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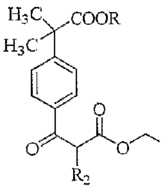
(54) **Title:** INTERMEDIATES USEFUL FOR THE PREPARATION OF ANTIHISTAMINIC PIPERIDINE DERIVATIVE



(I)

(57) **Abstract:** The present invention relates to process for preparing antihistaminic piperidine derivative, specifically fexofenadine and its pharmaceutically acceptable salts by using novel synthetic intermediates of following formula (I), *wherein R is lower alkyl; R_2 is H, cyclopropyl, $R_1$is alkyl, 4-(hydroxy-diphenyl-methyl)-piperidin-l-yl.*

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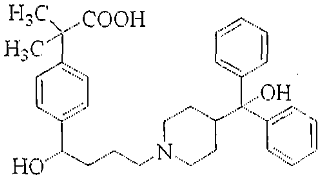
'INTERMEDIATES USEFUL FOR THE PREPARATION OF ANTIHISTAMINIC PIPERIDINE DERIVATIVE'

FIELD OF THE INVENTION

The present invention relates to process for preparing antihistaminic piperidine derivative, specifically fexofenadine. This invention also relates to novel synthetic intermediates useful in the preparation of antihistaminic piperidine derivative.

BACKGROUND OF THE INVENTION

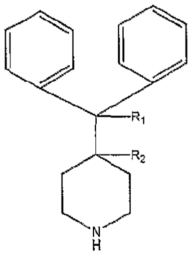
Fexofenadine, namely 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]1-hydroxybutyl]-α,α-dimethylbenzene acetic acid of formula-I is an H_1 receptor antagonist and a useful antihistamine drug.



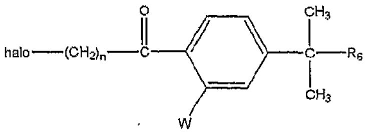
Formula I

It is a terfenadine carboxylic acid metabolite. Terfenadine has been linked to potentially fatal abnormal heart rhythms in some patients with liver disease or who also take the antifungal drug ketoconazole or the antibiotic erythromycin. In animal and human metabolic studies, terfenadine was shown to undergo high first-pass effect, which results in readily measurable plasma concentrations of the major metabolite 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]1-hydroxybutyl]-α,α-dimethylbenzene acetic acid, also known as terfenadine carboxylic acid metabolite. The terfenadine carboxylic acid metabolite also possesses anti-histaminic activity in animal models and may lack the cardiac side effects seen with terfinadine.

Piperidine derivatives were first disclosed in United States Patent No. 4,254,129. In this patent, methyl4-[4-[4-(hydroxy diphenyl methyl)-4-piperidinyl]-1-oxobutyl]-α,α -dimethyl phenyl acetate and related compounds are prepared by alkylation of a substituted piperidine derivative of formula:

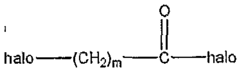


with a ω-haloalkyl substituted phenyl ketone of the formula:



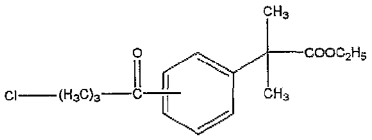
wherein the substituents halo, R_1, R_2, n, W and R_6 are described therein. The alkylation reaction is carried out in a suitable solvent, preferably in the presence of a base.

It is further described that the ω-haloalkyl substituted phenyl ketone wherein W is hydrogen can be prepared by reacting an appropriate straight or branched lower alkyl $C_{1\text{-}6}$ ester of α, α-dimethyl phenyl acetic acid with compound of following formula:



under the general condition of Friedel-crafts acylation, wherein halo and m are disclosed in United States Patent No. 4,254,129. The preferred solvent for the reaction is carbon disulfide.

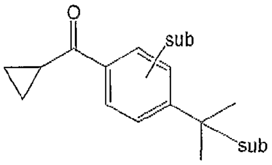
The above process produces a mixture of acylated regioisomers of the formula:



which are not separable by standard techniques of thin layer chromatography, or column chromatography. When the mixture of acylated regioisomers of the preceding formula is reacted with a piperidine, another mixture of aromatic regioisomers is obtained and thus the impurities continue till the end product i.e. fexofenadine wherein the monosubstituted meta, para mixture of regioisomers are obtained.

Various other synthetic routes to fexofenadine have been proposed in the literature. J. Org Chem 1994, 59, 2620-2622, (Kawai et al) proposes a route which requires attachment of a four carbon chain to a phenyl acetic acid moiety followed by coupling with the requisite piperidine ring. The method involves palladium catalysed coupling of a terminal alkyne and aromatic bromide followed by regioselective hydration using environmentally unfriendly mercury after piperidine coupling.

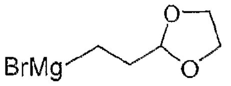
United States Patent No. 5,750,703 discloses a process which involves the reaction of azacyclonol with a cyclopropyl ketone derivative of general formula:



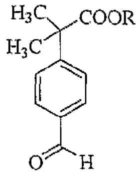
The process is, however, severely limited by the need to provide a substantially pure cyclopropyl regioisomer for reacting with azacyclonol. The cyclopropyl ketone derivative is prepared by the acylation of an aromatic ester derivative with an acid chloride in the presence of a Lewis acid catalyst. The resulting benzyl derivative comprises a mixture of regioisomers. After formation of a mixture of cyclopropyl ketone regioisomers, the desired para isomer is isolated laboriously by fractional crystallization of the corresponding cinchonidine salt. This process exhibits several disadvantages such as use of expensive cinchonidine, its toxicity, low yield.

