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(54) **Title:** AN IMPROVED PROCESS FOR THE MANUFACTURE OF MONTELUKAST SODIUM

(57) **Abstract:** Process for the manufacture of 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropane acetic acid, sodium salt [montelukast sodium (I)] consisting of: i. Converting methyl 1-(mercaptomethyl)-cyclopropaneacetate to a metal salt (X) using a metal hydroxide, ii. Subjecting the metal salt (X) to monometallation to provide a dimetallide (XI). iii. Converting a diol of formula (II) to a mesylate of formula (III) and reacting (III) in situ with (XI) affordin the metal salt of 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropane acetic acid. iv. Reacting the metal salt in-situ with a base and purifying to afford an amine salt (XII). v. Treating (XII) with a sodium base and precipitating out montelukast sodium (I).

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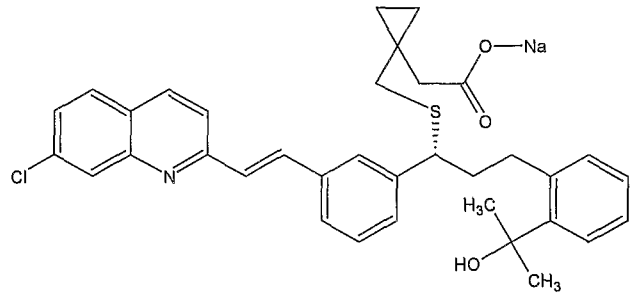
'AN IMPROVED PROCESS FOR THE MANUFACTURE OF MONTELUKAST SODIUM'

BACKGROUND OF THE INVENTION

The present invention relates to an improved process for the manufacture of 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropane acetic acid, sodium salt I, which is known as Montelukast sodium.

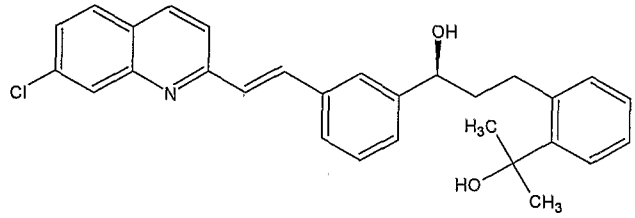


I

The compound of the formula I is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor. These compounds are effective in the treatment of asthmatic disorders, etc. Several processes for the manufacture of the same are reported.

PRIOR ART

The European Patent No. 480717 discloses a class of novel anti-asthmatic compounds including montelukast sodium of structural formula I, having activity as leukotriene antagonists and to methods for their preparation. This patent provided a process for the preparation of the title compound I, which comprises of converting an alcohol of the formula II to a mesylate of the formula III. The mesylate is then condensed, in presence of cesium carbonate, with methyl (1-acetylthiomethyl) cyclopropaneacetate of the formula IV, after treatment of the latter with hydrazine, to obtain a compound of the formula V



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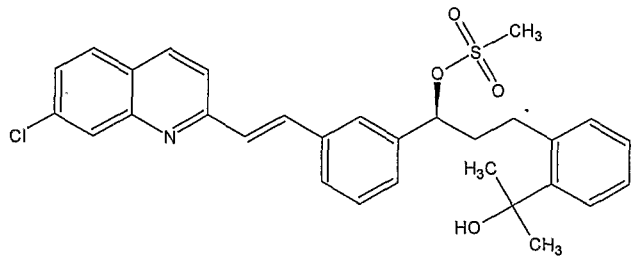

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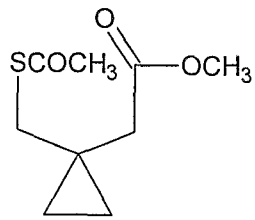

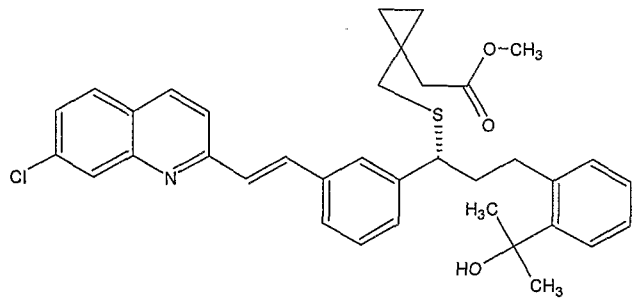

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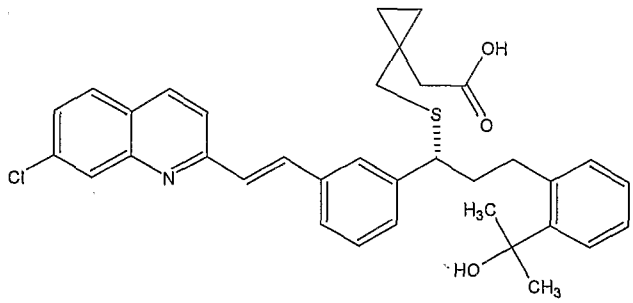
(V)

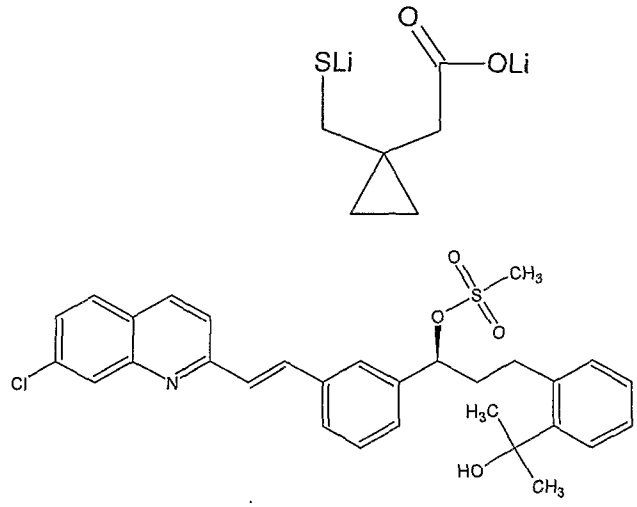


(VI)

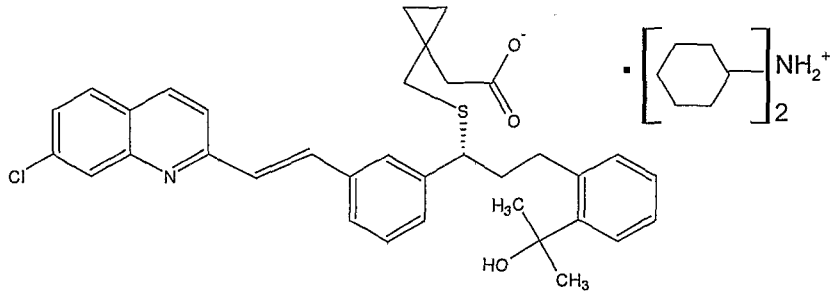
Finally the acid of the formula VI was prepared by hydrolysis of the methyl ester V in presence of pyridinium p-toluenesulphonate. The acid VI was, then, taken up in ethanol, treated with an equivalent amount of NaOH and the resultant oil was freeze dried to afford the compound of the formula I. This process afforded the title compound in low yields and purities and required purification by chromatography at intermediate stages.

European Patent No. 500360 relates to quinoline-containing ketoacids having activity as leukotriene antagonists and to methods for their preparation. This patent again provides processes as exemplified in EP 480717 and hence suffers from the same drawbacks.

The European Patent No. 737186 relates to a process for the preparation of a compound of the formula I which comprises of reacting the dilithium dianion of 1-(mercaptomethyl) cyclopropaneacetic acid (VII) with methanesulphonyloxy compound of the formula III to afford after suitable workup the acid VI which was in situ converted to its dicyclohexyl amine (DCHA) salt having the formula VIII.



VII III



VIII

The dicyclohexylamine salt was purified by leaching with solvents and dried. The dried salt VIII was taken up in toluene and treated with acetic acid to generate free acid VI, the toluene solution of which was subsequently treated with an equivalent quantity of sodium hydroxide and the sodium salt so formed (I) was crystallized from a solvent mixture comprising of toluene-acetonitrile. This process suffers from multiplicity of steps involving formation of VI, conversion of the latter to its dicyclohexylamine salt, purification of the dicyclohexylamine salt, regeneration of acid VI before it is converted to montelukast sodium which is crystallized, making it very tedious and industrially unattractive.

The provisional patent application WO 03/066598 discloses an anhydrous amorphous form of montelukast sodium of the formula I which comprises of preparing the montelukast free acid from montelukast dicyclohexylamine salt by acidification, dissolving the free acid of montelukast in a C_1-C_2 halogenated solvent or in C_7-C_8 aromatic hydrocarbon solvent and converting the dissolved acid to the corresponding alkali salt using an alkaline metal hydroxide/an alkaline metal alkoxide/alcoholic alkaline metal hydroxide/ alcoholic alkaline metal alkoxide in presence of C_1-C_4 straight or branched chain alcohol and isolating amorphous form of montelukast alkali salt by adding a C_5-C_7 acyclic or C_5-C_8 cyclic hydrocarbon. This process affords the compound of the formula in yields less than 70% of theory, which renders the process unattractive.

The provisional patent application WO 04/108679 relates to an improved method for the preparation of montelukast acid sodium salt in an amorphous form which comprises

of generating the dilithium dianion of 1-(thiomethyl)cyclopropaneacetic acid (VII) and coupling said dianion with wet mesylate of the formula III to get montelukast acid VI in crude form followed by conversion of the latter to its DCHA salt, purifying the DCHA salt and converting the DCHA salt to montelukast acid in the pure form and finally reacting the pure montelukast acid with a sodium base followed by evaporation of the solvent and triturating the residue with nonpolar water immiscible solvent to obtain the title compound, I. This long drawn procedure affects the overall yield of the final product.

The US application US2005/0187245 discloses a stable non-hygroscopic amorphous form of the compound of the formula I, which comprises of dissolving the montelukast sodium in a solvent/ a combination of solvents followed by spray drying the resultant solution. As a comparative example the patent also reports that a product prepared according to the process disclosed in EP 480717 which comprises of freeze drying an aqueous solution of montelukast sodium, provides an amorphous form as confirmed by the X-ray Diffraction data of the product. The patent does not disclose the yields obtained by following the procedure and is thus not clear.

SUMMARY

It is an objective of the present invention to provide a process for the manufacture of the compound of formula I in good yields by reducing the number of steps while still achieving good purities.

The process of the present invention utilizes 3 novel concepts for the manufacture of the compound of the formula I-

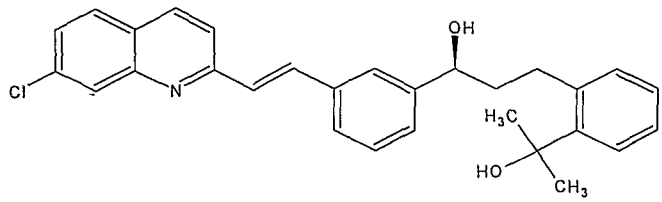
1. An important concept of the present invention is to utilize the ease of isolation of metal carboxylate salts wherein an ester compound of the formula IX is hydrolytically converted to a monometal salt of the formula X that can be isolated by filtration and thereafter can be dried to desired limits. These mono metallides can thereafter be converted to the dimetallides by use of a metal hydride, metal alkyl derivatives etc. This step serves the function of converting the mercapto end of 1-(mercaptomethyl)-cyclopropane acetate metal salt, X to

its dimetal salt, XI. Thus the process of the present invention utilizes lesser quantities of metal alkyl derivatives.

