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Mansonone F and Biflorin which are the members of the naturally occurring ortho-naphthoquinone consist of the unusual oxaphenalene skeleton. Biflorin, the first oxaphenalene natural product, was found to have antibiotic properties. More interestingly, mansonone F of a tricyclic sesquiterpenoid has been reported as a phytoalexin which is accumulated in the heartwood of the genus Ulmus in response to infections. Recently, mansonone F has been also isolated from the root bark of Ulmus davidiana which has been traditionally used as a medicinal plant for the infection diseases in Korea. In addition, the highly potent anti-MRSA activities of mansonne F comparable to that of vancomycin have been disclosed in our laboratory. However, the paucity of natural mansonone F as well as its inherent structural constraint has limited the optimization of its biological properties by structural modification and its therapeutic application. These reasons prompted us to develop a practical and divergent synthetic route to mansonone F .
The total synthesis of mansonone F has been accomplished via 10 step sequence, starting from the readily available 5-methoxy-1-tetralone. The key part of this synthesis involves an efficient preparation of 1,6-dimethyl-5-alkoxynaphthalene as a divergent cyclization precursor and its facile conversion to the oxaphenalene skeleton by peri ring closure.
This concise and practical synthetic procedure, providing a variety of substituents at C3, C6 and C9 positions, offers a useful synthetic route to the important anti-MRSA drug prospect.

[OD-3] [04/21/2000 (Fri) 11:40 - 11:55 / Rm B113, Bldg 26]

Kalopanaxsaponin A Is a Basic Saponin Structure for the Antitumor Activity of Hederagenin Monodesmosides

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Hederagenin (1), delta-hederin (2), kalopanaxsaponin A {3, hederagenin 3-O-alpha-L-rhamnosyl (1-2)-alpha-L-arabinoside}, kalopanaxsaponin I {4, hederagenin 3-O-beta-D-xylosyl (1-3)-alpha-L-rhamnosyl (1-2)-alpha-L-arabinoside} and sapindoside C {5, hederagenin 3-O-beta-D-glucosyl (1-4)-beta-D-xylosyl (1-3)-alpha-L-rhamnosyl (1-2)-alpha-L-arabinoside} were isolated from a saponin fraction of the MeOH extract of Kalopanax pictus Nakai (Araliaceae). 1 disaccharide (3), 1 trisaccharide (4), 1 tetrasaccharide (5) showed significant cytotoxicity on several tumor cell lines in contrast to no cytotoxicity of 1 monosaccharide (delta-hederin). We found that 3 commonly named also alpha-hederin is a basic structure of most 1 monodesmosides for the cytotoxicity. When the mice were treated with 37.5 mg/kg and 75 mg/kg of 3 or 15 mg/kg of cisplatin, a significant antitumor activity was obtained against colon cancer (% T/C of 124-169) and lung cancer (% T/C of 175.5-205), respectively. Throughout the cytotoxicities of 3 derivatives on several tumors, many saponins such as 1 disaccharides bearing (1-2) glycoside linkage and their serial saponins were suggested to have significant anti-tumor effect.

[OD-4] [04/21/2000 (Fri) 11:55 - 12:10 / Rm B113, Bldg 26]

Inhibitory Effect of Gyrophora esculenta on α-Glucosidase

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Diabetes mellitus is classified into insulin-dependent diabetes mellitus(IDDM) and noninsulin-dependent diabetes mellitus(NIDDM). It makes serious problems caused by its subsequent complications rather than by its own symptoms. α-Glucosidases are the key enzymes for these carbohydrate digestion. Therefore, α-glucosidase inhibitors could prevent and improve the

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.