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RESEARCH ARTICLE

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SYNTHESIS OF MONTELUKAST SODIUM VIA A NITRILE INTERMEDIATE; SYNTHESIS AND CHARACTERIZATION OF IMPURITIES

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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.

KEY WORDS

Synthetic approach, Montelukast sodium, leukotriene receptor antagonist

INTRODUCTION

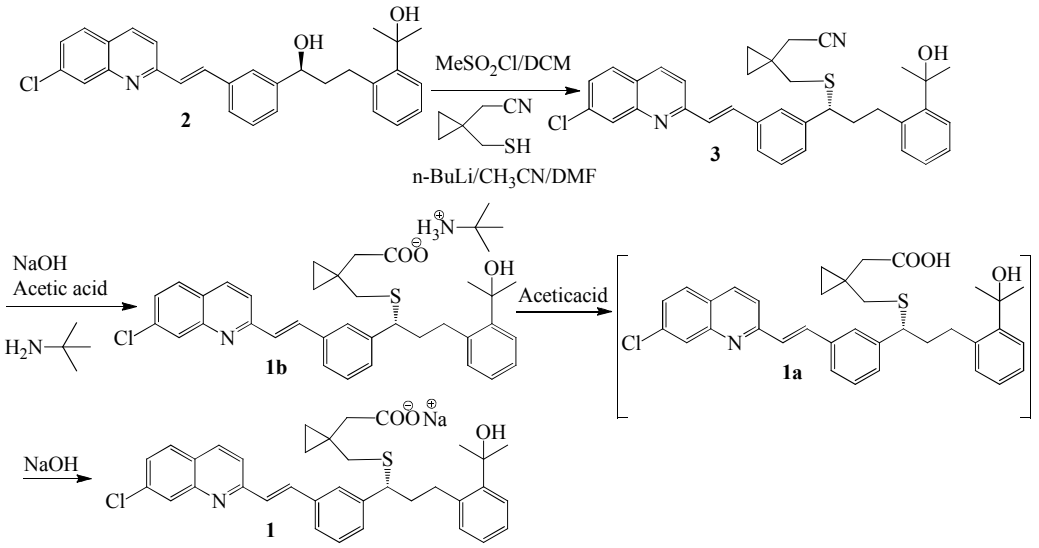
The sodium salt of Montelukast is a leukotriene receptor antagonist (LTD4). It is useful in treatment of asthma, inflammation, allergies, angina, cerebral spasm, glomerular nephritis, hepatitis, endotoxemia, uveitis and allograft rejection. [1]

Leukotrienes constitute a group of locally acting hormones 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 converted to the 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 were reported in literature. [2-8] As a part of the ongoing research and development program with an objective of providing simple and commercially viable synthetic processes,[9] the present work relates to novel synthetic approaches 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 of the present work.

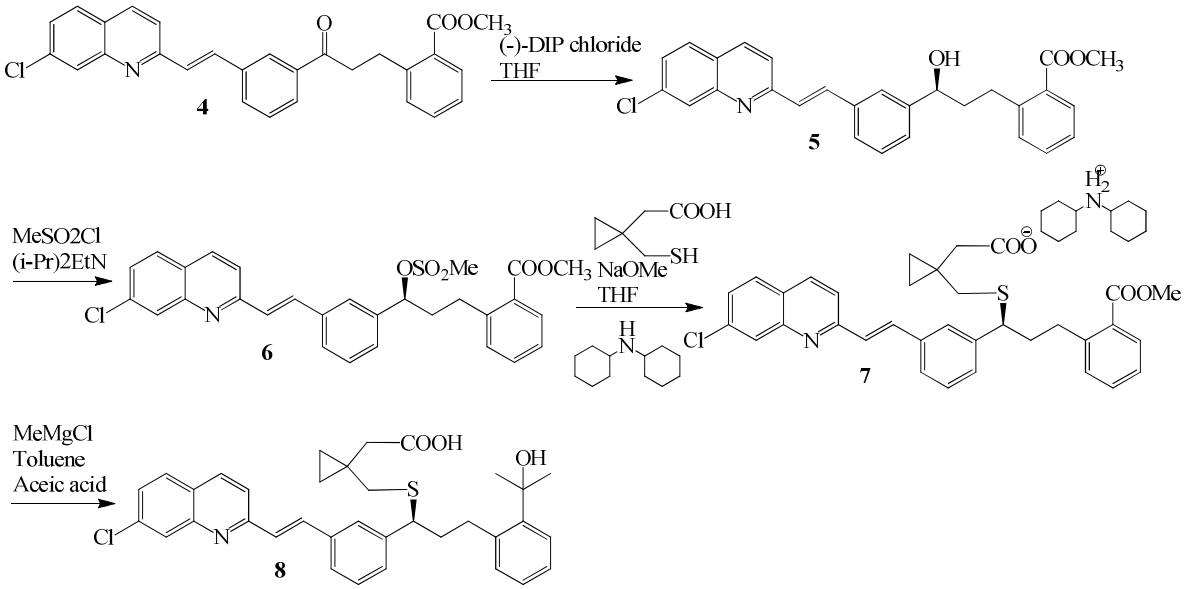
Novel synthetic approaches are depicted in scheme-1 and 2 respectively and the details are as follows:

