CHAPTER-4
SYNTHESIS AND CHARACTERIZATION
OF ZAFIRLUKAST ANALOGS
4.1 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 4.1) 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 4.1: Structure of zafirlukast 1

Leukotrienes (LTs), including LTB4 and cysteinyI-LTs (Cys-LTs) (LTC4, LTD4, and LTE4) are potent inflammatory lipid mediators which are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and play a crucial role in asthma pathophysiology by causing bronchoconstriction, mucus production and an increase in vascular
permeability. They represent one of the most effective approaches to the treatment of asthma and convincing proof for a causative role of Cys-LTs in asthma comes from the clinical effectiveness of Cys-LT1 receptor antagonists (e.g., montelukast, zafirlukast, pranlukast) and 5-LO inhibitors (e.g., zileuton) in patients. In recent years there has been particular interest in searching for dual H1/cys-LT1 antagonists in the hope of managing asthma by synergistic effects.

4.2 LITERATURE REVIEW

The literature survey revealed the following literature precedence for various analogs of zafirlukast.

Matassa et al.,2,3 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 group4 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 cPLA2a.5,6

4.3 PRESENT WORK

4.3.1 Objective

As part of a research program in the development of new indole derivatives, the preparation of zafirlukast analogs was undertaken.
Herein, synthesis and characterization of four new series of zafirlukast analogs have been described.

4.3.2 Results and discussion

Based on the literature, four new series of zafirlukast analogs (figure 4.2) has been designed. These analogs were synthesized by modifying the substitution on indole nitrogen, C-5 position of indole moiety and amide nitrogen.

Figure 4.2: Structures of zafirlukast analogs, 2, 3, 4 and 5
4.3.2.1 Synthesis and characterization of zafirlukast analogs, 2a–y

Synthesis of first series of analogs 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. Where as, different sulfonamides such as m-tolyl, p-tolyl, phenyl and benzyl sulfonamides were used instead of o-tolylsulfonamide.

Scheme 4.1: 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 nitroindole and (ii) reduction of nitro group.\(^7\) 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\(_2\)O to furnish the acid 8a. Subsequently, the acid
8a was coupled with o-toluene sulfonamide under DCC/DMAP conditions to yield the analog 2a (scheme 4.1).

Structure of analog 2a was confirmed based on the IR, mass and NMR spectral data and described as compound 15 in previous chapter-3.

To demonstrate the generality, this methodology was extended to synthesize other derivatives (2b–y) starting from the amino ester 6 (scheme 4.1). In all the cases good yields were obtained (table 4.1). Analogs, 2b–y were characterized based on the IR, mass and 1H NMR spectral data in the similar manner as 2a was characterized. Spectral data of 2b–y provided in the experimental section (4.5.3.2 – 4.5.3.25).

Table 4.1: Synthesis of zafirlukast analogs 2a–y

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compd.</th>
<th>R₁</th>
<th>R₂</th>
<th>Mp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>methyl</td>
<td>o-tolyl</td>
<td>118–122</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>methyl</td>
<td>p-tolyl</td>
<td>185–190</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>methyl</td>
<td>m-tolyl</td>
<td>145–150</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>methyl</td>
<td>phenyl</td>
<td>145–150</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>methyl</td>
<td>benzyl</td>
<td>200–206</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>ethyl</td>
<td>o-tolyl</td>
<td>179–186</td>
<td>71</td>
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<tr>
<td>7</td>
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<td>ethyl</td>
<td>p-tolyl</td>
<td>178–180</td>
<td>65</td>
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<td>8</td>
<td>2h</td>
<td>ethyl</td>
<td>m-tolyl</td>
<td>179–182</td>
<td>74</td>
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<td>9</td>
<td>2i</td>
<td>ethyl</td>
<td>phenyl</td>
<td>174–178</td>
<td>73</td>
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<tr>
<td>12</td>
<td>2l</td>
<td>isopropyl</td>
<td>p-tolyl</td>
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<td>2n</td>
<td>isopropyl</td>
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<td>75–80</td>
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<td>15</td>
<td>2o</td>
<td>isopropyl</td>
<td>benzyl</td>
<td>100–105</td>
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<td>2p</td>
<td>butyl</td>
<td>o-tolyl</td>
<td>120–125</td>
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<td>17</td>
<td>2q</td>
<td>butyl</td>
<td>p-tolyl</td>
<td>185–192</td>
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<td>18</td>
<td>2r</td>
<td>butyl</td>
<td>m-tolyl</td>
<td>115–120</td>
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<td>19</td>
<td>2s</td>
<td>butyl</td>
<td>phenyl</td>
<td>118–124</td>
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<tr>
<td>20</td>
<td>2t</td>
<td>butyl</td>
<td>benzyl</td>
<td>98–102</td>
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<td>21</td>
<td>2u</td>
<td>cyclopentyl</td>
<td>o-tolyl</td>
<td>142–145</td>
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<td>22</td>
<td>2v</td>
<td>cyclopentyl</td>
<td>p-tolyl</td>
<td>248–252</td>
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<td>23</td>
<td>2w</td>
<td>cyclopentyl</td>
<td>m-tolyl</td>
<td>204–210</td>
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<tr>
<td>24</td>
<td>2x</td>
<td>cyclopentyl</td>
<td>phenyl</td>
<td>142–147</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>2y</td>
<td>cyclopentyl</td>
<td>benzyl</td>
<td>115–125</td>
<td></td>
</tr>
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</table>

