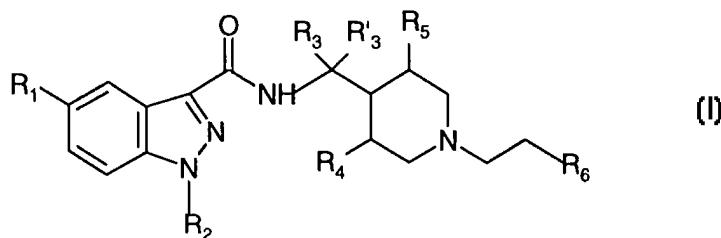


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/00		A2	(11) International Publication Number: WO 98/46589
			(43) International Publication Date: 22 October 1998 (22.10.98)
(21) International Application Number: PCT/EP98/02129			(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 2 April 1998 (02.04.98)			
(30) Priority Data: MI97A000867 15 April 1997 (15.04.97) IT			
(71) Applicant (for all designated States except US): ANGELINI RICERCHE S.P.A. SOCIETA' CONSORTILE [IT/IT]; Piazzale della Stazione, I-00040 S. Palomba (IT).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): ALISI, Alessandra [IT/IT]; Via Nemorense, 188, I-00199 Roma (IT). BRUFANI, Mario [IT/IT]; Via Aldo Moro, 28, I-00040 Castel Gandolfo (IT). CAZZOLLA, Nicola [IT/IT]; Via Virbio, 56, I-00040 Ariccia (IT). GIANNANGELI, Marilena [IT/IT]; Via Clelia, 88, I-00181 Roma (IT). PINZA, Mario [IT/IT]; Via per Cesano Boscone, 24, I-20094 Corsico (IT).			
(74) Agents: MARCHI, Massimo et al.; Marchi & Partners s.r.l., Via Pirelli, 19, I-20124 Milano (IT).			

(54) Title: INDAZOLE AMIDE COMPOUNDS AS SEROTONINERGIC AGENTS



(57) Abstract

A compound having general formula (I) wherein R₁, R₂, R₃, R'₃, R₄, R₅ and R₆ have the meanings stated in the description, acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

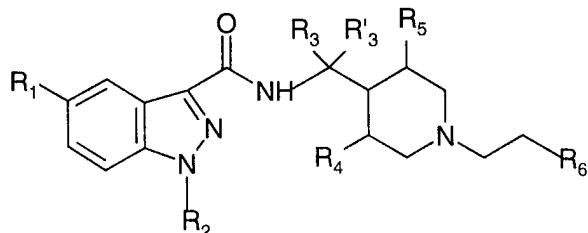
"Indazole amide compounds as serotonergic agents"

The present invention relates to an indazole amide compound possessing a serotonergic action, a method for preparing thereof and 5 the pharmaceutical compositions containing the same.

Amongst the numerous known families of serotonin receptors, the 5HT₄ receptors have only recently been identified in the urinary bladder, smooth and cardiac muscle and specific areas of the central nervous system. Compounds possessing agonistic, partially agonistic and 10 antagonistic actions against such receptors are of potential interest in pharmacological treatment of disorders of gastrointestinal motility, disorders of the central nervous system, urinary incontinence and cardiac arrhythmia. The action of such compounds in fact takes place by mimicking or antagonising the ability of serotonin to stimulate intestinal 15 motility by activation of the enteric neurons, to modulate important cerebral processes such as training, memory and anxiety, to induce relaxation of the urinary bladder and to increase frequency of atrial contraction.

A family of indazole amide compounds has now been found which 20 possess affinity with 5HT₄ receptors and which act as partial agonists or antagonists of serotonin.

It is therefore a first object of the present invention to provide an indazole amide compound having the general formula:



wherein

R₁ is hydrogen;

R₂ is isopropyl;

R₃ and R'₃ are hydrogen;

5 R₄ and R₅ are hydrogen;

R₆ is selected from the group comprising C₁₋₃ alkyl, C₃₋₇ cycloalkyl, heterocyclic ring having from 5 to 6 members where 1 to 4 members are heteroatoms, the same or different from each other, selected from the group comprising N, O and S, dimethylamino C₁₋₃ alkyl, methoxy C₁₋₃ alkyl, N-phenyl amide, aminosulphonylmethyl, dihydroxy C₂₋₃ alkyl, aryl, aryl substituted by at least a group selected from halogen and hydroxy, aryl C₁₋₃ alkyl; acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof.

15

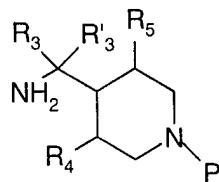
Preferred examples of aryl are phenyl, naphthyl and biphenyl.

Preferred examples of heterocyclic rings are thienyl, furanyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, furazanyl, pyrrolinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, 20 piperidinyl, piperazinyl, morpholinyl, triazinyl, thiazolyl, tetrazolyl and thiadiazolyl. Typical examples of R₆ are cyclopropyl, cyclohexyl, pyridinyl, tetrazolyl, morpholinyl, methoxymethyl, methoxypropyl, phenyl, chlorophenyl, bromophenyl, hydroxyphenyl, phenethyl, dimethylaminomethyl, and aminosulphonylmethyl.

