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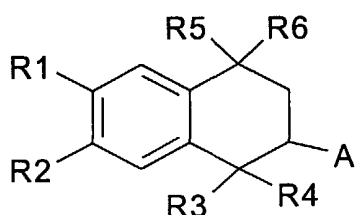
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(54) Title: 2,6,7-SUBSTITUTED TETRALINES USEFUL FOR THE PREPARATION OF MEDICAMENTS WITH PHOSPHODIESTERASE IV INHIBITORY ACTIVITY



(I)

(57) Abstract: Formula (I) compounds are described where the groups are as defined in the description, as well as processes for their preparation and their use as medicaments, particularly for the preparation of medicaments with phosphodiesterase IV inhibitory activity.

**2,6,7-substituted tetralines useful for the preparation of
medicaments with phosphodiesterase IV inhibitory activity**

The invention described herein relates to compounds for use as
medicaments, to processes for their preparation, to pharmacological
5 compositions containing them and to their use for the preparation of
medicaments, and more particularly for medicaments useful as
selective phosphodiesterase IV inhibitors.

The phosphodiesterases are a large family of enzymes which
act on different substrates over an extensive area of metabolic
10 regulation. For a review of the subject see C. David et al. TIPS –
January 1991 (vol. 12); 19-27.

It is well known that there are at least 5 distinct families of
phosphodiesterase isoenzymes (briefly PDE I-V) (see Beavo &
Houslay, Isoenzymes of Cyclic Nucleotide Phosphodiesterase.
15 Chichester: Wiley & Sons – 1990).

There is therefore still a need for selective phosphodiesterase
inhibitors.

In particular, the invention described herein tackles the
problem of supplying selective inhibitors of phosphodiesterase IV
20 (briefly, also referred to as PDE IV).

Phosphodiesterase IV inhibitors are also known to be useful
agents in the treatment of respiratory tract diseases, particularly as
anti-inflammatory agents and bronchodilators.

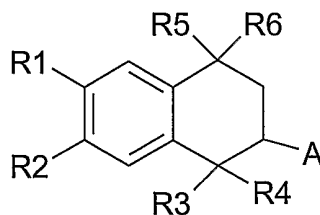
Among the most studied PDE IV inhibitors, we mention here rolipram (Reeves et al. Biochem J., 241, 535-541 (1987), US 4193926 and US 5059612) and denbufylline (Nicholson et al. Br. J. of Pharmacol., 97, 889-897 (1989)), as useful agents for the treatment of asthma thanks to their bronchodilator properties.

2-aminotetralines are described, for example, in Italian patent IT 1232359, as antihypertensive agents; in US patent 5637614, as immunomodulators; and in US 5591777, WO98/33762, WO99/15494, as agents useful for the treatment and prevention of septic shock.

WO 9704775 describes substituted dihydropyridopyrimidines as selective inhibitors of PDE IV.

It has now been found that 2,6,7-substituted tetralines are selective inhibitors of phosphodiesterase IV.

Compounds of general formula (I) are the subject matter of the invention described herein:



(I)

where:

R₁ and R₂, which may be the same or different, are halogen, hydroxy, straight or branched C₁-C₄ alkoxy, C₅-C₆ cycloalkoxy;

R₃ and R₄ together form a =O, =NOH group, or, R₃ and R₄, which may be the same or different, are -H, -OH;

R₅ and R₆ together form a =O, =NOH group; or, R₅ and R₆, which may be the same or different, are -H, -OH;

5 A is

- the -NHR₇ group, in which R₇ is -H, alkanoyl, C₁-C₄ alkylcarbamoyl, in which the alkyl may be substituted with halogens;

- arylcarbamoyl;

10 - -NCO;

- -COOR₈ in which R₈ is -H, C₁-C₄ alkyl, optionally substituted with one or more halogen atoms;

- -CONHOH;

their enantiomers, diastereoisomers and mixtures of the same, and

15 their pharmaceutically acceptable salts.

A first preferred group of formula (I) compounds are those in which R₁ is halogen and R₂ alkoxy or cycloalkoxy; in particular, within this group, a particular preference goes to compounds in which R₂ is cyclopentyloxy.

20 A second preferred group of formula (I) compounds are those in which R₅ and R₆ together are the keto group, or the corresponding oxime.

A third preferred group of formula (I) compounds are those in which A is the -COOR₈, -NCO or -CONHOH group.

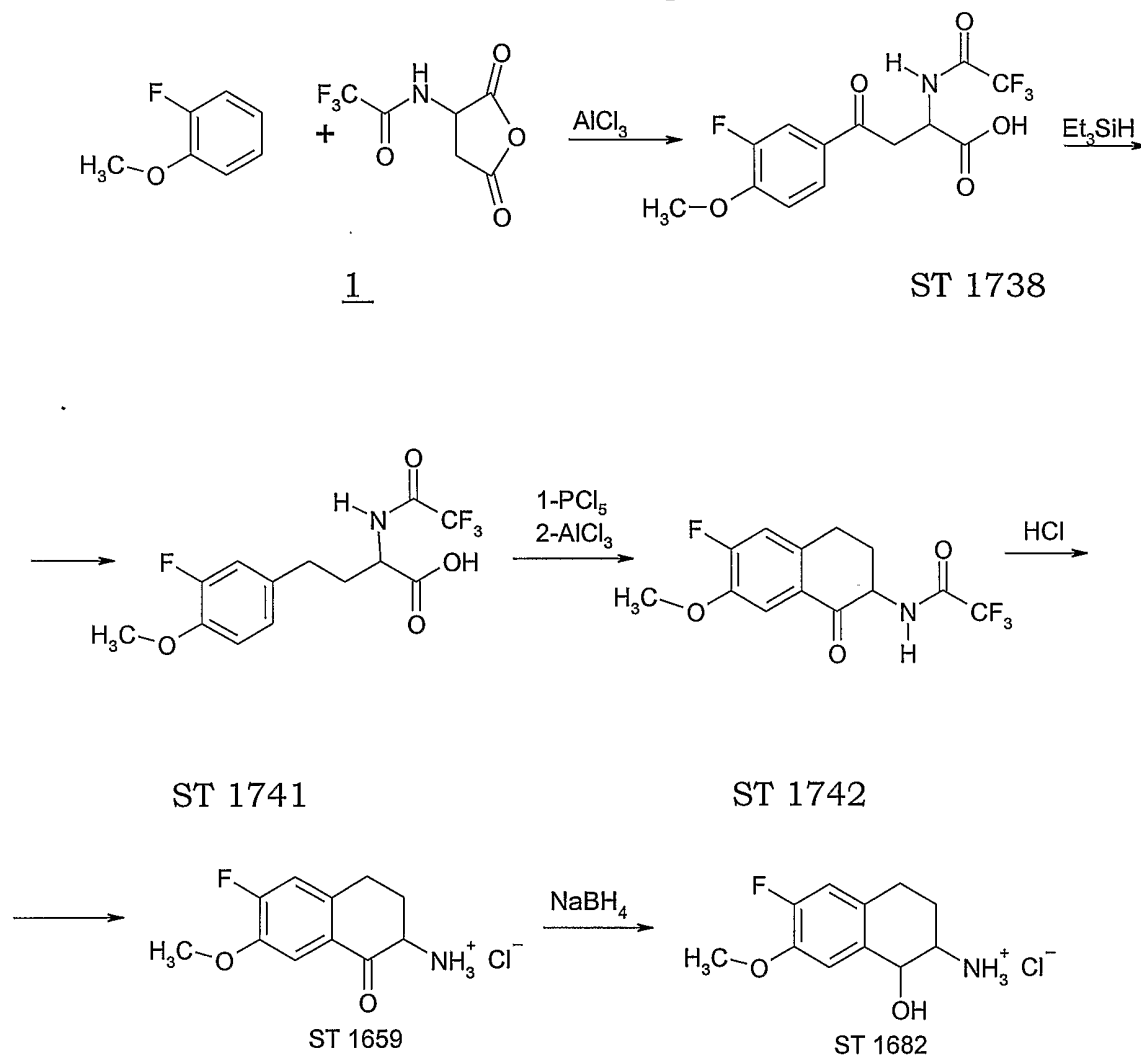
The following compounds are preferred:

