subsquent complication of diabetes mellitus.
During the screening program to discover such compounds from crude drugs, Gyrophora esculenta, a edible mushroom, was found to show the inhibitory activity through in vitro and in vivo experiment. GE974 isolated from Gyrophora esculenta showed a significant inhibitory activities on maltase, sucrase, and nonspecific α-glucosidase in vitro. Furthemore, it dose-dependently inhibited blood glucose elevation in normal or diabetic mice loaded various saccharides.

[OD-5] [04/21/2000 (Fri) 12:10 - 12:25 / Rm B113, Bldg 26]

CRM646-A and -B, novel fungal metabolites that inhibit heparinase

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Heparin-like glycosaminoglycans (HLGs) which polysulfated coplymers of alternating 1 →4 linked glucosamine and hexuronic acid were found both at the cell surface and in the extracellular matrix (ECM). To degrade extracellular HLGs, cells express endoglycosidases that cleave HLG chains. The enzyme may be involved in the remodeling of the ECM and aid migration of cells such as macrophages and tumor cells. These endoglycosidases such as heparinase and heparanase were also reported in relating to metastasis, inflammation and angiogenesis. Thus, in the course of screening for heparinase inhibitors from microbial metabolite through a modified assay system for heparinase, we isolated novel inhibitors, CRM646-A (1) and -B (2) from Acremonium sp. MT70646. Structure of 1 and 2 were determined by spectroscopic methods such as 1H-, 13C-, 1H-1H COSY, HMBC, FAB-MS and EI-MS spectrum. Compounds 1 and 2 inhibited heparinase in a dose-dependent manner with IC50 values of 3 μM and 10 μM, respectively. In matrigel invasion assay, Compound 2 showed inhibtion of B16-F10 cell migration as well as antiangiogenic activity ((IC50 = 5 μM, 10 μM, respectively). Thus, CRM646-A and -B is expected to be therapeutics in preventing cancer metastasis.

[OE-1] [04/21/2000 (Fri) 15:25 - 15:40 / Rm B113, Bldg 26]

Pharmacokinetic approach for the development of bioavailable ipriflavone formula

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Ipriflavone is a well-known anti-osteoporosis drug. However, this drug has an extremely poor bioavailability due to water insolubility. In an attempt to enhance oral bioavailability, we have developed a new ipriflavone formulation, named SIP-IV, by physical attachment of polymer polyvinylpyrrolidone to ipriflavone using a solid dispersion method. Pharmacokinetic studies including oral bioavailability were assessed with a single and multiple administration regimens in SD rats and healthy adults. The drug was analyzed in the plasma using an HPLC-UVD system. Following a single administration of 50 mg/kg to rats, SIP-IV showed a marked increase of oral absorption profile compared to unmodified ipriflavone and teobone, a commercially available ipriflavone formulation. The AUC and Cmax of SIP-IV were 6-10 times higher than those of teobone. Similar results were obtained from the multiple oral administration study at 50 mg/kg of SIP-IV (b.i.d.) and teobone (t.i.d.). The AUC and Cmax of SIP-IV, obtained from the terminal phase of 7-day treatment, were 4-8 times higher than those of teobone. The marked increase of oral absorption was also confirmed in the healthy humans receiving SIP-IV at 200 mg dose for two days. The AUC and Cmax of SIP-IV (b.i.d.) were 4-5 times higher than those of teobone (t.i.d.). Therefore, it can be summarized that the approach employing PVP polymer attachment is very effective for improving bioavilability of ipriflavone.