INHIBITORY ACTIVITIES AGAINST TOPOISOMERASE I AND II BY ISOAUROSTATIN DERIVATIVES AND THEIR ANTI-OXIDIZING ACTIVITIES

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Isoaurostatin A (1) isolated from Thermomonospora alba showed weak inhibition against topoisomerase (topo) I (IC$_{50}$ =307 μM). To enhance their inhibitory activity their derivatives (2-4) were prepared and their structure-activity relationships were investigated. The addition of hydroxyl group on aromatic rings increased the activities. 3-(3,4,5-Trihydroxybenzylidene)-5-hydroxy-3H-benzofuran-2-one (2, R$_1$=R$_2$=R$_3$=OH) showed strong inhibition (IC$_{50}$ =3 μM) against topo I. The increasing of hydroxyl group enhanced growth inhibition against a variety of cancer cells. The indolinone derivatives 3 exhibited weak activity. Benzothiazole derivatives with galloyl group (4, R$_1$=R$_2$=R$_3$=OH)) indicated IC$_{50}$ =8.2 μM. Unlike camptothecin and etoposide, compounds 2 and 3 neither stabilized DNA-topo cleavable complex nor intercalated into DNA, and they inhibited topo I and II noncompetitively. Their inhibitory mechanism was speculated to show allosteric effect by molecular docking.

From the result the increase of phenolic hydroxyl group enhanced inhibitory activities against topo, their anti-oxidizing activities were also expected and compounds 2 and 4 (R$_1$=R$_2$=R$_3$ =OH) indicated IC$_{50}$ =6.0 and 6.8 μM which are 3.5 to 4.0 times as potent as ascorbic acid (IC$_{50}$=24 μM).