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

Yoon Yeojun°, Yi Wonhui, Lee Bongyong

유한양행 중앙연구소 신약연구센터

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.
[This study was supported by a grant of the National R&D Program, Ministry of Science & Technology, Korea (CH1-3-12)]

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

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

Baik GunHa°[1], Chung BongYoung[1], Cho JungHyuck[2], Oh ChangHyun[2], Hong JoonHee[3*]

1 Department of Chemistry, Korea University, 1,5-Ka, Anam-dong, Sungbuk-ku, Seoul 136-701, 2 Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul 130-650, 3 College of Pharmacy, Chosun University, Kwangju 501-759.

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