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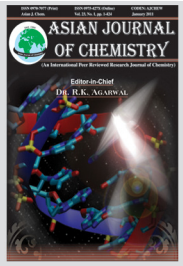

Identification, Synthesis and Characterization of Impurities of Montelukast Sodium

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Montelukast sodium is a selective leukotriene receptor antagonist which inhibits cysteinyl leukotriene $CysLT_1$ receptor. Various synthesis of Montelukast is published. During laboratory optimization and later in bulk synthesis formation of various impurities was detected. Besides, pharma Europa draft mention nine process related impurities. However, the method of preparation of most of these impurities is not available in literature. Also, different route of synthesis will have different impurity profile and those process related impurities are not covered in pharmacopeias. In this study we report the synthesis of possible process impurities, including seven impurities (A-H) mentioned in pharma Europa.

Key Words: Montelukast sodium, Leukotriene antagonists, Impurities.

INTRODUCTION

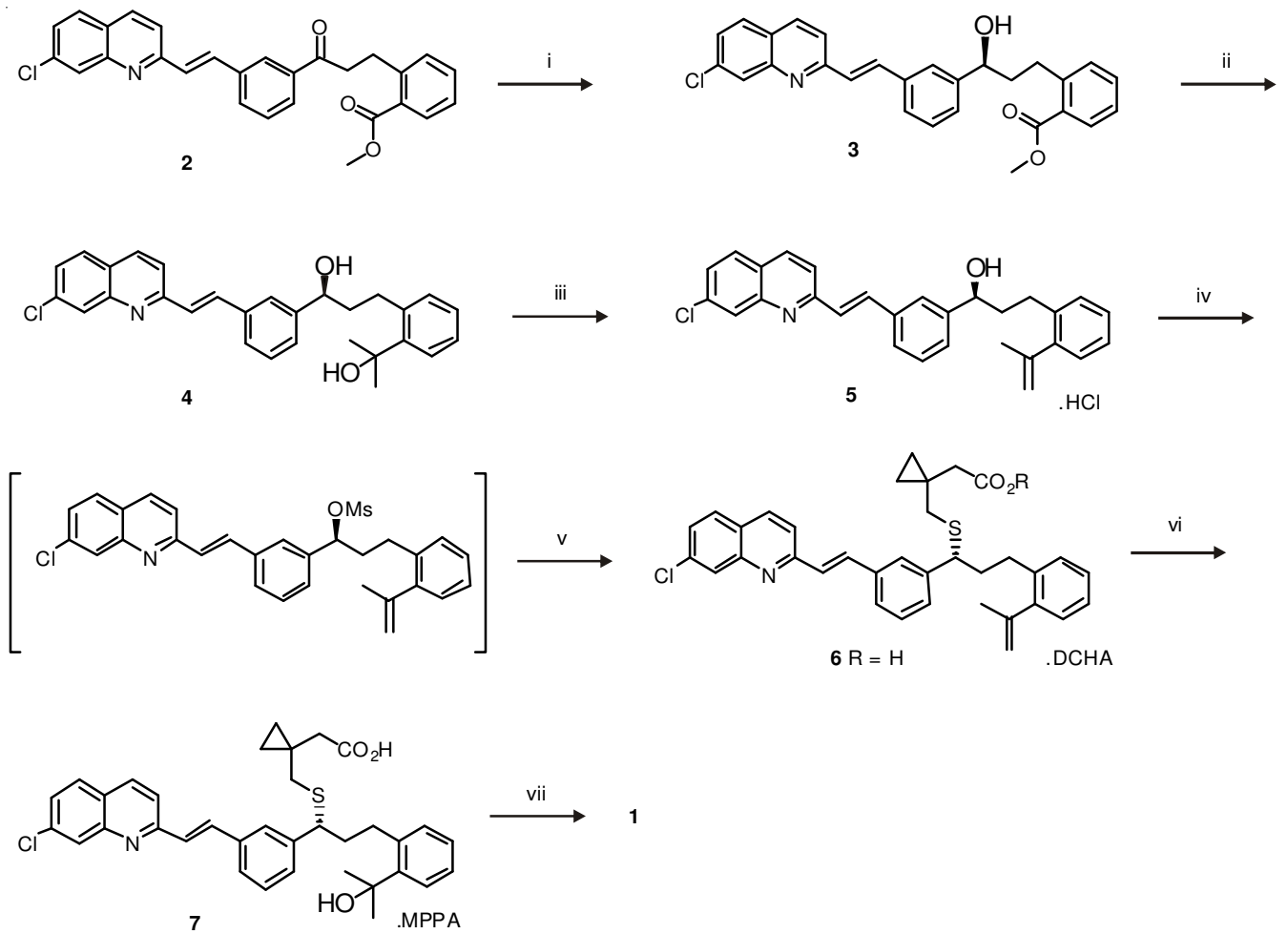
Montelukast sodium, [R-E]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1- methylethyl)-phenyl]propyl]thio]methyl]cyclopropane acetic acid sodium salt (**1**), is use as antiasthmatic, antiallergic, antiinflammatory, cytoprotective agent and hence useful in the treatment of angina, cerebral spasm, glomerular nephritis, hepatic, endtoxemia, uveitis and allograft rejection. The published synthesis[1] of montelukast **1** required stereoselective reduction of the keto-functionality in **2**, followed by Grignard reaction on the ester moiety of compound **3** to afford the diol **4**. The *tert*-alcohol was protected by a THP group and the *sec*-alcohol was activated by a mesyl group. Nucleophilic displacement of the O-mesyl moiety with 2-(1-(mercaptomethyl) cyclopropyl)acetic acid (MCAA) and subsequent deprotections afforded. Montelukast sodium **1** (transformation similar to that shown in **Scheme-I**, except that in literature[1] the *tert*-alcohol in **3** was protected with THP moiety, while in **Scheme-I** the *tert*-alcohol is converted into a masked styrene protecting group.

Due to its commercial value, many alternate synthesis of Montelukast have been reported[2] and recently a commercially viable process was published from our laboratory[3]. During its laboratory synthesis and bulk production various impurities, including those mentioned in pharma Europa[4] (Fig. 1) were detected by HPLC analysis and their structure tentatively assigned as **8-19** on the basis of their LC-MS data. As per the guidelines recommended by ICH, the amount of acceptable level for a known and unknown related compound (impurity) is less than 0.15 and 0.10 %, respectively in an API. In order to quantify and limit the impurities in the final drug substance, it is mandatory to have standard for the impurities. It was decided to synthesize these impurities as synthetic details for many of these are not reported in literature[5] and they are not commercially available.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz Avance Ft-NMR spectrometer; the chemical shifts were reported on δ ppm relative to either internal standard or tetramethylsilane. The FT-IR spectra were recorded on Perkin-Elmer 100 FT-IR spectrophotometer and only prominent peaks are reported. The electrospray ionization ESI-MS studies were carried on a quadrupole mass spectrometer Waters Quatro Micro API. HRMS studies were carried on an Agilent 6520 accurate-Mass Q-TOF LC/MS system. All the reagents used were of LR grade and used as such without further purification. All the anhydrous reactions were carried out under nitrogen atmosphere. Silica gel (120-200 mesh) was used for column chromatograph.

1S-{(3-[(E)-2-(7-Chloroquinolin-2-yl) vinyl] phenyl}-3- [2-(prop-1-en-2-yl) phenyl] propan-1-ol hydrochloride (8): To a suspension of hydroxyl styrene hydrochloride **5** (20 g, 41.9 mmol) in anhydrous CH_2Cl_2 (200 mL), at 25-30 ºC, under inert atmosphere, was added N,N-diisopropylethyl amine



Scheme-I: Reagents and conditions: (i) (-) DIPCl, CH_2Cl_2, -5 to 0 ºC; (ii) MeMgCl (3M solution in THF), $CeCl_3$, THF, 0-5 ºC; (iii) (a) acetic anhydride, Et_3N, DMAP, CH_2Cl_2, 0-5 ºC; (b) *p*-TsOH, CH_2Cl_2, 25-30 ºC; (c) NaOH, H_2O, MeOH, THF, 25-30 ºC; (d) HCl, EtOAc, 25-30 ºC; (iv) MsCl, DIPEA, CH_2Cl_2, 25-30 ºC; (v) MCAA, NaOMe (25 % solution in MeOH), DMF, 0-5 ºC; (b) DCHA, EtOAc, 25-30 ºC; (vi) (a) 80 % aq H_2SO_4, 5-10 ºC; (b) silica gel column purification, (c) MPPA, EtOAc, 25-30 ºC; (vii) AcOH, H_2O, CH_2Cl_2, 25-30 ºC; (b) NaOH, EtOH, 25-30 ºC. DIPCl = diisopinocampheylchloroborane; DIPEA = N,N-diisopropylethyl amine; MCAA = 2-[1-(mercaptomethyl) cyclopropyl]acetic acid; DCHA = dicyclohexyl amine; MPPA = 1-methyl-3-phenylpropylamine

(DIPEA, 11 mL). The clear solution obtained was cooled to 0-5 ºC and mesyl chloride (4.2 mL, 54.2 mmol) was added dropwise. The reaction mixture was stirred at 0-5 ºC and the progress of the reaction was monitored by analytical TLC. After 1 h, TLC revealed the completion of the reaction where upon ice-cold 7 % aq. $NaHCO_3$ (200 mL) was added, slowly, to the reaction mixture, while maintaining temperature below 10 ºC. The layers were separated and the aqueous layer back extracted with CH_2Cl_2 (40 mL). The combined organic layer was washed with water (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford the styrene mesylate (20.0 g) as thick viscous oil, which was used in the next step without further purification.

