Jeong TaeCheon, Lee EungSeok*

College of Pharmacy, Yeungnam University, Kyongsan 712-749, Korea, 1School of Medicine, Catholic University of Daegu, Daegu 705-034, Korea

It has been reported that 2-bromopropane might be a causative agent for reproductive toxicity and have immunotoxic effects. 1-Bromopropane known as an alternative to ozone depleting solvents, which has structural similarity to 2-bromopropane, has been reported to be neurotoxic to rats in long-term inhalation exposure.
To elucidate mechanisms of 1- or 2-bromopropane-induced toxicities in the molecular level, formation of N7-guanine adducts by 1- or 2-bromopropane was investigated in vitro. N7-Guanine adducts of 1- and 2-bromopropane (N7-propyl guanine and N7-isopropyl guanine, respectively) were chemically synthesized in three steps in relatively high yields and structurally characterized by analyses of 1H NMR, 13C NMR, UV, HPLC and LC/MS/MS (ESI) to use as standard materials. N7-Propyl guanine and N7-isopropyl guanine were detected and identified by UV, HPLC and LC/MS/MS analyses after incubation of calf thymus DNA with 1- or 2-bromopropane at a physiological condition for 16 hr, followed by thermal hydrolysis. In addition, time response and dose response effect of DNA adduct formation were investigated. Furthermore in vivo treatment of 2-bromopropane resulted in detection of RNA adduct of 2-bromopropane after analyses of ESI LC/MS/MS. The present results suggest that 1- and 2-bromopropane may form a DNA adducts at N7-position of 2'-deoxyguanosine at a physiological condition, which may be responsible for certain toxicities.

[PD1-37] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

PPAR-γ ligands binding energy and bioactivity

Lee HyeSun°, Chae ChongHak, Yoo SungEun, Park KyungLae

Lab. of CADD, KRICT, Daejon 305-343. Dept. of Pharmacy Chungnam National Univ. Daejeon 305-764

PPAR-γ(Peroxisome Proliferator-Activated Receptor γ) 리간드들은 논문 조사를 통해 이루어졌다. PPAR-γ의 45개 알려진 화합물들을 찾았고, 12 생물활성 화합물을 선택했다. 리간드(rosiglitazone)과 단백질의 결합된 구조는(1fm6)는 PDB로부터 획득했고, 단백질 coordinate를 가져와 PPAR 의 활성 영역 잔기들은 확인했다.(2TYR, 1SER, 1HIS). CoMFA와 Flexi Dock을 통해 단백질과 리간드 사이의 상호작용과 결합에너지에 대한 상호 관계를 밝혔다.

[PD1-38] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

3D-QSAR and docking studies of selective COX-2 inhibitors

Kim HyeJung°, Chae ChongHak, Yoo SungEun, Park KyungLae

Lab. of CADD, KRICT, Taejon 305-343. Dept. of Pharmacy Chungnam National Univ, Daejeon 305-764.

The three-dimensional quantitative structure-activity relationship (3D-QSAR) approach using comparative molecular field analysis (CoMFA) and comparative molecular similarity analysis (CoMSIA) was applied to 62 derivatives known as COX-2 selective inhibitors. Partial least square (PLS) analyses produced good predicted models with q2 value of 0.803 (s=0.285, F=215.401, r2=0.951) and 0.769 (s=0.192, F=245.364, r2=0.980) for CoMFA and CoMSIA, respectively. The

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.

Kong HyeSik°, Kim InHo, Kim YoungSoo, Choi Bohlm, Doh MinJu, Kim YoungMi

College of Pharmacy, Pusan National University

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

Im CU, Kim YH°, Jyung ML, Lim CB

College of Pharmacy, Chung-ang University

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]