In this presentation, we will report novel regio- and stereocontrolled synthetic method for the precursors of polyhydroxyamines using CSI.

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

Regioselective Substitution of 6,7-Dichloroquinoline-5,8-dione: Synthesis, Cytotoxicity, and X-ray crystal stucture of 4a,10,11-Triazabenzo[3,2-a]fluorene-5,6-diones

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6,7-Dicholroquinoline-5,8-dione reacted with 2-aminopyridine derivatives. Out of the four possible products which could be achieved in this reaction, condensation and rearrangement product, 4a,10,11-triazabenzo[3,2-a] fluorine-5,6-dione was obtained as major product. The definite structure was identified with X-ray crystallographic study. The preparation of ortho-quinones via nucleophilic substitution at C7 position was an unexpected result when considered the para-quinones via substitution at C6 position which prepared in reaction of 6,7-Dicholroquinoline-5,8-dione with ethyl acetoactate in our previous work. The antitumor activity of 4a,10,11-triazabenzo[3,2-a]fluorine-5,6-dione was superior or similar to doxorubicin and much higher than etoposide. Therefore, nucleophilic substitution at C7 position could provide the effective and simple synthetic rout to prepare biologically active ortho-quinone derivatives.

[PD1-11] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Efficient Solid Phase Library Synthesis of 7-Alkoxy-1,3,4,5-tetrahydro-benzo[e][1,4]diazepin-2-one

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The β-turn has been implicated as an important conformation for biological recognition of peptides or proteins. Benzodiazepine classes have been known as one of the nonpeptide β-turn mimic scaffolds. We have developed an efficient approach for the synthesis and derivatization of a scaffold of hydroxytetrahydrodizepinone class in order to screen compound library in various protein targets for new lead generations as well as for structure activity relationships of the scaffold. Amino acid esters and aromatic or alkyl halides for the introduction of amino acid side chains were used for building blocks in the library synthesis. Starting from 5-hydroxy-2-nitrobenzaldehyde, the benzodiazepin-2-one scaffold was synthesized in 4 steps in high yields. The validation of the scheme for the next solid phase derivatization of the scaffold has been expedited in a solution phase synthesis using a solid support mimic group, which was 2,4,6-trimethoxybenzaldehyde. After the validation, the scaffold was loaded in PL-FDMP resin through reductive amination and the alkylations of 7-hydroxyl and amide nitrogen were accomplished. TFA cleavages resulted in the initial 48 members of peptidomimetic library in high yields (50-60% purified yield, for the 4 step solid phase synthesis).

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

Synthesis and hypoglycemic Activity of the Substituted Pyrrolidine Thiazolidinedione Derivatives

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Non-insulin dependent diabetes mellitus (NIDDM) is characterized by hyperglycemia, hyperinsulinemia, and impaired insulin action. Insulin resistance is considered to be the underlying mechanism in the pathogenesis of

type 2 diabetes, which also leads to dyslipidemia, hypertension, and obesity. Thiazolidinediones are a class of oral insulin-sensitizing agents that improve glucose utilization without increasing insulin release. They significantly reduce glucose, lipid, and insulin levels in rodent models of NIDDM and obesity, and recent clinical data support their efficacy in obese diabetic patients.
In order to obtain novel thiazolidinedione derivatives which have more potent PPARγ agonism without liver toxicity and cardiac hypertrophy, we designed and synthesized a series of novel thiazolidinedione derivatives containing substituted pyrrolidine moieties using molecular modeling study. We also evaluated their in vitro activities in L6 myocytes and cytotoxicities in rat hepatocytes. Several N-benzyl pyrrolidine derivatives (Entry No. 18, 19, 20, 21,and 69) showed more potent enhancing activity on glucose utilization than reference compounds (rosiglitazone and troglitazone) in L6 myocytes cell assay. Among these compounds, the substituted N-benzyl pyrrolidine derivative (Entry No. 18) showed the most potent activity.

[PD1-13] [10/17/2002 (Thr) 09:30 ~ 12:30 / Hall C]

Synthesis of selective COX-2 inhibitors : Novel 1,5-diarylhydantoins via cyclization of methyl α-aminoacetates with aralkyl isocyanate

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Nonsteroidal antiinflammatory drugs(NSAIDs) are widely used to treat pain, fever and inflammatory condition. But chronic-disease patients suffer from gastro-intestinal disturbances such as discomfort, nausea, peptic ulcer and severe bleeding because NSAIDs inhibit not only COX-2 associated with anti-inflammatory activity but also COX-1 associated with adverse gastro-intestinal effects. 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 which contain phenyl group at 5-position, phenyl, sulfonamidylphenyl and p-methoxyphenyl groups at 1-position and ethyl, butyl, pentyl, phenyl, 4-chlorophenyl, 4-bromophenyl and benzyl groups at 3-position. These compounds were prepared through esterification, bromination, α-substitution and cyclization from commercially available phenylacetic acid. Especially, N-aralkyl groups could be introduced in 3-position of hydantoin ring by one-pot reaction of methyl α-aminoacetates with aralkyl isocyanate or isothiocyanate.

[PD1-14] [10/17/2002 (Thr) 09:30 ~ 12:30 / Hall C]

5-Arylidene-2(5H)-furanone Derivatives: Synthesis and Structure-Activity Relationship toward Cytotoxicity

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Ranunculin (RAN), isolated from Ranunculaceae, exhibited significant cytotoxic activity against KB and Bel-7402 cells with ED_{50} values of 0.21 and 0.35 μM, respectively. Under physiological condition, the ranunculin was deglycosylated to be protoanemonin, an active form containing α,β-unsaturated ketone moiety, which successively dimerized to be anemonin, inactive form. From this result, we envisioned that introduction of relatively stable aromatic ring instead of hydrogen in 5-methylene moiety might prevent the active moiety dimerizing and being changed inactive form.
On this rationale, we synthesized thirty-eight of 5-arylidene-2(5H)-furanone derivatives, and evaluated their cytotoxic activity against some cancer cell lines. On the whole, eletron-withdrawing group such as nitro and sulfonyl group on aromatic ring improve the cytotoxic activity, on the other hand, eletron-donating group including methoxy group did not improve the activity. Among analogues synthesized, 5'-(3-nitrobenzylidene)-2(5H)-furanone (AF21), 5'-(4-chlorobenzylidene)-2(5H)-furanone(AF17), 5'-(3-bromobenzylidene)-2(5H)-furanone (AF16) showed a significant cytotoxic activity against all cell lines tested.