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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 413/14, A61K 31/465	A1	(11) International Publication Number: WO 99/35144
		(43) International Publication Date: 15 July 1999 (15.07.99)

(21) International Application Number: PCT/EP98/08497

(22) International Filing Date: 29 December 1998 (29.12.98)

(30) Priority Data:
9702718 30 December 1997 (30.12.97) ES

(71) Applicant *(for all designated States except US)*: FERRER INTERNACIONAL, S.A. [ES/ES]; Gran Via Carlos III, 94, E–08028 Barcelona (ES).

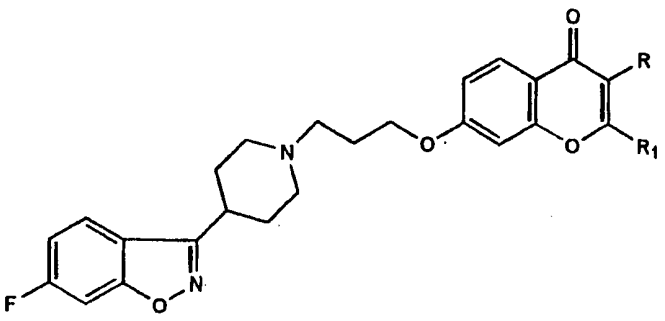
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: FOGUET, Rafael [ES/ES]; Lluçanès, 8, E–08022 Barcelona (ES). BOLOS, Jordi [ES/ES]; Avenida Josep Tarradellas, 35, E–08029 Barcelona (ES). SACRISTAN, Aurelio [ES/ES]; Santa Amèlia, 2, E–08034 Barcelona (ES). CASTELLO, Josep, M. [ES/ES]; Príncep d'Asturies, 35, E–08012 Barcelona (ES). ORTIZ, José, A. [ES/ES]; Còrsega, 429, E–08037 Barcelona (ES).

(74) Agents: KINZEBACH, Werner Reitstötter, Kinzebach & Partner et al.; Postfach 86 06 49, D–81633 München (DE).

(81) Designated States: AU, BR, CA, CZ, IL, JP, KR, MX, NO, NZ, PL, RO, RU, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 7–[(PIPERIDIN–1–YL)–PROPOXY]–CHROMEN–4–ONE DERIVATIVES, THEIR PREPARATION AND THEIR PHARMACEUTICAL USE



(I)

(57) Abstract

7–[3–[4–(6–Fluorobenzo[d]isoxazol–3–yl)piperidin–1–yl]propoxy]–chromen–4–one derivatives having formula (I) wherein R is hydrogen, CHO, CH_2OR_2 or COOH; R_1 is hydrogen or CH_2OH; and R_2 is alkyl having 1 to 4 carbon atoms with the proviso that one of substituents R and R_1 should be hydrogen, as well as their pharmaceutically acceptable salts. The process for their preparation and the pharmaceutical compositions containing them are also described. The compounds are new and are useful in the treatment of psychosis, schizophrenia and allergy.

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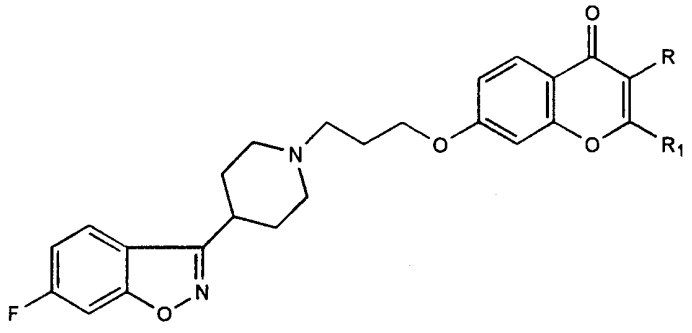
7-[(PIPERIDIN-1-YL)-PROPOXY]-CHROMEN-4-ONE DERIVATIVES, THEIR PREPARATION AND THEIR PHARMACEUTICAL USE

The present invention relates to 7-[3-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]propoxy]-chromen-4-one derivatives having the general formula (I):



