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S-Adenosylhomocysteine hydrolase (SAH) catalyzes the hydrolysis of S-adenosylhomocysteine to adenosine and L-homocysteine and has been an attractive target for the development of broad spectrum antiviral agents. Based on the potent inhibitory activity of neplanocin A against SAH, we have reported the synthesis and novel mechanism of action of fluoro-neplanocin A. Fluoro-neplanocin A exhibited potent antiviral activity against several viruses such as HIV-1, HSV-1, HSV-2, HBV, and VSV (vesicular stomatitis virus), but high cytotoxicity was also observed. Since this high cytotoxicity was thought to come from the phosphorylation of the 5'-hydroxyl group of fluoro-neplanocin A or strong inhibition of SAH, we designed 5'-substituted adenosine analogues (SH, NH2, and F) of fluoro-neplanocin A which can not be phosphorylated at the 5'-position and pyrimidine analogues of fluoro-neplanocin A which can not be substrates for SAH, respectively. For the synthesis of pyrimidine analogues of fluoro-neplanocin A, the key intermediate, D-fluorocyclopentenol was synthesized via critical electrophilic vinyl fluorination (n-BuLi, N-fluorobenzenesulfonimide) and then condensed with pyrimidine bases. For the synthesis of 5'-substituted adenosine analogues (SH, NH2, and F) of fluoro-neplanocin A, D-fluorocyclopentenol was condensed with adenine and then transformed to the 5'-substituted adenosine analogues. Synthesis and biological activity of the target nucleosides will be discussed in the meeting.

[PD1-35] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Construction of Indole Library for Serotonin Related Drugs and Macrocyclization Using Selenium Chemistry in Solid-Phase Reaction.

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Hetero chain compounds have high possibilities of being good medicinal candidate because of their well-known medicinal activity and relatively low subtitled carbon. By constructing the method of making this compound library, this research has the purpose to create a new medicinal candidate materials based on an easy medicinal search.
The first step is to construct an Indole library in a compounding process with the design of a linker connecting a solid-state resin and a substrate. The designed linkers in this research are of 3 kinds and a linker used in compounding of indole is a linker 3 that puts an oxygen atom in the middle. The second step was to establish a reaction condition in a solvent of a designed linker and application of Fischer indole compound method in solid state suitable for a solid-state resin. The third step was to select 20 kinds of ketone compounds and compound an indole through a Fischer indole compounding method by applying an established condition in a solvent state and a previously made linker 3. We had experimented with 10 kinds of activities and among the compounded indole compounds, the compounds Ind-5, 6 had anti-inflammation effect and Ind-7 had a cytotoxicity effect.
In general, a macrolactonization reaction within a molecule reacts in a weak concentration of about 103~105 by a high dilution method in order to escape the reaction of molecules. Because much solvent is consumed when macrolactonization reaction is carried out in a solution-phase, we studied a solid-phase macrolactonization reaction in order to overcome this problem.

[PD1-36] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Synthesis, Characterization and Identification of In Vitro and In Vivo DNA adducts of 1- and 2-Bromopropane

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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

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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

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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