Synthesis, Antimicrobial and Antioxidant Activity of Some Oxindoles

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Rindhe, et al.: Bioactive Oxindole Derivatives

The present work describes the synthesis and spectral analysis of some new 3(Z)-{4-[4-(arylsulfonyl)piperazin-1-ylbenzylidene]-1,3-dihydro-2H-indol-2-one (5a-j). Ten of the synthesized compounds were screened in vitro against six species of microorganisms, Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Pseudomonas aeruginosa, Aspergillus niger and Aspergillus clavatus. Most of the compounds exhibited significant antimicrobial activity. All of these compounds were also screened in vitro for the antioxidant activity using DPPH assay. Most of them have shown very significant antioxidant activity.

Key words: Antibacterial, antifungal and antioxidant activity, oxindole

Oxindole and other related ring systems, have several interesting biological activities[1-4]. According to the literature survey, 1-substituted aminomethyl-3-cyclohexylthiosemicarbazone-2-indolinones have shown significant antifungal, antibacterial and antiviral activities both in vivo and in vitro[5]. The new 1,3-dihydro-3-hydroxy-3-[2-hydroxyimino-2-(substituted phehyl)ethyl]-2H-indol-2-ones were synthesized and tested for antimicrobial activity and majority of the compounds were found to exhibit promising antibacterial and antifungal activities[6]. 3-amino-1-hydroxy-oxindole and related compounds have found to show significant antimicrobial activity[7]. Oxindole and related indole derivatives have also been found to show very good antioxidant activity[8,9].

Sulfonamide based drugs are known for their antimicrobial activities[10]. Arylsulfonamide-oxindole hybrid[11] has been explored for their anticancer activity, but few attempts have been made to explore the antimicrobial and antioxidant activity of aryl sulfonamide-oxindole hybrid. We herein, report the synthesis and biological testing of some 3(Z)-{4-[4-(arylsulfonyl)piperazin-1-ylbenzylidene]-1,3-dihydro-2H-indol-2-one (5a-j). These sulfonamide based oxindole derivatives were tested for antibacterial, antifungal and antioxidant activity.

All the recorded melting points were determined in open capillary and are uncorrected. IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc. 1H NMR and 13C NMR spectra were recorded on 400 MHz spectrophotometer in DMSO-d$_6$ as a solvent and TMS as an internal standard. Peak values are shown in δ ppm. Mass spectra were obtained using a Waters mass spectrometer.

General procedure for the synthesis of t-butyl-4-[4[(Z)-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]phenyl]piperazine-1-carboxylate (3) used was as follows; a mixture of 1 (0.01 mol) and 2 (0.01 mol) was dissolved in toluene and ammonium acetate (0.03 mol) was added to it. The reaction mixture stirred at 80° for 6 h. The reaction mixture was cooled to room temperature and poured into Hexane. Solid was obtained by filtration and crystallized from alcohol.

Compound (3): m.p.186°, Anal. Calcd. for C$_{24}$H$_{27}$N$_3$O$_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.00; H, 6.69; N, 10.33. IR (KBr)$\nu_{max}$ (cm$^{-1}$): 3621, 3380, 2887, 2336, 1693, 1590, 1340, 1078, 1030, 951. 1H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 1.40 (9H, s), 3.31 (4H, s), 3.45 (4H, s), 6.82 -6.98 (4H, m), 7.16 (1H, dt), 7.52 (1H, s, alken H), 7.63 (1H, m), 7.76 (1H, d), 8.44 (1H, d), 10.48 (1H, s, NH). 13C NMR (400 MHz, DMSO-d$_6$) δ (ppm): 169.38, 167.71, 137.51, 136.79, 134.59, 127.69, 125.97, 124.48, 123.95, 122.16, 121.70,
120.88, 118.92, 114.45, 110.19, 79.26, 46.93 and 28.24. MS m/z: 405 (M+) with all isotopic and other peaks.

General procedure for the synthesis of (Z)-3-(4-piperazin-1-ylbenzylidene)-1,3-dihydro-2H-indol-2-one (4) was as follows, compound 3 (0.01 mol) was dissolved in 10 ml methylene dichloride and 3 ml trifluoroacetic acid was added slowly to the reaction mixture (Scheme 1). The reaction mixture stirred at room temperature for 3 h and concentrated under vacuum. The reaction mixture was basified by liquor NH$_3$ and extracted by ethyl acetate. Ethyl acetate layer separated, dried over Na$_2$SO$_4$ and concentrated under vacuum.

