

Example G12

3-[2-(2,4-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

20

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-(2,4-dimethoxy-phenyl)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 404.2 (M-H)⁻

25

Example G13

4-Hydroxy-3-[2-(4-methoxy-2-methyl-phenyl)-acetyl]-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-(4-methoxy-2-methyl-phenyl)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 390.3 (M+H)⁺

5

Example G14

4-Hydroxy-3-[3-(4-methoxy-phenyl)-propionyl]-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 3-(4-methoxy-phenyl)-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

10

MS: 388.2 (M-H)⁻

Example G15

4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(3-phenyl-butyryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 3-phenyl-butyric acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

15

MS: 372.2 (M-H)⁻

Example G16

3-[3-(2,5-Dimethoxy-phenyl)-propionyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

20

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2,5-dimethoxy-phenyl)-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 418.2 (M-H)⁻

25

Example G17

4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(3-m-tolyl-propionyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 3-m-tolyl-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 372.2 (M-H)⁻

5 Example G18

4-Hydroxy-3-[3-(3-methoxy-phenyl)-propionyl]-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 3-(3-methoxy-phenyl)-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 388.1 (M-H)⁻

Example G19

4-Hydroxy-3-[2-(3-methoxy-phenoxy)-acetyl]-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

15 The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-(3-methoxy-phenoxy)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 390.3 (M-H)⁻

Example G20

20 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(2-m-tolyloxy-acetyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-m-tolyloxy-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 376.4 (M+H)⁺

25 Example G21

4-Hydroxy-3-[2-(2-methoxy-phenoxy)-acetyl]-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-(2-methoxy-phenoxy)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 392.2 (M+H)⁺

5

Example G22

3-[2-(2,3-Dimethyl-phenoxy)-acetyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-(2,3-Dimethyl-phenoxy)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

10

MS: 390.3 (M+H)⁺

Example G23

4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(4-phenyl-butyryl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 4-phenyl-butyric acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

15

MS: 372.2 (M-H)⁻

Example G24

4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(2-naphthalen-2-yl-acetyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-naphthalen-2-yl-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

20

MS: 396.3 (M+H)⁺

Example G25

4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-[2-(naphthalen-1-yloxy)-acetyl]-5H-furan-2-one

25

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-(naphthalen-1-yloxy)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 410.3 (M-H)⁻

5

Example G26

4-Hydroxy-3-(2-1H-indol-3-yl-acetyl)-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-1H-indol-3-yl-acetic acid instead of 3-methyl-sulfanyl-propionic acid in step c).

10 MS: 385.3 (M+H)⁺

Example G27

4-Hydroxy-3-(3-1H-indol-3-yl-propionyl)-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

15 The title compound was obtained in comparable yields according to the procedures described for example G1 using 3-1H-indol-3-yl-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 399.4 (M+H)⁺

Example G28

20 3-[2-(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-(2-acetyl-1,2-dihydro-isoquinolin-1-yl)-acetic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 414.4 (M+H)⁺

25

Example G29

3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 3,3-diphenyl-propionic acid (commercially available) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 436.4 (M+H)⁺

5

Example G30

4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(2-9H-thioxanthen-9-yl-acetyl)-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example G1 using 2-9H-thioxanthen-9-yl-acetic acid (prepared according to Jilek, Jiri O.; Holubek, Jiri; Svatek, Emil; Ryska, Miroslav; Pomykacek, Josef; Protiva, Miroslav. Collection of Czechoslovak Chemical Communications (1979), 44(7), 2124-2138) instead of 3-methyl-sulfanyl-propionic acid in step c).

MS: 466.3 (M+H)⁺

Example H1

15 5-[2-(4-Benzoyloxy-phenyl)-ethyl]-3-(4-cyclohexyl-butyryl)-4-hydroxy-5H-furan-2-one

a) 5-[2-(4-Benzoyloxy-phenyl)ethyl]-4-methoxy-5H-furan-2-one

To a solution of 20 ml of LDA (2M in THF) and 130 ml of THF was added at -95°C to -100°C a solution of 5.47 g of 3(E)-methoxy-acrylic acid methyl ester in 4.5 ml of THF within 1 min, stirring was continued at the same temperature for 5 min, which was followed by the addition of a pre-cooled (-78°C) solution of 33 mmole of the 3-(4-benzyloxy-phenyl)-propionaldehyde in 4.5 ml of THF within 2 min and stirring was continued at -100°C for 30 min and at -78°C for 1 h. The cold solution was poured onto 130 ml of ice-water, the pH was adjusted to 4 with 6.5 ml of aqueous HCl (37%) and the layers were separated. The aqueous layer was extracted twice with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was chromatographed on silica (n-heptane/AcOEt, various ratios) to give the 5-[2-(4-benzyloxy-phenyl)ethyl]-4-methoxy-5H-furan-2-one in 30-40% yield.

MS: 325.2 (M+H)⁺

b) 5-[2-(4-Benzoyloxy-phenyl)-ethyl]-4-hydroxy-5H-furan-2-one

30 A mixture of the 5-[2-(4-benzyloxy-phenyl)ethyl]-4-methoxy-5H-furan-2-one (10 mmole) and 15 ml of aqueous HCl (37%) was stirred at 40°C until completion of the

reaction. The suspension was filtered and the residue washed with ice-cold water and dried. An oily reaction mixture was extracted with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was either triturated with AcOEt/hexane or chromatographed with dichloromethane/MeOH (various ratios) to give 5-[2-(4-benzyloxy-phenyl)-ethyl]-4-hydroxy-5H-furan-2-one in 60- 90% yield.

MS: 310.2 (M)⁺

c) 5-[2-(4-Benzyloxy-phenyl)-ethyl]-3-(4-cyclohexyl-butyryl)-4-hydroxy-5H-furan-2-one

To as suspension of the 5-[2-(4-benzyloxy-phenyl)-ethyl]-4-hydroxy-5H-furan-2-one (0.2 mmole), NEt₃ (0.68 mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was added at 22°C 4-cyclohexyl-butyric acid (0.22 mmole) (commercial available) and stirring was continued until completion of the reaction. The pH of the reaction mixture was adjusted to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic layer was separated, washed with brine dried and evaporated. The residue was purified on preparative HPLC (RP-18, CH₃CN/H₂O, gradient) to give the 5-[2-(4-benzyloxy-phenyl)-ethyl]-3-(4-cyclohexyl-butyryl)-4-hydroxy-5H-furan-2-one in 10-60% yield.

MS: 463.2 (M+H)⁺

Example I1

3-Cyclohexanecarbonyl-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one

a) 4-Methoxy-5-methyl-5-phenethyl-5H-furan-2-one

To as solution of 20 ml of LDA (2M in THF) and 130 ml of THF was added at -95°C to -100°C a solution of 5.47 g of 3(E)-methoxy-acrylic acid methyl ester in 4.5 ml of THF within 1 min, stirring was continued at the same temperature for 5 min, which was followed by the addition of a pre-cooled (-78°C) solution of 33 mmole of the 4-phenyl-butan-2-one in 4.5 ml of THF within 2 min and stirring was continued at -100°C for 30 min and at -78°C for 1 h. The cold solution was poured onto 130 ml of ice-water, the pH was adjusted to 4 with 6.5 ml of aqueous HCl (37%) and the layers were separated. The aqueous layer was extracted twice with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was chromatographed on silica (n-heptane/AcOEt, various ratios) to give 4-methoxy-5-methyl-5-phenethyl-5H-furan-2-one in 30-40% yield.

MS: 233.2 (M+H)⁺

b) 4-Hydroxy-5-methyl-5-phenethyl-5H-furan-2-one

A mixture of the the 4-methoxy-5-methyl-5-phenethyl-5H-furan-2-one (10 mmole) and 15 ml of aqueous HCl (37%) was stirred at 40°C until completion of the reaction. The suspension was filtered and the residue washed with ice-cold water and dried. An oily
5 reaction mixture was extracted with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was either triturated with AcOEt/hexane or chromatographed with dichloromethane/MeOH (various ratios) to give 4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one in 60- 90% yield.

MS: 218.2 (M)⁺

c) 3-Cyclohexanecarbonyl-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one

To as suspension of the 4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one (0.2 mmole), NEt₃ (0.68 mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was added at 22°C cyclohexanecarboxylic acid (0.22 mmole) (commercially available) and
15 stirring was continued until completion of the reaction. The pH of the reaction mixture was adjusted to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic layer was separated, washed with brine dried and evaporated. The residue was purified on preparative HPLC (RP-18, CH₃CN/H₂O, gradient) to give the 3-cyclohexanecarbonyl-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one in 10-60% yield.

