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(54) Title: IMPROVED PROCESS FOR MANUFACTURING ANHYDROUS (E)-3-[2-BUTYL-1- {(4-CARBOXYPHENYL) METHYL}-1H-IMIDAZOLE-5-YL]-(THIOPHEN-2- YLMETHYL)PROP-2-ENOIC ACID METHANE SULFONATE

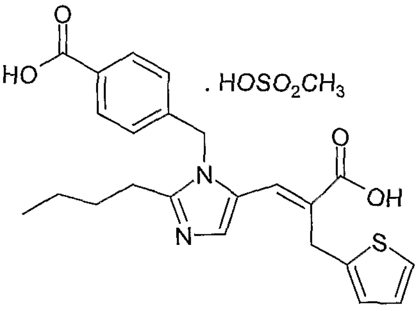
(57) Abstract: The present invention relates to a simple efficient and cost effective process for commercial manufacture of (E)-3-[2-Butyl-1-{(4-carboxyphenyl) methyl}-1H-imidazole-5-yl]- 2-(thiophen-2-ylmethyl)prop-2-enoic acid and its conversion to substantially pure anhydrous mesylate salt as shown in Formula (I), with a purity level of 99.85% and single individual impurity of less than 0.10 %.

WO 2009/084028 A2

IMPROVED PROCESS FOR MANUFACTURING ANHYDROUS (E)-3-[2-BUTYL-1-{(4-CARBOXYPHENYL) METHYL}-1H-IMIDAZOLE-5-YL]-2-(THIOPHEN-2-YLMETHYL)PROP-2-ENOIC ACID METHANE SULFONATE

FIELD OF THE INVENTION

The present invention relates to a simple, efficient and cost effective process for commercial manufacture of (E)-3-[2-Butyl-1-{(4-carboxyphenyl) methyl}-1H-imidazole-5-yl]-2-(thiophen-2-ylmethyl)prop-2-enoic acid and its conversion to substantially pure anhydrous mesylate salt as shown in Formula I, with a purity level of 99.85% and single individual impurity of less than 0.10 %. This compound is known to be angiotensin II receptor antagonist and is useful in regulating hypertension induced by angiotensin II and in the treatment of congestive heart failure, renal failure and glaucoma.

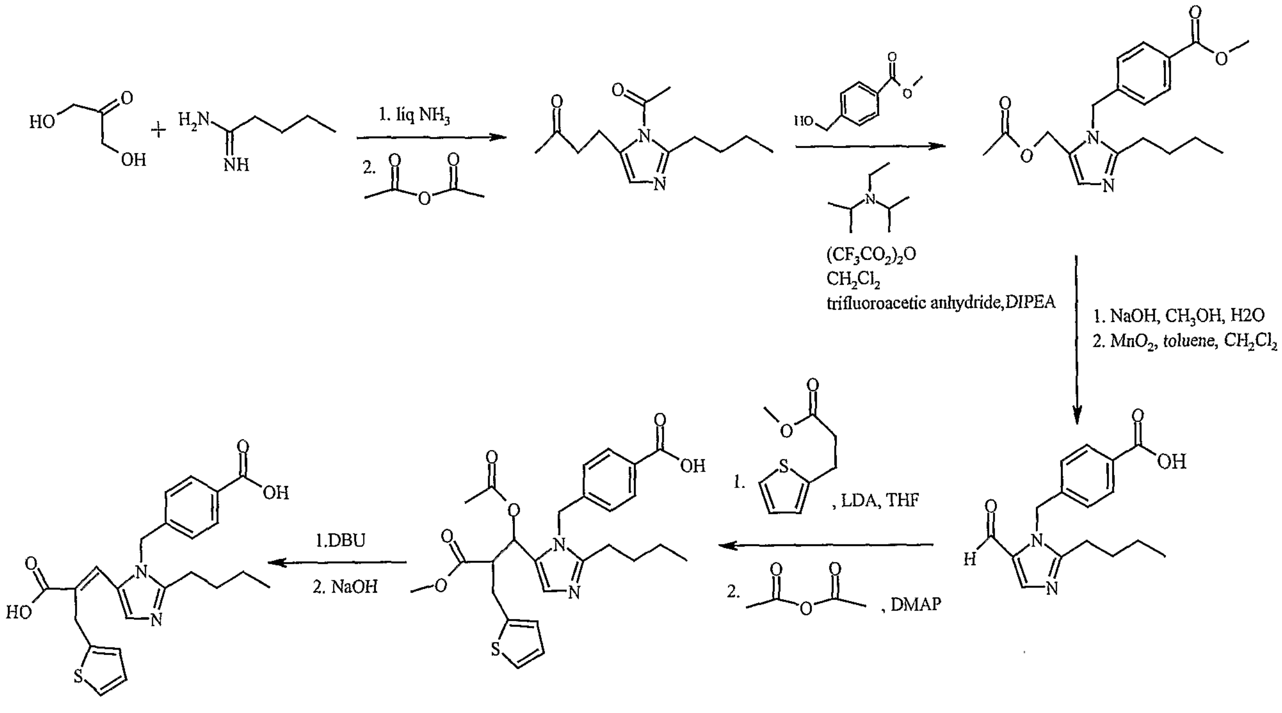


Formula I

BACKGROUND OF THE INVENTION

U.S.Pat. No. 5185351 describes the process for preparation of imidazole compounds, particularly the preparation of Eprosartan. The process comprises condensation of valerimidine methyl ester with dihydroxyacetone to give a diacetate which was treated with 4-carboxymethylbenzyl alcohol in the presence of triflic acid to give 2n-butyl-5-acetoxymethyl-1-(4-carboxyphenyl)-methyl-1H-imidazole. Thus obtained compound on further oxidization with manganese dioxide and thereafter condensation with methyl-3-(3-(2-theinyl)-propionate in the presence of n-butyl lithium at -78°C gives an ester which is hydrolysis gives Eprosartan. Eprosartan is further converted to its desired salt form. The form of the product obtained here is anhydrous in nature. The process can be best represented by Scheme I shown below;