25

It is a second object of the present invention to provide a process for preparing a compound of the formula (I), acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof, comprising:
a) acylating a 4-aminomethyl piperidine of the formula:

- 3 -



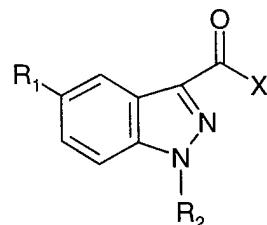
(II)

wherein

R_3 , R'_3 , R_4 and R_5 have the above mentioned meanings, and

5 P is a suitable protecting group;

by means of a 1-alkyl-indazole-3-carboxylic acid halide of the formula:



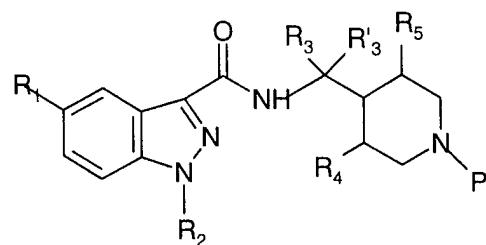
(III)

10 wherein

R_1 and R_2 have the above mentioned meanings, and

X is halogen,

to give a compound of the formula:



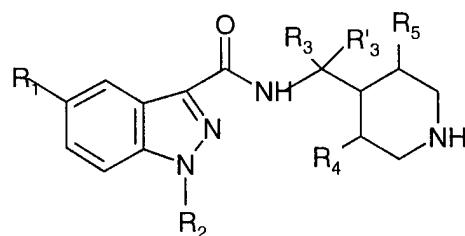
(IV)

wherein

R_1 , R_2 , R_3 , R'_3 , R_4 , R_5 and P have the above mentioned meanings,

b) de-protecting a compound of the formula (IV) to give a compound of
20 the formula:

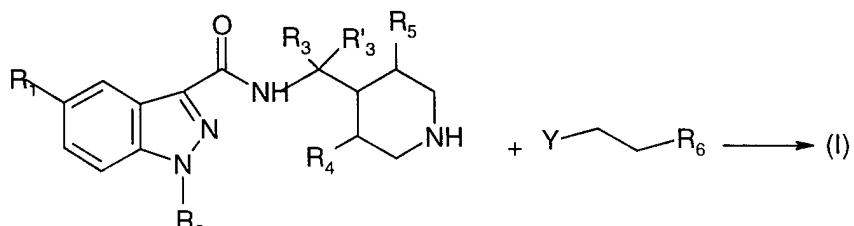
- 4 -



(V)

wherein R₁, R₂, R₃, R'₃, R₄ and R₅ have the above mentioned meanings,

5 c) alkylating a compound of the formula (V) with a compound of the formula (VI) to give a compound of the formula (I) according to the following reaction scheme:



10

(V)

(VI)

wherein

R₁, R₂, R₃, R'₃, R₄, R₅ and R₆ have the above mentioned meanings,
and

Y is halogen,

15 d) optionally forming an acid addition salt of an indazole amide compound of the formula (I) with a pharmaceutically acceptable organic or inorganic acid, or a pharmaceutically acceptable quaternary salt of an indazole amide compound of the formula (I).
Typical examples of protecting groups (P) are benzyloxycarbonyl, benzyl, terbutoxycarbonyl and trimethylsilylethoxycarbonyl.

20 Step a) is preferably carried out by reacting a compound of the formula (II) with a compound of the formula (III) in which X is chlorine, in

- 5 -

the presence of a suitable diluent and at a temperature of from 0 to 140°C for a period of time of from 0.5 to 20 hours.

Preferably the diluent is aprotic, polar or apolar. Still more preferably, it is aprotic apolar. Examples of suitable aprotic apolar diluents are 5 aromatic hydrocarbons such as, for example, benzene, toluene and xylenes. Examples of suitable aprotic polar diluents are dimethylformamide and dimethylsulphoxide.

Still more preferably, the reaction is performed at a temperature of from 15 to 40°C for a period of time of from 1 to 14 hours.

10 In turn, step (b) is carried out according to techniques known to the person skilled in the art of the protecting group (Theodora W. Greene and Peter G.M. Wuts, "Protective groups in organic synthesis", pp. 309-406, John Wiley & Sons, Inc., N.Y., 1991). In the case of benzyl and benzyloxycarbonyl, the deprotection of the protecting group is preferably 15 carried out by catalytic hydrogenation. An example of a suitable catalyst is palladium on activated carbon.

20 Preferably the deprotection is carried out by hydrogenation in the presence of a suitable diluent such as, for example, a low aliphatic alcohol, a low aliphatic acid and mixtures thereof. An example of a preferred diluent is an ethyl alcohol /acetic acid mixture.

25 Step c) is preferably performed with a compound of the formula (VI), in which Y is chlorine or bromine in the presence of a suitable acceptor of acids such as, for example, alkali carbonates and bicarbonates, low trialkylamines and a suitable diluent such as, for example, aromatic hydrocarbons, dimethylformamide and aliphatic low alcohols.

Typical examples of preferred organic and inorganic acids for forming addition salts of the present invention (step d) are oxalic, maleic, tartaric, methanesulphonic, sulphuric, phosphoric acid, hydrogen bromide and hydrogen chloride.

