Synthesis of some new condensed heterocyclic 6-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives of 2-naphthoxyacetic acid as potent anti-inflammatory agents with reduced ulcerogenicity

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A series of triazolo-thiadiazole derivatives have been synthesized from 2-naphthoxyacetic acid and evaluated for their anti-inflammatory and analgesic activity. Compounds which show good anti-inflammatory activity in comparison to standard drug naproxen have been further evaluated for their ulcerogenic and lipid peroxidation activity. The compounds 6-(2-chlorophenyl)-3-[(naphthalen-2-yloxy)methyl]-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole \(3b\) and 6 - (2,4-dichlorophenyl)-3-[(naphthalene -2-yloxy)methyl]-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole \(3c\) show maximum anti-inflammatory activity with reduced ulcerogenic potential and have also been evaluated for their hepatotoxicity and histopathological characteristics.

**Keywords:** Triazolo-thiadiazole, anti-inflammatory, ulcerogenicity, lipid peroxidation, hepatotoxic, histopathological studies

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs in all therapeutic agents. These drugs are often taken without prescription for minor aches, inflammation and pains. Inflammation is a normal and essential response to any infection and tissue injury. The most widely used nonsteroidal anti-inflammatory drugs (like aspirin, naproxen, ibuprofen and diclofenac sodium) inhibit the cyclooxygenase (COX) enzyme and control the release of inflammatory mediators responsible for inflammation. Generally, all currently available NSAIDs therapy effectively reduces the symptoms of many painful arthritic syndromes by inhibiting the cyclooxygenase (COXs) enzymes, but invites adverse gastrointestinal (GI) complications ranging from stomach irritation to life threatening GI ulceration, bleeding, and perforation to more serious small-bowel ulceration\(^1\). In order to reduce GI toxicity various COX-2 selective inhibitors \(viz.\) celecoxib, rofecoxib have been developed which showed marked anti-inflammatory activity but induce less GI side effect in comparison to non selective COX inhibitors\(^2,3\). But long term uses of these drugs cause cardiovascular side effects\(^4\). Therefore, development of NSAIDs with improved safety profile is still a necessity.

Studies have suggested that ulcerogenicity of NSAIDs can be reduced by derivatization of the carboxylic group. Different synthetic approaches and chemical modifications of NSAIDs have been studied to improve their safety profile\(^5,8\). Literature survey have shown that heterocyclic compounds bearing symmetrical 1,2,4-triazolo or 1,3,4-thiadiazole moieties possess broad spectrum of pharmacological properties including potential anti-inflammatory and analgesic activities\(^9,10\). Moreover, studies have revealed that compounds bearing triazolo-thiadiazole moieties were found to have diverse pharmacological properties\(^11,12\) along with anti-inflammatory activity with reduced GI toxicity\(^13,14\).

Therefore, in continuation of our earlier research work, it was thought worthwhile to synthesize some novel condensed heterocyclic compounds in which the COOH group of 2 naphthoxyacetic acid has been replaced with 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole moiety\(^15,16\). Thus we are reporting here the synthesis and biological evaluation of 6-(4-substitutedphenyl)-3-[(naphthalen-2-yloxy) methyl]-[1,2,4] triazolo [3,4 b] [1,3,4] thia diazoles, \(3a-j\) and 4-(submittedphenyl)-3-[(naphthalen-2-yloxy) methyl]-[1,2,4] triazolo [3,4-b] [1,3,4]thiadiazol-6-amine, \(4a-d\) analogs as possible anti-inflammatory and analgesic agents with reduced ulcerogenic effect.

**Result and Discussion**

The reaction sequence leading to the formation of the desired heterocyclic compounds \(3a-j\) and \(4a-d\) are outlined in Scheme I. The intermediate products potassium 2- [2-(naphthalen-2-yloxy)acytel] hydrazine-
Carbodithioate (1) and 4-amino-5-[naphthalen-2-yloxy)methyl]-4H-1,2,4-triazole-3-thiol (2) were synthesised according to literature method by slightly modifying reaction conditions. Compound 3a-j were synthesized by treating 4-amino-5-[naphthalen-2-yloxy)methyl]-4H-1,2,4-triazole-3-thiol (2) with substituted aromatic acids in the presence of phosphorous oxychloride to give the corresponding 6-(4-substitutedphenyl)-3-[naphthalen-2-yloxy)methyl]-1,2,4-triazolo[3,4-b] [1,3,4] thiadiazoles (3a-j), whereas reaction of 2 with aryl/alkyl isothiocynates in the presence of DMF provided 4-(sustitutedphenyl)- 3 -[naphthalen-2-yloxy)methyl] [1,2,4]triazolo [3,4-b] [1,3,4]thiadiazol-6-amine (4a-d). The purity of the compounds was checked by elemental analyses. Both the analytical and spectral data (IR, $^1$H NMR, $^{13}$C NMR and Mass) of the compounds were in full harmony with the proposed structures. The results of elemental analysis (C, H and N) were within ± 0.3% of the theoretical values.