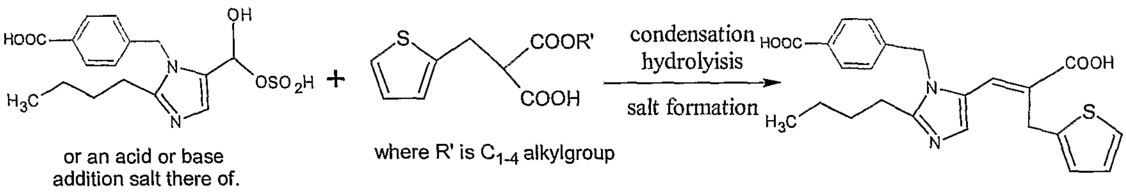
Scheme I



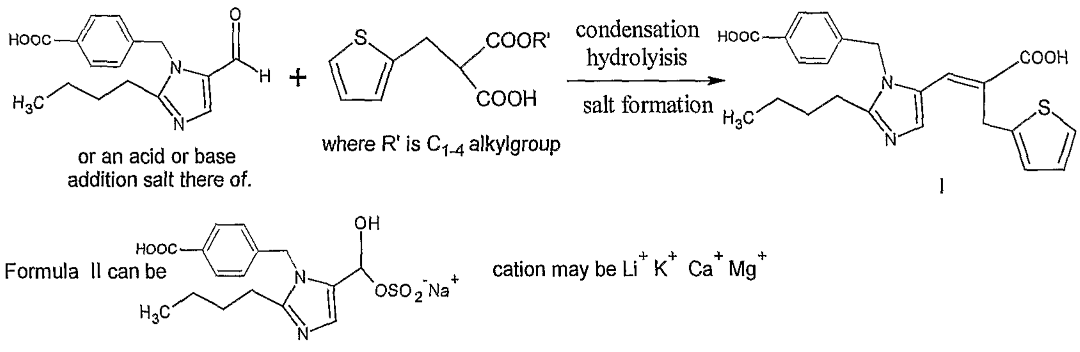
Although the process described here could be used for the preparation of Eprosartan , it has a few drawbacks when used on a commercial manufacturing scale, which are, the use of hazardous reagents such as n-butyl lithium, DBU and triflic acid which are not suitable to use at manufacturing scale because of their high cost and safety reasons. The temperature of the reaction has to be maintained at -78°C which is difficult to achieve and maintain all the time at manufacturing scale. Moreover, the overall yields are also very low about 40%.

US6172237 (EP0970073) discloses the condensation of 4-[(2-Butyl-5-formyl-1H-imidazol-1-yl)methyl]benzoic acid or the bisulfite addition compound of 4-[(2-Butyl-5-formyl-1-yl-imidazol-1-yl)methyl]benzoic acid and 2-(Thienylmethyl)propanedioic acid (Scheme II) or 2-(Thienylmethyl)propanedioic acid monoethyl ester (Scheme III) at reflux temperature in toluene under reduced pressure 9-13 inches Hg in presence of piperidine as a catalyst followed by hydrolysis of the intermediate ethyl ester to give Eprosartan which is further converted to its desired salt form, best represented by Scheme II shown below, the form of the product obtained here is anhydrous form;

Scheme II



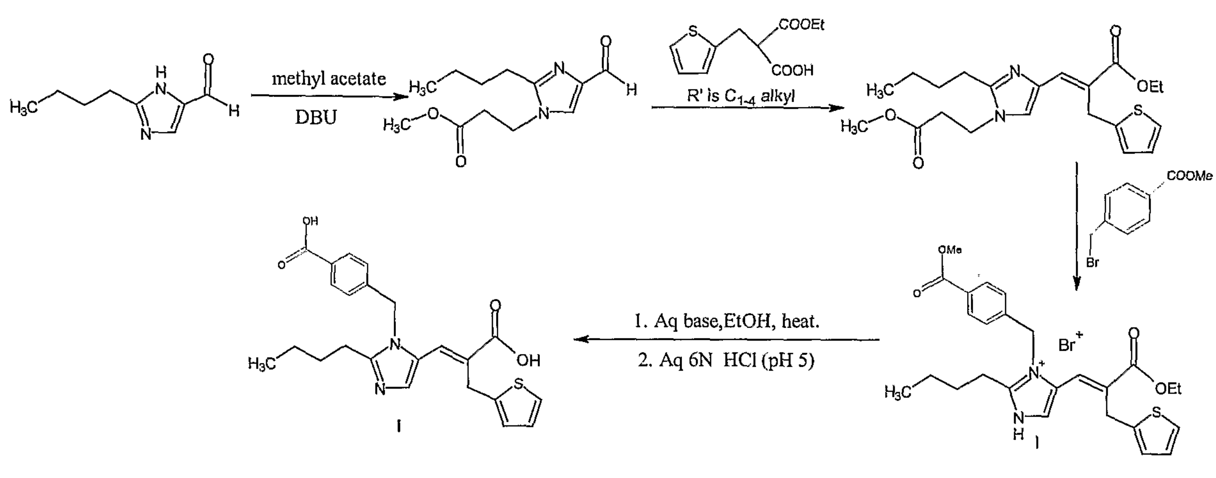
Scheme III



The major drawbacks of these processes are, the condensation is done at reduced pressure of 9-13 inches Hg which is very difficult to maintain all the time at higher scale of production, the reaction is time consuming and when used as potassium or sodium salts gives low yield.

