Synthesis and Properties of Selected 4-Substituted Anhydro Sugars

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Abstract

Piperazine and its derivatives belong to a class of structures exhibiting a broad spectrum of biological activities [1–4]. Some of the 1,4-disubstituted piperazine derivatives show anticonvulsant [5], bronchospasmolytic [6], antipsychotic [7] and antibacterial activities [8]. We therefore considered it to be of interest to extend our ongoing research and introduce some 4-substituted piperazines, morpholines and perhydro-1,4-thiazines, respectively, to test their antibacterial activity. The characterized series of new compounds was tested in vitro against E. coli ATCC11229, S. aureus ATCC6538 and C. albicans SATCC10231.

Bioassay

All the newly synthesized compounds 3a-g and 6a-g were tested in vitro, as hydrochloride salts in aqueous solutions against E. coli ATCC11229,
The in vitro antibacterial activity was evaluated by the minimal inhibitory concentration (MIC) technique according to the macrodilution method [17]. As positive control, the commercial antibiotic Ciprofloxacin was used. However, none of the above compounds showed any significant activity at concentrations = 500 μg/ml.

In conclusion, introduction of 2,3-anhydro-pyranosides at position 4 of the piperazine moiety decreases the biological activity against selected types of bacteria and fungi, compared to piperazine derivatives containing aryl or alkyl substituents. Therefore, it is worth to test these new compounds after hydrogenation of the benzyl group not only against bacteria or fungi, but also as its CNS depressant activity, since a large number of piperazine derivatives are CNS depressant compounds. This study is now under investigation and will be published separately.

**Experimental**

The compounds were purified by column chromatography (Silica gel, 70–230 mesh ASTM, Merck) using an ethyl acetate/dichloromethane elution system and by thin-layer chromatography (TLC) on precoated 0.25 mm silica gel glass plates (60 F254, Merck), employing the elution system dichloromethane/ethyl acetate (70:30). Melting points of the compounds were recorded with a digital apparatus of Bachofer and optical rotations were measured at room temperature with a Zeiss digital polarimeter, Model LEP A2. ^1^H NMR spectra were performed with a Bruker AC 250 spectrometer and ^13^C NMR spectra were recorded with GASPE (Gated Spin-Echo) on the same instrument in deuteriochloroform and TMS was used as reference standard. All chemical shifts are given in parts per million and the coupling constants (J) are given in Hertz. Mass spectra were recorded on a Varian MAT 711 spectrometer. Tetrahydrofuran was distilled from sodium-benzophenone under an argon atmosphere. Other reagents and chemicals were used as received (from Aldrich).

**General procedure for the preparation of compounds 3a–g and 6a–g**

To a stirred solution of epoxy trflate 2 or 5 (1 mmol) in 10 ml dry THF 3 mmol of the corresponding substituted piperazine, morpholine or perhydro-1,4-thiazine was added. The reaction...
mixture was then stirred until the TLC analysis showed no more starting material. The aqueous workup yields the 4-substituted lyxopyranoside derivatives.

**Benzyl-2,3-anhydro-4-deoxy-4-(4-methyl-1-piperazinyl)-α-D-lyxopyranoside (3a)**

$^1$H NMR (250 MHz, CDCl$_3$): $\delta = 7.28-7.38$ (m, 5H, C$_6$H$_5$), 4.99 (s, 1H, 1-H), 4.80 (d, J = 11.9 Hz, 1H, OCH$_2$Ph), 4.56 (d, J = 11.6 Hz, 1H, OCH$_2$Ph), 3.74 (dd, J = 10.7, 11.0 Hz, 1H, 5A-H), 3.52 (dd, J = 0.9, 6.4, 11.0 Hz, 1H, 5B-H), 3.35 (d, J = 3.7 Hz, 1H, 1-H), 3.09 (d, J = 4.0 Hz, 1H, 3-H), 2.91 (dd, J = 6.4, 10.7 Hz, 1H, 4-H), 2.61-2.85 (m, 8H, H-2', H-3', H-5', H-6'), 2.28 (s, 3H, N-CH$_3$). GASPE NMR (63 MHz, CDCl$_3$): $\delta = 44.5$ (N-CH$_3$), 47.9, 53.8 (C-2', C-3', C-5', C-6'), 48.6, 51.1 (C-2, C-3), 54.1 (C-5), 54.4 (C-4), 68.3 (OCH$_2$Ph), 92.5 (C-1), 126.4-127.0, 137.0 (C$_6$H$_5$). FAB-MS: $m/z = 305$; $\alpha$D = +77.3° (c = 0.35, CH$_2$Cl$_2$).

