2.1. INTRODUCTION

Multi-component Reactions (MCRs) are single vessel processes of convergent reactions where more than three starting components take part in the reaction and yielded into a product that essentially possess portions of all the components simultaneously\(^1\). These types of processes have got pronounced attentiveness and especially bring about the compound libraries suitable for the purpose of biological screening and such type of diversity oriented synthesis are of great importance in the field of drug discovery. In the area of MCRs, the Ugi four-component reaction (U-4CR)\(^2\) is amazing reaction, in which reaction between a carboxylic acid, a carbonyl compound, a primary amine, and an isocyanide produces α-aminoacyl carboxamides. This is a marvellous example of domino reaction with four points of diversity and is being extensively used to get complex molecular structures to boost drug discovery (Scheme in table 2.3).

2.2. BASIS OF WORK

Many synthetic heterocyclic molecules have prevalent attentiveness as herbicides, dyes, organic conductors and drugs. One of the sulphur containing heterocycle, e.g. benzothiophene, has gained considerable attention of medicinal chemists due to diversified array of biological activities of its derivatives. Benzothiophene show varied biological activities such as antimicrobial\(^3\) (methoxy oxazino quinolin-6-methylbenzo[b]thiophene-2-carboxamide), anti-inflammatory\(^4\) (3-isopropoxy-5-methoxybenzo[b]thiophene-2-carboxamide and 3-hydroxy-N-phenylbenzo[b]thiophene-2-carboxamide), antimalarial\(^5\) (3-bromo-N-(4-fluorobenzyl)benzo[b]thiophene-2-carboxamide),
Chapter 2
Synthesis of novel N, N-disubstituted benzo[b]thiophene-2-carboxamide library in aqueous media via Ugi four component reaction as antimicrobial agents

antidepressant$^6$ (oxazepan-3-ylcarbamoylphenylbenzo[b]thiophene-2-carboxamide), antitumor$^7$ (N-hydroxybenzo[b]thiophene-2-carboxamide), analgesic$^8$ (2-phenyl-2,3-dihydrobenzo[b]thiophen-3-yl)piperazine), and lipid lowering$^9$ (2-phenyl-3-N,N-disubstituted benzo[b]thiophene) and is the major pharmacophore in many of the drug candidate viz. raloxifen$^{10}$ which is a well-known drug for osteoporosis and Zileuton$^{11}$, a marketed drug with the trade name of Zyklofor for maintenance treatment of asthma (Figure 2.1).

Figure 2.1. pharmacological importance of benzothiophene and our designed molecular framework with the same core
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Moreover, the story of an ideal synthetic strategy comprises of one which is economic in reaction steps and waste, ecologically benign, safe, and simple and gives maximum yield. Ugi reaction is typically carried out in ethanol or dichloromethane\(^{12} \). It is environmentally as well as industrially unsafe to use volatile organic solvents. Thus for the reason of being vigilant towards nature one has to find ways to stop or at least avoid the use of such solvents and to infer harmless solvents such as water or ionic liquids,\(^{13} \) because the safe disposal of these solvents without impairing nature is a tedious job.

In light of these findings and facts, we have synthesised novel \( N,N \)-disubstituted benzo[\( b \)]thiophene-2-carboxamide combinatorial library, starting from benzo[\( b \)]thiophene-2-carboxylic acid using non-ionic surfactant, TritonX-100 \([C_{14}H_{22}O(C_2H_4O)_n] \) where \( n = 9-10 \), in aqueous media.

2.3 RESULT AND DISCUSSION

In continuation of our work on multicomponent reactions (MCRs) to synthesize various biologically active heterocyclic compounds,\(^{14} \) we have synthesized Novel \( N, N \)-disubstituted benzo[\( b \)]thiophene-2-carboxamide combinatorial library by reacting benzo[\( b \)]thiophene-2-carboxylic acid with different aldehydes, amines and isocyanides using TritonX-100 in water as solubilising agent.

The starting acid was prepared from 2-nitrobenzaldehyde and methyl thioglycolate via previously reported procedure by J. R. Beck\(^{15} \) followed by hydrolysis. Further this acid was used in typical U-4CR in combination with varying aldehydes, amines and isocyanides. The
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The reaction was first carried out in conventional Ugi solvent i.e. ethanol. The reaction took 24 h to complete the reaction with 47% yield (Table 4.1, entry 6). To observe the effect of solvent we examined other polar protic solvents such as methanol and water. In case of methanol yield was reduced with same reaction time (Table 2.1, entry 5) whereas in case of water yield as well as reaction time increased (Table 2.1, entry 7). Then we thought to try polar aprotic solvents viz. acetonitrile, tetrahydrofuran, dichloromethane and chloroform but no rewarding results were observed (Table 2.1, entry 1-4). We have also tried the reaction with non-polar solvents viz. toluene and xylene and found that reaction didn’t even take place (Table 2.1, entry 8-9). The solvent screening results are summarized in table 2.1.

