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Synthesis and characterization of new analogs of zafirlukast

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Abstract: Design, synthesis and characterization of four novel series of Zafirlukast analogs are described. The modifications are substitution on indole nitrogen, C-5 position of indole moiety and amide nitrogen of zafirlukast.

Keywords: Zafirlukast; anti asthma; new analogs; *N*-desmethyl zafirlukast analogs; DCU analogs.

1. Introduction

Indole derivatives have attracted enormous interest due to their diverse biological activities. However, since the isolation of indole alkaloids, these derivatives have been explored for their potential application as antibiotics, anti-inflammatory, anti-hypertensive and antitumor agents. Zafirlukast (figure 1) is one of the promising drugs (leukotriene antagonist) indicated for the treatment of mild to moderate asthma, but the drug has been associated with occasional idiosyncratic hepatotoxicity. Zafirlukast 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]

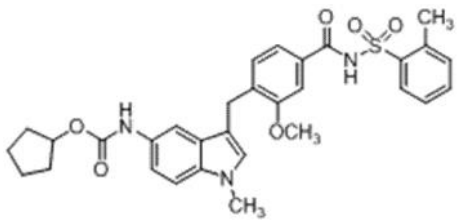

Figure 1. Structure of zafirlukast **1**

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2. Results and discussion

There are several reports on the synthesis of zafirlukast analogs in the literature. Matassa et al.,[2-7] reported zafirlukast analogs, that were prepared by changing the substitution on indole nitrogen, phenyl ring of sulfonamide moiety and C-5 position of indole moiety. Browns group[4,8] explored the N-carbamoyl analogs of zafirlukast and found the enhanced invitro potency. Some of the zafirlukast analogs were synthesized by modifying the substituent on indole nitrogen of zafirlukast and demonstrated that increasing in the bulkiness of the substituent increased the affinity for cPLA2α.[9,10]

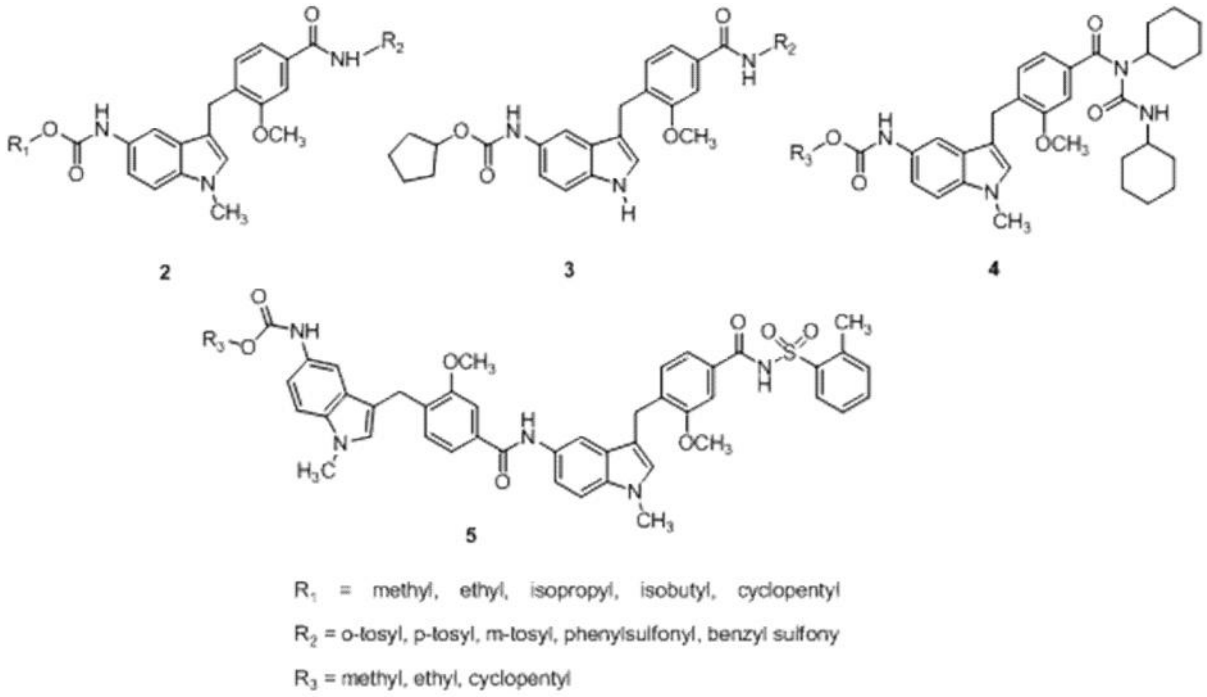


Figure 2. Structures of zafirlukast analogs, **2**, **3**, **4** and **5**

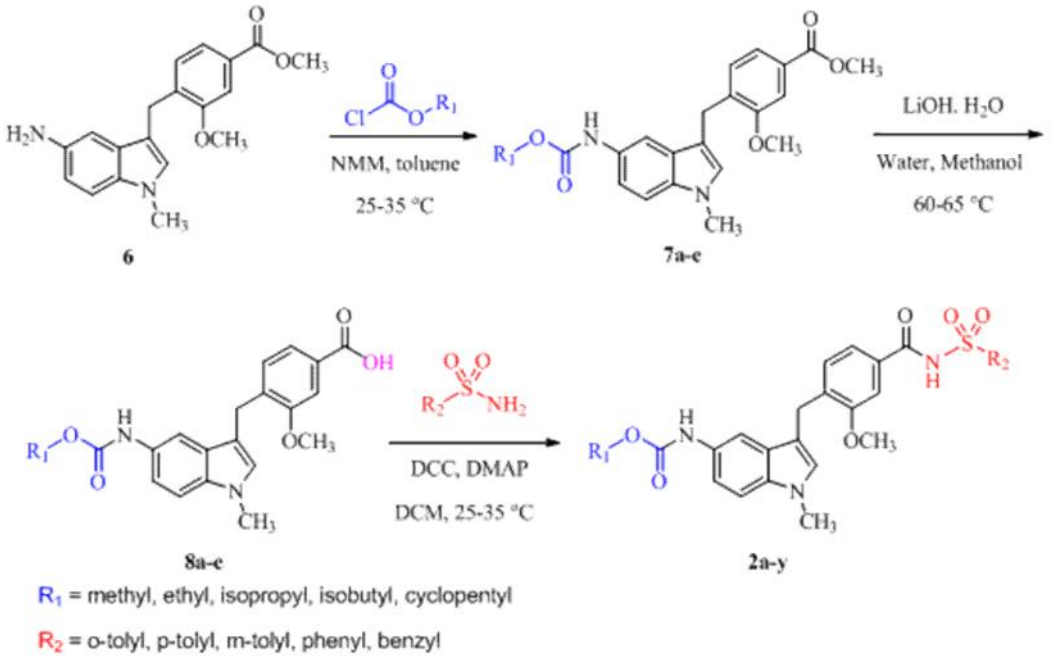
As part of a research program in the development of new indole derivatives, the preparation of zafirlukast analogs was undertaken. Herein, we describe design, synthesis and characterization of four new series of zafirlukast analogs. All the analogs were thoroughly characterized by spectral data.

2.1. Synthesis and characterization of zafirlukast analogs, ***2a–y***

Synthesis of first series of analogs was planned by changing the two functional groups cyclopentyl and *o*-tolylsulfonamide in zafirlukast. Cyclopentyl group was replaced with different alkyl groups such as methyl, ethyl, isopropyl and isobutyl. Whereas, different sulfonamides such as *m*-tolyl, *p*-tolyl, phenyl and benzyl sulfonamides were used instead of *o*-tolylsulfonamide.