MS: 327.2 (M-H)⁻

20

Example I2**3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one**

The title compound was obtained in comparable yields according to the procedures described for example F1 using 4-cyclohexyl-butyric acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

25 MS: 369.2 (M-H)⁻

Example I3**3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one**

The title compound was obtained in comparable yields according to the procedures
30 described for example F1 using 3-(4-tert-Butyl-phenyl)-2-methyl-propionic acid (prepared according to Kuchar, Miroslav; Rejholec, Vaclav; Roubal, Zdenek; Nemecek,

Oldrich; Collect. Czech. Chem. Commun. (1979), 44(1), 183-93) instead of cyclohexanecarboxylic acid in step c).

MS: 419.2 (M-H)⁻

Example I4

5 4-Hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5-methyl-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example F1 using (2-methoxy-phenoxy)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 381.2 (M-H)⁻

10

Example I5

4-Hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-methyl-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example F1 using (1H-indol-3-yl)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

15 MS: 374.2 (M-H)⁻

Example I6

3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example F1 using 3,3-diphenyl-propionic acid (commercially available)
20 instead of cyclohexanecarboxylic acid in step c).

MS: 425.3 (M-H)⁻

Example I7

3-[(9H-Fluoren-9-yl)-acetyl]-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures
25 described for example F1 using (9H-fluoren-9-yl)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 423.2 (M-H)⁻

Example J1

3-Cyclohexanecarbonyl-4-hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one

a) 4-Methoxy-5-phenethyl-5-phenyl-5H-furan-2-one

To a solution of 20 ml of LDA (2M in THF) and 130 ml of THF was added at -95°C to -100°C a solution of 5.47 g of 3(E)-methoxy-acrylic acid methyl ester in 4.5 ml of THF within 1 min, stirring was continued at the same temperature for 5 min, which was followed by the addition of a pre-cooled (-78°C) solution of 33 mmole of the 1,3-diphenyl-propan-1-one in 4.5 ml of THF within 2 min and stirring was continued at -100°C for 30 min and at -78°C for 1 h. The cold solution was poured onto 130 ml of ice-water, the pH was adjusted to 4 with 6.5 ml of aqueous HCl (37%) and the layers were separated. The aqueous layer was extracted twice with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was chromatographed on silica (n-heptane/AcOEt, various ratios) to give 4-methoxy-5-phenethyl-5-phenyl-5H-furan-2-one in 30-40% yield.

MS: 294.2 (M)⁺

b) 4-Hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one

A mixture of the 4-methoxy-5-phenethyl-5-phenyl-5H-furan-2-one (10 mmole) and 15 ml of aqueous HCl (37%) was stirred at 40°C until completion of the reaction. The suspension was filtered and the residue washed with ice-cold water and dried. An oily reaction mixture was extracted with dichloromethane, the organic layers were washed with brine, dried and evaporated. The residue was either triturated with AcOEt/hexane or chromatographed with dichloromethane/MeOH (various ratios) to give 4-hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one in 60-90% yield.

MS: 176.0 (M-C₈H₈)⁺

c) 3-Cyclohexanecarbonyl-4-hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one

To a suspension of the 4-hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one (0.2 mmole), NEt₃ (0.68 mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was added at 22°C cyclohexanecarboxylic acid (0.22 mmole) (commercially available) and stirring was continued until completion of the reaction. The pH of the reaction mixture was adjusted to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic layer was separated, washed with brine, dried and evaporated. The residue was purified on preparative HPLC (RP-18, CH₃CN/H₂O, gradient) to give the 3-cyclohexanecarbonyl-4-hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one in 10-60% yield.

MS: 389.1 (M-H)⁻

Example J2

4-Hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5-phenethyl-5-phenyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example J1 using (2-methoxy-phenoxy)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 443.1 (M-H)⁻

Example J3

4-Hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-phenethyl-5-phenyl-5H-furan-2-one

The title was obtained in comparable yields according to the procedures described for example J1 using (1H-indol-3-yl)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 436.1 (M-H)⁻

Example J4

3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example J1 using 3,3-diphenyl-propionic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 384.2 (M-C₈H₈)⁺

Example J5

3-[(9H-Fluoren-9-yl)-acetyl]-4-hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one

The title compound was obtained in comparable yields according to the procedures described for example F1 using (9H-Fluoren-9-yl)-acetic acid (commercially available) instead of cyclohexanecarboxylic acid in step c).

MS: 485.2 (M-H)⁻

Example K1

4-Hydroxy-3-(3-methylsulfanyl-propionyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one

a) Rac-{1-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene)-hydroxy-methyl]-3-phenyl-propyl}-carbamic acid tert-butyl ester

To a solution of 4.00 g of rac-homophenylalanine in 80 ml of dichloromethane was subsequently added at 22°C 2.17 g of Meldrum's acid and 4.02 g of DMAP followed by a
5 solution of 3.16 g of DCC in 20 ml of dichloromethane over 5 min and stirring was continued for 16 h. The suspension was filtered, the filtrate washed with aqueous HCl and water, dried and evaporated. The residue was triturated with 60 ml of methanol over 15 min, the suspension was diluted with 60 ml of diethylether, filtered and the residue
10 was washed with MeOH/diethylether (1:1, 20 ml) and dried to give 3.54 g of rac-{1-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene)-hydroxy-methyl]-3-phenyl-propyl}-carbamic acid tert-butyl ester as a white solid.

MS: 423.2 (M+NH₄)⁺.

b) Rac-3-hydroxy-5-oxo-2-phenethyl-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester

15 A suspension of 3.40 g of rac-{1-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidene)-hydroxy-methyl]-3-phenyl-propyl}-carbamic acid tert-butyl ester and 40 ml of methanol was heated to reflux temperature for 1 h and evaporated to give 2.53 g of rac-3-hydroxy-5-oxo-2-phenethyl-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester as a colourless foam.

20 MS: 304.1 (M+H)⁺

c) Rac-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

A solution of 1.58 g of rac-3-hydroxy-5-oxo-2-phenethyl-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester in 32 ml of dichloromethane was treated at 22°C with 2.0 ml of trifluoroacetic acid and stirring was continued for 16 h. The solution was
25 evaporated to dryness, the residue dissolved in 8 ml of diethylether and stirring was continued until the crystallization set in. The suspension was diluted with 8 ml of n-heptane, stirred for 15 min and filtered. The residue was washed with n-heptane and dried to give 0.85 g of rac-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one as a white solid.

30 MS: 204.2 (M+H)⁺

d) 4-Hydroxy-3-(3-methylsulfonyl-propionyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one

To a suspension of the rac-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one (0.2 mmole), NEt_3 (0.68 mmole), DMAP (0.066 mmole) and EDC (0.44 mmole) in 2 ml of THF was added at 22°C 3-methylsulfanyl-propionic acid (0.22 mmole) (commercially available) and stirring was continued until completion of the reaction. The pH of the reaction mixture was adjusted to 3 using aqueous HCl (2 N), the aqueous solution was saturated with NaCl, the organic layer was separated, washed with brine dried and evaporated. The residue was purified on preparative HPLC (RP-18, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, gradient) to give the 4-hydroxy-3-(3-methylsulfanyl-propionyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one in 20-60% yield.

MS: 304.1 (M-H)⁻

Example K2

3-Cyclopropanecarbonyl-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using cyclopropanecarboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 270.3 (M-H)⁻

Example K3

4-Hydroxy-3-(1-methyl-cyclopropanecarbonyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 1-methyl-cyclopropanecarboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 283.3 (M-H)⁻

Example K4

4-Hydroxy-5-phenethyl-3-(tetrahydro-furan-2-carbonyl)-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using tetrahydro-furan-2-carboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 302.2 (M+H)⁺

Example K5

3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 4-cyclohexyl-butyric acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

5 MS: 356.2 (M+H)⁺

Example K6

4-Hydroxy-5-phenethyl-3-(thieno[2,3-c]pyridine-7-carbonyl)-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using thieno[2,3-c]pyridine-7-carboxylic acid (prepared
10 according to Bass, R. J.; Popp, F. D.; Kant, J. Journal of Heterocyclic Chemistry (1984), 21(4), 1119-20) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 365.1 (M+H)⁺

Example K7

4-Hydroxy-3-(5-methyl-pyrazine-2-carbonyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one

15 The title compound was obtained in comparable yields according to the procedures described for example K1 using 5-methyl-pyrazine-2-carboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 324.1 (M+H)⁺

Example K8

20 4-Hydroxy-3-(isoquinoline-3-carbonyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using isoquinoline-3-carboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 358.1 (M+H)⁺

25

Example K9

3-(Benzo[1,2,3]thiadiazole-5-carbonyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using benzo[1,2,3]thiadiazole-5-carboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 364.1 (M-H)⁻

5

Example K10

4-Hydroxy-3-(3-methyl-furan-2-carbonyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 3-methyl-furan-2-carboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

10 MS: 319.2 (M-H)⁻

Example K11

3-(2,3-Dihydro-benzofuran-7-carbonyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

15 The title compound was obtained in comparable yields according to the procedures described for example K1 using 2,3-dihydro-benzofuran-7-carboxylic acid (prepared according to Voelter, Wolfgang; El-Abadelah, Mustafa M.; Sabri, Salim S.; Khanfar, Monther A. Zeitschrift fuer Naturforschung, B: Chemical Sciences (1999), 54(11), 1469-1473) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 348.2 (M-H)⁻

