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(54) Title: PROCESS FOR PREPARING RIMONABANT

(57) Abstract: Processes for preparing rimonabant.

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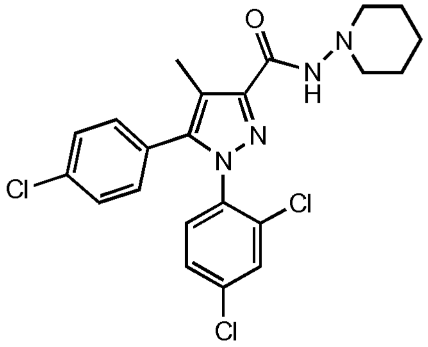
PROCESS FOR PREPARING RIMONABANT

INTRODUCTION TO THE INVENTION

The present invention relates to processes for the preparation of rimonabant and its pharmaceutically acceptable salts.

Rimonabant has a chemical name N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide, has the research designation SR 141716, and is structurally represented by Formula I.



Formula I

Rimonabant is an antagonist of the CB1 cannabinoid receptors and is useful as an antiobesity agent. Rimonabant is currently in clinical development in the U.S. for the treatment of obesity. It is available in the European market under the trademark ACOMPLIA as 20 mg oral film-coated tablets.

U.S. Patent No. 5,624,941 discloses rimonabant, its related compounds and processes for their preparation. In brief, the process comprises reacting a lithium salt of hexamethyldisilazane with 4-chloropropiophenone to afford a lithium salt of ethyl 4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate of Formula II, which on further reaction with 2,4-dichlorophenylhydrazine of Formula III affords ethyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylate of Formula V, which is then hydrolyzed to afford 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI. The carboxylic acid is then chlorinated followed by reaction with 1-aminopiperidine to afford rimonabant of Formula I, which can be purified by column chromatography.

U.S. Patent Application Publication Nos. 2007/0015810 and 2007/0015811 describe 5-(S)-substituted pyrazoline compounds and processes for their preparation.

The synthetic routes disclosed in the above patents require several steps, give low yields, are not suitable for large scale manufacturing processes and are also burdened by the use of hazardous chemicals such as thionyl chloride. It would be desirable to have a simple, efficient, industrial process for producing rimonabant which gives high yields and high purity without the need of applying complicated and time-consuming purification treatments such as column chromatography.

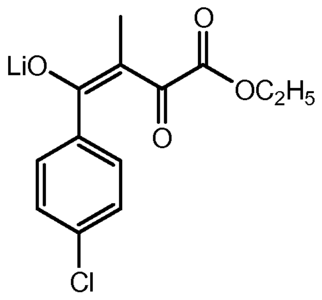
The present invention provides processes for the preparation of rimonabant that are environmentally friendly, have reduced reaction times, are easy to practice, produce high yields of rimonabant, are economical and can be adapted to use on an industrial scale.

SUMMARY OF THE INVENTION

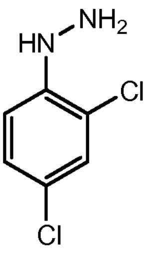
The present invention relates to processes for the preparation of rimonabant and its pharmaceutically acceptable salts.

One aspect of the present invention provides a process for the preparation of rimonabant of Formula I. In an embodiment, the process for the preparation of rimonabant comprises:

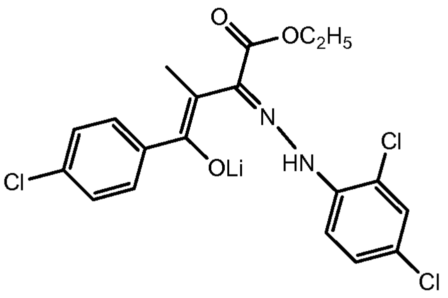
a) reaction of a lithium salt of ethyl-4-(4-chlorophenyl) -3-methyl-4-oxydo-2-oxo buten-3-oate of Formula II with dichlorophenylhydrazine of Formula III to give a lithium salt of 4-(4-chlorophenyl)-2-[(2, 4-dichlorophenyl)-hydrazono]-3-ethoxycarbonyl-2-methyl-propen-1-ol of Formula IV, which optionally is not isolated;



Formula II



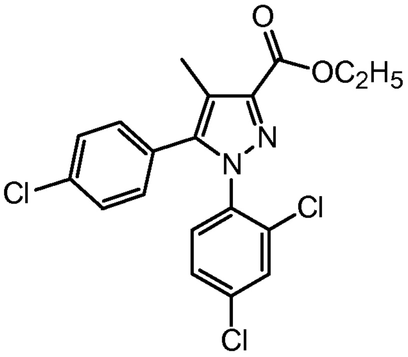
Formula III



Formula IV

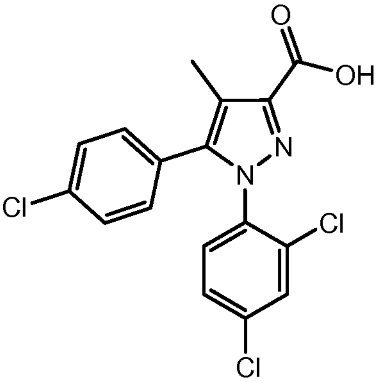
b) cyclization of the lithium salt of 4-(4-chlorophenyl)-2-[(2, 4-dichlorophenyl)-hydrazono]-3-ethoxycarbonyl-2-methyl-propen-1-ol of Formula IV in the presence of a suitable acid to afford ethyl-5-(4-chlorophenyl)-1-(2, 4-

dichloro phenyl)-4-methyl-pyrazole-3-carboxylate of Formula V, which optionally is not isolated.



Formula V

c) hydrolysis of ethyl-5-(4-chlorophenyl)-1-(2, 4-dichloro phenyl)-4-methyl-pyrazole-3-carboxylate of Formula V in the presence of a suitable base to give 5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI.



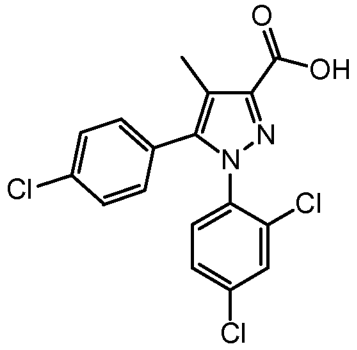
Formula VI

d) reacting 5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI with a chlorinating agent to form the compound of Formula VIb (see Fig. 1) and then reacting with 1-aminopiperidine to give rimonabant of Formula I.

Suitably, one or more of the sequential steps a) and b) are carried out without isolating intermediate compounds that form. In one embodiment of the invention, steps a) and b) are carried out without isolating the formed intermediates, followed by isolation of the compound of Formula VI.

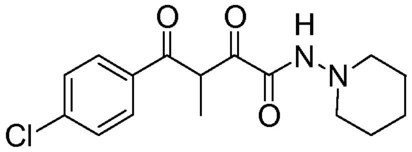
Another aspect of the present invention provides a process for the preparation of rimonabant of Formula I comprising reacting 5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI with 1-

aminopiperidine in the presence of a suitable reagent and a suitable organic solvent.



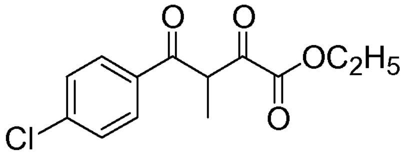
Formula VI

Yet another aspect of the present invention provides 4-(4-chlorophenyl)-3-methyl-2,4-dioxo-N-piperidin-1-yl-butyramide of Formula VII.



Formula VII

Still another aspect of the present invention provides a process for the preparation of 4-(4-chlorophenyl)-3-methyl-2, 4-dioxo-N-piperidin-1-yl-butyramide of Formula VII comprising reacting ethyl-4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxo-buten-3-oate of Formula VIII with 1-aminopiperidine.



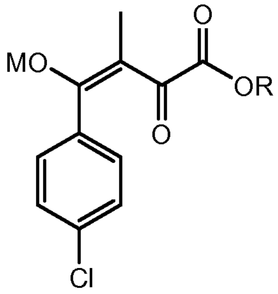
Formula VIII

A further aspect of the present invention provides a process for the preparation of rimonabant or a salt thereof from 4-(4-chlorophenyl)-3-methyl-2, 4-dioxo-N-piperidin-1-yl-butyramide of Formula VII comprising reacting 4-(4-chlorophenyl)-3-methyl-2, 4-dioxo-N-piperidin-1-yl-butyramide of Formula VII with dichlorophenylhydrazine of Formula III to give rimonabant of Formula I.

