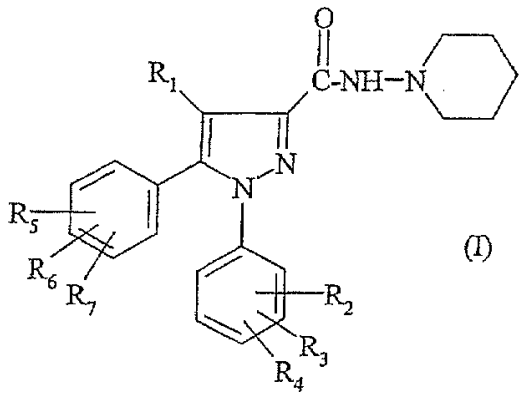
METHOD FOR PREPARING N-PIPERIDINO-1,5-DIPHENYLPYRAZOLE-3-CARBOXAMIDE DERIVATIVES

A subject matter of the present invention is a process for the preparation of a compound of formula:



(I)

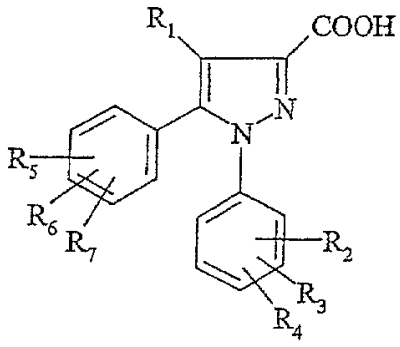
in which:

- R_1 represents a hydrogen or halogen atom or a (C_1-C_4)alkyl group;
- R_2, R_3, R_4, R_5, R_6 and R_7 represent, each independently of one another, a hydrogen or halogen atom or a (C_1-C_4)alkyl, (C_1-C_4)alkoxy or trifluoromethyl group;

and of its salts.

The compounds of formula (I) are disclosed in various patents or patent applications, EP 0 656 354 B, EP 1 150 961 B, as cannabinoid CB_1 receptor antagonists. More particularly, N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide or rimonabant has shown a clinical activity in obesity and in stopping people from smoking.

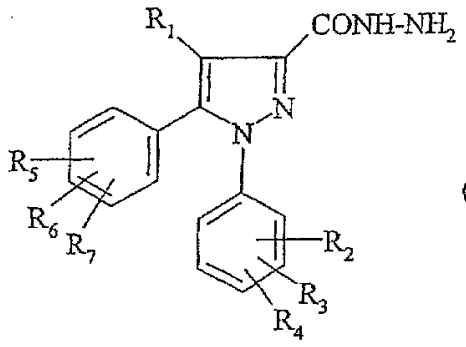
In the prior art, it is known to prepare a compound of formula (I) by the action of N-aminopiperidine on a functional derivative of the acid:



(A)

This synthetic process is disclosed in particular in patent EP 0 656 354 B for the preparation of rimonabant. Use is made, as functional derivative, for example, of an alkyl ester or the acid chloride.

According to the present invention, a compound of formula (I) is prepared by a process, characterized in that a pentane derivative of formula $X-(CH_2)_5-X'$ (II), in which X and X' each independently represent a halogen atom or a YSO_2O- group in which Y represents a (C_1-C_4)alkyl group, a (C_1-C_4)perfluoroalkyl group, an unsubstituted phenyl group or a phenyl group substituted by a methyl, chloro or nitro group, is reacted with a pyrazole-3-carbohydrazide derivative of formula:



(III)

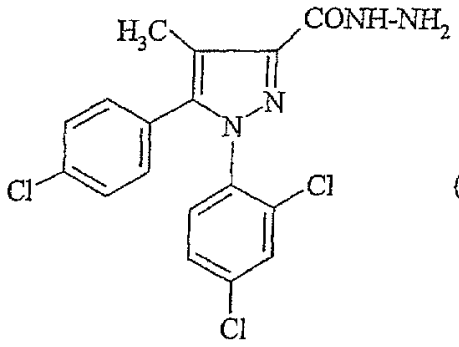
in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are as defined above for (I).

The reaction is carried out in the presence of a base, in a solvent and at a temperature between ambient temperature and the reflux temperature of the solvent.

Use is particularly made, in the process according to the invention, of a compound of formula (II) in which X and X' each independently represent a halogen atom.

Use is also particularly made of a compound of formula (II) in which X and X' each independently represent a YSO_2O- group in which Y is as defined above.

A particular embodiment of the present invention is characterized in that rimonabant is prepared by the action of a compound of formula (II) on 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbohydrazide of formula:



(IIIa)

According to a particular embodiment, a 1,5-dihalopentane of formula (II) is reacted with 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbohydrazide (IIIa).

More particularly, 1,5-dibromopentane is reacted with 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbohydrazide (IIIa).

