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(54) **NOVEL DERIVATIVES OF ARYL-{4-HALOGENO-4-[AMINOMETHYL]-PIPERIDIN-1-
YL}-METHANONE, THEIR METHOD OF PREPARATION AND THEIR USE AS MEDICINAL
PRODUCTS**

NEUE ARYL-{4-HALOGENO-4-[AMINOMETHYL]-PIPERIDIN-1-YL}-METHANONDERIVATE, IHR
HERSTELLUNGSVERFAHREN UND IHRE VERWENDUNG ALS MEDIZINPRODUKTE

NOUVEAUX DÉRIVÉS DE L'ARYL-{4-HALOGÉNO-4-[AMINOMÉTHYLE]-PIPÉRIDIN-1-
YLE}-MÉTHANONE, LEUR PROCÉDÉ DE PRÉPARATION ET LEUR UTILISATION EN TANT QUE
PRODUITS MÉDICINAUX

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• **A-S BOURLOT ET AL: "New substituted 1,4-
benzoxazine derivatives with potential
intracellular calcium activity" JOURNAL OF
MEDICINAL CHEMISTRY, AMERICAN CHEMICAL
SOCIETY, WASHINGTON, US, vol. 41, no. 17, 1
January 1998 (1998-01-01), pages 3142-3158,
XP002136635 ISSN: 0022-2623 cited in the
application**

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- ZHOU D ET AL: "Studies toward the discovery of the next generation of antidepressants. Part 5: 3,4-Dihydro-2H-benzo[1,4]oxazine derivatives with dual 5-HT_{1A} receptor and serotonin transporter affinity" *BIOORGANIC & MEDICINAL CHEMISTRY LETTERS*, PERGAMON, ELSEVIER SCIENCE, GB, vol. 16, no. 5, 1 March 2006 (2006-03-01), pages 1338-1341, XP025106349 ISSN: 0960-894X [retrieved on 2006-03-01]
- HERBERT BARTSCH, OTTO SCHWARZ: "Studien zur Chemie der 1,4-Oxazine, 5. Mitt. Zur Chemie 2-substituierter Dihydro-1,4-benzoxazine" *ARCHIV DER PHARMAZIE*, vol. 315, no. 6, 1982, pages 538-545, XP002594445 DOI: 10.1002/ardp.19823150611

Description

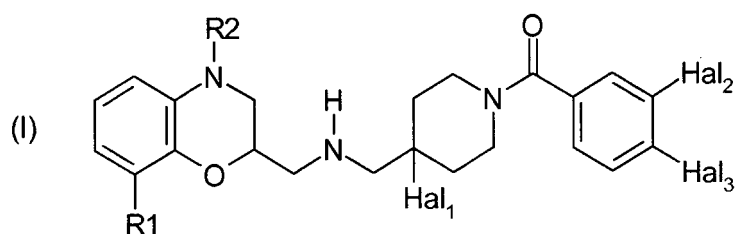
[0001] The 5-HT_{1A} receptor is structurally, pharmacologically and functionally the serotonergic receptor that is best characterized. Its involvement in the pathophysiology of numerous disorders and psychiatric illnesses is well known (Curr Drug Targets CNS Neurol Dis. 2004, 3, 1; Neurosci Biobehav Rev. 1990, 14, 35). For example, clinical trials on compounds with agonist activity for serotonergic receptors of sub-type 5-HT_{1A} have shown that the 5-HT_{1A} agonists are effective in the treatment of anxiety (J. Clin. Psychiatry 1987, 48, 3S) and depression (Int. J. Neuropsychopharmacology 1998, 1, 18). In addition, in animals, the 5-HT_{1A} agonists have shown neuroprotective properties (Arch. Int. Pharmacodyn. 1995, 329, 347) and analgesic properties (Behav. Brain Res. 1995, 73, 1/2, 69).

[0002] Having regard to the major therapeutic potential of compounds with agonistic activity for the serotonergic receptors of sub-type 5-HT_{1A}, the discovery of novel compounds having said activity is highly desirable.

[0003] Although a very high number of compounds have been described as 5-HT_{1A} agonists, only two are clinically available (i.e. buspirone: Europe and United States and tandospirone: Japan). These two compounds belong to the same chemical family however (i.e., arylpiperazine) and have a relatively similar pharmacological profile: limited affinity for the 5-HT_{1A} receptors and insufficient level of activity in depression and pain models.

[0004] It appears that 5-HT_{1A} agonists of different structures have different pharmacological profiles (Eur. J. Pharmacol. 2001, 420, 103-112).

[0005] The subject of the present invention is a novel family of compounds derived from aryl-{4-halogeno-4-[aminomethyl]-piperidin-1-yl}-methanone, which has the following general formula (1):



in which

R1 is:

- a hydrogen atom, or a halogen e.g. a fluorine atom, a chlorine atom, a bromine atom or an iodine atom,
- a straight or branched C₁-C₆ alkyl group e.g. a straight or branched C₁-C₃ alkyl group, or a C₁-C₃ fluoroalkyl group e.g. a fluoromethyl or difluoromethyl or trifluoromethyl group,
- a straight or branched C₁-C₆ alkoxy group e.g. a straight or branched C₁-C₃ alkoxy group,
- a carbamyl group, N-substituted or not by one or two, straight or branched C₁-C₃ alkyl groups, or
- a cyano group (CN)

R2 is a hydrogen atom or a straight or branched C₁-C₆ alkyl group e.g. a straight or branched C₁-C₃ alkyl group,

Hal₁, Hal₂ and Hal₃ are:

- a halogen, for example a fluorine atom, a chlorine atom, a bromine atom or an iodine atom,

their addition salts with pharmaceutically acceptable mineral acids or organic acids, and their enantiomer forms.

[0006] According to the invention, the compounds of general formula (1) are those in which:

Hal₁ and Hal₃ are:

- a fluorine atom

and Hal₂ is:

- a chlorine atom

[0007] In one particular embodiment of the invention, the formula (1) compounds are those in which:

5 R1 is:

- a hydrogen atom, or a chlorine atom or a fluorine atom,
- a straight or branched C₁-C₃ alkyl group, or a fluoromethyl, or difluoromethyl or trifluoromethyl group,
- 10 - a straight or branched C₁-C₃ alkoxy group,
a carbamyl group (CONH₂) N-substituted or not by one or two, straight or branched C₁-C₃ alkyl groups, or
- a cyano group (CN)

15

R2 is a hydrogen atom, or a straight or branched C₁-C₃ alkyl group,

Hal₁ and Hal₃ are:

20

- a fluorine atom

and Hal₂ is:

25

- a chlorine atom

their addition salts with pharmaceutically acceptable mineral acids or organic acids, and their enantiomer forms.

[0008] In another embodiment of the invention, the formula (1) compounds are those in which:

30 R1 is:

- a hydrogen atom, or a chlorine atom, or a fluorine atom
- a methyl group (CH₃)
- 35 - a methoxy group (O-CH₃)
- a non-substituted carbamyl group (CONH₂) or
- a cyano group (CN)

40

R2 is:

- a hydrogen atom or a methyl group

45

Hal₁ and Hal₃ are:

- a fluorine atom

Hal₂ is:

50

- a chlorine atom

their addition salts with pharmaceutically acceptable mineral acids or organic acids, and their enantiomer forms.

[0009] According to the invention, the compounds of general formula (1) are those in which:

55

- R1 is chosen from the group consisting of a hydrogen atom, and a carbamyl group N-substituted or not by one or two, straight or branched C₁-C₃ alkyl groups.

[0010] According to the invention, the compounds of general formula (1) are those in which:

- R2 is a hydrogen atom.

5 **[0011]** According to the invention, the compounds of general formula (1) are those in which:

- R1 and R2 are: a hydrogen atom.

10 **[0012]** The invention also concerns the mineral or organic salts of the formula (1) compounds with pharmaceutically acceptable mineral acids or organic acids and their enantiomer forms.

[0013] The compounds of the invention contain an asymmetric carbon atom in their structure. On this account they exist in enantiomer form. The invention concerns both each pure enantiomer i.e. associated with less than 5 % of the other enantiomer, and the racemic or non-racemic mixtures. However, among the compounds of formula (1), the enantiomer whose carbon atom of the dihydro-benzoxazine methanamine fragment is of absolute configuration (S) is preferred.

15 **[0014]** The descriptors R and S, used to specify the absolute configuration of the stereogenic carbon atoms contained in the molecules of formula (1), are defined such as defined in the priority rule of Cahn-Ingold-Prelog (E.L. Eliel and S.H. Wilen Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., chap. 5, 104-12, 1994).

[0015] By « halogen atom », in the meaning of the present invention, is meant a chlorine atom, a fluorine atom, a bromine atom or an iodine atom.

20 **[0016]** By « alkyl group », in the meaning of the present invention, is meant a straight or branched, saturated or unsaturated hydrocarbon chain comprising the indicated number of carbons.

[0017] By « alkoxy group », in the meaning of the present invention, is meant a straight or branched, saturated or unsaturated hydrocarbon chain bound to an oxygen atom (O-alkyl) and comprising the indicated number of carbons.

25 **[0018]** By « fluororalkyl group », in the meaning of the present invention, is meant a straight or branched, saturated or unsaturated hydrocarbon chain in which one or more hydrogen atoms have been replaced by a fluorine atom and which comprises the indicated number of carbons.

[0019] By « carbamyl group (CONH₂) N-substituted or not by one or two, straight or branched C₁-C₃ alkyl groups », in the meaning of the present invention, is meant the CONH₂ group in which the nitrogen atom can be substituted by one or two, straight or branched C₁-C₃ alkyl groups.

30 **[0020]** A further subject of the invention concerns pharmaceutical compositions containing, as active ingredient, at least one compound of general formula (1) or one of its pharmaceutically acceptable salts with pharmaceutically acceptable mineral acids or organic acids, or one of its enantiomers in combination with one or more pharmaceutically acceptable excipients, adjuvants or vehicles. As an example, mention may be made of inclusion complexes in particular those formed by the compounds of the invention and cyclodextrins.

35 **[0021]** The pharmaceutical compositions of the invention may be compositions which can be administered via oral, nasal, sublingual, rectal or parenteral route. It is generally advantageous to formulate said pharmaceutical compositions in unit dose form. Each dose then contains a predetermined quantity of active ingredient associated with the suitable vehicles, excipients and/or adjuvants, calculated to obtain a given therapeutic effect. As an example of unit dose form which can be administered via oral route, mention may be made of tablets, capsules, granules, powders and oral solutions or suspensions.

40 **[0022]** The suitable formulations for the chosen form of administration are known and described for example in Remington, The Science and Practice of Pharmacy, 19th Edition, 1995, Mack Publishing Company, and can therefore easily be prepared by persons skilled in the art.

