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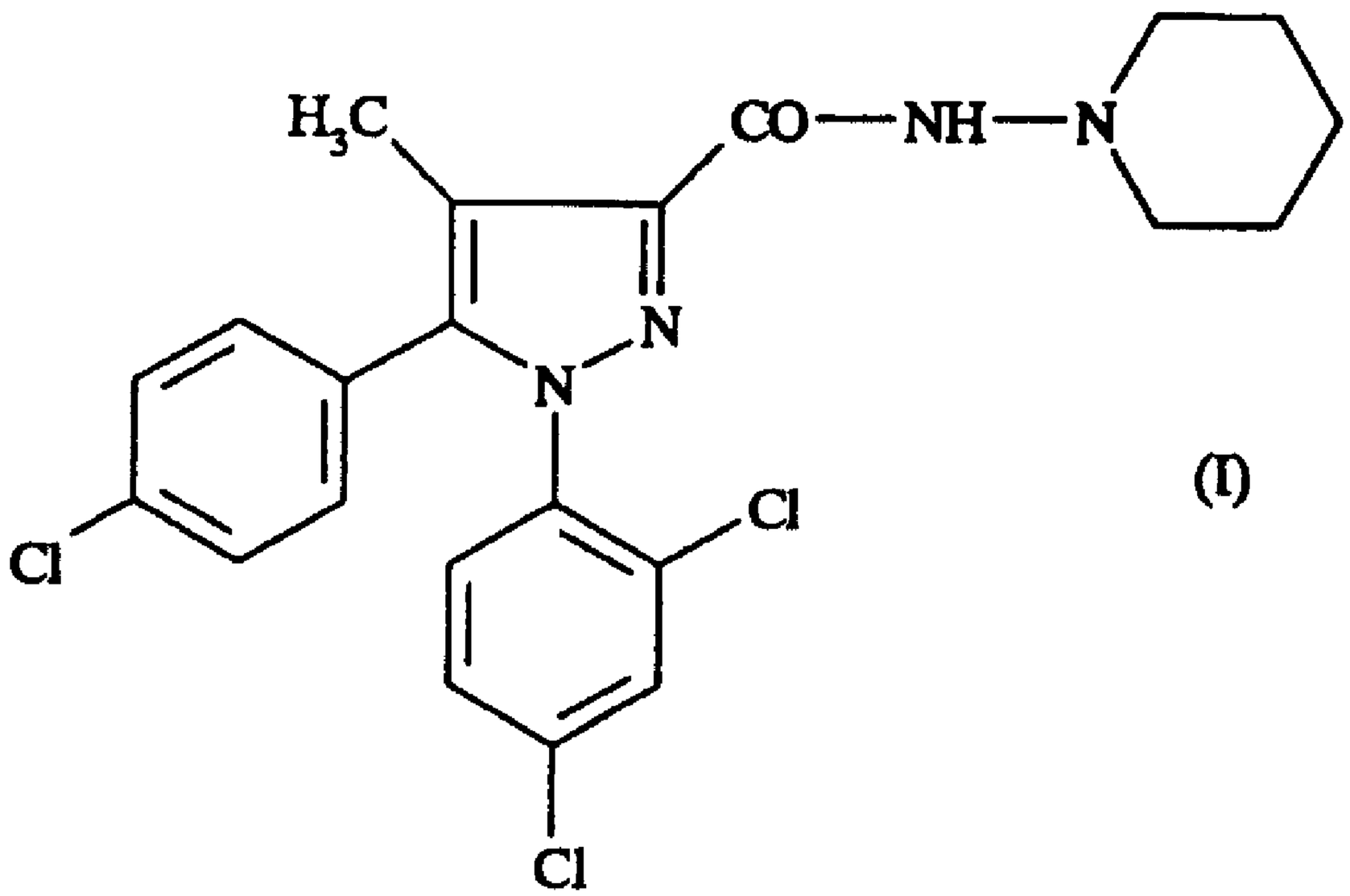
(54) Titre : N-PIPERIDINOPYRAZOLE-3-CARBOXAMIDE SUBSTITUES
(54) Title: SUBSTITUTED N-PIPERIDINO-PYRAZOLE-3-CARBOXAMIDE

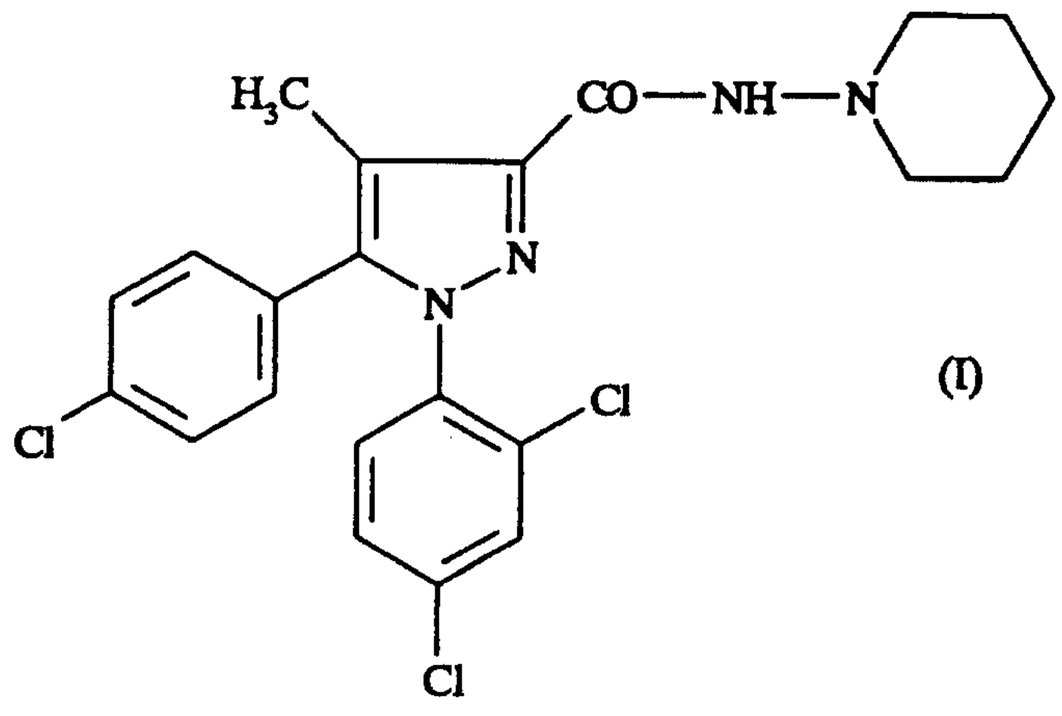


(I)

(57) Abrégé/Abstract:
N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide of the formula: (see formula I) its pharmaceutically acceptable salts and their solvates, are potent antagonists of the central cannabinoid receptors. They are prepared by reaction of a functional derivative of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylic acid with 1-aminopiperidine and, optionally, formation of a salt.

