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2-ARYLINDOLE DERIVATIVES AS NPGES-1 INHIBITORS

5 The present invention relates to a 2-arylindole compound substituted in position 5, to a pharmaceutical composition comprising it, to intermediate compounds and to a preparation process therefor.

More particularly, the present invention relates to a 2-arylindole compound substituted in position 5, which has inhibitory activity on
10 mPGEs-1.

It is known that prostaglandins (PG) are oxygenated fatty acids synthesized and released into the extracellular space, and then into the plasma, urine and other biological fluids.

They are important bioregulators, but also inflammation mediators
15 that modulate intracellular reactions and intercellular communication.

The prostaglandins E₂ (PGE₂) have an important physiological role of regulating renal function, vascular homeostasis, bone remodelling, induction of fever, gastrointestinal function and pregnancy. Besides these physiological functions, the PGE₂ prostaglandins behave as
20 potent mediators of acute inflammation (inducing hyperalgesia, vasodilatation and discharge of fluids from vessels: Vane J.R. and Botting R.M. 1997 "Anti-inflammatory drugs and their mechanism of action" Inflamm. Res. 47 (2): p. 78) and chronic inflammation.

Specifically, the PGE₂ prostaglandins are particularly abundant in
25 articular inflammatory pathologies. PGE₂ prostaglandins also play a role in pain and are potent pyretic agents (Ayoub S.S. et al., 2004 "A ceta-minophen-induced hypothermia in mice is mediated by a prostaglandin endoperoxide synthase 1 gene-derived protein", PNAS 101: 11165-11169; Ivanov A. et al. 2002 "Prostaglandin E₂ – synthesizing enzymes
30 in fever: differential transcriptional regulation", Am. J. Physiol. Regul.

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Integr. Comp. Physiol. 283: R1104-R1117).

The enzyme responsible for the synthesis of PGE₂ prostaglandins is prostaglandin E synthase (PGES), which converts the endoperoxide PGH₂, formed from arachidonic acid by the action of cyclooxygenases,
5 into PGE₂. The activity of PGES has been found both in the cytosolic fraction and membrane-bound in various types of cells.

Three enzymatic forms have been identified (Kudo I. et al. 2005 "Prostaglandin E synthase, a terminal enzyme for prostaglandin E₂ biosynthesis", Journal of Biochemistry and Molecular Biology 38,
10 633-638); among these, microsomal PGES-1 (mPGES-1) is a membrane-bound enzyme that requires glutathione as an essential cofactor for its activity.

The expression of mPGES-1 is induced by pro-inflammatory stimuli such as IL-1 β or LPS (Proc. Natl. Acad. Sci. 96: 7220, 1999). It is co-
15 localized together with COX-2 on the endoplasmatic reticulum and on the nuclear envelope (Lazarus M. et al. 2002 "Biochemical characterization of mouse microsomal prostaglandin E synthase-1 and its colocalization with cyclooxygenase-2 in peritoneal macrophages" Arch. Biochem. Biophys. 397: 336; Murakami M. et al. 2000 "Regulation of
20 prostaglandin E₂ biosynthesis by inducible membrane-associated prostaglandin E₂ synthase that acts in concert with cyclooxygenase-2" J. Biol. Chem. 275: 32783; Yamagata K. et al. 2001 "Coexpression of microsomal-type prostaglandin E synthase with cyclooxygenase-2 in brain endothelial cells of rats during endotoxin-induced fever"
25 J. Neurosci. 15;21(8): 2669-77). Although the two enzymes (COX-2 and mPGES-1) have a functional connection and co-expression, their rate of induction differs in a few cellular systems, indicating different regulatory induction mechanisms (J. Immunol. 167: 469, 2001).

Drugs that inhibit the enzyme COX-2 have been shown to be
30 effective in alleviating inflammation and pain in chronic inflammatory

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pathologies such as arthritis, but their prolonged use may induce tissue damage caused by an overproduction of cytokines, for instance $\text{TNF}\alpha$ and $\text{IL-1}\beta$ (Stichtenoth D.O. 2001 "Microsomal prostaglandin E synthase is regulated by proinflammatory cytokines and glucocorticoids in primary rheumatoid synovial cells" J. Immunol. 167: 469). In addition, the prolonged use of these drugs is associated with cardiovascular side effects. This has led to the withdrawal from the market of a number of selective COX-2 inhibitors and to a revision of the indications for the entire class of these drugs.

Recent research efforts are directed towards overcoming the side effects of COX-2 inhibitors by studying mPGES-1 inhibitors for the purpose of developing drugs that are active in the treatment of inflammation and pain.

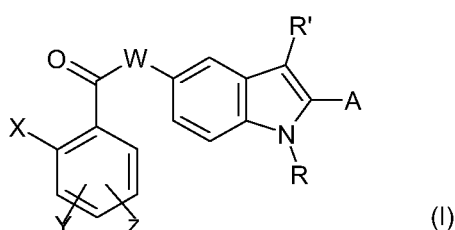
In addition, numerous studies have demonstrated that the PGE_2 prostaglandins are tumour-promoting factors (Castellone M.D. et al. 2005 "Prostaglandin E_2 promotes colon cancer growth through a novel Gs-Axin-B-catenin", Science 310, 1504-1510; Mehrotra S., et al. 2006 "Microsomal prostaglandin E_2 in breast cancer: a potential target for therapy", J. Pathol. 208(3): 356-63; Nakano et al. 2006 "Induction of macrophagic prostaglandin E_2 synthesis by glioma cells" J. Neurosurgery 104(4), 574-582) that are involved in angiogenesis, cell proliferation and cell migration functions. Selective FANS and COX-2 inhibitors are also found to inhibit various types of tumours, including colorectal, oesophageal, breast, lung and bladder tumours by means of inhibiting PGE_2 . PGE_2 prostaglandins derived from COX-2 induce tumour growth by means of binding to the actual receptors and activating signals for controlling cell proliferation, migration, apoptosis and angiogenesis (Wang D. et al. 2006 "Prostaglandin and cancer" Gut. 55 (1):115-22; Han C. et al. 2006 "Prostaglandin E_2 receptor EP1 transactivates EGFR/MET receptor tyrosine kinases and enhances

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invasiveness in human hepatocellular carcinoma cells", Journal of Cellular Physiology 207: 261-270).

A 2-arylindole compound substituted in position 5 that has selective inhibitory activity on mPGES-1 has now been found.

- 5 In a first aspect, the present invention relates to a 2-arylindole compound substituted in position 5, of formula (I):



in which:

- 10 X is a halogen atom or a (C₁-C₃)alkyl, trifluoromethyl, nitro, amino, cyano, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, phenyl or (C₁-C₃)alkylphenyl group;
- Y and Z, which may be identical or different, are an H or halogen atom, or a (C₁-C₃)alkyl, trifluoromethyl, nitro, amino, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, phenyl, COOH, (C₁-C₃)alkyl-COOH, (C₂-C₃)alkenyl-COOH, COOR, CONH₂, SO₂CH₃, SO₂NHCH₃ or NHSO₂CH₃ group;
- 15 W is an O atom or a CH₂ or NH group;
- R is a hydrogen atom or a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups;
- 20 R' is an H atom or a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups;
- A is a phenyl, naphthyl or pyridine group optionally substituted with 1 to 3 substituents, which may be identical or different, chosen from halogen, (C₁-C₆)alkyl optionally substituted with 1 to 3 hydroxy groups, trifluoromethyl, nitro, amino, di(C₁-C₃)alkylamino, hydroxy,
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(C₁-C₃)alkoxy, benzyloxy, COOH, COOR, SO₂CH₃,
SO₂NHCH₃, NHSO₂CH₃, POR₁R₂, OPOR₁R₂, (C₁-
C₆)alkyl-COOH, (C₂-C₆)alkenyl-COOH, phenyl and (C₁-
C₃)alkylphenyl,

5 in which, in turn,

R₁ and R₂, which may be identical or different, are (C₁-C₃)alkyl;
and the physiologically acceptable addition salts, stereoisomers,
enantiomers, hydrates, solvates and polymorphic forms thereof.

The chain of the various alkyl groups that may be present in the
10 compound of formula (I) may be linear or branched.

In the case of certain substituents, the compound of formula (I)
according to the present invention may contain an asymmetric carbon
atom and may thus be in the form of stereoisomers and enantiomers.
Typical examples of such substituents are 2-butanol, 2-methylbutyl,
15 2-butenic acid, 2-methylpropanoic acid and 1,2-pentane diol.

Preferably, the halogen is bromine, chlorine or fluorine.

Preferred meanings of X are halogen, (C₁-C₃)alkyl, trifluoromethyl,
nitro, cyano and (C₁-C₃)alkoxy. Particularly preferred meanings of X are
Cl, Br, F, trifluoromethyl and nitro.

20 Preferred meanings of Y and Z are H, halogen, nitro, COOH, (C₁-
C₃)alkyl, trifluoromethyl and (C₁-C₃)alkoxy. Particularly preferred
meanings of Y and Z are Cl, Br, F, trifluoromethyl, nitro, COOH, methyl,
ethyl, methoxy and ethoxy.

Preferred meanings of R are methyl, ethyl, propyl, isopropyl and
25 cyclohexyl.