Table 1. Synthesis of zafirlukast analogs **2a**–**y**

Compounds	R_1	R_2	Mp (°C)	Yield (%)
2a[9,10]	methyl	*o*-tolyl	120–122	79
2b	methyl	*p*-tolyl	185–187	76
2c	methyl	*m*-tolyl	148–150	82
2d	methyl	phenyl	146–148	79
2e	methyl	benzyl	200–202	72
2f	ethyl	*o*-tolyl	182–184	71
2g	ethyl	*p*-tolyl	178–180	65
2h	ethyl	*m*-tolyl	180–182	74
2i	ethyl	phenyl	174–176	73
2j	ethyl	benzyl	198–200	68
2k	isopropyl	*o*-tolyl	120–122	76
2l	isopropyl	*p*-tolyl	188–190	74
2m	isopropyl	*m*-tolyl	115–118	78
2n	isopropyl	phenyl	78–80	72
2o	isopropyl	benzyl	103–105	64
2p	butyl	*o*-tolyl	121–123	88
2q	butyl	*p*-tolyl	189–191	82
2r	butyl	*m*-tolyl	118–120	80
2s	butyl	phenyl	120–122	73
2t	butyl	benzyl	100–102	79
2u[14,15]	cyclopentyl	*o*-tolyl	142–143	86
2v[14,15]	cyclopentyl	*p*-tolyl	250–252	83
2w[14,15]	cyclopentyl	*m*-tolyl	206-208	95
2x[2]	cyclopentyl	phenyl	142–144	78
2y	cyclopentyl	benzyl	120–123	78



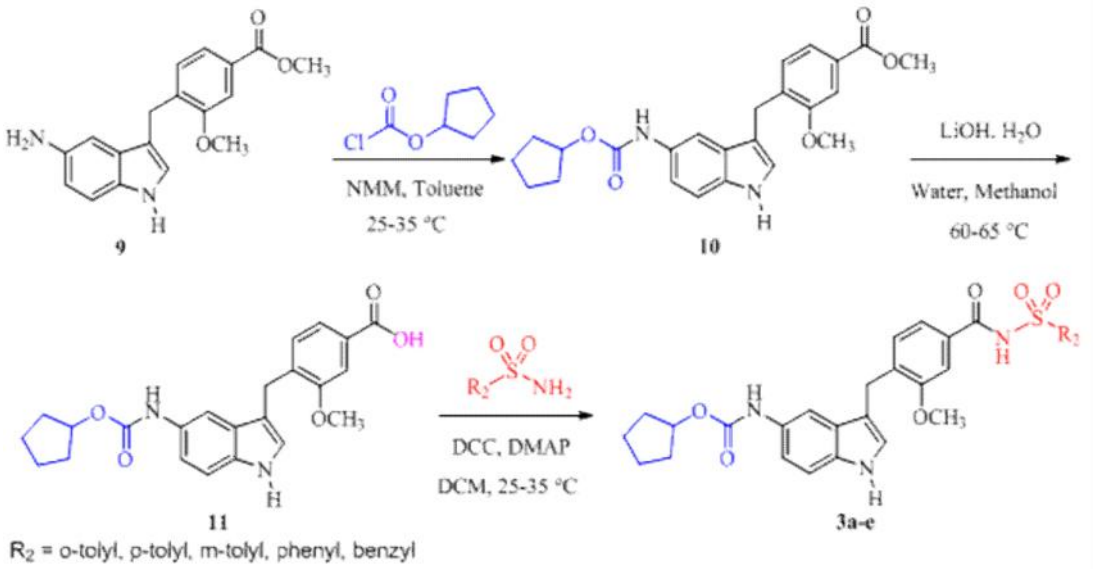
Scheme 1. Synthesis of zafirlukast analogs, **2a**–**y**

Compound **6** was found to be the appropriate starting material for the synthesis of analogs **2a**–**y**, which was prepared in two steps (i) alkylation of *N*-methyl 5-nitro indole and (ii) reduction of nitro group.[11] Compound **6** was treated with methyl chloroformate in toluene to provide derivative **7a**. The resulted compound **7a** was subjected for the alkaline hydrolysis with LiOH.H_2O to furnish the acid **8a**. Subsequently, the acid **8a** was coupled with *o*-toluene sulfonamide under DCC (dicyclohexyl carbodiimide) / DMAP (dimethyl amino pyridine) conditions to yield the analog **2a** (scheme 1).

To demonstrate the generality, this methodology was extended to synthesize other derivatives (**2b**–**y**) starting from the amino ester **6** (scheme 1). In all the cases good yields were obtained (table 1). Analogs, **2b**–**y** were characterized based on the IR, MS, NMR spectral data and Ana.calclated data.

2.2. Synthesis and characterization of des N-methyl zafirlukast analogs, **3a**–**e**

Second series of derivatives were synthesized from des *N*-methyl zafirlukast using different sulfonamides such as *o*-tolyl, *m*-tolyl, *p*-tolyl, phenyl and benzyl sulfonamides. These analogs were synthesized same as analogs **2a**–**y**, but compound **9** was used instead of compound **6**. Compound **9** was synthesized from 5-nitro indole by doing alkylation[2] followed by reduction of nitro group.[2-7,11]Reaction of amine **9** with cyclopentyl chloroformate in the presence of NMM (*N*-Methyl morpholine) in toluene yielded **10**. Hydrolysis of ester **10** using LiOH.H_2O in aq. methanol furnished acid **11**, which was coupled with *o*-toluene sulfonamide under DCC/DMAP coupling conditions to provide the des *N*-methyl zafirlukast derivative **3a** (scheme 2).



Scheme 2. Synthesis of des N-methyl zafirlukast analogs, **3a-e**

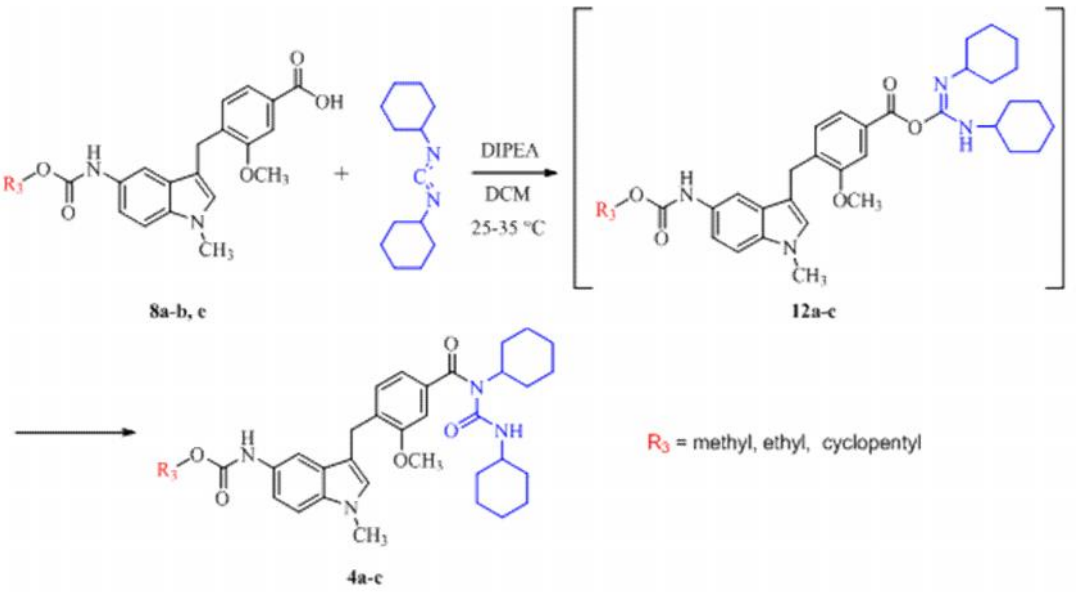
A similar procedure was utilized to synthesize other derivatives, **3b–e** (scheme 2). In all the cases good yields were obtained (table 2). Spectral data of these compounds provided in the experimental section.