**Biological Studies**

The synthesized compounds were evaluated for their anti-inflammatory, analgesic, ulcerogenic, lipid peroxidation, hepatotoxic and histopathological properties. The Wister rats and albino mice used in the present study were housed and kept in accordance with the Hamdard University Animal Care Unit, which applies the guidelines and rules laid down by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. All the test compounds and standard drug were administered in the form of solution (0.5% w/v carboxymethyl cellulose as a vehicle) by an oral route. Each group consisted of six animals. All the animals were procured from the CPCSEA and maintained in colony cages at 25 ± 2°C, relative humidity of 45–55%, under a 12 h light and dark cycle and were fed a standard animal feed. All the animals were clematises for a week before use. The anti-inflammatory activity of the test compounds...
were compared with the control. The analgesic, ulcerogenic and lipid peroxidation activities were compared with the standard drug naproxen. Data were analysed by student’s t test for n=6.

**Ant-inflammatory activity**

All the synthesized compounds were screened for their anti-inflammatory activity by carrageenan induced rat paw edema as described by Winter et al.\(^1\) at an equimolar dose relative to standard drug naproxen 30 mg/Kg body weight. The results revealed that the anti-inflammatory activity of triazolo-thiadiazole of 3a-j series was found in the range of 48.36% to 79.25%. Compounds having 2-chlorophenyl group (3b) and 2,4-dichlorophenyl group (3c) at 6\(^{th}\) position of triazolo-thiadiazole ring showed more anti-inflammatory activity (77.21% and 79.25% respectively) than standard drug naproxen (74.62%). The compound having 4-chlorophenyl (3a), 2-methylphenyl (3d), 2-bromophenyl (3g), 2-chloro-4-bromophenyl (3i) and 2,4-dichlorophenoxy methyl (3j) groups also showed good activity viz. 69.88%, 66.28%, 64.43%, 62.49% and 61.76% respectively. Other compounds of the series showed moderate to poor activity. The compounds of 4a-d series showed moderate anti-inflammatory activity in the range of 36.47% to 59.80% (Table I). Thus it was found that the presence of 2-chlorophenyl and 2,4-dichlorophenyl groups at 6\(^{th}\) position of triazolo-thiadiazole ring resulted in high anti-inflammatory activity.

**Analgesic activity**

Compounds (3a-c, g and 3i-j) which showed anti-inflammatory activity more than 60% were further tested for their analgesic effect by tail immersion method\(^1\) at the same oral dose as used for the anti-inflammatory activity. The analgesic activity of triazolo-thiadiazole derivatives was found in the range of 42.94% to 79.63%. Compound having 2,4-dichlorophenyl group (3c) at 6\(^{th}\) position of triazolo-thiadiazole ring showed maximum analgesic activity (79.63%) than standard drug naproxen (74.18%). When 2,4-dichlorophenyl group was replaced with 2-chlorophenyl group (3b) there was slight decrease in activity (74.95%) but still more than standard drug naproxen (74.18%). The compound having 4-chlorophenyl (3a), 2-methylphenyl (3d) and 2-bromophenyl (3g) also showed good activity viz. 60.96%, 65.72% and 65.30% respectively. The other compounds showed moderate to poor analgesic activity in the range of 42.94% to 51.37% (Table II). Thus it was found that the presence of 2-chlorophenyl and 2,4-dichlorophenyl groups at 6\(^{th}\) position of triazolo-thiadiazole ring resulted in high analgesic activity.