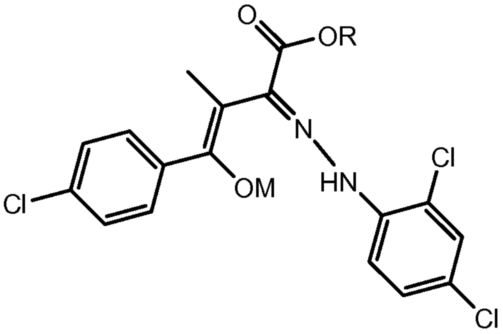
In a yet further aspect, the present invention provides a process for purifying rimonabant comprising reacting rimonabant with an acid to form a salt, and reacting the salt with a base.

An embodiment of the invention provides a process for preparing rimonabant, comprising:

a) reacting a compound having a formula:

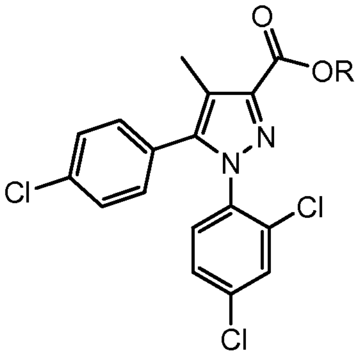


where M is an alkali metal and R is a C_1-C_6 straight chain, branched or cyclic alkyl group, with 2,4-dichlorophenylhydrazine to form an intermediate compound having a formula:



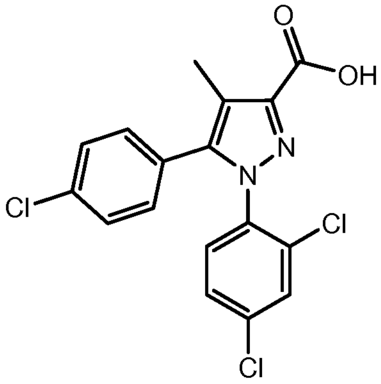
and, optionally without isolation of an intermediate compound,

b) further reacting with an acid to form a second intermediate compound having a formula:



and, optionally without isolation of a second intermediate compound,

c) reacting with a base to form a compound having a formula:



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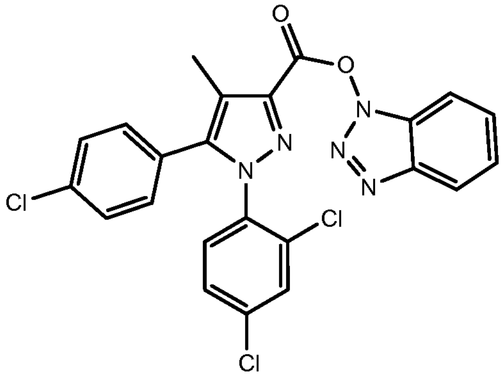
Another embodiment of the invention provides a compound having a formula:



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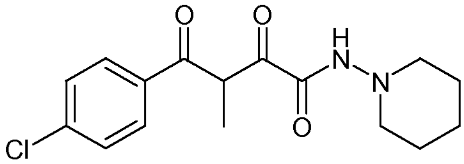
A further embodiment of the invention provides a compound having a formula:



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In an additional embodiment, the invention provides rimonabant or a salt thereof having a purity at least about 99 percent by weight.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic representation of a process for the preparation of rimonabant, starting from the intermediate having Formula VI.

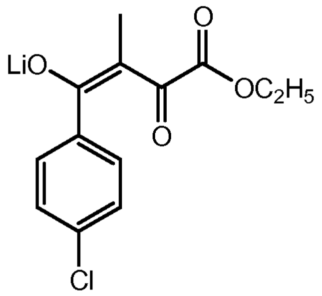
Fig. 2 is a schematic representation of a process for the preparation of rimonabant, starting from the intermediate having Formula VIII.

DETAILED DESCRIPTION OF THE INVENTION

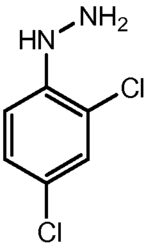
The present invention relates to processes for the preparation of rimonabant and its pharmaceutically acceptable salts.

One embodiment of the present invention provides a process for the preparation of rimonabant of Formula I, which comprises:

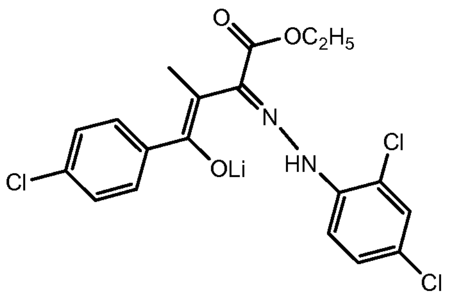
a) reacting a lithium salt of ethyl-4-(4-chlorophenyl) -3-methyl-4-oxydo-2-oxo buten-3-oate of Formula II with dichlorophenylhydrazine of Formula III to give 4-(4-chlorophenyl)-2-[(2, 4-dichlorophenyl)-hydrazono]-3-ethoxycarbonyl-2-methyl-propen-1-ol of Formula IV, which optionally is not isolated.



Formula II

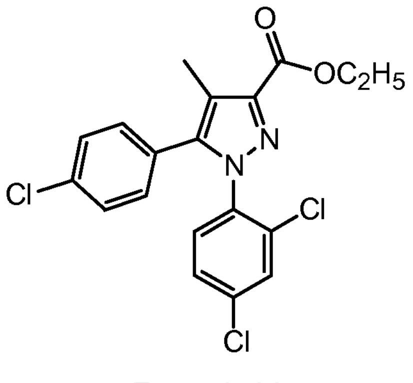


Formula III



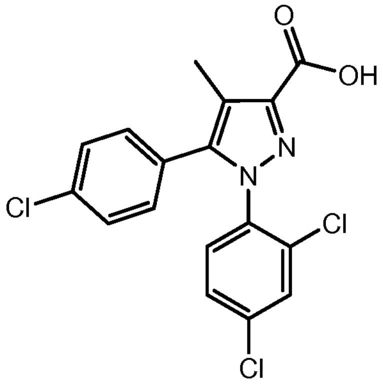
Formula IV

b) cyclizing 4-(4-chlorophenyl)-2-[(2, 4-dichlorophenyl)-hydrazono]-3-ethoxycarbonyl-2-methyl-propen-1-ol of Formula IV to afford ethyl-5-(4-chlorophenyl)-1-(2, 4-dichloro phenyl)-4-methyl-pyrazole-3-carboxylate of Formula V, which optionally is not isolated.



Formula V

c) hydrolyzing ethyl-5-(4-chlorophenyl)-1-(2, 4-dichloro phenyl)-4-methyl-pyrazole-3-carboxylate of Formula V to give 5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI; and



Formula VI

d) reacting 5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI with a chlorinating agent to form the compound of Formula VIb, and then reacting with 1-aminopiperidine to give rimonabant of Formula I.

Suitably, one or more of sequential steps a) and b) are carried out without isolating intermediate compounds that are formed. In one embodiment of the invention, steps a) and b) are carried out without isolating the formed intermediates, followed by isolation of the compound of Formula VI.

Step a) involves reacting a metal salt of ethyl-4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxo buten-3-one, such as the lithium salt of Formula II, with dichlorophenylhydrazine of Formula III to give 4-(4-chlorophenyl)-2-[(2, 4-dichlorophenyl)-hydrazono]-3-ethoxycarbonyl-2-methyl-propen-1-ol of Formula IV, which optionally is not isolated. This reaction is step a of Fig. 1.

Suitable organic solvents which can be used include but are not limited to: alcohols such as ethanol, n-propanol, isopropanol, n-butanol, isobutanol and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform and the like; hydrocarbon solvents such as toluene, xylene, n-heptane, n-hexane, cyclohexane, methylcyclohexane and the like; ethers such as tetrahydrofuran, 1,4-dioxane and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA) and the like; and mixtures thereof.

