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Prostaglandins are synthesized by the enzyme cyclooxygenase (COX). Both constitutive (COX-1) and inducible (COX-2) isoforms have been identified. COX-2 expression is stimulated by inflammatory mediators such as growth factors and cytokines. Most non-steroidal anti-inflammatory drugs (NSAIDS) inhibit both isoforms of COX. Recent evidence suggests that selective inhibitors of COX-2 may possess diminished side effects relative to common NSAIDS. Novel isothiazoles and isoxazoles were identified as selective inhibitors of cyclooxygenase-2 (COX-2).
We synthesized those compounds in general and flexible methods. And we report here the results of SAR (Structure & Activity Relationships) study of both isothiazole and isoxazole derivatives.

[PD1-48] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis of Novel Dimethylcyclopropyl Nucleosides as Potential Antiviral Agents

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The carbocyclic nucleosides have extensively studied as a promising antiviral agents having chemical and metabolical stability. In our research program for discovery of antiviral drugs, some novel dimethylcyclopropyl nucleosides possessing additional methyl spacer between purine bases and the ring was synthesized. The important intermediate, dimethylcyclopropyl alcohol was synthesized from ethyl chrysanthemate via its ozonolysis, isomerization, reduction, its protection using TBDPSCl and reduction of the ethyl ester by DIBAL-H gave the silylated cyclopropyl alcohol in good yield, which was condensed with purine bases by Mizunov reaction to give some cyclopropyl nucleosides after deprotection.

[PD1-49] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

CoMFA of 1-phenyl-2-substituted thioureas for their cytotoxicity

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The structure of 1-phenyl-2-substituted thiourea derivatives have been studied and optimized for their cytotoxic 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 cytotoxic activity.

[PD1-50] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Molecular Dynamics Simulation of Enantioselectivity in Metoprolol in complex

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Metoprolol (MT) is one kinds of adrenergic beta-blockers. Its (S)-enantiomer is known to be more active than the (R). Recently, the x-ray structure of beta-blocker, (S)-propranolol (a-naphthyl analogue), complexed in a mould fungal cellulase, Cel7A, was reported and the (R)-form did not build any complex. And in our previous study the conformation and stability of MT in carboxymethylated beta-cyclodextrin (BCD) complex was determined by NMR, HPLC, UV and electrophoresis measurement. Optically active BCD is often used as a chiral selector for the separation of drug enantiomers. From this study (R)-MT complex was found to be more stable than the (S)-MT

by a factor of 1.1 when carboxymethylated BCD was used as chiral discriminator. In this work the chiral discrimination energetics was modeled by an inclusion complex of MT in BCD and of MT in Cel7A using molecular dynamics(MD) simulation. With software SYBYL6.5 the aromatic ring of MT was inserted into the BCD cavity corresponding to the NMR structure. And MT was inserted into Cel7A binding pocket corresponding to X-ray structure of (S)-propranolol-Cel7A complex. Starting Coordinate from this structures performed 1ns MD simulations in water using GROMACS 3.0 program package with GROMOS96 (43a1) force field, respectively. In the normal MD phenoxy oxygen atom, OH and NH group of both MT enantiomers were involved in intensive H-bonding with O2 groups of glycosidyl rings of BCD. Furthermore free energy calculation for the transition of (S)- to (R)-form was performed using slow-growth, to yield a free energy change from (S)-MT-BCD to (R)-MT-BCD of 2.73kJ/mol, which rationalizes the bigger stability of (R)-MT-BCD complex than that of (S)-isomer. Also a realative free energy difference is 4.23 kJ/mol from (S)-MT-Cel7A to (R)-MT-Cel7A. Cel7A was confirm a chiral discriminator for the separation of beta-blocker theoretically.

[PD1-51] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

The 3-D QSAR study of antitumor arylsulfonylimidazolidinone derivatives by CoMFA and COMSIA

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Three-dimensional quantitative activity relationship (3D-QSAR) study for a series of arylsulfonylimidazolidinone derivatives with antitumor activity was conducted using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices anaysis (CoMSIA). The in vitro cytotoxicity against human lung carcinoma (A549) exhibited a strong correlation with steric and electrostatic factors of the molecules. However the contribution of steric factor was high and compounds with bulky side chain on indoline nitrogen are expected to have antitumor activity. The statistical result, cross-validated q2 (0.577 and 0.581) and conventional r2 (0.901 and 0.917) values, gave reliability to the prediction of the antitumor activities of this series.

[PD1-52] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis and in vitro/in vivo properties of prednisolone 21-sulfate sodium as a colon-specific prodrug of prednisolone

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Corticosteroids have been used most frequently for inflammatory bowel disease.They are well absorbed and only a limited fraction of the dose is delivered to the inflammatory site in the colon. To reduce side effects by the systemic absorption, colon-specific delivery is highly desirable. We prepared prednisolone 21-sulfate sodium (PDS) and investigated its suitability as a colon-specific prodrug of prednisolone(PD). If PDS is nonabsorbable and stable in the upper intestine, it will be delivered to the colon, where the sulfate group may hydrolyze to release PD by the sulfatase originated from microbes. METHOD: PDS was obtained by reacting PD and sulfatrioxide triethylamine, and subsequently treating the product with NaCl solution. Stability in pH 1.2 and 6.8 buffer solutions and apparent partition coefficient in 1-octanol/pH 6.8 buffer were determined. Prodrug conversion was determined by incubating PDS with the contents of various segments of gastrointestinal(GI) tract of rats. After oral administration, rats were sacrificed at predetermined time interval, and PD and PDS in the contents of GI tract and plasma were determined. RESULTS: PDS was stable and apparent partition coefficient of PD and PDS was 21.8 and 0.11, respectively. PDS was chemically stable on incubation with the contents of the stomach or small intestine (SI). With the cecal contents, PDS was decreased to 54% to give PD 29% of the dose in 6 h. The amount of PD was always less than the decreased PDS, which suggested that reduction of steroid took place by the cecal contents. After oral administration of PDS, neither PDS nor PD was detected from the plasma, and small amount of PD was recovered from the cecal contents but not from the SI. CONCLUSION: PDS is stable and nonabsorbable in the upper GI tract and release PD in the cecum, which implies that sulfate ester of glucocorticoid can be a promising colon-specific prodrug.