SYNTHESIS OF SOME NEW 1,2,3-TRIAZOLE DERIVATIVES OF INDOLE WITH POTENTIAL ANTIMICROBIAL ACTIVITY

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ABSTRACT

Seven novel [1-(1-benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]-acetic acid ethyl ester and their derivatives (5a-g) have been synthesized through cyclization from the intermediate, (1-prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester (3) by using (1H-indol-3-yl)-acetic acid ethyl ester (1) and 3-bromo-propyne (2) as raw materials. The chemical structures of these compounds have been established by IR, 1H, 13C-NMR, Mass spectral data and elemental analysis. The newly synthesized compounds were used to find their ability towards antibacterial activity.

KEYWORDS: Seven novel, newly synthesized compounds, antibacterial activity.

INTRODUCTION

1,2,3-Triazoles have been the subject of considerable research, mainly due to their usefulness in synthetic organic chemistry and also due to their variety of interesting biological activities, forming part of the scaffolds of antibacterial and antituberculosis agents [1], neuraminidase inhibitors [2], anticancer compounds [3], antiviral agents [4], analgesic compounds [5], fungicidal activity [6], protein tyrosine phosphatase inhibitors [7] and assorted biomolecules (nucleosides and nucleotides) [8].
RESULTS AND DISCUSSION

On the basis of these findings, we have designed and synthesized a novel series of indole based 1,2,3-triazoles as good antimicrobial agents. The synthetic route leading to the title compounds is summarized in scheme 1. Thus the key intermediate, (1-prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester (3) has been prepared from commercially available (1H-indol-3-yl)-acetic acid ethyl ester (1) and 3-bromo-propyne (2) in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile solvent at reflux temperature on constant stirring for 15 h. Finally, the intermediate 3 on cyclization with benzyl halide or substituted benzyl halide (4a-g) and sodium azide in ethanol solvent at reflux temperature on uniform stirring for 5-7 h to get the title compounds [1-(1-benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]-acetic acid ethyl ester and their derivatives (5a-g) in good yields. The chemical structures of these compounds have been established by IR, $^1$H & $^{13}$C-NMR, mass spectral data and elemental analysis. Finally, the newly synthesized compounds were used to find their ability towards antibacterial activity.

ANTIMICROBIAL ACTIVITY

The antibacterial activity in terms of minimum inhibitory concentration (MIC) of the newly synthesized title compounds, [1-(1-benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]-acetic acid ethyl ester and their derivatives (5a-g) was evaluated by the agar diffusion method [9] using two representative gram positive bacteria like Micrococcus luteus (ATCC 9341) and Staphylococcus aureus (ATCC 25923) and two gram negative bacteria such as Escherichia coli (ATCC 27853) and Pseudomonas aeruginosa (ATCC 27853) on tryptic soya agar media. Dimethylsulfoxide and Cephalexin were used as solvent and standard respectively for the test compounds. Among the products 5a-g, the compounds 5e, 5f and 5g were the most potent and were found almost to be equipotent to standard. The remaining compounds performed moderate to good antibacterial activity (Table 1). It is interesting to note that none of the compound is inactive against employed any bacterial strain. The outstanding properties of this new class of antibacterial substances deserve further investigation in order to clarify the mode of action at molecular level, responsible for the activity observed. More extensive study is also warranted to determine additional physicochemical and biological parameters to have a deeper insight into structure-activity relationship and to optimize the effectiveness of this series of molecules.
Scheme 1: (i) DBU, CH$_3$CN, Reflux, 15 h; (ii) NaN$_3$, EtOH, Reflux, 5-7 h

4 X a) = Cl, b) = Cl, c) = Cl, d) = Br, e) = Br, f) = Br, g) = Cl

4/5 Y a) = H, b) = 4-F, c) = 4-Cl, d) = 4-Br, e) = 4-I, f) = 2-CH$_3$, g) = 4-OCH$_3$

Table 1: Antibacterial activity of the newly synthesized compounds 4a-g

<table>
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<th>Entry</th>
<th>Compound</th>
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<td>14</td>
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<tr>
<td>2</td>
<td>5b</td>
<td>20</td>
<td>18</td>
<td>17</td>
<td>12</td>
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<td>3</td>
<td>5c</td>
<td>16</td>
<td>15</td>
<td>16</td>
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<tr>
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<td>5d</td>
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<tr>
<td>8</td>
<td>Cephalexin</td>
<td>26</td>
<td>23</td>
<td>22</td>
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</tbody>
</table>

EXPERIMENTAL

All reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were obtained on a PerkinElmer BX series FT-IR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for $^1$H NMR and 100 MHz spectrometer for $^{13}$C NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Synthesis of (1-prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester (3)

