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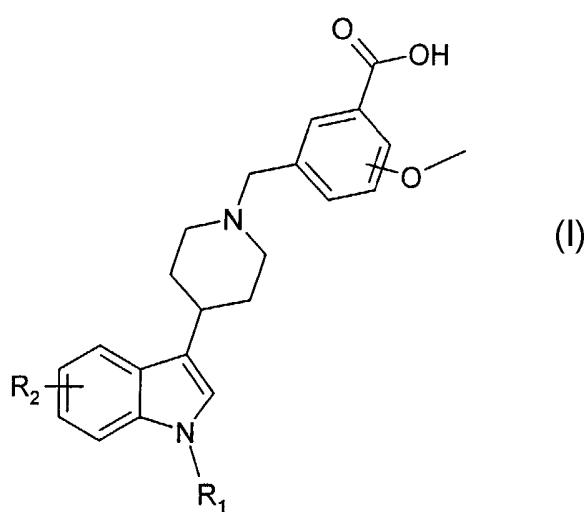
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(54) Title: NEW INDOLYLPIPERIDINE DERIVATIVES AS POTENT ANTIHISTAMINIC AND ANTIALLERGIC AGENTS



(57) Abstract: This invention is directed to new potent and selective antagonists of H₁ histamine receptors having the general formula (I) to processes for their preparation; to pharmaceutical compositions comprising them; and to their use in therapy as antiallergic agents.

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NEW INDOLYLPIPERIDINE DERIVATIVES AS POTENT ANTIHISTAMINIC AND ANTIALLERGIC AGENTS

- The present invention relates to a novel class of indolylpiperidine derivatives and
- 5 pharmaceutically acceptable salts thereof. These compounds are selective antagonists of H₁ histamine receptors and have more potent antihistaminic activity *in vivo*. They are thus particularly useful for the treatment of bronchial asthma, allergic rhinitis, conjunctivitis, dermatitis, urticaria and other allergic diseases.
- 10 WO 0075130 discloses selective antagonists of H₁ histamine receptors having an indolylpiperidine core. It has now been found that a specific group of compounds falling under the general formula in WO 0075130, but which are not explicitly disclosed there, show an increased selectivity on H₁ histamine receptors with respect to 5HT-2 serotonin receptors and, at the same time, are significantly more potent antihistaminic compounds
- 15 *in vivo*.

Thus, the present invention provides a selection of indolylpiperidine compounds having more potent and selective antiallergic effects. This allows to achieve a clinical improvement of the symptoms of allergic diseases with lower doses, preventing almost

20 completely the occurrence of sedative and cardiovascular side effects, which are characteristic of most commercial antihistamines.

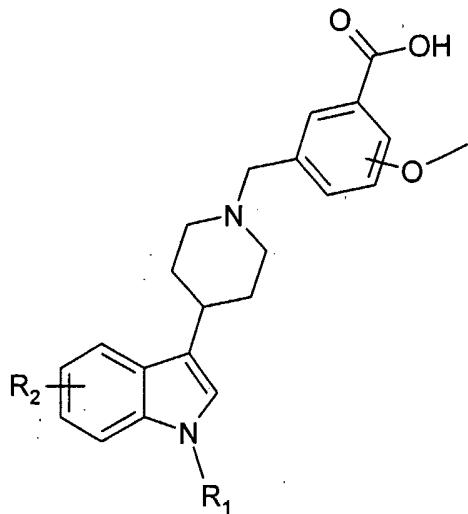
Further objectives of the present invention are to provide a method for preparing said compounds; pharmaceutical compositions comprising an effective amount of said

25 compounds; the use of the compounds in the manufacture of a medicament for the treatment of diseases susceptible of being improved by antagonism of H₁ histamine receptors, such as allergic diseases; and methods of treatment of diseases susceptible to amelioration by antagonism of H₁ histamine receptors, such as allergic diseases, comprising the administration of the compounds of the invention to a subject in need of

30 treatment.

With respect to the compounds explicitly disclosed in WO 0075130 the advantageous effects of the compounds of the invention are due to their distinguishing structural features. More specifically, the compounds of the invention are characterised by the

35 general structure of formula (I)



Formula I

wherein:

- 5 R₁ represents an alkyl, alkenyl, alkoxyalkyl or cycloalkylalkyl group;
R₂ represents a hydrogen or halogen atom;
the methoxy group substituting the benzoic acid is in position ortho with respect to the
carboxy group.

10 and pharmaceutically acceptable salts thereof

As used herein, an alkyl group or moiety is a linear straight or branched group or moiety.

Typically it is a C₁-C₁₀ group or moiety, preferably a C₁-C₆ group or moiety. Examples include methyl, ethyl, i-propyl, n-propyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl.

- 15 1-ethylpropyl, 1,2-dimethylpropyl, n-hexyl or 1-ethylbutyl. Most preferably it is a straight C₁-C₄ group or moiety.

As used herein, an alkenyl group or moiety is a linear straight or branched group or moiety. Typically it is a C₂-C₁₀ group or moiety, preferably a C₂-C₆ group or moiety, most

- 20 preferably it is a straight C₁-C₄ group or moiety. Examples include allyl or 2-propenyl.

As used herein, the alkyl chains present in the alkoxyalkyl and cycloalkylalkyl groups are typically linear straight or branched alkyl chains containing from 1 to 6 carbon atoms, most

preferably from 1 to 4 carbon atoms. In the alkoxyalkyl groups they may be the same or different.

As used herein, a cycloalkyl group is typically unsubstituted and has from 3 to 6 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. It is preferably cyclopropyl, cyclopentyl or cyclohexyl.

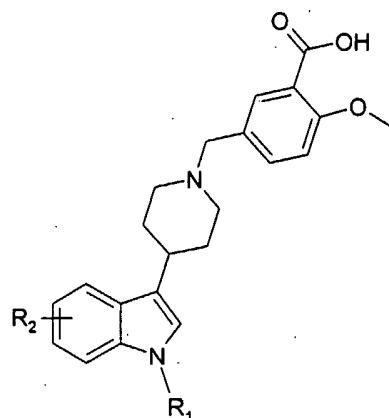
As used herein a halogen atom is one of chlorine, fluorine, bromine or iodine. Preferably chlorine or fluorine.