### 4.3.2.2 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 followed by reduction of nitro group. Reaction of amine 9 with cyclopentyl chloroformate in the presence of NMM in toluene yielded 10.
Hydrolysis of ester 10 using LiOH.H₂O in aq.methanol furnished acid 11, which was coupled with o-toluene sulfonamide under DCC/DMAP coupling conditions to provide the des N-methyl derivative 3a (scheme 4.2).

Scheme 4.2: Synthesis of des N-methyl zaflrulkast analogs

The deprotonated molecular ion appeared at m/z 560 in the mass spectrum (figure 4.3) as a base peak. FT-IR spectra (figure 4.4) showed bands at 1690 and 1313 & 1161 cm⁻¹ for carbonyl and sulfonyl groups respectively.

The ¹H NMR spectra (figure 4.5) revealed, three singlets at δ 3.94, 3.91 and 2.59 corresponding to benzylic, O-methyl and aromatic methyl protons, respectively. Three singlets corresponding to NH due to sulfonamide, carbamate and indole displayed at δ 12.55, 10.73 and 9.15 respectively. Two multiplets at δ 5.07-5.02 and 1.91-1.50 corresponding to cyclopentyl group. All the aromatic protons displayed between δ 7.0-8.1
and account for desmethyl derivative 3a, which is consistent with the assigned structure of derivative 3a.

**Figure 4.3:** Mass spectrum of compound 3a

**Figure 4.4:** IR spectrum of compound 3a
Figure 4.5: $^1$H NMR spectrum of compound 3a

In the $^{13}$C NMR spectrum, signals at $\delta 76.5$ and $55.4$ for OCH and OCH$_3$ respectively (figure 4.6). The peaks at $\delta 165.0$ and $157.4$ for
carbonyl carbon and other aromatic carbons appeared in their respective regions confirmed the assigned structure 3a.

A similar procedure was utilized to synthesize other derivatives, 3b–e (scheme 4.2). In all the cases good yields were obtained (table 4.2). Spectral data of these compounds provided in the experimental section (4.5.6.2–4.5.6.5).

**Table 4.2: Synthesis of des N-methyl zafirlukast analogs 3a–e**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compd.</th>
<th>R₂</th>
<th>Mp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>o-tolyl</td>
<td>130–135</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>p-tolyl</td>
<td>175–185</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>m-tolyl</td>
<td>210–220</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>phenyl</td>
<td>185–190</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>benzyl</td>
<td>135–147</td>
<td>65</td>
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**4.3.2.3 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 using DIPEA in dichloromethane provided dicyclohexyl urea analog 4a via o-acyl intermediate, 12a (scheme 4.3).
Scheme 4.3: Synthesis of zafirlukast DCU analogs, 4a–c

Structure of analog 4c was confirmed based on the IR, mass NMR (1H and 13C) spectral data and described as compound 19 in previous chapter-3.

This methodology was extended to make other similar analogs 4a and 4b and confirmed by spectral data (experimental section 4.5.7.1–4.5.7.3). The results were summarized in table 4.3.

