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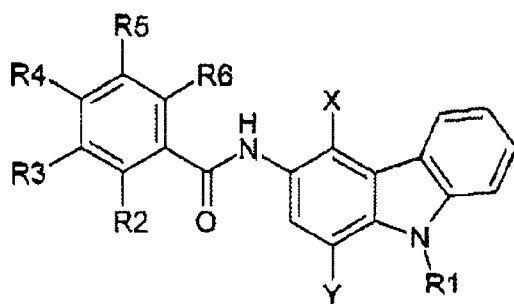
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(54) Title: 3-AMINOCARBAZOLE COMPOUNDS, PHARMACEUTICAL COMPOSITION CONTAINING THE SAME AND METHOD FOR THE PREPARATION THEREOF



(I)

(57) Abstract: A compound of formula (I), in which R1, R2, R3, R4, R5, R6, X and Y have the meanings indicated in the description, and the pharmaceutically acceptable salts thereof. A pharmaceutical composition containing a compound of formula (I) or a pharmaceutically acceptable salt thereof. A method for preparing the abovementioned compound of formula (I) and the pharmaceutically acceptable salts thereof.

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"3-aminocarbazole compound, pharmaceutical composition containing the same and method for the preparation thereof"

FIELD OF THE INVENTION

5 The present invention relates to a 3-aminocarbazole compound, to a pharmaceutical composition containing the same and to a method for the preparation thereof.

More particularly, the present invention relates to a 3-aminocarbazole compound that is useful for treating or preventing disturbances
10 associated with the production of prostaglandin E₂ (PGE₂), for instance inflammatory processes, tumours, Alzheimer's disease and atherosclerosis.

PRIOR ART

The value of the E₂ prostaglandins (PGE₂) arises from the role that
15 they play as bioregulators, together with other prostanoids produced metabolically from arachidonic acid, and as inflammation mediators.

Prostanoids are a class of compounds including prostaglandins, thromboxanes and prostacyclins. Prostanoids are lipid mediators that act as local hormones on the cells adjacent to the site of their release.
20 Prostanoids are mainly produced from arachidonic acid by cyclooxygenase-activated enzymatic oxidation. Cyclooxygenases (prostaglandin G/H synthases) catalyse the sequential formation of PGG₂ and PGH₂ from arachidonic acid. PGH₂ is then converted by means of specific enzymes into various prostanoids. The D₂
25 prostaglandins (PGD₂), E₂ prostaglandins (PGE₂), F_{2α} prostaglandins (PGF_{2α}), I₂ prostaglandins (PGI₂) and A₂ thromboxanes (TXA₂) are formed in this way.

With the ejection of seminal fluid, the prostanoids are not accumulated. Following various stimuli (inflammatory, immunological,
30 hormonal, ultraviolet light, tumoral agents and also mechanical

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agitation), they are synthesized and released into the extracellular space, from where they pass into the plasma, the urine and other biological fluids.

Prostanoids play an important role in the defence mechanisms of the functioning of organs and in the integrity of the body. This is demonstrated by the cytoprotective function in the gastrointestinal tract, by the regulation of the renal function and of capillary circulation, by the regulation of platelet aggregation and blood clotting, the involvement in the differentiation of immune cells and in wound repair, bone metabolism and ovulation.

In particular, the vasoprotective action of the PGI₂ prostanoids, which are essential for maintaining vascular tonus and for preventing thromboembolism and atherosclerosis at the endothelial level, and the anti-inflammatory and antiproliferative action of the PGD₂ prostanoids, the metabolite of which, 15d-PGJ₂, is capable of exerting anti-inflammatory effects by means of activation of the PPAR_γ (peroxisome proliferator-activated receptor-gamma) nuclear receptors (Inoue et al., 2000), should be underlined.

Prostanoids are thus bioregulators, but also important mediators of inflammation and of other pathologies.

In particular, the PGE₂ prostanoids are abundant in the sites of inflammation and are responsible for various pathological aspects of acute and chronic inflammation, for instance oedema, the formation of erythemas, inflammatory pain, articular inflammation and fever. In point of fact, the PGE₂ prostanoids represent potent pro-inflammatory and algogenic agents. Anti-PGE₂ antibodies have anti-inflammatory activity and animals lacking PGE₂ receptors show a reduced response to inflammatory stimuli (Portanova et al., 1996, Ueno et al., 2001) and an absent febrile response to pyrogenic stimuli (Ushikubi et al., 1998).

The non-steroidal anti-inflammatory drugs (NSAIDs) and selective

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COX-2 drugs currently in use reduce the inflammation-related symptoms by means of the non-selective inhibition of the production of eicosanoids (PGE₂, PGD₂, PGF_{2α}, PGI₂ and TXA₂) on account of their inhibitory action on the cyclooxygenases 1 and 2 (FitzGerald and
5 Patrono, 2001).

In particular, the selective COX-2 drugs currently marketed have reduced gastrointestinal toxicity when compared with conventional non-steroidal anti-inflammatory drugs (NSAIDs). However, the said selective COX-2 drugs reduce the production of vascular prostacyclin (PGI₂,
10 which is produced predominantly from COX-2), altering the normal equilibrium between the prothrombotic and antithrombotic eicosanoids in favour of the prothrombotic (TXA₂, which is produced predominantly from COX-1), and give rise to an increased risk of thrombotic-cardiovascular events (S. Malhotra, MD, DM; N. Shafiq, MD; P. Pandhi,
15 MD Medscape General Medicine 6(1), 2004; D. Mukherjee and E.J. Topol Cardiovascular risk and COX-2 inhibitors, Arthritis Res. Ther. 2003, 5:8-11-2002).

Various 3-aminocarbazole compounds have been studied for their ability to selectively bind to the human Y5 receptor and to modulate its
20 activity. This ability makes them useful in the treatment of appetite and metabolic disorders, for instance obesity, bulimia nervosa, anorexia nervosa, sleep disturbances, morphine dependency and epileptic attacks (WO 01/07409 A1, WO 02/051806, WO 02/096902 and US 6 399 631).

25 SUMMARY OF THE INVENTION

Surprisingly, it has now been found, that certain 3-aminocarbazole compounds are capable of selectively inhibiting the production of prostaglandin E₂ (PGE₂).

These compounds are capable of reducing the production of PGE₂
30 and are thus active in all the pathological conditions in which PGE₂ acts

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as a mediator (for example: inflammatory processes, pain, fever, tumours, Alzheimer's disease and atherosclerosis).

Typical examples of such inflammatory processes are oedema, erythema, articular inflammation, rheumatoid arthritis and arthrosis.

5 Typical examples of such tumours are colorectal and pulmonary carcinoma and adenocarcinoma.

The compounds of the present invention selectively inhibit the synthesis of PGE₂. This selectivity has the advantage of inhibiting a potent mediator of inflammation, pain and fever, while leaving unaltered
10 the production of the other prostanoids produced simultaneously in the arachidonic acid cascade, such as PGF_{2α}, TXA₂, PGI₂ and PGD₂. All the defence mechanisms of the functioning of organs and of the integrity of the body that are typical of the activity of the other prostanoids thus remain unchanged.

15 Similarly to conventional non-steroidal anti-inflammatory drugs, the compounds of the present invention have anti-inflammatory, antipyretic and analgesic properties, and are thus active in pathologies such as inflammation, pain, fever, rheumatoid arthritis and arthrosis. In addition, since the involvement of PGE₂ in tumours, Alzheimer's disease and
20 atherosclerosis is known in the literature, the compounds of the present invention also have applications in the prevention and treatment of these pathologies.

Advantageously, these compounds however show few side effects when compared with NSAIDs and selective COX-2 drugs, which, by
25 inhibiting cyclooxygenases, do not discriminate between the prostanoids.

In particular, these derivatives are useful in both the treatment and the prevention of inflammatory processes.

In particular, the compounds of the present invention show reduced
30 gastrointestinal, renal and vascular toxicity.

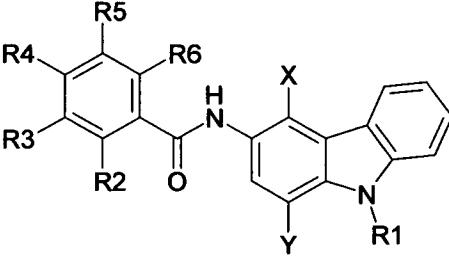
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DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present invention relates to a 3-aminocarbazole compound characterized in that it is selected from the group comprising the compounds of Table 1 below:

5

TABLE 1

 (I)								
Compound No.	R1	R2	R3	R4	R5	R6	X	Y
1	CH ₃	Cl	H	H	H	H	H	H
2	CH(CH ₃) ₂	Cl	H	H	H	H	H	H
3	PhCH ₂	Cl	H	H	H	H	H	H
4	CH ₃ CH ₂	CF ₃	H	H	H	H	H	H
5	CH ₃ CH ₂	CH ₃	H	H	H	CH ₃	H	H
6	CH ₃ CH ₂	F	H	H	H	CF ₃	H	H
7	CH ₃ CH ₂	CF ₃	H	F	H	H	H	H
8	CH ₃ CH ₂	Br	H	H	H	OCH ₃	H	H
9	CH ₃ CH ₂	Cl	H	H	Cl	OCH ₃	H	H
10	PhCH ₂	NH ₂	H	H	H	H	H	H
11	CH ₃ CH ₂	N(CH ₃) ₂	H	H	H	H	H	H

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12	CH ₃ (CH ₂) ₄	Cl	H	H	H	H	H	H
13	CH ₃ OCH ₂ CH ₂	Cl	H	H	H	H	H	H
14	HOOC(CH ₂) ₃	Cl	H	H	H	H	H	H
15	CH ₃ CH ₂	Cl	H	H	H	H	CH ₃	CH ₃
16	CH ₃ CH ₂	Cl	H	H	H	H	CH ₃	H
17	CH ₃ CH ₂	Cl	H	H	H	H	H	CH ₃
18	CH ₃ CH ₂	Cl	H	H	H	H	CH ₃	OCH ₃

and the pharmaceutically acceptable salts thereof.