45 **[0023]** It is known that dosage varies from one person to another, depending on the type and intensity of the disorder, the chosen route of administration, the weight, age and sex of the patient. Therefore, the efficient doses are to be determined in relation to these parameters by specialists in the matter. By way of indication, the efficient doses could range from 0.001 mg/Kg to 100 mg/Kg/day.

[0024] The compounds of general formula (1) may exist in several tautomer forms. Said tautomer forms, although not explicitly reported in the present application to simplify formula representation, are nonetheless included in the field of application of the invention.

50 **[0025]** A further subject of the present invention is a compound of formula (1) or one of its pharmaceutically acceptable salts with pharmaceutically acceptable mineral acids or organic acids, or one of its enantiomers for its use as medicinal product.

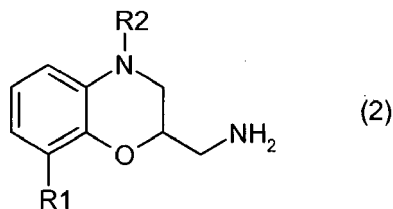
55 **[0026]** A further subject of the invention is a compound of formula (1) or one of its pharmaceutically acceptable salts with pharmaceutically acceptable mineral acids or organic acids, or one of its enantiomers for its use as medicinal product intended for the treatment of depression.

[0027] The subject of the present invention is a formula (1) compound or one of its pharmaceutically acceptable salts with pharmaceutically acceptable mineral acids or organic acids, or one of its enantiomers for its use as medicinal product

intended to treat pain.

[0028] The subject of the present invention also consists of a formula (1) compound or one of its pharmaceutically acceptable salts with pharmaceutically acceptable mineral acids or organic acids, or one of its enantiomers for its use as medicinal product intended to treat pathological pain and/or physiological pain.

[0029] The invention also extends to the synthesis intermediates of formula (2)



15 in which:

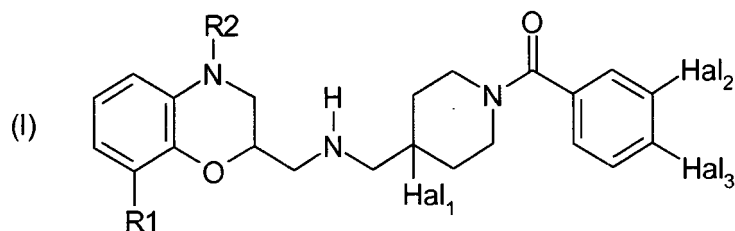
R1 is:

- 20
- a hydrogen atom,
 - a chlorine or fluorine atom, or a straight or branched C₁-C₆ alkyl group, or a fluoromethyl or difluoromethyl or trifluoromethyl group,
 - a straight or branched C₁-C₆ alkoxy group, or
 - a carbamyl group N-substituted or not by one or two, straight or branched C₁-C₃ alkyl groups,
- 25

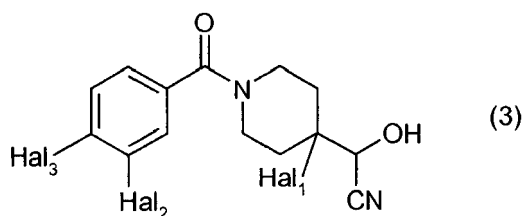
R2 is a hydrogen atom, or a straight or branched C₁-C₆ alkyl group,

30 used for the preparation of compounds of general formula (1).

[0030] The invention extends to the method to prepare compounds of general formula (1):



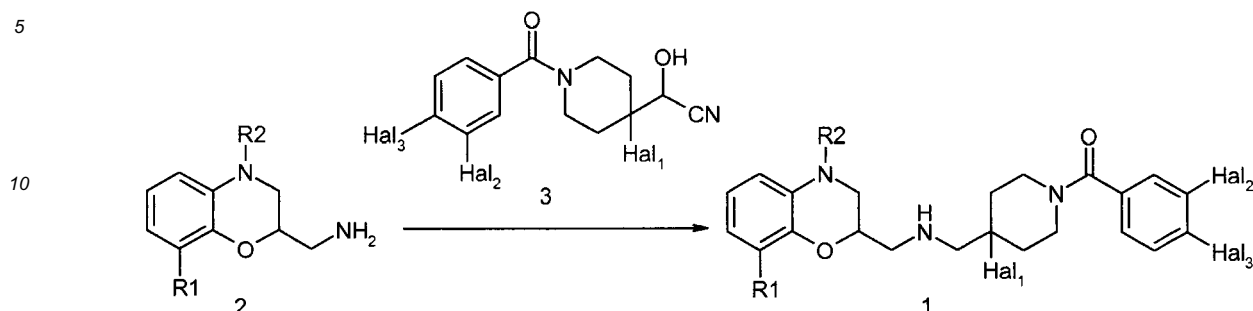
characterized in that it uses the condensation between an intermediate of type 3,4-dihydro-2H-1,4-benzoxazine-2-methanamine of formula (2) and cyanohydrine of formula (3):



in the presence of a reducing agent and optionally a base.

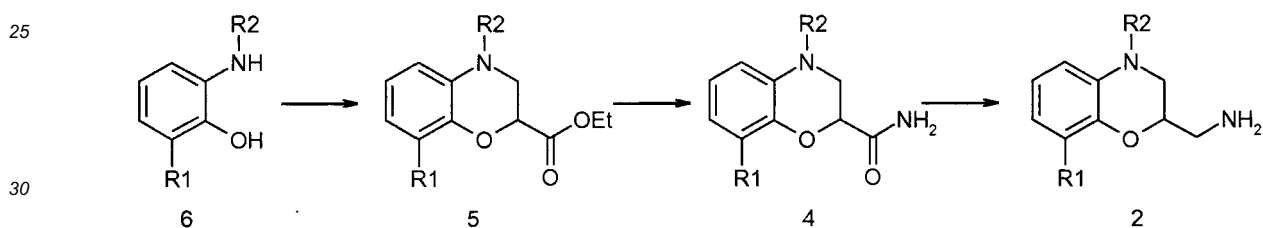
[0031] The formula (1) compounds were prepared following the reaction sequence indicated in scheme A.

Scheme A



[0032] Cyanohydrine (3) is prepared as described in patent WO 02/064585. The fragment 3,4-dihydro-2H-1,4-benzoxazine-2-methanamine of formula (2a) [102908-68-9] is prepared following the method reported in the literature (J. Med. Chem. 1998, 41, 3142). Regarding the novel intermediates of formula (2), these were prepared following the reaction sequence illustrated in scheme B.

Scheme B



[0033] Therefore 2-aminophenol of formula (6) is condensed with ethyl 2,3-dibromo-propionate in a basic medium following the method described in J. Med. Chem. 2003, 16, 1338, to give the ester of formula (5). Compound (5) is then converted to the amide (4) by treatment with ammonia according to a protocol well known to those skilled in the art. The formed amide of formula (4) is then reduced to the expected amine (2) using aluminium lithium hydride in aprotic medium, by analogy with the method described in Archiv der Pharmazie, 1982, 315, 538.

[0034] The following examples illustrate the invention but do not in any way limit the invention.

[0035] In the examples below:

(i) the progress of the reactions is monitored by thin layer chromatography (TLC) and therefore the reaction times are only given by way of indication.

(ii) different crystalline shapes may give different melting points, the melting points given in the present application are those of products prepared following the described method and are not corrected.

(iii) the structure of the products obtained according to the invention is confirmed by nuclear magnetic resonance (NMR) spectra, centesimal analysis, the purity of the end products is verified by TLC.

(iv) the NMR spectra are recorded in the indicated solvent. Chemical shifts (δ) are expressed in parts per million (ppm) relative to tetramethylsilane. Signal multiplicity is indicated by: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet.

(v) the different unit symbols have their usual meaning: mg (milligram); g (gram); mL (millilitre); cm (centimetre); °C (degree Celsius); mmol (millimole); min (minute).

(vi) The abbreviations have the following meaning: MP (melting point); BP (boiling point); Tr (retention time).

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(vii) By « ambient temperature » is meant a temperature of between 20°C and 25°C.

Intermediate 1

5 (+) and (-)-3,4-Dihydro-2H-1,4-benzoxazine-2-methanamine (2a)

[0036] The enantiomers of (\pm)-3,4-dihydro-2H-1,4-Benzoxazine-2-methanamine (8, 1g) are separated by chiral phase chromatography, Chiralpack AD, using as eluting solvent a mixture of hexane-ethanol-diethylamine (90:10:0.05). (+)-3,4-dihydro-2H-1,4-Benzoxazine-2-methanamine (2a1), 4,0g; Tr = 16.6 min ; $[\alpha]_D = +0.57^\circ$ (c 0.93, MeOH).
10 (-)-3,4-dihydro-2H-1,4-Benzoxazine-2-methanamine (2a2), 4,0g ; Tr = 21.3 min ; $[\alpha]_D = -0.67^\circ$ (c .1.34 MeOH).

Intermediate 2

15 3,4-Dihydro-8-fluoro-2H-1,4-benzoxazine-2-ethyl carboxylate (5b)

[0037] A mixture of 2-amino-6-fluorophenol (2g, 8.3 mmol), of ethyl 2,3-dibromopropionate (1.46 mL, 9.96 mmol) and of K_2CO_3 (3.44g, 24.9 mmol) in acetone (80mL) is heated under reflux for 9 h 15 min. The mixture is cooled and filtered. The filtrate is vacuum concentrated, the residue dissolved in iced aqueous NaOH solution (1N, 10mL) and extracted with ethyl ether. The ethereal phase is washed in water then saline water, dried over $MgSO_4$ and concentrated under
20 reduced pressure. The residue is purified by filtering through silica gel using dichloromethane as eluting solvent. The title compound is obtained in oil form (1.1 g, 59 %).

1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3H), 3.61 (m, 2H), 3.87 (s, 1H), 4.26 (q, 2H), 4.88 (t, 1H), 6.37 (d, 1H), 6.53 (t, 1H), 6.67 (t, 1H).

Intermediate 3

25 3,4-Dihydro-8-fluoro-2H-1,4-benzoxazine-2-carboxamide (4b)

[0038] To a solution of 5b (1.1 g, 4.89 mmol) in ethanol (20mL) an ammonia solution is added (32 %, 5mL). The solution obtained is agitated 14 h at ambient temperature then 10mL of ammonia are added and the mixture agitated for 48 h. The solution is concentrated under reduced pressure and the residue is dissolved in petroleum ether. The formed precipitate is filtered, washed in petroleum ether and vacuum dried (0.75g, 78%).

1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 2H), 3.50 (dd, 1H), 3.73 (dd, 1H), 4.69 (m, 1H), 5.60 (s, 1H), 6.41 (d, 1H), 6.52 (t, 1H), 6.71 (m, 1H).

