The reverse transriptase (RT) of HIV-1 is a proven target for inhibition of HIV-1 replication. Many nonnucleoside RT inhibitors (NNRTIs) are in development stage for the clinical use. Among them, trovirdine (PETT), (thiophene) ethylpyridylthioureas (TET), and phenylethylpyridylureas (urea-PETT) are simple and flexible arylalkylarylureas. These are now considered to be very important as a potential therapeutics with remarkable antiviral activity against various mutant strains. The effective conformation of these analogs for binding pocket of RT are well determined as a butterfly conformation by x-ray crystallography of their RT complex. To find out new analogs conformationally fixed, N-arylalkylbenzimidazolones, N-arylalkylbenzimidazolethiones, 3-arylalkyl-3,4-dihydro-1H-quinazolinones, and 3-arylalkyl-3,4-dihydro-1H-quinazoline thinones were designed and regioselectively prepared. These compounds were tested against HIV-1 and HIV-2 viruses. Although the conformations of these compounds were considered to be similar to the active conformation of PETTs, these do not show any activity. The synthesis and comparative conformational analysis of these analogs will be discussed.

[PD1-42] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Straightforward synthesis of 4'α-C-hydroxymethyl branched novel carbocyclic nucleosides

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Carbocyclic nucleosides are unique class in which a methylene group replaces the oxygen in the furan, which result in metabolic stability to endogenous phosphorylase. The biologically active natural carbocyclic nucleosides such as aristeromycin and neplanocin were found to possess interesting biological properties including antiviral and antitumor activity.
Recently, a number of 4'α-substituted nucleoside analogues have been synthesized and showed significant antitumor or antiviral activities. Among them, 4'α-C-methyl-2-deoxycytidine, 4'α-C-fluoromethyl-2-deoxycytidine and 4'α-C-hydroxymethylthymidine demonstrated very potent biological activities, but their high toxicity rendered them ineffectual as drugs.
On the basis of these interesting results and as part of our drug discovery programs, we have designed novel 4'α-hydroxymethyl substituted carbocyclic nucleosides which hybrid the properties of enzyme resistant carbocyclic as well as biologically active 4'α-C-branched furanose nucleosides. Herein, we disclose their de novo synthetic routes employing very versatile three step sequences ([3,3]-sigmatropic rearrangement, ring-closing metathesis, and Pd(0)-catalyzed allylic alkylation) from very simple acyclic precursor '1,3-dihydroxy acetone'.

[PD1-43] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

3,4-Diaryl-2(5H)-Furanone Derivatives: Synthesis, Cytotoxicity, and Antitumor Activity

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Fifty of 3,4-diaryl-2(5H)-furanone derivatives were synthesized and evaluated for their cytotoxicity in a small panel of cancer cell lines. Eleven compounds in this series, were found to have significant cytotoxic activities with ED_{50} values of less than 1 μM in most of the cell lines tested. Compound RTM51, 3-(3,4,5-trimethoxyphenyl)-4-(3-amino-4-methylamino)-2(5H)-furanone exhibited the most potent cytotoxic activity with ED_{50} value of 0.003 μM and antitumor activity on BDF1 mice bearing Lewis lung carcinoma cells with inhibition ratio of 72 %.

[PD1-44] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Structural Requirement of Isoflavonones for the Inhibitory Activity of Interleukin-5

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