[PD1-15] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis of Novel 3-Aminohydantoinyl-1,2-benzothiazine Derivatives for the COX-2 inhibitors

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We report the synthesis of several new 3-aminohydantoinyl-1,2-benzothiazine derivatives and propose an another mechanism of the cyclization to the hydantoins for the development candidates of COX-2 inhibitors. 3-Aminohydantoins 3a-d were prepared through cyclization of the condensation products that were formed by heating amino acids and tert-butyl carbazate in quinoline according to the method of Lalezari. Three compounds of 7a-c were synthesized through the process of chlorosulfonation, ammonolysis and oxidation of p-halotoluene, Gabriel-Colman rearrangement after condensation of sodium halo(or H)saccharin with methyl chloroacetate. Novel 7-halo(or H)-1,2-benzothiazine-3-carboxamide derivatives 8a-i were synthesized through the condensation of 7-halo(or H)-4-hydroxy-2H- 1,2-benzothiazine-3-carboxylic acid methyl ester 1,2-dioxides (7a-c) with 3-amino-5-alkylimidazolidine-2,4-diones (3a-d) in xylene.
The reaction mechanism of the formation of the 3-aminohydantoins (3a-d) involves the amidation and cyclization between α-amino acid and tert-butyl carbazate. One molecule of tert-butanol is generated from intermediate 2a-d by the intramolecular nucleophillic attack of amino group to the electron deficient carbonyl carbon of ester. In general, compounds 3a-d can be easily formed because tert-butoxyl group is very good leaving group. The cyclization products of amino acids and tert-butyl carbazate were found to be 3-aminohydantoins (3a-d) rather than hexahydro-1,2,4-triazine-3,6-diones (4a-d).

[PD1-16] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis of Azaisoflavones and Evaluation of Their Inhibitory Effects on IL-5

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Sophoricoside analogs are natural isoflavonoids isolated from fruits of Sophora japonica L. and exhibited an inhibitory effect on IL-5. Many synthetic variations on isoflavonoids has been reported, but relatively few examples of quinolone analogs have been described.
As part of our endeavor to develop novel and effective IL-5 inhibitor, we have synthesized azaisoflavones by cyclization of the key intermediate, 2'-aminochalocone obtained from substituted aniline. The synthesized azaisoflavones were evaluated for their inhibitory activities on IL-5 comparing with natural Sophoricoside analogs. None of the azaisoflavones showed promising inhibitory effects in the assay. Nevertheless, assay data indicated that 5, 7-phenolic hydroxy groups on the A-ring and alkyl substituent on N1 seemed to play an important role in the IL-5 bioassay.

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

Revisit to Unfulfilled Premise of Arylsulfonylimidazolidinones as Anticancer Agent

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For the development of novel anticancer agent, we have designed, synthesized, and tested novel 4-phenyl-1(N)-arylsulfonylimidazolidinones. As a result, much more potent cytotoxicities of these compounds against the various cancer cell lines than those of doxorubicin were demonstrated. Elaboration on aryl motif on sulfonyl moiety led us

to find highly potent 4-phenyl-1-(N-acylindoline-5-sulfonyl)imidazolidinones. Among them, 4-phenyl-1-[N-(p-aminobenzoyl)indoline-5-sulfonyl]imidazolidinone (PA) was proved to have good pharmacological profile. Without any significant change of body weight, PA shows 84.3%, 55.6%, 67.0%, and 87% suppression of tumour growth for murine tumor 3LL, Colon26, and human xenograft NCI-H23, and SW620, respectively (at dose of 65mg/kg/2day x 5 perorally). Although this compound has excellent activity in mice, the results of pliclinical toxicological study with dog hampers the further development. To find out the better derivatives, modification of indoline moiety of PA has been attempted. As a result, many analogs shows better pharmacological profiles compared to PA. Especially 4-acylamino-3-alkyl(or halogeno)benzenesulfonyl-4-phenylimidazolidinones show outstanding cytotoxicity against human solid cancer cell lines. Structure activity relationship of this series will be discussed.

[PD1-18] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis of 2,6-Diaromatic Substituted Pyridine Derivatives and Their Antitumor Activities

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α-terthienyl the first isolated from natural products shows potent antitumor activity, which encouraged us to study terpyridine and its biological properties. Terpyridine has also been reported as having carcinogenicity, and it's derivatives showed high cytotoxic activities against several human cancer cell lines and topoisomerase I inhibitory activity. Mannich free base from condensation reaction was allowed to react with pyridinum salts to give diaromatic substituted pyridine. In the present study, twenty 2,6-diaromatic substituted pyridine derivatives including phenyl, furyl, thienyl or pyridyl units were prepared. We have also tried to introduce monoaldehyde, dialdehyde, monohydroxymethyl and dihydroxymethyl functional groups in substituted moiety. Prepared compounds were evaluated their antitumor activities. Most of prepared compounds displayed moderate cytotoxic activities against several human cancer cell lines compared to doxorubicin, although they did not have significant inhibitory activities against topoisomerase I.

[PD1-19] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Stereoselective synthesis of novel 4'α-C-methyl branched novel carbocyclic nucleosides

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Recently, 4'α-C homologated furanose nucleosides, especially alkyl branches, are molecules of considerable current interest. One of reasons for this prominence arises from the notable biological activities as antiviral and antitumor agents, as shown in 4'α-C-methyl-2-deoxythymidine (EC_{50} = 7.2μM against HIV in MT-4 cell), 4'α-C-fluoromethyl-2-deoxycytidine, 4'α-C-hydroxymethylthymidine and 4'α-C-azidomethyl-thymidine. Furthermore, recently, we have reported synthetic routes of a series of novel 4'α-C-alkyl branched nucleosides having diverse functionality and stereochemistry employing versatile [3,3]-sigmatropic rearrangement as key reaction. As a part of our drug discovery program for antiviral agents, herein we report stereoselective synthetic route of novel carbocyclic nucleosides having methyl group at 4'α-position employing our versatile three step sequences ([3,3]-sigmatropic rearrangement, ring-closing metathesis, and Pd(0)-catalyzed allylic alkylation) from very simple acyclic precursor 'acetol'.

[PD1-20] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Diastereoselective Synthesis of (+)-Frontalin

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