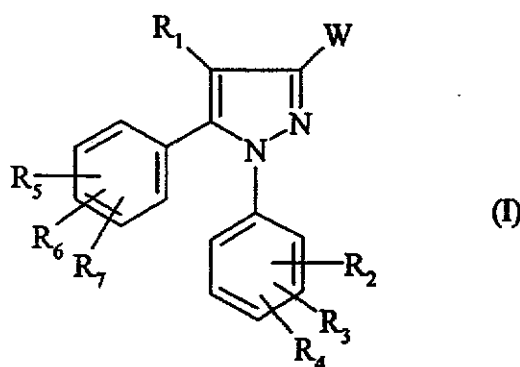


The present invention relates to a novel process for preparing 1,5-diphenylpyrazole-3-carboxylic acid derivatives.

1,5-Diphenyl-4-methylpyrazole-3-carboxylic acid esters are described in particular in European Patent EP 576 357 and American Patent US 5 624 941. These esters are useful intermediates for preparing 1,5-diphenyl-4-methylpyrazole-3-carboxylic acid derivatives that are cannabinoid CB₁ receptor antagonists.

More particularly, ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylate, described in European Patent EP 656 354, is a useful intermediate for preparing N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, the international non-proprietary name of which is rimonabant.

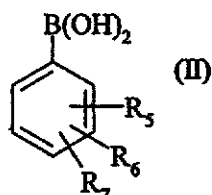
The subject of the present invention is a process for preparing a compound of formula:



in which:

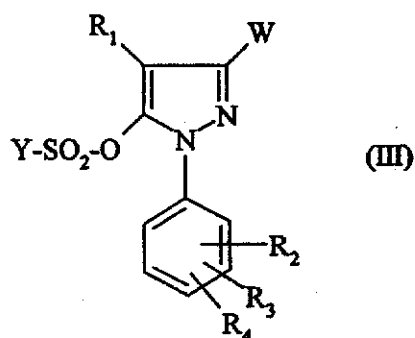
- W represents a group -COOR or a radical -CN;

- 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 each represent, independently of one another a hydrogen or halogen atom or a (C_1-C_4) alkyl, (C_1-C_4) alkoxy or trifluoromethyl group;
- R represents a (C_1-C_4) alkyl or benzyl group; characterized in that a phenylboronic acid derivative of formula:



10

in which R_5, R_6 and R_7 are as defined for (I), is reacted, in a solvent, in the presence of a catalyst in a basic medium, with a compound of formula:

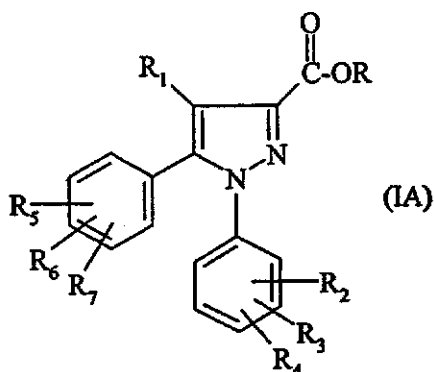


15 in which:

- W, R_1, R_2, R_3 and R_4 are as defined for (I);
- Y represents a (C_1-C_4) alkyl group, a (C_1-C_4) perfluoroalkyl group or a phenyl group that is unsubstituted or substituted with a methyl, chloro or nitro group.

20

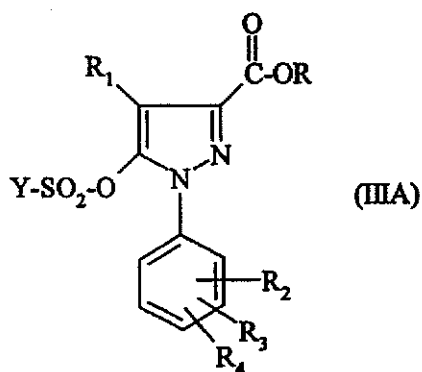
Particularly, a subject of the present invention is a process for preparing a compound of formula:



5 in which:

- R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R are as defined for a compound of formula (I);

characterized in that a phenylboronic acid derivative of formula (II) as defined above is reacted, in a solvent, in the presence of a catalyst in a basic medium, with a compound of formula:

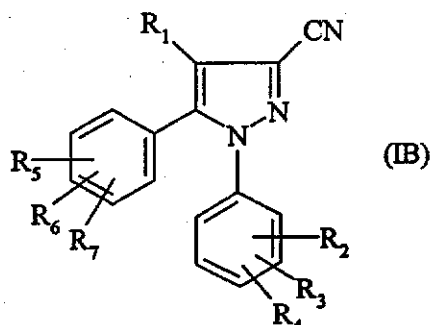


in which:

- Y , R , R_1 , R_2 , R_3 and R_4 are as defined above.

15 A subject of the present invention is in particular also a process for preparing a compound of

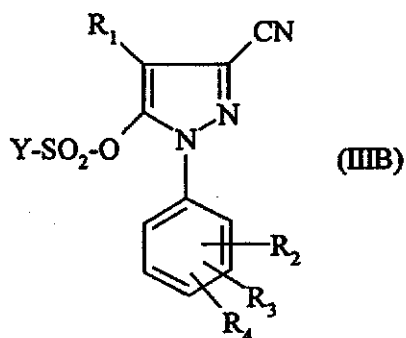
formula:



in which:

- R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are as defined for a
5 compound of formula (I);

characterized in that a phenylboronic acid derivative of formula (II) as defined above is reacted, in a solvent, in the presence of a catalyst in a basic medium, with a compound of formula:



10

in which:

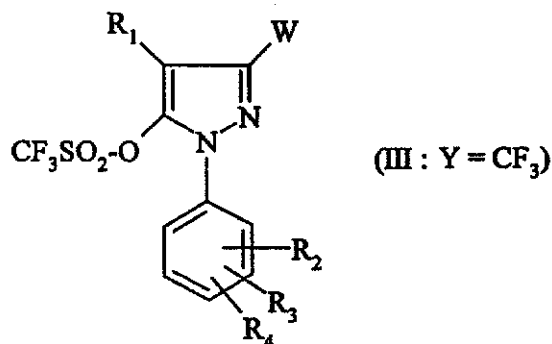
- Y , R_1 , R_2 , R_3 and R_4 are as defined above.

Preferably, the reaction of a compound of formula (II) with a compound of formula (III), (IIIA) or (IIIB) is carried out in an aromatic solvent, for example toluene, or in an ethereal solvent, for example tetrahydrofuran or dimethoxyethane or in dioxane, in the presence of a palladium complex, for example

tetrakis(triphenylphosphine)palladium, and in a basic medium, for example in the presence of an alkali metal carbonate, such as sodium carbonate or potassium carbonate.

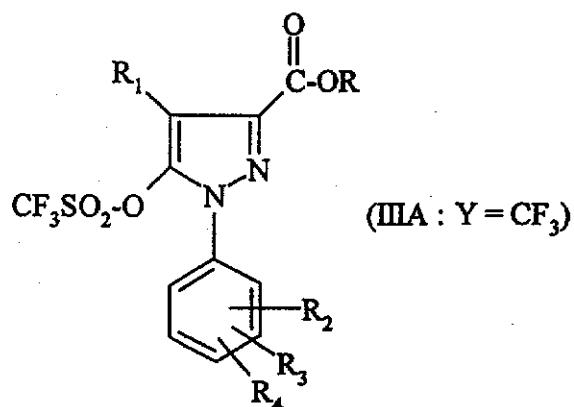
5 According to a preferred embodiment, the reaction is carried out in a two-phase medium, in the presence of tetrakis(triphenylphosphine)palladium, the basic medium consisting of sodium carbonate in an aqueous solution.