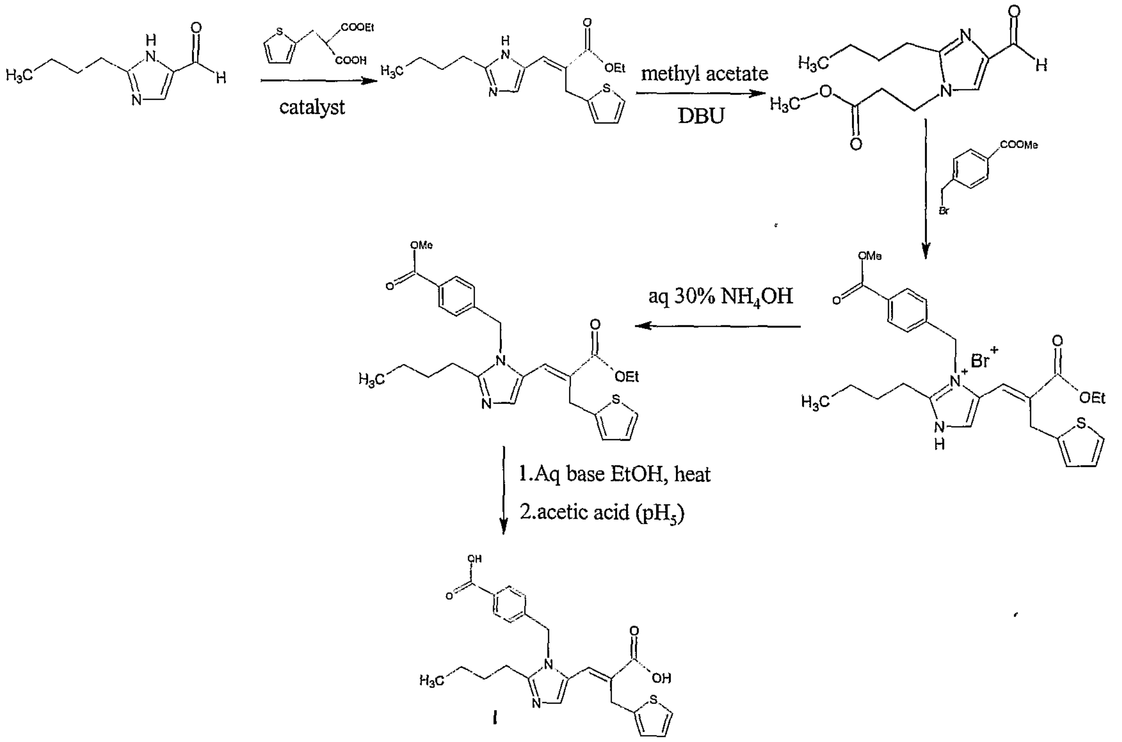
US6458963 (EP973769) discloses regioselective protection of nitrogen of the 2-n-butyl-4-formyl-1H-imidazole ring followed by treatment with (2-thienylmethyl)propanedioic acid, mono methyl ester under reduced pressure treatment with methyl-4-bromomethyl-benzoate and hydrolysis of the ester, followed by deprotection to give Eprosartan which is converted to its suitable salt form as shown in Scheme IV below,

Scheme IV



Alternatively US6458963 (EP973769) also discloses another process as in Scheme V whereby 2-n-butyl-4-formyl-1H-imidazole is first condensed with (2-thienylmethyl) propanedioic acid, mono methyl ester then the product is regioselectively protected condensed and deprotected to give Eprosartan which is converted to its suitable salt form,

Scheme V



The drawbacks of these processes as in Scheme IV and Scheme V are that there is frequent protection followed by deprotection which leads to lower yield, use of costlier reagents like DBU is not advisable at manufacturing scale. The condensation is carried out under reduced pressure which is difficult to maintain all the time at higher scale of production.

J. Med. Chem. (1991), 34, 1514-1517 discloses a process for the preparation of Eprosartan in which the condensation of the aldehyde with (2-thienylmethyl) propanedioic acid monomethyl ester in the presence of piperdine using toluene as solvent wherein the reported yield was only 40%.

US6517871 (EP1098634) disclose and claims amorphous ammonium salt of Eprosartan and process of preparation which comprises dissolving Eprosartan or Eprosartan mesylate in ammonium hydroxide in the presence of crystallization inhibitor(polyvinyl pyrrolidine).

EP889880 (US2001003187) discloses Eprosartan methanesulfonate dihydrate and the process of preparation thereof from anhydrous Eprosartan methanesulfonate.

US6262102 (EP991647) discloses Eprosartan methanesulfonate monohydrate and the process of preparation thereof for anhydrous Eprosartan methanesulfonate.

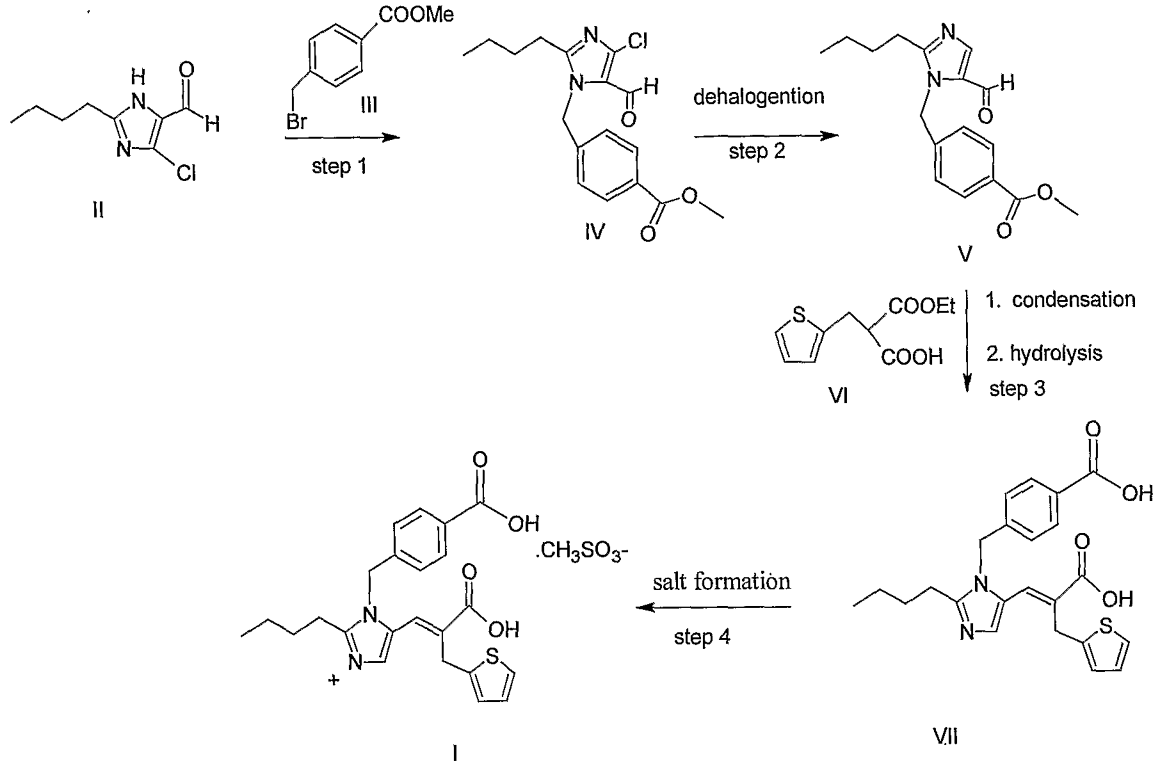
It is apparent from most of the prior-art that, the preparation of Eprosartan has certain disadvantages such as the use of hazardous and costly raw materials like n-butyl lithium, DBU and triflic acid, low reaction conditions like temperature below -78°C which is difficult to maintain all the time at higher scale of production, steps of protection followed by deprotection and high impurity levels and low yields. Therefore, there is a continuing need for developing a new process for the preparation of substantially pure Eprosartan mesylate which is cost effective and industrially viable.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for commercial manufacturing of Eprosartan , which is chemically known as (E)-3-[2-Butyl-1-{(4-carboxyphenyl) methyl}-1H-imidazole-5-yl]-2-(thiophen-2-ylmethyl)prop-2-enoic acid and its conversion to the substantially pure anhydrous Eprosartan mesylate of Formula I ,