**Benzyl-2,3-anhydro-4-deoxy-4-(4-ethyl-1-piperazinyl)-α-D-lyxopyranoside (3b)**

$^1$H NMR (250 MHz, CDCl$_3$): $\delta = 7.27-7.70$ (m, 5H, C$_6$H$_5$), 4.99 (s, 1H, 1-H), 4.79 (d, J = 11.6 Hz, 1H, OCH$_2$Ph), 4.56 (d, J = 11.9 Hz, 1H, OCH$_2$Ph), 3.75 (dd, J = 10.7, 11.0 Hz, 1H, 5A-H), 3.50 (dd, J = 0.9, 6.4, 11.0 Hz, 1H, 5B-H), 3.36 (d, J = 3.7 Hz, 1H, 1-H), 3.10 (d, J = 4.0 Hz, 1H, 3-H), 2.91 (dd, J = 6.1, 10.4 Hz, 1H, 4-H), 2.39-2.86 (m, 10H, H-2', H-3', 5B-H, H-6', N-CH$_2$CH$_3$), 1.09 (t, J = 7.2 Hz, 3H, N-CH$_2$CH$_3$). GASPE NMR (63 MHz, CDCl$_3$): $\delta = 11.9$ (N-CH$_2$CH$_3$), 49.4, 53.0 (C-2', C-3', C-5', C-6'), 50.1, 52.3 (C-2, C-3), 52.7 (N-CH$_2$CH$_3$), 55.7 (C-5), 56.0 (C-4), 68.9 (OCH$_2$Ph), 94.0 (C-1), 128.0-128.5, 137.3, (C$_6$H$_5$). FAB-MS: $m/z = 319$; $\alpha$D = +71.1° (c = 0.37, CH$_2$Cl$_2$).

**Benzyl-2,3-anhydro-4-deoxy-4-(4-phenyl-1-piperazinyl)-α-D-lyxopyranoside (3c)**

$^1$H NMR (250 MHz, CDCl$_3$): $\delta = 6.85-7.39$ (m, 10H, C$_6$H$_5$, C$_6$H$_5'$), 5.28 (s, 1H, 1-H), 5.10 (d, J = 11.8 Hz, 1H, 3-H), 2.91 (dd, J = 6.1, 10.4 Hz, 1H, 4-H), 2.39-2.86 (m, 10H, H-2', H-3', 5B-H, H-6', N-CH$_2$CH$_3$), 1.09 (t, J = 7.2 Hz, 3H, N-CH$_2$CH$_3$). GASPE NMR (63 MHz, CDCl$_3$): $\delta = 11.9$ (N-CH$_2$CH$_3$), 49.4, 53.0 (C-2', C-3', C-5', C-6'), 50.1, 52.3 (C-2, C-3), 52.7 (N-CH$_2$CH$_3$), 55.7 (C-5), 56.0 (C-4), 68.9 (OCH$_2$Ph), 94.0 (C-1), 128.0-128.5, 137.3, (C$_6$H$_5$). FAB-MS: $m/z = 319$; $\alpha$D = +71.1° (c = 0.37, CH$_2$Cl$_2$).

