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An Improved and Scalable Process for Zafirlukast: An Asthma Drug†

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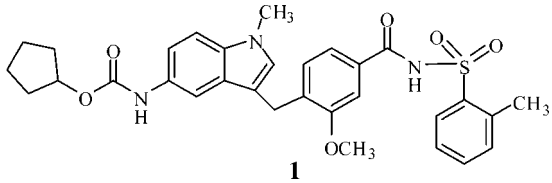
Abstract:

An improved and scalable process for the large-scale production of zafirlukast (Accolate), an important drug for asthma, is discussed along with impurity and scale-up-related issues.

Introduction

Zafirlukast **1**, is a potential drug used for the treatment of pulmonary disorders such as asthma. It acts by antagonizing one or more of the arachidonic acid metabolites, such as leukotriene, which inhibits the activity of cytochrome isozymes CYP 3A4 and CYP 2C9. The CYP 3A4 isozyme is also responsible for the metabolism of many other drugs.[1]



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In the literature several synthetic methods were reported for the preparation of zafirlukast 1.[2−5] We have earlier reported a laboratory synthesis of zafirlukast **1** (Scheme 1),[4] which presented several problems during the process development for large-scale production.[6] The problems include the following: (i) use of chloroform solvent for brominating **2** with DBDMH/AIBN led to poor-quality product and formation of a dibromo impurity **9a** beyond acceptable limits; (ii) removal of chloroform, a class-2 solvent,[7] from the reaction mixture reduced the yield of **3** drastically; and (iii) Friedel−Crafts alkylation of **4** with **3** in the presence of zinc bromide in 1,4-dioxane yielded polysubstituted indole derivatives as impurities.

Hence, we reviewed the earlier synthesis, modified the reaction conditions, and developed a process that obviates the above problems. This improved method, whose details are presented in this paper, is suitable for large-scale production of the drug in pure form and conforms to all the regulatory requirements.

Results and Discussion

In the present approach (Scheme 2), commercially available 3-methoxy-4-methylbenzoic acid (**2**) was first converted to the ester **8** in 98.0% yield and 99.0% purity, by treating with thionyl chloride in methanol. Alkyl bromination of **8** was achieved using cyclohexane as solvent instead of chloroform, and by adding the brominating agent (DBDMH) lot-wise. The benzyl bromide **9** was obtained in 84.0% yield with 99.0% purity. HPLC examination revealed the presence of the dibromo impurity **9a** in less than 1.0%.

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(1) Phipatanakul, W.; Eggleston, P. A.; Conover-Walker, M. K.; Kesavanathan, J.; Sweitzer, D.; Wood, R. A. *J. Allergy Clin. Immunol.* **2000**, *105* (4), 704**.**

(2) Bernstein, P. R.; Brown, F. J.; Matassa, V. G.; Yee, Y. K. U.S. Patent 4,859,692, 1989.

(3) Gutman, A.; Nisenevich, G.; Zaltzman, I.; Ponomarev, V.; Sotrihin, M. WO 02/46153 A2, 2002.

(4) Srinivas, K.; Srinivasan, N.; Krishna, M. R.; Reddy, C. R.; Arunagiri, M.; Lalitha, R.; Reddy, K. S. R.; Reddy, B. S.; Reddy, G. M.; Reddy, P. P.; Kumar, M. K.; Reddy, M. S. *Org. Process Res. Dev.* **2004**, *8*, 952–954**.**

(5) Ansell, C. L.; Derrick, I.; Moseley, J. D.; Stott, J. A. *Org. Process Res. Dev.* **2004**, *8*, 808–813**.**

(6) In the literature several synthetic methods (refs 2−5) were reported for the preparation of zafirlukast **1**. We have taken up one of the synthetic methods reported by us for process development for large-scale production (Scheme 1).[4] With this processes we have faced many problems during the laboratory development to achieve the quality of the final product **1**, and we discuss some of the issues/points as follows. Friedel−Crafts alkylation of **4** with **3** in the presence of zinc bromide in 1,4-dioxane medium afforded the product **5** with poor yield and quality. Indoles **4** have two active positions, i.e. 2 and 3; during the Friedel−Crafts reaction alkylations may occur at positions 2 and 3, which lead to the formation of impurities. These impurities also participate in the subsequent reactions. Attempts were made to remove the polysubstituted impurities corresponding to derivatives of **6** in different solvents, but this was not successful. Related polysubstituted impurities of **7** were converted into hydrochloride salt, and attempts were made to remove the impurities of **7** in different solvents, but this was not successful. Thus, to meet the regulatory requirements, quality was impacted on preparation of **1** in Scheme 1. Hence, Scheme 1 is not suitable for commercial production of **1**, and meeting the drug substance with regulatory requirements is very tough using Scheme 1. Finally, we selected Scheme 2 for process development in the laboratory; we achieved the regulatory requirements, and it was implemented in commercial scale also.