Table 2. Synthesis of des *N*-methyl zafirlukast analogs **3a–e**

Compounds	R_2	Mp (°C)	Yield (%)
3a[6,7]	*o*-tolyl	131–133	77
3b	*p*-tolyl	180-182	75
3c	*m*-tolyl	216-219	72
3d[6,7]	phenyl	188-190	78
3e[2]	benzyl	142-144	65

*2.3. Synthesis and characterization of zafirlukast DCU analogs, **4a–c***

Synthesis of third series of derivatives began from carbamate protected carboxylic acid **8**. Coupling of acid **8a** with DCC (dicyclohexyl carbodiimide) using DIPEA (*N,N*- di iso propyl ethyl amine) in dichloromethane (DCM) provided dicyclohexyl urea (DCU) analog **4a** *via* *o*-acyl intermediate, **12a** (scheme 3).



Scheme 3. Synthesis of zafirlukast DCU analogs, ***4a–c***

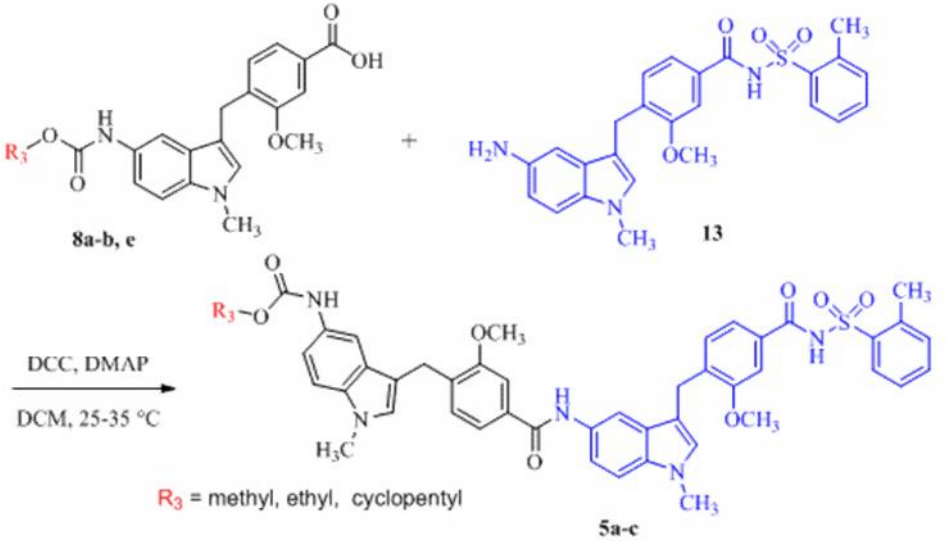
This methodology was extended to make other similar analogs **4a** and **4b** and confirmed by spectral data and the results were summarized in table 3.

Table 3. Synthesis of zafirlukast DCU analogs **4a–c**

Compounds	R_3	Mp (°C)	Yield (%)
4a	methyl	98-100	33
4b	ethyl	131-133	47
4c[15]	cyclopentyl	98-100	49

2.4. Synthesis and characterization of zafirlukast dimer analogs, ***5a–c***

The final series of dimer analogs were prepared in one step by coupling of amine **13** with different *N*-protected acids **8a–b** & **e** under DCC/DMAP conditions in dichloromethane (scheme 4). Compound **13** was synthesized by following the reported process.[12] Coupling of carbamate protected acid **8e** with amine **13** under DCC/DMAP conditions provided dimer **5c** in 21 % yield.



Scheme 4. Synthesis of zafirlukast dimer analogs, **5a–c**

Synthesis of other derivatives **5a** and **5b** was achieved under the same conditions with moderate yields (table 4). These derivatives were confirmed by spectral data.

Table 4. Synthesis of zafirlukast dimer analogs **5a**–**c**

Compounds	R_3	Mp (°C)	Yield (%)
5a	methyl	135-138	42
5b	ethyl	185-190	32
5c [12,15]	cyclopentyl	88-92	21

3. Conclusion

In conclusion, design and synthesis of new class of zafirlukast analogs were synthesized utilizing well known chemical reactions. All the analogs were well characterized by using mass, NMR and IR spectral data. These analogs will be tested against different therapeutic activities to find the target.

4. Experimental

4.1 General

The ^{1}H spectra were measured in CD_3OD and DMSO–d_6 200, 400 and 500 MHz on a Varian Gemini (200 MHz) and Mercury Plus (Varian 400, 500 MHz) FT–NMR spectrometer, the chemical shifts were reported in δ ppm. The FT–IR spectra were recorded in solid state as KBr dispersion using Perkin-Elmer 1650 FT–IR spectrophotometer. The mass spectrum (70eV) 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. Column chromatography was performed with silicagel 60-120 mesh. Yield reported was the isolated yield after purification of the compounds. The solvents and reagents were used without further purification.

4.2 Synthesis

4.2.1 General procedure for chloroformate coupling

To a solution of amine **6** (1.0 mmol) and *N*-methylmorpholine (1.2 mmol) in toluene (2 volumes to the amine) was added corresponding chloroformate (1.5 mmol) drop wise at 25-35 °C. The resulting reaction mass was maintained at room temperature for 45-60 min. After completion of reaction, the solvent was distilled from reaction mass, methanol (3 volumes to the amine) was added and stirred for 60 min. Filtered the precipitated compound under vacuum, and washed with methanol (0.5 volumes to the amine). The obtained wet solid was dried at 50-55 °C for 2-3 h to afford the carbamate.

The following compounds were synthesized using this method:

Methyl 4-((5-(ethoxycarbonylamino)-1-methyl-1*H*-indol-3-yl) methyl)-3-methoxy benzoate (7b): Yield: 97 %; Mp: 120–122 °C; IR (KBr, cm^{-1}): 3389 (NH), 1719 (C═O, ester), 1704 (C═O, carbamate), 1292 (OCH_3); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 9.30 (s, 1H), 7.59 (s, 1H), 7.48 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.04 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.96 (s, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 1.22 (t, J =

7.2 Hz, 3H); MS (*m/z*): 397 [M^+ + H], 419 (M^+ + Na]; Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.52; H, 6.14; N, 7.13; O, 20.18, Found : C, 66.72; H, 6.10; N, 7.07; O, 20.11.

Methyl 4-((5-(isopropoxycarbonylamino)-1-methyl-1H-indol-3-yl)methyl)-3-methoxy benzoate (7c): Yield: 94 %; Mp: 122–124 °C; IR (KBr, cm^{-1}): 3292 (NH), 1711 (C═O, ester), 1686 (C═O, carbamate), 1290 (OCH_3); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 9.24 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.16-7.11 (m, 2H), 7.04 (s, 1H), 4.88-4.82 (m, 1H), 3.96 (s, 2H), 3.92 (s, 3H), 3.83 (s, 3H), 3.69 (s, 3H), 1.22 (d, J = 6.0 Hz, 6H); MS (*m/z*): 411 [M^+ + H]; Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82; O, 19.49, Found : C, 67.43; H, 6.42; N, 6.79; O, 19.36.

