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During the last two decades, the increasing prevalence of antibiotic-resistant bacteria has had an enormous impact on infection control policies. In particular, the resistances to multiple antibiotics of strains of Gram-positive Staphylococci, methicillin-resistant Staphylococcus aureus (MRSA), are now significant clinical problem. Even though vancomycin and teicoplanin, a class of glycopeptide antibiotics, are widely used clinically in the treatment of MRSA infections, the structural complexity and toxic side effects of these antibiotics have prompted increased efforts to find and investigate new and effective antibiotics.

Towards this end, we have recently reported the isolation of a potent anti-MRSA sesquiterpenoid ortho-quinone, mansonone F, from the Korean medicinal plant which has traditionally been used to treat infectious diseases. It has been shown to have antibacterial activities against Gram-positive bacteria and, in particular, MRSA (with an MIC90 of 2 mg/ml in vitro), comparable to vancomycin. Mansonone F is structurally simple and unique ortho-naphthoquinone with conjugated tricyclic ring skeleton, and its energy-minimized structure turned out to be complete flat and highly strained.

In continuation of pharmacophore identification and investigation into the structure-anti-MRSA activity relationship of sesquiterpenoids based on the natural mansonone F, the systemically modified analogues of mansonone F were synthesized and assayed against MRSA strains.

Consequently, we have established the partial structure-activity relationship of mansonone F.

[PD1-22] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis and in vitro Antibiotic Activity of C-9 modified Derivatives of Erythromycin A.

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Since its discovery by Mcgurie et al. in 1952, erythromycin A (EM-A) has been the most widely used against many diseases, owing to its safety and effectiveness, especially respiratory tract infections. A major drawback to erythromycin is its instability in the acidic medium of the stomach. To minimize the acid instability and improve the activity, C-9 modified derivatives of erythromycin A were designed. The improvement of activity of erythromycin 9-oxime against gram-positive bacteria by introducing phenyl groups and isoxazole groups into the aliphatic chain was attempted. And also phenyl substituents were introduced at the C-9 position of erythromycin for forming C=C bond instead of C=O bond. Thus, prepared antibiotics were evaluated biologically by measuring the minimum inhibitory concentrations (MIC) against various bacterial strains. This new class of macrolide antibiotics showed reduced MIC value compared with those of erythromycin A and clarithromycin.

[PD1-23] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Lupane Derivatives Bearing Aminoacetyl Moiety

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Lupane derivatives showed good cytotoxic activity and it was reported that their cytotoxic activity mainly

came from the induction of apoptosis. Nowadays, there is a increasing interest in their potential for antitumor agent. But, the weak water solubility is one of their difficulties for in vivo application.
To increase the water solubility, sixteen derivatives of lupane which bearing aminoacetyl moiety at C3 were synthesized. Their cytotoxic activities against three cancer cell lines, SK-MEL-2, A-549, and B16-F10, were tested.
Of synthesized derivatives, only six derivatives were cytotoxic against certain cell lines. On the whole, the activities were weaker than their lead compound, betulinic acid. The cause of reduction of cytotoxic activity might come from the steric effects.

[PD1-24] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Evaluation of Morphogenic Regulatory Activity of Farnesoic acid and Its Derivatives against Candida albicans Dimorphism

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The yeast Candida albicans has a distinguishing feature, dimorphism, which is the ability to switch between two morphological forms: a budding yeast form and a multicellular invasive filamentous form. This ability has been postulated to contribute to the virulence of this organism. Studies on the morphological transition from a filamentous to a budding yeast form in C. albicans have shown that this organism excretes an autoregulatory
substance into the culture medium. This substance was extracted and purified by normal-phase and reversed-phase HPLC. The autoregulatory substance was structurally identified as 3,7,11-trimethyl-2,6,10-dodecatrienoate(farnesoic acid) by NMR and mass spectrometry. Growth experiments suggest that this substance does not inhibit filamentous growth. A series of farnesoic acid derivatives was prepared and their morphogenic regulatory activities were evaluated. Their inhibitory activities against yeast cell growth and yeast-to-hypha transition using C. albicans cells are sensitive to the chain length as well as the substitution patterns on the isoprenoid template. The preliminary structure-activity relationship of theses compounds is described to elucidate the essential structural requirements. These findings have implications for developmental signaling by the fungus and might have medical value in the development of antifungal therapies.

[PD1-25] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Practical Synthesis of (S)-7-(2-Isopropylamino)ethylcamptothecin Hydrochloride, Potent Topoisomerase I Inhibitor

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In our efforts to find a practical large-scale synthetic method for CKD-602, (S)-7-(2-Isopropylamino) ethylcamptothecin hydrochloride, under phase II clinical trials as a anti-cancer drug candidate, we have developed a semi-synthetic method employing the Mannich reaction. Unusually, dimethyl sulfoxide which was used as a solvent, worked as a formaldehyde source in the Mannich reaction of (S)-7-methylcamptothecin with isopropylamine hydrochloride.

[PD1-26] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]