Intermediate 4

Dihydro-8-fluoro-2H-1,4-benzoxazine-2-methanamine (2b)

[0039] To a solution of 4b (0.75 g, 3.83 mmol) in anhydrous THF (20 mL) held at ambient temperature in an inert atmosphere, is added dropwise a solution of $LiAlH_4$ in THF (13.4mL, 13.4 mmol). When addition is completed, the mixture is heated to 60°C for 11 h. The mixture obtained is cooled to 0°C then an aqueous solution of hydrochloric acid (1N) is added slowly until a pH of 3 is reached. The mixture is concentrated under reduced pressure then the residue is made alkaline through the addition of an aqueous NaOH solution (1N). The mixture is extracted with ethyl acetate, the organic phase is washed with water then with salt water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified by silica gel chromatography using a dichloromethane-methanol mixture (85:5) as eluting solvent. The title compound is obtained in oil form (1.1 g, 59 %). 1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 2H), 2.98 (m, 2H), 3.26 (dd, 1H), 3.42 (dd, (1H), 3.80 (s, 1H), 4.12 (m, 1H), 6.35, (d, 1H), 6.47 (t, 1H), 6.64 (t, 1H).

Intermediate 5

Dihydro-8-methyl-2H-1,4-benzoxazine-2-carboxamide (4c)

[0040] This compound is obtained using the same experimental conditions as those used for the synthesis of intermediate (4b) but replacing 3,4-dihydro-8-fluoro-2H-1,4-benzoxazine-2-ethyl carboxylate (5b) with 3,4-dihydro-8-methyl-2H-1,4-benzoxazine-2-ethyl carboxylate (5c), [220120-58-1]. The title compound of formula (4c) is obtained.

1H NMR ($CDCl_3$, 400 MHz) δ 1.55 (s, 1H), 2.23 (s, 3H), 3.46 (dd, 1H), 3.67 (dd, 1H), 3.81 (s, 1H), 4.69 (m, 1H), 5.56 (s, 1H), 6.50 (d, 1H), 6.58 (d, 1H), 6.74 (t, 1H).

Intermediate 6

Dihydro-8-methyl-2H-1,4-benzoxazine-2-methanamine (2c)

5 **[0041]** This compound is obtained using the same experimental conditions as those used for the synthesis of intermediate 2b but by replacing 3,4-dihydro-8-fluoro-2H-1,4-benzoxazine-2-carboxamide (4b) with 3,4-dihydro-8-methyl-2H-1,4-benzoxazine-2-carboxamide (4c). The title compound of formula (2c) is obtained.

¹H NMR (CDCl₃, 400 MHz) δ 1.6 (s, 2H), 2.19 (s, 3H), 2.92 (m, 2H), 3.19 (dd, 1H), 3.37 (dd, 1H), 4.11 (m, 1H), 6.17 (d, 1H), 6.54 (d, 1H), 6.67 (t, 1H).

10

Intermediate 7

Dihydro-8-chloro-2H-1,4-benzoxazine-2-carboxamide (4d)

15 **[0042]** This compound is obtained using the same experimental conditions as those used for the synthesis of intermediate 4b but replacing 3,4-dihydro-8-fluoro-2H-1,4-benzoxazine-2-ethyl carboxylate (5b) with 3,4-dihydro-8-chloro-2H-1,4-benzoxazine-2-ethyl carboxylate (5d), [73268-47-0]. The title compound of formula (4d) is obtained.

¹H NMR (CDCl₃, 400 MHz) δ 3.60 (dd, 1H), 3.85 (dd, 1H), 4.87 (m, 1H), 5.36 (s, 1H), 6.70-6.90 (m, 2H), 6.73 (d, 1H), 7.20 (s, 2H).

20

Intermediate 8

Dihydro-8-chloro-2H-1,4-benzoxazine-2-methanamine (2d)

25 **[0043]** This compound is obtained following the same experimental conditions as those used for the synthesis of intermediate 2b but replacing 3,4-dihydro-8-fluoro-2H-1,4-benzoxazine-2-carboxamide (4b) with 3,4-dihydro-8-chloro-2H-1,4-benzoxazine-2-carboxamide (4d). The title compound of formula (2d) is obtained.

¹H NMR (CDCl₃, 400 MHz) δ 3.10 (m, 2H), 3.31 (dd, 1H), 3.56 (dd, 1H), 4.16 (m, 1H), 5.11 (s, 2H), 5.28 (s, 1H), 6.70-6.90 (m, 2H), 6.73 (d, 1H).

30

Intermediate 9

Dihydro-8-methoxy-2H-1,4-benzoxazine-2-methanamine (2e)

35 **[0044]** This compound is obtained using the same reaction sequence and the same experimental conditions as those used for the synthesis of intermediate 2b but replacing 2-amino-6-fluorophenol with 2-amino-6-methoxyphenol. This gives the title compound of formula (2e).

¹H NMR (CDCl₃, 400 MHz) δ 2.98 (m, 2H), 3.23 (dd, 1H), 3.38 (dd, 1H), 3.85 (s, 3H), 4.14 (m, 1H), 4.67 (s, 2H), 6.26 (d, 1H), 6.34 (d, 1H), 6.70 (t, 3H).

40

Intermediate 10

Dihydro-8-cyano-2H-1,4-benzoxazine-2-methanamine (2f)

45 **[0045]** This compound is obtained using the same reaction sequence and the same experimental conditions as those used for the synthesis of intermediate 2b but replacing 2-amino-6-fluorophenol with 2-amino-6-cyanophenol. The title compound of formula (2f) is obtained.

¹H NMR (CDCl₃, 400 MHz) δ 1.48 (s, 2H), 2.99 (m, 2H), 3.28 (dd, 1H), 3.46 (dd, 1H), 4.19 (s, 1H), 4.20 (m, 1H), 6.73-6.80 (m, 2H), 6.90 (d, 1H).

50

Intermediate 11

Dihydro-4-methyl-2H-1,4-benzoxazine-2-methanamine (2g)

55 **[0046]** This compound is obtained following the same experimental conditions as those used for the synthesis of intermediate 2b but replacing 3,4-dihydro-8-fluoro-2H-1,4-benzoxazine-2-carboxamide (4b) with 3,4-dihydro-4-methyl-2H-1,4-benzoxazine-2-carboxamide (4g) [84831-37-8]. The title compound of formula (2g) is obtained.

¹H NMR (CDCl₃, 400 MHz) δ 2.67-3.16 (m, 3H), 2.85 (s, 3H), 3.38 (d, 1H), 4.3 (s, 1H), 6.55 (t, 1H), 6.63 (d, 1H), 6.70-6.74

(m, 2H), 8.48 (s, 2H).

Intermediate 12

5 Dihydro-8-carbamoyl-2H-1,4-benzoxazine-2-methanamine (2h)

[0047] This compound is obtained following the same experimental conditions as those used for the synthesis of intermediate (2b) but replacing 3,4-dihydro-8-fluoro-2H-1,4-benzoxazine-2-carboxamide (4b) with 3,4-dihydro-4-methyl-2H-1,4-benzoxazine-2-carboxamide (4h). The title compound of formula (2h) is obtained.

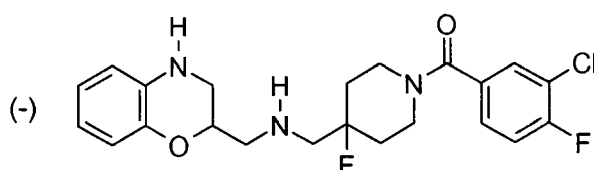
10 ¹H NMR (DMSO, 400 MHz) δ 1.62 (s, 2H), 2.69-2.83 (m, 2H), 3.07 (dd, 1H), 3.40 (dd, 1H), 4.00 (m, 1H), 6.28 (s, 1H), 6.76-6.84 (m, 3H).

EXAMPLE 1: (-)-(3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1a1)

15

[0048]

20



25 **[0049]** To a solution of (-)-3,4-dihydro-2H-1,4-benzoxazine-2-methanamine (2a2, 4.1 g, 25 mmol) in methanol (500mL) are successively added the compound of formula 3 (8.28 g, 26 mmol), iron sulphate (8.3 g, 30 mmol) and sodium cyanoborohydride (2.0 g, 32 mmol). The mixture is heated 6 h at 50°C then cooled to ambient temperature, filtered and concentrated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water then salt water, dried over MgSO₄ and filtered. The solvent is removed by vacuum evaporation and the product is purified by silica chromatography using a dichloromethane-methanol mixture (95:5) as eluting solvent. 1.6 g of the title compound (1a1) is obtained. Salification of this compound with fumaric acid allows the oxalate to be obtained in the form of white crystals (6.0 g).

30

$C_{22}H_{24}ClF_2N_3O_2$, $C_4H_4O_4$

MP: 185°C

35

$[\alpha]_D = -30.9$ (0.4 EtOH).

¹H NMR (DMSO d₆) δ 1.65-1.93 (m, 4H), 2.76-2.84 (m, 4H), 3.00 (dd, 1H), 3.32 (dd, 1H), 2.74-3.56 (m, 7H), 4.07 (m, 1H), 4.26 (s, 1H), 6.47 (t, 1H), 6.55 (d, 1H), 6.62-6.67 (m, 4H), 7.43-7.51 (m, 2H), 7.66 (d, 1H).

Theoretical % C 56.58, H 5.11, N 7.61

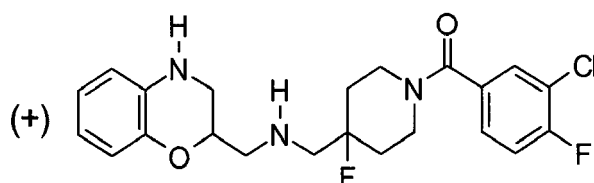
Actual % C 56.37, H 5.16, N 7.45.

40

EXAMPLE 2: (+)-(3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1a2)

[0050]

45



50

[0051] Using (+)-3,4-dihydro-2H-1,4-benzoxazine-2-methanamine (2a1) instead of (-)-3,4-dihydro-2H-1,4-Benzoxazine-2-methanamine (2a2) the title compound is obtained which is salified with fumaric acid to give the compound of formula (1a2).

55

$C_{22}H_{24}ClF_2N_3O_2$, $C_4H_4O_4$

MP: 185°C

$[\alpha]_D = +37.0$ (0.41 MeOH).

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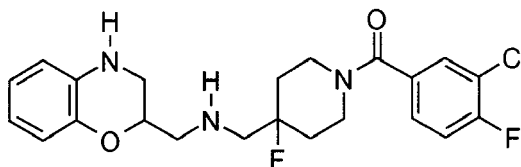
¹H NMR (DMSO d₆) δ 1.65-1.93 (m, 4H), 2.76-2.84 (m, 4H), 3.00 (dd, 1H), 3.32 (dd, 1H), 2.74-3.56 (m, 7H), 4.07 (m, 1H), 4.26 (s, 1H), 6.47 (t, 1H), 6.55 (d, 1H), 6.62-6.67 (m, 4H), 7.43-7.51 (m, 2H), 7.66 (d, 1H).
Theoretical % C 56.58, H 5.11, N 7.61
Actual % C 56.78, H 5.25, N 7.56.

