[PD1-24] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Design and Synthesis of Benzoquinoxalinediones

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In cancer chemotherapy, it is becoming increasingly clear that the DNA topoisomerases play an active role in the expression of the cytotoxic action of drugs. The amino substituted azaanthraquinones have attracted much interest due to their possible role as topoisomerase inhibitors. In connection with our interests in the design and synthesis of potent topoisomerase inhibitor, we herein described the preparation of a series of benzoquinoxalinedione derivatives. These were designed based on the SAR of azaanthraquinones and structural analysis of products which are fitted with doxorubicin.

[PD1-25] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Diasteroselective synthesis of long chained keto amino acids derivatives

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The unusal keto amino acid, (s)-2-amino-8-oxodecanoic acid(Aoda) is a biologically important constituent of the naturally occurring cyclic tetrapeptides such as apicidins. Consequently extensive chemical modifications of Aoda residue of apicidin were studied, and we are obtained the practical and versatile synthesis of the long-chained keto amino acids in enantiomerically pure form by alkylation with bromoketone and chiral Scholkopf auxiliary.

[PD1-26] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Design, Synthesis and Antitumor Evaluation of Terpyridine Derivatives Containing Pyridines at 4'-Position

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Recent study indicated that terpyridine and its derivatives displayed highly active antitumor properties. In this presentation, derivatives of terpyridines having three pyridine moieties at 2',4',6'-position of central pyridine skeleton were prepared, and evaluated their cytotoxicity against several human cancer cell lines and topoisomerase I inhibitory activities. Most of the prepared compounds showed strong cytotoxicity compared to doxorubicin. In addition, several compounds displayed better cytotoxicity than that of doxorubicin. Structure-activity relationship study was also performed to be indicated that [2,2':6',2"]terpyridine skeleton is important to show strong cytotoxicity. Significant topoisomerase I inhibitory activity was not observed for prepared compounds.

[PD1-27] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Synthesis and Antiinflammatory Activity of 1,5- and 4,5-Disubstituted Imidazoles

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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 inhibtors 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

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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-arylisoquinolinamines and 3D-Quantitative Structure Activity Relationships Study

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The significant antitumor activities of 3-arylisoquinolines promoted us to explore the structure-activity relationship of these compounds. A series of 3-Arylisoquinoline 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-Arylisoquinolines using the comparative molecular field analysis (CoMFA) method. CoMFA has been a useful technique in defining important 3-dimentional (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-phenyliosquinolin-(2H)-one. Two types of structures having different torsion angel 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 R2 (Q2) values and pharmacophore models. A synthesis of 3-arylisoquinolinamines and a 3D-QSAR study will be discussed.

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

(-)-β-Narcotine: A Facile Synthesis and the Degradation with Ethyl Chloroformate