[PD1-32] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Polyoxygenated Flavone Analogs as Inhibitors of PGE2 Production

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As part of our research to discover novel synthetic flavonoids which can be applied to chronic inflammation diseases, many structurally modified flavone analogs have been synthesized to obtain information concerning the relationships between structures and the anti-inflammatory activities. We previously reported that 7-methoxyflavone analogs generally exhibited strong inhibitory activities against cyclooxygenase-2 catalyzed prostaglandin production. 7-Methxoyflavone analogs with the polyoxygenated B ring were synthesized and evaluated the inhibitory activity of cyclooxygenase-2 catalyzed prostaglandin production. Polyoxygenated flavone analogs were prepared from 2,4-dihydroxyacetophenone in 3 steps. The inhibitory activity of the synthesized flavone analogs against prostaglandin production from lipopolysaccharide-treated RAW 264.7 cells were measured. 2,4,7-Trimethoxyflavone showed best results.

[PD1-33] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Synthesis of Brefeldin A Lactam Analogue

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(+)-Brefeldin A (1) has been, since its isolation1 and structural elucidation2 many years ago, one of the most attractive targets for synthetic chemists due to its wide range of biological activities and well-functionalized macrolide structure. Its biological mode of action has been disclosed by a number of important discoveries. Especially the ability of brefeldin A to induce DNA fragmentation associated with apoptosis in cancer cells has stimulated a great deal of recent interest in its preclinical development as an anticancer agent. Since Corey's first total synthesis of 1 in 1976, a number of synthetic routes to this macrolide antibiotic have been explored. In particular, the exciting biological activities of brefeldin A, combined with the impracticality of the previously developed syntheses led us to take on the challenge of the total synthesis of brefeldin A. In planning our approach, we hoped to develop a versatile, practical, and stereocontrolled route that would minimize protecting group manipulations and adapt a platform that leads to a variety of analogues of Brefeldin A. This paper fully describes our synthetic studies9 toward (+)-brefeldin A Lactam Analogue

[PD1-34] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Structure-activity Relationship Study of Fluoro-Neplanocin A as Potential Antiviral and Antitumor Agents

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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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