(7) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Q3C(R3): Impurities: Guideline for Residual Solvents. 1997.

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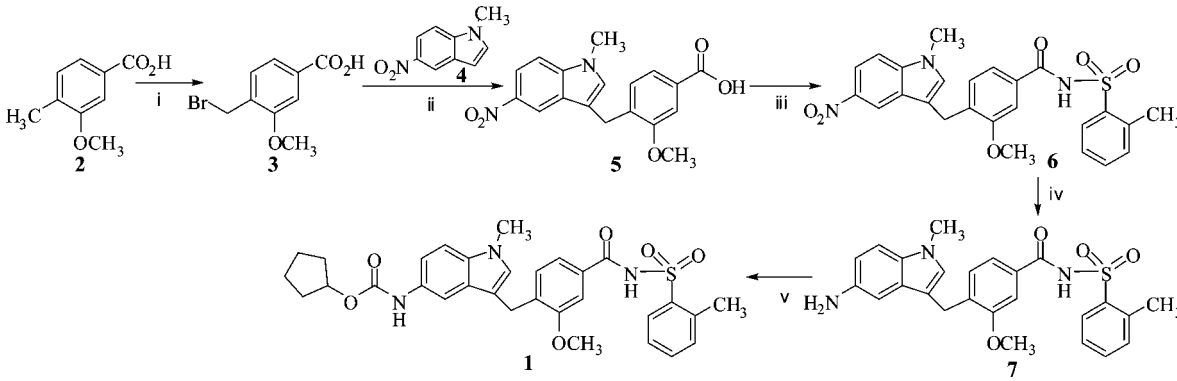
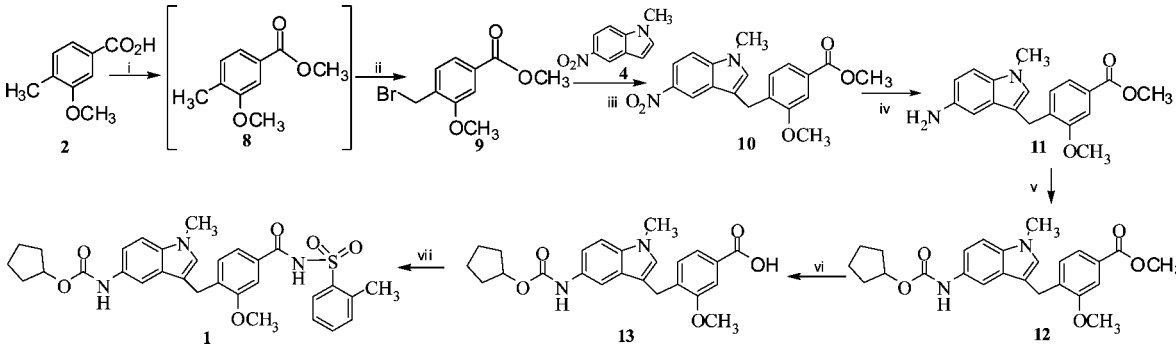
Scheme 1[a]



[a] Reagents and conditions: i) DBDMH /AIBN/$CHCl_3$, reflux, 81%; ii) zinc bromide/1,4-dioxane/60−65 °C, 62%; iii) DCC, DMAP, *o*-toluenesulfonamide, CH_2Cl_2, 63%; iv)Ra-Ni, THF, H_2, 88%; v) cyclopentylchloroformate/*N*-methylmorpholine, CH_2Cl_2, 85%.

Scheme 2[a]



[a] Reagents and conditions: i) $SOCl_2$, MeOH, 98%; ii) DBDMH, AIBN, cyclohexane, reflux, 84%; iii) cuprous oxide, 1,4-dioxane, EtOAc, MeOH, 85.0%; iv) Ra-Ni, EtOAc, H_2, 44%; v) cyclopentylchloroformate, *N*-methylmorpholine, toluene, MeOH, 97.0%; vi) $LiOH \cdot H_2O$, MeOH, 98.0%; vii) DCC, DMAP, *o*-toluenesulfonamide, CH_2Cl_2, ACN, 86% (tech).