United States Patent No. 6,147,216 provides an alternate technique to obtain enriched para regioisomer by high vacuum fractional distillation of methyl or ethyl ester of the mixture of isomeric acids followed by repeated fractional crystallization at low temperatures. This process is operationally tedious, inefficient; yields are low and therefore, are not amenable to industrial scale.

United States Patent No. 6,147,217 describes reaction of Grignard reagent 2-(2-bromomagnesium)-1,3-dioxolane of following formula



with alkyl ester intermediate of formula II

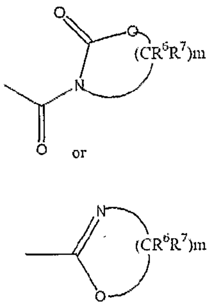


Formula II

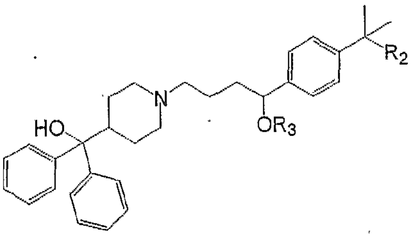
followed by reductive amination of the lactol to prepare fexofenadine and derivatives.

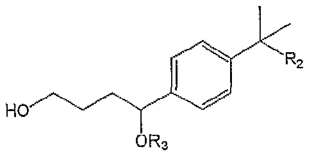
United States Patent No. 6,559,312 discloses the use of open chain and closed chain intermediates and reaction of the same with piperidine derivative to result in the preparation of Fexofenadine and analogues thereof. This process also suffers from a major drawback that the reaction conditions result in the formation of regioisomers that are difficult to resolve.

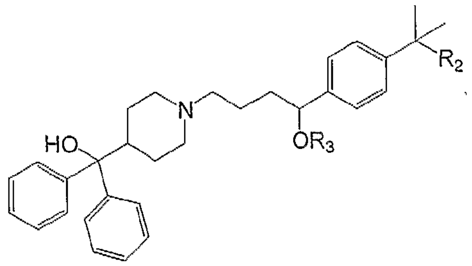
United States Patent No. 6,153,754 is a process patent which claims a process to prepare fexofenadine and its penultimate keto derivatives through ketocyclopropane intermediate, wherein phenyl ring is substituted with Z having following groups:



US Patent application 2003/0166682 discloses process for the preparation of fexofenadine involving novel intermediates having the following formulae:

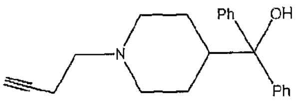






wherein the substituents are described in the specification comprising the use of silver nitrate and copper compounds. Silver nitrate is reported to cause toxicity to humans, including carcinogenicity, reproductive and developmental toxicity, neurotoxicity, and acute toxicity.

United States Patent No 6,815,549 claims for a compound of following formula



which is an intermediate for the preparation of fexofenadine.

PCT application WO 2004/043922 A1 discloses reaction of Grignard reagent (derived from 1-halo-3 -propanol and magnesium) with intermediate of formula II followed by azacyclonol coupling with mesylate derivative.

Several other processes for the preparation of fexofenadine and intermediates are disclosed in United States Patent Nos. 5,578,610, 5,589,487, 5,581,011, 5,663,412, 5,618,940, 5,562,370, 5,654,433, 5,663,353, 5,675,009, 5,375,693, 6,903,232.

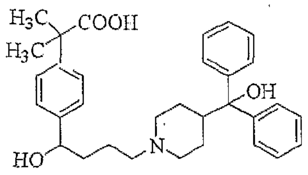
In view of the above, mainly two approaches have been followed for the preparation of fexofenadine and intermediates. First one involves acylation of the mono substituted benzene derivative (α,α-dimethylphenylacetic acid methyl ester) which results in mixture of meta and para isomers and hence lacks regioselectivity as disclosed in US patents 4,254,129,, 5,589,487, 5,581,011, 5,663,412, 5,750,703 etc. Second approach comprises Grignard reaction on 1,4-disubstituted benzene derivatives of formula II, thus incorporating regioselectivity from the beginning as described in US 6,147,217 and WO 2004/043922 A1.

There still remains the need to provide alternative methods for synthesizing fexofenadine and derivatives thereof which overcome the limitations of the prior art processes, e.g. in avoiding the use of unsafe chemicals and the need for laborious and time consuming regioisomeric separation techniques and recrystallization methods.

Thus, the present invention provides a process for the preparation of fexofenadine or its salts which exclusively affords para isomer, does not involve use of Grignard reagents, amenable to scale up and affords fexofenadine hydrochloride of high purity.

