SYNTHESE, ANTICONVULSANT AND ANTIMICROBIAL EVALUATION OF SOME NEW 3-[5-(SUBSTITUTED-PHENYL)-[1,3,4]OXADIAZOLE-2-YL]-1-NAPTHALEN-2-YL-PROPAN-1-ONE

Arvind Kumar¹, Baby Rabiya Parveen and Vaishali

Department of Pharmaceutical Chemistry, S. D. College of Pharmacy and Vocational Studies, Bhopa Road, Muzaffarnagar - 251001, India.

ABSTRACT
A series of 3-[5-(Substituted-phenyl)-[1,3,4]oxadiazole-2-yl]-1-napthalen-2-yl-propan-1-one were synthesized, and characterized by ¹H NMR, IR and Mass spectroscopy. All synthesized compounds were evaluated for anticonvulsant activity and antibacterial activity. The anticonvulsant activity was carried out on maximal electroshock seizure (MES) model. The compounds 3-[5-(4-Hydroxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-napthalen-2-yl-propan-1-one (AR-2) and 3-[5-(4-Flouro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-napthalen-2-yl-propan-1-one (AR-3) showed comparable result of anticonvulsant activity as standard. Whereas Compound 3-[5-(4-Flouro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-napthalen-2-yl-propan-1-one (AR-3) showed recognizable antimicrobial activity against MTCC-521 gram (-)ve bacteria.

Keywords: 1,3,4-Oxadiazole derivatives, Anticonvulsant activity and antibacterial activity.

INTRODUCTION
Epilepsy, derived from Greek word epi lam banein, means to attack or seize. An epileptic seizure is a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain¹. Epilepsy is one of the most common neurological conditions, occurring in about 1% of the global population. It is the second most common disorder after stroke. Estimates suggest that available medication controls the seizures in only 50% of patients or decreases the incidence in only 75% of patients². The search for antiepileptic agents with more selectivity and lower toxicity continues to be an area of investigation in medicinal chemistry.³ The mechanisms of action of the antiepileptic drugs (AEDs) consist in the blockade of voltage-dependent Na⁺ channels or T-type Ca²⁺ channels, inhibition of glutamatergic transmission and facilitation of γ-aminobutyric acid (GABA) inhibitory neurotransmission.⁴ Oxadiazole, a heterocyclic nucleus with molecular formula C₅H₅N₂O. There are four possible isomers of oxadiazole depending on the position of nitrogen atom in the ring namely 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4-oxadiazoles, out of these 1,3,4-oxadiazoles are found to be most potent biologically.⁵ Six 1,3,4-Oxadiazoles compounds are not intermediates, it is very effective organic compounds in their own right. It has become an important construction motif for the development of new drugs. Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum⁶ such as anticonvulsant,⁷ anti-inflammatory,⁸ analgesic,⁷ antimalarial,³¹ antiviral²⁵ and hypoglycemic activities.²⁶-³¹ The aim of the present study was to synthesize new 1,3,4-Oxadiazole derivatives from 4-Naphthalen-2-yl-4-oxo-butyric acid hydrazide and
evaluate their anticonvulsant and antibacterial activities.

**EXPERIMENTAL**

**Chemistry**

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), CDH (India) and S.D. Fine were used without further purification. Thin layer chromatographic analysis of compounds was performed on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.25 mm on previously cleaned TLC plates of 20x5 cm using conventional spreader. The plates were placed in hot air oven at 105°C for 30 min. The solutions of compounds were applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of compounds. Melting points were determined by using open capillary melting point apparatus and are reported uncorrected. FT-IR spectra (KBr) were recorded on a Perkin-Elmer Spectrometer BX-II spectrophotometer. The 1H-NMR and spectra were recorded on Bruker 400 MHz High Resolution NMR spectrometer using TMS as an internal standard. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t) and multiplet (m) (Scheme - 1).

**Synthesis of 4-Naphthalen-2-yl-4-oxo-butyric acid (3)**

The compound 4-Naphthalen-2-yl-4-oxo-butyric acid were synthesized by the mixing of Naphthalene 12.8 g (0.1M) and Succinic anhydride 10.0 g (0.1M) in benzene (50 ml) and anhydrous Aluminium chloride 13.33 g (0.1M) and stirred on magnetic stirrer at room temperature for 48 hrs. After completion the reaction was refluxed for 24 h in the presence of concentrated H2SO4 (few drops). The resultant mixture was concentrated, cooled and poured into crushed ice. The oily matter thus separated out. The physico-chemical data was calculated: Rf value 0.62, % yield 52.19, brown color and oily in nature.