Preferred meanings of R' are H, methyl, ethyl, propyl, isopropyl and
cyclohexyl.

Preferred meanings of A are phenyl, naphthyl and pyridine optionally
substituted with 1 or 2 substituents, which may be identical or different,
30 selected from halogen, (C₁-C₃)alkyl, (C₁-C₃)alkoxy and benzyloxy.

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A first particularly preferred meaning of A is phenyl optionally substituted with 1 or 2 substituents, which may be identical or different, selected from Br, Cl, F, methyl, ethyl, methoxy, ethoxy and benzyloxy.

5 A second particularly preferred meaning of A is naphthyl optionally substituted with 1 or 2 substituents, which may be identical or different, selected from Br, Cl, F, methyl, ethyl, methoxy, ethoxy and benzyloxy.

A third particularly preferred meaning of A is pyridine optionally substituted with 1 or 2 substituents, which may be identical or different, selected from Br, Cl, F, methyl, ethyl, methoxy, ethoxy and benzyloxy.

10 Depending on the nature of the substituents, the compound of formula (I) may form addition salts with physiologically acceptable organic or mineral acids or bases.

Typical examples of physiologically acceptable mineral acids are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and
15 nitric acid.

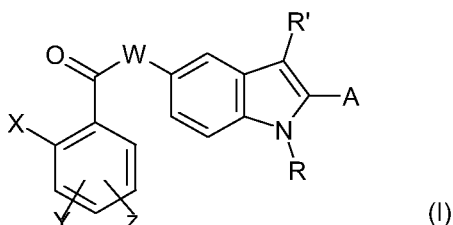
Typical examples of suitable physiologically acceptable organic acids are acetic acid, ascorbic acid, benzoic acid, citric acid, fumaric acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-toluenesulfonic acid, succinic acid, tannic acid and tartaric acid.

20 Typical examples of suitable physiologically acceptable mineral bases are: ammonia, calcium, magnesium, sodium and potassium.

Typical examples of suitable physiologically acceptable organic bases are: arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, N-methylglucamine, glucamine, glucosamine, histidine, N-(2-hydroxyethyl)piperidine, N-(2-hydroxyethyl)pyrrolidine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, theobromine, triethylamine,
25 trimethylamine, tripropylamine and tromethamine.

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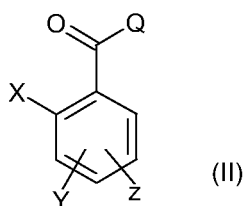
In a second aspect, the present invention relates to a process for preparing a 2-arylindole compound substituted in position 5, of formula (I):



5

in which A, X, Y, Z, W, R and R' have the meanings given above, and the physiologically acceptable addition salts, stereoisomers, enantiomers, hydrates, sulfates and polymorphic forms thereof, a) by reacting a compound of formula (II):

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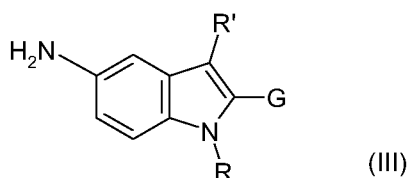
in which

X, Y and Z have the meanings given above, and

15

Q is a halogen atom or a hydroxy group,

with a compound of formula (III):



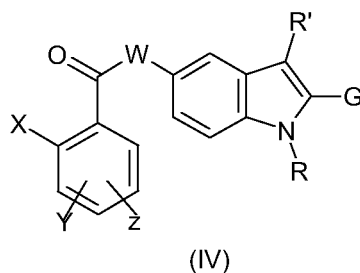
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in which

R and R' have the meanings given above, and

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G has the same meanings as A or is a hydrogen atom,
to give a compound of formula (IV):



5

in which

X, Y, Z, W, G, R and R' have the meanings given above,
and

10 b) when G is H, by reacting the compound of formula (IV) with a
compound of formula (V):



in which

I is an iodine atom, and

A has the meanings given above,

15 to give the compound of formula (I), and

c) forming, if so desired, a physiologically acceptable addition salt of
the compound of formula (IV) from step (a) in which G is other
than H or of the compound of formula (I) from step (b).

Clearly, the compound of formula (IV) in which G is other than H is
20 none other than the compound of formula (I). Thus, in the
abovementioned step (c), a physiologically acceptable addition salt of
the compound of formula (I) of the present invention is always obtained.

According to a first embodiment, the abovementioned step (a) is
performed by reacting a compound of formula (II) in which Q is Cl with
25 an amine of formula (III) in the presence of a suitable acid acceptor
according to standard techniques.

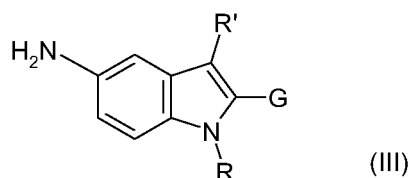
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According to a second embodiment, the abovementioned step (a) is performed by reacting a compound of formula (II) in which Q is OH with an amine of formula (III) in the presence of a suitable coupling agent according to standard techniques.

- 5 The reaction in the abovementioned step (b) between a compound of formula (IV) in which G is H and an aryl iodide of formula (V) is also performed according to standard techniques.

The intermediate compounds of formula (III) are novel.

- 10 According to a third aspect, the present invention also relates to a compound of formula (III):



in which

- 15 R is a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups;
- R' is an H atom or a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups,
- 20 G is a phenyl, naphthyl or pyridine group optionally substituted with 1 to 3 substituents, which may be identical or different, selected from halogen, (C₁-C₆)alkyl optionally substituted with 1 to 3 hydroxy groups, trifluoromethyl, nitro, amino, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, benzyloxy, COOH, COOR, SO₂CH₃, SO₂NHCH₃, NHSO₂CH₃, POR₁R₂, OPOR₁R₂, (C₁-C₆)alkyl-COOH,
- 25 (C₂-C₆)alkenyl-COOH, phenyl and (C₁-C₃)alkylphenyl,
- in which, in turn,
- R₁ and R₂, which may be identical or different, are (C₁-C₃)alkyl;
- on condition, however, that G is not an unsubstituted phenyl group

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when R is methyl and R' is H.

Preferred meanings of R are methyl, ethyl, propyl, isopropyl and cyclohexyl.

Preferred meanings of R' are H, methyl, ethyl, propyl, isopropyl and
5 cyclohexyl.

A first particularly preferred meaning of A is phenyl substituted with 1 or 2 substituents, which may be identical or different, selected from Br, Cl, F, methyl, ethyl, methoxy, ethoxy and benzyloxy.

A second particularly preferred meaning of A is naphthyl optionally
10 substituted with 1 or 2 substituents, which may be identical or different, selected from Br, Cl, F, methyl, ethyl, methoxy, ethoxy and benzyloxy.

A third particularly preferred meaning of A is pyridine optionally substituted with 1 or 2 substituents, which may be identical or different, selected from Br, Cl, F, methyl, ethyl, methoxy, ethoxy and benzyloxy.

15 The investigations on the biological properties of the compound of formula (I) according to the present invention demonstrated that it has an unexpected selective property of inhibiting mPGES-1 and pronounced anti-nociceptive activity in inflammatory pain.

In a fourth aspect, the present invention thus relates to a
20 pharmaceutical composition containing an effective amount of a compound of formula (I), or of a physiologically acceptable addition salt, stereoisomer, enantiomer, hydrate, solvate or polymorphic form thereof, and at least one pharmaceutically acceptable inert ingredient.

In the present description and in the claims, the term "effective
25 amount" refers to an amount that gives an evaluable improvement in at least one symptom or parameter of a specific disorder.

The pharmaceutical composition according to the present invention will be used in the treatment or prevention of disorders associated with the production of prostaglandin E₂ (PGE₂), for instance inflammatory
30 processes, pain, tumours, neurodegenerative disorders and

atherosclerosis.

Advantageously, the pharmaceutical composition according to the present invention will be used in the treatment of pain in chronic inflammatory pathologies such as arthritis, or of tumours, particularly colorectal, oesophageal, breast, lung and bladder tumours.

Preferably, the pharmaceutical compositions of the present invention are prepared in suitable dosage forms comprising an effective dose of at least one compound of formula (I) or of a physiologically acceptable addition salt, stereoisomer, enantiomer, hydrate, solvate or polymorphic form thereof, and at least one pharmaceutically acceptable inert ingredient.

Examples of suitable dosage forms are tablets, capsules, coated tablets, granules, solutions and syrups for oral administration; creams, ointments and antiseptic plasters for topical administration; suppositories for rectal administration and sterile solutions for administration by injection or aerosol or ophthalmic administration.

The dosage forms may also contain other conventional ingredients, for instance: preserving agents, stabilizers, surfactants, buffers, salts for regulating the osmotic pressure, emulsifiers, sweeteners, colorants, flavourings and the like.

If required for particular therapies, the pharmaceutical composition of the present invention may contain other pharmacologically active ingredients whose simultaneous administration is beneficial.

The amount of compound of formula (I) or of a physiologically acceptable addition salt, stereoisomer, enantiomer, hydrate, solvate or polymorphic form thereof, and at least one pharmaceutically acceptable inert ingredient in the pharmaceutical composition of the present invention may vary within a wide range depending on known factors, for instance the type of disease to be treated, the severity of the disease, the body weight of the patient, the dosage form, the chosen route of

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administration, the number of daily administrations and the efficacy of the chosen compound of formula (I). However, the optimum amount may be easily and routinely determined by a person skilled in the art.