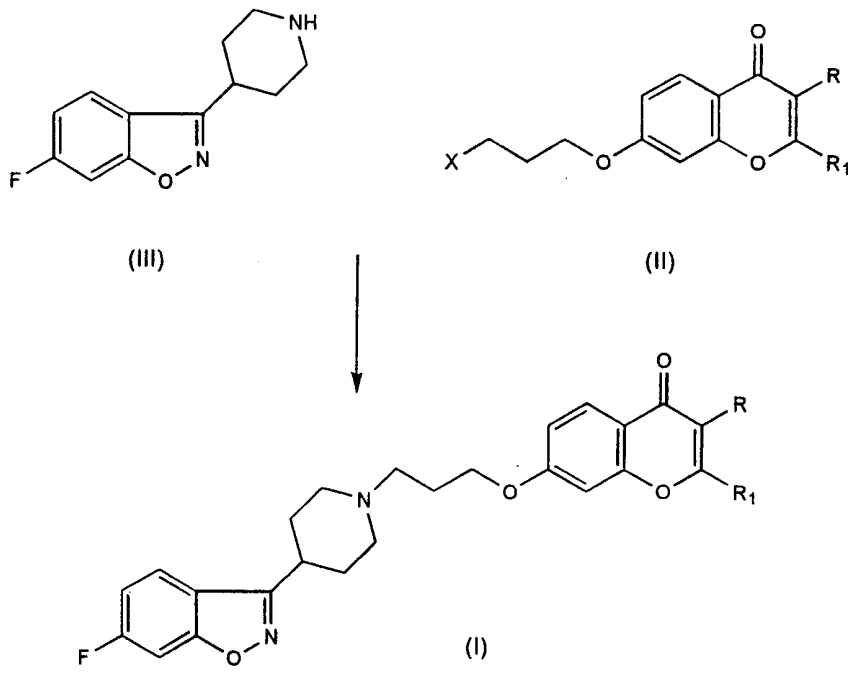
(I)

wherein R is hydrogen, CHO, CH_2OR_2 or COOH; R_1 is hydrogen or CH_2OH; and R_2 is alkyl having 1 to 4 carbon atoms with the proviso that one of substituents R and R_1 should be hydrogen, as well as their pharmaceutically acceptable addition salts.

The compoounds of the present invention are new and are obtained by reacting 2 (or 3)-substituted 7-(3-halopropoxy)-4H-1-benzopyran-4-one of general formula (II), wherein R and R_1 is as defined for (I) and X is a halogen selected

preferably between chlorine or bromine, with 6-fluoro-3-(4-piperidinyl)-benzo[d]isoxazole (III), according to Scheme 1, in the presence of a base selected between an alkali or earth-alkali metal carbonate or bicarbonate and a catalytic quantity of potassium iodide. The reaction occurs conveniently under heating and in a nonpolar medium, such as that composed of a solvent selected from N,N-dimethyl-formamide, acetonitrile or the like.

Scheme 1



Alternatively, the compounds (I, R:CHO, R_1:H) and (I, R:CH_2OR_2, R_1:H) can also be obtained from 7-[3-[4-(6-fluoro-benzo[d]isoxazole-3-yl)piperidin-1-yl]propoxy]-3-(hydroxymethyl)-chromen-4-one (Spanish Patent Application No. 9600323) by oxidation or by alkylation, respectively. The oxidation is conducted conveniently with oxalyl chloride and

dimethyl sulfoxide in a halogenated solvent, preferably dichloromethane. The alkylation is conducted conveniently with the corresponding alcohol R_2-OH (IV), wherein R_2 is as defined for (I), in an acid medium and at the boiling temperature of the mixture. From the new compounds of general formula (I), their salts may be obtained by adding respective acids according to conventional methods of Organic Chemistry.

Spanish Patent Applications No. 9500737 and 9600323 describe chromene derivatives with neuroleptic and anxiolytic action.