ABSTRACT OF THE DISCLSOURE

N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide of the formula:



(I)

its pharmaceutically acceptable salts and their solvates, are potent antagonists of the central cannabinoid receptors. They are prepared by reaction of a functional derivative of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylic acid with 1-aminopiperidine and, optionally, formation of a salt.

The present invention relates to a novel pyrazole derivative and its salts, to a method of preparing it and to the pharmaceutical compositions in which it is present.

Numerous pyrazole derivatives have been described in the literature; more particularly, EP-A- 268554 and DE-A-3910248 claim pyrazoles possessing herbicidal properties, EP-A-430186 and JP-A-3 031840 claim compounds useful for photography, and EP-A-418845 claims pyrazoles possessing antiinflammatory, analgesic and antithrombotic activity.

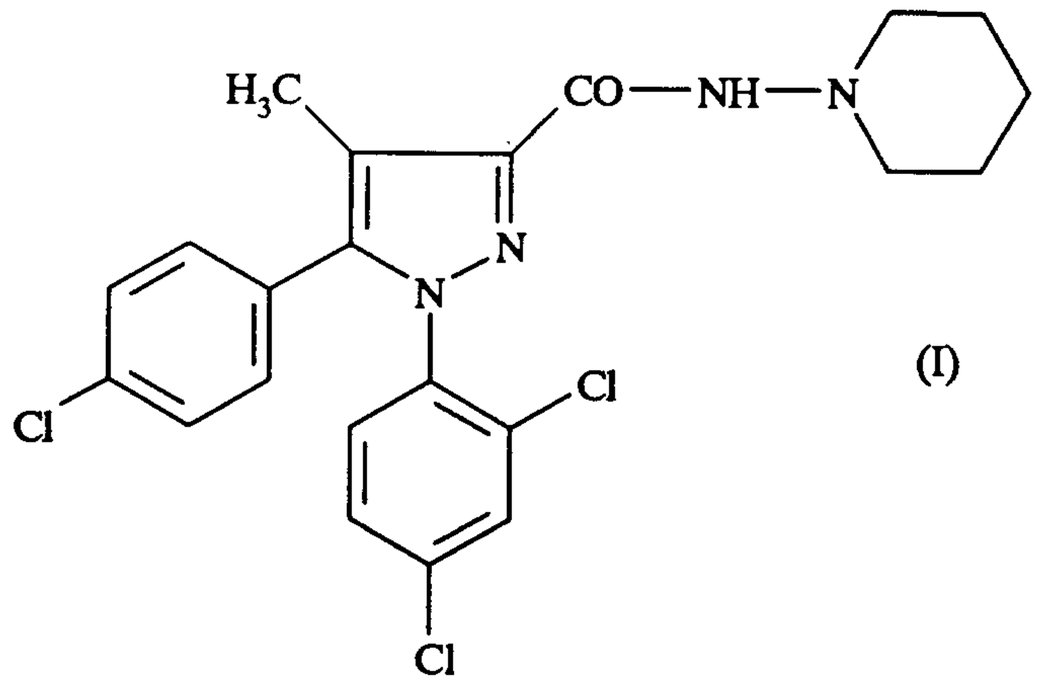
It has now been found that a N-piperidino-pyrazole-3-carboxamide has a very good affinity for the cannabinoid receptor and is useful in the therapeutic areas in which cannabis is known to be involved.

Δ^9-Tetrahydrocannabinol, or Δ^9-THC, is the main active constituent extracted from *Cannabis sativa* (Tuner, 1985; In Marijuana 84, Ed. Harvey, DY, IRL Press, Oxford).

The effects of cannabinoids are due to an interaction with specific high-affinity receptors present in the central nervous system (Devane et al., Molecular Pharmacology, 1988, 34, 605-613) and peripheral nervous system (Nye et al., The Journal of Pharmacology and Experimental Therapeutics, 1985, 234, 784-791; Kaminski et al., 1992, Molecular Pharmacology, 42, 736-742; Munro et al., Nature, 1993, 365, 61-65).

Characterization of this receptor has been made possible by the development of specific synthetic ligands such as the agonists WIN 55212-2 (J. Pharmacol. Exp. Ther., 1993, 264, 1352-1363) or CP 55,940 (J. Pharmacol. Exp. Ther., 1988, 247, 1046-1051).

According to one of its features, the present invention relates to the N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide of the formula :

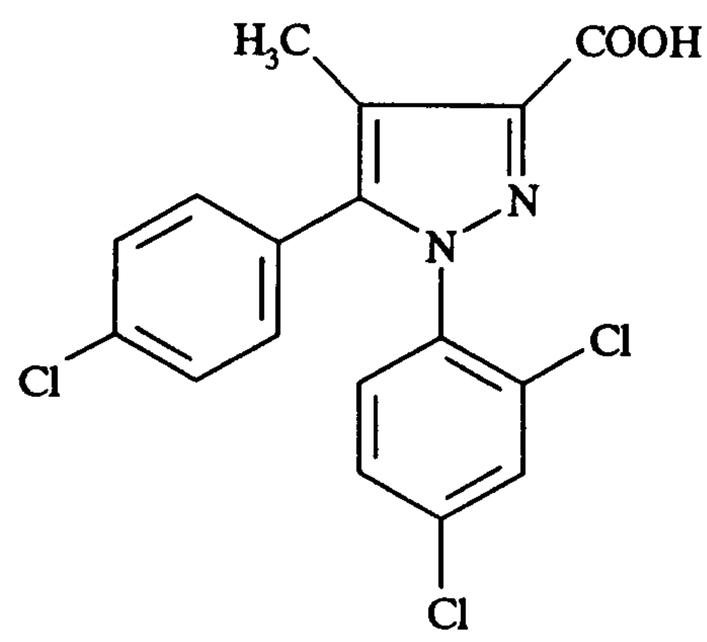


(I)

to its pharmaceutically acceptable salts and to their solvates.

The pharmaceutically acceptable salts of the compound of formula (I) include the acid addition salts such as the hydrochloride, hydrobromide, sulfate, hydrogensulfate, dihydrogenphosphate, methanesulfonate, methylsulfate, oxalate, maleate, fumarate, naphthalene-2-sulfonate, glyconate, gluconate, citrate, isethionate and paratoluene-sulfonate.

According to another of its features, the present invention relates to a method of preparing the above compound (I), its salts and their solvates, which comprises treating a functional derivative of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylic acid of the formula :



(II)

with 1-aminopiperidine in an organic solvent in the presence of a base, and optinally converting the resulting compound into one of its salts or one of their solvates.

The acid chloride, the anhydride, the mixed anhydride, a straight or branched C_1-C_4 alkyl ester, an activated ester such as p-nitrophenyl ester, or the free acid appropriately activated, for example by N,N-dicyclohexylcarbodiimide or benzotriazol-N-oxotris-(dimethylamino)phosphonium hexafluorophosphate (BOP) can be used as the functional derivative of the acid (II).