Table 2.1. Screening of solvent for the synthesis of $N,N$-disubstituted benzo[b]thiophene-2-carboxamide derivatives

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Solvent$^a$</th>
<th>Time (h)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ACN</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>CHCl$_3$</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>MeOH</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>EtOH</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>H$_2$O</td>
<td>36</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>72</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>Xylene</td>
<td>72</td>
<td>NR</td>
</tr>
</tbody>
</table>

$^a$1-4= Polar aprotic Solvent, 5-7=Polar protic solvent, 8-9=Nonpolar solvent, NR=No reaction; $^b$Isolated Yield.
Chapter 2
Synthesis of novel N, N-disubstituted benzo[b/thiophene-2-carboxamide library in aqueous media via Ugi four component reaction as antimicrobial agents

By screening of various solvent systems we found that water is the best with 55% yield. Since it is environmentally benign, safe and cheap solvent, we next moved to optimise the conditions to get best results with the same. As the organic reactants fail to completely dissolve in water, we used surfactants to solubilise reactants and provide the uniform environment to the reaction mixture.

Table 2.2. Effect of surfactant on the synthesis of N, N-disubstituted benzo[b]thiophene-2-carboxamide derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Mol%</th>
<th>Time (h.)</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Triton X-100</td>
<td>20(^a)</td>
<td>24</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>Triton X-100</td>
<td>15</td>
<td>24</td>
<td>77</td>
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<td>3</td>
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<td>10</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Triton X-100</td>
<td>5</td>
<td>24</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Triton CF-10</td>
<td>20</td>
<td>36</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>Tween-20</td>
<td>20</td>
<td>36</td>
<td>61</td>
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<td>7</td>
<td>Tween-80</td>
<td>20</td>
<td>48</td>
<td>58</td>
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<tr>
<td>8</td>
<td>SDS</td>
<td>20</td>
<td>48</td>
<td>60</td>
</tr>
</tbody>
</table>

\(^a\)Best results with 20 mol% of Triton X-100, \(^b\)Isolated Yield.

Firstly we used anionic surfactant 20 mol% of Sodium Dodecyle Sulfate (SDS) and found very nominal change in yield and reaction time also increased. Then we moved to non-ionic surfactants and get the best results with 20 mol% Triton X-100 in yield as well as time. We also observed that amount of surfactant also effects the yield of product (Table 4.2).
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Synthesis of novel $N, N$-disubstituted benzo[b/thiophene-2-carboxamide library in aqueous media via Ugi four component reaction as antimicrobial agents

After optimized reaction conditions in hand, we next moved to observe the catholicity of these conditions. For this we reacted a series of aldehydes, amines and isocyanides with benzo[b/thiophene-2-carboxylic acid by applying above reaction conditions to synthesized $N, N$-disubstituted benzo[b/thiophene-2-carboxamide library. The results are shown in table 4.3. The reaction took 24 h to complete and good to excellent yields were obtained. These results clearly throw a good light on the utility of the procedure.

Table 2.3. Synthesis of $N, N$-disubstituted benzo[b/thiophene-2-carboxamide derivatives$^{a, b}$ 5a-5n

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Entry</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$R^3$</th>
<th>Yield$^c$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>4-ClC$_6$H$_4$</td>
<td>Bn</td>
<td>tert-butyl</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>2,4-Cl$_2$C$_6$H$_3$</td>
<td>Bn</td>
<td>tert-butyl</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>3,4-(MeO)$_2$C$_6$H$_3$</td>
<td>Bn</td>
<td>tert-butyl</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>4-FC$_6$H$_4$</td>
<td>Bn</td>
<td>tert-butyl</td>
<td>89</td>
</tr>
</tbody>
</table>
Chapter 2
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<tbody>
<tr>
<td>5</td>
<td>5e</td>
<td>2-NO$_2$C$_6$H$_4$</td>
<td>Bn</td>
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<tr>
<td>6</td>
<td>5f</td>
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<tr>
<td>7</td>
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<td>Bn</td>
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</tr>
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<td>8</td>
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<tr>
<td>9</td>
<td>5i</td>
<td>4-ClC$_6$H$_4$</td>
<td>3-MeOBn</td>
<td>tert-butyl</td>
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<tr>
<td>10</td>
<td>5j</td>
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<td>3-MeOBn</td>
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<td>11</td>
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<td>12</td>
<td>5l</td>
<td>4-ClC$_6$H$_4$</td>
<td>Bn</td>
<td>Cyclohexyl</td>
</tr>
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<tr>
<td>14</td>
<td>5n</td>
<td>4-BnOC$_6$H$_4$</td>
<td>Bn</td>
<td>Cyclohexyl</td>
</tr>
</tbody>
</table>