10

Compounds of formula (I) containing one or more chiral centre may be used in enantiomerically or diastereoisomerically pure form, or in the form of a mixture of isomers.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases, for example alkyl amines, aralkyl amines and heterocyclic amines.

Preferred compounds of the invention are those wherein the methoxy group substituting the benzoic acid is both in position ortho with respect to the carboxy group and in position para with respect to the carbon atom which is bound to the indolylpiperidine moiety of the molecule as shown in formula Ia.



Formula Ia

Preferred compounds of the invention are those wherein R₁ is selected from ethyl, n-propyl, n-butyl, methoxymethyl, methoxyethyl, ethoxyethyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, allyl, 2-propenyl, 2-propoxyethyl and 3-methoxypropyl. Most preferably R₁ is methoxyethyl, ethoxyethyl, butyl, 5 cyclopropylmethyl or allyl.

Also preferred are compounds wherein R₂ is hydrogen, fluorine or chlorine. Most preferably, R₂ is hydrogen or fluorine.

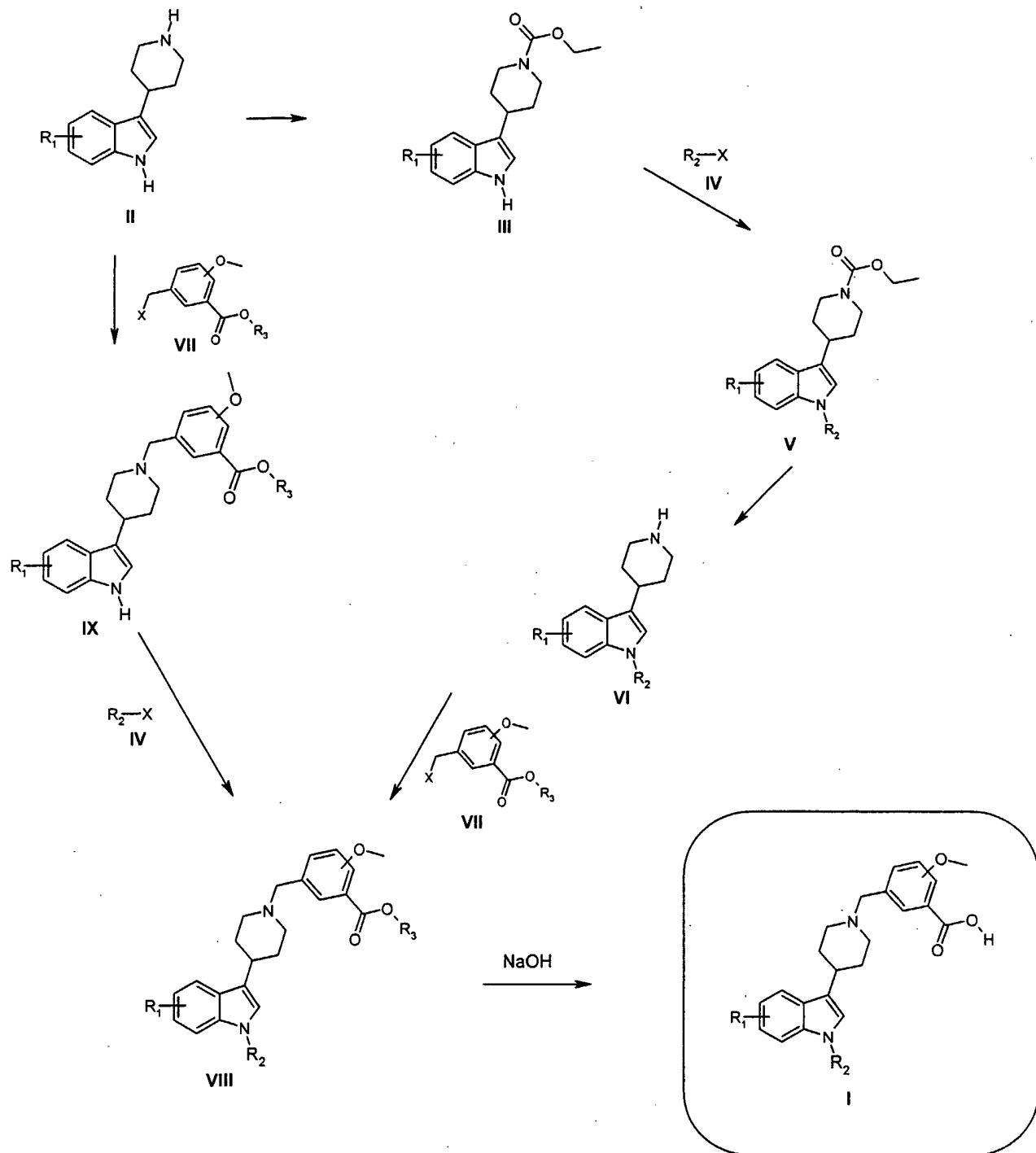
10 Particular individual compounds of the invention include:

1. 5-{4-[1-(2-ethoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic acid
2. 2-methoxy-5-{4-[1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-benzoic acid
3. 5-[4-(1-butyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
4. 5-{4-[1-(2-ethoxyethyl)-6-fluoro-1H-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic acid
5. 5-{4-[6-fluoro-1-(2-methoxyethyl)- 1H-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic acid
6. 5-[4-(1-butyl-6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
7. 5-[4-(5-bromo-1-propyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
8. 3-[4-(5-chloro-1-ethyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
9. 3-[4-(1-cyclopropylmethyl-5-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
10. 5-[4-(5-chloro-1-cyclohexylmethyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
11. 2-methoxy-5-{4-[1-(2-propoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-benzoic acid
12. 3-{4-[5-bromo-1-(3-methoxypropyl)-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid
13. 3-[4-(1-allyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
14. 3-[4-(1-allyl-6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
15. 5-{4-[5-chloro-1-(2-propenyl)-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid
16. 5-[4-(1-cyclopentylmethyl-6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid

17. 3-{4-[6-fluoro-1-methoxymethyl-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid
18. 3-{4-[1-cyclopropylethyl-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid
19. 3-{4-[5-chloro-1-(2-methoxyethyl)-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-
- 5 methoxybenzoic acid
20. 3-{4-[1-(2-ethoxyethyl)-5-fluoro-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid.