The mixture of (1H-indol-3-yl)-acetic acid ethyl ester (1) (0.01 mol) in acetonitrile (10 ml) and DBU (0.02 mol) was uniformly stirred for a few minutes to get homogeneous solution. Subsequently, 3-bromo-propyne (2) (0.01 mol) was added and the whole reaction mixture was refluxed for 15 h on constant stirring. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum and CH$_2$Cl$_2$ (20 ml) was added. The organic phase was washed with aqueous NH$_4$Cl solution (5%, 20 ml), dried with anhydrous Na$_2$SO$_4$
and concentrated under vacuum. The residue was purified by column chromatography (CH2Cl2) and recrystallized from CH2Cl2/hexane (1:1 v/v) to obtain pure (1-prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester (3).

**Synthesis of [1-(1-benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]-acetic acid ethyl ester and their derivatives (5a-g)**

The mixture of compound 3 (0.01 mol), sodium azide (0.03 mol) and benzyl halide or substituted benzyl halide (4a-g) (0.01 mol) in ethanol solvent (15 ml) was constantly stirred at reflux temperature for 5-7 h. After accomplishment of the reaction (examined by TLC), the reaction mixture was poured in ice-cold water and obtained solid was filtered off, washed with H2O, then with hexane and dried under vacuum. The crude product was purified by column chromatography (CH2Cl2/EtOH 98:2 v/v) and recrystallized from CH2Cl2/hexane (1:1 v/v) to afford [1-(1-benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]-acetic acid ethyl ester and their derivatives (5a-g) in pure form.

**PHYSICAL AND SPECTRAL DATA**

(1-Prop-2-ynyl-1H-indol-3-yl)-acetic acid ethyl ester (3) Color: Yellow solid; Yield: 71 (%); M.P: 125-127 °C; IR (KBr) cm⁻¹: 3290 (C-H, H-C≡C), 3024 (Ar-H), 2962 (C-H, CH₂), 2210 (C=C), 1740 (C=O), 1588 (C=C), 1210 (C-O); ¹H-NMR (CDCl₃) δ: 7.85 (1H, s, CH), 7.68-7.37 (4H, m, Ar-H), 4.26 (1H, s, H-C≡C), 4.10 (2H, s, CH₂), 4.04 (2H, q, J = 5.6 Hz, CH₂), 3.85 (2H, s, CH₂), 1.26 (3H, t, J = 5.6 Hz, CH₃); ¹³C-NMR (CDCl₃) δ: 168.3, 142.5, 136.3, 125.6, 123.7, 121.4, 115.6, 117.4, 112.5, 78.6, 69.5, 57.4, 44.2, 33.5, 13.4; MS m/z: 241 (M⁺); Elemental analysis calculated for C₁₅H₁₅N₂O₂: C-74.67, H-6.27, N-5.81, O-13.26. Found: C-72.36, H-5.98, N-5.21, O-12.78.

[1-(1-Benzyl-1H-[1,2,3]triazol-4-ylmethyl)-1H-indol-3-yl]-acetic acid ethyl ester (5a) Color: Pale yellow solid; Yield: 74 (%); M.P: 112-124 °C; IR (KBr) cm⁻¹: 3036 (C-H, Ar), 2965 (C-H, CH₂), 2161 (N=N), 1735 (C=O), 1594 (C=C), 1220 (C-O); ¹H-NMR (CDCl₃) δ: 7.81 (1H, s, CH), 7.62-7.31 (9H, m, Ar-H), 4.29 (1H, s, CH), 4.21 (2H, s, CH₂), 4.09 (2H, q, J = 5.2 Hz, CH₂), 3.92 (2H, s, CH₂), 3.76 (2H, s, CH₂), 1.21 (3H, t, J = 5.2 Hz, CH₃); ¹³C-NMR (CDCl₃) δ: 170.5, 146.3, 141.0, 136.5, 135.2, 132.4, 130.2, 129.6 (2), 127.6 (2), 124.0, 123.6, 121.5, 118.4, 114.8, 113.6, 58.6, 57.6, 57.1, 34.8, 12.8; MS m/z: 374 (M⁺); Elemental analysis calculated for C₂₂H₂₂N₄O₂: C-70.57, H-5.92, N-14.96, O-8.55. Found: C-69.23, H-5.26, N-13.56, O-7.98.
{1-[1-(4-Fluoro-benzyl)-1H-[1,2,3]triazol-4-ylmethyl]-1H-indol-3-yl]acetic acid ethyl ester (5b) Color: Brown solid; Yield: 70 (%); M.P: 130-132 °C; IR (KBr) cm⁻¹: 3029 (C-H, Ar), 2970 (C-H, CH₂), 2167 (N=N), 1741 (C=O), 1565 (C=C), 1223 (C-O); ¹H-NMR (CDCl₃) δ: 7.77 (1H, s, CH), 7.70 (2H, d, J = 7.4 Hz, Ar-H), 7.64-7.35 (4H, m, Ar-H), 7.32 (2H, d, J = 7.4 Hz, Ar-H), 4.20 (1H, s, CH), 4.14 (2H, s, CH₂), 4.01 (2H, q, J = 5.4 Hz, CH₂), 3.88 (2H, s, CH₂), 3.72 (2H, s, CH₂), 1.23 (3H, t, J = 5.4 Hz, CH₃); ¹³C-NMR (CDCl₃) δ: 172.3, 161.0, 142.3, 141.2, 135.2, 134.2, 132.0, 130.7 (2), 125.3, 122.3, 121.2, 118.4, 116.2 (2), 114.2, 113.2, 58.4, 57.4, 56.4, 34.2, 12.9; MS m/z: 392 (M⁺); Elemental analysis calculated for C₂₂H₂₁FN₄O₂: C=67.33, H=5.39, F=4.84, N=14.28, O=8.15. Found: C=66.21, H=5.06, F=4.23, N=13.65, O=7.69.

