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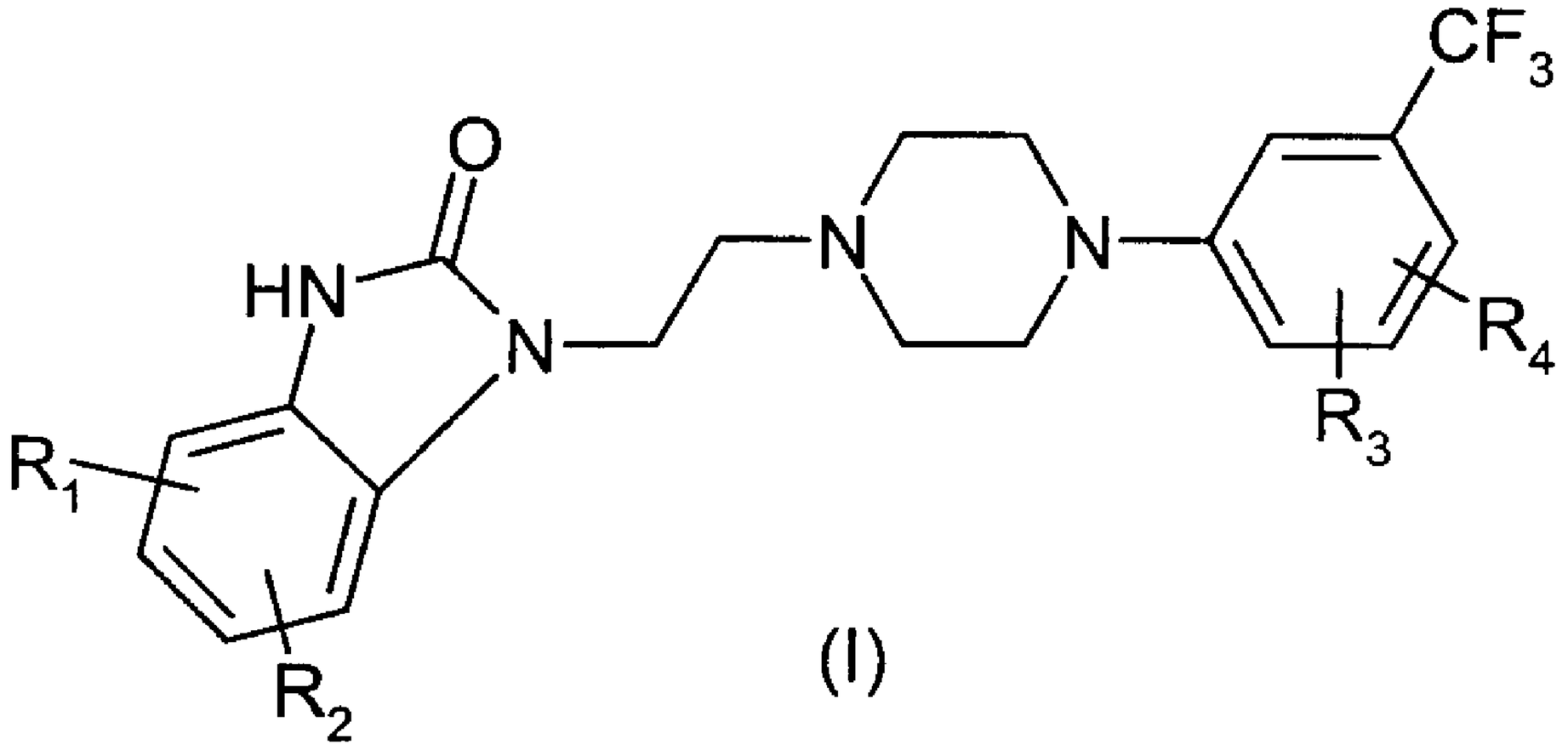
(54) Titre : NOUVEAUX DERIVES DE BENZIMIDAZOLONE POSSEDANT UNE AFFINITE MIXTE ENVERS LES RECEPTEURS DE SEROTONINE ET DE DOPAMINE

(54) Title: NEW BENZIMIDAZOLONE DERIVATIVES HAVING MIXED SEROTONINE AND DOPAMINE RECEPTORS AFFINITY



(I)

(57) Abrégé/Abstract:
The present invention pertains to compounds of general formula (I) wherein R_1, R_2, R_3, and R_4 denote hydrogen or hydroxy with the proviso that R_1, R_2, R_3, and R_4 cannot simultaneously represent hydrogen. These compounds bind to the Serotonine and dopamine receptors and are useful in the treatment of CNS disorders.

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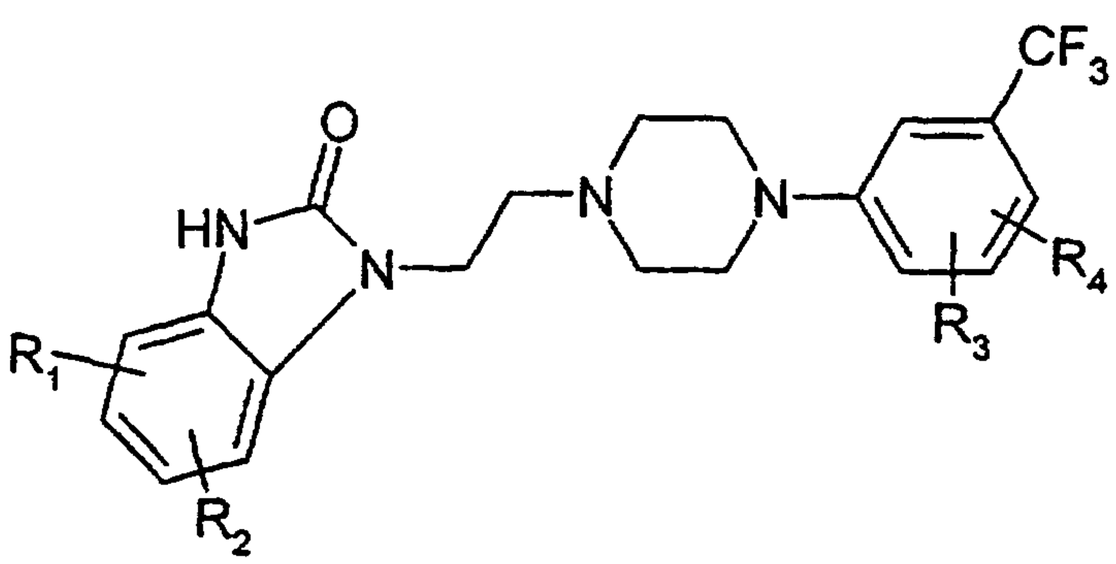


(I)

(57) Abstract: The present invention pertains to compounds of general formula (I) wherein R_1, R_2, R_3, and R_4 denote hydrogen or hydroxy with the proviso that R_1, R_2, R_3, and R_4 cannot simultaneously represent hydrogen. These compounds bind to the Serotonine and dopamine receptors and are useful in the treatment of CNS disorders.