Methyl iodide is a typical example of a preferred compound forming a pharmaceutically acceptable quaternary salt of the invention.

5 The preparation of the above mentioned salts comprises addition (step d) of a pharmaceutically acceptable organic or inorganic acid, or of methyl iodide to an indazole amide compound of the formula (I) obtained in step c).

The intermediates of formula (IV) and (V) are new. They are therefore a further object of the present invention.

10 Alternatively, indazole amide compound of the formula (I) can be prepared by acylation of a suitable 4-aminomethyl piperidine with a compound of the formula (III).

15 Typical examples of pathological conditions which might benefit from treatment with a pharmaceutical composition according to this invention are all the pathologies which are responsive to treatment with antagonists of 5-HT₄ receptor such as, for example, gastrointestinal disorders associated with high intestinal motility, such as IBS (irritable bowel syndrome), urinary incontinence, and cardiac arrhythmias such as atrial fibrillation.

20 Preferably, the pharmaceutical compositions of the present invention will be prepared in suitable dosage forms comprising an effective dose of at least one compound of the formula (I) or a pharmaceutically acceptable addition salt thereof or a quaternary salt thereof and at least one pharmaceutically acceptable inert ingredient.

25 Examples of suitable dosage forms are tablets, capsules, coated tablets, granules, solutions and syrups for oral administration; creams, ointments and medicated adhesive strips for topical administration; suppositories for rectal administration and sterile solutions for injectable, aerosol or ophthalmic administration.

30 The dosage forms may also contain other conventional ingredients such as stabilizing agents, preservatives, surfactants, buffers, salts for

- 7 -

adjusting the osmotic pressure, emulsifiers, sweeteners, coloring agents, flavoring agents, and the like.

When required by particular therapies, the pharmaceutical composition of the present invention may contain other 5 pharmacologically active ingredients whose concomitant administration is therapeutically useful.

The amount of the compound of formula (I) or of a pharmaceutically acceptable salt thereof may vary within a wide range depending on known factors such as, for example, the type of disease to be treated, the 10 severity of the disease, the patient's body weight, the dosage form, the chosen route of administration, the number of dosage forms administered per day and the effectiveness of the chosen compound of formula (I). However, the optimum amount may be easily and routinely determined by a person skilled in the art.

15 Typically, the amount of the compound of formula (I) or of a salt thereof in the pharmaceutical composition of this invention will be such as to insure an administered dosage level of from 0.001 to 50 mg/kg/day.

The dosage forms of the pharmaceutical composition according to this invention may be prepared according to methods which are known to the 20 pharmaceutical chemist and comprise mixing, granulation, compression, dissolution, sterilization, and the like.

The following Examples are intended to illustrate the present invention, without limiting it in any way.

EXAMPLE 1

25 Preparation of 1-isopropyl-1H-3-indazolecarbonyl chloride

(III: R₁ = H, R₂ = C₃H₇)

a) 2-methylpropyl-1-isopropyl-1H-3-indazolecarboxylate

To a solution of 2-methylpropyl-1H-3-indazolecarboxylate (50 g; 0.24 moles) in 1,2-dimethoxy-ethane (300 ml) a solution of isopropyl bromide (27.5 ml; 0.29 moles) in 1,2-dimethoxy-ethane (100 ml) and 30

- 8 -

KOH (13.5 g; 0.24 moles) was added and the mixture was heated under reflux for 8 hours. After removal of the solvent, the residue was dissolved in toluene (300 ml), the thus obtained solution was washed with 1N NaOH (100 ml), H₂O (2x100 ml) and then dried and 5 concentrated *in vacuum*. The residue was purified from the isomer 2-methylpropyl-2-isopropyl-2H-3-indazolecarboxylate via flash chromatography (eluent, hexane : ethyl acetate = 95:5) to give the title compound (23 g) as an oil.

10 ¹H NMR (CDCl₃, δ): 1.07 (d, J=7Hz, 6H); 1.66 (d, J=7Hz, 6H); 1.95-2.48 (m, 1H); 4.26 (d, J=7Hz, 2H); 4.96 (hept. J=7Hz, 1H); 7.15-7.70 (m, 3H); 8.03-8.33 (m, 1H).

15 b) 1-isopropyl-1H-3-indazolecarboxylic acid

A suspension of the compound of the Example 1a) (10 g; 0.04 moles) in 0.75N NaOH (100 ml) was heated under reflux for 12 hours. The 15 solution was then cooled, acidified with 6N HCl (40 ml), the solid precipitate was filtered and recrystallized from 1:1 hexane/ethyl acetate to give the title compound (5.5 g), m.p. 162-3° C (Harada H. et al., "Chem. Pharm. Bull.", 43(11), 1912-1930, 1995).

20 ¹H NMR (DMSO, δ); 1.54 (d, J=7Hz, 6H); 5.13 (hept, J=7Hz, 1H); 7.20-7.65 (m, 2H); 7.85 (d, J=8Hz, 1H); 8.14 (d, J=7Hz, 1H); 13.08 (s broad, 1H).