{1-[1-(4-Chloro-benzyl)-1H-[1,2,3]triazol-4-ylmethyl]-1H-indol-3-yl]acetic acid ethyl ester (5c) Color: White solid; Yield: 74 (%); M.P: 162-164 °C; IR (KBr) cm⁻¹: 3038 (C-H, Ar), 2962 (C-H, CH₂), 2172 (N=N), 1738 (C=O), 1574 (C=C), 1232 (C-O); ¹H-NMR (CDCl₃) δ: 7.74 (1H, s, CH), 7.68 (2H, d, J = 7.0 Hz, Ar-H), 7.60-7.41 (4H, m, Ar-H), 7.29 (2H, d, J = 7.0 Hz, Ar-H), 4.41 (1H, s, CH), 4.12 (2H, s, CH₂), 3.96 (2H, q, J = 6.0 Hz, CH₂), 3.80 (2H, s, CH₂), 3.68 (2H, s, CH₂), 1.31 (3H, t, J = 6.0 Hz, CH₃); ¹³C-NMR (CDCl₃) δ: 172.5, 144.2, 142.0, 136.4, 135.1, 134.8, 131.5 (2), 130.2, 129.5 (2), 127.4, 123.4, 117.4, 116.2, 113.6, 61.2, 59.6, 54.8, 36.2, 14.5, 12.98; MS m/z: 408 (M⁺); Elemental analysis calculated for C₂₂H₂₁ClN₄O₂: C=64.62, H=5.18, Cl=8.67, N=13.70, O=7.83. Found: C=63.20, H=4.89, Cl=7.98, N=12.65, O=7.21.

{1-[1-(4-Bromo-benzyl)-1H-[1,2,3]triazol-4-ylmethyl]-1H-indol-3-yl]acetic acid ethyl ester (5d) Color: Yellow solid; Yield: 72 (%); M.P: 154-156 °C; IR (KBr) cm⁻¹: 3044 (C-H, Ar), 2974 (C-H, CH₂), 2162 (N=N), 1740 (C=O), 1565 (C=C), 1241 (C-O); ¹H-NMR (CDCl₃) δ: 7.71 (1H, s, CH), 7.68 (2H, d, J = 7.2 Hz, Ar-H), 7.65-7.39 (4H, m, Ar-H), 7.24 (2H, d, J = 7.2 Hz, Ar-H), 4.31 (1H, s, CH), 4.25 (2H, s, CH₂), 4.12 (2H, q, J = 6.2 Hz, CH₂), 3.84 (2H, s, CH₂), 3.68 (2H, s, CH₂), 1.36 (3H, t, J = 6.2 Hz, CH₃); ¹³C-NMR (CDCl₃) δ: 171.6, 145.2, 141.7, 137.2, 136.4, 133.1, 130.2 (2), 129.4, 128.7 (2), 128.4, 124.5, 119.6, 117.1, 114.9, 63.2, 58.4, 55.3, 38.4, 16.2, 13.65; MS m/z: 453 (M⁺); Elemental analysis calculated for C₂₂H₂₁BrN₄O₂: C=58.29, H=4.67, Br=17.63, N=12.36, O=7.06. Found: C=57.46, H=4.25, Br=16.87, N=11.95, O=6.79.