Table 4.3: Synthesis of zafirlukast DCU analogs 4a–c

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compd.</th>
<th>R₁</th>
<th>Mp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>methyl</td>
<td>95–102</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>ethyl</td>
<td>130–135</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>cyclopentyl</td>
<td>98–100</td>
<td>49</td>
</tr>
</tbody>
</table>
4.3.2.4 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 4.4). Compound 13 was synthesized by following the reported process.\(^8\) Coupling of carbamate protected acid 8e with amine 13 under DCC/DMAP conditions provided dimer 5c in 21 % yield.

![Scheme 4.4: Synthesis of zafirlukast dimer analogs, 5a–c](image)

Structure of analog 5c was confirmed based on the IR, mass NMR (\(^1\)H and \(^{13}\)C) spectral data and described in previous chapter-3 as compound 18.
Synthesis of other derivatives 5a and 5b achieved under the same conditions with moderate yields (table 4.4). These derivatives were confirmed by spectral data (experimental section 4.5.8.1–4.5.8.3).

Table 4.4: Synthesis of zafirlukast dimer analogs 5a–c

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compd.</th>
<th>R₁</th>
<th>Mp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>methyl</td>
<td>135–138</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>ethyl</td>
<td>185–190</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>cyclopentyl</td>
<td>88-92</td>
<td>21</td>
</tr>
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</table>

4.4 CONCLUSION

Synthesized of new analogs of zafirlukast has been achieved utilizing well known chemical reaction. All the analogs were well characterized by using mass, NMR and IR spectral data.

In continuation chapter (Chapter-5), illustrates an alternate novel synthesis of tadalafil. Also described the complete impurity profile of tadalafil, including identification, synthesis, characterization and root cause of their formation in two commercial viable schemes.

4.5 EXPERIMENTAL SECTION

4.5.1 General procedure for chloroformate coupling

To a solution of amine 6 (1.0 mmol) and N-methylmorpholine (1.2 mmol) in toluene (2 times 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 times to the amine) was added and stirred for 60 min. Filtered the precipitated compound under vacuum, and washed with methanol (0.5 times to the amine). The obtained wet solid was dried at 50-55 °C for 2-3 h to afford the carbamate.

4.5.1.1 Methyl 3-methoxy-4-((5-(methoxycarbonyl amino)-1-methyl-1H-indol-3-yl) methyl) benzoate (7a)

Spectral data of 7a provided in chapter-3 experimental section 3.5.6.1 as compound 23

4.5.1.2 Methyl 4-((5-(ethoxycarbonylamino)-1-methyl-1H-indol-3-yl) methyl)-3-methoxybenzoate (7b)

**Mp:** 120–125 °C.

**IR (KBr, cm⁻¹):** 3389 (NH), 1719 (C=O, ester), 1704 (C=O, carbamate), 1292 (OCH₃).
$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ 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).

### 4.5.1.3 Methyl 4-((5-(isopropoxycarbonylamino)-1-methyl-1H-indol-3-yl)methyl)-3-methoxybenzoate (7c)

![Chemical Structure](image)

**Mp:** 122–126 °C.

**IR (KBr, cm$^{-1}$):** 3292 (NH), 1711 (C=O, ester), 1686 (C=O, carbamate), 1290 (OCH$_3$).

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ 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].
4.5.1.4 Methyl 4-((5-(isobutoxycarbonylamino)-1-methyl-1H-indol-3-yl) methyl)-3-methoxybenzoate (7d)

\[
\begin{align*}
\text{Mp:} & \quad 132–135 \degree C. \\
\text{IR (KBr, cm}^{-1}) & : \quad 3263 (\text{NH}), 1717 (\text{C}=\text{O, ester}), 1696 (\text{C}=\text{O, carbamate}), 1282 (\text{OCH}_3). \\
\text{H NMR (400 MHz, DMSO–}\text{d}_6) & : \quad \delta \text{H 9.30 (s, 1H), 7.61 (s, 1H), 7.48 (s, 1H), 7.44 (d, } J = 7.6 \text{ Hz, 1H), 7.28 (d, } J = 8.8 \text{ Hz, 1H), 7.19-7.11 (m, 2H), 7.05 (s, 1H), 3.96 (s, 2H), 3.91 (s, 3H), 3.83 (s, 2H), 3.82 (s, 3H), 3.69 (s, 3H), 1.95-1.85 (m, 1H), 0.91 (d, } J = 6.4 \text{ Hz, 6H).} \\
\text{MS (m/z):} & \quad 425 [M^+ + H].
\end{align*}
\]

