SYNTHESIS AND EVALUATION OF NAPROXEN DERIVATIVES AND ITS PHARMACOLOGICAL ACTIVITY

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Keywords:
Naproxen, 2-(6-methoxynaphthalen-2-yl)propanehydrazide, anti-analgesic, anti-ulcerogenic, Benzoic acid, 1,3,4-oxadiazole

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ABSTRACT

Objective- The main aim of the present study is to replace the carboxylic acid group of Naproxen and form various 1, 3, 4-oxadiazole derivatives. These derivatives are evaluated for Analgesic activity and reduce ulcerogenic effects.

Method- Various 1,3,4-Oxadiazole derivatives of Naproxen was prepared by cyclization of 2-(6-methoxynaphthalen-2-yl)propanehydrazide under various reaction conditions. The cyclization derivatives were screened for their anti-analgesic and ulcerogenic activities.

Result & Conclusion- Naproxen derivatives of Benzoic acid H, 2-Cl, 2-Br showed maximum analgesic activity, while compounds 4-Cl, 3-NH₂, 4-NH₂, 4-Br was found to be showed moderate analgesic activity. On the other hand, compounds H, 2-Cl, 2-Br showed maximum ulcerogenic activity. Naproxen derivatives of Benzoic acid H, 2-Cl, 2-Br showed maximum analgesic activity, while compounds 4-Cl, 3-NH₂, 4-NH₂, 4-Br was found to be showed moderate analgesic activity. On the other hand, compounds H, 2-Cl, 2-Br showed maximum ulcerogenic activity. Our findings indicate that the Benzoic acid derivatives of Naproxen possess anti-analgesic as well as anti-ulcerogenic activity.
INTRODUCTION
Naproxen is synthesized from 2-methoxynaphthalene and the (+)-isomer obtained by resolution with cinchonidine. It was introduced in the United Stated in 1976 and as a generic drug, has consistently been among the more popular NASIDs. As an inhibitor of prostaglandin biosynthesis, it is 12 times more potent than aspirin, 10 times more potent then phenylbutazone, three to four times more potent than ibuprofen, and four times more potent than fenoprofen, but it is approximately 300 times less potent than indomethacin. In the carrageenan induced rat paw edema assay, it is 11 times more potent than phenyl butazone and 55 times as potent as aspirin, but only 0.7 times potent then indomethacin.[1,2,3,4,5,6,7,8,9,10,11,12,13,14]

Oxadiazoles are five membered heterocyclic compounds with two nitrogen atoms and one oxygen atom. They are synthesized by ring condensation and rearrangements Depending on the position of hetero atoms they are named as 1,2,3, - 1,2,4,- 1,2,5, and 1,3,4- oxadiazoles. All of them were reported to possess one or the other biological activities. [13, 14].Some of the recent studies have shown that oxadiazoles are reported to possess antitubercular, antileprotic, analgesic, antiphlogistic, paralytic hypnotic and sedative activity, hypoglycemic, anti-malarial and pesticidal actions.[15,16,17,18,19,20] 1,3,4–oxadiazoles are well known compounds that are found to possess varied biological and pharmacological activities. They were associated with antibacterial, antifungal, tuberculostatic, anticonvulsant, analgesic, anti-inflammatory, diuretic, antiemetic and insecticidal properties. Recently they were found to possess nonulcerogenic anti-inflammatory, antitumour and antiviral activities. The incorporation of oxadiazoles with iron complexes showed excellent antitumour activity [21,22,23,24,25]. The compound 1,3,4-oxadiazole (1) is a thermally stable, neutral aromatic molecule.

