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Oxygen radicals are produced in many pathophysiologic states whether the event is a causal factor of illness or is a result of their progression. Oxygen radicals including superoxide anions, hydrogen peroxide are thought to be involved in a number of type of acute, and chronic pathologic condition in the brain and neural tissue. So the antioxidants have recently received much attention as therapeutic agent for the treatment of neurodegenerative disease.
In this study, we describe synthesis of a series of chromenone derivatives as antioxidant agents. The target compounds are designed to include the structural feature of caffeic acid, flavonoid, and tocopherol known as antioxidants.

[PD1-39] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis and Antifungal Activities of 2,5-Disubstituted-6-Arylamino-4,7-benzimidazolediones

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2,5-Disubstituted-6-arylamino-4,7-benzimidazolediones were synthesized and tested for in vitro antifungal activities against pathogenic fungi. The 2-aryl-6-arylamino-5-chloro-4,7-benzimidazolediones were prepared by nucleophilic substitution on 2-Aryl-5,6-dichloro-4,7-benzimidazolediones with appropriate arylamines in good yields. The synthesized 4,7-benzimidazolediones were tested in vitro for their growth inhibitory activities against pathogenic fungi by the standard method. The MIC values were determined by comparison to flucytosine as a fungicidal standard agent. The most active potential among the 4,7-benzimidazoledione series was found for 6-arylamino-2-(2-pyridyl)-4,7-benzimidazolediones, which showed generally good activities against all tested Candida species and A. niger.

[PD1-40] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis and evaluation of antifungal activities of 5-arylamino-6-chloro-4,7-dioxoindazoles

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5-Arylamino-6-chloro-4,7-dioxoindazoles (DZs) were newly synthesized for the evaluation of antifungal activities. The compounds DZs were prepared by regioselective nucleophilic substitution of 5,6-dichloro-4,7-dioxoindazoles with appropriate arylamines in high yield. DZs were tested for their growth inhibitory activities against Candida species and Aspergillus niger. The MIC values were determined by the two-fold dilution method. In general, DZs showed in vitro antifungal activities. Among the tested compounds, DZ1, 3, 6, 7and 12 showed potent antifungal activities against Candida species and Aspergillus niger. DZ7 was the most effective in preventing the growth of Candida species.

[PD1-41] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis of N-arylalkylbenzimidazolones(thiones) and 3-arylalkyl-3,4-dihydro-1H-quinazolinones (thinones) as conformatonally restricted PETT analogs for inhibition of HIV-1 reverse transcriptase

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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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