To a solution of the crude styrene mesylate (20 g) in toluene (100 mL), at 25-30 ºC, under inert atmosphere, was sequentially added DMAP (2.56 g, 20.9mmol) and CsOAc (40.2 g, 209.4 mmol). The reaction temperature was raised to 110 ºC and maintained at the same temperature for another 8 h, when analytical TLC showed the completion of the reaction. Toluene was removed completely under reduced pressure and the residue was diluted with EtOAc (200 mL) and washed sequentially with water (100 mL), 1N aq HCl (100 mL) and 5 % aq. NaCl solution (100 mL). The organic layer was concentrated under reduced pressure to afford the styrene acetate (23.8 g) as thick viscous oil, which was used in the next step without further purification.

To a solution of the crude styrene acetate (23.8 g) in a mixture of MeOH (100 mL) and THF (10 mL), at 25-30 ºC, was added 15 M aq NaOH (13.4 mL, 200 mmol). After stirring at 25-30 ºC for 2 h, analytical TLC showed the completion of the reaction. The reaction mass was concentrated to one-fourth of the original volume, under reduced pressure and the residue obtained was diluted with EtOAc (200 mL) and washed with water (100 mL). The pH was adjusted to 6.5-7.0 by the addition of 6N aq HCl, the layers separated and the aqueous layer back extracted with EtOAc (100 mL). The combined organic layer washed with water (100 mL). The organic layer dried (Na_2SO_4) and concentrated under reduced pressure to afford the desired inverted alcohol **8** (15.7 g, 85.1 % overall yield, HPLC purity 98.5 %) as a off-white solid material. IR (KBr, ν_{max}, cm^{-1}): 3341, 3050, 2986, 2915, 1752, 1599. ^1H NMR (DMSO-d_6): δ 8.80 (d, *J* = 8.7, 1H), 8.35 (d, *J* = 2.1, 1H), 8.27 (d, *J* = 16.5, 1H), 8.26 (d, *J* = 8.7, 1H), 8.17 (d, *J* = 8.7, 1H), 7.77 (dd, *J* = 2.1 and 8.7, 1H), 7.72 (s, 1H), 7.70 (d, *J* = 16.5, 1H), 7.61 (d,

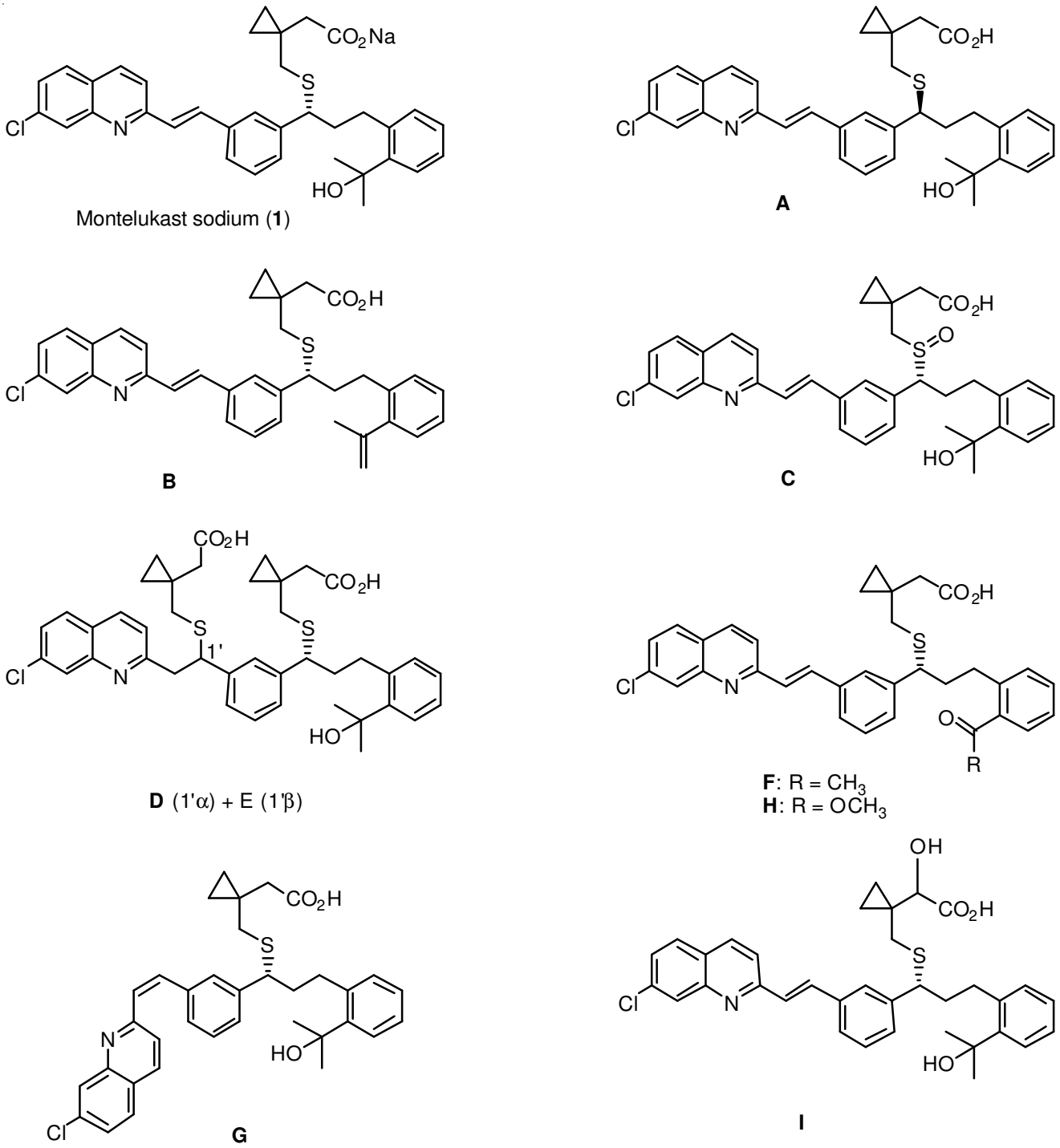


Fig. 1. Montelukast sodium and process related impurities

J = 7.5, 1H), 7.43 (d, *J* = 7.5, 1H), 7.40 (s, 1H), 7.19-7.06 (m, 3H), 7.01 (m, 1H), 5.09 (t, *J* = 1.8, 1H), 4.70 (m, 1H), 4.62 (t, *J* = 6.3, 1H), 2.67 (m, 1H), 2.60 (m, 1H), 1.92 (s, 3H), 1.88 (m, 2H). ESI-MS: m/z 440 ($[MH]^+$, $C_{29}H_{26}ClNO$ calcd. (%) 439), 442 $\{MH + 2\}^+$.

[S,E]-1-[[[1-[3-(2-(7-Chloro-2-quinolinyl)ethenyl)phenyl]-3-[2-(prop-1-en-2-yl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid dicyclohexylamine salt (9): To a suspension of hydroxy styrene hydrochloride (**8**) (10 g, 20.9 mmol) in anhydrous CH_2Cl_2 (100 mL), at 25-30 ºC, under inert atmosphere, was added N,N-diisopropylethyl amine (DIPEA, 5.5 mL). The clear solution obtained was cooled to 0-5 ºC and mesyl chloride (2.1 mL, 27.1 mmol) was added dropwise. The reaction mixture was stirred at 0-5 ºC and the progress of the reaction was monitored by analytical TLC. After 1.5 h, TLC revealed the completion of the reaction where upon ice-cold 7 % aq $NaHCO_3$ (100 mL) was added, slowly, to the reaction mixture, while maintaining temperature below 10 ºC. The layers were separated and the aqueous layer back extracted with CH_2Cl_2 (40 mL). The combined organic layer was washed with water (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford the styrene mesylate (10.6 g) as thick viscous oil, which was used in the next step without further purification.

A solution of 1-mercaptomethyl cyclopropylacetic acid (MCAA, 4.0 g, 27.4 mmol) in THF (75 mL) was cooled -15 to -10 ºC, under inert atmosphere. *n*-BuLi (15 % w/w in hexanes, 33.8 mL, 79.2 mmol) was added carefully over a period of 2 h, while maintaining temperature below -10 ºC. The temperature was allowed to rise to -5 to 0 ºC and a solution of crude styrene mesylate (10.6 g, dissolved in 50 mL anhydrous THF) was added over a period of 1 h. The reaction mixture was stirred at -2 to 2 ºC for 18 h, when analytical TLC showed the completion of the reaction. The reaction mass was diluted with EtOAc (100 mL) and then ice-cold 10 % aq NaCl solution (100 mL) was added. The layers were separated and the aqueous layer back extracted with EtOAc (50 mL). The combined organic layer washed sequentially with 5 % aq tartaric acid solution (50 mL) and water (100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. To the residue obtained (11.6 g) was added EtOAc (60 mL) and temperature raised to 40-45 ºC, whereupon a clear solution was obtained. The temperature was allowed to cool to 25-30 ºC and dicyclohexyl amine (DCHA, 5.4 mL, 27.07 mmol) was added and maintained for 15 h at the same temperature, under inert atmosphere. *n*-Hexane (120 mL) was added and the heterogeneous mass was further stirred, at 25-30 ºC, for another 6 h. The white precipitate was filtered off and washed with *n*-hexane (10 mL × 2). The material obtained was dried for 8 h at 50-55 ºC to afford the desired compound **9** as a white solid material (11 g, 70 % yield). IR (KBr, ν_{max}, cm^{-1}): 3344, 2936, 2856, 1608, 1538. ^1H NMR ($CDCl_3$): δ 8.10 (d, *J* = 8.4, 1H), 8.06 (d, *J* = 1.8, 1H), 7.71 (d, *J* = 8.7, 1H), 7.68 (d, *J* = 16.5, 1H), 7.66 (d, *J* = 8.4, 1H), 7.64 (s, 1H), 7.48 (m, 1H), 7.45 (dd, *J* = 2.1 and 8.7, 1H), 7.39 (d, *J* = 16.5, 1H), 7.32 (m, 1H), 7.27 (m, 1H), 7.20-7.00 (m, 4H), 5.08 (t, *J* = 1.2, 1H), 4.76 (d, *J* = 1.2, 1H), 3.88 (dd, *J* = 6.6 and 8.1, 1H), 2.78-2.70 (m, 2H), 2.69-2.53 (m, 4H), 2.36 (s, 2H), 2.22-2.05 (m, 2H), 2.00-1.89 (m, 4H), 1.93 (s, 3H), 1.80-1.65 (m, 4H), 1.64-1.56 (m, 2H), 1.39-1.05 (m, 10H), 0.53-0.45 (m, 2H), 0.40-0.31 (m, 2H). ESI-MS: m/z 568 ($[MH\text{-}DCHA]^+$, $C_{36}H_{34}NO_2SCl{\cdot}C_{12}H_{23}N$ calcd. (%) 748), 570 $[MH + 2\text{-}DCHA]^+$.