20

Example K12

4-Hydroxy-5-phenethyl-3-(1,2,5-trimethyl-1H-pyrrole-3-carbonyl)-1,5-dihydro-pyrrol-2-one

25 The title compound was obtained in comparable yields according to the procedures described for example K1 using 1,2,5-trimethyl-1H-pyrrole-3-carboxylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 337.2 (M-H)⁻

Example K13

4-Hydroxy-5-phenethyl-3-phenylacetyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using phenyl-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 320.1 (M-H)⁻

5

Example K14

4-Hydroxy-3-(2-naphthalen-2-yl-acetyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 2-naphthalen-2-yl-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

10 MS: 370.2 (M-H)⁻

Example K15

4-Hydroxy-3-[2-(3-oxo-indan-1-yl)-acetyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 2-(3-oxo-indan-1-yl)-acetic acid (prepared according to

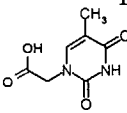
15 Thompson, Hugh W.; Brunskull, Andrew P. J.; Lalancette, Roger A. *Acta Crystallographica*, Section C: Crystal Structure Communications (1998), C54(6), 829-831) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 374.2 (M-H)⁻

Example K16

20 1-[2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-5-methyl-1H-pyrimidine-2,4-dione

The title compound was obtained in comparable yields according to the procedures

described for example K1 using  (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

25 MS: 368.1 (M-H)⁻

Example K17

4-Hydroxy-5-phenethyl-3-(2-phenyl-propionyl)-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 2-phenyl-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 336.2 (M+H)⁺

5

Example K18

4-Hydroxy-3-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 2-(6-methoxy-naphthalen-2-yl)-propionic acid
10 (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 414.2 (M-H)⁻

Example K19

4-Hydroxy-5-phenethyl-3-(3-m-tolyl-propionyl)-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures
15 described for example K1 using 3-m-tolyl-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 348.2 (M-H)⁻

Example K20

4-Hydroxy-3-[3-(3-methoxy-phenyl)-propionyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one

20 The title compound was obtained in comparable yields according to the procedures described for example K1 using 3-(3-methoxy-phenyl)-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 364.2 (M-H)⁻

Example K21

25 4-Hydroxy-3-[3-(2-methoxy-phenyl)-propionyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 3-(2-methoxy-phenyl)-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 364.2 (M-H)⁻

Example K22

4-Hydroxy-3-[3-(4-methoxy-phenyl)-propionyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures
5 described for example K1 using 3-(4-methoxy-phenyl)-propionic acid (commercially
available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 364.2 (M-H)⁻

Example K23

3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5-phenethyl-1,5-dihydro-
10 pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures
described for example K1 using 3-(4-tert-butyl-phenyl)-2-methyl-propionic acid
(prepared according to Kuchar, Miroslav; Rejholec, Vaclav; Roubal, Zdenek; Nemecek,
Oldrich; Collect. Czech. Chem. Commun. (1979), 44(1), 183-193) instead of 3-
15 methylsulfanyl-propionic acid in step d).

MS: 406.4 (M+H)⁺

Example K24

4-Hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures
20 described for example K1 using (2-methoxy-phenoxy)-acetic acid (commercially
available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 368.2 (M+H)⁺

Example K25

4-Hydroxy-5-phenethyl-3-(4-phenyl-butyryl)-1,5-dihydro-pyrrol-2-one

25 The title compound was obtained in comparable yields according to the procedures
described for example K1 using 4-phenyl-butyric acid (commercially available) instead of
3-methylsulfanyl-propionic acid in step d).

MS: 348.2 (M-H)⁻

Example K26

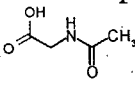
3-[4-(3,4-Dimethoxy-phenyl)-butyryl]-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 4-(3,4-dimethoxy-phenyl)-butyric acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 408.3 (M-H)⁻

Example K27

N-[2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-acetamide

The title compound was obtained in comparable yields according to the procedures described for example K1 using  (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

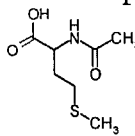
MS: 301.1 (M-H)⁻

15

Example K28

N-[1-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-3-methylsulfanyl-propyl]-acetamide

The title compound was obtained in comparable yields according to the procedures

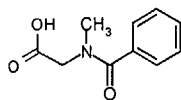
described for example K1 using  (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 377.2 (M+H)⁺

Example K29

N-[2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-N-methyl-benzamide

The title compound was obtained in comparable yields according to the procedures



described for example K1 using (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

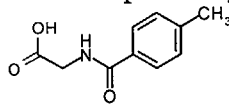
MS: 379.2 (M+H)⁺

5

Example K30

N-[2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-4-methylbenzamide

The title compound was obtained in comparable yields according to the procedures



described for example K1 using (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

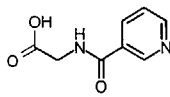
10

MS: 379.2 (M+H)⁺

Example K31

N-[2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-nicotinamide

15 The title compound was obtained in comparable yields according to the procedures



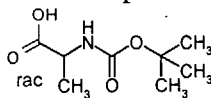
described for example K1 using (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 364.2 (M-H)⁻

Example K32

20 [2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-1-methyl-2-oxo-ethyl]-carbamic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures



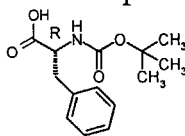
described for example K1 using (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

25 MS: 375.3 (M+H)⁺

Example K33

[1-Benzyl-2-(4-hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures



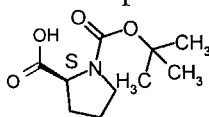
- 5 described for example K1 using (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 451.2 (M+H)⁺

Example K34

- 10 2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures



described for example K1 using (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

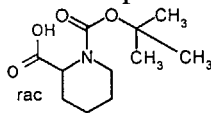
MS: 401.4 (M+H)⁺

15

Example K35

2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures



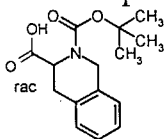
- 20 described for example K1 using (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 415.3 (M+H)⁺

Example K36

3-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures



described for example K1 using (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

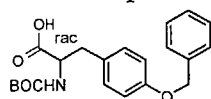
MS: 463.3 (M+H)⁺

5

Example K37

[1-(4-Benzyloxy-benzyl)-2-(4-hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester

The title compound was obtained in comparable yields according to the procedures



described for example K1 using (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

10

MS: 574.3 (M+NH₄)⁺

Example K38

3-[2-Amino-3-(4-benzyloxy-phenyl)-propionyl]-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one; compound with trifluoro-acetic acid

- 15 The title compound compound was prepared from the corresponding BOC-protected precursor (Example K37) by deprotection using CF₃COOH.

MS: 457.2 (M+H)⁺

Example K39

4-Hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one

- 20 The title compound was obtained in comparable yields according to the procedures described for example K1 using -[(1H-indol-3-yl)-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 361.1 (M+H)⁺

Example K40

3-[[1-(4-Fluoro-benzyl)-1H-indol-3-yl]-acetyl]-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 1-(4-Fluoro-benzyl)-1H-indol-3-yl]-acetic acid
5 (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 469.2 (M+H)⁺

Example K41

4-Hydroxy-3-(indol-1-yl-acetyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures
10 described for example K1 using indol-1-yl-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 361.2 (M+H)⁺

Example K42

4-Hydroxy-3-(3-1H-indol-3-yl-propionyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one

15 The title compound was obtained in comparable yields according to the procedures described for example K1 using 3-1H-indol-3-yl-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 373.1 (M-H)⁻

Example K43

20 3-(2-Benzo[b]thiophen-3-yl-acetyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 2-benzo[b]thiophen-3-yl-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 378.2 (M+H)⁺

25

Example K44

3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 3,3-diphenyl-propionylic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

MS: 412.2 (M+H)⁺

5

Example K45

3-(2,3-Diphenyl-propionyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

The title compound was obtained in comparable yields according to the procedures described for example K1 using 2,3-Diphenyl-propionic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

10 MS: 412.3 (M+H)⁺

Example K46

3-(Carbazol-9-yl-acetyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one

15 The title compound was obtained in comparable yields according to the procedures described for example K1 using carbazol-9-yl-acetic acid (commercially available) instead of 3-methylsulfanyl-propionic acid in step d).