Typically, the amount of compound of formula (I) or of a
5 physiologically acceptable addition salt, stereoisomer, enantiomer, hydrate, solvate or polymorphic form thereof, and at least one pharmaceutically acceptable inert ingredient in the pharmaceutical composition of the present invention will be such that it provides a level of administration of between 0.0001 and 100 mg/kg/day and even more
10 preferably between 0.01 and 10 mg/kg/day.

Clearly, the pharmaceutical formations of the present invention do not necessarily need to contain the entire amount of the compound of formula (I) since the said effective amount may be added by means of administration of a plurality of doses of the pharmaceutical composition
15 of the present invention.

The dosage forms of the pharmaceutical composition of the present invention may be prepared according to techniques that are well known to pharmaceutical chemists, including mixing, granulation, compression, dissolution, sterilization and the like.

20 The examples that follow serve to further illustrate the invention without, however, limiting it.

EXAMPLE 1

Preparation of intermediate compounds

a) 1-methyl-2-phenyl-1H-indol-5-amine

25 To a solution of 2-phenyl-5-nitroindole (prepared as described in J. Org. Chem. (1966), 31(1), 65-9) (1 g; 4.2 mmol) in DMF (10 ml) was added sodium hydride (50% suspension) (0.20 g; 4.2 mmol); the mixture was left under stirring for 30 minutes.

To the mixture thus obtained was then added dropwise iodomethane
30 (0.60 g; 4.2 mmol) dissolved in DMF (10 ml) and the resulting mixture

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was left under stirring at room temperature for 18 hours. The mixture was then poured into water (50 ml) and extracted with ethyl acetate (2 × 50 ml).

The organic phases were combined and dried over Na₂SO₄, and the solution was evaporated under reduced pressure. The residue thus obtained was purified by flash chromatography (eluent: 7/3 hexane/ethyl acetate) to give 1 g of 1-methyl-5-nitro-2-phenyl-1H-indole, which was used in the following reaction without any further purification.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.83 (s, 3 H) 6.88 (d, *J*=0.70 Hz, 1H) 7.47 – 7.68 (m, 5 H) 7.73 (d, *J*=9.06 Hz, 1 H) 8.08 (dd, *J*=9.06, 2.34 Hz, 1 H) 8.59 (d, *J*=2.05 Hz, 1 H)

To a suspension of 1-methyl-5-nitro-2-phenyl-1H-indole (1 g; 4 mmol) in 95° ethanol (100 ml) was added 10% Pd/C (0.1 g; 0.1 mmol) and the mixture underwent hydrogenation in a Parr hydrogenator (30 psi) for 4 hours.

The reaction mixture was filtered and the solution was evaporated under reduced pressure to give 1-methyl-2-phenyl-1H-indol-5-amine (0.8 g), which was used without any further purification.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.64 (s, 3 H) 4.51 (br, s, 2 H) 6.28 (d, *J*=0.88 Hz, 1H) 6.59 (dd, *J*=8.62, 2.19 Hz, 1 H) 6.70 (d, *J*=1.46 Hz, 1 H) 7.17 (d, *J*=8.48 Hz, 1 H) 7.25 – 7.59 (m, 5 H)

b) 1-ethyl-2-phenyl-1H-indol-5-amine

The process described above in Example 1a) was used, except that iodoethane was used instead of iodomethane.

1-ethyl-5-nitro-2-phenyl-1H-indole: ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.21 (t, *J*=7.16 Hz, 3 H) 4.30 (q, *J*=7.16 Hz, 2 H) 6.83 (d, *J*=0.58 Hz, 1 H) 7.48 – 7.63 (m, 5 H) 7.77 (d, *J*=9.21 Hz, 1 H) 8.07 (dd, *J*=9.21, 2.34 Hz, 1 H) 8.58 (d, *J*=2.34 Hz, 1 H)

1-ethyl-2-phenyl-1H-indol-5-amine: ¹H NMR (300 MHz, chloroform-*d*)

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δ ppm 1.28 (t, $J=6.94$ Hz, 3 H) 3.59 (br, s, 2 H) 4.13 (q, $J=7.16$ Hz, 2 H) 6.37 (d, $J=0.73$ Hz, 1 H) 6.82 (dd, $J=8.48, 2.19$ Hz, 1 H) 7.09 (d, $J=1.90$ Hz, 1 H) 7.23 (d, $J=8.62$ Hz, 1 H) 7.33 – 7.54 (m, 5 H)

c) 1-isopropyl-2-phenyl-1H-indol-5-amine

- 5 The process described above in step a) was used, except that isopropyl bromide was used instead of iodomethane.

1-isopropyl-5-nitro-2-phenyl-1H-indole:

Monoisotopic mass = 280.1; LC/MS ($M+H$)⁺ = 281.2

d) 1-ethyl-2-(2-fluorophenyl)-1H-indol-5-amine

- 10 To a suspension containing caesium acetate dried under vacuum overnight at 140°C (3.6 g; 19 mmol) in N,N-dimethylacetamide (DMA, 5 ml), under an inert atmosphere, were added palladium acetate (12 mg; 0.05 mmol), triphenylphosphine (55 mg; 0.21 mmol), 1-ethyl-5-nitro-1H-indole (2 g; 10 mmol) (prepared as described in Bioorg. Med. Chem. 13 (2005), 3531-3541) and 1-iodo-2-fluorobenzene (2.53 g; 11 mmol).

- The reaction mixture was left under stirring at 140°C under an inert atmosphere for 18 hours. The mixture was then cooled to room temperature, dichloromethane (50 ml) was added and the mixture thus obtained was filtered under vacuum through Celite.

The organic solution was transferred into a separating funnel, washed with H₂O (2 × 50 ml) and dried over Na₂SO₄.

- The organic solvent was removed by evaporation under reduced pressure and the residue was purified by flash chromatography on silica gel to give 1-ethyl-2-(2-fluorophenyl)-5-nitro-1H-indole (0.7 g), which was used without any further purification.

- ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.15 (t, $J=7.16$ Hz, 3 H) 4.18 (q, $J=7.02$ Hz, 2 H) 6.87 (s, 1 H) 7.35 – 7.50 (m, 2 H) 7.51 – 7.70 (m, 2 H) 7.79 (d, $J=9.06$ Hz, 1 H) 8.10 (dd, $J=9.06, 2.34$ Hz, 1 H) 8.62 (d, $J=2.34$ Hz, 1 H)

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To a suspension containing 1-ethyl-2-(2-fluorophenyl)-5-nitro-1H-indole (0.78 g; 2.75 mmol) in 95° ethanol (100 ml) was added 10% Pd/C (0.1 g; 0.1 mmol) and the mixture underwent hydrogenation in a Parr hydrogenator (30 psi) for 4 hours. The mixture was filtered and the
5 solution was evaporated under reduced pressure to give 1-ethyl-2-(2-fluorophenyl)-1H-indol-5-amine (0.8 g), which was used without any further purification.

e) 1-ethyl-2-(3-fluorophenyl)-1H-indol-5-amine

The process described above in Example 1d) was used, except that
10 3-fluoro-1-iodobenzene was used instead of 1-iodo-2-fluorobenzene.

1-ethyl-2-(3-fluorophenyl)-5-nitro-1H-indole: ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.20 (t, *J*=7.16 Hz, 3 H) 4.32 (q, *J*=7.31 Hz, 2 H) 6.90 (s, 1 H) 7.31 – 7.51 (m, 3 H) 7.55 – 7.67 (m, 1 H) 7.79 (d, *J*=9.06 Hz, 1 H) 8.09 (dd, *J*=9.06, 2.34 Hz, 1 H) 8.59 (d, *J*=2.05 Hz, 1 H)

15 f) 1-ethyl-2-(4-fluorophenyl)-1H-indol-5-amine

The process described above in Example 1d) was used, except that 4-fluoro-1-iodobenzene was used instead of 1-iodo-2-fluorobenzene.

1-ethyl-2-(4-fluorophenyl)-5-nitro-1H-indole: ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.19 (t, *J*=7.16 Hz, 3 H) 4.28 (q, *J*=7.02 Hz, 2 H) 6.83 (s, 1 H) 7.34 – 7.45 (m, 2 H) 7.60 – 7.68 (m, 2 H) 7.77 (d, *J*=9.35 Hz, 1 H) 8.07 (dd, *J*=9.35, 2.34 Hz, 1 H) 8.58 (d, *J*=2.34 Hz, 1 H)
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1-ethyl-2-(4-fluorophenyl)-1H-indol-5-amine: ¹H NMR (300 MHz, chloroform-*d*) δ ppm 1.24 (t, *J*=7.16 Hz, 3 H) 4.08 (q, *J*=7.16 Hz, 2 H) 6.33 (s, 1 H) 6.94 (dd, *J*=8.55, 2.27 Hz, 1 H) 7.09 – 7.25 (m, 4 H) 7.41 (d, *J*=8.77, 5.41 Hz, 2 H)
25

g) 1-ethyl-3-methyl-2-phenyl-1H-indol-5-amine

The process described above in Example 1a) was used, except that 2-phenyl-3-methyl-5-nitroindole (prepared as described in Tetrahedron 1965, Vol. 21, 823-829) and iodoethane were used instead of 2-phenyl-
30 5-nitroindole and iodomethane.