### Table I. Physical and analytical data for compounds (3a-g and 6a-g).

<table>
<thead>
<tr>
<th>Compd</th>
<th>Yield (%)</th>
<th>m.p. [°C]</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
<th>Analysis [%] (Calcd/Found)</th>
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<tr>
<td>3a</td>
<td>85</td>
<td>oil</td>
<td>C$<em>7$H$</em>{24}$N$_2$O$_3$</td>
<td>304.2</td>
<td>67.08/7.95/9.20</td>
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<tr>
<td>3b</td>
<td>81</td>
<td>oil</td>
<td>C$<em>{12}$H$</em>{26}$N$_2$O$_3$</td>
<td>318.2</td>
<td>67.90/8.23/8.80</td>
</tr>
<tr>
<td>3c</td>
<td>86</td>
<td>118–119</td>
<td>C$<em>{22}$H$</em>{26}$N$_2$O$_3$</td>
<td>366.2</td>
<td>72.11/7.15/7.64</td>
</tr>
<tr>
<td>3d</td>
<td>83</td>
<td>oil</td>
<td>C$<em>{22}$H$</em>{26}$FN$_2$O$_3$</td>
<td>384.2</td>
<td>68.73/6.55/7.29</td>
</tr>
<tr>
<td>3e</td>
<td>83</td>
<td>94–95</td>
<td>C$<em>{22}$H$</em>{26}$FN$_2$O$_3$</td>
<td>384.2</td>
<td>68.70/6.51/7.28</td>
</tr>
<tr>
<td>3f</td>
<td>89</td>
<td>oil</td>
<td>C$<em>{22}$H$</em>{25}$FN$_2$O$_3$</td>
<td>381.2</td>
<td>62.52/6.89/4.56</td>
</tr>
<tr>
<td>3g</td>
<td>86</td>
<td>oil</td>
<td>C$<em>{22}$H$</em>{25}$FN$_2$O$_3$</td>
<td>384.2</td>
<td>62.50/6.88/4.55</td>
</tr>
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11.6 Hz, 1H, OCH/Ph), 4.58 (d, J = 11.7 Hz, 1H, OCH/Ph), 4.09 (dd, J = 10.6, 10.7 Hz, 1H, 5a-H), 3.85 (dd, J = 6.1, 11.0 Hz, 1H, 5b-H), 3.70 (b,d, J = 3.4 Hz, 1H, 2-H), 3.50 (bt, J = 4.6 Hz, 4H, C2-H, C3-H). 3.41 (d, J = 4.0 Hz, 1H, 3-H), 3.07–3.30 (m, 5H, 4-H, C2-H, C6-H).

\[ \text{FAB-MS: } m/z = 319; [\alpha]_D = +49.0^\circ (c = 0.24, \text{CH}_2\text{Cl}_2). \]

**Benzyl-2,3-anhydro-4-deoxy-4-[4-(2-fluoro-phenyl)-1-piperazinyl]-a-D-lyxopyranoside** (6d)

\[ \text{1H NMR (250 MHz, CDCl}_3\): } \delta = 7.25–7.38 (m, 5H, C6-Hs), 6.91–7.07 (m, 4H, C4-Hd), 5.00 (s, 1H, 1-H), 4.83 (d, J = 11.9 Hz, 1H, OCH/Ph), 4.59 (d, J = 11.9 Hz, 1H, OCH/Ph), 3.86 (dd, J = 10.1, 10.7 Hz, 1H, 5a-H), 3.60 (dd, J = 5.6, 11.3 Hz, 1H, 5b-H), 3.47 (bs, 1H, 2-H), 2.92–3.17 (10H, m, 3-H, 4-H, C2-H, C3-H, C5-H, C6-H).

\[ \text{GASPE NMR (63 MHz, CDCl}_3\): } \delta = 49.8, 50.6 (C-2', C-3', C-5', C-6'), 50.3, 52.1 (C-2, C-3), 55.0 (C-5), 57.4 (C-4), 70.0 (OCH/Ph), 94.1 (C-1), 116.3, 120.1, 129.8, 137.1, 155.2 (C6-Hs, C4-Hd).

\[ \text{FAB-MS: } m/z= 376; [\alpha]_D = +58.5^\circ (c = 0.13, \text{CH}_2\text{Cl}_2). \]

**Benzyl-2,3-anhydro-4-deoxy-4-[4-(4-fluoro-phenyl)-1-piperazinyl]-a-D-lyxopyranoside** (6e)

\[ \text{1H NMR (250 MHz, CDCl}_3\): } \delta = 7.31–7.39 (m, 5H, C6-Hs), 6.90–7.00 (m, 4H, C4-Hd), 5.03 (s, 1H, 1-H), 4.82 (d, J = 11.9 Hz, 1H, OCH/Ph), 4.57 (d, J = 11.9 Hz, 1H, OCH/Ph), 3.80 (dd, J = 10.5, 10.7 Hz, 1H, 5-H), 3.57 (ddd, J = 0.9, 6.4, 11.3 Hz, 1H, 5b-H), 3.41 (d, J = 3.7 Hz, 1H, 2-H), 2.74–3.13 (m, 10H, 3-H, 4-H, C2-H, C3-H, C5-H, C6-H).

\[ \text{GASPE NMR (63 MHz, CDCl}_3\): } \delta = 49.8, 50.9 (C-2', C-3', C-5', C-6'), 50.3, 52.7 (C-2, C-3), 55.7 (C-5), 56.1 (C-4), 69.9 (OCH/Ph), 94.1 (C-1), 116.0, 116.3, 119.2, 123.0, 124.5, 128.1–128.6, 137.1, 155.2 (C6-Hs, C4-Hd).