As is known to those skilled in the art, the pharmaceutically acceptable salts of the compounds of Table 1 will be:

- acid-addition salts when the compound is basic, for instance compound 10 or 11, or
- base-addition salts when the compound is acidic, for instance compound 14.

Examples of suitable pharmaceutically acceptable acids are mineral acids such as HCl, HBr, H₂SO₄ and H₃PO₄, and organic acids such as oxalic acid, tartaric acid, methanesulfonic acid, p-toluenesulfonic acid, maleic acid, succinic acid, lactic acid and citric acid.

Examples of suitable pharmaceutically acceptable bases are alkali metals and alkaline-earth metals such as Na⁺, K⁺, Mg⁺⁺ and Ca⁺⁺, and organic bases such as tromethamine, choline and lysine.

- 15 In a second aspect, the present invention relates to a pharmaceutical composition characterized in that it comprises a therapeutically effective dose of a 3-aminocarbazole compound selected from the group comprising the compounds of Table 1 above or a pharmaceutically acceptable salt thereof together with at least one pharmaceutically acceptable inert vehicle.
- 20

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Preferably, the pharmaceutical compositions of the present invention are prepared in suitable dosage forms.

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

Advantageously, these dosage forms are formulated so as to ensure a controlled release over time of a compound of Table 1 above or of a
10 pharmaceutically acceptable salt thereof. Specifically, depending on the type of therapy, the required release time may be very short, normal or long.

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

In addition, when required for particular therapies, the pharmaceutical composition of the present invention may also contain other pharmacologically active ingredients whose simultaneous
20 administration is useful.

The amount of the compound of the present invention in the pharmaceutical composition may vary within a wide range as a function of 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,
25 the selected route of administration, the number of daily administrations and the efficacy of the selected compound. However, the optimum amount may be readily and routinely determined by a person skilled in the art.

Typically, the amount of compound of the present invention in the
30 pharmaceutical composition will be such that it ensures a level of

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administration of between 0.0001 and 100 mg/kg/day and even more preferably between 0.01 and 10 mg/kg/day.

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

In a third aspect, the present invention relates to a method for treating or preventing inflammatory processes, tumours, Alzheimer's disease and atherosclerosis in mammals, comprising the administration
10 of a therapeutically effective amount of a 3-aminocarbazole compound selected from the group comprising the compounds of Table 1 above or a pharmaceutically acceptable salt thereof to a person in need thereof.

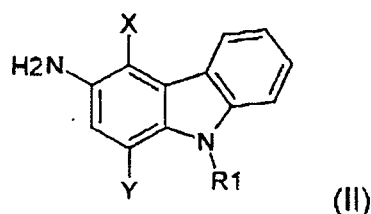
Preferably, the inflammatory process is selected from the group comprising oedema, erythema, articular inflammation, rheumatoid
15 arthritis and arthrosis, and the tumour is selected from the group comprising colorectal or pulmonary carcinoma and adenocarcinoma.

The 3-aminocarbazoles of Table 1 above may be prepared according to known methods, for instance by reacting an acid, or a reactive derivative thereof, with the selected amine (patent application
20 WO 02/096902 A1, WO 02/051806, J. Med. Chem. 2002 vol. 45, pp. 3509-3523). Typical examples of reactive derivatives are acyl halides, anhydrides or esters.

In a fourth aspect, the present invention thus relates to a method for preparing a 3-aminocarbazole of Table 1 above, characterized in that it
25 comprises the following steps:

a) reacting an amine of formula (II)

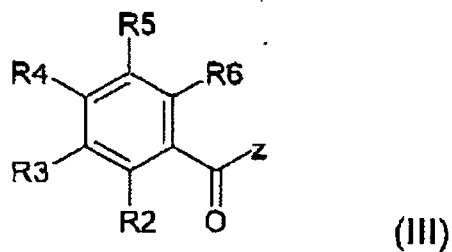
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in which R1, X and Y have the meanings indicated in Table 1,

with a compound of formula (III)

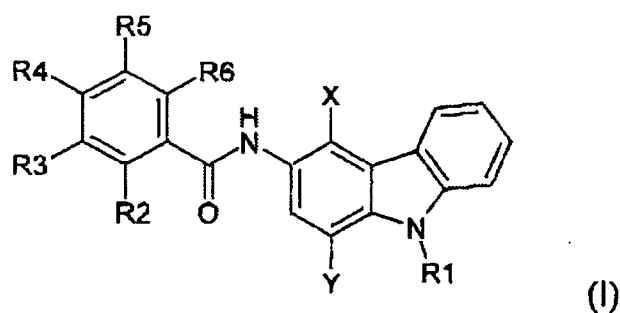
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in which R2, R3, R4, R5 and R6 have the meanings indicated in Table 1, and Z is selected from the group comprising Cl, Br, OH, OR and OC(O)R, in which R is a linear or branched alkyl containing from 1 to 6 carbon atoms,

to give a 3-aminocarbazole compound of formula (I)

10



in which R1, R2, R3, R4, R5, R6, X and Y have the meanings indicated in Table 1, and

15

b) optional formation of a pharmaceutically acceptable salt of the compound of formula (I) thus obtained.

Typically, step (a) is performed in the presence of a suitable diluent

at a temperature within the range between 0 and 140°C, for a time within the range between 0.5 and 24 hours. Preferably, the reaction temperature is within the range between 15 and 40°C. Advantageously, the reaction time ranges from 2 to 18 hours.

5 Preferably, the diluent is aprotic, polar or apolar. Even more preferably, it is a polar aprotic diluent. Examples of suitable polar aprotic diluents are dimethylformamide and dichloromethane.

In the embodiment in which Z is Cl or Br, the reaction is advantageously performed in the presence of a suitable organic or mineral acid acceptor. Examples of suitable organic acceptors are diisopropylethylenediamine, triethylethylamine, pyridine and dimethylaminopyridine. Examples of suitable mineral acceptors are alkali metal carbonates or bicarbonates.

In the embodiment in which Z is OH, the reaction is preferably performed in the presence of a suitable coupling agent, for instance dicyclohexylcarbodiimide (also supported on polystyrene resin) or carbonyldiimidazole.

The examples that follow are given to illustrate the invention in greater detail without, however, limiting it.

20 Example 1

Preparation of Compound 1

(R1=CH₃, R2=Cl, R3=R4=R5=R6=X=Y=H)

a) 9-methyl-9*H*-carbazole

25 To a solution of carbazole (5 g; 0.030 mol) in dimethylformamide (50 ml) was added portionwise sodium hydride (60% suspension in mineral oil, 1.15 g; 0.030 mol) and the suspension obtained was stirred at room temperature for 0.5 hour. Iodomethane (1.43 ml; 0.030 mol) was then added dropwise.

The suspension thus obtained was stirred for 16 hours and H₂O was
30 then added cautiously until precipitation was complete. The precipitate

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was collected by filtration under vacuum and dried in a vacuum oven.

5.3 g of the desired product were thus obtained and were used without further purification.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.87 (s, 3 H), 7.20 (t, *J* = 7.5 Hz, 2 H), 7.43 - 7.49 (m, 2 H), 7.56 - 7.61 (m, 2 H), 8.15 (d, *J* = 7.5 Hz, 2 H).

b) 9-methyl-3-nitro-9H-carbazole

The product obtained as described in step a) above (3.9 g; 0.022 mol) was dissolved in glacial acetic acid (70 ml). A mixture containing fuming nitric acid (1.05 ml) in glacial acetic acid (3.11 ml) was then added dropwise over 30 minutes.

The solution thus obtained was stirred for a further 30 minutes. The reaction mixture was then poured into H₂O and ice, stirred for 15 minutes and filtered. The residue thus obtained (4 g) was purified by flash chromatography, eluting with an 85/15 hexane/ethyl acetate mixture.

The desired product (2.2 g) was thus obtained.

¹H NMR (300 MHz, chloroform-*d*) δ ppm 3.92 (s, 3 H), 7.27 - 7.51 (m, 3 H), 7.54 - 7.63 (m, 1 H), 8.15 (d, *J* = 7.9 Hz, 1 H), 8.40 (dd, *J* = 8.9, 2.2 Hz, 1 H), 9.01 (d, *J* = 2.0 Hz, 1 H).

c) 9-methyl-9H-carbazole-3-amine

The product obtained as described in step b) above (1.94 g; 0.009 mol) was dissolved in absolute ethanol (20 ml). Stannous chloride dihydrate (8.16 g; 0.043 mol) was then added. The mixture thus obtained was refluxed for 16 hours.