**Synthesis of 4-Naphthalen-2-yl-4-oxo-butyric acid hydrazide (5)**

4-Naphthalen-2-yl-4-oxo-butyric acid ethyl ester (50 mmol) and hydrazine hydrate 99% (50 mmol) in the presence of ethanol were refluxed for 20–24 h. This reaction was monitored with TLC. After the completion of reaction, excess solvent was removed under vacuum and the residue was filtered under suction, washed with water, and dried in air. The solid mass thus recrystallized from ethanol. The physicochemical data was calculated: Rf value 0.66, % yield 48.10, melting point 142-144°C, greenish yellow color and powdered form.

**Synthesis of 3-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one. 6a (AR-1)**

3-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one was prepared by the reaction of 4-Methoxybenzaldehyde (0.1 mmol) in the presence of Phosphorous oxychloride in a 100-ml round bottle flask. The reaction mixture was refluxed for 3 h. The resultant mixture was cooled, poured into crushed ice and neutralized by dissolving in sodium bicarbonate. The solid mass thus separated out was dried and recrystallized from ethanol.

Light brown colored flakes, M.f. C22H18N2O3, m.p. 210-212 0°C, Rf 0.42, % yield 45.61; IR (KBr, cm⁻¹, u): 3055.11(-CH3); 1639.89(-C=O); 1509.57(-C-C); 1269.80(-O-). 1H NMR (500 MHz, DMSO-d₆), δ 7.129-7.983 (m, 11H, Ar-H), 3.745 (s, 3H, -OCH₃), 2.216-3.238 (t, 4H, CH₂-CH₂). MS (m/z+) [M⁺] 359.39

**Synthesis of 3-[5-(4-Hydroxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one. 6b (AR-2)**

3-[5-(4-Hydroxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one was prepared by the reaction of 4-Hydroxy benzaldehyde (0.1 mmol) in the presence of Phosphorous oxychloride in a 100-ml round bottle flask. The reaction mixture was refluxed for 3 h. The resultant mixture was cooled, poured into
crushed ice and neutralize by dissolving in sodium bicarbonate. The solid mass thus separated out was dried and recrystallized from ethanol. Palish yellow colored flakes, M.f. C_{21}H_{16}N_{2}O_{3}, m.p. 205-207 °C, Rf 0.64, % yield 50.21, IR (KBr, cm\(^{-1}\), v): 2822.57(-CH); 1690.12(-C=O); 1474.41(-C-C); 1439.08(O-H); 1265.41(-O-).

\[^1\text{H} \text{ NMR (500 MHz, DMSO-d)}\], \(\delta\) 7.119-7.996 (m, 11H, Ar-H), 4.316 (s, 1H, -OH), 2.212-3.241 (t, 4H, CH\(_2\)-CH\(_2\)); MS (m/z+) [M\(^+\)] 345.36.

\text{Napthalene (1) + Dihydro-furan-2,5-dione (2) \rightarrow AlCl\(_3\) (Anhydrous) stirring for 48 hrs}

\text{4-Naphthalen-2-yl-4-oxo-butryc acid (3)}

\text{4-Naphthalen-2-yl-4-oxo-butryc acid ethyl ester (4)}

\text{4-Naphthalen-2-yl-4-oxo-butryc acid hydrazide (5)}

\text{1,3,4-Oxadiazole derivatives (6)}

\begin{center}
\begin{tabular}{l}
\textbf{Compound No.} & 6a & 6b & 6c \\
\textbf{R} & -OCH\(_3\), -OH, -F
\end{tabular}
\end{center}

\text{Synthetic Scheme-1}
Synthesis of 3-[5-(4-Fluoro-phenyl)-1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one. 6c (AR-3)
3-[5-(4-Fluoro-phenyl)-1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one was prepared by the reaction of 4-Fluorobenzaldehyde (0.1 mmol) in the presence of Phosphorous oxychloride in a 100-ml round bottle flask. The reaction mixture was refluxed for 3 h. The resultant mixture was cooled, poured into crushed ice and neutralize by dissolving in sodium bicarbonate. The solid mass thus separated out was dried and recrystallized from ethanol.

Brown colored flakes, M. f. C_{21}H_{19}FN_{2}O_{2}, m. p. 215-217 °C, Rf 0.54, % yield 54.44, IR (KBr, cm^{-1}, ν): 3049.22(-CH3); 1609.16(-C=O); 1274.24(-O-); 904.06(-C-F). ^1H NMR (500 MHz, DMSO-d), δ 7.121-7.980 (m, 11H, Ar-H), 2.210-3.232 (t, 4H, CH2-CH2). MS (m/z+) [M+1]^1347.35

RESULT AND DISCUSSION
Anticonvulsant Activity
The synthesized compounds were showed protection against MES test, indicative of their ability to inhibit the seizure spread. The results are shown in Table 1. The compounds AR-1, AR-2 and AR-3 were active in MES test. The compounds 3-[5-(4-Methoxy-phenyl)-1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-1), 3-[5-(4-Hydroxy-phenyl)-1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-2) and 3-[5-(4-Fluoro-phenyl)-1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-3) show protection at a dose of 50 mg/kg. None of these compounds showed neurotoxicity in the highest administered dose (300 mg/kg).