[S,E]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]-cyclopropane acetic acid sodium salt (A): 80 % aq H_2SO_4 (50 mL), under inert atmosphere, was cooled to 0-5 ºC and styrene dicyclohexyl amine salt (**9**) (10 g, 13.3 mmol) was added in 5 lots, over a period of 1 h. The reaction mixture was stirred for 1 h at 5-10 ºC, diluted with EtOAc (100 mL) and quenched by the sequential addition of *t*-BuOH (100 mL) and water (100 mL), while maintaining internal temperature below 10 ºC. The pH of the reaction mass adjusted to 3.0-4.0 by the addition of a solution of 20% aq. NaOH (*ca.* 20 mL), over a period of 1h, while maintaining temperature below 15 ºC. Water (100 mL) was added and the temperature was allowed to rise to 25-30 ºC. The layers were separated and the aqueous layer extracted with EtOAc (50 mL). The combined organic layer washed with 5 % aq NaCl solution (100 mL × 2). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. To the residue obtained (9.5 g) was purified by silica gel column chromatography. Elution with 5 % MeOH in dichloromethane (v/v) afforded the hydrated compound (5.0 g). The material was dissolved in EtOAc (30 mL) at 40-45 ºC, under inert atmosphere. The solution was cooled to 25-30 ºC and 1-methyl-3-phenylpropyl amine (MPPA, 1.6 mL, 9.88 mmol) was added. After stirring for 18 h, the reaction mixture was diluted with *n*-hexane (60 mL) and stirring continued for additional 6 h. The white precipitate formed was filtered and washing was performed with *n*-hexane (10 mL). The S-Montelukast MPPA salt was dried for 8 h at 45-50 ºC. The MPPA salt (4.8 g) obtained was converted into the desired sodium salt by disolving it in CH_2Cl_2 (50 mL). Water (25 mL) added and pH adjusted to 3.5-4.0 with 50 % aq. AcOH, over 0.5 h. After stirring for 0.5 h, the layers were separated and the aqueous layer extracted with CH_2Cl_2 (25 mL). The combined organic layer was washed with water (50 mL × 2). To a stirred CH_2Cl_2 phase was added an ethanolic solution of NaOH (0.25 g, dissolved in a mixture of 12.5 mL EtOH and 0.1 mL H_2O), at 25-30 ºC and stirred for 0.5 h. The reaction mixture was concentrated under reduced pressure and the residue obtained was dissolved in MeOH (40 mL). To the clear solution carbon (PS-133, 0.5 g) was added, stirred for 0.5 h at 40-45 ºC and filtered over hyflow bed. The solvent was removed completely, dried at 85-90 ºC for 12 h, to afford the desired S-isomer of Montelukast sodium (impurity A, 3.36 g, 41.5 % yield and HPLC purity 99.4 %) as off white solid material. IR (KBr, ν_{max}, cm^{-1}): 3394, 1636, 1608, 1595, 1557, 1497. ^1H NMR ($CDCl_3$): δ 8.37 (d, *J* = 8.7, 1H), 8.00 (d, *J* = 1.8, 1H), 7.97 (d, *J* = 9.0, 1H), 7.92 (d, *J* = 8.7, 1H), 7.86 (d, *J* = 16.5, 1H), 7.70 (s, 1H), 7.58 (d, *J* = 7.2, 1H), 7.55 (dd, *J* = 2.1 and 9.0, 1H), 7.48 (d, *J* = 16.5, 1H), 7.41-7.34 (m, 2H), 7.32 (d, *J* = 7.2, 1H), 7.07 (m, 3H), 3.99 (t, *J* = 7.5, 1H), 3.04 (td, *J* = 4.5 and 12.0, 1H), 2.75 (m, 1H), 2.65 (d, *J* = 12.6, 1H), 2.52 (d, *J* = 12.6, 1H), 2.17 (m, 1H), 2.12-1.96 (m, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.20 (brs, 1H), 0.42-0.30 (m, 2H), 0.25-0.13 (m, 2H). ESI-HRMS: m/z 586.2142 ($[MH\text{-}Na]^+$, $C_{35}H_{37}NO_3SCl$ calcd. (%) 586.1991).

[R,E]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]-phenyl]-3-[prop-1-en-2-yl)phenyl]propyl]sulfinyl]methyl]-cyclopropaneacetic acid (10) and [R,E]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[prop-1-en-2-yl)phenyl]-propyl]sulfonyl]methyl]cyclopropane acetic acid (11): To a solution of styrene thioether **6** (10 g, 17.6 mmol) in CH_2Cl_2 (100 mL) was added a solution of *m*-chloroperbenzoic acid (3.95 g, 22 mmol; dissolved in 30 mL CH_2Cl_2) at 25-30 ºC. The reaction mass was stirred for 2 h, analytical TLC revealed the absence of the starting material and the formation of two oxidized products. The reaction mass was quenched by the addition of water (100 mL). The layers separated and organic layer washed with water (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure and the residue obtained was purified by column chromatography. Elution with 0.1-0.5 % MeOH in CH_2Cl_2 (v/v) afforded initially the sulphone **11** followed by the sulphoxide **10** (as a mixture of diastereomers), both as pale-yellow solid materials. Sulphoxide **10** (4.0 g, 39.2 % yield). IR (KBr, ν_{max}, cm^{-1}): 3425, 3013, 2915, 1715, 1608, 1497. ^1H NMR ($CDCl_3$, major diastereomer): δ 8.11-8.05 (m, 2H), 7.70 (d, *J* = 8.7, 1H), 7.68 (d, *J* = 16.5, 1H), 7.62 (d, *J* = 8.4, 1H), 7.66 (m, 1H), 7.56 (m, 1H), 7.49 (s, 1H), 7.45 (dd, *J* = 2.1 and 8.7, 1H), 7.43-7.39 (m, 2H), 7.21-7.00 (m, 5H),

5.03 (m, 1H), 4.74 (m, 1H), 4.08 (dd, *J* = 3.0 and 11.4, 1H), 3.35 (d, *J* = 13.8, 1H), 3.01 (d, *J* = 16.2, 1H), 2.72 (m, 1H), 2.60 (m, 2H), 2.19 (m, 1H), 2.14 (d, *J* = 13.8, 1H), 2.04 (d, *J* = 16.2, 1H), 1.88 (s, 3H), 0.72-0.50 (m, 4H). ESI-HRMS: m/z 584.1992 ($[MH]^+$, $C_{35}H_{35}NO_3SCl$ calcd. (%) 584.1831). Sulphone **11** (0.5 g, 4.7 % yield, HPLC purity 99.0 %). IR (KBr, ν_{max}, cm^{-1}): 3439, 3068, 3011, 2964, 2925, 1713, 1609. ^1H NMR ($CDCl_3$): δ 8.10 (d, *J* = 8.7, 1H), 8.05 (d, *J* = 1.2, 1H), 7.76 (s, 1H), 7.71 (d, *J* = 8.7, 1H), 7.65 (d, *J* = 8.7, 1H), 7.62 (d, *J* = 16.2, 1H), 7.58 (d, *J* = 7.8, 1H), 7.46 (dd, *J* = 2.1 and 8.7, 1H), 7.44 (d, *J* = 16.2, 1H), 7.44 (t, *J* = 7.8, 1H), 7.33 (d, *J* = 7.8, 1H), 7.22-7.01 (m, 4H), 5.07 (s, 1H), 4.76 (s, 1H), 4.05 (m, 1H), 3.02 (d, *J* = 14.4, 1H), 2.95 (d, *J* = 14.4, 1H), 2.76-2.52 (m, 5H), 1.91 (s, 3H), 0.72-0.55 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 174.8, 156.5, 148.0, 145.0, 143.7, 137.2, 136.5, 135.8, 134.5, 133.6, 129.9, 129.4, 129.1, 128.6, 128.3, 128.1, 127.7, 127.5, 127.4, 127.0, 126.2, 125.6, 119.1, 115.1, 69.8, 56.2, 40.1, 30.0, 29.0, 24.9, 12.4, 12.1, 11.6. ESI-HRMS: m/z 600.1969 ($[MH]^+$, $C_{35}H_{35}NO_4SCl$ calcd. (%) 600.1825). The styrene sulphone **11** and sulphoxide **10** were hydrated with 80 % aq H_2SO_4 in a mixture of water and CH_2Cl_2 to afford the montelukast sulphone **12** and sulphoxide **C**, respectively. The spectral data was similar to those obtained by the direct oxidation of the montelukast sodium (see below).