5

EXAMPLE 3: (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1a3)

[0052]

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15

[0053] Using 3,4-dihydro-2H-1,4-benzoxazine-2-methanamine, commercially available, instead of (-)-3,4-dihydro-2H-1,4-Benzoxazine-2-methanamine (2a2), the title compound is obtained which is salified with hydrochloric acid to give the compound of formula (1a3).

20

C₂₂H₂₄ClF₂N₃O₂, H₂Cl₂

MP: 175°C

¹H NMR (DMSO d₆) δ 1.68-2.14 (m, 4H), 3.12-3.21 (m, 4H), 3.37-3.50 (3, 7H), 4.32 (s, 1H), 4.58 (m, 1H), 6.59 (t, 1H), 6.71 (d, 1H), 6.74-6.77 (m, 2H), 7.44-7.55 (m, 2H), 7.70 (dd, 1H), 9.48 (s, 2H).

25

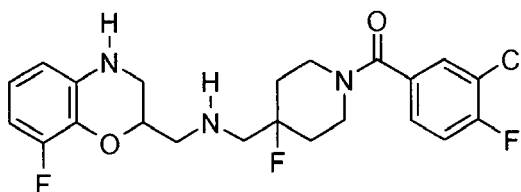
Theoretical % C 51.93, H 5.15, N 8.26

Actual % C 5.81, H 5.30, N 8.22.

EXAMPLE 4: (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-fluoro-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1b)

30

[0054]



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[0055] The same operating mode is used as for the preparation of (-)-(3-chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1a1) but by replacing (-)-3,4-dihydro-2H-1,4-benzoxazine-2-methanamine (2a2) with (±)-dihydro-8-fluoro-2H-1,4-benzoxazine-2-methanamine (2b). The compound obtained is then salified to fumarate form.

45

C₂₂H₂₃ClFN₃O₂, C₉H₄O₄

MP: 100°C

¹H NMR (DMSO d₆) δ 1.61-2.00 (m, 4H), 2.76-2.84 (m, 4H), 3.03-3.45 (m, 9H), 4.06 (m, 1H), 4.23 (s, 1H), 5.96 (s, 1H), 6.34-6.38 (m, 2H), 6.59-6.63 (m, 2H), 7.43-7.49 (m, 2H), 7.67 (d, 1H).

50

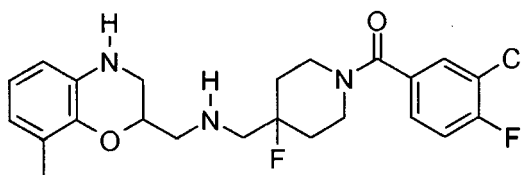
Theoretical % C 54.79, H 4.77, N 7.37

Actual % C 54.57, H 4.88, N 7.13.

EXAMPLE 5: (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-methyl-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1c)

55

[0056]



[0057] The same operating mode is followed as for the preparation of (-)-(3-chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1a1) but by replacing (-)-3,4-dihydro-2H-1,4-benzoxazine-2-methanamine (2a2) with dihydro-8-methyl-2H-1,4-benzoxazine-2-methanamine (2c). The compound obtained is then salified to dihydrochloride form.

$C_{23}H_{26}ClF_2N_3O_2$, H_2Cl_2

MP: 180°C

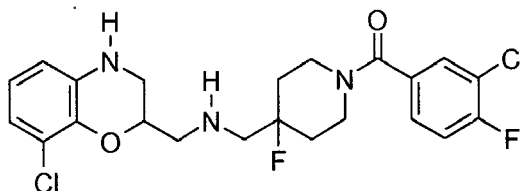
1H NMR (DMSO d_6) δ 1.85-2.08 (m, 4H), 2.13 (s, 3H), 3.09-3.46 (m, 10H), 4.31 (s, 1H), 4.59 (m, 1H), 6.50-6.55 (m, 2H), 6.63-6.67 (m, 1H), 7.45-7.54 (m, 2H), 7.69 (d, 1H), 9.52 (s, 2H).

Theoretical % C 52.84, H 5.40, N 8.04

Actual % C 53.55, H 5.67, N 7.65.

EXAMPLE 6: (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-chloro-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1d)

[0058]



[0059] The same operating mode is used as for the preparation of (-)-(3-chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1a1) but by replacing (-)-3,4-dihydro-2H-1,4-benzoxazine-2-methanamine (2a2) with dihydro-8-chloro-2H-1,4-benzoxazine-2-methanamine (2d). The compound obtained is then salified to dihydrochloride form.

$C_{22}H_{23}Cl_2F_2N_3O_2$, H_2Cl_2

MP: 136°C

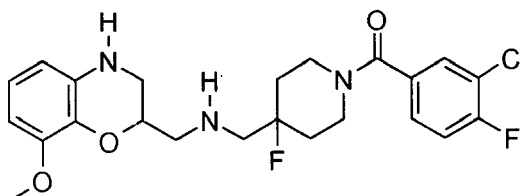
1H NMR (DMSO d_6) δ 1.82-1.94 (m, 4H), 3.11-3.75 (m, 10H), 4.06 (m, 1H), 4.35 (s, 1H), 4.64 (m, 1H), 6.57-6.64 (m, 2H), 6.73 (m, 1H), 7.45-7.68 (m, 2H), 7.68 (d, 1H), 9.59 (d, 2H).

Theoretical % C 48.63, H 4.64, N 7.73

Actual % C 48.57, H 4.54, N 7.42.

EXAMPLE 7: (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-methoxy-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1e)

[0060]



[0061] The same operating mode is followed as for the preparation of (-)-(3-chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1a1) but by replacing (-)-3,4-dihydro-2H-1,4-benzoxazine-2-methanamine (2a2) with dihydro-8-methoxy-2H-1,4-benzoxazine-2-methanamine (2e). The com-

compound obtained is the salified to dihydrochloride form.

$C_{23}H_{26}ClF_2N_3O_3$, H_2Cl_2

MP: 187°C

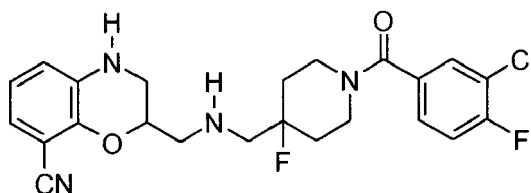
1H NMR (DMSO d_6) δ 1.75-2.10 (m, 4H), 3.09-3.70 (m, 10H), 3.71 (s, 3H), 4.27 (s, 1H), 4.59 (m, 1H), 6.31-6.36 (m, 2H), 6.68 (t, 1H), 7.46-7.53 (m, 2H), 7.69 (d, 1H), 9.86 (s, 2H).

Theoretical % C 51.26, H 5.24, N 7.79

Actual % C 51.15, H 5.37, N 7.53.

EXAMPLE 8: (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-cyano-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1f)

[0062]



[0063] The same operating mode is followed as for the preparation of (-)-(3-chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1a1) but by replacing (-)-3,4-dihydro-2H-1,4-benzoxazine-2-methanamine (2a2) with dihydro-8-cyano-2H-1,4-benzoxazine-2-methanamine (2f). The compound obtained is then salified to dihydrochloride form.

$C_{23}H_{23}ClF_2N_4O_2$, H_2Cl_2

MP: 149°C

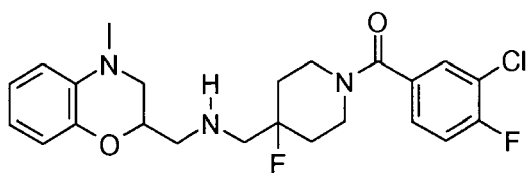
1H NMR (DMSO d_6) δ 1.72-2.13 (m, 4H), 3.14-3.63 (m, 10H), 4.26 (s, 1H), 4.72 (m, 1H), 6.87-6.94 (m, 3H), 7.45-7.64 (m, 2H), 7.67 (d, 1H), 9.60 (s, 2H).

Theoretical % C 51.75, H 4.72, N 10.50

Actual % C 51.36, H 4.71, N 10.28.

EXAMPLE 9: (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-4-methyl-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1g)

[0064]



[0065] The same operating mode is followed as for the preparation of (-)-(3-chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone (1a1) but by replacing (-)-3,4-dihydro-2H-1,4-benzoxazine-2-methanamine (2a2) with dihydro-4-methyl-2H-1,4-benzoxazine-2-methanamine (2g). The compound obtained is then salified to fumarate form.

$C_{23}H_{26}ClF_2N_3O_2$, $C_4H_4O_4$

MP: 125°C

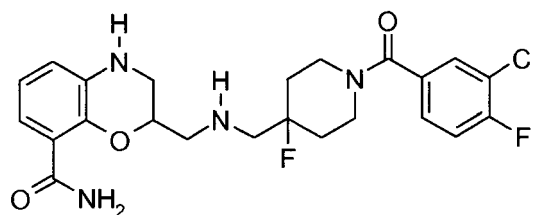
1H NMR (DMSO d_6) δ 1.60-2.08 (m, 4H), 2.81 (s, 3H), 2.76-3.51 (m, 10H), 4.22 (m, 2H), 6.56-6.76 (m, 4H), 7.46-7.65 (m, 2H), 7.67 (d, 1H).

Theoretical % C 48.80, H 5.34, N 7.42

Actual % C 48.72, H 5.42, N 7.33.

EXAMPLE 10: (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-carbamoyl-1,4-benzoxazine-2-methanami-
no)-methyl]-piperidin-1-yl}-methanone (1h)

[0066]



[0067] The same operating mode is followed as for the preparation of (-)-(3-chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-
dihydro-2H-1,4-benzoxazine-2-methanami-
no)-methyl]-piperidin-1-yl}-methanone (1a1) but by replacing (-)-3,4-dihydro-
2H-1,4-benzoxazine-2-methanamine (2a2) with dihydro-8-carbamoyl-2H-1,4-benzoxazine-2-methanamine (2h). The
compound obtained is then salified to dihydrochloride form.

$C_{23}H_{25}ClF_2N_4O_3$, H_2Cl_2

MP: 170°C

1H NMR (DMSO d_6) δ 1.80-2.12 (m, 4H), 3.12-3.73 (m, 10H), 4.45 (s, 1H), 4.64 (m, 1H), 6.87-6.93 (m, 3H), 7.45-7.66
(m, 2H), 7.68 (d, 1H), 9.40 (d, 2H).

Theoretical % C 50.06, H 4.93, N 10.15

Actual % C 49.73, H 4.68, N 10.00.