New Benzimidazolone derivatives having mixed serotonine and dopamine receptors affinity

The present invention relates to novel pharmacologically active benzimidazolone derivatives and their addicton salts which bind the serotonine and dopamine receptors, to their preparation and their use for therapeutic purposes. These compounds, owing to their pharmacological activity, are useful in the treatment of CNS disorders.

Background of the invention

Serotonine (5-HT) and Dopamine recognise several well defined cell surface receptors. Among these, 5-HT_{1A}, 5-HT_{2A} and D_4 at which serotonine and dopamine, respectively, have high affinity, are known to be implicated in many Central Nervous System disorders such as depression, anxiety, schizophrenia, Parkinson and neurodegenerative diseases.

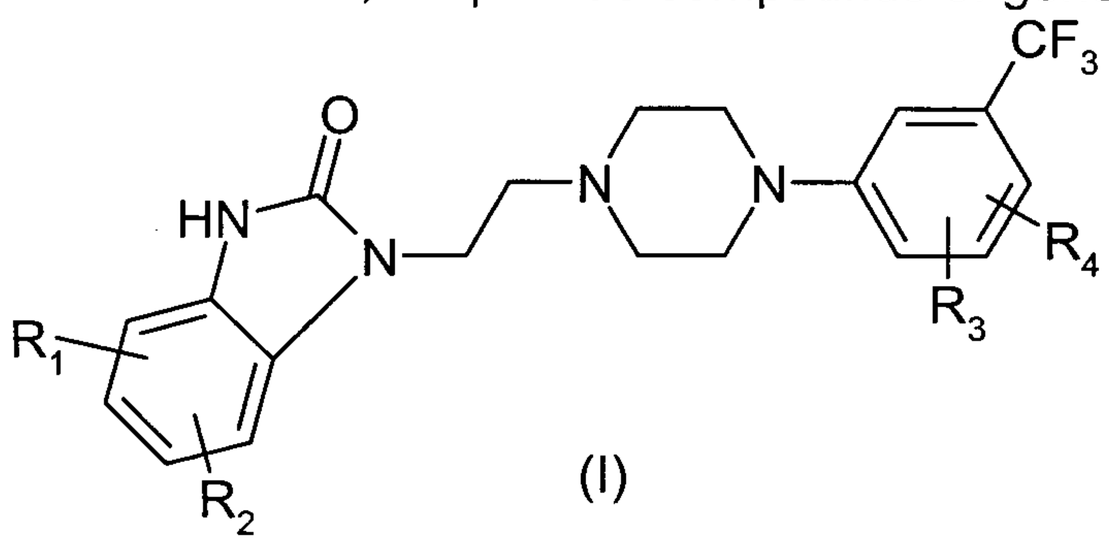
In the previous art, several classes of compounds able to interfere with the neurotransmission at serotonine or dopamine receptor subtypes are known. Particularly, derivatives based on the core structure of the arylpiperazine and benzimidazolone have been described (e.g. GB 2023594, U.S. Pat. 3,472,854, U.S. Pat. 4,954,503 and WO 98/33784), and targeted both to generic serotonine or dopamine receptors and to a specific receptor subtype. In another patent (US 5,576,318) compounds based both on the benzimidazolone and phenyl piperazine structures are described: in this latter case the described affinities are limited to 5-HT_{1A} and 5-HT_{2A} receptor subtypes.

Detailed description of the invention

Here we describe, and this is the object of the present invention, new hydroxylated derivatives based on the benzimidazolone phenyl piperazine structure. Surprisingly it was discovered that the compounds according to this invention possess an interesting affinity profile at the said serotonine and dopamine receptor subtypes: indeed, some of them have a high and preferential affinity at a given site (e.g. 5-HT_{1A}, 5-HT_{2A} or D_4) whereas some other have a mixed affinity at all the said receptors.

Owing to their peculiar profile, the present compounds may play a role in the regulation of neurotransmission at the serotonine and/or the dopamine sites and thus may be of value in the treatment of those diseases where an altered functioning of neurosignal transmission is present. Examples of these CNS disorders include depression, schizophrenia, Parkinson, anxiety, sleep disturbances, sexual and mental disorders and age associated memory impairment.

According to the present invention, we provide compounds of general formula (I)



(I)

wherein

R_1, R_2, R_3, and R_4 denote hydrogen or hydroxy with the proviso that R_1, R_2, R_3, and R_4 cannot simultaneously represent hydrogen.

Preferred compounds according to the invention are those of general formula (I) wherein two or three of the four radicals R_1, R_2, R_3, and R_4 denote hydrogen.

Also preferred are compounds of general formula (I) wherein one of the radicals R_1, R_2, R_3, and R_4 denotes hydroxy, whilst the other radicals represent hydrogen.