4.5.1.5 Methyl 4-((5-(cyclopentyloxycarbonylamino)-1-methyl-1H-indol-3-yl) methyl)-3-methoxybenzoate (7e)

\[
\begin{align*}
\text{Spectral data of 7e given in chapter-2 experimental section 2.5.6.5 as compound 9}
\end{align*}
\]
4.5.2 General procedure for hydrolysis of ester with LiOH.H₂O

To a stirred solution of methyl ester, 7a–e (1.0 mmol) in methanol (6 times to the ester) was added a solution of lithium hydroxide monohydrate (1.5 mmol) in water (1.5 times 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.

4.5.2.1 4-((5-(Methoxycarbonyl amino)-1-methyl-1H-indol-3-yl)methyl)-3-methoxybenzoic acid (8a)

Spectral data of 8a given in chapter-3 experimental section 3.5.6.2 as compound 24
4.5.2.2 4-((5-(Ethoxycarbonyl amino)-1-methyl-1H-indol-3-yl)methyl)-3-methoxybenzoic acid (8b)

**M.p:** 185-191°C.

**IR (KBr, cm⁻¹):** 3435 (OH), 3286 (NH), 1688 (C=O, acid), 1298 (OCH₃).

**¹H NMR (400 MHz, DMSO-d₆):** 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].

4.5.2.3 4-((5-(Isopropoxycarbonylamino)-1-methyl-1H-indol-3-yl)methyl)-3-methoxybenzoic acid (8c)

**M.p:** 218-222 °C.

**IR (KBr, cm⁻¹):** 3276 (NH), 1686 (C=O, acid), 1299 (OCH₃).
$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ 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$^- - H$].

4.5.2.4 4-((5-(Isobutoxycarbonylamino)-1-methyl-1H-indol-3-yl)-methyl)-3-methoxybenzoic acid (8d)

Mp: 135-141 °C.

IR (KBr, cm$^{-1}$): 3421 (OH), 3294 (NH), 1689 (C=O, acid), 1307 (OCH$_3$).

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ 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$^- - H$].
4.5.2.5 4-((5-(Cyclopentyloxycarbonylamino)-1-methyl-1H-indol-3-yl)-methyl)-3-methoxybenzoic acid (8e)

Spectral data of 8e given in chapter-2 experimental section 2.5.6.6 as compound 10

4.5.3 General procedure 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 times 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 times to the acid). The filtrate was separated, washed with 50 % diluted aq. HCl (2 times to the acid) and followed by water (10 times 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 and dried under vacuum at 70-75 °C to furnish amide.
4.5.3.1 Methyl 3-(2-methoxy-4-(o-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-ylcarbamate (2a)

Spectral data of 2a given in chapter-3 experimental section 3.5.6.3 as compound 15

4.5.3.2 Methyl 3-(2-methoxy-4-(p-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-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-\(d_6\)): \(\delta\)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].

### 4.5.3.3 Methyl 3-(2-methoxy-4-(m-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2c)

**IR (KBr, cm⁻¹):** 3327 (NH), 1691 (C=O, carbamate), 1626 (C=O, amide), 1311 & 1157 (SO₂, asym. and sym.).

**¹H NMR (400 MHz, DMSO-d₆):** 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].

### 4.5.3.4 Methyl 3-(4-(benzylsulfonylcarbamoyl)-2-methoxybenzyl)-1-methyl-1H-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-\(\text{d}_6\)): \(\delta_H\) 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, 6H), 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].

4.5.3.5 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-\(\text{d}_6\)): \(\delta_H\) 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].
4.5.3.6 Ethyl 3-(2-methoxy-4-(o-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2f)

![Chemical Structure Image]

**IR (KBr, cm⁻¹):** 3294 (NH), 1709 (C=O, carbamate), 1646 (C=O, amide) 1350 & 1112 (SO₂, asym. and sym.).

**¹H NMR (400 MHz, DMSO-d₆):** δH 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].

4.5.3.7 Ethyl 3-(2-methoxy-4-(p-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2g)

![Chemical Structure Image]
IR (KBr, cm\(^{-1}\)): 3305 (NH), 1694 (C=O, carbamate), 1668 (C=O, amide), 1349 & 1164 (SO\(_2\), asym. and sym.).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta_H\) 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].

