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Carbonucleosides has extensively been studied as a promising antiviral agents having chemical and metabolical stability. As yet there are no rules relating the structures of carbocyclic nucleosides to their therapeutic activity, although trends among certain kinds of structure have been tentatively put forward. Some vinyl cyclobutyl nucleosides can be considered to be analogue of exomethylene cyclopentyl nucleosides, BMS-200475. In our research program for discovery of anti-viral drugs, the key intermediate containing vinyl group has been synthesized from D-glucose, via several steps involving ring contraction reaction by zirconium complex.

[PD1-23] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Structure-transport relationship of drugs in Caco-2 monolayer system: through sildenafil derivatives and dopamine receptor antagonists

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To investigate about prediction of intestinal absorption is very important process in drug discovery, development of lead drug candidates derived by combinatorial synthesis and combinatorial screening paradigms. Researches for predictable factor of intestinal absorption already accomplished and tried means every possible in several places. Polar surface area (PSA) and Log P, well-known factors of chemical structure, are compared with apparent permeability coefficient (Papp), a single factor of transport assay of in vitro system. However, those studies are tended to diminish why the flaw, have no connection with structure and absorption of in vivo. The aim of this study is to make clear of complicated relationship between predictable factors and absorption in vivo. 24 compounds, derivatives of sildenafil and dopamine receptor antagonist, examined and calculated apparent permeability coefficient (Papp). Polar surface area (PSA) and Log P of these compounds obtained by Sybyl 6.7 (software).

[PD1-24] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Oxidation of Methyl Substituted Benzo- or Pyridoquinoxalinediones

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The high temperature and pressure oxidative reaction using 18% nitric acid is known to oxidize benzylic methyl group of a quinone containing aromatic ring system to a carboxylic acid. We have previously reported the oxidation of 3-methylazaanthraquinone and 7,8-dimethylazaanthraquinone to give the azaanthraquinone carboxylic acids.
However, an interesting result was obtained in the same reaction of 7,8-dimethylbenzo quinoxalinedione, 7-methylpyridoquinoxalinedione, 8-methylbenzoquinoxalinedione.
Both benzylic methyl group and 2- and 3-carbon of quinoxalinediones were oxidized.
Oxidation of quinoxaline that is not to go by way of quinoxaline oxide intermediate is rare. The only reported example of the direct method is to reflux a mixture of quinoxaline and ammonium peroxosulfate in water (42%).

[PD1-25] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

CoMFA Analysis of 2-Alkylureido-1-phenyl propanols for N-SMase inhibitory activity

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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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College of Pharmacy, Pusan National University

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