10 According to a preferred process for preparing a compound of formula (I), a phenylboronic acid derivative of formula (II) is reacted with a compound of formula (III) in which Y represents a group CF_3 , namely a compound of formula:

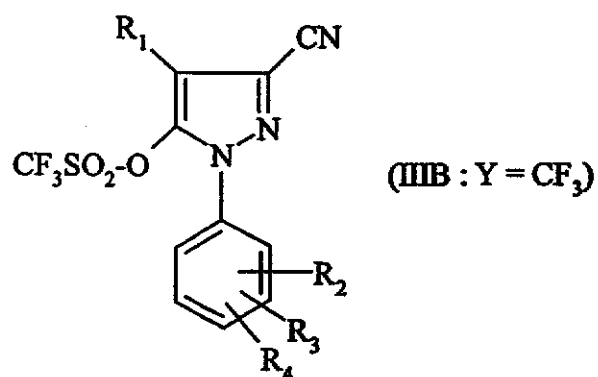


15

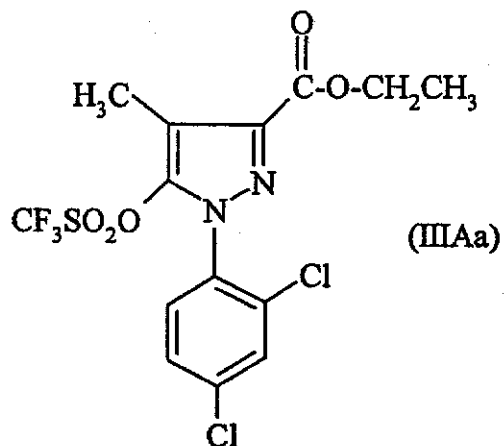
In addition, according to a preferred process for preparing a compound of formula (IA), a phenylboronic acid derivative of formula (II) is reacted with a compound of formula (IIIA) in which Y
 20 represents a group CF_3 , namely a compound of formula:



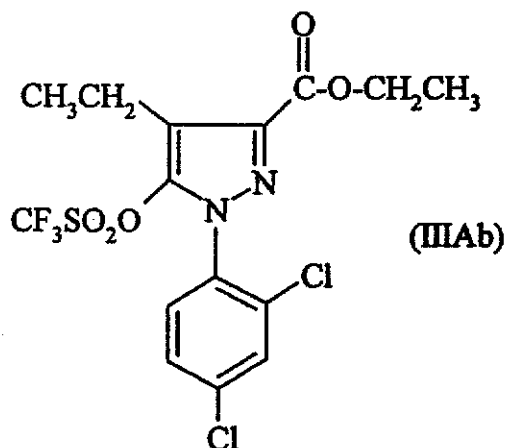
Finally, according to a preferred process for preparing a compound of formula (IB), a phenylboronic acid derivative of formula (II) is reacted with a
 5 compound of formula (IIIB) in which Y represents a group CF₃, namely a compound of formula:



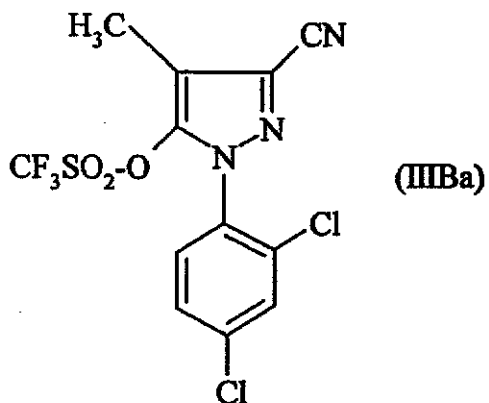
More preferably, 4-chlorophenylboronic acid is reacted with a compound of formula:



Also more preferably, 4-bromophenylboronic acid is reacted with a compound of formula:

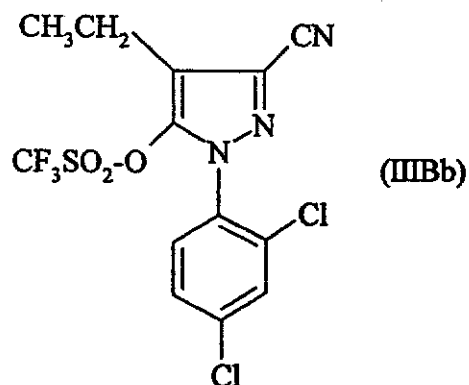


Even more preferably, 4-chlorophenylboronic acid is reacted with a compound of formula:

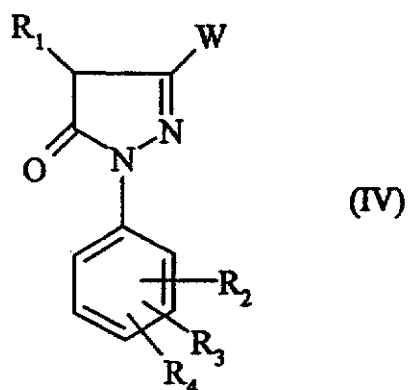


Finally, more preferably, 4-bromophenylboronic acid

acid is reacted with a compound of formula:

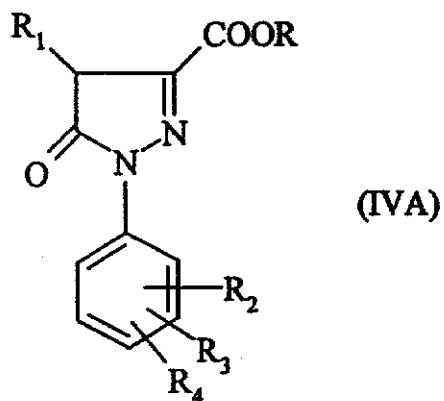


The compound of formula (III) is obtained from a pyrazolone derivative of formula:



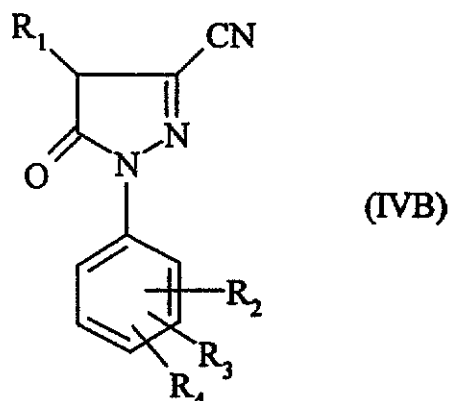
5

In particular, the compound of formula (IIIA) is obtained from a pyrazolone derivative of formula:



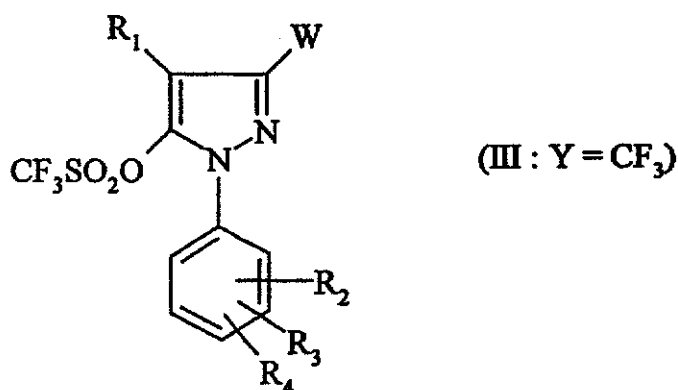
Also in particular, the compound of formula
10 (IIIB) is obtained from a pyrazolone derivative of

formula:



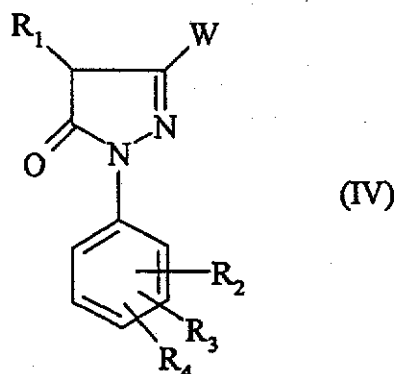
To prepare a compound of formula (III), (IIIA) or (IIIB), an anhydride of formula $(YSO_2)_2O$ or a
 5 chloride of formula YSO_2Cl is reacted with a compound of formula (IV), (IVA) or (IVB), the reaction being carried out in the presence of a base, preferably a tertiary amine.