4.5.3.8 Ethyl 3-(2-methoxy-4-(m-tolysulfonylcarbamoyl)benzyl)-1-methyl-1H-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.).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta_H\) 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].
4.5.3.9  Ethyl 3-(4-(benzylsulfonylcarbamoyl)-2-methoxybenzyl)-1-methyl-1H-indol-5-yl-carbamate (2i)

**IR (KBr, cm⁻¹):** 3325 (NH), 1681 (C=O, carbamate), 1697 (C=O, amide), 1340 & 1152 (SO₂, asym. and sym.).

**¹H NMR (400 MHz, DMSO-d₆):** 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].

4.5.3.10  Ethyl 3-(2-methoxy-4-(phenylsulfonylcarbamoyl)benzyl)-1-methyl-1H-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.).

**\(^{1}\)H NMR (400 MHz, DMSO-\(d_6\))**: \(\delta_H\) 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].

4.5.3.11 **Isopropyl 3-(2-methoxy-4-(o-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-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.).

**\(^{1}\)H NMR (400 MHz, DMSO-\(d_6\))**: \(\delta_H\) 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].
4.5.3.12 Isopropyl 3-(2-methoxy-4-(p-tolylsulfonylcarbamoyl)-benzyl)-1-methyl-1H-indol-5-yl-carbamate (2l)

IR (KBr, cm⁻¹): 3322 (NH), 1691 (C=O, carbamate), 1677 (C=O, amide), 1342 & 1165 (SO₂, asym. and sym.).

¹H NMR (400 MHz, DMSO–d₆): δH 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].

4.5.3.13 Isopropyl 3-(2-methoxy-4-(m-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2m)
**IR (KBr, cm\(^{-1}\))**: 3357 (NH), 1690 (C=O, carbamate), 1341 & 1157 (SO\(_2\), asym. and sym.).

**\(^1\)H NMR (400 MHz, DMSO-\(d_6\))**: \(\delta_H\) 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).

4.5.3.14 *Isopropyl 3-(4-(benzylsulfonylcarbamoyl)-2-methoxy benzyl)-1-methyl-1H-indol-5-yl-carbamate (2n)*

![Chemical Structure](image)

**IR (KBr, cm\(^{-1}\))**: 3362 (NH), 1692 (C=O, carbamate), 1338 & 1154 (SO\(_2\), asym. and sym.).

**\(^1\)H NMR (400 MHz, DMSO-\(d_6\))**: \(\delta_H\) 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).
4.5.3.15 Isopropyl 3-(2-methoxy-4-(phenylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2o)

IR (KBr, cm$^{-1}$): 3371 (NH), 1692 (C=O, carbamate), 1344 & 1162 (SO$_2$, asym. and sym.).

$^1$H NMR (400 MHz, DMSO–d$_6$): $\delta_H$ 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].

4.5.3.16 Isobutyl 3-(2-methoxy-4-(o-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-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-\(d_6\)):** \(\delta_H\) 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].

**4.5.3.17 Isobutyl 3-(2-methoxy-4-(p-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2q)**

![Chemical Structure]

**IR (KBr, cm\(^{-1}\)):** 3318 (NH), 1682 (C=O, carbamate), 1342 & 1162 (SO\(_2\), asym. and sym.).

**\(^{1}\)H NMR (400 MHz, DMSO-\(d_6\)):** \(\delta_H\) 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].

4.5.3.18 Isobutyl 3-(2-methoxy-4-(m-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2r)

IR (KBr, cm⁻¹): 3332 (NH), 1693 (C=O, carbamate), 1340 & 1158 (SO₂, asym. and sym.).

¹H NMR (500 MHz, DMSO-d₆): δH 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].

4.5.3.19 Isobutyl 3-(4-(benzylsulfonylcarbamoyl)-2-methoxybenzyl)-1-methyl-1H-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$_6$): $\delta$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].