- 2-(N-trifluoroacetyl)amino-6,7-diethoxy-1-tetralone (ST1359);
- 2-amino-6,7-diethoxy-1-tetralone hydrochloride (ST1374);
- (R,S)-6-methoxy-7-cyclopentyloxy-1,2,3,4-tetrahydro-2-naphthoic
5 acid (ST1506);
- (R,S)-2-amino-6-fluoro-7-methoxy-1-tetralone hydrochloride
(ST1659);
- (R,S)-6-methoxy-7-cyclopentyloxy-2-benzyloxy-carbonylamino-
tetraline (ST1678);
- 10 - (R,S)-1-hydroxy-(R,S)-2-amino-6-fluoro-7-methoxy-tetraline
hydrochloride (ST1682);
- (R,S)-2-amino-6-methoxy-7-cyclopentyloxy-tetraline
hydrochloride (ST1683);
- 7-(cyclopentyloxy)-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-
15 naphthalenecarboxylic acid (ST1702);
- (4E)-7-(cyclopentyloxy)-4-(hydroxyimino)-6-methoxy-1,2,3,4-
tetrahydro-2-naphthalenecarboxylic acid (ST1703);
- (4E)-7-(cyclopentyloxy)-N-hydroxy-4-(hydroxyimino)-6-methoxy-
1,2,3,4-tetrahydro-2-naphthalenecarboxamide (ST1704);
- 20 - 2,2,2-trifluoro-N-(6-fluoro-7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-
naphthalenyl)acetamide (ST1742);
- methyl 7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetrahydro-2-naph-
thalenecarboxylate (ST1743);

- 7-(cyclopentyloxy)-2-isocyanate-6-methoxy-1,2,3,4-tetrahydro-2-naphthalene (ST1744);
- methyl 7-(cyclopentyloxy)-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (ST1763).

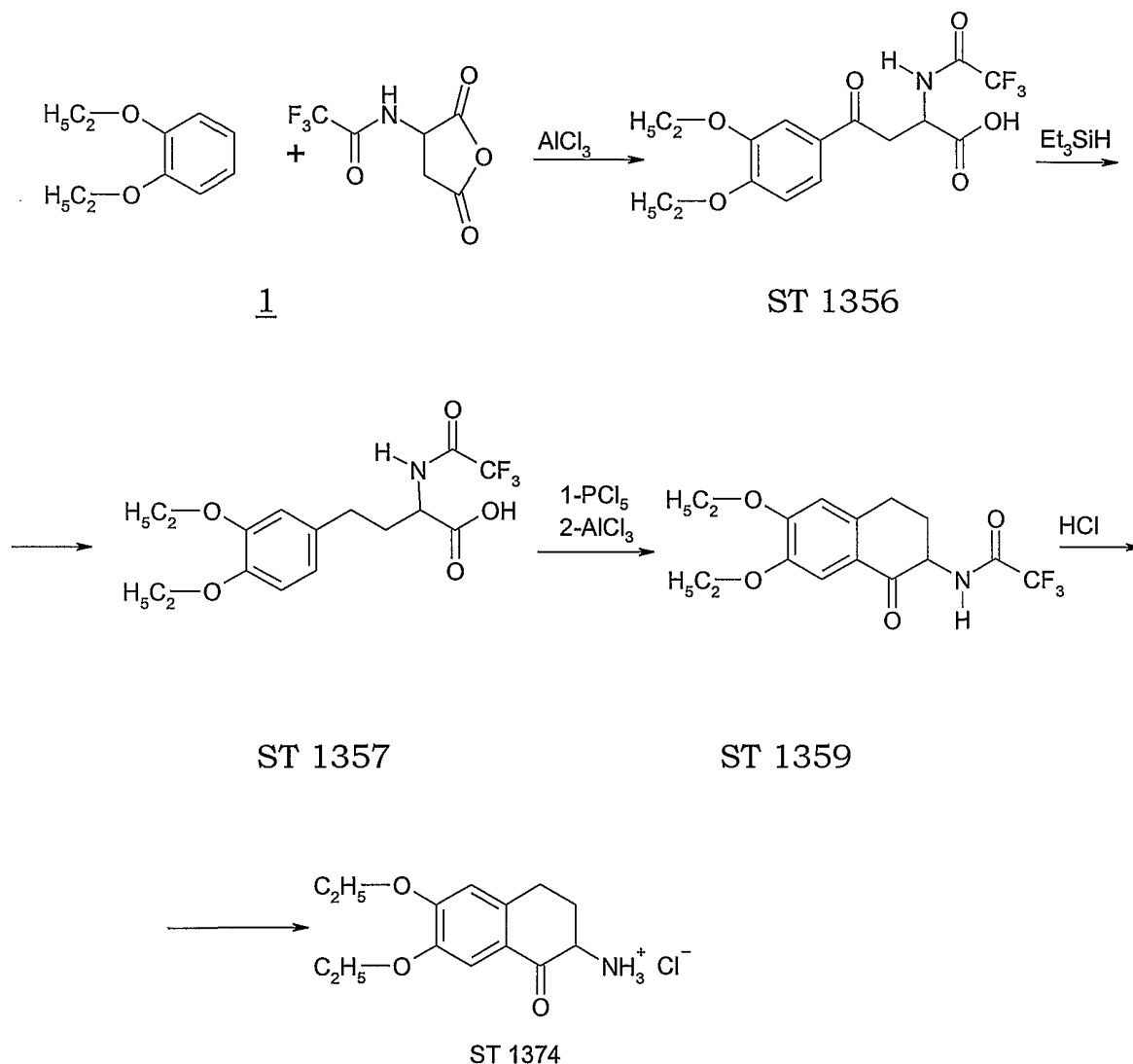
5 The compounds according to the invention described herein can be prepared according to known methods.

 In particular, in the case of the formula (I) compounds in which A is a -NHR₇ group, the R₁ and R₂ groups are halogen and hydroxy or alkoxy or cycloalkoxy, R₃ and R₄ are independently
10 hydrogen and hydroxyl, and the R₅ and R₆ groups are both hydrogen, these are preferably prepared with the process described, entirely by way of an example, for compounds ST1659 and ST1682, which involves a series of reactions according to the reaction diagram indicated here below.

Diagram 1

It is understood that the expert in the field is capable of preparing all the formula (I) compounds, in which R_1 and R_2 are as specified in the general description, selecting the appropriate starting compounds. By way of an example, an appropriate starting compound will be selected from the group consisting of benzene 1,2, substituted with the groups R_1 and R_2 indicated above, such as 2-halophenol (2-chlorophenol, 2-fluorophenol, 2-bromophenol, 2-iodophenol), ethers with C_1 - C_4 alkyl or C_5 - C_6 cycloalkyl of 2-alkoxyphenol (2-chlorophenol methyl ether, 2-fluorophenol methyl ether, 2-bromophenol methyl ether, 2-iodophenol methyl ether and higher ethers). These compounds are commercially available or can be prepared with methods known in the literature.