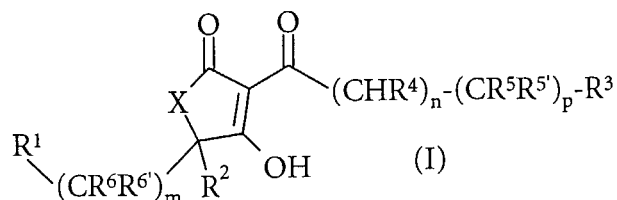
MS: 411.3 (M+H)⁺

¹H-NMR (300 MHz, internal standard TMS, *J* values in Hz, d₆-DMSO): 9.20 (s, br., 1H), 8.15 (d, *J* = 7.7, 2H), 7.50-7.10 (m, 11H), 5.69 (s, 2H), 4.00 (*J* = 7.6 and 4, 1H), 2.95 (s, br. 1H), 2.80-2.65 (m, 2H), 2.20-2.00 (m 1H), 1.95-1.80 (m, 1H)

20

Claims

1. A compounds of the general formula I



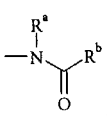
wherein

5 X is O or NH;

R¹ is lower alkyl, cycloalkyl, heterocycloalkyl or aryl, wherein the aryl ring is unsubstituted or substituted by benzyloxy;

R² is H, lower alkyl or aryl;

R³ is lower alkyl, -SCH₃, acetyl,

10 , wherein R^a is H or lower alkyl, R^b is lower alkyl, heteroaryl, -OC(CH₃)₃ or aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl,

cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by lower alkyl or aryl,

15 heterocycloalkyl, wherein the heterocycloalkyl ring is unsubstituted or substituted by -COOC(CH₃)₃;

(CH=CR')_o-aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl, alkoxy, hydroxyl, benzyloxy, halogen, acetyl, -(CH₂)₂NHSO₂Ph, -NHCO(CH₂)₂NHCOOC(CH₃)₃ or -(CH₂)₂NHCOC₆H₃OCH₃Cl, or for the non aromatic part of fused ring system also by oxo,

20 o is 0 or 1;

R' is H or lower alkyl,

aryloxy, wherein the aryl ring is unsubstituted or substituted by lower alkyl or alkoxy, or

25 (CH=CH)_q-heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by lower alkyl, acetyl, alkoxy, halogen, -COOC(CH₃)₃ or by halogen substituted

benzyl, or for the non aromatic part of fused ring system also by oxo;
q is 0 or 1;

R^4 is H, lower alkyl, $-(CH_2)_2SCH_3$, $-NHCOCH_3$, $-NHSO_2p\text{-Cl-Ph}$, amino,
 $-NHCOOC(CH_3)_3$, hydroxyl, aryl, benzyl or halogen substituted benzyl;

5 $R^5, R^{5'}$ are independently from each other H, lower alkyl or aryl;

$R^6, R^{6'}$ are independently from each other H, lower alkyl or $-SCH_3$;

m is 1, 2 or 3;

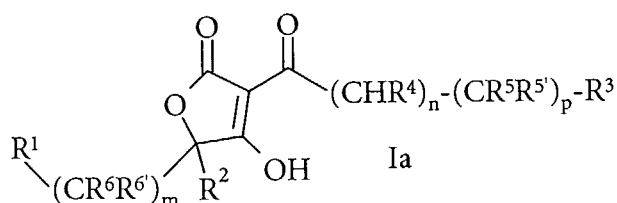
n is 0 or 1; and

p is 0, 1, 2 or 3;

10 and pharmaceutically acceptable salts thereof,

with the exception that the compound is not 3-acetyl-4-hydroxy-5-isobutyl-1,5-dihydro-pyrrol-2-one or 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-5H-furan-2-one.

2. The compound of formula I of claim 1, wherein said compound has the formula
Ia



15

wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^{6'}$, m, n and p are defined in claim 1,

and pharmaceutically acceptable salts thereof,

with the exception that the compound is not 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-5H-furan-2-one.

20 3. The compound of formula Ia according to claim 2, wherein

R^1 is lower alkyl, cycloalkyl, heterocycloalkyl, or aryl, wherein the aryl ring is unsubstituted or substituted by benzyloxy;

R^2 is H, lower alkyl or aryl;

R^3 is lower alkyl, $-SCH_3$, acetyl,

cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by lower alkyl or aryl,

heterocycloalkyl,

(CH=CR')_o-aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl, alkoxy, hydroxyl, benzyloxy, halogen, acetyl, -(CH₂)₂NHSO₂Ph, -NHCO(CH₂)₂NHCOOC(CH₃)₃ or -(CH₂)₂NHCOC₆H₃OCH₃Cl, o is 0 or 1; R' is H or lower alkyl,

aryloxy, wherein the aryl ring is unsubstituted or substituted by lower alkyl or alkoxy, or

(CH=CH)_q-heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by lower alkyl, acetyl, alkoxy, halogen, or by halogen substituted benzyl; q is 0 or 1;

R⁴ is H, lower alkyl, -(CH₂)₂SCH₃, -NHSO₂p-Cl-Ph, amino, -NHCOOC(CH₃)₃, hydroxyl, aryl, benzyl or halogen substituted benzyl;

R⁵, R^{5'} are independently from each other H, lower alkyl or aryl;

R⁶, R^{6'} are independently from each other H, lower alkyl or -SCH₃;

m is 1, 2 or 3;

n is 0 or 1; and

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts thereof,

with the exception that the compound is not 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-5H-furan-2-one.

4. The compound of formula Ia according to claim 3, wherein

R¹ is methyl, cyclohexyl, phenyl, morpholin-4-yl or 4-benzyloxy-phenyl;

R² is H, methyl or phenyl;

R³ is methyl, -SCH₃, acetyl,

cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by methyl, tert-butyl or phenyl,

tetrahydro-furan-2-yl, pyrrolidine-2-yl, 1-tert-butyloxycarbonylpyrrolidine-2-yl, piperidine-2-yl, 1-tert-butyloxycarbonyl piperidine-2-yl,

- 5 (CH=CR')_o-aryl, wherein the aryl ring is unsubstituted or substituted by methyl, tert-butyl, methoxy, hydroxyl, benzyloxy, chloro, fluoro, acetyl, -(CH₂)₂NHSO₂Ph, -NHCO(CH₂)₂NHCOOC(CH₃)₃ or -(CH₂)₂NHCO-3-chloro-2-methoxybenzene, o is 0 or 1;
R' is H or methyl,

- 10 aryloxy, wherein the aryl ring is unsubstituted or substituted by methyl or methoxy, or

(CH=CH)_q-heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by methyl, acetyl, methoxy, chloro, or by chloro or fluoro substituted benzyl;
q is 0 or 1;

- 15 R⁴ is H, methyl, ethyl, -(CH₂)₂SCH₃, -NHSO₂p-Cl-Phenyl, amino, -NHCOOC(CH₃)₃, hydroxyl, phenyl, benzyl or chloro substituted benzyl;

R⁵, R^{5'} are independently from each other H, methyl or phenyl;

R⁶, R^{6'} are independently from each other H, methyl or -SCH₃;

m is 1, 2 or 3;

- 20 n is 0 or 1; and

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts thereof,

with the exception that the compound is not 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-5H-furan-2-one.

- 25 5. The compound of formula Ia according to claim 4, wherein

R¹ is methyl, cyclohexyl, phenyl, morpholin-4-yl or 4-benzyloxy-phenyl;

R² is H, methyl or phenyl;

- R^3 is methyl, -SCH₃, acetyl, cyclopropanyl, 2,2,3,3-tetramethyl-cyclopropanyl, 2-phenyl-cyclopropanyl, cyclopent-2-enyl, cyclohexanyl, 4-tert-butyl-cyclohexanyl, tetrahydro-furan-2-yl, pyrrolidine-2-yl, 1-tert-butyloxycarbonylpyrrolidine-2-yl, piperidine-2-yl, 1-tert-butyloxycarbonylpiperidine-2-yl,
- 5 phenyl, 2-toluenyl, 3-toluenyl, 4-tert-butyl-phenyl, 4-fluoro-phenyl, 4-chloro-phenyl, 4-hydroxy-phenyl, 4-benzyloxy-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, -CH=C-phenyl, 2,4-dimethoxy-phenyl, 2,5-dimethoxy-phenyl, 3,4-dimethoxy-phenyl, 3,5-dimethoxy-phenyl, 4,5-dimethoxy-phenyl, 4-methoxy-2-methyl-phenyl, 4-methoxy-3-methyl-phenyl, -phenyl-4-
- 10 (CH₂)₂NHSO₂Ph, -phenyl-4-NHCO(CH₂)₂NHCOOC(CH₃)₃, -phenyl-4-(CH₂)₂NHCO-3-chloro-2-methoxybenzene, naphthalen-2-yl, 6-methoxy-naphthalen-2-yl, 2-acetyl-naphthalen-1-yl, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl, 9H-fluoren-9-yl,
- 15 phenoxy, 3-dimethyl-phenoxy, 2,3-dimethyl-phenoxy, 2-methoxy-phenoxy, 3-methoxy-phenoxy, naphthalene-1-yloxy, -CH=CH-pyridin-3-yl, indol-1-yl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 4-fluoro-benzyl-1H-indol-3-yl, 1-(4-chloro-benzyl)-5-methoxy-2-methyl-1H-indol-3-yl, 1-(4-chloro-benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl, 2-acetyl-1,2-
- 20 dihydro-isoquinolin-1-yl, 1,2,3,4-tetrahydro-isoquinoline-2-yl, (3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester)-3-yl, 2-methyl-benzofuran-3-yl, 5-chloro-benzofuran-3-yl, benzo[b]thiophen-3-yl, or 9H-thioxanthen-9-yl,
- R^4 is H, methyl, ethyl, -(CH₂)₂SCH₃, -NHSO₂p-Cl-Phenyl, amino, -NHCOOC(CH₃)₃, hydroxyl, phenyl, benzyl or chloro substituted benzyl;
- 25 $R^5, R^{5'}$ are independently from each other H, methyl or phenyl;
- $R^6, R^{6'}$ are independently from each other H, methyl or -SCH₃;
- m is 1, 2 or 3;
- n is 0 or 1; and
- p is 0, 1, 2 or 3;
- 30 and pharmaceutically acceptable salts thereof,

with the exception that the compound is not 3-acetyl-5-benzyl-4-hydroxy-1,5-dihydro-5H-furan-2-one.

