Synthesis and Antiviral Activity of Methylene Cyclopropyl Pyrimidine Nucleosides

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Some methylene cyclopropyl pyrimidine nucleosides were synthesized from the intermediate, Feist's acid as a series of purine nucleosides to find potent antiviral agents. The key intermediate 7, cyclopropyl compound was synthesized via esterfication, reduction, and the partial protection by using TBDPS-Cl, bulky protecting group which was activated by tosylation. Its condensation with some 5-substituted pyrimidine bases in the presence of potassium carbonate and a crown compound and its deprotection by using n-Bu_4NF gave corresponding cyclopropyl nucleosides in low yield, respectively. The thymine nucleoside among the synthesized compounds showed moderate anti-HBV activity.

[PD1-3] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis and structure-activity relationship of novel FTase inhibitors containing imidazole and urea moieties

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Ras proteins play an important role in signal transduction process involved in cell proliferation. Mutated Ras proteins have been found in 30% of human cancers including 50% of colon cancer, 90% of pancreas cancer, 50% of lung cancer and thyroid gland cancers. A series of posttranslational modifications are required for its biological function. The first step is alkylation of cystein residue of its C-terminus with a farnesyl group by farnesyltransferase(FTase), which was identified as a potential target for the discovery of anticancer agents.
Based on the C-terminal CAAX (C: cystein, A: aliphatic amino acid, X: serine or methionine) box of ras protein, varies types of CAAX mimetic FTase inhibitors have been reported.
In this presentation, the synthesis, structure-activity relationship, and biological properties of novel FTase inhibitors containing imidazole group will be described. Cysteine of CAAX box was replaced with imidazole substituent and AAX moiety was replaced with simple urea derivatives. Biological activity was evaluated by FTase assay and MTT based cell growth inhibition assay. Many FTase inhibitors showed potent inhibition against K-ras farnesylation as well as ras-transformed cell growth without showing cytotoxicity.

[PD1-4] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

An Efficient Synthesis of Cyclic α,α-Disubstituted α-Amino Acids

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Development of conformationally constrained amino acid analogues attracts much attention in the design of biologically active compounds such as enzyme inhibitors and receptor agonists/antagonists. It is very important to develop synthetic methodology allowing the ready synthesis of those amino acids. We have devised an efficient method for the synthesis of cyclic α,α-disubstituted α-amino acids such as 2-aminotetraline-2-carboxylic acid (Atc), 1-amino-4-phenylcyclohexane-1-carboxylic acid (Apc), and 4-amino-1-phenylpiperidine-4-carboxylic acid (Appc). Key features of the synthesis involve hydantoin formation, mild hydrolysis of hydantoin and efficient resolution of resulting racemic or

diastereomeric mixtures.

[PD1-5] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthesis and Antitumor Activity of 4'-O-Aminoacyl-, Carbamate-, and Carbonate Prodrugs of 4'-Demethyl-1-Deoxypodophyllotoxin

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Deoxypodophyllotoxin (DPT), first isolated from *Anthricus sylvestris* is a potent inhibitor of mitosis, and showed a potent cytotoxic activity against a wide variety of cancer cell lines. But, DPT still did not show a potent antitumor activity comparable to its potent cytotoxic activity. This was considered to be due to poor aqueous solubility and bioavailability of DPT. To obtain compounds with pharmaceutically acceptable properties and improved antitumor activity, we designed 4'-demethyl-1-DPT derivatives in which the methyl group at 4'-position was replaced with various aminoacyl, carbamoyl, oxycarbonyl groups. Among them, 4'-demethyl-4'-*O*-(8-aminooctanoyl)-1-DPT, 4'-demethyl-4'-*O*-(2-hyroxyethylcarbamoyl)-1-DPT, and 4'-demethyl-4'-*O*-(2-chloroethylcarbonyl)-1-DPT showed inhibition ratio (IR) of 87%, 95%, and 89%, respectively, much higher than the IR (78%) of etoposide which was used as positive control.

[PD1-6] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Stereoselective synthesis hydroxylated cyclopentane carbocycle for nucleosides via sequential Claisen rearrangement and RCM reaction

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Extensive efforts in the search of chemotherapeutic agents against viral infection and cancers have led to the discovery of a variety of biologically active nucleoside analogs, including carbocyclic nucleosides (i.e. abacavir).
As part of our drug discovery program, we have determined to synthesize carbocyclic nucleosides with hydroxy group at 5'-position. Herein, We would like to introduce synthetic method of cyclopentane carbocycle intermediate for the synthesis of 5'-hydroxy carbocyclic nucleosides using sequential Claisen rearrangement and ring closing metathesis from D-mannitol.

[PD1-7] [10/19/2001 (Fri) 14:00 - 17:00 / Hall D]

Synthetic Approaches to the Generation of New COX-2 Inhibitor through the Modification of Indomethacin

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All nonsteroiddal antiinflammatory drugs(NSAIDs) inhibit coclooxygenase(COX) isoenymes to different extents, which accounts for their antiinflammatory and analgesic activities and their gastrointestinal(GI)