Scheme-1:



According to scheme-1, Montelukast sodium (1) was prepared by:
(i) mesylation of 2-(2-(3(S)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)phenyl)-3-hydroxypropyl)phenyl)-2-propanol **(2)** using methane sulfonyl chloride in presence of N,N-diisopropyl ethyl amine in acetonitrile solvent; (ii) condensation of the resulting mesylate in a mixture acetonitrile and N,N-dimethyl formamide with lithium salt of 1-(mercapto methyl) acetonitrile that is prepared by treating it with n-butyl lithium to provide (R)-E-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)ethenyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propyl)thio)methyl)cyclopropyl) acetonitrile **(3)**; (iii) hydrolysis of **(3)** with aqueous sodium hydroxide to provide Montelukast acid **(1a)**; (iv) converting it in to tertiary butyl amine salt of Montelukast **(1b)** by treating with tertiary butyl amine in acetone and purifying the isolated butyl amine salt of Montelukast **(1b)** by recrystallization from acetone;
(v) converting the purified tertiary butyl amine salt of Montelukast **(1b)** in to Montelukast sodium **(1)**.

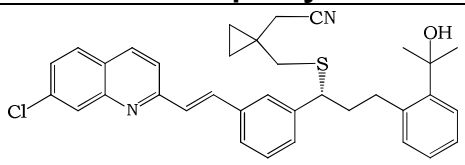
Scheme-2:

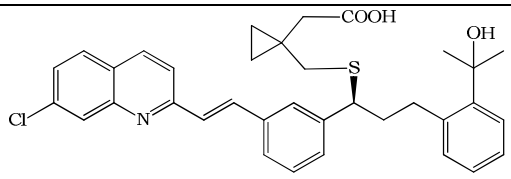
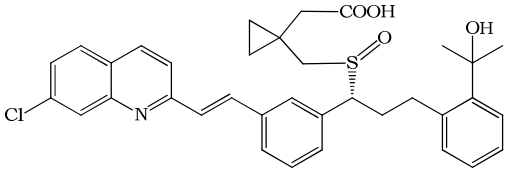
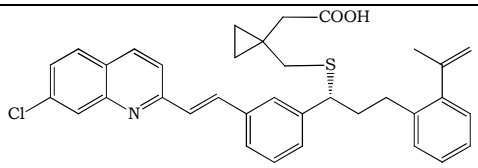


The starting materials **2 & 4** were prepared by known methods for e.g., by a method known in Belley *et al*.

During the synthesis of montelukast sodium **(1)**, the following compounds were identified as impurities in Montelukast sodium and 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
3		(R,E)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propyl)thio)methyl)cyclopropyl)acetonitrile

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
9		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
10		(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

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. 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)-2-(1-(((1-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propyl)thio) methyl)cyclopropyl)acetonitrile (3):

***General procedure*:** 10 grams (0.0218 mol) of **2** was added in 50 ml of toluene, and the mixture was heated to reflux. Reaction mixture was concentrated by simultaneous azeotropic removal of water. 90 ml of acetonitrile was added after room temperature was attained by the resulting mass and was stirred at 50-60°C for 30-45 minutes. Resulting mass was further cooled to -10 to -15°C and 5.33 ml of N,N-diisopropyl ethylamine was added and was stirred for about 30 minutes. 9.3 ml of methane sulfonyl chloride was added and reaction mass was aged at -10 to -15°C for about 9 hours. The reaction mass was filtered and washed with acetonitrile followed by hexanes to provide 10.0 g of mesylate of **2**.

