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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