NSAIDS (non-steroidal anti-inflammatory drugs) now a day inflammation is one of the most common disease and treatment is mainly done through topical administra-tion. A large number of marketed preparations are available among which NSAIDS are most commonly used drugs for the treatment of inflammation. Chemically hete-rogeneous large groups of
drugs which suppress inflammation in a manner similar to steroids but less side effects of sedation, respiratory depression or addiction then steroids. They are widely used for the treatment of inflammatory disorders and painful condition such as rheumatoid arthritis, gout bursitis, painful menstruation and headache. They are effetely in the relief of pain and fever. NSAIDs inhibit the cyclooxygenase (Cox) activity resulting in decreased synthesis of prostaglandin, leukotriene and thromboxane precursors such as ubiquitous enzyme which catalyzes the initial steps in the synthesis of prostanoids. Prostanoids is any group of a C-20 fatty acids complex with an internal five or six carbon rings such as prostaglandins, prostanic acids, prostacyclins and thromboxane; from derived from arachidonic acid(C-20 polyunsaturated fatty acid with four cis double bonds). The action or the synthesis of prostanoids are involved in the modulation of a variety of pathophysiologic processes including inflammation, homeostasis, thrombosis, cytoprotection, ulceration, hemodynamic and other the progression of kidney diseases. Thus, NSAIDs as non-selective inhibitors of the cyclooxygenases (both the cyclooxygenase-1 and cyclooxygenase-2 isoenzymes) may have beneficial as well as unwanted effects on a variety of human diseases. Low stomach prostanoid levels caused by COX-1 inhibitors can result in ulceration and internal bleeding and perforation. The selective COX-2 inhibitors such as oxicam, meloxicam, and coxibs do not interfere with COX-1.[26,27,28,29,30,31,32,33]

Gastrointestinal problem are a common reason for after cancer at the primary care clinic as well as the out-patient clinic of the hospital. Many of these consultations (approx 75%) are for symptoms related to non-organic diseases.[34]

An ulcer is a local defect or excavation of the surface of an organ or tissue, which is produced by the sloughing of the inflammatory narcotic tissue. The term “Peptic ulcer” refers to a group of ulcerative disorders of the upper gastrointestinal tract which appear to have in common the participation of acids-pepsin in the pathogenesis.

METHODOLOGY

STEP 1-Preparation of Ester-In a 500 ml round bottomed flask place a mixture of 56gm (0.246 mol) of Naproxen, 85 ml (2.5 mol) of absolute ethanol and 2.7ml concentrated sulphuric acid. Add a few small chips of porous porcelain, attach a reflux condenser and boil the mixture gently for 10 hrs. Distil off the excess of alcohol on a water bath and allow to cool. The solid precipitated was collected, dried.
(STEP 1)

**STEP 2 – Preparation of 2-(6-methoxynaphthalen-2-yl)** - In a 500 ml round bottomed flask place a mixture of 2.58gm (0.01 mol) of Ester, 1 ml of Hydrazine Hydrate and 10 ml of ethanol. Add a few small chips of porous porcelain, attach a reflux condenser and boil the mixture gently for 4 hrs reflux on a water bath. The compound was collected, dried and recrystallized from ethanol.

<table>
<thead>
<tr>
<th>Yield: 40gm (71%)</th>
<th>Molecular Formula: C_{16}H_{18}O_{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>R_f Value: 0.6</td>
<td>Solvent System for TLC: Chloroform:Ethyl Acetate(8:2)</td>
</tr>
</tbody>
</table>

(STEP 2)

**STEP 3: Preparation of Derivatives** - Take a mixture of Hydrazide (0.001 mole) and the appropriate aromatic acid (0.001 mole) were dissolved in Phosphorus oxychloride in round bottomed flask and reflux for 18-26hrs. The reaction mixture was slowly pour over crushed ice and kept overnight. The solid thus precipitated was filtered, washed with water, dried and recrystallized from ethanol.

<table>
<thead>
<tr>
<th>Yield: 64%</th>
<th>Molecular Formula: C_{14}H_{16}N_{2}O</th>
</tr>
</thead>
<tbody>
<tr>
<td>R_f value: 0.5</td>
<td>Solvent System for TLC: Chloroform: Ethyl Acetate (8:2)</td>
</tr>
</tbody>
</table>
R-COOH
\[
\text{POCl}_3
\]

R=Different substituted Benzoic acids

**PHARMACOLOGICAL EVALUATION**

**Study Protocol for Antiulcer Activity**-

**Experimental Protocol**- Albino rats of either sex were used in experiment for antiulcer activity. Standard drugs Naproxen and their derivatives were suspended in 0.1% C.M.C. The animals were fasted for 24 hours prior to dosing. The compounds were administered orally by gavage in a volume of 5mg/kg to the animals. Doses equivalent to 5mg/kg for derivatives.

The animals received the following treatment in 0.1% CMC as a suspending agent for a day.