6. The compound of formula Ia according to claim 5, which is

- (RS)-4-Hydroxy-5-isobutyl-3-(3-methyl-butyryl)-5H-furan-2-one;
- 5 4-Hydroxy-5-isobutyl-3-(3-methylsulfanyl-propionyl)-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-(4-methyl-pentanoyl)-5H-furan-2-one;
- 1-(4-Hydroxy-5-isobutyl-2-oxo-2,5-dihydro-furan-3-yl)-2-methyl-pentane-1,4-dione;
- 4-Hydroxy-5-isobutyl-3-(2,2,3,3-tetramethyl-cyclopropanecarbonyl)-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-(tetrahydro-furan-2-carbonyl)-5H-furan-2-one;
- 10 3-Cyclohexanecarbonyl-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-(4-tert-Butyl-cyclohexanecarbonyl)-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-(Cyclopent-2-enyl-acetyl)-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-(2-Cyclohexyl-acetyl)-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 15 4-Hydroxy-5-isobutyl-3-(2-phenoxy-benzoyl)-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-phenylacetyl-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-o-tolylacetyl-5H-furan-2-one;
- 3-[(4-Chloro-phenyl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-[2-(4-methoxy-3-methyl-phenyl)-acetyl]-5H-furan-2-one;
- 20 3-[2-(3,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-[2-(2,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-[2-(2,4-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-(2-phenyl-propionyl)-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-(2-phenyl-butyryl)-5H-furan-2-one;

- 4-Hydroxy-5-isobutyl-3-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-(3-phenyl-propionyl)-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-(3-m-tolyl-propionyl)-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-[3-(3-methoxy-phenyl)-propionyl]-5H-furan-2-one;
- 5 4-Hydroxy-5-isobutyl-3-[3-(4-methoxy-phenyl)-propionyl]-5H-furan-2-one;
- 3-[3-(2,5-Dimethoxy-phenyl)-propionyl]-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-[3-(4-Chloro-phenyl)-2-methyl-propionyl]-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-(3-phenyl-butyryl)-5H-furan-2-one;
- 10 4-Hydroxy-5-isobutyl-3-((R)-(R)-2-phenyl-cyclopropanecarbonyl)-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-[2-(2-methoxy-phenoxy)-acetyl]-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-[2-(naphthalen-1-yloxy)-acetyl]-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-(2-phenoxy-propionyl)-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-(4-phenyl-butyryl)-5H-furan-2-one;
- 15 3-[4-(3,4-Dimethoxy-phenyl)-butyryl]-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-((Z)-2-methyl-5-pyridin-3-yl-pent-4-enoyl)-5H-furan-2-one;
- 4-Hydroxy-5-isobutyl-3-((Z)-2-methyl-5-phenyl-hex-4-enoyl)-5H-furan-2-one;
- 4-Hydroxy-3-(2-1H-indol-3-yl-acetyl)-5-isobutyl-5H-furan-2-one;
- 4-Hydroxy-3-(3-1H-indol-3-yl-propionyl)-5-isobutyl-5H-furan-2-one;
- 20 4-Hydroxy-5-isobutyl-3-(2-naphthalen-2-yl-acetyl)-5H-furan-2-one;
- 3-[2-(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-Diphenylacetyl-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-isobutyl-5H-furan-2-one;

- 4-Hydroxy-5-isobutyl-3-[(9H-thioxanthen-9-yl)-acetyl]-5H-furan-2-one;
- 3-[(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetyl]-4-hydroxy-5-isobutyl-5H-furan-2-one;
- 4-Hydroxy-3-(3-methylsulfanyl-propionyl)-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 5 one;
- 3-Cyclopropanecarbonyl-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2,2,3,3-tetramethyl-cyclopropanecarbonyl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(tetrahydro-furan-2-carbonyl)-5H-furan-2-one;
- 10 one;
- 3-Cyclohexanecarbonyl-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 3-(4-tert-Butyl-cyclohexanecarbonyl)-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 3-(2-Cyclohexyl-acetyl)-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 15 3-(4-Cyclohexyl-butyl)-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-phenylacetyl-5H-furan-2-one;
- 4-Hydroxy-3-[2-(4-methoxy-3-methyl-phenyl)-acetyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 3-[2-(3,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 20 2-one;
- 3-[2-(2,4-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 3-[2-(2,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 25 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-naphthalen-2-yl-acetyl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-phenyl-propionyl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-phenyl-butyl)-5H-furan-2-one;

- 4-Hydroxy-3-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(3-phenyl-propionyl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(3-m-tolyl-propionyl)-5H-furan-2-one;
- 5 4-Hydroxy-3-[3-(3-methoxy-phenyl)-propionyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 4-Hydroxy-3-[3-(4-methoxy-phenyl)-propionyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 3-[3-(2,5-Dimethoxy-phenyl)-propionyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 10 3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(3-phenyl-butyryl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-((R)-(R)-2-phenyl-cyclopropanecarbonyl)-5H-furan-2-one;
- 15 4-Hydroxy-3-[2-(2-methoxy-phenoxy)-acetyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 4-Hydroxy-3-[2-(2,3-Dimethyl-phenoxy)-acetyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 20 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-phenoxy-propionyl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-phenoxy-butyryl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-[2-(naphthalen-1-yloxy)-acetyl]-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(4-phenyl-butyryl)-5H-furan-2-one;
- 25 3-[4-(3,4-Dimethoxy-phenyl)-butyryl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 4-Hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;

- 4-Hydroxy-3-(3-1H-indol-3-yl-propionyl)-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 3-[2-(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetyl]-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 5 3-Diphenylacetyl-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-(2-methylsulfanyl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(2-methylsulfanyl-propyl)-3-(2-9H-thioxanthen-9-yl-acetyl)-5H-furan-2-one;
- 3-(2-10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl-acetyl)-4-hydroxy-5-(2-
- 10 methylsulfanyl-propyl)-5H-furan-2-one;
- 3-Cyclohexanecarbonyl-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 3-Cyclohexylacetyl-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 5-Cyclohexylmethyl-3-(3-cyclohexyl-propionyl)-4-hydroxy-5H-furan-2-one;
- 3-(4-Cyclohexyl-butyryl)-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 15 4-Chloro-N-[3-cyclohexyl-1-(5-cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-carbonyl)-propyl]-benzenesulfonamide;
- 5-Cyclohexylmethyl-3-(5-cyclohexyl-pentanoyl)-4-hydroxy-5H-furan-2-one;
- 5-Cyclohexylmethyl-4-hydroxy-3-(2-methyl-3-phenyl-propionyl)-5H-furan-2-one;
- 3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-5-cyclohexylmethyl-4-hydroxy-5H-
- 20 furan-2-one;
- 3-[3-(4-Benzoyloxy-phenyl)-2-methyl-propionyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- (2-{4-[3-(5-Cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-2-methyl-3-oxo-propyl]-phenylcarbamoyl}-ethyl)-carbamic acid tert-butyl ester;
- 25 N-(2-{4-[3-(5-Cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-2-methyl-3-oxo-propyl]-phenyl}-ethyl)-benzenesulfonamide;