The reaction mixture was cooled to room temperature and the solvent was then removed under reduced pressure. The residue was taken up in H₂O. The pH was brought to 7.5 by adding saturated sodium bicarbonate solution and the mixture was transferred into a separating funnel. The organic phase was extracted with ethyl acetate

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(2 × 100 ml). The organic extracts were combined and washed with water saturated with NaCl (2 × 100 ml). The organic phase was separated out and dried over Na₂SO₄. The organic phase was separated out and dried over Na₂SO₄. The solvent was then removed
 5 by evaporation under reduced pressure and the residue thus obtained (1.5 g) was used without further purification.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.76 (s, 3 H), 4.72 (br, s, 2 H), 6.84 (dd, J = 8.8, 2.0 Hz, 1 H), 7.04 - 7.11 (m, 1 H), 7.25 - 7.30 (m, 2 H), 7.32 - 7.39 (m, 1H), 7.44 (d, J = 8.1 Hz, 1 H), 7.93 (dt, J = 7.6, 1.0 Hz,
 10 1 H).

d) 2-chloro-*N*-(9-methyl-9*H*-carbazol-3-yl)benzamide

The product obtained as described in step c) above (1.5 g; 0.008 mol) was dissolved in dichloromethane (20 ml). Diisopropylethylenediamine (1.19 g; 0.009 mol) and 2-chlorobenzoyl
 15 chloride (1.16 ml; 0.009 mol) were then added to the solution. The mixture thus obtained was stirred for 3 hours.

The reaction mixture was transferred into a separating funnel and washed with 1N HCl solution (50 ml), with 1N NaOH (50 ml) and with H₂O (50 ml). The organic phase was separated out and dried over
 20 Na₂SO₄. The solvent was then removed by evaporation under reduced pressure and the residue thus obtained (3 g) was crystallized from a 1/2 hexane/ethyl acetate mixture.

2-Chloro-*N*-(9-methyl-9*H*-carbazol-3-yl)benzamide (1.2 g) was thus obtained.

25 m.p.: 206°C

Elemental analysis

for C₂₀H₁₅ClN₂O

	C	H	N
Found %	71.81	4.34	8.37
Calculated %	71.75	4.52	8.37

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^1H NMR (300 MHz, DMSO- d_6) δ ppm 3.88 (s, 3 H), 7.20 (t, J = 6.9 Hz, 1 H), 7.43 - 7.73 (m, 8 H), 8.09 (d, J = 7.6 Hz, 1 H), 8.57 (d, J = 1.7 Hz, 1 H), 10.48 (br, s, 1 H).

Example 2

5

Preparation of Compound 2

(R1=CH(CH₃)₂, R2=Cl, R3=R4=R5=R6=X=Y=H)

a) 9-(1-methylethyl)-9H-carbazole

Carbazole (5 g; 0.03 mol) was reacted with isopropyl bromide (5.61 ml; 0.06 mol) by working in a manner similar to that described in
10 Example 1a).

The solid product obtained after filtration (4 g) was purified by flash chromatography, eluting with a 97/3 hexane/ethyl acetate mixture to give 3.3 g of the desired product.

^1H NMR (300 MHz, DMSO- d_6) δ ppm, 1.63 (d, J = 7.0 Hz, 6 H), 5.11
15 (hept, J = 7.0, Hz, 1 H), 7.18 (t, J = 7.5 Hz, 2 H), 7.38 - 7.45 (m, 2 H), 7.69 (d, J = 8.2 Hz, 2 H), 8.15 (dt, J = 7.6, 1.0 Hz, 2 H).

b) 9-(1-methylethyl)-3-nitro-9H-carbazole

The product obtained as described in step a) above (3.3 g; 0.016 mol) was reacted by working in a manner similar to that described
20 in Example 1b).

The solid product obtained after filtration (3.7 g) was purified by flash chromatography, eluting with a 95/5 hexane/ethyl acetate mixture to give 1.8 g of the desired product.

^1H NMR (300 MHz, DMSO- d_6) δ ppm, 1.67 (d, J = 7.0 Hz, 6 H), 5.23
25 (hept, J = 7.0, Hz, 6 H), 7.33 (t, J = 7.0 Hz, 1 H), 7.53 - 7.60 (m, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.90 (d, J = 9.2 Hz, 1 H), 8.31 (dd, J = 9.2, 2.3 Hz, 1 H), 8.43 (dq, J = 8.0, 0.7 Hz, 1 H), 9.18 (d, J = 2.3 Hz, 1 H).

c) 9-(1-methylethyl)-9H-carbazole-3-amine

The product obtained as described in step b) above (1.7 g; 0.007 mol) was reacted by working in a manner similar to that described
30

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in Example 1c).

The product thus obtained (1.3 g) was used without further purification.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.57 (d, *J* = 7.0 Hz, 6 H), 4.71
5 (br, s, 2 H), 4.95 (hept, *J* = 7.0 Hz, 1 H), 6.80 (dd, *J* = 8.6, 2.2 Hz, 1 H),
7.04 (t, *J* = 6.9 Hz, 1 H), 7.25 - 7.34 (m, 2 H), 7.38 (d, *J* = 8.8 Hz, 1 H),
7.53 (d, *J* = 8.6 Hz, 1 H), 7.92 (dq, *J* = 7.8, 0.7 Hz, 1 H).

d) 2-chloro-*N*-[9-(1-methylethyl)-9*H*-carbazol-3-yl]benzamide

The product obtained as described in step c) above (1.2 g;
10 0.005 mol) was reacted by working in a manner similar to that described
in Example 1d).

The product thus obtained (2.2 g) was crystallized twice from a 1/9
hexane/ethyl acetate mixture.

2-Chloro-*N*-[9-(1-methylethyl)-9*H*-carbazol-3-yl]benzamide (1.1 g)
15 was thus obtained.

m.p.: 195°C

Elemental analysis

for C₂₂H₁₉ClN₂O

	C	H	N
Found %	72.71	5.16	7.88
Calculated %	72.82	5.28	7.72

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.63 (d, *J* = 6.9 Hz, 6 H), 5.09
20 (hept, *J* = 6.9 Hz, 1 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 7.38 - 7.73 (m, 8 H),
8.08 (d, *J* = 7.3 Hz, 1 H), 8.56 (d, *J* = 1.7 Hz, 1 H), 10.47 (br, s, 1 H).

Example 3

Preparation of Compound 3

(R₁=CH₂Ph, R₂=Cl, R₃=R₄=R₅=R₆=X=Y=H)

25 a) 9-(phenylmethyl)-9*H*-carbazole

Carbazole (5 g; 0.03 mol) was reacted with benzyl bromide (7.11 ml;
0.06 mol) by working in a manner similar to that described in

Example 1a).

The solid product obtained after filtration (8 g) washed with hexane to give 7.2 g of the desired product.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 5.66 (s, 2 H), 7.13 - 7.47 (m, 9 H), 7.62 (d, *J* = 8.2 Hz, 2 H), 8.18 (d, *J* = 7.6 Hz, 2 H).

b) 3-nitro-9-(phenylmethyl)-9*H*-carbazole

The product obtained as described in step a) above (6.7 g; 0.026 mol) was reacted by working in a manner similar to that described in Example 1b).

10 The solid product obtained after filtration (7 g) was purified by flash chromatography, eluting with a 95/5 hexane/ethyl acetate mixture to give 2.5 g of the desired product.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 5.78 (s, 2 H), 7.15 - 7.39 (m, 6 H), 7.52 - 7.60 (m, 1 H), 7.75 (d, *J* = 8.5 Hz, 1 H), 7.85 (d, *J* = 9.1 Hz, 1 H), 8.34 (dd, *J* = 9.1, 2.3 Hz, 1 H), 8.45 (d, *J* = 7.3 Hz, 1 H), 9.22 (d, *J* = 2.3 Hz, 1 H).

c) 9-(phenylmethyl)-9*H*-carbazole-3-amine

The product obtained as described in step b) above (1 g; 0.003 mol) was reacted by working in a manner similar to that described in

20 Example 1c).

The product thus obtained (1 g) was used without further purification.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 4.75 (br, s, 2 H), 5.52 (s, 2 H), 6.79 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.05 - 7.36 (m, 9 H), 7.48 (d, *J* = 8.5 Hz, 1 H), 7.95 (d, *J* = 7.3 Hz, 1 H).

25 d) 2-chloro-*N*-[9-(phenylmethyl)-9*H*-carbazol-3-yl]benzamide

The product obtained as described in step c) above (0.9 g; 0.003 mol) was reacted by working in a manner similar to that described in Example 1d).

The product thus obtained (1.5 g) was crystallized from ethyl acetate.

30 2-Chloro-*N*-[9-(phenylmethyl)-9*H*-carbazol-3-yl]benzamide (550 mg)

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was thus obtained.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 5.66 (s, 2 H), 7.11 - 7.31 (m, 6 H), 7.39 - 7.68 (m, 8 H), 8.12 (d, $J = 7.6$ Hz, 1 H), 8.59 (d, $J = 1.4$ Hz, 1 H), 10.48 (br, s, 1 H).