**Treatment**-

**Group-I**- Normal (Received Distill Water)

**Group-II**- Control Drug received indomethacin (20 mg/kg,p.o.)

**Group-III**- Animals received standard drug ranitidine (70 mg/kg,p.o.)

**Group-IV**- Derivative A+ Indomethacin   **Group-V**- Derivative B+ Indomethacin

**Group-VI**- Derivative C+ Indomethacin   **Group-VII**- Derivative D+ Indomethacin

**Group-VIII**- Derivative E+ Indomethacin **Group-IX**- Derivative F+ Indomethacin

**Group-X**- Derivative G+ Indomethacin   **Group-XI**- Derivative H+ Indomethacin

**Group-XII**- Derivative I+ Indomethacin

**Analgesic Activity**

**Experimental Protocol**- Albino rats of either sex were used in experiment for analgesic activity. Standard drugs Aspirin and test derivatives were suspended in 0.1% C.M.C. The Aspirin administered orally by gavage in a volume of 25mg/kg to the animals. Dose equivalent to 5mg/kg for derivatives.

The animals received the following treatment in 0.1% CMC as a suspending agent for a day.
RESULTS AND DISCUSSION

All the various compounds were synthesized with physicochemical data (Table-1), and spectrl analysis with respect to 1H NMR spectra and IR spectra.

Synthesized compounds were screened for Ulcerogenic activity (Shown in table 2)

Synthesized compounds were screened for Analgesic activity (Shown in table 3)

**Physiochemical Characterization**

**Table 1:** The result of the reaction of various R=Different substituted Benzoic acids

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound Code</th>
<th>R</th>
<th>M.Pt.(°C)</th>
<th>%Yield</th>
<th>Rf Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>BEN-1</td>
<td>C6H5</td>
<td>220-225</td>
<td>68</td>
<td>0.52</td>
</tr>
<tr>
<td>2.</td>
<td>BEN-2</td>
<td>C6H4Cl</td>
<td>216-224</td>
<td>70</td>
<td>0.56</td>
</tr>
<tr>
<td>3.</td>
<td>BEN-3</td>
<td>C6H4Cl</td>
<td>215-222</td>
<td>69</td>
<td>0.80</td>
</tr>
<tr>
<td>4.</td>
<td>BEN-4</td>
<td>C6H6N</td>
<td>230-240</td>
<td>71</td>
<td>0.72</td>
</tr>
<tr>
<td>5.</td>
<td>BEN-5</td>
<td>C6H6N</td>
<td>236-242</td>
<td>68.40</td>
<td>0.66</td>
</tr>
<tr>
<td>6.</td>
<td>BEN-6</td>
<td>C6H5Br</td>
<td>238-244</td>
<td>70</td>
<td>0.58</td>
</tr>
<tr>
<td>7.</td>
<td>BEN-7</td>
<td>C6H5Br</td>
<td>232-238</td>
<td>66</td>
<td>0.54</td>
</tr>
<tr>
<td>8.</td>
<td>BEN -8</td>
<td>SH</td>
<td>234-246</td>
<td>68.20</td>
<td>0.88</td>
</tr>
<tr>
<td>9.</td>
<td>BEN -9</td>
<td>NH2</td>
<td>235-242</td>
<td>69</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**Pharmacological Characterization**

**A. Effects of Naproxen Derivatives on Ulcerogenic Activity** - Six hours after the oral administration of compounds, the animals were sacrificed using diethyl ether. An incision was made along the midline of abdomen to cut open the stomach and 3 cm of duodenum was removed. The stomach was opened along the lesser curvature and washed with distilled water. The mucous was wiped off and numbers of lesions were examined by means of 10X magnifying lens. The numbers of ulcer were noted and the severity recorded with the following scores:
Evaluation of Ulcer Index

An ulcer index $U_1$ of all the compounds were calculated, applying following formula:

$$U_1 = \frac{U_N}{U_S}$$

Where, $U_N$ = average number of ulcers per animal,

$U_S$ = average of severity score,

$U_p$ = percentage of animals with ulcers

B. Effects of Naproxen Derivatives on Analgesic Activity - The basal reaction time of the animals to radiant heat source was taken by placing the tip (last 1-2 cm) of the tail at the radiant heat source. The tail-withdrawal from the heat source (flacking response) was taken as the end point and considered as reaction time. The basal reaction time was noted before drug administration and after 5,15,30,45,60,90,120 min. of the drug administration. The reaction time of treated animals was compared before and after drug treatment.