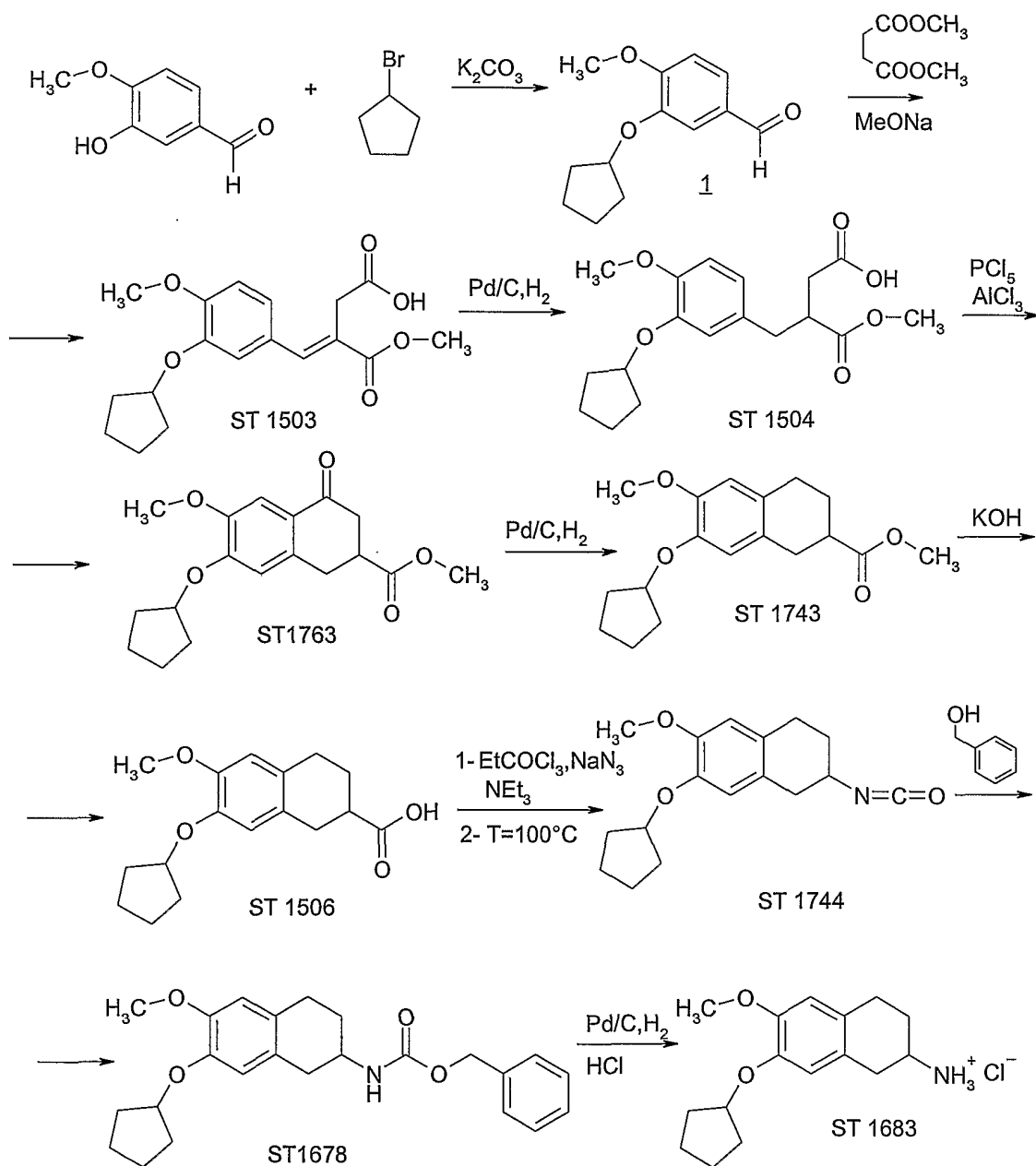
In the case of the formula (I) compounds in which A is a $-NHR_7$ group, the R_1 and R_2 groups are both alkoxy or cycloalkoxy, R_3 and R_4 together are the keto group, and the R_5 and R_6 groups are both hydrogen, these are preferably prepared with the process described, entirely by way of an example, for compound ST 1374, which involves a series of reactions according to the diagram indicated here below:

Diagram 2

It is understood that the expert in the field is capable of preparing all the formula (I) compounds, in which R_1 and R_2 are as specified in the general description, selecting the appropriate starting compounds. By way of an example, an appropriate starting compound will be selected from the group consisting of benzene 1,2, substituted with the groups R_1 and R_2 indicated above, such as 2,3-dimethoxybenzene, 2,3-diethoxybenzene, 2,3-dipropoxybenzene, 2,3-

dibutoxybenzene, and the branched isomeric analogues, or 2,3-dicyclopentyloxybenzene, 2,3-dicyclohexyloxybenzene. Starting compounds carrying different R_1 and R_2 groups are also envisaged. These compounds are commercially available or can be prepared with known methods in the literature.

In the case of the group of particularly preferred formula (I) compounds, in which A is a $-NHR_7$ group, group R_1 is alkoxy or cycloalkoxy, the R_2 group is cyclopentyloxy, R_3 and R_4 are both hydrogen, and the R_5 and R_6 groups are both hydrogen, these are preferably prepared with the process described, entirely by way of an example, for compound ST1683, which involves a series of reactions according to the diagram indicated here below:

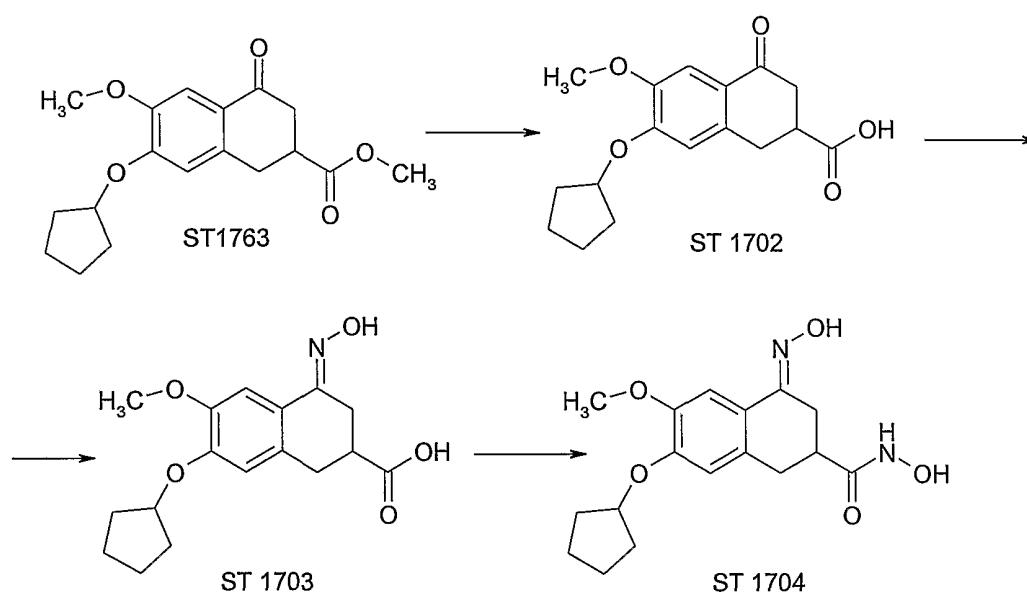
Diagram 3

As can be seen, the process described in diagram 3 conveniently makes it possible to obtain formula (I) compounds, in which A is COOR₈, -NCO, and R₅ and R₆, together, form the keto group.

Of course, the chemical expert in the field will be capable of judging which procedural variants will enable him or her to obtain the compounds desired within the formula (I) framework described above, with the possible combinations envisaged for the various groups.

It is understood that the expert in the field is capable of preparing all the formula (I) compounds. For example, in the second step, esters of glutaric acid can be used as envisaged in the definition of R₈, alkyl with 1 to 4 carbon atoms, or, the keto group in 4- on the tetraline ring can be conserved up until the end compound. The starting compounds are commercially available or can be prepared with the methods known in the literature.

In the case of the group of particularly preferred formula (I) compounds, in which A is a -CONHOH group, the R₁ group is alkoxy or cycloalkoxy, the R₂ group is cyclopentyloxy, R₃ and R₄ are both hydrogen, and the R₅ and R₆ groups together are the -NOH group, these are preferably prepared with the process described, entirely by way of an example, for compound ST1704, which involves a series of reactions according to the diagram indicated here below:

Diagram 4

It is understood that the expert in the field is capable of preparing all the formula (I) compounds, selecting the appropriate starting compounds.

The following examples further illustrate the invention.

5

EXAMPLE 1 (Diagram 1)

Preparation of 2-amino-6-fluoro-7-methoxy-1-tetralone hydrochloride (ST1659)

a) Preparation of N-trifluoroacetyl-aspartic anhydride (1)

Aspartic acid (100 g: 0.75 mol) is suspended in trifluoroacetic
10 acid (300 ml) under mechanical stirring and cooled with an ice and
salt bath; trifluoroacetic anhydride is added drop-wise (300 ml: 2.16
mol), adjusting the addition in such a way as not to let the
temperature rise above 10°C. On completing the addition, the
suspension is left to stir vigorously for half an hour at a temperature
15 below 10°C after which the temperature is allowed to rise slowly. The
suspension is reacted for 2 hours at 45°C and for one night at room
temperature. Extraction is done with acetone (300 ml) with cooling
to solubilise the mass which is of very firm consistency and then the
solution is concentrated to dryness. The solid obtained is washed
20 twice with 500 cc of n-hexane and again with 1 litre of n-
hexane/ethyl ether at a ratio of 4:1, triturating and vacuum filtering.
135 g of product are obtained which can be used as is if the
analyses are compliant. Crystallisation by n-hexane/EtOAc is
performed obtaining 119 g of product which is vacuum dried

thoroughly at 40°C. Yield 75%.