Thus, in the method of the invention, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylic acid chloride, obtained by reaction of thionyl chloride with the acid of formula (II), can be reacted with 1-aminopiperidine in a solvent such as dichloromethane in an inert atmosphere, at a temperature between 0°C and room temperature, in the presence of a base such as triethylamine.

Alternately, the mixed anhydride of the acid of formula (II) can be prepared by reaction of ethylchloroformate with the said acid in the presence of a base such as triethylamine, and then reacted with 1-aminopiperidine in a solvent such as dichloromethane in an inert atmosphere, at room temperature, in the presence of a base such as triethylamine.

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

The compound of formula (I) can be isolated 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 said salt with a mineral or organic base such as sodium or ammonium hydroxide or triethylamine, or with an alkali metal carbonate or bicarbonate such as sodium or potassium carbonate or bicarbonate, and converted into

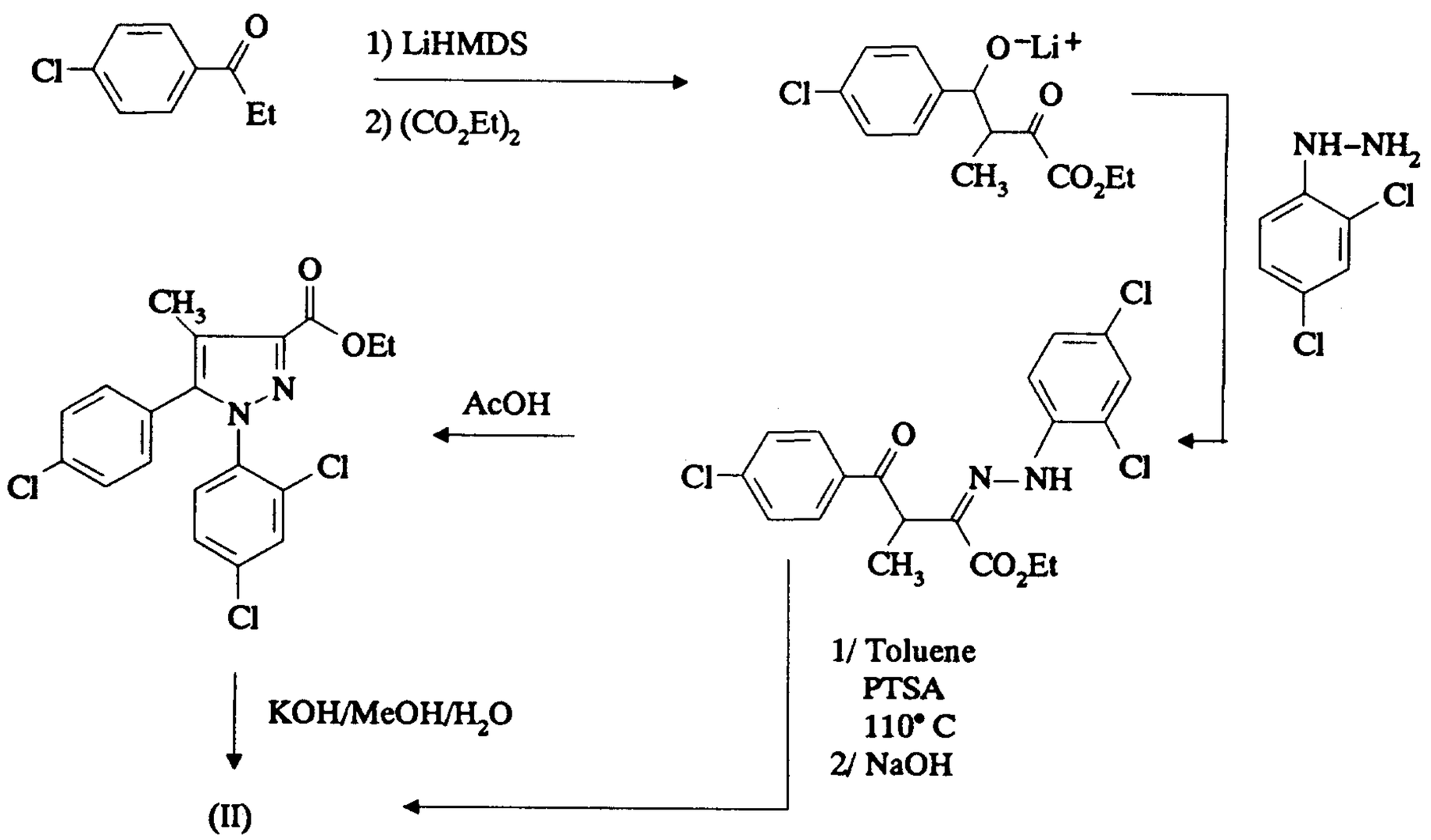
another salt such as the methanesulfonate, fumarate or naphtalene-2-sulfonate.

When the compound (I) is obtained in the form of the free base, a salt is formed by treatment with the chosen acid in an organic solvent. Treatment of the free base, for example dissolved in an ether such as diethylether, or in acetone, with a solution of the acid in the same solvent gives the corresponding salt, which is isolated by the conventional techniques.

The acid of formula (II) used as starting compound in the method of the present invention can be prepared according to conventionnal methods. Some of these methods are illustrated therafter in the preparations.

Preparations 1 and 2 are similar. They are carried out according to the reaction scheme below (route 1) :