4.5.3.20 Isobutyl 3-(2-methoxy-4-(phenylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2t)

IR (KBr, cm$^{-1}$): 3367 (NH), 1693 (C=O, carbamate), 1341 & 1165 (SO$_2$, asym. and sym.).

$^1$H NMR (400 MHz, DMSO–d$_6$): $\delta$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].
4.5.3.21 Cyclopentyl 3-(2-methoxy-4-(o-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2u)

Spectral data of 2u given in chapter-2 experimental section 2.5.6.9 as compound 1

4.5.3.22 Cyclopentyl 3-(2-methoxy-4-(p-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2v)

Spectral data of 2v given in chapter-3 experimental section 3.5.5 as compound 14
4.5.3.23 Cyclopentyl 3-(2-methoxy-4-(m-tolylsulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl-carbamate (2w)

Spectral data of 2w given in chapter-3 experimental section 3.5.4 as compound 13

4.5.3.24 Cyclopentyl 3-(4-(benzylsulfonylcarbamoyl)-2-methoxybenzyl)-1-methyl-1H-indol-5-yl-carbamate (2x)

**IR (KBr, cm$^{-1}$):** 3327 (NH), 1689 (C=O, carbamate), 1626 (C=O, amide), 1340 & 1155 (SO$_2$, asym. and sym.).

**$^1$H NMR (400 MHz, DMSO–d$_6$):** $\delta$H 11.95 (s, 1H), 9.21 (s, 1H), 7.62 (s, 1H), 7.48 (s, 1H), 7.41 (d, $J = 7.2$ Hz, 1H), 7.39–7.26 (m, 6H), 7.12 (t, $J = 7.2$ Hz, 2H), 7.05 (s, 1H), 5.07–5.02 (m, 1H), 4.83 (s, 2H), 3.95 (s, 2H), 3.90 (s, 3H), 3.69 (s, 3H), 1.90–1.50 (m, 8H).

**MS (m/z):** 607 [M$^+$ + MeOH], 621.3 [M$^+$ + 2 Na].
4.5.3.25 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 (SO₂, asym. and sym.).

¹H NMR (400 MHz, DMSO-d₆): δH 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].

4.5.4 Methyl 4-((5-(cyclopentylxoycarbonylamino)-1H-indol-3-yl)methyl)-3-methoxybenzoate (10)
Same process followed as mentioned in the experimental section 4.5.1, but amine 9 was used instead of amine 6.

**Mp**: 88–92 °C.

**IR (KBr, cm⁻¹)**: 3339 (NH), 1702 (C=O, ester), 1629 (C=O, carbamate), 1292 (OCH₃).

**¹H NMR (400 MHz, CD₃OD)**: δH 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].

**4.5.5 4-((5-(Cyclopentyloxycarbonylamino)-1H-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 (OCH₃)
1H NMR (200 MHz, DMSO-d6): δH 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].

4.5.6 General procedure for zafirlukast analogs, 3a–e

Same process followed as mentioned in the experimental section 4.5.3, but acid 11 was used instead of acid 8a–e.

4.5.6.1 Cyclopentyl 3-(2-methoxy-4-(o-tolylsulfonylcarbamoyl)benzyl)-1H-indol-5-yl-carbamate (3a)

IR (KBr, cm⁻¹): 3328 (NH), 1690 (C=O, carbamate), 1626 (C=O, amide), 1313 & 1161 (SO₂, asym. and sym.).

1H NMR (400 MHz, DMSO-d6): δH 12.55 (s, 1H), 10.73 (s, 1H), 9.15 (s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.60–7.55 (m, 2H), 7.49 (s, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.40–7.35 (m, 2H), 7.21 (d, J = 8.8 Hz, 1H), 7.07 (s, 1H), 7.06 (d, J = 7.6 Hz, 2H), 5.07–5.02 (m, 1H), 3.94 (s, 2H), 3.91 (s, 3H), 2.59 (s, 3H), 1.91–1.50 (m, 8H).

13C NMR (100 MHz, CDCl₃): δC 165.0, 157.4, 157.0, 137.6, 136.9, 135.9, 133.7, 133.4, 132.3, 131.3, 130.0, 130.0, 129.4, 127.6, 126.2,
123.8, 119.7, 113.3, 111.3, 109.6, 77.5, 55.4, 49.1, 33.7, 32.7, 25.5, 25.2, 24.8, 23.6, 20.3.

