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Studies on alternate synthetic routes of Montelukast sodium, a heterocyclic compound of potent medicinal interest

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ABSTRACT

An alternate approach for the synthesis of leukotriene antagonist drug substance Montelukast sodium is discussed.

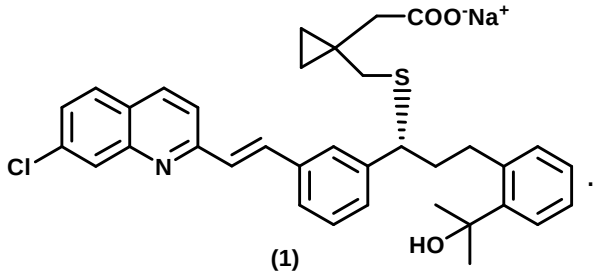
KEYWORDS

Montelukast sodium;
Anti-asthmatic;
Leukotriene;
Antagonist;
Alternate synthesis.

INTRODUCTION

Montelukast sodium is a selective leukotriene receptor antagonist which inhibits cysteinyl leukotriene $CysLT_1$ receptor. It is useful as anti-asthmatic[1-3], anti-allergic, anti-inflammatory, cytoprotective agent and hence useful in the treatment of angina, cerebral spasm, glomerular nephritis, hepatic, endtoxemia, uveitis and allograft rejection. Leukotrienes are a group of local harmones derived from arachidonic acid in the body and representative examples of leukotrienes include leukotriene B4 (LTB4), leukotriene C4 (LTC4), leukotriene D4 (LTD4), and leukotriene E4 (LTE4). Montelukast sodium is described chemically as [R-E]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl) ethenyl] phenyl] -3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid and is structurally represented as figure 1.

Montelukast sodium is one of the top 10 selling drugs in the world. Due to its commercial importance several synthetic routes are reported[4-8]. Most of the synthetic routes as well as intermediates are protected in several patents by various generic companies. It is a stiff challenge for organic chemists at this juncture to design an alternate novel synthetic route bifurcating the most crowded patent protection. In this context we are successful in designing various alternate cost-effective methods to synthesize Montelukast Sodium. In our study we have focused on alternate approaches by replacing



(1)

Figure 1 : Structure of [R-E]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl) ethenyl] phenyl] -3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid

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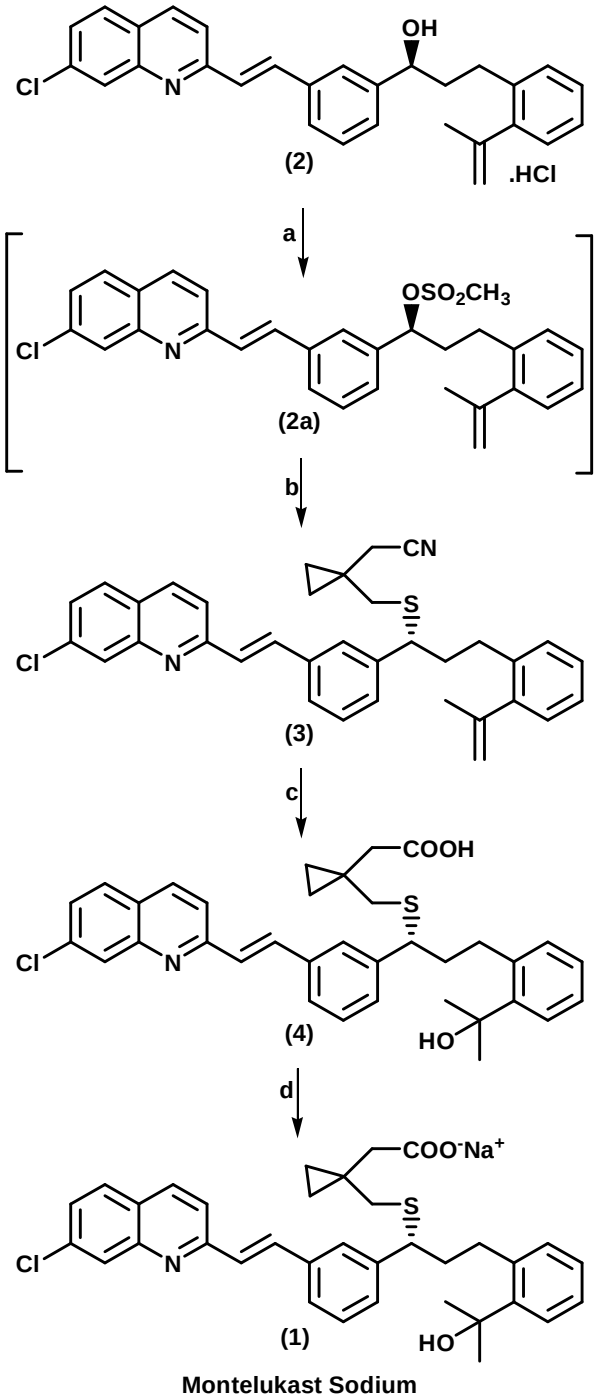
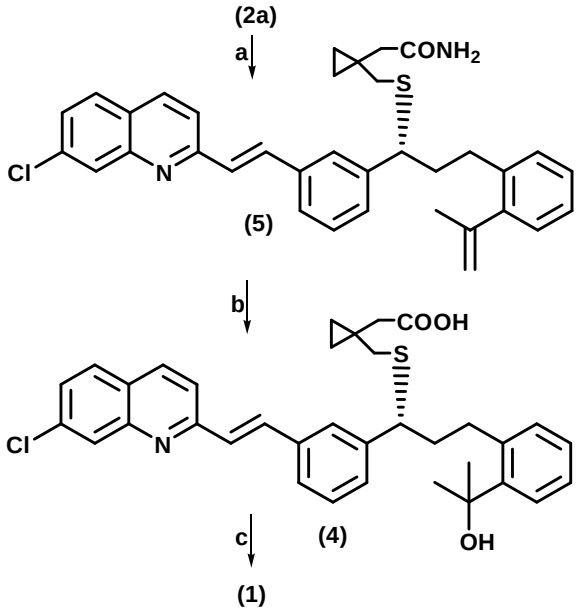
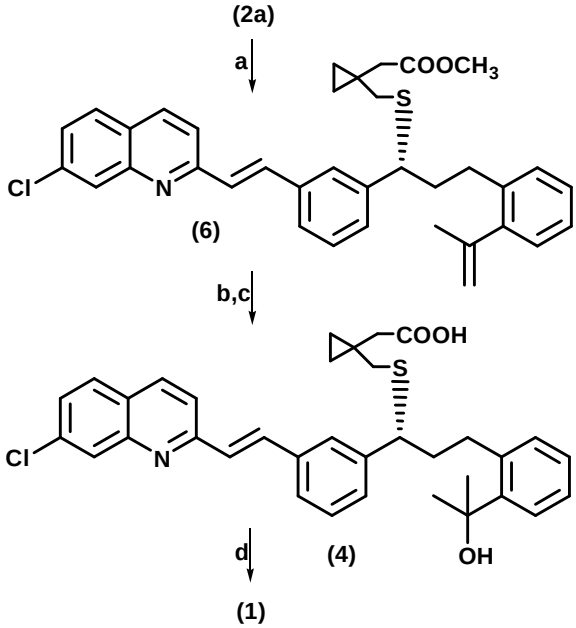


Scheme 1 : Reagents and solvents: (a) Methane sulphonyl chloride, DIPEA/MDC (b) 2-(1-(mercaptomethyl) cyclopropyl) acetonitrile, 25% NaOMe in MeOH, DMF (c) 80%H2SO4 (d)NaOH, MeOH, n-heptane



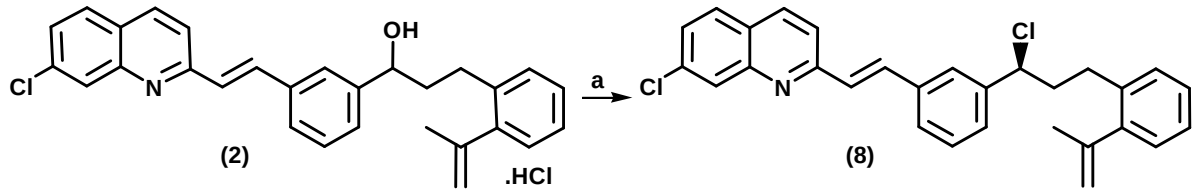
Scheme 2 : Reagents and solvents: (a) 60%NaH, DMF, 2-(1-(mercaptomethyl) cyclopropyl)acetamide (b) 80% H2SO4; (c) NaOH, MeOH