Of particular interest are compounds selected from the group consisting of:

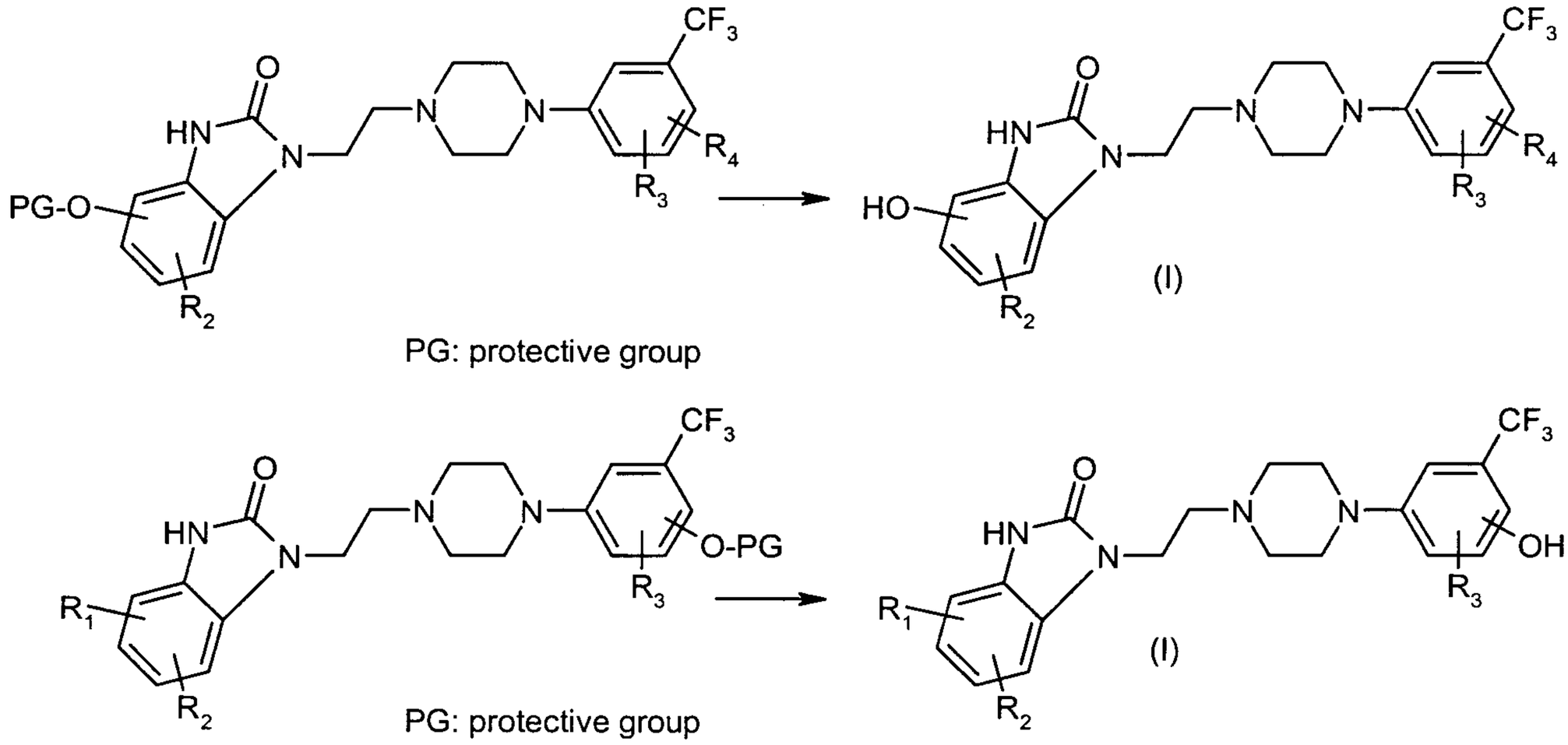
- 5-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one;
- 6-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one;
- 4-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzimidazol-2-one;
- 7-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one;
- 1-{2-[4-(4-Hydroxy-3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one;
- 1-{2-[4-(3-Hydroxy-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one;
- 1-{2-[4-(2-Hydroxy-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzimidazol-2-one;
- 1-{2-[4-(2-Hydroxy-3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzimidazol-2-one;

For the pharmaceutical use the compounds of general formula (I) may be used either as free base or in the form of physiologically acceptable acid addition salts. The term “acceptable acid addition salts“ includes both organic and inorganic acids such as

maleic, citric, tartaric, methanesulphonic, acetic, benzoic, succinic, gluconic, isethionic, glycinic, lactic, malic, mucoic, glutamic, sulphamic and ascorbic acid; inorganic acids include hydrochloric, hydrobromic, nitric, sulfuric, or phosphoric acid.

The compounds of general formula (I) may be conveniently prepared by a variety of synthetic processes analogous to those known in the art using conventional methods and starting from suitable intermediates in which the hydroxy function (generally in the form of a methoxy precursor group) is inserted in a well defined position, and suitable for originating the final target compound. When a masked (i.e. protected) hydroxy function is used throughout all the synthetic process, the hydroxy function is generated in the last step as exemplarily outlined in scheme 1.

Scheme 1:



As protective groups conventional ether protective groups are applicable (e.g.: methyl, methoxymethyl, benzyl). The preferred protecting group according to the invention is the methyl ether. The deprotection of the hydroxy group can be easily carried out by conventional known procedures. In case of the preferred protecting group methoxy the deprotection is achieved by treatment with strong acqueous acids such as 48% hydrobromic acid at high temperatures or alternatively by treatment with boron derivatives, such as BBr_3, at low temperatures in chlorurated solvents such as methylene dichloride.

As mentioned before, the compounds of formula (I) according to the present invention, surprisingly show interesting pharmacological properties owing to their different profile at the serotonine or dopamine receptor subtypes, such as 5-HT_{1A}, 5-

HT_{2A} and D_4. The biochemical profile of the compounds was assessed by evaluating their affinity for the 5-HT_{1A}, 5-HT_{2A} and D_4 receptors, according to the methods described below.

Receptor Binding studies

Binding studies were carried out to determine the affinity of the compounds for 5-HT_{1A}, 5-HT_{2A} and D_4 receptors

5-HT_{1A} receptor

Tissue preparation:

Male Sprague-Dawley rats (200-250 g) were used. The hippocampus taken from these animals was homogenized in 10 volumes of ice cold 50 mM TRIS buffer (pH 7.4). The homogenate was diluted 1:400 (w:v) in the same buffer to have a final protein concentration of about 200 µg/ml, filtered and incubated at 37° C for 10 min before use.

Binding assay:

Displacement experiments were performed by incubating the homogenate (980 µl) in the presence of [^{3}H]-8-OH-DPAT (10 µl; 1.0-1.2 nM) and different concentrations of the test compounds dissolved in DMSO (10 µl), at 30° C for 15 min (final volume: 1 ml). Non specific binding was determined in the presence of 10 µ M 5-HT (10 µl). The reaction was stopped by rapid filtration through Inotech IH 201 filters using Inotech Cell Harvester. The radioactivity was counted by liquid scintillation spectrometry.

