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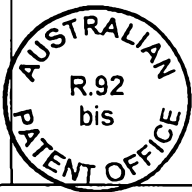
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(54) Title: PYRAZOLECARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM			
(54) Titre: DERIVES D'ACIDE PYRAZOLECARBOXYLIQUE, LEUR PREPARATION, LES COMPOSITIONS PHARMACEUTIQUES EN CONTENANT			
(57) Abstract <p>The invention concerns N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide, the salts and solvents thereof which are powerful antagonists of cannabinoid CB₁ receptors. The method for preparing them consists in reacting a functional derivative of 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxylic acid with 1-aminopiperidine with subsequent optional salification.</p>			
(57) Abrégé <p>Le N-pipéridino-5-(4-bromophényl)-1-(2,4-dichloro phényl)-4-éthylpyrazole-3-carboxamide, ses sels et solvants sont des puissants antagonistes des récepteurs aux cannabinoïdes CB₁. Ils sont préparés par réaction d'un dérivé fonctionnel de l'acide 5-(4-bromophényl)-1-(2,4-dichlorophényl)-4-éthylpyrazole-3-carboxylique avec la 1-aminopipéridine puis salification éventuelle.</p>			

PYRAZOLECARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to a novel
5 pyrazole derivative, to its salts and to the solvates
thereof, to a process for their preparation and to
pharmaceutical compositions containing them.

Patent applications EP-A-576 357,
EP-A-658 546 and WO-97/19063 describe pyrazole
10 derivatives with affinity for cannabinoid receptors.
More particularly, patent application EP-A-656 354
describes N-piperidino-5-(4-chlorophenyl)-
1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide,
also known as SR 141 716, and the pharmaceutically
15 acceptable salts thereof which have very good affinity
for the central cannabinoid receptors.

Compounds similar to SR 141716 have been
described in the literature, in particular
N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-
20 4-methylpyrazole-3-carboxamide, referred to hereinbelow
as compound A, which is described by B.F. Thomas et al.
in J. Pharm. Exp. Therap., 1998, 285, 285-292.

The effects of cannabinoids are due to an
interaction with specific high-affinity receptors
25 present at the central level (Devane et al., Mol.
Pharmacol., 1988, 34, 605-613) and at the peripheral

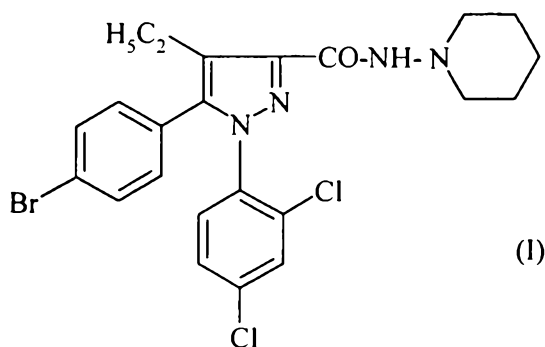


level (Nye et al., Pharmacol. and Experimental Ther., 1985, 234, 784-791 ; Kaminski et al., 1992, Mol. Pharmacol., 42, 736-742 ; Munro et al., Nature, 1993, 365, 61-65).

5 Characterization of the receptors was made possible by the development of synthetic ligands specific for cannabinoid receptors, such as the agonists WIN 55212-2 (J. Pharmacol. Exp. Ther., 1993, 264, 1352-1363) or CP 55,940 (J. Pharmacol. Exp. Ther.,
10 1988, 247, 1046-1051). The pharmacology of the CB₁ and CB₂ cannabinoid receptor subtypes is outlined in Pharmacol. Ther., 1997, 74, 129-130.

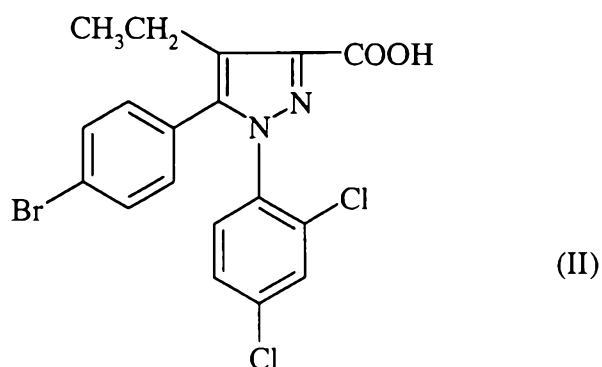
A novel N-piperidino-3-pyrazolecarboxamide derivative has now been found which has very good
15 affinity for the CB₁ subtype of cannabinoid receptors (CB₁ receptors) with long-lasting action, which is useful in the therapeutic fields in which cannabinoids are known to be involved.

According to one of its aspects, the present
20 invention relates to N-piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide, of formula:



to its pharmaceutically acceptable salts and to the solvates thereof.

According to another of its aspects, the present invention relates to a process for preparing compound (I) above, its salts and the solvates thereof, characterized in that a functional derivative of 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxylic acid, of formula:



10

is treated with 1-aminopiperidine, in an organic solvent and in the presence of a base; and the compound thus obtained is optionally converted into one of its salts or one of the solvates thereof.

15

The reaction is carried out in basic medium, for example in the presence of triethylamine in an inert solvent such as dichloromethane or tetrahydrofuran.

20

Functional derivatives of the acid (II) which may be used are the acid chloride, the anhydride, a mixed anhydride, a C₁-C₄ alkyl ester in which the alkyl is straight or branched, an activated ester, for



example the p-nitrophenyl ester, or the suitably activated free acid, for example activated with N,N-dicyclohexylcarbodiimide or with benzotriazole-N-oxotris(dimethylamino)phosphonium (BOP)

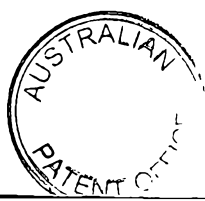
5 hexafluorophosphate.