The properties of the compounds of the present invention are different from those of the compounds disclosed in the aforesaid patents. In fact, the applicants have found out that the compounds of the general formula (I) exhibit, in addition to a potent action on D_2 and 5-HT_{2A} receptors which is of their own as antipsychotic agents, an important action on histamine H_1 receptors. In contrast, a H_1-antihistamic action has not been previously reported for any of the compounds of the preceding patents.

D_2 receptors: A 2-nM solution of radioactive spiperone ([^{3}H]spiperone), which acts as a specific ligand, was incubated with the membrane corresponding to 20 mg of rat striatum for 20 min at 35°C buffered at pH 7.4 with Tris.HCl. The non-specific binding was then determined by addition of a micromolar concentration of unlabelled spiperone. IC_{50} (inhibitory concentration 50%) was calculated from the

inhibition rate of the specific binding obtained by addition of eleven different concentrations of the compounds to be tested. After the incubation was completed, the sample was filtered through a glass fiber filter and then washed three times with Tris.HCl buffer. The amount of receptor-bound radioactivity was retained on the membrane and determined by liquid scintillation counting.

5-HT_{2A} receptors: A 0.5 nM solution of radioactive ketanserin ([^{3}H]ketanserin, which acts as a specific ligand, was incubated with the membrane corresponding to 1 mg of rat cortex for 30 min at 35°C buffered at pH 7.4 with Tris.HCl. Non-specific binding was then determined by addition of 5 micromolar concentration of unlabelled mianserin. IC_{50} (inhibitory concentration 50%) was calculated from the inhibition rate of the specific binding obtained by addition of eleven different concentrations of the compounds to be tested. After the incubation was completed, the sample was filtered through a glass fiber filter and then washed three times with Tris.HCl buffer. The amount of receptor-bound radioactivity was retained on the membrane and determined by liquid scintillation counting.

H_1 receptors: Testing for activity was performed by incubation of guinea-pig cerebellum membranes, in the presence or absence of test compounds, in a 1 nM solution of [^{3}H]-pyrilamine as a specific marker at 25°C for 60 minutes. The bound radioactivity was separated by filtration (Whatman

GF/B) in a Brandel Harvester. The amount of receptor-bound radioactivity present in the filters was determined using a Packard 1800TR counter. The specific binding was established with a 1 μM concentration of tripolidine.

The biochemical results expressed as IC_{50} in molar concentrations are presented comparatively to the compound of Example 2' in Spanish Patent Application No. 9600323 and to standard haloperidol in Table 1 for D_2 and 5-HT_{2A} receptors, and comparatively to the compound of Example 2' in Spanish Patent Application No. 9600323 and to standard promethazine in Table 2 for H_1 receptors.

Table 1

Compound	D_2	5-HT_{2A}
Example 1	1.31×10^{-8}	2.11×10^{-9}
Example 2	1.28×10^{-8}	5.94×10^{-10}
Ex. 2' (ES 9600323)	1.72×10^{-8}	3.08×10^{-9}
Haloperidol	1.37×10^{-8}	1.04×10^{-7}

From the data of Table 1 it can be concluded that the compounds of Examples 1 and 2 of the present invention are more potent as ligands of D_2 and 5-HT_{2A} receptors than the compound of Example 2' of Spanish Patent Application No. 9600323. The ratio D_2/5-HT_{2A} shows that all the compounds are superior to standard haloperidol, which results in a lower risk of extrapyramidal effects.

Table 2

Compound	H_1
Example 3	3.39×10^{-10}
Example 6	1.01×10^{-9}
Ex. 2' (ES 9600323)	1.20×10^{-9}
Promethazine	8.93×10^{-10}

Similarly, from the data of Table 2 it can be concluded that the compounds of Examples 3 and 6 of the present invention are more potent as ligands of H_1 receptors than the compounds of Example 2' in the Spanish Patent Application No. 9600323 and of the same order as promethazine. In addition, the potency of the compound of Example 1 is greater than that of standard promethazine.