The reaction is carried out in the presence of an organic base, such as a tertiary amine, for example triethylamine, or of an inorganic base, such as NaOH, KOH, K_2CO_3, Na_2CO_3 or Cs_2CO_3.

The reaction is carried out in an aromatic solvent, for example toluene or chlorobenzene, in an ethereal

solvent, for example tetrahydrofuran, dimethoxyethane or dioxane, or in a nitrile solvent, such as acetonitrile or propionitrile.

Preferably, the reaction is carried out in acetonitrile in the presence of triethylamine or Na_2CO_3 or K_2CO_3.

Very particularly preferably, the reaction is carried out in acetonitrile heated at reflux in the presence of Na_2CO_3.

A subject matter of the present invention is very particularly a process for the preparation of N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide and of its salts, characterized in that 1,5-dibromopentane is reacted with a compound of formula (IIIa) in the presence of Na_2CO_3 in acetonitrile heated to reflux.

The term "halogen atom" is understood to mean a bromine, chlorine or iodine atom.

Compounds of formula (III) and their preparation are known in the prior art: Canadian J. Chem., 1963, 41(7), 1813-1818; J. Chem. Engineering Data, 1977, 22(1), 104-110; J. Med. Chem., 2002, 45, 2708-2719.

The publication of J. Med. Chem., 2002, describes in particular 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbohydrazide and its preparation from the corresponding acid chloride.

The following examples illustrate the invention without, however, limiting it.

In these examples and in the description, the following abbreviations are used:
DCM: dichloromethane.

The mass spectra are measured in electrospray (ES) ionization mode.

The proton nuclear magnetic resonance (^{1}H NMR) spectra are recorded at 200 MHz or at 300 MHz in d_6-DMSO or in $CDCl_3$. The chemical shifts δ are expressed in parts per million (ppm).

The signals observed in NMR are expressed thus: s: singlet; bs: broad singlet; d: doublet; sd: split doublet; t: triplet; st: split triplet; q: quartet; bup: broad unresolved peak; mt: multiplet.

Preparation 1
5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbohydrrazide.

20 g of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carbonyl chloride in 100 ml of ethanol are placed under nitrogen and the mixture is heated at reflux for 2 hours. It is allowed to return to a temperature of 20-25°C, then 50 g of hydrazine hydrate are added and the mixture is again heated at reflux for 3 and a half hours. The reaction medium is filtered while hot and then the ethanol is evaporated. The reaction medium is concentrated, then taken up in 150 ml of DCM and separated by settling. The aqueous phase is discarded, the organic phase is washed twice with 100 ml of water and then the DCM is evaporated. After drying under vacuum, 16.9 g of the expected compound are obtained.
ES^+: $[M+Na]^+$ = 417, 419, 421, 423
ES^-: $[M-H]^-$ = 393, 395, 397, 399
NMR ($CDCl_3$, ^{1}H at 300 MHz): 2.35 ppm: s: 3H; 4.0 ppm: d: 2H; 7.04 ppm: m: 2H; 7.25 ppm: bm: 4H; 7.41 ppm: d: 1H; 8.04 ppm: m: 1H.

EXAMPLE 1

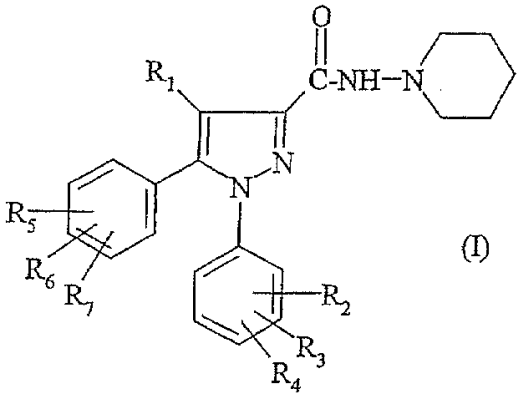
N-Piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide

10 g of the compound obtained in Preparation 1 and 5.3 g of sodium carbonate are placed under nitrogen in 100 ml of acetonitrile. The reaction medium is heated to reflux of the acetonitrile, a total of 6.9 ml of 1,5-dibromopentane is added and then heating is maintained at reflux over 45 hours. The medium is hydrolyzed by addition of 50 ml of water, separation by settling is allowed to take place and the aqueous phase is discarded. The organic phase is washed twice with 50 ml of a saturated aqueous NaCl solution. The acetonitrile is evaporated to dryness and 18.4 g of a crude product are obtained. The crude product obtained is chromatographed on silica gel (eluent cyclohexane/acetone: 75/25; v/v). The product obtained is taken up in 100 ml of methylcyclohexane and recrystallized. 5.7 g of the pure expected compound are obtained.