Methyl 4-((5-(isobutoxycarbonylamino)-1-methyl-1*H*-indol-3-yl) methyl)-3-methoxy benzoate (7d): Yield: 96 %; Mp: 132–134 °C; IR (KBr, cm^{-1}): 3263 (NH), 1717 (C═O, ester), 1696 (C═O, carbamate), 1282 (OCH_3); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 9.30 (s, 1H), 7.61 (s, 1H), 7.48 (s, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.19-7.11 (m, 2H), 7.05 (s, 1H), 3.96 (s, 2H), 3.91 (s, 3H), 3.83 (s, 2H), 3.82 (s, 3H), 3.69 (s, 3H), 1.95-1.85 (m, 1H), 0.91 (d, J = 6.4 Hz, 6H); MS (*m/z*): 425 [M^+ + H]; Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60; O, 18.85, Found : C, 67.80; H, 6.73; N, 6.55; O, 18.92.

4.2.2 General procedure for hydrolysis of ester with $LiOH.H_2O$

To a stirred solution of methyl ester, **7a**–**e** (1.0 mmol) in methanol (6 volumes to the ester) was added a solution of lithium hydroxide monohydrate (1.5 mmol) in water (1.5 volumes to the ester). The resulting reaction mass was heated to reflux (60-65 °C) and maintained under reflux for 2-3 h. The reaction mixture was cooled to 25-35 °C and acidified to pH 1.0-2.0 with diluted HCl. The reaction mixture was stirred for 1-2 h and filtered the precipitated solid. The wet solid was washed with water and dried under vacuum at 70-75 °C to give acid.

The following compounds were synthesized using this method:

4-((5-(Ethoxycarbonyl amino)-1-methyl -1*H*-indol-3-yl) methyl)-3-methoxybenzoic acid (8b): Yield: 97 %; Mp: 187-189 °C; IR (KBr, cm^{-1}): 3435 (OH), 3286 (NH), 1688 (C═O, acid), 1298 (OCH_3); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.84 (s, 1H), 9.30 (s, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.04 (s, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.95 (s, 2H), 3.91 (s, 3H), 3.69 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); MS (*m/z*): 382.9 [M^+ + H], 405 [M^+ + Na]; Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33; O, 20.92, Found : C, 66.08; H, 5.84; N, 7.27; O, 20.81.

4-((5-(Isopropoxycarbonylamino)-1-methyl-1*H*-indol-3-yl) methyl)-3-methoxybenzoic acid (8c): Yield: 95 %; Mp: 220-222 °C; IR (KBr, cm^{-1}): 3430 (OH), 3276 (NH), 1686 (C═O, acid), 1299 (OCH_3); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.83 (s, 1H), 9.24 (s, 1H), 7.61 (s, 1H), 7.48 (s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 6.8 Hz, 1H), 7.03 (s, 1H), 4.87-4.82 (m, 1H), 3.95 (s, 2H), 3.90 (s, 3H), 3.68 (s, 3H), 1.23 (d, J = 6.0 Hz, 6H); MS (*m/z*): 395.1 [M^- – H]; Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07; O, 20.18, Found : C, 66.52; H, 6.12; N, 7.00; O, 20.27.

4-((5-(Isobutoxycarbonylamino)-1-methyl-1*H*-indol-3-yl)-methyl)-3-methoxybenzoic acid (8d): Yield: 95 %; Mp: 139-141 °C; IR (KBr, cm^{-1}): 3421 (OH), 3294 (NH), 1689 (C═O, acid), 1307 (OCH_3); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.82 (s, 1H), 9.31 (s, 1H), 7.61 (s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.19-7.15 (m, 1H), 7.12 (d, J = 6.8 Hz, 1H), 7.03 (s, 1H), 3.96 (s, 2H), 3.90 (s, 3H), 3.82 (d, J = 6.8 Hz, 2H), 3.69 (s, 3H), 1.96-1.85 (m, 1H), 0.92 (d, J = 6.4 Hz, 6H); MS (*m/z*): 409.1 [M^- – H]; Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82; O, 19.49, Found : C, 67.16; H, 6.40; N, 6.92; O, 19.52.

4.2.3 General procedure of DCC/DMAP coupling for zafirlukast analogs, ***2a–y***

To a stirred mixture of corresponding acid, **8a**–**e** (1.0 mmol), DMAP (1.2 mmol), corresponding sulfonamide (1.2 mmol) in dichloromethane (10 volumes to the acid) was added DCC (1.1 mmol) and maintained the reaction at 25-35 °C for 3-4 h. The unwanted solid (DCU) was filtered and washed with dichloromethane (2 volumes to the acid). The filtrate was separated, washed with 50 % diluted aq. HCl (2 volumes to the acid) and followed by water (10 volumes to the acid). The organic layer was distilled completely under vacuum below 45 °C to obtain solid. The crude compound was isolated and purified by column chromatography [by eluting with ethyl acetate/hexane (1:1)] and dried under vacuum at 70-75 °C to furnish amide.

The following compounds were synthesized using this method:

Methyl3-(2-methoxy-4-(*p*-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2b): IR (KBr, cm^{-1}): 3300 (NH), 1697 (C=O, carbamate), 1670 (C=O, amide), 1349 & 1165 (SO_2, asym. and sym.) ; ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.41 (br, 1H), 9.30 (s, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.55 (s, 1H), 7.44 (t, J = 8.0 Hz, 3H), 7.35 (dd, J = 1.2, 7.2 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 3.93 (s, 2H), 3.90 (s, 3H), 3.68 (s, 3H), 3.62 (s, 3H), 2.39 (s, 3H); MS (*m/z*): 520 [M^- – H]; Anal. Calcd for $C_{27}H_{27}N_3O_6S$: C, 62.17; H, 5.22; N, 8.06; O, 18.40; S, 6.15, Found : C, 62.20; H, 5.30; N, 8.02; O, 18.31; S, 6.17.

Methyl 3-(2-methoxy-4-(*m*-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2c): IR (KBr, cm^{-1}): 3327 (NH), 1691 (C=O, carbamate), 1626 (C=O, amide), 1311 & 1157 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.40 (br, 1H), 9.30 (s, 1H), 7.68 (s, 2H), 7.55 (s, 1H), 7.50 (s, 1H), 7.48 (dd, J = 2.0, 11.2 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.37-7.32 (m, 3H), 7.08 (d, J = 7.2 Hz, 1H), 7.02 (s, 1H), 3.93 (s, 2H), 3.90 (s, 3H), 3.68 (s, 3H), 3.61 (s, 3H), 2.39 (s, 3H); MS (*m/z*): 520.1 [M^- – H]; Anal. Calcd for $C_{27}H_{27}N_3O_6S$: C, 62.17; H, 5.22; N, 8.06; O, 18.40; S, 6.15, Found : C, 62.22; H, 5.31; N, 8.00; O, 18.30; S, 6.17.

