The ability of Ras oncoproteins to cause malignant transformation requires their post-translational modification by prenyl group. Prenylation allows the ras oncoprotein to localize to the plasma membrane where it plays a pivotal role in growth factor signalling and malignancy. For this reason, inhibition of Ras prenylation is being pursued as a way of developing anticancer drug. Ras prenylation, covalent attachment of a farnesyl group to the sulfhydryl group of cysteine in the C-terminal CAAX box, is catalyzed by farnesyltransferase (FPTase). Based on the C-terminal CAAX box of Ras proteins, many types of peptidomimetic FTase inhibitors have been reported.
We will discuss the synthesis and structure-activity relationship of novel FTase inhibitors containing a cysteine or imidazole acetic acid as a cysteine surrogate linked to proline instead of isoleucine. They strongly inhibited K-ras farnesylation as well as Ras-transformed cell growth without showing cytotoxicity. This study was supported by a grant of the Korea Health 21 R & D project, Ministry of Health & Welfare, Republic of Korea (HMP-98-D-7-0010).

[PD1-30] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

SYNTHESIS AND HIV-1 PROTEASE INHIBITORY ACTIVITIES OF 4-HYDROXYPYRONE DERIVATIVES

Sun Nam Kim1, Yong Sil Lee°1, Jae Yeol Lee1, Chong-Kyo Lee2, Hokoon Park1, and Yong Sup Lee1

1 Division of Life Science, Korea institute of Science and Technology; 2 Korea Research Institute of Chemical Technology

Human immunodeficiency virus(HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS). Several enzymes are important to the life cycle of this virus. Therefore, reverse transcriptase integrase and protease are considered to be promising targets for the development of anti-AIDS drugs. The HIV-1 protease, which has a C2 symmetric homodimeric structure, plays a key role in viral maturation. Based on the structure of HIV-1 protease, we reported the design and synthesis of new nonpeptidic protease inhibitors. A number of 4-hydroxypyrone based inhibitors have proven to be effective inhibitors of HIV protease, so we investigated the structure-activity relationships of 4-hydroxypyrone derivatives on HIV-1 protease inhibitory activity. In this presentation, the synthesis and inhibitory activity of various 4-hydroxypyrone derivatives will be discussed in detail.

[PD1-31] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

Comparative Molecular Field Analysis (CoMFA) of Ceramide Derivatives

Im CU°, Choi SK, You JH, Yim CB

Division of Medicinal Chemistry, College of Pharmacy, Chungang University

Ceramide derivatives have been optimized for their cytotoxic activity and three dimensional quantitative structure-activity relationship (QSAR) was investigated using the comparative molecular field analysis (CoMFA). The result suggested that the electrostatic and steric factors of ceramide derivatives were strongly correlated with the cytotoxicity.

[PD1-32] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

Synthesis and cyclooxygenase-2 inhibitory activities of 7-bromo-1,2-benzothiazine derivartives

Shin HS, CHoi HJ, Kwon SK, Park MS

College of Pharmacy, Duksung Women's University, Seoul, Korea

The ability of non-steroidal anti-inflammatory drugs(NSAIDs) to inhibit cyclooxygenase-2(COX-2) may well explain their therapeutic efficacy as anti-inflammatory drugs by blocking prostaglandins formation, whereas inhibition of cyclooxygenase-1(COX-1) may well explain their unwanted the gastric and renal side effects. In this study, a series of analogues were prepared to develope new useful COX-2 inhibitors. Novel 7-bromo-1,2-benzothiazine derivatives, which could exhibit potential anti-inflammtory activity, were synthesized through 1,2-benzothiazine and 4-bromotoluene over the sulfonation, amination and oxidation, by Gabriel-Colman rearrangement. These compounds were evaluated for their ability of inhibiting cyclooxygenase-2 in murine macropharge RAW 264.7 cell line. To investigate the structure-activity relationship of 7-bromo-1,2-benzothiazine derivatives, accumulation of prostaglandins by the selective expression of COX-2, which was expressed by the lipopolysaccharide-stimulated macropharges, were screened.

[PD1-33] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

6-(1-Alkoxyiminoalkyl)-5,8-Dimethoxy-1,4-Naphthoquinones : Synthesis, Evaluation of Cytotoxic Activity and Antitumor Activity

You YJ°, Kim Y, Ahn BZ

College of Pharmacy, Chungnam National University

2-Acyl-1,4,5,8-Tetramethoxynaphthalene (TN) derivatives were treated with hydroxylamine to produce 2-(1-hydroxyiminoalkyl)-TN derivatives. These were oxidatively demethylated to 6-(1-hydroxyiminoalkyl)-5,8-dimethoxy
-1,4-naphthoquinone (DMNQ) derivatives. These DMNQ derivatives were tested for cytotoxic activity against L1210 cells and anitumor activity using S-180 fluid tumor. Their ED50 values on L1210 cells ranged over 0.1~0.3mg/ml. They generally exhibited a potent anitumor activity. It was found that the activity was dependent on size of the side chains with longer chain being more potent. Among the compounds tested, nine exhibited a higher T/C value than 300 %.

[PD1-34] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

Synthesis of New Allyl Sulfonate Analogues as Potential Antitumor Agents

Jin cheng hua°, Lee MJ, Kang HO, Kim DK*, Moon HI, Lee KR, Chung KH, Zee OP, Jung YH

College of pharmacy Sungkyunkwan University, Woosuk University*

Much attention has been focused on developing new chemotherapeutic agents for a treatment of cancer from natural products. As parts of a program, aimed at developing new antitumor agents, a monoterpenoid compound (10-isobutyloxy-8,9-epoxythymol isobutyrate) isolated from *Carpesium divaricatum* S. *et* Z. and its derivatives have been synthesized and their structure-activity relationships have been investigated. At this time, to study the effect of *p*-methoxy substituent on biological activity, we designed and synthesized *p*-methoxy epoxythymol. And we modified ester bond to relatively stable sulfonyl ester bond because the ester bond is easily hydrolyzed by esterase in the body. Furthermore, modification of aromatic moiety in thymol skeleton with intact allyl sulfonate has been carried out. The in vitro cytotoxic activities of the synthetic compound against human cancer cell lines were evaluated.

[PD1-35] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]