Antibacterial activity
A series of 3-[5-(Substituted-phenyl)-1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one were synthesized. The results are shown in Table 2. The compound AR-1, AR-2 and AR-3 showed very good inhibitory characteristics with stronger antimicrobial activity against MTCC-521 gram (-)ve bacteria were evaluated after Cup-plate method. The studied products are still under investigation. Their antibiotic properties have promising applications in the control of infections.

Table 1: Anticonvulsant activity of compounds

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>Various phase of convulsions (time in sec)</th>
<th>Flexion</th>
<th>Extensor</th>
<th>Stupor</th>
<th>Recovery</th>
<th>%Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Tween 80</td>
<td>Flexion</td>
<td>4.41±0.43</td>
<td>14.88±0.31</td>
<td>80.68±0.19</td>
<td>122.1±0.91</td>
<td>0</td>
</tr>
<tr>
<td>Std.</td>
<td>25</td>
<td>Flexion</td>
<td>0.59±0.1</td>
<td>1.22±0.13</td>
<td>29.01±0.92</td>
<td>61.47±0.46</td>
<td>100</td>
</tr>
<tr>
<td>AR-1</td>
<td>50</td>
<td>Extensor</td>
<td>2.92±0.30</td>
<td>12.96±0.28</td>
<td>71.25±0.24</td>
<td>100.5±0.50</td>
<td>66.66</td>
</tr>
<tr>
<td>AR-2</td>
<td>50</td>
<td>Stupor</td>
<td>1.77±0.30</td>
<td>9.22±0.40</td>
<td>64.84±0.35</td>
<td>85.48±0.10</td>
<td>83.33</td>
</tr>
<tr>
<td>AR-3</td>
<td>50</td>
<td>Recovery</td>
<td>2.12±0.42</td>
<td>11.62±0.12</td>
<td>59.23±0.23</td>
<td>97.68±0.38</td>
<td>83.33</td>
</tr>
</tbody>
</table>

Values represent the mean ± SD of six animals each group (n=6). AR-1, AR-2, AR-3 test compounds.

*indicates p<0.05, **indicates p<0.02 and ***indicates p<0.01 when compared to the control group.
(The mean difference was considered significant at 0.01 level.)

Graph 1.
### Table 2: Antibacterial activity of compounds

<table>
<thead>
<tr>
<th>COMPOUND CODE</th>
<th>Zone of inhibition in mm</th>
<th>E. coli (MTCC-521)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 μg/ml</td>
<td>30 μg/ml</td>
</tr>
<tr>
<td>AR-1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>AR-2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>AR-3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Graph 2.**

**CONCLUSION**

A series of substituted 1,3,4-Oxadiazole derivatives were synthesized, their anticonvulsant activity were evaluated after oral administration on MES model. The compounds 3-[5-(4-Hydroxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-2) and 3-[5-(4-Flouro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-3) displayed significant anticonvulsant activity and compound 3-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-1) shown mild activity. However, further studies need to be carried out to ascertain the precise mechanism of action of anticonvulsant activity of these compounds. The Compound 3-[5-(4-Flouro-phenyl)-[1,3,4]oxadiazole-2-yl]-1-naphthalen-2-yl-propan-1-one (AR-3) showed significant inhibitory characteristics with stronger antimicrobial activity against MTCC-521 gram (-)ve bacteria.

**ACKNOWLEDGEMENT**

The authors are thanks to animal house of S. D. College of Pharmacy & Vocational Studies, Muzaffarnagar to providing animals for pharmacological screening. Thanks are also due to JNU Delhi for recording the $^1$HNMR and IR spectra of the synthesized compounds.

**REFERENCES**


26. Shivarama BH, Gonsalves R, Sheony S, 
   Ibid, Synthesis of substituted 1,3,4-
   Oxadiazole, Journal of Science, 2000; 35:
   267.
27. Shafiee A, Sayadi A, Roozbahani MH, 
   Foroumadi A, Kamal F, Imidazole as an 
   important moiety, Arch. Pharm. Med. Chem., 
   2002; 10: 495.
   1,3,4-Oxadiazole, Ind. J. Chem., 1999; 
   38(B):1066.
29. Gulerman N, Rollas S, Kiraz M, Ekinci AC, 
   Vidin A, Farmaco, Synthesis of substituted 
   4-[(1,2,4]triazolo[3,4-b]-[1,3,4]thiadiazol-6-
30. Muhi-Eldeen Z, Nadir M, Aljobory NR, 
   Husseyn F, Stohs S, Synthesis of New 
   biologically active Triazoles derivative, Eur. 
31. Saini R, Chaturvedi S, Kesari AN, 
   Kushwaha S, Synthesis, Characterization 
   and biological Evaluation of 1,3,4-
   Oxadiazole, Der. Pharm. Chemica., 2010; 