M.P.: 134-136°C

¹H-NMR (DMSOd₆), Varian 300 MHz, δ (p.p.m.): 2.85-3.3 (2H,m,CH₂); 4.95-5.1 (1H,m,CHNH); 9.6-9.8 (1H,bd,CHNHCOCF₃).

5 b) Preparation of 4-(3-fluoro-4-methoxyphenyl-4-oxo-2-(N-trifluoroacetyl)-aminobutanoic acid (ST1738)

The N-trifluoroacetyl aspartic anhydride (1) (58 g: 0.275 mol) is suspended in 100 ml of anhydrous CH₂Cl₂; 2-fluoroanisol (77 ml; 0.68 mol) is then added at room temperature and in a nitrogen
10 atmosphere with mechanical stirring. The temperature is then brought down to +10°C with an ice bath and AlCl₃ (82 g, 0.616 mol) is added in two portions. The cooling is removed and the suspension is left to reach room temperature. The reaction is left under mechanical stirring at room temperature for 2 days. After
15 approximately 5 hours, when the reaction has taken on a red colour, and has started to become less fluid, another 100 ml of CH₂Cl₂ are added. When the reaction is completed, 300 ml of CH₂Cl₂ are added, the reaction mixture is left under vigorous stirring to triturate the solid and is then vacuum filtered. The dried solid is
20 transferred portion-wise into a beaker containing 2 litres of HCl 6N under vigorous stirring and cooling with ice. A flaky precipitate is formed, the whole is extracted several times with a total of 1 litre of AcOEt or CH₂Cl₂, the organic phase is separated and brought to dryness after anhydrification on anhydrous Na₂SO₄. A clear solid or

oil is obtained which is crystallised by n-hexane-EtOAc 7:5. Filtration is done by concentrating the mother liquors from which more product is recovered which is recrystallised and added to the first crystallised product after TLC control. 43 g of product are
5 obtained. Yield 47%.

M.P.: 116-118°C

$^1\text{H-NMR}$ (CD_3OD) Varian 300 MHz, δ (ppm): 3.6 (2H,m, CH_2NH), 3,96 (3H,s, PhOCH_3); 4.88-5.01 (1H,m, CH_2CHNH); 7.18-7.22 (1H,t,Ar); 7.7-7.8 (1H, dd, Ar); 7.82-7.9 (1h, bd, NH)

10 a) Preparation of 4-(3-fluoro-4-methoxyphenyl-2-(N-trifluoroacetyl)aminobutanoic acid (ST1741)

4-(3-fluoro-4-methoxyphenyl-4-oxo-2-(N-trifluoroacetyl)aminobutanoic acid (ST1738) (28.8 g, 0.087 mol) is dissolved in 150 ml of CF_3COOH or even less, and, under a nitrogen atmosphere,
15 triethylsilane (54.9 g, 0.348 mol) is added; the solution is slightly refluxed for 8 hours and one night at room temperature. The trifluoroacetic acid is completely eliminated by vacuum evaporation at the lowest possible temperature; the residual oil is cooled with an ice and salt bath and then treated under stirring in a beaker with a
20 saturated solution of NaHCO_3 and then with solid NaHCO_3 , under vigorous stirring, adding ether from time to time to avoid excessive frothing. The aqueous phase is washed with ethyl ether and carefully acidified cold with HCl 6N to pH 3. The product precipitates and is then extracted several times with CH_2Cl_2 . The organic

extracts are gathered, washed with little water, dried on anhydrous Na_2SO_4 and then vacuum dried. The solid or oil obtained is crystallised by n-hexane/EtOAc obtaining a white solid which is vacuum dried in an oven. 21 g of product are obtained. Yield 75%.

5 M.P.: 107-108°C

^1H -NMR (CDCl_3), Varian 300 MHz, δ (p.p.m.): 2.0-2.18 (1H,m,CHHCHNH); 2.22-2.36 (1H,m,CHHCHNH); 2.6-2.7 (2H,t,PhCH₂CH₂); 3.84 (3H,s,PhOCH₃); 4.6-4.7 (1H,m,CH₂CHNH), 6.78 (1H, dd, CHNHCOCF₃); 6.8-6.92 (2H,m,Ar).

10 d) Preparation of 2-(N-trifluoroacetyl)-amino-6-fluoro-7-methoxy-1-tetralone (ST1742)

35 g of 4-(3-fluoro-4-methoxyphenyl)-2-(N-trifluoroacetyl)-aminobutanoic acid (ST 1741) (0.108 mol) are suspended in anhydrous methylene chloride (500 ml). 23 g of phosphorus pentachloride are added at room temperature under stirring and under light nitrogen flow. After 5 minutes the solubilisation is complete. The solution is left to stir at room temperature in a nitrogen atmosphere for approximately one hour. 43 g (0.324 mol) of aluminium chloride are added with a rise in temperature and reflux
15 of the solvent, controlling the temperature with a water and ice bath. When the temperature has dropped to 25° the solution is left to react for another 1.5 hours. It is poured into water and ice after stirring, leaving the complex to decompose for at least half an hour under stirring. The phases are separated, and the opalescent organic
20

phase is washed 4-5 times with water to pH 6. The chlorinated solvent is concentrated to dryness after anhydrification, treated with AcOEt (800 ml) and the organic solution is washed several times with water to pH 6. After anhydrification with anhydrous sodium sulphate, a crude solid is obtained, which, when dried for half an hour using a mechanical pump, weighs 33 g. The solid is crystallised with AcOEt/isopropyl ether (220 ml-300 ml) obtaining 16 g of filtered and dried solid; the mother liquors are concentrated to dryness and crystallised in turn by the same solvent (80 ml-130 ml), yielding 6 g of solid which, when filtered and dried, is added to the previous solid, obtaining 22 g of product. Yield 67%.

M.P.: 184-185°C

$^1\text{H-NMR}$ (CDCl_3), Varian 300 MHz, δ (p.p.m.): 1.83-2.2 (1H,m,CH $\underline{\text{H}}$ CHNH); 2.8-2.88 (1H,m,CH $\underline{\text{H}}$ CHNH); 2.9-3.0 (1H,m,CH $\underline{\text{H}}$ CH $\underline{\text{H}}$); 3.15-2.26 (1H,m,CH $\underline{\text{H}}$ CH $\underline{\text{H}}$); 3.92 (3H,s,OCH $\underline{\text{H}}$); 4.53-4.62 (1H,m,CH $\underline{\text{H}}$ CH $\underline{\text{N}}$ HCOCF $\underline{\text{H}}$); 6.88 (1H,d,Ar); 7.57 (1H,d,Ar); 7.43 (1H,bs,CHN $\underline{\text{H}}$ HCOCF $\underline{\text{H}}$).

e) Preparation of 2-amino-6-fluoro-7-methoxy-1-tetralone hydrochloride (ST1659)

1 g of 2-(N-trifluoroacetyl)-amino-6,7-dimethoxy-1-tetralone (ST1742) is suspended in 50 ml of anhydrous methanol and 10 ml of 37% hydrochloric acid and reacted under nitrogen and stirring for one night (18 hours) at the reflux temperature of the solvent. The reaction solution is dried several times, treating the white residue

with MeOH to completely eliminate the residual hydrochloric acid. Extraction is done with acetone under stirring, with the formation of a filterable solid which is oven-dried. 750 mg of product are obtained.

5 M.P.: 239-241°C

^1H -NMR (D_2O), Varian 300 MHz, δ (p.p.m.): 2.0-2.2 (1H,m, CHHCHNH_3^+); 2.38-2.5 (1H,m, CHHCHNH_3^+); 2.85-3.1 (2H,m, CH_2Ar); 3.75 (3H,m, OCH_3); 4.2-4.3 (1H,dd, CHNH_3^+); 6.9-7.0 (1H,d,Ar); 7.35-7.45 (1H,d,Ar).