In particular, the compound of formula:



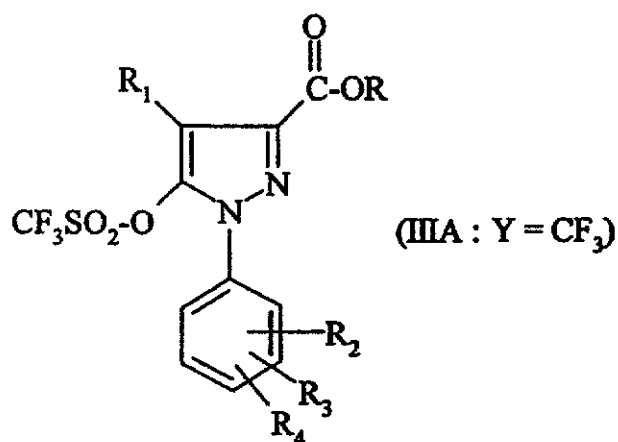
10

is obtained by reaction of triflic anhydride with a pyrazolone derivative of formula:



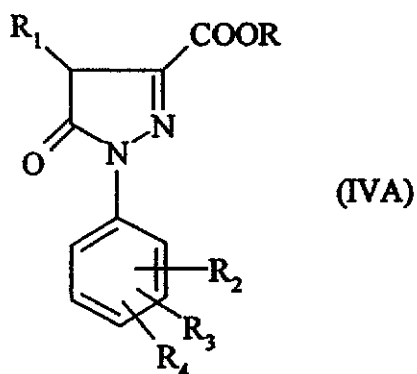
in the presence of a base, such as a tertiary amine, and in a solvent, such as dichloromethane.

Also in particular, the compound of formula:



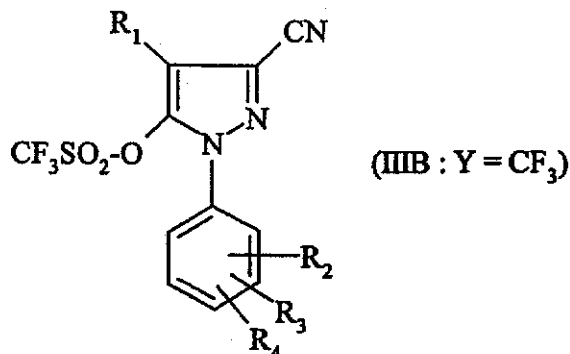
5

is obtained by reaction of triflic anhydride with a pyrazolone derivative of formula:

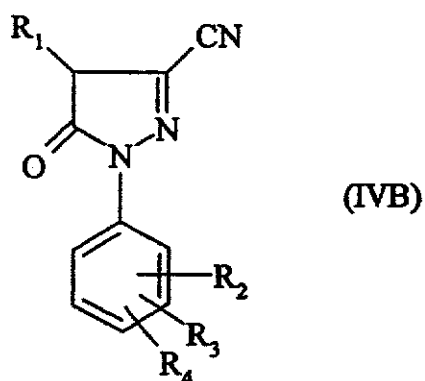


10 in the presence of a base, such as tertiary amine, and in a solvent, such as dichloromethane.

Finally in particular, the compound of formula:



is obtained by reaction of triflic anhydride with a pyrazole derivative of formula:

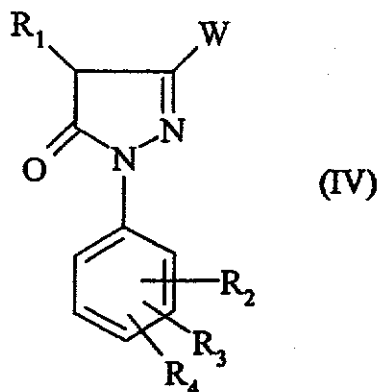


5

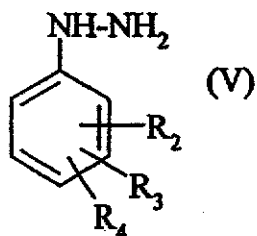
in the presence of a base, such as tertiary amine, and in a solvent, such as dichloromethane.

Preferably, the compound of formula (III),
 (IIIA) or (IIIB), in which Y represents CF₃, is obtained
 10 by the action of triflic anhydride and triethylamine in
 an equimolecular mixture, in dichloromethane, at a
 temperature of between -5°C and +5°C.

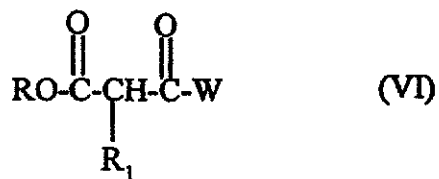
The compound of formula:



is obtained by reaction of a hydrazine derivative of formula:



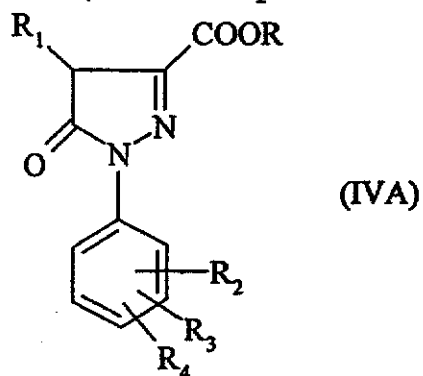
5 in which R_2 , R_3 and R_4 are as defined for (I), with a derivative of formula:



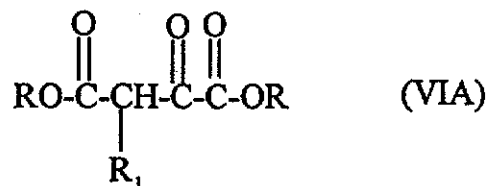
in which R , R_1 and W are as defined above for (I).

10

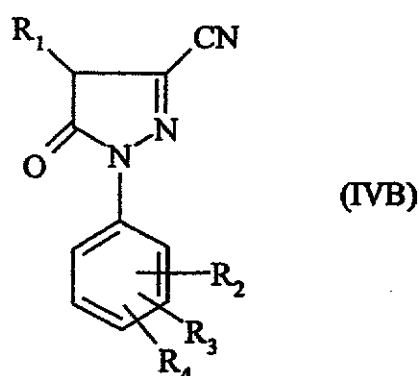
In particular, the compound of formula:



is obtained by reaction of a hydrazine derivative of formula (V) with a derivative of formula:

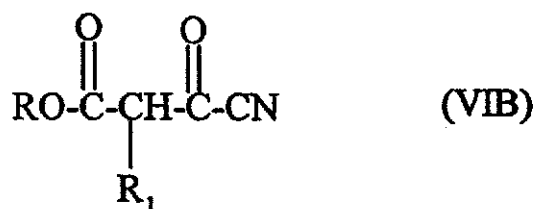


Also in particular, the compound of formula:



5

is obtained by reaction of a hydrazine derivative of formula (V) with a derivative of formula:

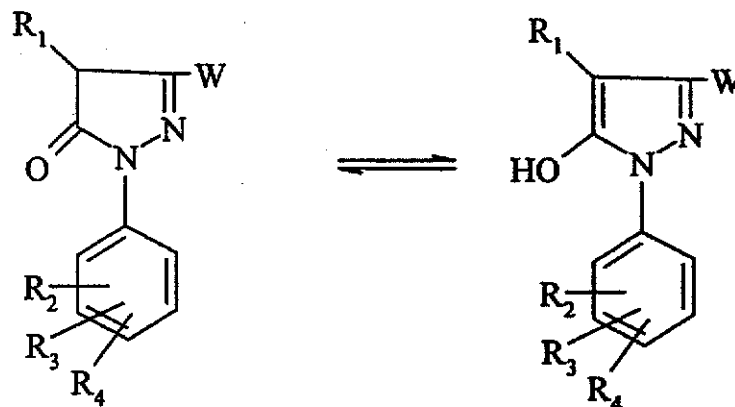


Preferably, a hydrazine hydrochloride of
10 formula (V) is used in a solvent, in an acid medium,
for example in acetic acid; or in toluene in the
presence of hydrochloric acid, acetic acid or
trifluoroacetic acid.

