Synthesis, Characterization and Anti-Inflammatory Activity of Some 1,3,4-Oxadiazole Derivatives

Arvind Kumar Singh\textsuperscript{a,*}, M. Lohani\textsuperscript{b} and R. Parthsarthy\textsuperscript{a}

\textsuperscript{a}Kamla Nehru Institute of Management and Technology, Faculty of Pharmacy, Sultanpur, India. \textsuperscript{b}Integral University Lucknow, Uttar Pradesh, India.

Abstract

A series of five-membered heterocyclic rings were synthesized by the reaction between benzoyl chloride and various chloro-nitro-benzoyl chlorides and semi-carbazide to form (C\textsubscript{1}-C\textsubscript{7}) compounds and was tested for their anti-inflammatory activity determined by rat-paw-oedema method. All the synthesis compounds have been characterized by \textsuperscript{1}HNMR, IR and Mass spectral data. The compounds were purified by column chromatography. All synthesized derivatives were determined by the carrageenan-induced rat-paw-oedema model for anti-inflammatory activity. The entire compound gives good response for the anti-inflammatory activity: [3-Chloro-N-[5-(3-Chloro-phenyl)-[1,3,4] oxadiazole-2yl] benzamide (C\textsubscript{4}), and [4-Nitro-N-[5-(4-Nitro-phenyl)-[1,3,4] oxadiazole-2yl] benzamide (C\textsubscript{7}). For this activity, indometacin was used as a standard drug and compared to new synthesized drugs. Some new synthesized drugs have shown better activities for the anti-inflammation.

Keywords: 1,3,4-Oxadiazoles; Anti-inflammatory; Synthesis; Heterocyclic.

Introduction

1, 3, 4-oxadiazole derivatives are heterocyclic compounds containing one oxygen and two nitrogen atoms in a five-membered ring. 1,3,4-oxadiazole derivatives have played a major role in the pharmaceutical chemistry. The number of so many synthetic compounds with oxadiazole nucleus used for antibacterial (1-5), antifungal (6-9), analgesic and anti-inflammatory activities (10-13). Derivatives of 1,3,4-oxadiazole with suitable substitution at 2,5-position have already been reported to have possible biological activities. 1,3,4-oxadiazole derivatives act as anticonvulsant and diuretics (14). These observations and our interest in the pharmaceutical chemistry of heterocyclic compounds promoted us to have synthesized different derivatives of 1,3,4-oxadiazole with different substituent at 2 and 5-positions. These derivatives have been also screened for their anti-inflammatory activity. Mostly, five-membered-ring aromatic systems having three heteroatoms at symmetrical position have been studied because of their physiological properties (15-16). It is also well established that various derivatives of 1,3,4-oxadiazole exhibit broad spectrum of pharmacological properties such as antibacterial and antifungal activities (17-18). 1,3,4-oxadiazole showed antibacterial properties similar to those of well known sulphonamide drugs (19).

Experimental

All chemicals were supplied by (Merck and
of animals. The initial paw volume and also the paw volume after 3 and 6 h of administrating carrageenan were measured. Percent paw oedema inhibition was calculated.

Results and Discussion

At the end of the experiment, it has been concluded that the compounds synthesized in the project have good yield value. The synthesized oxadiazole compounds were identified and characterized by IR, $^1$H NMR and MASS spectra. Then, the pharmacological activity was done. The entire compound had a good response for Anti-inflammatory activity : [3-Chloro-N-[5-(3-Chloro-phenyl)-[1,3,4] oxadiazole-2yl] benzamide (C$_3$),and [4-Nitro-N-[5-(4-Nitro-phenyl)-[1,3,4] oxadiazole-2yl]benzamide (C$_5$). Substitution of 2-chloro-benzoic acid at 2,5-position anti-inflammatory activity greater (C$_2$) than 3-chloro substituted compound (C$_3$) and 4-cloro-benzoic acid compound (C$_4$) substituted at 2,5 position anti-inflammatory activity greater than 2-chloro-substituted compound (C$_2$). While substitution of 4-nitro-compounds (C$_7$) at 2,5-position greater than other 2-nitro and 3-nitro substituted compounds (C$_5$ and C$_6$).

Compound 1: [N-(5-Phenyl-[1, 3, 4] oxadiazol-2-yl)-benzamide]
IR( KBr,cm$^{-1}$) : 3214( NH) ,1664(C=O) ,1070( N-N) ,1232(C-O-C) ; $^1$HNMR(DMSO-$d_6$,400 MHz), 8.72 (s, 1H, J = 7.6 Hz) , 7.72 (d, 3H, J = 7.9 Hz), 7.62 (d, 1H, J = 7.9 Hz), 7.62 (d, 1H, J = 7.6 Hz, MASS (ESI):m/z (%), 266 (23), 262 (14), 260 (100), 249 (17), 248 (100), analytical calculated for C$_{15}$H$_{11}$N$_3$O$_2$ c = 67.90, H = 4.23, N = 15.86, O = 12.12, found = C = 67.92, H = 4.15, N = 15.84, O = 12.07.