agent and conditions: Aldehyde (1 mmol), amine (1 mmol), acid (1 mmol), isocyanide (1 mmol), triton X-100 (20 mol%), water (10 mL), stirring at room temp, 24h; Reactions took 24 h to complete, Isolated Yield.
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Figure 2.2. Proposed reaction mechanism for the synthesis of N,N-disubstituted benzo[b/thiophene-2-carboxamide.

The reaction possibly proceeds with the formation of the shiff’s base from aldehyde and amine inside the hydrophobic core of micelle and gets protonated with carboxylic acid to form iminium ion. The iminium ion reacts with isocyanide and then attacked by carboxylate ion to form an intermediate. This intermediate finally undergoes mumm rearrangement to afford the final product (figure 4.2).

2.4. BIOLOGICAL ACTIVITY

2.4.1. MATERIAL AND METHOD

Biological significance of all the synthesized compounds have been studied for their in-vitro antifungal activity against different fungal strain. The strains chosen for the study are: Candida albicans, Cryotococcus neoformans, Sporothrix schenckii, Trichophyton mentagrophytes, Aspergillus fumigates and Candida parapsilosis
(ATCC-22019). The antifungal activity was compared with those of standard drugs Fluconazole and Amphotericin B. The in-vitro antibacterial activity was studied against five strains of pathogenic bacteria namely, *Streptococcus faecalis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* and the activity was compared with those of standard antibacterial drugs Gentamycin and Ampicillin. The inhibitory activities are expressed as minimum inhibitory concentration (MIC, µg/ml).

### 2.4.2. EVALUATION OF ANTI-FUNGAL AND ANTI-BACTERIAL ACTIVITY

**Table 2.4.** In vitro antibacterial activity of compounds (5a-5n).

<table>
<thead>
<tr>
<th>Comp</th>
<th>Minimum inhibitory conc. (MIC) µg /ml</th>
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<tbody>
<tr>
<td>5a</td>
<td>&gt;50</td>
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<tr>
<td>5b</td>
<td>&gt;50</td>
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</table>
Chapter 2
Synthesis of novel \( N, N \)-disubstituted benzo/\( b \)/thiophene-2-carboxamide library in aqueous media via Ugi four component reaction as antimicrobial agents

<table>
<thead>
<tr>
<th></th>
<th>5c</th>
<th>5d</th>
<th>5e</th>
<th>5f</th>
<th>5g</th>
<th>5h</th>
<th>5i</th>
<th>5j</th>
<th>5k</th>
<th>5l</th>
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<tr>
<td>Vacomycin</td>
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</table>

The results in Table 4.4 demonstrate that almost all the compounds synthesized exhibited potent antifungal activity. Compounds are showing significant inhibition against the *Trichophyton mentagrophytes* test (MIC in the range of 6.25-12.5 µg/ml).
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2.5. CONCLUSION

In conclusion, we have synthesized and reported herein an efficient, eco-friendly and novel $N,N$-disubstituted benzo[b]thiophene-2-carboxamide combinatorial library using 20 mol% TritonX-100 surfactant to make a uniform reaction atmosphere in water. This method avoids the use of volatile organic solvents hence profitable, gives good yield and has “green” protocol. The synthesized compounds are having active benzo[b]thiophene-2-carboxamide pharmacophore hence may serve as imminent drug candidate or their intermediate.