Table 1. **Experimental results of compound 10 with different Lewis acids**

S. No	reagent	yield of **10** (%)	% of **10**[a]	% of **10a**[a]	% of **10b**[a]	% of **4**[a]
1	Ag_2O	65.0	51.4	5.65	16.85	1.20
2	CuCl	30.0	33.4	4.09	7.55	38.31
3	ZnO	60.0	49.1	41.09	4.35	1.83
4	$AlCl_3$[b]	−	−	−	−	−
5	Al_2O_3[c]	95.0	6.7	ND[d]	ND[d]	34.99
6	$ZnBr_2$	62.0	53.2	18.2	9.55	4.8
7	Cu_2O	85.0	85.3	8.18	3.60	0.99

[a] Results reported based on HPLC area %. [b] Reactant is not converted to product [based on TLC]. [c] Very little purity observed. [d] ND = not detected.

1-Methy-5-nitroindole required in the present study was prepared in 99.0% yield and 99.0% purity by treating 5-nitroindole with dimethylsulfate and by using very mild reaction conditions. Earlier, the same methylation was conducted by using expensive reagents like dimethylcarbonate[8] and methyliodide,[2] that required harsh reaction conditions and longer reaction times.

Preparation of compound **10** involves Friedel−Craft alkylation[9] of **4** with **9** in the presence of an acid. To achieve the optimum product yield and quality, several Lewis acids such as silver oxide, zinc bromide, cuprous oxide, cuprous chloride, zinc oxide, aluminum chloride, and alumina were examined, and cuprous oxide was found to be the best amongst all (Table 1). Further, the impact of solvent on the yield and quality of the product was also studied. Use of 1,4-dioxane as solvent gave the product in highest yield (85.0%) and purity (85.0%) (Table 2). The impurity profile by HPLC revealed the presence of polysubstituted indoles (**10a** and **10b**) in the product.

Attempts to separate and purify **10** from the impurities **10a** and **10b** by washing with different solvents failed. Therefore, crude **10** was taken as such for reduction with Ra-Ni in ethyl acetate medium. Usual work up yielded the amine **11** in 65−70.0% purity (HPLC). The crude amine was converted to its hydrochloride in ethyl acetate/water mixture, and purified by slurry in dichloromethane/water mixture (Table 3). The free base **11** was liberated from its hydrochloride by neutralizing with 10% aqueous sodium carbonate, and was further purified

(8) Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. K. *Org. Process Res. Dev.* **2001**, *5*, 604–608.
(9) Mahadevan, A.; Sard, H.; Gonzalez, M.; McKew, J. C. *Tetrahedron Lett.* **2003**, *44*, 4589–4591.

Table 2. **Experimental results of compound 10 with different solvents**

S. No	solvent	yield of **10** (%)	% of **10**[a]	% of **10a**[a]	% of **10b**[a]	% of **4**[a]
1	toluene	95.0	49.2	44.34	3.32	1.23
2	acetonitrile	65.0	50.6	4.78	2.81	2.08
3	methyl ethyl ketone	93.0	51.5	24.34	13.72	5.29
4	methyl isobutyl ketone	54.0	81.5	8.18	3.60	0.99
5	ethyl acetate	86.0	52.3	33.24	2.97	7.98
6	dichloromethane[b]	–	–	–	–	–
7	*tert*-butyl acetate	58.5	77.8	9.75	4.78	1.31
8	1,4-dioxane	85.0	85.3	8.18	3.60	0.99
9	tetrahydro furan	55.0	39.64	5.54	5.64	42.77

[a] Results reported based on HPLC area %. [b] Reactant is not converted to product [based on TLC].

Table 3. **Solubility data of hydrochloride salts of compounds 11, 11a, and 11b**

S. No	cmpd	DCM[a]	EA[a]	water[a]	methanol[a]
1	**11**	++	++	++	++++
2	**11a**	++	++	++++	++++
3	**11b**	++++	++	++	++++

[a] + = very slightly soluble; + + = slightly soluble; + + + = sparingly soluble; + + + + = soluble.

Table 4. **Impurity levels in 11 by HPLC in each stage of isolation**

S.No	purification of **11** in solvent	% of **11**[a]	% of **11a**[a]	% of **11b**[a]
1	reaction medium	64.70	7.977	12.56
2	after isolation from mixture of in EA and water	97.75	1.61	0.30
3	DCM and water	99.26	0.61	0.08
4	free base	99.27	0.62	0.09
5	methanol	99.54	0.36	0.05

[a] Results reported based on HPLC area %.

by treating with methanol (Table 4).[10] HPLC examination of the product indicated that **11** was obtained in 45% yield, and has 99.5% purity along with 0.36% of **11a** and less than 0.10% of **11b**.