General procedure for the synthesis of 5 (a-j) was as follows; compound 4 (0.01 mol) and aromatic sulfonyl chloride (0.01 mol) were dissolved in tetrahydrofuran in presence of pyridine (0.03 mol) and catalytic amount of dimethyl aminopyridine. The reaction mixture was stirred at room temperature for 8 h and then poured into water. Aqueous layer extracted by ethyl acetate. Ethyl acetate layer separated, dried over Na$_2$SO$_4$ and concentrated under vacuum. The crude product obtained, was crystallized by alcohol. The Melting point and yield of the 5 (a-j) is given in Table 1.

**TABLE 1: STRUCTURAL DATA OF THE SYNTHESIZED OXINDOLES**

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>m.p. (°)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>2-naphthyl</td>
<td>157</td>
<td>80</td>
</tr>
<tr>
<td>5b</td>
<td>6-coumarin</td>
<td>181</td>
<td>82</td>
</tr>
<tr>
<td>5c</td>
<td>4-phenoxyphenyl</td>
<td>143</td>
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<tr>
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<td>4-ethylphenyl</td>
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<td>85</td>
</tr>
<tr>
<td>5e</td>
<td>4-methylphenyl</td>
<td>225</td>
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</tr>
<tr>
<td>5f</td>
<td>4-N-acetylphenyl</td>
<td>240</td>
<td>90</td>
</tr>
<tr>
<td>5g</td>
<td>5-dimethylamino-2-naphthyl</td>
<td>154</td>
<td>67</td>
</tr>
<tr>
<td>5h</td>
<td>4-t-butylphenyl</td>
<td>144</td>
<td>78</td>
</tr>
<tr>
<td>5i</td>
<td>4-trifluoromethoxyphenyl</td>
<td>250</td>
<td>89</td>
</tr>
<tr>
<td>5j</td>
<td>4-isopropylphenyl</td>
<td>138</td>
<td>77</td>
</tr>
</tbody>
</table>

Compound 5a, Anal. Calcd. for C$_{25}$H$_{25}$N$_3$O$_3$S: C, 70.28; H, 5.08; N, 8.48. Found: C, 70.21; H, 5.06; N, 8.45. IR (KBr)_max (cm$^{-1}$): 3621, 3380, 3277, 2887, 2336, 1693, 1592, 1355, 1236, 1055, 951, $^1$H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 3.01 (4H, s), 3.47 (4H, s), 6.53-8.76 (16H, m, aromatic protons), 10.52 (1H, s, NH). MS m/z: 495 (M+) with all isotopic and other peaks. Compound 5b, Calcd. for C$_{28}$H$_{23}$N$_3$O$_5$S: C, 65.48; H, 4.51; N, 8.18. Found: C, 65.35; H, 4.49; N, 8.15. IR (KBr)_max (cm$^{-1}$): 3583, 3342, 2887, 1735, 1693, 1592, 1355, 1236, 1055, 951, $^1$H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 3.08 (4H, s), 3.44 (4H, s), 6.67-8.39 (14H, m, aromatic protons), 10.52 (1H, s, NH). MS m/z: 513 (M+) with all isotopic and other peaks. Compound 5c, Calcd. for C$_{31}$H$_{27}$N$_3$O$_4$S: C, 69.26; H, 5.06; N, 7.82. Found: C, 69.20; H, 5.05;
S. aureus and the fungi used were...
acid (an antioxidant agent) as a positive control. The compounds were tested for antioxidant activity at 200, 100 and 50 µg/ml concentrations. Amongst the compounds screened for antioxidant activity, 5b, 5c, 5f, 5g and 5i showed very good antioxidant activities as shown in Table 4. Compounds 5a, 5d, 5e, 5h and 5j do not show significant antioxidant activity. The compounds with alkyl substituent do not show any radical scavenging activity while the compounds with heterocyclic ring system like coumarin or the one with substituents like N(CH$_3$)$_2$, OCF$_3$ and N-acetyl show very significant antioxidant activity. It suggests the significant role played by these substituents as radical scavengers.

In conclusion, a series of oxindole derivatives were synthesized and tested for antifungal, antibacterial and antioxidant activity. Most of the compounds have shown very good antimicrobial and antioxidant activity, which suggest a possible clinical significance of 3(Z)-{4-[4-(arylsulfonyl)piperazin-1-ylbenzylidene)-1,3-dihydro-2H-indol-2-ones.
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Accepted 2 April 2011
Revised 14 March 2011
Received 15 March 2010