2. A very important concept of the present invention is to convert an alcohol derivative and of the formula II to alkyl sulfonate compounds of the formula III, which are, reacted in-situ with the compound of the formula XI. It is well known to those conversant in the art that compounds of the formula III are relatively unstable and their isolation by operations such as filtration etc becomes an industrially critical operation which need special handling systems and hence the process of the present invention provides an efficient and hitherto unreported method of utilizing in-situ the thus obtained alkyl sulfonate which thereby affords much improved yields and also makes the process industrially easy to carry out. Thus the process for the manufacture of the compound of the formula I is rendered simple, easy and convenient to carry out on a large scale.
3. Another important concept of the present invention is to provide the synthetic utility of bases particularly the chirally pure bases such as α–methyl benzylamine, brucine, strychnine, quinine, cinchonidine, ephedrine, amphetamine, phenylpropanol amine etc for isolation and purification of the respective salts of montelukast. These chiral bases afford the title compound in better efficiencies and purities which thereby affords a process for the manufacture of the compound of the formula I that is highly economical and commercially advantageous.

DETAILED DESCRIPTION

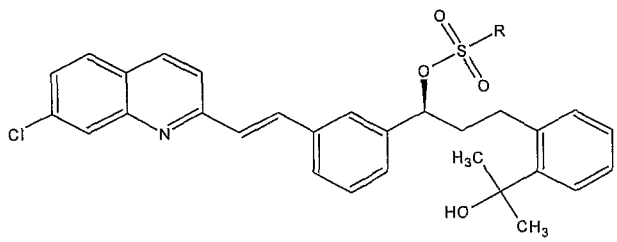
In an attempt to devise a more efficient process for montelukast sodium (I), it was conceived that the ester of the formula IX that has been reported in EP480717 could be readily converted to metal salts (X). These metal salts of the formula X apart from protecting the carboxylic acid can also be isolated as stable crystalline salts, which can be characterized. These mono metallides can be reacted with anhydrous metallide forming reagents affording the dimetallide derivatives, which can have potential uses for onward coupling with suitable substrates.



(II)

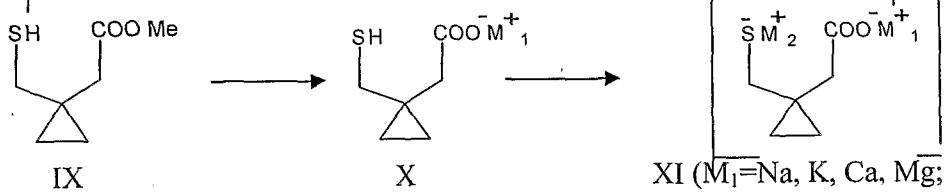
RSO_2X

(R=Me, Et, Pr; X=Cl, Br, I)



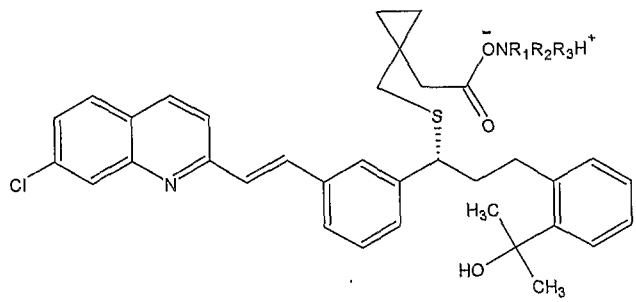
(III)

(R=Me, Et, Pr)



IX X XI (M_1=Na, K, Ca, Mg;

M_2=Li, Na,



XII (R_1,R_2,R_3=H, achiral or chiral alkyl, cycloalkyl, heteroalkyl or heterocycloalkyl)

According to the invention there is provided a process for the manufacture of the compound of the formula I consisting of converting methyl 1-(mercaptomethyl)-cyclopropane acetate of the formula IX to metal salts of the formula X in a suitable

solvent at 0 to 50°C wherein M_1 can be alkali metal or an alkaline earth metal such as Na^+, K^+, Ca^{+2}, Mg^{+2} etc. The compounds of the formula X are dried and characterized. These are then converted to the dimetal salt of the formula XI in a suitable solvent at 0 to -50°C wherein M_1 is as described above and M_2 is an alkali metal such as Li^+, Na^+, K^+ etc. The process is so carried out that simultaneously as XI is being synthesized, a compound of the formula II is converted to compounds of the formula III. This alkyl sulfonation affords compounds of the formula III which is monitored by HPLC (herein described in the examples) which without isolation are condensed "in-situ" with the simultaneously prepared compounds of the formula XI in a suitable solvent at 0 to -50°C. This reaction is again monitored by HPLC. After the specified limits are achieved the reaction mass is quenched and extracted with a suitable solvent. The organic layer is thereafter treated with a suitable base, preferably a chirally pure base. This affords the crystallization of montelukast salt (XII) with a base preferably a chirally pure base, which is isolated by filtration. The compound of the formula XII is then purified by crystallization from a suitable solvent. It was important to establish that during the in-situ condensation of alkyl sulfonate III with the dimetalide XI, complete inversion occurs at the carbon carrying the alkyl sulfonate group, to give the desired enantiomer XII and that the proportion of the undesired enantiomer XIII does not increase as compared to the standard procedure reported in EP 737186. This was done by preparing XII where the chiral base used is (R)-(+)-α-methylbenzyl amine and also preparing (R)-(+)-α-methylbenzyl amine salt of montelukast obtained according to the procedure described in EP 737186 wherein instead of adding DCHA as prescribed in the process α–methyl benzylamine was added. The specific optical rotations of the two salts were comparable.

To obtain montelukast sodium (I), the purified salt XII is dissolved in a suitable solvent and treated with a stoichiometric amount of a sodium base at 0 to 50°C followed by trituration of the resultant solution in an antisolvent. An amorphous powder of pure montelukast sodium (I) is obtained.

As a suitable solvent for the saponification of the compound of the formula IX affording X one can use methanol, ethanol, n- or isopropanol, preferably methanol. As

a suitable solvent for the isolation of compound of the formula X one can utilize the hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, THF, acetonitrile, preferably toluene.

As a suitable base for the saponification of the compound of the formula IX affording X one can use sodium hydroxide, potassium hydroxide, calcium hydroxide or magnesium hydroxide, preferably sodium hydroxide.

The saponification of the compound of the formula IX affording X is carried out at -10 to 80°C preferably 50°C.

As a suitable solvent for the dimetallation of the compound of the formula X affording XI one can utilize the hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, THF, acetonitrile, preferably THF.

As a suitable base for the dimetallation of the compound of the formula X affording XI one can use n-butyl lithium, sodium hydride, sodium methoxide, potassium hydride, potassium methoxide, calcium hydride, magnesium oxide, phenyl sodium, preferably n-butyl lithium. The molar quantity of the base used for dimetallation can be varied between 0.95 and 0.99 moles but preferably 0.98 moles with respect to the compound of the formula IX.

The temperatures employed for the dimetallation of the compound of the formula X affording XI is carried out at -20 to 20°C preferably -10°C.

As a suitable solvent for the conversion of the compound of the formula II to the compound of the formula III, one can utilize the ethers such as dialkyl ethers, where alkyl connotes methyl, ethyl, n- & iso propyl, cyclic ethers such as THF, 1,4-dioxane, etc. More preferred ones are the cyclic ethers like tetrahydrofuran and 1,4-dioxane.

As a suitable reagent for the conversion of the compound of the formula II to the compound of the formula III, one can utilize the routinely available alkyl sulfonyl halide such as methanesulfonyl chloride, ethane sulfonyl chloride, propane sulfonyl

chloride; methanesulfonyl bromide, ethane sulfonyl bromide, propane sulfonyl bromide; methanesulfonyl iodide, ethane sulfonyl iodide, propane sulfonyl iodide. More preferred ones are the methanesulfonyl chloride, ethane sulfonyl chloride.

The molar quantity of the alkyl sulfonyl halide used for the conversion of the compound of the formula II to the compound of the formula III can be varied between 1.0 and 1.5 but preferably 1.1-1.2 moles with respect to the compound of the formula II.

The temperatures employed for the conversion of the compound of the formula II to the compound of the formula III is carried out at -50 to 20°C preferably -20°C.

The reaction temperatures employed for the condensation between the compound of the formula III with the compound of the formula XI is carried out at -50 to 20°C preferably -10°C.

The molar quantity of the dimetallide XI used with respect to the compound of the formula III can be varied between 1.0-2.0 moles but preferably 1.4 to 1.5 moles with respect to the compound of the formula III.

As a suitable base for the conversion of the compound of the formula XI affording XII one can use either an achiral base like benzhydryl amine (aminodiphenylmethane) or the commercially available chirally pure bases such as α–methyl benzylamine, brucine, strychnine, quinine, cinchonidine, ephedrine, amphetamine, 3-nitro-α–methyl benzylamine, 4-nitro-α–methyl benzylamine, phenyl alinol, 1R,2R-2-amino-1,2-diphenylethanol, α–methyl naphthylethylamine, phenyl propanolamine etc. More preferred ones are the chirally pure bases. The molar quantity of the base used for this salt formation can be varied between 1.0 to 1.5 moles but preferably 1.1-1.2 moles with respect to the compound of the formula II.

As an organic solvent for purification of the compound of the formula XII one can utilize halogenated organic solvents, ethers, alkyl acetates, aromatic hydrocarbons, etc. More preferred are the alkyl acetates preferably ethyl acetate.

The organic solvent for dissolving the purified compound of the formula XII is selected from hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, ketones such as acetone, methyl ethyl ketone or methyl isobutyl ketone or esters such as methyl acetate, ethyl acetate or n-butyl acetate. More preferred one is toluene.

As a base for generating the sodium salt one can utilize the alkali metal hydroxides such as sodium hydroxide, the alkali metal carbonates such as sodium carbonate, the alkali metal bicarbonates such as sodium bicarbonate, alkali metal acetates such as sodium acetate, or alkali metal alkoxides such as sodium methoxide. More preferred one is sodium methoxide.

The suitable antisolvent for precipitating the compound of the formula I is selected from hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, ketones such as acetone, methyl ethyl ketone or methyl isobutyl ketone or esters such as methyl acetate, ethyl acetate or n-butyl acetate, preferably n-heptane.

The process does not proceed via the dilithio salt. The process of the present invention does not utilize any isolated mesylate. The process of the present invention does not employ the dicyclohexylamine salt as an intermediate. The process of the present invention does not utilize any freeze dryer for the isolation of the compound of the formula I. The process of the present invention does not proceed via the montelukast free acid.