Reaction of **11** with cyclopentyl chloroformate in toluene containing *N*-methylmorpholine at room temperature yielded **12** in 97.0% yield and 99.50% purity (HPLC). *N*-Methylmorpholine content was found to be less than 0.10% in area %.[11] Hydrolysis of **12** with lithium hydroxide in aqueous methanol provided the corresponding acid **13** in 98.0% yield and 99.2% purity. Condensation of **13** with *o*-toluenesulfonamide in the presence of DCC and DMAP gave the crude zafirlukast **1**.[12]

(10) The solubility of each compound has been measured in analytical research and development (AR&D) as per the USP general guidelines for solubility measurements. Soluble = 1 g /30 mL. Sparingly soluble = 1 g /100 mL. Slightly soluble = 100 mg /100 mL. Very slightly soluble = 10 mg /100 mL.

(11) Byproduct *N*-methylmorpholine hydrochloride is highly soluble in methanol, and after isolation of **12**, the *N*-methylmorpholine content is less than 0.10 area % by HPLC.

(12) Attempts were made to form the amide linkage between **13** and *o*-toluenesulfonamide: (i) Boric acid catalyzed in toluene and *o*-xylene medium the reactant was not converted to product **1**. (ii) Acid derivative of **13** is converted to acid chloride derivative in dichloromethane by using thionyl chloride followed by condensation with *o*-toluenesulfonamide, but yield is very less (less than 50.0% theoretical) and the obtained zafirlukast description is brown in color, and it is very difficult to achieve the white to off-white colour as mentioned in RX list. Hence, the aforementioned problems render this process not suitable.

Table 5. **Results of crude zafirlukast 1 by HPLC before silica gel purification**

S. No.	% of **1**[a]	% of **1a**[a]	% of **1b**[a]	% of **1c**[a]	% of **12**[a]	% of **Imp-A**[a]
1	96.53	0.01	0.03	0.21	1.01	0.42
2	97.47	ND	0.06	0.35	0.73	0.43
3	97.68	0.07	0.04	0.24	0.75	0.60
4	98.43[b]	0.06	0.08	0.23	0.66	0.15
5	97.62[b]	0.08	0.09	0.14	0.63	0.49

[a] Results reported are based on HPLC area %; ND = not detected. [b] Laboratory experiments results.

Table 6. **Results of pure zafirlukast 1by HPLC after silica gel purification**

S. No.	% of **1**[a]	% of **1a**[a]	% of **1b**[a]	% of **1c**[a]	% of **12**[a]	% of **Imp-A**[a]
1	99.65	ND	ND	0.09	0.06	0.05
2	99.57	ND	0.01	0.08	0.07	0.07
3	99.63	ND	ND	0.07	0.05	0.04
4	99.78[b]	0.02	ND	0.04	0.09	0.02
5	99.85[b]	ND	ND	0.04	0.06	0.04

[a] Results reported based on HPLC area %; ND = not detected. [b] Laboratory experiments results.

The DCU content in the product was reduced by treating it with methanol,[13] but an unknown impurity (**Imp-A**) whose M^+ was at *m*/*z* 867.4 (LC/MS) was detected in the crude at 0.15 to 0.70% level. This impurity could neither be characterized nor separated from the crude by any means. However, the crude zafirlukast was treated with silica gel to obtain the product that meets the description of the drug substance as mentioned in the RX list[14] (white to off-white). The overall purity of the pure zafirlukast obtained from this process at scale-up level is 99.5% (by HPLC), and all the impurity levels are less than 0.10%. The results are summarized in Tables 5 and 6. See also Scheme 3.

Amorphous polymorph of zafirlukast was prepared as the finished drug substance by evaporating the solution of zafirlukast under nitrogen pressure at 50 °C by using a spray drier (Table 7).[15]

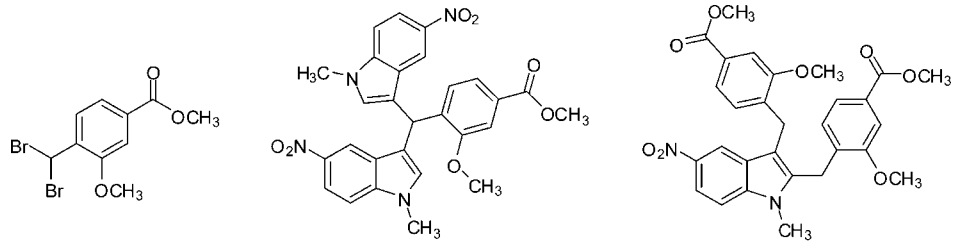
Conclusion

In conclusion, we have developed an improved and scalable manufacturing process for the synthesis of **1**. The product

(13) DCU will be filtered as a by-product during the DCC coupling reaction, and it is highly soluble in methanol; after methanol purification the DCU content is less than 0.05% by HPLC.

(14) http://www.Rxlist.com.