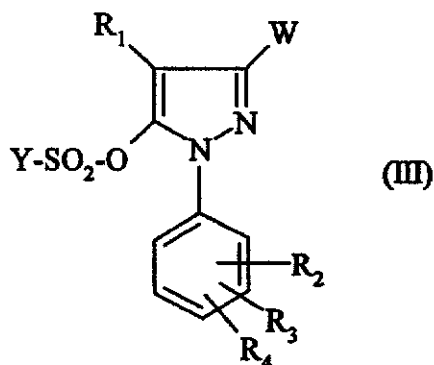
The 3-oxosuccinate derivatives of formula (VI),
15 (VIA) or (VIB) are known or are prepared by known
methods such as Claisen condensation of an ester

enolate with an oxalic acid ester.

The compound of formula (IV) can exist in 2 tautomeric forms:



5 According to another of its aspects, a subject of the present invention is the compounds of formula:



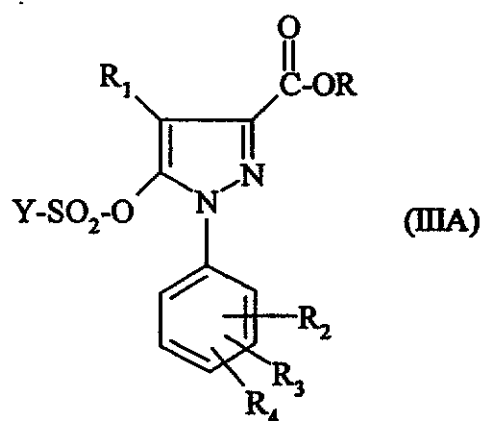
in which:

- W represents a group -COOR or a radical -CN;
- 10 - Y represents a (C₁-C₄)alkyl group, a (C₁-C₄)perfluoroalkyl group or a phenyl group that is unsubstituted or substituted with a methyl, chloro or nitro group;
- R₁ represents a hydrogen or halogen atom or a
- 15 (C₁-C₄)alkyl group;
- R₂, R₃ and R₄ each represent, independently of one

another, a hydrogen or halogen atom or a (C₁-C₄)alkyl, (C₁-C₄)alkoxy or trifluoromethyl group;

- R represents a (C₁-C₄)alkyl or benzyl group.

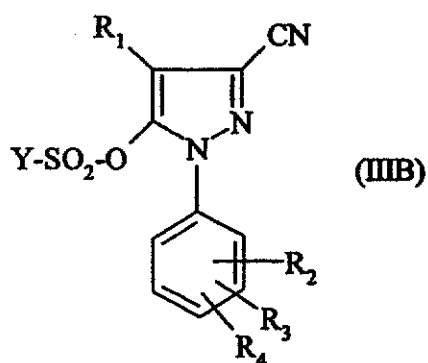
5 Preferably, a subject of the present invention is the compounds of formula:



in which:

- Y, R, R₁, R₂, R₃ and R₄ are as defined above.

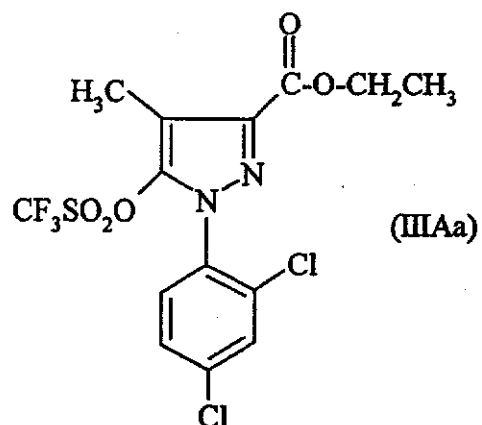
10 Preferably, a subject of the present invention is the compounds of formula:



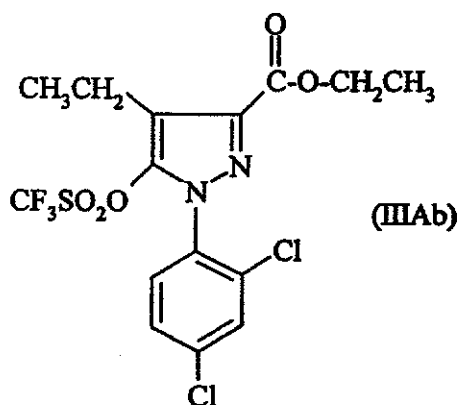
in which:

- Y, R₁, R₂, R₃ and R₄ are as defined above.

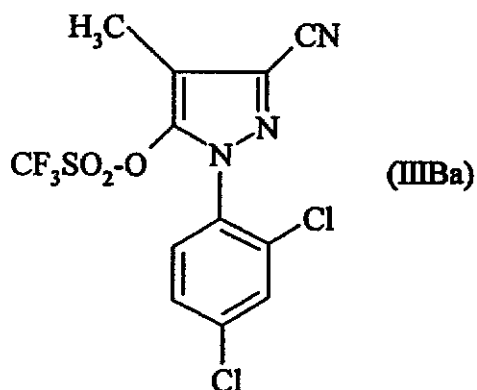
15 More preferably, a subject of the present invention is the compound of formula:



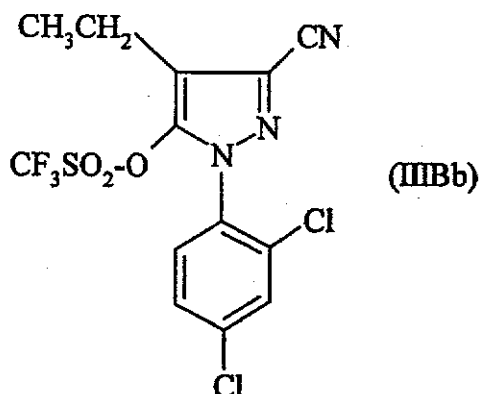
Also more preferably, a subject of the present invention is the compound of formula:



5 Even more preferably, a subject of the present invention is the compound of formula:



Finally more preferably, a subject of the present invention is a compound of formula:



The following example is not limiting; it illustrates one embodiment of the invention.

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

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

10 EXAMPLE 1

Preparation of ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate

A) Ethyl 1-(2,4-dichlorophenyl)-4-methyl-5-oxo-4,5-dihydro-1H-pyrazole-3-carboxylate

15 12.6 g of 2,4-dichlorophenylhydrazine hydrochloride in 100 ml of toluene are placed under nitrogen; after stirring, 10 g of diethyl 2-methyl-3-oxosuccinate are added and the mixture is then heated and 5 ml of TFA are added at 55°C. The mixture is left
20 at the reflux of the solvent for 4 and a half hours, with stirring. The mixture is allowed to return to

ambient temperature and is then heated to 75°C and the reaction medium is hydrolyzed with 30 ml of water. The mixture is separated by settling out, the aqueous phase is discarded and the organic phase is then evaporated

5 in order to eliminate the residual TFA. The organic phase is taken up with 10 ml of toluene and the expected product then crystallizes, $m = 10.2$ g.