The process of the invention does not utilize solvents such as acetonitrile during the final stages of crystallization, which have a stringent limit in ICH.

All the above collectively make the process economically more viable providing high yields and high purities for the final product.

The following examples are illustrative of the invention but not limitative to the scope thereof.

EXPERIMENTAL SECTION

HPLC method for reaction monitoring:

Column: Cosmosil silica, 250 x 4.6 mm, 5.0 μ; wavelength: 280 n.m; injection volume: 10μL; Column temperature: 30°C; Run time: 30 min; Mobile phase: Hexane, dioxane & THF in the ratio of 85:15:2 and degassed.

EXAMPLE 1

Sodium 1-(mercaptomethyl)-cyclopropane acetate:

A solution of methyl 1-(mercaptomethyl)-cyclopropane acetate (50 gm, 0.31 mol) (IX) in methanol (250 ml) was treated with sodium hydroxide solution (62.0 gm in 200 ml distilled water) and stirred at 45°C for 2 hrs. The hydrolysis was monitored by TLC and the reaction mass was concentrated to a residual mass, which was dissolved in 300 ml of water and pH adjusted to 4.0 and reaction was extracted with 200ml of toluene. Toluene extract was stripped of toluene. The residue containing (X) was slurried in cyclohexane and filtered under nitrogen atmosphere, washed with cyclohexane (50 ml x 2) and dried under vacuum at 35°C to afford 44.61 gm of sodium 1-(mercaptomethyl)-cyclopropane acetate.

Yield = 85% (of theory)

NMR (CDCl3): δ 2.13-2.32 (m,4H), 0.27-0.44 (m, 4H)

XRD: As per fig-1

Montelukast α-methyl benzyl amine salt

A suspension of 17 gm sodium 1-(mercaptomethyl)-cyclopropane acetate (X) (0.101 mol) in 75 ml THF was cooled to -40°C. To this 64.4 ml of n-butyl lithium (0.099 mol) was added followed by maintaining the reaction mass at -20 to -40°C for an additional 30 min to provide a mass of XI.

Simultaneously in another assembly the alcohol (II) (33 gm, 0.072 mol) was dissolved in 330 ml methylene chloride. To this N-methyl morpholine (10.91 gm, 0.108 mol) was added and the reaction mass was thereafter cooled to -25°C. Mesyl chloride (III) (9.76 gm, 0.085 mol) dissolved in 20 ml methylene chloride was added to the reaction mass

and the reaction was stirred at -15 to -20°C for 2 hrs. The reaction mass was monitored by HPLC to check that the unreacted II was below 1%. Thereafter the reaction mass was further cooled to -40°C, filtered and the filtrate was concentrated in vacuum and the residue was dissolved in 600 ml THF. The resultant clear solution was cooled to -45°C. To this the simultaneously prepared XI mass was added and the reaction was maintained at -10 to -15°C for 12 hrs and the reaction was again monitored by HPLC to check that the unreacted III was below 2%. The reaction mass was thereafter poured in a mixture of 1000 ml each of ethyl acetate and water and acidified with acetic acid to pH of 3.5. The layers were separated and the organic layer was washed with 200 ml water followed by 100 ml of 20% sodium chloride. The ethyl acetate solution was treated with charcoal, filtered through celite and treated with (R)-(+)- α-methylbenzyl amine (9.6 gm, 0.079 mol) to afford the crude salt. The resultant salt was filtered and purified by crystallization from 200 ml ethyl acetate to afford 43.8 gm of the α-methylbenzyl amine salt of montelukast.

Yield: 86% (of theory)

M.P: 126-7°C.

IR: 3336, 1604, 1541, 1496

NMR: δ 8.12-8.14 (d, 1H), 8.04-8.05 (d, 1H), 7.81 (s, 1H), 7.61-7.64 (bs, 1H), 7.70-7.74 (dd, 2H), 7.60-7.64 (d, 1H), 7.10-7.52 (m, 13H), 4.12-4.13 (q, 1H), 4.01-4.04 (t, 1H), 3.11-3.13 (m, 1H), 2.92-2.95 (m, 1H), 2.64-2.68 (d, 1H), 2.20-2.65 (m, 5H), 1.60-1.62 (2s, 6H), 1.40-1.41 (d, 3H), 0.46-0.55 (m, 4H)

Assay (by HPLC): 98.4%

Water content (by Karl Fisher): 0.12%

XRD: As per Fig-2

EXAMPLE-2

The procedure of example 1 was followed with 23.33 gm of cinchonidine instead of (R)-(+)- α-methylbenzyl amine and the isolated product dried at 40°C under vacuum to give 53.5gm of cinchonidine salt of montelukast.

Yield: 84.4% (of theory)

M.P: 98 to 105°C.

IR: 3238, 2924; 1606;1593;1377;838;759 cm^{-1}

NMR: δ 6.88-8.60 (m, 21H); 5.66-5.68 (m, 1H); 5.07-5.09 (d, 1H); 4.69-4.78 (t, 2H); 1.97-3.78 (m, 14H); 1.17-1.21 (m, 15 H); δ 0.15-0.55 (m, 4H)

Assay (by HPLC): 98.5%

Water content (by Karl Fisher): 0.15%

XRD: As per Fig-3

EXAMPLE-3

The procedure of example 1 was followed with 25.71 gm of quinine instead of (R)-(+)-α-methylbenzyl amine and the isolated product dried at 40°C under vacuum to give 54.12 gm of quinine salt of montelukast.

Yield: 82.5% (of theory)

M.P: 80 to 90°C.

IR: 3069; 2924, 1606; 1593; 1433; 861;760 cm^{-1}

NMR: δ 6.88 to 8.45 (m, 20H); 5.57-5.91 (m, 1H); 5.06-5.09 (d, 1H); 4.69-4.79 (t, 3H); 1.99-3.03 (m, 11H); 1.17-1.18 (d, 12 H); 1.22 (d, 6H); 0.15-0.23 (m, 6H)

Assay (by HPLC): 98.1%

Water content (by Karl Fisher): 0.18%

XRD: As per Fig-4

EXAMPLE-4

The procedure of example 1 was followed with 26.5 gm of strychnine instead of (R)-(+)-α-methylbenzyl amine and the isolated product dried at 40°C under vacuum to give 55gm strychnine salt of montelukast.

Yield: 83% (of theory)

M.P: 76 to 85°C.

IR: 3415, 1672, 1595, 1480; 761.8 cm^{-1}

NMR: δ 6.81-8.19 (m, 19H); 5.5-5.6(d, 1H); 3.12-4.36(m, 5H); 1.93-2.87(m, 19H); 0.99-1.75 (m, 10H); 0.14-0.26 (m, 4H)

Assay (by HPLC): 98.6%

Water content (by Karl Fisher): 0.19%

XRD: As per Fig-5

EXAMPLE-5

The procedure of example 1 was followed with 10.85 gm of (+) phenylpropanolamine instead of (R)-(+)- α-methylbenzyl amine and the isolated product dried at 40°C under vacuum to give 43.6 gm phenylpropanolamine salt of montelukast.

Yield: 82% (of theory)

M.P: 156 to 159°C.

Assay (by HPLC): 98.1%

Water content (by Karl Fisher): 0.67%

XRD: As per Fig-6

EXAMPLE-6

The procedure of example 1 was followed with 14.51 gm of benzhydrylamine instead of (R)-(+)- α-methylbenzyl amine and the isolated product dried at 40°C under vacuum to give 47.33 gm benzhydrylamine salt of montelukast.

Yield: 85.4% (of theory)

M.P: 128 to 134°C.

IR: 3371, 2667, 1606, 1542, 1497,1451,837, 759 in cm^{-1}

NMR: δ 8.67 to δ 7.08 (25 H (m) Aromatic & olefinic) ; δ 5.08 (s,1H) ; δ 3.95 (s,2H) ; δ 3.15 to 2.13 (m, 11H); δ 1.41 (s, 6H); δ 0.81 to 0.32 (m, 4H)

Assay (by HPLC): 98.5%

Water content (by Karl Fisher): 0.77%

XRD: As per Fig-7

Montelukast sodium salt

The α-methyl benzyl amine salt (30 gm, 0.042mol) was dissolved in 240 ml toluene and to the resultant solution 2.4 gm of sodium methoxide (0.044mol) was added and the

contents stirred for 30 min at 25-30°C followed by addition of 1.5 gm charcoal. The mass was stirred at 25-30°C for 1 hr and filtered through celite. The clear filtrate was added drop-wise into 900 ml n-heptane. The product mass was stirred for an additional 10 min at 25-30°C and filtered. The product was dried at 50°C under vacuum to get 24 gm of montelukast sodium.

Yield: 93% (of theory)

Water content (by Karl Fisher): 1.3%

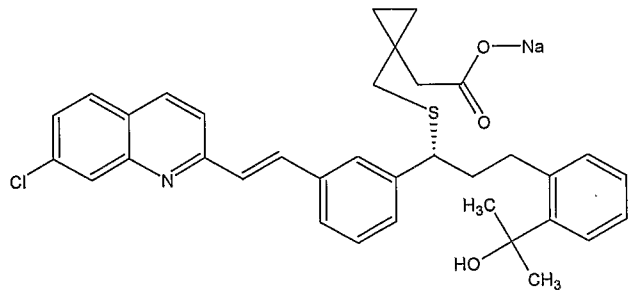
Assay (by HPLC): 99.6%

SOR: + 98.12

XRD: As per Fig-8

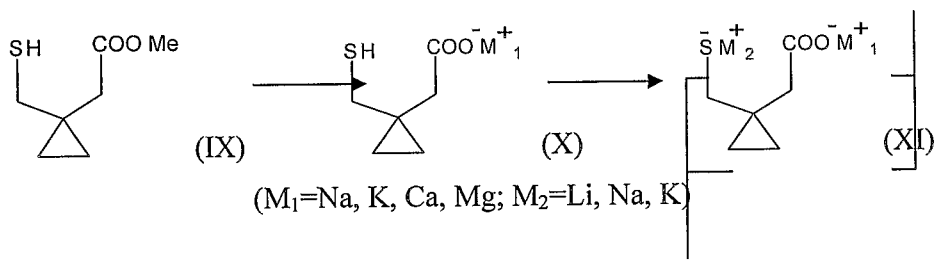
WE CLAIM:

1. A process for preparing 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropane acetic acid, sodium salt [montelukast sodium (I)], the said process comprising steps of-