In accordance with another embodiment, the present invention provides a method for
10 preparing the indolylpiperidine compounds represented by formula I. These compounds are prepared according to Scheme 1 starting from an intermediate of general formula VIII wherein R₁ and R₂ are as defined above and R₃ is an alkyl group.

Scheme 1



The intermediate of formula VIII is treated with sodium or potassium hydroxide in a solvent such as methanol, ethanol or tetrahydrofuran at a temperature between 25°C and 60°C.

Further treatment with an inorganic acid such as hydrochloric acid provides the corresponding indolylpiperidine derivatives of general formula I wherein R₁ and R₂ are as defined above.

- 5 The compound of formula VIII can be prepared following two different pathways (see Scheme 1).

According to the first pathway, a compound of general structure II wherein R₁ is as defined above, is treated with ethyl chloroformate in the presence of a base such as triethylamine 10 or pyridine at a temperature between 0°C and room temperature to give a compound of formula III wherein R₁ is as defined above.

- The alkylation of compound III with a reactive intermediate of formula IV wherein R₂ is as defined above and X is a leaving group, such as a chlorine or a bromine atom or a 15 methane sulphonate, p-toluenesulphonate or a benzenesulphonate group, gives a compound of general formula V, wherein R₁ and R₂ are as defined above. This reaction is preferably carried out in an inert solvent such as dimethylformamide, tetrahydrofuran or ethyl ether at a temperature between 0°C and 80°C in the presence of an inorganic base such as sodium hydride or sodium amide.
- 20 Compound V is deprotected by boiling it in the presence of an excess of sodium or potassium hydroxide in an alcoholic solvent such as ethanol, isopropanol or n-butanol at a temperature between 80°C and 180°C. This leads to a compound of general formula VI, wherein R₁ and R₂ are as defined above.
- 25 Further alkylation of compound VI with a reactive intermediate of formula VII wherein R₃ is as defined above and X is a leaving group, such as a chlorine or a bromine atom or a methane sulphonate, p-tolene sulphonate or a benzene sulphonate group, gives a compound of formula VIII wherein R₁, R₂ and R₃ are as defined above. This 30 reaction is preferably carried out in an organic solvent such as toluene, dichloromethane, dioxane or methyl isobutylketone at a temperature between 25°C and 140°C in the presence of a base such as an alkali metal carbonate or bicarbonate, triethylamine or diisopropylethylamine.
- 35 Alternatively, the novel indolylpiperidine derivatives of the present invention can be prepared according to a different strategy as shown in Scheme 1.

- A compound of formula II is alkylated with a reactive intermediate of formula VII wherein R₃ is as defined above and X is a leaving group such as a chlorine or a bromine atom or a methane sulphonate, p-toluene sulphonate or a benzene sulphonate group to give a
- 5 compound of general formula IX wherein R₁ and R₃ are as defined above. This reaction is preferably carried out in an organic solvent such as toluene, dichloromethane, dioxane or methyl isobutylketone at a temperature between 25°C and 140°C in the presence of a base such as an alkali metal carbonate or bicarbonate, triethylamine or diisopropylethylamine.
- 10 The alkylation of compound IX with a reactive intermediate of general formula IV wherein R₂ is as defined above and X is a leaving group, such as a chlorine or a bromine atom or a methane sulphonate, p-toluensulphonate or a benzenesulphonate group, gives a compound of general formula VIII wherein R₁, R₂ and R₃ are as defined above. This
- 15 reaction is preferably carried out in an inert solvent such as dimethylformamide, tetrahydrofuran or ethyl ether at a temperature between 0°C and 80°C in the presence of an inorganic base such as sodium hydride or sodium amide.
- The final products of formula I are purified by chromatography or by recrystallisation.
- 20 Occasionally, the products are purified by preparative HPLC-MS, using a C-18 column. The starting compounds of formula II are prepared from 4-piperidone following known procedures (*J. Med. Chem.* 1992, 35, 4813).
- Example 1**
- 25 **Preparation of 5-[4-[1-(2-ethoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl]-2-methoxybenzoic acid**
- A. Preparation of 3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole
- 30 30 g (0.26 mol) of indole were dissolved in a solution of potassium hydroxide (77.6 g, 1.38 mol) in methanol (692 ml). 4-piperidone monohydrate hydrochloride (102.3 g, 0.66 mol) was added in one portion and the mixture was heated to reflux for 5 h. Potassium chloride precipitated upon cooling at room temperature and it was filtered off. The liquid phase was concentrated until only one third of the liquid remained in the round-bottom flask. The solid
- 35 formed during the concentration of the liquid phase was filtered and washed thoroughly

with ethanol and, finally, with ethyl ether. 31.9 g (63% of yield) of the final product were obtained.

Melting point : 183-185°C

5 B. Preparation of 3-piperidin-4-yl-1H-indole

19.03 g (0.096 mol) of 3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole were hydrogenated in a Parr apparatus during 18 h at 3 bar with 2.2 g of Pd/C 10% in 600 ml of methanol. After standard work-up, 16.76 g (87% of yield) of the desired product were obtained.

10 Melting point : 210-212°C

C. Preparation of 4-(1H-indol-3-yl)-piperidine-1-carboxylic acid ethyl ester

To a suspension of 30 g (0.15 mol) of 3-piperidin-4-yl-1H-indole and 28 mL (0.2 mol) in 15 185 ml of anhydrous dichloromethane, 17 ml (0.18 mol) of ethyl chloroformate were added dropwise keeping the temperature of the reaction below 20°C. After 2h at room temperature, the crude mixture was poured into 100 ml of water. The organic layer was separated and dried with sodium sulphate. After filtration, the solvent was removed under reduced pressure affording 39 g (95% of yield) of the expected product.