PHARMACOLOGICAL STUDY ON THE PRODUCTS OF THE INVENTION

[0068] The compounds of this invention were compared with buspirone (4-butyl-4-methyl-1-[4-(4-pyridin-2-yl)-piperazin-1-yl]-butyl]-piperidine-2,6-dione) which is an agonist of 5-HT_{1A} receptors used clinically. The affinity of the compounds of the invention for the rat 5-HT_{1A} receptor was measured conventionally from competitive experiments with a radiolabelled 5-HT_{1A} agonist. The antidepressant activity of the compounds of the invention and of buspirone was assessed after oral administration in rats with the forced swimming test (Eur. J. Pharmacol. 1978, 47, 379). This test is widely used since it is predictive of antidepressant action in man. Analgesic activity was determined after intra-peritoneal administration to rats, both with a physiological pain model and a pathological pain model. By physiological pain, the inventors designate pain whose origin is a lesion and/or organic ill-function such as pain caused by excessive nociceptive stimuli. On the contrary, by pathological pain the inventors designate pain which has no apparent pathological cause and therefore does not play a physiological role (e.g. alarm signal); this latter category includes some pain of neuropathic origin for example.

[0069] The physiological pain model chosen by the inventors to determine the analgesic activity of the compounds of the invention uses excess nociceptive stimuli (injection of formol) to cause a painful sensation in animal (Eur. J. Pharmacol. 2001, 421, 109). For the so-called pathological pain model in animal, the inventors chose to use pain induced by the injection of a cytotoxic agent such as oxaliplatin (Eur. J. Cancer 2007, 2658).

1- Measurement of the affinity of the compounds of the invention for the 5-HT_{1A} receptors

PROTOCOL

[0070] The *in vitro* affinity of the compounds of the invention for the 5-HT_{1A} receptors was determined by measuring the shift of (3H) 8-OH-DPAT (agonist of 5HT_{1A} receptors labelled with tritium, TRK 850; 160-240 Ci/mmol).

[0071] The study on binding with the 5-HT_{1A} receptor was conducted as described in Naunyn-Schmiedeberg's Arch. Pharmacol. 1991, 343, 106. For these experiments, rat cerebral cortices were used. After unfreezing the brain in Tris-HCl buffer 50 mmol, pH = 7.40 at 25°C, the cerebral cortex is sampled and homogenized in 20 volumes of buffer held at 4°C. The homogenate is centrifuged at 39000 g for 10 min, the centrifuge residue is suspended in the same volume of buffer and again centrifuged. After further suspension under the same conditions, the homogenate is incubated for 10 min at 37°C then again centrifuged. The final residue is suspended in cold reaction buffer Tris-HCl 50 mmol, pH = 7.40 at 25°C containing 10 mmol of pargyline, 4 mmol of CaCl₂ and 0.10 % ascorbic acid. The final concentration of the tissue in the incubation medium is 10 mg/tube.

[0072] The reaction tubes contain 0.10 mL of (3H) 8-OH-DPAT (final 0.20 nmol), 0.10 mL of product to be tested 6-7 concentrations and 0.80 mL of tissue. Non-specific binding is defined using 10 nmol of 5-HT. The reaction tubes are

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incubated at 23°C for 30 min then their content is rapidly vacuum filtered through Whatman GF/B filters, the tubes are rinsed with 2 x 5mL of Tris-HCl buffer 50 mmol, pH = 7.4 at 25°C. Radioactivity is collected on the filter and analyzed by liquid scintillation by adding 4mL of scintillating liquid (Emulsifier Safe, Packard). All experiments were performed in triplicate.

5 **[0073]** The inhibition constants (K_i) of the products of the invention are estimated from shift experiments using the non-linear regression programme RADLIG version 4 by EBDA (Equilibrium Binding Data Analysis Biosoft, Cambridge, UK, Mc Pherson, 1985). The dissociation constant of the radioactive ligand used for calculations is 0.31 mmol for (^3H)8-OH-DPAT. The values of pK_i ($-\log K_i$) are given in the form mean \pm SEM of at least 3 experiments.

10 2- Forced swimming test: antidepressant activity of the compounds of the invention

PROTOCOL

15 **[0074]** The rats (Male Sprague Dawley rats (ICO: OFA SD [IOPS], Iffa Credo, France), are placed in a cylinder (45cm high and 20cm in diameter) filled with water at 25°C \pm 0.5 up to a height of 17 cm. This depth allows rats to swim or float without their tail touching the bottom of the cylinder.

20 **[0075]** 24 h before the test day, the rats are placed in the cylinder for 15 min, a lapse of time after which they no longer attempt to escape and remain immobile. On the test day the animals are replaced in the cylinder and the duration of animal immobility is measured by direct observation followed by verification of an audiovisual recording for 5 min. The products of the invention are administered by oral route 60 min before the test. A rat is considered to be immobile if it allows itself to float and only makes small movements to remain on the surface. Two rats are observed at the same time.

3- Formol test: analgesic activity against so-called physiological pain

25 PROTOCOL

30 **[0076]** The rats (Male Sprague Dawley rats (ICO: OFA SD [IOPS], Iffa Credo, France) are placed in plexiglass observation boxes above an angled mirror so as to facilitate observation of the hind paws. After thirty minutes of habituation, the animals are given an injection of formol diluted to 2.5% on the plantar surface of the right hind paw. The injection of formol produces behavioural responses which occur in two phases:

- an acute phase, from 0 to 5 min after injection of the formol, corresponding to stimulation of receptors specialized in the transmission of pain messages to the spinal cord.
- a late phase which occurs 20 to 30 min after the injection. This phase corresponds to stimulation of receptors by inflammatory mediators and/or to hyper-excitability of the dorsal horn induced during the first phase. This late phase therefore involves central sensitization.

40 **[0077]** For the study of the compounds of the invention we selected two expressions of painful behaviour and chose two periods of observation which correspond to the two pain phases (i.e. 0-5 min and 22.5-27.5 min). During these two 5-min periods the animals are observed every 30 seconds and are given scores for the following behaviours: paw licking or not of the injected paw, and lifting or non-lifting of the injected paw. Ten observations give a maximum score of 10 for each parameter for each of the 2 phases. The products of the invention are administered via intraperitoneal route 15 min before the injection of formol.

45 4- Oxaliplatin test: analgesic activity against so-called pathological pain

PROTOCOL

50 **[0078]** The rats (Male Sprague Dawley rats (ICO: OFA SD [IOPS], Iffa Credo, France) are tested a first time on the Friday to determine their mechanical sensitivity threshold (von Frey test). They are then given an intra-peritoneal injection (i.p.) of oxaliplatin (anticancer treatment causing neuropathic pain in patients) at a dose of 8 mg/kg. This dose in rat induces neuropathy which translates as mechanical hypersensitivity (allodynia) which develops 3 days after the injection with a peak on day five. For the study of the compounds of the invention, the animals are re-tested on day five, 15 min after administration of the compound via intra-peritoneal route.

55

STATISTICAL ANALYSES OF RESULTS

[0079] Quantification of the effect of the compounds of the invention on the forced swimming tests and on the formol

test is conducted by one-factor variance analysis between groups (ANOVA analysis) followed by a multiple comparison test (Dunnett's test) versus control animals. The ED₅₀ value is calculated using Litchfield and Wilcoxon analysis from the percentage of responding animals.

5 FIGURES

[0080]

10 Figure 1 gives the results obtained during the forced swimming test after oral administration (p.o.) of the compound of formula (1a1) or of buspirone, namely the observed time of animal immobility (in seconds) compared with the logarithm of the dose of the administered compound (in mg/kg).

15 Figure 2 gives the observed results (either for paw lifting or paw licking) for the formol test after intra-peritoneal administration (i.p.) of the compound of formula (1a1) or of buspirone. For this test, the animals are observed every 30 seconds during two periods of 5 min. The following behaviours are noted: paw licking or not of the injected paw, and paw lifting or not of the injected paw. Ten observations give a maximum score of 10 for each parameter for each of the 2 phases, measuring either paw lifting or paw licking. This test was also performed by comparison with administration of the vehicle (veh) alone.

20 Figure 3 shows the results obtained with the von Frey test with oxaliplatin. For each experiment, pressure is exerted on the paw of the animals, either non-treated with oxaliplatin (basal), or treated with oxaliplatin and after intra-peritoneal administration of a saline solution or of compound (1a1) (at a dose of 0.01, 0.04 or 0.16 mg/kg) or of buspirone (at a dose of 0.63 or 2.5 mg/kg). The pressure force is then measured (in g) at which withdrawal of the paw of the animals is observed.

25

RESULTS

1) Measurement of the affinity of the compounds of the invention for the 5-HT_{1A} receptors.

30 [0081] Table 1, as an example, gives the pKi values for some derivatives of the invention compared with buspirone chosen as reference product.

Table 1

35

Compound	5-HT _{1A} affinity (pKi)
1a1	8.99
1b	9.20
1c	8.91
1d	8.64
1e	8.82
1f	9.19
1g	9.10
1h	9.13
buspirone	7.65

40

45

50 [0082] The test results show that the compounds of formula (1) have strong affinity for the serotonergic receptors of sub-type 5-HT_{1A}. The 5-HT_{1A} affinity of the compounds of the invention is additionally much higher than that of buspirone.

2) Forced swimming test: antidepressant activity of the compounds of the invention.

55

[0083] The forced swimming test (Figure 1), after oral administration in the rat, shows that the compound of formula (1a1), representing the series, exerts central action. For example, the formula (1a1) compound is capable of reducing the animal's immobility time in dose-dependent fashion [F(7.50) = 43.67; P<0.001]. This compound is both very powerful

(ED₅₀ = 0.08 mg/Kg) and highly efficient since none of the animals remains immobile on and after the dose of 10 mg/Kg. By comparison buspirone, even at a dose of 40 mg/Kg, has no effect on animal immobility [F(5.61)= 0.51 P>0.05]. To conclude, compound (1a1), and the compounds belonging to this chemical series in general, exhibit fully remarkable antidepressant properties after administration via oral route.

3) Formol test: analgesic activity against so-called physiological pain.

[0084] The formol test (Figure 2), using administration via intra-peritoneal route, shows that the formula (1a1) compound, representing this chemical series, exerts remarkable analgesic activity against pain of physiological origin. The formula (1a1) compound shows dose-dependent inhibition of the 2 measured parameters (paw lifting and paw licking) for each of the 2 phases: [F(5.36) = 323.80; P<0.001], [F(5.36) = 41.13; P<0.001], [F(5.36) = 50.19; P<0.001] and [F(5.36) = 39.67; P<0.0011, respectively.