Thus, by means of the process according to the invention, it is possible to react the acid chloride of formula (II) obtained by reacting thionyl chloride with the acid of formula (II) in an inert
10 solvent, such as benzene or toluene, or a chlorinated solvent (for example dichloromethane, dichloroethane or chloroform), an ether (for example tetrahydrofuran or dioxane), or an amide (for example N,N-dimethylformamide) under an inert atmosphere, at a
15 temperature of between 0°C and the reflux point of the solvent.

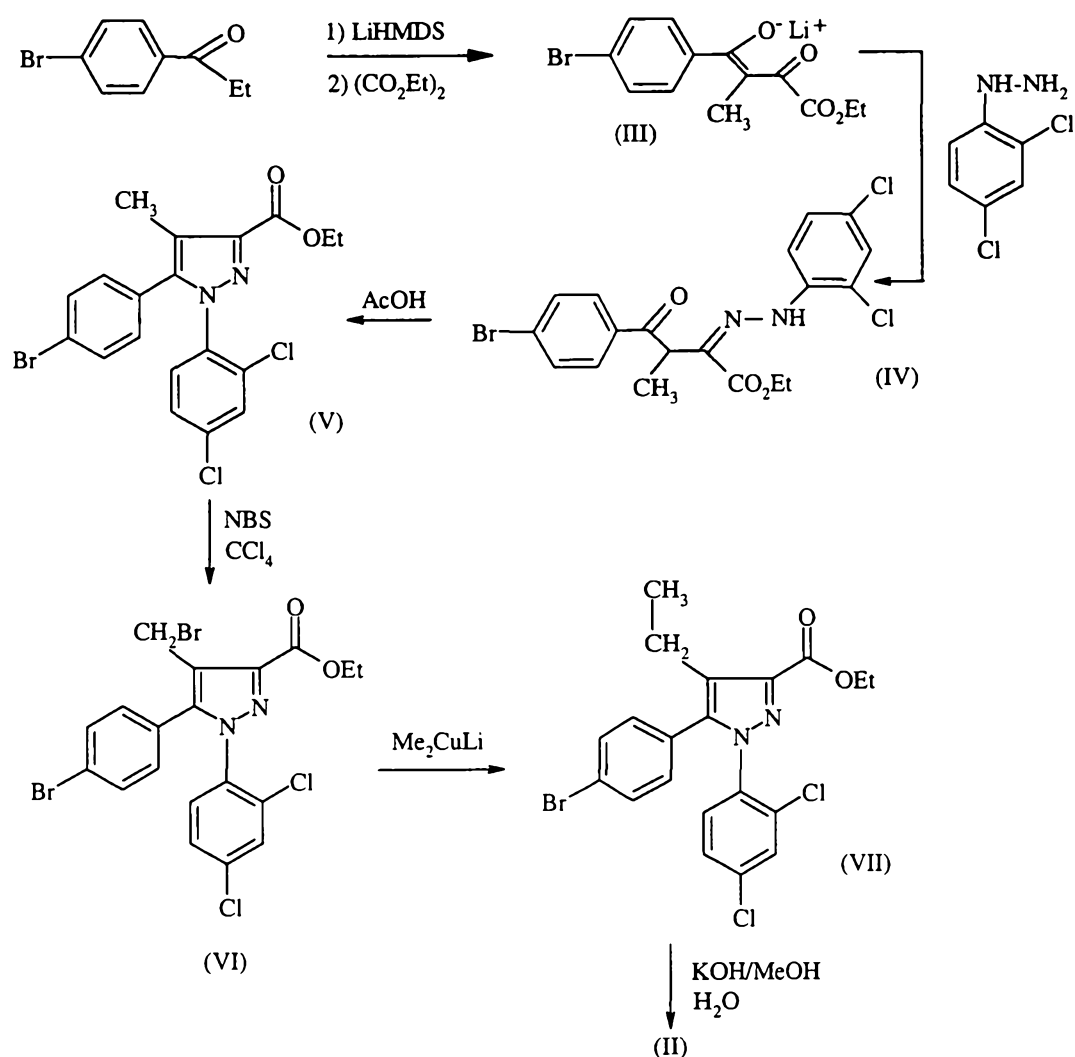
One variant of the procedure consists in preparing the mixed anhydride of the acid of formula (II) by reacting ethyl chloroformate with the acid of
20 formula (II), in the presence of a base such as triethylamine.

The acid of formula (II) can be prepared according to the reaction scheme described below, in which:

25 LiHMDS = lithium hexamethyldisilazide
NBS = N-bromosuccinimide.



SCHEME 1

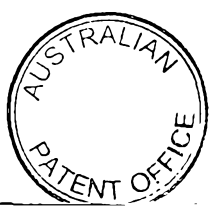


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The first step is carried out according to J. Heterocyclic. Chem., 1989, 26, 1389. In the penultimate step, the conversion of the 4-bromomethyl substituent of the pyrazole into 4-ethyl is carried out according to J. Am. Chem. Soc., 1968, 90, 5615.

10

The 1-aminopiperidine used is a commercial product.

