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RESEARCH ARTICLE

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SYNTHESIS OF MONTELUKAST SODIUM VIA AN ESTER INTERMEDIATE; SYNTHEIS AND CHARACTERIZATION OF IMPURITIES

CHANDRA SEKHAR BVVN [$A], RAMESH KUMAR N [A], KALYAN CHAKRAVARTHY A [A] AND MUKKANTI K [B]

[A] Dr Reddy's Laboratories Limited, Bachupalli, Qutubullapur, Rangareddy District-72, Andhra Pradesh, India. Fax: 91 40 4434 6285

[B] Institute of Science and Technology, JNTU, Hyderabad.

[$]CHANDRA SEKHAR BVVN

Dr Reddy's Laboratories Limited, Bachupalli, Qutubullapur, Rangareddy District-72

ABSTRACT

The objective is to study novel synthetic approaches for the synthesis of leukotriene receptor antagonist, Montelukast sodium. The current study also deals with synthesis and characterization of impurities of Montelukast sodium.

KEYWORDS

Montelukast sodium, leukotriene receptor antagonist, synthetic approach

INTRODUCTION

The sodium salt of Montelukast is a leukotriene receptor antagonist (LTD4). It is useful in treatment of asthma, inflammation, allergies, angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis and allograft rejection. [1]

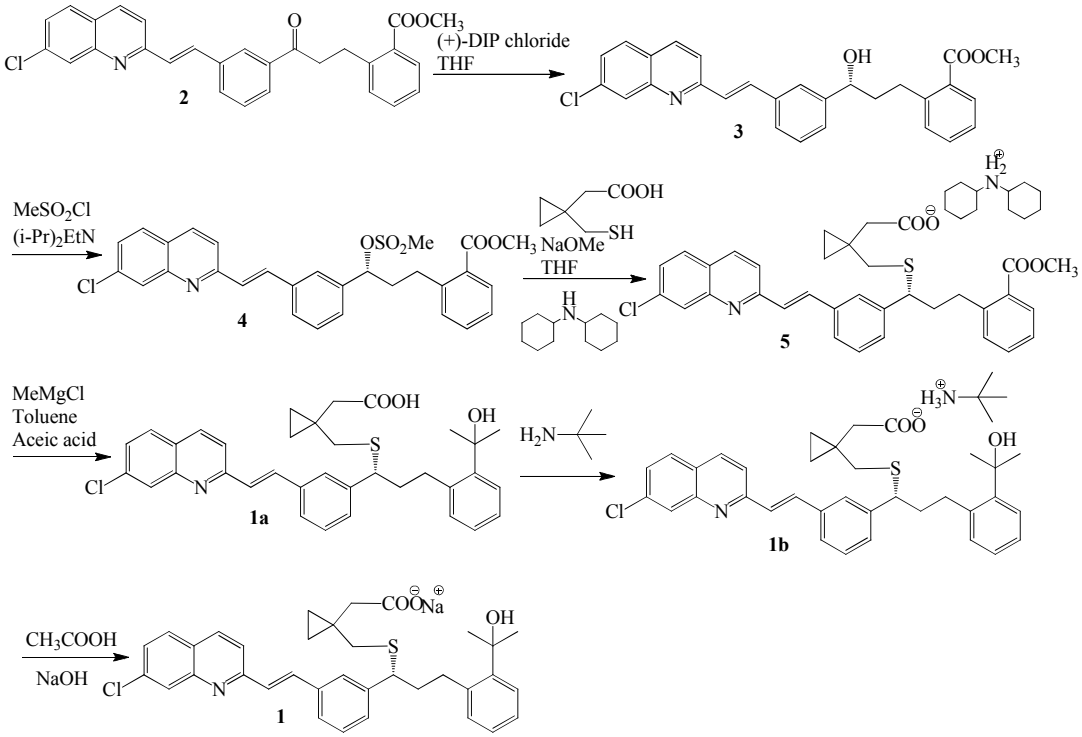
Leukotrienes constitute a group of locally acting hormones that are produced, in living systems, from arachidonic acid. Major leukotrienes are Leukotriene B4 (abbreviated as LTB4), LTC4, LTD4, and LTE4. Biosynthesis of these leukotrienes begins with the action of the enzyme 5-lipoxygenase on arachidonic acid to produce the epoxide known as Leukotriene A4 (LTA4), which is then converted to other leukotrienes by subsequent enzymatic steps. Further details of the biosynthesis as well as the metabolism of the leukotrienes are to be found in the book Leukotrienes and Lipoxygenases, Ed. J. Rokach, Elsevier, Amsterdam (1989). The actions of the leukotrienes in living systems and their contribution to various disease states are also discussed in the book by Rokach. [2]

