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]