Scheme 3 : Reagents and solvents: (a) 15% n-butyl lithium solution in THF, Methyl 2-(1-(mercaptomethyl) cyclopropyl) acetate (b) 80% H2SO4; (c) NaOH, Acetic acid; (d) NaOH, MeOH

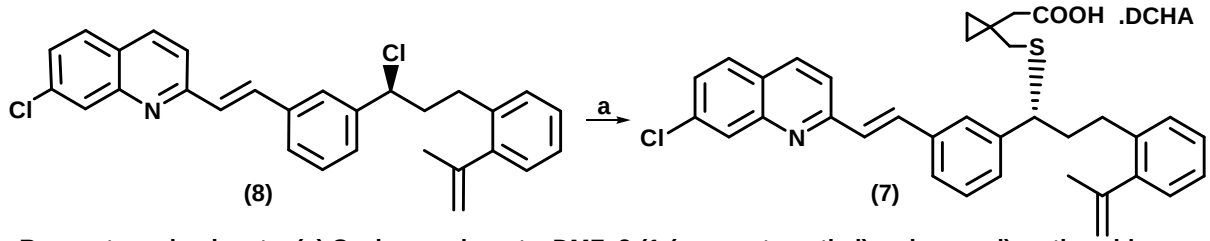
the claimed and costly intermediate 2-(1-(mercaptomethyl) cyclopropyl) acetic acid with much cheaper and commercially available alternatives.

The first approach (Scheme 1) involves mesylation of (S)-1-(3-((E)-2-(7-chloroquinolin-2-yl) vinyl) phenyl)-3-(2-(prop-1-en-2-yl) phenyl) propan-1-ol hydrochloride **(2)**, [Hydroxy styrene] with methane sulphonyl-chloride to give (S)-1-(3-((E)-2-(7-chloro- quinolin-2-yl)vinyl)phenyl)-3-(2-(prop-1-en-2-yl) phenyl)propyl methanesulfonate **(2a)** and in situ subjected to conden-



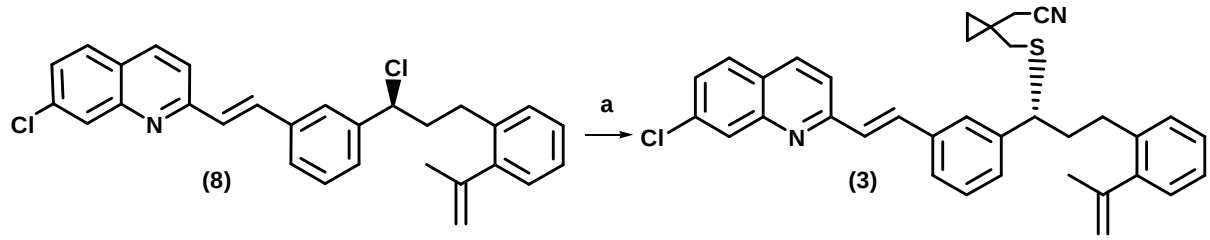
Reagent and solvent : (a) Thionyl chloride, DMF

Scheme 4



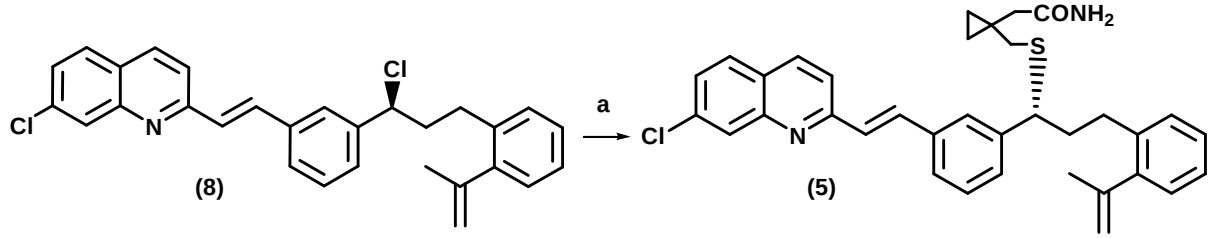
Reagents and solvents: (a) Cesium carbonate, DMF, 2-(1-(mercaptomethyl)cyclopropyl)acetic acid, Dicyclohexylamine (DCHA)