MS (m/z): 560 [M⁻ - H].

4.5.6.2 Cyclopentyl 3-(2-methoxy-4-(p-tolylsulfonylcarbamoyl)benzyl)-1H-indol-5-yl-carbamate (3b)

IR (KBr, cm⁻¹): 3388 (NH), 1688 (C=O, carbamate), 1597 (C=O, amide), 1340 & 1165 (SO₂, asym. and sym.).

¹H NMR (400 MHz, DMSO-d₆): δH 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].
4.5.6.3 Cyclopentyl 3-(2-methoxy-4-\textit{m}-tolylsulfonylcarbamoyl)benzyl)-1\textit{H}-indol-5-yl-carbamate (3c)

IR (\textit{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--\textit{d}_6): $\delta$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].

4.5.6.4 Cyclopentyl 3-(4-(phenylsulfonylcarbamoyl)-2-methoxybenzyl)-1\textit{H}-indol-5-ylcarbamate (3d)

IR (\textit{KBr, cm}^{-1}): 3410 (NH), 1710 (C=O, carbamate), 1620 (C=O, amide), 1345 & 1130 (SO$_2$, asym. and sym.).
\textbf{\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}):} \ \delta_{H} 12.50 \text{ (brs, 1H)}, 11.10 \text{ (s, 1H)}, 9.31 \text{ (s, 1H)}, 7.95 \text{ (d, } J = 7.6 \text{ Hz, 2H}), 7.65 \text{ (t, } J = 7.6 \text{ Hz, 1H}), 7.60 \text{ (d, } J = 7.6 \text{ Hz, 2H}), 7.50 \text{ (s, 1H)}, 7.45 \text{ (s, 1H)}, 7.32 \text{ (dd, } J = 1.3, 7.6 \text{ Hz, 1H}), 7.24 \text{ (t, } J = 8.6 \text{ Hz, 1H}), 7.15-7.10 \text{ (m, 2H)}, 7.04 \text{ (d, } J = 8.0 \text{ Hz, 1H}), 7.00 \text{ (s, 1H)}, 5.08-5.02 \text{ (m, 1H)}, 3.93 \text{ (s, 2H)}, 3.92 \text{ (s, 2H)}, 3.90 \text{ (s, 3H)}, 1.30-1.10 \text{ (m, 8H)}.

\textbf{MS (m/z):} 548 [M\textsuperscript{+} + H].

\textbf{4.5.6.5 Cyclopentyl 3-(4-(benzylsulfonylcarbamoyl)-2-methoxy benzyl)-1H-indol-5-ylcarbamate (3e)}

\textbf{IR (KBr, cm\textsuperscript{-1}):} 3327 (NH), 1698 (C=O, carbamate), 1648 (C=O, amide), 1335 & 1151 (SO\textsubscript{2}, asym. and sym.).

\textbf{\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}):} \ \delta_{H} 11.95 \text{ (s, 1H)}, 10.74 \text{ (s, 1H)}, 9.17 \text{ (s, 1H)}, 7.59 \text{ (s, 1H)}, 7.48 \text{ (s, 1H)}, 7.43-7.30 \text{ (m, 6H)}, 7.22 \text{ (d, } J = 8.8 \text{ Hz, 1H)}, 7.11-7.06 \text{ (m, 3H)}, 5.07-5.03 \text{ (m, 1H)}, 4.83 \text{ (s, 2H)}, 3.96 \text{ (s, 2H)}, 3.91 \text{ (s, 3H)}, 1.92-1.53 \text{ (m, 8H)}.

\textbf{MS (m/z):} 584 [M\textsuperscript{+} + Na].
4.5.7 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 times 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 times to the acid). The organic layer was washed with 50 % aq. HCl (2 times to the acid), followed by water (10 times 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 was and washed with methanol (2 times to the acid) to afford compounds 4a–c.

4.5.7.1 Methyl 3-(4-(cyclohexyl(cyclohexylcarbamoyl)carbamoyl)-2-methoxy benzyl)-1-methyl-1H-indol-5-ylcarbamate (4a)

IR (KBr, cm⁻¹): 3322 (NH), 2931 (Ali, CH), 1701 (C=O, urea), 1628 (C=O, amide), 1237 (OCH₃).