The compounds of the present invention were compared with the compound of Example 2' of Spanish Patent Application No. 9600323 in Animal Pharmacology by the inhibition test of apomorphine-induced climbing behaviour (P.Protais et al: "Psychopharmacology", 50, 1-6, 1976). For the practical performance of this experiment, male Swiss mice weighing 22-24 g were used. One week prior to experiment, animals were kept in our facilities at a temperature of 20-22°C and 12/12 h light-dark cycle, and had free access to food and water. Two hours prior to experiment, the animals were placed in individual cages without access to food.

Animals were administered orally with test drug or 0.25% agar at time 0. After 60 minutes, apomorphine was subcutaneously injected at a dose of 1 mg/kg, and after further 70 minutes the animal's behaviour was assessed. Two additional assessments were performed at 10-min intervals.

For assessment, each animal was placed on the bottom of a small upright box (11x7.5x4.5 cm). The walls of the box were made of translucent methacrylate except one of the lateral surfaces (7.5 cm wide) which was a 3-mm wire mesh. The position of the animal was scored for 2 minutes according to the following criteria: 0 = four paws on the floor; 1 = three paws on the floor; 2 = two paws on the floor; 3 = one paw on the floor; and 4 = four paws holding the wire mesh. If an animal keeps several positions within the 2-min observation, the seconds elapsed in each position will be recorded. Finally, mean scoring was calculated. The cataleptic activity of the compounds by the oral route was simultaneously assessed in rats and expressed as effective dose 50% (ED_{50}). The results obtained are tabulated in Table 3 as inhibitory dose 50% (ID_{50}, mg/kg) in the climbing behaviour test and as ED_{50} (mg/kg) in the catalepsy test. The therapeutic index (TI), which is a safety measurement for the use of test compounds, is also shown in Table 3.

Table 3

Compound	Climbing ID_{50}	Catalepsy ED_{50}	$TI=ED_{50}/ID_{50}$
Example 3	0.21	6.79	32.3
Example 6	5.87	>100 (*)	>17 (*)
Ex.2'ES9600323	0.25	3.8	15.2
Haloperidol	0.32	2.00	6.25

(*) undetermined

According to the data of Table 3, the compounds of Examples 3 andy 6 of the present invention have a higher therapeutic index than the compound of Example 2' of Spanish Patent Application No. 9600323 and than haloperidol, which confirms the advantage of a lower risk of extrapyramidal effects at the therapeutic doses.

The compounds of the present invention may be used as antipsychotic agents for the treatment of psychosis and schizophrenia by the oral, inyectable or rectal route at daily doses ranging from 1 to 500 mg, preferably between 2 and 50 mg inclusive. The usual oral administration forms as antipsychotic agents are solutions, tablets, coated-tablets, capsules, granules, syrups and the like. The compounds of the present invention may also be used as antihistamines for the treatment of allergy by the oral, injectable or rectal route at daily doses ranging from 1 and 500 mg, preferably between 2 and 150 mg inclusive. For the oral administration of these compounds in the treatment of allergy, solutions, tablets, coated-tablets, capsules, granules, syrups and the like may be administered. As antiallergic agents, they may also be

administered in topical formulations, such as cream, ointment, lotion, powder and the like at concentrations ranging from 0.5 to 5%, preferably between 1 and 2% inclusive.

Example 1: 7-[3-[4-(6-fluorobenzo[d]isoxazole-3-yl)piperidin-1-yl]propoxy]-3-formyl-chromen-4-one

To a solution of 2 mL (23 mmoles) of oxalyl chloride in 35 mL of dry dichloromethane, cooled at -70°C, was added drop by drop a solution of 3 mL (42 mmoles) of dimethyl sulfoxide dissolved in 10 mL of dichloromethane and the mixture was stirred for 5 minutes. Then 5 g (11 mmoles) of 7-[3-[4-(6-fluorobenzo[d]isoxazole-3-yl)piperidin-1-yl]propoxy]-3-(hydroxymethyl)-chromen-4-one (Patent ES 9600323) were added in several portions for 15 minutes and stirred for further 30 minutes at -70°C. 15 mL (107 moles) of triethylamine were added drop by drop and stirred overnight while allowed to warm to room temperature gradually. By cooling at -20°C, 50 mL of water were added, the mixture was allowed to warm to room temperature and the organic phase was decanted, dried over sodium sulphate and evaporated. The solid obtained was purified by chromatography on a silica gel column. Elution of the column with $CHCl_3$:CH_3OH (98:2, v/v) gave 2.12 g of 7-[3-[4-(6-fluorobenzo[d]isoxazole-3-yl)piperidin-1-yl]propoxy]-3-formyl-chromen-4-one in 43% yield, mp 163-5°C.