5 HT_{2A} receptor

Tissue preparation:

Male Sprague-Dawley rats (200-250 g) were used. Cerebral cortex was homogenized in 10 volumes of ice cold 0.32 M sucrose. After the centrifugation of the homogenate (1,000 x g for 10 min) the supernatant was then recentrifuged at 48,000 x g for 15 min. The resulting pellet was suspended in 10 volumes of 50 mM TRIS buffer (pH 7.4), incubated at 37° C for 10 min and recentrifuged at 48,000 x g for 15 min. The residue was then resuspended in 10 volumes of 50 mM TRIS buffer (pH 7.4).

Binding assay:

The tissue was diluted 1:100 (w:v) in 50 mM TRIS buffer (pH 7.4) to have a final concentration of about 200 µg/ml. Displacement experiments were performed by incubating the homogenate (980 µl) in the presence of [^{3}H]-Ketanserine (10 µl; 0.5-0.6 nM) and different concentrations of the test compounds dissolved in DMSO (10 µl) at 37° C for 10 min (final volume: 1 ml). Non specific binding was determined in

the presence of 100 µM Methysergide (10 µl). The reaction was stopped by rapid filtration through Inotech IH 201 filters using Inotech Cell Harvester. The radioactivity was counted by liquid scintillation spectrometry.

D_4 Receptor

Cell culture:

Cells were grown in monolayer at 37°C in 95% air/5% CO2 in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 7.5% (v/v) heat-inactivated foetal bovine serum (FBS), 2.5% (v/v) heat-inactivated horse serum donor herd, 2% of a stock solution containing 5000 I.U./ml penicillin and 5000 µg/ml streptomycin, 1% (v/v) of a solution MEM containing non-essential amino acid, 2 mM glutamine and 200 µg/ml geneticin. Cells were passaged twice a week using a trypsin/EDTA solution and the split rate was 1:4. Cells were not subcultured more than 17 times.

Preparation of cell membranes:

The cells grown to confluence were washed twice with Dulbecco's PBS buffer and were detached adding VERSENE (PBS containing 0.2 g/l EDTA) for 10 min at 37°C. The cell suspension was centrifuged at 1,000 rpm for 10 min and the pellet was harvested in DMEM with 10% DMSO and stored at –80 °C. Before use, cells were thawed, centrifuged at 1,000 rpm for 10 min and the pellet was resuspended in PBS. The cells were centrifuged again at 270 x g for 10 min at 4 °C and the pellet was resuspended in a lysis buffer (10 mM Tris-HCl pH 7.4, 5 mM Na_2EDTA and protease inhibitors) and incubated for 30 min on ice. Cells were homogenised with an Ultra Turrax homogeniser. Unbroken cells and nuclei were removed by an initial centrifugation at 270 x g for 10 min at 4 °C and crude membranes were collected from the supernatant by a 60 min spin at 130,000 x g. The pelleted membranes were resuspended in the same lysis buffer with 20 strokes by a Potter homogeniser. The final cell membrane suspension, corresponding to about 1 x 10^7 original cells/ml, was aliquoted and immediately frozen at –80°C.

Membrane preparation:

D_4 receptor binding studies were carried out in membranes from CHO cells prepared as above.The membranes were dilute in incubation buffer (50 mM TRIS-HCl pH 7.4 , 5mM Mg $Cl_2.6H_2O$, 5mM KCl, 1.5 mM $CaCl_2.2H_2O$, 5mM EDTA) according to their receptor density.

Binding assay:

Displacement experiment were performed in 1000 µl total volume incubating the membranes (980 µl) in the presence of [^{3}H] -YM 09151-2 (10 µl; 0.15-0.25 nM) and different concentrations of the test compounds dissolved in DMSO (10µl) at 27° C for two hours. Non specific binding was determined in the presence of 10 µM of Clozapine (10 µl). The reaction was stopped by rapid filtration through Inotech IH 201

filters (pre-soaked in 0.1 % Polyethylenimine) using Inotech cell harvester. The radioactivity was counted by liquid scintillation spectrometry.

Data analysis:

The affinity values (Ki) for the compounds were obtained by a non linear least squares regression analysis on the basis of a one binding site model. The values were corrected on the basis of the radioligand occupancy on the receptors according to the equation: $Ki = IC_{50} / (1 + [C] / Kd)$, where [C] and Kd represent the concentration and the dissociation constant of the used radioligands ([^{3}H]-8-OH-DPAT for the 5-HT_{1A} binding, [^{3}H]-Ketanserine for the 5-HT_{2A} binding and [^{3}H]-YM 09151-2) for the D_4 binding, respectively).

The following table (Table I) collects the affinity values (Ki, nM) at the said receptors of the new compounds.

TABLE I. Ki (nM) for 5-HT_{1A}, 5-HT_{2A} and D_4 receptors

Compound	5-HT_{1A} (rat hippocampus tissue)	5-HT_{2A} (Rat cortex tissue)	D_4 (CHO cell membranes)
1	40.8	58.5	287
2	333	33.8	804
3	15.4	43.8	33.9
4	1590	23.8	652
5	369	705	17.8
6	156	328	24.8
7	>10000	4436	-

As a further feature of the present invention there are provided pharmaceutical compositions comprising as an active ingredient at least one compound of formula (I), as before defined, or a physiologically acceptable addition salt thereof in addition with one or more pharmaceutical carrier, diluents or excipients. For pharmaceutical administration the compounds of general formula (I) and their physiologically acceptable acid addition salts may be incorporated into the conventional pharmaceutical preparation in solid, liquid or spray form. The composition may, for example, be presented in a form suitable for oral, rectal, parenteral administration or for nasal inhalation: preferred forms includes for example, capsules, tablets, coated tablets, ampoules, suppositories and nasal spray.

The active ingredient may be incorporated in excipients or carriers conventionally used in pharmaceutical compositions such as, for example, talc, arabic gum, lactose, gelatine, magnesium stearate, corn starch, acqueous or non acqueous vehicles, polyvynil pyrrolidone, semisynthetic glicerides of fatty acids, benzalconium chloride, sodium phosphate , EDTA, polysorbate 80.