¹H NMR (400 MHz, DMSO-d₆): δH 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].

### 4.5.7.2 Ethyl 3-(4-(cyclohexyl(cyclohexylcarbamoyl)carbamoyl)-2-
methoxy benzyl)-1-methyl-1H-indol-5-ylcarbamate (4b)

![Chemical Structure](image)

**IR (KBr, cm⁻¹):** 3322 (NH), 2931(Ali, CH), 1719 (C=O, urea), 1698 (C=O,
carbamate), 1627 (C=O, amide), 1234 (OCH₃).

**¹H NMR (400 MHz, DMSO-d₆):** δH 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].
4.5.7.3 Cyclopentyl 3-(4-(cyclohexyl(cyclohexylcarbamoyl)carbamoyl)-2-methoxybenzyl)-1-methyl-1H-indol-5-ylcarbamate (4c)

Spectral data of 4c given in chapter-3 experimental section 3.5.10 as compound 19

4.5.8 General procedure for zafirlukast dimer analogs, 5a–c

Same process was followed as mentioned in the experimental section 4.5.3, but amine 13 was used instead of sulfonamide.

4.5.8.1 Methyl 3-(2-methoxy-4-(3-(2-methoxy-4-((o-tolylsulfonyl)carbamoyl) benzyl)-1-methyl-1H-indol-5-ylcarbamoyl) benzyl)-1-methyl-1H-indol-5-ylcarbamate (5a)

IR (KBr, cm⁻¹): 3370 (NH), 2940 (Ali, CH), 1702 (C=O, carbamate), 1645 (C=O, amide), 1320 & 1163 (SO₂, asym. and sym.), 1242 (OCH₃).
\[ ^1H \text{NMR (400 MHz, DMSO-}\text{d}_6\text{): } \delta_H 12.62 \text{ (bs, 1H), 9.96 (s, 1H), 9.36 (s, 1H), 7.97 (d, } J = 8.0 \text{ Hz, 1H), 7.83 (s, 1H), 7.61 (s, 1H), 7.55-7.28 \text{ (m, 9H), 7.20-7.03 (m, 6H), 3.96 (s, 4H), 3.94 (s, 3H), 3.88 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.63 (s, 3H), 2.56 (s, 3H).} \]

MS (m/z): 814 [M+ + H].

4.5.8.2 Ethyl 3-(2-methoxy-4-(3-(2-methoxy-4-(o-tolylsulfonyl carbamoyl)benzyl)-1-methyl-1H-indol-5-ylcarbamoyl)benzyl)-1-methyl-1H-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\(_3\)).

\[ ^1H \text{NMR (400 MHz, DMSO-}\text{d}_6\text{): } \delta_H 12.55 \text{ (s, 1H), 9.95 (s, 1H), 9.29 (s, 1H), 8.02 (d, } J = 7.6 \text{ Hz, 1H), 7.84 (s, 1H), 7.63 (s, 1H), 7.60-7.33 \text{ (m, 8H), 7.28 (d, } J = 8.8 \text{ Hz, 1H), 7.20-7.07 (m, 4H), 7.05 (d, } J = 8.8 \text{ Hz, 2H), 4.09 (q, } J = 6.8 \text{ Hz, 2H), 3.96 (s, 4H), 3.94 (s, 3H), 3.91 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 2.58 (s, 3H), 1.22 (t, } J = 6.8 \text{ Hz, 3H).} \]

MS (m/z): 828 [M+ + H], 850 [M+ + Na].
4.5.8.3 Cyclopentyl 3-(2-methoxy-4-(3-(2-methoxy-4-(o-tolyl sulfonylcarbamoyl)benzyl)-1-methyl-1H-indol-5-yl carbamoyl)benzyl)-1-methyl-1H-indol-5-ylcarbamate (5c)

Spectral data of 5c given in chapter-3 experimental section 3.5.9.3 as compound 18

4.6 REFERENCES


4. (a) Brown, M. F.; Marfat, A.; Antognoli, G.; Chambers, R. J.; Cheng, J. B.; Damon, D. B.; Liston, T. E.; McGlynn, M. A.;