5

Example 4

Preparation of Compound 4

($\text{R}_1 = \text{CH}_3\text{CH}_2$, $\text{R}_2 = \text{CF}_3$, $\text{R}_3 = \text{R}_4 = \text{R}_5 = \text{R}_6 = \text{X} = \text{Y} = \text{H}$)

a) N-(9-ethyl-9H-carbazol-3-yl)-2-(trifluoromethyl)benzamide

To a solution of 3-amino-9-ethylcarbazole (4 g; 0.019 mol) in
10 dichloromethane (30 ml) were added triethylamine (2.9 ml; 0.021 mol)
and 2-(trifluoromethyl)benzoyl chloride (3.1 ml; 0.021 mol). The mixture
thus obtained was stirred for 16 hours.

The reaction mixture was transferred into a separating funnel and
washed with H_2O (2×50 ml). The organic phase was separated out
15 and dried over Na_2SO_4 , the solvent was removed by evaporation under
reduced pressure and the residue thus obtained (4 g) was crystallized
from ethanol.

N-(9-Ethyl-9H-carbazol-3-yl)-2-(trifluoromethyl)benzamide (3.5 g)
was thus obtained.

20 m.p.: 206-207°C

Elemental analysis

for $\text{C}_{22}\text{H}_{17}\text{F}_3\text{N}_2\text{O}$

	C	H	N
Found %	68.87	4.26	7.30
Calculated %	69.01	4.48	7.33

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 1.32 (t, $J = 7.1$ Hz, 3 H), 4.44
(q, $J = 7.1$ Hz, 2 H), 7.16 - 7.23 (m, 1 H), 7.42 - 7.50 (m, 1 H), 7.55 -
25 7.90 (m, 7 H), 8.09 (d, $J = 7.7$ Hz, 1 H), 8.51 (d, $J = 1.2$ Hz, 1 H), 10.53
(br, s, 1 H).

Example 5

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Preparation of Compound 5

(R1=CH₃CH₂, R2=R6=CH₃, R3=R4=R5=X=Y=H)a) 2,6-Dimethylbenzoyl chloride

To a mixture of 2,6-dimethylbenzoic acid (3 g; 0.02 mol) in toluene
 5 (50 ml) was added thionyl chloride (3.6 ml; 0.05 mol). The mixture thus
 obtained was refluxed for 2 hours. The solvent and the excess thionyl
 chloride were then evaporated off under reduced pressure. The residue
 thus obtained was taken up in toluene (50 ml) three times and
 evaporated under reduced pressure. The product thus obtained (3.6 g)
 10 was used without further purification.

b) N-(9-ethyl-9H-carbazol-3-yl)-2,6-dimethylbenzamide

The product obtained as described in step a) above (3.3 g;
 0.020 mol) was reacted by working in a manner similar to that described
 in Example 4.

15 The product obtained (2.4 g) was crystallized from isopropanol. N-(9-
 Ethyl-9H-carbazol-3-yl)-2,6-dimethylbenzamide (1.4 g) was thus
 obtained.

m.p.: 192-193°C

Elemental analysis

20 for C₂₃H₂₂N₂O

	C	H	N
Found %	80.57	6.48	8.16
Calculated %	80.67	6.48	8.18

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.31 (t, *J* = 7.1 Hz, 3 H), 2.34 (s,
 6 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 7.08 - 7.27 (m, 4 H), 7.41 - 7.49 (m, 1 H),
 7.54 - 7.62 (m, 2 H), 7.68 (dd, *J* = 8.8, 1.8 Hz, 1 H), 8.10 (d, *J* = 7.6 Hz,
 1 H), 8.59 (d, *J* = 1.8 Hz, 1 H), 10.34 (br, s, 1 H).

25

Examples 6-9

Preparation of Compounds 6-9

A suspension containing 9-ethyl-3-aminocarbazole (0.1 g;

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0.48 mmol) and the appropriate benzoic acid (0.70 mmol) in which R2, R3, R4, R5 and R6 have the meanings indicated in Table 1, in dichloromethane (4 ml) and DMF (0.8 ml), was stirred for 10 minutes.

Polystyrene-divinylbenzene carbodiimide resin (PS-carbodiimide) (0.73 g; 0.9 mmol) was added to the reaction mixture thus obtained, under an inert atmosphere.

The suspension was then stirred for 16 hours.

The reaction mixture was filtered and the solid product obtained was washed with dichloromethane. The solution was then treated with Amberlyst 15 resin (200 mg; 0.8 mmol) and Amberlyst A21 resin (250 mg; 1 mmol) and stirred for 2 hours. The resins were separated out by filtration and washed with dichloromethane (2 × 5 ml) and the organic solvent was evaporated off under reduced pressure to give the desired product.

15

Compound No.	M.W.	Yield (mg)	LC/MS (M+H) ⁺
6	400.38	51	401.3
7	400.38	129	401.3
8	423.31	80	423.2
9	413.31	18	413.1

Example 10

Preparation of Compound 10

(R1= PhCH₂, R2= NH₂, X=R3=R4=R5=R6=Y=H)

a) 2-[(terbutoxycarbonyl)amino]benzoic acid

20 A mixture of anthranilic acid (6.8 g; 0.050 mol), di-tert-butyl dicarbonate (16.4 ml; 0.071 mol), 0.5N NaOH (100 ml), dioxan (50 ml) and acetonitrile (10 ml), was kept under stirring at room temperature for 16 hours. The solvent was removed by evaporation under reduced pressure and the residue was treated with a mixture of 100 g of ice and 25 100 ml of a 10% aqueous solution of citric acid. The solution was

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extracted with ethyl acetate (3 x 100 ml). The combined organic phases were washed with a saturate solution of NaCl (50 ml) and then dried on Na₂SO₄.

After filtration the solvent was removed by evaporation under reduced pressure. The thus obtained residue was crystallized from a mixture of hexane : ethyl acetate = 3 : 1 to yield the product of the title (4.9 g).

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.49 (s, 9 H), 7.07 (td, *J*=7.80, 7.50, 1.20 Hz, 1 H), 7.57 (td, *J*=8.53, 7.22, 1.82 Hz, 1 H), 7.96 (dd, *J*=7.97, 1.72 Hz, 1 H), 8.28 (dd, *J*=8.58, 0.91 Hz, 1 H), 10.51 (s, 1 H), 13.55 (br. s., 1 H).

b) 2-amino-N-(9-benzyl-9H-carbazol-3-yl)benzamide hydrochloride

4-dimethylaminopyridine (0.31 g, 0.0025 mol) and 9-(phenylmethyl)-9H-carbazol-3-amine, obtained as described in Example 3c) (0.626 g, 0.0023 mol), were added to a solution of the product obtained in the previous step a) (0.496 g, 0.0021 mol) in dichloromethane (5 ml).

The mixture was stirred at room temperature for 5 minutes, added with N,N-dicyclohexylcarbodiimide (0.475 g, 0.0023 mol) and kept under stirring at room temperature for 2 days.

Afterwards the mixture was diluted with dichloromethane (15 ml) and filtered through a silica layer. The solution washed with a 10% aqueous solution of citric acid (3x 10 ml), water (2 x 10 ml) and a saturate solution of NaCl (10 ml), respectively. The organic phase was dried on Na₂SO₄ and the solvent was removed under reduced pressure.

The thus obtained product (1.3 g) was purified by flash chromatography by eluting with a mixture of hexane : ethyl acetate = 7 : 3, and then crystallized from a mixture hexane : ethyl acetate = 95 : 5.

The thus obtained product (350 mg, 0.712 mmol) was dissolved in ethyl acetate (50 ml) and treated with a solution of HCl in ethanol 3M (26 ml). The solvent was removed by evaporation under reduced

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pressure and the residue was crystallized from a mixture of absolute ethanol : ethyl acetate = 1 : 1. The 2-amino-N-(9-benzyl-9H-carbazol-3-yl)benzamide hydrochloride (0,2 g) was thus obtained.

1H NMR (300 MHz, DMSO- d_6) δ ppm 5.66 (s, 2 H), 7.01 (t, $J=7.51$ Hz, 1 H), 7.08 - 7.50 (m, 12 H), 7.62 (d, $J=8.59$ Hz, 2 H), 7.70 (dd, $J=8.82$, 1.80 Hz, 1 H), 7.84 (dd, $J=7.76$, 0.99 Hz, 1 H), 8.10 (d, $J=7.60$ Hz, 1 H), 8.56 (d, $J=1.65$ Hz, 1 H), 10.34 (br. s., 1 H).

Example 11

Preparation of Compound 11

10 (R1= CH₃CH₂, R2= N(CH₃)₂, R3=R4=R5=R6=X=Y=H)

a) 2-dimethylamino-N-(9-ethyl-9H-carbazol-3-yl)benzamide hydrochloride

3-amino-9-ethylcarbazole (0.484 g, 0.0023 mol) was reacted with N-dimethyl anthranilic acid (0.347 g, 0.0021 mol) by working in a similar manner to Example 10b.

The thus obtained product (0.9 g) was purified by flash chromatography by eluting with a mixture of hexane : ethyl acetate = 8 : 2. Afterwards, it was dissolved in ethanol, treated with a solution of HCl in 3M ethanol (2.0 ml) and kept at room temperature for 3 hours. Then the solvent was removed under reduced pressure and the residue was crystallized from a mixture of isopropyl alcohol : isopropyl ether = 1 : 3.