**Ulcerogenic activity**

The compounds 3a-e, 3g, 3i-j which showed significant anti-inflammatory and good analgesic activity were further tested for their acute ulcerogenicity by the method of Ciolli et al.\(^2\) (Table II). The compounds were tested at an equimolar oral dose relative to 90 mg/Kg naproxen. The tested compounds showed severity index ranging of 0.250 ± 0.11 to 0.833 ± 1.66 in comparison to standard drug naproxen (severity index 0.666 ± 0.10). The compounds having 2-chlorophenyl group (3b) showed minimum ulcerogenicity (severity index 0.250 ± 0.11) whereas compound having 2,4-dichloro phenoxy methyl group (3j) showed maximum ulcerogenicity (severity index 0.833 ± 1.66). The other compound 3a and 3c also showed ulcerogenicity (0.416 ± 0.083 and 0.333 ± 0.105 respectively) lower than standard drug naproxen.

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**Table I — Anti-inflammatory activity of triazolo-thiadiazole derivatives 3a-j and 4a-d**

<table>
<thead>
<tr>
<th>Compd</th>
<th>After 3 h</th>
<th>After 4 h</th>
<th>Compd</th>
<th>After 3 h</th>
<th>After 4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>67.62 ± 0.71</td>
<td>69.86 ± 0.79(^d)</td>
<td>3i</td>
<td>60.59 ± 1.34</td>
<td>66.75 ± 1.20(^c)</td>
</tr>
<tr>
<td>3b</td>
<td>73.24 ± 1.11</td>
<td>77.21 ± 1.07</td>
<td>3j</td>
<td>59.04 ± 0.55</td>
<td>61.76 ± 0.62(^a)</td>
</tr>
<tr>
<td>3c</td>
<td>75.80 ± 0.75</td>
<td>79.25 ± 0.72</td>
<td>4a</td>
<td>53.36 ± 1.31</td>
<td>54.91 ± 1.40(^a)</td>
</tr>
<tr>
<td>3d</td>
<td>60.38 ± 0.91</td>
<td>66.28 ± 1.29(^c)</td>
<td>4b</td>
<td>51.73 ± 0.88</td>
<td>59.80 ± 0.62(^a)</td>
</tr>
<tr>
<td>3e</td>
<td>59.91 ± 0.51</td>
<td>64.43 ± 1.06(^b)</td>
<td>4c</td>
<td>41.64 ± 0.96</td>
<td>45.25 ± 1.13(^a)</td>
</tr>
<tr>
<td>3f</td>
<td>45.16 ± 0.95</td>
<td>48.36 ± 0.45(^a)</td>
<td>4d</td>
<td>29.81 ± 0.82</td>
<td>36.47 ± 0.51(^a)</td>
</tr>
<tr>
<td>3g</td>
<td>58.45 ± 0.56</td>
<td>62.49 ± 1.21(^b)</td>
<td>3j</td>
<td>70.85 ± 1.25</td>
<td>74.62 ± 1.08</td>
</tr>
<tr>
<td>3h</td>
<td>42.44 ± 1.14</td>
<td>46.59 ± 0.91(^c)</td>
<td>Naproxen</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Test compounds and naproxen were tested at 30 mg/kg body weight.

\(^{a}\)Mean ± SEM, n = 6.

Significance levels compared to the control: \(^{a}\)p < 0.0001, \(^{b}\)p < 0.001, \(^{c}\)p < 0.01, \(^{d}\)p < 0.05
whereas compound 3d and 3g showed ulcerogenicity higher than standard drug.

**Lipid peroxidation activity**

All the compounds screened for ulcerogenic activity were also analyzed for lipid peroxidation according to the method of Ohkawa et al.\textsuperscript{21} The lipid peroxidation was measured as nanomoles of malondialdehyde (MDA/100 mg) of gastric mucosa tissue. Triazolo-thiadiazole derivatives having 2-chlorophenyl (3b) and 2,4-dichloro phenyl group (3c) showed maximum reduction 3.75 ± 0.08, 3.72 ± 0.155 and 3.81 ± 0.174 respectively whereas standard naproxen showed lipid peroxidation activity 6.08 ± 0.16 and control group showed 3.23 ± 0.04. Thus these studies showed that the synthesized compounds have inhibited the induction of gastric mucosal lesions and the results further suggested that their protective effect might be related to the inhibition of lipid peroxidation in the gastric mucosa (Table II).