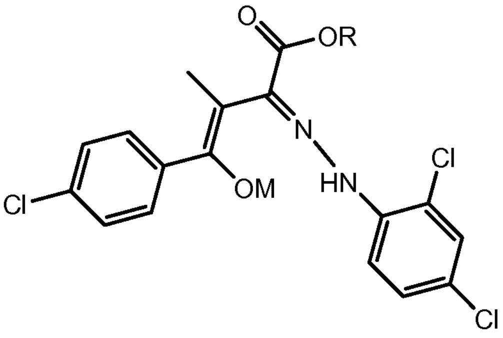
Suitable temperatures for conducting the reaction range from about 0 to about 200 °C, or from about 20 to about 100 °C.

Suitably, the reaction is conducted in the presence of an acid. Suitable acids which can be used include, but are not limited to, sulfuric acid, hydrochloric acid, acetic acid and the like, or mixtures of any two or more thereof.

Optionally, the acid may be used as its aqueous solution. Suitably, aqueous solutions containing about 5% to 50%, or about 10% to 20%, (w/v) of the acid can be used.

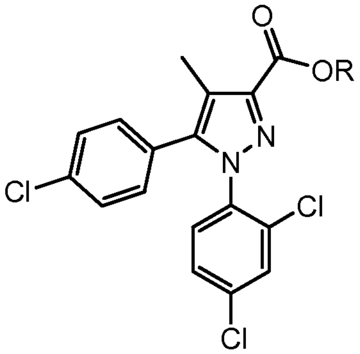
Suitably, instead of the lithium salt, a salt of any alkali metal such as a sodium salt or potassium salt of ethyl-4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxo buten-3-one can be used as the starting material, to give the corresponding alkali metal salt of the product 4-(4-chlorophenyl)-2-[(2, 4-dichlorophenyl)-hydrazono]-3-ethoxycarbonyl-2-methyl-propen-1-ol. The “Li” in Formula II and Formula IV can be replaced by “M” to denote an alkali metal. For convenience, the discussion in this description will refer to the lithium salt.

Further, metal salts of esters other than the ethyl ester of Formula II can be used in the process. Suitably, instead of the ethyl ester, any C_1-C_6 straight chain, branched or cyclic alkyl esters such as the methyl, propyl, isopropyl and t-butyl esters can be used, and the more general representation of the compound of Formula IV is Formula IVa:



Formula IVa

where R is a C_1-C_6 straight chain, branched or cyclic alkyl group, and the more general representation of the compound of Formula V is Formula Va. For convenience, the discussion in this description will refer to the group as “ethyl.”



Formula Va

The lithium salt of 4-(4-chlorophenyl)-2-[(2, 4-dichlorophenyl)-hydrazono]-3-ethoxycarbonyl-2-methyl-propen-1-ol of Formula IV formed in the reaction medium is optionally progressed to step b) without isolating the compound.

Step b) involves cyclizing the 4-(4-chlorophenyl)-2-[(2, 4-dichlorophenyl)-hydrazono]-3-ethoxycarbonyl-2-methyl-propen-1-ol salt, such as the lithium salt of Formula IV, in the presence of a suitable acid to afford ethyl-5-(4-chlorophenyl)-1-(2, 4-dichloro phenyl)-4-methyl-pyrazole-3-carboxylate of Formula V. This reaction is step b of Fig. 1.

Suitable acids which can be used include, but are not limited to, sulfuric acid, hydrochloric acid, acetic acid and the like, or mixtures of any two or more thereof.

Optionally, the acid may be used as its aqueous solution. Suitably, aqueous solutions containing about 5% to 50%, or about 10% to 20%, (w/v) of the acid can be used.

In an embodiment, the acid used in sulfuric acid. Sulfuric acid results in the conversion of the compound of Formula IV to the compound of Formula V directly, resulting in reduction of reaction time and is less expensive when compared to acetic acid used in the prior art.

Suitable solvents which can be used for the reaction include, but are not limited to: alcohols such as ethanol, n-propanol, isopropanol, n-butanol, isobutanol and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform and the like; hydrocarbon solvents such as toluene, xylene, n-heptane, n-hexane, cyclohexane, methylcyclohexane and the like; and mixtures thereof.

Suitable temperatures for cyclization range from about 20 °C to 200 °C, or from about 50 °C to 200 °C.

After the completion of cyclization, the product formed can optionally be used directly in the next step without isolation.

Step c) involves hydrolyzing ethyl-5-(4-chlorophenyl)-1-(2, 4-dichloro phenyl)-4-methyl-pyrazole-3-carboxylate of Formula V to give 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI. This reaction is step c of Fig. 1.

Hydrolysis can be carried out in the presence of a suitable base. Suitable bases which can be used include, but are not limited to: alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like; bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate, and the like; ammonia; and mixtures thereof. These bases can be used in the form of solids or in the form of aqueous solutions.

Suitably, aqueous solutions containing about 5% to 50%, or about 10% to 20%, (w/v) of the corresponding base can be used. Any concentration is useful, which will convert the acid addition salt to a free base.

Suitable temperatures for conducting the reaction range from about 20 °C to 200 °C, or from about 25 °C to 100 °C.

5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid obtained above can optionally be purified by recrystallization, slurrying or a combination thereof in an organic solvent to obtain pure compound.

Suitable solvents which can be used for purification include, but are not limited to: ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; alcohols like methanol, ethanol, isopropyl alcohol, n-propanol, and the like; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the like; nitriles such as acetonitrile, propionitrile and the like; and mixtures thereof.

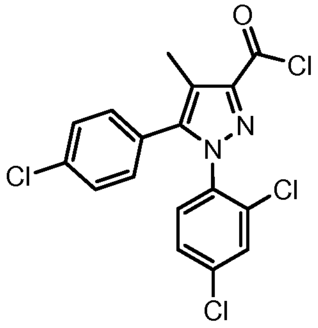
Step d) involves reacting 5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI with a chlorinating agent to form compound of Formula VIb and then reacting with 1-aminopiperidine to give rimonabant of Formula I.

Suitable chlorinating agents which can be used include, but are not limited to, thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, and the like, or mixtures thereof.

Suitable solvents which can be used include, but are not limited to: ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like, esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the like; nitriles such as acetonitrile, propionitrile and the like; and mixtures thereof.

Suitable temperatures for conducting the reaction range from about 20 °C to 200 °C, or from about 25 °C to 100 °C.

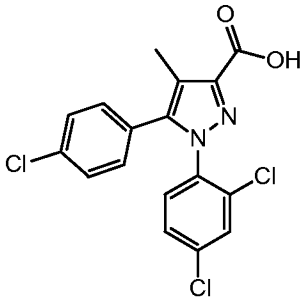
The chlorinating agent converts the acid of Formula VI to its active acid chloride derivative of Formula VIb. This reaction is Step d of Fig. 1.



Formula VIb

Suitably, this intermediate then is reacted with 1-aminopiperidine to give rimonabant of Formula I.

Another aspect of the present invention provides a process for the preparation of rimonabant comprising reacting 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI with 1-aminopiperidine in the presence of a suitable reagent and a suitable organic solvent.



Formula VI

5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI can be obtained by any known methods or by a process described above in the present invention.

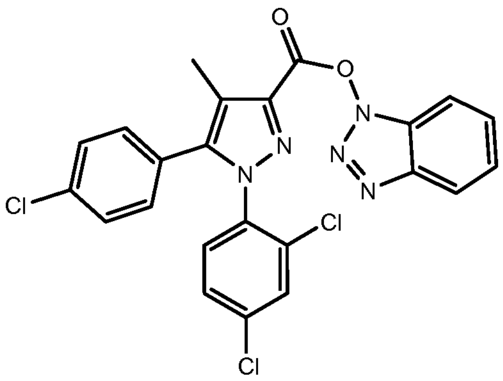
Suitable reagents which can be used for the reaction include, but are not limited to: coupling agents such as the carbodiimide compounds 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI), dicyclohexyl carbodiimide (DCC), and diisopropylcarbodiimide (DIPCDI), optionally in the presence of catalytic auxiliary nucleophiles like 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimede (HOSu), and N-hydroxy-5-norbene-endo-2,3-dicarboxamide (HONB); or dehydrating agents like carbonyldiimidazole, boric acid, phosphorus pentoxide, acetic anhydride, sulfuric acid and the like.