25 c) 1-isopropyl-1H-3-indazolecarbonyl chloride

Thionyl chloride (4 ml, 0.054 moles) was added to a stirred solution of the compound of the Example 1b) and the mixture was stirred under reflux for 2 hours. After removal of the solvent *in vacuum*, the residue was recrystallized from hexane to give 3.5 g of the title compound, m.p. 63-4° C.

- 9 -

Elemental analysis for	C	H	N
C ₁₁ H ₁₁ CIN ₂ O			
% found:	59.29	5.20	12.76
% calculated:	59.33	4.98	12.58

¹H NMR (CDCl₃, δ): 1.69 (d, J=7Hz, 6H); 5.00 (hept., J=7Hz, 1H); 7.20-7.70 (m, 3H); 8.03-8.33 (m, 1H).

EXAMPLE 2

Preparation of N3-{{1-(2-phenylethyl)-4-piperidinyl}methyl}-1-isopropyl-

1H-3-indazolecarboxamide hydrochloride (AFR 306)

(I: R₁ = R₃ = R'₃ = R₄ = R₅ = H, R₂ = C₃H₇, R₆ = C₆H₅)

[1-(2-phenylethyl)-1-piperidinyl]methylamine (3 g; 0.014 moles), prepared as described in EP-A-0 343 307, in toluene (30 ml) was dropped into a suspension of the compound of the Example 1c) (3 g, 0.014 moles) in toluene (30 ml). After 3 hours at room temperature, the solid was filtered, dissolved in H₂O, made basic with 6N NaOH solution and extracted with CH₂Cl₂ (2x200 ml). The solvent was removed by evaporation, the residue was purified on SiO₂ column (eluent, CHCl₃ : MeOH = 95 : 5) and transformed into the corresponding hydrochloride. The obtained product (2 g) melted at 211-212° C.

Elemental analysis for C H N Cl⁻

C₂₅H₃₃CIN₄O

% found:	68.13	7.52	12.78	8.03
% calculated:	68.09	7.54	12.70	8.04

¹H NMR (DMSO, δ): 1.56 (d, J=7Hz, 6H); 1.50-2.30 (m, 5H); 2.70-3.90 (m, 10H); 5.10 (hept, J=7Hz, 1H); 7.05-7.63 (m, 7H); 7.81 (d, J=8Hz, 1H); 8.21 (d, J=8Hz, 1H); 8.47 (t, J=6Hz, 1H); 11.05 (s broad, 1H).

IR (KBr): ν_{co} 1652cm⁻¹.

EXAMPLE 3

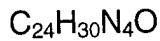
Preparation of N3-{{1-(phenylmethyl)-4-piperidinyl}methyl}-1-isopropyl-1H-3-indazolecarboxamide

- 10 -

(IV: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $P = -CH_2C_6H_5$)

To a stirred solution of 1-isopropyl-1H-3-indazolecarbonyl chloride (52 g; 0.234 moles) in toluene (300 ml) it was added dropwise a solution of [1-(phenylmethyl)-4-piperidinyl]methylamine, prepared as described in 5 WO 94/10174, (47.7 g; 0.234 moles) in toluene (200 ml). After 5 hours, the solvent was removed by evaporation under reduced pressure. The reaction mixture was treated with 2N NaOH, extracted with dichloromethane and concentrated *in vacuum*. The solid residue (95 g) was recrystallized from 7:3 hexane/ethyl acetate to afford the title 10 compound as a white solid (45 g), m.p. 72-74° C.

Elemental analysis for C H N



% found:	73.78	7.87	14.35
% calculated:	73.81	7.74	14.35

¹H NMR (CDCl₃, δ): 1.59 (d, J=7Hz, 6H); 1.10-2.25 (m, 7H); 2.80-3.15 (m, 2H); 3.27-3.60 (m, 4H); 4.86 (hept, J=7Hz, 1H); 7.00-7.60(m, 9H); 8.27-8.52(m, 1H).

IR (KBr): ν_{co} 1641cm⁻¹.

15

EXAMPLE 4

Preparation of N3-(4-piperidinylmethyl)-1-isopropyl-1H-3-indazolecarboxamide hydrochloride

(V: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$)

A suspension of the product of the Example 3 (28 g; 0.076 moles) in 20 ethyl alcohol (1500 ml) and glacial acetic acid (66 ml) was hydrogenated over 10% Pd-C (13.4 g) at 35 psi for 24 hours. The mixture was filtered and the filtrate concentrated *in vacuum*. The residue was dissolved in water, treated with 5N NaOH and stirred for 2 hours at room temperature. The solid obtained was filtered off (16.6 g) and converted to the 25 corresponding hydrochloride (9.5 g), m.p. 211-214° C (dec.)

- 11 -

Elemental analysis for	C	H	N
$C_{17}H_{25}ClN_4O \cdot 1/2H_2O$			
% found:	58.82	7.68	16.36
% calculated:	59.03	7.58	16.20

1H NMR (DMSO, δ): 1.55 (d, $J=7$ Hz, 6H); 1.31-2.18 (m, 5H); 2.58-3.64 (m, 7H); 5.09 (hept, $J=7$ Hz, 1H); 7.12-7.60 (m, 2H); 7.80 (d, $J=8$ Hz, 1H); 8.20 (d, $J=8$ Hz, 1H); 8.41 (t, $J=6$ Hz, 1H); 8.82-9.60 (m, 2H).
IR (KBr): ν_{co} 1658 cm^{-1} .