[R,E]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl) ethenyl]-phenyl]-3-[2-(-hydroxy-1-methylethyl) phenyl]propyl]-sulfinyl] methyl] cyclopropaneacetic acid sodium salt (C) and [R,E]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl) ethenyl]phenyl]-3-[2-(hydroxy-1-methylethyl)phenyl]propyl]-sulfonyl]methyl]-cyclopropane acetic acid sodium salt (12): To a solution of Montelukast **7** (10 g, 17.1 mmol) in CH_2Cl_2 (100 mL) was added a solution of *m*-chloroperbenzoic acid (3.83 g, 22.2 mmol; dissolved in 30 mL of CH_2Cl_2) at 25-30 ºC. The reaction mass was stirred for 2 h, analytical TLC revealed the absence of the starting material and the formation of two oxidized products. The reaction mass was quenched by the addition of ice-cold water (100 mL). The layers separated and aqueous layer extracted with CH_2Cl_2 (30 mL). The combined organic layer washed with water (100 mL × 2), dried (Na_2SO_4) and concentrated under reduced pressure and the residue obtained was purified by column chromatography. Elution with 0-5 % MeOH in CH_2Cl_2 (v/v) afforded initially the montelukast sulphone **12** followed by the montelukast sulphoxide C, both as pale-yellow solid materials. **Sulphoxide C:** The fractions containing the diastereomeric mixture were further purified by first converting it into its dicyclohexyl amine salt followed by acidification to liberate the sulphoxide as free acid. To the column purified sulphoxide (*ca.* 4.0 g) was added EtOAc (24 mL) and stirred for 10 min at 25-30 ºC. To the homogeneous solution was added dicyclohexyl amine (1.6 mL, 8.0 mmol) and stirring continued for another 12 h. *n*-Hexane (48 mL) was added stirring continued for additional 6 h. The white precipitate formed was filtered, washed with *n*-hexane (10 mL) and dried for 8 h at 45-50 ºC. To the suspension of the sulphoxide dicyclohexyl amine salt (*ca.* 4.5 g) in CH_2Cl_2 (45 mL) was added water (22 mL). The pH was adjusted to 4 with the addition of 50 % aq AcOH solution (c*a*. 1.5 mL) and stirred for 0.5 h. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (30 mL). The combined organic layer washed with water (20 mL × 2), dried (Na_2SO_4) and concentrated under reduced pressure. To the residue was added *n*-hexane (45 mL) and the slurry stirred for 2 h at 25-30 ºC. The pale-yellow solid material was filtered, washed with *n*-hexane (10 mL) and dried for 8 h at 45-50 ºC to yield the desired compound **C** (3.3 g, 32.3 % yield). IR (KBr, ν_{max}, cm^{-1}): 3372, 2972, 1714, 1604, 1637. ^1H NMR (DMSO-d_6, major diastereomer): identical to reported in literature[5a]. ESI-MS: m/z 602 ($[MH]^+$, $C_{35}H_{36}ClNO_4S$ calcd. (%) 601, 604 $[MH + 2]^+$. Sulphone **12** (0.6 g, 5.7 % yield). IR (KBr, ν_{max}, cm^{-1}): 3450, 3067, 2976, 2927, 1715, 1638, 1609, 1499, 1302. ^1H NMR ($CDCl_3$): δ 8.08 (d, *J* = 8.7, 1H), 8.03 (d, *J* = 1.5, 1H), 7.83 (s, 1H), 7.70 (d, *J* = 8.7, 1H), 7.63 (d, *J* = 8.7, 1H), 7.59 (d, *J* = 16.2, 1H), 7.52 (m, 1H), 7.45 (dd, *J* = 16.2 1H), 7.44 (dd, *J* = 2.1 and 8.7, 1H), 7.43-7.40 (m, 2H), 7.29 (m, 1H), 7.19-7.07 (m, 3H), 4.50 (brs, 1H), 4.23 (m, 1H), 3.13 (d, *J* = 14.1, 1H), 3.08 (m, 1H), 3.05 (d, *J* = 14.1, 1H), 2.82-2.69 (m, 2H), 2.61 (s, 1H), 2.41 (m, 1H), 1.56 (s, 3H), 1.54 (s, 3H), 0.75-0.67 (m, 2H), 0.67-0.55 (m, 2H). ESI-MS: m/z 618 ($[MH]^+$, $C_{35}H_{36}NO_5SCl$ calcd. (%) 617, 620 $[MH + 2]^+$.

[R,E]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)-2(RS)-[(carboxymethyl)cyclopropyl]methyl]thio]ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]-cyclopropane acetic acid (D and E): The *sec*-alcohol of the diol **4** was activated as a mesylate. To diol **4** (50 g, 109.2 mmol), anhydrous toluene (200 mL) was added and *ca.* 50 mL was removed by azeotropic distillation. Acetonitrile (450 mL) was added and the homogeneous solution was cooled to 0-5 ºC, DIPEA (26.3 mL) was added and the solution stirred for 0.5 h. The reaction mass was cooled to -25 ºC, mesylate chloride (11.2 mL, 144.7 mmol) was added over 2 h and maintained at the same temperature for another 3 h. The precipitate formed was filtered and washed with ice-cold *n*-hexane (100 mL × 2). In another flask 2-[1-(mercaptomethyl) cyclopropyl]acetic acid methyl ester (42 g, 229.6 mmol) was dissolved in DMF (300 mL) and the solution cooled to -15 ºC. A solution of 25 % NaOMe in MeOH (71 mL, 229.6 mmol) was added over a period of 0.5 h and the reaction mixture stirred, at -15 ºC, for another 0.5 h. The temperature was allowed to rise to -5 to 0 ºC and the solution of the diol mono-mesylate (75 g, dissolved in 150 mL DMF and cooled to -5 to 0 ºC) was added over 2 h and maintained at 0-5 ºC for 8 h. Analytical TLC revealed the absence of diol mono-mesylate and the formation of two products. The reaction mixture was poured into a mixture of ice-cold 10 % aqueous NaCl solution (600 mL) and EtOAc (750 mL). The layers were separated and aqueous layer extracted with EtOAc (500 mL). The combined organic layer washed sequentially with 7.5 % aqueous tartaric acid solution (300 mL) and water (550 mL). The solvent was removed under reduced pressure and the residue obtained (*ca.* 53 g) was dissolved in MeOH (250 mL). 6N aqueous NaOH solution (150 mL) was added and heated to 60-65 ºC and maintained for 3 h, when analytical TLC revealed the completion of de-esterification. Water (300 mL) and EtOAc (150 mL) were charged and pH adjusted to 4.0-4.5 by addition of 6N aqueous HCl. The layers separated and aqueous layer extracted with EtOAc (50 mL). The combined organic layer dried (Na_2SO_4)

and concentrated under reduced pressure and the residue obtained (*ca.* 55 g) was purified by column chromatography. Elution with 10-12 % MeOH in CH_2Cl_2 (v/v) afforded the Michael addition products **D + E**, as an inseparable mixture. The fractions containing the product were pooled and concentrated under reduced pressure, slurred in *n*-hexane (100 mL), filtered, washed with *n*-hexane (25 mL) and dried at 50 ºC for 5 h to yield **D + E** (10 g, 12.5 % yield) as pale-yellow solid material. The ^{1}H NMR spectral data is identical to that reported for montelucast diastereoisomer-II, reported in literature, but synthesized by an alternate route, *i.e*., by addition of MCCA to a mixture of montelucast sodium **1**, PEG-300 and sodium *tert*-butoxide in toluene-THF [5j].

Alternately, the mixture of Michael addition products D + E were also synthesized by the condensation of styrene **6** with 2-[1-(mercaptomethyl) cyclopropyl]acetic acid (MCAA), followed by hydration of the styrene moiety with aqueous sulphuric acid. To a suspension of **6** (20 g; 35 mmol) in DMF (100 mL) was added a solution of 25 % NaOMe in methanol (30.4 mL, 140 mmol) at 25-30 ºC. The temperature was raised to 40-45 ºC and MCAA (11.3 g; 77 mmol) was added over a period of 2 h. The reaction mass was maintained at 40-45 ºC for 24 h, where upon TLC revealed the disappearance of styrene **6**. The reaction mass was cooled to 25-30 ºC and quenched into 10 % aqueous NaCl solution (200 mL). EtOAc (250 mL) was added, layers seperated and the organic layer sequentially washed with a 5 % aqueous solution of tartaric acid (40 mL) and water (80 mL). The organic layer under reduced dried (Na_2SO_4) and concentrated under reduced pressure and the residue obtained (*ca.* 19 g) was purified by column chromatography. Elution with 8-10 % MeOH in CH_2Cl_2 (v/v) afforded the Michael addition products **13** (3.1 g, 12.4 % yield) as pale-yellow solid material. IR (KBr, ν_{max}, cm^{-1}): 3424, 2971, 2922, 1706, 1614. ^{1}H NMR ($CDCl_3$, major diastereomer): δ 8.10 (d, 1H), 8.05 (d, 1H), 7.64 (d, 1H), 7.46-7.38 (m, 2H), 7.36 (m, 1H), 7.34 (m, 1H), 7.30 (m, 1H), 7.27 (m, 1H), 7.17-7.08 (m, 4H), 5.06 (t, 1H), 4.70(m, 1H), 4.34 (dd, 1H), 3.96 (t, 1H), 3.73 (dd, 1H), 3.29 (dd, 1H), 3.02 (d, 1H), 2.94 (m, 1H), 2.82 (m, 1H), 2.68 (d, 1H), 2.48 (d, 1H), 2.46 (d, 1H), 2.32 (d, 1H), 2.16 (d, 1H), 2.12 (m, 1H), 2.02 (m, 1H), 1.99 (d, 1H), 1.94 (d, 1H), 1.87 (s, 3H), 0.65-0.32 (m, 8H). ESI-MS: m/z 714 ([M + H]$^+$, $C_{41}H_{44}ClNO_4S_2$ calcd. (%) 713, 716 [M + 2]$^+$. Under inert atmosphere, 80 % aq H_2SO_4 (15 mL) was cooled to 0-5 ºC and **13** (2.5 g, 3.5 mmol) was added over a period of 0.5 h. The reaction mixture was stirred for 2 h at 5-10 ºC, diluted with EtOAc (25 mL) and quenched by the sequential addition of *t*-BuOH (25 mL) and water (25 mL). The pH of the reaction mass adjusted to 3-4 by the addition of aq NaOH. Water (30 mL) was added, layers separated and the aqueous layer extracted with EtOAc (15 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure and the residue obtained (*ca.* 2.5 g) was purified by silica gel column chromatography. Elution with 8-10 % MeOH in dichloromethane (v/v) afforded product **D + E** (0.9 g; 35.3 %), whose spectral data were identical as above and to that reported in literature [5j].