Scheme 5



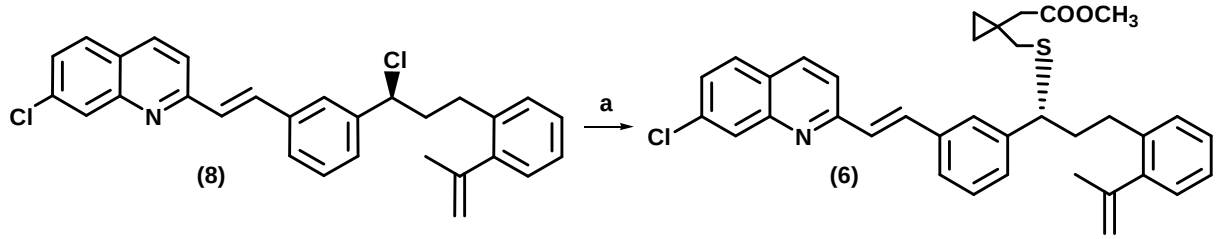
Reagents and solvents: (a) NaOMe, DMF, 2-(1-(mercaptomethyl) cyclopropyl)acetonitrile

Scheme 6



Reagents and solvents: (a) NaH, DMF, 2-(1-(mercaptomethyl) cyclopropyl)acetamide

Scheme 7



Reagents and solvents: (a) Cesium carbonate, DMF, Methyl 2-(1-(mercaptomethyl) cyclopropyl)acetate

Scheme 8

sation with 2-(1-(mercaptomethyl) cyclopropyl) acetonitrile in the presence of sodium methoxide solution in methanol affords2-(1-(((R)-1-(3-((E)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(prop-1-en-2yl)phenyl) propylthio)methyl)cyclopropyl) aceto nitrile **(3)**. The nitrile **(3)** was purified by column chromotography and subjected to one pot hydration of the styrene moiety and hydrolysis of the nitrile group with 80% H_2SO_4 affords 2-[1-[1(R)-[3-[2(E)-(7-chloroquinolin-2-yl)vinyl] phenyl] -3-[2-hydroxy-1-methylethyl) phenyl] propyl sulfanylmethyl] cyclopropyl] acetic acid **(4)**, as free acid. The free acid **(4)** upon treatment with alcoholic sodium hydroxide solution affords Montelukast sodium **(1)**.

The second approach (Scheme 2) involves condensation of (S)-1-(3-((E)-2-(7-chloroquinolin-2-yl) vinyl) phenyl)-3-(2-(prop-1-en-2-yl) phenyl) propyl methane Sulfonate **(2a)** with 2-(1-(mercaptomethyl) cyclopropyl) acetamide in the presence of sodium hydride in N,N-dimethylformamide affords 2-(1-(((R)-1-(3-((E)-2-(7-chloroquinolin-2-yl) vinyl) phenyl)-3-(2-(prop-1-en-2-yl) phenyl) propylthio) methyl) cyclopropyl) acetamide **(5)**, which is further subjected to hydration with 80% H_2SO_4 followed by column chromatography affords 2-[1-[1(R)-[3-[2(E)-(7-Chloroquinolin-2-yl)vinyl]phenyl]-3-[2-hydroxy-1-methylethyl) phenyl] propylsulfanylmethyl] cyclopropyl] acetic acid **(4)** as free acid. Treatment of **(4)** with methanolic sodium hydroxide affords Montelukast sodium **(1)**.

The third approach (Scheme 3) involves condensation of (S)-1-(3-((E)-2-(7-chloroquinolin-2-yl)vinyl) phenyl)-3-(2-(prop-1-en-2-yl)phenyl)propyl methanesulfonate **(2a)** with methyl 2-(1-(mercaptomethyl) cyclo propyl)acetate in the presence of 15% n-butyl lithium solution in tetrahydrofuran affords methyl-2-(1(((R)-1-(3-((E)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(prop-1-en-2-yl)phenyl) propylthio) methyl) cyclopropyl)acetate **(6)**, which is subjected further to hydration with 80% H_2SO_4 and hydrolysis with sodium hydroxide followed by column purification affords 2-[1-[1(R)-[3-[2(E)-(7-Chloroquinolin-2-yl)vinyl] phenyl]-3-[2-hydroxy-1-methylethyl) phenyl] propylsulfanylmethyl] cyclopropyl] acetic acid **(4)**. Treatment of **(4)** with methanolic sodium hydroxide affords Montelukast sodium **(1)**.