ES⁻: $[M-H]^- = 313.0$.

NMR (DMSO-d₆ 1H at 300 MHz): 1.26 ppm: t: 3H;
10 2.11 ppm: s: 3H; 4.23 ppm: q: 2H; 7.57 ppm: m: 2H;
7.87 ppm: bs: 1H; 11.04 ppm: bs: 1H.

B) Ethyl 1-(2,4-dichlorophenyl)-4-methyl-5-
(((trifluoromethyl)sulphonyl)oxy)-1H-pyrazole-3-
carboxylate

15 5 g of pyrazolone obtained in the preceding step are suspended in 25 ml of DCM, under nitrogen, and the mixture is cooled to 0°C with stirring. 2.4 ml of TEA followed by 3 ml of triflic anhydride are added and the stirring is maintained at 0°C for 15 minutes. The
20 reaction medium is hydrolyzed with 20 ml of DCM. The reaction medium is separated by settling out and the organic phase is then washed with 20 ml of water. The aqueous phase is discarded. The organic phase is evaporated and the oil obtained is chromatographed on
25 silica, elution being carried out with a pentane/EtOAc mixture (90/10; v/v). The fractions containing the expected compound are combined and evaporated to

dryness. 6.77 g of the expected product are obtained.

ES⁺: [M+Na]⁺ = 468.8

NMR (DMSO-d₆ 1H at 300 MHz): 1.31 ppm: t: 3H;
2.27 ppm: s: 3H; 4.34 ppm: q: 2H; 7.72 ppm: sd: 1H;
5 7.79 ppm: d: 1H; 8.04 ppm: d: 1H.

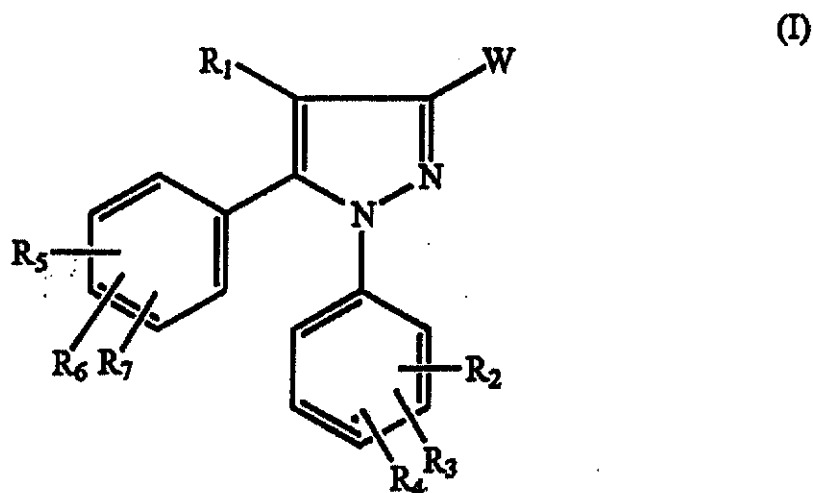
C) Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate

2.55 g of the pyrazole triflate of the preceding step, 1.08 g of 4-chlorophenylboronic acid
10 and 67 mg of tetrakis(triphenylphosphine)palladium are mixed, under nitrogen; 25 ml of toluene and 7.1 ml of a 2M aqueous sodium carbonate solution are added. The reaction medium is stirred at 65°C for 6 hours. The reaction medium is separated by settling out, the
15 aqueous phase is discarded, and the organic phase is then washed with 10 ml of water. After separation by settling out, the organic phase is evaporated off. The product obtained is purified by chromatography on silica, elution being carried out with a
20 cyclohexane/EtOAc mixture (85/15; v/v). 1.890 g of the expected compound are obtained.

NMR (DMSO-d₆ 1H at 300 MHz): 1.31 ppm: t: 3H;
2.23 ppm: s: 3H; 4.32 ppm: q: 2H; 7.24 ppm: d: 2H;
7.46 ppm: d: 2H; 7.57 ppm: sd: 1H; 7.73 ppm: d: 1H;
25 7.77: d: 1H.

What is claimed is:

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



in which:

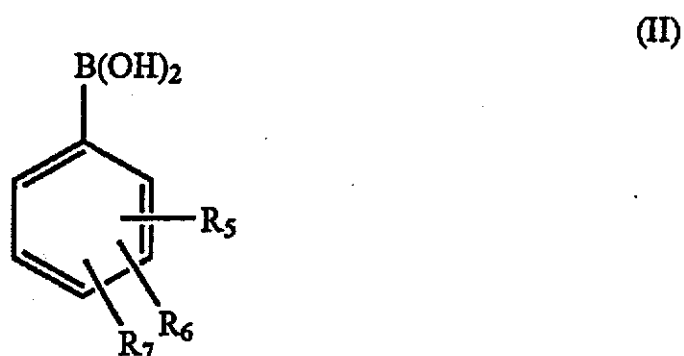
W represents a group —COOR or a radical —CN;

R₁ represents a hydrogen or halogen atom or a (C₁-C₄) alkyl group;

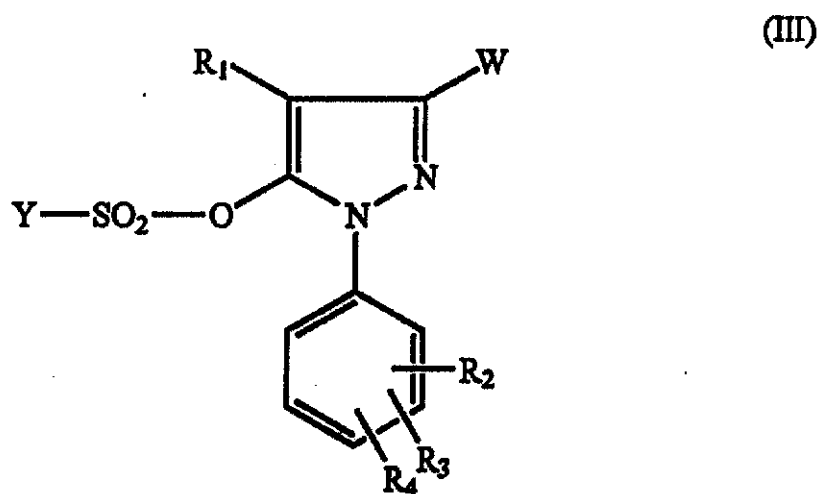
R₂, R₃, R₄, R₅, R₆ and R₇ each represent, independently of one another a hydrogen or halogen atom or a (C₁-C₄) alkyl, (C₁-C₄) alkoxy or trifluoromethyl group;

R represents a (C₁-C₄) alkyl or benzyl group;

wherein a phenylboronic acid derivative of formula (II):



in which R₅, R₆ and R₇ are as defined above for (I), is reacted with a compound of formula (III):