- 5-Chloro-N-(2-{4-[3-(5-cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-2-methyl-3-oxo-propyl]-phenyl}-ethyl)-2-methoxy-benzamide;
- [1-(4-Benzoyloxy-benzyl)-2-(5-cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester;
- 5 [2-(5-Cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-carbamic acid tert-butyl ester ;
- 3-[2-Amino-3-(4-hydroxy-phenyl)-propionyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one; compound with trifluoro-acetic acid;
- 5-Cyclohexylmethyl-4-hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5H-furan-2-one;
- 10 5-Cyclohexylmethyl-4-hydroxy-3-[(1H-indol-3-yl)-acetyl]-5H-furan-2-one;
- 5-Cyclohexylmethyl-4-hydroxy-3-[(1-methyl-1H-indol-3-yl)-acetyl]-5H-furan-2-one;
- 5-Cyclohexylmethyl-3-[[1-(4-fluoro-benzyl)-1H-indol-3-yl]-acetyl]-4-hydroxy-5H-furan-2-one;
- 3-[[1-(4-Chloro-benzyl)-5-methoxy-2-methyl-1H-indol-3-yl]-acetyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 15 3-[[1-(4-Chloro-benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-acetyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 5-Cyclohexylmethyl-4-hydroxy-3-(indol-1-yl-acetyl)-5H-furan-2-one;
- 5-Cyclohexylmethyl-4-hydroxy-3-(3-1H-indol-3-yl-propionyl)-5H-furan-2-one;
- 20 5-Cyclohexylmethyl-4-hydroxy-3-[(2-methyl-benzofuran-3-yl)-acetyl]-5H-furan-2-one;
- 3-[(5-Chloro-benzofuran-3-yl)-acetyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 3-(Benzo[b]thiophen-3-yl-acetyl)-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 5-Cyclohexylmethyl-3-(3,3-diphenyl-propionyl)-4-hydroxy-5H-furan-2-one;
- 5-Cyclohexylmethyl-3-(2,3-diphenyl-propionyl)-4-hydroxy-5H-furan-2-one;
- 25 5-Cyclohexylmethyl-3-[3-(4-fluoro-phenyl)-2-phenyl-propionyl]-4-hydroxy-5H-furan-2-one;
- 3-(2-Benzyl-3-phenyl-propionyl)-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;

- 3-[2-(4-Chloro-benzyl)-3-(4-chloro-phenyl)-propionyl]-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 5-Cyclohexylmethyl-3-[(9H-fluoren-9-yl)-acetyl]-4-hydroxy-5H-furan-2-one;
- 3-(Carbazol-9-yl-acetyl)-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 5 5-Benzyl-3-cyclohexanecarbonyl-4-hydroxy-5H-furan-2-one;
- 5-Benzyl-3-[3-(4-tert-butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5H-furan-2-one;
- 5-Benzyl-4-hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5H-furan-2-one;
- 5-Benzyl-3-(4-cyclohexyl-butyryl)-4-hydroxy-5H-furan-2-one;
- 5-Benzyl-4-hydroxy-3-[(1H-indol-3-yl)-acetyl]-5H-furan-2-one;
- 10 5-Benzyl-3-(3,3-diphenyl-propionyl)-4-hydroxy-5H-furan-2-one;
- 5-Benzyl-3-[(9H-fluoren-9-yl)-acetyl]-4-hydroxy-5H-furan-2-one;
- Rac-4-Hydroxy-3-(3-methyl-sulfanyl-propionyl)-5-phenethyl-5H-furan-2-one;
- Rac-3-(2(R,S),4-dimethyl-pentanoyl)-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-4-hydroxy-3-(2(R,S)-methyl-hexanoyl)-5-phenethyl-5H-furan-2-one;
- 15 Rac-3-cyclopropane-carbonyl-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-3-cyclohexane-carbonyl-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-3-(2-cyclohexyl-acetyl)-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-3-(4-cyclohexyl-butyryl)-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-4-hydroxy-5-phenethyl-3-phenylacetyl-5H-furan-2-one;
- 20 Rac-4-hydroxy-5-phenethyl-3-(2-o-tolyl-acetyl)-5H-furan-2-one;
- Rac-4-hydroxy-5-phenethyl-3-(2(R,S)-phenyl-propionyl)-5H-furan-2-one;
- Rac-4-hydroxy-5-phenethyl-3-(2(R,S)-phenyl-butyryl)-5H-furan-2-one;
- Rac-3-[2-(2,5-dimethoxy-phenyl)-acetyl]-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-3-[2-(2,4-dimethoxy-phenyl)-acetyl]-4-hydroxy-5-phenethyl-5H-furan-2-one;

- Rac-3-[2-(3,5-dimethoxy-phenyl)-acetyl]-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-4-hydroxy-5-phenethyl-3-(3-phenyl-propionyl)-5H-furan-2-one;
- 4-Hydroxy-5-phenethyl-3-((R)-(R)-2-phenyl-cyclopropanecarbonyl)-5H-furan-2-one;
- Rac-4-hydroxy-5-phenethyl-3-(3(R,S)-phenyl-butyryl)-5H-furan-2-one;
- 5 Rac-4-hydroxy-3-(2(R,S)-hydroxy-3-phenyl-propionyl)-5-phenethyl-5H-furan-2-one;
- Rac-4-hydroxy-5-phenethyl-3-(3-m-tolyl-propionyl)-5H-furan-2-one;
- Rac-4-hydroxy-3-[2-(2-methoxy-phenoxy)-acetyl]-5-phenethyl-5H-furan-2-one;
- Rac-4-hydroxy-3-[3-(3-methoxy-phenyl)-propionyl]-5-phenethyl-5H-furan-2-one;
- Rac-4-hydroxy-3-[3-(4-methoxy-phenyl)-propionyl]-5-phenethyl-5H-furan-2-one;
- 10 Rac-3-[3-(2,5-dimethoxy-phenyl)-propionyl]-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-3-[3-(4-tert-butyl-phenyl)-2(R,S)-methyl-propionyl]-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-3-[3-(4-chloro-phenyl)-2(R,S)-methyl-propionyl]-4-hydroxy-5-phenethyl-5H-furan-2-one;
- 15 4-Hydroxy-5-phenethyl-3-(4-phenyl-butyryl)-5H-furan-2-one;
- 3-[4-(3,4-Dimethoxy-phenyl)-butyryl]-4-hydroxy-5-phenethyl-5H-furan-2-one;
- 4-Hydroxy-3-(2-naphthalen-2-yl-acetyl)-5-phenethyl-5H-furan-2-one;
- Rac-4-hydroxy-3-[2(R,S)-(6-methoxy-naphthalen-2-yl)-propionyl]-5-phenethyl-5H-furan-2-one;
- 20 3-[(2-Acetyl-naphthalen-1-yl)-acetyl]-4-hydroxy-5-phenethyl-5H-furan-2-one;
- 3-[2-(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetyl]-4-hydroxy-5-phenethyl-5H-furan-2-one;
- 4-Hydroxy-3-(2-1H-indol-3-yl-acetyl)-5-phenethyl-5H-furan-2-one;
- Rac-4-hydroxy-3-(3-1H-indol-3-yl-propionyl)-5-phenethyl-5H-furan-2-one;

- Rac-4-hydroxy-3-[2-(naphthalen-1-yloxy)-acetyl]-5-phenethyl-5H-furan-2-one;
- Rac-3-(3,3-diphenyl-propionyl)-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-3-(2-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl-acetyl)-4-hydroxy-5-phenethyl-5H-furan-2-one;
- 5 Rac-4-hydroxy-5-phenethyl-3-(2-9H-thioxanthen-9-yl-acetyl)-5H-furan-2-one;
- Rac-3-(2-9H-fluoren-9-yl-acetyl)-4-hydroxy-5-phenethyl-5H-furan-2-one;
- Rac-[2-(4-hydroxy-2-oxo-5-phenethyl-2,5-dihydro-furan-3-yl)-1(R,S)-methyl-2-oxo-ethyl]-carbamic acid tert-butyl ester;
- Rac-3-(2(R,S)-amino-propionyl)-4-hydroxy-5-phenethyl-5H-furan-2-one;
- 10 [1(R)-Benzyl-2-(4-hydroxy-2-oxo-5(R,S)-phenethyl-2,5-di-hydro-furan-3-yl)-2-oxo-ethyl]-carbamic acid tert-butylester;
- 3-(2(R)-Amino-3-phenyl-propionyl)-4-hydroxy-5(R,S)-phenethyl-5H-furan-2-one;
- Rac-[1(R,S)-(4-benzyloxy-benzyl)-2-(4-hydroxy-2-oxo-5-phenethyl-2,5-dihydro-furan-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester;
- 15 [1(S)-(4-Benzyloxy-benzyl)-2-(4-hydroxy-2-oxo-5(R,S)-phenethyl-2,5-dihydro-furan-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester;
- [1(R)-(4-Benzyloxy-benzyl)-2-(4-hydroxy-2-oxo-5(R,S)-phenethyl-2,5-dihydro-furan-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester;
- Rac-3-[2(R,S)-amino-3-(4-benzyloxy-phenyl)-propionyl]-4-hydroxy-5-phenethyl-5H-furan-2-one;
- 20 furan-2-one;
- 2-(4-Hydroxy-2-oxo-5(R,S)-phenethyl-2,5-dihydro-furan-3-carbonyl)-pyrrolidine-1(S)-carboxylic acid tert-butyl ester;
- 4-Hydroxy-5(R,S)-phenethyl-3-(pyrrolidine-2(S)-carbonyl)-5H-furan-2-one;
- Rac-2(R,S)-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-furan-3-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester;
- 25 Rac-4-hydroxy-5-phenethyl-3(R,S)-(piperidine-2-carbonyl)-5H-furan-2-one;