Methyl3-(4-(benzylsulfonylcarbamoyl)-2-methoxybenzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2d): IR (KBr, cm^{-1}): 3340 (NH), 1700 (C=O, carbamate), 1681 (C=O, amide), 1345 & 1150 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 11.92 (s, 1H), 9.32 (s, 1H), 7.59 (s, 1H), 7.48 (s, 1H), 7.42 (d, J = 6.4 Hz, 1H), 7.38–7.27 (m, *6*H), 7.14 (t, J = 7.6 Hz, 2H), 7.06 (s, 1H), 4.84 (s, 2H), 3.95 (s, 2H), 3.90 (s, 3H), 3.69 (s, 3H), 3.63 (s, 3H); MS (*m/z*): 522 [M^+ + H]; Anal. Calcd for $C_{27}H_{27}N_3O_6S$: C, 62.17; H, 5.22; N, 8.06; O, 18.40; S, 6.15, Found : C, 62.27; H, 5.19; N, 8.00; O, 18.37; S, 6.17.

Methyl 3-(2-methoxy-4-(phenylsulfonylcarbamoyl)benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2e): IR (KBr, cm^{-1}): 3325 (NH), 1714 (C=O, carbamate), 1626 (C=O, amide), 1347 & 1134 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.50 (br, 1H), 9.31 (s, 1H), 7.99 (d, J = 7.6 Hz, 2H), 7.71 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 2H), 7.55 (s, 1H), 7.46 (s, 1H), 7.36 (dd, J = 1.2, 7.6 Hz, 1H), 7.27 (t, J = 8.8 Hz, 1H), 7.17-7.12 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 3.93 (s, 2H), 3.91 (s, 3H), 3.68 (s, 3H), 3.62 (s, 3H);MS (*m/z*): 506.1 [M^- – H]; Anal. Calcd for $C_{26}H_{25}N_3O_6S$: C, 61.53; H, 4.96; N, 8.28; O, 18.91; S, 6.32, Found : 61.42; H, 5.01; N, 8.34; O, 18.99; S, 6.24.

Ethyl 3-(2-methoxy-4-(*o*-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2f): IR (KBr, cm^{-1}): 3294 (NH), 1709 (C=O, carbamate), 1646 (C=O, amide) 1350 & 1112 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.37 (s, 1H), 9.25 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.54 (s, 1H), 7.47-7.39 (m, 3H), 7.32 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 4.05 (q, J = 6.8 Hz, 2H), 3.91 (s, 2H), 3.88 (s, 3H), 3.65 (s, 3H), 2.36 (s, 3H), 1.19 (t, J = 6.8 Hz, 3H); MS (*m/z*): 534 [M^- – H]; Anal. Calcd for $C_{28}H_{29}N_3O_6S$: C, 62.79; H, 5.46; N, 7.85; O, 17.92; S, 5.99, Found : C, 62.81; H, 5.50; N, 7.88; O, 17.98; S, 5.98.

Ethyl 3-(2-methoxy-4-(*p*-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2g): IR (KBr, cm^{-1}): 3305 (NH), 1694 (C═O, carbamate), 1668 (C═O, amide), 1349 & 1164 (SO_2, asym. and sym.); ^1H NMR (400 MHz, DMSO–d_6): δ_H 12.50 (br, 1H), 9.27 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.53 (t, J = 7.2 Hz, 1H), 7.49 (s, 1H), 7.48-7.26 (m, 3H), 7.26 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.93 (s, 2H), 3.89 (s, 3H), 3.68 (s, 3H), 2.58 (s, 3H), 1.22 (t, J = 6.8 Hz, 3H); MS (*m/z*): 534 [M^- – H]; Anal. Calcd for $C_{28}H_{29}N_3O_6S$: C, 62.79; H, 5.46; N, 7.85; O, 17.92; S, 5.99, Found : C, 62.84; H, 5.52; N, 7.95; O, 17.79; S, 5.90.

Ethyl3-(2-methoxy-4-(*m*-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1*H*-indol-5-yl-carbamate(2h): IR (KBr, cm^{-1}): 3328 (NH), 1694 (C═O, carbamate), 1627 (C═O, amide), 1346 & 1159 (SO_2, asym. and sym.) ; ^1H NMR (400 MHz, DMSO–d_6): δ_H 12.45 (br, 1H), 9.27 (s, 1H), 7.78 (s, 2H), 7.62-7.45 (m, 3H), 7.47 (s, 1H), 7.36 (dd, J = 1.2, 7.6 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 7.2 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 4.07 (q, J = 6.8 Hz, 2H), 3.93 (s, 2H), 3.91 (s, 3H), 3.67 (s, 3H), 2.40 (s, 3H), 1.21 (t, J = 6.8 Hz, 3H); MS (*m/z*): 536 [M^+ + H], 567 [M^+ + Na]; Anal. Calcd for $C_{28}H_{29}N_3O_6S$: C, 62.79; H, 5.46; N, 7.85; O, 17.92; S, 5.99, Found : C, 62.84; H, 5.39; N, 7.72; O, 17.88; S, 6.17.

Ethyl 3-(4-(benzylsulfonylcarbamoyl)-2-methoxybenzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2i): IR (KBr, cm^{-1}): 3325 (NH), 1681 (C═O, carbamate), 1697 (C═O, amide), 1340 & 1152 (SO_2, asym. and sym.); ^1H NMR (400 MHz, DMSO–d_6): δ_H 12.55 (s, 1H), 9.26 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.40-7.25 (m, 6H), 7.13 (t, J = 7.6 Hz, 1H), 7.06 (s, 1H), 6.97 (t, J = 8.4 Hz, 1H), 4.83 (s, 2H), 4.08 (q, J = 6.8 Hz, 2H), 3.95 (s, 2H), 3.90 (s, 3H), 3.69 (s, 3H), 1.22 (t, J = 6.8 Hz, 3H); MS (*m/z*): 534.1 [M^- – H]; Anal. Calcd for $C_{28}H_{29}N_3O_6S$: C, 62.79; H, 5.46; N, 7.85; O, 17.92; S, 5.99, Found : C, 62.69; H, 5.51; N, 7.90; O, 17.90; S, 6.00.

Ethyl 3-(2-methoxy-4-(phenylsulfonylcarbamoyl)benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2j): IR (KBr, cm^{-1}): 3291 (NH), 1713 (C═O, carbamate), 1645 (C═O, amide), 1348 & 1136 (SO_2, asym. and sym.); ^1H NMR (400 MHz, DMSO–d_6): δ_H 12.50 (br, 1H), 9.26 (s, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.68-7.56 (m, 4H), 7.47 (s, 1H), 7.36 (dd, J = 1.6, 8.0 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.00 (s, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.92 (s, 2H), 3.89 (s, 3H), 3.67 (s, 3H), 1.21 (t, J = 6.8 Hz, 3H); MS (*m/z*): 520 [M^- – H]; Anal. Calcd for $C_{27}H_{27}N_3O_6S$: C, 62.17; H, 5.22; N, 8.06; O, 18.40; S, 6.15, Found : C, 62.22; H, 5.28; N, 8.01; O, 18.32; S, 6.17.

Isopropyl 3-(2-methoxy-4-(*o*-tolylsulfonylcarbamoyl)-benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2k): IR (KBr, cm^{-1}): 3365 (NH), 1693 (C═O, carbamate), 1647 (C═O, amide), 1337 & 1161 (SO_2, asym. and sym.); ^1H NMR (400 MHz, DMSO–d_6): δ_H 12.80 (br, 1H), 9.21 (s, 1H), 8.19 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H), 7.40-7.24 (m, 4H), 7.14 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 7.04 (s, 1H), 6.96 (d, J = 7.2 Hz, 1H), 4.90-4.81 (m, 1H), 3.92 (s, 2H), 3.88 (s, 3H), 3.67 (s, 3H), 2.57 (s, 3H), 1.22 (d, J = 6.4 Hz, 6H); MS (*m/z*): 550 [M^+ + H]; Anal. Calcd for $C_{29}H_{31}N_3O_6S$: C, 63.37; H, 5.68; N, 7.65; O, 17.47; S, 5.83, Found : C, 63.23; H, 5.74; N, 7.54; O, 17.52; S, 5.97.