20 ESI/MS m/e = 272 [(M+1)+, C16 H20 N2 O2]

¹H-NMR (300 MHz, DMSO) δ = 1.16-1.23 (t, 2H), 1.41-1.65 (m, 2H), 1.92-1.99 (m, 2H), 2.90-3.10 (m, 3H), 3.99-4.10 (m, 4H), 6.95-7.10 (m, 3H), 7.31-7.34 (d, 1H), 7.53-7.57 (d, 1H), 10.81 (s, 1H).

25 D. Preparation of 4-[1-(2-ethoxyethyl)-1H-indol-3-yl]-piperidine-1-carboxylic acid ethyl ester

Under inert atmosphere, a solution of 12.5 g (0.045 mol) of 4-(1H-indol-3-yl)-piperidine-1-carboxylic acid ethyl ester in 50 ml of anhydrous DMF was added dropwise to a 30 suspension containing 2.75 g (0.068 mol) of sodium hydride (60% in mineral oil) in 200 ml of anhydrous DMF. After stirring at room temperature for 1 hour, 6.6 ml (0.06 mol) of 1-bromo-2-ethoxyethane were added. The reaction mixture was heated at 60°C for 3 hours. The crude mixture was poured into water and extracted with ethyl acetate. After drying, the solvent was removed under reduced pressure and 16 g of a crude oil were obtained 35 and used in the next step without purification.

E. Preparation of 1-(2-ethoxyethyl)-3-piperidin-4-yl-1H-indole

To a solution of 16 g (0.054 mol) of 4-[1-(2-ethoxyethyl)-1H-indol-3-yl]-piperidine-1-carboxylic acid ethyl ester in 10 ml of iso-propanol, a solution of 32 g of potassium hydroxide in 270 ml of iso-propanol was added. The crude mixture was refluxed for 16 hours. After cooling at room temperature, the solvent was removed at reduced pressure and the crude mixture was extracted between ethyl acetate and water. The organic layer was dried with sodium sulphate and after filtration, the solvent was removed under reduced pressure affording 9.6 g (71% of yield) of an oil which corresponds to the expected product.

F. Preparation of 5-[4-[1-(2-ethoxyethyl)-1H-indol-3-yl]-piperidin-1-ylmethyl]-2-methoxybenzoic acid

15 A solution of 1.9 g (0.0071 mol) of 5-bromomethyl-2-methoxy-benzoic acid methyl ester in 5 ml of methyl isobutylketone was added to a suspension of 1.8 g (0.065 mol) of 1-(2-ethoxyethyl)-3-piperidin-4-yl-1H-indole and 1.8 g (0.013 mol) of potassium carbonate in 45 ml of methyl isobutylketone. The reaction mixture was heated at 60°C for 20 h. The crude mixture was filtered to remove inorganic salts and the solvent was removed under reduced pressure affording 3.5 g of a crude oil. The crude mixture was purified by flash chromatography over silica gel affording 1.8 g (48% of yield) of 5-[4-[1-(2-ethoxyethyl)-1H-indol-3-yl]-piperidin-1-ylmethyl]-2-methoxy-benzoic acid ethyl ester. This ester was dissolved in 18 ml of ethanol and hydrolysed with 2N NaOH at room temperature for 20 hours. The crude mixture was neutralised with 2N HCl aqueous solution and the solvent was removed under reduced pressure. The crude residue was extracted between dichloromethane and water. After drying, filtering and removing the solvent under reduced pressure, the residue obtained was recrystallised with ethanol affording 0.77 g (27% of overall yield) of the expected acid.

25 30 Melting point: 225.8-226.5°C

¹H-RMN (DMSO) δ = 1.02-1.06 (t, 3H), 1.61-1.72 (m, 2H), 1.90-1.94 (d, 2H), 2.10-2.17 (t, 2H), 2.72-2.79 (t, 1H), 2.89-2.93 (d, 2H), 3.37-3.41 (m, 2H), 3.49 (s, 2H), 3.63-3.69 (t, 2H), 3.81 (s, 3H), 4.22-4.26 (t, 2H), 6.95-6.99 (t, 1H), 7.07-7.12 (m, 3H), 7.40-7.46 (t, 2H), 7.53-7.59 (m, 2H).

Example 2**Preparation of 2-methoxy-5-{4-[1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-benzoic acid**

A. Preparation of 4-[1-(2-methoxyethyl)-1H-indol-3-yl]-piperidine-1-carboxylic acid

5 ethyl ester

This compound was prepared following the procedure described in example 1, part D, starting with 5.5 g (0.02 mol) of 4-(1H-indol-3-yl)-piperidine-1-carboxylic acid ethyl ester and 2.3 ml (0.0233 mol) of 1-bromo-2-methoxyethane. The reaction mixture was stirred at room temperature for 24 h and after standard work-up, 6.5 g (98% of yield) of 4-[1-(2-methoxyethyl)-1H-indol-3-yl]-piperidine-1-carboxylic acid ethyl ester were obtained.

B. Preparation of 1-(2-methoxyethyl)-3-piperidin-4-yl-1H-indole

This compound was prepared following the procedure described in example 1, part E, starting with 6.5 g (0.02 mmol) of 4-[1-(2-methoxyethyl)-1H-indol-3-yl]-piperidine-1-carboxylic acid ethyl ester. After standard work-up, 4.6 g (92% of yield) of 1-(2-methoxyethyl)-3-piperidin-4-yl-1H-indole were obtained.

C. Preparation of 2-methoxy-5-{4-[1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-benzoic acid ethyl ester

20 Over a solution of 6.5 g (0.025 mol) of 1-(2-methoxyethyl)-3-piperidin-4-yl-1H-indole in 90 ml of dichloromethane and 3.9 ml (0.026 mol) of triethylamine, a solution of 7.2 g (0.026 mol) of 5-bromomethyl-2-methoxy-benzoic acid ethyl ester in 15 ml of dichloromethane was added. The crude mixture was stirred at room temperature for 24 hours. After standard work-up and purification by chromatography over silica gel, 9.9 g (70% of yield) 25 of 2-methoxy-5-{4-[1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-benzoic acid ethyl ester were obtained.