- Rac-3(R,S)-(4-hydroxy-2-oxo-5-phenethyl-2,5-dihydro-furan-3-carbonyl)-3,4-dihydro-1H-iso-quinoline-2-carboxylic acid tert-butyl ester;
- Rac-4-hydroxy-5-phenethyl-3(R,S)-(1,2,3,4-tetrahydro-isoquinoline-3-carbonyl)-5H-furan-2-one;
- 5 3-4-Cyclohexanecarbonyl-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one;
- 3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one;
- 3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one;
- 4-Hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5-(3-phenyl-propyl)-5H-furan-2-one;
- 10 4-Hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-(3-phenyl-propyl)-5H-furan-2-one;
- 3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one;
- 3-[(9H-Fluoren-9-yl)-acetyl]-4-hydroxy-5-(3-phenyl-propyl)-5H-furan-2-one;
- 4-Hydroxy-3-(3-methylsulfanyl-propionyl)-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 15 3-Cyclopropanecarbonyl-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(2,2,3,3-tetramethyl-cyclopropanecarbonyl)-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(tetrahydro-furan-2-carbonyl)-5H-furan-2-one;
- 20 3-Cyclohexanecarbonyl-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 3-(2-Cyclohexyl-acetyl)-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-phenylacetyl-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(2-phenyl-propionyl)-5H-furan-2-one;
- 25 3-[2-(3,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;

- 3-[2-(2,5-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 3-[2-(2,4-Dimethoxy-phenyl)-acetyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 5 4-Hydroxy-3-[2-(4-methoxy-2-methyl-phenyl)-acetyl]-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 4-Hydroxy-3-[3-(4-methoxy-phenyl)-propionyl]-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(3-phenyl-butyryl)-5H-furan-2-one;
- 10 3-[3-(2,5-Dimethoxy-phenyl)-propionyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(3-m-tolyl-propionyl)-5H-furan-2-one;
- 4-Hydroxy-3-[3-(3-methoxy-phenyl)-propionyl]-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 15 4-Hydroxy-3-[2-(3-methoxy-phenoxy)-acetyl]-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(2-m-tolyloxy-acetyl)-5H-furan-2-one;
- 4-Hydroxy-3-[2-(2-methoxy-phenoxy)-acetyl]-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 20 3-[2-(2,3-Dimethyl-phenoxy)-acetyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(4-phenyl-butyryl)-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(2-naphthalen-2-yl-acetyl)-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-[2-(naphthalen-1-yloxy)-acetyl]-5H-furan-2-one;
- 25 2-one;
- 4-Hydroxy-3-(2-1H-indol-3-yl-acetyl)-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 4-Hydroxy-3-(3-1H-indol-3-yl-propionyl)-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;

- 3-[2-(2-Acetyl-1,2-dihydro-isoquinolin-1-yl)-acetyl]-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-(3-morpholin-4-yl-propyl)-5H-furan-2-one;
- 4-Hydroxy-5-(3-morpholin-4-yl-propyl)-3-(2-9H-thioxanthen-9-yl-acetyl)-5H-furan-2-one;
- 5 [2-(4-Benzoyloxy-phenyl)-ethyl]-3-(4-cyclohexyl-butyryl)-4-hydroxy-5H-furan-2-one;
- 3-Cyclohexanecarbonyl-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one;
- 3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one;
- 3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one;
- 10 4-Hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5-methyl-5-phenethyl-5H-furan-2-one;
- 4-Hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-methyl-5-phenethyl-5H-furan-2-one;
- 3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one;
- 3-[(9H-Fluoren-9-yl)-acetyl]-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one;
- 15 3-Cyclohexanecarbonyl-4-hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one;
- 4-Hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5-phenethyl-5-phenyl-5H-furan-2-one;
- 4-Hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-phenethyl-5-phenyl-5H-furan-2-one;
- 3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one; or
- 3-[(9H-Fluoren-9-yl)-acetyl]-4-hydroxy-5-phenethyl-5-phenyl-5H-furan-2-one.

20 7. The compound of formula Ia according to claim 6, which is

- Rac-4-hydroxy-5-isobutyl-3-[(9H-thioxanthen-9-yl)-acetyl]-5H-furan-2-one;
- 3-[3-(4-tert-Butyl-phenyl)-2(R,S)-methyl-propionyl]-5(R,S)-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;
- 5-Chloro-N-(2-{4-[3-(5(R,S)-cyclohexylmethyl-4-hydroxy-2-oxo-2,5-dihydro-furan-3-yl)-2(R,S)-methyl-3-oxo-propyl]-phenyl}-ethyl)-2-methoxy-benzamide;
- 25

Rac-5-cyclohexylmethyl-4-hydroxy-3-[(1H-indol-3-yl)-acetyl]-5H-furan-2-one;

Rac-5-cyclohexylmethyl-3-{[1-(4-fluoro-benzyl)-1H-indol-3-yl]-acetyl}-4-hydroxy-5H-furan-2-one;

Rac-5-cyclohexylmethyl-3-[(9H-fluoren-9-yl)-acetyl]-4-hydroxy-5H-furan-2-one;

5 Rac-3-(carbazol-9-yl-acetyl)-5-cyclohexylmethyl-4-hydroxy-5H-furan-2-one;

5(R,S)-Benzyl-3-[3-(4-tert-butyl-phenyl)-2(R,S)-methyl-propionyl]-4-hydroxy-5H-furan-2-one;

Rac-4-hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5-phenethyl-5H-furan-2-one;

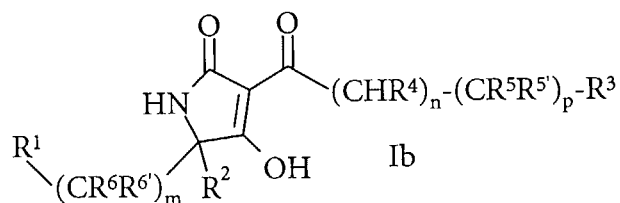
Rac-4-hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-phenethyl-5H-furan-2-one;

10 Rac-3-(3,3-diphenyl-propionyl)-4-hydroxy-5-phenethyl-5H-furan-2-one;

Rac-4-hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-(3-phenyl-propyl)-5H-furan-2-one; or

Rac-3-[(9H-fluoren-9-yl)-acetyl]-4-hydroxy-5-methyl-5-phenethyl-5H-furan-2-one.

8. The compound of formula I of claim 1, wherein said compound has the formula Ib



15

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^5' , R^6 , R^6' , m , n and p are defined in claim 1,

and pharmaceutically acceptable salts thereof,

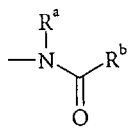
with the exception that the compound is not 3-acetyl-4-hydroxy-5-isobutyl-1,5-dihydro-pyrrol-2-one.

20 9. The compound of formula Ib according to claim 8, wherein

R^1 is aryl;

R^2 is H;

R^3 is $-SCH_3$,



, wherein R^a is H or lower alkyl, R^b is lower alkyl, heteroaryl, -OC(CH₃)₃ or aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl,

cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by lower alkyl,

- 5 heterocycloalkyl, wherein the heterocycloalkyl ring is unsubstituted or substituted by -COOC(CH₃)₃;

aryl, wherein the aryl ring is unsubstituted or substituted by lower alkyl, alkoxy, benzyloxy or for the non aromatic part of fused ring system also by oxo,

aryloxy, wherein the aryl ring is unsubstituted substituted by alkoxy, or

- 10 heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by lower alkyl, -COOC(CH₃)₃ or by halogen substituted benzyl, or for the non aromatic part of fused ring system also by oxo;

R⁴ is H, lower alkyl, -NHCOCH₃, amino, -NHCOOC(CH₃)₃, aryl or benzyl;

R⁵, R^{5'} are H;

- 15 R⁶, R^{6'} are H;

m is 2;

n is 0 or 1; and

p is 0, 1, 2 or 3;

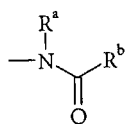
and pharmaceutically acceptable salts thereof.

- 20 10. The compound of formula Ib of claim 9, wherein

R¹ is phenyl;

R² is H;

R³ is -SCH₃,



, wherein R^a is H or methyl, R^b is methyl, 1H-pyrrol-3-yl, $-OC(CH_3)_3$ or aryl, wherein the aryl ring is unsubstituted or substituted by methyl,

cycloalkyl, wherein the cycloalkyl ring is unsubstituted or substituted by methyl,

heterocycloalkyl, wherein the heterocycloalkyl ring is unsubstituted or substituted by $-COOC(CH_3)_3$;

aryl, wherein the aryl ring is unsubstituted or substituted by methyl, tert-butyl, methoxy, benzyloxy or for the non aromatic part of fused ring system also by oxo,

aryloxy, wherein the aryl ring is substituted by methoxy, or

heteroaryl, wherein the heteroaryl ring is unsubstituted or substituted by methy, $-COOC(CH_3)_3$ or by 4-fluoro-benzyl-1-yl, or for the non aromatic part of fused ring system also by oxo;

R^4 is H, methyl, $-NHCOCH_3$, amino, $-NHCOOC(CH_3)_3$, phenyl or benzyl;

$R^5, R^{5'}$ are H;

$R^6, R^{6'}$ are H;

m is 2;

n is 0 or 1; and

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts thereof.