SUMMARY OF THE INVENTION

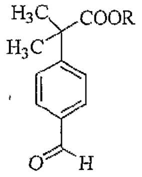
Accordingly, the present invention relates to the preparation of fexofenadine of formula I or its pharmaceutically acceptable salts,



Formula-I

which comprises,

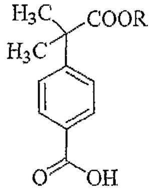
oxidizing 2-(4-formyl-phenyl)-2-methyl-propionic acid alkyl ester of formula II,



Formula-II

wherein R is lower alkyl

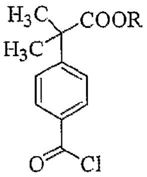
to prepare acid derivative of formula IIIa,



Formula-IIIa

wherein R is lower alkyl

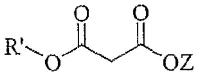
converting the resulting acid derivative to acid chloride of formula IIIb,



Formula-IIIb

wherein R is lower alkyl

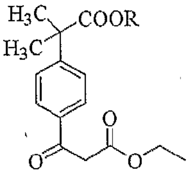
condensing the resulting acid chloride with keto ester of formula IV,



Formula-IV

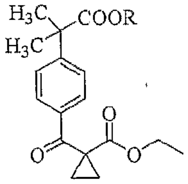
wherein R' is C_{1-6} *lower alkyl such as methyl, ethyl etc; Z is alkali or alkaline earth metal*

to prepare a β-keto ester derivative of formula V,



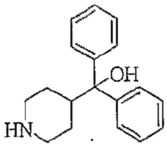
Formula-V

treating the resulting β-keto ester derivative with 1,2-dihaloethane in the presence of base and optionally in the presence of phase transfer catalyst to prepare a activated cyclopropane derivative of formula VI,



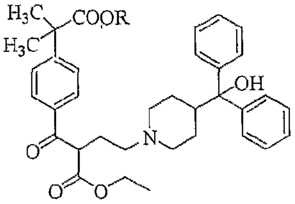
Formula-VI

condensing the resulting activated cyclopropane derivative of formula VI with piperidine derivative of formula VII,



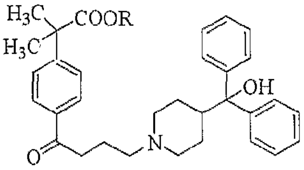
Formula-VII

to afford the α-carboethoxy derivative of formula VIII,



Formula-VIII

hydrolyzing the resulting α-carboethoxy derivative of formula VIII to prepare keto ester of formula IX.



Formula-IX

and converting keto ester of formula IX to fexofenadine or its salts by the conventional methods.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to processes for preparing certain piperidine derivatives, including fexofenadine and pharmaceutically acceptable salts.

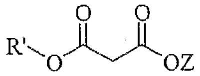
According to process, 2-(4-formyl-phenyl)-2-methyl-propionic acid alkyl ester of formula-II is oxidized suitably to afford compound of the formula IIIa.

The compounds of formula II and IIIa are commercially available and their preparations are well documented.

The oxidation of formyl group can be carried out by using suitable oxidizing agent such as chromic acid, $KMnO_4$, atmospheric O_2, silver oxide, H_2O_2, $tBuO_2H$, RuO4, HNO_3 and the like. Particularly the oxidation reaction is carried out using alkali chlorite such as sodium chlorite etc and preferably sodium chlorite is used in the presence of alkyl sulfoxides. The reaction is carried out in solvents such as dimethylsulfoxide, acetonitrile at a temperature ranging from 20°C to 60°C. After completion of reaction, to the reaction mass, aqueous sodium sulphite is added.

Thereafter solvent is distilled off completely and reaction mass is treated with bicarbonate. Optionally the reaction mixture is washed with solvent such as isopropyl ether, methyl tertiary butyl ether, methylene dichloride, toluene and the like. The desired acid derivative is precipitated by adding concentrated hydrochloric acid and isolated by filtration. The acid derivative is then converted to its chloride derivative of formula IIIb. The acid chloride formation is carried out using reagents like thionyl chloride, phosphorous trichloride, phosphorous oxychloride, phosphorous pentachloride and the like. Acid chloride formation is carried out with or without solvent at reflux temperature. After completion of reaction solvent is distilled off completely under vacuum to remove traces of reagent.

Compound of the formula IIIb is further reacted with suitable reagent like metal alkylmalonate of formula-IV,



Formula-IV

wherein R' is C_{1-6} lower alkyl such as methyl, ethyl etc; Z is alkali or alkaline earth metal

in a suitable solvent to afford β-keto ester derivative of the formula V, namely 2-[4-(2-ethoxycarbonyl-acetyl)-phenyl]-2-methyl-propionic acid alkyl ester.

The reaction is carried out using solvent which can be selected from hydrocarbon such as toluene and the like, chlorinated hydrocarbon such as methylene chloride and the like,. ethers such as isopropyl ether and the like, acetate such as ethyl acetate and the like, and preferably ethyl acetate, in the presence of base like pyridine, trialkylamine and preferably triethylamine in the presence of magnesium chloride. The reaction is conducted at -40°C to ambient temperature. After completion of reaction, the reaction mixture is quenched with dilute hydrochloric acid and compound is extracted in suitable solvent like toluene.