The 2-dimethylamino-N-(9-ethyl-9H-carbazol-3-yl)benzamide hydrochloride (0,25 g) was thus obtained.

1H NMR (300 MHz, DMSO- d_6 + D₂O) δ ppm 1.29 - 1.38 (m, $J=7.01$, 7.01 Hz, 3 H), 3.21 (s, 6 H), 4.45 (q, $J=7.16$ Hz, 2 H), 7.24 (td, $J=7.86$, 7.05, 0.88 Hz, 1 H), 7.50 (td, $J=8.26$, 7.09, 1.17 Hz, 1 H), 7.56 - 7.69 (m, 3 H), 7.73 - 7.83 (m, 2 H), 7.91 (d, $J=8.00$ Hz, 1 H), 8.09 - 8.16 (m, 2 H), 8.56 (d, $J=1.75$ Hz, 1 H).

Example 12

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Preparation of Compound 12

(R1= CH₃(CH₂)₄, R2= Cl, R3=R4=R5=R6=X=Y=H)

a) 9-pentyl-9H-carbazole

Carbazole (5 g, 0.030 mol) was reacted with 1-bromopentane (7.5 ml, 0.06 mol) by working in a similar manner to Example 1a).

The solid product obtained after cool filtration (8 g) was purified by filtration through a silica layer by eluting with a mixture of hexane : ethyl acetate = 8 : 2.

It was thus obtained the desired product (6 g).

¹H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 0.82 - 0.94 (m, *J*=7.00, 7.00 Hz, 3 H), 1.28 - 1.44 (m, 4 H), 1.79 - 1.94 (m, 2 H), 4.28 (t, *J*=7.23 Hz, 2 H), 7.21 (td, *J*=7.86, 6.76, 1.32 Hz, 2 H), 7.36 - 7.49 (m, 4 H), 8.09 (d, *J*=7.75 Hz, 2 H).

b) 3-nitro-9-pentyl-9H-carbazole

The product obtained as described in the preceding step a) (1 g, 0.0042 mol) was reacted by working in a similar manner to Example 1b).

The thus obtained product (0.9 g) was purified by flash chromatography by eluting with a mixture of hexane : ethyl acetate = 10 : 1 and the resulting product (0.54 g) was used without further purification.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.75 - 0.85 (m, *J*=7.00, 7.00 Hz, 3 H), 1.19 - 1.37 (m, 4 H), 1.70 - 1.86 (m, 2 H), 4.47 (t, *J*=7.10 Hz, 2 H), 7.33 (td, *J*=7.90, 7.00, 0.80 Hz, 1 H), 7.58 (td, *J*=7.68, 1.16 Hz, 1 H), 7.72 (d, *J*=8.42 Hz, 1 H), 7.78 (d, *J*=9.08 Hz, 1 H), 8.33 (dd, *J*=9.17, 2.39 Hz, 1 H), 8.40 (d, *J*=7.76 Hz, 1 H), 9.17 (d, *J*=2.31 Hz, 1 H).

c) 9-pentyl-9H-carbazol-3-amine

The product obtained as described in the preceding step b) (2.6 g, 0.0092 mol) was reacted by working in a similar manner to Example 1c).

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The thus obtained product (2 g) was purified by crystallization from hexane to yield the desired product (1.3 g).

GC/MS (m/z): 252 (molecular ion), 195 (basic peak)

d) 2-chloro-*N*-(9-pentyl-9*H*-carbazol-3-yl)benzamide

- 5 The product obtained as described in the preceding step c) (0.6 g, 0.0024 mol) was reacted by working in a similar manner to Example 1d).

- 10 The thus obtained product (0.9 g) was purified by crystallization from a mixture of hexane : ethyl acetate = 4 : 1. The 2-chloro-*N*-(9-pentyl-9*H*-carbazol-3-yl)benzamide (0.3 g) was thus obtained.

¹H NMR (300 MHz, DMSO- d_6) δ ppm 0.81 (t, $J=7.00$ Hz, 3 H), 1.21 - 1.36 (m, 4 H), 1.71 - 1.86 (m, 2 H), 4.38 (t, $J=6.97$ Hz, 2 H), 7.19 (td, $J=7.90, 7.00, 0.80$ Hz, 1 H), 7.41 - 7.71 (m, 8 H), 8.09 (d, $J=7.49$ Hz, 1 H), 8.56 (d, $J=1.74$ Hz, 1 H), 10.47 (s, 1 H).

- 15 Example 13

Preparation of Compound 13

(R1= CH₃OCH₂CH₂, R2=Cl, R3=R4=R5=R6=X=Y=H)

a) 9-(2-methoxyethyl)-9*H*-carbazole

- 20 Cesium carbonate (19.5 g, 0.06 mol) was added to a solution of carbazole (5 g, 0.030 mol) in DMF (100 ml) and the mixture was kept under stirring for 1 hour at room temperature. 2-bromoethylmethylether (5.6 ml, 0.06 mol) was added and the mixture was kept under stirring at 90°C for 5 hours.

- 25 Afterwards the reaction mixture was poured into water (300 ml) and stirred at room temperature for 2 hours. The solid (4,8 g) was filtered and used without any further purification.

- 30 ¹H NMR (300 MHz, DMSO- d_6) δ ppm 3.18 (s, 3 H), 3.71 (t, $J=5.41$ Hz, 2 H), 4.55 (t, $J=5.41$ Hz, 2 H), 7.19 (td, $J=7.80, 7.10, 1.00$ Hz, 2 H), 7.44 (td, $J=8.26, 7.09, 1.17$ Hz, 2 H), 7.60 (d, $J=8.18$ Hz, 2 H), 8.14 (dt, $J=7.75, 0.90$ Hz, 2 H).

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b) 3-nitro-9-(2-methoxyethyl)-9H-carbazole

The product obtained as described in the preceding step a) (6 g, 0.027 mol) was reacted by working in a similar manner to Example 1b).

The thus obtained product (7.2 g) was purified by crystallization from
5 toluene to yield the desired product (4.5 g).

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.16 (s, 3 H), 3.74 (t, *J*=5.19 Hz, 2 H), 4.66 (t, *J*=5.19 Hz, 2 H), 7.33 (ddd, *J*=8.00, 7.00, 0.88 Hz, 1 H), 7.57 (ddd, *J*=8.25, 7.20, 1.17 Hz, 1 H), 7.74 (dt, *J*=8.18, 0.88 Hz, 1 H), 7.79 (d, *J*=9.06 Hz, 1 H), 8.33 (dd, *J*=9.21, 2.34 Hz, 1 H), 8.40 (dt,
10 *J*=7.75, 0.88 Hz, 1 H), 9.16 (d, *J*=2.34 Hz, 1 H).

c) 9-(2-methoxyethyl)-9H-carbazol-3-amine

The product obtained as described in the preceding step b) (3 g, 0.011 mol) was reacted by working in a similar manner to Example 1c).

The thus obtained product (2.7 g) was crystallized from a mixture of
15 hexane : ethyl acetate = 2 : 1 to yield the desired product (1.1 g).

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.18 (s, 3 H), 3.66 (t, *J*=5.55 Hz, 2 H), 4.42 (t, *J*=5.48 Hz, 2 H), 4.70 (s, 2 H), 6.81 (dd, *J*=8.48, 2.19 Hz, 1 H), 7.06 (ddd, *J*=7.80, 7.00, 0.88 Hz, 1 H), 7.26 (d, *J*=1.90 Hz, 1 H), 7.29 (d, *J*=8.48 Hz, 1 H), 7.32 (ddd, *J*=8.25, 7.00, 1.25 Hz, 1 H), 7.46
20 (dt, *J*=8.25, 0.88 Hz, 1 H), 7.91 (dt, *J*=7.60, 0.88 Hz, 1 H).

d) 2-chloro-*N*-[9-(2-methoxyethyl)-9H-carbazol-3-yl]benzamide

The product obtained as described in the preceding step c) (0.58 g, 0.0024 mol) was reacted with 2-chlorobenzoyl chloride (0.36 ml, 0.0028 mol) by working in a similar manner to Example 1d).

25 The thus obtained product (0.9 g) was crystallized from a mixture of hexane : ethyl acetate = 2 : 1. It was thus obtained the 2-chloro-*N*-[9-(2-methoxyethyl)-9H-carbazol-3-yl]benzamide (0.5 g).

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.18 (s, 3 H), 3.72 (t, *J*=5.28 Hz, 2 H), 4.55 (t, *J*=5.37 Hz, 2 H), 7.19 (ddd, *J*=7.90, 7.00, 0.88 Hz, 1 H),

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7.39 - 7.69 (m, 8 H), 8.08 (d, $J=7.76$ Hz, 1 H), 8.54 (d, $J=1.82$ Hz, 1 H), 10.47 (s, 1 H).

Example 14

Preparation of Compound 14

5 (R1= HOOC(CH₂)₃, R2= Cl, R3=R4=R5=R6=X=Y=H)

a) 4-(9H-carbazol-9-yl)butanenitrile

Carbazole (10 g, 0.060 mol) was reacted with 4-bromobutyronitrile (11.9 ml, 0.12 mol) by working in a similar manner to Example 1a).