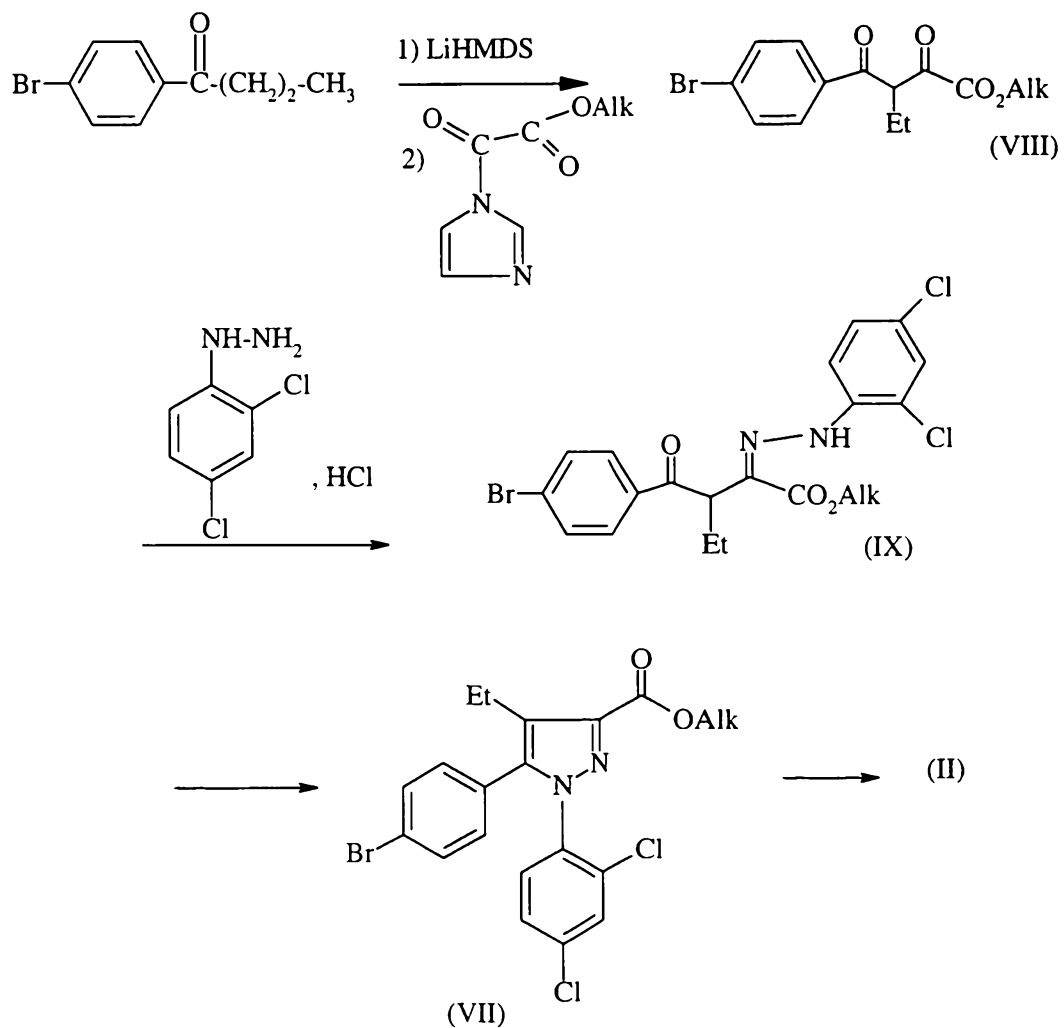


The ester of formula (VII) and the acid of formula (II) can be prepared according to another process which constitutes a further subject of the present invention.

5 This process is illustrated by the reaction scheme below, in which Alk represents a (C₁-C₆)alkyl and represents an ethyl.

SCHEME 2

10



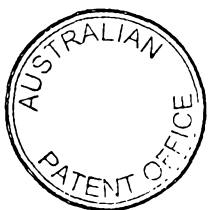
This process is characterized in that an alkyl ester, preferably the ethyl ester, of 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxylic acid is prepared by
 5 cyclization of an alkyl ester, preferably the ethyl ester, of 3-(4-bromobenzoyl)-2-(2-(2,4-dichlorophenyl)-hydrazono)pentanoic acid (IX).

This reaction is carried out in a protic solvent such as an alcohol, for example a C₁-C₄ alcohol, preferably ethanol, at a temperature of between room
 10 temperature and 80°C, preferably in refluxing ethanol.

According to the invention, the alkyl ester, preferably the ethyl ester, of 3-(4-bromobenzoyl)-2-(2-(2,4-dichlorophenyl)hydrazono)pentanoic acid is
 15 prepared by the action of a 2,4-dichlorophenylhydrazine salt, preferably the hydrochloride, on an alkyl ester, preferably the ethyl ester, of 4-bromobenzoyl-2-oxopentanoic acid (VIII).

The reaction is carried out in a protic solvent, for example a C₁-C₄ alcohol, preferably ethanol.
 20

According to the invention, the alkyl ester, preferably the ethyl ester, of 4-bromobenzoyl-2-oxopentanoic acid is prepared by the action of LiHMDS
 25 and then of an alkyl ester, preferably the ethyl ester, of 2-(1-imidazolyl)-2-oxoacetic acid on bromobutyrophenone.



The reaction is carried out in an organic solvent such as an aromatic solvent or an ether, preferably methyl tert-butyl ether. The first step of this reaction is carried out at low temperature, for example at a temperature between 0°C and -60°C, preferably at a temperature in the region of -20°C; the second step is carried out at a temperature of between room temperature and -20°C, preferably at room temperature.

Thus, according to Scheme 2, the preparation of an alkyl ester of 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxylic acid (VII) is carried out starting with 4-bromobenzoyl-2-oxopentanoic acid (VIII) by the action of a 2,4-dichlorophenylhydrazine salt, followed by cyclization.

Bromobutyrophenone is commercially available.

The ethyl ester of 2-(1-imidazolyl)-2-oxoacetic acid is described and prepared according to J. Org. Chem., 1981, 46 (1), 211-213.