D. Preparation of 2-methoxy-5-{4-[1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-benzoic acid

30 Over a solution of 0.9 g (0.002 mol) of 2-methoxy-5-{4-[1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-benzoic acid ethyl ester in 9 ml of methanol and 5 ml of tetrahydrofuran, 5 ml of a 1N aqueous sodium hydroxide were added. The crude mixture was stirred at room temperature for 20 hours and then neutralised with 1N aqueous HCl. The product precipitated from the mixture. The solid obtained was filtrated and washed

with ethanol and ethyl ether. 0.55 g (65% of yield) of 2-methoxy-5-{4-[1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-benzoic acid were obtained.

Melting point: 241.9-242.9°C

¹H-RMN (DMSO) δ = 1.59-1.74 (m, 2H), 1.89-1.93 (d, 1H), 2.07-2.15 (t, 2H), 2.71-2.77 (m, 5 1H), 2.87-2.91 (d, 2H), 3.20 (s, 3H), 3.47 (s, 2H), 3.59-3.63 (t, 2H), 3.79 (s, 3H), 4.22-4.25 (t, 2H), 6.93-6.98 (t, 1H), 7.00-7.10 (m, 3H), 7.39-7.45 (m, 2H), 7.51-7.58 (m, 2H).

Example 3

Preparation of 5-[4-(1-butyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid

This compound was prepared using the procedure described in Example 1 using 1-bromobutane instead of 1-bromo-2-ethoxyethane in step D. Step F was performed using 1.3 g (0.0051 mol) of 1-butyl-3-piperidin-4-yl-1H-indole. Overall yield 85% (1.4 g).

15 Melting point: 229.7-235.4°C

¹H-RMN (DMSO) δ = 0.86-0.91 (t, 3H), 1.11-1.30 (m, 4H), 1.68-1.73 (t, 2H), 1.76-2.15 (m, 5H), 2.79-3.16 (m, 2H), 3.74-3.76 (m, 2H), 3.85 (s, 3H), 4.08-4.12 (t, 2H), 6.81-7.19 (m, 4H), 7.38-7.42 (m, 1H), 7.58-7.62 (m, 2H), 7.76-7.80 (m, 1H).

20 Example 4

Preparation of 5-{4-[1-(2-ethoxyethyl)-6-fluoro-1H-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic acid

A. Preparation of 6-fluoro-3-piperidin-4-yl-1H-indole

25

This compound was prepared following the procedure described in Example 1 (steps A and B) starting with 1 g (7.4 mmol) of 6-fluoroindol and 2.84 g (18.5 mmol) of 4-piperidone monohydrate hydrochloride. In this case, the hydrogenation step took place for 1 hour at 2 bar and the catalyst used was platinum (IV) oxide. 0.640 g (51% yield) of 6-fluoro-3-piperidin-4-yl-1H-indole were obtained.

30 ESI/MS m/e = 219 [(M+1)+, C13 H15 F N2].

B. Preparation of 4-(6-fluoro-1H-indol-3-yl)-piperidine-1-carboxylic acid ethyl ester

This compound was prepared following the procedure described in Example 1 (step C) starting with 4.4 g (20 mmol) of 6-fluoro-3-piperidin-4-yl-1H-indole. After standard work-up, 5.2 g (90% of yield) of 4-(6-fluoro-1H-indol-3-yl)-piperidine-1-carboxylic acid ethyl ester were obtained.

5

C. Preparation of 5-[4-[1-(2-ethoxyethyl)-6-fluoro-1H-indol-3-yl]piperidin-1-ylmethyl]-2-methoxybenzoic acid

This compound was prepared the procedure described in Example 1 (steps D, E and F) 10 starting with 5.1 g (0.017 mmol) of 4-(6-fluoro-1H-indol-3-yl)-piperidine-1-carboxylic acid ethyl ester. Overall yield 47% (1.4 g)

Melting point: 232.7-233.7°C

¹H-RMN (DMSO) δ = 1.01-1.06 (t, 3H), 1.59-1.67 (m, 2H), 1.89-1.92 (d, 2H), 2.07-2.14 (t, 2H), 2.71-2.75 (m, 1H), 2.87-2.91 (d, 2H), 3.25-3.30 (m, 2H), 3.47 (s, 2H), 3.62-3.65 (t, 2H), 3.80 (s, 3H), 4.19-4.23 (t, 2H), 6.80-6.84 (m, 1H), 7.06-7.12 (m, 2H), 7.27-7.32 (dd, 1H), 7.41-7.45 (d, 1H), 7.50-7.57 (m, 2H).

Example 5

Preparation of 5-[4-[6-fluoro-1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl]-2-methoxybenzoic acid

This compound was prepared following the procedure described in Example 1 (steps D, E and F) starting with 4.4 g (0.015 mmol) of 4-(6-fluoro-1H-indol-3-yl)-piperidine-1-carboxylic acid ethyl ester and 1.7 ml (0.018 mmol) of 1-bromo-2-methoxyethane. Overall 25 yield 30% (0.85 g).

Melting point: 247.0-248.1°C

¹H-RMN (DMSO) δ = 1.56-1.75 (m, 2H), 1.87-1.95 (m, 2H), 2.05-2.13 (t, 2H), 2.67-2.71 (t, 1H), 2.86-2.90 (d, 2H), 3.19 (s, 3H), 3.46 (s, 2H), 3.51-3.53 (m, 2H), 3.79 (s, 3H), 4.19-4.23 (m, 2H), 6.78-6.82 (m, 1H), 6.98-7.10 (m, 2H), 7.26-7.30 (dd, 1H), 7.41-7.43 (m, 1H), 30 7.50-7.55 (m, 2H).