Route 1



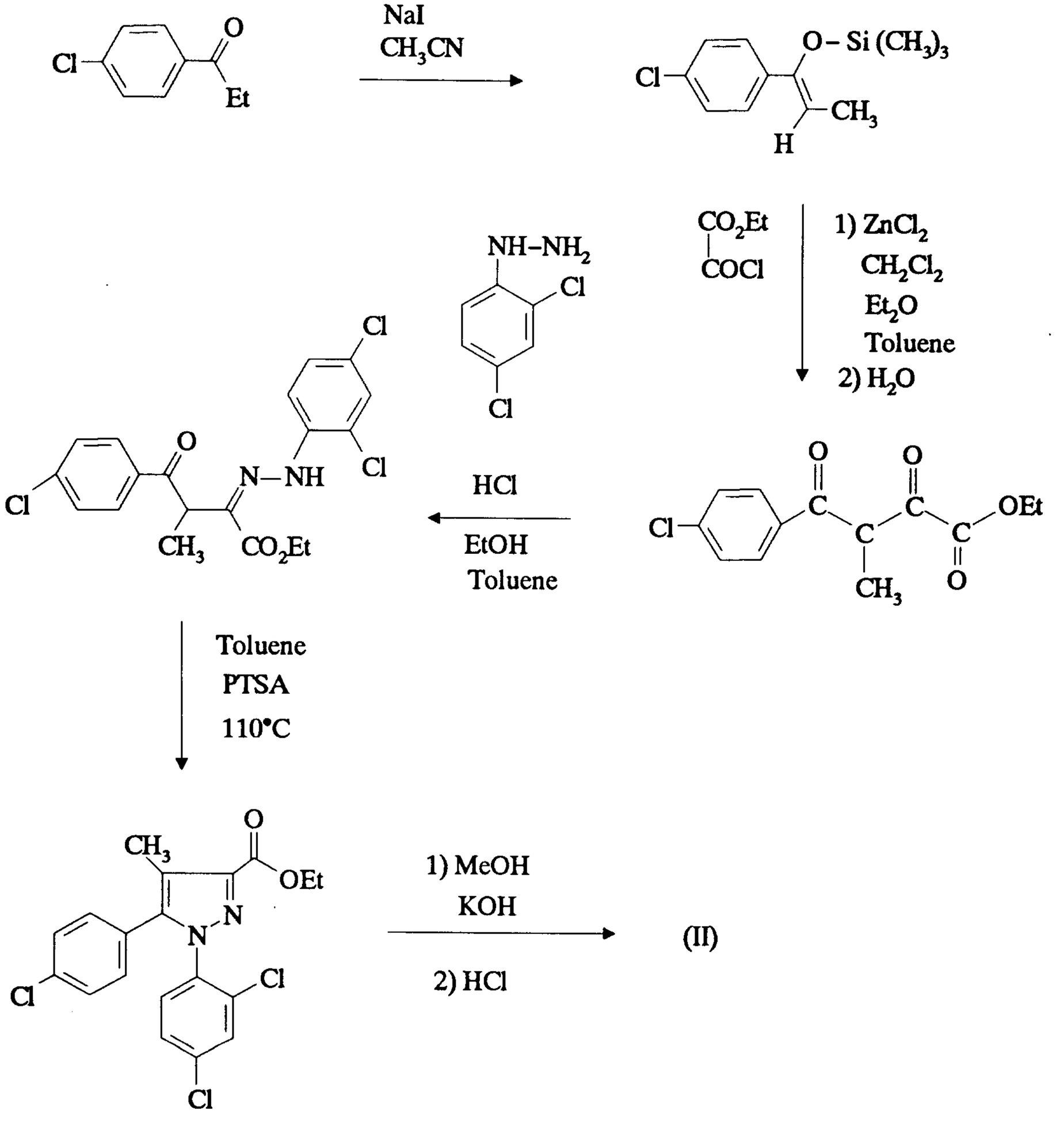
LiHMDS : lithium salt of hexamethyldisilazane

PTSA : paratoluenesulfonic acid.

The first step is carried out according to J. Heterocyclic Chem., 1989, 26, 1389.

Preparation 3 is carried out according to the scheme below (route 2) :

Route 2



TMSCl : chlorotrimethylsilane

PTSA : paratoluenesulfonic acid

The first step is carried out according to the method described by E.S. SCHWEIZER in J. Org. Chem., 1987, 52, 1324-1332. The second step is carried out according to the method described by R.E. TIRPAK et *al.* in J. Org. Chem., 1982, 47, 5099-5102.

The other reagent used in the method of the present invention, 1-aminopiperidine, is commercially available.

The compound of formula (I) exhibits a very good affinity *in vitro* for the central cannabinoid receptors under the experimental conditions described by Devane et al., Molecular Pharmacology, 1988, 34, 605-613.

More particularly, the compound of the present invention, as such or in the form of one of its pharmaceutically acceptable salts, is a potent and selective antagonist of the central cannabinoid receptors and has a Ki of about 2nM. It is from 500 to 1000 times more active on the central receptor as on the peripheral receptor; it is also active upon oral administration and penetrates the blood-brain barrier.

The good penetration of the compound of the present invention in the central nervous system as well as its antagonist character are confirmed by the results obtained with the model of the antagonism of hypothermia induced by an agonist of cannabinoid receptors. Especially, the compound of the present invention antagonizes the hypothermia induced by WIN 55212-2 in mice with an ED_{50} of 0.3 mg/kg i.p. and 0.4 mg/kg per os. In this test (Pertwee R.G., 1985 : 263-277 ; in Marijuana 84, Ed. Harvey, D.Y., IRL Press, Oxford), the above compound exerted its action for 8 to 10 hours after oral administration of a dose of 3 mg/kg.

In addition, the compound (I) alone, upon subcutaneous administration, improves the memory capacities of rats in the test of the central memory (A Pério et *al.* in Psychopharmacology, 1989, 97, 262-268).

Thanks to its remarkable properties, especially its high affinity, its selectivity towards the central receptor as well as its capacity to penetrate the blood-brain barrier, the compound (I), as such or optionally in the form of a pharmaceutically acceptable salt or a solvate, can be used as the active principle of drugs intended for the treatment of the diseases of the central nervous system in mammals.

The toxicity of compound (I) is compatible with its use as a psychotropic drug, especially for the treatment of thymic disorders, anxiety disorders, mood disorders, vomiting, memory disorders, cognitive disorders, neuropathies, migraine, stress, psychosomatic-induced diseases, epilepsy, dyskinesia or Parkinson's disease.

The compound (I) according to the invention can also be used as a drug for the treatment of appetite disorders, especially as an anorexic, for the treatment of schizophrenia, delirious disorders, psychotic disorders in general as well as for the treatment of disorders associated with the use of psychotic substances. Furthermore, the compound (I) according to the invention can be used in cancer chemotherapy.

The use of the compound according to the invention as a drug for the treatment of appetite disorders, anxiety disorders, mood disorders, schizophrenia, psychotic disorders, memory disorders, cognitive disorders and dyskinesia, as well as its use in cancer chemotherapy, constitute a further feature of the present invention.

The compound according to the invention is generally administered in dosage units.

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 features, the present invention relates to pharmaceutical compositions in which a compound of formula (I) or one of its

pharmaceutically acceptable salts or one of their solvates is present as the active principle.

The compound of formula (I) above and its pharmaceutically acceptable salts can be used in daily doses of 0.01 to 100 mg per kilogram of body weight of the mammal to be treated, preferably in daily doses of 0.1 to 50 mg/kg. In humans, the dose can preferably vary from 0.5 to 4000 mg per day, more particularly from 2.5 to 1000 mg, depending on the age of the subject to be treated or the type of treatment: prophylactic or curative.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration, the active principle can be administered to animals and humans in unit forms of administration, mixed with conventional pharmaceutical carriers. The appropriate unit forms of administration include forms for oral administration, such as tablets, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, forms for sublingual and buccal administration, aerosols, implants, forms for subcutaneous, intramuscular, intravenous, intranasal or intraocular administration and forms for rectal administration.

In the pharmaceutical compositions of the present invention, the active principle is generally formulated as dosage units containing from 0.5 to 1000 mg, preferably from 1 to 500 mg, more preferably from 2 to 200 mg of said active principle per dosage unit for daily administrations.

When preparing a solid composition in the form of tablets, a wetting agent such as sodium laurylsulfate can be added to the active principle optionally micronized, which is then mixed with a pharmaceutical vehicle such as silica, starch, lactose, magnesium stearate, talc or the like. The tablets can be coated with sucrose, with various polymers or other appropriate substances or else they can be treated so as to have a prolonged or delayed activity

and so as to release a predetermined amount of active principle continuously.