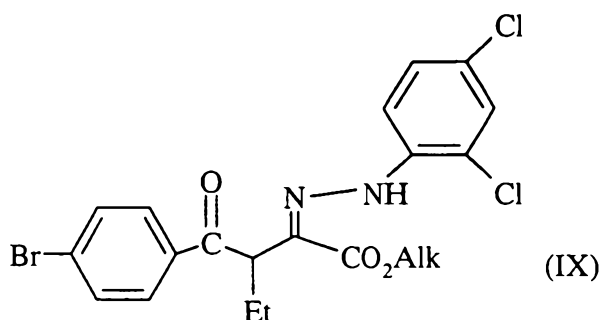
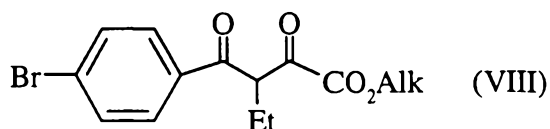
The present invention also comprises a process for preparing an alkyl ester, preferably the ethyl ester, of 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxylic acid, from 4-bromobenzoyl-2-oxopentanoic acid, by the action of a 2,4-dichlorophenylhydrazine salt, preferably the hydrochloride, in a protic solvent, for example a C₁-C₄ alcohol, preferably ethanol. The



reaction is carried out at a temperature of between room temperature and 80°C, preferably in refluxing ethanol.

The compounds of formula:

5



in which Alk represents a (C₁-C₆)alkyl are novel and form part of the invention. Preferably, Alk represents an ethyl.

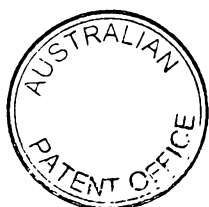
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The compound of formula (I) obtained by the process according to the invention is isolated, in the form of the free base or of a salt or solvate, according to the conventional techniques.

15

The pharmaceutically acceptable salts of the compound of formula (I) comprise the addition salts with acids, such as the hydrochloride, the hydrobromide, the sulphate, the hydrogen sulphate, the dihydrogen phosphate, the methanesulphonate, the methyl sulphate, the oxalate, the maleate, the fumarate, the

20



2-naphthalenesulphonate, the glyconate, the gluconate, the citrate, the isethionate, the para-toluenesulphonate or the succinate.

The compound of formula (I) can be isolated
5 in the form of one of its salts, for example the hydrochloride or the oxalate; in this case, the free base can be prepared by neutralizing the said salt with an inorganic or organic base, such as sodium hydroxide or ammonium hydroxide, triethylamine or an alkali metal
10 carbonate or bicarbonate such as sodium or potassium carbonate or bicarbonate, and converted into another salt such as the methanesulphonate, fumarate or 2-naphthalenesulphonate.

When the compound of formula (I) is obtained
15 in the form of the free base, the salification is carried out by treatment with the acid chosen in an organic solvent. By treating the free base, dissolved, for example, in an ether such as diethyl ether or in acetone, with a solution of the acid in the same
20 solvent, the corresponding salt is obtained and is then isolated according to the conventional techniques.

The compounds of formula (I) have very good
in vitro affinity for the CB₁ cannabinoid receptors, under the experimental conditions described by Devane
25 et al., Mol. Pharmacol., 1988, 34, 605-613.

Thus, the compound according to the invention has very strong affinity for human CB₁ cannabinoid receptors ($K_i = 5.4$ nM) which compares favourably with



that of SR 141716 for the same receptors, determined under the same conditions ($K_i = 34$ nM).

The compound according to the invention was also compared with N-piperidino-5-(4-bromophenyl)-
5 1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, (compound A). The affinity of this compound for human CB_1 cannabinoid receptors, measured under the same conditions, is reflected by a K_i value of 8 nM.

Moreover, the duration of occupation of the
10 CB_1 receptors present in the brain by the 3 compounds below was compared:

- the compound of formula (I) according to the invention,
- SR 141716,
- 15 - compound A.

The study was performed *in vivo* in mice, after oral administration of each of the compounds at a dose of 10 mg/kg, according to the technique described in M. Rinaldi-Carmona et al., Life Sciences, 1995, 56,
20 1941-1947. The results obtained are collated in the table below.

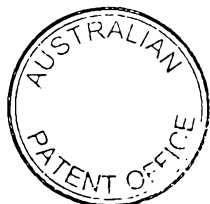


TABLE 1

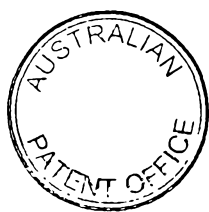
	% of occupation of the receptors	
	1 hour	24 hours
Compound of formula (I)	82%	44%
SR 141716	69%	4%
Compound A	89%	4%

Surprisingly, it is observed that the compound of formula (I) according to the invention is
5 the only compound which shows appreciable occupation (44%) 24 hours after its administration.

Moreover, the antagonist nature of the compound of formula (I) was demonstrated by the results obtained in models of adenylate-cyclase inhibition as
10 described in M. Rinaldi-Carmona et al., J. Pharmacol. Exp. Ther., 1996, 278, 871-878.

More particularly, the compound of the present invention, in its native form or in the form of one of its pharmaceutically acceptable salts, is a
15 powerful and selective antagonist of the CB₁ cannabinoid receptors.

The antagonist nature of the compound according to the invention, as well as its good penetration into the central nervous system, are
20 confirmed by the results obtained in the model of



antagonism of the hypothermia induced with a cannabinoid receptor agonist. Thus, the compound of formula (I) according to the invention antagonizes the hypothermia induced with WIN 55212-2 in mice, with an oral ED₅₀ of 0.3 mg/kg in the test described by Pertwee R.G. et al. in Marijuana, 84, Ed. Harvey, D.Y. Oxford IRL Press, 1985, 263-277. In this test, the activity and the duration of action of 3 compounds were compared. The results obtained are collated in the table below:

TABLE 2

Antagonism of the hypothermia induced

	Duration of action		
	oral ED ₅₀	oral dose	24 h
Compound of formula (I)	0.3 mg/kg	1 mg/kg	active
SR 141716	0.4 mg/kg	1 mg/kg 10 mg/kg	not active active
Compound A	0.3 mg/kg	1 mg/kg 10 mg/kg	not active active

It is found that the compound of the present invention has an ED₅₀ which is comparable with those of the compounds of the prior art, but its duration of action is markedly longer.

Thus, whereas 24 hours after their administration, SR 141716 and compound A are only



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active at a dose of 10 mg/kg/p.o., the compound of formula (I) according to the invention is active 24 hours after its administration, at a dose 10 times lower (1 mg/kg/p.o.).

