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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

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(-)-α-narcotine(1R,9S) is one of the major bases in Papaver somniferum L., the sourse plant for opium, while (-)-β-narcotine(1R,9R) is a synthetic phthalideisoquinoline alkaloid. Although some advanced methods for the preparation of α-narcotine have been developed using modified Bischler-Napieralski cyclization, the facile synthesis of β-narcotine has not further been attempted, supposingly because of its no clinical efficacy contrary to α-narcotine having an antitussive effect. We could conveniently prepare β-narcotine using cotarnine as a starting material. Direct condensation of cotarnine and iodomeconine prepared by aromatic iodination using thallium trifluoroacetate/ KI and by the successive reduction of resulting iodo-β-narcotine with aluminum amalgam. Its structure including a stereochemistry was confirmed by instrumental analyses. This synthetic alkaloid was degraded with ethyl chloroformate at room temperature to afford the chloro-carbamate as a crystalline intermediate, which was unexpectedly converted into the carbinol by exchange of Cl with OH of water contained in the solvents and the ethoxy-carbamate, probably because of ethanol added to chloroform as a solvent stabilizer during the purification by column chromatography.

[PD1-31] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Acyclic Vanilloid Receptor Antagonist Based on Capsazepine

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Capsaicin, the pungent component of chili pepper, opens a novel cation selective ion channel in the plasma membrane of peripheral sensory neurons. Capsaicin channel agonists induce pain upon topical application in the early stage, which is followed by a period of desensitization. Although the agonists have been studied as a analgesics, their initial irritancy became sever side effect. So competitive antagonists have been pursued as a novel pharmacological agent for analgesics, rather than agonists. Since the introduction of the first competitive antagonist, capsazepine by forming 7-membered rigid ring system, the more potent antagonist has not been reported yet. As part of our program to find a new scaffold for a competitive antagonist against the capsaicin receptor, we modified capsazepine by opening the 7-membered rigid ring system, which has a virtually similar orthogonal conformation. In this communication, we report the synthesis of N,N,N-trisubstituted acyclic thiourea derivatives and their biological activities.

[PD1-32] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Cleavage of Benzyl and p-Methoxybenzyl Ethers Using Chlorosulfonyl Isocyanate Reaction

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Deprotection of the benzyl group has been widely used in multi-step organic synthesis with a variety of reaction conditions, including catalytic hydrogenolysis, Lewis acids such as $FeCl_3$ or $MgBr_2$ and lithium naphthalenide. However, these procedures sometimes can be problematic with multifunctional substrates, such as unsaturated bonds during hydrogenolysis, an acid-labile moiety in $FeCl_3$, and a easily reducible functional group in lithium naphthalenide.

Also, there are various methods for selectively removing of the p-methoxybenzyl group which include Lewis acid-catalyzed cleavage (TMSCl-$SnCl_2$-anisole, Me_2BBr, BF_3OEt_2-$NaCNBH_3$, $AlCl_3$-EtSH, $CeCl_3$-NaI), oxidation (2,3-dichloro-5,6-dicyanobenzoquinone, ceric ammonium nitrate), trifluoroacetic acid, and clay-supported ammonium nitrate-irradiation. Many of these procedures sometimes have one or more problems, for example, use of a heavy metal, a side reaction, low yield, or the cost of the reagent. Especially, DDQ is inclined to overoxidize allylic p-methoxybenzyl ether to an unsaturated ketone.

These facts prompt us to find a milder and more widely applicable method for deprotection of benzyl and p-