[0085] The efficiency of the formula (1a1) compound and of the compounds of the invention in general, is clearly apparent with regard to the paw lifting parameter. Compound (1a1) not only proves to be very powerful (ED₅₀ = 0.05 mg/Kg) for inhibition of this parameter, but it is also very efficient insofar as it prevents paw lifting in all the rats injected with formol on and after a dose of 0.63 mg/Kg. Full analgesia is obtained irrespective of the pain phase under consideration (acute or late) and is also expressed for the paw licking parameter. By comparison, buspirone only affects the paw lifting parameter during the acute phase and late phase on and after a dose of 2.5 mg/kg ([F(3.24) = 8.20; P<0.001] and [F(3,24) = 4.57; P=0.01]). Buspirone inhibits paw licking on and after a dose of 0.63 mg/kg for the acute phase and 2.5 mg/kg for the late phase ([F(3.24) = 47.04; P<0.001] and [F(3.24) = 40.50; P<0.001]). To conclude, compound (1a1), and the compounds belonging to this chemical series in general, exhibit analgesic properties against physiological pain that are fully remarkable after intra-peritoneal administration.

4-) Oxaliplatin test: analgesic activity against so-called pathological pain.

[0086] The test for oxaliplatin-induced pain (Figure 3), via intra-peritoneal administration, shows that the formula (1a1) compound, representative of this chemical series, exerts powerful analgesic activity against so-called pathological pain. For example the formula (1a1) compound shows dose-dependent inhibition of allodynia developed by animals treated with oxaliplatin. Full analgesia is obtained on and after a dose of 0.04 mg/kg of compound 1a1. By comparison, buspirone does not produce any significant analgesia even at a dose of 2.5 mg/kg.

[0087] To summarize, compound (1a1), and the compounds belonging to this chemical series in general, display analgesic properties against pathological pain that are fully remarkable after administration via i.p. route.

[0088] It arises from these tests that the compounds of the invention exhibit:

- affinity for the serotonergic receptors of sub-type 5-HT_{1A} that is greater than that of buspirone,
- antidepressant activity that is greater than that of buspirone,
- broad analgesic activity since it addresses pain of both physiological and pathological origin. This analgesic activity proves to be greater than that of buspirone, a 5-HT_{1A} agonist given human clinical use.

[0089] In this respect, the compounds of the invention are therefore potentially useful for the treatment of pathologies involving serotonergic ill-functioning, in particular for the treatment of depression and pain for which therapeutic needs are considerable.

[0090] The administration of the compounds of the invention can use oral, nasal, sublingual, rectal or parenteral routes. As a non-limiting example of formulations, one preparation of the compounds of the invention is given below. The ingredients and other therapeutically acceptable ingredients can be added in other proportions without modifying the scope of the invention. The terms « active ingredient » used in the examples of formulation given below refer to a compound of formula (1) or an addition salt or optionally to a hydrate of an addition salt of the formula (1) compound with a pharmaceutically acceptable mineral acid or organic acid or one of the enantiomers of the formula (1) compound.

Example of pharmaceutical composition:

[0091] Formula to prepare 1000 tablets each containing 10 mg of active ingredient:

Active ingredient	10 g
Lactose	100 g

(continued)

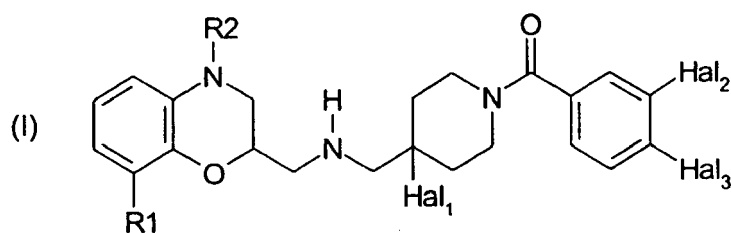
Wheat starch	10 g
Magnesium stearate	3 g
Talc	3 g

5

Claims

10 1. Compounds of general formula (1)

15



20

wherein

R1 is:

25

- a hydrogen atom or a halogen,
- a straight or branched C₁-C₆ alkyl group or a C₁-C₃ fluoroalkyl group,
- a straight or branched C₁-C₆ alkoxy group,
- a carbamyl group, N-substituted or not by one or two, straight or branched C₁-C₃ alkyl groups, or
- a cyano group (CN)

30

R2 is:

- a hydrogen atom or a straight or branched C₁-C₆ alkyl group,

35

Hal₁, Hal₂ and Hal₃ are:

- a halogen

their addition salts with pharmaceutically acceptable mineral acids or organic acids, and their enantiomer forms.

40

2. Compound according to claim 1, **characterized in that** Hal₁ and Hal₃ are a fluorine atom and Hal₂ is a chlorine atom.3. Compound according to any of claims 1 to 2, **characterized in that** R1 is chosen from the group consisting of: a hydrogen atom and a carbamyl group N-substituted or not by one or two, straight or branched C₁-C₃ alkyl groups.

45

4. Compound according to any of claims 1 to 3 **characterized in that** R2 is a hydrogen atom.5. Compound according to any of claims 1 to 4 **characterized in that** R1 and R2 are a hydrogen atom.

50

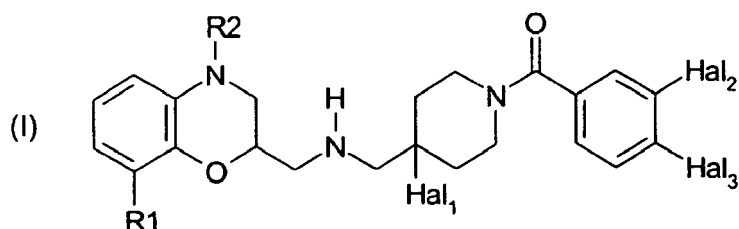
6. Compound according to either of claims 1 to 2, **characterized in that** it is chosen from the group consisting of:

- (-)-(3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone,
- (+)-(3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone,
- (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone,
- (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-fluoro-1,4-benzoxazine-2-methanamino)-me-

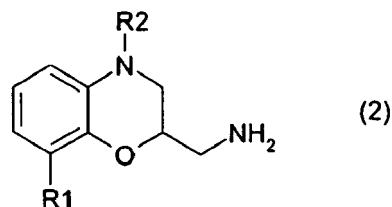
55

thyl]-piperidin-1-yl)-methanone,
 - (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-methyl-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone,
 - (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-chloro-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone,
 - (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-methoxy-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone,
 - (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-cyano-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone,
 - (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-4-methyl-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone,
 - (3-Chloro-4-fluoro-phenyl)-{4-fluoro-4-[(3,4-dihydro-2H-8-carbamoyl-1,4-benzoxazine-2-methanamino)-methyl]-piperidin-1-yl}-methanone.

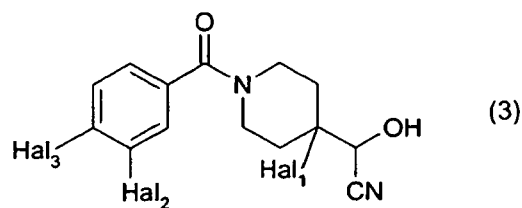
7. Compound of formula (1) such as defined in any of claims 1 to 6 for its use as medicinal product.
8. Compound according to claim 7, **characterized in that** the medicinal product is intended for the treatment of pain.
9. Compound according to claim 7, **characterized in that** the medicinal product is intended for the treatment of pathological pain and/or physiological pain.
10. Compound according to claim 7, **characterized in that** the medicinal product is intended for the treatment of depression.
11. Pharmaceutical composition **characterized in that** it comprises at least one compound of formula (1) such as defined according to any of claims 1 to 6 in combination with one or more suitable and pharmaceutically acceptable excipients, adjuvants or vehicles.
12. Method to prepare compounds of general formula (1)



wherein the radicals R_1 , R_2 , Hal_1 , Hal_2 and Hal_3 have the designations given in claim 1, **characterized in that** it uses the condensation between an intermediate of type 3,4-dihydro-2H-1,4-benzoxazine-2-methanamine of formula (2)



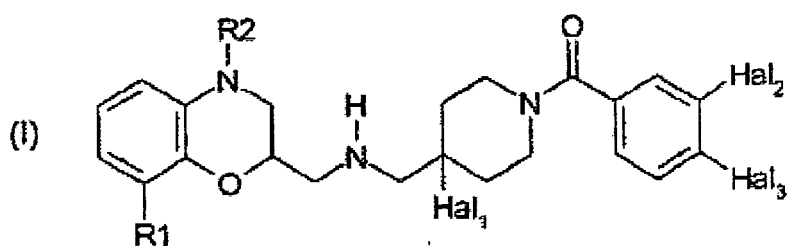
in which R_1 and R_2 have the designations given previously for formula (1), and cyanohydrine of formula (3)



10 in which Hal₁, Hal₂ and Hal₃ have the designations given previously for formula (1), in the presence of a reducing agent and optionally a base.

Patentansprüche

15 1. Verbindungen der allgemeinen Formel (1)



worin

30 R1:

- ein Wasserstoffatom oder ein Halogen,
- eine gerad- oder verzweigt-kettige C₁-C₆-Alkylgruppe oder eine C₁-C₃-Fluoralkylgruppe,
- eine gerad- oder verzweigt-kettige C₁-C₆-Alkoxygruppe,
- eine Carbamylgruppe, die durch eine oder zwei gerad- oder verzweigt-kettige C₁-C₃-Alkylgruppen N-substituiert oder nicht substituiert ist, oder
- eine Cyanogruppe (CN) ist;

40 R2:

- ein Wasserstoffatom oder eine gerad- oder verzweigt-kettige C₁-C₆-Alkylgruppe ist,

Hal₁, Hal₂ und Hal₃:

- ein Halogen sind,

deren Additionssalze mit pharmazeutisch annehmbaren Mineralsäuren oder organischen Säuren und deren Enantiomerformen.

- 50 2. Verbindung nach Anspruch 1, **dadurch gekennzeichnet, dass** Hal₁ und Hal₃ ein Fluoratom sind und Hal₂ ein Chloratom ist.
3. Verbindung nach einem der Ansprüche 1 bis 2, **dadurch gekennzeichnet, dass** R1 aus der Gruppe bestehend aus: einem Wasserstoffatom und einer Carbamylgruppe, die durch eine oder zwei gerad- oder verzweigt-kettige C₁-C₃-Alkylgruppen N-substituiert oder nicht substituiert ist, ausgewählt ist.
- 55 4. Verbindung nach einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, dass** R2 ein Wasserstoffatom ist.