[R,E]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-[prop-1-en-2-yl)phenyl]propyl]thio]methyl]cyclopropane acetic acid methyl ester (14): Hydroxy styrene hydrochloride (**5**) (10 g, 20.9 mmol) was dissolved in a mixture of CH_2Cl_2 (300 mL) and DIPEA (16.5 mL) was added. The reaction mass was cooled to 0-5 ºC and mesylate chloride (6.3 mL, 81.4 mmol) added and stirred at the same temperature for 1 h. Ice-cold 7 % aqueous solution of $NaHCO_3$ (300 mL) was added and layers separated. Aqueous layer was extracted with CH_2Cl_2 (100 mL) and combined organic layer washed with water (150 mL), dried (Na_2SO_4), concentrated under reduced pressure and the residue obtained was dissolved in DMF (90 mL). In the meanwhile, in another flask 2-[1-(mercaptomethyl) cyclopropyl] acetic acid methyl ester (12.1 g, 75.6 mmol) was dissolved in DMF (90 mL) and the solution cooled to -5 ºC. A solution of 25 % NaOMe in MeOH (17.3 mL, 80.0 mmol) was added over a period of 0.5 h and the reaction mixture stirred, at -5 to 0 ºC, for another 0.5 h. The solution of the styrene mesylate in DMF was added over 1 h and maintained at 0-5 ºC for 20 h. The reaction mixture was poured into ice-cold 5 % aqueous NaCl solution (300 mL) and EtOAc (300 mL) was added. The layers were separated and aqueous layer extracted with EtOAc (150 mL). The combined organic layer washed with water (150 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue obtained (*ca.* 14 g) was purified by column chromatography, 2-5 % MeOH in CH_2Cl_2 (v/v) eluted the desired ester **14** (10.3 g, 86 % yield) as thick viscous oil. IR (KBr, ν_{max}, cm^{-1}): 3008, 2949, 1736, 1637, 1608, 1595, 1497. ^{1}H NMR ($CDCl_3$): δ 8.10 (d, *J* = 8.7, 1H), 8.07 (d, *J* = 2.1, 1H), 7.71 (d, *J* = 16.5, 1H), 7.71 (d, *J* = 8.7, 1H), 7.65 (d, *J* = 8.7, 1H), 7.60 (s, 1H), 7.51 (m, 1H), 7.44 (dd, *J* = 2.1 and 8.7, 1H), 7.39 (d, *J* = 16.5, 1H), 7.35 (t, *J* = 7.5, 1H), 7.28 (m, 1H), 7.19-7.04 (m, 4H), 5.10 (m, 1H), 4.77 (m, 1H), 3.84 (m, 1H), 3.60 (s, 3H), 2.69 (m, 1H), 2.60 (m, 1H), 2.48 (d, *J* = 12.9, 1H), 2.43 (d, *J* = 15.6, 1H), 2.42 (d, *J* = 12.9, 1H), 2.35 (d, *J* = 15.6, 1H), 2.17-2.11 (m, 2H), 1.94 (s, 3H), 0.64-0.32 (m, 4H), the sample was contaminated by traces of DMF and CH_2Cl_2. ^{13}C NMR ($CDCl_3$): δ 172.5, 156.8, 148.6, 145.3, 143.6, 137.9, 136.4, 136.0, 135.5, 135.0, 129.1, 128.8, 128.6, 128.5, 128.2, 128.1, 127.0, 126.8, 126.0, 125.7, 125.6, 119.5, 114.9, 53.3, 51.3, 49.8, 39.8, 39.1, 38.6, 31.1, 24.9, 16.5, 12.6, 12.3. ESI-HRMS: m/z 582.2206 ([MH]$^+$, $C_{36}H_{37}ClNO_2S$ calcd. (%) 582.2108. Alternately, compound **14** was also obtained by esterification of styrene acid **6**. To a stirred solution of **6** (10 g, 52 mmol) in a mixture of MeOH (45 mL) and toluene (45 mL), at 25-30 ºC, was added sulphuric acid (5.54 g, 56 mmol). The reaction mixture was heated to reflux temperature and maintained for 15 h. The reaction mixture was concentrated under reduced pressure and the residue obtained was dissolved in CH_2Cl_2 (180 mL) and washed sequentially with water (90 mL × 2), 5 % aqueous $NaHCO_3$ solution (90 mL) and water (90 mL). The organic layer was concentrated under reduced pressure and the residue obtained was purified by column chromatography to yield the desired ester **14** (8.1 g, 81 % yield), whose spectral data were identical to that described above.

[R,E]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-[(2-hydroxypropan-2-yl)phenyl]propyl]thio] methyl]-cyclopropane acetic acid methyl ester (15): To diol **4** (50 g, 109.2 mmol), anhydrous toluene (200 mL) was added and

ca. 50 mL was removed by azeotropic distillation. Acetonitrile (450 mL) was added and the homogeneous solution was cooled to 0-5 ºC, DIPEA (26.3 mL) was added and the solution stirred for 0.5 h. The reaction mass was cooled to -25 ºC, mesylate chloride (11.2 mL, 144.7mmol) was added over 2 h and maintained at the same temperature for another 3 h. The precipitate formed was filtered and washed with ice-cold *n*-hexane (100 mL × 2). In another flask 2-[1-(mercaptomethyl) cyclopropyl]-acetic acid methyl ester (18.4 g, 115 mmol) was dissolved in DMF (150 mL) and the solution cooled to -15 ºC. A solution of 25 % NaOMe in MeOH (26.3 mL, 115 mmol) was added over a period of 0.5 h and the reaction mixture stirred, at -15 ºC, for another 0.5 h. The temperature was allowed to rise to -5 to 0 ºC and the solution of the diol mesylate (75 g, dissolved in 150 mL DMF and cooled to -15 ºC) was added over 1 h and maintained at 0-5 ºC for 24 h, when analytical TLC revealed the absence of diol mesylate. The reaction mixture was poured into a mixture of ice-cold 10 % aqueous NaCl solution (500 mL) and EtOAc (500 mL). The layers were separated and aqueous layer extracted with EtOAc (500 mL). The combined organic layer washed sequentially with 5 % aqueous tartaric acid solution (250 mL) and water (500 mL). The solvent was removed under reduced pressure and the residue obtained (*ca.* 48 g) was purified by column chromatography. 5-10 % EtOAc in *n*-hexane (v/v) eluted the ester **15** (20 g, 30.5 % yield) as thick viscous oil. IR (KBr, ν_{max}, cm^{-1}): 3447, 3058, 2974, 2950, 1733, 1637, 1608, 1497. ^{1}H NMR ($CDCl_3$): δ 8.10 (d, *J* = 8.8, 1H), 8.06 (d, *J* = 2.1, 1H), 7.71 (d, *J* = 8.8, 1H), 7.66 (d, *J* = 8.7, 1H), 7.65 (d, *J* = 16.5, 1H), 7.64 (s, 1H), 7.51 (m, 1H), 7.43 (m, 1H), 7.38 (d, *J* = 8.7, 1H), 7.36 (d, *J* = 16.5, 1H), 7.35-7.32 (m, 2H), 7.17 (m, 1H), 7.16 (m, 1H), 7.12 (m, 1H), 3.93 (t, *J* = 6.3, 1H), 3.60 (s, 3H); 3.13 (m, 1H), 2.86 (m, 1H), 2.52-2.49 (m, 2H), 2.43-2.40 (m, 2H), 2.21-2.17 (m, 2H), 1.59 (2s, 3H each), 0.53-0.41 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 172.7, 156.8, 148.6, 145.3, 143.6, 140.0, 136.4, 136.0, 135.4, 135.0, 131.5, 128.8, 128.6, 128.5, 128.1, 127.0, 126.8, 126.0, 125.6, 125.5, 125.3, 119.5, 73.5, 51.3, 50.3, 39.9, 39.8, 39.2, 32.3, 31.8, 16.8, 12.6, 12.3. ESI-HRMS: m/z 600.2318 ($[MH]^+$, $C_{36}H_{39}NO_3SCl$ calcd. (%) 600.2262). Alternatively, compound **15** was also obtained by esterification of montelukast **7**. To a solution of montelukast (10 g, 17 mmol) in a mixture of MeOH (45 mL) and toluene (45 mL) at 25-30 ºC was added sulphuric acid (5.54 g, 56 mmol). Heated the mass to reflux temperature and maintained for 5 h. The reaction mass was concentrated under vacuum and the residue obtained was dissolved in CH_2Cl_2 (180 mL) and washed sequentially with water (90 mL × 2) and 5 % aqueous $NaHCO_3$ solution (90 mL). The organic layer was concentrated under reduced pressure and the residue obtained was purified by column chromatography to yield the desired ester **15** (6 g, 58.8 % yield), whose spectral data were identical to that described above.