### Table II — Analgesic, ulcerogenic and lipid peroxidation activities of synthesized triazolo-thiadazole derivatives 3a-e, 3g and 3i,j

<table>
<thead>
<tr>
<th>Compd</th>
<th>Pre-treatment/normal 0 h</th>
<th>Post-treatment /after 4 h</th>
<th>% Inhibition</th>
<th>Ulcerogenic activity (Severity index)</th>
<th>nmol MDA content /100 mg tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>1.62 ± 0.01</td>
<td>2.61 ± 0.01</td>
<td>60.96 ± 1.32</td>
<td>0.416 ± 0.08</td>
<td>4.72 ± 0.12</td>
</tr>
<tr>
<td>3b</td>
<td>1.51 ± 0.01</td>
<td>2.65 ± 0.02</td>
<td>74.95 ± 1.56</td>
<td>0.250 ± 0.11</td>
<td>3.72 ± 0.15</td>
</tr>
<tr>
<td>3c</td>
<td>1.48 ± 0.01</td>
<td>2.66 ± 0.02</td>
<td>79.63 ± 0.99</td>
<td>0.333 ± 0.10</td>
<td>3.81 ± 0.17</td>
</tr>
<tr>
<td>3d</td>
<td>1.39 ± 0.00</td>
<td>2.30 ± 0.01</td>
<td>65.72 ± 1.36</td>
<td>0.750 ± 0.11</td>
<td>5.50 ± 0.21</td>
</tr>
<tr>
<td>3e</td>
<td>1.68 ± 0.01</td>
<td>2.40 ± 0.01</td>
<td>42.94 ± 1.09</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3g</td>
<td>1.59 ± 0.01</td>
<td>2.64 ± 0.01</td>
<td>65.30 ± 1.18</td>
<td>0.833 ± 0.16</td>
<td>6.24 ± 0.10</td>
</tr>
<tr>
<td>3i</td>
<td>1.48 ± 0.00</td>
<td>2.22 ± 0.01</td>
<td>51.37 ± 1.04</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3j</td>
<td>1.67 ± 0.01</td>
<td>2.46 ± 0.01</td>
<td>47.23 ± 0.98</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Control</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.000 ± 0.00</td>
<td>3.31 ± 0.06</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.64 ± 0.01</td>
<td>2.85 ± 0.03</td>
<td>74.18 ± 0.99</td>
<td>0.666 ± 0.10</td>
<td>6.08 ± 0.16</td>
</tr>
</tbody>
</table>

Test compounds and naproxen were tested at 30 mg kg\textsuperscript{-1} body weight.

\(\text{#Mean} \pm \text{SEM, n = 6.} \)

Significance levels compared to the standard drug: \(a p < 0.0001, b p < 0.001, c p < 0.01, d p < 0.05\)

### Table III — Effect of compounds 3a and 3c on serum enzymes, total proteins and total albumin

<table>
<thead>
<tr>
<th>Compd</th>
<th>Alkaline Phosphatase</th>
<th>SGOT</th>
<th>SGPT</th>
<th>Total Protein (g/100 mL)</th>
<th>Albumin (g/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>45.62 ± 0.72</td>
<td>161.04 ± 2.29</td>
<td>51.96 ± 0.82</td>
<td>1.83 ± 0.00</td>
<td>1.74 ± 0.01</td>
</tr>
<tr>
<td>Naproxen</td>
<td>47.72 ± 1.30</td>
<td>165.57 ± 2.32</td>
<td>53.14 ± 1.53</td>
<td>1.90 ± 0.01</td>
<td>1.68 ± 0.01</td>
</tr>
<tr>
<td>3b</td>
<td>41.36 ± 1.21</td>
<td>154.71 ± 3.05</td>
<td>44.11 ± 1.56</td>
<td>1.77±0.01</td>
<td>1.69 ± 0.01</td>
</tr>
<tr>
<td>3c</td>
<td>42.12 ± 1.16</td>
<td>142.04 ± 3.81</td>
<td>46.81 ± 1.58</td>
<td>1.82±0.01</td>
<td>1.75 ± 0.02</td>
</tr>
</tbody>
</table>

Test compounds and naproxen were tested at 30 mg kg\textsuperscript{-1} body weight.