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1-ethyl-3-methyl-5-nitro-2-phenyl-1H-indole: ^1H NMR (300 MHz, DMSO- d_6) δ ppm 1.10 (t, $J=7.10$ Hz, 3 H) 2.23 (s, 3 H), 4.16 (q, $J=7.27$ Hz, 2 H) 7.44 – 7.63 (m, 5 H) 7.71 (d, $J=9.25$ Hz, 1 H) 8.07 (dd, $J=9.25$, 2.31 Hz, 1 H) 8.53 (d, $J=2.31$ Hz, 1 H)

- 5 1-ethyl-3-methyl-2-phenyl-1H-indol-5-amine: ^1H NMR (300 MHz, chloroform- d) δ ppm 1.17 (t, $J=7.16$ Hz, 3 H) 2.16 (s, 3 H) 3.35 (br, s, 2 H) 4.00 (q, $J=7.16$ Hz, 2 H) 6.76 (dd, $J=8.48$, 2.19 Hz, 1 H) 6.96 (d, $J=1.75$ Hz, 1 H) 7.17 (d, $J=8.33$ Hz, 1 H) 7.31 – 7.53 (m, 5 H)

h) 5-amino-2-phenyl-1-cyclohexylindole

- 10 To a suspension of caesium acetate dried under vacuum overnight at 140°C (1.8 g; 9.5 mmol) in N,N-dimethylacetamide (5 ml), under an inert atmosphere, were added palladium acetate (6 mg; 0.05 mmol), triphenylphosphine (28 mg; 0.1 mmol), 1-cyclohexylindole (prepared as described in Synthesis 1977, 5, 335-336) (1 g; 5 mmol) and 1-iodo-4-
15 methylbenzene (1.26 g; 6 mmol).

- The reaction mixture was left under stirring at 140°C under an inert atmosphere for 18 hours. It was then cooled to room temperature and dichloromethane (50 ml) was added. The reaction mixture was filtered under vacuum through Celite. The filtrate was transferred into a
20 separating funnel and the organic phase was washed with H_2O (2 $\times$ 50 ml) and dried over Na_2SO_4 .

- The organic solvent was removed by evaporation under reduced pressure and the residue was purified by flash chromatography on silica gel (97/3 hexane/ethyl acetate) to give 1-cyclohexyl-2-(4-methylphenyl)-
25 1H-indole (200 mg), which was used without any further purification.

^1H NMR (300 MHz, chloroform- d_6) δ ppm 1.13 – 1.98 (m, 8 H) 2.25 – 2.41 (m, 2 H) 2.43 (s, 3 H) 4.21 (tt, $J=12.42$, 3.80 Hz, 1 H) 6.42 (br. s., 1 H) 7.05 – 7.11 (m, 1 H) 7.15 (ddd, $J=7.90$, 7.20, 1.30 Hz, 1H) 7.22 – 7.35 (m, 4 H) 7.57 – 7.67 (m, 2 H)

- 30 To a solution of 1-cyclohexyl-2-(4-methylphenyl)-1H-indole (100 mg,

- 17 -

0.3 mmol) in 2 ml of concentrated H₂SO₄ at 5°C was added dropwise a solution of NaNO₃ (34 mg; 0.4 mmol) in H₂SO₄ (1 ml).

Once the addition was complete, the mixture was left under stirring at 5°C for 10 minutes. It was then poured into H₂O and ice (10 ml) and the solid thus formed was filtered off and purified by flash chromatography on silica gel (99/1 hexane/ethyl acetate) to give 1-cyclohexyl-2-(4-methylphenyl)-5-nitro-1H-indole (45 mg), which was used without any further purification.

¹H NMR (300 MHz, chloroform-*d*) δ ppm 1.15 – 1.42 (m, 4 H)
1.64 - 2.01 (m, 4 H) 2.16 – 2.41 (m, 2 H) 2.45 (s, 3 H) 4.24 (tt, *J*=12.42, 3.80 Hz, 1 H) 6.59 (s, 1 H) 7.28 – 7.35 (m, 4 H) 7.64 (d, *J*=9.35 Hz, 1 H) 8.06 (dd, *J*=9.35, 2.34 Hz, 1 H) 8.54 (d, *J*=2.34 Hz, 1 H)

To a suspension of 1-cyclohexyl-2-(4-methylphenyl)-5-nitro-1H-indole (45 mg; 0.13 mmol) in absolute ethanol (5 ml) was added stannous chloride dihydrate (152 mg; 0.67 mmol) and the mixture was left under stirring at 70°C for 18 hours. The reaction mixture was cooled to room temperature and then poured into H₂O and ice (20 ml), NaHCO₃ (saturated solution) was added to pH 8 and the mixture was left under stirring for 20 minutes.

The mixture was then poured into a separating funnel and extracted with ethyl acetate (2 × 30 ml). The organic phases were combined and dried over Na₂SO₄, and the solvent was removed by evaporation under reduced pressure to give 5-amino-2-(4-methylphenyl)-1-cyclohexylindole (30 mg), which was used without any further purification.

¹H NMR (300 MHz, chloroform-*d*₆) δ ppm 1.12 – 1.42 (m, 4 H) 1.62 – 1.94 (m, 4 H), 2.17 – 2.38 (m, 2 H) 2.41 (s, 3 H) 4.05 – 4.20 (m, 1 H) 4.23 (br. s., 2 H) 6.25 (s, 1 H) 6.69 (dd, *J*=8.62, 2.19 Hz, 1 H) 6.98 (d, *J*=2.34 Hz, 1 H) 7.19 – 7.33 (m, 4 H) 7.45 (d, *J*=8.77 Hz, 1 H)

i) 2-chloro-N-(1-ethyl-1H-indol-5-yl)benzamide

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To a solution of 1-ethyl-1H-indol-5-amine (prepared as described in Bioorg. Med Chem. 13 (2005), 3531-3541) (27 g; 170 mmol) in dichloromethane (300 ml) was added N,N-diisopropylethylenediamine (26.1 g; 202 mmol), followed by dropwise addition of 2-chlorobenzoyl chloride (35.4 g; 202 mmol) dissolved in dichloromethane (50 ml).

Once the additions were complete, the mixture was left under stirring at room temperature for 2 hours. Water (400 ml) was then added and the organic phase was separated out and dried over Na₂SO₄.

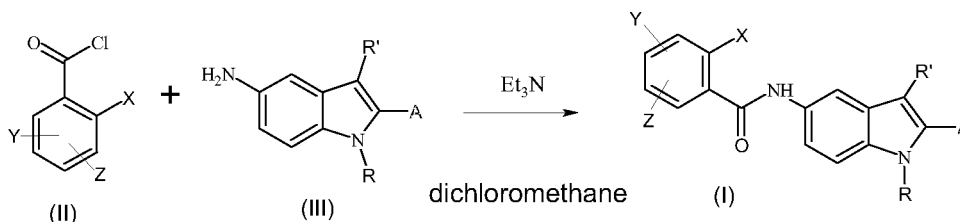
The organic solution was evaporated under reduced pressure. The crude product obtained was purified by crystallization with ethyl acetate to give the desired product (37 g).

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.35 (t, *J*=7.27 Hz, 3 H) 4.19 (q, *J*=7.05 Hz, 2 H) 6.41 (dd, *J*=2.97, 0.66 Hz, 1 H) 7.34 – 7.60 (m, 7 H) 8.00 (d, *J*=1.32 Hz, 1 H) 10.26 (s, 1 H)

EXAMPLE 2

Preparation of compounds of the invention

a) Example of a first variant of the preparation process:

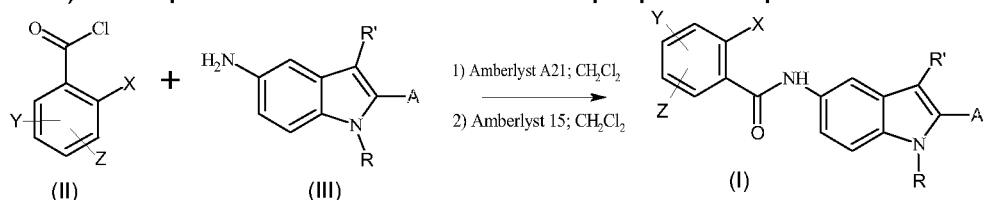


To a solution of a 5-aminoindole (III) (2 mmol) in dichloromethane (10 ml) was added triethylamine (2.2 mmol), followed by dropwise addition of an acyl chloride (II) (2.2 mmol) dissolved in dichloromethane (10 ml). Once the additions were complete, the mixture was left under stirring at room temperature for 20 hours. Water (50 ml) was then added and the organic phase was separated out and dried over Na₂SO₄. The solution was evaporated under reduced pressure. The crude product obtained was purified to give compound (I) in which X, Y,

- 19 -

Z, R, R' and A have the meanings given above.