{1-[1-(4-Iodo-benzyl)-1H-[1,2,3]triazol-4-ylmethyl]-1H-indol-3-yl]acetic acid ethyl ester (5e) Color: White solid; Yield: 75 (%); M.P: 147-149 °C; IR (KBr) cm⁻¹: 3056 (C-H, Ar),
2969 (C-H, CH₂), 2174 (N=N), 1744 (C=O), 1570 (C=C), 1248 (C-O); ¹H-NMR (CDCl₃) δ: 7.81 (1H, s, CH), 7.74 (2H, d, J = 7.6 Hz, Ar-H), 7.61-7.36 (4H, m, Ar-H), 7.36 (2H, d, J = 7.6 Hz, Ar-H), 4.25 (1H, s, CH), 4.21 (2H, s, CH₂), 4.18 (2H, q, J = 5.8 Hz, CH₂), 3.91 (2H, s, CH₂), 3.71 (2H, s, CH₂), 1.41 (3H, t, J = 5.8 Hz, CH₃), 1.34 (3H, q, J = 7.6 Hz, Ar); ¹³C-NMR (CDCl₃) δ: 172.0, 143.6, 142.1, 139.6, 137.4, 135.2, 132.1 (2), 130.5, 129.7 (2), 127.5, 126.7, 121.0, 119.4, 116.1, 65.7, 59.4, 53.7, 40.2, 17.4, 15.6; MS m/z: 500 (M⁺); Elemental analysis calculated for C₂₂H₂₁N₄O₂: C=52.81, H=4.25, I-25.36, N-11.20, O-6.40. Found: C=51.36, H=4.02, I-24.52, N-10.87, O-5.98.

1-[1-{2-Methyl-benzyl]-1H-[1,2,3]triazol-4-ylmethyl}-1H-indol-3-yl]-acetic acid ethyl ester (5f) Color: Pale yellow solid; Yield: 77 (%); M.P: 133-135 °C; IR (KBr) cm⁻¹: 3062 (C-H, Ar), 2961 (C-H, CH₂), 2170 (N=N), 1748 (C=O), 1578 (C-C), 1252 (C-O); ¹H-NMR (CDCl₃) δ: 7.78 (1H, s, CH), 7.71 (2H, d, J = 7.6 Hz, Ar-H), 7.69-7.31 (4H, m, Ar-H), 7.29 (2H, d, J = 7.6 Hz, Ar-H), 4.31 (1H, s, CH), 4.28 (2H, s, CH₂), 4.21 (2H, q, J = 5.8 Hz, CH₂), 3.88 (2H, s, CH₂), 3.68 (2H, s, CH₂), 2.85 (3H, s, CH₃), 1.38 (3H, t, J = 5.8 Hz, CH₃); ¹³C-NMR (CDCl₃) δ: 168.2, 145.3, 141.2, 138.6, 136.3, 134.2, 131.2 (2), 129.3, 128.4 (2), 126.3, 124.8, 120.2, 117.4, 115.3, 64.8, 60.2, 56.3, 44.4, 25.3, 19.3, 16.2; MS m/z: 388 (M⁺); Elemental analysis calculated for C₂₃H₂₄N₄O₂: C=71.11, H=6.23, N-14.42, O-8.24. Found: C=70.41, H=5.89, N-13.98, O-7.84.

1-[1-{4-Methoxy-benzyl]-1H-[1,2,3]triazol-4-ylmethyl}-1H-indol-3-yl]-acetic acid ethyl ester (5g) Color: Yellow solid; Yield: 74 (%); M.P: 141-143 °C; IR (KBr) cm⁻¹: 3074 (C-H, Ar), 2968 (C-H, CH₂), 2166 (N=N), 1752 (C=O), 1578 (C-C), 1258 (C-O); ¹H-NMR (CDCl₃) δ: 7.81 (1H, s, CH), 7.77 (2H, d, J = 7.6 Hz, Ar-H), 7.70-7.36 (4H, m, Ar-H), 7.31 (2H, d, J = 7.6 Hz, Ar-H), 4.35 (1H, s, CH), 4.30 (2H, s, CH₂), 4.19 (2H, q, J = 5.8 Hz, CH₂), 3.78 (2H, s, CH₂), 3.71 (3H, s, OCH₃), 3.65 (2H, s, CH₂), 1.44 (3H, t, J = 5.8 Hz, CH₃); ¹³C-NMR (CDCl₃) δ: 170.4, 147.1, 144.7, 140.3, 138.4, 133.6, 132.7 (2), 130.4, 129.1 (2), 127.6, 126.2, 124.7, 119.2, 117.5, 68.4, 62.1, 58.4, 46.9, 28.4, 21.0, 17.8; MS m/z: 404 (M⁺); Elemental analysis calculated for C₂₃H₂₄N₄O₃: C=68.30, H=5.98, N-13.85, O-11.87. Found: C=67.69, H=5.25, N-12.95, O-11.21.

REFERENCES