In case it is desired to further increase the solubilty of the compounds of general formula (I) or of their physiologically acceptable salts, surfactants, non ionic surfactants such as PEG 400, cyclodextrin, metastable polymorphs, inert adsorbents such as bentonite, may be incorporated. Furthermore some techniques may be employed by preparing for example eutectic mixtures and/or solid dispersion by using mannitol, sorbitol, saccharose, succinic acid or physical modified forms by using hydrosoluble polymers, PVP, PEG 4000-20.000.

The compositions are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose of the active ingredient. Each dosage unit may conveniently contain from 0,01 mg to 100 mg, preferably from 0,1 to 50 mg.

Experimental part

The following examples illustrate the preparation of compounds according to the invention. It should be understood that the invention is not limited to the given examples of chemical methods and processes for the preparation of the substances, as other conventional methods well known to those skilled in the art, are suitable too.

Description 1

2-Bromo-N-(4-methoxy-2-nitro-phenyl)–acetamide

A solution of 2-bromoacetylbromide (17.9 ml; 0.20 moles) in CH_2Cl_2 (30 ml) was slowly added to a mixture of 4-methoxy-2-nitro aniline (30 g; 0.18 moles) and triethylamine (28 ml; 0,2 moles) in CH_2Cl_2 (300 ml). The reaction mixture was stirred at room temperature overnight, then poured into water. The aqueous layer was extracted with additional CH_2Cl_2, dried over $MgSO_4$ and evaporated under vacuum. The crude product was crystallized from a 7/3 Et_2O/ EtOH mixture to give the title compound as a white solid.

31.5 g, m.p. 94-98 °C

Description 2

N-(4-Methoxy-2-nitro-phenyl)–2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-acetamide

To a mixture of 2- bromo- N- (4-methoxy-2-nitro-phenyl)-acetamide (13 g; 0.045 mol) and Na_2CO_3 (4.8 g) in anhydrous ethanol, 1-(3-trifluoromethylphenyl)-piperazine (8.22 ml; 0.045 mol) was added dropwise. The mixture was stirred at room

temperature overnight. The solvent was evaporated, the residue was dissolved into toluene and washed with water. From the evaporated organic layer, a crude solid was obtained. This was crystallized from a 9/1 Et_2O/EtOH mixture to give the title compound as a yellow solid.

10.7 g, m.p. 98-100 °C

According to the above described procedure, the following compounds were prepared:

6-methoxy-1-{2-[4-(3-trifluoromethyl)-phenyl-piperazin-1-yl]-ethyl}2,3-dihydro-2-oxo-1H-benzimidazole

The reaction mixture was refluxed for 10 hours in the presence of a catalytic amount of KI. The title compound was recrystallized from 95% EtOH to give a white solid.
m.p. 208-210 °C

2-methoxy-6-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-acetylamino}-phenyl)-carbamic acid benzyl ester

The reaction mixture was heated at 100° C for 3 hours in anhydrous DMF in the presence of a catalytic amount of KI. The title compound was crystallized from diethyl ether to give a white solid.

m.p. 153-155°C

7-methoxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1.3-dihydro-benzimidazol-2-one

The reaction mixture was heated at 100° C for 3 hours in anhydrous DMF in the presence of a catalytic amount of KI. The title compound was recrystallised from ethyl acetate and used without further purification.

1-{2-[4-(4-methoxy-3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzimidazol-2-one

The reaction mixture was heated for 8 hours in DMF. The title compound was purified by flash chromatography (silica gel; eluent: CH_2Cl_2/MeOH/NH_4OH 95:5:0.5)

1-{2-[4-(3-methoxy-5-trifluoromethyl-phenyl)-piperazin-1yl]-ethyl}-1,3-dihydro-benzimidazol-2-one

The reaction mixture was heated for 6 hours in DMF. The title compound was crystallized from 95% EtOH as hydrochloride salt.

Description 3

4-methoxy-N-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-benzene-1,2 diamine

To a solution of N-(4-methoxy-2-nitro-phenyl)-2-[4-(3-trifluoro methyl-phenyl)-piperazin-1-yl] -acetamide (9 g; 0.021 mol) in tetrahydrofurane (THF) a 1 M solution of BH_3 in THF (168 ml, 0.168 mol) was added dropwise keeping the temperature at 10-15 °C. The solution was heated at 50 °C for 4 hours and stirred at room temperature overnight. The reaction was acidified to pH 2 with 10% aqueous HCl and heated at 60 °C for 1 hour, then it was cooled and basified to pH 9 with Na_2CO_3. The product was extracted from the aqueous phase with CH_2Cl_2 and purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH 95-5-0.5) to give the title compound as a white solid. 2.2 g, m.p. 57-60 °C

According to the above described procedure, additionally the following compound was prepared:

3-methoxy-N-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-benzene-1,2-diamine

Description 4

5-methoxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzimidazol-2-one

To a solution of trichloromethyl chloroformate (0.12 ml, 1.1 mmoles) a solution of 4-methoxy-N-1{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-benzene-1,2-diamine (0.4 g; 1.0 mmol) and triethylamine (0.14 ml; 1.1mmol) in CH_2Cl_2, was added dropwise keeping the temperature at 25 °C. The mixture was stirred at room temperature for 3 hours and a precipitate was formed. The crude solid was filtered off and recrystallized from isopropanol to give the title compound as hydrochloride salt. 0.02 g, m.p. 212-216 °C dec.

According to the above described procedure, the following compounds were prepared:

5-methoxy-2-oxo-2,3-dihydro-benzimidazole-1-carboxylic acid-ethyl ester

The title compound was obtained from extraction in organic solvent (CH_2Cl_2) and recrystallization from isopropanol. White solid.

m.p.180-183 °C

4-methoxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1yl]-ethyl}-1,3-dihydro-benzimidazol-2-one

The crude compound was used without further purification.

4-methoxy-1,3-dihydro-benzimidazol-2-one

Brown solid. The crude compound was used without further purification.