2.6. EXPERIMENTAL DETAILS WITH SPECTRAL ANALYTICAL DATA

1. All reactions were monitored by TLC over silica gel plate. The spots on TLC plates were visualized under UV lamp or by iodine vapors.
2. For column chromatography, Silica (60-120 or 100-200 mesh) was used.
3. Room temperature mentioned ranges between 15-35°C (throughout the year).
4. $^1$H-NMR, and $^{13}$C-NMR spectra were recorded on Bruker Avance DPX-300 MHz or Avance DPX-200 MHz FT Bruker spectrometers, using deuteriated solvents and TMS as an internal standard. Data expresses the chemical shift values in δ ppm from downfield to upfield in both $^1$H-NMR and $^{13}$C-NMR spectra. For all compounds, $^1$H-NMR data is reported in the following order: Chemical shift (multiplicity, $J$ value, number of protons).
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5. ES mass spectra were recorded in Merck M-8000 LCMS system or Micromass Quadro LCMS system and HR/EI mass were done on JEOL-600H at 70eV.

6. Elemental analyses were carried out on Carlo-Erba-1108 instrument or Elementar’s Vario EL III microanalysers.

2.6.1. GENERAL PROCEDURE FOR THE SYNTHESIS OF COMPOUNDS 5a-5n

In a typical experimental procedure, the aldehyde (1 mmol), benzylamine (1 mmol), isocyanide (1 mmol) and benzo[b]thiophene-2-carboxylic acid (1 mmol) with tritonX-100 (20 mol\%) were taken in water (10 mL) into a round-bottom flask and was stirred at room temperature for 24h. On completion of the reaction (as monitored by TLC) precipitated product was filtered and washed twice with fresh water. The crude product was recrystallized using ethanol as solvent.

\( N\)-benzyl-\(N\)-(2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)benzo\(b\)/thiophene-2-carboxamide (5a):

Off white solid; yield: 81%; M p. 155-157 °C; ESI MS \((m/z) = 490 \text{(M+H)}\); IR (KBr): \( \nu = 3424, 1650, 1403, 1216, 767 \); \( ^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta = 7.84 \text{ (d, } J= 5.9, 1\text{H}), 7.72 \text{ (d, } J= 6.2, 1\text{H}), 7.58 \text{ (s, } 1\text{H}), 7.38-7.19 \text{ (m, } 11\text{H}), 5.78 \text{ (s, } 1\text{H}), 5.57 \text{ (s, } 1\text{H}), 5.08 \text{ (d, } J=11.1, 1\text{H}), 4.77 \text{ (br, } 1\text{H}), 1.33 \text{ (s, } 9\text{H}); \( ^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta = 167.4, 166.5, 141.0, 138.4, 136.4, 136.5, 135.3, 133.8, 133.1, 132.5, 130.1, 128.6, 128.4, 127.4, 127.1, 126.4, 126.0,
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125.3, 124.9, 124.5, 122.3, 70.1, 64.5, 52.2, 28.5; Elemental Analysis calculated for C\textsubscript{28}H\textsubscript{27}ClN\textsubscript{2}O\textsubscript{2}S: C, 68.49; H, 5.54; N, 5.70; found: C, 68.45; H, 5.53; N, 5.74.

\textit{N-benzyl-N-(2-(tert-butylamino)-1-(2,4-dichlorophenyl)-2-oxoethyl)benzo/b thiophene-2-carboxamide (5b):}

Off white solid; yield: 84%; M p. 160-161 °C; ESI MS (m/z) = 524 (M+H); IR (KBr): ν= 3424, 3019, 2400, 1619, 1384, 1215, 1049, 757, 669; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ = 7.87 (d, J= 6.7 Hz, 1H), 7.76 (d, J= 6.5 Hz, 1H), 7.61-7.56 (m, 2H), 7.39 (m, 2H), 7.28-7.17(m, 7H), 6.00 (s, 1H), 5.69 (s, 1H), 5.03 (br, 1H), 4.78 (d, J= 16.2 Hz, 1H), 1.34 (s, 9H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ= 167.4, 166.5, 141.2, 138.5, 136.4, 137.0, 135.5, 133.4, 133.7, 132.6, 130.0, 128.4, 128.1, 127.4, 127.1, 126.7, 126.2, 125.4, 124.8, 124.2, 123.5, 68.7, 64.7, 52.1, 28.5; Elemental Analysis calculated for C\textsubscript{28}H\textsubscript{26}Cl\textsubscript{2}N\textsubscript{2}O\textsubscript{2}S: C, 64.00; H, 4.99; N, 5.33; found: C, 64.05; H, 4.95; N, 5.35

\textit{N-benzyl-N-(2-(tert-butylamino)-1-(3,4-dimethoxyphenyl)-2-oxoethyl)benzo/b thiophene-2-carboxamide (5c):}