5

EXAMPLE 5

Preparation of N3-{[1-(4-phenylbutyl)-4-piperidinyl]methyl}-1-isopropyl-1H-3-indazolecarboxamide oxalate (AFR603)

(I: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $R_6 = -CH_2CH_2C_6H_5$)

To a stirred suspension of the product of Example 4 as free base (5.27 g; 15.6 mmoles) in ethyl alcohol (20 ml), K_2CO_3 (6.5 g; 50 mmoles) and 4-phenylbromobutane ("Braun", B-44, 2872, 1911) (3.6 g, 17.1 mmoles) were added. The reaction mixture was stirred at reflux for 10 hours. After removal of the solvent, the residue was partitioned between ethyl acetate and 1N HCl. The water phase was made basic with 2N NaOH, extracted with ethyl acetate and concentrated *in vacuum*. The solid was converted to the corresponding oxalate salt (2 g), m.p. 154-155° C.

15

Elemental analysis for

$C_{29}H_{38}N_4O_5 \cdot 1/2H_2O$

	C	H	N
% found:	65.87	7.47	10.62
% calculated:	65.52	7.39	10.54

20

1H NMR (DMSO, δ): 1.55 (d, $J=7$ Hz, 6H); 1.31-2.18 (m, 5H); 2.30-3.64 (m, 14H); 5.08 (hept, $J=7$ Hz, 1H); 7.12-7.60 (m, 7H); 7.80 (d, $J=8$ Hz, 1H); 8.19 (d, $J=8$ Hz, 1H); 8.41 (t, $J=6$ Hz, 1H).

- 12 -

EXAMPLE 6

Preparation of N3-[(1-(2-cyclohexylethyl)-4-piperidinyl)methyl]-1-isopropyl-1H-3-indazolecarboxamide hydrochloride (AFR604)

(I: R₁ = R₃ = R'₃ = R₄ = R₅ = H, R₂ = C₃H₇, R₆ = C₆H₁₁)

5 Following the procedure of Example 5, N3-(4-piperidinylmethyl)-1-isopropyl-1H-3-indazolecarboxamide (4.42 g) and (2-bromoethyl)-cyclohexane ("J.A.C.S.", 48, 1089-1093, 1926) (4.63 g) gave the title compound (2.5 g), m.p. 244-246° C (dec.)

Elemental analysis for	C	H	N	Cl ⁻
C ₂₅ H ₃₉ N ₄ O.1/2 H ₂ O				
% found:	65.51	9.05	12.57	7.89
% calculated:	65.83	8.84	12.28	7.77

10 ¹H NMR (DMSO, δ): 1.55 (d, J=7Hz, 6H); 0.68-2.18 (m, 17H); 2.63-3.70 (m, 10H); 5.09 (hept, J=7Hz, 1H); 7.12-7.60 (m, 2H); 7.80 (d, J=8Hz, 1H); 8.20 (d, J=8Hz, 1H); 8.41 (t, J=6Hz, 1H); 10.70 (s broad 1H).
IR (KBr): ν_{co} 1656 cm⁻¹.

EXAMPLE 7

Preparation of N3-[(1-[3-(dimethylamino)propyl]-4-piperidinyl)methyl]-1-isopropyl-1H-3-indazolecarboxamide dimaleate (AFR606)

(I: R₁ = R₃ = R'₃ = R₄ = R₅ = H, R₂ = C₃H₇, R₆ = -CH₂NC₂H₆)

15 Following the procedure of Example 5, N3-(4-piperidinylmethyl)-1-isopropyl-1H-3-indazolecarboxamide (3 g) and N-(3-chloropropyl)-N,N-dimethylamine hydrochloride (580 mg) gave the title compound (950 mg), m.p. 155-156° C.

Elemental analysis for	C	H	N
C ₃₀ H ₄₃ N ₅ O ₉ .1/2H ₂ O			
% found:	57.83	7.01	11.11
% calculated:	57.50	7.08	11.18

- 13 -

¹H NMR (DMSO, δ): 1.55 (d, $J=7$ Hz, 6H); 1.68-2.28 (m, 7H); 2.81 (s, 6H); 2.75-3.75 (m, 11H); 5.09 (hept, $J=7$ Hz, 1H); 6.09 (s, 4H); 7.12-7.60 (m, 2H); 7.81 (d, $J=8$ Hz, 1H); 8.20 (d, $J=8$ Hz, 1H); 8.45 (t, $J=6$ Hz, 1H).

EXAMPLE 8

5 Preparation of N3-({1-[2-(4-morpholinyl)ethyl]-4-piperidinyl}methyl)-1-isopropyl-1H-3-indazolecarboxamide dihydrochloride (AFR607)

(I: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $R_6 = C_4H_4NO$)

10 Following the procedure of Example 5, N3-(4-piperidinylmethyl)-1-isopropyl-1H-3-indazolecarboxamide (3 g) and 4-(2-chloroethyl)-morpholine (3.42 g) gave the title compound (3.2 g), m.p. 266-267° C (dec.)