\[ \text{FAB-MS: } m/z= 385; [\alpha]_D = +67.3^\circ (c = 0.11, \text{CH}_2\text{Cl}_2). \]

**Benzyl-2,3-anhydro-4-deoxy-4-[4-morpholino]-a-D-lyxopyranoside** (6f)

\[ \text{1H NMR (250 MHz, CDCl}_3\): } \delta = 7.27–7.41 (5H, m, C6-Hs), 4.99 (s, 1H, 1-H), 4.80 (d, J = 11.9 Hz, 1H, OCH/Ph), 4.57 (d, J = 11.9 Hz, 1H, OCH/Ph), 3.73 (m, 5H, 5a-H, C2-H, C3-H). 3.54 (ddd, J = 1.2, 6.4, 11.3 Hz, 5b-H), 3.37 (d, J = 3.7 Hz, 1H, 2-H), 3.11 (d, J = 3.7 Hz, 1H, 3-H), 2.59–2.92 (m, 4H, C2-H, C6-H).

\[ \text{GASPE NMR(63 MHz, CDCl}_3\): } \delta = 50.2 (C2, C6), 67.1 (C3, C5), 50.0, 52.3 (C-2, C-3), 55.6 (C-5), 56.4 (C-4), 69.9 (OCH/Ph), 94.1 (C-1), 128.1–128.6, 137.0, 157.7 (C6-Hs).

\[ \text{FAB-MS: } m/z= 292; [\alpha]_D = +81.3^\circ (c = 0.51, \text{CH}_2\text{Cl}_2). \]
Benzyl-2,3-anhydro-4-deoxy-4-(4-phenyl-1-piperazinyl)-β-L-lyxopyranoside (6e)

$^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 6.84–7.41 (m, 10H, C$_6$H$_5$, C$_6$H$_5$), 6.90 (d, $J$ = 2.7 Hz, 1H, 1-H), 4.74 (d, $J$ = 12.2 Hz, 1H, OCH$_2$Ph), 4.54 (d, $J$ = 12.2 Hz, 1H, OCH$_2$Ph), 3.84 (dd, $J$ = 3.4, 12.6 Hz, 1H, 5'-H), 3.67 (d, $J$ = 12.5 Hz, 1H, 5''-H), 3.34 (m, 2H, 2-H, 3-H), 3.34 (bs, 4H, C$_3$-H, C$_3$-H). 2.92 (m, 5H, 4-H, C$_2$-H, C$_5$-H). GASPE NMR (63 MHz, CDCl$_3$): $\delta$ = 49.6 (C-2', C-3', C-5', C-6'), 51.8 (C-2, C-3), 56.7 (C-5), 57.3 (C-4), 69.2 (OCH$_2$Ph), 92.3 (C-1), 116.3, 120.0, 127.0–129.2, 137.2 (C$_6$H$_5$), 138.5. FAB-MS: $m/z$ = 367; $[\alpha]_D^{20}$ = +22.1° (c = 0.11, CH$_2$Cl$_2$).

Benzyl-2,3-anhydro-4-deoxy-4-[4-(2-fluoro-phenyl)-1-piperazinyl]-β-L-lyxopyranoside (6d)

$^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 7.28–7.41 (m, 5H, C$_6$H$_5$), 6.99–7.10 (m, 4H, C$_6$H$_4$), 5.05 (d, $J$ = 2.7 Hz, 1H, 1-H), 4.81 (d, $J$ = 12.2 Hz, 1H, OCH$_2$Ph), 4.62 (d, $J$ = 12.2 Hz, 1H, OCH$_2$Ph), 3.92 (dd, $J$ = 3.1, 12.5 Hz, 1H, 5'-H), 3.77 (d, $J$ = 13.1 Hz, 1H, 5''-H), 3.48 (bs, 1H, 3-H), 3.39 (dd, $J$ = 2.9, 3.1 Hz, 2-H), 3.00–3.17 (9H, m, 4-H, C$_2$-H, C$_3$-H, C$_5$-H, C$_6$-H). GASPE NMR (63 MHz, CDCl$_3$): $\delta$ = 50.7 (C-2', C-3', C-5', C-6'), 51.9, 51.5 (C-2, C-3), 56.2 (C-5), 57.1 (C-4), 69.9 (OCH$_3$Ph), 92.3 (C-1), 116.0, 119.2, 124.5, 127.9–128.5, 137.1 (C$_6$H$_5$), 138.5. FAB-MS: $m/z$ = 385; $[\alpha]_D^{20}$ = +36.8° (c = 0.10, CH$_2$Cl$_2$).