Off white solid; yield: 79%; M p. 132-135 °C; ESI MS (m/z) = 516 (M+H); IR (KBr): ν= 3293, 2927, 1653, 1608, 1517, 1456, 1219, 1027,
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757; \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.85\) (d, \(J = 7.9, 1\)H), 7.72 (d, \(J = 7.1, 1\)H), 7.55 (s, 1H), 7.42-7.37 (m, 2H), 7.35-7.20 (m, 5H), 6.95 (d, \(J = 8.3, 2\)H), 6.86-6.75 (m, 1H), 5.59 (s, 1H), 5.08 (d, \(J = 17.3, 1\)H), 4.75 (d, \(J = 17.3, 1\)H), 3.86 (s, 3H), 3.75 (s, 3H), 1.35 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 167.4, 166.6, 162.3, 146.2, 141.3, 138.5, 136.4, 131.0, 128.4, 128.1, 127.4, 127.1, 126.7, 126.2, 125.4, 124.8, 124.2, 123.5, 116.4, 114.3, 70.7, 63.3, 58.1, 52.3, 28.5; Elemental Analysis calculated for C\(_{30}\)H\(_{32}\)N\(_2\)O\(_4\)S: C, 69.74; H, 6.24; N, 5.42; found: C, 69.70; H, 6.29; N, 5.46;

\(N\)-benzyl-\(N\)-(2-(tert-butylamino)-1-(4-fluorophenyl)-2-oxoethyl)benzo/b/thiophene-2-carboxamide (5d):

Off white solid; yield: 89%; M p. 138-140 \(^0\)C; ESI MS (m/z) = 474 (M+H); IR (KBr): \(\nu = 3684, 3448, 3020, 2401, 1599, 1520, 1434, 1344, 1216, 1035, 928, 760, 671\); \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 7.87\) (d, \(J = 5.6, 1\)H), 7.76 (d, \(J = 6.3, 1\)H), 7.58 (s, 1H), 7.38-7.18 (m, 11H), 5.77 (s, 1H), 5.58 (s, 1H), 5.11 (d, \(J = 11.1, 1\)H), 4.77 (br, 1H), 1.35 (s, 9H), \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 167.4, 166.5, 162.0, 141.1, 138.4, 136.5, 136.3, 135.3, 133.7, 133.0, 132.5, 130.1, 128.4, 127.0, 126.4, 125.9, 125.3, 124.8, 124.5, 122.3, 118.9, 70.4, 64.3, 52.0, 28.5; Elemental Analysis
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calculated for \(C_{28}H_{27}FN_2O_2S\): C, 70.86; H, 5.73; N, 5.90; found: C, 70.82; H, 5.70; N, 5.94.

\(N\)-benzyl-\(N\)-(2-(tert-butylamino)-1-(2-nitrophenyl)-2-oxoethyl)benzo/[\(b\)]thiophene-2-carboxamide (5e):

Off white solid; yield: 80%; M p. 145-147 °C; ESI MS (\(m/z\)) = 501 (M+H); IR (KBr): \(\nu=3422, 3019, 2401, 1682, 1615, 1525, 1415, 1216, 762, 670\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) = 8.06-7.54 (m, 7H), 7.47-7.43 (m, 3H), 7.01-6.94 (m, 5H), 6.38 (s, 1H), 5.09 (d, \(J=15.3\), 1H), 4.54 (br, 1H), 1.22 (s, 9H); \(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta=167.5, 166.5, 148.3, 140.7, 138.6, 136.7, 136.5, 136.4, 135.2, 130.0, 129.4, 128.6, 128.4, 127.5, 126.3, 125.0, 124.9, 124.8, 123.2, 122.3, 70.5, 64.5, 52.0, 28.5;
Analysis calculated for \(C_{28}H_{27}N_3O_4S\): C, 67.05; H, 5.43; N, 8.38; found: C, 67.09; H, 5.40; N, 8.40

\(N\)-benzyl-\(N\)-(2-(tert-butylamino)-1-(4-nitrophenyl)-2-oxoethyl)benzo/[\(b\)]thiophene-2-carboxamide (5f):