IR(KBr): 1691, 1652, 1619, 1441 cm^{-1}.

NMR ($CDCl_3$): 2.10 (m, 6H), 2.20 (m, 2H), 2.60 (t, 2H), 3.10

(m, 3H), 4.19 (t, 2H), 6.96 (d, 1H), 7.05 (m, 2H), 7.24 (dd, 1H), 7.69 (dd, 1H), 8.19 (d, 1H), 8.47 (s, 1H), 10.37 (s, 1H).

Example 2: 7-[3-[4-(6-fluorobenzo[d]isoxazole-3-yl)piperidin-1-yl]propoxy]-4-oxochromene-3-carboxylic acid hydrochloride

A mixture of 0.87 g (3 mmoles) of 7-(3-chloropropoxy)-4-oxochromene-3-carboxylic acid, 0.7 g (3 mmoles) of 6-fluoro-3-(4-piperidinyl)-benzo[d]isoxazole hydrochloride, 0.85 g (6 mmoles) of anhydrous potassium carbonate and a catalytic amount of potassium iodide in 25 mL of N,N-dimethylformamide was heated to 89-90°C for 24 hours. After being cooled, the solution was poured onto 125 mL of water and then neutralized with HCl at pH 7. The precipitate obtained was filtered, washed with water and dried at vaccum. The solid was dissolved in 60 mL of 0.1M NaOH, diluted with water to 300 mL and the solution was washed with ethyl acetate. The aqueous solution was acidified with HCl to pH 1-2, and the precipitate obtained was filtered and dried at vaccum to give 0.62 g of 7-[3-[4-(6-fluorobenzo[d]isoxazole-3-yl)piperidin-1-yl]propoxy]-4-oxochromene-3-carboxylic acid hydrochloride in 40% yield.

IR(KBr): 3100-3700, 1698, 1616, 1447, 1384, 1165, 1121 cm^{-1}.

NMR (DMSO): 2.13 (m, 6H), 2.30 (m, 2H, piperidine -$2H_a$ and -$6H_a$), 2.67 (t, J=7.5 Hz, 2H, O-CH_2-CH_2-$\underline{CH_2}$-N), 3.16 (d+m, 3H, piperidine -$2H_e$, -4H and -$6H_e$), 4.10 (t, J=6Hz, 2H, O-CH_2), 6.67 (s, 1H, 8-H), 6.79 (d, J=8.7 Hz, 1H, 6-H), 7.10 (td,

J=8.4 and 2.1 Hz, 1H, benzisoxazole-5H), 7.27 (dd, J=8.4 and 2.1 Hz, 1H, benzisoxazole-7H), 7.79 (dd, J=8.4 and 5.4 Hz, 1H, benzisoxazole-4H), 7.97 (d, J=8.7 Hz, 1H, -5H), 9.86 (s, 1H, 2-H).

Example 3: 7-[3-[4-(6-fluorobenzo[d]isoxazole-3-yl)piperidin-1-yl]propoxy]-3-methoxymethyl-chromen-4-one hydrochloride

A solution of 2 g (4.4 mmoles) of 7-[3-[4-(6-fluorobenzo[d] isoxazole-3-yl)piperidin-1-yl]propoxy]-3-(hydroxymethyl)-chromen-4-one in 20 mL of 2M HCl in methanol was heated at reflux for 2 hours. The solvent was evaporated and the residue was dissolved in dichloromethane and washed with saturated CO_3HNa solution. The organic phase was evaporated, dissolved in acetonitrile and precipitated by addition of etheral HCL solution. The solid obtained was recrystallized from methanol to give 0.75 g of 7-[3-[4-(6-fluorobenzo[d] isoxazole-3-yl)piperidin-1-yl]propoxy]-3-methoxymethyl-chromen-4-one hydrochloride in 34% yield, mp 219-221°C.