5 The long-lasting action of the compound of formula (I) according to the invention is particularly noteworthy and represents an important advantage for its use as a medicinal product.

10 The toxicity of compounds (I) is compatible with their use as a medicinal products.

15 According to another of its aspects, the present invention relates to the use of a compound of formula (I), or one of the pharmaceutically acceptable salts or solvates thereof, for the preparation of medicinal products intended for treating diseases involving the CB₁ cannabinoid receptors.

20 According to yet another of its aspects, the present invention relates to a method of treating diseases or disorders involving the CB₁ cannabinoid receptors in a mammal comprising administering a compound of the invention or a pharmaceutical composition of the invention to said mammal.

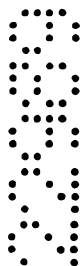
25 For example, and in a non-limiting manner, the compound of formula (I) is useful as a psychotropic medicinal product, in particular for the treatment of anxiety disorders, mood disorders, delirium disorders, psychotic disorders in general, for the treatment of schizophrenia and depression, as well as for the treatment of disorders associated with the use of



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psychotropic substances, in particular in the case of
abuse of a substance and/or dependence on a substance,
including alcohol dependency and nicotine dependency.

The compound of formula (I) according to the
5 invention can be used as medicinal product for treating



neuropathies, migraine, stress, diseases of psychosomatic origin, epilepsy, locomotor disorders, in particular dyskinesias or Parkinson's disease.

The compound of formula (I) according to the invention can also be used as a medicinal product in the treatment of memory disorders, cognitive disorders, in particular in the treatment of senile dementia and Alzheimer's disease, as well as in the treatment of attention disorders or vigilance disorders.

Furthermore, the compound of formula (I) may be useful as a neuroprotective agent, in the treatment of neurodegenerative diseases.

The compound of formula (I) according to the invention can be used as a medicinal product in the treatment of appetite disorders, cravings (for sugars, carbohydrates, drugs, alcohol or any appetizing substance) and/or eating disorders, in particular as an anorexigenic agent or for the treatment of obesity or bulimia, as well as for the treatment of type II diabetes or non-insulin-dependent diabetes.

Furthermore, the compound of formula (I) according to the invention can be used as a medicinal product in the treatment of gastrointestinal disorders, diarrheic disorders, ulcers, vomiting, urinary and bladder disorders, cardiovascular disorders, fertility disorders, inflammatory phenomena, infectious diseases and as a medicinal product for anticancer chemotherapy.



According to the present invention, the compound of formula (I) is most particularly useful for treating psychotic disorders, in particular schizophrenia; for treating appetite disorders and obesity, for treating for memory and cognitive disorders; for treating alcohol dependency or nicotine dependency, i.e. for withdrawal from alcohol and for withdrawal from tobacco.

According to one of its aspects, the present invention relates to the use of a compound of formula (I), its pharmaceutically acceptable salts and the solvates thereof for the treatment of the disorders and diseases indicated above.

According to another of its aspects, the present invention also relates to the use of the compounds of formula (I), in their native form or in radiolabelled form, as a pharmacological tool in man or animals, for detecting and labelling the CB₁ receptors.

The compound according to the invention is generally administered as a dosage unit.

The said dosage units are preferably formulated in pharmaceutical compositions in which the active principle is mixed with a pharmaceutical excipient.

Thus, according to another of its aspects, the present invention relates to pharmaceutical compositions containing, as active principle, a



compound of formula (I), one of its pharmaceutically acceptable salts or a solvate thereof.

The compound of formula (I) above and its pharmaceutically acceptable salts or solvates can be used at daily doses of from 0.01 to 100 mg per kg of body weight of the mammal to be treated, preferably at daily doses of from 0.02 to 50 mg/kg. In human beings, the dose can preferably range from 0.05 to 4000 mg per day, more particularly from 0.1 to 1000 mg per day depending on the age of the individual to be treated or the type of treatment, i.e. prophylactic or curative treatment. Although these doses are examples of average situations, it is possible to have special cases in which higher doses or lower doses are suitable, and such doses also belong to the invention. According to the usual practice, the dose which is suitable for each patient is determined by the doctor according to the method of administration and the age, weight and response of the said patient.

In the pharmaceutical compositions of the present invention for oral, sublingual, inhaled, subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration, the active principle can be administered in unit administration form, as a mixture with conventional pharmaceutical supports, to animals and to human beings. The appropriate unit forms of administration comprise oral-route forms such as tablets, gel capsules, powders, granules and oral



solutions or suspensions, sublingual and buccal administration forms, aerosols, topical administration forms, implants, subcutaneous, intramuscular, intravenous, intranasal or intraocular administration forms and rectal administration forms.

In the pharmaceutical compositions of the present invention, the active principle is generally formulated in dosage units containing from 0.05 to 1000 mg, advantageously from 0.1 to 500 mg and preferably from 1 to 200 mg, of the said active principle per dosage unit for daily administrations.

When a solid composition is prepared in tablet form, a wetting agent such as sodium lauryl sulphate can be added to the micronized or non-micronized active principle, and the whole is mixed with a pharmaceutical vehicle such as silica, gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose, various polymers or other suitable materials or alternatively they can be treated such that they have sustained or delayed activity and such that they release a predetermined amount of active principle continuously.

A preparation in gel capsule form is obtained by mixing the active principle with a diluent such as a glycol or a glycerol ester and by incorporating the mixture obtained into soft or hard gel capsules.



A preparation in the form of a syrup or elixir can contain the active principle together with a sweetener, preferably a calorie-free sweetener, methyl paraben and propyl paraben as antiseptic agents, as
5 well as a flavour enhancer and a suitable colorant.

The water-dispersible powders or granules can contain the active principle as a mixture with dispersants, wetting agents or suspending agents, such as polyvinylpyrrolidone, as well as with sweeteners or
10 flavour enhancers.