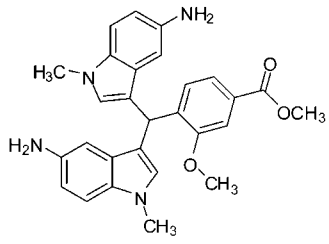
(15) Holohan, J. J.; Edwards, I. J. (Imperial Chemical Industries PLC). U.S. Patent 5,319,097, 1994.



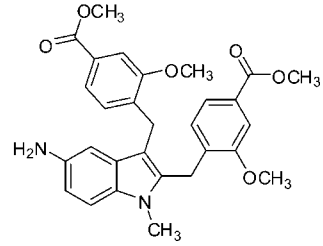
9a

10a

10b



11a



11b

obtained by this process conforms to all the regulatory requirements.

Experimental Section

The ^{1}H NMR spectra were measured in $CDCl_3$ and DMSO on a Varian 200 MHz/Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in solid state as KBr dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on HP-5989A LC/MS spectrometer. Melting points were determined by using the capillary method on POLMON (model MP-96) melting point apparatus. The X-ray powder diffraction pattern was recorded on Bruker axes D8 advance, equipped with Bragg−Brentano θ:θ goniometer having lynx-eye detector. The pattern was recorded at a tube voltage of 40 kV and a tube current of 40 mA, with a step size of 0.013° and time step of 0.1 s over an angular range of 3−45° 2θ. The sample was gently ground and placed into a sample holder by top-loading method. The sample was exposed to the Cu Kα radiations (λ = 1.5418 Å). The thermal analysis was performed on TGA, Q500 of TA Instruments. The thermogram was recorded from 25 to 250 °C under the nitrogen gas purge at a flow of 40 mL/min for balance and 60 mL/min for sample at a heating rate of 10 °C/min. The thermal analysis was carried out on TA Q1000. The thermogram was recorded from 40 to 250 °C under the nitrogen flow of 50 mL/min at a heating rate of 10 °C/min. A sample of about 3−4 mg was weighed into an aluminum pan and was distributed uniformly as a thin layer. The sample and reference pans were placed in the furnace and heated with the above said parameters. The solvents and reagents were used without further purification.

Preparation of 4-Bromomethyl-3-methoxybenzoic Acid Methyl Ester (9). To a solution of 3-methoxy-4-methylbenzoic acid (**2**, 5.0 kg, 30.12 mol) in methanol (7.5 L), was slowly added thionyl chloride (2.5 L, 33.9 mol) during a period of 2 h. After the addition was completed, the reaction mixture was heated to 55−60 °C and maintained at that temperature for 2−3 h. The reaction mass was then quenched with chilled water (5−10 °C). The precipitated solid was filtered and washed with 10% aqueous sodium carbonate (10.0 L). The wet compound (5.4 kg, 2.20% water content by Karl Fischer reagent) was dissolved in cyclohexane (30.0 L). 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH, 4.0 kg, 17.48 mol) and 2, 2′-azobisisobutyronitrile (30.0 g, 0.182 mol) were added to the above solution. The resultant reaction mass was refluxed (78−82 °C) for 3−4 h and then cooled to room temperature. 1,3-Dibromo-5,5-dimethylhydantoin (1.0 kg, 4.37 mol) and, 2,2′-azobisisobutyronitrile (10.0 g, 0.06 mol) were added. The reflux was then continued for an additional 1−2 h. Then water (20.0 L) was added to the reaction mass, and the reaction was maintained for 45−60 min at 55−60 °C. The organic layer was separated, cooled to 10−15 °C, and kept aside for 45−60 min. The solid obtained was filtered, washed with cyclohexane (5.0 L), and dried under vacuum at 45−50 °C for 3−4 h to afford 6.5 kg (84%) of the title compound with 99.12% of purity by HPLC.

Mass (*m*/*z*): 283.2 (M^+ + H + Na); **7** (KBr, cm^{-1}): 1717 (–C═O), 2951 (−C–H), 1276 (−C–O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.9 (s, 3H), 4.0 (s, 3H), 4.5 (s, 2H), 7.2−7.6 (m, 3H).

Preparation of 1-Methyl-5-nitro-1H-indole (4). To a solution of 5-nitroindole (5.0 kg, 30.86 mol) and sodium hydroxide (2.6 kg, 65.0 mol) in dimethyl formamide (20.0 L) was slowly added dimethylsulfate (4.55 kg, 36.11 mol), and the reaction mass was maintained at 25−35 °C for 2−4 h. After completion of the reaction (by TLC), water (50.0 L) was added, and the mixture was maintained for 45−60 min. The obtained solid was filtered, washed with water (25.0 L), and dried under vacuum at 50−60 °C for 3−4 h to afford 5.36 kg (98.7%) of the title compound with 99.63% of purity by HPLC.