Suitable organic solvents which can be used for the above reaction include, but are not limited to: hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; ethers such as tetrahydrofuran, 1,4-dioxane and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), and the like or mixtures thereof; halogenated solvents such as dichloromethane, chloroform and the like; and mixtures thereof.

Suitable temperatures for conducting the reaction range from about -10 to about 200 °C, or from about 30 to about 100 °C.

In an embodiment, the reagent used for reaction is a combination of the coupling agent dicyclohexyl carbodiimide and the auxillary nucleophile 1-hydroxybenzotriazole (HOBt). This reaction is Step f of Fig. 1.

During the reaction, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI reacts with dicyclohexyl carbodiimide to form a reactive intermediate 5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid benzotriazol-1-yl ester of Formula VIa.

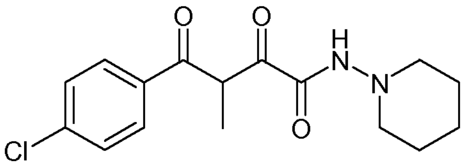


Formula VIa

Suitably, the intermediate then is reacted with 1-aminopiperidine to give rimonabant of Formula I.

In another embodiment, the reagent used is carbonyldiimidazole, which acts as a dehydrating agent. This reaction is Step e of Fig. 1.

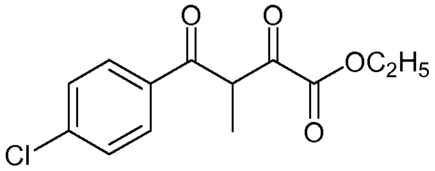
Yet another aspect of the present invention provides 4-(4-chlorophenyl)-3-methyl-2,4-dioxo-N-piperidin-1-yl-butyramide of Formula VII.



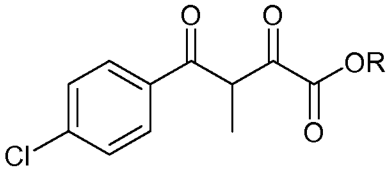
Formula VII

4-(4-chlorophenyl)-3-methyl-2,4-dioxo-N-piperidin-1-yl-butyramide of Formula VII acts as an intermediate for the preparation of rimonabant and its related compounds.

Still another aspect of the present invention provides a process for the preparation of 4-(4-chlorophenyl)-3-methyl-2,4-dioxo-N-piperidin-1-yl-butyramide of Formula VII. In an embodiment, the process comprises reacting ethyl-4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxo-buten-3-oate of Formula VIII with 1-aminopiperidine. Although the ethyl ester is shown in Formula VIII, those skilled in the art will recognize that esters formed from alcohols other than ethanol can also be used, and the invention includes any other such esters where the ethyl group is replaced by any other C_1-C_6 straight chain, branched or cyclic alkyl group; thus, the Formula VIII structure can more generally be represented by the structure of Formula VIIIa where R is a C_1-C_6 straight chain, branched or cyclic alkyl group. This reaction is step a of Fig. 2.



Formula VIII



Formula VIIIa

Suitably the reaction can be carried out in the presence of reagents which include, but are not limited to lithium hexamethyldisilazamide, n-butyllithium, sodium methoxide, potassium tertiary-butoxide, sodium hydride, lithium aluminium hydride, potassium carbonate, sodium carbonate, lithium hydride, triethylamine, diisopropyl ethylamine, and the like.

The reaction can also be conducted in the absence of any such reagents because 1-aminopiperidine itself acts as a base.

Suitable organic solvents which can be used include but are not limited to: alcohols such as ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, and the like; hydrocarbon solvents such as toluene, xylene, methylcyclohexane, and the like; ethers such as tetrahydrofuran, 1,4-dioxane, and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), and the like; and mixtures thereof or their combinations with water in various proportions.

Suitable temperatures for conducting the reaction range from about 0 °C to about 200 °C, or form about 20 °C to about 100 °C.

Suitably, instead of the ethyl ester, any C_1-C_6 straight chain, branched or cyclic alkyl esters such as the methyl, propyl, isopropyl and t-butyl esters of 4-(4-chlorophenyl)-3-methyl-2,4-dioxobutanoic acid can be used to prepare the compound of Formula VII.

A further aspect of the present invention provides a process for the preparation of rimonabant from 4-(4-chlorophenyl)-3-methyl-2,4-dioxo-N-piperidin-1-yl-butyramide of Formula VII. In an embodiment, the process comprises of reacting 4-(4-chlorophenyl)-3-methyl-2,4-dioxo-N-piperidin-1-yl-butyramide of Formula VII with dichlorophenylhydrazine of Formula III to give rimonabant of Formula I. This reaction is Step b of Fig. 2

The reaction can be carried out in the presence of a suitable base. Suitable bases which can be used include but are not limited to: organic bases such as pyridine, triethylamine, dimethylamine, methylamine, aqueous ammonia, and the like.

Suitable organic solvents which can be used for the reaction include, but are not limited to: alcohols such as ethanol, n-propanol, isopropanol, n-butanol, isobutanol, and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, and the like; hydrocarbon solvents such as toluene, xylene, methylcyclohexane, and the like; ethers such as tetrahydrofuran, 1,4-dioxane, and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), and the like; and mixtures thereof or their combinations with water in various proportions.

Rimonabant obtained above can be purified by recrystallization or slurrying in a suitable solvent, or by converting it to an acid addition salt followed by purification of the salt, and recovering rimonabant from the salt.

Suitable organic solvents which can be used for recrystallization or slurry formation include but are not limited to: alcoholic solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, n-butanol, and the like; halogenated solvents such as dichloromethane, 1,2-dichloroethane, and the like; esters such as ethyl acetate, n-butyl acetate, tertiary-butyl acetate, and isopropyl acetate and the like; ketonic solvents such as acetone, ethyl methyl ketone, and the like; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; nitrile solvents such as acetonitrile, propionitrile and the like; and mixtures thereof in various proportions.

When the slurry technique is used for purification, a solvent in which rimonabant has a low solubility will frequently be employed, to enhance the product recovery.

The concentration of rimonabant in the solvent can range from about 40 to 80% or more. For recrystallization, a solution can be prepared at an elevated temperature if desired to achieve a desired concentration. Any temperature is acceptable for the dissolution as long as a clear solution of the rimonabant is obtained and is not detrimental to the drug substance chemically or physically. The solution may be brought down to room temperature for further processing if required or an elevated temperature may be used.

In a still further aspect the present invention provides a process for purifying rimonabant comprising reacting with an acid to form a salt, and reacting the salt with a base.

When purification is carried out by formation of a salt of rimonabant suitable acids which can be used for salt formation include but are not limited to: inorganic acids such as hydrochloric acid, hydrobromic acid, and the like; and organic acids such as oxalic acid, trifluoroacetic acid, tartaric acid, formic acid, acetic acid, para-toluene sulfonic acid and the like.

The acid addition salt of rimonabant can be purified further by recrystallization or slurrying in a suitable solvent. The solvents which have been mentioned for purification of rimonabant can be used.

The acid addition salt can be converted to rimonabant by treating with a base. Suitable bases that can used for conversion of the acid addition salt of rimonabant to its free base include but are not limited to: alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like; bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate, and the like; ammonia; and mixtures thereof. These bases can be used in the form of solids or in the form of aqueous solutions.

Suitably, aqueous solutions containing about 5% to 50%, or about 10% to 20%, (w/v) of the corresponding base can be used. Any concentration is useful, which will convert the acid addition salt to the free base.

Rimonabant obtained according to any of the processes described above can be converted to its pharmaceutically acceptable salts by reacting it with the desired acid in the presence of a suitable solvent.

Suitable acids which can be used include, but are not limited to: inorganic acids like hydrochloric acid, hydrobromic acid; and organic acids like tartaric acid, acetic acid, citric acid and the like.

Rimonabant and its salts obtained according to the process of the present invention are substantially pure. By “substantially pure rimonabant” it is meant that rimonabant and its salts prepared in accordance with the process of the present invention have a purity of more than about 99%, or more than about 99.5%. It contains less than about 0.5%, or less than about 0.15%, by weight of any of the process related impurities.

Certain specific aspects and embodiments of this invention are described in further detail by the examples below, which examples are provided only for the purpose of illustration and are not intended to limit the scope of the appended claims in any manner.

