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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In a continuity of our search for a novel angiogenesis inhibitor(s) for anticancer therapy from natural sources, we have screened a large number of Vietnamese medicinal plants. It was found that seven out of fifty-eight of methanol extracts of Vietnamese medicinal plant materials showed strong to moderate antiangiogenic activity in vitro angiogenesis assay using HUVEC model. These plants include Ephedra sinica (herba), Ceiba pentandra (stem), Ceiba pentandra (leaves), Coix lachryma jobi (semen), Drynaria fortunei (rhizoma), Illicium verum (fructus), Illicium verum (stem), and Bombax ceiba (stem). Of these, the methanol (MeOH) extracts of Ephedrae sinicae herba, Ceibae pentandrae stem exhibited the strongest inhibitory effects on in vitro tube formation (inhibition ratios of 89.12 and 87.54 % at 30, and 100 ug/mL, respectively).

[PD1-27] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

Study of the Amyloid Precursor Protein(APP) Changes in Transmembrane Domain Using Cellular Automata(CAs)

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Alzheimer's disease is caused by the penetration, aggregation and deposition of β-amyloid peptide(βAP). An βAP has the characteristics of amphiphilic peptide with a hydrophilic and a hydrophobic segment. This hydrophobic segment is C-terminus domain, which interacts with lipid membrane. The segment is located at the transmembrane domain of the amyloid precursor protein (APP). A βAP is formed after mutations and cleavages of an APP those are occurred in transmembrane. For this reason, the mutations and cleavages of an APP are very significant. In this study, we studied structure characteristics of an APP. Structural changes of an APP and formation of a βAP were simulated using cellular automata(CAs). In CAs simulation, large extracellular domain, transmembrane domain, and cytoplasmic tail were depicted by different colors. The mutation and cleavages were shown by other colors, also. From the results, it seems that CAs effectively simulated the phenomena in transmembrane domain.

[PD2-1] [10/20/2000 (Fri) 11:30 - 12:30 / [Hall B]]

A Simple and Sensitive Enzyme-linked Immunosorbent Assay for the Determination of Ginsenoside F1

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Panax ginseng C. A. Meyer contains many kinds of glucosides of dammarane type triterpenes, protopanaxadiol (PPD) and protopanaxatriol (PPT), as main constituents. Ginsenoside F_1 ($G\text{-}F_1$), a PPT type saponin, was isolated from the leaves of this plant. In order to evaluate the quality of commercial ginseng extracts, a specific and highly sensitive ELISA of $G\text{-}F_1$ was explored.

High titer polyclonal antibodies were raised against $G\text{-}F_1$-BSA conjugate. The optimum antibody dilution for the assay was found to be 80,000-fold and 6 μ g/ml of $G\text{-}F_1$-ovalbumin was used for solid phase coating. The working range of this assay is 1.25 pg/well~ 125 pg/well. Cross reactivity of the antibody was investigated to determine its specificity.
As a result, the antibodies showed 34.79% of cross-reactivity with PPT, the aglycone of $G\text{-}F_1$.