Mass (*m*/*z*): 177.0 (M^+ + H); IR (KBr, cm^{-1}): 2921 (−C−H), 1612, 1580 (Ar−C═C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.9 (s, 3H), 6.7 (d, 1H), 7.2 (d, 2H), 7.4 (d, 1H), 8.1 (d, 1H), 8.5 (s, 1H).

Preparation of 3-Methoxy-4-(1-methyl-5-nitro-1H-indol-3-ylmethyl)benzoic Acid Methyl Ester (10). A mixture of 4-bromomethyl-3-methoxybenzoic acid methyl ester (**9**, 3.82 kg, 14.74 mol), 1-methyl-5-nitro-1H-indole (**4,** 2.0 kg, 11.36 mol, and cuprous oxide (4.88 kg, 34.12 mol) in 1,4-dioxane (14.0 L) was heated at 95−100 °C for 24−30 h. The reaction mass was filtered through Hyflow and washed with 1,4-dioxane

Scheme 3. **Synthetic scheme of zafirlukast carry-over impurities from 10**

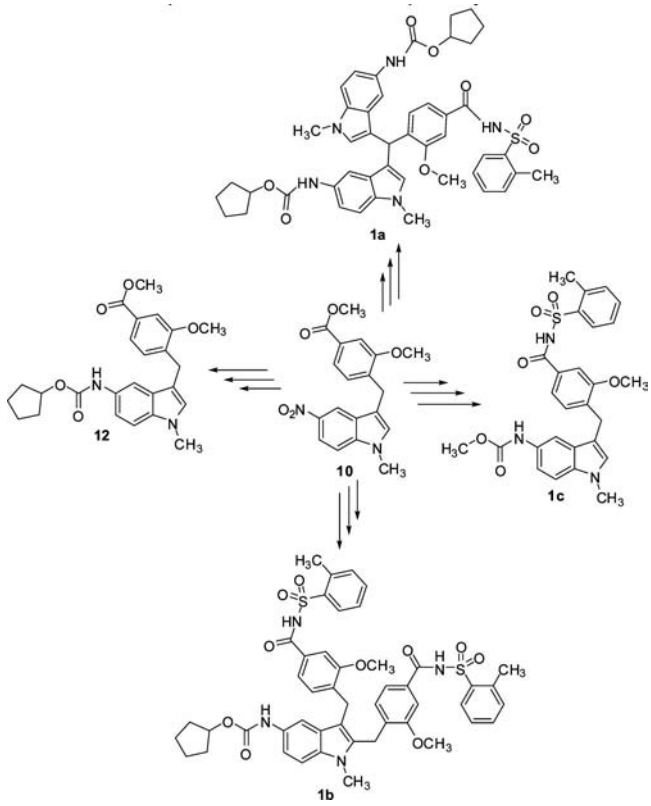


Table 7. **Organic volatile impurities results of compound amorphous polymorphs of zafirlukast 1 by GC**

S. No	XRD	DCM (ppm)[a]	acetonitrile (ppm)[a]
1	amorphous	339	43
2	amorphous	122	79
3	amorphous	ND	59

[a] Results reported based on gas chromatography; ND = not detected.

(4.0 L). The filtrate was concentrated; to the residue was added methanol (18.0 L) and ethyl acetate (2.0 L). The mixture was then refluxed for 60 min, cooled to 25−35 °C, and kept aside for 4 h. The solid obtained was filtered and dried at 50−55 °C to afford 3.42 kg (85.0%) of the title compound with 84.7% purity by HPLC.

MS (*m*/*z*): 377 (M^+ + H + Na); IR (KBr, cm^{-1}): 2949 (−C−H), 1709 (−C═O), 1618 and 1579 (Ar−C═C), 1291 (−C−O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.8 (s, 3H), 3.9 (s, 3H), 3.95 (s, 3H), 4.1 (s, 2H), 6.8 (s, 1H), 7.1−7.4 (m, 2H), 7.6 (m, 2H), 8.0−8.2 (dd, 1H), 8.6 (d, 1H).