EXAMPLE 1

PREPARATION OF 5-(4-CHLOROPHENYL)-1-(2,4-DICHLOROPHENYL)-4-METHYL-PYRAZOLE-3-CARBOXYLIC ACID (FORMULA VI)

8.0 g of the lithium salt of ethyl 4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-oate of Formula II and 200 ml of ethanol were charged into a clean and dry round bottom flask followed by stirring for 10 minutes. 6.19 g of 2,4-dichlorophenylhydrazine hydrochloride of Formula III was added followed by addition of 80 ml of 50% aqueous sulfuric acid. The reaction mass was heated to 90 °C and maintained for 7 hours followed by distillation of solvent completely at 90 °C under a vacuum of 300 mm Hg. 160 ml of 50% aqueous sulfuric acid was added to the residue followed by heating to about 140° C. The reaction mass was maintained at 140 °C for 12 hours. The reaction mass was then cooled to 30 °C followed by quenching with 200 ml of ice water. The mixture was stirred for 20 minutes. The separated solid was filtered and washed with 80 ml of water to afford a crude form of the title compound.

24.5 g of the above crude compound and 500 ml of water were taken into a clean and dry round bottom flask and stirred for 10 minutes. pH of the reaction mass was adjusted to 12 by the addition of 5 g of sodium hydroxide followed by washing the solution with 2×150 ml of petroleum ether. Organic and aqueous phases were separated followed by adjusting the pH of the aqueous layer to about 2, by addition of 4.6 ml of 12 N hydrochloric acid. The resultant suspension was stirred for 10 minutes followed by filtration of the separated solid. The solid was washed with 3 liters of water. The solid obtained was dried at 35 °C under a vacuum of 700 mm Hg for 2 hours to afford 17.5 g of the title compound.

EXAMPLE 2

PREPARATION OF 5-(4-CHLOROPHENYL)-1-(2,4-DICHLOROPHENYL)-4-METHYLPYRAZOLE-3-CARBOXYLIC ACID CHLORIDE (FORMULA VIb)

17 g of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI and 525 ml of toluene were charged into a clean and dry round bottom flask followed by the addition of 15.9 ml of thionyl chloride at 30 °C. The reaction solution was heated to 110 °C and maintained for 4 hours. The solvent was then distilled off completely at 110 °C under a vacuum of 700 mm Hg. 700 ml of toluene was added to the residue and was distilled completely at 110° C under a vacuum of 700 mm Hg, followed by addition of an additional 700 ml of toluene and distilling completely at 110 °C to afford 16.8 g of the title compound.

EXAMPLE 3

PREPARATION OF N-PIPERDINO-5-(4-CHLOROPHENYL)-1-(2,4-DICHLOROPHENYL)-4-METHYLPYRAZOLE-3-CARBOXAMIDE (FORMULA I)

8.4 g of 1-aminopiperidine and a solution of 27 ml of triethylamine in 179.9 ml of dichloromethane were taken into a clean and dry round bottom flask, followed by cooling to 15 °C. A solution of 16.8 g of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxylic acid chloride of Formula VIb in 179.9 ml of dichloromethane was added dropwise at about -15 to -10 °C. The resultant reaction mixture was stirred for 30 minutes followed by quenching the reaction mass by addition of the reaction mass to 749.7 ml of ice water. Organic and aqueous layers were separated and the aqueous layer was extracted with 600 ml (2×300 ml) of dichloromethane. Organic and aqueous layers were separated and both the organic layers were combined followed by washing the total organic layer with 600 ml of a saturated solution of sodium chloride. Organic and aqueous layers were separated and the organic layer was dried over 62.2 g of anhydrous sodium sulfate. The solvent was distilled off at 40 °C under a vacuum of 300 mm Hg to afford 25 g of the title compound. The resultant residue was purified by column chromatography using petroleum ether and ethyl acetate in the ratio of 88:12 as eluent. Collected fractions were distilled completely at 55 °C followed by addition of 25 ml of petroleum ether and stirring for 30 minutes.

Separated solid was filtered and the solid was dried at 40 °C under vacuum for 2 hours to afford 11.8 g of the title compound.

EXAMPLE 4

PREPARATION OF 4-(4-CHLOROPHENYL)-3-METHYL-2,4-DIOXOBUTYRIC ACID ETHYL ESTER (FORMULA VIII)

300 ml of methylcyclohexane was taken into a clean and dry round bottom flask under a nitrogen atmosphere followed by addition of 300 ml of lithium hexamethyldisilazamide. The mixture was cooled to 15 °C followed by addition of a mixture of 50 g of 4-chloropropiophenone and 125 ml of methylcyclohexane. The resultant reaction mixture was stirred for 3 hours followed by addition of 47.8 of diethyl oxalate. The reaction mixture was stirred for 15 hours, the separated solid was filtered, and the solid was washed with 50 ml of methylcyclohexane followed by slurrying the obtained solid in 200 ml of methylcyclohexane and filtering under a nitrogen atmosphere. The solid was dissolved in 250 ml of water, filtered and the pH of the filtrate was adjusted to 2 by the addition of 24 ml of hydrochloric acid (12N). Separated solid was filtered and the filtrate was extracted with 3×250 ml of ethyl acetate and the total organic layer was dried over anhydrous sodium sulfate (20 g) followed by distillation of the solvent completely at 65 °C under a vacuum of 700 mm Hg to afford 21.5 g of the title compound as a residue.

EXAMPLE 5

PREPARATION OF 4-(4-CHLOROPHENYL)-3-METHYL-2,4-DIOXO-N-PIPERIDIN-1-YL-BUTYRAMIDE (FORMULA VII)

21.5 g of 4-(4-chlorophenyl)-3-methyl-2,4-dioxobutyric acid ethyl ester of Formula VIII, 8.04 g of 1-aminopiperidine, and 8.04 g of triethylamine were taken into a clean and dry round bottom flask followed by stirring for 3 hours. After the completion of reaction, 500 ml of ethyl acetate was added followed by separation and washing of the organic layer with 3×500 ml of water. Total organic layer was dried over 20 g of anhydrous sodium sulphate, followed by separation and distillation of solvent completely at about 65 °C under a vacuum of 700 mm Hg to give 19.5 g of the title compound as a residue.

EXAMPLE 6

PREPARATION OF N-PIPERDINE-5-(4-CHLOROPHENYL)-1-(2,4-DICHLOROPHENYL)-4-METHYLPYRAZOLE-3-CARBOXAMIDE (FORMULA I)

19.4 g of 4-(4-chlorophenyl)-3-methyl-2,4-dioxo-N-piperidin-1-yl-butyramide, 12.85 g of (2,4-dichlorophenyl)hydrazine hydrochloride, and 240 ml of ethanol were taken into a clean and dry round bottom flask. The suspension was stirred for 8 hours followed by filtration of the separated solid. The solid was washed with 20 ml of ethanol. Solvent from the filtrate was distilled off completely at 65 °C under a vacuum of 700 mm Hg to afford 23.2 g of residue. 200 ml of dichloromethane was added to the residue and stirred for 30 minutes followed by filtration of separated solid. The solid was washed with 10 ml of dichloromethane. Solvent from the resultant filtrate was distilled completely at 40 °C under a vacuum of 700 mm Hg to afford 21.5 g of crude compound. The crude compound was dissolved in 200 ml of dichloromethane and was adsorbed onto 42 g of silica gel in a100×200 mm chromatography column. The compound fractions were collected using 1-13% ethyl acetate as eluant followed by distillation of solvent completely from the combined fractions at about 55-65° C, followed by charging of 50 ml of acetone and stirring for about 5-10 minutes. Separated solid was filtered to afford 0.5 g of the title compound.

EXAMPLE 7

PREPARATION OF THE LITHIUM SALT OF ETHYL 4-(4-CHLOROPHENYL)-3-METHYL-4-OXYDO-2-OXOBUTEN-3-OATE (FORMULA II)

300 g of the lithium salt of hexamethyldisilazane and 300 ml of methylcyclohexane were taken into a clean and dry round bottom flask followed by cooling to 20 °C. 50 g of 1-(4-chloro-phenyl)-propan-1-one dissolved in 300 ml of methylcyclohexane was added slowly to the above reaction mixture followed by stirring for 3 hours. 47.8 g of oxalic acid diethyl ester was added to the reaction mass at 20 °C. The resultant reaction mixture was stirred for 8 hours. Separated solid was filtered and washed with 250 ml of methylcyclohexane to afford a crude form of the title compound.