Elemental analysis for	C	H	N	Cl ⁻
$C_{23}H_{37}Cl_2N_5O_2 \cdot 1/2 H_2O$				
% found:	55.74	7.61	13.96	14.12
% calculated:	55.75	7.73	14.13	14.31

15 ¹H NMR (DMSO, δ): 1.55 (d, $J=7$ Hz, 6H); 1.30-2.25 (m, 5H); 2.75-4.30 (m, 19H); 5.09 (hept, $J=7$ Hz, 1H); 7.12-7.60 (m, 2H); 7.81 (d, $J=8$ Hz, 1H); 8.20 (d, $J=8$ Hz, 1H); 8.45 (t, $J=6$ Hz, 1H); 10.80 (s broad, 1H); 10.60 (s broad, 1H).

IR (KBr): ν_{co} 1652 cm⁻¹.

EXAMPLE 9

20 Preparation of N3-[(1-{2-[(methylsulphonyl)amino]ethyl}4-piperidinyl)methyl]-1-isopropyl-1H-3-indazolecarboxamide hydrochloride (AFR703)

(I: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $R_6 = CH_3SO_2NH-$)

25 Following the procedure of Example 5, N3-(4-piperidinylmethyl)-1-isopropyl-1H-3-indazolecarboxamide (5 g) N-(2-bromoethyl)-methane sulphonamide (WO 93/18036) (3 g) gave the title compound (1.5 g), m.p. 186-187° C (dec.)

- 14 -

Elemental analysis for	C	H	N	S	Cl ⁻
C ₂₀ H ₃₂ ClN ₅ O ₃ S					
% found:	52.15	7.22	15.30	6.98	7.77
% calculated:	52.45	7.04	15.29	7.00	7.74
¹ H NMR (DMSO, δ); 1.55 (d, J=7Hz, 6H); 1.40-2.30 (m, 5H); 3.00 (s, 3H); 2.75-3.80 (m, 10H); 5.09 (hept, J=7Hz, 1H); 7.12-7.70 (m, 3H); 7.80 (d, J=8Hz, 1H); 8.20 (d, J=8Hz, 1H); 8.45 (t, J=6Hz, 1H); 10.73 (s broad, 1H).					
5 IR (KBr): ν_{co} 1651cm ⁻¹ .					

EXAMPLE 10

Preparation of N3-(1-[2-(2-pyridinyl)ethyl] 4-piperidinyl)methyl)-1-isopropyl-1H-3-indazolecarboxamide hydrochloride (AFR605)

(I: R₁ = R₃ = R'₃ = R₄ = R₅ = H, R₂ = C₃H₇, R₆ = C₅H₄N)

10 To a stirred suspension of the product of Example 4 as free base (10 g; 33.3 mmoles), 2-vinylpyridine (3.6 g; 34 mmoles), glacial acetic acid (2 ml) and water (2.5 ml) were added. After 16 hours at 95° C, the reaction mixture was made basic with 2N NaOH, extracted with ethyl acetate and concentrated *in vacuum*. The residue was purified by flash silica-gel chromatography with CHCl₃:MeOH = 97 : 3 as eluent to yield a solid which was converted to hydrochloride salt (5 g), m.p. 122-123° C (dec.)

15

Elemental analysis for	C	H	N	Cl ⁻
C ₂₄ H ₃₂ ClN ₅ O.H ₂ O				
% found:	62.80	7.42	15.18	7.78
% calculated:	62.66	7.45	15.22	7.71
¹ H NMR (DMSO, δ); 1.55 (d, J=7Hz, 6H); 1.68-2.30 (m, 5H); 2.80-3.78 (m, 12H); 5.10 (hept, J=7Hz, 1H); 7.12-7.60 (m, 4H); 7.68-8.00 (m, 2H); 8.21 (d, J=7Hz, 1H); 8.33-8.70 (m, 2H); 11.05 (s broad, 1H).				
20 IR (KBr): ν_{co} 1644 cm ⁻¹ .				

TEST 1

Antagonistic Action on 5-HT₄ Receptor

- 15 -

The antagonistic action of the compounds of the formula (I) was evaluated by testing the influence of the compound under evaluation on serotonin-induced relaxation of rat oesophageal tunica pre-contracted with carbachol according to the method described by J.D. Gale et al. in 5 "Br. J. Pharmacol.", 111, 332-338, (1994).

All the tested compounds of the invention showed a $pA_2 > 8$. The specific values for AFR 603, AFR 604, AFR 605 and AFR 306 are shown Table 1 below.

Table 1

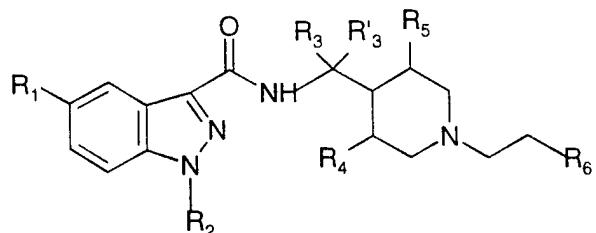
Compound	pA_2	s.e.
AFR 603	9.12	1.42
AFR 604	8.19	0.99
AFR 605	10.8	1.90
AFR 306	9.36	0.38

10 s.e. = standard error

- 16 -

CLAIMS

1. A compound having the general formula



(I)