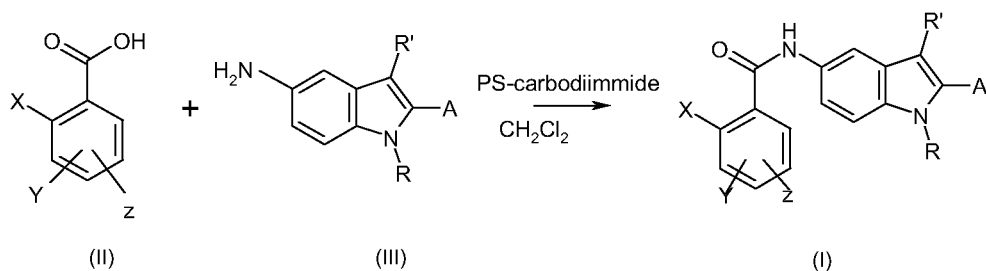
b) Example of a second variant of the preparation process:



5 To a suspension of a 5-aminoindole (III) (0.9 mmol) were added Amberlyst A21 resin (0.9 g) in dichloromethane (3 ml) and an acyl chloride (II) (0.28 mmol) in dichloromethane (3 ml). The mixture was left under stirring for 20 hours. The Amberlyst A21 resin was then removed by filtration and washed with dichloromethane (5 ml). The organic

10 phases were combined, diluted with dimethylformamide (1 ml) and stirred with Amberlyst 15 resin (0.9 g) for 5 hours. This treatment was repeated twice. The Amberlyst 15 resin was removed by filtration and the solution was evaporated under centrifuge to give compound (I) in which X, Y, Z, R, R' and A have the meanings indicated above.

15 c) Example of a third variant of the preparation process:

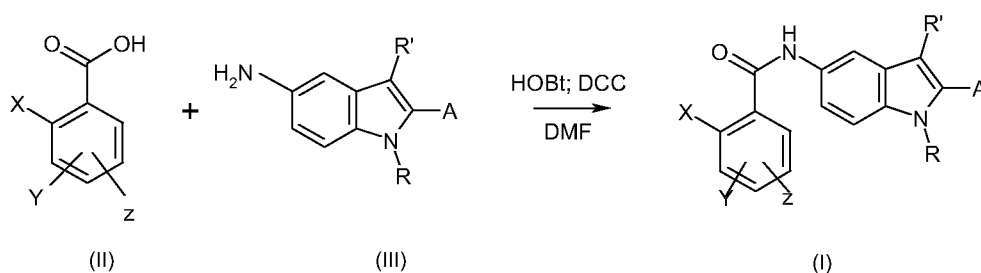


20 Under an inert atmosphere, a benzoic acid (II) (0.67 mmol) and a 5-aminoindole (III) (0.45 mmol) were dissolved in dichloromethane (8 ml) and dimethylformamide (0.8 ml). After leaving the mixture stirring at room temperature for 10 minutes, PS-carbodiimide resin (0.73 g) was added.

- 20 -

After leaving the reaction mixture stirring for 20 hours, the resin was removed by filtration and washed with dichloromethane (2×5 ml). The solution was evaporated under centrifugation to give compound (I) in which X, Y, Z, R, R' and A have the meanings given above.

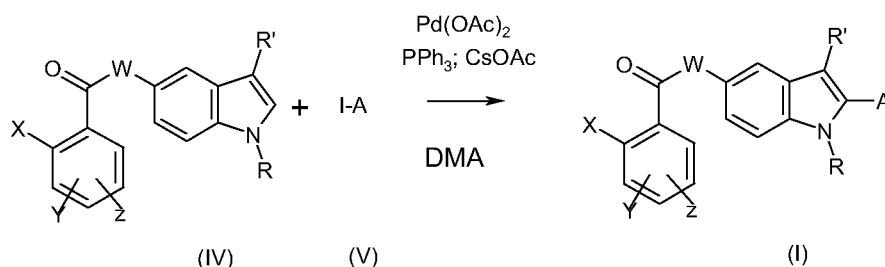
5 d) Example of a fourth variant of the preparation process:



To a solution of a benzoic acid (II) (10 mmol) in dimethylformamide
10 (40 ml) with stirring at 0°C were added 1-hydroxybenzotriazol (HOBt) (10 mmol) and dicyclohexylcarbodiimide (DCC) (10 mmol). The mixture was left under stirring at 0°C for 30 minutes and a 5-aminoindole (III) (9 mmol) dissolved in dimethylformamide (20 ml) was added.

The mixture was left under stirring at 0°C for a further 30 minutes,
15 and then at room temperature for 18 hours. The mixture was filtered, 2N hydrochloric acid was added to pH 2, and the precipitate thus formed was filtered off and purified to give compound (I) in which X, Y, Z, R, R' and A have the meanings given above.

e) Example of a fifth variant of the preparation process:



20 To a suspension of caesium acetate dried under vacuum overnight at 140°C (6.02 mmol) in N,N-dimethylacetamide (DMA) (3 ml), under an

- 21 -

inert atmosphere, were added palladium acetate (0.017 mmol), triphenylphosphine (0.067 mmol), indole (V) (3.35 mmol) and an aryl iodide (V) (3.68 mmol).

The reaction mixture was left under stirring at 140°C under an inert atmosphere for 18 hours. The reaction mixture was cooled to room temperature, dichloromethane (50 ml) was added and the resulting mixture was filtered under vacuum through Celite. The filtered organic solution was transferred into a separating funnel. The organic phase was washed with H₂O (2 × 50 ml), dried over Na₂SO₄ and evaporated under reduced pressure.

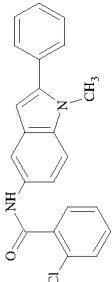
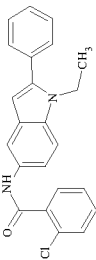
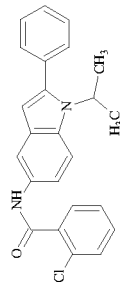
The residue was purified to give compound (I) in which X, Y, Z, R, R' and A have the meanings given above.

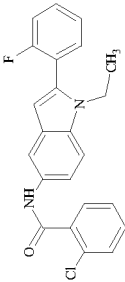
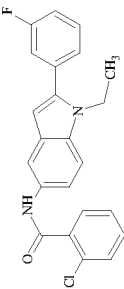
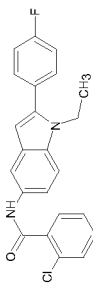
The compounds of formula (I) shown in Table 1 below, in which

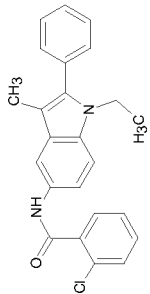
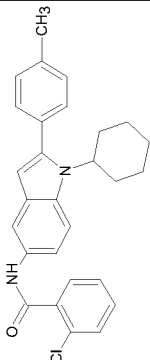
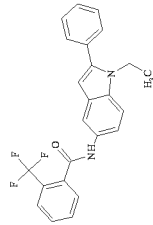
	Purification A	=	Crystallization
15	Purification B	=	Flash chromatography on silica gel
	i-PrOH	=	Isopropanol
	(i-Pr) ₂ O	=	Diisopropyl ether
	EtOAc	=	Ethyl acetate
	Hex	=	Hexane
20	EtOH	=	Ethanol
	CHCl ₃	=	Chloroform
	MeOH	=	Methanol
	AcOH	=	Acetic acid

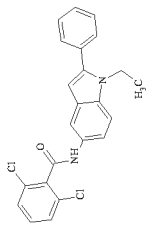
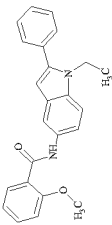
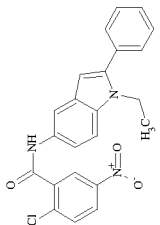
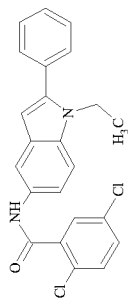
were thus prepared.

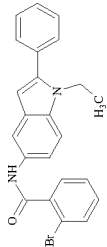
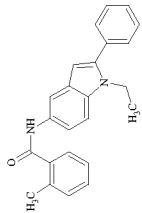
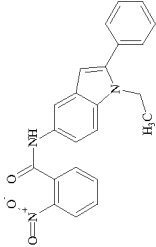
TABLE 1

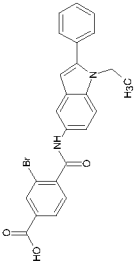
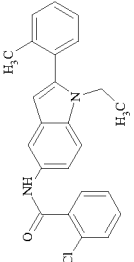
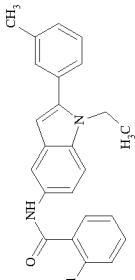
Compound	Structural Formula	Example	Purification	Monoisotopic Mass	LC/MS (M+H) ⁺	¹ H NMR (300 MHz)
1		2(a)	A (EtOH 95°)	360,1	361,4	DMSO-d ₆ δ ppm 3,75 (s, 3 H) 6,58 (s, 1 H) 7,36 - 7,70 (m, 11 H) 8,06 (s, 1 H) 10,33 (s, 1 H)
2		2(a)	A (i-prOH/(i-pr) ₂ O = 1/1)	374,1	375,4	DMSO-d ₆ δ ppm 1,19 (dd, J=7,00 Hz, 3 H) 4,21 (q, J=7,10 Hz, 2 H) 6,53 (s, 1 H) 7,39 - 7,63 (m, 11 H) 8,04 (d, J=1,65 Hz, 1 H) 10,31 (s, 1 H)
3		2(a)	A (EtOH 95°)	388,1	389,3	DMSO-d ₆ δ ppm 1,54 (d, J=6,95 Hz, 6 H) 4,51 - 4,68 (m, J=7,00, 7,00, 7,00, 7,00, 7,00, 7,00 Hz, 1 H) 6,43 (s, 1 H) 7,32 - 7,72 (m, 11 H) 8,04 (d, J=1,83 Hz, 1 H) 10,31 (s, 1 H)