10 The solid product obtained after cool filtration (18 g) was purified by flash chromatography by eluting with a mixture of hexane : ethyl acetate = 8 : 2. It was thus obtained the desired product (10 g).

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 2.03 - 2.15 (m, $J=7.23$, 7.23, 7.23, 7.23 Hz, 2 H), 2.55 (t, $J=7.23$ Hz, 2 H), 4.46 (t, $J=7.16$ Hz, 2 H), 7.21 (td, $J=7.86$, 7.05, 1.02 Hz, 2 H), 7.47 (td, $J=8.26$, 7.09, 1.32 Hz, 2 H), 7.62 (dt, $J=8.22$, 0.79 Hz, 2 H), 8.16 (dq, $J=7.75$, 0.73, 0.58 Hz, 2 H).

b) 4-(3-nitro-9H-carbazol-9-yl)butanenitrile

20 The product obtained as described in the preceding step a) (5 g, 0.0213 mol) was reacted by working in a similar manner to Example 1b).

The thus obtained product (5.2 g) was crystallized from 95° ethanol to yield the desired product (4.8 g).

GC/MS (m/z): 279 (molecular ion), 225 (basic peak)

c) 4-(3-amino-9H-carbazol-9-yl)butanenitrile

25 The product obtained as described in the preceding step b) (2.3 g, 0.0082 mol) was reacted by working in a similar manner to Example 1c).

30 The thus obtained product (2.3 g) was purified by flash chromatography by eluting with a mixture of hexane : ethyl acetate = 4 : 6. It was thus obtained the desired product (1.4 g).

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1H NMR (300 MHz, DMSO- d_6) δ ppm 1.95 - 2.12 (m, $J=7.20$, 7.20, 7.20, 7.20 Hz, 2 H), 2.50 (t, $J=7.20$ Hz, 2 H), 4.33 (t, $J=7.16$ Hz, 2 H), 4.74 (s, 2 H), 6.84 (dd, $J=8.62$, 2.19 Hz, 1 H), 7.09 (td, $J=7.90$, 7.00, 1.00 Hz, 1 H), 7.28 (d, $J=1.90$ Hz, 1 H), 7.31 (d, $J=8.62$ Hz, 1 H), 7.36
5 (td, $J=8.22$, 7.05, 1.24 Hz, 1 H), 7.48 (d, $J=8.30$ Hz, 1 H), 7.94 (d, $J=7.45$ Hz, 1 H).

d) 4-(3-amino-9H-carbazol-9-yl)butanoic acid

The product obtained as described in the preceding step c) (0.7 g, 2.81 mmol) was reacted in water (5 ml) with 95% sulfuric acid (2.8 ml,
10 50 mmol) at reflux for one night.

Then the reaction mixture was cooled, poured on ice (50 g) and the solid product was collected by filtration. It was thus obtained the desired product (0.83 g), which was used in the next reaction without any further purification.

15 e) 4-([3-(2-chlorobenzamido)]-9H-carbazol-9-yl)butanoic acid

The product obtained as described in the preceding step d) (0.3 g, 1,19 mmol) was reacted with 2-chlorobenzoyl chloride (0.171 ml, 1,35 mmol) by working in a similar manner to Example 1d).

The reaction mixture was washed with 1N HCl (3 x 6 ml). The
20 organic phases were separated. The solvent was removed from the combined organic phases under reduced pressure.

It was thus obtained the 4-([3-(2-chlorobenzamido)]-9H-carbazol-9-yl)butanoic acid (0,15 g).

1H NMR (300 MHz, DMSO- d_6) δ ppm 1.92 - 2.07 (m, $J=7.00$, 7.00, 7.00, 7.00 Hz, 2 H), 2.27 (t, $J=7.00$ Hz, 2 H), 4.41 (t, $J=7.14$ Hz, 1 H),
25 7.20 (td, $J=7.80$, 7.00, 0.80 Hz, 1 H), 7.37 - 7.80 (m, 9 H), 8.10 (d, $J=7.50$ Hz, 1 H), 8.57 (d, $J=1.83$ Hz, 1 H), 10.48 (s, 2 H).

Example 15

Preparation of Compound 15

30 (R1= CH₃CH₂, R2= Cl, X=Y= CH₃, R3=R4=R5=R6=H)

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a) 6-bromo-9-ethyl-1,4-dimethyl-3-nitro-9H-carbazole

6-bromo-1,4-dimethyl-3-nitro-9H-carbazole (prepared as described in Chem. Pharm. Bull 35(1), 425-428 (1987), (4.8 g, 0.015 mol) was reacted with iodoethane by working in a similar manner to Example 1a).

- 5 The solid product obtained after filtration (5.1 g) was used without any further purification.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.34 (t, *J*=7.02 Hz, 3 H), 2.83 (s, 3 H), 2.93 (s, 3 H), 4.67 (q, *J*=7.21 Hz, 2 H), 7.71 (dd, *J*=8.70, 1.70 Hz, 1 H), 7.77 (d, *J*=8.50 Hz, 1 H), 7.88 (s, 1 H), 8.38 (d, *J*=1.75 Hz, 1 H).

10 b) 6-bromo-9-ethyl-1,4-dimethyl-3-amino-9H-carbazole

The product obtained as described in the preceding step a) (5 g, 0.014 mol) was reacted by working in a similar manner to Example 1c).

The solid product obtained after filtration (5.1 g) was used without any further purification.

- 15 GC/MS (*m/z*): 316, 318 (molecular ion, basic peak)

c) 9-ethyl-1,4-dimethyl-3-amino-9H-carbazole

- A solution of the product obtained in the preceding step b) (2 g, 0.006 mol) in THF (25 ml) was added to a suspension of LiAlH₄ (0.95 g, 0.025 mol) in anhydrous THF (25 ml). The suspension was refluxed for 24
20 hours. Afterwards, the suspension was left to cool to room temperature and added with a mixture of H₂O and THF 1:1 and NaOH (1,9 g).

- THF was removed by evaporation under reduced pressure and the aqueous residue was placed into a separatory funnel and extracted with ethyl acetate (2x50 ml). The organic phase was separated and dried on
25 Na₂SO₄. The solvent was removed by evaporation under reduced pressure and the thus obtained residue (1.3 g) was used without any further purification.

GC/MS (*m/z*): 238 (molecular ion), 209 (basic peak).

d) 2-chloro-N-(9-ethyl-1,4-dimethyl-9H-carbazol-3-yl)benzamide

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The product obtained as described in the preceding step c) (1.2 g, 0.005 mol) was reacted by working in a similar manner to Example 1d).

The thus obtained product (2 g) was purified by flash chromatography by eluting with a mixture of hexane : ethyl acetate = 8 :

5 2 and then crystallized from a mixture of chloroform : hexane = 1 : 1.

It was thus obtained the 2-chloro-*N*-(9-ethyl-1,4-dimethyl-9*H*-carbazol-3-yl)benzamide (0,2 g).

1H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.32 (t, *J*=7.00 Hz, 3 H), 2.72 (s, 3 H), 2.79 (s, 3 H), 4.65 (q, *J*=6.94 Hz, 2 H), 7.17 (s, 1 H), 7.22 (td, 10 *J*=8.00, 7.00, 0.80 Hz, 1 H), 7.42 - 7.70 (m, 6 H), 8.21 (d, *J*=7.93 Hz, 1 H), 10.03 (s, 1 H).

Example 16

Preparation of Compound 16

(R1= CH₃CH₂, R2= Cl, X= CH₃, R3=R4=R5=R6=Y=H)

15 a) 9-ethyl-9*H*-carbazole

Carbazole (4 g, 0.024 mol) was reacted with iodoethane by working in a similar manner to Example 1a).

The solid product obtained after filtration (4.4 g) was used without any further purification.

20 1H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.31 (t, *J*=7.16 Hz, 3 H), 4.44 (q, *J*=7.02 Hz, 2 H), 7.16 - 7.23 (m, *J*=7.90, 7.00, 1.00 Hz, 2 H), 7.45 (td, *J*=8.30, 7.00, 1.10 Hz, 2 H), 7.60 (d, *J*=8.18 Hz, 2 H), 8.15 (d, *J*=7.60 Hz, 2 H).

b) 9-ethyl-3-nitro-9*H*-carbazole

25 The product obtained as described in the preceding step a) (4 g, 0.0014 mol) was reacted by working in a similar manner to Example 1b).

The thus obtained product (6 g) was purified by flash chromatography by eluting with a mixture of hexane : ethyl acetate = 8 : 2. It was thus obtained the desired product (2.8 g).

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1H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.35 (t, *J*=7.16 Hz, 3 H), 4.54 (q, *J*=7.31 Hz, 2 H), 7.34 (ddd, *J*=8.20, 7.40, 0.80 Hz, 1 H), 7.59 (ddd, *J*=8.20, 7.30, 1.30 Hz, 1 H), 7.74 (dt, *J*=8.18, 0.80 Hz, 1 H), 7.80 (d, *J*=9.06 Hz, 1 H), 8.35 (dd, *J*=9.06, 2.34 Hz, 1 H), 8.41 (dt, *J*=7.60, 0.80 Hz, 1 H), 9.18 (d, *J*=2.34 Hz, 1 H).

c) 9-ethyl-4-methyl-3-nitro-9*H*-carbazole

The product obtained as described in the preceding step b) (2.8 g, 0.0012 mol) was dissolved in anhydrous THF (about 100 ml). The solution was brought at -15°C in an inert atmosphere. A 3M solution of CH₃MgCl in THF (5.7 ml, 0.012 mol) was added and the reaction mixture was kept under stirring for 1 hour at -15°C. Afterwards, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (4.5 g, 0.0020 mol) was added and the reaction mixture was allowed to reach room temperature and maintained under stirring for 48 hours.