5

wherein:

R₁ is hydrogen;

R₂ is isopropyl;

R₃ and R'₃ are hydrogen;

R₄ and R₅ are hydrogen;

10 R₆ is selected from the group comprising C₁₋₃ alkyl, C₃₋₇ cycloalkyl,

heterocyclic ring having from 5 to 6 members where 1 to 4
members are heteroatoms, the same or different from each
other, selected from the group comprising N, O and S,

dimethylamino C₁₋₃ alkyl, methoxy C₁₋₃ alkyl, N-phenyl amide,

15 aminosulphonylmethyl, dihydroxy C₂₋₃ alkyl, aryl, aryl substituted
by at least a group selected from halogen and hydroxy, aryl C₁₋₃
alkyl;

acid addition salts thereof with pharmaceutically acceptable organic
and inorganic acids and pharmaceutically acceptable quaternary
salts thereof.

20

2. A compound according to claim 1, characterized in that aryl is selected from the group comprising phenyl, naphthyl and biphenyl.
3. A compound according to claim 1, characterized in that heterocyclic rings are thieryl, furanyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, furazanyl,

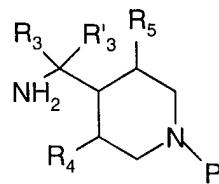
25

- 17 -

pyrrolinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, morpholinyl, triazinyl, thiazolyl, tetrazolyl and thiadiazolyl.

4. A compound according to claim 1, characterized in that R₆ is selected from the group comprising cyclopropyl, cyclohexyl, pyridinyl, tetrazolyl, morpholinyl, methoxymethyl, methoxypropyl, phenyl, chlorophenyl, bromophenyl, hydroxyphenyl, phenethyl, dimethylaminomethyl, and aminosulphonylmethyl.
5. A compound according to claim 1, characterized in that R₁, R₃, R'₃, R₄ and R₅ are hydrogen, R₂ is isopropyl and R₆ is phenyl.
10. A compound according to claim 1, characterized in that R₁, R₃, R'₃, R₄ and R₅ are hydrogen, R₂ is isopropyl and R₆ is phenethyl.
7. A compound according to claim 1, characterized in that R₁, R₃, R'₃, R₄ and R₅ are hydrogen, R₂ is isopropyl and R₆ is cyclohexyl.
8. A compound according to claim 1, characterized in that R₁, R₃, R'₃, R₄ and R₅ are hydrogen, R₂ is isopropyl and R₆ is pyridinyl.
15. A compound according to claim 1, characterized in that R₁, R₃, R'₃, R₄ and R₅ are hydrogen, R₂ is isopropyl and R₆ is dimethylaminomethyl.
10. A compound according to claim 1, characterized in that R₁, R₃, R'₃, R₄ and R₅ are hydrogen, R₂ is isopropyl and R₆ is morpholinyl.
20. A compound according to claim 1, characterized in that R₁, R₃, R'₃, R₄ and R₅ are hydrogen, R₂ is isopropyl and R₆ is aminosulphonylmethyl.
11. A process for preparing a compound of the formula (I), acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof, comprising:
 - a) acylating a 4-aminomethyl piperidine of the formula:

- 18 -



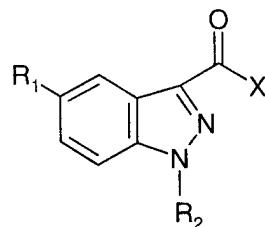
(II)

wherein

R_3 , R'_3 , R_4 and R_5 have the above mentioned meanings, and

5 P is a suitable protecting group;

by means of a 1-alkyl-indazole-3-carboxylic acid halide of the formula:



(III)

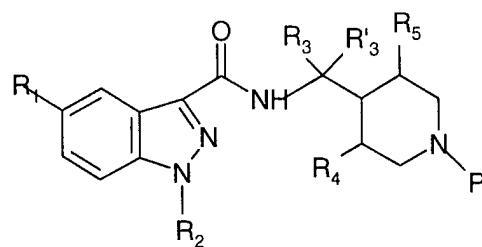
10

wherein

R_1 and R_2 have the above mentioned meanings, and

X is halogen,

to give a compound of the formula:



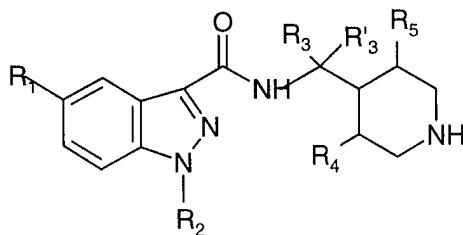
(IV)

wherein

R_1 , R_2 , R_3 , R'_3 , R_4 , R_5 and P have the above mentioned meanings,

b) de-protecting a compound of the formula (IV) to give a compound
20 of the formula:

