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

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We report the synthesis of several new 3-aminomethyl-1,2-benzothiazine derivatives and propose an another mechanism of the cyclization to the hydantoin 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 Lei et al. 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)salicylaldehyde 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-alkylimidazoline-2,4-diones (3a–d) in toluene.

The reaction mechanism of the formation of the 3-aminohydantoins (3a–d) involves the amidation and cyclization of the new α-amino acid and tert-butyl carbazate. One molecule of tert-butanol is generated from intermediate 2a–d by the intramolecular nucleophilic 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).

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-aminochalcone 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.

Revisit to Unfulfilled Premise of Arylsulfonylmidazolimidinones 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)-arylsulfonylmidazolimidinones. 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