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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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Prostaglandins are synthesized by the enzyme cyclooxygenase (COX). Both constitutive (COX-1) and inducible (COX-2) isoforms have been identified. COX-2 expression is stimulated by inflammatory mediators such as growth factors and cytokines. Most non-steroidal anti-inflammatory drugs (NSAIDS) inhibit both isoforms of COX. Recent evidence suggests that selective inhibitors of COX-2 may possess diminished side effects relative to common NSAIDS. Novel isothiazoles and isoxazoles were identified as selective inhibitors of cyclooxygenase-2 (COX-2).
We synthesized those compounds in general and flexible methods. And we report here the results of SAR (Structure & Activity Relationships) study of both isothiazole and isoxazole derivatives.

[PD1-48] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis of Novel Dimethylcyclopropyl Nucleosides as Potential Antiviral Agents

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The carbocyclic nucleosides have extensively studied as a promising antiviral agents having chemical and metabolical stability. In our research program for discovery of antiviral drugs, some novel dimethylcyclopropyl nucleosides possessing additional methyl spacer between purine bases and the ring was synthesized. The important intermediate, dimethylcyclopropyl alcohol was synthesized from ethyl chrysanthemate via its ozonolysis, isomerization, reduction, its protection using TBDPSCl and reduction of the ethyl ester by DIBAL-H gave the silylated cyclopropyl alcohol in good yield, which was condensed with purine bases by Mizunov reaction to give some cyclopropyl nucleosides after deprotection.

[PD1-49] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

CoMFA of 1-phenyl-2-substituted thioureas for their cytotoxicity

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The structure of 1-phenyl-2-substituted thiourea derivatives have been studied and optimized for their cytotoxic activity. The three dimensional quantitative structure activity relationship (3D-QSAR) was investigated using comparative molecular field analysis (CoMFA). The result suggested that electrostatic and steric factors of 2-alkylureido-1-phenyl propanol derivatives were correlated well with cytotoxic activity.

[PD1-50] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Molecular Dynamics Simulation of Enantioselectivity in Metoprolol in complex

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Metoprolol (MT) is one kinds of adrenergic beta-blockers. Its (S)-enantiomer is known to be more active than the (R). Recently, the x-ray structure of beta-blocker, (S)-propranolol (a-naphthyl analogue), complexed in a mould fungal cellulase, Cel7A, was reported and the (R)-form did not build any complex. And in our previous study the conformation and stability of MT in carboxymethylated beta-cyclodextrin (BCD) complex was determined by NMR, HPLC, UV and electrophoresis measurement. Optically active BCD is often used as a chiral selector for the separation of drug enantiomers. From this study (R)-MT complex was found to be more stable than the (S)-MT