The reaction mixture was diluted with dichloromethane (100 ml) and washed with water (2x60ml). The organic phase was separated and dried on Na₂SO₄.

The solvent was then removed by evaporation under reduced pressure and the thus obtained residue was purified by flash chromatography by eluting with a mixture of hexane : ethyl acetate = 8 : 2. The pure fractions were combined to give the desired product (0.6 g). 1H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.33 (t, *J*=7.16 Hz, 3 H), 3.03 (s, 3 H), 4.53 (q, *J*=7.31 Hz, 2 H), 7.35 (ddd, *J*=8.18, 7.00, 1.20 Hz, 1 H), 7.59 (ddd, *J*=8.20, 7.30, 1.20 Hz, 1 H), 7.67 (d, *J*=9.06 Hz, 1 H), 7.77 (d, *J*=8.18 Hz, 1 H), 8.10 (d, *J*=9.06 Hz, 1 H), 8.33 (d, *J*=8.18 Hz, 1 H).

d) 9-ethyl-4-methyl-9*H*-carbazol-3-amine

The product obtained as described in the preceding step c) (0.4 g, 0.0016 mol) was reacted by working in a similar manner to Example 1c).

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The thus obtained product (0.5 g) was purified by flash chromatography by eluting with a CHCl_3 . It was thus obtained the desired product (0.3 g).

1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 1.24 (t, $J=7.02$ Hz, 3 H), 2.57 (s, 3 H), 4.32 (q, $J=7.02$ Hz, 2 H), 4.55 (s, 2 H), 6.91 (d, $J=8.48$ Hz, 1 H), 7.09 (ddd, $J=8.18$, 7.00, 1.00 Hz, 1 H), 7.18 (d, $J=8.48$ Hz, 1 H), 7.35 (ddd, $J=8.00$, 7.20, 1.20 Hz, 1 H), 7.48 (d, $J=8.18$ Hz, 1 H), 8.15 (d, $J=7.89$ Hz, 1 H).

d) 2-chloro-*N*-(9-ethyl-4-methyl-9*H*-carbazol-3-yl)benzamide

10 The product obtained as described in the preceding step d) (0.3 g, 0.0013 mol) was reacted by working in a similar manner to Example 1d).

The thus obtained product (0.5 g) was crystallized 2 times from a mixture of hexane : ethyl acetate = 1 : 2. It was thus obtained the 2-chloro-*N*-(9-ethyl-4-methyl-9*H*-carbazol-3-yl)benzamide (0.23 g).

15 1H NMR (300 MHz, $\text{DMSO}-d_6$) δ ppm 1.31 (t, $J=7.10$ Hz, 3 H), 2.77 (s, 3 H), 4.47 (q, $J=7.05$ Hz, 2 H), 7.23 (ddd, $J=8.00$, 7.00, 1.00 Hz, 1 H), 7.39 - 7.72 (m, 8 H), 8.23 (d, $J=7.93$ Hz, 1 H), 10.09 (s, 1 H).

Examples 17 and 18

20 Preparation of Compounds 17 and 18

Compounds 17 and 18 may be prepared by working in a manner similar to that described in Examples 1-16 above.

Example 19

Preparation of Comparative Compound A

25 (R1= CH_3CH_2 , R2=OH, R3=R4=R5=R6=X=Y=H)

a) *N*-(9-ethyl-9*H*-carbazol-3-yl)-2-methoxybenzamide

3-Amino-9-ethylcarbazole (5.6 g; 0.027 mol) was reacted with 2-methoxybenzoyl chloride (4.35 ml; 0.029 mol) by working in a manner similar to that described in Example 4.

30 The residue thus obtained (3.5 g) was crystallized from isopropanol

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to give the desired product (2.5 g).

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.32 (t, *J* = 7.1 Hz, 3 H), 3.96 (s, 3 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 7.10 (td, *J* = 7.4, 1.0 Hz, 1 H), 7.15 - 7.24 (m, 2 H), 7.41 - 7.48 (m, 1 H), 7.48 - 7.55 (m, 1 H), 7.55 - 7.61 (m, 2 H),
5 7.70 - 7.79 (m, 2 H), 8.10 (d, *J* = 7.6 Hz, 1 H), 8.58 (d, *J* = 1.8 Hz, 1 H), 10.13 (br, s, 1 H).

b) N-(9-ethyl-9*H*-carbazol-3-yl)-2-hydroxybenzamide

To a solution containing boron tribromide (1M in dichloromethane, 0.2 ml; 0.001 mol) in dichloromethane (10 ml) was added the product
10 obtained as described in step a) above (0.5 g; 0.001 mol). The mixture thus obtained was stirred for 16 hours.

The reaction mixture was transferred into a separating funnel and washed with H₂O (2 × 50 ml). The organic phase was separated out and dried over Na₂SO₄. The solvent was removed by evaporation under
15 reduced pressure and the residue thus obtained (0.4 g) was crystallized from ethanol.

N-(9-Ethyl-9*H*-carbazol-3-yl)-2-hydroxybenzamide (0.25 g) was thus obtained.

¹H NMR (300 MHz, DMSO-*d*₆, 70°C), δ ppm 1.37 (t, *J* = 7.1 Hz, 3 H),
20 4.45 (q, *J* = 7.1 Hz, 2 H), 5.55 (br, s, 1H), 6.94 - 7.02 (m, 2 H), 7.21 (t, *J* = 7.0 Hz, 1 H), 7.41 - 7.77 (m, 5 H), 8.04 - 8.15 (m, 2 H), 8.42 - 8.48 (m, 1 H), 10.33 (br, s, 1 H).

Example 20

Preparation of Comparative Compound B

25 (R₁=CH₃CH₂, R₂=SCH₃, R₃=R₄=R₅=R₆=X=Y=H)

Comparative Compound B was prepared in a manner similar to that described with respect to Compounds 6-9, starting with 9-ethyl-3-aminocarbazole and 2-methylmercaptobenzoic acid.

LC/MS (M+H)⁺ = 361.2.

30

Example 21

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Test of *in vitro* activity

This test allows evaluation of the inhibitory capability on the production of the PGE₂ prostaglandins and the selectivity relative to the production of the PGF_{2α} prostaglandins.

- 5 The cell line A549, human pulmonary adenocarcinoma, was used, which is particularly sensitive to stimulation with pro-inflammatory 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).
- 10 The cells were stimulated with IL-1_β (1 ng/ml) and simultaneously treated with the test compound for 18 hours in an appropriate culture medium (DMEM - Dulbecco's Modified Eagle's Medium) supplemented with 5% foetal calf serum and L-glutamine (4 mM final) in an incubator at 37°C and at a CO₂ concentration of 5%.
- 15 After 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 compounds used were indomethacin (Sigma-Aldrich), a non-steroidal anti-inflammatory drug that inhibits in equal
- 20 measure both PGE₂ and PGF_{2α}, and also the compounds of formula (I) in which R1=CH₃CH₂, R2=OH, R3=R4=R5=R6=X=Y=H (comparative compound A) and R1=CH₃CH₂, R2=SCH₃, R3=R4=R5=R6=X=Y=H (comparative compound B).
- The results, given as percentages of inhibition of the production of
- 25 PGE₂ and of PGF_{2α} at a concentration of 10 μm, are shown in Table 2.

TABLE 2

Compound	% inhibition at 10 μM	
	PGE ₂	PGF _{2α}
1	59	27
2	90	66

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3	86	7
4	67	0
5	93	60
6	76	26
7	90	48
8	77	16
A	88	84
B	na	na
indomethacin	100	100

na = not active at the experimental concentration

For illustrative purposes, Table 3 shows the pIC₅₀ values of certain compounds of the invention, where pIC₅₀ is the negative logarithm of the IC₅₀ value, which, in turn, is the concentration of compound that inhibits 50% of the production of PGE₂ or of PGF_{2α} relative to cells that have been stimulated but not treated with the same compound.

TABLE 3

Compound	pIC ₅₀	
	PGE ₂	PGF _{2α}
2	6.1	5
3	5.9	< 4
4	6.2	4
6	6.4	< 4
7	5.7	< 4
8	5.4	< 4
indomethacin	8.3	8.6

Example 22Test of *in vivo* activity

10 This test allows evaluation of the activity of the compounds of the invention in a nociceptive test of inflammatory origin.

The test compounds were evaluated in an experimental model that

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causes stretching induced with acetic acid in mice (Stock J.L. et al., J. Clin. Inv. 2001, 107: 325-331). Female CD-1 mice weighing 25-30 g were used for the test.

5 The animals were treated orally with the compound (30 mg/kg) suspended in methylcellulose (MTC). The control animals were treated orally with the vehicle alone (MTC).

One hour after treatment, an intraperitoneal injection of acetic acid (0.7% v/v in physiological saline, 16 μ l/g of body weight) was given to the animals to induce inflammatory pain and to check the effects of the
10 treatment on the nociceptive response.