10 **EXAMPLE 2 (Diagram 1)**

Preparation of 2-amino-6-fluoro-7-methoxy-1-hydroxy-tetraline hydrochloride (ST1682)

1.8 g (0.0073 mol) of 2-amino-6-fluoro-7-methoxy-1-tetralone hydrochloride (ST1659) are solubilised in MeOH at -10°C ; 0.6 g
15 (0.0156 moli) of NaBH_4 are added and then after 2 hours another 0.6 g. The solution is left to react for one night at room temperature, the methanol is then concentrated and extraction is done several times with little water and AcOEt. Anhydrous HCl is bubbled into the organic solutions anhydrified on anhydrous sodium sulphate and
20 the solution is cooled. The precipitate obtained is filtered obtaining 1.1 g of product. Yield 61%.

^1H -NMR (D_2O), Varian 300 MHz, δ (p.p.m.): 1.5-1.9 (1H,m, CHHCHNH_3^+); 2.1-2.2 (1H,m, CHHCHNH_3^+); 2.6-2.85 (2H,m, CH_2Ar); 3.25-3.35 (1H,dd, CHNH_3^+); 3.45-3.55

(1H,dd,CHNH₃⁺); 3.75 (3H,m,OCH₃); 6.75-7.1 (2H,2dd,Ar) .

EXAMPLE 3 (Diagram 2)

Preparation of 2-amino-6,7-diethoxy-1-tetralone hydrochloride
(ST 1374)

5 a) Preparation of trifluoro-acetyl aspartic anhydride (1)

See Example 1a.

b) Preparation of 4-(3,4-diethoxyphenyl-4-oxo-2-(N-trifluoroacetyl)-
aminobutanoic acid (ST 1356)

12 g (0.56 mol) of trifluoroacetyl-aspartic anhydride (1) are
10 suspended in 100 ml of anhydrous CH₂Cl₂ with 16.6 g (0.1 mol) of
1,2-diethoxybenzene. Then, under stirring and a nitrogen
atmosphere, 22 g (0.16 mol) of AlCl₃ are added portion-wise, leaving
the solution to react for 4 days. The reaction solution is dried,
obtaining a dark pitch which is treated with 100 ml of HCl 6N. The
15 acid solution is extracted with ethyl ether, washing several times
with water, anhydrifying on anhydrous sodium sulphate and
concentrating to dryness. The pitchy residue is left to stir for one
night in a mixture of ethyl ether and n-hexane by which the crude
product is crystallised; the product is then crystallised again by
20 AcOEt /n-hexane, washed with petroleum ether and oven-dried,
giving 11 g of product. Yield 52%.

M.P.: 160-161°C

¹H-NMR (CDCl₃) Varian 300 MHz, δ (ppm): 1.3-1.7
(6H,m,CH₃CH₂); 3.4-4.0 (2H,m,CH₂CHNH); 4.0-4.3

(4H,m,PhOCH₂CH₃); 4.88-5.01 (1H,m,CH₂CHNH); 6.8-7.0 (1H,d,Ar); 7.5 (1H, s, Ar); 7.4-7.6 (1H, m, Ar); 8.4-9.0 (1H.bs,COOH).

c) Preparation of 4-(3,4-diethoxyphenyl-2-(N-trifluoroacetyl)-amino-butanoic acid (ST1357)

5 9.5 g (0.025 mol) of 4-(3,4-diethoxyphenyl-4-oxo-2-(N-trifluoroacetyl)-aminobutanoic acid (ST 1356) are suspended in 40 ml of trifluoroacetic acid, and 19 ml of triethylsilane are then added under stirring and a nitrogen atmosphere. The solution is heated at reflux temperature for 8 hours, then cooled and treated by carefully
10 adding a saturated solution of NaHCO₃ until an alkaline pH is obtained. The solution is washed with ethyl ether and then carefully brought to acid pH with HCl 6N, extracting several times with CH₂Cl₂. The organic solution is dried after anhydrification, obtaining a light pitch which is crystallised by ethyl ether/n-hexane. 6.5 g of
15 product are obtained. Yield 72%.

M.P.: 106-108°C

¹H-NMR (CDCl₃) Varian 300 MHz, δ (ppm): 1.35-1.5 (6H,m,CH₃CH₂); 2.1-2.4 (2H,m,CH₂CHNH); 2.6-2.7 (2H,m,CH₂CH₂CHNH); 4.0-4.2 (4H,m,PhOCH₂CH₃); 4.6-4.8
20 (1H,m,CH₂CHNH); 6.6-6.9 (3H,m,Ar).

d) Preparation of 2-(N-trifluoroacetyl)-amino-6,7-diethoxy-1-tetralone (ST1359)

2.5 g (0.0069 mol) of 4-(3,4-diethoxyphenyl-2-(N-trifluoroacetyl)-aminobutanoic acid (ST1357) are solubilised in 100 ml of

CH₂Cl₂ to which 1.9 g (0.009 mol) of PCl₅ are added at room temperature under a nitrogen atmosphere. The solution is left to react under stirring and nitrogen for 30 minutes, whereupon 1.3 g (0.01 mol) of AlCl₃ are added, heating then at reflux temperature for 2 hours. To the cooled solution are added 100 ml of water and ice; the phases are separated and the aqueous phase is extracted with CH₂Cl₂. The merged organic phases are washed with water, anhydriified on anhydrous sodium sulphate and dried. The solid obtained is speciated and then crystallised by ethyl ether. 1.8 g of product are obtained. Resa 76 %.

M.P.: 162-163°C

¹H-NMR (CDCl₃), Varian 300 MHz, δ (p.p.m.): 1.3-1.5 (6H,m,CH₃CH₂); 1.8-2.0 (1H,m,CHHCHNH₃⁺); 2.7-3.0 (2H,m,CH₂Ar); 3.1-3.2 (1H,m, CHHCHNH₃⁺); 4.0-4.2 (6H,m,OCH₂CH₃); 4.4-4.55 (1H,m,CHNH₃⁺); 6.6 (1H,s,Ar); 7.4 (1H,s,Ar); 7.4-7.6 (1H,bs,NH).

e) Preparation of 2-amino-6,7-diethoxy-1-tetralone hydrochloride (ST1374)

0.9 g of 2-(N-trifluoroacetyl)-amino-6,7-diethoxy-1-tetralone (ST1359) are solubilised in 50 ml of anhydrous methanol and 10 ml of 37% hydrochloric acid and reacted, under nitrogen and stirring, for one night (18 hours) at the reflux temperature of the solvent. The reaction solution is dried several times, treating the white residue obtained with MeOH to completely eliminate any residual HCl.

Extraction is then done with acetone under stirring, with formation of a filterable solid which is oven-dried. 700 mg of product are obtained (Yield 74%).

M.P.: 216°C with decomposition

5 $^1\text{H-NMR}$ (D_2O), Varian 300 MHz, δ (p.p.m.): 1.4-1.6 (6H,m, CH_3CH_2); 2.2-2.4 (1H,m, CHHCHNH_3^+); 2.5-2.65 (1H,m, CHHCHNH_3^+); 3.0-3.3 (2H,m, CH_2Ar); 4.1-4.3 (6H,m, OCH_2CH_3); 4.2-4.4 (1H,dd, CHNH_3^+); 6.9-7.0 (1H,s,Ar); 7.4-7.45 (1H,s,Ar).

10

EXAMPLE 4 (Diagram 3)

Preparation of 7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetrahydro-2-naphthaleneammonium chloride (ST1683)

a) Preparation of 3-cyclopentyloxy-4-methoxy-benzaldehyde (1)

27.6 g (0.18 mol) of 3-hydroxy-4-methoxy-benzaldehyde are
15 solubilised in 110 ml of anhydrous N,N-dimethylformamide, and, under vigorous magnetic stirring, 37.5 g (0.28 mol) of anhydrous K_2CO_3 are added at room temperature and after 30 minutes 25 ml (0.23 mol) of cyclopentyl bromide dissolved in 10 ml of N,N-dimethylformamide are added drop-wise. The reaction mixture is
20 heated to reflux temperature for 16 hours until the reaction is complete and then filtered, washing the solid with AcOEt and n-hexane; the organic solutions are washed several times with water, with a saturated solution of K_2CO_3 and again with water until neutral pH is obtained. The organic solution is anhydrified with

anhydrous sodium sulphate and concentrated to dryness, obtaining an orange-coloured oil weighing 29 g after oil-pump drying, which is used as is, in view of its considerable purity. Yield 73%.