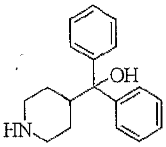
β-Keto ester derivative of formula V, is novel and is another object of the invention, is then treated with 1,2-dihaloethane in the presence of base optionally using phase transfer catalyst to afford activated cyclopropane derivative of the formula VI, namely, 1-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-cyclopropane carboxylic acid ethyl ester.

Further object of the present invention is the preparation of activated cyclopropane derivative of formula VI, which is an important intermediate in the preparation of fexofenadine.

The base can consist of carbonates of alkali metal such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate etc.

The phase transfer catalyst comprises arylalkylammonium halide, tetraalkyl ammonium halide, phosphonium salts and preferably benzyltriethylammonium chloride is used. The reaction is carried out in any solvent like hydrocarbons such as benzene, toluene, xylene; chlorinated hydrocarbon such as methylene chloride and the like; acetates such as ethyl acetate; ethers such as dioxane, tetrahydrofuran; acetonitrile, dimethylacetamide, dimethylformamide, n-methylpyrrolidine, dimethylsulfoxide and the like, at a temperature ranging from ambient temperature to 80°C. The progress of the reaction is monitored by high performance liquid chromatography. After completion of reaction the solvent is distilled off under vacuum. To the reaction mass another solvent is added which can be selected from toluene, ethylacetate, isopropylether, methyl tertiarybutyl ether, diethylether, cyclohexane, methylene chloride and the like. The reaction mixture is filtered to remove inorganic salts. Solvent is distilled to isolate cyclopropane derivative of formula VI. The crude product can be purified by treating with an amine. The amine can consist of dialkylamine, cyclic secondary amine, monoalkylpiperazine and the like such as morpholine, piperidine, pyrrolidine.

Activated cyclopropane derivative of formula VI is condensed with piperidine derivative (azacyclonol) of formula-VII,

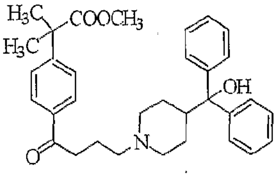


Formula-VII

under suitable reaction conditions to prepare α-carboethoxy derivative of formula-VIII, 4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-2-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-butyric acid ethyl ester. The reaction is conducted at 40-90°C and preferably at 55-70°C and it takes 20-60 hours for completion of reaction. The solvent used in the reaction consists of dimethylformamide, dimethylacetamide, n-methylpyrrolidine, methylisobutyl ketone, acetonitrile, acetone, methyl ethyl ketone, dimethylsulfoxide and the like. After completion of condensation, the solvent is distilled off and to the residue another solvent is added in which azacyclonol is not soluble. The solvent can be isopropyl ether, methyltertiarybutyl ether, diethylether, xylene, ethylbenzene, toluene and the like.

The crude product can be purified by preparing acid addition salts. The acid can be any suitable acid such as citric acid, fumaric acid, maleic acid, pthalic acid, isopthalic acid, p-terepthalic acid, oxalic acid and the like.

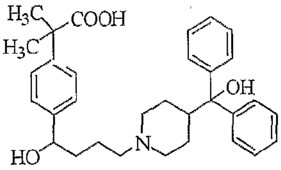
The α-carboethoxy derivative of formula VIII is novel, and is another object of the invention, is further hydrolyzed under suitable reaction conditions to afford keto ester of the formula IX, 2-(4-{4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyryl}-phenyl) -2-methyl-propionic acid methyl ester.



Formula-IX

The hydrolysis is carried out using base in alcoholic solvent. The base can be selected from metal carbonates such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate etc. The product obtained can be purified using alcoholic solvent, aqueous alcoholic solvent and the like, optionally an anti solvent can also be used which can be selected from n-alkanes, toluene, ethyl benzene, xylene, ethers such as isopropyl ether and methyl tert-butyl ether and the like.

The keto ester of the formula IX can be converted into fexofenadine of formula-I,



Formula- I

and pharmaceutically acceptable salts thereof by the methods known in prior art. Generally keto ester of the formula IX is reduced first with the help of reducing agent such as sodium borohydride and thereafter hydroxyl ester is hydrolyzed to fexofenadine *in situ* or optionally by isolating the corresponding hydroxyl ester intermediate. Alternatively, keto ester of the formula IX can be hydrolyzed first and thereafter keto group is reduced to hydroxyl to form fexofenadine which is converted to fexofenadine salts such as hydrochloride having purity greater than 99.5%. Major advantages realized in the present invention is that process provides exclusively para isomer thus no need of extensive purification and affords fexofenadine hydrochloride in high purity.

The present invention will now be illustrated by the following examples, which are not intended to limit the effective scope of the claims. Consequently, any variations of the invention described above are not to be regarded as departure from the spirit and scope of the invention as claimed. The present invention has been described in terms of its specific embodiments and various modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of present invention.

EXAMPLES

Preparation of 4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoic acid (formula IIIa)

To a stirred solution of 2-(4-formyl-phenyl)-2-methyl-propionic acid methyl ester of the formula II (48g, 233 mmol) in acetonitrile (120 ml), dimethylsulfoxide (20ml, 1.2 mole equivalent) and water (40 ml) were added. Thereafter a solution of sodium chlorite (42.1g, 466 mmol) in water (202 ml) was added slowly at 25 – 40°C and reaction mixture was stirred for 1 hour. After completion of reaction (absence of starting material) aqueous sodium sulphite (20g in 48 ml of water) was added to the reaction mixture. Solvent was distilled off under vacuum. To the residue saturated aqueous solution of sodium bicarbonate (250 ml) was added and stirred for 10 minutes. The aqueous solution was washed with toluene (200 ml x3) and treated with concentrated hydrochloric acid (100ml) at 5 – 10°C. The solid, which precipitated out was filtered, washed with water and dried to afford 44.4g of title compound having purity 98.8% by HPLC.