In an alternate approach compounds **(3)**, **(5)**, **(6)**, and **(7)** are synthesized by an SN^2 reaction on the chloro derivative **(8)**. The (S) configured alcohol 2 upon reaction with thionyl chloride in the presence of N,N-dimethylformamide gave 2-(3-((S)-1-chloro-3-(2-(prop-1-en-2-yl) phenyl) propyl) ethenyl)-7-chloro quinoline **(8)** (Scheme 4). Surprisingly, the chiral HPLC revealed it to be a mixture of 80% of desired S-isomer and 20% of R-isomer. The unwanted R-isomer is easily removed in the subsequent steps of the synthesis.

Condensation of compound **(8)** with 2-(1-(mercaptomethyl)cyclopropyl)acetic acid in the presence of cesium carbonate affords 2-(1-(((R)-1-(3-((E)-2-(7-chloroquinolin-2-yl) vinyl) phenyl)-3-(2-(prop-1-en-2-yl) phenyl) propylthio) methyl) cyclopropyl)acetic acid **(7)** which is isolated as dicyclohexylamine salt (Scheme 5).

Condensation of compound **(8)** with 2-(1-(mercaptomethyl) cyclopropyl) acetonitrile in the presence of sodium methoxide affords 2-(1-(((R)-1-(3-((E)-2-(7-chloroquinolin-2-yl)vinyl) phenyl)-3-(2-(prop-1-en-2-yl)phenyl)propylthio)methyl)cyclopropyl) acetonitrile **(3)** (Scheme 6).

Condensation of compound **(8)** with 2-(1-(mercaptomethyl) cyclopropyl)acetamide in the presence of sodium hydride affords 2-(1-(((R)-1-(3-((E)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(prop-1-en-2-yl) phenyl) propylthio) methyl) cyclopropyl) acetamide **(5)** (Scheme 7).

Condensation of compound **(8)** with methyl 2-(1-(mercaptomethyl) cyclopropyl)acetate in the presence of cesium carbonate affords methyl 2-(1-(((R)-1-(3-((E)-2-(7-chloroquinolin-2-yl) vinyl) phenyl)-3-(2-(prop-1-en-2-yl) phenyl) propylthio) methyl) cyclopropyl) acetate **(6)** (Scheme 8).

To conclude we have explored cost-effective commercially viable and scalable alternative routes for the synthesis of Montelukast sodium.

The experimental details for all the routes discussed and spectral data for new compounds **(3)**, **(5)**, **(6)**, **(8)** available in supplementary material file.

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REFERENCES

[1] A.Markham, D.Faulds; Drugs, **56(2)**, 251, **(1998)**.

[2] M.Labelle, M.Belley, Y.Gareau, J.Y.Gauthier, D.Guay, R.Gordon, S.G.Grossman, T.R.Jones, Y.Leblanc; Bioorg.Med.Chem.Lett., **5(3)**, 283, **(1995)**.

[3] M.J.Noonan, P.Chervinsky, M.Brandon, J.Zhang, S.Kundu, J.Mcburney, T.F.Reiss; Eur.Respir.J., **11**, 1232 **(1998)**.

[4] B.R.Reguri, S.Bollikonda, S.B.V.V.Chandra, R.K.Kasturi, S.K.Aavula; US 20050107612 A1, **(2005)**.

[5] A.Overeem, R.G.Gieling, J.Zhu, L.Thijs; WO 2005105749 A2, **(2005)**.

[6] M.L.Belley, S.Leger, P.Roy, Y.B.Xiang, M.Labelle, D.Guay; EP 0480717 B1, **(1991)**.

[7] M.Bhupathy, J.M.McNamara, D.R.Sidler, R.P.Volante, J.J.Bergan, EP 0737186 B1, **(1994)**.

[8] E.Shapiro, R.Yahalomi, V.Niddam-Hildesheim, G.Sterimbaum, K.Chen; WO 2005105751 A1, **(2005)**.