The process for preparation of Eprosartan can be best described by the scheme VI discussed below, which comprises;

Scheme VI



- reacting n-Butyl-4-chloro-5-formyl-1H-imidazole of Formula II with Methyl-4-(bromo methyl)benzoate of Formula III to give a compound of formula IV as in Step 1
- dehalogenating the compound of Formula IV to give a compound of formula V as in Step 2
- condensation of the compound of Formula V with a compound of Formula VI followed by hydrolysis to give a compound of Formula VII as in Step 3
- forming methanesulfonate salt of the compound of formula VII in a suitable organic solvent to give anhydrous Eprosartan mesylate of Formula I as shown in step 4

The reaction of the 2-n-butyl-4-chloro-5-formyl-1H-imidazole with methyl-4-(bromo methyl)benzoate can be carried out in an organic solvent selected from N,N-Dimethyl formamide,DMSO most preferably N,N-Dimethyl formamide; in presence of a suitable base selected from sodium carbonate or potassium carbonate most preferably potassium carbonate to give compound of formula IV as in step 1.

The dehalogenation of the compound of Formula IV is carried out under reduced pressure in presence of palladium-carbon or Raney Nickel in an organic solvent selected from methanol, ethanol or ethyl acetate; most preferably methanol to give a compound of Formula V as in Step 2.

The reaction of the compound of formula V with the compound of Formula VI is carried out in the presence of suitable base selected from piperidine, pyridine, morpholine, N-methyl pyrrolidine, most preferably piperidine in an organic solvent selected from group consisting of diisopropyl ether, toluene, cyclohexane, hexane; most preferably diisopropyl ether under reduced pressure. The compound formed as above was hydrolysed *in situ.* in an organic solvent selected from a group consisting of methanol, ethanol or isopropyl alcohol; most preferably methanol with a suitable base selected from sodium hydroxide or potassium hydroxide most preferably sodium hydroxide.

The reaction mass after hydrolysis, was acidified with suitable acid selected from acetic acid or dilute hydrochloric acid; most preferably dilute hydrochloric acid in an organic solvent selected from diisopropyl ether, to give a compound of Formula VII as shown in Step 3.

Eprosartan of formula VII which has major XRD peaks at 6.73, 7.15, 7.92, 8.43, 9.02, 9.22, 9.69, 10.15, 10.29, 11.61, 12.74, 13.08, 13.62, 15.31, 15.85, 16.35, 16.98, 17.27, 17.77, 18.15, 18.30, 18.94, 19.22, 20.21, 20.65, 20.87, 21.44, 21.67, 21.97, 22.47, 22.64, 22.76, 23.24, 23.86, 24.10, 24.52, 25.06, 25.43, 25.92, 26.33, 26.65, 27.13, 27.88, 28.35, 28.68, 29.32, 30.22, 30.88, 31.38, 31.74, 33.64, 34.05, 36.06, 37.14, 38.12, 39.03, 41.69, 44.17, 45.01, 47.55 at 2? values.

The methane sulphonate salt formation of compound of formula VII is carried out in the presence of methane sulphonic acid in an organic solvent selected form acetic acid, isopropanol or ethanol; most preferably acetic acid to give a compound of Formula I.

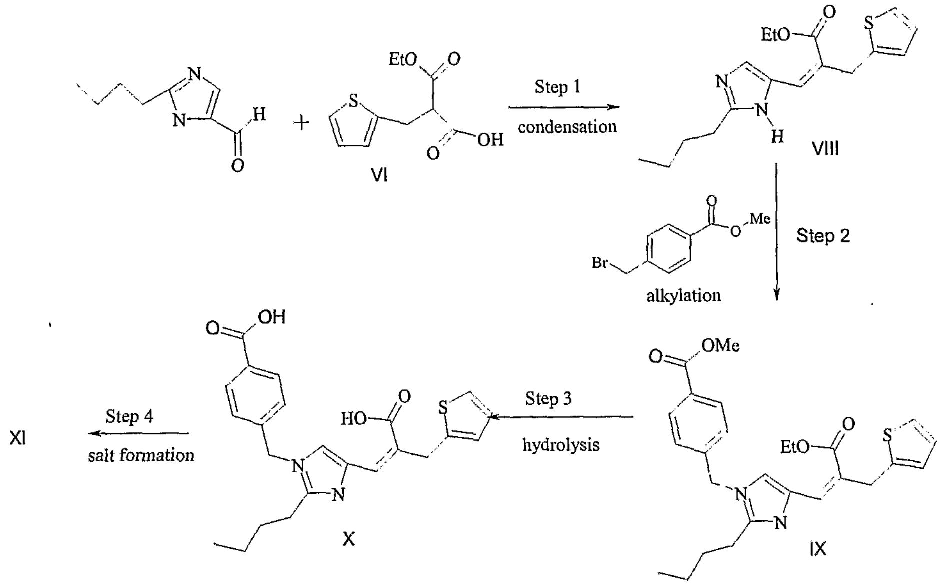
The present invention also provides a pharmaceutically acceptable active ingredient which is substantially pure with a purity level of 99.85% and impurity level of less than 0.10%.

The anti-solvent used to precipitate the compound is selected from isopropyl acetate

The solvent used for the purification of the crude is acetic acid, ethanol or methanol most preferably acetic acid.

