

Recently it has been demonstrated that selective cyclooxygenase-2 (COX-2) inhibitors retain the antiinflammatory effect but with markedly reduced GI toxicity compared to non selective inhibitors such as traditional NSAIDs. As a consequence, intense efforts have been made to develop selective COX-2 inhibitors during the last decade. Two compounds in this class, celecoxib and rofecoxib, are already in the market and are proved as potent and selective COX-2 inhibitors with much better gastric tolerance. However, there are still strong demands for a COX-2 inhibitor with improved efficacy and safety profiles.

Here we report the synthesis and biological profiles of 1,5- and 4,5-disubstituted imidazole analogues as structural equivalents of celecoxib and rofecoxib. The imidazole analogues are overlapped well with the 3D structures of celecoxib and rofecoxib.

[PD1-28] [ 10/17/2002 (Thr) 09:30 - 12:30 / Hall C ]

#### Synthesis and Biological Studies of A Novel Series of Catechol Ether Type Derivatives as Potential Phosphodiesterase(PDE) IV Inhibitors

Lee, JaeMok, Lee KounHo<sup>O</sup>, Kim JongHoon, Song SeogBeom, Chun HyungOk, Yeon KyuJeong, Kwon SoonJi, Rhee ChungK., Xiang MyungXik

Department of Medicinal Chemistry, Cheil Jedang Corp.

We synthesized various catechol ether type derivatives substituted by the hydrazine moiety and evaluated for their ability to inhibit PDE IV (Phosphodiesterase IV). These new compounds were synthesized from 4-methoxy-3-hydroxy benzaldehyde through 5 or 7 steps. Some of them have similar or more potent inhibitory activity against PDE IV than known PDE IV inhibitor, Ariflo ( SB 207499 ). Structure activity relationship (SAR) and biological studies of described compounds will be discussed in detail.

[PD1-29] [ 10/17/2002 (Thr) 09:30 - 12:30 / Hall C ]

#### Synthesis of 3-arylisquinolinamines and 3D-Quantitative Structure Activity Relationships Study

Min SunYoung<sup>O</sup>, Cho WonJea

College of Pharmacy, Chonnam National University

The significant antitumor activities of 3-arylisquinolines promoted us to explore the structure-activity relationship of these compounds. A series of 3-Arylisquinoline derivatives, which related to Benzo[c]phenanthridine alkaloids, were evaluated for antitumor cytotoxicity against human lung tumor cell (A 549). We tried to study structure-activity relationship (SAR) of 3-Arylisquinolines using the comparative molecular field analysis (CoMFA) method. CoMFA has been a useful technique in defining important 3-dimensional (3-D) properties and postulated pharmacophore model can be derived from CoMFA study. To obtain further insight into the relationship between the structure and function of these compounds as antitumor agents, we have carried out three dimensional quantitative structure-activity relationship (3D QSAR) studies using the comparative molecular field analysis (CoMFA) method. CoMFA is not only one of the most used 3D-QSAR methods, but also has been applied to a number of different classes of compounds. The method is based on ligand-receptor interaction and can be a powerful tool for designing of ligand when the receptor site is unrecognized. In order to carry out conformational search of these compounds, we tried to determine the X-ray crystallographic structure of 7,8-dimethoxy-3-phenylisquinolin-(2H)-one. Two types of structures having different torsion angle between the isoquinoline ring and 3-aryl ring were found in the crystals. Therefore, CoMFA was performed two different, overlapping ways. As a result, we could get good Cross-Validated R<sup>2</sup> (Q<sup>2</sup>) values and pharmacophore models. A synthesis of 3-arylisquinolinamines and a 3D-QSAR study will be discussed.

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

#### (-)- $\beta$ -Narcotine: A Facile Synthesis and the Degradation with Ethyl Chloroformate