form a tetrahydropyran system, and a 10-membered ring lactone bearing a side chain with a doubly unsaturated acylenamine moiety. Here we report a formal synthesis of apicularen core unit and its synthetic derivatives. In retrosynthetic analysis, we equated the introduction of an acetate unit to a two-step procedure involving allylation followed by ozonolysis. The reiterations of the allylation-ozonolysis sequence were to be performed in the designated order. These steps not only would "mimic" nature's polyacetate biosynthetic pathway to apicularen A, but also would have the potential of yielding the correct stereochemistry at each chiral center of the target molecule through the judicious choice of appropriate reagents and conditions. After fifth allylation, exposure of intermediate to NaH for 2h followed by addition of water furnished the macrolide lactone. Then terminal homoallyl group was ozonolyzed followed by semicarbazonation and derivatizations. Another derivatizations was carried out as follows, the terminal homoallyl group was homologated by hydroboration-oxidation, then the alcohol obtained was oxidized by TPAP to give the corresponding aldehyde, which was also semicarbazonated and derivatized.

[PD1-3] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Synthesis and COX-2 Inhibitory Properties of Luotonin A Homologues

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Luotonin A was isolated from Peganum nigellastrum Bunge (Zygophyllaceae) which was named Luo-Tuo-Hao in China and used as a Chinese traditional medicine for the treatment of rheumatism, abscess, and inflammation. The basic fractions of P. nigellastrum showed antitumor activtity, and the origin of such an activity was recently revealed by identifying its constituent luotonin A which inhibited the growth of leukemia P-388 cells (IC_{50} = 1.8 μg/mL). Such an intriguing properties of luotonin A led developments of efficient methods for total synthesis. Although Luo-Tuo-Hao has been used more likely for the treatment of inflammation-related symptoms, no efforts towards to explore antinflammatory activity of P. nigellastrum itself as well as its components have been pursued as yet. Our continuing interests in the conformational effects on biological activity as well as search for anti-inflammatory agents spurred us to design a series of lutonin A related compounds in which the dihedral angles between planar 4(3H)-quinazolinone and quinoline rings could be controlled in a regular fashion by a methylene bridge connecting N3 of 4(3H)-quinazolinone and C2 of quinoline. We herein described the synthesis and properties of homologous series of luotonin A.

[PD1-4] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Protective effects of synthetic of 3-Alkoxy-6-allylthiopyridazine against aflatoxin B_1-induced hepatotoxicity

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3-Alkoxy-6-allylthiopyridazine derivatives showed the strongest protective effect against oxidative stress and their anticancer effect determined on the growth of SK-Hep-1 hepatocellular carcinomar cells. The allythio group as a pharmacologically active group was introduced into pyridazine nucleus and a substituent such as halogen or alkoxy was also introduced into paraposition of allylthio group. Five kinds of 3-alkoxy-6-allylthiopyridazine derivatives were synthesized and their chemoprotective activities examined in rats exposed to aflatoxin B_1-toxicant. Rats were pretreated with five 3-alkoxy-6-allylthiopyridazine derivatives at daily oral doses of 50 mg/kg for 10consecutive days, and during this period with one or three repeated doses of the potent hepatotoxin, aflatoxin B_1. The hepatoprotective effects of the 3-alkoxy-6-allylthiopyridazine derivatives against aflatoxin B_1 administration were showed the significantly normal as compared with control in body and liver weights. Aspartate aminotransferase and alanine aminotransferase levels were markedly elevated after aflatoxin B_1 administration, and pretreatment with 3-alkoxy-6-allylthiopyridazine derivatives, before aflatoxin B_1 administration, resulted in decreased levels of these enzymes. In addition, the 3-alkoxy-6-allylthiopyridazine derivatives,

K6(methoxy-), K8(chloro-), K16(ethoxy-) and K17(n-propoxy), induced elevated hepatic GSH levels. Four kinds of 3-alkoxy-6-allylthiopyridazine derivatives investigated were effective against aflatoxin B_1-induced hepatotoxicity.

[PD1-5] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Natural TACE (TNF-α Convertase) Inhibitor, Gelastatin Hydroxamate: Biological Evaluation and Target Validation

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One of attractive target for Rheumatoid Arthritis (RA) therapy is the cytokine, tumor necrosis factor –alpha (TNF-α), which has been shown to be overproduced in the joint of RA patients. The clinical success of anti-TNFR biologics has validated TNF-α as a drug discovery target. Thus, inhibiting of formation of TNF-α has been emerged to an intriguing approach for RA therapy. TNF-α is processed from its membrane bound precursor by the metalloprotease TNF-α converting enzyme (TACE), Here, biological evaluation, mode of action of natural TACE inhibitor, Gelastatin hydroxamate, are addressed. The correlation of α-secetase and TACE is evaluated based on cellular APP-α inhibition assay

[PD1-6] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

N-4-Substituted-benzyl-N'-tert-butylbenzyl Thioureas as Vanilloid Receptor Ligands: Investigation on the Role of Methanesulfonamido group in Antagonistic Activity

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Vanilloid receptor 1 (VR1) is a nonselective cation ion channel placed in the plasma membrane of peripheral sensory neurons that is potential target for analgesia. A series of N-4-substituted-benzyl-N'-tert-butylbenzyl thioureas were prepared for the study of their agonistic/antagonistic activities to the vanilloid receptor in rat DRG. Their structure-activity relationship in reveals that not only the two oxygens and amide hydrogen of sulfonamido group but also the optimal size of methyl in methanesulfonamido group play an integral role for the antagonistic activity on vanilloid receptor.

[PD1-7] [2003-10-10 14:00 - 17:30 / Grand Ballroom Pre-function]

Efficient Synthesis of Nucleoside Phosphonates using Olefin Cross-Metathesis

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In recent years, olefin cross-metathesis (CM) has emerged as a powerful and convenient synthetic technique in organic chemistry; however, as a general synthetic method, CM has been limited by the lack of predictability in product selectivity and stereoselectivity. A number of excellent studies have recently appeared in the literature which have shown that with the correct catalyst and reaction conditions CM can be used to access a variety of di- and trisubstituted olefinic products in moderate to high yield with good E/Z ratios. Grubbs et al have recently published a method for the synthesis of vinylphosphonates via an olefin cross-metathesis reaction. As part of our ongoing research program examining the synthesis and biological application of backbone-modified nucleic acids, we had reason to examine a novel synthetic approach to nucleoside phosphonates, and we now wish to report our results in this area, which led to the formation of nucleoside phosphonates using olefin cross-metathesis reaction.