The above wet compound and 250 ml of methylcyclohexane were taken into a clean and dry round bottom flask followed by cooling to 25-30 °C. The mixture was stirred for 90 minutes. Separated solid was filtered and the solid was washed with 100 ml methylcylcohexane. The wet solid was dried at 35 °C under a vacuum of 700 mm Hg for 2 hours to afford 42.4 g of the title compound.

EXAMPLE 8

PREPARATION OF 5-(4-CHLOROPHENYL)-1-(2,4-DICHLOROPHENYL)-4-METHYL-PYRAZOLE-3-CARBOXYLIC ACID (FORMULA VI)

42.0 g of the lithium salt of ethyl 4-(4-chlorophenyl)-3-methyl-4-oxydo-2-oxobuten-3-one of Formula II and 1200 ml of ethanol were taken into a clean and dry round bottom flask and stirred for 20 minutes. 32.6 g of 2,4-dichlorophenylhydrazine hydrochloride of Formula III was added to it followed by the addition of 420 ml of 50% aqueous sulfuric acid. The reaction mass was heated to 90 °C and maintained for 5 hours followed by distillation of solvent completely at 80 °C under a vacuum of 300 mm Hg. 840 ml of 50% aqueous sulfuric acid was added to the residue obtained and heated to 130 °C. The reaction mass was maintained at 130 °C for 12 hours. The reaction mass was then cooled to 28 °C followed by quenching by adding the reaction mass to 1025 ml of ice water. The mixture was stirred for 20 minutes. The separated solid was filtered and washed with 123 ml of water to afford a crude form of the title compound.

42 g of the above obtained crude form of the title compound and 420 ml of methanol were charged into a clean and dry round bottom flask and stirred for 10 minutes. 14.4 g of potassium hydroxide dissolved in 294 ml water was added followed by heating to 90 °C and stirring for 3 hours. The reaction mass was cooled to 28 °C. The reaction mass was then added to 2840 ml of ice water and the mixture was stirred for 20 minutes. pH of the reaction mass was then adjusted to 2 by addition of 4.6 ml of 12N hydrochloric acid. The resultant suspension was stirred for 30 minutes followed by filtration of the separated solid and washing the solid with 3 liters of water. The solid obtained was dried at 35 °C under a vacuum of 700 mm Hg for 2 hours to afford 17.5 g of the title compound.

EXAMPLE 9

PREPARATION OF N-PIPERIDONO-5-(4-CHLOROPHENYL)-1(2,4-DICHLOROPHENYL)-4-METHYL-PYRAZOLE-3-CARBOXAMIDE (FORMULA I)

45.0 g of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI, 18.7 g of 1-hydroxybenzotriazole, and 450 ml of dichloromethane were taken into a clean and dry round bottom flask and stirred for 20 minutes. A solution of 29.3 g of dicyclohexylcarbodiimide in 900 ml of dichloromethane was added slowly followed by stirring for 20 minutes at 30 °C. The resultant reaction mixture was stirred for 30 minutes at 0 °C. Reaction completion was checked using thin layer chromatography. After completion of the reaction, the reaction mass was filtered to separate the unwanted byproduct. The filter cake was washed with 135 ml of dichloromethane. The resultant clear filtrate was distilled completely under a vacuum of 650 mm Hg at 40 °C to afford 5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid benzotriazol-1-yl ester of Formula VIa.

67.1 g of the above obtained compound and 900 ml of dichloromethane were taken into a clean and dry round bottom flask and stirred for 10 minutes. 15.35 g of potassium carbonate was added and stirred for 20 minutes. A solution of 11.8 g of 1-aminopiperdine of Formula II in 450 ml of dichloromethane was added slowly through a dropper at 30 °C. Reaction completion was checked using thin layer chromatography. After completion of the reaction, the reaction mass was filtered to separate the unwanted byproduct. The filter cake was washed with 135 ml of dichloromethane. The solvent was distilled completely under a vacuum of 300 mm Hg at 45 °C. The residue was dissolved in 450 ml of petroleum ether and taken into a clean dry round bottom flask and stirred for 3 hours at 0 °C. Separated solid was filtered and the solid was washed with 225 ml of petroleum ether and drying under ambient conditions for 6 hours to afford 47.0 g of a crude form of the title compound of Formula I, with a purity by HPLC of 95%.

47 g of the above crude compound and 235 ml of acetone were taken into a clean and dry round bottom flask and stirred for 2 hours at 60 °C. The pH was adjusted to 2 by addition of 10 ml of 12 normal hydrochloric acid at 50 °C. The resultant suspension was stirred for 30 minutes at 0-3 °C. The separated solid

was filtered and washed with 47 ml of acetone. The wet solid was maintained at 25 °C under aerial drying for 2 hours to afford 43.0 g of the compound.

43 g of the above compound and 235 ml of methanol were taken into a clean and dry round bottom flask and stirred for 20 minutes at 26 °C. pH of the reaction mass was adjusted to a value between 10 to 12 by addition of 8 ml of aqueous sodium hydroxide solution at 26 °C. 470 ml of water was then added and the resultant suspension was stirred for 2 hours at 26 °C. The separated solid was filtered and washed with 470 ml of water. The wet solid was dried at 50 °C under a reduced pressure of 700 mm Hg for 10 hours to afford 37.0 g of the title compound.

Purity by HPLC of 99.66%.

EXAMPLE 10

PREPARATION OF THE LITHIUM SALT OF ETHYL 4-(4-CHLOROPHENYL)-3-METHYL-4-OXYDO-2-OXOBUTEN-3-OATE (FORMULA II)

60 ml of the lithium salt of hexamethyldisilazane and 60 ml of cyclohexane were taken into clean and dry round bottom flask followed by cooling to 15 °C. 10 g of 1-(4-chloro-phenyl)-propan-1-one was dissolved in 30 ml of methylcyclohexane and this solution was added slowly to the above reaction mixture followed by stirring for 3 hours. 8.7 g of oxalic acid diethyl ester was added to the reaction mass at 15 °C. The resultant reaction mixture was stirred for 8 hours. Separated solid was filtered and the solid was washed twice with 30 ml of cyclohexane. The wet solid was dried at 30 °C under a vacuum of 700 mm Hg for 2 hours to afford 10 g of the title compound.

EXAMPLE 11

PREPARATION OF N-PIPERIDONO-5-(4-CHLOROPHENYL)-1(2,4-DICHLOROPHENYL)-4-METHYL-PYRAZOLE-3-CARBOXAMIDE (FORMULA I)

10.0 g of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI, 6.3 g 1,1'-carbonyldiimidazole, and 100 ml of THF were taken into a clean and dry round bottom flask and stirred for 20 minutes. 2.88 g of N-aminopiperidine was added and the reaction mass was heated to 70 °C. The reaction mass was maintained at 65 to 70 °C for 2 hours. Reaction completion was checked using thin layer chromatography. After completion of the reaction, the solvent was distilled completely under a vacuum of 300 mm Hg at a temperature of 50 °C to afford a residue. The residue was dissolved in 100 ml of diisopropyl ether and washed twice with water and then with 50 ml of saturated vacuum salt solution. The organic layer was dried over sodium sulfate and filtered. The solvent was distilled completely under a vacuum of 300 mm/Hg at 50 °C. The residue obtained was dissolved in 30 ml of diisiopropyl ether. The solution was then cooled to 25 °C and further cooled to 0 °C. The separated solid was filtered and washed with 10 ml of n-heptane. The wet compound was dried at 60 °C for 5 hours to afford 9.0 g of a crude form of the title compound of Formula I.

5.0 g of the above crude compound and 25 ml of methanol were taken into a clean and dry round bottom flask and stirred for about 30 minutes at 65 °C. The mixture was then cooled to 28 °C and stirred for 30 minutes at 28 °C. The separated solid was filtered and washed with 5 ml of methanol. The solid obtained was dried at 60 °C under a reduced pressure of about 700 mm Hg for 10 hours to afford 3.1 g of the title compound.

Purity by HPLC 98.97%.