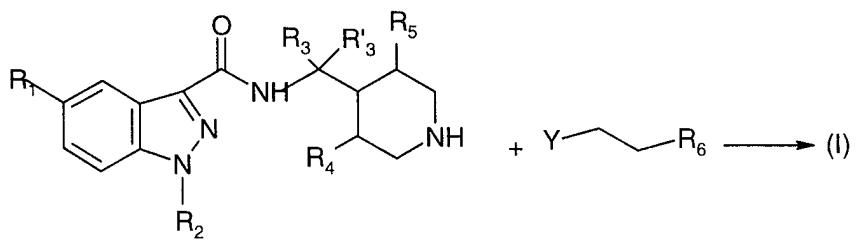
- 19 -



(V)

wherein R₁, R₂, R₃, R'₃, R₄ and R₅ have the above mentioned meanings,

5 c) alkylating a compound of the formula (V) with a compound of the formula (VI) to give a compound of the formula (I) according to the following reaction scheme:



10

(V)

(VI)

wherein

R₁, R₂, R₃, R'₃, R₄, R₅ and R₆ have the above mentioned meanings, and

Y is halogen,

15 d) optionally forming an acid addition salt of an indazole amide compound of the formula (I) with a pharmaceutically acceptable organic or inorganic acid, or a pharmaceutically acceptable quaternary salt of an indazole amide compound of the formula (I).

13. A process according to claim 12, characterized in that P is selected from the group comprising benzyloxycarbonyl, benzyl, terbutoxycarbonyl, trimethylsilylethoxycarbonyl.

20 14. A process according to claims 12 or 13, characterized in that step a) is carried out by reacting a compound of the formula (II) with a

- 20 -

compound of the formula (III) in which X is chlorine, in the presence of a diluent and at a temperature of from 0 to 140°C for a period of time of from 0.5 to 20 hours.

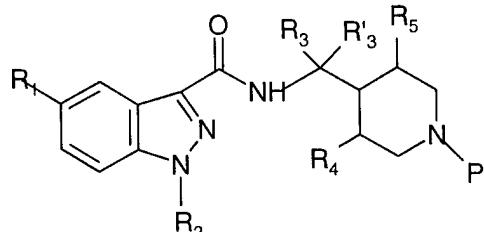
15. A process according to claim 13, characterized in that when P is
5 benzyl or benzyloxycarbonyl, step b) is carried out by catalytic
hydrogenation.

16. A process according to any of the preceding claims from 12 to 14,
characterized in that when, in a compound of the formula (VI), Y is
10 chlorine or bromine, step c) is performed in the presence of an
acceptor of acids and in the presence of a diluent.

17. A process according to claim 12, characterized in that methyl iodide
forms a pharmaceutically acceptable quaternary salt of a compound
of formula (I), step d).

18. An intermediate compound having the general formula:

15



(IV)

wherein

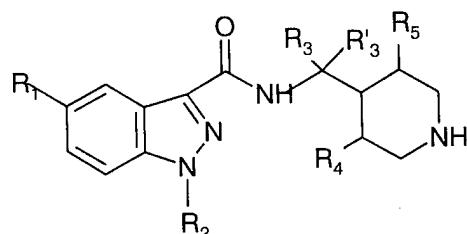
20 R₁ is hydrogen;
R₂ is isopropyl;
R₃ and R'₃ are hydrogen;
R₄ and R₅ are hydrogen; and
P is a protecting group.

19. A compound according to claim 18, characterized in that P is
25 selected from the group comprising benzyloxycarbonyl, benzyl,
terbutoxycarbonyl, trimethylsilylethoxycarbonyl.

- 21 -

20. A compound according to claim 18, characterized in that R₁, R₃, R'₃, R₄ and R₅ are hydrogen, R₂ is isopropyl and P is benzyl.

21. An intermediate compound having the general formula:



5

(V)

wherein

R₁ is hydrogen;

R₂ is isopropyl;

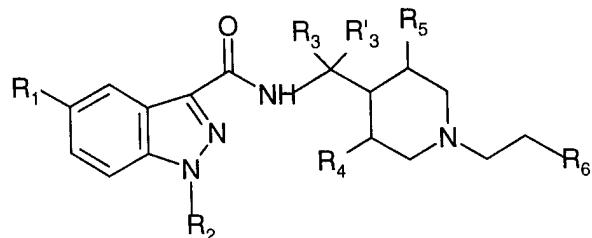
10 R₃ and R'₃ are hydrogen;

R₄ and R₅ are hydrogen.

22. A compound according to claim 17, characterized in that R₁, R₃, R'₃, R₄ and R₅ are hydrogen and R₂ is isopropyl.

23. A pharmaceutical composition, characterized in that the said

15 composition comprises an effective dose of at least one compound of the formula:



(I)

20 wherein

R₁ is hydrogen;

- 22 -

R₂ is isopropyl;
R₃ and R'₃ are hydrogen;
R₄ and R₅ are hydrogen;
R₆ is selected from the group comprising C₁₋₃ alkyl, C₃₋₇ cycloalkyl,
5 heterocyclic ring having from 5 to 6 members where 1 to 3
members are heteroatoms, the same or different from each
other, selected from the group comprising N, O and S,
dimethylamino C₁₋₃ alkyl, methoxy C₁₋₃ alkyl, N-phenyl amide,
aminosulphonylmethyl, dihydroxy C₂₋₃ alkyl, aryl, aryl substituted
10 by at least a group selected from halogen and hydroxy, aryl C₁₋₃
alkyl;
acid addition salts thereof with pharmaceutically acceptable organic
and inorganic acids and pharmaceutically acceptable quaternary
salts thereof.