Isopropyl 3-(2-methoxy-4-(*p*-tolylsulfonylcarbamoyl)-benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2l): IR (KBr, cm^{-1}): 3322 (NH), 1691 (C═O, carbamate), 1648 (C═O, amide), 1342 & 1165 (SO_2, asym. and sym.); ^1H NMR (400 MHz, DMSO–d_6): δ_H 12.43 (br, 1H), 9.21 (s, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.58 (s, 1H), 7.46 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.0 (s, 1H), 4.88–4.80 (m, 1H), 3.92 (s, 2H), 3.89 (s, 3H), 3.67 (s, 3H), 2.37 (s, 3H), 1.22 (d, J = 6.4 Hz, 6H); MS (*m/z*): 550 [M^+ + H]; Anal. Calcd for $C_{29}H_{31}N_3O_6S$: C, 63.37; H, 5.68; N, 7.65; O, 17.47; S, 5.83, Found : C, 63.26; H, 5.72; N, 7.55; O, 17.55; S, 5.92.

Isopropyl 3-(2-methoxy-4-(*m*-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2m): IR (KBr, cm^{-1}): 3357 (NH), 1690 (C═O, carbamate), 1604 (C═O, amide), 1341 &, 1157 (SO_2, asym. and sym.); ^1H NMR (400 MHz, DMSO–d_6): δ_H 12.45 (s, 1H), 9.21 (s, 1H), 7.78 (s, 2H), 7.64-7.56 (m, 1H), 7.54-7.50 (m, 1H), 7.47 (s, 1H), 7.46-7.35 (m, 1H), 7.31 (s, 1H), 7.26 (d, J = 8.8 Hz,

1H), 7.13 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 4.88-4.82 (m, 1H), 3.93 (s, 2H), 3.91 (s, 3H), 3.67 (s, 3H), 2.40 (s, 3H), 1.23 (d, J = 6.0 Hz, 6H); MS (*m/z*): 550 (M^+ + H); Anal. Calcd for $C_{29}H_{31}N_3O_6S$: C, 63.37; H, 5.68; N, 7.65; O, 17.47; S, 5.83, Found : C, 63.29; H, 5.74; N, 7.69; O, 17.50; S, 5.78.

Isopropyl 3-(4-(benzylsulfonylcarbamoyl)-2-methoxy benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2n):IR (KBr, cm^{-1}): 3362 (NH), 1692 (C=O, carbamate), 1624 (C=O, amide), 1338 & 1154 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 11.91 (s, 1H), 9.23 (s, 1H), 7.63 (s, 1H), 7.48 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.39-7.27 (m, 6H), 7.14 (t, J = 7.6 Hz, 1H), 7.06 (s, 1H), 6.83 (s, 1H), 4.87-4.82 (m, 3H), 4.26 (s, 1H), 3.95 (s, 1H), 3.90 (s, 3H), 3.69 (s, 3H), 1.23 (d, J = 6.4 Hz, 6H); MS (*m/z*): 550 (M^+ + H); Anal. Calcd for $C_{29}H_{31}N_3O_6S$: C, 63.37; H, 5.68; N, 7.65; O, 17.47; S, 5.83, Found : C, 63.42; H, 5.59; N, 7.59; O, 17.54; S, 5.86.

Isopropyl 3-(2-methoxy-4-(phenylsulfonylcarbamoyl) benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2o):IR (KBr, cm^{-1}): 3371 (NH), 1692 (C=O, carbamate), 1625 (C=O, amide), 1344 & 1162 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.44 (s, 1H), 9.21 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.72 (t, J = 7.2 Hz, 1H), 7.64 (t, J = 7.6 Hz, 2H), 7.60 (s, 1H), 7.48 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 4.90-4.83 (m, 1H), 3.93 (s, 2H), 3.91 (s, 3H), 3.67 (s, 3H), 1.22 (d, J = 6.0 Hz, 6H); MS (*m/z*): 536 [M^+ + H]; Anal. Calcd for $C_{28}H_{29}N_3O_6S$: C, 62.79; H, 5.46; N, 7.85; O, 17.92; S, 5.99, Found : C, 62.37; H, 5.56; N, 7.93; O, 18.02; S, 6.12.

Isobutyl 3-(2-methoxy-4-(*o*-tolylsulfonylcarbamoyl) benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2p):IR (KBr, cm^{-1}): 3327 (NH), 1692 (C=O, carbamate), 1627 (C=O, amide), 1340 & 1160 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.58 (s, 1H), 9.27 (s, 1H), 8.02 (d, J = 7.2 Hz, 1H), 7.56 (t, J = 8.0 Hz, 2H), 7.49 (s, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.40-7.34 (m, 2H), 7.27 (d, J = 8.8 Hz, 1H), 7.18-7.12 (m, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 3.93 (s, 2H), 3.90 (s, 3H), 3.82 (d, J = 6.8 Hz, 2H), 3.68 (s, 3H), 2.59 (s, 3H), 1.97-1.84 (m, 1H), 0.91 (d, J = 6.8 Hz, 6H); MS (*m/z*): 564 [M^+ + H]; Anal. Calcd for $C_{30}H_{33}N_3O_6S$: C, 63.92; H, 5.90; N, 7.45; O, 17.03; S, 5.69, Found : C, 64.08; H, 5.95; N, 7.38; O, 16.98; S, 5.61.

Isobutyl 3-(2-methoxy-4-(*p*-tolylsulfonylcarbamoyl) benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2q): IR (KBr, cm^{-1}): 3318 (NH), 1682 (C=O, carbamate), 1585 (C=O, amide), 1342 & 1162 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.39 (s, 1H), 9.27 (s, 1H), 7.86 (d, J = 7.6 Hz, 2H), 7.57 (s, 1H), 7.48-7.40 (m, 3H), 7.35 (dd, J = 1.6, 8.0 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.20-7.15 (m, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 3.93 (s, 2H), 3.90 (s, 3H), 3.82 (d, J = 6.4 Hz, 2H), 3.68 (s, 3H), 2.38 (s, 3H), 1.96-1.85 (m, 1H), 0.91 (d, J = 6.4 Hz, 6H); MS (*m/z*): 564 [M^+ + H]; Anal. Calcd for $C_{30}H_{33}N_3O_6S$: C, 63.92; H, 5.90; N, 7.45; O, 17.03; S, 5.69, Found : C, 63.82; H, 5.85; N, 7.38; O, 17.23; S, 5.72.

Isobutyl 3-(2-methoxy-4-(*m*-tolylsulfonylcarbamoyl) benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2r): IR (KBr, cm^{-1}): 3332 (NH), 1693 (C=O, carbamate), 1630 (C=O, amide), 1340 & 1158 (SO_2, asym. and sym.); ^{1}H NMR (500 MHz, DMSO–d_6): δ_H 12.50 (br, 1H), 9.27 (s, 1H), 7.72 (s, 2H), 7.55 (s, 1H), 7.50–7.40 (m, 3H), 7.34 (dd, J = 1.5, 8.0 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.18-7.12 (m, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.00 (s, 1H), 3.91 (s, 2H), 3.88 (s, 3H), 3.80 (d, J = 7.0 Hz, 2H), 3.66 (s, 3H), 2.37 (s, 3H), 1.95-1.87 (m, 1H), 0.89 (d, J = 7.0 Hz, 6H); MS (*m/z*): 564 [M^+ + H]; Anal. Calcd for $C_{30}H_{33}N_3O_6S$: C, 63.92; H, 5.90; N, 7.45; O, 17.03; S, 5.69, Found : C, 64.04; H, 5.95; N, 7.37; O, 17.11; S, 5.53.