Benzyl-2,3-anhydro-4-deoxy-4-[4-(4-fluorophenyl)-1-piperazinyl]-β-L-lyxopyranoside (6e)

$^1$H NMR (250 MHz, CDCl$_3$): $\delta$ = 7.28–7.41 (m, 5H, C$_6$H$_5$), 6.84–7.00 (m, 4H, C$_6$H$_4$), 5.05 (d, $J$ = 3.1 Hz, 1H, 1-H), 4.81 (d, $J$ = 12.2 Hz, 1H, OCH$_2$Ph), 4.61 (d, $J$ = 12.2 Hz, 1H, OCH$_2$Ph), 3.92 (bd, $J$ = 11.3 Hz, 1H, 5-H), 3.74 (bd, $J$ = 11.3 Hz, 1H, 5''-H), 3.38 (m, 2H, 2-H, 3-H), 2.94–3.15 (m, 9H, 4-H, C$_2$-H, C$_3$-H, C$_5$-H, C$_6$-H). GASPE NMR (63 MHz, CDCl$_3$): $\delta$ = 50.6 (C-2', C-3', C-5', C-6'), 54.5 (C-2, C-3), 55.7 (C-5), 56.1 (C-4), 69.2 (OCH$_3$Ph), 92.1 (C-1), 116.0–128.5, 137.3, 157.7, 155.1 (C$_6$H$_5$), FAB-MS: $m/z$ = 385; $[\alpha]_D^{20}$ = +33.9° (c = 0.36, CH$_2$Cl$_2$).

Benzyl-2,3-anhydro-4-deoxy-4-(4-morpholino)-β-L-lyxopyranoside (6f)

$^1$H NMR (250 MHz, CDCl$_3$): 7.27–7.40 (m, 5H, C$_6$H$_5$), 5.02 (d, $J$ = 3.1 Hz, 1H, 1-H), 4.80 (d, $J$ = 12.2 Hz, 1H, OCH$_2$Ph), 4.60 (d, $J$ = 12.2 Hz, 1H, OCH$_2$Ph), 3.89 (dd, $J$ = 3.4, 12.8 Hz, 1H, 5'-H), 3.68–3.74 (m, 5H, 5''-H, C$_3$-H, C$_5$-H), 3.36–3.43 (m, 2H, 2-H, 3-H), 2.77–2.40 (m, 5H, 4-H, C$_2$-H, C$_6$-H). GASPE NMR (63 MHz, CDCl$_3$): $\delta$ = 51.0 (C$_2$, C$_6$), 67.1 (C$_3$, C$_5$), 50.9, 51.8 (C-2, C-3), 56.8 (C-5), 57.6 (C-4), 69.1 (OCH$_2$Ph), 92.2 (C-1), 127.9–128.5, 137.5 (C$_6$H$_5$). FAB-MS: $m/z$ = 292; $[\alpha]_D^{20}$ = +47.2° (c = 0.18, CH$_2$Cl$_2$).

Benzyl-2,3-anhydro-4-deoxy-4-(perhydro-1,4-thiazin-4-yl)-β-L-lyxopyranoside (6g)

$^1$H NMR (250 MHz, CDCl$_3$): 7.27–7.39 (m, 5H, C$_6$H$_5$), 5.00 (d, $J$ = 2.7 Hz, 1H, 1-H), 4.80 (d, $J$ = 12.5 Hz, 1H, OCH$_2$Ph), 4.61 (d, $J$ = 12.2 Hz, 1H, OCH$_2$Ph), 3.87 (d, $J$ = 11.9 Hz, 1H, 5'-H), 3.71 (d, $J$ = 12.5 Hz, 1H, 5''-H), 3.34 (bs, 2H, 2-H, 3-H), 3.00 (bs, 5H, 4-H, C$_2$-H, C$_3$-H), 2.67 (bs, 4H, C$_5$-H, C$_6$-H). GASPE NMR (63 MHz, CDCl$_3$): $\delta$ = 27.6 29.2 (C$_2$, C$_5$, C$_2$, C$_6$), 51.8 (C-2, C-3), 53.00 (C-5), 58.7 (C-4), 69.2 (OCH$_3$Ph), 92.2 (C-1), 127.9–128.5 (C$_6$H$_5$). FAB-MS: $m/z$ = 308; $[\alpha]_D^{20}$ = +46.7° (c = 0.10, CH$_2$Cl$_2$).