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

A preparation in the form of a syrup or elixir can contain the active principle together with a sweetener, which is preferably calorie-free, methylparaben and propylparaben as antiseptics, as well as a flavoring and an appropriate color.

The water-dispersible powders or granules can contain the active principle mixed with dispersants, wetting agents or suspending agents such as polyvinyl-pyrrolidone, and also with sweeteners or taste correctors.

Rectal administration is effected using suppositories prepared with binders which melt at the rectal temperature, for example cacao butter or polyethylene glycols.

Parenteral administration is effected using aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersants and/or solubilizers, for example propylene glycol or polyethylene glycol.

Thus a cosolvent, for example an alcohol such as ethanol or a glycol such as polyethylene glycol or propylene glycol, and a hydrophilic surfactant such as Tween® 80, can be used to prepare an aqueous solution injectable by intravenous route. The active principle can be solubilized by a triglyceride or a glycerol ester to prepare an oily solution injectable by intramuscular route.

Transdermal administration is effected using multilaminated patches or reservoirs into which the active principle is in the form of an alcoholic solution.

The active principle can also be formulated as microcapsules or microspheres, optionally with one or more carriers or additives.

The active principle can also be presented 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 prolonged-release forms which are useful in the case of chronic treatments, implants can be used. 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 following Examples illustrate the invention without however implying a limitation.

The melting or decomposition points of the products, M.p., were measured in a capillary tube with a Tottoli apparatus ; in some cases, differential scanning calorimetry (DSC) was used to measure the melting temperature.

The following abbreviations are used in the preparations and in the examples :

THF : tetrahydrofuran

Ether : diethyl ether

Iso ether : diisopropyl ether

EtOH : ethanol

AcOEt : ethyl acetate

MeOH : methanol

DCM : dichloromethane

KOH : potassium hydroxide

AcOH : acetic acid

HCl : hydrochloric acid

NaCl : sodium chloride

RT : room temperature

DSC : differential scanning calorimetry

M.p. : melting point

The following abbreviations are used in the interpretation of the NMR spectra :

s : singlet

d : doublet

t : triplet

q : quadruplet

m : unresolved signals or multiplet

PREPARATION 1

A) Lithium salt of ethyl 4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate

125 ml of a 1M solution of the lithium salt of hexamethyldisilazane in THF are added under a nitrogen atmosphere to 500 ml of ether. The mixture is cooled to -78° C and a solution of 21 g of 4-chloropropiophenone in 100 ml of ether is added dropwise. After stirring for 45 minutes, 19.2 ml of ethyl oxalate are added rapidly and the mixture is stirred for 16 hours while allowing the temperature to rise to RT. The precipitate formed is filtered off, washed with ether and dried under vacuum to give 12.6 g of the expected product.

B) Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylate

9.8 g of 2,4-dichlorophenylhydrazine are added to a solution of 12.6 g of the lithium salt obtained above in 70 ml of EtOH and the mixture is stirred for 16 hours at RT. The precipate formed is filtered off, washed with EtOH and then ether and dried under vacuum to give 12.6 g of hydrazone. This is dissolved in 100 ml of AcOH, the mixture is refluxed for 24 hours and then poured into 500 ml of iced water. The mixture is extracted with AcOEt, washed with water and then a saturated solution of NaCl. After drying over magnesium sulfate and evaporation under vacuum, the crude product is crystallized from iso ether to give 9.6 g of the expected product. M.p. = 124° C.

C) 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid

A solution of 3.3 g of KOH in 70 ml of water is added to a solution of 9.6 g of the ester obtained above in 70 ml of MeOH. The mixture is refluxed for 3 hours, poured into 200 ml of iced water and the reaction mixture is acidified to pH = 1 upon addition of a 10 % solution of HCl. The precipitate formed is filtered off, washed with water and dried under vacuum to give 8.8 g of the expected acid. M.p. = 211° C.

Preparation 1 is improved using the operating conditions described in preparation 2 below :

PREPARATION 2

A) Lithium salt of ethyl 4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate

2008 g of the lithium salt of hexamethyldisilazane are dissolved, in a reactor, under a nitrogen atmosphere, in 10.1 l of methylcyclohexane. A solution of 1686 g of 4-chloropropiophenone in 4 l of methylcyclohexane is then added slowly at 20 ± 5° C. After stirring for 4 and a half hours, 1607 g of ethyl oxalate are added over 35 minutes at 20 ± 5° C. The mixture is stirred for 17 hours at the same temperature. The solid formed is filtered off, washed with methylcyclohexane and dried under vacuum to give 1931 g of the expected product.

B) 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid

1/ 1921 g of the lithium salt obtained above are dissolved, in a reactor, under a nitrogen atmosphere, in 11 l of EtOH. 1493 g of 2,4-dichlorophenylhydrazine hydrochloride are then immediatly added at 20 ± 5° C. The mixture is stirred for 1 hour and 2.88 l of deionized water are then added, and stirring is continued for 17 hours at 20 ± 5° C. The precipitate formed is filtered off, washed with 80 % (v/v)

ethanol and dried under vacuum to give 2280 g of the expected hydrazone. M.p. = 140° C.

2/ 2267 g of hydrazone are dissolved, in a reactor, under a nitrogen atmosphere, in 11.3 l of toluene. 201.6 g of paratoluenesulfonic acid are then added and the mixture is refluxed for 3 hours. The mixture is cooled to 20 ± 5° C and paratoluenesulfonic acid is removed by extraction with deionized water. 120.75 g of benzyltriethylammonium chloride and then a solution of 636 g of NaOH in 1180 ml of deionized water are added to the toluene solution. The mixture is heated for 4 hours at 68 ± 3° C with vigorous stirring, sodium hydroxide is then neutralized and the reaction mixture is acidified with 1500 ml of HCl (d = 1.19). The mixture is cooled to 20 ± 5° C, the precipitate formed is filtered off, washed with toluene and then deionized water, and dried under vacuum to give 1585 g of the expected product. M.p. = 210° C.

PREPARATION 3

A) 1-(4-chlorophenyl)-1-trimethylsilyloxypropene

13.47 g of chlorotrimethylsilane are slowly added to 12.55 g of triethylamine, under a nitrogen atmosphere, at 20 ± 3° C. 16.86 g of 4-chloropropiophenone (endothermic mixture) and then a solution of 18.58 g of sodium iodide in 125 ml of acetonitrile are further added while maintaining the temperature at 18 ± 2° C. The mixture is then heated for 3 hours at 40 ± 5° C, the acetonitrile is removed under reduced pressure and 150 ml of toluene are added to the solid residue. 50 ml of solvent are distilled under reduced pressure to drive the residual acetonitrile off. The inorganic materials are extracted with 100 ml of iced water, the organic phase is washed with 100 ml of iced water and dried over magnesium sulfate. The toluene is removed under reduced pressure and complete removal of the

solvents is performed for 15 hours at 60° C under a pressure of 1 mbar to give 22.7 g of an oil.