5. Verbindung nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, dass** R1 und R2 ein Wasserstoffatom sind.

6. Verbindung nach einem der Ansprüche 1 bis 2, **dadurch gekennzeichnet, dass** sie ausgewählt ist aus der Gruppe bestehend aus:

- (-)-(3-Chlor-4-fluorphenyl)-{4-fluor-4-[(3,4-dihydro-2H-1,4-benzoxazin-2-methanamino)-methyl]-piperidin-1-yl}methanon,
- (+)-(3-Chlor-4-fluorphenyl)-{4-fluor-4-[(3,4-dihydro-2H-1,4-benzoxazin-2-methanamino)-methyl]-piperidin-1-yl}methanon,
- (3-Chlor-4-fluorphenyl)-{4-fluor-4-[(3,4-dihydro-2H-1,4-benzoxazin-2-methanamino)-methyl]-piperidin-1-yl}methanon,
- (3-Chlor-4-fluorphenyl)-{4-fluor-4-[(3,4-dihydro-2H-8-fluor-1,4-benzoxazin-2-methanamino)-methyl]-piperidin-1-yl}methanon,
- (3-Chlor-4-fluorphenyl)-{4-fluor-4-[(3,4-dihydro-2H-8-methyl-1,4-benzoxazin-2-methanamino)-methyl]-piperidin-1-yl}methanon,
- (3-Chlor-4-fluorphenyl)-{4-fluor-4-[(3,4-dihydro-2H-8-chlor-1,4-benzoxazin-2-methanamino)-methyl]-piperidin-1-yl}methanon,
- (3-Chlor-4-fluorphenyl)-{4-fluor-4-[(3,4-dihydro-2H-8-methoxy-1,4-benzoxazin-2-methanamino)-methyl]-piperidin-1-yl}methanon,
- (3-Chlor-4-fluorphenyl)-{4-fluor-4-[(3,4-dihydro-2H-8-cyano-1,4-benzoxazin-2-methanamino)-methyl]-piperidin-1-yl}methanon,
- (3-Chlor-4-fluorphenyl)-{4-fluor-4-[(3,4-dihydro-2H-4-methyl-1,4-benzoxazin-2-methanamino)-methyl]-piperidin-1-yl}methanon,
- (3-Chlor-4-fluorphenyl)-{4-fluor-4-[(3,4-dihydro-2H-8-carbamoyl-1,4-benzoxazin-2-methanamino)-methyl]-piperidin-1-yl}methanon.

7. Verbindung der Formel (1), wie in einem der Ansprüche 1 bis 6 definiert, für deren Verwendung als ein medizinisches Erzeugnis.

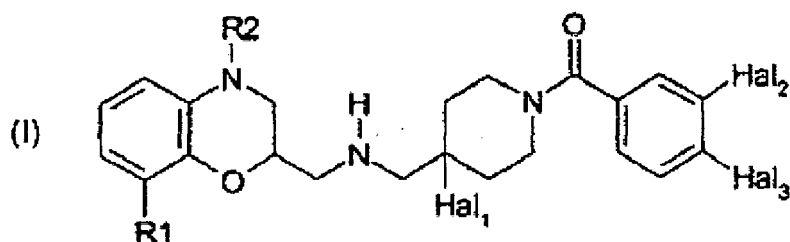
8. Verbindung nach Anspruch 7, **dadurch gekennzeichnet, dass** das medizinische Erzeugnis für die Behandlung von Schmerz bestimmt ist.

9. Verbindung nach Anspruch 7, **dadurch gekennzeichnet, dass** das medizinische Erzeugnis für die Behandlung von pathologischem Schmerz und/oder physiologischem Schmerz bestimmt ist.

10. Verbindung nach Anspruch 7, **dadurch gekennzeichnet, dass** das medizinische Erzeugnis für die Behandlung von Depression bestimmt ist.

11. Pharmazeutische Zusammensetzung, **dadurch gekennzeichnet, dass** sie mindestens eine Verbindung der Formel (1), wie gemäß einem der Ansprüche 1 bis 6 definiert, in Kombination mit einem oder mehreren geeigneten und pharmazeutisch annehmbaren Trägern, Adjuvantien oder Vehikeln umfasst.

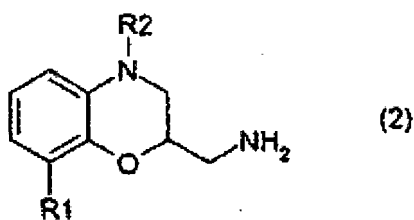
12. Verfahren zum Herstellen von Verbindungen der allgemeinen Formel (1)



worin die Reste R₁, R₂, Hal₁, Hal₂ und Hal₃ die in Anspruch 1 angegebenen Bezeichnungen haben, **dadurch gekennzeichnet, dass** es die Kondensation zwischen einer Zwischenstufe vom Typ 3,4-Dihydro-2H-1,4-benzoxa-

zin-2-methanamin der Formel (2)

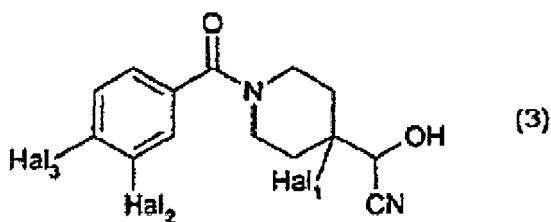
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10

in welcher R_1 und R_2 die zuvor für Formel (1) angegebenen Bezeichnungen haben, und Cyanhydrin der Formel (3)

15



20

25 in welcher Hal_1 , Hal_2 und Hal_3 die zuvor für Formel (1) angegebenen Bezeichnungen haben, in Gegenwart eines Reduktionsmittels und gegebenenfalls einer Base einsetzt.

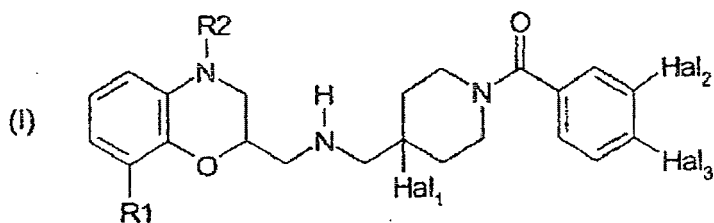
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Revendications

30

1. Composés de formule générale (1)

35



40

dans laquelle

R1 est :

45

- un atome d'hydrogène ou un halogène,
- un groupe alkyle C_1-C_6 linéaire ou ramifié ou un groupe fluoroalkyle C_1-C_3 ,
- un groupe alcoxy C_1-C_6 linéaire ou ramifié,
- un groupe carbamyle, N-substitué ou non par un ou deux groupes alkyle C_1-C_3 linéaires ou ramifiés, ou
- un groupe cyano (CN)

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R2 est :

- un atome d'hydrogène ou un groupe alkyle C_1-C_6 linéaire ou ramifié,

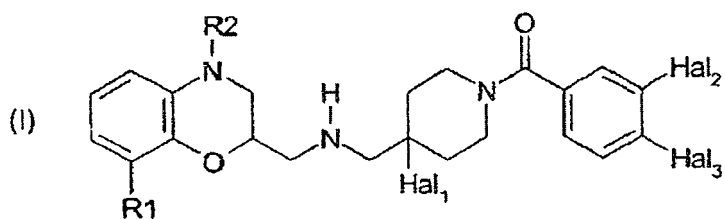
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Hal_1 , Hal_2 et Hal_3 sont :

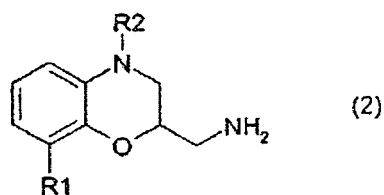
- un halogène

leurs sels d'addition avec des acides inorganiques ou des acides organiques pharmaceutiquement acceptables, et leurs formes énantiomères.

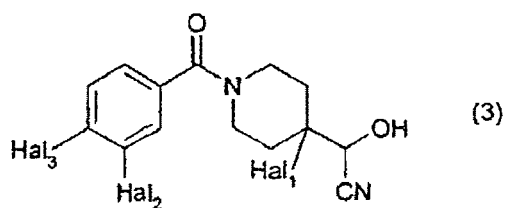
- 5
2. Composé selon la revendication 1, **caractérisé en ce que** Hal₁ et Hal₂ sont un atome de fluor et Hal₃ est un atome de chlore.
- 10
3. Composé selon l'une quelconque des revendications 1 à 2, **caractérisé en ce que** R1 est choisi dans le groupe constitué par : un atome d'hydrogène et un groupe carbamyle N-substitué ou non par un ou deux groupes alkyle C₁-C₃ linéaires ou ramifiés.
- 15
4. Composé selon l'une quelconque des revendications 1 à 3 **caractérisé en ce que** R2 est un atome d'hydrogène.
5. Composé selon l'une quelconque des revendications 1 à 4 **caractérisé en ce que** R1 et R2 sont un atome d'hydrogène.
- 20
6. Composé selon l'une ou l'autre des revendications 1 à 2, **caractérisé en ce qu'il** est choisi dans le groupe constitué par :
- (-)-(3-chloro-4-fluoro-phényl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-méthanamino)-méthyl]-pipéridin-1-yl}-méthanone,
 - (+)-(3-chloro-4-fluoro-phényl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-méthanamino)-méthyl]-pipéridin-1-yl}-méthanone,
 - (3-chloro-4-fluoro-phényl)-{4-fluoro-4-[(3,4-dihydro-2H-1,4-benzoxazine-2-méthanamino)-méthyl]-pipéridin-1-yl}-méthanone,
 - (3-chloro-4-fluoro-phényl)-{4-fluoro-4-[(3,4-dihydro-2H-8-fluoro-1,4-benzoxazine-2-méthanamino)-méthyl]-pipéridin-1-yl}-méthanone,
 - (3-chloro-4-fluoro-phényl)-{4-fluoro-4-[(3,4-dihydro-2H-8-méthyl-1,4-benzoxazine-2-méthanamino)-méthyl]-pipéridin-1-yl}-méthanone,
 - (3-chloro-4-fluoro-phényl)-{4-fluoro-4-[(3,4-dihydro-2H-8-chloro-1,4-benzoxazine-2-méthanamino)-méthyl]-pipéridin-1-yl}-méthanone,
 - (3-chloro-4-fluoro-phényl)-{4-fluoro-4-[(3,4-dihydro-2H-8-méthoxy-1,4-benzoxazine-2-méthanamino)-méthyl]-pipéridin-1-yl}-méthanone,
 - (3-chloro-4-fluoro-phényl)-{4-fluoro-4-[(3,4-dihydro-2H-8-cyano-1,4-benzoxazine-2-méthanamino)-méthyl]-pipéridin-1-yl}-méthanone,
 - (3-chloro-4-fluoro-phényl)-{4-fluoro-4-[(3,4-dihydro-2H-4-méthyl-1,4-benzoxazine-2-méthanamino)-méthyl]-pipéridin-1-yl}-méthanone,
 - (3-chloro-4-fluoro-phényl)-{4-fluoro-4-[(3,4-dihydro-2H-8-carbamoyl-1,4-benzoxazine-2-méthanamino)-méthyl]-pipéridin-1-yl}-méthanone.
- 30
- 40
7. Composé de formule (1) tel que défini dans l'une quelconque des revendications 1 à 6 pour son utilisation à titre de produit à visée médicale.
8. Composé selon la revendication 7, **caractérisé en ce que** le produit à visée médicale est destiné à traiter la douleur.
- 45
9. Composé selon la revendication 7, **caractérisé en ce que** le produit à visée médicale est destiné à traiter la douleur pathologique et/ou la douleur physiologique.
- 50
10. Composé selon la revendication 7, **caractérisé en ce que** le produit à visée médicale est destiné à traiter la dépression.
11. Composition pharmaceutique **caractérisée en ce qu'elle** comprend au moins un composé de formule (1) tel que défini dans l'une quelconque des revendications 1 à 6 en association avec un ou plusieurs excipients, adjuvants ou véhicules convenables et pharmaceutiquement acceptables.
- 55
12. Procédé de préparation de composés de formule générale (1)



10 dans laquelle les radicaux R_1 , R_2 , Hal_1 , Hal_2 et Hal_3 ont les significations indiquées dans la revendication 1, **carac-**
térisé en ce qu'il utilise la condensation entre un intermédiaire de type 3,4-dihydro-2H-1,4-benzoxazine-2-méthana-
 mine de formule (2)



25 dans laquelle R_1 et R_2 ont les significations indiquées précédemment pour la formule (1),
 et une cyanhydrine de formule (3)



35 dans laquelle Hal_1 , Hal_2 et Hal_3 ont les significations indiquées précédemment pour la formule (1), en présence
 d'un agent de réduction et éventuellement d'une base.