Different synthetic approaches are reported in literature. [2-8] As a part of the ongoing research and development program, and with an objective of providing simple and commercially viable synthetic processes[9], the present work relates to novel synthetic approaches that are followed for the preparation of Montelukast sodium. It is also the objective of the present work to identify and characterize the process related impurities of the novel synthetic approaches experimented in the present work.

Novel synthetic approaches are depicted in the following scheme and the details are as follows:

MATERIALS AND METHODS

Scheme:



According to the above scheme, Montelukast sodium (1) was prepared by:

(i) reducing (E)-methyl 2-(3-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-oxopropyl)benzoate **(2)** using (+)-B-chloro diisopinocampheylborane as a chiral reducing reagent in dichloromethane solvent which is followed by quenching the reaction mixture with aqueous ammonia. Isolating the resulting precipitate and further purifying in a mixture of methanol and water to provide pure (R,E)-methyl 2-(3-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-hydroxypropyl)benzoate **(3)**;

(ii) mesylating the resulting purified hydroxy ester **(3)** with methane sulphonyl chloride in presence of diisopropyl ethyl amine in dichloromethane solvent to provide the mesylate **(4)**;

(iii) reacting the mesylate **(3)** with disodium salt of 1-(mercapto methyl) cyclpropane acetic acid that is prepared by treating 1-(mercapto methyl) cyclpropane acetic acid with sodium methoxide, in a mixture of dichloromethane and N,N-dimethyl formamide to provide an ester analog of Montelukast. Further converting it into dicyclohexyl amine salt by treating with dicyclohexylamine in acetone solvent to provide dicyclohexyl amine salt of 2-(2-((((R)-1-(3-((E)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(methoxycarbonyl) phenyl) propyl)thio)methyl)cyclopropyl) acetic acid **(5)**;

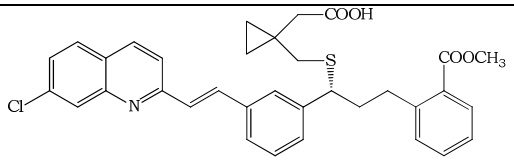
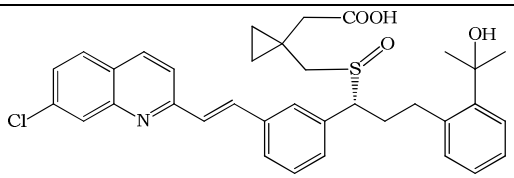
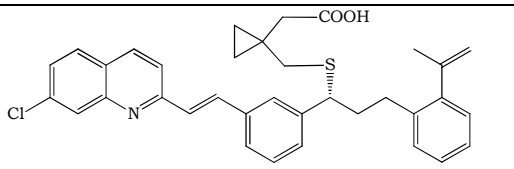
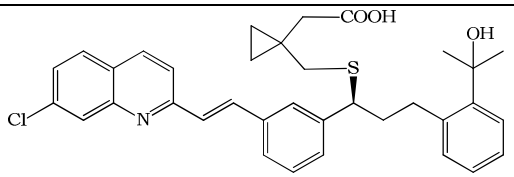
(iv) reacting the ester **(5)** with methyl magnesium chloride in THF under Grignard's reaction conditions in toluene solvent to convert the ester **5** in to Montelukast (1a).

The starting materials **2** was prepared by known methods for e.g., by a method known in Belley *et al*.