\(\text{#Mean} \pm \text{SEM, n = 6.} \)

Significance levels compared to the control: \(a p < 0.0001, b p < 0.001, c p < 0.01, d p < 0.05\)

Hepatotoxic and histopathological activity

Compounds 3b and 3c showing potent anti-inflammatory and analgesic activities with reduced ulcerogenicity and lipid peroxidation, were further studied for their hepatotoxic effect. Assessment of liver function such as serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) were estimated by a reported method.\textsuperscript{22} The alkaline phoshatase, total protein and total albumin were measured according to reported procedures\textsuperscript{23,24} as shown in Table III. The liver function tests like alkaline phosphatase, SGOT, SGPT and total protein were carried out on serum collected from the treated rats. The compound 3b and 3c showed decrease in alkaline phosphatase, SGOT, SGPT, total protein level in comparison to reference drug naproxen. Histopathological testing of these compounds was also carried out by reported method.\textsuperscript{25} The histopatho-logical studies of liver do not show any...
significant pathological changes in comparison to standard drug naproxen (Figure 1).

**Experimental Section**

The melting points were determined in open capillary tubes in a Hicon melting point apparatus and are uncorrected. Elemental analysis (C, H, N, S) was performed on the CHNS Elimentar (Analyses systime, GmbH) Germany Vario EL III. FTIR spectra were recorded as KBr pellets on a Jasco FT/IR 410 spectrometer and frequency was expressed in cm$^{-1}$. $^1$H NMR spectra were recorded on a Bruker model DPX 400 NMR spectrometer. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane (TMS). Mass spectra were measured on a Jeol SR-102 (FAB) mass spectrometer. Unless otherwise specified, all reactions were carried out in oven-dried glassware, and commercially available starting materials were used without further purification.

**Potassium 2- [2- (naphthalen-2-yloxy) acetyl] hydrazinecarbodithioate, 1**

Potassium hydroxide (0.03 mole) was dissolved in absolute ethanol (50 mL). The solution was cooled in an ice bath and diphenyl acetic hydrazide (0.02 mole) was added to it with stirring. To this solution carbondisulphide (0.025 mole) was added in small portions with constant stirring. The reaction mixture was agitated continuously for 13 h at RT. The precipitated potassium dithiocarbazinate was collected by filtration, washed with anhydrous ether (100 mL) and dried in vacuum. The potassium salt thus obtained in quantitative yield and was used in the next step without further purification.

**4-Amino-5-[(naphthalen-2-yloxy)methyl]-4H-1,2,4-triazole-3-thiol, 2**

A suspension of compound 1 (0.02 mole) in water (10 mL) and hydrazine hydrate (99%, 0.04 mole) was refluxed for 16 h with occasional shaking. The colour of the reaction mixture changed to green with the evaluation of hydrogen sulfide gas. A homogenous reaction mixture was obtained during the reaction process. The progress of reaction was monitored by aluminum coated Merck TLC plates using T:E:F (5:4:1) as solvent system. The reaction mixture was cooled to RT and diluted with water (20 mL). On acidification with acetic acid the required triazole was

![Figure 1 — Histopathological studies of the liver](image)
The compound so obtained was dried and recrystallized and washed thoroughly with cold water. The progress of reaction was monitored by aluminum coated Merck TLC plates using 40% ethyl acetate-hexane solvent system. The reaction mixture was cooled to RT and then gradually poured on to crushed ice with stirring. The mixture was allowed to stand overnight and the solid separated out was filtered, treated with dilute sodium hydroxide solution and washed thoroughly with cold water. The compound so obtained was dried and recrystallized with ethanol.

General procedure for synthesis of 6-(4-substitutedphenyl) -1,2,4] triazolo[3,4-b][1,3,4]thiadiazoles, 3a-j

An equimolar mixture of compound 2 (0.01 mole) and substituted aromatic acid (0.01 mole) in phosphorus oxychloride (10 mL) was refluxed for 5-7 h. The progress of reaction was monitored by aluminum coated Merck TLC plates using 40% ethyl acetate-hexane solvent system. The reaction mixture was allowed to cool and refluxed. The solid separated out was filtered, washed with dilute sodium hydroxide solution and washed thoroughly with cold water. The compound so obtained was dried and recrystallized.