EXAMPLE 12

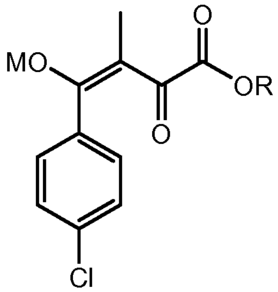
PREPARATION OF N-PIPERIDONO-5-(4-CHLOROPHENYL)-1(2,4-DICHLOROPHENYL)-4-METHYL-PYRAZOLE-3-CARBOXAMIDE (FORMULA I)

150 ml of toluene and 5 g of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid of Formula VI were taken into a round bottom flask and stirred at 29 °C for 10 minutes. 0.08 g of boric acid was added and stirred for another 10 minutes. The reaction mass was then heated to 40 °C and a solution of 1.31 g of 1-aminopiperidine in 15 ml toluene was added. The reaction mass was maintained at 40 °C for 30 minutes and then further heated to 112 °C. The reaction mass was maintained at 111 °C for 12 hours. The reaction mass was then cooled to 29 °C and 100 ml of n-heptane was added to it and stirred for 15 minutes. The formed solid was filtered and washed with 50 ml of n-heptane. The wet solid was dried at 50 °C for 8 hours to yield 3.6 g of the title compound.

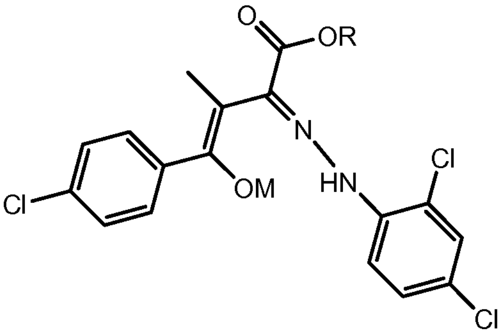
CLAIMS:

1. A process for preparing rimonabant, comprising:

a) reacting a compound having a formula:

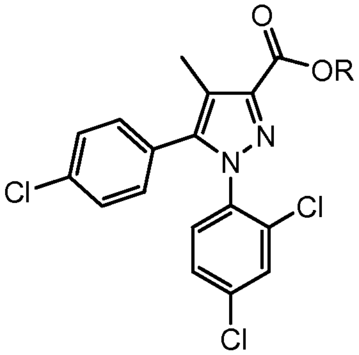


where M is an alkali metal and R is a C_1-C_6 straight chain, branched or cyclic alkyl group, with 2,4-dichlorophenylhydrazine to form an intermediate compound having a formula:



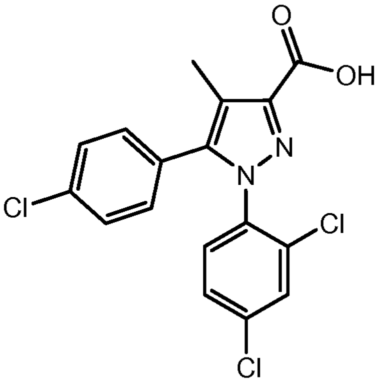
and, optionally without isolation of an intermediate compound,

b) further reacting with an acid to form a second intermediate compound having a formula:



and, optionally without isolation of a second intermediate compound,

c) reacting with a base to form a compound having a formula:



.

2. The process of claim 1, wherein M comprises sodium.

3. The process of either of claims 1 or 2, wherein R comprises an ethyl group.

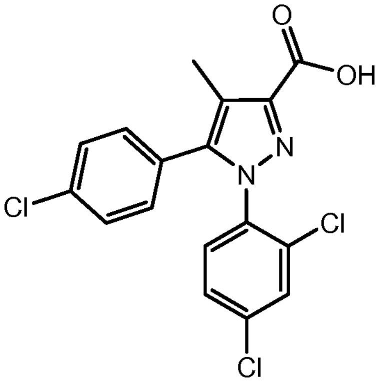
4. The process of any one of claims 1-3, wherein an intermediate compound is not isolated.

5. The process of any one of claims 1-3, wherein a second intermediate compound is not isolated.

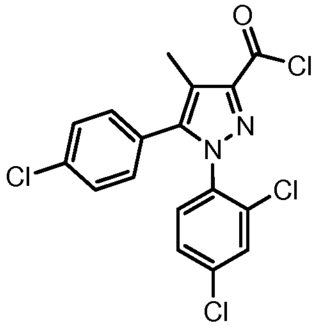
6. The process of any one of claims 1-3, wherein an intermediate compound and a second intermediate compound are not isolated.

7. The process of any one of claims 1-6, wherein an acid in b) comprises sulfuric acid.

8. The process of any one of claims 1-7, further comprising chlorinating a compound having a formula:

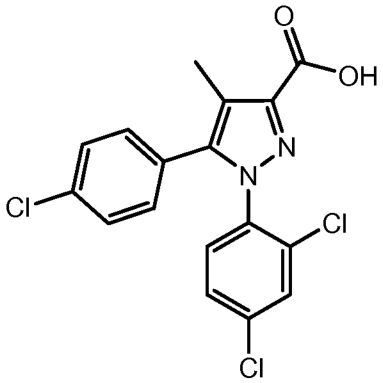


to form a compound having a formula:

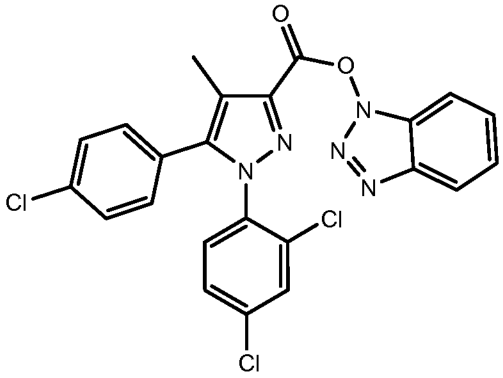


and then further reacting with 1-aminopiperidine.

9. The process of any one of claims 1-7, further comprising coupling a compound having a formula:

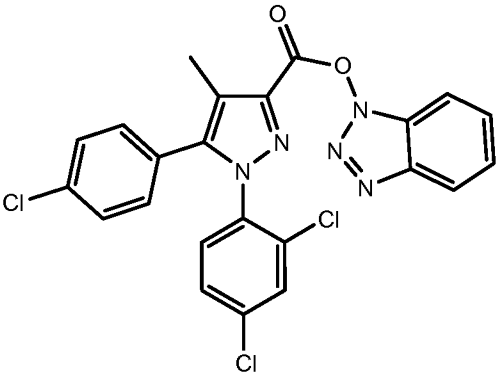


with 1-hydroxybenzotriazole, in the presence of dicyclohexylcarbodiimide, to form a compound having a formula:



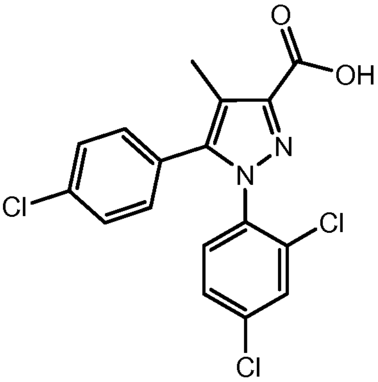
.

10. The process of claim 9, further comprising reacting a compound having a formula:



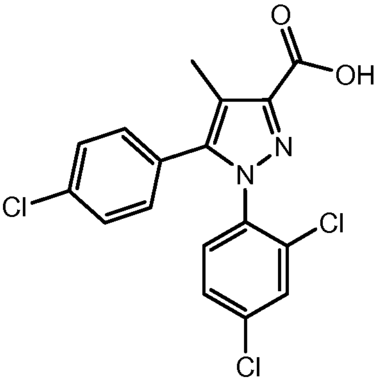
with 1-aminopiperidine.

11. The process of any one of claims 1-7, further comprising reacting a compound having a formula:



with boric acid, then further reacting with 1-aminopiperidine.

12. The process of any one of claims 1-7, further comprising coupling a compound having a formula:

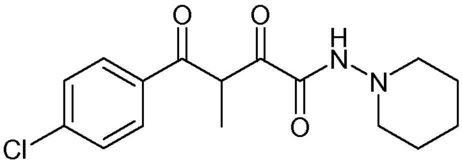


with 1-aminopiperidine, in the presence of a carbodiimide coupling agent or a dehydrating agent.