11. The compound of formula Ib according to claim 10, wherein

R^1 is phenyl;

R^2 is H;

R^3 is $-SCH_3$, $-NHCOCH_3$, $-NHCO$ -phenyl, $-NHCO$ -(4-methyl-phenyl), $-NHCO$ -(2,5-dihydro-1H-pyrrol-3-yl), $NHCOOC(CH_3)_3$,

cyclopropanyl, 1-methyl-cyclopropanyl, cyclohexanyl,

1-tert-butyloxycarbonylpyrrolidine-2-yl, 1-ter-butyloxycarbonylpiperidine-2-yl, tetrahydro-furan-2-yl,

phenyl, toluenyl, 4-tert-butyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-benzoxo-phenyl, 3,4-dimethoxy-phenyl, naphthalene-2-yl, 6-methoxy-
 5 naphthalen-2-yl, 3-oxo-indan-1-yl,

2-methyl-phenoxy,

1,2,5-trimethyl-1H-pyrrole-3-yl, 5-methyl-pyrazine-2-yl, 5-methyl-2,4-dioxo-1H-pyriminine-1-yl, 3-methyl-furan-2-yl, indol-1-yl, 1H-indol-3-yl, (4-fluoro-benzyl)-1H-indol-3-yl, isoquinoline-3-yl, 3,4-dihydro-1H-isoquinoline-2-carboxylic acid
 10 tert-butyl ester, thieno[2,3-c]pyridine-7-yl, benzo[1,2,3]thiadiazole-5-yl, 2,3-dihydro-benzofuran-7-yl, 2-benzo[b]thiophen-3-yl, or carbazol-9-yl,

R⁴ is H, methyl, -NHCOCH₃, amino, -NHCOOC(CH₃)₃, phenyl or benzyl;

R⁵, R^{5'} are H;

R⁶, R^{6'} are H;

15 m is 2;

n is 0 or 1; and

p is 0, 1, 2 or 3;

and pharmaceutically acceptable salts thereof.

12. The compound of formula Ib according to claim 11, which is

20 4-Hydroxy-3-(3-methylsulfanyl-propionyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one;

3-Cyclopropanecarbonyl-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one;

4-Hydroxy-3-(1-methyl-cyclopropanecarbonyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one;

4-Hydroxy-5-phenethyl-3-(tetrahydro-furan-2-carbonyl)-1,5-dihydro-pyrrol-2-one;

3-(4-Cyclohexyl-butyryl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one;

25 4-Hydroxy-5-phenethyl-3-(thieno[2,3-c]pyridine-7-carbonyl)-1,5-dihydro-pyrrol-2-one;

4-Hydroxy-3-(5-methyl-pyrazine-2-carbonyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one;

- 4-Hydroxy-3-(isoquinoline-3-carbonyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 3-(Benzo[1,2,3]thiadiazole-5-carbonyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 4-Hydroxy-3-(3-methyl-furan-2-carbonyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 5 3-(2,3-Dihydro-benzofuran-7-carbonyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 4-Hydroxy-5-phenethyl-3-(1,2,5-trimethyl-1H-pyrrole-3-carbonyl)-1,5-dihydro-pyrrol-2-one;
- 4-Hydroxy-5-phenethyl-3-phenylacetyl-1,5-dihydro-pyrrol-2-one;
- 10 4-Hydroxy-3-(2-naphthalen-2-yl-acetyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 4-Hydroxy-3-[2-(3-oxo-indan-1-yl)-acetyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 1-[2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-5-methyl-1H-pyrimidine-2,4-dione;
- 4-Hydroxy-5-phenethyl-3-(2-phenyl-propionyl)-1,5-dihydro-pyrrol-2-one;
- 15 4-Hydroxy-3-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 4-Hydroxy-5-phenethyl-3-(3-m-tolyl-propionyl)-1,5-dihydro-pyrrol-2-one;
- 4-Hydroxy-3-[3-(3-methoxy-phenyl)-propionyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 20 4-Hydroxy-3-[3-(2-methoxy-phenyl)-propionyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 4-Hydroxy-3-[3-(4-methoxy-phenyl)-propionyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 3-[3-(4-tert-Butyl-phenyl)-2-methyl-propionyl]-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 25 4-Hydroxy-3-[(2-methoxy-phenoxy)-acetyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 4-Hydroxy-5-phenethyl-3-(4-phenyl-butyryl)-1,5-dihydro-pyrrol-2-one;

- 3-[4-(3,4-Dimethoxy-phenyl)-butyryl]-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- N-[2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-acetamide;
- 5 N-[1-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-3-methylsulfanyl-propyl]-acetamide;
- N-[2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-N-methyl-benzamide;
- 10 N-[2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-4-methyl-benzamide;
- N-[2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-nicotinamide;
- [2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-1-methyl-2-oxo-ethyl]-carbamic acid tert-butyl ester;
- 15 [1-Benzyl-2-(4-hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester;
- 2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester;
- 2-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester;
- 20 3-(4-Hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrole-3-carbonyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester;
- [1-(4-Benzyloxy-benzyl)-2-(4-hydroxy-2-oxo-5-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2-oxo-ethyl]-carbamic acid tert-butyl ester;
- 25 3-[2-Amino-3-(4-benzyloxy-phenyl)-propionyl]-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one; compound with trifluoro-acetic acid;
- 4-Hydroxy-3-[(1H-indol-3-yl)-acetyl]-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 3-{[1-(4-Fluoro-benzyl)-1H-indol-3-yl]-acetyl}-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one;

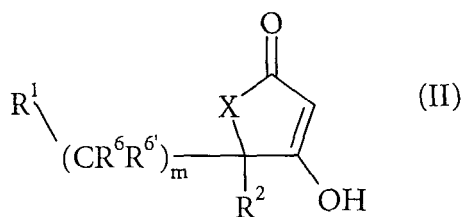
- 4-Hydroxy-3-(indol-1-yl-acetyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 4-Hydroxy-3-(3-1H-indol-3-yl-propionyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 3-(2-Benzo[b]thiophen-3-yl-acetyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 3-(3,3-Diphenyl-propionyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one;
- 5 3-(2,3-Diphenyl-propionyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one; or
- 3-(Carbazol-9-yl-acetyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one.

13. The compound of formula Ib according to claim 12, which is

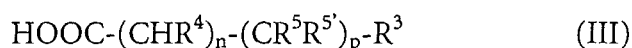
- 4-Hydroxy-3(R,S)-[2-(6-methoxy-naphthalen-2-yl)-propionyl]-5(R,S)-phenethyl-1,5-dihydro-pyrrol-2-one;
- 10 [1-(4-Benzyloxy-benzyl)-2-(4-hydroxy-2-oxo-5(R,S)-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-2(R,S)-oxo-ethyl]-carbamic acid tert-butyl ester;
- Rac-4-hydroxy-3-(indol-1-yl-acetyl)-5-phenethyl-1,5-dihydro-pyrrol-2-one; or
- Rac-3-(carbazol-9-yl-acetyl)-4-hydroxy-5-phenethyl-1,5-dihydro-pyrrol-2-one.

14. A process for producing a compound of formula I of claim 1, comprising

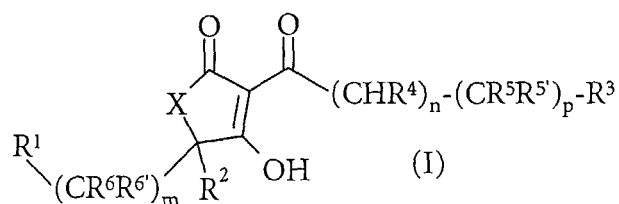
- 15 acylation of a compound of formula II



with a carboxylic acid of formula III



to produce a compound of formula I



wherein X, R¹, R², R³, R⁴, R⁵, R^{5'}, R⁶, R^{6'}, m, n and p are defined in claim 1, and
if desired, converting the compounds obtained into pharmaceutically acceptable salts.

15. The compound of formula I or a pharmaceutically acceptable salt thereof according to claim 1, whenever prepared by a process according to claim 14.

5 16. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of formula I or a pharmaceutically acceptable salt thereof according to any one of claim 1 to 13 in admixture with one or more pharmaceutically acceptable carrier for the treatment of diseases.

10 17. The compound of formula I or a pharmaceutically acceptable salt thereof according to claim 1 for the use as medicament.

18. Use of one or more compounds of formula I or a pharmaceutically acceptable salt thereof according to claim 1 for the manufacture of a medicament for the treatment or prevention of a disease state which is modulated by an inhibitor of β -secretase.

19. The use of claim 18, wherein the disease state comprises disorders of CNS.

15 20. The use of claim 19, wherein the disease state comprises Alzheimer's disease.

21. The invention is hereinbefore described.