For rectal administration, use is made of suppositories which are prepared with binders that melt at the rectal temperature, for example cocoa butter or polyethylene glycols.

15 For parenteral, intranasal or intraocular administration, aqueous suspensions, isotonic saline solutions or sterile, injectable solutions which contain pharmacologically compatible dispersants and/or solubilizing agents, for example propylene glycol or
20 polyethylene glycol, are used.

Thus, to prepare an aqueous solution which can be injected intravenously, a co-solvent such as, for example, an alcohol, for instance ethanol or a glycol such as polyethylene glycol or propylene glycol,
25 and a hydrophilic surfactant such as Tween® 80, can be used. To prepare an oily solution which can be injected intramuscularly, the active principle can be dissolved with a triglyceride or a glycerol ester.



Creams, ointments or gels can be used for local administration.

For transdermal administration, patches in multilayer form or containing a reservoir in which the active principle may be in alcoholic solution can be used.

For administration by inhalation, an aerosol is used containing, for example, sorbitan trioleate or oleic acid as well as trichlorofluoromethane, dichlorofluoromethane, dichlorotetrafluoroethane or any other biologically compatible propellant gas; it is also possible to use a system containing the active principle alone or combined with an excipient, in powder form.

The active principle can also be formulated in the form of microcapsules or microspheres, optionally with one or more supports or additives.

The active principle can also be in the form of a complex with a cyclodextrin; for example α -, β - or γ -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin or methyl- β -cyclodextrin.

Among the forms for sustained release which are useful in the case of chronic treatments, it is possible to use implants. These can be prepared in the form of an oily suspension or in the form of a suspension of microspheres in an isotonic medium.

The pharmaceutical compositions of the present invention can contain, along with the compound



of formula (I) or one of its pharmaceutically acceptable salts or solvates, other active principles which can be useful in the treatment of the disorders or diseases indicated above.

5 In the present description, the following abbreviations are used:

DCM: dichloromethane

LiHMDS: lithium hexamethyldisilazide

TMSCl: chlorotrimethylsilane

10 PTSA: para-toluenesulphonic acid

NBS: N-bromosuccinimide

MTBE: methyl tert-butyl ether

RT: room temperature

m.p.: melting point

15 TLC: thin layer chromatography

NMR: nuclear magnetic resonance. The NMR spectra are recorded at 200 MHz in DMSO-d₆

s: singlet; d: doublet; t: triplet; q: quadruplet;

m: broad peak or multiplet; dd: doubled doublet.

20

PREPARATION 1

Ethyl 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-
4-ethylpyrazole-3-carboxylate

A) Lithium ethyl 4-(4-bromophenyl)-3-methyl-4-oxido-
25 2-oxobutenoate

21.6 g of LiHMDS are placed in 340 ml of anhydrous ether under nitrogen and the solution is cooled to -60°C, followed by addition of 4 g of



bromopropiophenone dissolved in 150 ml of anhydrous ether. This mixture is allowed to warm to -30°C and 17.53 ml of ethyl oxalate are then added. After stirring overnight at RT, the precipitate formed is
5 filtered off and then rinsed with ether and dried under vacuum. 21.8 g of the expected compound are obtained.

B) Ethyl 4-(4-bromophenyl)-2-[(2,4-dichlorophenyl)-hydrazono]-3-methyl-4-oxobutyrates

16.8 g of the compound prepared in the above
10 step and 12.5 g of 2,4-dichlorophenylhydrazine hydrochloride in 150 ml of ethanol are mixed together and left stirring for 2 and a half hours. The precipitate formed is filtered off, rinsed with ethanol and then dried under vacuum. 16.24 g of the expected
15 compound are obtained.

C) Ethyl 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylates

16.24 g of the compound obtained in the above step are heated for 24 hours in 200 ml of acetic acid
20 and the reaction medium is then poured into 1 litre of ice-cold water; the precipitate formed is filtered off, rinsed with water and dried under vacuum. 12.8 g of the expected compound are obtained, and this product is recrystallized from methylcyclohexane, m.p. = 133°C .

25 D) Ethyl 4-bromomethyl-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)pyrazole-3-carboxylates

12.8 g of the ester obtained in the above step are placed in 130 ml of carbon tetrachloride and



5.27 g of N-bromosuccinimide are added, followed by 24 mg of benzoyl peroxide. The mixture is refluxed for 4 hours and is then filtered and concentrated under vacuum. The residue is chromatographed on silica, eluting with a toluene/ethyl acetate mixture (97/3; v/v). 7.24 g of the expected compound are obtained, m.p. = 116°C.

E) Ethyl 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxylate

10 2.26 g of CuBr are introduced as a suspension in 100 ml of ether, under argon, followed by dropwise addition at -20°C of a solution containing 20 ml of 1.6 M methyllithium in ether diluted in 20 ml of ether. After stirring for 10 minutes at -20°C, the suspension
15 decolorizes and then becomes clear. The resulting mixture is cooled to -78°C and 7 g of the compound prepared in the above step are added as a solution in 100 ml of ether, over 30 minutes, after which the mixture is allowed to warm to RT. After stirring for
20 2 hours, the mixture is hydrolysed by addition of saturated ammonium chloride solution. The resulting mixture is extracted with ether and washed with water, and then with saturated NaCl solution. This solution is dried over MgSO₄ and then evaporated to dryness. The
25 residue is chromatographed on silica, eluting with a toluene/ethyl acetate mixture (96/4; v/v). 3.7 g of the expected compound are obtained, m.p. = 108°C.



NMR: 1.05 ppm: t: 3H; 1.30 ppm: t: 3H; 2.60 ppm: q: 2H;
4.30 ppm: q: 2H; 7.15 ppm: d: 2H; 7.50-7.75 ppm: m: 5H.

PREPARATION 2

5 5-(4-Bromophenyl)-1-(2,4-dichlorophenyl)-
4-ethylpyrazole-3-carboxylic acid (II).