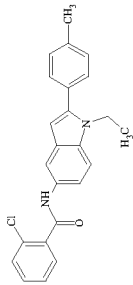
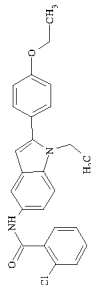
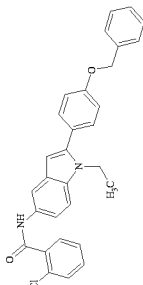
4		2(a)	B (Es/AcOEt = 8/2)			DMSO-d ₆ δ ppm 1,13 (t, J=6,94 Hz, 3 H) 4,08 (q, J=6,72 Hz, 2 H) 6,54 (s, 1 H) 7,30 - 7,67 (m, 10 H) 8,07 (d, J=1,65 Hz, 1 H) 10,34 (s, 1 H)
5		2(a)	B (Es/AcOEt = 8/2)			DMSO-d ₆ δ ppm 1,19 (t, J=7,10 Hz, 3 H) 4,23 (q, J=7,27 Hz, 2 H) 6,61 (s, 1 H) 7,23 - 7,65 (m, 10 H) 8,06 (d, J=1,98 Hz, 1 H) 10,34 (s, 1 H)
6		2(a)	B (Es/AcOEt = 7/3)			DMSO-d ₆ δ ppm 1,18 (t, J=7,00 Hz, 3 H) 4,19 (q, J=7,27 Hz, 2 H) 6,53 (s, 1 H) 7,29 - 7,67 (m, 10 H) 8,05 (d, J=1,65 Hz, 1 H) 10,32 (s, 1 H)

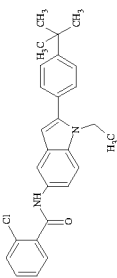
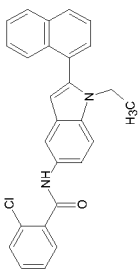
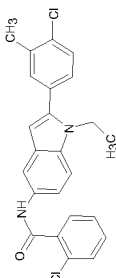
7		2(a)	B (Es/AcOEt = 9/1)			DMSO-d ₆ δ ppm 1,08 (t, J=7,14 Hz, 3 H) 2,16 (s, 3 H) 4,07 (q, J=7,03 Hz, 2 H) 7,37 - 7,64 (m, 11 H) 8,02 (d, J=1,39 Hz, 1 H) 10,32 (s, 1 H)
8		2(a)	B (Es/AcOEt = 9/1)	442,2	443,3	CHLOROFORM-d δ ppm 1,11 - 1,44 (m, 4 H) 1,64 - 1,97 (m, 4 H) 2,23 - 2,41 (m, 2 H) 2,43 (s, 3 H) 4,20 (tt, J=12,35, 3,65, 3,51 Hz, 1 H) 6,42 (s, 1 H) 7,21 - 7,50 (m, 8 H) 7,61 (d, J=8,77 Hz, 1 H) 7,77 - 7,84 (m, 1 H) 7,87 (s, 1 H) 7,93 (d, J=2,05 Hz, 1 H)
9		2(b)	-	408,1	409,4	

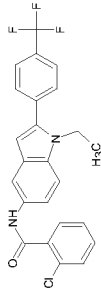
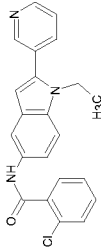
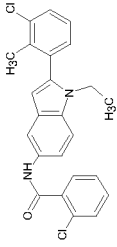
10		2(b)	-	408,1	409,4	
11		2(b)	-	370,2	371,3	
12		2(c)	-	419,1	420,3	
13		2(c)	-	408,1	409,4	

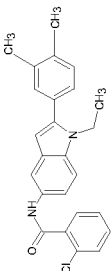
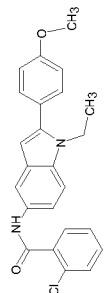
14		2(c)	-	418,1	419,3	
15		2(c)	-	354,2	355,4	
16		2(c)	-	385,1	386,3	

17		2(d)	B CHCl ₃ /MeOH/AcO H = 95/5/0,1	462,1	463,3	DMSO-d ₆ δ ppm 1,20 (t, J=7,06 Hz, 3 H) 4,21 (q, J=6,86 Hz, 2 H) 6,54 (s, 1 H) 7,37 - 7,61 (m, 7 H) 7,70 (d, J=7,67 Hz, 1 H) 7,98 - 8,07 (m, 2 H) 8,17 (d, J=1,21 Hz, 1 H) 10,42 (s, 1 H) 13,46 (br, s, 1 H)
18		2(e)	B (Es/AcOEt = 8/2)	388,1	389,3	DMSO-d ₆ δ ppm 1,05 (t, J=7,05 Hz, 3 H) 2,16 (s, 3 H) 3,95 (q, J=6,97 Hz, 2 H) 6,39 (s, 1 H) 7,26 - 7,65 (m, 10 H) 8,02 (d, J=1,57 Hz, 1 H) 10,31 (s, 1 H)
19		2(e)	B (Es/AcOEt = 8/2)	388,1	389,4	DMSO-d ₆ δ ppm 1,19 (dd, J=7,00 Hz, 3 H) 2,40 (s, 3 H) 4,21 (q, J=6,94 Hz, 2 H) 6,50 (s, 1 H) 7,20 - 7,67 (m, 10 H) 8,03 (d, J=1,65 Hz, 1 H) 10,32 (s, 1 H)

20		2(e)	B (Es/AcOEt = 8/2)	388,1	389,2	DMSO-d ₆ δ ppm 1,18 (t, J=6,94 Hz, 3 H) 2,39 (s, 3 H) 4,19 (q, J=6,94 Hz, 2 H) 6,48 (s, 1 H) 7,28 - 7,63 (m, 10 H) 8,02 (d, J=1,65 Hz, 1 H) 10,31 (s, 1 H)
21		2(e)	B (Es/AcOEt = 8/2)	418,1	419,4	DMSO-d ₆ δ ppm 1,19 (t, J=7,10 Hz, 3 H) 1,37 (t, J=6,94 Hz, 3 H) 4,10 (q, J=6,94 Hz, 2 H) 4,13 - 4,23 (m, 2 H) 6,44 (s, 1 H) 7,02 - 7,11 (m, 2 H) 7,24 - 7,77 (m, 8 H) 8,01 (d, J=1,65 Hz, 1 H) 10,30 (s, 1 H)
22		2(e)	B (Es/AcOEt = 7/3)	480,2	481,4	DMSO-d ₆ δ ppm 1,19 (t, J=7,02 Hz, 3 H) 4,15 - 4,22 (m, 2 H) 5,19 (s, 2 H) 6,45 (s, 1 H) 7,12 - 7,23 (m, 2 H) 7,25 - 7,64 (m, 13 H) 8,00 - 8,03 (m, 1 H) 10,30 (s, 1 H)

23		2(e)	B (Es/AcOEt = 85/15)	430,2	431,5	DMSO-d ₆ δ ppm 1,22 (t, J=7,10 Hz, 3 H) 1,35 (s, 9 H) 4,20 (q, J=7,10 Hz, 2 H) 6,49 (s, 1 H) 7,37 - 7,64 (m, 10 H) 8,03 (d, J=1,65 Hz, 1 H) 10,31 (s, 1 H)
24		2(e)	B (Es/AcOEt = 8/2)	424,1	425,3	DMSO-d ₆ δ ppm 1,00 (t, J=7,10 Hz, 3 H) 3,62 - 4,21 (m, 2 H) 6,57 (d, J=0,66 Hz, 1 H) 7,41 - 7,71 (m, 11 H) 8,01 - 8,12 (m, 3 H) 10,35 (s, 1 H)
25		2(e)	B (Es/AcOEt = 85/15)	422,1	423,2	DMSO-d ₆ δ ppm 1,14 - 1,22 (m, J=6,94, 6,94 Hz, 3 H) 2,43 (s, 3 H) 4,21 (q, J=6,94 Hz, 2 H) 6,55 (s, 1 H) 7,36 - 7,62 (m, 9 H) 8,04 (d, J=1,65 Hz, 1 H) 10,33 (s, 1 H)

