The flavonoids are a very large and important group of polyphenolic natural product, which exhibit a wide range of biological properties. To decipher the relationship between the stuructural modification of flavone B ring moiety and anti-inflammatory activity, we synthesized flavone analogs substituted with a heteroaryl group at the B ring position.
2'-Hydroxyacetophenone was reacted with various heteroaromatic aldehydes in alcoholic KOH to produce chalcones in good yields. Reactions in iodine-DMSO conditions provide a large number of synthetic flavones as crystalline products. The preparation of these products along with their anti-inflammatory activity will be discussed.

[PD1-18] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Peptidyl 2-Ketoimdiazole Libraries for Protease Inhibitors

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Recently, it has been reported that 2-ketoheterocycles, eletrophilic ketones, generate the transition-state mimetic in the process of proteolysis. Therefore, it is suggested 2-ketoheterocycles exhibit reversible mode of inhibition on serine proteases. We designed and prepared 2-ketoheterocycle libraries for the discovery of potent and specific protease inhibitors.
In the synthesis of tetra-peptidyl 2-ketoimidazole libraries (P4-P3-P2-P1-ketoimidazole), 2-ketoimidazole was obtained by the reaction of Weinreb amide originated from several natural and unnatural amino acids with 2-lithiated 1-methylimidazole in high yield. In order to obtain the peptidyl 2-ketoimidazole libraries, the parallel solution phase synthetic method was used for the introduction of various P2, P3, and P4 building blocks. We synthesized approximately 600 compounds being 2-ketoimidazole with diverse residues on P1~P4, and used this library for the discovery of serine protease inhibitors, such as HCV NS3 protease and elastases, etc.
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[PD1-19] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Stereocontrolled synthesis of novel 6'(β)-hydroxy-carbocyclic nucleosides

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Since 6'-hydroxymethyl substituted carbovir showed good biological activity as potent anti-HIV agent, many medicinal chemists started to explorer 6'-modified carbocyclic nucleosides. Unfortunately, most of the known 6'-modified carbocyclic nucleosides have been synthesized as racemic mixture, probably due to the synthetic difficulties. Therefore enantiomeric synthesis of the novel 6'-substituted carbocyclic nucleosides would be synthetic challenging and biologically interesting. Furthermore, the recent approval of abacavir by FDA as an anti-HIV agent strongly warranted the further explorer of carbocyclic nucleosides as chemotherapeutic agents.
On the other hand, much attention has been paid to unnatural L-nucleosides since some of the L-enantiomers have been shown to possess more improved biological profiles than its D-counterpart. Among them, 3TC, FTC, L-FddC, L-FMAU were reported to be the promising antiviral agents. For example, L-FMAU showed greater potency against HBV and lower toxicity than D-FMAU. Recent approval of 3TC by Food and Drug Administration for the treatment of HIV and HBV infected individual shows the therapeutic significance of L-nucleosides.
In line with these interesting observations and as part of our ongoing drug discovery efforts, we have designed novel nucleosides with hydroxy group at 6'(β)-position of L-carbocyclic nucleosides that would hybrid the properties of 2',3'-dideoxy carbocyclic nucleosides and L-nucleosides. Herein, we would like to present an enantiomeric synthetic route of novel 6'(β)-hydroxy-2',3'-dideoxy-L-carbocyclic nucleosides, of which stereochemistry was successfully controlled by sequential chelation controlled Claisen

rearrangement, Grubbs' ring closing metathesis, and Trost's allylic alkylation. The reiterative three-step sequence (i.e. sigmatropic rearrangement, ring closing methathesis, and allylic alkylation) can also provide acess to further synthesis of structually complicated novel carbocyclic nucleosides.

[PD1-20] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Synthesis of Novel 1,5-diarylhydantoins as Selective COX-2 Inhibitors

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The most common side-effects of NSAIDs are generally gastro-intestinal disturbances such as discomfort, nausea, peptic ulcer and severe bleeding. It has been proposed that NSAIDs act through inhibition of cyclooxygenase-1(COX-1) and cyclooxygenase-2(COX-2) and that inhibition of COX-1 is associated with adverse gastro-intestinal effects while inhibition of COX-2 is associated with anti-inflammatory activity. On the basis of this fact, specific COX-2 inhibitors such as celecoxib and rofecoxib are introduced in the drug market. The distinguished feature of these drugs is that the 5-membered heterocycle ring is substituted with two aryl groups. This study reports on synthesis of novel 1,5-diarylhydantoin derivatives, candidates for selective COX-2 inhibitors. These compounds were synthesized through esterification, bromination, α-substitution and cyclization from commercially available phenylacetic aicd.

[PD1-21] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Novel Dimeric Cinchona Alkaloid Ammonium Salts with 2,7-Naphthalene Ligand: Highly Enantioselective and Practical Phase-Transfer Catalysts for the Synthesis of alpha-Amino acids

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Phase-transfer catalysis (PTC) is one of the most useful methodologies for the practical syntheses because of the operational simplicity and mild reaction conditions, which enable this method to be applied to the industrial process. Recently, PTC has been extensively applied for the asymmetric synthesis by using chiral quaternary ammonium salts. Chiral phase-tranfer catalysts derived from the cinchona alkaloids have been developed and successfully applied to various useful organic reactions. Based on the fact that the introduction of a bulky subunit at the N(1)-position of cinchona alkaloids leads to enhance the enantioselectivity, we recently reported the efficient dimeric and trimeric catalyst by using benzene as a ligand. The enhancement of stereoselectivity is due to the screening effect of each two Cinchona unit, which can make the substrate approach to only one direction. As part of our program to develop practical catalyst which can be used in industrial process, we further investigate the more optimal dimeric catalyst by modifying ligand instead of benzene ligand. In this poster, we report the preparation of new symmetrical dimeric cinchona alkaloid-derived catalysts having naphthalene moiety as a new optimal ligand and their application to the catalytic enantioselective phase-transfer alkylation of N-(diphenylmethylene)glycine tert-butyl ester.

[PD1-22] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

The Cyclobutyl Intermediate for Synthesis of Novel Carbocyclic Nucleosides , Potential Antiviral Agents

Kook MinChul°, Choi BoGil