¹H-NMR (CDCl₃), Varian 200 MHz, δ (p.p.m.): 1.4-2.1
5 (8H,m,cyclopentyl); 3.83 (3H,s,OCH₃); 4.7-4.95 (1H,m,OCH); 6.8-6.95 (1H,d,Ar); 7.2-7.4 (3H,m,Ar); 9.73 (1H,s,H_C=O).

b) Preparation of (3E)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-(methoxycarbonyl)-3-butenic acid (ST1503)

To a solution of sodium methoxide in methanol, prepared by
10 dissolving 4 g (0.174 mol) of sodium methylate in 100 ml of methanol, is added drop-wise, under a nitrogen atmosphere, a solution of 32.5 g (0.147 mol) of 3-cyclopentyloxy-4-methoxybenzaldehyde (1) and 19.8 ml (0.15 mol) of dimethyl succinate.

15 The solution is then heated under stirring for 4 hours to reflux and, after cooling, is concentrated to dryness, obtaining an oily product, which after treatment with a saturated solution of NaHCO₃ at alkaline pH, is washed several times with ethyl ether. The aqueous solution is acidified with HCl 6N at pH 4 and the product is
20 extracted several times with ethyl ether, washing with water until neutral pH is obtained.

The organic phase is anhydried with anhydrous sodium sulphate and concentrated to dryness. The crude solid obtained is crystallised by n-hexane/AcOEt, giving 20 g of product. Yield 41%.

M.P.: 119-121°C

¹H-NMR (CDCl₃), Varian 300 MHz, δ (p.p.m.): 1.5-1.7 (2H,m,cyclopentyl); 1.7-2.0 (6H,m,cyclopentyl); 3.6 (2H,s,CH₂COOH); 3.85 (3H,s,COOCH₃); 3.87 (3H,s,OCH₃); 4.75-4.82 (1H,m,OCH);
5 6.85-7.0 (3H,m,Ar); 7.26 (1H,s,ArCH=).

c) Preparation of 3-[3-(cyclopentyloxy)-4-methoxybenzyl]-4-methoxy-4-oxobutanoic acid (ST 1504)

16.5 g (0.049 mol) of (3E)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-(methoxycarbonyl)-3-butenic acid (ST1503) are
10 solubilised in 450 ml of AcOEt, heating slightly; 1.8 g of Pd/C are added and the solution is hydrogenated in Parr at 52 psi for 3 hours. The suspension is filtered on a celite bed and concentrated to dryness, obtaining an oil, which solidifies after washing with petroleum ether. A crude product is obtained which when
15 crystallised by n-hexane/AcOEt gives 12 g of product. Yield 73%.

M.P.: 68-70°C

¹H-NMR (CDCl₃), Varian 300 MHz, δ (p.p.m.): 1.5-1.7 (2H,m,cyclopentyl); 1.7-2.0 (6H,m,cyclopentyl); 2.38-2.5 (1H,m,CH₂COOH); 2.6-2.8 (2H,m,CH₂COOH,CH₂Ar); 2.9-3.13
20 (2H,m,CHCOOCH₃,CH₂Ar); 3.65 (3H,s,COOCH₃); 3.8 (3H,s,OCH₃); 4.68-4.8 (1H,m,OCH); 6.6-6.82 (3H,m,Ar).

d) Preparation of methyl 7-(cyclopentyloxy)-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (ST 1763)

10.5 g (0.031 mol) of 3-[3-(cyclopentyloxy)-4-methoxybenzyl]-4-methoxy-4-oxobutanoic acid (ST 1504) are solubilised in 110 ml of anhydrous CH_2Cl_2 and 7.1 g (0.034 mol) of PCl_5 are added in one portion, cooling with an ice bath under a nitrogen atmosphere. After
5 30 minutes' stirring, 4.65 g (0.035 mol) of AlCl_3 in one portion at room temperature are added. The solution is left at this temperature for another thirty minutes, and is then poured into water and ice, separating the phases. The aqueous phase is extracted again with CH_2Cl_2 , and the merged organic phases, washed with water to
10 neutral pH and anhydried with anhydrous sodium sulphate, are concentrated to dryness, obtaining an oil which solidifies. The crude product is then crystallised by n-hexane/AcOEt, obtaining 7.8 g of product. Yield 78%.

M.P.: 121-123°C

15 ^1H -NMR (CDCl_3), Varian 200 MHz, δ (p.p.m.): 1.5-2.1 (8H,m,cyclopentyl); 2.7-3.0 (2H,m, COCH_2); 3.1-3.2 (3H,m, CHCOOCH_3 , ArCH_2); 3.73 (3H,s, COOCH_3); 3.85 (3H,s, OCH_3); 6.65 (1H,s,Ar); 7.48 (1H,s,Ar).

e) Preparation of methyl 7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (ST 1743)
20

4 g (0.013 mol) of methyl 7-(cyclopentyloxy)-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (ST1763) are solubilised in 100 ml of anhydrous ethanol with 20 ml of glacial acetic acid. 1 g of 10% Pd/C is added and the solution is

hydrogenated in Parr for 5.5 hours at an H₂ pressure of 55 psi The solution is filtered on a celite bed and then concentrated to dryness, extracting several times with cyclohexane. The solid obtained is crystallised by cyclohexane/AcOEt giving 3.5 g of product. Yield
5 88%.

¹H-NMR (CDCl₃), Varian 200 MHz, δ (p.p.m.): 1.5-2.05 (9H,m,cyclopentyl,CH₂CHCOOCH₃); 2.1-2.25 (1H,m,CH₂CHCOOCH₃); 2.7-2.83 (3H,m,CHCOOCH₃,CH₂Ar); 2.83-2.98 (2H,d,CHCH₂Ar); 3.7 (3H,s,COOCH₃); 3.8 (3H,s,ArOCH₃); 4.6-4.8
10 (1H,m,OCH); 6.5-6.6 (2H,m,Ar).

f) Preparation of 7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (ST1506)

2.4 g (0.079 mol) of methyl 7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (ST1743) are
15 suspended in 100 ml of a 50% water-methanol solution, in which 0.9 g (0.016 mol) of KOH have previously been solubilised. The solution is heated at reflux temperature for 1.5 hours, and then the methanol is eliminated by vacuum evaporation and addition of water. The alkaline aqueous solution is washed with ether, acidified
20 to pH 3 with HCl 6N, and the product is extracted several times with AcOEt, anhydrifying it on anhydrous sodium sulphate. The organic solution, when dried, yields 1.7 g of crude product which is crystallised by n-hexane/AcOEt obtaining 1.1 g of product. Yield 48%.

M.P.: 132-134°C

¹H-NMR (CDCl₃), Varian 300 MHz, δ (p.p.m.): 1.5-1.7 (2H,m,cyclopentyl); 1.75-2.0 (7H,m,cyclopentyl, CH₂CH₂CH); 2.18-2.3 (1H,m, CH₂CH₂CH); 2.7-2.85 (3H,m,CHCOOH,CH₂Ar); 2.9-3.0 (2H,d,CHCH₂Ar); 3.8 (3H,s,OCH₃); 4.68-4.8 (1H,m,OCH); 6.5-6.63 (2H,m,Ar).

g) Preparation of 7-(cyclopentyloxy)-2-isocyanate-6-methoxy-1,2,3,4-tetrahydronaphthalene (ST1744)

7 g (0.024 moli) of 7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (ST1506) are solubilised in 40 ml of anhydrous acetone to which are added under stirring 3.67 ml (0.026 mol) of triethylamine. After cooling at -5°C, 2.5 ml (0.026 mol) of ethylchloroformate dissolved in 5 ml of anhydrous acetone are added. The solution is left to react for 20 minutes, allowing the temperature to rise to not more than 5°C, and then 3.12 g (0.048 mol) of NaN₃ dissolved in 80 ml of water are slowly added drop-wise, maintaining a stable temperature. The mixture is reacted for 1.5 hours at a 0°C, whereupon 100 ml of cold water are added to the suspension and extraction is done several times with toluene, anhydrifying the organic phase on anhydrous sodium sulphate. The anhydrous solution is added to 50 ml of previously heated toluene and heated further at 105°C for 1.5 hours. The solution is dried, obtaining a dense oily crude product which, after oil-pump drying,

weighs 6 g. This crude product is pure enough to be used as is in the next reaction. Yield 87%.