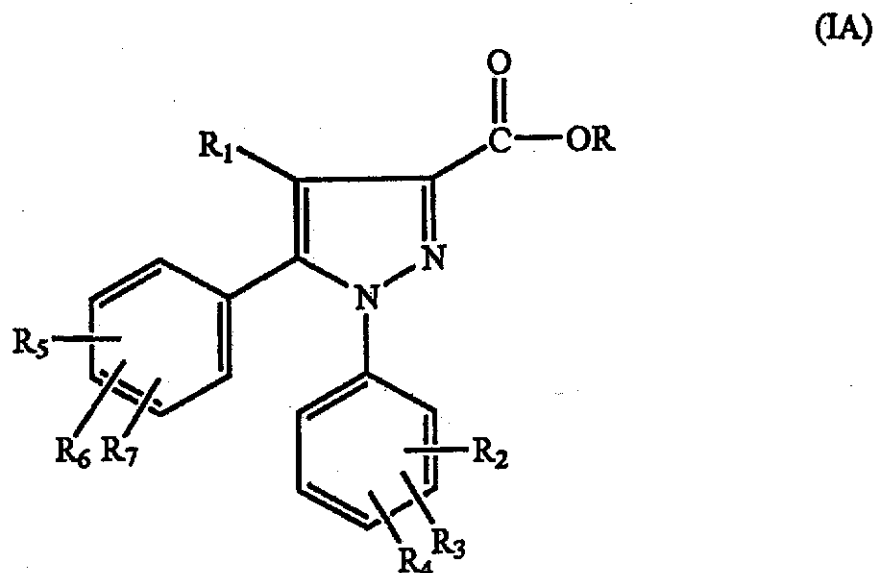


in which:

W, R₁, R₂, R₃ and R₄ are as defined above for (I);

Y represents a (C₁-C₄)alkyl group, a (C₁-C₄) perfluoroalkyl group or a phenyl group that is un-substituted or substituted with a methyl, chloro or nitro group.

2. The process according to claim 1, for preparing a compound of formula (IA):

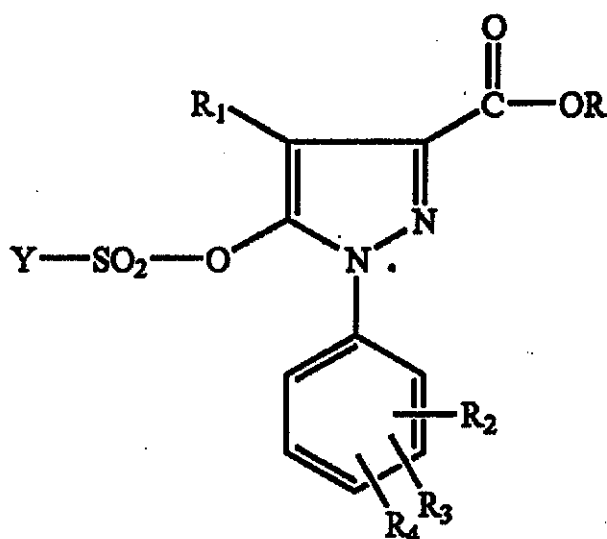


in which:

$R_1, R_2, R_3, R_4, R_5, R_6, R_7$ and R are as defined for a compound of formula (I) in claim 1;

wherein a phenylboronic acid derivative of formula (II) as defined in claim 1 is reacted with a compound of formula (IIIA):

(IIIA)

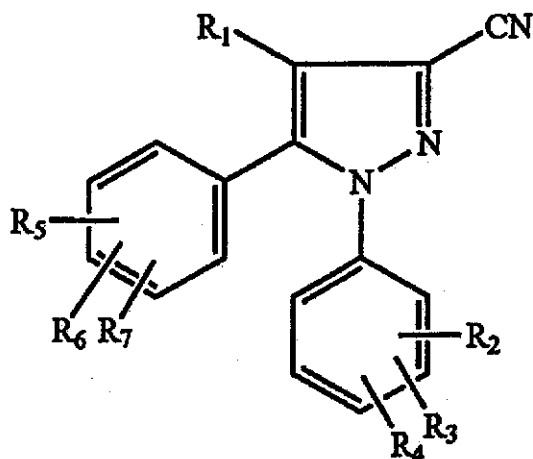


in which:

Y, R, R_1, R_2, R_3 and R_4 are as defined with respect to formula I in claim 1.

3. The process as recited in claim 1 for the preparation of a compound of formula (IB):

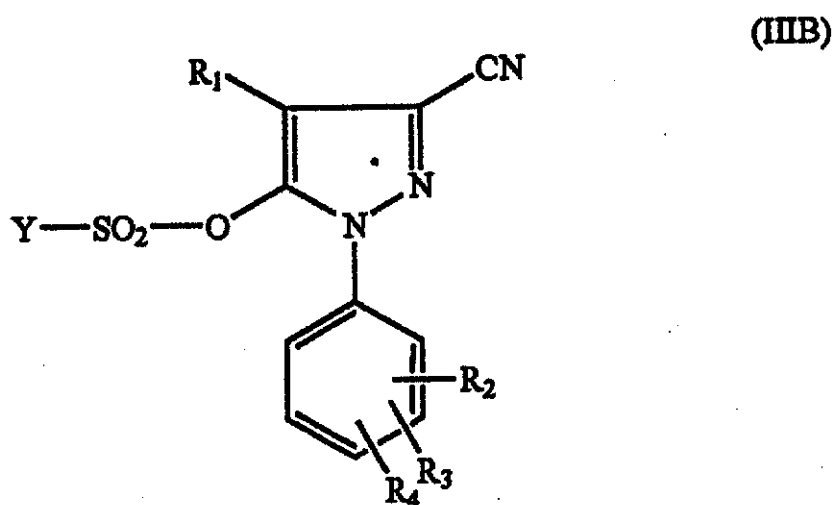
(IB)



in which

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are as defined for a compound of formula (I) in claim 1;

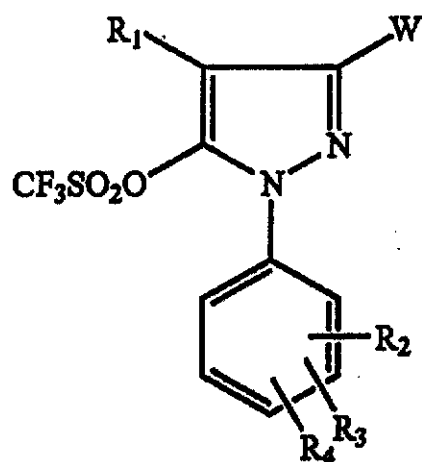
wherein a phenylboronic acid derivative of formula (II) as defined in claim 1 is reacted with a compound of formula (IIIB):



in which:

Y , R_1 , R_2 , R_3 and R_4 are as defined in claim 1.

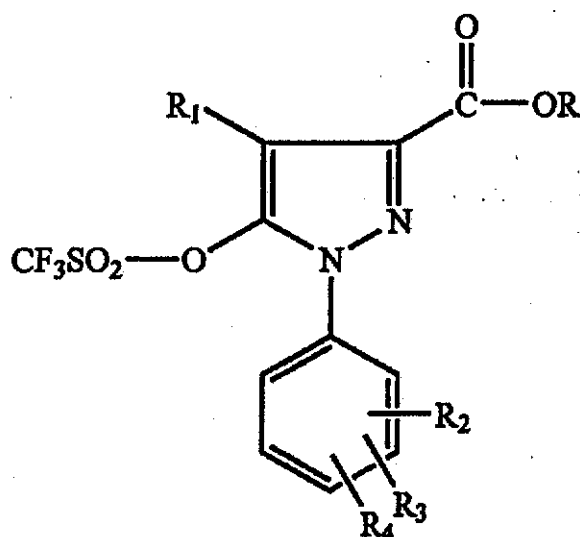
- 45 4. The process according to claim 1, wherein a phenylboronic acid derivative of formula (II) as defined in claim 1 is reacted with a compound of formula (III):

(III; Y = CF₃)

in which:

W, R₁, R₂, R₃ and R₄ are as defined in claim 1.