During the synthesis of montelukast sodium **(1)**, the following compounds were identified as impurities in Montelukast sodium obtained in the process of the present work and

the same were characterized. The structures of the impurities are depicted in Table 1.

Table-1
Structure of related impurities of Montelukast sodium (1) prepared according to present work

Compound	Structure of impurity	Chemical name
5		(R,E)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(methoxycarbonyl)phenyl) propyl)thio)methyl)cyclopropyl)acetic acid
6		2-(1-(((R)-((R)-1-(3-((E)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propyl)sulfinyl)methyl)cyclopropyl)acetic acid
7		(R,E)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(prop-1-en-2-yl)phenyl)propyl)thio)methyl)cyclopropyl)acetic acid
8		(S,E)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propyl)thio)methyl)cyclopropyl)acetic acid

Experimental

All the reactions were monitored by TLC and IR spectra were recorded on Perkin-Elmer model-1600 spectrophotometer. 1H-NMR spectra of the compounds were recorded on Perkin-Elmer EM-390-200 MHz spectrophotometer, using TMS as an internal standard.

Synthesis of (R,E)-methyl 2-(3-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-hydroxypropyl)benzoate (3):

General procedure: 100 grams (0.219 mol) of **2** was dissolved in 500 ml of dichloromethane. 180 ml of (+)-DIP chloride (0.346 mol) was taken separately in 500 ml of dichloromethane and cooled to -5^{O}C with stirring. The above solution of **2** in dichloromethane was added, slowly drop-wise, to (+)-DIP chloride in dichloromethane at -5 to 0^{O}C. After addition, the reaction mixture was aged at -5 ^{O}C to 0^{O}C for 10 hours. The resultant reaction mixture was quenched with aqueous ammonia and stirred for 60 minutes. Aqueous sodium chloride solution was added to the reaction mixture and stirred for 30 minutes. Then, the layers were separated and the organic layer was washed with aqueous sodium chloride solution. Dichloromethane was distilled from the organic layer. The resulting crude was purified from a mixture of methanol and water to yield 80 grams (Theoretical yield: 80%) of **(3)**. (Purity by HPLC: 98%). Specific optical rotation (SOR) $[\alpha]_D^{25}$ of +34^{O} (C=1 in chloroform). The obtained

product was characterized as **3** based on FT-IR, Mass and ^{1}H-NMR spectral data as depicted in Table 2.

Synthesis of dicyclohexyl amine salt of (R,E)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl) phenyl)-3-(2-(methoxycarbonyl)phenyl) propyl)thio)methyl)cyclopropyl) acetic acid (5):