Isobutyl 3-(4-(benzylsulfonylcarbamoyl)-2-methoxy benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2s): IR (KBr, cm^{-1}): 3323 (NH), 1695 (C=O, carbamate), 1641 (C=O, amide), 1335 & 1151 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.40 (br, 1H), 9.30 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.60 (s, 1H), 7.49 (s, 1H), 7.42-7.30 (m, 5H), 7.20-7.15 (m, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.03 (s, 1H), 6.95 (d, J = 7.6 Hz, 1H), 4.66 (s, 2H), 3.93 (s, 2H), 3.88 (s, 3H), 3.83 (d, J = 6.8 Hz, 2H), 3.69 (s, 3H), 1.95-1.86 (m, 1H), 0.92 (d, J = 6.8 Hz, 6H); MS (*m/z*): 564 [M^+ + H]; Anal. Calcd for

$C_{30}H_{33}N_3O_6S$: C, 63.92; H, 5.90; N, 7.45; O, 17.03; S, 5.69, Found : C, 64.05; H, 5.78; N, 7.39; O, 17.11; S, 5.67.

Isobutyl 3-(2-methoxy-4-(phenylsulfonylcarbamoyl) benzyl)-1-methyl-1*H*-indol-5-yl-carbamate (2t): IR (KBr, cm^{-1}): 3367 (NH), 1693 (C═O, carbamate), 1635 (C═O, amide), 1341 & 1165 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.39 (s, 1H), 9.27 (s, 1H), 7.75 (d, J = 7.6 Hz, 2H), 7.57 (s, 1H), 7.48-7.42 (m, 3H), 7.36 (d, J = 7.5 Hz, 1H), 7.32-7.25 (m, 2H), 7.19–7.13 (m, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 3.93 (s, 2H), 3.89 (s, 3H), 3.82 (d, J = 7.0 Hz, 2H), 3.68 (s, 3H), 1.97-1.88 (m, 1H), 0.91 (d, J = 7.0 Hz, 6H); MS (*m/z*): 550 [M^+ + H]; Anal. Calcd for $C_{29}H_{31}N_3O_6S$: C, 63.37; H, 5.68; N, 7.65; O, 17.47; S, 5.83, Found : C, 63.50; H, 5.60; N, 7.62; O, 17.54; S, 5.74.

Cyclopentyl 3-(2-methoxy-4-(phenylsulfonylcarbamoyl) benzyl)-1-methyl-1H-indol-5-yl-carbamate (2y): IR (KBr, cm^{-1}): 3448 (NH), 1693 (C═O, carbamate), 1667 (C═O, amide), 1342 & 1170 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.50 (br, 1H), 9.20 (s, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.71 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 8.0 Hz, 2H), 7.58 (s, 1H), 7.46 (s, 1H), 7.36 (dd, J = 1.2, 8.0 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.18-7.10 (m, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 5.07-5.02 (m, 1H), 3.93 (s, 2H), 3.91 (s, 3H), 3.67 (s, 3H),1.91-1.50 (m, 8H) ; MS (*m/z*): 584 [M^+ + Na]; Anal. Calcd for $C_{30}H_{31}N_3O_6S$: C, 64.15; H, 5.56; N, 7.48; O, 17.09; S, 5.71, Found : C, 64.20; H, 5.65; N, 7.48; O, 16.93; S, 5.74.

Methyl 4-((5-(cyclopentyloxycarbonylamino)-1*H*-indol-3-yl) methyl)-3-methoxy benzoate (10): Mp: 88–92 °C; IR (KBr, cm^{-1}): 3339 (NH), 1702 (C═O, ester), 1629 (C═O, carbamate), (s,1292 (OCH_3) ; ^{1}H NMR (400 MHz, CD_3OD): δ_H 12.59 (s, 1H), 10.73 (s, 1H), 7.53 (s, 1H), 7.51 (bs, 1H), 7.45 (dd, J = 1.6 Hz, 8.0 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 12.0 Hz, 1H), 6.95 (s, 1H), 5.13-5.07 (m, 1H), 4.04 (s, 2H), 3.90 (s, 3H), 3.84 (s, 3H), 1.93-1.55 (m, 8H) ; MS (*m/z*): 445 [M^+ + Na]; Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63; O, 18.94, Found : C, 68.13; H, 6.20; N, 6.71; O, 18.96.

4-((5-(Cyclopentyloxycarbonylamino)-1*H*-indol-3-yl)methyl)-methoxybenzoic acid (11):Same process was followed as mentioned in the experimental section 4.5.2, but ester **10** was used instead of acid **7a**–**e**.Mp: 185-188 °C; IR (KBr, cm^{-1}): 3500 (OH), 3280 (NH), 1690 (C═O, acid), 1260 (OCH_3); ^{1}H NMR (200 MHz, DMSO–d_6): δ_H 12.50 (s, 1H), 10.71 (s, 1H), 7.80-7.30 (m, 4H), 7.45-7.05 (m, 3H), 6.85 (s, 1H), 5.25-5.22 (m, 1H), 4.10 (s, 2H), 3.90 (s, 3H), 1.30-1.10 (m, 8H); MS (*m/z*): 409 [M^+ + H], Anal. Calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86; O, 19.59, Found : C, 67.50; H, 5.88; N, 6.90; O, 19.72.

4.2.4. General procedure for zafirlukast analogs, 3a–e

Cyclopentyl 3-(2-methoxy-4-(*p*-tolylsulfonylcarbamoyl) benzyl)-1*H*-indol-5-yl-carbamate (3b): IR (KBr, cm^{-1}): 3388 (NH), 1688 (C═O, carbamate), 1597 (C═O, amide), 1340 & 1165 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.38 (s, 1H), 10.72 (s, 1H), 9.14 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.45 (s, 1H), 7.41 (d, J = 7.6 Hz, 2H), 7.34 (dd, J = 1.2, 8.0 Hz, 2H), 7.21 (d, J = 8.4 Hz, 1H), 7.05 (s, 1H), 7.04 (d, J = 7.6 Hz, 2H), 5.06-5.01 (m, 1H), 3.93 (s, 2H), 3.90 (s, 3H), 2.38 (s, 3H), 1.90-1.50 (m, 8H); MS (*m/z*): 584 [M^+ + Na], Anal. Calcd for $C_{30}H_{31}N_3O_6S$: C, 64.15; H, 5.56; N, 7.48; O, 17.09; S, 5.71, Found : C, 64.05; H, 5.62; N, 7.41; O, 17.00; S, 5.92.

Cyclopentyl 3-(2-methoxy-4-(*m*-tolylsulfonylcarbamoyl) benzyl)-1*H*-indol-5-yl-carbamate (3c) : IR (KBr, cm^{-1}): 3384 (NH), 1693 (C═O, carbamate), 1675 (C═O, amide), 1330 & 1157 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.41 (s, 1H), 10.73 (s, 1H), 9.15 (s, 1H), 7.78 (s, 2H), 7.54 (s, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.50 (s, 1H), 7.36 (dd, J = 1.6, 8.0 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.07 (s, 1H), 7.06 (d, J = 7.2 Hz, 2H), 5.05-5.01 (m, 1H), 3.94 (s, 2H), 3.91 (s, 3H), 2.40 (s, 3H), 1.90-1.50 (m, 8H); MS (*m/z*): 584 [M^+ + Na]; Anal. Calcd for $C_{30}H_{31}N_3O_6S$: C, 64.15; H, 5.56; N, 7.48; O, 17.09; S, 5.71, Found : C, 64.10; H, 5.58; N, 7.53; O, 17.21; S, 5.58.