Example 6

Preparation of 5-[4-(1-butyl-6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid

A. Preparation of 5-[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid ethyl ester

A suspension containing 0.5 g (2.2 mmol) of 6-fluoro-3-piperidin-4-yl-1H-indole, 0.8 g (2.7 mmol) of 5-bromomethyl-2-methoxybenzoic acid methyl ester and 0.6 g (4.3 mmol) of potassium carbonate in 10 ml of ethyl isobutylketone was heated at 90°C for 16 hours. The inorganic solid was filtrated and the solvent was removed under reduced pressure. 0.91 g (97% of yield) of the expected product was obtained.

10 B. Preparation of 5-[4-(1-buty-6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid

Under inert atmosphere, a solution of 0.07 g (0.17 mmol) of 5-[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid ethyl ester in 0.5 ml of anhydrous DMF was added dropwise to a suspension containing 0.012 g (0.24 mol) of sodium hydride (60% in mineral oil) in 1 ml of anhydrous DMF. After stirring at room temperature for 1 hour, a solution of 0.044 g (0.24 mol) of 1-bromobutane in 0.5 ml of DMF was added. The reaction mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure. This ester was dissolved in a mixture of 1ml of ethanol and hydrolysed with 2N NaOH at room temperature for 20 hours. The crude mixture was neutralised with 2N HCl aqueous solution and the solvent was removed under reduced pressure. The crude residue was purified by HPLC-MS chromatography affording 0.0053 g of the expected acid.

ESI/MS m/e = 439 [(M+1)+, C26 H31F N2O3]

25 Also included within the scope of the present invention are pharmaceutical compositions which comprise, as the active ingredient, at least one indolylpiperidine derivative of general formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier or diluent. Preferably the composition is made up in a 30 form suitable for oral, parenteral or topical administration. The pharmaceutically acceptable carriers or diluents which are mixed with the active compound or compounds, or salts thereof, to form the composition of this invention are well-known "per se" and the actual excipients used depend "inter alia" on the intended method of administration of the compositions.

- Compositions of this invention are preferably adapted for oral administration. In this case, the compositions may take the form of tablets, capsules or effervescent granules or of liquid preparations such as elixirs, syrups or suspensions, all containing one or more compounds of the invention; such preparations may be made by methods well known in the art. The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired.

- Tablets or capsules may conveniently contain between 0.2 and 500 mg, preferably from 10 0.5 to 100 mg, of active ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof. The compounds may be incorporated into pellets coated with an appropriate natural or synthetic polymer known in the art to produce sustained release characteristics. They can also be incorporated with polymers into tablet form to produce the same characteristics.

- 15 The liquid composition adapted for oral use may be in the form of solution or suspension. The solution may be an aqueous solution of an acid addition salt of the indolylpiperidine derivative in association with, for example, sucrose or sorbitol to form a syrup. The suspension may comprise an insoluble or microencapsulated form of an active compound 20 of the invention in association with water or other pharmaceutically acceptable liquid medium together with a suspending agent or flavouring agent.

- Compositions for parenteral injection may be prepared from soluble salts of the indolylpiperidine derivatives, which may or may not be freeze-dried and which may be 25 dissolved in water or an appropriate parenteral injectable fluid.
- Compositions for topical administration may take the form of a cream, lotion, ointment or the like. They can be prepared as suspensions or emulsions of the type oil-in-water or water-in-oil, using the excipients usual in the art..

- 30 In human therapy, the doses of the compound of general formula I depend on the desired effect and duration of treatment; adult doses are generally between 0.2 mg and 500 mg per day and preferably between 0.5 mg and 100 mg per day. In general, the physician will decide the dosing regime taking into account the age and weight of the patient being treated.

Pharmacological Action

The following assays were carried out to demonstrate the excellent pharmacological activities of the compounds of the present invention.

5

- (1) In vitro histamine H₁ receptor binding assay, to measure the affinity of the compounds.
- (2) Histamine-induced skin vascular permeability in rats, to evaluate antiallergic activity *in vivo*.

10

- (3) Serotonin 5HT2 receptor binding assay, to assess selectivity.

(1) Histamine-H₁ receptor binding assay

15 The study of binding to histamine-H₁ receptors was performed in guinea pig cerebellum membranes as described by Chang et al., *J. Neurochem*, 1979, 32, 1653-1663. Briefly, the membrane suspensions (160 μ g/ml) were incubated at 30°C with 0.7 nM [³H]-mepyramine and different concentrations of the test compounds in a final volume of 250 μ l. Binding reactions were terminated by filtration after 30 min of incubation and the 20 bound radioactivity was determined. The non-specific binding was measured in the presence of 10 μ M of promethazine. The affinity of each test compound to the receptor was determined by using at least six different concentrations run in duplicate. IC₅₀ values were obtained by non-linear regression by use of SAS on a DEC AXP computer.

25 (2) Histamine-induced skin vascular permeability in rats

Male Wistar rats (180-210 g) were treated orally with the test compound or vehicle. Either one, four, eight or 24 hours later the rats were lightly anaesthetised with ether and a 30 cutaneous reaction was induced by two intradermal injections of 50 μ l of histamine (100 μ g/ml) onto the back, followed by an intravenous injection of 3 ml/kg of Evan's Blue (5 mg/ml), both dissolved in saline. Sixty minutes later, the rats were killed by cervical dislocation and the back skin dissected free. The diameter (in millimetres) of the papule was measured in two directions and the area was calculated. Results are given as the % of inhibition at a given dose compared with the vehicle treated group.

35

(3) Serotonin- 5HT2 Receptor Binding Assay

The study of binding to serotonin-5HT2 receptors was performed in human frontal cerebral cortex membranes as described previously (Pazos et al., Eur. J. of Pharmacol, 5 1985, 106, 531-538). Briefly, the membrane suspensions (170 μ g/ml) were incubated at 37 °C with 1 nM 3H-Ketanserin and different concentrations of the test compounds in a final volume of 250 μ l. Binding reactions were terminated by filtration after 30 minutes of incubation under constant shaking and the bound radioactivity was measured. The non-specific binding was estimated in the presence of 10 μ M mianserin. The affinity of each 10 test compound to the receptor was determined by using at least six different concentrations run in duplicate. IC50 values were calculated by non-linear regression using SAS.