Off white solid; yield: 82%; M p. 130-131 °C; ESI MS (\(m/z\)) = 501 (M+H); IR (KBr): \(\nu=3684, 3620, 3426, 3019, 2976, 2400, 1603, 1522, 1476, 1350, 1216, 1046, 849, 767, 669\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta=8.08-8.03\) (m, 3H), 7.88-7.85 (m, 1H), 7.67-7.63 (m, 1H), 7.51-
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7.43 (m, 3H), 7.25-7.16 (m, 2H), 7.14-6.97 (m, 4H), 6.11 (s, 1H), 5.14 (d, J=17.2, 1H), 4.74 (d, J= 17.2, 1H), 1.23 (s, 9H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta=$ 167.3, 166.5, 147.8, 140.7, 138.6, 136.7, 136.6, 136.3, 135.3, 129.4, 128.6, 128.4, 127.5, 127.0, 126.1, 125.0, 124.8, 123.2, 122.3, 71.1, 64.7, 52.0, 28.5;
Elemental Analysis calculated for C$_{28}$H$_{27}$N$_3$O$_4$S: C, 67.05; H, 5.43; N, 8.38; found: C, 67.08; H, 5.41; N, 8.35

$N$-benzyl-$N$-(2-(tert-butylamino)-1-(3-methoxyphenyl)-2-oxoethyl)benzo[b]thiophene-2-carboxamide (5g):

Off white solid; yield: 77%; M p. 109-111 $^\circ$C; ESI MS (m/z) = 486 (M+H); IR (KBr):
$\nu$ = 3419, 3013, 1678, 1609, 1518, 1455, 1217, 1046, 758, 668; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta = 8.01-7.89$ (m, 3H), 7.63 (br, s, 1H), 7.43 (m, 2H), 7.25-7.02 (m, 7H), 6.85-6.77 (m, 2H), 5.99 (s, 1H), 4.98 (br, 2H), 3.64 (s, 3H), 1.23 (s, 9H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta = 167.3$, 166.6, 162.3, 141.3, 138.5, 136.4, 131.0, 128.4, 128.1, 127.4, 127.1, 126.7, 126.2, 125.4, 124.8, 124.2, 123.5, 116.4, 14.3, 70.7, 63.3, 58.4, 52.3, 28.5; Analysis calculated for C$_{29}$H$_{30}$N$_2$O$_3$S: C, 71.58; H, 6.21; N, 5.76 found: C, 71.60; H, 6.26; N, 5.77.
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\( N \)-benzyl-\( N \)-(1-(4-(benzyloxy)phenyl)-2-(tert-butylamino)-2-oxoethyl)benzo[\( b \)]thiophene-2-carboxamide (5h):

\[
\text{Off white solid; yield: 83\%; M p. 146-148^\circ C; ESI MS (m/z) = 562 (M+H); IR (KBr): } \nu = 3422, 3018, 2399, 1678, 1610, 1510, 1454, 1384, 1216, 1027, 928, 769, 669, 497; {^1}H NMR (400 MHz, DMSO-\( d_6 \)) \delta = 8.01(s, 1H), 7.87-7.81 (m, 1H), 7.62(s, 1H), 7.43-7.31 (m, 8H), 7.19 (d, \( J = \) 7.8, 2H), 7.13-7.04 (m, 3H), 6.99 (d, \( J = \) 7.0, 2H), 6.89 (d, \( J = \) 8.4, 2H), 5.95 (br, 1H), 5.18 (d, \( J = \)11.1, 1H), 5.03 (s, 2H), 1.23 (s, 9H); {^{13}}C NMR (101 MHz, DMSO-\( d_6 \)) \delta = 167.9, 166.7, 160.8, 146.1, 141.9, 138.5, 136.5, 136.4, 128.9, 128.4, 128.6, 128.3, 127.4, 127.1, 126.6, 126.2, 125.4, 124.8, 124.2, 123.5, 123.1, 122.9, 122.7, 115.7, 71.2, 70.7, 63.3, 52.3, 28.5;
\]
Elemental Analysis calculated for \( \text{C}_{35}\text{H}_{34}\text{N}_{2}\text{O}_{3}\text{S} \): C, 74.70; H, 6.09; N, 4.98; found: C, 74.74; H, 6.07; N, 4.99