26		2(e)	B (Es/AcOEt = 8/2)	442,1	443,3	DMSO-d ₆ δ ppm 1,20 (t, J=7,10 Hz, 3 H) 4,25 (q, J=7,10 Hz, 2 H) 6,68 (s, 1 H) 7,41 - 7,64 (m, 6 H) 7,76 - 7,92 (m, 4 H) 8,09 (d, J=1,65 Hz, 1 H) 10,36 (s, 1 H)
27		2(e)	B (Es/AcOEt = 7/3)	375,1	376,3	DMSO-d ₆ δ ppm 1,20 (t, J=7,10 Hz, 3 H) 4,22 (q, J=7,05 Hz, 2 H) 6,66 (s, 1 H) 7,41 - 7,64 (m, 7 H) 8,00 (dt, J=8,09, 1,98, 1,82 Hz, 1 H) 8,08 (t, J=1,88 Hz, 1 H) 8,65 (dd, J=4,62, 1,65 Hz, 1 H) 8,78 (dd, J=2,31, 0,99 Hz, 1 H) 10,35 (s, 1 H)
28		2(e)	B (Es/AcOEt = 8/2)	422,1	423,0	DMSO-d ₆ δ ppm 1,06 (t, J=7,10 Hz, 3 H) 2,18 (s, 3 H) 3,94 (br, s, 2 H) 6,43 (s, 1 H) 7,30 - 7,63 (m, 9 H) 8,04 (d, J=1,65 Hz, 1 H) 10,32 (s, 1 H)

29		2(e)	B (Es/AcOEt = 8/2)	402,1	403,3	DMSO-d ₆ δ ppm 1,18 (t, J=7,10 Hz, 3 H) 2,29 (s, 3 H) 2,31 (s, 3 H) 4,19 (q, J=6,94 Hz, 2 H) 6,46 (s, 1 H) 7,21 - 7,63 (m, 9 H) 8,02 (d, J=1,98 Hz, 1 H) 10,30 (s, 1 H)
30		2(e)	B (Es/AcOEt = 8/2)	404,1	405,4	DMSO-d ₆ δ ppm 1,19 (t, J=7,10 Hz, 3 H) 3,83 (s, 3 H) 4,18 (q, J=6,94 Hz, 2 H) 6,45 (s, 1 H) 7,04 - 7,13 (m, 2 H) 7,36 - 7,63 (m, 8 H) 8,01 (d, J=1,65 Hz, 1 H) 10,30 (s, 1 H)

EXAMPLE 3

In vitro biological activity

The test used makes it possible to evaluate the inhibitory capacity of the test compounds on the production of PGE₂ and the selectivity relative to the production of PGF_{2α}. The human pulmonary adenocarcinoma cell line A549 was used, which is particularly sensitive to stimulation with proinflammatory cytokines, for instance IL-1_β, and, in response to this stimulation, is particularly active in the production and release of two prostanoids: PGE₂ and PGF_{2α} (Thoren S. Jakobsson P-J, 2000).

The cells were stimulated with IL-1_β (10 ng/ml) and simultaneously treated with the test compound for 22 hours in a suitable culture medium (DMEM – Dulbecco's Modified Eagles Medium) enriched with 5% fetal calf serum and L-glutamine (4 mM final) in an incubator at 37°C and with a CO₂ concentration of 5%.

At the end of the incubation, the amount of PGE₂ and PGF_{2α} produced and released into the supernatant were assayed using an EIA kit (produced and sold by Cayman Chemicals, Ann Arbor, MI, USA).

The comparative compound used was indomethacin at a concentration of 10 nM (Sigma-Aldrich), which is a non-steroidal anti-inflammatory drug that inhibits in equal measure both PGE₂ and PGF_{2α}.

The results, expressed as a percentage of inhibition of the production of PGE₂ and of PGF_{2α} at a concentration of 10 μm, are given in Table 2, in which "ia" (inactive) indicates an inhibitory activity of less than 20%.

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TABLE 2

Compound	% inhibition at 10 μ m	
	PGE ₂	PGF _{2α}
1	63	ia
2	76	ia
3	91	34
4	72	ia
5	91	36
6	82	ia
7	90	39
9	100	ia
10	76	ia
12	75	ia
13	100	36
16	74	ia
18	66	ia
19	87	43
20	75	ia
21	66	ia
22	79	ia
24	79	ia
25	89	ia
28	65	ia
29	91	ia
30	75	ia
Indomethacin (10 nM)	100	100

For illustrative purposes, Table 3 collates the pIC₅₀ values of a

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number of compounds of the invention, where pIC_{50} represents the negative logarithm of the IC_{50} , which, in turn, represents the concentration of compound that inhibits the production of PGE_2 or $\text{PGF}_{2\alpha}$ by 50% relative to cells that are stimulated but not treated with the same compound.

In Table 3, "nd" means not determinable.

TABLE 3

Compound	pIC_{50}	
	PGE_2	$\text{PGF}_{2\alpha}$
2	5.7	nd
6	5.8	nd
9	5.9	4.3
10	5.7	< 4
13	6.1	nd
18	5.6	nd
19	6.0	4
20	5.5	< 4
indomethacin	8.3	8.6

10

EXAMPLE 4*In vivo* biological activity

The test compound was evaluated in the model of acetic acid-induced stretching in mice (Stock J.L. et al., J Clin Inv 2001, 107: 325-331). This test makes it possible to evaluate the antinociceptive activity of the compounds of the invention in a model of inflammatory pain.

Female CD-1 mice weighing 25-30 g were used for the test.

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The animals were treated intraperitoneally with the test compound (0.1-10 mg/kg) suspended in methylcellulose (MTC). The control animals were treated with the vehicle alone (MTC) via the same route.

30 minutes after the treatment, the animals received an
5 intraperitoneal injection of acetic acid (0.7 v/v in physiological solution, 16 µl/g of body weight) in order to induce inflammatory pain and to check the effects of the test compound on the nociceptive response.

Immediately after the administration of acetic acid and for the following 20 minutes, the number of stretches, which represents the
10 parameter for evaluation of the nociceptive response, was measured.

As reported in Table 4, the compound of the invention induced, in a dose-dependent manner, a reduction in stretching in the 20 minutes following the administration of acetic acid, compared with the animals treated with MTC alone.

15

TABLE 4

Treatment	dose (mg/kg)	No. of stretches	% inhibition
Vehicle	-	52	-
Compound 2	0.1	38	27
	1	36	31
	10	25	52

EXAMPLE 5

20 Selectivity between isoforms of PGES

The test used makes it possible to evaluate the capacity of the compounds of the invention to inhibit the production of PGE₂ in a human lymphoma cell line U-937 that preferentially expresses an enzymatic isoform (cPGES), which is responsible for the production of
25 PGE₂ under basal conditions, in the absence of pro-inflammatory

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stimuli. This enzymatic form is different from the one predominantly expressed in the A549 cells (mPGES-1) after a pro-inflammatory stimulus.

5 The absence of inhibitory activity on PGE₂ in this cell model ensures the selectivity of the compound compared with the enzymatic form responsible for the production of PGE₂ in the presence of inflammatory stimuli.

The results, expressed as a percentage of inhibition of the production of PGE₂, are given in Table 5, in which "ia" (inactive) indicates an
10 inhibitory activity of less than 20%. The reference compound used was indomethacin at a concentration of 10 nM.

The compounds of the invention were found not to significantly inhibit the production of PGE₂ owing mainly to the action of cPGES.

15

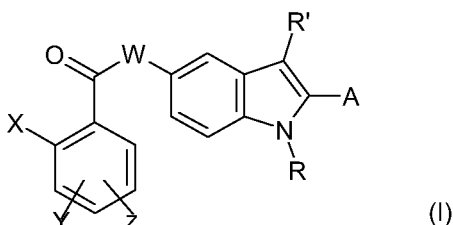
TABLE 5

Compound	% inhibition at 10 μ M
	PGE ₂
2	ia
6	ia
9	ia
10	22
13	30
18	ia
19	ia
20	ia
Indomethacin (10 nM)	78

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CLAIMS

1. A 2-arylindole compound substituted in position 5, of formula (I):



5

in which:

- X is a halogen atom or a (C₁-C₃)alkyl, trifluoromethyl, nitro, amino, cyano, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, phenyl or (C₁-C₃)alkylphenyl group;
- 10 Y and Z, which may be the same or different, are an H or halogen atom, or a (C₁-C₃)alkyl, trifluoromethyl, nitro, amino, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, phenyl, COOH, (C₁-C₃)alkyl-COOH, (C₂-C₃)alkenyl-COOH, COOR, CONH₂, SO₂CH₃, SO₂NHCH₃ or NHSO₂CH₃ group;
- 15 W is an O atom or a CH₂ or NH group;
- R is a hydrogen atom or a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups;
- R' is an H atom or a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups;
- 20 A is a phenyl, naphthyl or pyridine group optionally substituted with 1 to 3 substituents, which may be the same or different, selected from halogen, (C₁-C₆)alkyl optionally substituted with 1 to 3 hydroxy groups, trifluoromethyl, nitro, amino, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, benzyloxy, COOH, COOR, SO₂CH₃, SO₂NHCH₃, NHSO₂CH₃, POR₁R₂, OPOR₁R₂, (C₁-C₆)alkyl-COOH, (C₂-C₆)alkenyl-COOH, phenyl and (C₁-
- 25

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C₃)alkylphenyl,

in which, in turn,

R₁ and R₂, which may be the same or different, are (C₁-C₃)alkyl;