General procedure: A stirred mixture of 100 grams (0.219 mol) of **3** and 500 ml of toluene, was heated to reflux and removed water by azeotropic distillation using Dean-Stark apparatus. The mixture was cooled to 50°C and the remaining solvent was distilled under reduced pressure. The residue was re-dissolved in 200 ml of dichloromethane at ambient temperature and the solvent was distilled again under reduced pressure. Again, the residue was re-dissolved in 1000 ml of dichloromethane and the mixture was cooled to 0-5°C. 57.5 ml (0.328 mol) of diisopropyl ethylamine was added at once to the stirred mixture; and the reaction mass was stirred at 0-5°C for 15-30 minutes. 22 ml (0.284 mol) of methane sulfonyl chloride was added dropwise at 0-5°C with stirring. After the addition was completed, the cooling was discontinued, and the reaction mass was maintained at 25-35°C until completion of the reaction. 600 ml of water was added and the mass was stirred for another 30 minutes. The organic and aqueous layers were separated, and the aqueous layer was extracted with 200 ml of dichloromethane. The combined organic layers were washed with water (3 X 600 ml). Dichloromethane was distilled off atmospherically, followed by distillation under reduced pressure at a temperature of below 50°C. The resultant residue was re-dissolved in toluene (200 ml), which was again distilled off under reduced pressure and 45°C-50°C to obtain a residue of the mesylate intermediate **(4)**. 38.3 grams (0.262 mol) of 1-mercapto methyl cyclopropane acetic acid and 450 ml of methanol were stirred until clear dissolution at 25-35°C for 60 minutes. A mixture of the crude intermediate mesylate **(4)** was obtained as described above, to which dichloromethane and dimethyl formamide (450 ml) were added, and the resulting reaction mass was stirred for clear dissolution at 25-35°C. Besides, the reaction mass was heated and maintained at reflux temperature for 2-3 hours. 450 ml of water was charged to the reaction mixture and continued stirring for 15 minutes. The organic and aqueous layers were separated; the aqueous layer was extracted with 200 ml of dichloromethane. On the other hand, the combined organic layers were washed with a mixture of vacuum salt (37.5 grams) and water (400 ml) solution, then washed with a solution of acetic acid (45 ml) in water (400 ml), followed by a water wash (4 X 400 ml). The solvents were distilled off atmospherically from the organic layer; followed by distillation under reduced pressure at 45-50°C. The obtained residue was dissolved in 200 ml acetone; and acetone was distilled off under reduced pressure at 45-50°C. Thus the obtained residual crude product was re-dissolved in 500 ml acetone at 25-35°C. 52 ml (0.262 mol) of dicyclohexyl amine was added to the solution of the crude residue at 25-35°C; and the mass was stirred at 25-35°C until a solid separated. After filtering the solid that separated out, the wet compound was taken into 400 ml of acetone, and heated to reflux. The mass was maintained at reflux for 1-2 hours, then cooled to 25-35°C; stirring continued for 4-5 hours. The resulting solid was filtered and washed with 50 ml of acetone. The solid was dried in an oven at 45-50°C to afford the 49.7 grams of the title compound. 49 grams (0.0639 mol) of dicyclo hexyl amine salt of 2-[1-[1-(R)-3-[2-(E)-(7chloro quinolin-2-yl) vinyl [phenyl]-3-[2-methoxy carbonyl phenyl]propyl sulfonyl methyl]cyclo propyl]acetic acid and 490 ml of acetone were charged into a round bottomed flask, and the mixture was heated to reflux. The mass was maintained at reflux for 1-2 hours, cooled to 25-35°C slowly under stirring, and maintained at 25-35°C for another 4-5 hours. The separated solid was filtered; washed with acetone (49 ml) and dried at 50-55°C to afford 44.7 grams of purified title compound.

Synthesis of (R,E)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propyl)thio) methyl)cyclopropyl) acetic acid (Montelukast free acid) (1a):

General procedure: 100 grams (0.13 mol) of **5** and 1000 ml of toluene were charged to a round bottomed flask, and stirred for about 5 minutes. A mixture of acetic acid (15 ml) and water (500 ml) was added, and the mass was further stirred for another 30 minutes. The organic and aqueous layers were separated. The resultant organic layer was dried over anhydrous sodium sulphate after washing with water (3 X 500 ml). The solvent was removed under reduced pressure at a temperature below 50°C. The resulting crude residue was dissolved in a mixture of toluene (760 ml) and tetrahydrofuran (760 ml); the solution was then transferred into a round bottomed flask and cooled to 0°C under nitrogen atmosphere. 261 ml of 3 M solution of methyl magnesium chloride in tetrahydrofuran was added dropwise during 2-3 hours at 0-5°C. The reaction mass was maintained at 0-5°C for 6-7 hours, and cooled to 0°C. A mixture of acetic acid (90 ml) and water (750 ml) was slowly added at below 15°C for about one hour. The reaction mass was stirred at 25-35°C for another one hour until clear dissolution. The organic and aqueous layers were separated. Organic layer was washed with 5% sodium bicarbonate solution (2 X 750 ml), followed by a water wash (2 X 750 ml) and dried over anhydrous sodium sulphate. The solvent from the organic layer was removed under reduced pressure. The resulting residue was treated with additional amount of methyl magnesium chloride (50 ml) followed by work-up in the same procedure. The crude product was recrystallized from toluene to afford about 17.4 grams of the purified title compound.