\( N \)-(2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-\( N \)-(3-methoxybenzyl) benzo[\( b \)]thiophene-2-carboxamide (5i):

\[
\text{Off white solid; yield: 79\%; M p. 156-158^\circ C; ESI MS (m/z) = 520 (M+H); IR (KBr): } \nu = 3682, 3426, 3019, 2975, 2399, 1677, 1599, 1517, 1430, 1215, 1046, 928, 757, 669, 626, 497; ESI MS (m/z) = 522 (M+H), {^1}H NMR (400 MHz, DMSO-\( d_6 \)) \delta
\]
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\begin{align*}
\text{ Off white solid; yield: 80%; M p. 105-106}^\circ C; \text{ ESI MS (m/z) = 554 (M+H); IR (KBr): v= 3423, 3019, 2400, 1684, 1603, 1519, 1458, 1384, 1215, 1051, 929,756, 669, 497; } \text{\( ^1 \)H NMR (400 MHz, DMSO-\( d_6 \))} \\
\delta =8.06-7.89 \text{ (m, 3H), 7.52-7.35 \text{ (m, 5H), 7.14 \text{ (s, 1H), 6.98 \text{ (m, 1H), 6.63-6.51 \text{ (m, 3H), 5.87 \text{ (s, 1H), 5.09 \text{ (d, J= 16.1 Hz, 1H), 4.19 \text{ (br, 1H), 3.65 \text{ (s, 3H),1.32 \text{ (s, 9H); \( ^13 \)C NMR (101 MHz, DMSO-\( d_6 \))} \delta = 167.3, 166.5, 162.0, 141.1, 138.5, 136.3, 137.0, 135.5, 133.2, 133.7, 132.6, 130.0, 128.3, 128.1, 127.4, 127.1, 126.7, 126.2, 125.4, 124.8, 124.1, 123.5, 70.1, 64.7, 58.3, 52.1, 28.5; }} \text{ Elemental Analysis calculated for C}_{29}\text{H}_{28}\text{Cl}_{2}\text{N}_{2}\text{O}_{3}\text{S: C, 62.70; H, 5.08; N, 5.04; found: C, 62.68; H, 5.10; N, 5.09} \end{align*}
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\[ \textit{N-(1-(4-(benzyloxy)phenyl)-2-(tert-butylamino)-2-oxoethyl-} \textit{N-(3-methoxybenzyl)benzo(b/thiophene-2-carboxamide (5k):} \]

![Chemical Structure of 5k]

Off white solid; yield: 81%; M p. 122-123 °C; ESI MS (\( m/z \)) = 592 (M+H); IR (KBr): \( \nu = 3423, 3018, 2399, 1603, 1511, 1421, 1384, 1215, 1046, 928, 757, 669, 497 \); \(^1\)H NMR (400 MHz, pyridine-\( d_5 \)) \( \delta = 7.94 \) (br, s, 1H), 7.81-7.74 (m, 1H), 7.56-7.39 (m, 11H), 7.21 (t, \( J = 7.9 \) Hz, 1H), 7.06-7.00 (m, 4H), 6.83 (dd, \( J = 1.9 \) Hz, 7.8 Hz, 1H), 6.36 (br, 1H), 5.61 (d, \( J = 17 \) Hz, 1H), 5.11 (s, 2H), 3.67 (s, 3H),1.55 (s, 9H); \(^{13}\)C NMR (101 MHz, pyridine-\( d_5 \)) \( \delta = 167.9, 166.7, 162.3, 160.8, 146.4, 141.4, 138.3, 136.5, 136.7, 128.7, 128.5, 128.2, 128.1, 127.4, 127.3, 126.9, 126.5, 125.7, 124.8, 124.5, 123.5, 123.2, 122.8, 122.7, 115.2, 71.1, 70.8, 63.3, 58.2, 52.2, 28.5; Elemental Analysis calculated for \( C_{36}H_{36}N_2O_4S: \) C, 72.95; H, 6.12; N, 4.73; found: C, 73.00; H, 6.17; N, 4.69

\[ \textit{N-benzyl-N-(1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl)benzo(b/thiophene-2-carboxamide (5l):} \]