32.3 g (0.254 mol) of 1-(Mercaptomethyl)cyclopropane acetonitrile was dissolved in 400 ml of N,N-dimethylformamide and the mixture was cooled to -10 to -15°C. 317.5 ml of 3.4 M n-Butyl lithium was added drop wise in reaction mass. 80 g of above obtained mesylate of **2** was added to the reaction mass at -10 to -15°C and the reaction mass was aged at -10 to -15°C for about 8 hours. 500 ml of 15% sodium chloride solution was added followed by 800 ml of toluene and the reaction mass was stirred for about 30 minutes. Organic layer and aqueous layer were separated. Aqueous layer was extracted with toluene. Water was added to combined organic layers and the pH was adjusted to 5.0 using 48 ml of acetic acid and the reaction mass was stirred at 25°C for 30-40 minutes. Organic layer was washed with 640 ml of 5% Sodium bicarbonate solution followed by water. Removal of solvent under reduced pressure below 50°C afforded 80 g of **3**.

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, ter-butyl amine salt (1b):

General procedure: 65 g (0.114 mol) of **3** and 325 ml of caustic lye were added into round bottom flask and further stirred and heated to reflux at 118-122^{O}C for 6 to 8 hours. 130 ml of

water and 650 ml of toluene were added to the reaction mass below 90^{O}C and stirred for 30 minutes. **Separated the layers and the aqueous layer was** extracted with 325 ml of toluene at 60-70^{O}C. Combined organic layers were distilled under reduced pressure below 50^{O}C and washed with 720 ml of n-heptane at 25-35^{O}C. 300 ml of water and 200 ml of dichloromethane were added to the reaction mass.The pH was adjusted to 5 with acetic acid. Layers were separated and the aqueous layer was extracted with 200 ml of dichloromethane. Combined organic layer was washed with 1300 ml of water and distilled off solvent from organic layer at atmospheric pressure followed by distillation under reduced pressure below 50^{O}C to afford **1a**. 500 ml of acetone was added to the above obtained crude and distilled of acetone under reduced pressure below 50^{O}C to remove the traces of dichloromethane. 21 gm (0.287 mol) of tertiary butyl amine was added to the above reaction mass slowly at 25-30^{O}C. The reaction mass was stirred till thick solid separation at 25 35^{O}C for 8-10 hours. The separated solid was filtered and washed with acetone. It was then dried at 50 - 55^{O}C to afford 40 gm of **1b**. 30 grams of **1b** was purified by recrystallization from acetone to afford 23 grams of purified **1b**.

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 mls of methanol were added to the residue. The solvent was removed again under reduced pressure at a temperature below 45°C. A mixture of 0.307 grams of freshly prepared sodium pellets and 50 ml of methanol was added to the residue at 25-35°C. 0.5 grams of carbon were 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 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 (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):

(a) Synthesis of (S,E)-methyl 2-(3-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-hydroxypropyl)benzoate (5):

General procedure: 10 grams (0.0219 mol) of **4** was dissolved in 50 ml of dichloromethane. A cooled solution of 18 ml of (-)-DIP chloride (0.0346 mol) in 50 ml of dichloromethane to above solution of **4.** Reaction mixture was aged at -5 to 0^{O}C for 10 hours. Reaction mixture was quenched with aqueous ammonia and stirred 30 minutes. Aqueous sodium chloride solution was added and stirred for 30 minutes. Layers were separated and the organic layer was washed with aqueous sodium chloride solution. Dichloromethane was distilled from the organic layer. The resulting crude **5** obtained above was purified from a mixture of methanol to yield 8 grams (Theoretical yield: 80%) of **5**. (Purity by HPLC: 98%). Specific optical rotation (SOR): of -68^{O} (C=1 in chloroform).

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

***General procedure*:** A stirred mixture of 10 grams (0.0219 mol) of **5** and 50 ml of toluene,

heated to reflux and removed water by azeotropic distillation using Dean-Stark apparatus. Cooled the mixture to 50°C and the solvent remaining was distilled under reduced pressure. The residue was re-dissolved in 100 ml of dichloromethane and the mixture was cooled to 0-5°C. 5.75 ml (0.0328 mol) of diisopropyl ethylamine were added and the reaction mass was stirred at 0-5°C. 2.2 ml (0.0284 mol) of methane sulfonyl chloride were added dropwise at 0-5°C. After the addition was completed, the reaction mass was maintained at 25-35°C until reaction completion. 60 ml of water were added and layers were separated. Aqueous layer was extracted with 200 ml of dichloromethane. The combined organic layers were washed with water. Dichloromethane was distilled off to obtain mesylate of **5**.