Description 5

(4-methoxy-2-nitro-phenyl)-carbamic acid ethyl ester

To a cooled solution of 4-methoxy-2-nitro-aniline (25 g; 0.15 mol) in pyridine (370 ml), ethyl chloroformate (17.8 ml; 0.18 mol) was added dropwise. The mixture was refluxed for 10 hours, then cooled and poured into ice-water. The precipitated solid was collected and purified by flash chromatography (silica gel, eluent: hexane/diethyl ether 85:15) to yield the title compound as a yellow solid.

7.3 g, m.p. 56-57 °C

Description 6

(4-methoxy-2 amino-phenyl)-carbamic acid ethyl ester

A solution of (4-methoxy-2-nitro-phenyl)-carbamic acid ethyl ester (7.3 g; 0.03 mol) in 95% EtOH (500 ml), was hydrogenated at room temperature and pressure in the presence of 10% aqueous HCl (13 ml) and 10% Pd/C (0.35 g). When the theoretical amount of hydrogen was taken up, the catalyst was filtered off and the solution was evaporated to dryness to give the title compound (5 g) after crystallization from Et_2O/EtOH (85:15). The compound was used without further purification.

According to the above described procedure, the following compounds were prepared:

3-methoxy-benzene-1,2-diamine

The compound was used without further purification.

4-methoxy-3-trifluoromethyl-phenylamine

The compound was used without further purification.

2-amino-4-trifluoromethyl-phenol

Light brown solid; m.p. 115 °C

Description 7

3-(2-chloro-ethyl)-5-methoxy-2-oxo-2,3-dihydro-benzimidazole-1-carboxylic acid ethyl ester

A mixture of 5-methoxy 2-oxo-2,3-dihydro-benzimidazole-1-carboxylic acid ethyl ester and 80% NaH (0.38 g; 0.013 mol) in anhydrous DMF was stirred 20 minutes at room temperature. Then 1-bromo-2-chloro ethane (1.1 ml; 0.013 moles) was added and the solution was stirred overnight. After cooling, the reaction mixture was poured into water and the separated oil was extracted into ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated under vacuum to give the crude title compound which was crystallized with diisopropyl ether. White solid.
1.35 g; m.p. 116-118 °C

According to the above described procedure, additionally the following compound was prepared.

1-(2-chloro-ethyl)-7-methoxy-1,3-dihydro-benzimidazol-2-one

The reaction mixture was treated with aqueous KOH for 4 hours to cleave the 1-carboxylic acid phenyl-ester and the title compound was extracted in ethyl acetate and used without further purification.

Description 8

(2-methoxy-6-nitro-phenyl)-carbamic acid benzyl ester

To a solution of 2-methoxy-6-nitro-aniline (2g; 0.0119 moles) in anhydrous THF (20 ml), trichloroethyl chloroformate (1.43 ml; 0.01189 moles) was added dropwise. The reaction was heated for 45 min at 60 °C, the solvent was then removed under vacuum and the crude residue was dissolved in dioxane (20 ml). To this solution, benzyl alcohol (2.46 ml; 0.0237 mmoles) was added and the reaction mixture was refluxed for 8 hours. The solvent was then removed under vacuum and the crude residue was poured into diluted 10% HCl. The title compound was extracted into ethyl ether. The crude brown oil was crystallized with diisopropyl ether to give a light brown solid. 1.9 g; m.p. 78-80 °C

Description 9

(2-Amino-6-methoxy-phenyl)-carbamic acid benzyl ester

A mixture of (2-methoxy-6-nitro-phenyl) carbamic acid benzyl ester (17.5 g; 0.058 mol) and $SnCl_2 .2H_2O$ (65.3 g; 0.29 mol) in anhydrous ethanol, was heated at 70 °C for 2 hours. The solvent was then removed under vacuum and the residue was acidified with 10% aqueous HCl. The title compound was extracted with ethyl acetate and washed with diluted aqueous K_2CO_3. The precipitated solid was filtered off, the

organic layer was dried over $MgSO_4$ and evaporated under vacuum to give the title compound after crystallization with n-hexane. The compound was used without further purification. Yellow solid; 9.6 g.

Description 10

[2-(2-Chloro-acetylamino)-6-methoxy-phenyl]-carbamic acid benzyl ester

To a cool solution of (2-amino-6-methoxy-phenyl)-carbamic acid benzyl ester (9.5 g; 34.9 mmol) and triethylamine (5.8 ml; 42 mmol) in anhydrous THF (90 ml), chloroacetylchloride (3.3 ml; 42 mmol) was added dropwise. The mixture was stirred at 0 °C for 2 hours, the solvent was evaporated and the residue was dissolved in ethyl acetate. The organic layer was washed with 10% aqueous HCl and diluted aqueous Na_2CO_3 then it was dried and evaporated. The crude residue was crystallized with n-hexane to give the title compound as a white solid
10.8 g.

Description 11

2-methoxy-6-nitro-aniline

To a mixture of 2-hydroxy-6-nitro-aniline (41 g; 0.266 mol) and 85% KOH (17.5 g; 0.266 mol) in anhydrous DMF (80 ml), CH_3I (16.5 ml; 0.266 mol) was added dropwise. The reaction mixture was stirred at room temperature for 4 hours then poured into ice-water, the title compound precipitated as a brown solid.
40 g; m.p. 67-68 °C

Description 12

4-methoxy-2-oxo-2,3-dihydro-benzimidazole-1-carboxylic acid phenyl ester

To a solution of 4-methoxy-2-oxo-2,3-dihydro-benzimidazole (24 g; 0.146 mol) in pyridine (200 ml), phenylchloroformate (18.4 ml; 0.146 mol) was added dropwise. The reaction mixture was refluxed for 14 hours then was poured into ice-water. The precipitated solid was collected and dried to give the title compound.
30 g; m.p. 204-205 °C

Description 13

1-(4-methoxy-3-trifluoromethyl-phenyl)-piperazine

A mixture of 4-methoxy-3-trifluoromethyl-phenyl-amine (12 g; 0.0627 mol) and bis-(2-chloroethyl) ammonium chloride (11.2 g; 0.0627 mol) in n-butanol (120 ml) was refluxed for 10 hours. The reaction mixture was cooled at room temperature and the crude title compound precipitated as hydrochloride salt over night. The solid was collected and crystallized from acetone.
7 g; m.p. 244-245 °C