NMR run at 200 MHz ($CDCl_3$)

0.13 ppm : s : 9H

1.7 ppm : d : 3H

5.28 ppm : q : 1H

7.21-7.39 ppm : m : 4H.

B) Ethyl 3-(4-chlorobenzoyl)-3-methylpyruvate

10 g of anhydrous zinc chloride are suspended in 50 ml of toluene under a nitrogen atmosphere. Residual water is azeotropically driven off over 1 hour under atmospheric pressure. 20 ml of toluene and then 11.5 ml of ethyl ether are added to the mixture, cooled to 20 ± 3° C. A solution of 17 g of ethyl chloroglyoxylate diluted in 20 ml of dichloromethane is then slowly added to the mixture cooled to 0 ± 2° C. 14.5 g of the product obtained in the previous step are added over 1 and a half hours at the same temperature. The temperature is then allowed to rise to RT and the mixture is heated for 4 hours at 45° C. The organic phase is washed with a solution of sodium hydrogencarbonate and then water, and dried over magnesium sulfate. The solvents are removed under reduced pressure to give 17.6 g of an oil.

NMR run at 200 MHz ($CDCl_3$)

1.25 ppm : t : 3H

1.35 ppm : d : 3H

4.20 ppm : q : 2H

4.93 ppm : q : 1H

7.45-7.90 ppm : m : 4H.

C) Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylate

13.3 g of 2,4-dichlorophenylhydrazine hydrochloride are added to 17.6 g of the compound obtained in the previous step and the mixture is stirred for 18 hours at 20 ± 3° C. Without isolating the hydrazone, 0.56 g of paratoluenesulfonic acid are then added and the ternary

azeotrope (water, ethanol, toluene) is distilled. Toluene reflux is continued for 1 hour and the reaction mixture is then cooled to 20 ± 3° C. The insoluble material is filtered off and the toluene solution is then washed twice with 100 ml of water. The solvents are removed under reduced pressure to give a crude oil which is used as such in the next step.

D) 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid

8.1 g of KOH in pellets are added to a solution of the oil obtained in the previous step in 100 ml of MeOH. The mixture is left for 1 hour at 25 ± 3° C and the solvents are then removed under reduced pressure. The residue is taken up with 200 ml of water and 40 ml of toluene, the mixture is heated at 60 ± 3° C, decanted, and the aqueous phase is extracted three times, at this temperature, with 40 ml of toluene. Hydrochloric acid is then added to the aqueous phase until pH = 1.5. The white crystals formed are filtered off, washed with water and then iso ether and dried under vaccum to give 9.9 g of the expected product. M.p. = 210° C.

EXAMPLE 1

N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide

A) 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid chloride

5 ml of thionyl chloride are added to a suspension of 8.8 g of the acid obtained in step C of preparation 1 in 90 ml of toluene, the mixture is refluxed for 3 hours and then evaporated to dryness under vaccum. The residue is taken up in 90 ml of toluene and the solvent is evaporated again under vacuum to give 8.0 g of the expected acid chloride which is used as such in the following step.

B) N-piperidino-5-(4-chlorophenyl)-1(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide

A solution of 8.0 g of the acid chloride obtained above in 80 ml of DCM is added dropwise to a solution of 2.8 ml of 1-aminopiperidine and 3.6 ml of triethylamine in 100 ml of DCM, cooled to 0° C. The mixture is stirred for 3 hours while allowing the temperature to rise to RT and then poured into 200 ml of iced water. The mixture is extracted with DCM, washed with water and then a saturated solution of NaCl, dried over magnesium sulfate and evaporated under vaccum. The residue is purified by chromatography on silica gel using AcOEt/toluene (10/90; v/v) as the eluent. Crystallisation in iso ether gives 5.9 g of the expected product. M.p. = 148° C.

The compound of example 1 can also be prepared using operating conditions which are industrially more accessible.

A suspension of 1568.6 g of the acid obtained in step B of preparation 2 in 14.1 l of methylcyclohexane is heated, under a nitrogen atmosphere, to 83 ± 3° C, and a solution of 554.5 g of thionyl chloride in 1.57 l of methylcyclohexane is added thereto. The mixture is stirred for 3 hours at 83 ± 3° C and the temperature is then increased over 2 hours up to the reflux temperature of methylcyclohexane while removing the excess thionyl chloride by distillation. The mixture is cooled to 10 ± 3° C and a solution of 452.9 g of 1-aminopiperidine and 457.5 g of triethylamine in 3.14 l of THF is then slowly added. The mixture is stirred for 17 hours while allowing the temperature to rise to 20 ± 5° C, and the organic phase is successively washed, at 20 ± 5° C, with deionized water and a 4% aqueous solution of acetic acid. The organic phase is then washed, at 70 ± 3° C, with a 1.5 % solution of NaOH and then deionized water, and the THF and water are driven off by azeotropic distillation under atmospheric pressure. The mixture is allowed to cool to 20 ± 5° C. The expected

product crystallises, the precipate formed is filtered off, washed with methylcyclohexane and dried under vaccum to give 1627 g of the title compound.
DSC : endothermic peak centered at 155.5° C.

EXAMPLE 2

N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (solvate with ethanol)

10 g of the compound obtained in example 1 are suspended in 60 ml of absolute ethanol and the mixture is refluxed until complete dissolution of the compound. The mixture is allowed to cool to 20 ± 3° C and stirring is continued for 2 hours. The white crystals formed are filtered off, washed with ethanol and dried under vacuum to give 9.6 g of the expected product.
DSC : endothermic peak centered at 102.7° C.

% calculated	C : 56.5	H : 5.29	N : 10.98
% found	C : 56.43	H : 5.41	N : 11.05.

EXAMPLE 3

N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide hydrochloride

A saturated solution of gaseous HCl in ether is added dropwise to a solution of 5.9 g of the compound obtained in example 1 in 50 ml of ether until pH = 1. The precipitate formed is filtered off, washed with ether and dried under vacuum to give 6.0 g of the expected hydrochloride. M.p. = 224° C (decomposition).

EXAMPLE 4

N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide hydrochloride (solvate with ethanol)

40 g of the compound obtained in example 3 are suspended in 400 ml of absolute ethanol. The mixture is heated to the boiling point until complete dissolution of the compound and then stirred for 20 hours while progressively cooling it to 20 ± 3° C. The white crystals formed are filtered off, washed with ethanol and dried under vacuum to give 29.6 g of the expected product.

DSC : broad endothermic peak (175-230° C)

Thermogravimetry : weight loss : about 8.2 % starting at 100° C.

% calculated C : 53.04 H : 5.16 N : 10.31

% found C : 52.68 H : 5.23 N : 10.34.

EXAMPLE 5

N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide methanesulfonate (hemisolvate with acetone)

3.84 g of methanesulfonic acid are added at 20 ± 3° C to a solution of 18.55 g of the compound obtained in example 1 in 185 ml of acetone and the mixture is stirred for 20 hours at the same temperature. The white crystals formed are filtered off, washed with acetone and dried under vacuum to give 21.65 g of the expected product.