3.6 g of the ester obtained in Preparation 1
are placed in 54 ml of MeOH and a solution containing
1.08 g of KOH in 6.85 ml of water is added. The
10 reaction medium is refluxed for 3 hours and then
concentrated under vacuum. The residue is taken up in
ice-cold water, acidified to pH = 1 with 1 N HCl and
then extracted with DCM. 3.3 g of the expected compound
are obtained, m.p. = 218°C.
15 NMR: 1.10 ppm: t: 3H; 2.70 ppm: q: 2H; 7.25 ppm: d: 2H;
7.60-7.85 ppm: m: 5H.

PREPARATION 3

Ethyl 3-(4-bromobenzoyl)-2-oxopentanoate

20 A solution of 247 g of 4-bromobutyrophenone
in 1500 ml of MTBE is added to a solution of 210 g of
LiHMDS in 2500 ml of MTBE, while keeping the
temperature at -20°C. After stirring for 3 hours at
this temperature, 210 g of ethyl 2-(1-imidazolyl)-
25 2-oxoacetate in 1000 ml of MTBE are added over 1 hour,
at 10°C, and the mixture is left stirring for 18 hours
at room temperature. The lithium salt formed is
filtered off and then suspended in 800 ml of MTBE.



800 ml of 6 N hydrochloric acid are added to the suspension. After separation of the phases by settling, the ether phase is washed 4 times with 1000 ml of water and then concentrated under reduced pressure. The

5 expected compound is isolated (263 g). From the NMR analysis, it is a mixture containing 8% of the 4-bromobutyrophenone starting material.

NMR: 0.86 ppm: t: 3H; 1.10 ppm: t: 3H; 1.83 ppm: mt: 2H; 4.15 ppm: q: 2H; 5.19 ppm: t: 1H; 7.70 ppm: d: 2H;
10 7.98 ppm: d: 2H.

PREPARATION 4

Ethyl 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxylate

15 A) Ethyl 3-(4-bromobenzoyl)-2-(2-(2,4-dichlorophenyl)-hydrazono)pentanoate

A suspension of 155 g of 2,4-dichlorophenylhydrazine hydrochloride in 1200 ml of ethanol is prepared and 263 g of the compound of
20 Preparation 3 in 1000 ml of ethanol are added at room temperature.

A small portion of the intermediate formed can be isolated by filtration and characterized.

NMR: 0.92 ppm: t: 3H; 1.04 ppm: t: 3H; 1.89 ppm: mt: 2H; 4.16 ppm: q: 2H; 4.76 ppm: t: 1H; 7.42 ppm: mt: 2H;
25 7.60 ppm: s: 1H; 7.75 ppm: d: 2H; 7.93 ppm: d: 2H; 12.31 ppm: s: 1H.



B) Ethyl 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-
4-ethylpyrazole-3-carboxylate

The suspension obtained is refluxed for
4 hours and then left stirring for 18 hours at room
5 temperature. The product formed is filtered off and
then dried under vacuum at 50°C to give the expected
compound (247 g), m.p. = 108°C.

NMR: 1.07 ppm: t: 3H; 1.28 ppm: t: 3H; 2.58 ppm: q: 2H;
4.32 ppm: q: 2H; 7.16 ppm: d: 2H; 7.53 ppm: dd: 1H;
10 7.59 ppm: d: 2H; 7.73 ppm: d + small d: 2H.

EXAMPLE 1N-Piperidino-5-(4-bromophenyl)-
1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide

A) 5-(4-Bromophenyl)-1-(2,4-dichlorophenyl)-
15 4-ethylpyrazole-3-carboxylic acid chloride

3.2 g of the acid obtained in the above step
are placed in suspension in 32 ml of toluene, 1.6 ml of
thionyl chloride are added and the mixture is then
refluxed for 3 hours. The reaction medium is
20 concentrated under vacuum and then taken up in toluene.
The operation is repeated several times. 3.3 g of the
expected compound are obtained.

B) N-Piperidino-5-(4-bromophenyl)-1-(2,4-dichloro-
phenyl)-4-ethylpyrazole-3-carboxamide

25 A solution of 0.23 ml of N-aminopiperidine
and 0.29 ml of triethylamine in 20 ml of DCM is
prepared, under nitrogen, and is cooled to a
temperature of between 0°C and 5°C. 0.8 g of the acid



chloride obtained in the above step in 20 ml of DCM is added. After leaving overnight at RT, the resulting mixture is poured onto ice-cold water and the phases are separated by settling. The organic phase is

5 extracted with DCM and then washed with water, with 5% Na_2CO_3 solution and with saturated NaCl solution. The resulting solution is evaporated to dryness and the residue is then chromatographed on silica, eluting with a toluene/EtOAc mixture (80/20; v/v). 0.52 g of the

10 expected compound is obtained, m.p. = 113°C .

NMR: 1.05 ppm: t: 3H; 1.25-1.65 ppm: m: 6H; 2.65 ppm: q: 2H; 2.80 ppm: m: 4H; 7.15 ppm: d: 2H; 7.50-7.80 ppm: m: 5H; 9.10 ppm: s: 1H.

15 EXAMPLE 2

N-Piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide

A) 5-(4-Bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxylic acid chloride

20 A mixture containing 97 g of thionyl chloride and 118 g of the compound of Preparation 4 in 1200 ml of toluene is prepared and is heated gradually to reflux and is then maintained at reflux for 3 hours. The reaction medium is concentrated.



B) N-Piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide

The acid chloride formed is taken up in 380 ml of methylcyclohexane and 2.8 g of triethylamine in 218 ml of THF are introduced. The mixture is kept at 50°C.