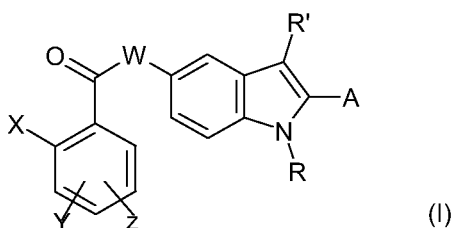
- 5 and the physiologically acceptable addition salts, stereoisomers, enantiomers, hydrates, solvates and polymorphic forms thereof.
2. A compound according to Claim 1, characterized in that X is halogen, (C₁-C₃)alkyl, trifluoromethyl, nitro or (C₁-C₃)alkoxy.
3. A compound according to Claim 2, characterized in that X is Cl, Br,
- 10 F, trifluoromethyl or nitro.
4. A compound according to Claim 1, characterized in that Y and Z are, independently of each other, H, halogen, nitro, COOH, (C₁-C₃)alkyl, trifluoromethyl or (C₁-C₃)alkoxy.
5. A compound according to Claim 4, characterized in that Y and Z are,
- 15 independently of each other, Cl, Br, F, trifluoromethyl, nitro, COOH, methyl, ethyl, methoxy or ethoxy.
6. A compound according to Claim 1, characterized in that R is methyl, ethyl, propyl, isopropyl or cyclohexyl.
7. A compound according to Claim 1, characterized in that R' is H,
- 20 methyl, ethyl, propyl, isopropyl or cyclohexyl.
8. A compound according to Claim 1, characterized in that A is phenyl, naphthyl or pyridine optionally substituted with 1 or 2 substituents, which may be the same or different, selected from halogen, (C₁-C₃)alkyl, (C₁-C₃)alkoxy and benzyloxy.
- 25 9. A compound according to Claim 8, characterized in that A is phenyl optionally substituted with 1 or 2 substituents, which may be the same or different, selected from Br, Cl, F, methyl, ethyl, methoxy, ethoxy and benzyloxy.
10. A compound according to Claim 8, characterized in that A is
- 30 naphthyl optionally substituted with 1 or 2 substituents, which may be

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the same or different, selected from Br, Cl, F, methyl, ethyl, methoxy, ethoxy and benzyloxy.

11. A compound according to Claim 8, characterized in that A is pyridine optionally substituted with 1 or 2 substituents, which may be identical or different, selected from Br, Cl, F, methyl, ethyl, methoxy, ethoxy and benzyloxy.

12. A process for preparing a 2-arylindole compound substituted in position 5, of formula (I):



in which:

X is a halogen atom or a (C₁-C₃)alkyl, trifluoromethyl, nitro, amino, cyano, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, phenyl or (C₁-C₃)alkylphenyl group;

Y and Z, which may be identical or different, are an H or halogen atom, or a (C₁-C₃)alkyl, trifluoromethyl, nitro, amino, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, phenyl, COOH, (C₁-C₃)alkyl-COOH, (C₂-C₃)alkenyl-COOH, COOR, CONH₂, SO₂CH₃, SO₂NHCH₃ or NHSO₂CH₃ group;

W is an O atom or a CH₂ or NH group;

R is a hydrogen atom or a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups;

R' is an H atom or a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups;

A is a phenyl, naphthyl or pyridine group optionally substituted with 1 to 3 substituents, which may be

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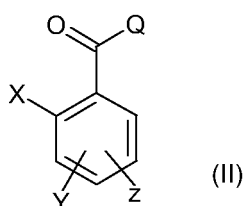
identical or different, selected from halogen, (C₁-C₆)alkyl optionally substituted with 1 to 3 hydroxy groups, trifluoromethyl, nitro, amino, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, benzyloxy, COOH, COOR, SO₂CH₃,
 5 SO₂NHCH₃, NHSO₂CH₃, POR₁R₂, OPOR₁R₂, (C₁-C₆)alkyl-COOH, (C₂-C₆)alkenyl-COOH, phenyl and (C₁-C₃)alkylphenyl,

in which, in turn,

R₁ and R₂, which may be identical or different, are (C₁-C₃)alkyl;

characterized in that:

a) a compound of formula (II):

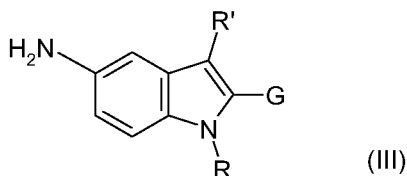


in which

X, Y and Z have the meanings given above, and

Q is a halogen atom or a hydroxy group,

is reacted with a compound of formula (III):



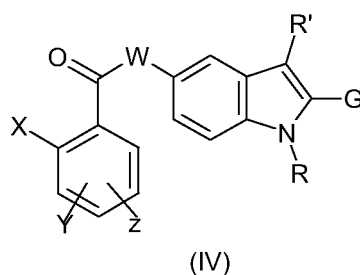
in which

R and R' have the meanings given above, and

G has the same meanings as A or is a hydrogen atom,

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to give a compound of formula (IV):



5 in which

X, Y, Z, W, G, R and R' have the meanings given above,
and

b) when G is H, the compound of formula (IV) is reacted with a
compound of formula (V):

10 IA (V)

in which

I is an iodine atom, and

A has the meanings given above,

to give the compound of formula (I), and

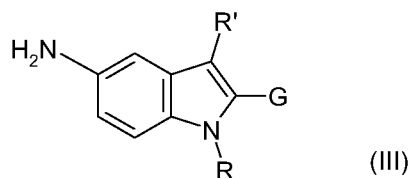
15 c) if so desired, a physiologically acceptable addition salt of the
compound of formula (IV) from step (a) in which G is other than H or
of the compound of formula (I) from step (b) is formed.

13. A process according to Claim 12, characterized in that step (a) is
performed by reacting a compound of formula (II) in which Q is Cl
20 with an amine of formula (III) in the presence of a suitable acid
acceptor according to standard techniques.

14. A process according to Claim 12, characterized in that step (a) is
performed by reacting a compound of formula (II) in which Q is OH
25 with an amine of formula (III) in the presence of a suitable coupling
agent according to standard techniques.

15. An intermediate compound of formula (III):

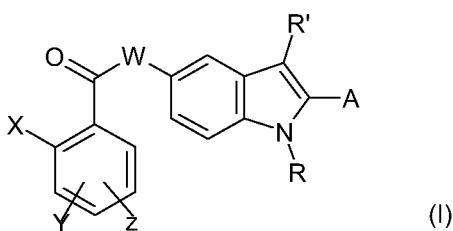
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in which

- 5 R is a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups;
 R' is an H atom or a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups,
 G is a phenyl, naphthyl or pyridine group optionally substituted with 1
 10 to 3 substituents, which may be identical or different, selected from halogen, (C₁-C₆)alkyl optionally substituted with 1 to 3 hydroxy groups, trifluoromethyl, nitro, amino, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, benzyloxy, COOH, COOR, SO₂CH₃, SO₂NHCH₃, NHSO₂CH₃, POR₁R₂, OPOR₁R₂, (C₁-C₆)alkyl-COOH,
 15 (C₂-C₆)alkenyl-COOH, phenyl and (C₁-C₃)alkylphenyl,
 in which, in turn,
 R₁ and R₂, which may be identical or different, are (C₁-C₃)alkyl;
 provided, however, that G is not an unsubstituted phenyl group when R is methyl and R' is H.
- 20 16. An intermediate compound according to Claim 15, characterized in that R is methyl, ethyl, propyl, isopropyl or cyclohexyl.
17. An intermediate compound according to Claim 15, characterized in that R' is H, methyl, ethyl, propyl, isopropyl or cyclohexyl.
18. A pharmaceutical composition containing an effective amount of a
 25 compound of formula (I):

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in which:

- 5 X is a halogen atom or a (C₁-C₃)alkyl, trifluoromethyl, nitro, amino, cyano, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, phenyl or (C₁-C₃)alkylphenyl group;
- 10 Y and Z, which may be identical or different, are an H or halogen atom, or a (C₁-C₃)alkyl, trifluoromethyl, nitro, amino, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, phenyl, COOH, (C₁-C₃)alkyl-COOH, (C₂-C₃)alkenyl-COOH, COOR, CONH₂, SO₂CH₃, SO₂NHCH₃ or NHSO₂CH₃ group;
- W is an O atom or a CH₂ or NH group;
- 15 R is a hydrogen atom or a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups;
- R' is an H atom or a (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl group optionally substituted with 1 to 3 hydroxy groups;
- 20 A is a phenyl, naphthyl or pyridine group optionally substituted with 1 to 3 substituents, which may be identical or different, selected from halogen, (C₁-C₆)alkyl optionally substituted with 1 to 3 hydroxy groups, trifluoromethyl, nitro, amino, di(C₁-C₃)alkylamino, hydroxy, (C₁-C₃)alkoxy, benzyloxy, COOH, COOR, SO₂CH₃, SO₂NHCH₃, NHSO₂CH₃, POR₁R₂, OPOR₁R₂, (C₁-C₆)alkyl-COOH, (C₂-C₆)alkenyl-COOH, phenyl and (C₁-C₃)alkylphenyl,
- 25 in which, in turn, R₁ and R₂, which may be identical or different, are (C₁-

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C₃)alkyl;

or of a physiologically acceptable addition salt, stereoisomer, enantiomer, hydrate, solvate or polymorphic form thereof, and at least one pharmaceutically acceptable inert ingredient.