DSC : melting, recrystallisation at about 175° C then melting at 191.5° C.

Thermogravimetry : weight less : about 5.2 % starting at 90° C.

% calculated C : 49.90 H : 4.75 N : 9.50

% found C : 49.70 H : 4.76 N : 9.44.

EXAMPLE 6

N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide hemifumarate

A solution of 0.038 g of fumaric acid in 6 ml of acetone is added dropwise to a solution of 0.30 g of the compound obtained in example 1 in 3 ml of acetone. The white crystals formed upon cooling to 0° C are filtered off, washed with acetone and dried under vacuum to give 0.23 g of the expected salt. M.p. = 168 °C.

EXAMPLE 7

N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide hydrogensulfate

0.018 ml of concentrated sulfuric acid are added to a solution of 0.30 g of the compound obtained in example 1 in 3 ml of acetone. The white crystals formed are filtered off, washed with acetone and then ether, and dried under vacuum to give 0.31 g of the expected salt. M.p. = 240° C.

EXAMPLE 8

N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide paratoluenesulfonate

7.61 g of paratoluenesulfonic acid are added at 20 ± 3° C to a solution of 18.55 g of the compound obtained in example 1 in 185 ml of acetone and the mixture is stirred for 20 hours at the same temperature. The white crystals formed are filtered off, washed with acetone and dried under vacuum to give 24.25 g of the expected product.
DSC : endothermic peak centered at 236.8° C
% calculated C : 54.76 H : 4.60 N : 8.72
% found C : 54.11 H : 4.71 N : 8.69.

EXAMPLE 9

N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide dihydrogenphosphate

4.61 g of 85 % phosphoric acid are added at 20 ± 3° C to a solution of 18.55 g of the compound obtained in example 1 in 185 ml of methylethylketone. Water is removed by distillation under atmospheric pressure of the azeotrope methylethylketone/water. The mixture is progressively cooled to 20 ± 3° C while stirring for 20 hours. The white crystals formed are filtered off, washed with methylethylketone and dried under vacuum to give 21 g of the expected product.

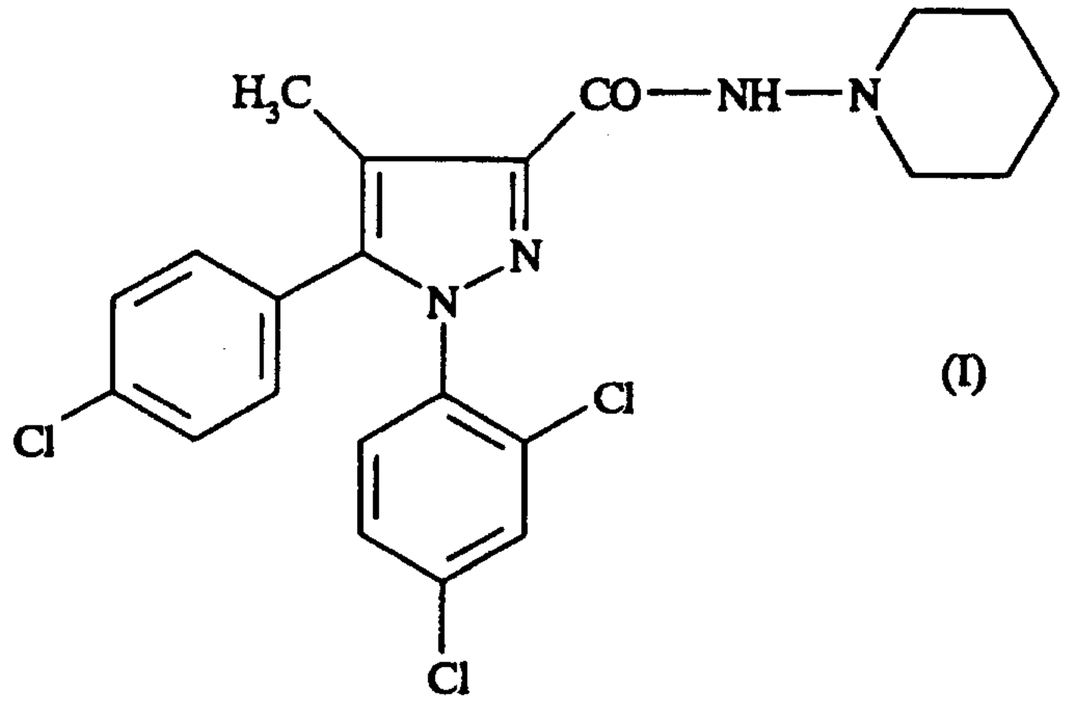
DSC : endothermic peak centered at 185.5° C

% calculated C : 47.04 H : 4.31 N : 9.97

% found C : 46.96 H : 4.62 N : 9.98.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, of the formula :



(I)

its pharmaceutically acceptable acid addition salts or their solvates.

2. N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide hydrochloride or its solvate with ethanol.

3. N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide methanesulfonate or its hemisolvate with acetone.

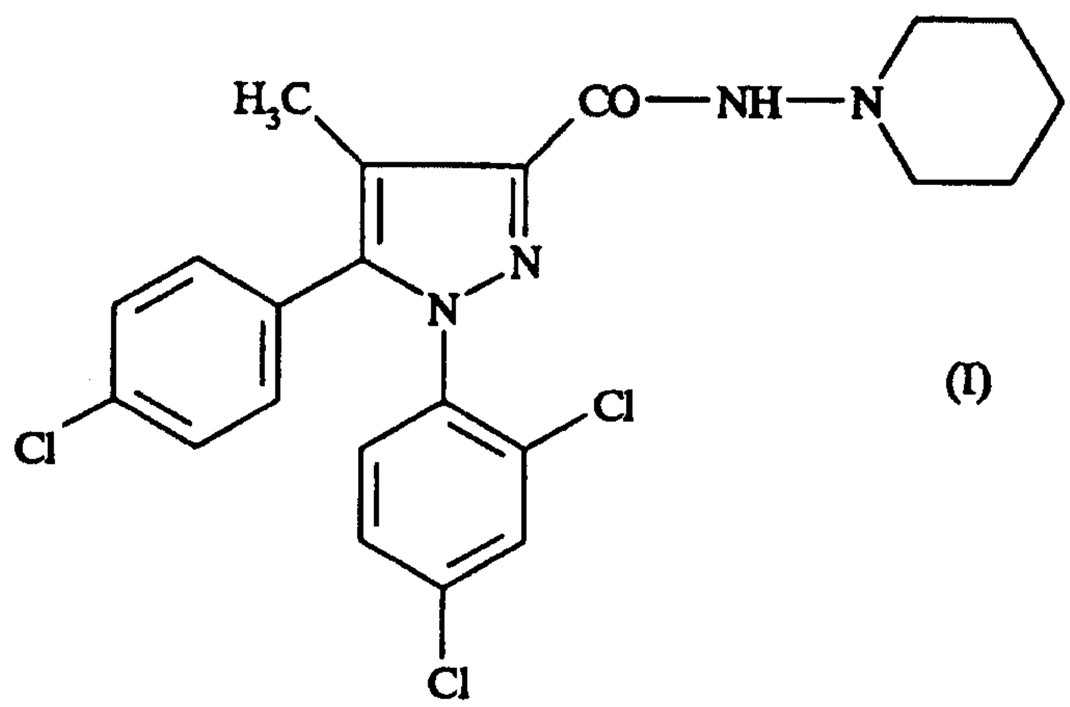
4. N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide hemifumarate.