IR(KBr): 1659, 1615, 1443, 1273, 1244 cm^{-1}.

NMR ($CDCl_3$-CD_3OD): 2.25 (m, 2H), 2.50 (m, 2H), 2.90 (m, 2H), 3.05 (m, 2H), 3.35 (m, 2H), 3.48 (s, 3H), 3.60 (m, 1H), 3.80 (d, 2H), 4.20 (m, 2H), 4.39 (s, 2H), 6.90 (d, 1H), 6.97 (d, 1H), 7.16 (td, 1H), 7.66 (dd, 1H), 7.95 (s, 1H), 8.10 (d, 1H), 8.20 (dd, 1H).

Example 4: 7-hydroxy-2-(hydroxymethyl)-chromen-4-one

To a suspension of 5 g (21 mmoles) of ethyl 7-hidroxy-4-oxo-chromen-2-carboxylate and 5 g (45 mmoles) of calcium chloride in 100 mL of absolute ethanol, cooled at 0°C, were added 3 g of sodium borohydride in several portions and the mixture was stirred at room temperature for 16 hours. Further 1 g of sodium borohydride was added and stirred for an additional 2 hours. The reaction mixture was suspended in 200 mL of water and acidified slowly with HCl. The precipitate was filtered, washed with water and dried at vaccum to give 2.7 g de 7-hydroxy-2-(hydroxymethyl)-chromen-4-one as a solid, yield 66%, mp 250-252°C.

IR(KBr): 2700-3500, 1650, 1634, 1570, 1458, 1326, 1250, 1101 cm^{-1}

NMR (d_6-DMSO): 3.50 (s, wide, 2H, OH), 4.40 (s, 2H, CH_2OH), 6.20 (s, 1H, 3-H), 6.82 (d, J=2.4 Hz, 1H, 8-H), 6.92 (dd, J=8.7 and 2.4 Hz, 1H, 6-H), 7.86 (d, J=8.7, 1H, 5-H).

Example 5: 7-(3-chloropropoxy)-2-(hydroxymethyl)-chromen-4-one

A mixture of 6 g (31 mmoles) of the compound obtained in Example 4, 6 mL (61 mmoles) of 1-bromo-3-chloropropane, 4.3 g (31 mmoles) of anhydrous potassium carbonate in 100 mL of acetone and 25 mL of N,N-dimethylformamide was heated at reflux for 16 hours. The reaction mixture was poured onto 100 mL of water and extracted with 100 mL of ethyl acetate. The

organic extracts were washed with two portions of 100 mL of water, dried over sodium sulphate and evaporated at vaccum. The residue obtained was suspended in 25 mL of ethyl ether, filtered and dried at vaccum to give 4.2 g of 7-(3-chloropropoxy)-2-(hydroxymethyl)-chromen-4-one in 50% yield, mp 110-112°C.

IR(KBr): 2600-3500, 1651, 1628, 1592, 1448, 1246, 1099 cm^{-1}

NMR ($CDCl_3$): 2.28 (m, 2H, O-CH_2-$\underline{CH_2}$), 3.76 (t, J=6 Hz, 2H, CH_2Cl), 4.16 (t, J=6 Hz, 2H, O-CH_2), 4.57 (s, 3H, $C\underline{H_2}OH$ + $O\underline{H}$), 6.44 (s, 1H, 3-H), 6.78 (d, J=2,1 Hz, 1H, 8-H), 6.90 (dd, J=8,7 and 2.1 Hz, 1H, 6-H), 7.99 (d, J=8.7 Hz, 1H, 5-H).