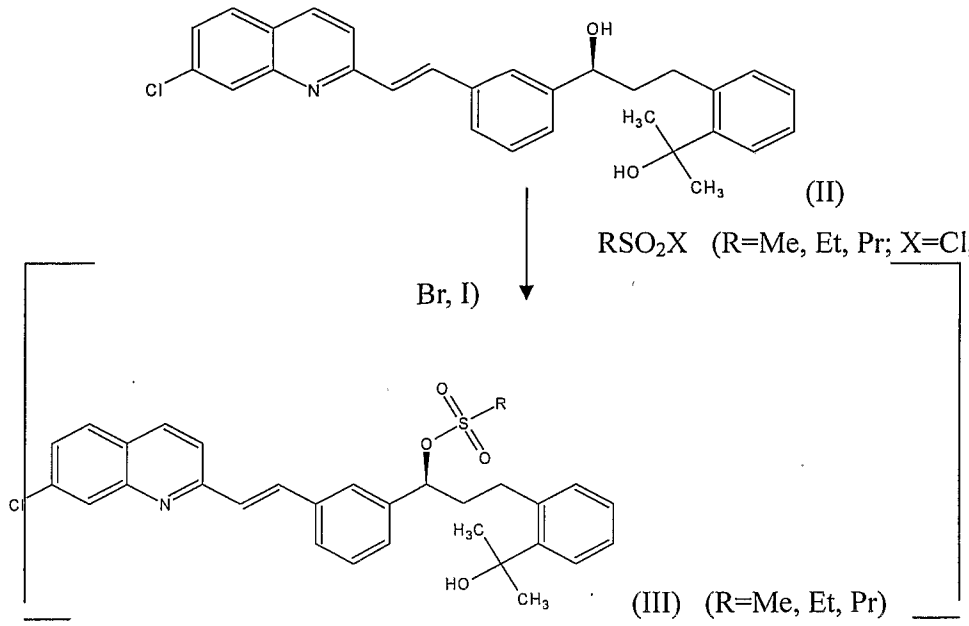
(I)

(a) treating methyl1-(mercaptomethyl)-cyclopropane acetate of formula IX, in 2-10 volumes of a suitable solvent with alkali metal or alkaline earth metal hydroxide at a temperature ranging from 20 to 80°C affording the monometallide salt of the structure X, which is isolated by concentrating the saponified mass followed by dehydrating the water by using a suitable base.



(b) treating the compound of the formula X with one molar equivalent of a metalide forming substance to get the dimetallide derivative of the formula XI, at a temperature ranging from -50 to 0°C,

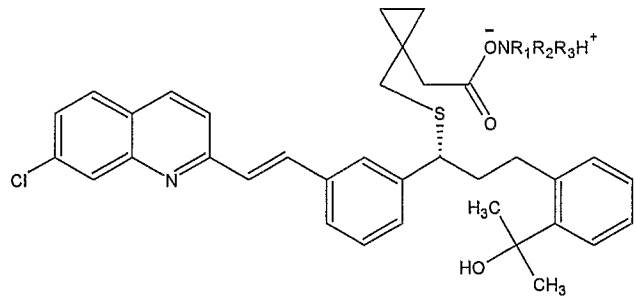
(c) treating the compound of the formula II with an alkylsulfonyl halide in a suitable solvent in presence of a base at a temperature ranging from -50 to 0°C followed by filtration and redissolution of the residue in a suitable solvent,



(d) mixing a solution of 2-(2-(3-(S)-(3-(2-(7-chloro-2-quinolinyl)-ethenyl)phenyl-3-alkylsulphonyloxypropyl)phenyl)-2-propanol (III) with a suspension of 1.1 to 1.5 moles of XI cooled to -20 to 0°C and maintained at that temperature for 8-20 hrs,

(e) extracting out the active substance, after adjusting the pH between 2-6, from the reaction mass by using a suitable solvent,

(f) reacting the montelukast solution with a suitable base in the molar equivalents of 1.0-2.0 molar to afford the montelukast salt (XII)



(XII)

(g) purifying XII by crystallization from 3 to 5 volumes of a suitable solvent at 50-80°C and cooling to ambient temperature,

(h) dissolving purified XII in 8-10 volumes of a suitable solvent and treating it with an equivalent quantity of sodium base at 25 to 50°C,

(i) adding 25-50 volumes of an antisolvent and keeping the contents at 25 to 50°C.

2. A process as claimed in claim 1, wherein in step (a) the suitable solvent for saponification of the compound of the formula IX to a monometallide salt of formula X is selected from methanol, ethanol, n- or isopropanol, preferably methanol.

3. A process as claimed in claim 1, wherein in step (a) the suitable solvent for the isolation of compound of the formula X is selected from the hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, THF, acetonitrile, preferably toluene.

4. A process as claimed in claim 1, wherein in step (a) the suitable base for the saponification of the compound of the formula IX affording X is selected from the group comprising sodium hydroxide, potassium hydroxide, calcium hydroxide or magnesium hydroxide, preferably sodium hydroxide.

5. A process as claimed in claim 1, wherein in step (a) the saponification of the compound of the formula IX affording X is carried out at 20 to 80°C preferably 50°C.

6. A process as claimed in claim 1, wherein in step (b) the suitable solvent for the dimetallation of the compound of the formula X affording XI is selected from the hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, THF, acetonitrile, preferably THF.

7. A process as claimed in claim 1, wherein in step (b) the suitable reagent for the dimetallation of the compound of the formula X affording XI is selected from lithium forming substances such as n-, sec- & tert-butyl lithium, lithium hydride, sodium forming substance such as sodium hydride, sodium methoxide,

phenyl sodium, potassium forming substance such as potassium hydride, potassium methoxide, calcium forming substance such as calcium hydride, magnesium forming substance such as magnesium oxide, more preferably n-butyl lithium.

8. .A process as claimed in claim 1, wherein in step (b) the temperatures employed for the dimetallation of the compound of the formula X affording XI is carried out at -20 to 20°C preferably -10°C.

9. A process as claimed in claim 1, wherein in step (c) the suitable solvent for the conversion of the compound of the formula II to the compound of the formula III is selected from the ethers such as dialkyl ethers, where alkyl connotes methyl, ethyl, n- & iso propyl, cyclic ethers such as THF, 1,4-dioxane, preferably the cyclic ethers like tetrahydrofuran and 1,4-dioxane.

10. A process as claimed in claim 1, wherein in step (c) the suitable alkyl sulfonyl halide for the conversion of the compound of the formula II to the compound of the formula III is selected from methanesulfonyl chloride, ethane sulfonyl chloride, propane sulfonyl chloride; methanesulfonyl bromide, ethane sulfonyl bromide, propane sulfonyl bromide; methanesulfonyl iodide, ethane sulfonyl iodide, propane sulfonyl iodide, more preferably methanesulfonyl chloride or ethane sulfonyl chloride.

11. A process as claimed in claim 1, wherein in step (c) the molar quantity of the alkyl sulfonyl halide used for the conversion of the compound of the formula II to the compound of the formula III can be varied between 1.0 and 1.5 but preferably 1.1-1.2 moles with respect to the compound of the formula II.

12. A process as claimed in claim 1, wherein in step (c) the temperatures employed for the conversion of the compound of the formula II to the compound of the formula III is carried out at -50 to 20°C, preferably -20°C.

13. A process as claimed in claim 1, wherein in step (d) the reaction temperatures employed for the condensation between the compound of the formula III with the compound of the formula XI is carried out at -50 to 0°C, preferably -10°C.

14. A process as claimed in claim 1, wherein in step (d) the molar quantity of XI employed is 1.0-2.0 moles with respect to the compound of the formula II but preferably 1.4 to 1.5 moles with respect to the compound of the formula II.

15. A process as claimed in claim 1, wherein in step (e) the suitable solvent for extracting out the active substance, after adjusting the pH, from the reaction mass is selected from hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, or esters such as methyl acetate, ethyl acetate or n-butyl acetate, more preferably ethyl acetate.

16. A process as claimed in claim 1, wherein in step (e) the suitable pH for adjustment is selected from 2 to 6 units, preferably 3.5.

17. A process as claimed in claim 1, wherein in step (f) the suitable base for the conversion of the compound of the formula II affording XII is selected from either an achiral base like benzhydryl amine (aminodiphenylmethane) or the commercially available chirally pure bases such as α–methyl benzylamine, brucine, strychnine, quinine, cinchonidine, ephedrine, amphetamine, 3-nitro-α–methyl benzylamine, 4-nitro-α–methyl benzylamine, phenyl alinol, 1R,2R-2-amino-1,2-diphenylethanol, α–methyl naphthylethylamine, phenyl propanolamine, more preferably the chirally pure bases, such as α–methyl benzylamine.

18. A process as claimed in claim 1, wherein in step (f) the molar quantity of the base used for this salt formation can be varied between 1.0 to 1.5 moles with respect to the compound of the formula II but preferably 1.1-1.2 moles with respect to the compound of the formula II.

19. A process as claimed in claim 1, wherein in step (g) the organic solvent for purification of the compound of the formula XII is selected from halogenated organic solvents, ethers, alkyl acetates, aromatic hydrocarbons, etc. more preferably alkyl acetates such as ethyl acetate.

20. A process as claimed in claim 1, wherein in step (h) the suitable solvent for dissolving the purified compound of the formula XII is selected from hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, ketones such as acetone, methyl ethyl ketone or methyl isobutyl ketone or esters such as methyl acetate, ethyl acetate or n-butyl acetate, more preferably toluene.

21. A process as claimed in claim 1, wherein in step (h) the suitable base for converting the purified compound of the formula XII to the sodium salt is selected from sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium alkoxide, where alkoxide connotes methoxide, ethoxide, n- & iso-propoxide, more preferably sodium methoxide.

22. A process as claimed in claim 1, wherein in step (i) the suitable antisolvent for precipitating the compound of the formula I is selected from hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, ketones such as acetone, methyl ethyl ketone or methyl isobutyl ketone or esters such as methyl acetate, ethyl acetate or n-butyl acetate, preferably n-heptane.

23. A process for the preparation of 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio] methyl] cyclopropane acetic acid, sodium salt [montelukast sodium(I)] essentially as described and with particular reference to the examples.

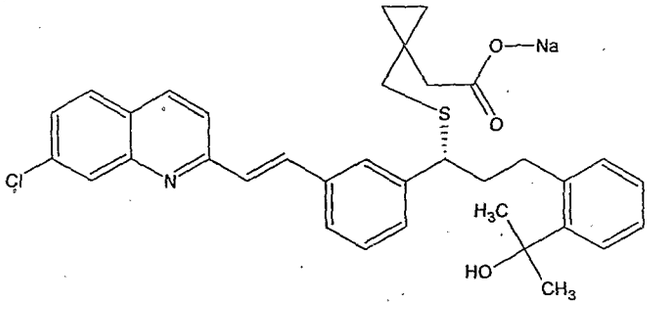
24. A process for the preparation of 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio] methyl] cyclopropane acetic acid, sodium salt [montelukast sodium(I)] whenever prepared by the process of any of the claims 1-23.

