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The structure of 2-alkylureido-1-phenyl propanol derivatives have been studied and optimized for their N-SMase inhibitory activity. The three dimensional quantitative structure activity relationship (3D-QSAR) was investigated using comparative molecular field analysis (CoMFA). The result suggested that electrostatic and steric factors of 2-alkylureido-1-phenyl propanol derivatives were correlated well with N-SMase inhibitory activity.

[PD1-26] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Studies on Colon-specific prodrugs: Structural effect of acyl moiety on the hydrolysis of N-aromatic acyl-glycine by the rat cecal contents.

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N-aromatic acyl-(2-drug substituted)-glycine can be a colon-specific prodrug because the amide bond of N-aromatic acyl-amino acid conjugates is known to be stable in the upper intestine and dissociated by the microbial enzymes in the colon. 2-DRUG-glycine, which forms after hydrolysis of amide bond, decomposes spontaneously to release drug molecule.
In the present study, structural effect of acyl moiety on the hydrolysis of N-aromatic acyl-glycine by the rat intestinal contents was studied. Incubation of N-aromatic acyl-glycine with rat cecal contents revealed that electron-withdrawing group enhanced the rate of hydrolysis and vice versa for electron-donating group. Substitution on 2- or 3-position retarded hydrolysis greatly due to the steric hindrance. Electronic effect was not significant compared with steric effect. To use N-aromatic acyl-glycine as a colon-specific promoiety, an aromatic ring with hydrophilic and electron-withdrawing substituent will be desirable to limit absorption in the upper intestine and enhance bioactivation in the colon. Insertion of a vulnerable spacer moiety, such as N-aromatic acyl-spacer-(2-DRUG)-glycine, will reduce the steric hindrance and enhance bioactivation of the prodrug.

[PD1-27] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Studies on Colon-specific prodrugs: Structural effect of amino acid on the hydrolysis of N-benzoyl-amino acid conjugate by the rat cecal contents.

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N-Aromatic acyl-amino acid conjugates are known to be stable in the upper intestine and dissociated by the microbial enzymes in the colon. For this reason, amino acid can be used as a colon-specific promoiety for aromatic acid drugs such as 5-aminosalicylic acid.
In the present study, structural effect of the amino acid (or amino acid analogue) moiety on the hydrolysis of N-benzoyl-amino acid conjugate by the rat intestinal contents was studied. It was noticed that steric hindrance imposed by the substituent on 2-position of amino acid reduced the rate of hydrolysis. Rate of hydrolysis was enhanced by the conjugate with the acidic amino acid. Hydrolysis was almost completely inhibited with the conjugates of D-amino acid or alkyl homologue of glycine. Hydrolysis did not take place with the conjugates of aminoalkylsulfonic acid, an isostere of the amino acid, except taurine.

[PD1-28] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Protective Activity of Allylthiopyridazine Derivatives on Aflatoxin B1- induced Hepatotoxicity in Rats

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Five allylthiopyridazine derivatives were synthesized and their chemoprotective activities were screened by aflatoxin B1 administration. Male Sprague-Dawley rat were treated with five allylthiopyridazine derivatives at the daily oral doses of 50 mg/kg for 10 consecutive days, and during this period three repeated doeses of aflatoxin B1(1.0 mg/kg, i.p.) injected. The group of aflatoxin B1 (1.0 mg/kg, 3 times) administration showed the striking increase in body and liver weight, whereas the body and liver weight of allylthiopyridazine derivatives was normal as compared with vehicle. And the allylthiopyridazine derivatives showed remarkable inhibition for the AST and ALT activities of rat serum exposed by aflatoxin B1 toxin. But propoxy substituent compound, K18, did not show any activity, whereas other four allylthiopyridazine derivatives, K6, K8, K16 and K17 showed strong hepatoprotective activity.

[PD1-29] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Modeling of Binding Modes and Inhibition Mechanism of Apicidin Derivatives, Histone Deacetylase Inhibitors : A flexible Docking Study

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A novel fungal metabolite, apicidin has growth inhibition and detransforming activity against cancer cells. It is known that the biological activity of apicidin is due to the inhibition of histone deacetylase (HDAC) in low nanomolar concentration. Hydrazone, semicarbazone and carbohydrazone derivative of apicidin were synthesized and characterized in a human HDAC inhibition assay. All compounds have shown IC_{50} values between 0.17 and 0.71 μM, and revealed the HDAC inhibition activity comparable to apicidin.
In this study, we examined a possible mode of interaction between those compounds and HDAC by docking analysis. We conducted flexible docking of each compound into the histone deacetylase-like protein (HDLP) catalytic domain using a FlexX docking program. FlexX binding energy scores of the compounds were analyzed using consensus scoring method (CScore), which combines multiple scoring functions in binding affinity estimation.
The docked models predicted the interactions of the compound with the amino acid residues and Zn^{2+} at the active site of HDLP, and the data obtained from the CScore analysis correlated well with the HDAC inhibitory activity of the apicidin derivatives.

[PD1-30] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Diversity of compounds in Korea Chemical Bank

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Korea Chemical Bank project has started as an "infra" supporting the new drug development strategy of high efficiency and low costs. Now Korea Chemical Bank holds 50,000 compounds consigned from the domestic institutions.
We examined the consigned compounds to verify that the compounds have the adequate structure to new drug using Lipinski's rule. As a result, about 95% of compounds are validated as having proper structure for new drug.
And we compared the physical properties and diversity of compounds with the compounds of international compounds supplier(160,000 compounds from ChemDiv and 145,000 compounds from SPECS and BIOSPECS).