6-(4-Chlorophenyl)-3-[(naphthalen-2-yl)methyl]-1,2,4] triazolo[3,4-b][1,3,4] thia diazole, 3a:

- Yield: 79%; m.p.182-184°C; IR (KBr): 1619 (C=N), 714 cm\(^{-1}\) (C-S-C); \(^1^H\) NMR (DMSO-\(d_6\)): \(\delta\) 5.67 (s, 2H, OCH\(_2\)), 7.21-7.96 (m, 11H, ArH); \(^1^C\) NMR (DMSO-\(d_6\)): \(\delta\) 166.45, 155.78, 134.27, 132.80, 131.71, 131.55, 129.74, 129.47, 128.55, 128.05, 127.65, 127.04, 124.75, 124.26, 118.64, 110.78, 110.47, 59.67 (OCH\(_2\)); MS: \(m/z\) 392 (M\(^+\)), 394 (M\(^+\)+2). Anal. Calcd for C\(_{26}\)H\(_{15}\)ClN\(_5\)O\(_2\): C, 57.25; H, 3.14; N, 15.24. Found: C, 57.05; H, 3.11; N, 14.02%.

6-(2-Bromophenyl)-3-[(naphthalen-2-yl)methyl]-1,2,4] triazolo[3,4-b][1,3,4] thia diazole, 3b:

- Yield: 75%; m.p.92-94°C; IR (KBr): 1621 (C=N), 708 cm\(^{-1}\) (C-S-C); \(^1^H\) NMR (DMSO-\(d_6\)): \(\delta\) 5.48 (s, 2H, OCH\(_2\)), 7.29-7.87 (m, 11H, ArH); \(^1^C\) NMR (DMSO-\(d_6\)): \(\delta\) 167.53, 155.65, 135.28, 133.69, 132.44, 131.51, 130.56, 129.41, 129.53, 128.65, 127.58, 126.14, 124.32, 124.11, 119.34, 118.67, 108.64, 58.85 (OCH\(_2\)); MS: \(m/z\) 392 (M\(^+\)), 394 (M\(^+\)+2). Anal. Calcd for C\(_{26}\)H\(_{15}\)BrN\(_5\)O\(_2\): C, 57.25; H, 3.14; N, 15.24. Found: C, 57.09; H, 3.09; N, 14.08%.

6-(2-Bromophenyl)-3-[(naphthalen-2-yl)methyl]-1,2,4] triazolo[3,4-b][1,3,4] thia diazole, 3c:

- Yield: 72%; m.p.152-154°C; IR (KBr): 1617 (C=N), 710 cm\(^{-1}\) (C-S-C); \(^1^H\) NMR (DMSO-\(d_6\)): \(\delta\) 5.59 (s, 2H, OCH\(_2\)), 7.10-7.94 (m, 10H, ArH); \(^1^C\) NMR (DMSO-\(d_6\)): \(\delta\) 171.45, 167.53, 162.46, 156.78, 135.78, 134.63, 133.26, 131.52, 130.79, 129.58, 129.11, 127.85, 127.34, 126.28, 125.17, 124.86, 121.33, 118.39, 108.47, 59.63 (OCH\(_2\)); MS: \(m/z\) 426 (M\(^+\)), 428 (M\(^+\)+2). Anal. Calcd for C\(_{26}\)H\(_{15}\)BrN\(_5\)O\(_2\): C, 54.93; H, 3.00; N, 12.81. Found: C, 54.87; H, 2.81; N, 12.61%.
6-(4-Bromophenyl)-3-[(naphthalen-2-yloxy)methyl]-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole, 3h: Yield: 78%; m.p.108-110°C; IR (KBr): 1622 (C=N), 717 cm\(^{-1}\) (C=S-C); \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 5.65 (s, 2H, OCH\(_2\)), 7.24-7.94 (m, 11H, ArH); \(^13\)C NMR (DMSO-\(d_6\)): \(\delta\) 170.94, 157.48, 148.00, 143.43, 141.37, 135.65, 133.61, 130.89, 130.33, 129.32, 128.91, 128.74, 128.50, 128.14, 126.92, 124.27, 111.03, 61.68 (OCH\(_2\)); MS: \(m/z\) 438 (M\(^+\)), 440 (M\(^+\)+2). Anal. Calcd for C\(_{20}\)H\(_{15}\)BrN\(_3\)O\(_2\): C, 54.93; H, 3.00; N, 12.81. Found: C, 54.72; H, 3.17; N, 12.64%.