Cyclopentyl 3-(4-(phenylsulfonylcarbamoyl)-2-methoxy benzyl)-1*H*-indol-5-yl carbamate (3d): IR (KBr, cm^{-1}): 3410 (NH), 1710 (C═O, carbamate), 1620 (C═O, amide), 1345 & 1130 (SO_2, asym. and sym.); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.50 (brs, 1H), 11.10 (s, 1H), 9.31 (s, 1H), 7.95 (d, J = 7.6 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.50 (s, 1H), 7.45 (s, 1H), 7.32 (dd, J = 1.3, 7.6 Hz, 1H), 7.24 (t, J = 8.6 Hz, 1H), 7.15–7.10 (m, 2H), 7.04 (d, J = 8.0 Hz, 1H), 7.00 (s, 1H), 5.08-5.02 (m, 1H), 3.93 (s, 2H), 3.92 (s, 2H), 3.90 (s, 3H), 1.30-1.10 (m, 8H); MS (*m/z*): 548 [M^+ + H]; Anal. Calcd for $C_{29}H_{29}N_3O_6S$: C, 63.60; H, 5.34; N, 7.67; O, 17.53; S, 5.86, Found : C, 63.52; H, 5.38; N, 7.59; O, 17.60; S, 5.91.

*4.2.5 General procedure for zafirlukast DCU analogs, **4a–c***

To a stirred mixture of acid **8a**, **8b** or **8e** (1.0 mmol) and DCC (1.1 mmol) in dichloromethane (10 volumes to the acid) was added diisopropylethylamine (1.2 mmol) at 25-35 °C for 4-5 h. Filtered the unwanted solid (DCU) and washed with dichloromethane (2 volumes to the acid). The organic layer was washed with 50 % aq. HCl (2 volumes to the acid), followed by water (10 volumes to the acid). The organic layer was distilled under reduced pressure below 45 °C and methanol was added to the residue. The reaction mixture was heated to 60-65 °C and stirred for 10-15 min. The reaction mixture was cooled to 25-35 °C, stirred for 45 min, filtered the separated solid and washed with methanol (2 volumes to the acid) to afford compounds **4a**–**c**.

Methyl 3-(4-(cyclohexyl(cyclohexylcarbamoyl)carbamoyl)-2-methoxy benzyl)-1-methyl-1*H*-indol-5-ylcarbamate (4a): IR (KBr, cm^{-1}): 3322 (NH), 2931 (Ali, CH), 1701 (C═O, urea), 1628 (C═O, amide), 1237 (OCH_3); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 9.31 (bs, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.60 (bs, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.94 (s, 1H), 6.90 (d, J = 7.2 Hz, 1H), 4.18-4.11 (m, 1H), 3.89 (s, 2H), 3.82 (s, 3H), 3.67 (s, 3H), 3.63 (s, 3H), 3.13-3.05 (m, 1H), 1.85-1.59 (m, 8H), 1.40-0.95 (m, 12H); MS (*m/z*): 575 [M^+ + H]; Anal. Calcd for $C_{33}H_{42}N_4O_5$: C, 68.97; H, 7.37; N, 9.75; O, 13.92, Found : C, 68.82; H, 7.42; N, 9.80; O, 13.87.

Ethyl 3-(4-(cyclohexyl(cyclohexylcarbamoyl)carbamoyl)-2-methoxy benzyl)-1-methyl-1*H*-indol-5-ylcarbamate (4b): IR (KBr, cm^{-1}): 3322 (NH), 2931(Ali, CH), 1719 (C═O, urea), 1627 (C═O, amide), 1234 (OCH_3); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 9.27 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.62 (s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.16–7.10 (m, 1H), 7.06 (s, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 6.92 (t, J = 8.0 Hz, 1H), 4.20–4.06 (m, 3H), 3.89 (s, 2H), 3.82 (s, 3H), 3.66 (s, 3H), 3.15-3.06 (m, 1H), 1.86-1.60 (m, 8H), 1.40-0.95 (m, 15H); MS (*m/z*): 589 [M^+ + H]; Anal. Calcd for $C_{34}H_{44}N_4O_5$: C, 69.36; H, 7.53; N, 9.52; O, 13.59, Found : C, 69.42; H, 7.51; N, 9.55; O, 13.52.

*4.2.6 General procedure for zafirlukast dimer analogs, **5a–c***

Procedure same as general procedure of DCC/DMAP coupling

Methyl 3-(2-methoxy-4-(3-(2-methoxy-4-(*o*-tolylsulfonyl carbamoyl) benzyl)-1-methyl-1*H*-indol-5-ylcarbamoyl) benzyl)-1-methyl-1*H*-indol-5-ylcarbamate (5a): IR (KBr, cm^{-1}): 3370 (NH), 2940 (Ali, CH), 1702 (C═O, carbamate), 1645 (C═O, amide), 1320 & 1163 (SO_2, asym. and sym.), 1242 (OCH_3) ;^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.62 (bs, 1H), 9.96 (s, 1H), 9.36 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 7.61 (s, 1H), 7.55-7.28 (m, 9H), 7.20-7.03 (m, 6H), 3.96 (s, 4H), 3.94 (s, 3H), 3.88 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.63 (s, 3H), 2.56 (s, 3H); MS (*m/z*): 814 [M^+ + H]; Anal. Calcd for $C_{45}H_{43}N_5O_8S$: C, 66.41; H, 5.33; N, 8.60; O, 15.73; S, 3.94, Found : C, 66.53; H, 5.30; N, 8.57; O, 15.70; S, 3.90.

Ethyl 3-(2-methoxy-4-(3-(2-methoxy-4-(*o*-tolylsulfonyl carbamoyl)benzyl)-1-methyl-1*H*-indol-5-ylcarbamoyl)benzyl)-1-methyl-1*H*-indol-5-ylcarbamate (5b): IR (KBr, cm^{-1}): 3365 (NH), 2940 (Ali, CH), 1697 (C═O, carbamate), 1657 (C═O, amide), 1579 (C═O, amide), 1380 & 1166 (SO_2, asym. and sym.), 1232 (OCH_3); ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 12.55 (s, 1H), 9.95 (s, 1H), 9.29

(s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.84 (s, 1H), 7.63 (s, 1H), 7.60-7.33 (m, 8H), 7.28 (d, J = 8.8 Hz, 1H), 7.20–7.07 (m, 4H), 7.05 (d, J = 8.8 Hz, 2H), 4.09 (q, J = 6.8 Hz, 2H), 3.96 (s, 4H), 3.94 (s, 3H), 3.91 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 2.58 (s, 3H), 1.22 (t, J = 6.8 Hz, 3H); MS (*m/z*): 828 [M^+ + H], 850 [M^+ + Na]; Anal. Calcd for $C_{46}H_{45}N_5O_8S$: C, 66.73; H, 5.48; N, 8.46; O, 15.46; S, 3.87, Found : 66.69; H, 5.50; N, 8.48; O, 15.42; S, 3.91.

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