Statistical Analysis

Table-2-The Anti-Ulcerogenic effects of the synthesized compounds on (Mean±SEM) In Ulcerogenic Rats:

<table>
<thead>
<tr>
<th>Group</th>
<th>Severity Of Lesion</th>
<th>Ulcer Index $U_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Standard (Indomethacin)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Derivatives I</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>II</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>V</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>VI</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>VII</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>VIII</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>IX</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>

*No. of animals in each group= 5

Each value represents the Mean± SEM

*represents (p<0.01) compared to control vs. treated group
From the results of antiulcerogenic effect, it can be concluded that synthesized compounds have shown significant activity (P<0.05), when compared to the control group. Some of the synthesized compounds have shown reduction in ulcerogenic effect comparable to the control. However, the ulcerogenic effect is incomparable to that of the standard drug (Indomethacin; 20mg/kg).

Anti-analgesic Effects-

Data were analyzed using “Dunnett’s test” to determine the statistical significance of the change in BGL p<0.01 was considered significant

Table-3: The Anti Analgesic effects of the synthesized compounds on (Mean±SEM) In Analgesic Rats:

<table>
<thead>
<tr>
<th>Groups</th>
<th>Reaction Time Before drug adm. (min.)</th>
<th>Reaction Time After drug administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0min</td>
<td>15min</td>
</tr>
<tr>
<td>Standard</td>
<td>4.42±0.05</td>
<td>4.72±0.058</td>
</tr>
<tr>
<td>Normal</td>
<td>4.0±0.15</td>
<td>4.44±0.23</td>
</tr>
<tr>
<td>Derivatives</td>
<td>4.23±0.02</td>
<td>4.6±0.07</td>
</tr>
<tr>
<td>II</td>
<td>4.12±0.05</td>
<td>4.6±0.07</td>
</tr>
<tr>
<td>III</td>
<td>4.52±0.03</td>
<td>4.72±0.04</td>
</tr>
<tr>
<td>IV</td>
<td>4.42±0.01*</td>
<td>4.66±0.04*</td>
</tr>
<tr>
<td>V</td>
<td>4.52±0.05</td>
<td>4.74±0.07</td>
</tr>
<tr>
<td>VI</td>
<td>4.32±0.09</td>
<td>4.50±0.11</td>
</tr>
<tr>
<td>VII</td>
<td>3.60±0.04</td>
<td>3.98±0.058</td>
</tr>
<tr>
<td>VIII</td>
<td>4.59±0.06*</td>
<td>4.72±0.058*</td>
</tr>
<tr>
<td>IX</td>
<td>4.67±0.04*</td>
<td>4.72±0.058*</td>
</tr>
</tbody>
</table>

No. of animals in each group= 5, Each value represents the Mean±SEM, *represents (p<0.05) compared to control vs. treated group

Fig 1- Shows the effects of Standard and synthesized compounds on Anti-analgesic Effect (Mean + SEM) in Analgesics Rats on different minutes Treatment
From the results of antianalgesic effect, it can be concluded that synthesized compounds have shown significant activity (P<0.05), when compared to the control group. Some of the synthesized compounds have shown reduction in analgesic effect comparable to the control. However, the analgesic effect is incomparable to that of the standard drug (Aspirin; 25mg/kg).

**CONCLUSION**

Some Naproxen analogues were synthesized using different Benzoic acid derivatives subjective to Chemical and Spectral analysis. These compounds were then subjected to the evaluation of their anti-analgesic as well as ulcerogenic activity.

Compounds BEN-1, BEN-2 and BEN-6 exhibited analgesic activity comparable or superior to Aspirin. Compounds BEN-7, BEN-4, BEN-3, and BEN-5 exhibited moderate analgesic activity while compounds BEN-8 and BEN-9 were found to be less potent as compared to standard and other analogue.

Same as with ulcerogenic activity compounds BEN-1, BEN-2 and BEN-6 exhibited ulcerogenic activity comparable or superior to Indomethacin. Compounds BEN-7, BEN-4, BEN-3, and BEN-5 exhibited moderate ulcerogenic activity while compounds BEN-8 and BEN-9 were found to be less potent as compared to standard and other analogue.