According to the above described procedure, the following compounds were prepared:

1-(3-methoxy-5-trifluoromethyl-phenyl)-piperazine

White solid m.p. > 250°C (as hydrochloride salt)

2-piperazin-1yl-4-trifluoromethyl-phenol

White solid. m.p. > 250°C (as hydrochloride salt)

Example 1

5-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one (Compound 1)

A mixture of 5-methoxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzimidazol-2-one (0.6 g; 1.4 mmol) and 48% HBr (30 ml) was refluxed for 1 hour. The reaction was then cooled and water was added (30 ml). The precipitated solid was collected and recrystallized from 95% EtOH to give the title compound as a white solid 0.4 g; m.p. 275°C (as hydrobromide salt, from 95% ethanol)
^{1}H-NMR (DMSO; 200MHz): 10.82 (1H, s); 9.6,(1H, b); 9.11(1H, s); 7.47 (1H, m); 7.2÷7.4 (2H, ov); 7.16 (1H, d); 7.03 (1H, d); 6.4÷6.6 (2H, ov); 4.17 (2H, t); 4.03 (2H, d); 3.82 (2H, d); 3.51 (2H, b); 2.9÷3.5 (4H, ov)

According to the above described procedure, the following compounds were prepared:

6-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one (Compound 2)

m.p.> 250 °C (as hydrobromide salt, from 95% ethanol)
^{1}H-NMR (DMSO, 200 MHz);10.73 (1H, s); 9.6 (1H, b); 9.13 (1H, s); 7.48 (1H, m); 7.2÷7.4 (2H, ov); 7.16 (1H, d); 6.81 (1H, d); 6.69 (1H, d); 6.49 (1H, m); 4.18 (2H, t); 4.04 (2H, d); 3.84 (2H, d); 3.51 (2H, b); 2.9÷3.5 (4H, ov)

4-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzimidazol-2-one (Compound 3)

m.p. 110 °C (as hydrochloride salt, from 5% HCl)
^{1}H-NMR (DMSO, 200MHz); 10.92 (1H, s); 10.8 (1H, b); 9.83 (1H, s), 7.47 (1H, m); 7.2÷7.4 (2H, ov); 7.15 (1H, d); 6.7÷7.0 (2H, ov); 6.57 (1H, d); 4.25 (2H, b); 4.0 (2H, m); 3.8 (2H, m); 3.0÷3.6 (6H, ov)

7-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one (Compound 4)

m.p. 246 °C (as hydrochloride salt, from ethyl acetate)

^{1}H-NMR (DMSO, 200MHz); 10.95 (1H,s); 10.3 (1H, b); 10.07 (1H, s); 7.47 (1H, m); 7.2÷7.4 (2H, ov); 7.15 (1H, d); 6.83 (1H, m); 6.57 (1H, d); 6.52(1H, d); 4.34 (2H, t); 3.99 (2H, m); 3.81 (2H, m); 3.56 (2H, b); 3.0÷3.5 (4H, ov)

1-{2-[4-(4-Hydroxy-3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one (Compound 5)

m.p.> 250 °C (as hydrochloride salt, from acetone)

^{1}H-NMR (DMSO, 200MHz); 11.07 (1H , s); 10.7 (1H, b); 10.1 (1H, b); 7.33 (1H, m); 6.9÷7.2 (6H, ov); 4.7 (1H+HDO, b); 4.29 (2H, t); 3.6÷3.9 (4H, ov); 3.5 (2H, b); 3.23 (2H, m); 3.01 (2H, m)

1-{2-[4-(3-Hydroxy-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one (Compound 6)

m.p.170 °C (as hydrobromide salt, from 95% ethanol)

^{1}H-NMR (DMSO, 200MHz); 11.06 (1H,s); 9.97 (1H, s); 9.6 (1H, b), 7.27 (1H, m); 7.0÷7.1 (3H, ov); 6.8 (1H, b); 6.6 (1H, b); 6.5 (1H, b); 4.2 (2H, b); 3.95 (2H, d); 3.81 (2H, d); 3.5 (2H, b); 2.9÷3.5 (4H, ov)

Example 2

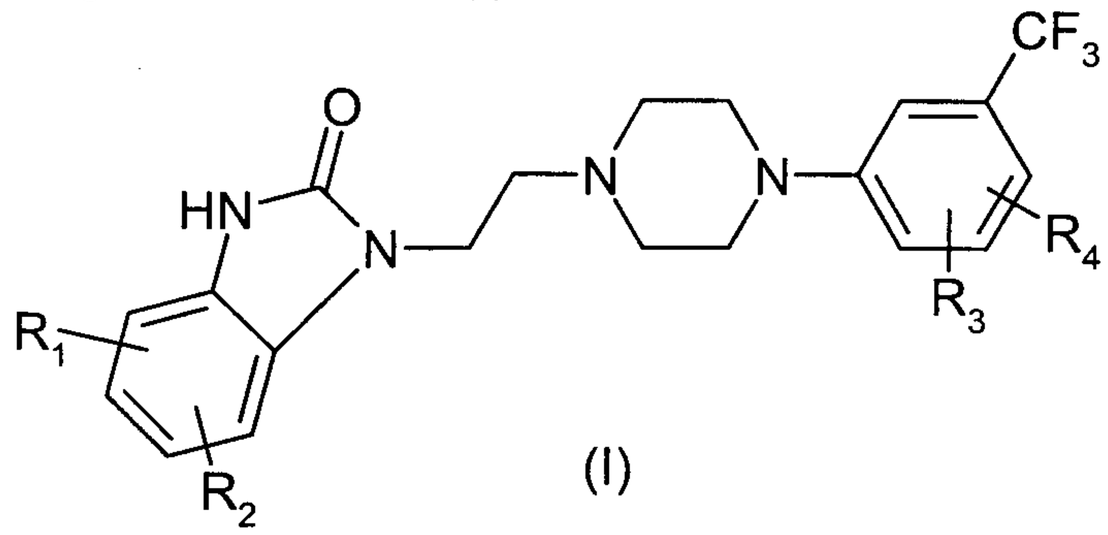
1-{2-[4-(2-Hydroxy-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzimidazol-2-one (Compound 7)

A mixture of 2-piperazin-1-yl-4-trifluoromethyl-phenol hydrochloride salt (0.17 g; 0.53 mmol), 80% NaH (0.03 g; 1.06 mmol) , K_2CO_3 (0.148 g; 1.06 mmol) and 1-(2-chloro-ethyl)-1.3-dihydro-benzimidazol-2-one (0.104 g; 0.53 mmol), was heated at 80 °C for 4 hours. After cooling, the reaction mixture was poured into water and the separated oil was extracted into ethyl acetate. The crude title compound was purified by flash chromatography (silica gel; eluent: CH_2Cl_2 /MeOH/NH_4OH 97:3:0.3) to give the free base of the title compound. The hydrochloride salt was obtained in ethyl acetate and ethereal HCl solution. White solid.