[R,E]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-methoxy-1-methylethyl)phenyl]propyl]thio]methyl]-cyclopropane acetic acid (17): A solution of montelukast free acid **7** (50 g, 85.3 mmol) in DMF (250 mL) was cooled to 0-5 ºC and NaH (60 % suspension in mineral oil, 12.3 g, 307 mmol) was added. The reaction mass was stirred for 0.5 h, MeI (72.7 g, 512 mmol) was added over 0.5 h and maintained at 0-5 ºC for another 2 h, where upon analytical TLC revealed the completion of the reaction. MeOH (100 mL) was added carefully and the reaction mass stirred for 15 min. CH_2Cl_2 (750 mL) was charged and washing was performed with water (500 mL × 2). The organic layer was dried (Na_2SO_4) and concentration under reduced pressure. The residue obtained **16** (*ca.* 50.7 g) was dissolved in MeOH (250 mL). The solution was cooled to 10-15 ºC and a solution of 1N aqueous NaOH (220 mL) was added. The reaction temperature was raised to 50-55 ºC and maintained for 5h, where upon analytical TLC revealed the completion of ester hydrolysis. The reaction mass was concentrated under reduced pressure and to get residue obtained was added EtOAc (500 mL) and water (500mL). The pH of the reaction mass was adjusted to 4.5-5.0 with 50 % aqueous AcOH (ca 41 mL). The layers were separated and the aqueous layer extracted with EtOAc (250 mL). The combined organic layer was washed with water (500 mL), dried (Na_2SO_4) and concentration under reduced pressure. The residue obtained was purified by column chromatography, 15-20 % EtOAc in *n*-hexane (v/v) eluted the ether **17** (15 g; 29.4 % yield) as a white solid material. IR (KBr, ν_{max}, cm^{-1}): 3429, 2977, 2930, 1706, 1611, 1501. ^{1}H NMR ($CDCl_3$): δ 8.08 (d, *J* = 8.7, 1H), 8.07 (d, *J* = 2.1, 1H), 7.77 (brs, 1H), 7.70 (d, *J* = 8.7, 1H), 7.67 (d, *J* = 8.7, 1H), 7.63 (d, *J* = 16.5, 1H), 7.46 (d, *J* = 16.5, 1H), 7.44 (dd, *J* = 2.1 and 8.7, 2H), 7.42 (m, 1H), 7.35-7.31 (m, 2H), 7.23 (d, *J* = 7.5, 1H), 7.21-7.17 (m, 2H), 7.12 (m, 1H), 5.15 (d, *J* = 2.1, 1H), 4.05 (t, *J* = 7.2, 1H), 3.29 (m, 1H), 3.03 (s, 3H), 2.97 (m, 1H), 2.68 (d, *J* = 13.2, 1H), 2.52 (d, *J* = 16.2, 1H), 2.37 (d, *J* = 16.2, 1H); 2.33 (d, *J* = 13.2, 1H), 2.17 (m, 2H), 1.59 (2s, 3H each), 0.62 (m, 1H), 0.54-0.46 (m, 2H), 0.43 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 175.1, 156.8, 147.8, 143.5, 141.5, 140.9, 136.6, 136.4, 135.5, 132.6, 130.4, 128.7, 128.6, 128.5, 127.5, 127.2, 127.1, 127.0, 126.6, 126.5, 126.3, 125.5, 119.1, 78.6, 50.4, 50.3, 40.3, 39.1, 38.8, 30.5, 28.2, 12.4, 12.1. ESI-HRMS: m/z 600.2135 ($[MH]^+$, $C_{36}H_{39}NO_3SCl$ calcd. (%) 600.2262.

[R,E]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(methoxycarbonyl)phenyl]propyl]thio]methyl]-cyclopropane acetic acid (H): A solution of hydroxyl ester **3** (50 g; 109 mmol) in a mixture of anhydrous CH_2Cl_2 (500 mL) and DIPEA (28.5 mL) was cooled to 0-5 ºC. Mesylate chloride (16.3 g, 142 mmol) was added over a period of 1 h and the reaction mixture maintained for another 2 h at 0-5 ºC, where upon analytical TLC revealed the absence of the hydroxyl ester **3**. Ice-cold aqueous 7 % $NaHCO_3$ (500 mL) was added and layers separated. Aqueous layer was extracted with CH_2Cl_2 (100 mL) and combined organic layer washed with water (250 mL), dried (Na_2SO_4), concentrated under reduced pressure and the residue obtained was dissolved in DMF (150 mL). In the meanwhile, in another flask 2-[1-(mercaptomethyl)cyclopropyl] acetic acid (19.1 g, 130 mmol) was dissolved in DMF (150 mL) and the solution cooled to -5 ºC. A solution of 25 % NaOMe in MeOH (60 mL, 277.7 mmol) was added over a period of 0.5 h and the reaction mixture stirred, at -5 to 0 ºC, for another 1 h. The solution of mesylate of **3** in DMF was added over 1 h and maintained at 0-5 ºC for 18 h. The reaction mixture was poured into ice-cold 5 % aqueous NaCl solution (500 mL) and EtOAc (500 mL) was added. The layers were separated and aqueous layer extracted with EtOAc (150 mL). The combined organic layer washed sequentially with 5 %

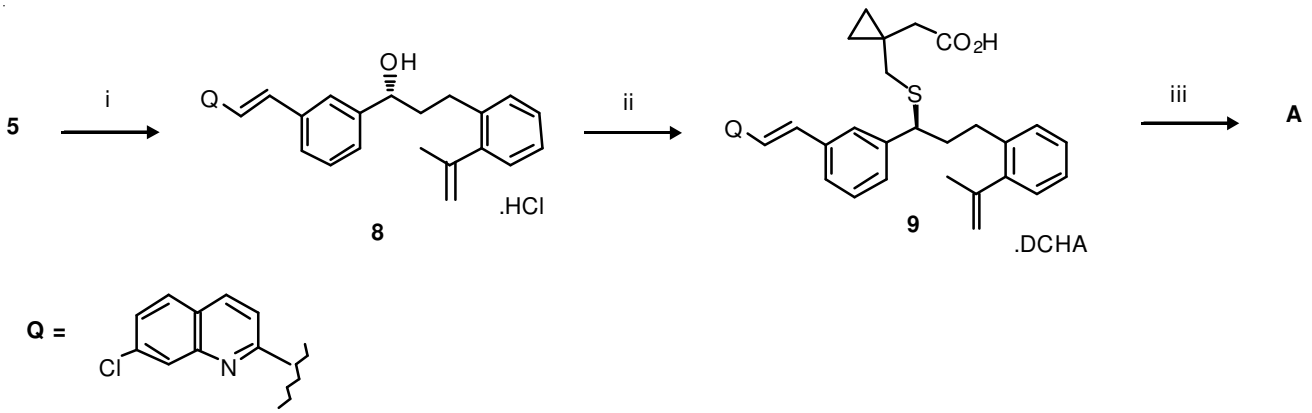
aqueous tartaric acid (250 mL) and water (150 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue obtained (*ca.* 60 g) was purified by column chromatography, 5-15 % EtOAc in *n*-hexane (v/v) eluted the desired ester **H** (20.8 g, 32.5 % yield) as a off-white solid material. IR (KBr, ν_{max}, cm^{-1}): 3018, 2949, 1718, 1609, 1498. ^1H NMR ($CDCl_3$): δ 8.06 (d, *J* = 8.4, 1H), 8.04 (d, *J* = 1.8, 1H), 7.85 (dd, *J* = 1.2 and 6.6, 1H), 7.72 (s, 1H), 7.68 (d, *J* = 8.4, 1H), 7.65 (d, *J* = 8.4, 1H), 7.60 (d, *J* = 16.2, 1H), 7.46 (d, *J* = 16.2, 1H), 7.44 (m, 1H), 7.40 (m, 1H), 7.35 (m, 1H), 7.29 (m, 1H), 7.25-7.19 (m, 3H), 3.93 (t, *J* = 7.2, 1H), 3.82 (s, 3H), 3.07 (m, 1H), 2.94 (m, 1H), 2.63 (d, *J* = 4.8, 1H), 2.58 (d, *J* = 8.1, 1H), 2.17-2.12 (m, 3H), 0.54-0.42 (m, 4H). 13C NMR (CDCl3): d 179.2, 166.2, 158.1, 156.2, 141.2, 140.2, 136.5, 136.4, 135.7, 135.5, 131.9, 130.9, 130.7, 128.9, 128.7, 128.6, 128.5, 128.0, 127.5, 127.1, 126.6, 126.5, 126.4, 126.0, 119.0, 51.8, 49.9, 40.0, 38.59, 38.57, 32.8, 12.2. ESI-HRMS: m/z 586.2158 ($[MH]^+$, $C_{34}H_{33}NO_4SCl$ calcd. (%) 586.1554.