Compound 2: [2-Chloro-N-[5-(2-chloro-phenyl)-[1,3,4]oxadiazol-2-yl]benzamide]
IR( KBr,cm-1): 3214(NH),1664(C=O) ,1070( N-N) ,1232(C-O-C) ; $^1$HNMR(DMSO-d$_6$,400 M Hz), 8.72 (s, 1H, J = 7.6 Hz) , 7.72 (d, 3H, J = 7.9 Hz), 7.62 (d, 1H, J = 7.9 Hz), 7.62 (d, 1H, J = 7.6 Hz, MASS (ESI):m/z (%), 266 (23), 262 (14), 260 (100), 249 (17), 248 (100), analytical calculated for C$_{15}$H$_{11}$N$_3$O$_2$Cl; c = 67.90, H = 4.23, N = 15.86, O = 12.12, found = C = 49.62, H = 2.86, N = 23.48.

Material and methods

General procedure for synthesis of compounds (C$_1$ to C$_7$):- (1:1 molar ratio) Aromatic, phosphorus pentachloride and benzene were taken in RBF, fitted with air condenser and calcium chloride guard tube. The mixture was heated gently to melt with vigorous shaking at around 50°C. After 30 min excess POCl$_3$ was distilled out. The residue was dried well and used for the next reaction. Then, semicarbazide was added to the respected acid chloride and reflux for 5 h. These programs of the reaction were monitored by checking the TLC. The excess benzene was distilled out, neutralizing with aq. NaHCO$_3$ and the compound was extracted with chloroform. The crude was obtained through distillation of chloroform under reduce pressure

Anti-inflammation activity

Anti-inflammation activity of all synthesized derivatives was determined by the carrageenan-induced rat paw oedema model. Albino rats (100-200 g) were divided into 3 groups as control, test and standard (six animals per group). Overnight fasted animals were used and during that period only tap water was given. Generally, indomethacin was used as standard drug. Both test and standard drugs were suspended in 1% carboxymethyl cellulose (CMC) and administered orally through gastric gavage needle. One percent of CMC was administered in control group. After 1 h of administrating the compound, we induced the carrageenan (1%) by the sub planner surface of the right hind paws
Compound 3: [4-Chloro-N-[5-(4-chlorophenyl)-[1,3,4] oxadiazol-2-yl]benzamide]

IR (KBr, cm-1) P: 3272 (NH), 1668 (C=O), 7.76 (d, 2H, J = 7.3 Hz), 7.68 (d, 1H, J = 7.2 Hz), 7.73 (d, 2H, J = 8.2 Hz); 1HNMR (DMSO-d$_6$, 400 MHz), 7.76 (d, 2H, J = 7.3 Hz), 7.68 (d, 1H, J = 7.2 Hz), 7.73 (d, 2H, J = 8.2 Hz); MASS (C-SI), m/z (%) analytical calculated for C$_{15}$H$_9$N$_3$O$_2$Cl$_2$, C = 48.98, H = 2.83, N = 23.48, found, C = 47.96, H = 2.81, N = 23.32.

Compound 4: [3-Chloro-N-[5-(3-Chlorophenyl)-[1,3,4] oxadiazole-2yl]benzamide]

IR (KBr, cm-1): 3268 (NH), 1668 (C=O), 7.72 (d, 2H, J = 8.4 Hz), 7.78 (m, 3H, J = 8.3 Hz); 1HNMR (DMSO-d$_6$, 400 MHz), 7.71 (d, 1H, J = 7.24 Hz), 7.77 (d, 1H, J = 7.3 Hz), 7.73 (d, 1H, J = 8.3 Hz), 7.22 (m, 1H, J = 8.21 Hz); MASS (C-SI), m/z (%) analytical calculated for C$_{14}$H$_9$N$_5$O$_6$, C = 48.92, H = 2.44, N = 30.47, found C = 48.46, H = 2.90, N = 30.42.

Compound 5: [2-Nitro-N-[5-(2-Nitrophenyl)-[1,3,4] oxadiazole-2yl]benzamide]

IR (KBr cm-1): 3272 (NH), 1670 (C=O), 7.70 (d, 1H, J = 7.25 Hz), 7.78 (d, 1H, J = 7.4 Hz), 7.73 (d, 1H, J = 8.3 Hz); 1HNMR (DMSO-d$_6$, 400 MHz), 7.70 (d, 1H, J = 7.25 Hz), 7.78 (d, 1H, J = 7.4 Hz), 7.73 (d, 1H, J = 8.3 Hz); MASS (C-SI), m/z (%) analytical calculated for C$_{15}$H$_9$N$_5$O$_6$, C = 48.97, H = 2.93, N = 30.48, found C = 48.27, N = 2.90, N = 30.42.