The IR studies of the compounds were done on the basis of analgesic as well as ulcerogenic activity shown by the analogue. Introduction of BEN-1, BEN-2 and BEN-6 groups to terminal Naproxen of NSAIDS increase the activity while BEN-3, BEN-4, BEN-5 and BEN-7 exhibited moderate analgesic as well as ulcerogenic activity, while compounds BEN-8 and BEN-9 were found to be less potent as compared to standard and other analogues.

**Table 4- List of Abbreviations**

<table>
<thead>
<tr>
<th>%</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg</td>
<td>Microgram</td>
</tr>
<tr>
<td>ºC</td>
<td>Degree Celsius</td>
</tr>
<tr>
<td>Ar</td>
<td>Aromatic</td>
</tr>
<tr>
<td>c.</td>
<td>About</td>
</tr>
<tr>
<td>D</td>
<td>Doublet</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethyl Formamide</td>
</tr>
<tr>
<td>Fig.</td>
<td>Figure</td>
</tr>
<tr>
<td>Gm</td>
<td>Gram</td>
</tr>
<tr>
<td>Hrs</td>
<td>Hour</td>
</tr>
<tr>
<td>IR</td>
<td>Infra Red</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>lt.</td>
<td>Liter</td>
</tr>
<tr>
<td>mg/dl</td>
<td>milligram per deciliter</td>
</tr>
<tr>
<td>M</td>
<td>Multiplet</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>Min</td>
<td>Minute</td>
</tr>
<tr>
<td>Mm</td>
<td>Millimeter</td>
</tr>
<tr>
<td>MI</td>
<td>Milliliter</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>No.</td>
<td>Number</td>
</tr>
<tr>
<td>Ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>Retention factor</td>
</tr>
<tr>
<td>S</td>
<td>Singlet</td>
</tr>
</tbody>
</table>

**BEN-1** 2-(6-methoxynaphthalen-2-yl) propanoate

**BEN-2** 2-(6-methoxynaphthalen-2-yl) propane hydrazide.

**BEN-3** 2-(4-chlorophenyl)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole

**BEN-4** 4-(1-(6-methoxynaphthaen-2-yl)ethyl)-1,3,4-oxadiazole aniline

**BEN-5** 3-(5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole aniline

**BEN-6** 2-(2-Bromophenyl)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole

**BEN-7** 2-(4-Bromophenyl)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole

**BEN-8** 1,3,4-oxadiazole-2-thiol-2-ethyl naphthalene

**BEN-9** 1,3,4-oxadiazole-2-ethyl naphthalene

**SEM** Standard Error Mean

**Str** Stretching

**sym.** Symmetric

**Std.** Standard

**TLC** Thin Layer Chromatography

**VLA** Very Late Antigen

**vol.** Volume

**Yrs** Years

**REPRESENTATIVE SPECTRAL ANALYSIS**

**1.1- BEN-1** 2-[1-(6-methoxynaphthalen-2-yl)ethyl]-5-phenyl-1,3,4-oxadiazole.

**IR (KBr) cm<sup>-1</sup>** 1550 (C=C str), 1530 (C=N str), 3100 (Ar-H), 2920 (C-H str), 1190 (C-O-C).

**NMR (DMSO, d<sub>6</sub>):** δ 3.83 (s, 1H, CH<sub>3</sub>), δ 1.68 (s, 1H, CH<sub>3</sub>), δ 7.18-8.05 (m, 11H, Ar-H), δ 4.23 (s, 1H, CH).

**1.2- BEN-2** 2-{(2-chlorophenyl)-5-[1-(6-methoxynaphthalen-2-yl)ethyl]}-1,3,4-oxadiazole.

**IR (KBr) cm<sup>-1</sup>** 1550 (C=C str), 1530 (C=N str), 3100 (Ar-H), 2920 (C-H str), 1190 (C-O-C), 730(Cl str)

**NMR (DMSO, d<sub>6</sub>):** δ 3.83 (s, 1H, CH<sub>3</sub>), δ 1.68 (s, 1H, CH<sub>3</sub>), δ 7.18-8.05 (m, 10H, Ar-H), δ 4.23 (s, 1H, CH).
1.3- BEN-3- 2-(4-chlorophenyl)-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole.