AMENDED CLAIMS

[Received by the International Bureau on 07 Mayl 2007 (07.05.07)]

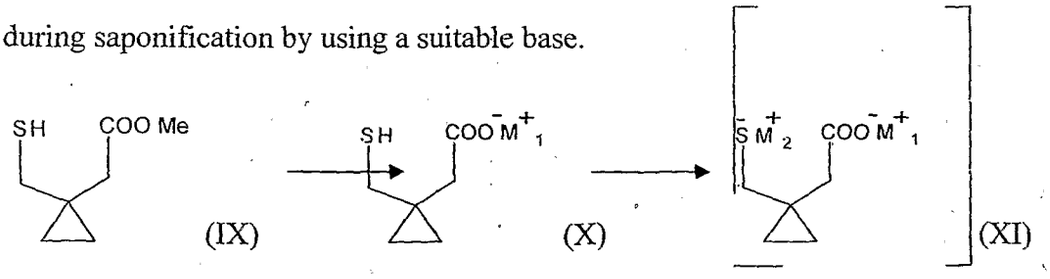
We claim:

1. A process for preparing 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropane acetic acid, sodium salt [Montelukast sodium (I)], the said process comprising steps of-



(I)

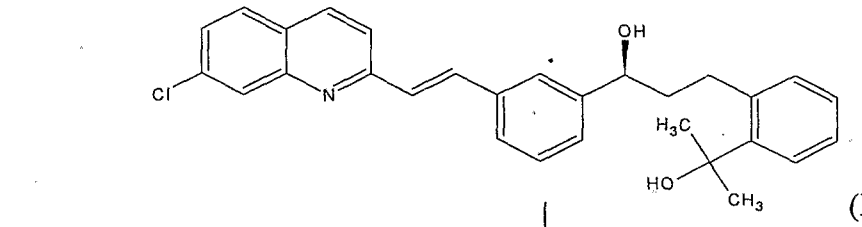
(a) treating methyl1-(mercaptomethyl)-cyclopropane acetate of formula IX, in 2-10 volumes of a suitable solvent for saponification, along with alkali metal or alkaline earth metal hydroxide at a temperature ranging from 20 to 80°C affording the monometallide salt of the structure X, which is isolated by concentrating the saponified mass in a suitable solvent followed by dehydrating the water formed during saponification by using a suitable base.



(M_1=Na, K, Ca, Mg; M_2=Li, Na, K)

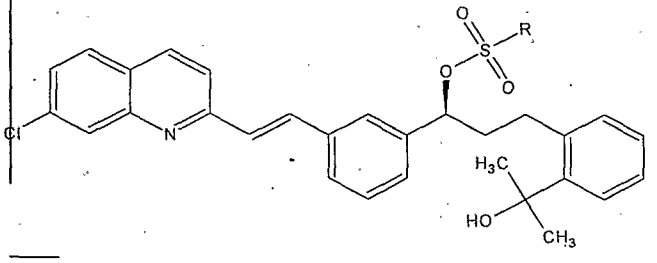
(b) treating the compound of the formula X with one molar equivalent of a metalide forming substance to get the dimetallide derivative of the formula XI, at a temperature ranging from -50 to 20°C,

(c) treating the compound of the formula II with an alkylsulfonyl halide in a suitable solvent in presence of a base at a temperature ranging from -50 to 20°C followed by filtration and redissolution of the residue in a suitable solvent,



(II)

RSO_2X (R=Me, Et, Pr; X=Cl, Br, I)

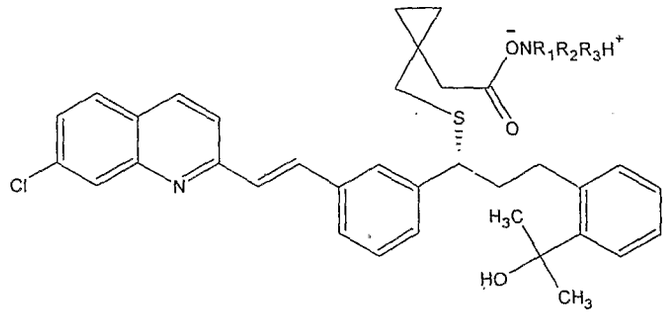


(III) (R=Me, Et, Pr)

(d) mixing a solution of 2-(2-(3-(S)-(3-(2-(7-chloro-2-quinolinyl)-ethenyl)phenyl-3-alkylsulphonyloxypropyl)phenyl)-2-propanol (III) with a suspension of 1.1 to 1.5 moles of XI cooled to -20 to 0°C and maintained at that temperature for 8-20 hrs,

(e) extracting out the active substance, after adjusting the pH between 2-6, from the reaction mass by using a suitable solvent,

(f) reacting the Montelukast solution with a suitable base in a ratio of 1: (1.0-20.)to afford the Montelukast salt (XII)



(XII)

(g) purifying XII by crystallization from 3 to 5 volumes of a suitable solvent at 50-80°C and cooling to ambient temperature,

(h) dissolving purified XII in 8-10 volumes of a suitable solvent and treating in 1:1 ratio with a suitable sodium base, at a temperature of 25 to 50°C,

(i) adding 25-50 volumes of an antisolvent and keeping the contents at 25 to 50°C,

2. A process as claimed in claim 1, wherein in step (a) the suitable solvent for saponification of the compound of the formula IX to a monometallide salt of formula X is selected from methanol, ethanol, n- or isopropanol, preferably methanol.

3. A process as claimed in claim 1, wherein in step (a) the suitable solvent for the isolation of compound of the formula X is selected from the hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertiary butyl ether, THF, acetonitrile, preferably toluene.

4. A process as claimed in claim 1, wherein in step (a) the suitable base for the saponification of the compound of the formula IX affording X is selected from the group comprising sodium hydroxide, potassium hydroxide, calcium hydroxide or magnesium hydroxide, preferably sodium hydroxide.

5. A process as claimed in claim 1, wherein in step (a) the saponification of the compound of the formula IX affording X is carried out at 20 to 80°C preferably 50°C.

6. A process as claimed in claim 1, wherein in step (b) the suitable solvent for the dimetallation of the compound of the formula X affording XI is selected from the hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertiary butyl ether, THF, acetonitrile, preferably THF.

7. A process as claimed in claim 1, wherein in step (b) the suitable reagent for the dimetallation of the compound of the formula X affording XI is selected from lithium forming substances such as n-, sec- & tert-butyl lithium, lithium hydride, sodium forming substance such as sodium hydride, sodium methoxide, phenyl sodium, potassium forming substance such as potassium hydride, potassium methoxide, calcium forming substance such as calcium hydride, magnesium forming substance such as magnesium oxide, more preferably n-butyl lithium.

8. .A process as claimed in claim 1, wherein in step (b) the temperatures employed for the dimetallation of the compound of the formula X affording XI is carried out at -20 to 20°C preferably -10°C.

9. A process as claimed in claim 1, wherein in step (c) the suitable solvent for the conversion of the compound of the formula II to the compound of the formula III is selected from the ethers such as dialkyl ethers, where alkyl connotes methyl, ethyl, n- & iso propyl, cyclic ethers such as THF, 1,4-dioxane, preferably the cyclic ethers like tetrahydrofuran and 1,4-dioxane.

10. A process as claimed in claim 1, wherein in step (c) the suitable alkyl sulfonyl halide for the conversion of the compound of the formula II to the compound of the formula III is selected from methanesulfonyl chloride, ethane sulfonyl chloride, propane sulfonyl chloride; methanesulfonyl bromide, ethane sulfonyl bromide, propane sulfonyl bromide; methanesulfonyl iodide, ethane sulfonyl iodide, propane sulfonyl iodide, more preferably methanesulfonyl chloride or ethane sulfonyl chloride.

11. A process as claimed in claim 1, wherein in step (c) the molar quantity of the alkyl sulfonyl halide used for the conversion of the compound of the formula II to the compound of the formula III can be varied between 1.0 and 1.5 but preferably 1.1-1.2 moles with respect to the compound of the formula II.

12. A process as claimed in claim 1, wherein in step (c) the temperatures employed for the conversion of the compound of the formula II to the compound of the formula III is carried out at -50 to 20°C, preferably -20°C.

13. A process as claimed in claim 1, wherein in step (d) the reaction temperatures employed for the condensation between the compound of the formula III with the compound of the formula XI is carried out at -50 to 0°C, preferably -10°C.

14. A process as claimed in claim 1, wherein in step (d) the molar quantity of XI employed is 1.0-2.0 moles with respect to the compound of the formula II but preferably 1.4 to 1.5 moles with respect to the compound of the formula II.

15. A process as claimed in claim 1, wherein in step (e) the suitable solvent for extracting out the active substance, after adjusting the pH, from the reaction mass is selected from hydrocarbons such as hexane, n-heptane, cyclohexane, toluene,

ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, or esters such as methyl acetate, ethyl acetate or n-butyl acetate, more preferably ethyl acetate.

16. A process as claimed in claim 1, wherein in step (e) the suitable pH for adjustment is selected from 2 to 6 units, preferably 3.5.

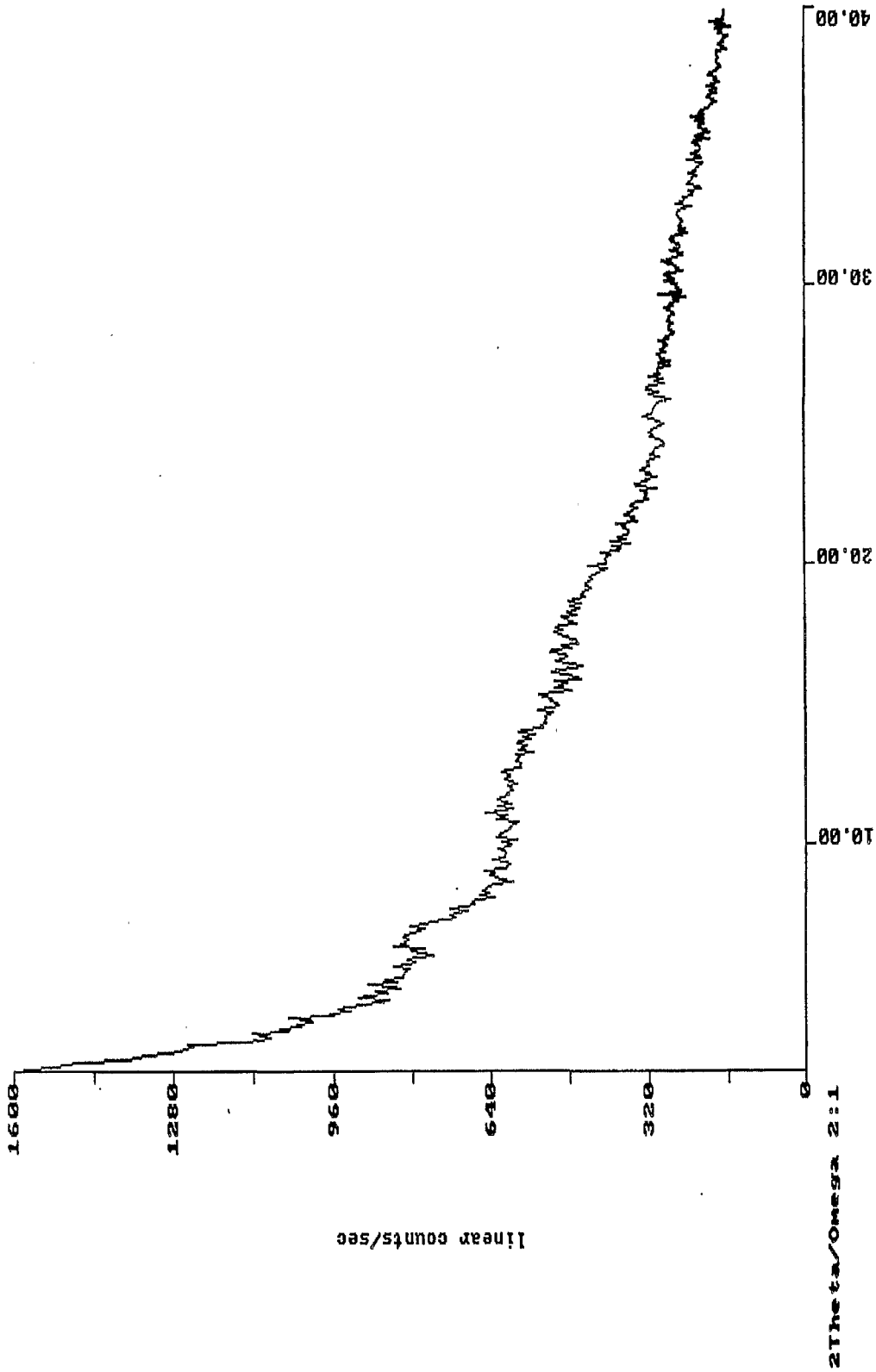
17. A process as claimed in claim 1, wherein in step (f) the suitable base for the conversion of the compound of the formula II affording XII is selected from either an achiral base like benzhydryl amine (aminodiphenylmethane) or the commercially available chirally pure bases such as α–methyl benzylamine, brucine, strychnine, quinine, cinchonidine, ephedrine, amphetamine, 3-nitro-α–methyl benzylamine, 4-nitro-α–methyl benzylamine, phenyl alinol, 1R,2R-2-amino-1,2-diphenylethanol, α–methyl naphthylethylamine, phenyl propanolamine, more preferably the chirally pure bases, such as α–methyl benzylamine.

