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Calcium channel blockers have been proven to be clinically useful agents in treating various cardiovascular disorders. The chemical structures of the major blockes are classified into three groups, dihydropyridines, phenylalkylamines and 1,5-benzothiazepines, which are represented by nifedipine, verapamil and diltiazem, respectively. Because of their highly clinical usefulness a number of modifications have been done on dihydropyridines and phenylalkylamines for the purpose improving their bioavailability and duration of action. However, there have been only a few reports concerning modifications of benzothiazepines. Diltiazem is usually administered twice or three times a day and its antihypertensive potency is far less than that of dihydropyridines. In order to synthesize a potent and long-lasting diltiazem congener, we intended to synthesize the hybrid structure of nifedipine and 8-chlorodiltiazem. 4-(1-pyrrolyl)amino-3-mercaptopyridine was synthesize from 4-amino-3-mercaptopyridine and 2,5-dimethoxytetrahydrofuran, and it was reacted with ethyl 2-(4-methoxyphenyl)-2-bromoacetate to give 2-(4-methoxy phenyl)-pyrrolo[2,1-d]-pyrido[3,4-b][1,5]thiazepine derivatives.

[PD1-22] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Asymmetric synthesis of (R)-(+)-etomoxir via enzymatic resolution

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An asymmetric synthesis of (R)-(+)-etomoxir 1, employing enzymatic resolution of ethyl 2-alkyl-2,3-dihydroxypropionate using Amano AK via transacylation is reported. Highly enantioselective enzymatic resolution of ethyl 2-alkyl-2,3-dihydroxypropionate was developed by using Amano AK in MTBE. By this process, (R)-(+)-etomoxir could be prepared in 30% yield and 98% ee over five steps from triehyl phosphonoacetate.

[PD1-23] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Comparative Molecular Field Analysis (CoMFA) Study of Antitumor 3 - Arylisoquinolines

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A three-dimensional quantitative structure-activity relationship (3D-QSAR) was performed for antitumor 3-arylisoquinoline derivatives by using comparative molecular field analysis (CoMFA) against four tumor cell-lines (A549, SK-OV-3, SK-MEL-2, and HCT15). CoMFA procedure was progressed with a set of 83 3-arylisoquinolines and x-ray crystal structure of 7,8-dimethoxy-3-(2-methylphenyl)isoquinolinone was used to determine molecular conformations. As a result we could get good Cross-Validated R^2 (Q^2) values and pharmacophore models. The synthesis and CoMFA of antitumor 3-arylisoquinoline will be discussed.

[PD1-24] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Synthesis and Structure- activity relationship of PDE4 inhibitors

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Research conducted over the last 20 years has established that inflamation of the airways is central to asthma. Althrough glucocorticosteroids are considered the most effective anti-inflammatory drugs currently available for asthma, they are non-selective. Thus new drugs with enhanced selectivity and improved adverse effect profiles clearly required. For this reason, selective PDE4 inhibitors have been synthesized. and we are going to apply pyrimidopyridine system to this type of inhibitor. About 50 compounds were synthesized and evaluated IC50 and selectivity for PDE4 inhibited. The structure-activity relationships will be discussed.

[PD1-25] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

SYNTHESIS AND IN VITRO/IN VIVO EVALUATION OF N,N′-BIS(5-AMINOSALICYL)-L-CYSTINE AS A COLON-SPECIFIC PRODRUG OF 5-AMINOSALICYLIC ACID

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SYNTHESIS AND IN VITRO/IN VIVO EVALUATION OF N,N′-BIS(5-AMINOSALICYL)-L-CYSTINE AS A COLON-SPECIFIC PRODRUG OF 5-AMINOSALICYLIC ACID
N,N′-Bis (5-amino-salicyl)-L-cystine dimethyl ester (5-ASA-Cys) was synthesized as a colon-specific prodrug of 5-aminosali-cylic acid (5-ASA) and its in vitro/in vivo properties were investigated.
5-Nitrosalicylic acid was reacted with cystein methyl ester in the presence of DCC and obtained N,N′-bis (5-nitro-salicyl)-L-cystine dimethyl ester (5-NSA-Cys). Reduction and hydrolysis of 5-NSA-Cys afforded 5-ASA-Cys. 5-ASA-Cys was stable in pH 1.2 and 6.8 buffer solution at 37℃. Incubation of 5-ASA-Cys with cecal contents released 5-ASA in 50 or 95% of the dose in 8 or 24 hrs, respectively. No 5-ASA was detected from the incubation with the homogenates of stomach or small intestine. After oral administration, 5-ASA-Cys was not detected in the plasma and the level of 5-ASA and N-acetyl-ASA was very low. From feces, about 45% of the orally administered dose were recovered as 5-ASA and N-acetyl-ASA, and none as 5-ASA-Cys, and from urine, 43% as 5-ASA and N-acetyl-ASA and 10 % as 5-ASA-Cys in 24 hrs. For comparison, where 5-ASA was administered orally, the fraction of the dose recovered from feces was only 7 % and more than 80 % was recovered from urine as 5-ASA and N-acetyl-ASA in 24 hrs.
Conclusions. 5-ASA-Cys was stable in the upper intestine and its absorption was limited in the upper GI tract. It was microbially activated in the colon to release 5-ASA.Concentration of 5-ASA and N-acetyl-ASA available in the large intestine was almost 6 times higher by the administration of 5-ASA-Cys than free 5-ASA. In contrast, concentration of 5-ASA in urine, which is related to systemic toxicity, was almost 2 times lower by the administration of 5-ASA-Cys than free 5-ASA. These results suggest that 5-ASA-Cys is a promising colon-specific prodrug of 5-ASA.

[PD1-26] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Antiangiogenesis Activity of Vietnamese Medicinal Plants

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