ER-35786, FR-21818, and IH201 are under clinical or preclinical stage.
We carried out the chemical modification on the pyrrolidine side chain of BO-2727, showing the potent antibacterial activity and high stability to DHP-I. To this end we tried the introduction of cyclic isoxazolidine, isoxazoline, and isoxazole derivatives via 1,3-dipolar cycloaddition reaction of 2-vinylpyrrolidine with nitrone and nitrile oxide instead of acyclic side chain of BO-2727 to give the rigid conformation. It was known that carbapenem derivatives directly linked with isoxazolidine or isoxazoline ring at C-2 position showed potent antibacterial activities.
We describe the synthesis of the 1β-methylcarbapenems containing 5'-isoxazolo-pyrrolidin-3'-ylthio derivatives as C-2 side chain and their biological properties.

[PD1-27] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

The new pyridopyrimidine derivatives as a PDE IV inhibitors

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A novel series of pyrido[2,3-d]pyrimidine compounds exhibiting selective inhibition for phosphodiesterase IV (PDE IV) were designed and synthesized by the reaction of 6-amino-5-iodo-1-methyl uracil with DMF-dimethylaceral, followed by reaction with various olefins in presence of a catalytic amount of Pd(OAc)2and K2CO3 in DMF at 100 oC to give the title compounds. Biological inhibitory potency for these compounds was evaluated as a PDE IV inhibitors. The result will be discussed.

[PD1-28] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

An efficient and selective 1-N-monoethylation of sisomicin : Process development of netilmicn(1-N-ethylsisomicin

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An efficient, newly improved practical synthetic method for the 1-N-ethylsisomicin (Netilmicin), a highly effective antibacterial agent for the refractory Psudomonas aeruginosa infections, was described. Sisomicin in starting material was converted to the 3,2',6'-triacylprotected sisomicin by chelation method, the tri-blocked sisomicin was reacted with mixture of sodium borohydride and acetic acid in methanol, which is a new reagent for selective mono ethylation at 1-aminogroup of sisomicin and new process suitable for mass production of netilmicin under less sensitive to air and moisture. Development efforts focus in optimizing mono-alkylation conditions having little by-product was achived in 87~96% yield. In this presentation, the results will be discussed.

[PD1-29] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

Synthesis and Structure-Activity Relationship of Non-peptide FPTase Inhibitors

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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