18. A process as claimed in claim 1, wherein in step (f) the molar quantity of the base used for this salt formation can be varied between 1.0 to 1.5 moles with respect to the compound of the formula II but preferably 1.1-1.2 moles with respect to the compound of the formula II.

19. A process as claimed in claim 1, wherein in step (g) the organic solvent for purification of the compound of the formula XII is selected from halogenated organic solvents, ethers, alkyl acetates, aromatic hydrocarbons, etc. more preferably alkyl acetates such as ethyl acetate.

20. A process as claimed in claim 1, wherein in step (h) the suitable solvent for dissolving the purified compound of the formula XII is selected from hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, ketones such as acetone, methyl ethyl ketone or methyl isobutyl ketone or esters such as methyl acetate, ethyl acetate or n-butyl acetate, more preferably toluene.
21. A process as claimed in claim 1, wherein in step (h) the suitable base for converting the purified compound of the formula XII to the sodium salt is selected from sodium hydroxide, sodium carbonate, sodium bicarbonate, sodium alkoxide, where alkoxide connotes methoxide, ethoxide, n- & iso- propoxide, more preferably sodium methoxide.
22. A process as claimed in claim 1, wherein in step (i) the suitable antisolvent for precipitating the compound of the formula I is selected from hydrocarbons such as hexane, n-heptane, cyclohexane, toluene, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, ketones such as acetone, methyl ethyl ketone or methyl isobutyl ketone or esters such as methyl acetate, ethyl acetate or n-butyl acetate, preferably n-heptane.
23. A process for the preparation of 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio] methyl] cyclopropane acetic acid, sodium salt [Montelukast sodium(I)] essentially as described and with particular reference to the examples.
24. A process for the preparation of 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl) ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio] methyl]

cyclopropane acetic acid, sodium salt [Montelukast sodium(I)] whenever prepared by the process of any of the claims 1-23.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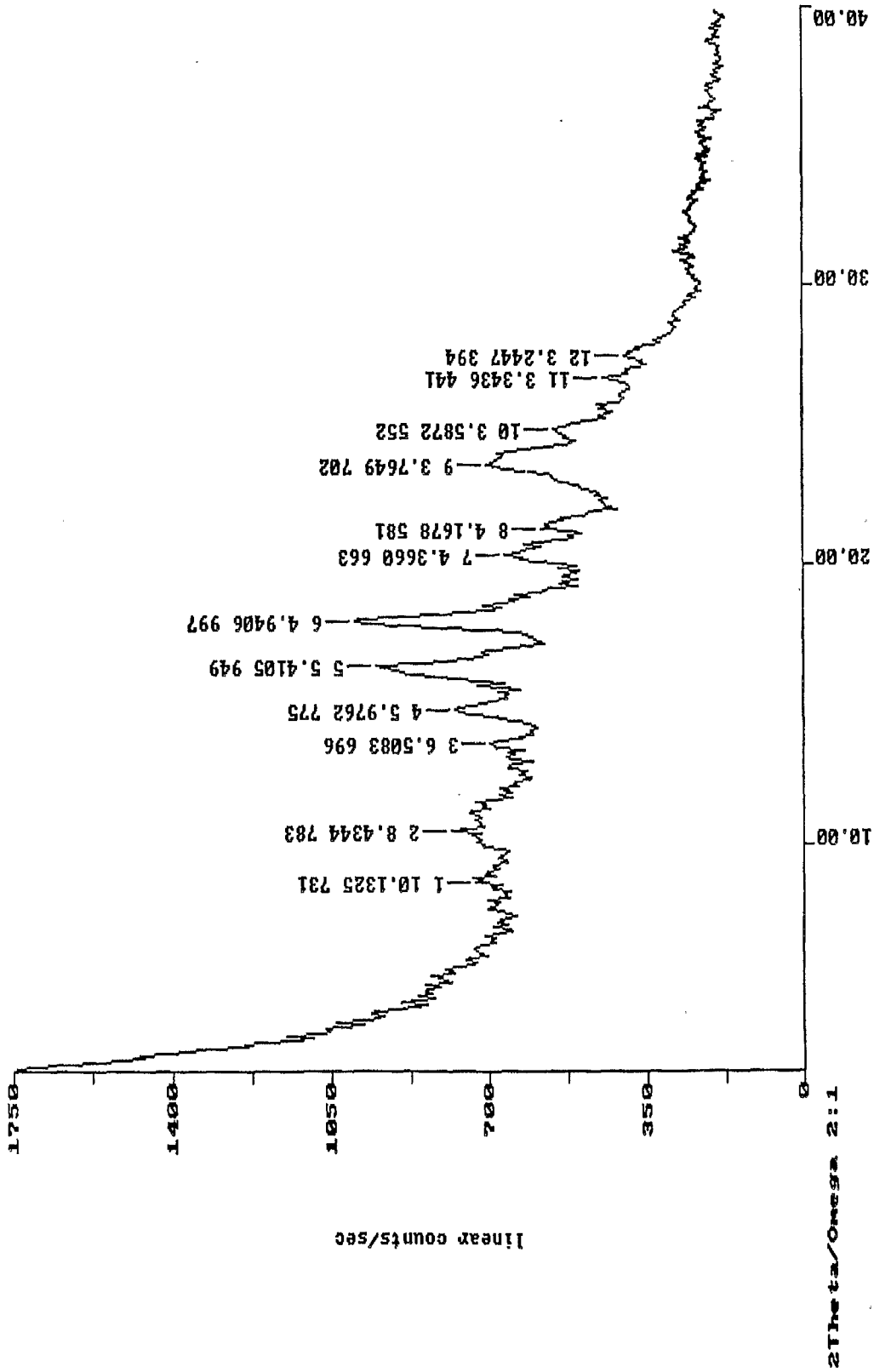
(Fig-1)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5 5.4105 949
6 4.9406 997
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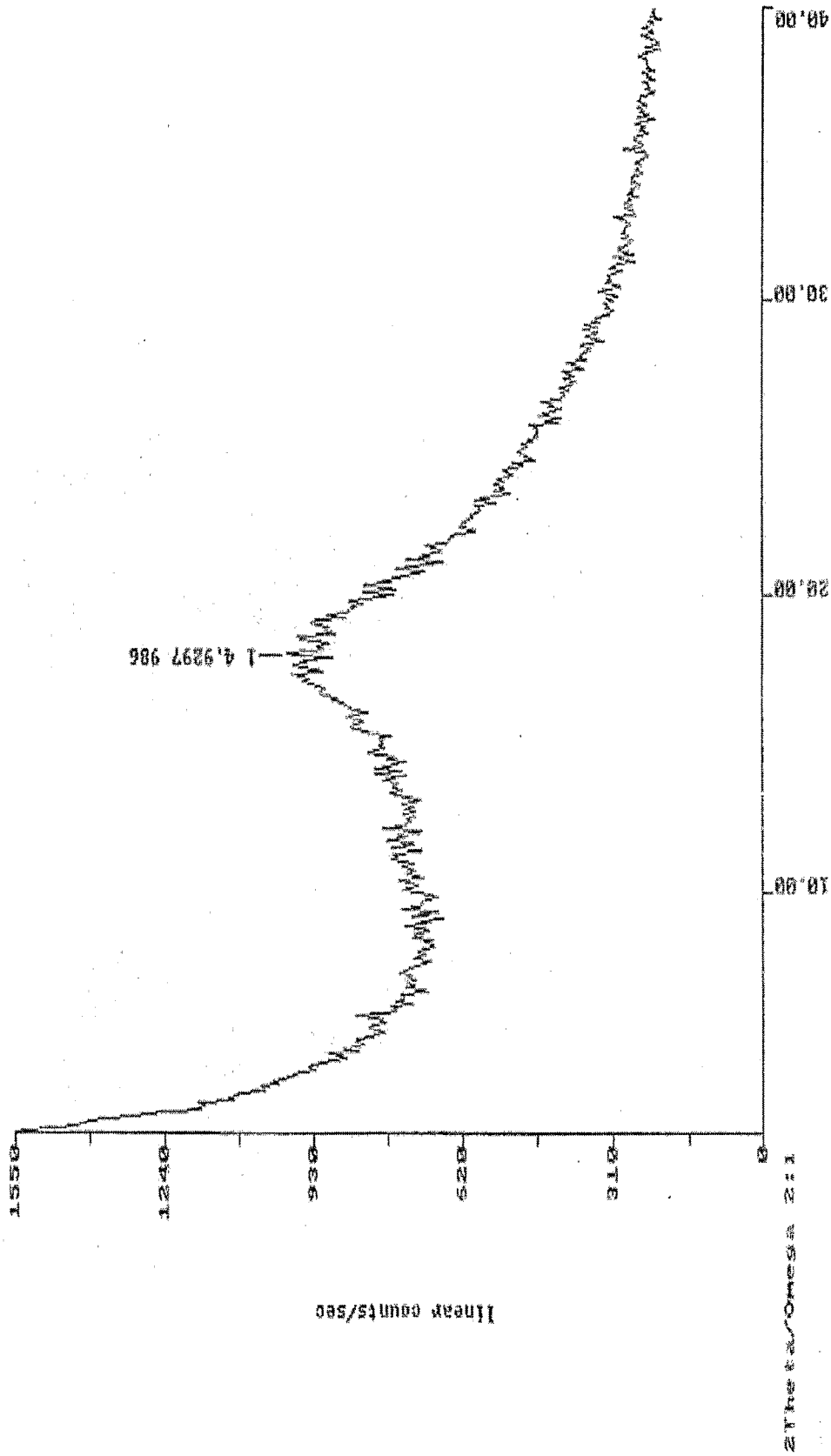
12 3.2447 394