Synthesis of (R,E)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propyl)thio) methyl)cyclopropyl)acetic acid tertiary butyl amine salt (Montelukast tertiary butyl amine salt) (1b):

General procedure: 8.6 grams (0.0147 mol) of **1a**, 155 ml of acetone and 17 ml of isopropyl alcohol were charged into a round bottomed flask and stirred at 25-35°C until clear dissolution. 2.3 ml (0.022 mol) of tertiary butyl amine was added and the mass was stirred at 25-35°C. The separated solid was filtered, washed with acetone (20 ml) and dried at 40-50°C. The dried residue was re-precipitated from a mixture of acetone (225 ml) and isopropyl alcohol (25 ml), affording 6 grams of the title compound.

Synthesis of (R,E)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propyl)thio) methyl)cyclopropyl)acetic acid sodium salt (Montelukast sodium) (1):

General procedure: 5 grams of **1b** and 50 ml of dichloromethane were mixed at 25-35°C. A mixture of 0.5 ml of acetic acid and 25 ml of water was added to the mass, and stirred at 25-35°C for 15 minutes. The organic and aqueous layers were separated; the organic layer was washed with water (4 X 25 ml) and dried over sodium sulphate. The solvent was removed under reduced pressure at a temperature below 45°C. 10 ml of methanol was added to the residue. The solvent was removed again under reduced pressure at a temperature of below 45°C. A mixture of 0.307 grams of freshly prepared sodium pellets and 50 ml of methanol were added to the residue at 25-35°C. 0.5 grams of carbon was added and the mass was stirred for about 30 minutes at 25-35°C and the solvent was removed under reduced pressure at a temperature below 45°C. The residue was re-dissolved in toluene (5 ml) and added to n-heptane under nitrogen atmosphere at 25-35°C. The mixture was stirred at 25-35°C for about 1 hour to form a precipitate, which was then filtered and washed with n-heptane under nitrogen atmosphere. The resulting solid was dried at 80°C under reduced pressure to afford 3.2 grams of the title compound.

Synthesis of 2-(1-(((R)-((R)-1-(3-((E)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propyl)sulfinyl) methyl)cyclopropyl)acetic acid (6):

General procedure: 2.0 grams of Montelukast **(1a)** was taken in 50 ml of methanol and 3 ml of hydrogen peroxide was added. Then, the reaction mixture was aged at ambient temperature for 3 hours. Reaction mixture was quenched with water and the compound was extracted into dichloromethane. Dichloromethane was distilled completely and the resulting residue was triturated with hexanes to afford 1.7 grams of **6**.

Synthesis of (R,E)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(prop-1-en-2-yl)phenyl)propyl)thio)methyl) cyclopropyl)acetic acid (7):

General procedure: 5.0 grams of Montelukast acid was dissolved in 200 ml of chloroform and added 0.8 ml of conc.H2SO4. Reaction mixture was aged at 50°C for 6 hours. Reaction mixture was cooled to room temperature and quenched with ice cooled water. Layers were separated and the organic layer was washed with water followed by aqueous sodium bi-carbonate solution. Chloroform was distilled completely to afford 4.6 grams of **7**.

***Synthesis of (S,E)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propyl)thio) methyl)cyclopropyl)acetic acid (8*)**: (8) is the enantiomer (S-isomer) of Montelukast. It was prepared starting from 10 grams of **2** according to the synthetic scheme given above except using (-)-DIP chloride in place of (+)-DIP chloride by following the procedure for Montelukast given above to afford 1.2 grams of **8** (Purity by HPLC – 98%). It has a specific optical rotation $[\alpha]_D^{25}$ of -101^{O} (C=1 in chloroform).

The characterization data of compounds 1, 3 and 5-8 are presented in Table 2.