Preparation of (2-[4-(2-ethoxycarbonyl-acetyl)-phenyl]-2-methyl-propionic acid methyl ester) of the formula (V)

To a stirred suspension of potassium ethyl malonate (15g, 88mmol) in ethylacetate (135 ml), triethylamine (30.1ml, 221 mmol) and anhydrous magnesium chloride (10g, 105 mmol) were added at 0°C and thereafter the reaction mass was stirred at 35°C for 6.5 hours. The reaction mixture was chilled to -15°C and to this 2-(4-chlorocarbonyl-phenyl)-2-methyl-propionic acid methyl ester (15g, 62.4 mmol) in ethyl acetate (15 ml) was added and was stirred at room temperature for 14 hours. To the reaction mixture dilute hydrochloric acid (180 ml) was added at 0°C and the reaction mass was extracted with toluene (20 ml x 3). The combined toluene extracts were washed with hydrochloric acid (45ml x 2) followed by water (15ml x2), dried over anhydrous Na_2SO_4 and concentrated to obtain 19g of the title compound having purity 97.5% by HPLC.

Preparation of 1-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-cyclopropane carboxylic acid ethyl ester (VI)

To the stirred solution of 2-[4-(2-ethoxycarbonyl-acetyl)-phenyl]-2-methyl-propionic acid methyl ester of the formula V (216g, 739 moles) in dry dimethylsulphoxide (864 ml), 1,2 dibromoethane (208.2g, 1.1082 moles), anhydrous potassium carbonate (255.3g, 1.847 moles), and benzyltriethylammonium chloride (8.41g, 37 mmols) were added at ambient temperature. The reaction mixture was then heated at 50-60°C for five hours. After completion of reaction (absence of starting β-ketoester monitored by HPLC), the reaction mixture was cooled to 20 - 25 °C and filtered. Dimethylsulphoxide was distilled off under vaccum and to the residue methylene chloride (100ml) was added and product was refiltered to remove potassium carbonate. Methylene chloride was distilled off to afford the title compound.

Purification of 1-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-cyclopropane carboxylic acid ethyl ester (VI)

To the crude of the formula VI (235g, 739mmols) as obtained above, was added dimethylsulphoxide (470 ml), morpholine (22.5g, 259 mmols), potassium iodide (6.13g, 37 mmols), benzyltriethylammonium chloride (8.41g, 37 mmols) and heated to 40 – 50°C with stirring for 5 hours. Dimethylsulphoxide was distilled off under vacuum and residue was dissolved in toluene (200 ml). The solution was washed with saturated brine (100 ml) dimineralized water (75ml), 1% hydrochloric acid (100ml) followed by dimineralized water (50 ml x1). The toluene layer was dried over anhydrous sodium sulphate and concentrated to obtain 172g of pure compound.

Preparation of 4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-2-[4-(1-methoxy carbonyl-1-methyl-ethyl)-benzoyl]-butyric acid ethyl ester (formula VIII)

To a solution of 1-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-cyclopropane carboxylic acid ethyl ester (100g, 314.5 mmol) of formula VI in dimethylsulfoxide (600 ml) was added azacyclonol (84g, 314.5 mmol) and heated to 60-65°C for 55 hours under nitrogen atmosphere. Dimethylsulfoxide was distilled off under reduced pressure. To the concentrate, toluene (1 lit) was added and stirred 10 minutes. The precipitated azacyclonol was filtered off. The toluene solution was washed with brine solution (250 ml) followed by dimineralized water (250 ml), dried over anhydrous sodium sulphate and concentrated to afford 184.5 gm of tile compound.

Purification of 4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-2-[4-(1-methoxy carbonyl-1-methyl-ethyl)-benzoyl]-butyric acid ethyl ester (formula VIII)

The above crude compound (184.5 g) was taken in ethylacetate (185 ml) and a solution of oxalic acid dihydrate (40 g, 314.5 m mol) in ethylacetate (740 ml) was added at ambient temperature. The reaction mixture was stirred for 3 hours and the precipitated salt was filtered and washed with ethylacetate and dried. To the salt, toluene (700 ml) and aqueous sodium carbonate (20%, 514 ml) were added and stirred for 3 hrs at ambient temperature. The two phase mixture was filtered to remove the insoluble particles. Toluene layer was separated and the aqueous layer was extracted with toluene (200 ml x 2). The combined organic layer was washed with water (150 ml x 2) and concentrated to afford pure 4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-2-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-butyric acid ethyl ester having purity 96% by HPLC.