The indolylpiperidines of the invention are characterised by the presence of a methoxy 15 group in ortho position of the benzoic acid moiety. The results obtained in the pharmacological assays show that this particular structural feature is responsible for an increased antiallergic potency, with respect to indolylpiperidines of otherwise identical structure but not having a methoxy group in ortho position of the benzoic acid moiety, as shown in table 1.

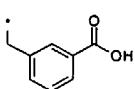
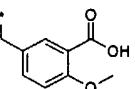
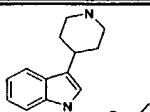
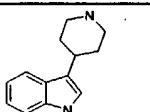
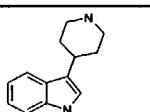
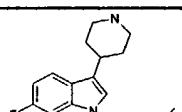
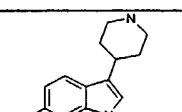
Indolylpiperidine core							Example
	H1 (nM)	5HT-2 (nM)	papule (4h) % inh a 1mg/Kg	H1 (nM)	5HT-2 (nM)	papule (4h) % inh a 1mg/Kg	
	218	1774	84%	145	5350	88%	1
	335	>10000	24%	470	>10000	96%	2
	—	—	—	130	4500	100%	3
	147	944	41%	160	4300	89%	4
	150	3850	44%	245	>10000	96%	5

TABLE 1

5

- The results in table 1 indicate that the compounds of the invention have an H₁ binding IC₅₀ which is comparable or even slightly higher than the IC₅₀ of the structurally similar indolylpiperidines not having the ortho-methoxy group. These implies a comparable affinity for histamine H₁ receptors *in vitro*. Consequently, the person skilled in the art 10 would have expected that both classes of indolylpiperidines would also have a comparable antiallergic activity *in vivo*.

Remarkably, the antihistaminic and antiallergic potency *in vivo* of the indolylpiperidines of the invention is significantly higher than that of compounds without an ortho-methoxy

group. This is evident from the comparison of the inhibitory effects of the two classes of compounds on the size of the papula induced by an injection of histamine, 4 hours after the oral administration of the compounds at a dose of 1 mg /Kg. The percentage of inhibition produced by the compounds of the invention is always higher than that of their 5 counterparts and ranges between 88 % and 100 %.

Furthermore, the affinity of the compounds of the invention for 5HT-2 receptors is in all cases significantly lower than the already relatively low affinity of the compounds not having an ortho-methoxy group. The affinity for 5HT-2 receptors is known to be directly 10 correlated with the occurrence of the serious cardiovascular side-effects which many commercial antihistamines induce. Therefore, it is highly desirable to develop compounds with increased 5HT-2 binding IC₅₀, because this results in a more selective antihistaminic effect. This is the case of the indolylpiperidines of the invention, which are expected to be devoid of cardiovascular effects.

15 In view of these results it can be concluded that the distinguishing structural features of the compounds of the invention represent a novel group of compounds selected from the generic class of antihistaminic indolylpiperidines, which results in a dramatic improvement of their selectivity and antiallergic potency and in a decreased risk of producing 20 cardiovascular side-effects.

They can thus be advantageously used at low doses for the treatment of allergic disorders, for instance, bronchial asthma, rhinitis, conjunctivitis, dermatitis and urticaria.

25 The invention thus provides a method for treating an allergic disorder comprising the step of administering to a subject in need of such treatment an effective amount of a compound of formula I.

30 The invention also provides the use of the compounds of formula I in the manufacture of a medicament for the treatment of an allergic disorder, as well as pharmaceutical compositions comprising a compound of formula I. Some examples of suitable compositions are shown below.

Formulation example 1

35 **Preparation of a pharmaceutical composition: syrup**

150 ml of a syrup are prepared as follows:

Active compound	750 mg
Glycerin	15 g
5 hydrogenated castor oil-ethylene oxide	1.5 g
sodium methyl p-hydroxybenzoate	240 mg
sodium propyl p-hydroxybenzoate	60 mg
sodium saccharin	300 mg
flavouring q.s.	
10 sodium hydroxide q.s. pH = 4	
demineralised water q.s. 150 ml	

Procedure:

- To a solution of the p-hydroxybenzoates and saccharin in 30 ml of demineralised water,
- 15 an aqueous glycerin solution and hydrogenated castor oil-ethylene oxide are added. After stirring, the active compound is added and homogenised to reach complete dissolution. The flavouring agent is then mixed into the solution with vigorous stirring, and the mixture was made up to final volume with demineralised water.

20 Formulation example 2

Preparation of a pharmaceutical composition: capsules

Capsules containing 20 mg of active compound are prepared from the following formulation:

25 Active compound	20 mg
magnesium stearate	4.5 mg
lactose spray dried	367 mg
cross-linked sodium carboxymethylcellulose	18 mg
sodium lauryl sulphate	9 mg

30

Procedure:

2-methoxy-5-{4-[1-(2-methoxy-ethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-piperidin-1-ylmethyl}-benzoic acid, sodium lauryl sulphate, lactose and cross-linked sodium carboxymethylcellulose were mixed together and passed through a screen with an

opening of 0.6 mm. The magnesium stearate was added and the mixture encapsulated into gelatine capsules of appropriate size.

Formulation example 3

5 Preparation of a pharmaceutical composition: tablets

Tablets containing 10 mg of active compound were prepared from the following formulation:

	Active compound	10 mg
10	microcrystalline cellulose	16.5 mg
	lactose spray dried	96.2 mg
	carboxymethyl starch	5.7 mg
	sodium stearyl fumarate	0.8 mg
	colloidal silicon dioxide	0.8 mg

15

Procedure:

All the powders were passed through a screen with openings of 0.6 mm. They were then all mixed for 30 minutes and compressed into 145 mg tablets using 6 mm discs and flat bevelled punches. The disintegration time of the tablets was about 60 seconds.