Off white solid; yield: 85%; M p. 112-113 °C; ESI MS (\( m/z \)) = 516 (M+H); IR (KBr): \( \nu = 3684, 3616, 3436, 3019, 2976, 2400, 1602, 1573, 1524, 1476, 1216, 1046, 928, 770, 669, 627; 1650, 1403, 1216, 767; \(^1\)H NMR (300 MHz, CDCl\( _3 \)) \( \delta = 7.86 \) (d, \( J = 5.8 \) Hz, 1H), 7.73 (d, \( J = 6.2 \) Hz, 1H),
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7.58 (s, 1H), 7.38-7.26 (m, 7H), 7.28-7.19 (m, 4H), 5.64 (s, 1H), 5.54 (s, 1H), 5.07 (br, 1H), 4.78 (d, J = 15.6, 1H), 2.84-2.71 (m, 1H), 1.72-1.61 (m, 2H), 1.67-1.63 (m, 3H), 1.55-1.25 (m, 5H); 13C NMR (75 MHz, CDCl3) δ = 167.3, 166.5, 141.1, 138.4, 136.6, 136.3, 135.3, 133.0, 132.5, 130.2, 128.6, 128.2, 127.4, 127.1, 126.5, 126.0, 125.3, 125.1, 124.5, 122.2, 69.8, 53.9, 52.2, 35.2, 27.1, 25.7; Elemental Analysis calculated for C30H29ClN2O2S: C, 69.68; H, 5.65; N, 5.42; found: C, 69.67; H, 5.66; N, 5.46.

N-benzyl-N-(2-(cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl)benzo[b]/thiophene-2-carboxamide (5m):

Off white solid; yield: 86%; M p. 125-126 °C; ESI MS (m/z) = 500 (M+H); IR (KBr): ν = 3684, 3621, 3435, 3019, 2400, 1572, 1523, 1476, 1423, 1215, 1047, 928, 877, 849, 770, 669, 626, 496; 1H NMR (300 MHz, CDCl3) δ = 7.87 (d, J = 5.6, 1H), 7.76 (d, J = 6.3, 1H), 7.58 (s, 1H), 7.38-7.18 (m, 11H), 5.77 (s, 1H), 5.58 (s, 1H), 5.11 (br, 1H), 4.77 (d, J = 16.7, 1H), 2.79-2.67 (m, 1H), 1.71-1.62 (m, 2H), 1.67-1.62 (m, 3H), 1.53-1.24 (m, 5H); 13C NMR (75 MHz, CDCl3) δ = 167.4, 166.3, 141.1, 138.3, 136.3, 136.3, 135.3, 133.8, 133.0, 132.5, 130.1, 128.6, 128.1, 127.4, 127.0, 126.5, 126.1, 125.3, 125.1, 124.5, 122.1, 70.2, 54.0, 52.3, 35.3, 27.4,
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25.6; Elemental Analysis calculated for C\textsubscript{30}H\textsubscript{29}FN\textsubscript{2}O\textsubscript{2}S: C, 71.97; H, 5.84; N, 5.60; found: C, 72.00; H, 5.88; N, 5.63.

\textit{N}-benzyl-N-(1-(4-(benzyloxy)phenyl)-2-(cyclohexylamino)-2-oxoethyl)benzo[b/thiophene-2-carboxamide (5n):}

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

Off white solid; yield: 80%; M p. 129-131 °C; ESI MS (m/z) = 588 (M+H); IR (KBr): ν = 3426, 3018, 1629, 1569, 1480, 1432, 1215, 865, 758, 669; \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}\textsubscript{6}) δ = 8.04(s, 1H), 7.88-781 (m, 1H), 7.63 (s, 1H), 7.41-7.31 (m, 8H), 7.19 (d, J = 7.7, 2H), 7.15-7.09 (m, 3H), 6.94 (d, J = 7.1, 2H), 6.87 (d, J = 8.3, 2H), 5.90 (br, 1H), 5.17 (d, J =11.3, 1H), 5.12 (s, 2H), 2.77-2.65 (m, 1H), 1.70-161 (m, 2H), 1.66-1.61 (m, 3H), 1.52-1.22 (m, 5H); \textsuperscript{13}C NMR (101 MHz, DMSO-\textit{d}\textsubscript{6}) δ = 167.9, 166.7, 160.8, 146.1, 141.9, 138.5, 136.5, 136.4, 128.9, 128.4, 128.6, 128.3, 127.4, 127.1, 126.6, 126.2, 125.4, 124.8, 124.2, 123.5, 123.1, 122.9, 122.7, 115.7, 71.2, 70.2, 54.2, 52.3, 35.2, 27.4, 25.5; Elemental Analysis calculated for C\textsubscript{37}H\textsubscript{36}N\textsubscript{2}O\textsubscript{3}S: C, 75.48; H, 6.16; N, 4.76; found: C, 75.53; H, 6.20; N, 4.75.
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2.7. REFERENCES


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$^1$H NMR of compound 5e

$^1$H NMR of compound 5f
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\[ ^1H \text{ NMR of compound 5i} \]

\[ ^1H \text{ NMR of compound 5k} \]