6-(4-Bromo-2-chlorophenyl)-3-[(naphthalen-2- yloxy)methyl]-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole, 3i: Yield: 76%; m.p.146-148°C; IR (KBr): 1632 (C=N), 711 cm\(^{-1}\) (C=S-C); \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 5.57 (s, 2H, OCH\(_2\)), 7.13-7.77 (m, 10H, ArH); \(^13\)C NMR (DMSO-\(d_6\)): \(\delta\) 168.97, 166.47, 155.68, 144.27, 134.26, 132.81, 131.71, 131.56, 130.26, 129.75, 129.46, 128.56, 127.79, 127.66, 126.95, 126.64, 124.27, 118.64, 107.80, 61.89 (OCH\(_2\)); MS: \(m/z\) 472 (M\(^+\)), 474 (M\(^+\)+2) 476 (M\(^+\)+4). Anal. Calcd for C\(_{20}\)H\(_{15}\)Cl\(_2\)N\(_3\)O\(_2\): C, 50.92; H, 2.56; N, 11.88. Found: C, 50.73; H, 2.34; N, 11.64%.

6-[(2,4-Dichlorophenoxy)methyl]-3-(naphthalen-2- yloxy)methyl]-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole, 3j: Yield: 68%; m.p.96-98°C; IR (KBr): 1617 (C=N), 709 cm\(^{-1}\) (C=S-C); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 5.29 (s, 2H, OCH\(_2\)), 5.59 (s, 2H, OCH\(_2\)), 7.16-7.81 (m, 10H, ArH); \(^13\)C NMR (CDCl\(_3\)): \(\delta\) 170.37, 168.49, 162.53, 152.71, 157.28, 131.47, 130.78, 130.53, 129.87, 129.12, 128.93, 127.84, 127.14, 126.98, 125.11, 121.53, 118.58, 117.35, 105.77, 63.42 (OCH\(_2\)), 59.57 (CH\(_2\)O); MS: \(m/z\) 456 (M\(^+\)), 458 (M\(^+\)+2). Anal. Calcd for C\(_{21}\)H\(_{14}\)Cl\(_2\)N\(_3\)O\(_2\): C, 55.15; H, 3.09; N, 12.25. Found: C, 54.91; H, 2.88; N, 12.03%.

General procedure for synthesis of 4-(Sustituted-phenyl)-3-[(naphthalen-2-yloxy)methyl]-1,2,4-triazolo[3,4-b][1,3,4]thiadiazol-6-amine, 4a-d

An equimolar mixture of compound 2 (0.01 mole), substituted phenylsulfonyl cyanates (0.01 mole) in dimethylformamide (20 mL) was refluxed for 8-10 hrs. The progress of reaction was monitored by aluminum coated Merck TLC using 40-50% ethyl acetate-hexane solvent system. The reaction mixture was cooled to RT and then gradually poured on to crushed ice with stirring. The mixture was allowed to stand overnight and the solid separated out was filtered, and washed thoroughly with cold water. The compound so obtained was dried and recrystallized with ethanol.

3-[(Naphthalen-2-yloxy)methyl]-N-phenyl-1,2,4-triazolo [3,4-b][1,3,4]thiadiazol-6 amine, 4a: Yield: 68%; m.p.136-138°C; IR (KBr): 1621 (C=N), 704 cm\(^{-1}\) (C=S-C); \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 4.94 (s, 2H, OCH\(_2\)), 7.08-7.84 (m, 12H, ArH), 9.37 (bs, 1H, NH); \(^13\)C NMR (DMSO-\(d_6\)): \(\delta\) 167.34, 162.45, 157.83, 153.45, 140.73, 130.14, 129.87, 129.54, 129.32, 128.15, 127.11, 126.94, 124.73, 123.22, 118.37, 110.03, 106.85, 61.63 (OCH\(_2\)); MS: \(m/z\) 373 (M\(^+\)). Anal. Calcd for C\(_{28}\)H\(_{15}\)N\(_5\)OS: C, 64.33; H, 4.05; N, 18.75. Found: C, 64.15; H, 3.85; N, 18.58%.

Conclusions

Fourteen triazolo-thiadiazole derivatives were synthesized and evaluated for their anti-inflammatory
and analgesics activity. Compounds showing high anti-inflammatory and analgesic activities were also tested for their ulcerogenic potential and lipid peroxidation. It was found that compound 3b and 3c showing high anti-inflammatory activity also exhibited reduced ulcerogenic potential and lipid peroxidation, with no hepatocyte necrosis or degeneration. In conclusion, this preliminary investigation showed that cyclisation of carboxyclic group of 2-naphthoxyacetic acid into triazolo-thiadiazole moieties resulted in significant biological activities with reduced GI toxicity.

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