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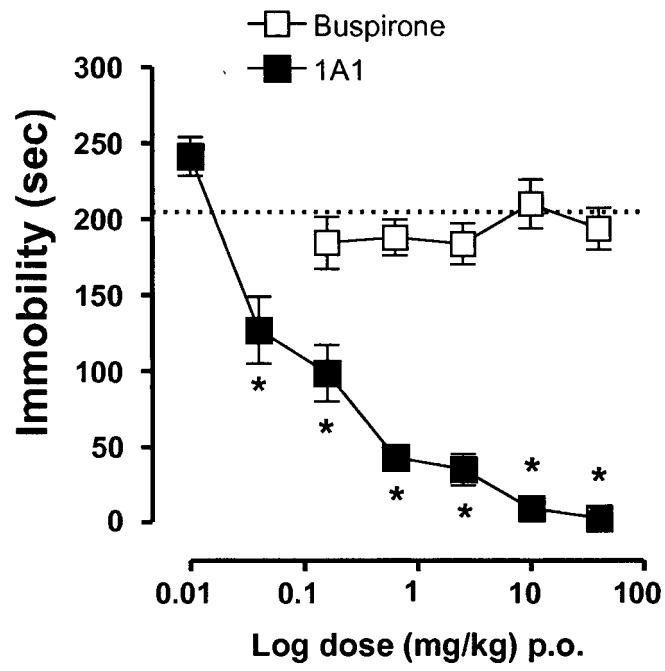


Figure 1

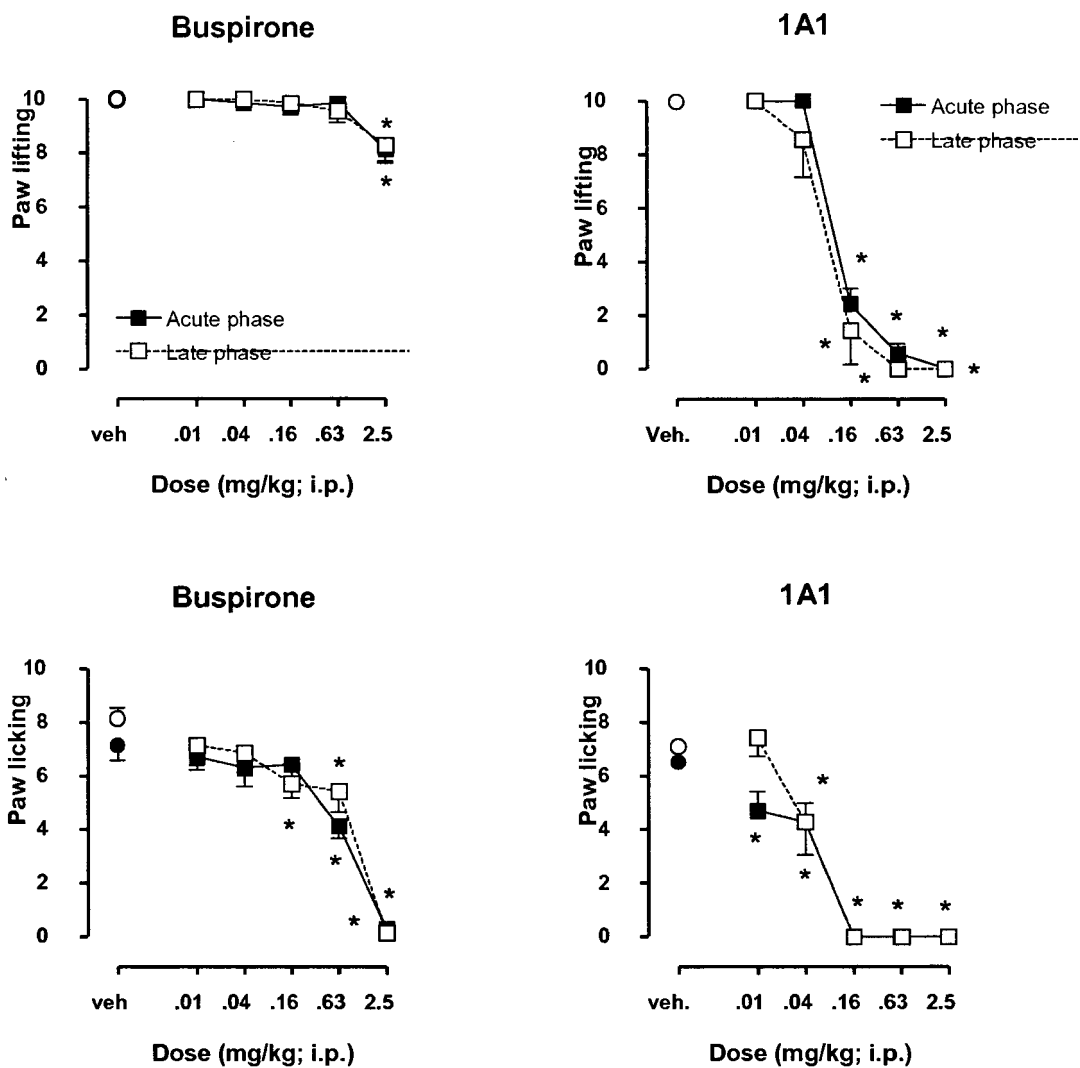


Figure 2

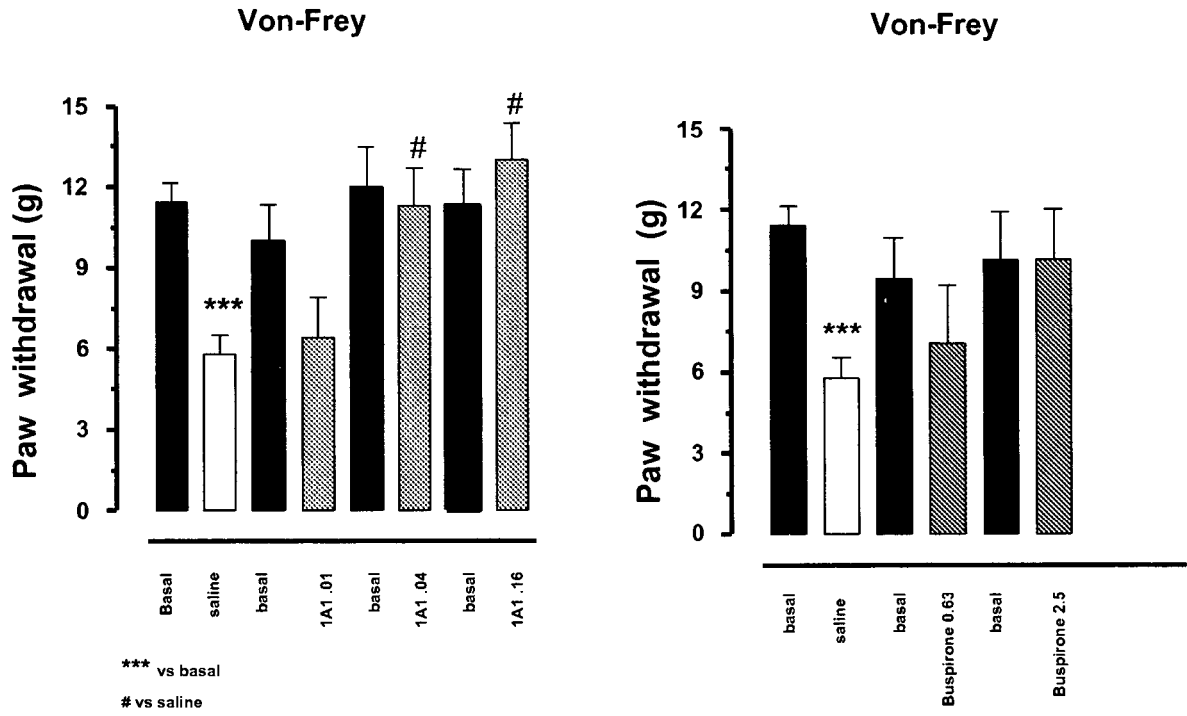


Figure 3

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 02064585 A [0032]

Non-patent literature cited in the description

- *Curr Drug Targets CNS Neurol Dis.*, 2004, vol. 3, 1 [0001]
- *Neurosci Biobehav Rev.*, 1990, vol. 14, 35 [0001]
- *J. Clin. Psychiatry*, 1987, vol. 48, 3S [0001]
- *Int. J. Neuropsychopharmacology*, 1998, vol. 1, 18 [0001]
- *Arch. Int. Pharmacodyn.*, 1995, vol. 329, 347 [0001]
- *Behav. Brain Res.*, 1995, vol. 73 (1/2), 69 [0001]
- *Eur. J. Pharmacol.*, 2001, vol. 420, 103-112 [0004]
- **E.L. ELIEL ; S.H. WILEN.** Stereochemistry of Organic Compounds. John Wiley & Sons, Inc, 1994, 104-12 [0014]
- Remington, The Science and Practice of Pharmacy. Mack Publishing Company, 1995 [0022]
- *J. Med. Chem.*, 1998, vol. 41, 3142 [0032]
- *J. Med. Chem.*, 2003, vol. 16, 1338 [0033]
- *Archiv der Pharmazie*, 1982, vol. 315, 538 [0033]
- *Eur. J. Pharmacol.*, 1978, vol. 47, 379 [0068]
- *Eur. J. Pharmacol.*, 2001, vol. 421, 109 [0069]
- *Eur. J. Cancer*, 2007, 2658 [0069]
- *Equilibrium Binding Data Analysis Biosoft*, 1985 [0073]