IR (KBr) cm\(^{-1}\): 1550 (C=C str), 1530 (C=N str), 3100 (Ar-H), 2920 (C-H str), 1190 (C-O-C), 730(Cl str) NMR (DMSO, d\(_6\)):\(\delta\) 3.83 (s, 1H, CH\(_3\)), \(\delta\) 1.68 (s, 1H, CH\(_3\)), \(\delta\) 7.18-8.05 (m, 10H, Ar-H), \(\delta\) 4.23 (s, 1H, CH).

1.4- BEN-4-4-(5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole aniline.

IR (KBr) cm\(^{-1}\): 1550 (C=C str), 1530 (C=N str), 3100 (Ar-H), 2920 (C-H str), 1190 (C-O-C), 3250(NH\(_2\) str) NMR (DMSO, d\(_6\)):\(\delta\) 3.83 (s, 1H, CH\(_3\)), \(\delta\) 1.68 (s, 1H, CH\(_3\)), \(\delta\) 6.58-7.90 (m, 10H, Ar-H), \(\delta\) 4.23 (s, 1H, CH), 6.27 (s, 1H, NH\(_2\)).

1.5- BEN-5-3-(5-(1--(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole aniline

IR (KBr) cm\(^{-1}\): 1550 (C=C str), 1530 (C=N str), 3100 (Ar-H), 2920 (C-H str), 1190 (C-O-C), 3250(NH\(_2\) str) NMR (DMSO, d\(_6\)):\(\delta\) 3.83 (s, 1H, CH\(_3\)), \(\delta\) 1.68 (s, 1H, CH\(_3\)), \(\delta\) 6.58-7.90 (m, 10H, Ar-H), \(\delta\) 4.23 (s, 1H, CH), 6.27 (s, 1H, NH\(_2\)).

1.6- BEN-6-2-(2-Bromophenyl-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole

IR (KBr) cm\(^{-1}\): 1550 (C=C str), 1530 (C=N str), 3100 (Ar-H), 2920 (C-H str), 1190 (C-O-C), 570(Br str) NMR (DMSO, d\(_6\)):\(\delta\) 3.83 (s, 1H, CH\(_3\)), \(\delta\) 1.68 (s, 1H, CH\(_3\)), \(\delta\) 7.18-8.05 (m, 10H, Ar-H), \(\delta\) 4.23 (s, 1H, CH).
1.7- BEN-7-2-(4-Bromophenyl-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-1,3,4-oxadiazole.

**IR (KBr) cm⁻¹**: 1550 (C=C str), 1530 (C=N str), 3100 (Ar-H), 2920 (C-H str), 1190 (C-O-C), 570(Br str)  
**NMR (DMSO, d₆):** δ 3.83 (s, 1H, CH₃), δ 1.68 (s, 1H, CH₃), δ 7.18-8.05 (m, 10H, Ar-H), δ 4.23 (s, 1H, CH).

1.8- BEN-8-5-[1-(6-methoxynapthalene-2-yl)ethyl]-1,3,4-oxadiazole-2-thiol.

**IR (KBr) cm⁻¹**: 1550 (C=C str), 1530 (C=N str), 3100 (Ar-H), 2920 (C-H str), 1190 (C-O-C), (SH).  
**NMR (DMSO, d₆):** δ 3.83 (s, 1H, CH₃), δ 1.68 (s, 1H, CH₃), δ 7.18-7.90 (m, 6H, Ar-H), δ 4.23 (s, 1H, CH), δ 13.05 (s, 1H, SH)

1.9-5-[1-(6-methoxynapthalene-2-yl) ethyl]-1,3,4-oxadiazole-2-amine

**IR (KBr) cm⁻¹**: 1550 (C=C str), 1530 (C=N str), 3100 (Ar-H), 2920 (C-H str), 1190 (C-O-C), 3200(NH₂ str)  
**NMR (DMSO, d₆):** δ 3.83 (s, 1H, CH₃), δ 1.68 (s, 1H, CH₃), δ 7.18-7.87 (m, 6H, Ar-H), δ 4.23 (s, 1H, CH), 6.99 (s, 1H, NH₂)

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