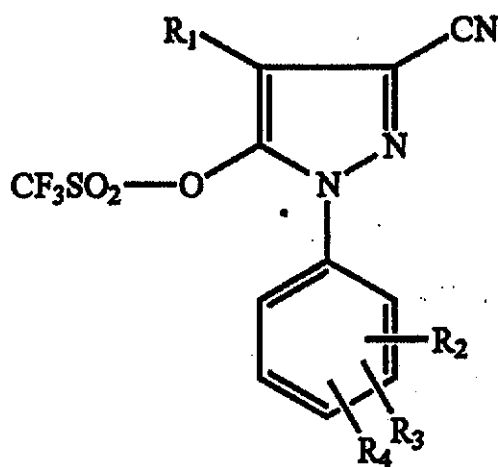
5. The process according to claim 2, wherein a phenylboronic acid derivative of formula (II) as defined in claim 1 is reacted with a compound of formula (IIIA);

(IIIA; Y = CF₃)

in which:

R , R_1 , R_2 , R_3 and R_4 are as defined in claim 1.

6. The process as recited in claim 3, wherein a phenylboronic acid derivative of formula (II) as defined in claim 1 is reacted with a compound of formula (IIIB):



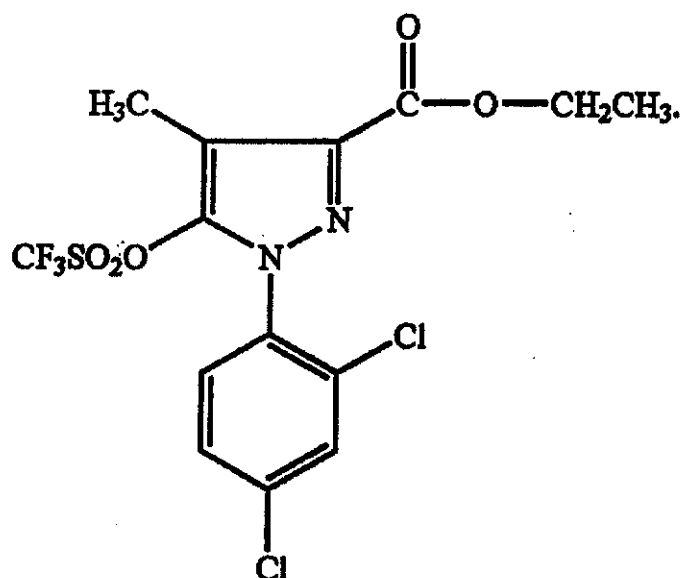
(IIIB; $Y = CF_3$)

in which:

R_1 , R_2 , R_3 and R_4 are as defined in claim 1.

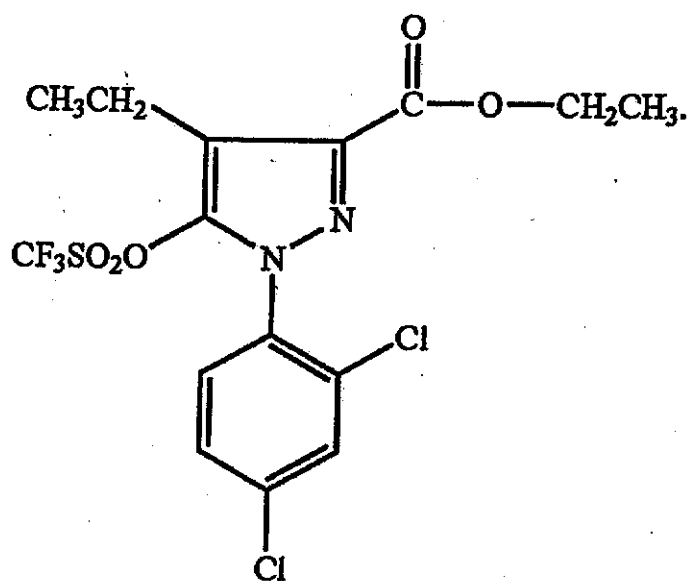
7. The process according to claim 5, wherein 4-chlorophenylboronic acid is reacted with a compound of formula (IIIAa):

(IIIAa)

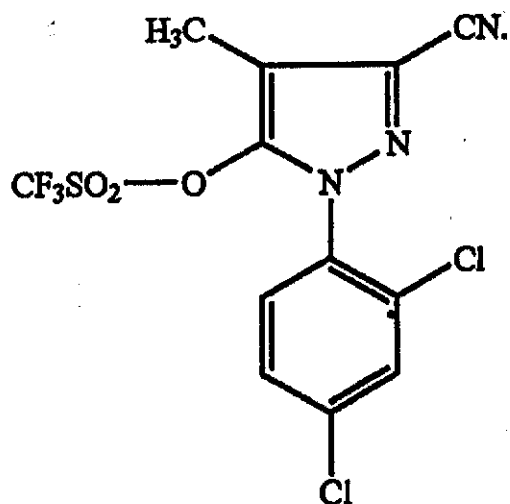


8. The process as recited in claim 5, wherein 4-bromophenylboronic acid is reacted with a compound of formula (IIIAb):

(IIIAb)

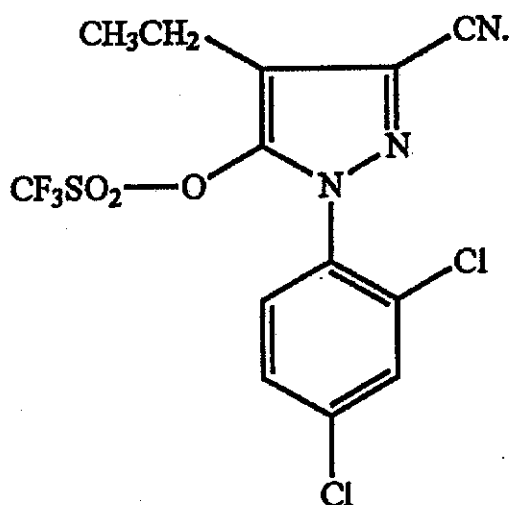


9. The process according to claim 6, wherein 4-chlorophenylboronic acid is reacted with a compound of formula (IIIBa):



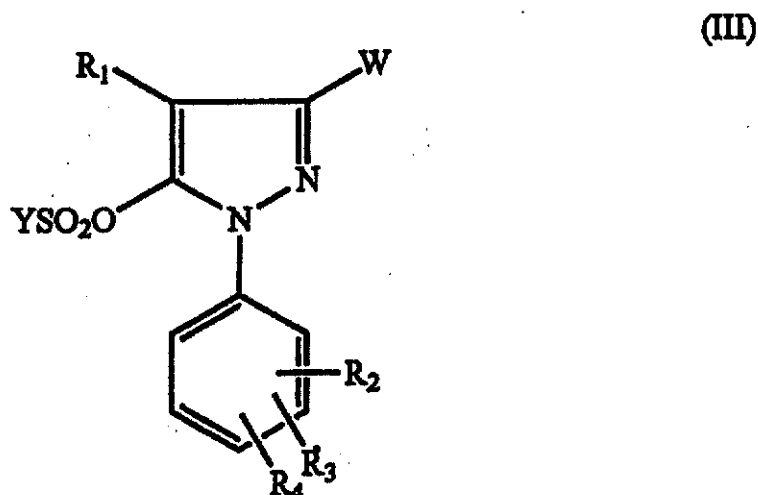
(IIIBa)

10. The process as recited in claim 6, wherein 4-bromophenylboronic acid is reacted with a compound of formula (IIIBb):



(IIIBb)

11. A compound as defined by formula (III):



in which:

W represents a group —COOR or a radical —CN ;