(Fig-2)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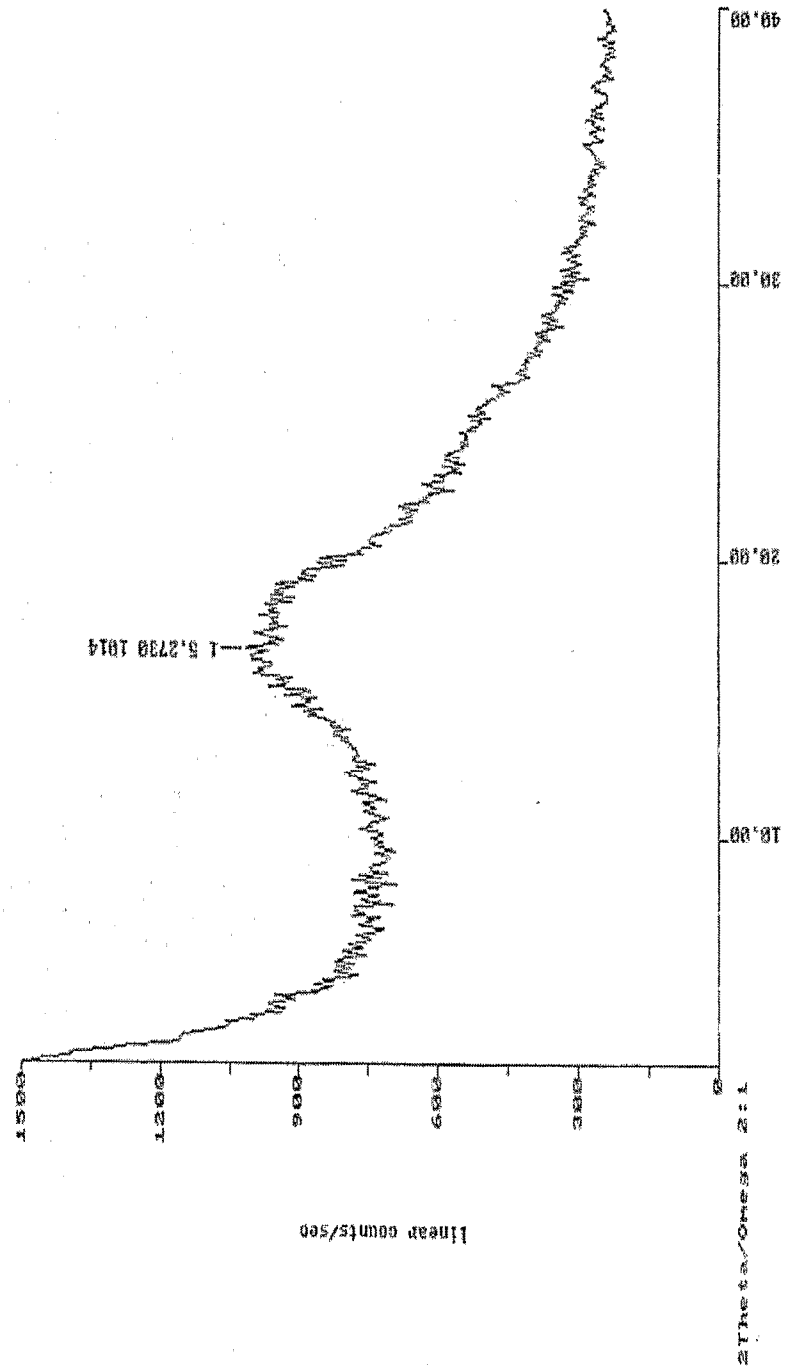
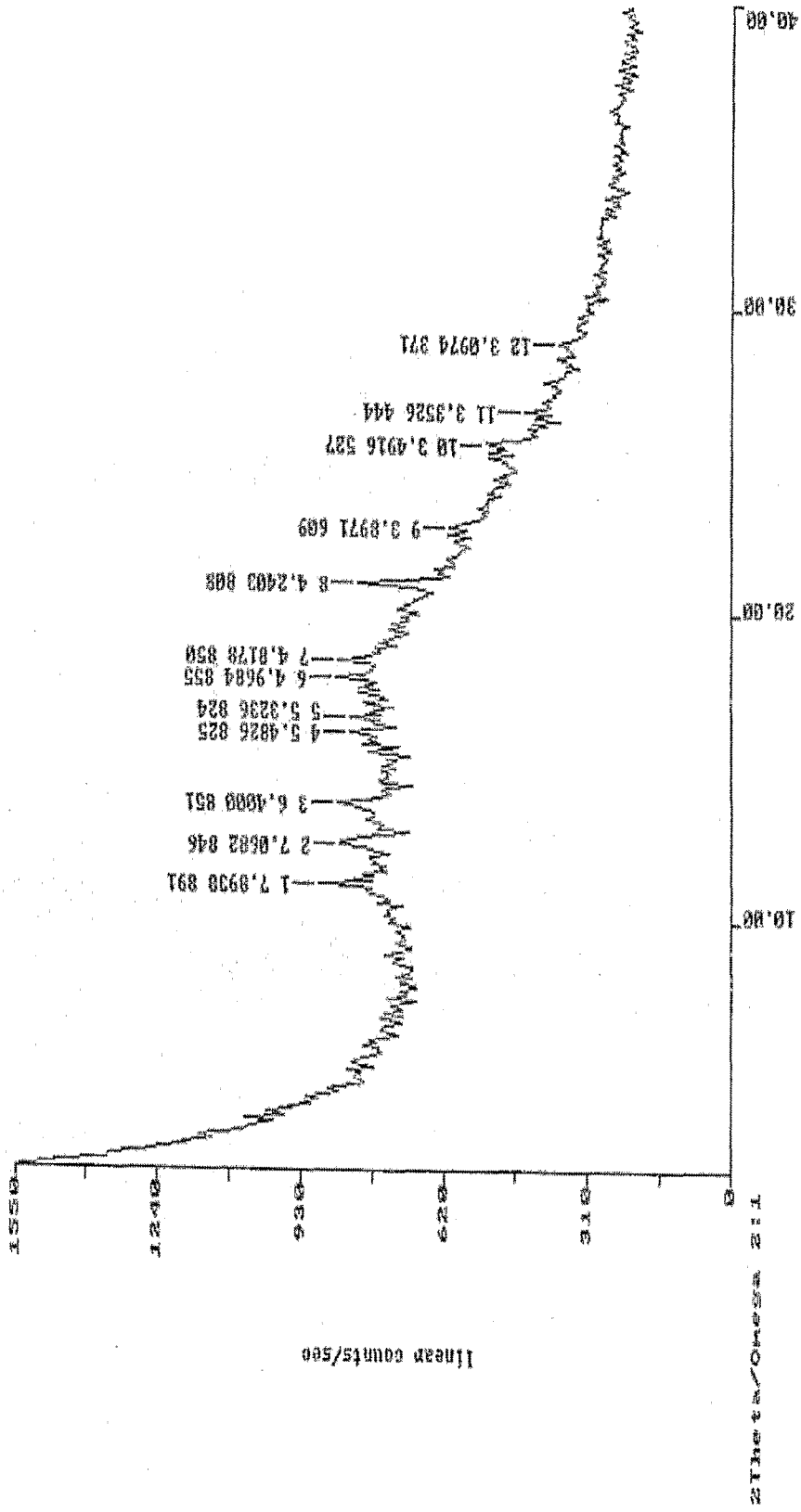
Linear counts/sec
2Theta/Omega 2:1

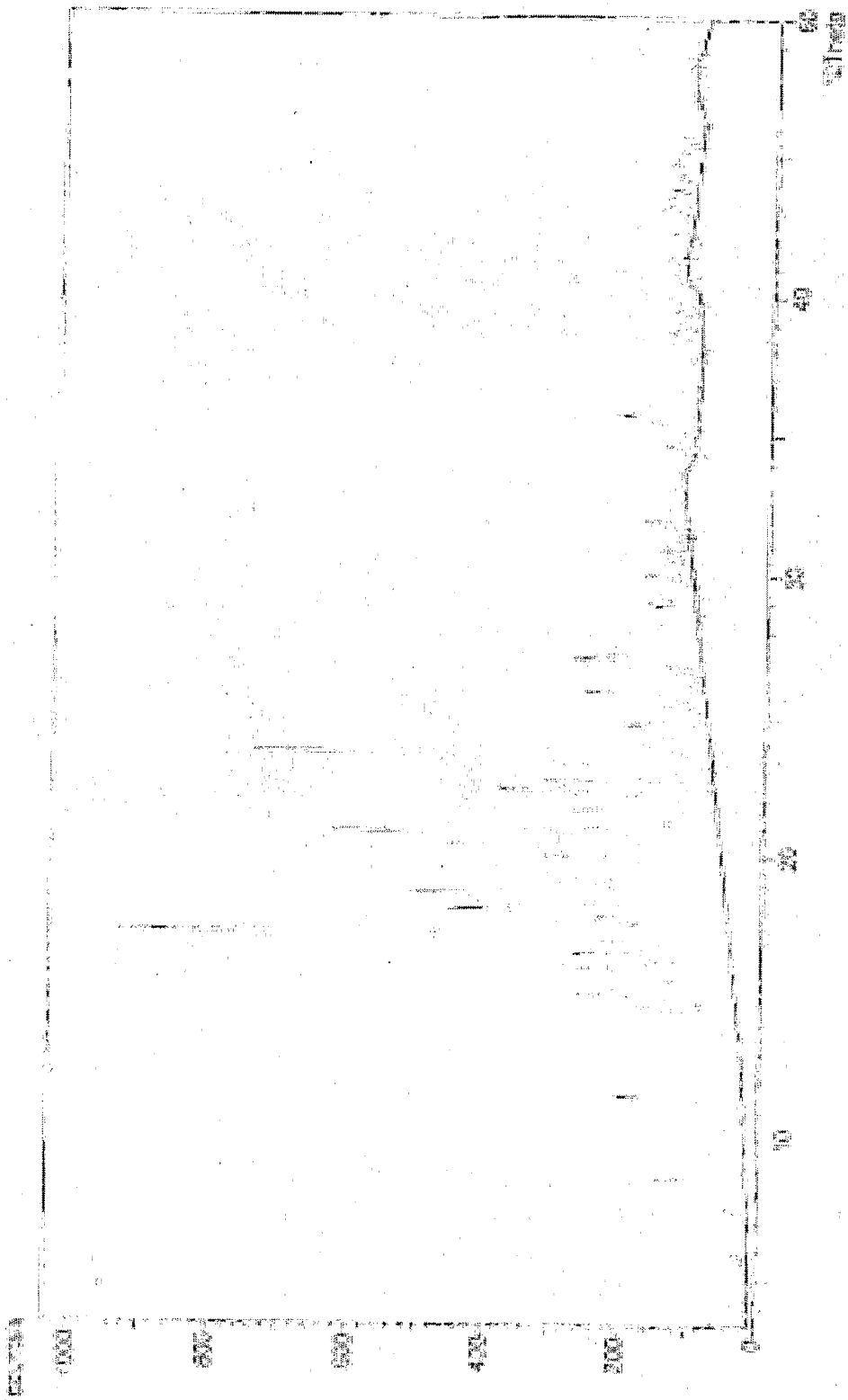
(Fig-3)