Preparation of 4-(5-Amino-1-methyl-1H-indole-3-yl-methyl)-3-methoxybenzoic Acid Methyl Ester (11). A mixture of 3-methoxy-4-(1-methyl-5-nitro-1*H*-indole-3-yl methyl)-benzoic acid methyl ester (**10**, 10.0 kg, 28.24 mol) and Raney-nickel (3.0 kg) taken in ethyl acetate (50.0 L) and water (10.0 L) was kept in a Paul-Knorr apparatus, and the reaction mass was maintained at hydrogen pressure (5−6 kg/cm^2) at 25−35 °C for 3−4 h. After the reaction, the catalyst was filtered through Hyflow and washed with ethyl acetate (50.0 L). The filtrate was acidified to pH 1−2 with dil. HCl (mixture of 50.0% water and 50.0% conc. HCl) and stirred for 30−45 min. The solid obtained was filtered. The wet compound was taken in a mixture of water (50.0 L) and dichloromethane (50.0 L) and stirred for 3−4 h at room temperature, basified to pH 7−8 with 10% aqueous sodium carbonate solution, and filtered. The precipitate was purified in methanol (10.0 L) to afford 4.01 kg (44%) of the title compound with 99.50% purity by HPLC.

MS (*m*/*z*): 325 (M^+ + H); IR (KBr, cm^{-1}): 3442 and 3360 (−NH_2), 2937 (−CH), 1703 (−C═O), 1297 (−C−O).

^{1}H NMR (200 MHz, CDCl3) δ 3.65 (s, 3H), 3.9 (s, 3H), 3.95 (s, 3H), 4.05 (s, 2H), 6.6−6.8 (m, 3H), 7.0−7.3 (m, 2H), 7.5−7.6 (m, 2H).

Preparation of 4-(5-cyclopentyloxycarbonylamino-1-methyl-1H-indol-3-yl methyl)-3-methoxybenzoic Acid Methyl Ester (12). To a solution of 4-(5-amino-1-methyl-1*H*-indole-3-yl methyl)-3-methoxybenzoic acid methyl ester (**11**, 14.0 kg, 43.20 mol) and *N*-methylmorpholine (5.29 kg, 52.37 mol) in toluene (70.0 L) was slowly added cyclopentyl chloroformate (9.66 kg, 65.05 mol) at 25−35 °C, and the resulting reaction mass was maintained at room temperature for 45−60 min. After completion of the reaction, the solvent was distilled off. Methanol (70.0 L) was added to the residue and filtered. The solid precipitate was washed with methanol (14.0 L) and dried at 50−55 °C for 2−3 h to afford 18.50 kg (98.4%) of the title compound with 99.73% of purity by HPLC.

MS (*m*/*z*): 437.4 (M^+ + H); IR (KBr, cm^{-1}): 3247 (−NH), 1719 (−C═O), 1692 (−C═O), 1232 (−C−O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1−2 (s, 8H), 3.7 (s, 3H), 3.8 (s, 3H), 3.9 (s, 3H), 4.0 (s, 2H), 5.1 (m, 1H), 7.0−7.6 (m, 7H).

Preparation of [4-(5-Cyclopentyloxycarbonylmethyl-1-methyl-1H-indol-3-ylmethyl)-3-methoxybenzoic Acid (13). To a mixture of 4-(5-cyclopentyloxycarbonylamino-1-methyl-1H-indol-3-ylmethyl)-3-methoxybenzoic acid methyl ester (**12**, 16.0 kg, 36.69 mol) and methanol (96.0 L) was added a solution of lithium hydroxide monohydrate (2.4 kg, 57.14 mol) and water (24.0 L). The resulting reaction mass was heated to reflux (60−65 °C) for 1−2 h, then cooled to 25−35 °C and acidified to pH = 1.0−2.0 with aqueous hydrochloride (mixture of 50.0% water and 50.0% conc. HCl) solution. The reaction mixture was set aside for 1−2 h, and the precipitate was filtered, washed with water, and dried under vacuum at 70−75 °C to afford 15.2 kg (98.2%) of the title compound with 99.21% of purity by HPLC.

MS (*m*/*z*): 423.3 (M^+ + H); IR (KBr, cm^{-1}): 3288 (−NH), 2957 (−C−H), 1696 (−C═O), 1264 (−C−O); H NMR (200 MHz, $CDCl_3$) δ 1−2 (s, 8H), 3.7 (s, 3H), 3.90 (s, 3H), 4.05 (s, 2H), 5.2 (m, 1H), 6.8 (s, 1H), 7.0−7.2 (m, 3H), 7.3−7.7 (m, 3H).

