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Oncogenic mutations of ras genes have been found in 30% of all human cancers including 50% of colon cancer, 90% of pancreas cancer, 50% of lung cancer and thyroid gland cancers. The transformed ras proteins, e.g., H-Ras, N-Ras, K-RasA, K-RasB etc., translated by the mutated ras genes result in the unregulated cell growth, thereby causing cell tumorization. This reaction is catalyzed by the enzyme, farnesyltransferase (FTase). Therefore, inhibitors of FTase should serve to block cell transforming activity by inhibiting the action of the mutated ras gene. Therefore, FTase has been focused as a new target for development of anticancer agents. Based on the N-terminal CAAX box of ras proteins, many types of peptidomimetic FTase inhibitors have been reported. The synthesis and the biological activity of non-peptide FTase inhibitors will be discussed in this presentation. Cysteine of the CAAX box have been replaced with imidazole substituent and isoleucyl moiety replaced with a various alkyl, cycloalkyl surrogates. Evaluation of biological activity was carried out with purified FTase and MTT based cell growth inhibition. Many FTase inhibitors showed strong inhibition against K-ras farnesylation as well as ras-transformed cell growth without showing cytotoxicity in wild type cell line, NIH3T3.

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[PD1-5] [ 04/20/2001 (Fri) 13:30 - 14:30 / Hall 4 ]

### Syntheses of Certain 3-Aryl-2-propenoates and Evaluation of their Cytotoxicity

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In our search for novel antitumor agents from natural sources, we isolated a phenyl propanoid, methyl 3,4-dihydroxycinnamate (methyl caffeate 4a), from the plant *Notopterygium incisum*. This compound showed a significant cytotoxicity against various cancer cell lines and greatly inhibited the invasion of B16 melanoma cells. Structurally, 4a possesses an alpha,beta-unsaturated carbonyl, which can be considered as a Michael acceptor, an active moiety often employed in the design of anticancer drugs. In addition, a number of alpha,beta-unsaturated ketones have demonstrated preferential activity toward thiol. Alkylation with a cellular thiol such as glutathione (GSH) may also occur with cinnamates like 4a, leading to adducts at beta-position. Hence, alpha,beta-unsaturated carbonyl-containing compounds may be free from problems of mutagenicity and carcinogenicity that are associated with many alkylating agents used in cancer chemotherapy. Taking into consideration this structural feature and the interesting bioactivity of the compound 4a, the present investigation aims at preparing a number of 4a analogues and related 3-aryl-2-propenoates in order to evaluate their cytotoxicity. Caffeates (4a ~ 4c) were obtained by refluxing caffeic acid in excess alcohol used as solvent in the presence of a catalytic amount of HCl. Other cinnamates (4d ~ 4m) were synthesized in good yields by a Wittig reaction. The two caffeamides 3a, 3b were synthesized through a sequence: protection of the phenol groups with methoxycarbonyls, coupling of the protected caffeic acid with hydroxylamine or aniline and deprotection by sodium methoxide. Reduction of the double bond of the propenoate 4d was carried out using hydrogen (1 atm) and Pd/C (10%) to afford the dihydrocinnamate 5 in a quantitative yield. E)-3-[2-(1,4-Dihydroxy-9,10-dione)anthracenyl]- and (E)-3-[2-(1,4-dihydroxy-5,8-dione)naphthalenyl]-2-propenoates were synthesized from 2-formyl-1,4-9,10-tetramethoxynaphthalene(6a) and 2-formyl-1,4,9,10-tetramethoxynaphthalene(6b). The synthesized compounds were evaluated for their cytotoxicities. It was found that methyl and ethyl 2,5-dihydroxycinnamates displayed a potent cytotoxicity against a variety of cancer cell lines. The simple analogues (E)-methyl/ethyl 3-[2-(1,4-dihydroxy-9,10-dione)anthracenyl]-2-propenoates exerted an

almost comparable cytotoxicity to adriamycin and (E)-methyl/ethyl 3-[2-(1,4-dimethoxy-5,8-dione)naphthalenyl]-2-propenoates showed strong cytotoxicity against various solid tumor cell lines.

[PD1-6] [ 04/20/2001 (Fri) 13:30 - 14:30 / Hall 4 ]

### Cinmetacin유도체의 합성과 진통항염활성

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Nine cinmetacin derivatives as potential nonsteroidal analgesic and antiinflammatory compounds were prepared and their analgesic-antiinflammatory activity was compared with cinmetacin. Salicylic acid and phenols were reacted with DCC to give phenyl saicylates. Cinmetacin was treated with DCC and phenol derivatives to yield cinmetacin esters. Some of compounds showed stronger analgesic activity than cinmetacin, but only one compound showed comparable antiinflammatory activity to cinmetacin.

[PD1-7] [ 04/20/2001 (Fri) 13:30 - 14:30 / Hall 4 ]

### Design and Synthesis of Isoindoloquinoline Derivatives as Potential Antitumor Agents

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The azaanthraquinones are a new class of antitumor agents that exhibit promising in vitro and in vivo activity against a wide spectrum of tumor cell lines. In an effort to develop novel antitumor intercalating agents that could overcome the shortcoming of anthracyclines, we recently reported the synthesis and biological evaluation of some azaanthraquinone derivatives and continued our efforts to design the related compounds.

In this study, we describe synthesis of a series of isoindoloquinoline derivatives. These were designed based on the structure-activity relationship of azaanthraquinones and structural analysis of products which are fitted with doxorubicin. A Diels-Alder reaction and a high temperature and pressure oxidative reaction were used as key synthetic steps.

[PD1-8] [ 04/20/2001 (Fri) 13:30 - 14:30 / Hall 4 ]

### Formation of Carbamates: Comparison of the Stability of Various Carbocations via CSI Reaction

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The cinnamyl alkyl ethers were treated with chlorosulfonyl isocyanate (CSI) to afford the corresponding N-protected allylic amines as a mixture of regioisomers. However, in the case of cinnamyl t-butyl ether, the corresponding allyl carbamate was obtained rather than N-allylcarbamates as a single product. These results may be rationalized by suggesting that the reaction pathways are determined in accord with the stability of carbocations obtained during the reaction process. From these results, we