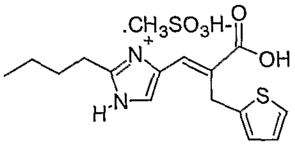
Alternatively an impurity of Eprosartan mesylate, which is (E)-3-[2-Butyl-1-{(4-carboxyphenyl) methyl}-1H-imidazole-4-yl]-2-(thiophen-2-ylmethyl)prop-2-enoic acid can also be manufactured as depicted below in Scheme VII whose process comprises;

Scheme VII



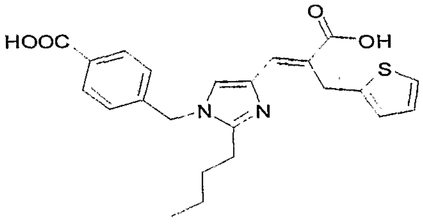
- reacting 2-n-butyl-4-formyl-1H-imidazole with (2-thienylmethyl)propanedioic acid monomethyl ester in which (2-thienylmethyl)propanedioic acid monomethyl ester was added in lots to 2-n-butyl-4-formyl-1H-imidazole in a suitable organic solvent over a period of 4-5 hrs to avoid decarboxylation of (2-thienylmethyl)propanedioic acid to give a compound of Formula VIII as shown in step 1
- treating the compound of formula VIII with methyl 4-(bromomethyl)benzoate to give a compound of Formula IX as shown in Step 2
- hydrolyzing the compound of Formula IX followed by acidification to give the compound of Formula X
- The compound of formula X was treated with methane sulfonic acid in a suitable organic solvent to give the salt of Formula XI as in step 4.

Another embodiment of the present invention is a process provided for the preparation of Eprosartan Mesylate which is substantially free from 4-(bromomethyl) benzoic acid and (E)-3-[2-n-butyl-1H-imidazole-5-yl]-2-(2-thienyl)methyl-2-propionic acid mono methanesulphonate of formula XII

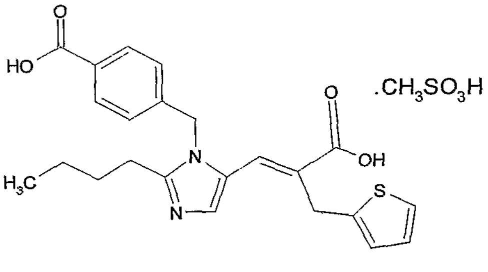


XII

Another embodiment of the present invention is a process provided for the preparation of Eprosartan Mesylate which is substantially free from (E)-3-[2-Butyl-1-{(4-carboxyphenyl) methyl}-1H-imidazole-4-yl]-2-(thiophen-2-ylmethyl)prop-2-enoic acid of formula X and its salt of Formula XI



X



XI

Another embodiment of the present invention is a process for the preparation of (E)-3-[2-Butyl-1-{(4-carboxyphenyl)methyl}-1H-imidazole-4-yl]-2-(thiophen-2-ylmethyl)prop-2-enoic acid of formula X and its salt of Formula XI as given in Scheme VII.

The invention is illustrated by the following example; the example is not intended to limit the scope of this invention as defined herein above and as claimed herein below.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 : XRD of (E)Entacapone polymorphic Form A

EXAMPLES

Example 1: Preparation of 2-Butyl-4-chloro-1[(carbomethoxy-phenyl)methyl]-1H-imidazole-5-carboxaldehyde

To dimethylformamide (400 ml) was added n-Butyl-4-chloro-5-formyl-1H-imidazole (100g, 0.536 mol) followed by the addition of anhydrous potassium carbonate (55.4 g, 0.4 mol) at a temperature of 25-30°C.The contents were stirred at this temperature for 30 minutes, followed by cooling the reaction mixture to 0-5°C. To this was added Methyl-4-(bromomethyl) benzoate (129.2 g, 0.564 mol) in four equal lots at intervals of 30 minutes, maintaining the temperature between 0-5°C.The reaction mixture was stirred for 8-10 hours below 10°C, heated to 28-30°C for 10-12 hours. After the completion of the reaction, it was poured into water (2000 ml) at 28-30°C,stirred for 1 hour at the same temperature, filtered , washed with water (1 X 200 ml). The product was dried at 50-55°C in hot air oven. The product was recrystallised by heating in methanol/water at 50-55°C. Mixture was stirred at 20-25°C for 2 hours, filtered, washed with methanol and dried at 50-55°C to get the desired compound (Dry wt. 147 g, Yield = 82.12 %) .

Example 2: Preparation of 2-Butyl-1-[(4-carbomethoxy-phenyl)methyl]-1H-imidazole-5-carboxaldehyde

The compound (100 g, 0.536 mol) as obtained from the Example 1 above was taken in methanol (1100mL) in an autoclave followed by the addition of potassium acetate at 25-30°C. To this was added palladium on carbon (10 g) under nitrogen atmosphere. Thereafter, the nitrogen was evacuated followed by hydrogen gas. The reaction mixture was stirred until completion maintaining a Hydrogen pressure of 2.8-3.0 kg/cm^2. The reaction mass was filtered through hyflow bed, washed with methanol. Solvent distilled off under vacuum maintaining a temperature less than 45°C. Water was added to the crude residue followed by ethyl acetate, pH was adjusted to 8.0-9.0 using 10% sodium bicarbonate solution. The organic layer was separated and distilled under vacuum, maintaining a temperature less than 50°C. The crude product was taken in diisopropyl ether (100 ml) heated the contents to a temperature of 40-45°C, hexane was slowly charged into it at the same temperature for a period of 1 hour. The contents cooled to 25°C, stirred for 3 hours, filtered, dried to get the desired compound (Dry wt. 69 g, Yield = 77 %)

Example 3: Preparation of Eprosartan.

To diisopropyl ether (125 ml) was added piperidine (4.7 g, 0.0551 mol) and hydrochloric acid (2.5ml) at 25-30°C. The contents were heated to 40-45°C, followed by addition of the compound (25 g,0.0833 mol) as prepared in Example 2 above. The reaction mass was heated to a temperature of 50-55°C and Ethyl 2-carboxy-3-(2-thienyl) propionate (43 g, 0.189 mol) added in 3 lots. The contents were heated to reflux under reduced pressure in a Dean-Stark apparatus until reaction completion. Thereafter the excess solvent was completely removed under vacuum, methanol was added to the crude residue, followed by sodium hydroxide solution. The contents were heated to reflux for 3 hours, cooled to 35-40°C, pH adjusted to 5.0-5.2 using 10% HCl. The contents were cooled to 20°C with stirring for 2 hours. The product was filtered and then washed with 50% aq. isopropyl alcohol (1X50 ml), and water (2X25 ml), dried for 1 hour to get the desired compound (40 g).

