[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