Preparation of 2-(4-{4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyryl}-phenyl) -2-methyl-propionic acid methyl ester (formula IX)

To a stirred solution of 4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-2-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-butyric acid ethyl ester (30 g, 51.22 mmol) in methanol (120 ml) was added a solution of potassium carbonate (17.7 g, 128 mmol) in water (30 ml) at 28-32°C. The reaction mixture was stirred at 28-32°C for 10 hours and then at 35-40°C for 6 hours. The reaction mixture was cooled to ambient temperature and water (60 ml) was added. The precipitated product was filtered, washed with aqueous methanol (35 ml) and dried to obtain 21.6g of 2-(4-{4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyryl}-phenyl)-2-methyl-propionic acid methyl ester. The product is purified using isobutanol.

Preparation of 2-(4-{1-hydroxy-4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyl}-phenyl)-2-methyl-propionic acid methyl ester (formula X)

To a stirred solution of 2-(4-{4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyryl}-phenyl)-2-methyl-propionic acid methyl ester (10 g, 19.47 mmol) of the formula IX in methanol (30 ml) at 0°C was added sodium borohydride (0.38 g, 10 mmol) in portions and stirred at 30-35°C for 1 hour. The completion of reaction was checked by HPLC (starting should be NMT 1%). Acetic acid (0.31 g) was added at 30-35°C and the reaction mixture was heated to 50-55°C for 30 minutes. Demineralized water (20 ml) was added slowly at 50-55°C and stirred for 30 minutes. The reaction mixture was cooled and stirred. The product obtained was filtered, washed with demineralized water and dried at 50-55°C for 6-8 hours to obtain 9.0 g of 2-(4-{1-hydroxy-4-[4-(hydroxyl -diphenyl-methyl)-piperidin-1-yl]-butyl}-phenyl)-2-methyl-propionic acid methyl ester.

Preparation of 2-(4-{1-hydroxy-4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyl}-phenyl)-2-methyl-propionic acid (fexofenadine)

To a stirred solution of sodium hydroxide (1.24 g, 31 mmols) in denatured spirit (30 ml) was added 2-(4-{1-hydroxy-4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyl}-phenyl)-2-methyl-propionic acid methyl ester (10 g, 19.4 mmols) at 30°C. The reaction mixture was heated to reflux for 3 hrs. HPLC was checked (starting material should be absent). After completion of reactions, ethanol was distilled off completely under vacuum and water 50 ml was added to make a clear solution. The resulting solution was washed with methyl tertiary butyl ether (20 ml x 4) and methylene dichloride. The aqueous solution was cooled to 0-5°C and the pH was adjusted to 6.0 – 6.5 with hydrochloric acid. The precipitated solid was filtered and dried at 50-55°C to afford 8.5 g of fexofenadine having purity 99.4% by HPLC.

Preparation of 4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoic acid (formula IIIa)

To a stirred solution of 2-(4-formyl-phenyl)-2-methyl-propionic acid methyl ester of the formula II (4.5 kg) in acetonitrile (11.25 litres) was added dimethylsulfoxide (2.05 kg) and water (3.7 lit). A solution of sodium chlorite (3.95kg) in water (18.9 lit) was added slowly at 25 – 40°C and reaction mixture was stirred for 1 hour. After completion of reaction (absence of starting material) aqueous sodium sulphite (1.87 kg in 4.5 lit of water) was added to the reaction mixture. Solvent was distilled off under vacuum. To the residue saturated aqueous solution of sodium bicarbonate (5.6 kg in 19 lit of water) was added and stirred for 30 minutes. The aqueous solution was washed with toluene (18 lit x3) and treated with hydrochloric acid (6.0 lit) at 5 – 10°C. The solid, which precipitated out was filtered, washed with water and dried to afford 3.58 kg of title compound.

Preparation of 2-(4-chlorocarbonyl-phenyl)-2-methyl-propionic acid methyl ester (formula IIIb)

To a stirred suspension of 4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoic acid (1.0 kg) of the formula IIIa in toluene (5 lit), thionyl chloride (0.492 lit) was added and reaction mass was stirred at 25°C for 1 hour followed by refluxing for 4 hours. Solvent was distilled off completely under reduced pressure to afford 1.08 kg of title compound.

Preparation of 2-[4-(2-ethoxycarbonyl-acetyl)-phenyl]-2-methyl-propionic acid methyl ester (formula V)

To a stirred suspension of potassium ethyl malonate (1.0 kg,) in ethylacetate (9.0 lit) was added triethylamine (2.05 lit) and anhydrous magnesium chloride (0.672 kg) at 0°C and thereafter the reaction mass was stirred at 30°C for 6.5 hours. The reaction mixture was cooled to -35°C and to this 2-(4-chlorocarbonyl-phenyl)-2-methyl-propionic acid methyl ester (1.083 kg) was added. Thereafter temperature was raised and reaction mixture was stirred at room temperature for 14 hours. To the reaction mixture dilute hydrochloric acid (12 litres) was added at 0°C and the reaction mass was extracted with toluene (1 lit x 3). The combined toluene extracts were washed with dilute hydrochloric acid (3.0 lit x 2) followed by water, dried over anhydrous sodium sulphate and concentrated to obtain 1.315 kg of the title compound.

