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

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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

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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