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

The animals treated with the compounds of the invention showed a
15 significant reduction in stretching in the 20 minutes following the administration of acetic acid, compared with the animals treated with MTC alone.

The results obtained with Compound 4 are shown in Fig. 1.

Example 23

20 Test on human primary endothelial cells (HUVEC)

This test allows evaluation of the capability of the compounds of the invention to inhibit the production of PGI₂.

The absence of inhibitory activity on this prostanoid can ensure maintenance of the vasoprotective action of the PGI₂ prostanoids and
25 provide useful pharmacological information regarding the absence of adverse side effects on the endothelium.

The action of the test compounds is evaluated in HUVEC cells under basal conditions and conditions of stimulation (J. Immunol. 1989, June 1; 142(11): 3993-9).

30 The results are given as a percentage of inhibition relative to the

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control enzymatic activity.

Indomethacin is used as reference compound.

The compounds of the invention did not show any significant inhibition of secretion of PGI_2 .

5 The results are shown in Table 4.

TABLE 4

Compound	LogM	Inhibition (%)	Comparison Compound	IC_{50}
2	-5	31	indomethacin	-8.0
4	-5	21	indomethacin	-8.0
6	-5	15	indomethacin	-8.0
7	-5	30	indomethacin	-8.0

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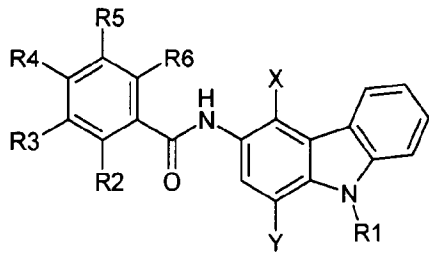
EPO - DG 1

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CLAIMS

1. A 3-aminocarbazole compound, characterized in that it is selected from the group comprising the compounds of Table 1 below:

TABLE 1

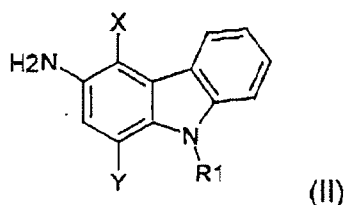
 (I)								
Compound No.	R1	R2	R3	R4	R5	R6	X	Y
1	CH ₃	Cl	H	H	H	H	H	H
2	CH(CH ₃) ₂	Cl	H	H	H	H	H	H
3	PhCH ₂	Cl	H	H	H	H	H	H
4	CH ₃ CH ₂	CF ₃	H	H	H	H	H	H
5	CH ₃ CH ₂	CH ₃	H	H	H	CH ₃	H	H
6	CH ₃ CH ₂	F	H	H	H	CF ₃	H	H
7	CH ₃ CH ₂	CF ₃	H	F	H	H	H	H
8	CH ₃ CH ₂	Br	H	H	H	OCH ₃	H	H
9	CH ₃ CH ₂	Cl	H	H	Cl	OCH ₃	H	H
10	PhCH ₂	NH ₂	H	H	H	H	H	H
11	CH ₃ CH ₂	N(CH ₃) ₂	H	H	H	H	H	H
12	CH ₃ (CH ₂) ₄	Cl	H	H	H	H	H	H
13	CH ₃ OCH ₂ CH ₂	Cl	H	H	H	H	H	H

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14	HOOC(CH ₂) ₃	Cl	H	H	H	H	H	H
15	CH ₃ CH ₂	Cl	H	H	H	H	CH ₃	CH ₃
16	CH ₃ CH ₂	Cl	H	H	H	H	CH ₃	H
17	CH ₃ CH ₂	Cl	H	H	H	H	H	CH ₃
18	CH ₃ CH ₂	Cl	H	H	H	H	CH ₃	OCH ₃

and a pharmaceutically acceptable salt thereof.

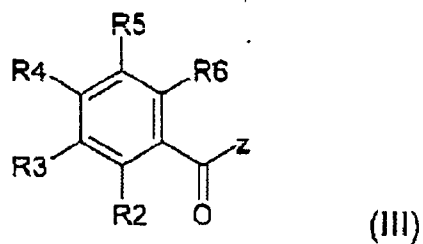
2. A pharmaceutical composition, characterized in that it comprises a therapeutically effective dose of a 3-aminocarbazole compound selected from the group comprising the compounds of Table 1 of Claim 1 above, or a pharmaceutically acceptable salt thereof,
- 5 together with at least one pharmaceutically acceptable inert vehicle.
3. A method for treating or preventing inflammatory processes, tumours, Alzheimer's disease and atherosclerosis in mammals, comprising the administration of a therapeutically effective amount of
- 10 a 3-aminocarbazole compound selected from the group comprising the compounds of Table 1 of Claim 1 above, or a pharmaceutically acceptable salt thereof, to a person in need thereof.
4. A method for preparing a 3-aminocarbazole of Table 1 of Claim 1 above, characterized in that it comprises the following steps:
- 15 a) reacting of an amine of formula (II)



in which R1, X and Y have the meanings indicated in said Table 1, with a compound of formula (III)

20

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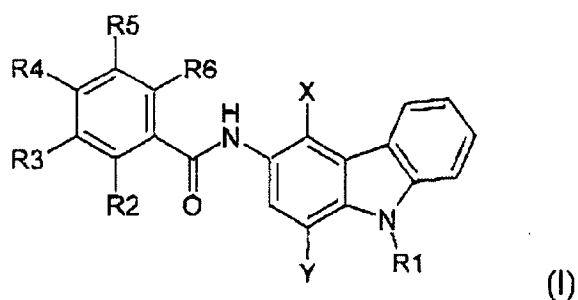


in which R2, R3, R4, R5 and R6 have the meanings indicated in said Table 1, and

Z is selected from the group comprising Cl, Br, OH, OR and OC(O)R,

5 in which R is a linear or branched alkyl containing from 1 to 6 carbon atoms,

to give a 3-aminocarbazole compound of formula (I)

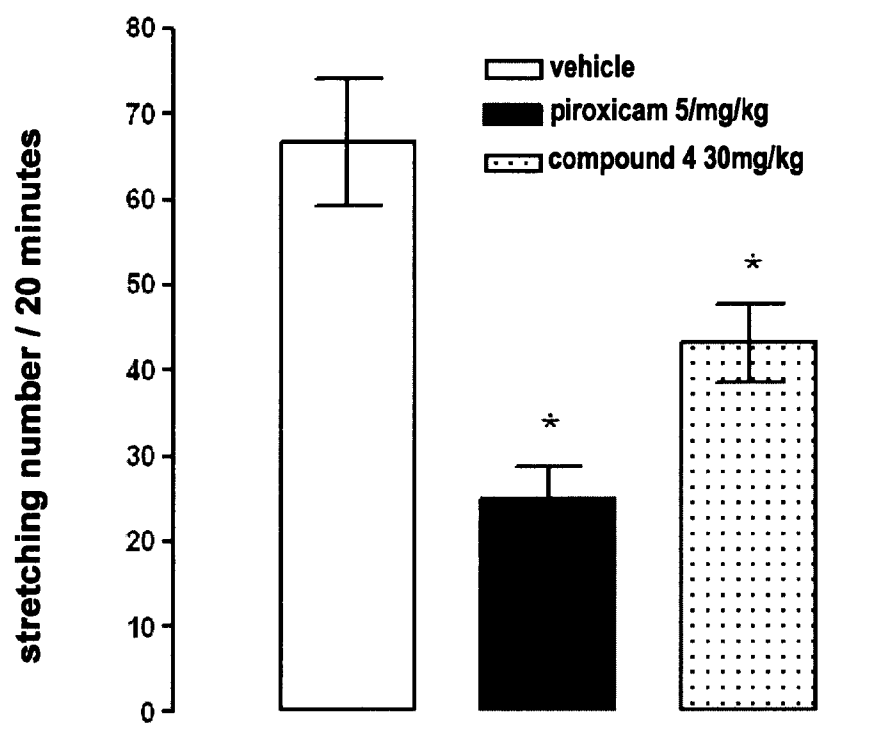


10 in which R1, R2, R3, R4, R5, R6, X and Y have the meanings indicated in said Table 1, and

b) optional formation of a pharmaceutically acceptable salt of the compound of formula (I) thus obtained.

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(41)



8 mice/group

* $p < 0.05$ vs vehicle treated group by ANOVA**Fig. 1**

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/007393

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D209/88 A61K31/403 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 310 179 A (MERCK FROSST CANADA INC) 5 April 1989 (1989-04-05) the whole document	1-4
A	WO 02/096902 A (BOEHRINGER INGELHEIM INTERNATIONAL GMBH; NOVO NORDISK A/S; RUDOLF, KLA) 5 December 2002 (2002-12-05) example 26-18	1-4

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 November 2006

Date of mailing of the international search report

13/11/2006

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/007393

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/007393

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0310179	A	05-04-1989	CA 1330344 C	21-06-1994
			DK 537288 A	25-05-1989
			JP 1132561 A	25-05-1989
WO 02096902	A	05-12-2002	CA 2447234 A1	05-12-2002
			DE 10125961 A1	12-12-2002
			EP 1395578 A1	10-03-2004
			MX PA03010757 A	02-03-2004