Preparation of 1-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-cyclopropane carboxylic acid ethyl ester (VI)

To the stirred solution of (2-[4-(2-ethoxycarbonyl-acetyl)-phenyl]-2-methyl-propionic acid methyl ester) of the formula V (395g) in dry dimethylsulphoxide (1580 ml) were added 1,2 dibromoethane (381.2g), anhydrous potassium carbonate (467.4g), and benzyltriethylammonium chloride (15.4g) at ambient temperature. The reaction mixture was then stirred at 50-60°C for five hours. After completion of reaction (absence of starting β-ketoester by HPLC) the reaction mixture was cooled to 20 - 25 °C and filtered. Dimethylsulphoxide was distilled off under vacuum and to the residue methylene chloride (100ml) was added and product was filtered to remove potassium carbonate. Methylene chloride was distilled off to afford 430 g of 1-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-cyclopropane carboxylic acid ethyl ester.

Purification of 1-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-cyclopropane carboxylic acid ethyl ester (VI)

To the crude compound of the formula VI (430.1g,) was added dimethylsulphoxide (860 ml), morpholine (41.24g), potassium iodide (11.2g), benzyltriethylammonium chloride (15.4g,) and heated to 40 – 50°C with stirring for 5 hours. Dimethylsulphoxide was distilled off under vacuum and residue was dissolved in toluene (300 ml). The solution was washed with saturated brine (100 ml) dimineralized water (100ml x 2), 1% hydrochloric acid (100ml) followed by dimineralized water (100 ml x1). The toluene layer was dried over anhydrous sodium sulphate and concentrated to obtain 350g of pure 1-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-cyclopropane carboxylic acid ethyl ester.

Preparation of 4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-2-[4-(1-methoxy carbonyl-1-methyl-ethyl)-benzoyl]-butyric acid ethyl ester (formula VIII)

To a solution of 1-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-cyclopropane carboxylic acid ethyl ester (350g) of formula VI in dimethylsulfoxide (2.1 lit) was added azacyclonol (294g) and heated to 60-65°C for 48 hours under nitrogen atmosphere. Dimethylsulfoxide was distilled off under reduced pressure and to the concentrate toluene (400 ml) was added and stirred 10 minutes. The precipitated azacyclonol was filtered off. The toluene solution was washed with

20% brine (100 ml x 1) followed by dimineralized water (100 ml x 1), dried over anhydrous sodium sulphate and concentrated to afford 640g of 4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-2-[4-(1-methoxy carbonyl-1-methyl-ethyl)-benzoyl]-butyric acid ethyl ester.

Purification:

The above crude (640 g) was taken in ethylacetate (2.0 lit) and a solution of oxalic acid dihydrate (151.7g) in ethylacetate (1.2 lit) was added at ambient temperature. The reaction mixture was stirred for 3 hours and the precipitated salt was filtered and washed with ethylacetate (100ml) and dried. To the salt, toluene (600 ml) and aqueous sodium carbonate (300 ml) were added and stirred for 3 hrs at ambient temperature. The two phase mixture was filtered to remove the insoluble particles. Toluene layer was separated and the aqueous layer was extracted with toluene (200 ml x 2). The combined organic layer was washed with dimineralized water (150 ml x 2) and concentrated to afford 340 g of pure 4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-2-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-butyric acid ethyl ester.

Preparation of 2-(4-{4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyryl}-phenyl) -2-methyl-propionic acid methyl ester (formula IX)

To a stirred solution of 4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-2-[4-(1-methoxycarbonyl-1-methyl-ethyl)-benzoyl]-butyric acid ethyl ester (340g) in methanol (1.36 lit) was added a solution of potassium carbonate (200.5g) in dimineralized water (340 ml). The reaction mixture was stirred at ambient temperature for 20 hours and then at 35-40°C for 6 hours. The reaction mixture was cooled to ambient temperature and dimineralized water (680 ml) was added. The precipitated product was filtered, washed with aqueous methanol (350 ml x 1) and dried to obtain 265g of title compound. The crude product was purified aqueous methanol.

Preparation of 2-(4-{1-hydroxy-4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyl}-phenyl)-2-methyl-propionic acid (Fexofenadine)

To a stirred solution of 2-(4-{4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyryl}-phenyl)-2-methyl-propionic acid methyl ester (165 g) of the formula IX in methanol (1650 ml), sodium borohydride (12.15 g) was added at room temperature and reaction mixture was stirred at 30-

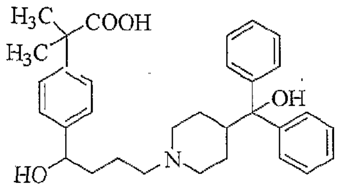
35°C for 1 hour. The temperature was further raised to 65-70°C and reaction mass was stirred for one hour. The solvent was distilled off and to the residue methanol (660 ml) and sodium hydroxide (25.7g) were added at 50-55°C and further heated at 70-75°C till less then 0.5% of fexofenadine methyl ester in HPLC. The reaction mixture was cooled to 50-55°C and pH was adjusted to 6.5-7.0 using hydrochloric acid. The reaction mixture was cooled to 0-5°C, stirred for 1.5 hours, filtered, washed with water and dried at 50-55°C for 6-8 hours to afford 155 g of fexofenadine. The product is purified using ethanol to obtain 152 g of pure fexofenadine.