$^1\text{H-NMR}$ (CDCl_3), Varian 200 MHz, δ (p.p.m.): 1.5-2.2

(10H,m,cyclopentyl, CH_2CHNCO); 2.7-3.2 (4H,m, CH_2Ar); 3.92
5 (3H,s, OCH_3); 3.9-4.0 (1H,m, CHNCO); 2.6-2.8 (1H,m, OCH); 6.5-
6.7(2H,d,Ar).

h) Preparation of benzyl 7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetra-
hydro-2-naphthalenylcarbamate (ST 1678)

3.5 g (0.0122 mol) of 7-(cyclopentyloxy)-2-isocyanate-6-
10 methoxy-1,2,3,4-tetrahydronaphthalene (ST 1744) are solubilised in
9 ml of anhydrous benzyl alcohol, heating at 100°C for 5 hours. The
oily solution is solubilised in di-isopropyl ether and precipitated by
addition of petroleum ether, obtaining a pitch. This treatment is
repeated several times. The pitchy residue is purified by means of a
15 chromatography column (stationary phase: silica, mobile phase: n-
hexane/AcOEt 8:2) and, after drying, 2.5 g of product are obtained.
Yield 52 %.

M.P.: 104-107°C

$^1\text{H-NMR}$ (CDCl_3), Varian 300 MHz, δ (p.p.m.): 1.5-1.7
20 (2H,m,cyclopentyl); 1.7-1.95 (7H,m,cyclopentyl, CHHCHNHCO); 1.95-
2.1 (1H,m, CHHCHNHCO); 2.5-2.63 (1H,Ar CHHCHNHCO); 2.6-2.9
(2H,m, CH_2Ar); 2.95-3.1 (1H,m,Ar CHHCHNHCO); 3.82 (3H,s, OCH_3);
3.95-4.1 (1H,m, CHNHCO); 4.65-4.75 (1H,m, OCH); 4.75-4.9

(1H,da,NHCO); 5.05-5.2 (2H,s,OCH₂Ph); 6.5-6.6 (2H,d,Ar); 7.25-7.4 (5H,m,Ar).

i) Preparation of 7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetrahydro-2-naphthaleneammonium chloride (ST 1683)

5 2.5 g (0.0063 mol) of benzyl 7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenylcarbamate (ST 1678) are solubilised in 90 ml of absolute ethanol, heating slightly; then, after adding 0.55 ml (0.0066 mol) of 37% HCl and 0.5 g of 10% Pd/C at room temperature, the solution is subjected in Parr to an H₂
10 pressure of 50 psi for 3 hours. The dispersion is filtered on a celite bed, and the filtrate is dried. The solid obtained is treated with acetone under stirring, filtered and crystallised by EtOH/n-hexane, obtaining 0.9 g of product after drying. Yield 48%.

M.P.: 193-196°C

15 ¹H-NMR (D₂O), Varian 300 MHz, δ (p.p.m.): 0 (TMS); 1.6-2.1 (9H,m,cyclopentyl,CH₂HCHNH₃⁺); 2.2-2.3 (1H,m,CH₂HCHNH₃⁺); 2.8-3.0 (3H,m,CH₂Ar, ArCH₂HCHNH₃⁺); 3.1-3.2 (1H,dd,ArCH₂HCHNH₃⁺); 3.6-3.7(1H,m, CHNH₃⁺); 3.82 (3H,s,OCH₃); 6.8-6.9 (2H,d,Ar).

EXAMPLE 5 (Diagram 4)

20 Preparation of (4E)-7-(cyclopentyloxy)-N-hydroxy-4-(hydroxyimino)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxamide (ST1704)

a) Preparation of methyl 7-(cyclopentyloxy)-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (ST1763)

See example 3d.

b) Preparation of 7-(cyclopentyloxy)-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (ST1702)

9.5 g (0.0312 moli) of methyl 7-(cyclopentyloxy)-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (ST1763) are
suspended in a solution of 3.5 g (0.0624 mol) of KOH in 200 ml of 50% water/methanol and reacted at 80°C for 15 minutes. The reaction mixture is dried, then treated with 100 ml of water and acidified to pH 3.5 with HCl 6 N; extraction is done several times
with EtOAc and the organic solution is washed with water and concentrated to dryness after anhydrification with anhydrous sodium sulphate. A solid is obtained, which is crystallised by hot filtering the insoluble residue, obtaining 6.5 g of product. Yield 68%.

M.P.: 175-178°C

¹H-NMR (CDCl₃), Varian 300 MHz, δ (p.p.m.): 1.5-2.1 (8H,m,cyclopentyl); 2.6-2.95 (2H,m,CH₂); 3.1-3.3 (3H,m,CH₂,CHCOOH); 3.85 (3H,s,OCH₃); 4.8-4.9 (1H,m,CH); 6.6-6.7 (1H,s,Ar); 7.5 (1H,s,Ar).

c) Preparation of (4E)-7-(cyclopentyloxy)-4-(hydroxyimino)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (ST1703)

1.38 g (0.0198 mol) of hydroxylamine hydrochloride are solubilised in 20 ml of water, and 1 g (0.0098 mol) of Na₂CO₃ is added cold in one portion under a nitrogen atmosphere. After 20

minutes under stirring, a solution of 3 g (0.00985 mol) of (4E)-7-(cyclopentyloxy)-4-(hydroxy-imino)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (ST 1703) in 100 ml of 95% ethanol is added dropwise at 5°C, bringing the solution to reflux temperature for 1.5 hours under stirring. The solution is concentrated to dryness, then added with 80 ml of water, acidifying to pH 3 with HCl 6N, cooling and then extracting the aqueous solution several times. The organic phase is anhydified on anhydrous sodium sulphate and concentrated to dryness, obtaining a solid which, when crystallised by n-hexane/ EtOAc gives 2.3 g of product. Yield 73%.

M.P.: 254-256°C

$^1\text{H-NMR}$ (DMSO-d_6), Varian 300 MHz, δ (p.p.m.): 1.8-2.2 (8H,m,cyclopentyl), 2.8-3.3 (5H,m,2CH₂,CHCOOH); 3.3-3.7 (1H,bs,COOH); 3.9 (3H,s,OCH₃); 4.95-5.0 (1H,m,CH); 6.95 (1H,s,Ar); 7.45 (1H,s,Ar); 11.1 (1H,s,=NOH).

d) Preparation of (4E)-7-(cyclopentyloxy)-N-hydroxy-4-(hydroxy-imino)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxamide (ST1704)

1.5 g (0.0047 mol) of (4E)-7-(cyclopentyloxy)-4-(hydroxyimino)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (ST1703) are suspended in 100 ml of CH₂Cl₂ with 0.3 ml of anhydrous DMF, cooled to 5°C and 0.85 ml (0.01 mol) of oxalyl chloride are added drop-wise under magnetic stirring. 7.9 ml (0.122 mol) of 50% hydroxylamine in water are added, cooling again to 5°C,

and then leaving the solution to react at room temperature under stirring for 3 hours. The precipitated solid is filtered and treated with HCl 2N at pH 3; extraction is done several times with EtOAc, washing with water. The organic phase, anhydried on anhydrous sodium sulphate is dried, obtaining a solid which when crystallised
5 by n-hexane/EtOAc gives 0.75 g of product. Yield 55%.

M.P.: 186-188°C

^1H -NMR (DMSO-d_6), Varian 300 MHz, δ (p.p.m.): 1.8-2.2 (8H,m,cyclopentyl), 2.4-2.7 (2H,m, CH_2); 2.8-3.0 (2H,m, CH_2); 3.15-
10 3.25 (1H,m, CHCOOH); 3.9 (3H,s, OCH_3); 4.95-5.0 (1H,m, CH); 6.95 (1H,s,Ar); 7.45 (1H,s,Ar); 8.8-9.2 (1H,bs, NH); 10.5-11.0 (1H,bs, OH); 11.5 (1H,s, $=\text{NOH}$).

The compounds according to the invention described herein are useful as phosphodiesterase IV (PDE IV) inhibitors.

15 Assays conducted with standard processes, e.g. as described by Cortij et al., Br. J. Pharmacol. 108:562, 1993 or Nicholsen CD et al., Trends Pharmacol. Sci. 12:19, 1991 have yielded the following results for compounds figuring among the examples envisaged within the framework of the invention described herein.