25 mg; m.p. 158-160 °C

Claims

1) Compounds of general formula (I)



(I)

wherein

R_1, R_2, R_3, and R_4 denote hydrogen or hydroxy with the proviso that R_1, R_2, R_3, and R_4 cannot simultaneously represent hydrogen.

2) Compounds of general formula (I) according to claim 1 wherein two or three of the four radicals R_1, R_2, R_3, and R_4 denote hydrogen.

3) 5-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one;

4) 6-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one;

5) 4-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzimidazol-2-one;

6) 7-Hydroxy-1-{2-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one;

7) 1-{2-[4-(4-Hydroxy-3-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one;

8) 1-{2-[4-(3-Hydroxy-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3 dihydro-benzimidazol-2-one;

9) 1-{2-[4-(2-Hydroxy-5-trifluoromethyl-phenyl)-piperazin-1-yl]-ethyl}-1,3-dihydro-benzimidazol-2-one;

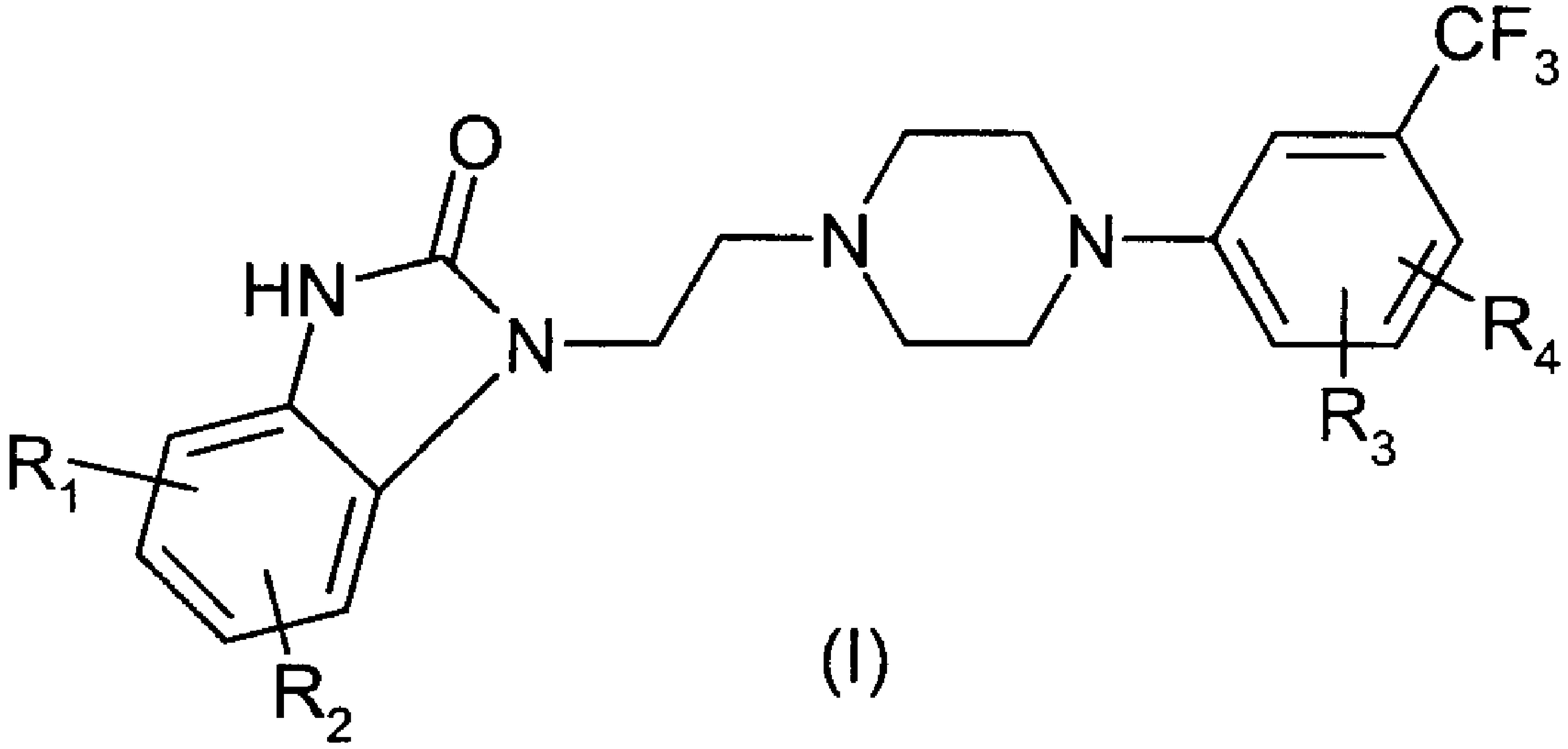
10) Physiologically acceptable acid addition salts of compounds of general formula (I) according to claims 1 to 9.

11) Salts according to claim 10, characterized in that the physiologically acceptable acids are hydrochloric, maleic or fumaric acid.

12) Process for the preparation of compounds of general formula (I) according to one of claims 1 to 9, characterized in that the last reaction step comprises liberation of the hydroxy group or groups by cleavage of the protective group.

13) Process for the preparation of compounds of general formula (I) according to claim 12, characterized in that the protective group is methyl.

14) Process for the preparation of compounds of general formula (I) according to claim 13, characterized in that the deprotection of the hydroxy group is carried out by treatment with strong acqueous acids such as hydrobromic acid at high temperatures or by treatment with boron derivatives, such as BBr_3, at low temperatures in chlorurated solvents.



(I)