Preparation of 2-(4-{1-hydroxy-4-[4-(hydroxy-diphenyl-methyl)-piperidin-1-yl]-butyl}-phenyl)-2- methyl- propionic acid hydrochloride (Fexofenadine hydrochloride)

To a cooled mixture of fexofenadine (150g) and isopropanol (450 ml) was added isopropanol hydrogen chloride at 5-10°C till pH was adjusted to 3.0 – 3.5 and was stirred for further 30 minutes. The reaction mass was charcolised and after filtering the carbon, isopropanol was distilled off and fresh isopropanol (75 ml) was added and reaction mass was heated to 40-45°C. To this ethyl acetate (750ml) was added and stirred at 40-45°C. The reaction mass was cooled to ambient temperature, filtered, washed with ethyl acetate and dried to afford 149 g of fexofenadine hydrochloride having purity 99.59% by HPLC.

CLAIMS:

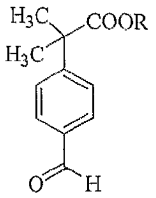
1. A process for the preparation of fexofenadine of formula I or its pharmaceutically acceptable salts,



Formula-I

which comprises,

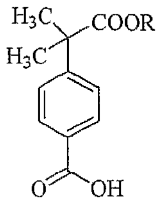
a) oxidizing 2-(4-formyl-phenyl)-2-methyl-propionic acid alkyl ester of formula II,



Formula-II

wherein R is lower alkyl

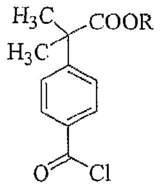
to prepare acid derivative of formula IIIa



Formula-IIIa

wherein R is lower alkyl

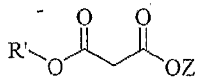
b) converting the resulting acid derivative to acid chloride of formula IIIb,



Formula-IIIb

wherein R is lower alkyl

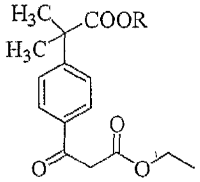
c) condensing the resulting acid chloride with keto ester of formula IV,



Formula-IV

wherein R' is lower alkyl, Z is alkali or alkaline earth metal

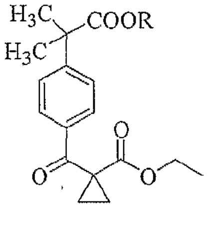
to prepare a β-keto ester derivative of formula V,



Formula-V

wherein R is lower alkyl

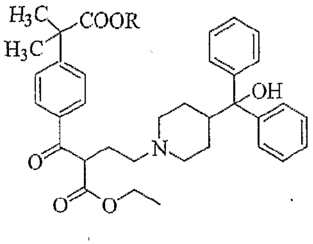
d) treating the resulting β-keto ester derivative with 1,2-dihaloethane in the presence of base and optionally in the presence of phase transfer catalyst to prepare activated cyclopropane derivative of formula VI,



Formula-VI

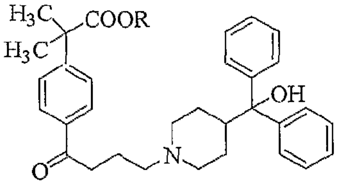
wherein R is lower alkyl

e) condensing the resulting activated cyclopropane derivative of formula VI with piperidine derivative (azacyclonol) of formula VII to afford the α-carboethoxy derivative of formula VIII,



Formula-VIII

f) hydrolyzing the resulting α-carboethoxy derivative of formula VIII to prepare keto ester of formula IX,



Formula-IX

g) converting keto ester of formula IX to fexofenadine or its salts by the conventional methods.

2. The process according to claim 1, wherein oxidation in step a is carried out using aqueous alkali chlorite such as sodium chlorite.

3. The process according to claim 1, wherein acid chloride in step b is prepared by using thionyl chloride, phosphorous trichloride, phosphorous oxychloride, phosphorous pentachloride.

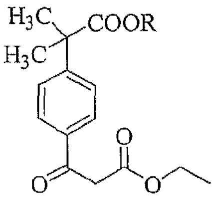
4. The process according to claim 1, wherein condensation in step c is carried out using base such as pyridine, trialkylamine, in the presence of magnesium chloride in solvent such as toluene, methylene chloride, isopropyl ether and ethyl acetate.

5. The process according to claim 1, wherein reaction in step d base is selected from alkali metal carbonates.

6. The process according to claim 1, wherein condensation reaction in step e is carried out at 40-90°C.

7. The process according to claim 1, wherein hydrolysis in step f is carried out using base which is selected from alkali metal carbonates.

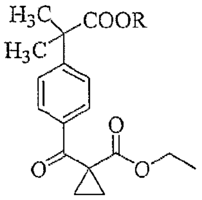
8. A β-keto ester derivative of formula V,



Formula-V

wherein R is lower alkyl

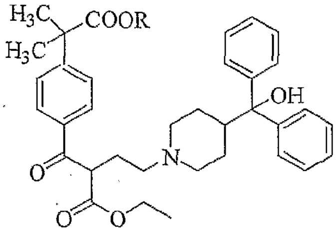
9. A compound of formula VI,



Formula-VI

wherein R is lower alkyl

10. A α-carboethoxy derivative of formula VIII and its acid addition salts,



Formula-VIII

wherein R is lower alkyl