5. N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide paratoluenesulfonate.

6. N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide hydrogensulfate.

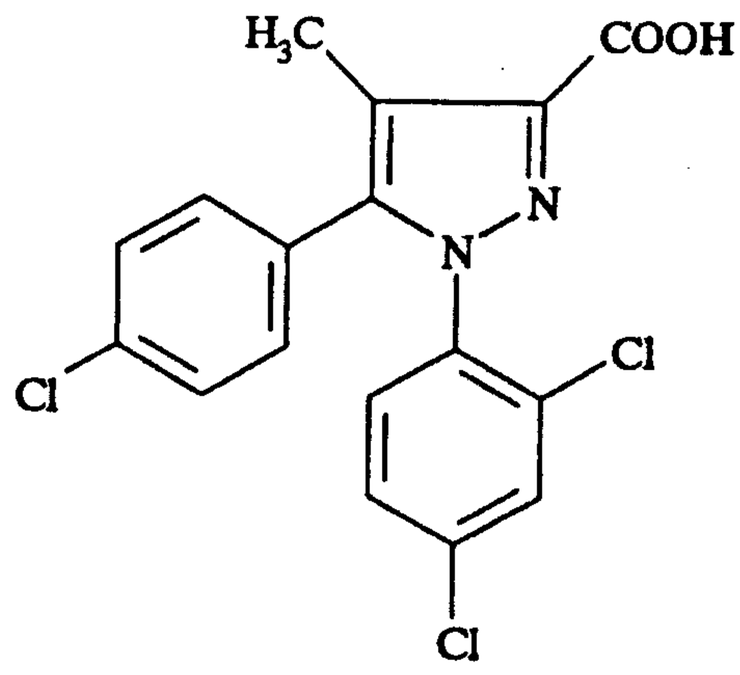
7. N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide dihydrogenphosphate.

8. A method of preparing N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamid of the formula:



(I)

its salts or their solvates, which comprises treating a functional derivative of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylic acid of the formula:

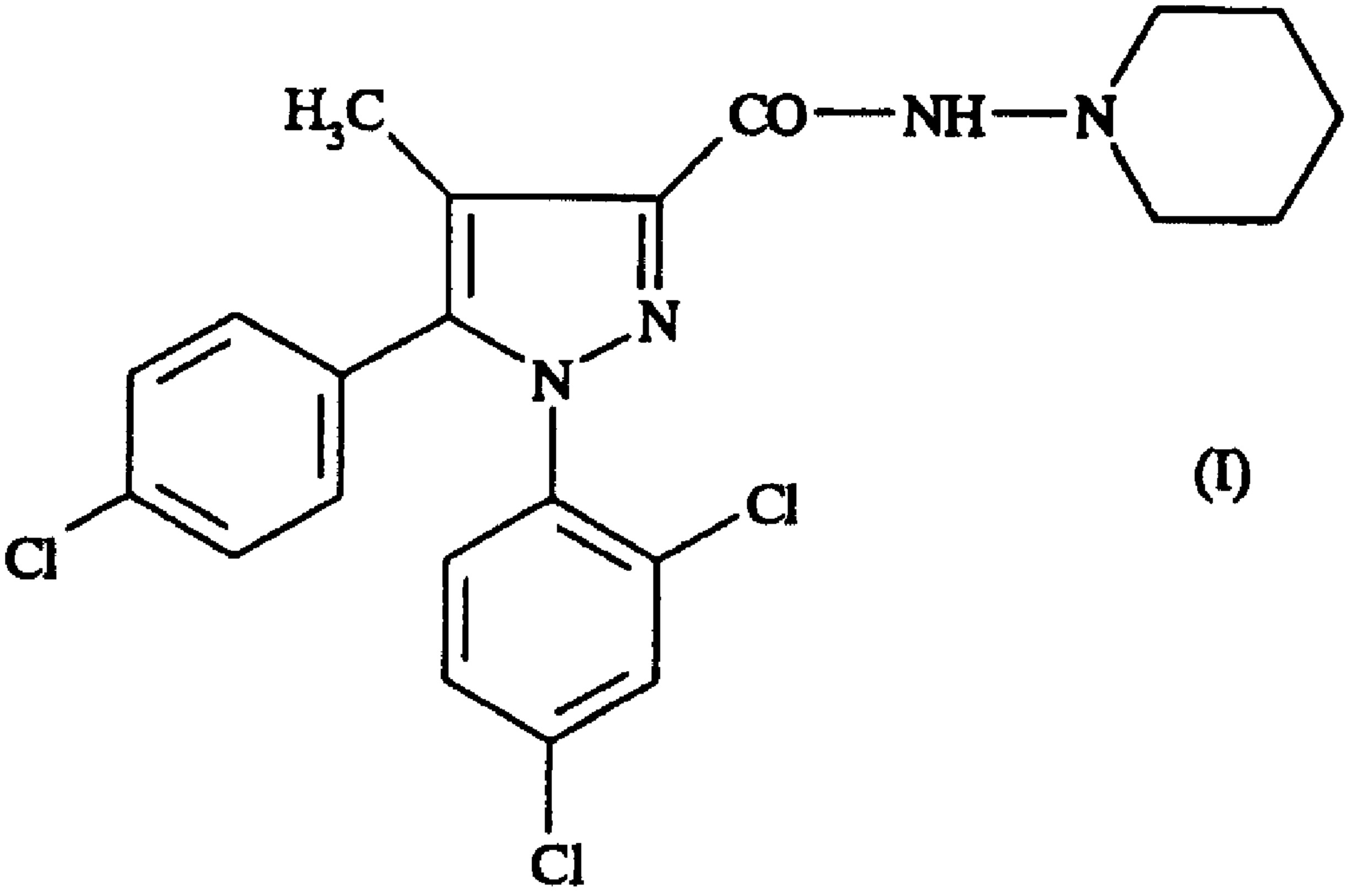


(II)

with 1-aminopiperidine in an organic solvent in the presence of a base, and optionally converting the resulting compound into one of its salts or one of their solvates.

9. A pharmaceutical composition which contains, as the active principle, a compound according to any one of claims 1 to 7 and in the form of a dosage unit in which the active principle is mixed with at least one pharmaceutical excipient.

10. A pharmaceutical composition according to claim 9, which contains from 0.5 to 1000 mg of active principle.



(I)