INTERACTION OF NAPHTHOMYCIN A WITH SULFHYDRYL COMPOUNDS

Sir:

We have reported that naphthomycin A exhibits antitumor activity in mice and the mechanism of cytotoxicity is the inhibition of various SH enzymes. We have further found that naphthomycin A interacts with a variety of SH compounds by replacing the CI group by an SR group. These results are presented in this communication.

Materials and Methods

Naphthomycin A (I) was prepared as described previously. I: C_{40}H_{46}CINO_9; FD-MS m/z 719 (M^+); shows UV \( \lambda_{\text{max}} \) nm (\( \varepsilon \)) 231 (38,900) and 275 (33,400). The elemental analysis revealed that I contains 4.49% Cl but no S. The retention time of I was 4.20 minutes by HPLC.

Methanethiol, ethanethiol and propanethiol were purchased from Nakarai Chemical Co., Tokyo. p-Bromothiophenol was a product of Aldrich Chemical Co., Wisconsin, U.S.A.

HPLC was performed on a reverse phase silica gel column (8NVC18 5 \( \mu \), 10 cm x 8 mm, diameter, Waters Associates) developing with MeOH - H_2O - AcOH (80: 20: 1). The column was eluted with a flow rate of 2.0 ml/minute and the eluate was monitored with a UV detector at 280 nm.

Fig. 1. The structure of naphthomycin A and its derivatives.

Table 1. Cytotoxicity of naphthomycin A and its derivatives.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>IC_{50} (\mu M)</th>
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<tbody>
<tr>
<td>I</td>
<td>1.2</td>
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<tr>
<td>II</td>
<td>1.2</td>
</tr>
<tr>
<td>III</td>
<td>3.8</td>
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<tr>
<td>IV</td>
<td>3.0</td>
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</tbody>
</table>

Experimental

Methanethiol Derivative (II) of Naphthomycin A

A mixture of naphthomycin A (8.9 mg) dissolved in 1/15 m phosphate buffer (7 ml, pH 7.4) and methanethiol (4.7 mg) dissolved in MeOH (0.5 ml) was kept at 37°C for 10 minutes. The reaction product was extracted with EtOAc and purified by preparative silica gel TLC developed with CHCl_3 - EtOAc (1: 2) to yield 4.9 mg of II. The retention time of II was 3.54 minutes by HPLC. II: C_{41}H_{49}NO_9S; MS m/z 731 (M^+); shows UV \( \lambda_{\text{max}} \) nm (\( \varepsilon \)) 230 (57,500) and 275 (33,200). The elemental analysis indicated that II contains 4.42% S but no Cl. The \(^1\text{H} \) NMR spectrum of II was similar to that of I, except additional SCH_3.

Ethanethiol (III) and Propanethiol (IV) Derivatives of Naphthomycin A

Naphthomycin A (11.1 mg) and ethanethiol or propanethiol were treated as described above to yield 7.3 mg of III or 10.9 mg of IV. MS m/z 745 (M^+) for III and 759 (M^+) for IV.

p-Bromothiophenol Derivative (V) of Naphthomycin A

Naphthomycin A (5.2 mg) and p-bromothiophenol (1 mg) were treated as described above to yield 7.3 mg of V. The retention time was 7.13 minutes by HPLC. MS m/z 871 (M^+).

Cytotoxicity of Naphthomycin A Derivatives

Although the cytotoxicity of naphthomycin A (I) was reversed by SH compounds such as 2-
mercaptoethanol, dithiothreitol and glutathione\textsuperscript{1)}, the alkanethiol derivatives II, III and IV showed cytotoxicity for L5178Y murine lymphoma. As presented in Table 1, II exhibited the same degree of inhibition of DNA synthesis as I, and III and IV less degree of inhibition.

The present result together with the previous studies\textsuperscript{1)} gave a molecular basis for the action of naphthomycin A.

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References