steric and electrostatic contour map generated by CoMFA model showed a good agreement with CoMSIA map. Docking of COMFA test set into the COX-2 active site by FlexiDock showed a good correlation (r2=0.802) between the bioactivity and fitness scores. Flexible docking by molecular dynamics generated reasonable binding configurations and the calculated binding energies were correlated (r2=0.650) with inhibitory activity. Then comparative binding energy (COMBINE) analysis was applied to a series of docking complexes.

[PD1-39] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

The inhibiory effect of glycyrrhizin and flavonoids on the reductive metabolism of glucocorticoid by the rat cecal contents.

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Glucocorticoids are used most widely for the treatment of inflammatory bowel disease (IBD). For the efficient treatment and reduction of side effects, colon-specific delivery of a glucocorticoid is highly desirable. Previously, we synthesized prednisolone 21-sulfate sodium (PDS) as a colon-specific prodrug of prednisolone (PD) expecting that it might be stable and nonabsorbable in the upper intestine and hydrolyze in the colon to release PD. Properties of PDS was suitable as a colon-specific prodrug except that a portion of the released PD underwent reductive metabolism (bioinactivation) by the cecal and colonic contents. To be used as an effective therapy for IBD, a glucocorticoid should be resistant to the reductive bioinactivation. In the present study, we investigated the liability of various glucocorticoid to the reductive metabolism by the rat intestinal contents and studied the inhibitory effect of glycyrrhizin and several flavonoids on the reductive metabolism. The liability of glucocorticoid to the reductive metabolism by the rat cecal contents was in the order of cortisone, hydrocortisone> prednisolone> methylprednisolone> triamcinolone> betamethasone≫dexamethasone, which revealed that 9-fluoro substituted glucocorticoids were most resistant. Glycyrrhizin inhibited the reductive metabolism of methylprednisolone 50% of the control at the concentration of 1x10-3M. Among the tested compounds, rutin was most effective on a molar basis. Selection of a suitable glucocorticoid and/or the use of a metabolism inhibitor might optimise the therapeutic effect of a glucocorticoid for IBD.

[PD1-40] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Cytotoxic activity of (2S, 3R, 4E) 5-Aryl-4-pentene-1,3-diol-2-aminoueras

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The 18 ureidoceramide derivatives had been investigated for their cytotoxic activity against HT-29 colon cancer, Caki-2 renal cancer, A549 lung cancer, PC-3 prostate cancer, HL-60 leukemia cell using MTT assay. Cytotoxic activity was strongly influenced by the substituted alkyl chain length and the optimal alkyl chain length for cytotoxicity was C9-C12. Some of ureidoceramide derivatives showed stronger activity than reference compound, B13. Specially, fluorophenyl derivative with C12 chain length showed 2~3 times stronger activity than B13 against all tested cancer cell.

[PD1-41] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Synthesis and cyclooxygenase-2 inhibitory activity of tetrahydroaminoacridine and their analogues

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A series of tetrahydroaminoacridine and their analogues were synthesized. Tetrahydroaminoacridine(tacrine) is an anticholinesterase agent used in the treatment of Alzheimer's disease. Introduction of piperidine group at the para position enhanced anti-inflamatory activity for Alzheimer's disease. We investigated their ability to inhibit cyclooxygenase-1 and 2 isoforms. This series has shown potent in vitro inhibition of the enzyme cyclooxygenase-2 with % inhibition = 70.3~23.6 at 10 μg/ml. Compound 3b was the most potential inhibitor with an IC_{50}s = 15.6 μg/ml. Compound 3a and 3c displayed weak in vitro inhibition of cyclooxygenase-2 with IC_{50}s 20.2~29.2 μg/ml. The most potent analogues in this series was compound 3b with a cyclooxygenase inhibitory activity of 1/2 in excess of 5 times. These data indicate that compound 3b is an cyclooxygenase-2 inhibitor with good selectivity profile when compared with tetrahydroaminoacridine.

[PD1-42] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

The Role of Korea Chemical Bank in "Hit to Lead" process of Drug Discovery

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The Korea Chemical Bank (KCB) has more than 80.000 compound collections, provided from many companies, academies and institutes. KCB has supported high-throughput screening (HTS) against 80 biological targets and identified a number of hits over 20 targets. These hits were first validated by confirming the purity and novelty of anticipated compound. We also determined their physiochemical properties. Information about structure/activity relationship (SAR), ADME, and 3D-QSAR in each compound was precisely examined and collected from molecular databases. Furthermore, we searched recent research trends for all biological targets screened. All of accumulated information were then provided to the drug development programs, which were organized in industries or institutes. Many screening hits are nonspecific (false positive). This is a serious problem in drug discovery. We recently found that many nonspecific hits from drug discovery screening projects have certain chemical structures and that they are often appeared as hits in every screening target. These data were also informed to research groups for successful lead generation. This post includes several success cases for "hit to lead" as well as a role of KCB in this process.

[PD1-43] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

3-D QSAR Studies on Thiazole and Triazole Antifungal Agents by CoMFA and CoMSIA

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