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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Interleukin (IL)-5 appears to be one of the main proinflammatory mediators among a growing number of cytokines and chemokines that induce eosinophilic inflammation. Sophoricoside and their analogs isolated from Sophora japonica show relatively potent inhibitory activity of interleukin (IL)-5 as a small molecule. To identify structural requirements of this isoflavonone for its inhibitory activity against IL-5, isoflavonones, isoflavanones, and their glycosides were prepared and tested their inhibitory activity against IL-5. Among them, 5-benzyloxy-3-(4-hydroxyphenyl)chromen-4-one (87.9 % inhibition at 50 μM, IC50 = 15.3 μM) shows the most potent activity, which is compatible activity with that of sophoricoside. The important structural requirements of these isoflavonone analogs exhibiting the inhibitory activity against IL-5 were recognized as 1) planarity of chromen-4-one ring, 2) existence of phenolic hydroxyl at 4-position of B ring, and 3) introduction of benzyloxy at 5 position, which may act as a bulky group for hydrophobic pocket in putative binding site. However glucopyranosyl moiety of sophoricoside would not be critical for the activity.

[PD1-45] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Design, Synthesis and Biological Activities of Novel Vanilloid Receptor (VR) Agonists and Antagonists

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Recently, we have reported that several lipoxygenases products directly activate the capsaicin-activated channel as intracellular messengers in neuron. In particular, 12-(*S*)-hydroperoxyeicosatetraenoic acid turned out to be the most potent endogenous VR activator. This finding prompted us to search for a novel non-vanilloid VR agonists and antagonists. We have designed and synthesized a series of non-vanilloid VR binding ligands based on the structural similarity between 12-HPETE and capsaicin, the natural VR agonist. Our recent studies on the development of selective vanilloid receptor agonists and antagonists will be presented.

[PD1-46] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthetic Approaches to Benzophenanthridines

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Benzo[c]phenanthridine alkaloids occurring in the Fumariaceae, Papaveraceae, and Rutaceae, posses numerous pharmacological activities, such as antitumor, antimicrobal and antifungal activities. Thus, they have attracted much interests of chemists and as the result, several total syntheses of these heterocycle structure were accomplished. Among that, procedures which involve 3-arylisoquinoline intermediates are useful methods and these synthons could be also applied to the preparation of other alkaloids. We have recently reported the convenient synthesis of benzophenanthridine skeleton via cyclization of 3-arylisoquinoline intermediate. In continuing research, the synthetic approaches to natural benzophenanthridines and its derivatization were carried out.

[PD1-47] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

EFFECTS OF ISOTHIAZOLE AND ISOXAZOLE DERIVATIVES AS SELECTIVE CYCLOOXYGENASE-2 INHIBITORS

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