R07. Identification of Antifungal Bisphosphocholines from Medicinal Gentiana Species

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IDENTIFICATION OF ANTFUNGAL BISPHEROCHOLINES FROM MEDICINAL GENTIANA SPECIES

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Abstract

Gentiana species including G. crassicaulis, G. macrophylla, G. dahurica, and G. straminea are used in traditional Chinese medicine (TCM) as “Qinjiao” for the treatment of rheumatism, hepatitis, and pain. Four antifungal bisphosphocholines [irlbacholine (2) and three new analogues, gentianalines A-C (1, 3, and 4)] were identified from G. crassicaulis by a bioassay-guided fractionation and structure elucidation approach. Subsequent chemical analysis of 56 “Qinjiao” samples (45 from G. crassicaulis, five from G. macrophylla, three from G. dahurica, and three from G. straminea) showed that bisphosphocholines were present in all four Gentiana species, with irlbacholine as the major compound ranging from 2.0–6.2 mg per gram dried material. irlbacholine exhibited potent in vitro antifungal activity against Cryptococcus neoformans, Aspergillus fumigatus, Candida albicans, and Candida glabrata with minimum inhibitory concentrations (MICs) values of 0.63, 1.25, 10.0, and 5.0 μg/mL, respectively. Identification of the bisphosphocholines, a rare class of antifungal natural products, in these medicinal plants provides scientific evidence to complement their medicinal use. The bisphosphocholines carrying a long aliphatic chain possess amphiphilic molecule-like properties with a tendency of retention in both normal and reversed-phase silica gel column chromatography, and thereby may be neglected in natural products discovery. This report may stimulate interest in this class of compounds that warrant the further study of other biological activities as well.

In Vitro Antifungal Activity of IrlbaIcholine (2) and Extracts

<table>
<thead>
<tr>
<th>Compound</th>
<th>C. neoformans ATCC 90113</th>
<th>A. fumigatus ATCC 204305</th>
<th>C. albicans ATCC 90028</th>
<th>C. glabrata ATCC 90030</th>
</tr>
</thead>
<tbody>
<tr>
<td>irlbacholine (2)</td>
<td>0.42 / 0.63</td>
<td>0.87 / 1.25</td>
<td>3.7 / 10.0</td>
<td>2.08 / 5.0</td>
</tr>
<tr>
<td>fraction a</td>
<td>1.15 / 2.5</td>
<td>2.06 / 2.5</td>
<td>15.0 / 20.0</td>
<td>7.3 / 20.0</td>
</tr>
<tr>
<td>EIOH extract</td>
<td>5.2 / 12.5</td>
<td>9.99 / 12.5</td>
<td>&gt;200 / &gt;200</td>
<td>34.4 / 100</td>
</tr>
<tr>
<td>CHCl₃ extract</td>
<td>14.9 / 25.0</td>
<td>44.3 / 100</td>
<td>&gt;200 / &gt;200</td>
<td>90.5 / 200</td>
</tr>
<tr>
<td>ammonothiuranin b</td>
<td>0.19 / 0.63</td>
<td>1.1 / 2.5</td>
<td>0.22 / 0.63</td>
<td>0.21 / 0.63</td>
</tr>
</tbody>
</table>

*IC₅₀ concentration responsible for 50% growth inhibition of fungal cells; MIC: minimum inhibitory concentration (lowest concentration that allows no detectable growth). The highest test concentrations for compounds, fractions, and crude extracts are 20, 20, and 200 μg/mL, respectively. *A fraction contains irlbacholine as major compound and also gentianalines A–C as minor compounds determined by LC-MS.

Acknowledgments

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