1 5.2738 1014
Linear counts/sec
2Theta/Omega 2:1
10.00
20.00
30.00
40.00
0
300
600
900
1200
1500

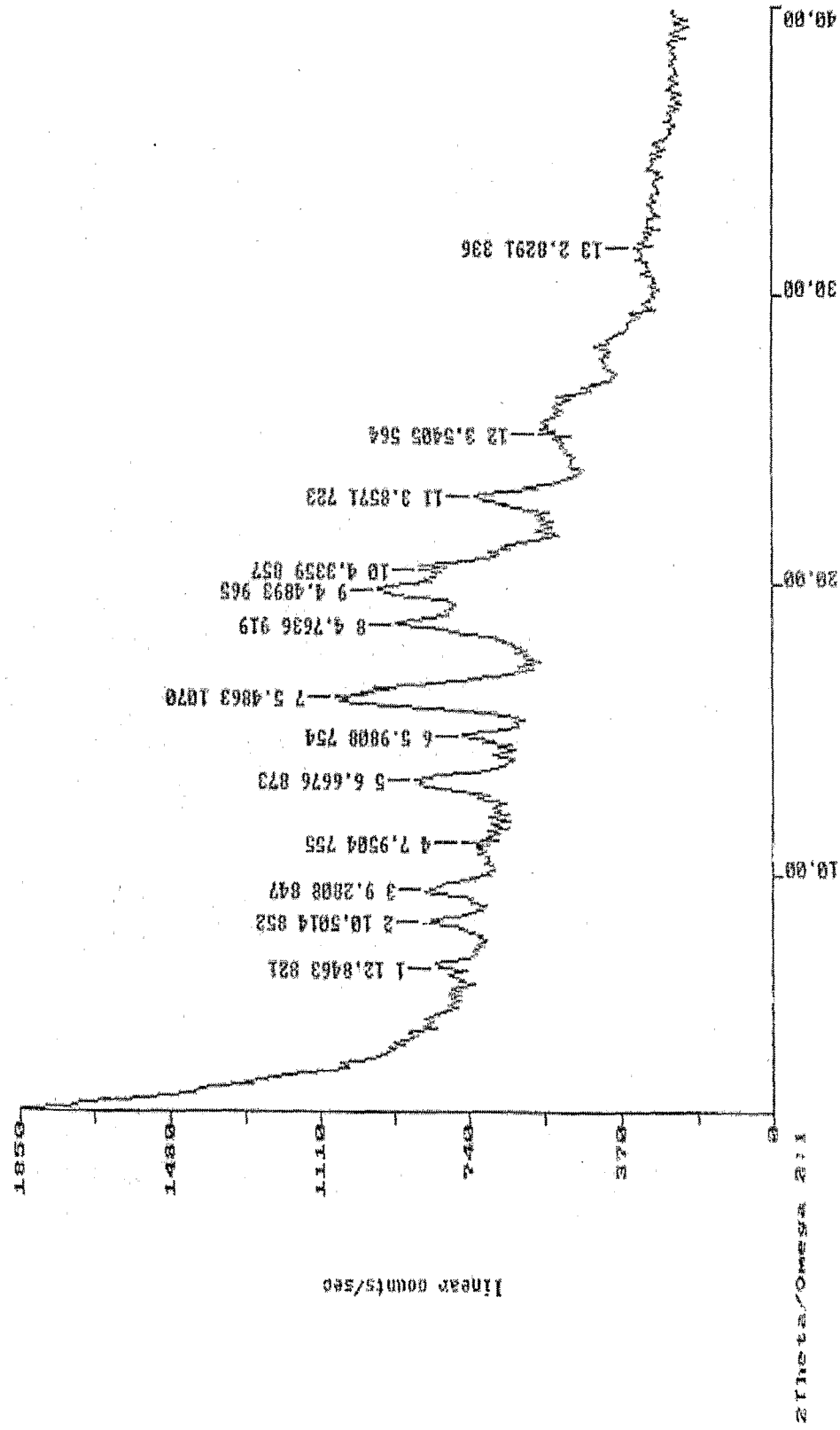
(Fig-4)


Linear counts/sec
2Theta/Omega
1 7,0938 891
2 7,0682 846
3 6,4008 851
4 5,4826 825
5 5,3236 824
6 4,9684 855
7 4,8178 850
8 4,2403 808
9 3,8971 609
10 3,4916 527
11 3,3526 444
12 3,0974 371

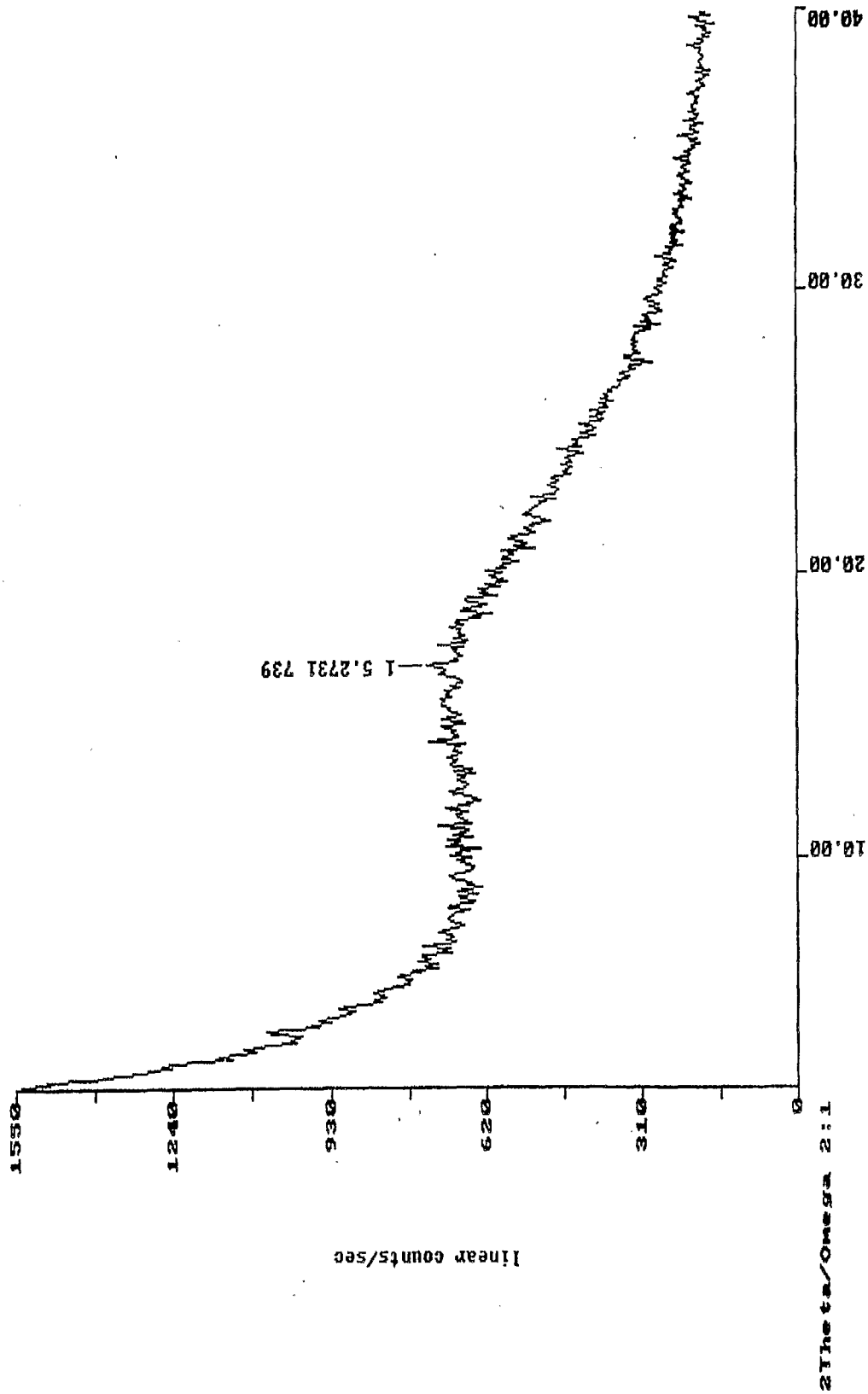
(Fig-5)



(Fig-6)


1 12,8463 821
2 10,5014 852
3 9,2808 847
4 7,9504 755
5 6,6676 873
6 5,9808 754
7 5,4863 1070
8 4,7636 919
9 4,4893 965
10 4,3359 857
11 3,8571 723
12 3,5405 564
13 2,8291 336
1850
1480
1110
740
370
0
10,00
20,00
30,00
40,00
Linear counts/sec
2Theta/Omega 2:1

(Fig-7)


1550
1240
930
620
310
0
Linear counts/sec
10.00
20.00
30.00
40.00
2Theta/Omega 2:1
1 5.2731 739

(Fig-8)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/002690

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C07D 215/18 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Database: STN; File: Medline, WPIDS, CA, Biosis; Keyword: montelukast, preparation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/108679 A1 (MOREPEN LABORATORIES LIMITED) 16 December 2004 Whole document, Scheme 2	1-24
X	EP 0 737 186 B1 (MERCK & CO., INC.) 19 August 1998 Whole document, Examples 6 and 7	1-24
A	WO 2006/008751 A2 (MATRIX LABORATORIES LTD) 26 January 2006 Whole document	1-24
P,X	WO 2006/058545 A1 (MEDICHEM S.A.) 8 June 2006 Whole document	1-24

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
16 February 2007	-2 MAR 2007
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **IAN DOWD** Telephone No : (02) 6283 2273

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/002690

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2006/064269 A2 (CIPLA LIMITED) 22 June 2006 Whole document	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IB2006/002690

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2004108679	AU	2003253247	CA	2528228	EP	1631550
EP	0737186	AU	14448/95	BG	100638	BR	9408452
		CA	2179407	CN	1139429	CN	1219535
		CY	2104	CZ	9601878	FI	962641
		HK	1009269	HR	941022	HU	76279
		LV	12313	NZ	278263	PL	315155
		US	5614632	US	6320052	WO	9518107
WO	2006008751						
WO	2006058545						
WO	2006064269						

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX