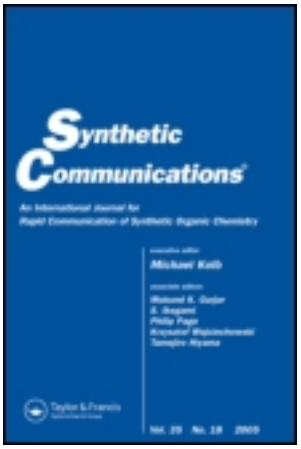

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CONCISE AND ALTERNATIVE SYNTHESIS OF ZAFIRLUKAST, AN ANTI-ASTHMA DRUG

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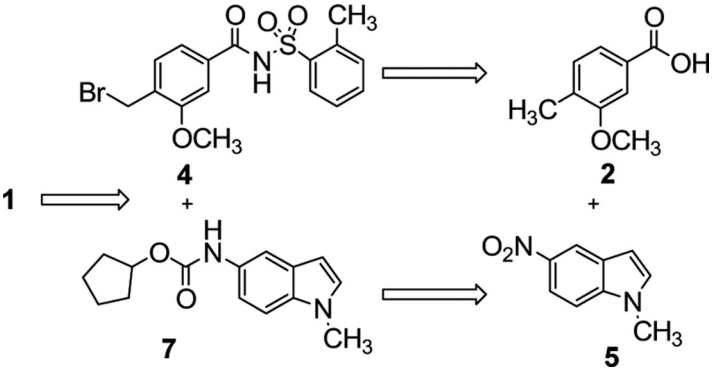
GRAPHICAL ABSTRACT



Abstract *Concise and alternative synthesis of zafirlukast (**1**) is described. The synthesis features fewer steps, convergent synthesis, and novel intermediates.*

Keywords Alternate synthesis; novel intermediates; selective bromination; zafirlukast

INTRODUCTION

Zafirlukast is a selective and competitive receptor antagonist of the cysteinyl leukotrienes D-4 and E-4, which is indicated for the prophylaxis and treatment of mild to moderate persistent and chronic asthma.[1] Leukotrienes are a class of

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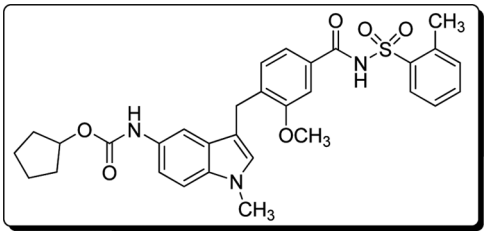


Figure 1. Structure of zafirlukast (**1**).

compounds that have been identified as responsible for the contraction of human airway and lung vascular smooth muscle. A chemical agent that is effective in blocking the induced constricting actions of leukotriene could be used to treat inflammatory processes in the pulmonary system. Zafirlukast works by directly blocking substances called leukotrienes, which are molecules that contribute to inflammation and narrowing in the airways, a process that leads to symptoms such as difficulty in breathing in patients with asthma.

The action of zafirlukast (trade name: Accolate) reduces inflammation and thus helps to control the symptoms of asthma and improve lung function. Zafirlukast is a potent, selective $CysLT_1$ receptor antagonist sold for the treatment of asthma as well as for the symptoms associated with allergic rhinitis. It binds to the human $CysLT_1$ and $CysLT_2$ receptors with IC_{50} values of approximately 5 and 7,400 nM, respectively.

In the literature several synthetic methods were available for the preparation of zafirlukast **1** including one route reported by our group.[2–8] Most of the reported syntheses of zafirlukast involved either linear or poor-yielding processes or excessive number of stages. In continuation of earlier work, herein we describe a convergent strategy for the synthesis of zafirlukast. The easily available 5-nitroindole derivative (**5**) and acid derivative (**2**) were effectively transformed to the target compound involving very straightforward reactions. Compounds **3** and **4** are novel and reported for the first time here, including synthesis and charcerization with spectral data. Compound **7** has been disclosed in the literature, and synthesis and characterization are not reported here.[9]

RESULTS AND DISCUSSION

In formulating the synthetic plan for zafirlukast, we envisioned a coupling between the sulfonamide **4** and carbamate **8**, allowing the synthesis of target compound **1** (Scheme 1). Indole derivative **8** could be obtained from reduction of nitro indole and subsequent carbamate formation. The other fragment could be synthesized via sulfamidation followed by selective bromination. Synthesis of these fragments started with inexpensive and readily available starting materials 5-nitroindole derivative (**5**) and benzoic acid derivative (**2**).

The chemical route for the synthesis of zafirlukast (**1**) is shown in Scheme 2. Synthesis of intermediate **4** commenced from benzoic acid **2**, and coupling of acid **2** with sulfonamide under peptide coupling conditions [N, N′-dicyclohexylacarbodiimide (DCC–dimethylaminopyridine DMAP)] furnished compound **3** in 95% yield.

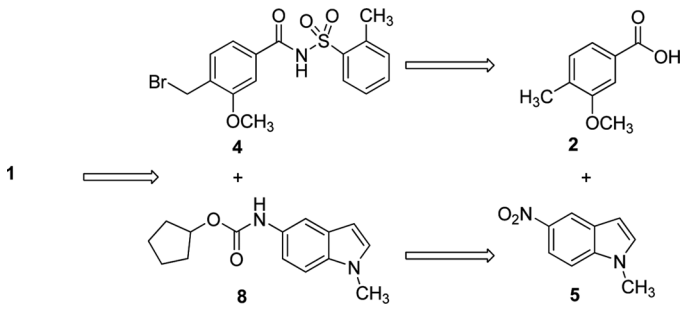
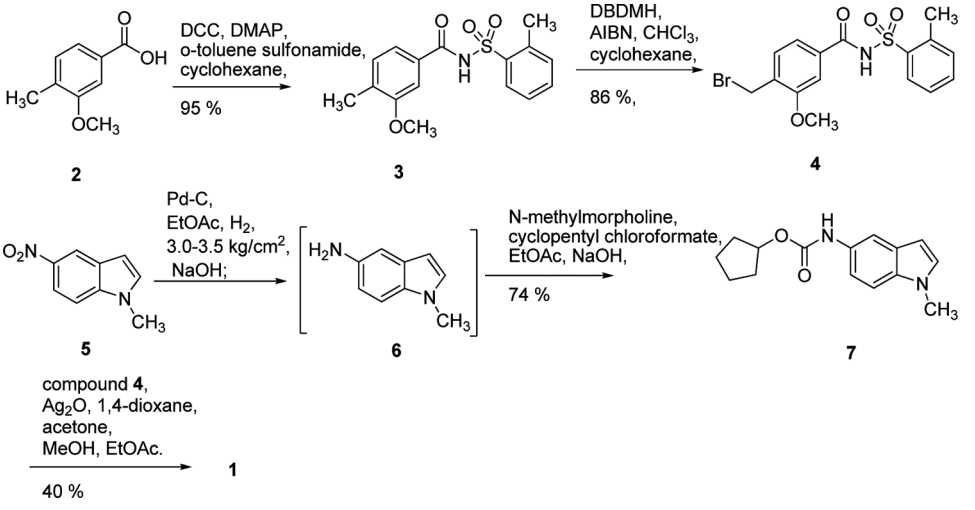


Figure 2. Retrosynthesis of zafirlukast.

Mass spectrum of compound **3** showed a m/z 318 [M-H] peak in the negative mode. Infrared (IR) spectrum displayed characteristic absorptions at 1700 cm^{-1} and 1336 and 1156 corresponding to carbonyl and sulfonyl stretching respectively. The proton NMR spectrum showed a singlet at δ 9.61 corresponding to the *N*H proton and three singlets at δ 3.77, 2.72, and 2.22 corresponding to OCH_3 and two aromatic methyl groups (adjacent to sulfonyl and methoxy groups). Aromatic protons appeared as double doublets at δ 8.27, a doublet at δ 7.16, and a multiplet at δ 7.60–7.24, confirming the structure of sulfonamide **3**.

The aim of selective bromination of sulfonamide **3** was achieved with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and azobisisobutyronitrile (AIBN) in chloroform to yield the monobromo compound **4** with 86% yield and 96.0% purity. Mass spectrum showed protonated molecular ion peak at m/z 398 and sodium adduct at m/z 420.^{1}H NMR spectrum of compound **4** is characterized by the presence of a multiplet at δ 7.61–7.27 and a double doublet at δ 8.28 corresponding to aromatic protons. The methoxy adjacent aromatic methyl group was deshielded



Scheme 1. Concise and alternative synthesis of zafirlukast.

and appeared as a singlet for two protons. Other methyl protons were unchanged, and the IR spectrum displayed characteristic absorptions at 1703 and 1336 and 1165 cm^{-1}, corresponding to carbamate carbonyl and sulfonyl stretching respectively, further confirming the assigned structure.

The other intermediate **7** was prepared by a two-step sequence starting from nitroindole derivative **5**. To get the carbamate functionality in the final molecule, the nitro group in **5** was reduced to amine **6** under catalytic hydrogenation conditions followed by carbamate ester **7** formations.

The nitro group in compound **5** was reduced to amine in the presence of Pd/C under a hydrogen atmosphere to give compound **6**, which was coupled with cyclopentyl chloroformate using *N*-methylmorpholine to afford compound **7**. Carbamate **7** was characterized by ^{1}H NMR, mass and IR spectral data. In the ^{1}H NMR, three singlets due to *O*-methyl, *N*-methyl, and aromatic methyl groups displayed at δ 3.89, 3.65, and 2.64, respectively. Aromatic protons appeared as a multiplet at δ 7.60–7.12, two doublets at δ 8.05 and 7.86, and a singlet at 6.65. A singlet at δ 3.75 corresponds to NCH_3 protons and multiplets at δ 5.25–5.19, 1.94–1.85, and 1.83–1.70 correspond to cyclopentyl group protons. IR spectrum showed disappearance of nitro group bands, amine absorptions at 1689 cm^{-1} for carbonyl group and mass spectrum showing the protonated molecular ion appeared at m/z 259, and the sodium adduct appeared at m/z 281, further supporting the structure of compound **7**.

Finally alkylation of compound **7** with compound **4** under silver oxide conditions provided zafirlukast in 40% yield. IR spectra showed bands at 1690, & 3331 and 1340, and 1161 cm^{-1} for carbamate, amide carbonyl, and sulfonyl groups respectively. The ^{1}H NMR spectra revealed four singlets at δ 4.00, 3.82, 3.68, and 2.68 corresponding to benzylic, *O*-methyl, *N*-methy, and aromatic methyl respectively. Cyclopentyl group protons appeared in the alicyclic region as two multiplets at δ 1.90–1.53 and δ 5.10–5.04. All the aromatic protons displayed between δ 7.0 and 8.25 and account for zafirlukast. In the mass spectrum, the protonated molecular ion appeared at m/z 576, which is consistent with the assigned structure of zafirlukast.

CONCLUSION

In conclusion, we have successfully prepared zafrilukast in an alternative concise and convergent synthesis of zafirlukast (**1**) from 5-nitroindole derivative (**5**) and acid derivative (**2**). Three novel intermediates (**3, 4**, and **7**) were synthesized, characterized, and confirmed by spectral data. These novel derivatives will be used as an intermediates to prepare for **1**.

EXPERIMENTAL

The ^{1}H and ^{13}C spectra were measured in $CDCl_3$ and dimethylsulfoxide (DMSO-d_6) at 50, 100, 200, and 400 MHz on Varian Gemini (200 MHz) and Mercury Plus (Varian 400 MHz) Fourier transform (FT)–NMR spectrometers, and the chemical shifts were reported in δ ppm. The FT-IR spectra were recorded in solid state as KBr dispersion using a Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on a HP–5989A LC/MS

spectrometer. Melting points were determined by using the capillary method on a Polmon (model MP-96) melting-point apparatus. The solvents and reagents were used without further purification.