Preparation of {3-[2-Methoxy-4-(toluene-2-sulfonylaminocarbonyl)benzyl]-1-methyl-1H-indol-5-yl}acetic Acid Cyclopentyl Ester (1). A mixture of [4-(5-cyclopentyloxycarbonylmethyl-1-methyl-1H-indol-3-ylmethyl)-3-methoxybenzoic acid (**14**, 8.0 kg, 18.94 mol), 4-(dimethylamino)pyridine (2.85 kg, 22.8 mol), 1,3-dicyclohexyl carbodiimide (DCC, 4.45 kg, 21.69 mol), *o*-toluenesulfonamide (3.88 kg, 22.72 mol), and dichloromethane (80.0 L) was maintained at 25−35 °C for 3−4 h. The reaction mass was then filtered under vacuum and washed with dichloromethane (13.7 L). The organic layer was quenched with dil. HCl (2.4 L of conc.HCl + 2.4 L of water) and

washed with water (40.0 L). The solvent was distilled off completely under vacuum below 45 °C. Acetonitrile (16.0 L) was added to the compound and distilled off completely under vacuum at below 80 °C. The obtained solid was cooled to 25 °C, acetonitrile (40.0 L) was added and heated to 80 °C. The reaction mass was then stirred for about 40 min at that temperature, cooled to 30 °C, and then stirred for about 50 min for complete solid separation. The separated solid was filtered and washed with acetonitrile (8.0 L). The compound was again taken in methanol (96.0 L) and stirred at 25−35 °C for 45 min, filtered, and washed with methanol (8.0 L). The wet compound was dried under vacuum at 70−75 °C to afford crude 9.25 kg (86%) of the title compound with 98.6% purity by HPLC.

Purification of Crude Zafirlukast 1. To a solution of crude zafirlukast (**1**, 7.0 kg) and dichloromethane (112 L), was charged silica gel (14.0 kg), and the mixture was stirred for about 60 min at 30 °C. The silica gel was filtered and washed with dichloromethane (2 × 70.0 L). The filtrate was distilled off completely under vacuum below 45 °C. The obtained compound was cooled to 25 °C, and acetonitrile (42.0 L) was added and then distilled off completely under vacuum at below 80 °C. The obtained solid was again cooled to 25 °C, acetonitrile (84.0 L) was added and then heated to 80 °C and stirred for about 40 min. The resultant reaction mass was cooled to 30 °C and stirred for about 50 min for complete solid separation. The separated solid was filtered and washed with acetonitrile (21.0 L) and suck dried for about 30 min (purity 99.3%). The obtained compound was taken in dichloromethane (67.0 L) and stirred for about 15 min at 30 °C for complete dissolution. Silica gel (8.4 kg) was charged into the above dichloromethane solution; this mixture was stirred for about 60 min at 30 °C, filtered, and washed with dichloromethane (2 × 35.0 L). The filtrate was distilled off completely under vacuum below 45 °C. The obtained compound was cooled to 25 °C, and acetonitrile (8.0 L) was added and distilled off completely under vacuum at below 80 °C; the obtained solid was cooled to 25 °C, and acetonitrile (22.0 L), was added and heated to 80 °C and stirred for about 40 min. The resultant reaction mass was cooled to 30 °C and stirred for about 50 min for complete solid separation. The separated solid was filtered and washed with acetonitrile (4.0 L) and suck dried for about 30 min, dried at 75 °C under vacuum for about 4 h to afford the 4.10 kg (58.5%) of pure compound with purity 99.5% by HPLC.

Melting range: 142−145 °C; MS (*m*/*z*): 576 ($M^+ + H$); IR (KBr, cm^{-1}): 3326 (NH), 1679 (−C═O), ^{1}H NMR ($CDCl_3$) δ 7.0−8.0 (m, 11H), 3.7 (s, 3H), 4.0 (s, 2H), 3.9 (s, 3H), 2.6 (s, 3H), 1.45−1.8 (s, 9H).

Preparation of the Amorphous Form of 1. A solution of pure zafirlukast (**1**, 800.0 g) in dichloromethane (12.0 L) was heated to about 40 °C and stirred for about 30 min for complete dissolution. The resultant solution was filtered through a microfilter and washed with dichloromethane (1.6 L). The clear solution obtained was passed into a spray drier through nitrogen pressure at 50 °C. The resultant solid was dried under vacuum at 70−75 °C for about 10−12 h to afford the 720.0 g (90.0%) of the amorphous form of **1** by PXRD with purity 99.6% by HPLC. DSC thermogram clearly shows two endotherms observed at 110.30 and 199.73 °C, and the first endotherm corresponds to amorphous of zafirlukast and the second endotherm corresponds to stable zafirlukast polymorph of form-X.[15]

Melting range: 115−120 °C; MS (*m*/*z*): 576 ($M^+ + H$); IR (KBr cm^{-1}): 3331 (−NH), 2960 (−C−H), 1690 (−C═O), 1455A (−C−H), 1340, 1162 (SO_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.0−8.0 (m, 11H), 3.7 (s, 3H), 4.0 (s, 2H), 3.9 (s, 3H), 2.6 (s, 3H), 1.45−1.8 (s, 9H).

Weight loss by TGA: 0.37% w/w.

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