NMR (d_6-DMSO, ^1H at 200 MHz): 1.31 ppm: bm: 2H; 1.55 ppm: bm: 4H; 2.22 ppm: s: 3H; 4.0 ppm: d: 2H; 7.22 ppm: d: 2H; 7.43 ppm: d: 2H; 7.56 ppm: sd: 1H; 7.71 ppm: d: 1H; 7.76 ppm: d: 1H; 9.02 ppm: s: 1H.

WHAT IS CLAIMED IS:

1. A process for the preparation of a compound of formula:



(I)

in which:

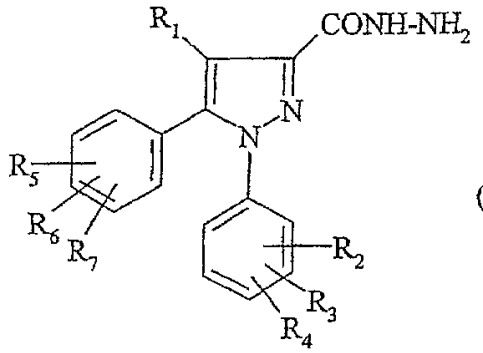
- R_1 represents a hydrogen or halogen atom or a (C_1-C_4)alkyl group;
- R_2, R_3, R_4, R_5, R_6 and R_7 represent, each independently of one another, a hydrogen or halogen atom or a (C_1-C_4)alkyl, (C_1-C_4)alkoxy or trifluoromethyl group;

and of its salts, characterized in that:

a pentane derivative of formula:

$$X-(CH_2)_5-X' \quad (II)$$

in which X and X' each independently represent a halogen atom or a YSO_2O- group in which Y represents a (C_1-C_4)alkyl group, a (C_1-C_4)perfluoroalkyl group, an unsubstituted phenyl group or a phenyl group substituted by a methyl, chloro or nitro group, is reacted with a pyrazole-3-carbohydrazide derivative of formula:



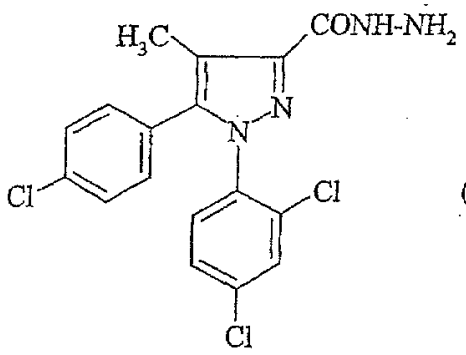
(III)

in which R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are as defined above for (I), in the presence of a base, in a solvent and at a temperature between ambient temperature and the reflux temperature of the solvent.

2. The process as claimed in claim 1, characterized in that, in the compound of formula (II), X and X' each independently represent a halogen atom.

3. The process as claimed in claim 1, characterized in that, in the compound of formula (II), X and X' each independently represent a Y-SO_2-O- group in which Y is as defined in claim 1.

4. The process as claimed in any one of claims 1 to 3 for the preparation of N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxamide and of its salts, characterized in that:
a compound of formula (II) is reacted with 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbohydrazide of formula:



(IIIa)

5. The process as claimed in claim 4, characterized in that a 1,5-dihalopentane is reacted with the compound of formula (IIIa).

6. The process as claimed in claim 5, characterized in that 1,5-dibromopentane is reacted with the compound of formula (IIIa).

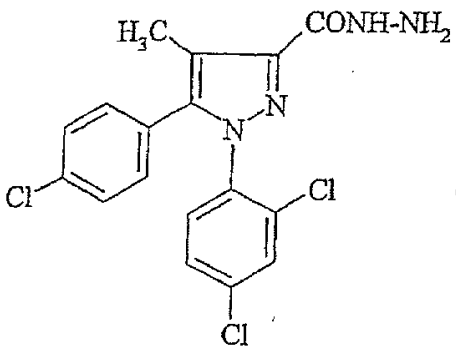
7. The process as claimed in any one of claims 1 to 6, characterized in that the base is chosen from triethylamine, NaOH, KOH, K_2CO_3, Na_2CO_3 or Cs_2CO_3.

8. The process as claimed in any one of claims 1 to 7, characterized in that the solvent is chosen from toluene, chlorobenzene, tetrahydrofuran, dimethoxyethane, dioxane, acetonitrile or propionitrile.

9. The process as claimed in any one of claims 1 to 8, characterized in that the reaction is carried out in the presence of triethylamine, of Na_2CO_3 or of K_2CO_3 in acetonitrile.

10. The process as claimed in any one of claims 1 to 9, characterized in that the reaction is carried out in the presence of Na_2CO_3 in acetonitrile heated at reflux.

11. A process for the preparation of N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxamide and of its salts, characterized in that 1,5-dibromopentane is reacted with a compound of formula:



(IIIa)

in the presence of Na_2CO_3 in acetonitrile heated at reflux.