3-Methoxy-4-methyl-*N*-(o-tolylsulfonyl) Benzamide (3)

A mixture of 3-methoxy-4-methyl benzoic acid **2** (100 g, 0.602 mol), 4-(dimethylamino)pyridine (90.3 g, 0.722 mol), 1,3-dicyclohexyl carbodiimide (149.0 g, 0.723 mol), and o-toluene sulfonamide (123.5 g, 0.722 mol) in dichloromethane (1000 mL) was stirred at 25–35 °C for 4–6 h. After completion of reaction, the unwanted solid by-product (dicyclohexylurea, DCU) was filtered and washed with dichloromethane (200 mL). Diluted HCl (200 mL) was added to the filtrate; the organic layer was separated and washed with water (500 mL). The filtrate was distilled completely under vacuum below 45 °C and cooled to 25 °C. Dichloromethane (100 mL) was charged to reaction mass and stirred for 15 min at 25–35 °C. Cyclohexane (1000 mL) was added to the compound, heated to 50–55 °C, and the reaction mass was stirred for about 40 min at that temperature. The reaction mass was cooled to 30 °C and then stirred for about 50 min. The separated solid was filtered and washed with cyclohexane (100 mL). The wet compound was dried under vacuum at 70–75 °C to furnish **3** (182.0 g, 94.7%). HPLC purity 95.2%; mp 145–150 °C; MS (m/z): 318 [M-H]; IR (KBr, ν_{max}, cm^{-1}): 3260, 2939, 1700, 1577, 1418, 1336, 1266, 1156, 1061, 881, 753; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.61 (s, 1H), 8.27 (dd, $J = 1.4$, 7.8 Hz, 1H), 7.60–7.24 (m, 5H), 7.16 (d, $J = 7.6$ Hz, Hz, 1H), 3.77 (s, 3H), 2.72 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 164.8, 157.1, 137.5, 136.8, 133.5, 132.3, 131.8, 130.4, 130.3, 130.0, 126.2, 120.6, 109.6, 55.4, 19.5, 16.1. Anal. calcd. for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 60.12; H, 5.34; N, 4.41.

N-(4-Bromomethyl-3-methoxybenzoyl)-2-methylbenzene Sulfonamide (4)

DBDMH (56.5 g, 0.63 moles) and AIBN (0.31 g, 0.006 mol) were added at room temperature to a stirred solution of 3-methoxy-4-methyl-*N*-(o-tolylsulfonyl) benzamide **3** (100 g, 0.313 mol) in chloroform (500 mL). The resulting reaction mass was heated to reflux (60–65 °C) and maintained for 6–8 h. After completion of reaction (monitored by thin-layer chromatography, TLC), the reaction mixture was quenched with 30% sodium carbonate solution (300 mL) and washed with water (200 mL). The organic layer was separated and dried over sodium sulfhate, and the solvent was removed under vacuum below 65 °C. Cyclohexane (1000 mL) was added to the residue, heated to 80 °C, and stirred for about 40 min at that temperature. The reaction mass was cooled to to 30 °C and stirred for about 50 min. The separated solid was filtered and washed with cyclohexane (100 mL). The wet compound was dried under vacuum at 60–65 °C to furnish **4** (107.0 g, 86.3%). HPLC purity 96.4%; mp 150–154 °C; MS (m/z): 398 [M^++H]; IR (KBr, ν_{max}, cm^{-1}): 3251, 2984, 1703, 1577, 1417, 1405, 1336, 1272, 1165, 880, 754; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.61 (s, 1H), 8.28 (dd, $J = 1.4$, 7.8 Hz, 1H), 7.61–7.27 (m, 6H), 4.49 (s, 2H), 3.85 (s, 3H), 2.72 (s, 3H). Anal. calcd. for $C_{16}H_{16}$ NO_4SBr: C,

48.25; H, 4.05; N, 3.52. Found: C, 48.20; H, 4.01; N, 3.51; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 163.7, 157.6, 137.6, 136.2, 134.2, 132.5, 132.2, 131.9, 131.5, 131.1, 126.5, 119.7, 110.4, 55.9, 27.1, 20.4.

Cyclopentyl 1-Methyl-1H-Indol-5-ylcarbamate (7)

A suspension of *N*-methyl-5-nitro indole **5** (100 g, 0.568 mol) and 10% Pd-C (15.0 g) in ethyl acetate (800 mL) was hydrogenated in a autoclave under hydrogen pressure (3.0–3.5 kg/cm^2) at 25–35 °C. The reaction mass was maintained at 25–35 °C for 3–4 h. After completion of the reaction (monitored by TLC), reaction mass was filtered through hyflow and washed with ethyl acetate (100 mL). The filtrate was washed with 10% sodium hydroxide solution (200 mL) and followed by saturated sodium chloride solution (200 mL). *N*-Methylmorpholine (63.1 g, 0.625 mol) was slowly added to the separated organic layer and followed by cyclopentyl chloroformate (93 g, 0.626 mol) at 25–35 °C. The resulting reaction mass was maintained at room temperature for 45–60 min. After completion of the reaction (monitored by TLC), the reaction mixture was washed with 10% sodium hydroxide solution (200 mL) and followed by saturated sodium chloride solution (200 mL). The solvent was distilled up to 80% of the reaction mass, cooled to 0–5 °C, and stirred for 1–2 h for complete solid precipitation. The separated solid was filtered and washed with ethyl acetate (50 mL). The wet compound was dried under vacuum at 50–55 °C to afford the title compound **7** (130 g, 73.6%). HPLC purity 99.2%; mp 104–108 °C; MS (*m*/*z*): 259.2 [$M^+ + H$], 281.3 [$M^+ + Na$]; IR (KBr, ν_{max}, cm^{-1}): 3284, 2953, 1689, 1541, 1496, 1291, 1245, 1162, 1039, 716; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.25 (s, 0.5 H), 7.20 (s, 0.5 H), 7.15 (d, $J = 8.8$ Hz, 1H), 7.01 (d, $J = 3.2$ Hz, 1H), 6.53 (s, 1H), 6.41 (d, $J = 3.2$ Hz, 1H), 5.25–5.19 (m, 1H), 3.75 (s, 3H), 1.94–1.85 (m, 2H), 1.83–1.70 (m, 4H), 1.68–1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 154.1, 133.8, 130.2, 129.5, 128.5, 114.9, 111.3, 109.2, 100.7, 32.8, 32.7, 23.6. Anal. calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.88; H, 7.06; N, 10.80.

[3-[[2-Methoxy-4-[[[(2-methyl phenyl)sulfonyl]amino]carbonyl]-phenyl]methyl]-1-methyl-1H-indole-5-yl] Carbamic Acid Cyclopentyl Ester (1)

Silver oxide (6.25 g, 0.0271 mol) was added to a solution of compound **7** (10.0 g, 0.0387 mol) and compound **4** (22.5 g, 0.0541 mol) in 1,4-dioxane (70.0 mL) at room temperature. The reaction mixture was heated to 95–100 °C and stirred for 12–15 h. The reaction mixture was filtered through hyflow and washed with acetone (90.0 mL). The filtrate was concentrated, and methanol (90.0 mL) and ethyl acetate (10.0 mL) were added. Subsequently, the mixture was heated to reflux, maintained for 60 min, cooled to 25–35 °C, and stirred for 1 h. The obtained solid was filtered and dried at 50–55 °C to provide 20.0 g (90%) of crude compound with 61.7% purity. The crude compound was purified by using column chromatography (dichloromethane–methanol 9:1) to afford the title compound **1** (8.9 g, 40.0%). HPLC purity 98.6%; mp: 205–209 °C; MS (*m*/*z*): 576 [$M^+ + H$]; IR (KBr, ν_{max}, cm^{-1}): 3370, 2960, 1690, 1581, 1455, 1340, 1226, 1161, 1034, 868, 758; ^{1}H NMR (400 MHz, $CDCl_3$): δ

9.35 (br, 1H), 8.24 (d, $J = 7.8$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 2H), 7.38 (t, $J = 7.6$ Hz, 1H), 7.30 (s, 1H), 7.27 (d, $J = 7.6$ Hz, 1H), 7.26 (s, 2H), 7.18 (d, $J = 8.8$ Hz, 1H), 7.10 (d, $J = 7.6$ Hz, 1H), 7.06 (d, $J = 7.6$ Hz, 1H), 6.74 (s, 1H), 6.54 (s, 1H), 5.22–5.18 (m, 1H), 4.00 (s, 2H), 3.82 (s, 3H), 3.68 (s, 3H), 2.68 (s, 3H), 1.90–1.53 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.8, 157.1, 154.3, 137.4, 136.7, 136.0, 134.0, 133.5, 132.1, 131.1, 129.7, 129.4, 128.0, 127.7, 127.7, 126.0, 119.8, 115.2, 111.7, 109.7, 109.4, 109.1, 77.5, 55.2, 32.5, 32.5 32.3, 24.8, 23.4, 23.4, 20.0.

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