A solution of 30 g of N-aminopiperidine and 28 g of triethylamine in 34 ml of methylcyclohexane is prepared and cooled to 10°C, and the mixture containing the acid chloride is added slowly. After stirring for 2 hours at 10°C, the product formed is filtered off, taken up in 2000 ml of DCM and washed twice with 2000 ml of water. The product is recrystallized from 4500 ml of methylcyclohexane and then filtered off and dried. 125 g of the expected compound are obtained.

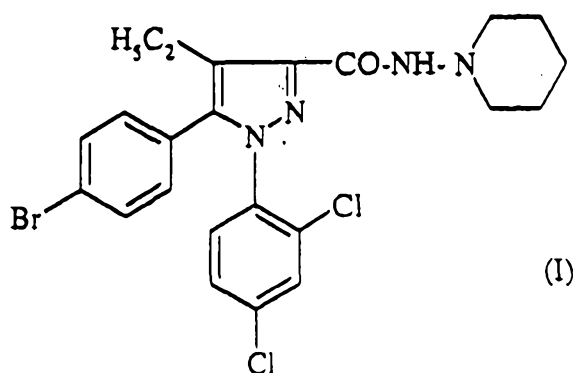
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. N-Piperidino-5-(4-bromophenyl)-
1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide,
5 of formula:

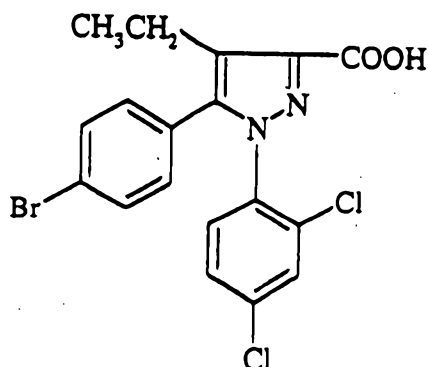


its pharmaceutically acceptable salts and the solvates
10 thereof.

2. Process for preparing N-piperidino-
5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-
4-ethylpyrazole-3-carboxamide, its salts and the
solvates thereof, characterized in that a functional
15 derivative of 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-
4-ethylpyrazole-3-carboxylic acid, of formula:



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is treated with 1-aminopiperidine, in an organic solvent and in the presence of a base; and the compound thus obtained is optionally converted into one of its salts or one of the solvates thereof.

3. Process according to claim 2, wherein the functional derivative of the compound of formula (II) is an alkyl ester, said alkyl ester of formula II prepared by cyclization of an alkyl ester of 3-(4-bromobenzoyl)-2-(2-(2,4-dichlorophenyl)-hydrazono)pentanoic acid (IX).

4. Process according to claim 3, wherein the alkyl ester of 3-(4-bromobenzoyl)-2-(2-(2,4-dichlorophenyl)hydrazono)pentanoic acid is prepared by the action of a 2,4-dichlorophenylhydrazine salt on an alkyl ester of 4-bromobenzoyl-2-oxopentanoic acid (VIII).

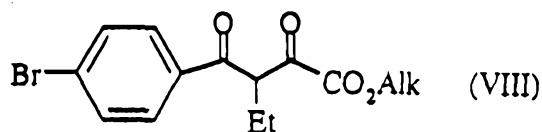
5. Process according to claim 4, wherein the alkyl ester of 4-bromobenzoyl-2-oxopentanoic acid is prepared by the action of LiHMDS and then an alkyl ester of 2-(1-imidazolyl)-2-oxoacetic acid on bromobutyrophenone.



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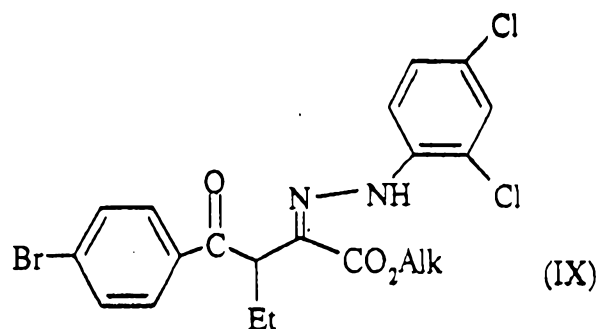
6. Process according to claim 2, wherein the functional derivative of the compound of formula (II) is an alkyl ester, said alkyl ester of formula (II) prepared from 4-bromobenzoyl-2-oxopentanoic acid by the action of a 2,4-dichlorophenylhydrazine salt, followed by cyclization.

7. Compound of formula:



in which Alk represents a (C₁-C₆) alkyl.

8. Compound of formula:



in which Alk represents a (C₁-C₆) alkyl.

9. Pharmaceutical composition containing, as active principle, a compound according to claim 1.



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10. Pharmaceutical composition according to claim 9, containing from 0.1 to 1000 mg of active principle, in unit dosage form, in which the active principle is mixed with at least one pharmaceutical
5 excipient.

11. Use of a compound according to claim 1, for the preparation of medicinal products intended for treating diseases or disorders involving the CB₁ cannabinoid
10 receptors.

12. Use of a compound according to claim 11, for the treatment of psychotic disorders, for the treatment of appetite disorders and obesity, for the treatment of memory and cognitive disorders; for the treatment of alcohol
15 dependency and for withdrawal from tobacco.

13. A method of treating diseases or disorders involving the CB₁ cannabinoid receptors in a mammal comprising administering a compound according to claim 1 or
20 a pharmaceutical composition according to claim 9 or claim 10 to said mammal.

14. A method according to claim 13, wherein the disease or disorder is selected from psychotic disorders,
25 appetite disorders and obesity, memory and cognitive disorders, alcohol dependency and withdrawal from tobacco.

15. Process for preparing N-piperindino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-
30 carboxamide, its salts and the solvates thereof according to claim 2, substantially as hereinbefore described with reference to the Examples.



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16. Pharmaceutical composition according to claim 9, substantially as hereinbefore described.

5 17. Use of a compound according to claim 11, substantially as hereinbefore described.

10 18. A method of treating diseases or disorders involving the CB₁ cannabinoid receptors according to claim 13, substantially as hereinbefore described.

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