20

Formulation example 4

Preparation of a cream

Components:

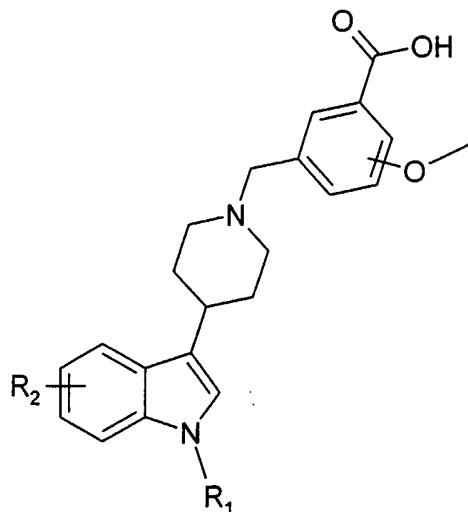
	Active compound	1 %
25	Cetyl alcohol	3 %
	Stearyl alcohol	4 %
	Gliceryl monostearate	4 %
	Sorbitan monostearate	0.8 %
	Sorbitan monostearate POE	0.8 %
30	Liquid vaseline	5 %
	Methylparaben	0.18 %
	Propylparaben	0.02 %
	Glycerine	15 %
	Purified water csp.	100 %

35

An oil-in-water emulsion cream is prepared with the ingredients listed above, using conventional methods.

CLAIMS

1. A compound of formula I



5 wherein:

R_1 represents an alkyl, alkenyl, alkoxyalkyl or cycloalkylalkyl group;

R_2 represents a hydrogen or halogen atom;

the methoxy group substituting the benzoic acid is in position ortho with respect to the
10 carboxy group.

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein the methoxy group substituting the benzoic
15 acid is both in position ortho with respect to the carboxy group and in position para with
respect to the carbon atom which is bound to the indolylpiperidine moiety of the molecule..

3 A compound according to any preceding claim wherein R_1 is selected from ethyl, n-
propyl, n-butyl, methoxymethyl, methoxyethyl, ethoxyethyl, cyclopropylmethyl,
20 cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, allyl, 2-propenyl, 2-propoxyethyl
and 3-methoxypropyl.

4. A compound according to claim 3, wherein R_1 is methoxyethyl, ethoxyethyl, butyl,
cyclopropylmethyl or allyl.

5. A compound according to any preceding claim wherein R2 is hydrogen, fluorine or chlorine.
- 5 6. A compound according to claim 5 wherein R2 is hydrogen or fluorine.
7. A compound according to claims 1 or 2, which is one of
- 5-{4-[1-(2-ethoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 10 2-methoxy-5-{4-[1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-benzoic acid
- 5-[4-(1-butyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
- 5-{4-[1-(2-ethoxyethyl)-6-fluoro-1H-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 5-{4-[6-fluoro-1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 15 5-[4-(1-butyl-6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
- 5-[4-(5-bromo-1-propyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
- 3-[4-(5-chloro-1-ethyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
- 3-[4-(1-cyclopropylmethyl-5-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
- 20 5-[4-(5-chloro-1-cyclohexylmethyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
- 2-methoxy-5-{4-[1-(2-propoxyethyl)-1H-indol-3-yl]-piperidin-1-ylmethyl}-benzoic acid
- 3-{4-[5-bromo-1-(3-methoxypropyl)-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 25 3-[4-(1-allyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
- 3-[4-(1-allyl-6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
- 5-{4-[5-chloro-1-(2-propenyl)-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 5-[4-(1-cyclopentylmethyl-6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
- 30 3-{4-[6-fluoro-1-methoxymethyl-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 3-{4-[1-cyclopropylethyl-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 3-{4-[5-chloro-1-(2-methoxyethyl)-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 3-{4-[1-(2-ethoxyethyl)-5-fluoro-1H-indol-3-yl]-piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 35 acid.

8. A compound according to claim 7, which is one of

- 5-{4-[1-(2-ethoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 5 2-methoxy-5-{4-[1-(2-methoxyethyl)-1H-indol-3-yl]piperidin-1-ylmethyl}-benzoic acid
- 5-[4-(1-butyl-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid
- 5-{4-[1-(2-ethoxyethyl)-6-fluoro-1H-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 5-{4-[6-fluoro-1-(2-methoxyethyl)- 1H-indol-3-yl]piperidin-1-ylmethyl}-2-methoxybenzoic acid
- 10 5-[4-(1-butyl-6-fluoro-1H-indol-3-yl)-piperidin-1-ylmethyl]-2-methoxybenzoic acid

9. A compound according to any one of claims 1 to 8 for use in the treatment of a pathological condition or disease susceptible to amelioration by antagonism of H₁ histamine receptors.

15

10. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 8 mixed with a pharmaceutically acceptable diluent or carrier.

11. Use of a compound as defined in any one of claims 1 to 8 in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible of being improved by antagonism of histamine H₁ receptors.

12. Use according to claim 11, wherein the pathological condition or disease is bronchial asthma, allergic rhinitis, conjunctivitis, dermatitis, urticaria or any other allergic disease.

25

13. A method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by antagonism of histamine H₁ receptors, which comprises administering to said subject an effective amount of a compound as defined in any one of claims 1 to 8.

30

14. A method according to claim 13, wherein the pathological condition or disease is bronchial asthma, allergic rhinitis, conjunctivitis, dermatitis, urticaria or any other allergic disease.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05222

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 A61K31/445 A61P43/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

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

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

WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 36589 A (ALMIRALL PRODESFARMA) 10 May 2002 (2002-05-10) page 0; claims 1,9; examples 68,80,117; table 2 ---	1-5,8-12
A	WO 00 75130 A (ALMIRALL PRODESFARMA) 14 December 2000 (2000-12-14) cited in the application page 0; claims; example 158 -----	1-5,8-12

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

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

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

Date of the actual completion of the international search

Date of mailing of the international search report

21 August 2003

01/09/2003

Name and mailing address of the ISA

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Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/EP 03/05222**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

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

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 13,14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/05222

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0236589	A 10-05-2002	ES 2172436 A1		16-09-2002
		AU 2365502 A		15-05-2002
		CA 2427589 A1		10-05-2002
		WO 0236589 A1		10-05-2002
		EP 1330453 A1		30-07-2003
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