The crude eprosartan base(40gm) is taken in 10% sodium hydroxide (125 ml) at 25-30°C and stirred for 15 minutes at 35-40°C, followed by filtration through hyflow bed, washed with water. The crude product was taken in isopropyl alcohol(62.5 ml),pH adjusted to 5.0-5.2 with 10% HCl at 35-40°C, product cooled to 20°C and stirred for 2 hours, filtered, washed with 50% aqueous isopropyl alcohol (50 ml) and water (2X25 ml) and dried to get the desired compound (Dry wt 25 g, Yield=70.92%).

Example 4: Preparation of Eprosartan mesylate

To acetic acid (300 ml) was added Eprosartan base(100 g), as obtained from Example 3 above at 25-30°C.To this was added methane sulphonic acid maintaining the same temperature. The contents were heated to 65-70°C until dissolution takes place, followed by filtration through hyflow bed and washing with hot acetic acid (25 ml). The filtrate was cooled to 40-45°C and isopropyl acetate (800 ml) was slowly added to it in 2 lots at an interval of 2 hours. The temperature was then lowered to 15-20°C and stirred for 4 hours, filtered and washed with isopropyl acetate(100 ml) and dried to get the desired compound (100 g, Yield=81.5%)

The crude product was taken in acetic acid(200 ml) and heated to 80°C until dissolution. Contents were cooled to 25°C and stirred for 2 hours, filtered, washed with ethanol (100 ml), dried at 40-45°C to get 75 g of Eprosartan Mesylate. (Yield=75%, HPLC Purity = 99.85%)

Example 5: Preparation of Diethyl-2-thienylidene malonate

To cyclohexane (2500 ml) was added piperidine(75 g) at 25-30°C.Acetic acid was then added to the mixture drop wise at the same temperature over 15-20 minutes, followed by the addition of Diethyl malonate (678 g,4.22 mol) and then Thiophen-2-aldehyde at 25-30°C.The contents were heated to reflux for 5-7 hours in a Dean-Stark apparatus until reaction completion. The cyclohexane was distilled out and ethyl acetate(2500 ml) was added to the crude residue, acidified with 10% HCl, stirred for 30 minutes. The organic layer was separated and 10% sodium bicarbonate solution added, stirred for 30 minutes followed by one water washing. The organic layer was separated followed by the addition of sodium metabisulfite, stirred for 30 minutes and the separation of organic layer. The ethyl acetate was distilled out under vacuum below 50°C to get the product (1050.0 g).

Example 6: Preparation of Diethyl (2-thienylmethyl)malonate:

The compound (500g, 1.96mol) obtained as from example 5 above was taken in methanol (2500 ml) at 25-30°C. The contents were cooled to 0°C and sodium borohydride (37.1 g, 0.98 mol) was added in 5 equal lots at an interval of 10 minutes. After the completion of the reaction, the pH was adjusted to 6.0-6.2 with acetic acid (250 ml), under cold conditions. The salt was filtered off. Methanol was distilled out from the filtrate, ethyl acetate (2500 ml) was added along with water at 25-30°C, stirred for 15 minutes. The organic layer was separated and 10% vacuum salt (250 g) was added and stirred for 15 minutes. The layers were separated, organic layer dried over sodium sulphate and distilled to get the desired compound (448 g).

Example 7: Preparation of 2-Carbethoxy-3-(2-thienyl)propanoic acid:

The compound (500 g,1.95 mol) as obtained from Example 6 above, was taken in ethanol (1500ml) and 10% sodium hydroxide (1.95 mol) solution was slowly added over 1 hour. The contents were stirred for 48 hours at 25-30°C.The solvent was distilled out and water (2500 ml) was added to it followed by Diisopropyl ether (1000ml). The aqueous layer was separated,acidified to pH 1 using 2N sulfuric acid, methylene chloride was added. The organic layer was separated and washed with water (3X1000 ml), dried over sodium sulfate (100 g), distilled the methylene chloride to get the compound (320 g).

Example 8: Preparation of Ethyl (2E)-3-(2-butyl-4,5-dihydro-1H-imidazol-5-yl)-2-(thiophen-2-ylmethyl)prop-2-enoate of formula VIII

To cyclohexane (250mL) and piperidine (9.4g) together was added conc. hydrochloric acid in a dropwise manner for a period of 10 minutes at 25-30°C. The temperature was raised to 45-50°C and the content was stirred for 15-20mintues followed by the addition of 2-n-butyl-4-formyl-1H-imidazole (50g) and the stirring was continued for 15-20 minutes at 30-35°C to obtain a clear solution. The temperature of the reaction mixture was raised 50-55°C and to it was added Ethyl 2-Carboxy-3-(2-thienyl)-propanoate (100g) in 4 lot, the temperature was further raised to 75°C followed by azeotropic removal of water with cyclohexane. To this reaction mixture Ethyl 2-Carboxy-3-(2-thienyl)-propanoate was added after every 1hour at 50-55°C and the reaction mixture was refluxed at 75-80°C for at atmospheric pressure for 15-18hrs. Excess of cyclohexane was distilled off completely below 45°C. The residue was taken in toluene at 25-30°C and water (1000mL) was added and stirring was continued for 20min. at 25-30°C, the two layers were separated. The organic layer is washed with sodium bicarbonate (1x100mL, 10% sodium metabisulphate (1x1000mL) and saturated NaCl solution (1x500mL)in a subsequent manner. The organic layer is separated, and evaporated under vacuum at 650-750mm Hg.(96gm)

Example 9: Preparation of compound of formula IX.