3.83 grams (0.0262 mol) of 1-mercapto methyl cyclopropane acetic acid and 45 ml of methanol were stirred until clear dissolution at 25-35°C for 60 minutes. A mixture of the mesylate **of 5** obtained as described above, dichloromethane and dimethyl formamide (45 ml, 1:1) were added, and the resulting reaction mass was stirred for clear dissolution at 25-35°C. The reaction mass was heated and maintained at reflux temperature for 2-3 hours. 45 ml of water were charged to the reaction mixture and continued stirring for 15 minutes. The organic and aqueous layers were separated; the aqueous layer extracted with 20 ml of dichloromethane. The combined organic layers were washed with aqueous sodium chloride solution, then washed with a aqueous acetic acid solution followed by water washing. The solvents were distilled off and the obtained residue was dissolved in 50 ml acetone; and acetone and 5.2 ml (0.0262 mol) of dicyclohexyl amine were added to the solution and stirred at 25-35°C until a solid separated. Filtered the solid and recrystallized from acetone to afford 4.9 grams of the title compound.

(c) 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):

General procedure: 10 grams (0.13 mol) of **7** and 100 ml of toluene were charged to a round bottomed flask, and stirred for about 5 minutes. A mixture of acetic acid (1.5 ml) and water (50 ml) was added, and the mass was further stirred for another 30 minutes. The organic and aqueous layers were separated. The solvent was removed from organic layer under reduced pressure at a temperature of below 50°C. The resulting crude residue was dissolved in a mixture of toluene (760 ml) and tetrahydrofuran (760 ml); the solution was transferred into a round bottomed flask and cooled to 0°C under nitrogen atmosphere. 26.1 ml of 3 M solution of methyl magnesium chloride in tetrahydrofuran were added dropwise during 2-3 hours at 0-5°C. The reaction mass was maintained at 0-5°C for 7 hours, and cooled to 0°C. A mixture of acetic acid (9 ml) and water (75 ml) was slowly added at below 15°C. 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 followed by a water wash. The solvent from the organic layer was removed under reduced pressure. The crude product was dissolved in toluene (10 ml) and stirred at 25-35°C. The separated solid was filtered, washed with toluene and dried to afford1.7 grams of **8**.

(Purity by HPLC – 98%). It has a specific optical rotation $[\alpha]_D^{25}$ of -99^O (C=1 in chloroform).

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 (9):

General procedure: 2.0 grams of Montelukast **(1a)** was taken in 50 methanol and added 3 ml of hydrogen peroxide and the reaction mixture was aged at ambient temperature for 3 hours. Reaction mixture was quenched with water and the compound was extracted in to dichloromethane. Dichloromethane was distilled completely and the resulting residue was triturated with hexanes to afford 1.7 grams of **9**.

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 (10):

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 **10**.

The characterization data of compounds 1, 3 and 9-10 are presented in Table 2.

Table 2
Characterization data of compounds 1, 3, 8-10

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	1743 & 1680 (two carbonyl stretchings); 2389 ($^+$N-H stretching); 3056 (aromatic C-H stretching); 2966 (aliphatic C-H); 1475 (C-N); 1255 & 1026 (C-O-C (aryl alkyl ether)	567	7.1-8.1 (m, 15H) corresponding to Ar-H & CH=CH; 3.9 (m, 1H) corresponding to CH-S; 3.1 (m, 1H) corresponding to OH; 3.2 (m, 1H) corresponding to thiazepine –N-CH2-CH2; 2.9 (s, 6H) corresponding to -N(CH3)2 and 1.9 (s, 3H) corresponding to -$COCH_3$.
8	3367 (OH stretching); 1637 (C=O stretching); 1607 (C=C stretching); 1498 (aromatic	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 CH2 groups (excluding CH2 groups of cyclopropyl ring) and 3O-OH (at 3.0); 1.5 (m, 6H) corresponding to methyl; 0.2 & 0.4 (two multiplets, 4H) corresponding to two CH2

	C=C stretching); 697 (C-S stretching).		groups of cyclopropyl ring. The signal at around 11 corresponding to COOH is missing as the spectrum is taken only up to 9.
9	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 3O-alcohol; 4.0 (t, 1H) corresponding to CH-S; 2.0-2.9 (m, 8H) corresponding to all CH2 groups (excluding CH2 groups of cyclopropyl ring); 1.4 (s, 6H) corresponding to methyl; 0.3-0.6 (m, 4H) corresponding to two CH2 groups of cyclopropyl ring.
10	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 =CH2 of styrene; 3.9 (t, 1H) corresponding to CH-S; 1.9-2.5 (m, 11H) corresponding to all CH2 groups (excluding CH2 groups of cyclopropyl ring) & methyl; 0.4 (m, 4H) corresponding to two CH2 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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