Example 6: 7-[3-[4-(6-fluorobenzo[d]isoxazole-3-yl)piperidin-1-yl]propoxy]-2-(hydroxymethyl)-chromen-4-one hydrochloride

A mixture of 3 g (11 mmoles) of the compound obtained in Example 5, 2.88 g (11 mmoles) of 6-fluoro-3-(4-piperidinyl)-benzo[d]isoxazole hydrochloride, 2.16 g (26 mmoles) of sodium bicarbonate and a catalytic amount of potassium iodide in 80 mL of acetonitrile was heated at reflux for 48 hours. The mixture was then allowed to cool, poured onto 100 mL of water and extracted with 100 mL of chloroform. The chloroform extract was washed with water, dried over sodium sulphate and evaporated. The residue obtained was suspended in ethyl ether, filtered and dried at vaccum to give 2 g of 7-[3-[4-(6-fluorobenzo[d]isoxazole-3-yl)piperidin-1-yl]propoxy]-2-(hydroxymethyl)-chromen-4-one in 40% yield.

NMR ($CDCl_3$): 2.0-2.2 (m, 8H), 2.60 (t, J=7.2 Hz, 2H, N-$\underline{CH_2}$-

CH_2-CH_2-O), 3.10 (d+m, 3H, piperidine -2H_e, -4H and -6H_a), 4.13 (t, J=6.6 Hz, 2H, O-$\underline{CH_2}$-CH_2-CH_2), 4.58 (s, 3H, $\underline{CH_2}$OH), 6.41 (s, 1H, 3-H), 6.89 (d, J=2,1 Hz, 1H, 8-H), 6.94 (dd, J=8.7 and 2.1 Hz, 1H, 6-H), 7.07 (td, J=8.7 and 2.4 Hz, 1H, benzisoxazole-5H), 7.25 (dd, J=8.7 and 2.4 Hz, 1H, benzisoxazole-7H), 7.71 (dd, J=8.7 and 5.1 Hz, 1H, benzisoxazole-4H), 8.04 (d, J=8.7 Hz, 1H, 5-H).

Hydrochloride: The product obtained was dissolved in a mixture of chloroform:methanol (3:1) and precipitated by addition of HCl methanol solution to give 1.4 g of 7-[3-[4-(6-fluorobenzo[d]isoxazole-3-yl)piperidin-1-yl]propoxy]-2-(hydroxymethyl)-chromen-4-one hydrochloride, as a solid, mp 248-251°C.

IR(KBr): 3300, 2500, 1648, 1603, 1439, 1329, 1122, 1094 cm^{-1}.

Example 7: 0.025% injection formulation

Composition for 1 ampoule

compound of Example 3	0.5 mg
methyl *p*-hydroxybenzoate.....	1.0 mg
propyl *p*-hydroxybenzoate	0.1 mg
bidistilled water q.s.	2.0 mL

Example 8: 0.1% oral solution formulation

Composition for 100 ml:

compound of Example 3	100 mg
methyl *p*-hydroxybenzoate	135 mg
propyl *p*-hydroxybenzoate	15 mg
sorbitol 70%	20 mg

sodium saccharin	50 mg
orange essence	0.25 mL
distilled water q.s.	100 mL

Example 9: 1 mg tablet formulation

Composition for 1 tablet:

compound of Example 3	1.0 mg
corn starc	32.4 mg
talc	4.5 mg
hydrogenated castor oil	1.5 mg
lactose q.s.	150.0 mg

Example 10: 5 mg tablet formulation

Composition for 1 tablet:

compound of Example 3	5.0 mg
corn starch	43.2 mg
talc	6.0 mg
hydrogenated castor oil	2.0 mg
lactose q.s.	200.0 mg

Example 11: 10 mg tablet formulation

Composition for 1 tablet:

compound of Example 3	10.0 mg
corn starch	40.0 mg
sodium lauryl sulphate	0.50 mg
pregelatinized corn starch	8.00 mg
magnesium stearate ..	1.20 mg
lactose q.s.	240.00 mg