Table 2

Characterization data of compounds 1, 3 and 5-8

Compound No.	IR (cm^{-1})	M^+ (m/z)	^1H NMR (ppm)
1	3350 (OH stretching); 1629 (C=O stretching); 2624 & 2536 (+N-H stretching); 1612 (C=C stretching); 1496 (aromatic C=C stretching); 697 (C-S stretching).	586	7.0-8.3 (m, 15H) corresponding to Ar-H, CH=CH; 5.2 (s, 1H) corresponding to OH; 3.9 (t, 1H) corresponding to CH-S; 2.0-3.2 (m, 8H) corresponding to all CH_2 groups (excluding CH_2 groups of cyclopropyl ring); 1.3 (s, 6H) corresponding to methyl; 0.4 (m, 4H) corresponding to two CH_2 groups of cyclopropyl ring.
3	3148 (OH stretching); 1716 (C=O stretching (ester); absence of peak corresponding to	458	7.3-8.3 (m, 15H) corresponding to Ar-H; CH=CH; 4.7 (m, 1H) CH-OH; 3.9 (s, 3H) corresponding to CH_3; 3.1 (s, 1H) corresponding to OH; 2.1 (m, 4H) corresponding to CH_2-CH_2.

	C=O stretching (Ketone); 1600 (vinylic C=C stretching); 1492 (Aromatic C=C stretching)		
5	3431 (N-H stretching); 2668, 2530, 2380 (+N-H stretching); 3056 (aromatic C-H stretching); 2926 & 2854 (aliphatic C-H); 1721 (C=O stretching); 1605 (–COO- Asym. Stretching); 1533 (C=C stretching); 1496 (aromatic C=C stretching); 697 (C-S stretching).	767	8.4 (m, 2H) corresponding to ammonium ($+NH_2$); 7.3-8.0 (m, 15H) corresponding to Ar-H, CH=CH; 3.9 (t, 1H) corresponding to CH-S; 3.7 (s, 3H) corresponding $COOCH_3$; 1.0-2.9 (m, 30H) corresponding to all CH_2 groups (excluding CH_2 groups of cyclopropyl ring) and CH groups of dicyclohexyl; 0.3-0.5 (m, 4H) corresponding to two CH_2 groups of cyclopropyl ring.
6	3402 (OH stretching); 1713 (C=O stretching); 1220 (S=O stretching); 697 (C-S stretching).	602	12 corresponding to proton of COOH; 7.1-8.4 (m, 15H) corresponding to Ar-H, CH=CH; 4.9 (s, 1H) corresponding to OH of 3^O-OH; 4.0 (t, 1H) corresponding to CH-S; 2.0-2.9 (m, 8H) corresponding to all CH_2 groups (excluding CH_2 groups of cyclopropyl ring); 1.4 (s, 6H) corresponding to methyl; 0.3-0.6 (m, 4H) corresponding to two CH_2 groups of cyclopropyl ring.
7	3429 (OH stretching); 1713 (C=O stretching); 1608 (C=C stretching); 1499 (aromatic C=C stretching); 697 (C-S stretching).	568	7.1-8.4 (m, 15H) corresponding to Ar-H, CH=CH; 5.1 & 4.7 (2 singlets, 2H) corresponding to hydrogens $=CH_2$ of styrene; 3.9 (t, 1H) corresponding to CH-S; 1.9-2.5 (m, 11H) corresponding to all CH_2 groups (excluding CH_2 groups of cyclopropyl ring) & methyl; 0.4 (m, 4H) corresponding to two CH_2 groups of cyclopropyl ring. The signal at around 11 corresponding to COOH is missing as the spectrum is taken only up to 9.
8	3367 (OH stretching); 1637 (C=O stretching); 1607 (C=C stretching);	586	7.0-8.0 (m, 15H) corresponding to Ar-H, CH=CH; 3.9 (t, 1H) corresponding to CH-S; 2.1-3.2 (m, 9H) corresponding to all CH_2 groups (excluding CH_2 groups of cyclopropyl ring) and 3^O-OH (at 3.0); 1.5 (m, 6H) corresponding to

1498 (aromatic C=C stretching); 697 (C-S stretching).	methyl; 0.2 & 0.4 (two multiplets, 4H) corresponding to two CH_2 groups of cyclopropyl ring. The signal at around 11 corresponding to COOH is missing as the spectrum is taken only up to 9.

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