[R,E]-1-[[[1-[3-[2-(7-Chloro-2-quinolinyl) ethenyl]phenyl]-3-[2-(methylcarbonyl)phenyl] propyl]thio]methyl]cyclopropane acetic acid dicyclohexyl amine salt (F): A solution of ester H (25 g, 42.6 mmol) in anhydrous THF (250 mL) was cooled to 0-5 ºC and MeMgCl (3 M solution in THF, 150 mL, 450 mmol) was added over a period of 3 h. The reaction mass was stirred for 6 h at 0-5 ºC, where upon TLC revealed the absence of ester **H**. To the reaction mixture was added ice-cold 50 % aqueous AcOH (250 mL) followed by EtOAc (250 mL), while maintaining internal temperature below 10 ºC. The layers separated and the aqueous layer extracted with EtOAc (125 mL). The combined organic layer washed sequentially with water (320 mL), 5 % aqueous $NaHCO_3$ solution (250 mL) and water (250 mL). The separated organic phase dried (Na_2SO_4) and concentrated under reduced pressure. The residue obtained (*ca.* 26 g) was purified by column chromatography, 0.5-2.0 % MeOH in CH_2Cl_2 (v/v) eluted the desired keto-free acid **F** (*ca.* 3.0 g). It was converted into its dicyclohexyl amine salt by dissolving in EtOAc (18 mL) and to the clear solution was added dicyclohexylamine (1.24 mL). The mixture was stirred for 6 h at 25-30 ºC and *n*-hexane (36 mL) added over a period of 0.5 h and the reaction mass stirred for another 3 h. The precipitate formed was filtered and washed with *n*-hexane (10 mL) and dried at 45-50 ºC for 8 h to afford ketone **19** (3.1 g, 12.7 % yield) as a yellow solid material. IR (KBr, ν_{max}, cm^{-1}): 3435, 2934, 2853, 1753, 1682, 1637, 1611, 1497. ^1H NMR (DMSO-d_6): δ 8.40 (d, *J* = 8.7, 1H), 8.02 (s, 1H), 8.00 (d, *J* = 8.7, 1H), 7.93 (d, *J* = 8.7, 1H), 7.88 (d, *J* = 16.5, 1H), 7.75 (d, *J* = 7.8, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 8.7, 1H), 7.59 (dd, *J* = 2.1 and 8.7, 1H), 7.50 (d, *J* = 16.5, 1H), 7.43 (m, 1H), 7.39 (d, *J* = 7.5, 1H), 7.32 (d, *J* = 7.8, 1H), 7.27 (m, 1H), 7.13 (m, 1H), 3.91 (t, *J* = 7.2, 1H), 2.80 (m, 1H), 2.61-2.45 (m, 8H), 2.25 (d, *J* = 9.5, 1H), 2.18 (d, *J* = 9.5, 1H), 2.15-2.04 (m, 2H), 1.86-1.74 (m, 4H), 1.70-1.61 (m, 4H), 1.61-1.50 (m, 2H), 1.28-0.96 (m, 10H), 0.55-0.42 (m, 4H). ESI-MS: m/z 570 ($[MH-DCHA]^+$, $C_{34}H_{32}NO_3SCl{\cdot}C_{12}H_{23}N$ calcd. (%) 750, 572 $[MH + 2\text{-}DCHA]^+$.

RESULTS AND DISCUSSION

Montelukast sodium **1** synthesized[3] is shown in **Scheme-I**. The keto-ester **2** is reduced stereoselectively to the hydroxyl-ester **3**, which upon treatment with excess MeMgCl afforded the diol **4**. The diol **4** is converted to styrene **5**, *via sec*-alcohol acetylation-dehydration-deacetylation to yield hydroxyl-styrene **5**. The *sec*-alcohol is activated by reaction of **5** with mesylate chloride and *in situ* displacement with 2-[1-(mercaptomethyl) cyclopropyl]acetic acid (MCAA) afforded styrene **6**, isolated as a dicyclohexyl amine (DCHA) salt. Hydration of **6** in the presence of 80 % aq H_2SO_4 afforded **7**, isolated as 1-methyl-3-phenylpropylamine (MPPA) salt. The MPPA salt **7** upon treatment with acetic acid and subsequently with sodium hydroxide afforded Montelukast sodium **1**.

In laboratory optimization of montelukast, many process related impurities were identified and their synthesis was undertaken. During reduction of keto-ester **2** with (-) DIP chloride, formation of 2-3 % of the undesired R-isomer was observed when analyzed by chiral-HPLC, its carry over throughout the synthesis leads to contamination of montelukast sodium with the isomeric impurity A. Impurity A was synthesized by a double inversion of the stereochemistry of *sec*-alcohol in hydroxyl styrene **5** (**Scheme-II**). Thus the *sec*-alcohol in **5** was activated with MsCl and the mesylated formed



Scheme-II: Reagents and conditions (and yields): (i) (a) MsCl, DIPEA, CH_2Cl_2, 0-5 ºC; (b) CsOAc, DMAP, toluene, 110 ºC; (c) 15M aq NaOH, THF, MeOH, 25-30 ºC; (d) 6N aq HCl, 25-30 ºC (85.1 %); (ii) (a) MsCl, DIPEA, CH_2Cl_2, 0-5 ºC; b) MCAA, *n*-BuLi (15 % w/w in hexanes), THF, -2 to 2 ºC; (c) DCHA, EtOAc, 25-30 ºC (70 %); (iii) (a) 80 % aq H_2SO_4, 5-10 ºC; (b) silica gel column purification, (c) MPPA, EtOAc, 25-30 ºC; (d) AcOH, H_2O, CH_2Cl_2, 25-30 ºC; (e) NaOH, H_2O, EtOH, 25-30 ºC (41.5 %). DIPEA = N,N-diisopropylethyl amine; MCAA = 2-[1-(mercaptomethyl) cyclopropyl]acetic acid; DCHA = dicyclohexyl amine; MPPA = 1-methyl-3-phenylpropylamine

was *in situ* displaced with an acetate ion, deacetylation with a mild base afforded the isomeric hydroxyl styrene **8**. Again, the *sec*-alcohol in **8** was activated and a S_N2 displaced with MCAA afforded isomeric styrene **9**. It was observed that the styrene **9** contamination in styrene **6** was never more than 0.15 %. Hydration of styrene **9** with 80 % aq H_2SO_4 afforded impurity A.

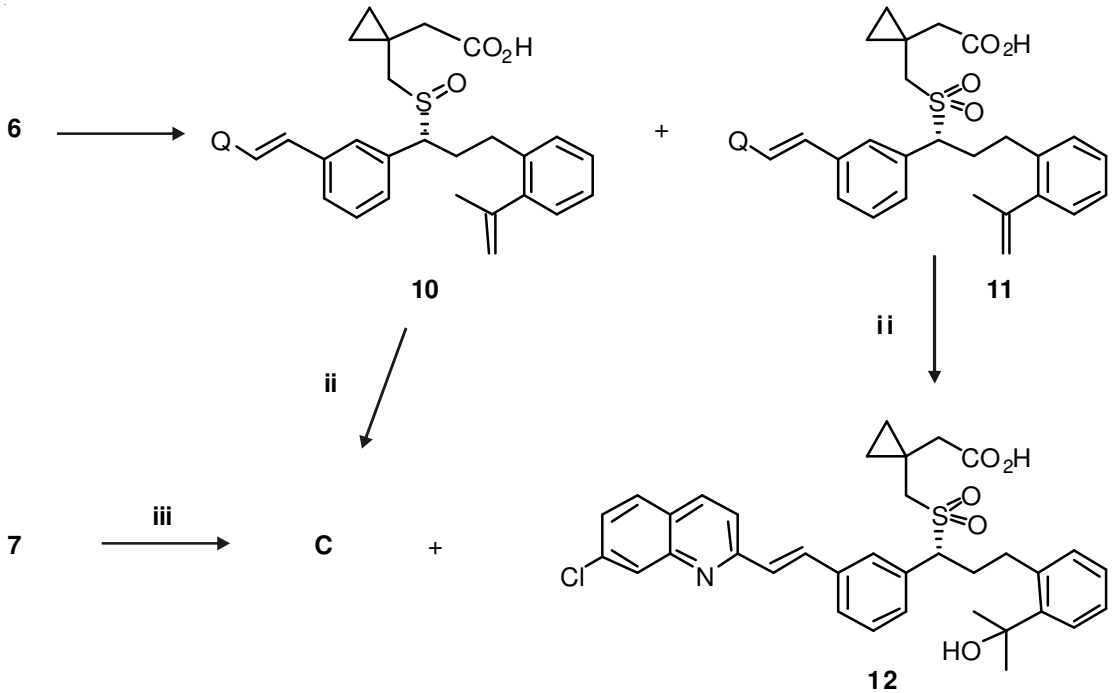
Since the *tert*-alcohol in Montelukast is prone to dehydration even under mild acidic condition, styrene **6** (impurity B) is a potential impurity and degradent. This impurity was found in innovator tablet singulair in the levels of 0.1 %. The draft pharmacopeia recommends this impurity limit of NMT 0.3 %. This compound **6** is one of the intermediate in our route of synthesis.

Few impurities were anticipated in MPPA addition reaction. The oxidized compounds, sulphoxide **10** and sulphone **11** are possible degradent and possibly formed due to air oxidation of the thioether moiety. Oxidation of styrene **6** with *m*-chloroperbenzoic acid afforded both these impurities in the ratio 9:1 and they were separated by silica gel column chromatography (**Scheme-III**). The less polar sulphone **11** eluted first followed by the more polar sulphoxide **10** (as an inseparable 1:5 mixture of diastereomers). Both of them were characterized by their ^{1}H NMR and mass spectral data. The styrene oxidized products were hydrated with 80 % aq H_2SO_4 to afford oxidized Montelukast sulpoxide C and sulphone **12**, respectively. Impurity C was also prepared by the literature procedure[5a] and found to be identical to the one synthesized above by the two step process from styrene **6**.

