

[OD1-1] [ 2003-10-11 09:30 - 09:45 / ASEM Hall Meeting Room 203 ]

**A versatile biomimetic total synthesis of benzo[c]phenanthridine and protoberberine alkaloids using lithiated toluamide-benzonitrile cycloaddition**

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Natural benzo[c]phenanthridine and protoberberine alkaloids which have been attractive to synthetic organic chemists and biochemists over the last 2 decades since such compounds have shown interesting biological properties such as antitumor, antiviral and antimicrobial activities. For the systematic research on these alkaloids, several total syntheses of these alkaloids have been reported. However, the bulk of reported benzo[c]phenanthridine synthetic studies to date have involved multistep sequences for assembly of the target molecules as well as lack of generality for synthesizing substituted molecules. We have tried to develop a new versatile synthetic method for these compounds using lithiated toluamide-benzonitrile cycloaddition. Retro-synthetic consideration of benzo[c]phenanthridine and protoberberines indicates that the coupling of o-methylbenzonitrile with o-toluamide might afford 3-arylisquinoline which could be transferred to the aldehyde or primary alcohol. Benzo[c]phenanthridines or protoberberines can be formed by an intramolecular ring cyclization method. Herein, we succeeded in synthesizing natural benzo[c]phenanthridine alkaloids such as oxysanguinarine, oxyvicine, oxychelerythrine, oxynitidine as well as protoberberines such as 8-oxocoptisine, 8-oxoberberine, 8-oxosedoberberine and 8-oxopsedocoptisine.

[OD1-2] [ 2003-10-11 09:45 - 10:00 / ASEM Hall Meeting Room 203 ]

**Molecular modeling of COX-2 inhibitors: 3D-QSAR and docking studies**

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88 selective COX-2 inhibitors belonging to three chemical classes (triaryl rings, diaryl cycloalkanopyrazoles, and diphenyl hydrazides) were studied using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). Partial least squares analysis produced statistically significant models with  $q^2$  values of 0.84 and 0.79 for CoMFA and CoMSIA, respectively. The key spatial properties were detected by careful analysis of the isocontour maps. The binding energies calculated from flexible docking correlated with inhibitory activities by the least-squares fit method. The three chemical classes of inhibitors showed reasonable internal predictability ( $r^2 = 0.51, 0.49, \text{ and } 0.54$ ), but the triaryl rings had a much lower binding energy than the others. Differences in binding energies were considered to be due to the electrostatic interaction energy between R513 of the COX-2 active site and the sulfonyl group of the triaryl ring. Comparative binding energy analyses gave  $q^2$  values of 0.64, 0.63, and 0.50 for triaryl rings, diaryl cycloalkanopyrazoles, and diphenyl hydrazides, respectively. In the QSAR models, some protein residues were highlighted as particularly important for inhibitory activity. The combination of ligand-based and structure-based models provided an improved understanding of the three chemical classes of inhibitors and their interactions with COX-2.

[OD1-3] [ 2003-10-11 10:00 - 10:15 / ASEM Hall Meeting Room 203 ]

**Total Synthesis of Bacillariolide III**

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Bacillariolide III was isolated from the culture medium of the marine diatom, *Pseudonitzschia multiseries*, a causative organism of amnesic shellfish poisoning by Shimizu et al. This extracellular metabolite features bicyclic system of hydroxycyclopentane and (Z)-pentenoic acid-bearing lactone ring. Bacillariolide I is known to possess significant inhibitory activity against phospholipase A<sub>2</sub>, but the biological function of bacillariolide III is still under investigation. The unique structural feature as well as the promising biological activity led us to the total synthesis of bacillariolide III. The total synthesis of bacillariolide III has been accomplished via 15 linear steps in a 15% overall yield from the known (R)- $\alpha$ -hydroxybutyrolactone. The key parts of this approach include the stereoselective construction of the cis-disubstituted hydroxycyclopentane skeleton and the convergent and stereocontrolled introduction of the (Z)-pentenoic