Y represents a $(\text{C}_1\text{—C}_4)$ alkyl group, a $(\text{C}_1\text{—C}_4)$ perfluoroalkyl group or a phenyl group that is unsubstituted or substituted with a methyl, chloro or nitro group;

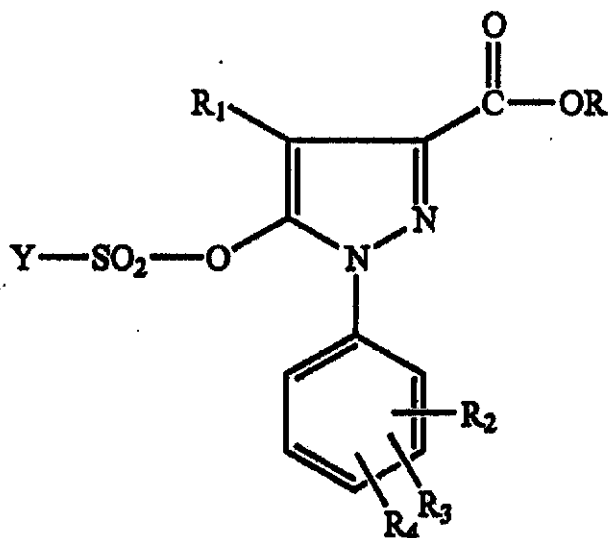
R_1 represents a hydrogen or halogen atom or a $(\text{C}_1\text{—C}_4)$ alkyl group;

R_2 , R_3 and R_4 each represent, independently of one another, a hydrogen or halogen atom or a $(\text{C}_1\text{—C}_4)$ alkyl, $(\text{C}_1\text{—C}_4)$ alkoxy or trifluoromethyl group;

R represents a $(\text{C}_1\text{—C}_4)$ alkyl or benzyl group.

12. The compound as recited in claim 11 defined by the formula (IIIA):

(IIIA)

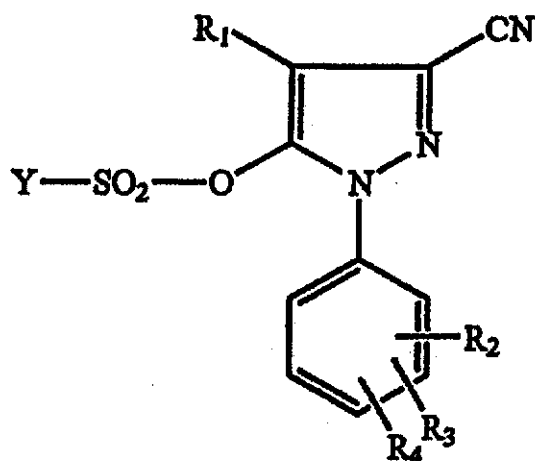


in which:

Y , R , R_1 , R_2 , R_3 and R_4 are as defined in claim 11.

13. The compound as recited in claim 11 defined by the formula (IIIB):

(IIIB)

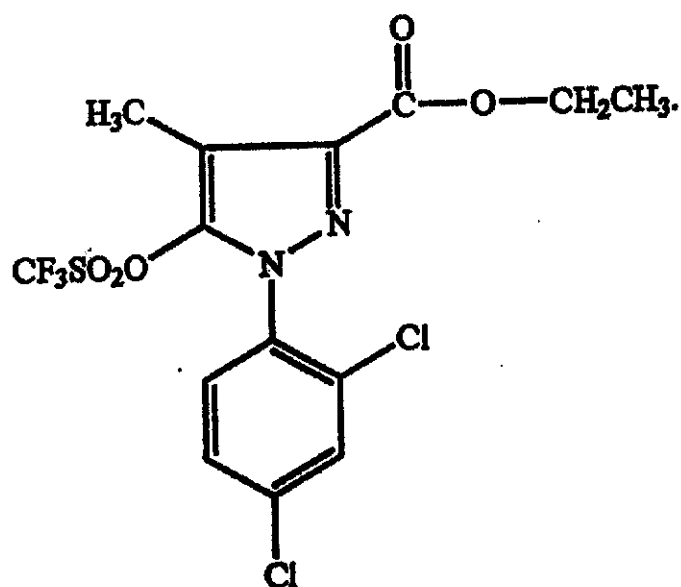


in which:

Y , R_1 , R_2 , R_3 and R_4 are as defined in claim 11.

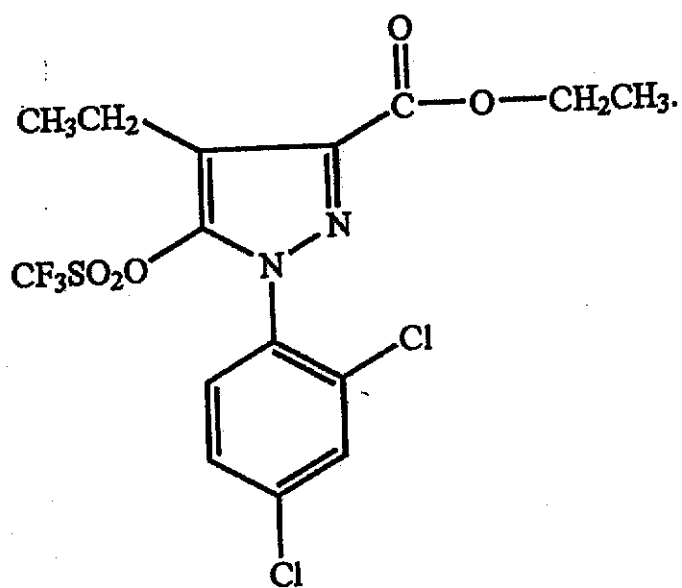
14. The compound as recited in claim 12, of formula (IIIAa):

(IIIAa)

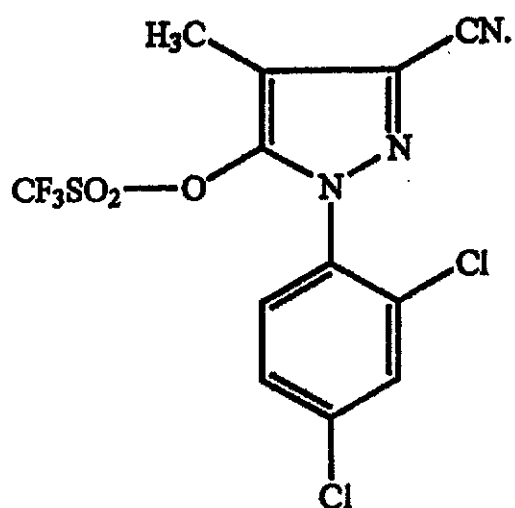


15. The compound as recited in claim 12, of formula (IIIAb):

(IIIAb)

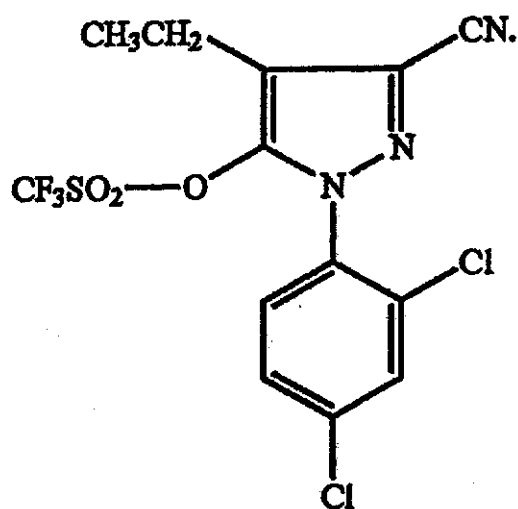


16. The compound as defined in claim 13, of formula (IIIBa):



(IIIBa)

17. The compound as defined in claim 13, of formula (IIIBb):



(IIIBb)