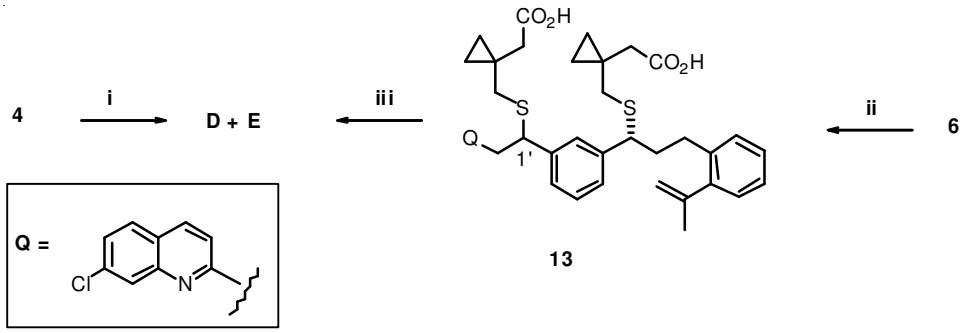
During the MCAA coupling reaction, apart from the oxidized product **10** and **11**, the Michael addition product **13** was also observed as a mixture of diastereoisomers. LC-MS (m/z 714, M + H) indicated the addition of two MCAA units and it was confirmed by their synthesis. Thus, sodium salt of MCAA was stirred with styrene **6** at 40-45 ºC for 24 h and crude material obtained was purified by column chromatography. Hydration of the diastereoisomers with 80 % aq H_2SO_4 afforded the desired impurities D and E (**Scheme-IV**). These compounds were also synthesized, following the literature method[5j], by the reaction of sodium salt of MCAA methyl ester with Montelukast **1** and subsequent hydrolysis of the ester moiety.

The hydration of styrene **6**, under acidic condition, didn't proceed to completion and the mixture of **6** and **7** had to be separated by column chromatography. Formation of three impurities was observed during column purification. As methanol was one of the eluent, aided by the acidic environment, formation of methyl esters was anticipated. Esterification of compounds **6** and **7** with methanol, in the presence of acid afforded the methyl esters **14** and **15**, respectively. In addition, another impurity with mass (m/z 582) similar to ester **15** was also detected, which was tentatively assigned as methyl ether **17**. Reaction of compound **7** with MeI, under strong alkaline conditions, yielded compound **16**, which upon saponification yielded the desired ether **17** (**Scheme-V**). Surprisingly, compound **16** was not at all detected in any of the fractions obtained from column chromatography

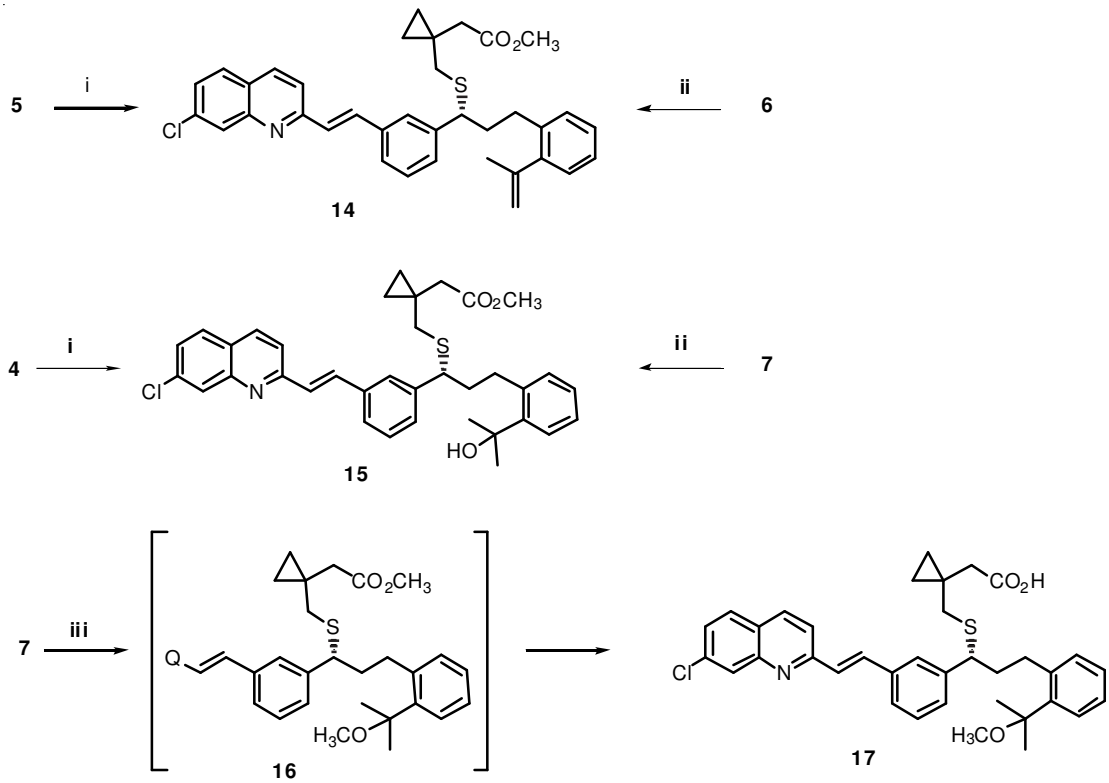
Impurity H was synthesized by mesylating of *sec*-alcohol in ester **3**, followed by the displacement of the O-mesyl moiety with MCAA (**Scheme-VI**). Compound **H** upon saponification afforded impurity **18**. The diol **4** is obtained by the Grignard reaction of MeMgCl with ester **3** in the presence of anhydrous $CeCl_3$. The completion of the reaction depends upon the quality of cerium chloride used and 0.2-0.5 % keto-intermediate **19** is



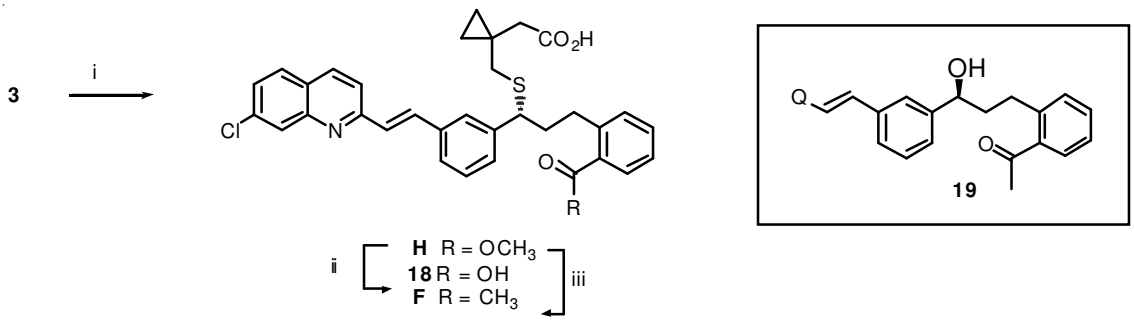
Scheme-III: Reagents and conditions (and yields): (i) (a) *m*-CPBA, CH_2Cl_2, 25-30 ºC; (b) silica gel column separation, (**10**: 39.2 %; **11**: 4.7 %); (ii) (a) 80 % aq H_2SO_4, 5-10 ºC; (b) silica gel column purification, (c) MPPA, EtOAc, 25-30 ºC; (iii) (a) *m*-CPBA, CH_2Cl_2, 25-30 ºC; (b) silica gel column separation, (C): 32.3 %; 12:5.7 %;). *m*-CPBA = *meta*-chloroperbenzoic acid



Scheme-IV: Reagents and conditions (and yields): (i) (a) MsCl, DIPEA, CH_2Cl_2, 0-5 ºC; (b) MCAA methyl ester, NaOMe (25 % solution in MeOH), DMF, -5 to 0 ºC; (c) 6M aq NaOH, MeOH, 60-65 ºC; (d) silica gel column purification (12.5 %); (ii) (a) MCAA, NaOMe (25 % solution in MeOH), DMF, 40-45 ºC; (b) silica gel column purification (12.4 %); (iii) (a) 80 % aq H_2SO_4, 5-10 ºC; (b) silica gel column purification, (35.3 %). DIPEA = N,N-diisopropylethyl amine; MCAA = 2-[1-(mercaptomethyl) cyclopropyl]acetic acid



Scheme-V: Reagents and conditions (and yields): (i) (a) MsCl, DIPEA, CH_2Cl_2, 0-5 ºC; (b) MCAA methyl ester, NaOMe (25 % solution in MeOH), DMF, 0-5 ºC; (c) silica gel column purification (**14**: 86 % from **5**; **15**: 30.5 % from **4**); (ii) (a) MeOH, H_2SO_4, toluene, reflux; (b) silica gel column purification, (**14**: 81 % from **6**; **15**: 58.8 % from **7**); (iii) (a) MeI, NaH (60 % suspension in mineral oil), DMF, 0-5 ºC; (b) 1M aq NaOH, MeOH, 50-55 ºC; (c) silica gel column purification, (29.4 %). DIPEA = N,N-diisopropylethyl amine; MCAA = 2-[1-(mercaptomethyl) cyclopropyl]acetic acid; DCHA = dicyclohexyl amine



Scheme-VI: Reagents and conditions (and yields): (i) (a) MsCl, DIPEA, CH_2Cl_2, 0-5 ºC; (b) MCAA, NaOMe (25 % solution in MeOH), DMF, 0-5 ºC; (c) silica gel column purification (32.5 %); (ii) (a) 2M aq NaOH, MeOH, THF, reflux; (c) silica gel column purification, (43.3 %); (iii) (a) MeMgCl (3M solution in THF), THF, 0-5 ºC; (b) DCHA, EtOAc, 25-30 ºC (12.7 %); DIPEA = N,N-diisopropylethyl amine; MCAA = 2-[1-(mercaptomethyl) cyclopropyl]acetic acid

observed and in some cases even up to 6 % of ketone **19** could be seen. In the absence of $CeCl_3$ reaction of ester **3** with MeMgCl afforded the keto-intermediate **19**, as the major product. Mesylation of **19** with MsCl, in the presence of base and *in situ* reaction with sodium salt of MCAA afforded the desired impurity F

Conclusion

For the better understanding of the synthetic pathway of an active pharmaceutical ingredient it is necessary to identify all the impurities/degradation products formed/anticipated. In this regard we have identified and synthesized different possible potential process-related impurities of montelukast sodium, including seven impurities reported in pharma Europa.

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