Compound	Species	Concentration (μ M)	% inhibition
ST 1702	human	100	77
ST 1703	human	100	75
ST 1704	human	100	74

The following determination of IC₅₀ for inhibition of PDE IV activity and competition at the rolipram receptor, conducted with standard processes, , e.g. as described by Duplantier A.J. et al., J. Med. Chem. 39: 120, 1996 and by Thorphy T.J. et al., J Pharmacol. Exp. Ther., 263: 1195, 1992 have yielded the following results for compounds figuring among the examples envisaged within the framework of the invention described herein

Compound	Origin	IC ₅₀ (μ M) PDE4 Activity (L)PDE4	Origin	IC ₅₀ (μ M) Rolipram receptor (H)PDE4	H/L
ST 1702	Human	12.1	Mouse brain	N.C.	-
ST 1703	Human	8.4	Mouse brain	N.C.	-
ST 1704	Human	46	Mouse brain	>10.0	>0.22

N.C. means value not calculable because of no inhibition at the highest test concentration, however it means low affinity for rolipram receptor.

As reported in WO 00/51598, authors: Christensen S.B.,
5 Barnette M.S. and Thorphy T.J. and widely confirmed by other
authors in related letterature, if a compound exhibits H/L IC₅₀
ratio of about 0.1 or greater calculated as the ratio of the IC₅₀
(H) for high affinity rolipram binding form (HPDE4) divided by
the IC₅₀ (L) for the form which binds rolipram with low affinity
10 (LPDE4), it will have an acceptable therapeutic index for
treating asthma or chronic obstructive pulmonary disease (COPD),
minimizing side effects tipical of phosphodiesterase IV inhibitors as
rolipram.

Selectivity of these compounds for inhibition of
15 phosphodiesterase IV (PDE4) activity over other phosphodiesterases
was demonstred by assays conducted with standard processes, e.g.
as described by Nicholsen CD et al., Trends Pharmacol. Sci. 12:19,
1991. These assays have yielded the following results for compounds
figuring among the examples envisaged within the framework of the
20 invention described herein.

% PDE inhibition at 100 µM						
Compound	PDE1 (bovine)	PDE2 (human)	PDE3 (human)	PDE4 (human)	PDE5 (human)	PDE6 (bovine)
ST 1702	27	-17	22	78	16	27

The compounds according to the invention described herein are useful as medicaments, and particularly as phosphodiesterase IV inhibitors. The compounds according to the invention can
5 therefore be used in the preparation of medicaments with phosphodiesterase IV inhibitory activity, particularly for the treatment of asthma or for the treatment of chronic obstructive pulmonary disease.

The compounds according to the invention also exert an
10 inhibitory action on the release of TNF (Tumor Necrosis Factor) induced by bacterial LPS (lipopolysaccharides). In *in-vitro* activity tests, conducted as described in international patent application WO 98/33762, the compounds according to the invention have demonstrated a TNF inhibitory action comparable to that shown by
15 the compounds described in WO98/33762.

Therefore, the compounds according to the invention are useful as medicaments, particularly for the treatment and prevention of septic shock.

As far as industrial applicability is concerned, the formula (I)
20 compounds described herein will be formulated in pharmaceutical compositions as active ingredients. Pharmaceutical compositions are conventionally known and contain a therapeutically effective amount of active ingredient in mixtures with pharmaceutically acceptable excipients and/or vehicles.

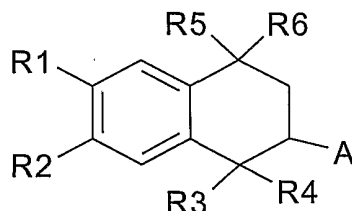
The subject matter of the invention described herein comprises pharmaceutical compositions containing as their active ingredient at least one formula (I) compound, either alone or in combination with one or more formula (I) compounds. The active ingredient according to the invention described herein will be in a mixture with appropriate vehicles and/or excipients commonly used in pharmacy, such as, for example, those described in "Remington's Pharmaceutical Sciences Handbook", latest edition. The compositions according to the invention described herein will contain a therapeutically effective amount of the active ingredient. The doses will be decided by the expert in the field, e.g. by the clinician or primary care physician according to the type of disease to be treated and the patient's condition, or concomitantly with the administration of other active ingredients. By way of an example, doses ranging from 0.1 to 100 mg/kg may be indicated.

Examples of pharmaceutical compositions are those that permit oral or parenteral, intravenous, intramuscular, subcutaneous, and transdermal administration as well as administration by nasal or oral spray. Pharmaceutical compositions suitable for the purpose are tablets, soft or rigid capsules, powders, solutions, suspensions, syrups, and solid forms for extempore liquid preparations. Compositions for parenteral administration include, for example, all the intramuscular, intravenous and subcutaneous injectable forms and those which can be administered in the form of

solutions, suspensions, or emulsions. We should also mention the liposomal formulations. The compositions also include forms entailing the controlled release of the active ingredient, whether in oral administration, as tablets coated with various layers, 5 microencapsulated powders, complexes with cyclodextrin, and depot forms, e.g. of the subcutaneous type, or as depot injections and implants.

CLAIMS

1. Formula (I) compounds



(I)

in which

R₁ and R₂, which may be the same or different, are halogen,
hydroxy, straight or branched C₁-C₄ alkoxy, C₅-C₆ cycloalkoxy;

R₃ and R₄ together form a =O, =NOH group, or, R₃ and R₄, which
may be the same or different, are -H, -OH;

R₅ and R₆ together form a =O, =NOH group; or, R₅ and R₆, which
may be the same or different, are -H, -OH;

A is

- the -NHR₇ group, in which R₇ is -H, alkanoyl, C₁-C₄
alkylcarbamoyl, in which the alkyl may be substituted with
halogens;
- arylcarbamoyl;
- -NCO;
- -COOR₈ in which R₈ is -H, C₁-C₄ alkyl, optionally substituted
with one or more halogen atoms;
- -CONHOH;

their enantiomers, diastereoisomers and mixtures of the same, and their pharmaceutically acceptable salts.

2. Compounds according to claim 1, in which R₁ is halogen and R₂ alkoxy or cycloalkoxy.
- 5 3. Compounds according to claim 1, in which R₅ and R₆ together are the keto group. or the corresponding oxime.
4. Compounds according to claim 1, in which A is the -COOR₈, -NCO or -CONHOH group.
5. Compound according to claim 1, selected from the group
10 consisting of:
 - 2-(N-trifluoroacetyl)amino-6,7-diethoxy-1-tetralone;
 - 2-amino-6,7-diethoxy-1-tetralone hydrochloride;
 - (R,S)-6-methoxy-7-cyclopentyloxy-1,2,3,4-tetrahydro-2-naphthoic acid;
 - 15 - (R,S)-2-amino-6-fluoro-7-methoxy-1-tetralone hydrochloride;
 - (R,S)-6-methoxy-7-cyclopentyloxy-2-benzyloxy-carbonylamino-tetraline;
 - (R,S)-1-hydroxy-(R,S)-2-amino-6-fluoro-7-methoxy-tetraline hydrochloride;
 - 20 - (R,S)-2-amino-6-methoxy-7-cyclopentyloxy-tetraline hydrochloride;
 - 7-(cyclopentyloxy)-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid;

- (4E)-7-(cyclopentyloxy)-4-(hydroxyimino)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid;
 - (4E)-7-(cyclopentyloxy)-N-hydroxy-4-(hydroxyimino)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxamide;
 - 5 - 2,2,2-trifluoro-N-(6-fluoro-7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl)acetamide;
 - methyl 7-(cyclopentyloxy)-6-methoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylate;
 - 7-(cyclopentyloxy)-2-isocyanate-6-methoxy-1,2,3,4-tetrahydro-2-naphthalene;
 - 10 - methyl 7-(cyclopentyloxy)-6-methoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate.
6. Compounds according to claim 1, for use as medicaments.
7. Use of compounds according to claim 1 for the preparation of a
15 medicament possessing phosphodiesterase IV inhibitory activity.
8. Use of compounds according to claim 1 for the preparation of a medicament useful for the treatment of asthma.
9. Use of compounds according to claim 1 for the preparation of a medicament useful for the prevention and/or treatment of septic
20 shock.
10. Pharmaceutical compositions containing at least one compound according to claim 1 in a mixture with at least one pharmaceutically acceptable vehicle or excipient.