The compound (50g) obtained from the example 8 above was taken in toluene(100mL) at 25-30°C and stirred till dissolution, followed by the addition of water(200ml), sodium Hydroxide flakes(6.2gm), and the stirring was continued for 10min at 25-30°C. To this reaction mixture was added methyl-4-(bromomethyl)-benzoate and stirred for 18-24 hrs. at 25-30°C. The two layer are separated and the organic layer is washed with DM Water (500ml)and evaporated at 50-55°C under vacuum 650-750mm Hg to get the crude diester (64gm)

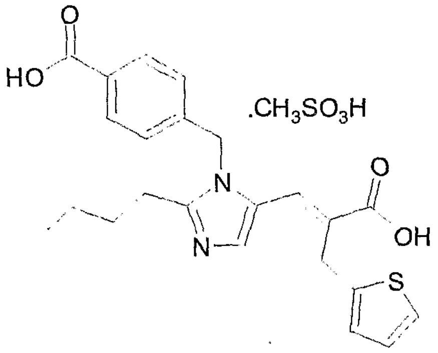
Example 10: Preparation of Compound of Formula X

The Compound IX (64gm) is taken in methanol (192ml) at 25-30°C and stirred till dissolution followed by the addition of water and sodium hydroxide and stirring was continued at 25-30°C for 15min, the reaction mixture is heated at 57-60°C for 3 hrs. and the methanol layer is distilled off under vacuum. The residue was taken in water (500mL) and washed with toluene

(2x500ml) and the pH is adjusted to 5.0-5.2 using glacial acetic acid at 20-25°C. The reaction mixture is stirred until the product separates out and cooled to 15-20°C and stirred for 2hrs at 15-20°C to allow complete precipitation of solid. The crude is filtered and dried under vacuum at 45-50°C for 2hrs to get yellow solid (40gm, %Yield= 68, HPLC=80%).

We claim

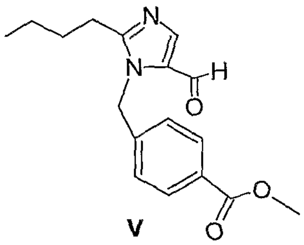
1) An improved process for preparation of Eprosartan, a compound of Formula I



I

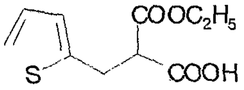
or a pharmaceutically acceptable salt thereof; which comprises of :

a) reacting methyl 4-[[2-butyl-5-formyl-1H-imidazol-1-yl]methyl]benzoate, of Formula V



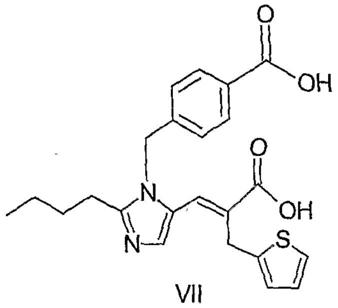
V

with ethyl 2-carboxy-3-(2-thienyl)propionate of Formula VI :



VI

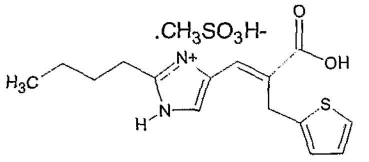
in the presence of a base in a solvent selected from diisopropyl ether to give a diester intermediate and was hydrolysed *in situ* with a base to obtain pure eprosartan of formula VII ; and



VII

b) converting the eprosartan formed into its mesylate salt to obtain eprosartan mesylate of Formula I

2) The process according to Claim 1, wherein anhydrous Eprosartan mesylate of formula I substantially free from 4-(bromomethyl) benzoic acid and (E)-3-[2-n-butyl-1H-imidazole-5-yl]-2-(2-thienyl)methyl-2-propionic acid mono methanesulphonate of formula VIII.



VIII

3) The process according to Claim 1, wherein the reaction in step a) is carried out at a temperature between 40°C and reflux temperature of the solvent used.

4) The process according to Claim 3, wherein the reaction is carried out at the reflux temperature of the solvent used.

5) The process according to Claim 1, wherein the solvent used in the step a) is diisopropyl ether.

6) The process according to Claim 1, wherein the base is used is selected from group consisting of piperidine, pyridine, morpholine, N-methylpyrrolidine and a salt thereof.

7) The process according to Claim 6, wherein the base used is piperidine or piperidine hydrochloride.

8) The process according to Claim 1, wherein the *in situ* hydrolysis is carried out

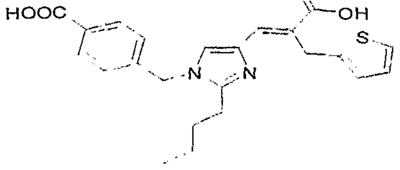
   a) in an organic solvent selected from group consisting of methanol, ethanol or isopropyl alcohol; most preferably methanol,

   b) in presence of a suitable base selected from group consisting of sodium or potassium hydroxide, most favourably sodium hydroxide.

9) A process according to claim 1-8 wherein the Eprosartan mesylate formed is anhydrous in nature.

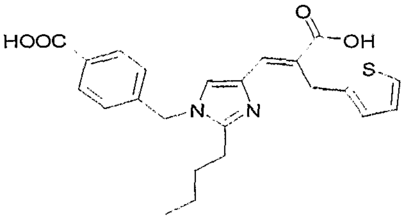
10) Substantially pure anhydrous form of Eprosartan mesylate of formula I, with purity level greater than 99.85% and single individual impurity less than 0.10%.

11) A process according to claim 1-8 wherein the Eprosartan mesylate formed is substantially free from