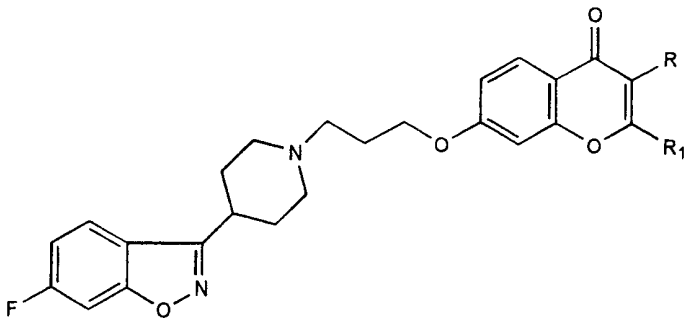
Example 12: 1% topical cream formulation

Composition for 100 g:

compound of Example 3	1.00 g
isopropyl myristate	9.00 g
cetostearyl alcohol	6.00 g
propylene glycol	3.00 g
fatty acid polyglycolic ester	5.00 g
oleic acid decyl ester	6.00 g
perfume	0.30 g
methyl *p*-hydroxybenzoate	0.15 g
propyl *p*-hydroxybenzoate	0.02 g
ethyl *p*-hydroxybenzoate	0.03 g
demineralized water q.s.	100.00 g

Claims

1. 7-[3-[4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl]propoxy]-chromen-4-one derivatives of formula (I):



(I)

wherein R is hydrogen, CHO, CH_2OR_2 or COOH; R_1 is hydrogen or CH_2OH; and R_2 is alkyl having 1 to 4 carbon atoms with the proviso that one of substituents R and R_1 should be hydrogen, as well as their pharmaceutically acceptable salts.

2. The derivatives according to claim 1 of formula (I) wherein R is CHO, CH_2OR_2 or COOH and R_1 is hydrogen, or R is hydrogen and R_1 is CH_2OH.

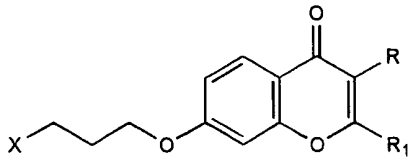
3. The compounds of formula (I), as well as their pharmaceutically acceptable additions salts, for use in the treatment of psychosis, schizophrenia and allergy.

4. A pharmaceutically composition comprising a compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

5. The use of a compound of claims 1 or 2 for preparing a pharmaceutical composition for the treatment of psychosis, schizophrenia and allergy.

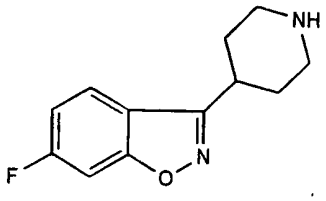
6. A method of treatment of psychosis, schizophrenia and allergy which comprises administering to a mammal an effective amount of a compound of formula (I) according to claim 1 or 2, or a pharmaceutically acceptable addition salt thereof.

7. A process for preparing a compound of formula (I) according to claim 1 or 2, which comprises reacting the intermediates of the formula (II):



(II)

wherein R and R_1 is as defined for (I) and X is a halogen selected preferably between chlorine or bromine, with the intermediate of formula (III):



(III)

followed by optional reaction with the corresponding acid if their pharmaceutically acceptable salts are to be obtained.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 98/08497

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/14 A61K31/465

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 6 C07D A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X X	WO 96 32389 A (FERRER) 17 October 1996 see page 1 - page 11; claims; examples 1-3 & ES 9 600 323 A (FERRER) cited in the application	1-7

☐ 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
29 April 1999	12/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/08497

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. [X] Claims Nos.: 6
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 6 is 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

Inter nal Application No
PCT/EP 98/08497

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9632389 A	17-10-1996	ES 2101646 A	01-07-1997
		AU 696494 B	10-09-1998
		AU 5500496 A	30-10-1996
		CA 2192596 A	17-10-1996
		EP 0765323 A	02-04-1997
		ES 2103237 A	01-09-1997
		JP 10501557 T	10-02-1998
		NO 965300 A	11-12-1996
		NZ 306447 A	24-06-1997
		US 5736558 A	07-04-1998