Compound 6: [3-Nitro-N-[5-(3-Nitrophenyl)-[1,3,4] oxadiazole-2yl]benzamide]

IR (KBr Cm-1): 3271 (NH), 1668 (C=O), 7.71 (d, 1H, J = 7.24 Hz), 7.77 (d, 1H, J = 7.3 Hz), 7.73 (d, 1H, J = 8.3 Hz), 7.22 (m, 1H, J = 8.21 Hz); 1HNMR (DMSO-d$_6$, 400 MHz), 7.71 (d, 1H, J = 7.24 Hz), 7.77 (d, 1H, J = 7.3 Hz), 7.73 (d, 1H, J = 8.3 Hz), 7.22 (m, 1H, J = 8.21 Hz); MASS (C-SI), m/z (%) analytical calculated for C$_{14}$H$_9$N$_5$O$_6$, C = 48.92, H = 2.44, N = 30.47, found C = 48.46, H = 2.90, N = 30.42.
Table 1. Physical properties of compounds (C₁ to C₇).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Yield (%)</th>
<th>Rf</th>
<th>MP(°C)</th>
<th>Mol. Formula</th>
<th>Mol. Wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₁</td>
<td>72%</td>
<td>0.715</td>
<td>212</td>
<td>C₁₃H₁₁N₅O₆</td>
<td>265.2</td>
</tr>
<tr>
<td>C₂</td>
<td>66%</td>
<td>0.692</td>
<td>214</td>
<td>o-C₁₅H₁₃N₅O₆Cl₂</td>
<td>334.16</td>
</tr>
<tr>
<td>C₃</td>
<td>79%</td>
<td>0.678</td>
<td>213</td>
<td>m-C₁₅H₁₃N₅O₆Cl₂</td>
<td>334.16</td>
</tr>
<tr>
<td>C₄</td>
<td>82%</td>
<td>0.682</td>
<td>211</td>
<td>p-C₁₅H₁₃N₅O₆Cl₂</td>
<td>334.16</td>
</tr>
<tr>
<td>C₅</td>
<td>80%</td>
<td>0.721</td>
<td>273</td>
<td>o-C₁₅H₁₃N₅O₆Cl₂</td>
<td>355.26</td>
</tr>
<tr>
<td>C₆</td>
<td>73%</td>
<td>0.761</td>
<td>266</td>
<td>m-C₁₅H₁₃N₅O₆Cl₂</td>
<td>355.26</td>
</tr>
<tr>
<td>C₇</td>
<td>78%</td>
<td>0.672</td>
<td>271</td>
<td>p-C₁₅H₁₃N₅O₆Cl₂</td>
<td>355.26</td>
</tr>
</tbody>
</table>

N = 30.45.

**Compound 7**: [4-Nitro-N-[5-(4-Nitro-phenyl]-[1, 3, 4] oxadiazole-2yl] benzamide

IR(KBr Cm⁻¹) :- 3272(NH), 1665 (C=O), 1078 (N-N), 1260 (C-O-C), 783(C-Cl)

H₁NMR (DMS+ds400M H₂):- 7.70(d, 1H, J = 7.23 H₂), 7.2 (d, 1H, J = 7.2 H₂), 7.74 (d, 1H, J = 8.4 H₂), 7.26 (m, 1H, J = 8.20 H₂),


Acknowledgment

We are thankful to Dr. R. PATH SARTHY kamla, Nehru institute of management of technology Sultanpur (up), for his kind support. We are also very grateful to Mr. Subrata Jana (the award of PhD) from Bengal Engineering and science university, Howrah India.

Table 2. Anti-inflammatory activities of compounds C₁ to C₇.

<table>
<thead>
<tr>
<th>Columns</th>
<th>Dose Mg/Kg</th>
<th>Inhibition of paw oedema after 3 h (%) ¹</th>
<th>Inhibition of paw oedema after 6 h (%) ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1</td>
<td>30</td>
<td>3.28 ± 0.28</td>
<td>58.24</td>
</tr>
<tr>
<td>C-2</td>
<td>30</td>
<td>2.48 ± 0.23</td>
<td>56.48</td>
</tr>
<tr>
<td>C-3</td>
<td>30</td>
<td>3.46 ± 0.22</td>
<td>51.16</td>
</tr>
<tr>
<td>C-4</td>
<td>30</td>
<td>1.62 ± 0.27</td>
<td>70.98</td>
</tr>
<tr>
<td>C-5</td>
<td>30</td>
<td>3.26 ± 0.241</td>
<td>59.48</td>
</tr>
<tr>
<td>C-6</td>
<td>30</td>
<td>3.22 ± 0.281</td>
<td>53.98</td>
</tr>
<tr>
<td>C-7</td>
<td>30</td>
<td>1.52 ± 0.271</td>
<td>69.54</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>0.36 ± 0.28</td>
<td>_</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>40</td>
<td>1.78 ± 0.340</td>
<td>66.44</td>
</tr>
</tbody>
</table>

¹: Dose for 1-7: 30 mg/Kg b.wt; 2: Dose for indomethacin 40 mg/Kg b.wt; mean ± SEM; n=6

References

7. Xia-Juan Zou, Lu-Hua Lai, Gui-Yu Jin and Zu-Xing Zhang. Synthesis and antimicrobial activities if 1,3,4...


This article is available online at http://www.ijpr.ir
کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت‌های کاربردی در تدوین و چاپ مقاله