IX

12) A compound of Formula IX

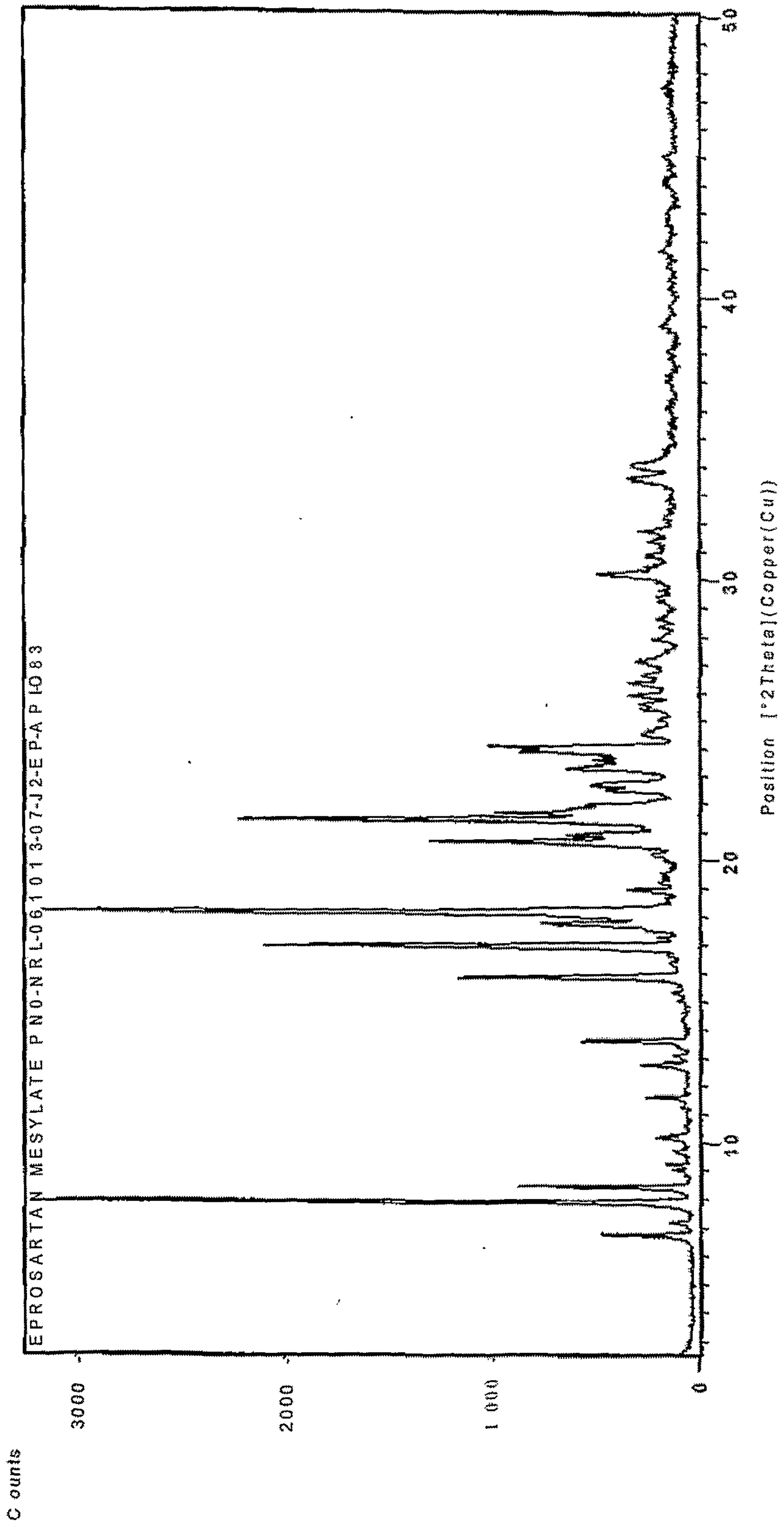


and the process for making the compound of Formula IX and its salt of Formula X, which comprises.

- reacting 2-n-butyl-4-formyl-1H-imidazole with (2-thienylmethyl)propanedioic acid monomethyl ester in which (2-thienylmethyl)propanedioic acid monomethyl ester was added in lots to 2-n-butyl-4-formyl-1H-imidazole in a suitable organic solvent over a period of 4-5 hrs to avoid decarboxylation of (2-thienylmethyl)propanedioic acid to give a compound of Formula VIII as shown in step 1
- treating the compound of formula VIII with methyl 4-(bromomethyl)benzoate to give a compound of Formula IX as shown in 2a or 2b
- hydrolyzing the compound of Formula IX followed by acidification to give Eprosartan of Formula X
- methane sulphonate salt formation of compound of formula X in a suitable organic solvent to give a compound of Formula XI as in step 4.

forming methane sulphonate salt of compound of formula X in a suitable organic solvent to give (E)-3-[2-Butyl-1-{(4-carboxyphenyl) methyl}-1H-imidazole-4-yl]-2-(thiophen-2-yl-methyl)prop-2-enoic acid methane sulfonate

Figure 1: XRD of (E) Entacapone polymorphic form A



Peak List:

Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]	Area [cps*°2Th.]
6.7337	13.12710	13.83	1.44
7.1547	12.35557	2.58	0.40
7.9172	11.16727	100.00	10.44
8.4329	10.48540	26.52	2.77
9.0234	9.80058	2.49	0.19
9.2174	9.59469	3.56	0.28
9.6961	9.12207	2.09	0.38
10.1548	8.71100	4.83	0.50
10.2857	8.60041	2.57	0.27
11.6149	7.61901	6.15	0.64
12.7396	6.94880	7.03	1.10
13.0774	6.77008	1.64	0.26
13.6178	6.50259	15.61	2.44
15.3093	5.78775	1.39	0.22
15.8514	5.59101	33.85	4.42
16.3549	5.42000	1.45	0.23
16.9839	5.22067	60.92	15.90
17.2665	5.13584	3.14	0.25
17.7698	4.99150	20.50	2.14
18.1494	4.88795	99.64	13.00
18.2996	4.84816	19.26	1.01
18.9447	4.68450	7.23	1.13
19.2151	4.61918	2.07	0.38
20.2129	4.39337	3.27	0.51
20.6467	4.30203	36.62	4.78
20.8681	4.25688	15.17	2.38
21.4412	4.14439	66.21	10.37
21.6692	4.10128	25.92	2.03
21.9758	4.04476	12.10	0.95
22.4666	3.95750	8.50	0.89
22.6373	3.92803	11.86	0.93
22.7584	3.90740	9.83	1.28
23.2390	3.82768	14.86	1.94
23.8577	3.72979	21.72	2.27
24.0982	3.69311	27.17	2.84
24.5154	3.63120	3.80	0.99
25.0583	3.55375	1.72	0.27
25.4301	3.50263	4.13	0.54
25.9192	3.43763	6.23	0.98
26.3295	3.38499	5.57	0.87
26.6475	3.34531	3.98	0.62
27.1269	3.28727	5.19	1.35
27.8843	3.19968	2.53	0.53
28.3485	3.14833	1.57	0.33
28.6839	3.11227	1.46	0.46
29.3213	3.04605	1.82	0.57

30.2197	2.95752	11.19	0.88
30.8753	2.89619	3.36	0.88
31.3771	2.85102	3.58	0.56
31.7434	2.81895	4.97	0.52
33.6418	2.66409	6.26	2.29
34.0494	2.63313	6.30	2.30
36.0647	2.49048	1.37	0.72
37.1404	2.42078	1.04	0.54
38.1222	2.36066	1.39	0.29
39.0346	2.30756	2.08	1.30
41.6955	2.16625	1.88	0.59
44.1748	2.05025	1.42	0.74
45.0115	2.01407	1.67	0.35
47.5514	1.91067	1.51	1.56