13. The process of claim 12, wherein a carbodiimide coupling agent is present with a catalytic auxiliary neucleophile.

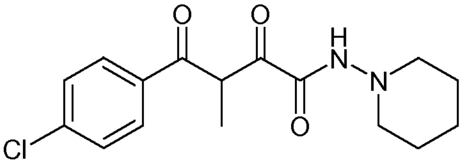
14. The process of claim 12, wherein a dehydrating agent comprises carbonyldiimidazole.

15. A process for preparing rimonabant, comprising reacting a compound having a formula:

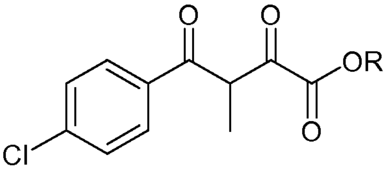


with a 2,4-dichlorophenylhydrazine salt.

16. The process of claim 15, wherein a compound having a formula:

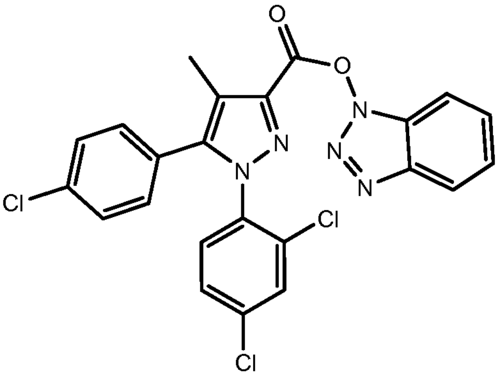


is prepared by reacting a compound having a formula:



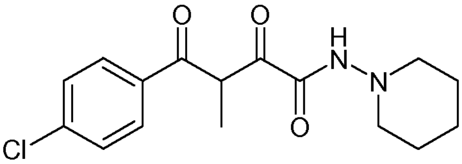
where R is C_1-C_6 straight chain, branched or cyclic alkyl group, with 1-aminopiperidine.

17. A compound having a formula:



.

18. A compound having a formula:



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19. A process for purifying rimonabant, comprising reacting rimonabant with an acid to form a salt, and reacting a salt with a base.

20. Rimonabant or a salt thereof having a purity at least about 99 percent by weight.

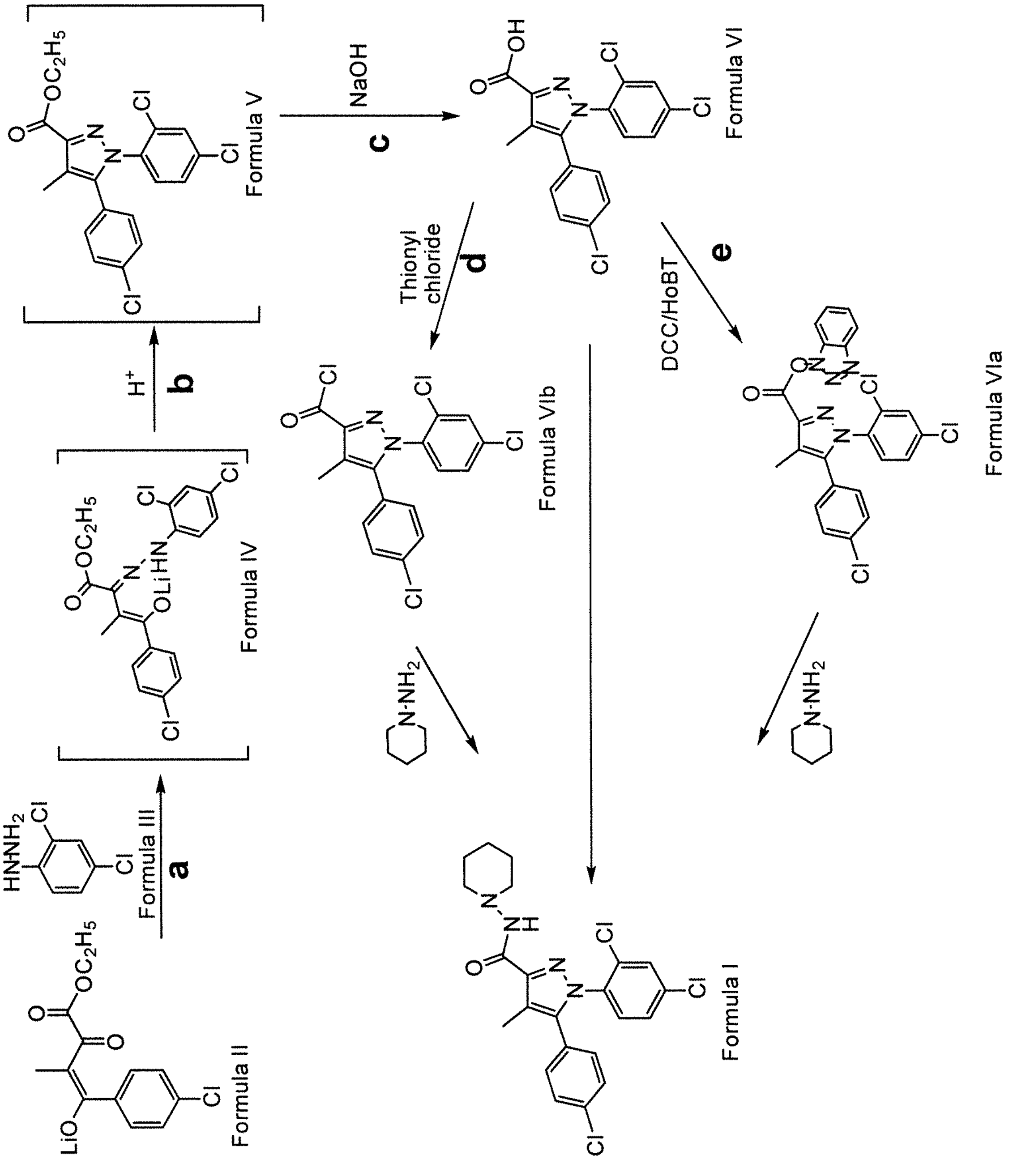
Formula II
LiO
OC$_2$H$_5$
HN·NH$_2$
Cl
Formula III
a
Formula IV
OLi HN
H$^+$
b
Formula V
NaOH
c
Formula VI
Thionyl chloride
d
Formula VIb
DCC/HoBT
e
Formula VIa
N·NH$_2$
Formula I
N
H

Fig. 1

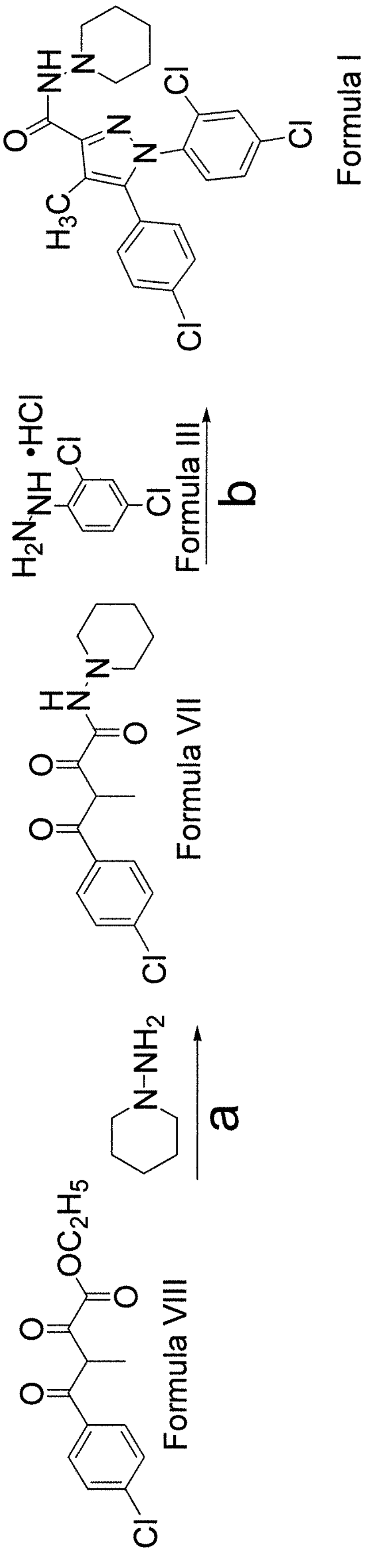

Fig. 2