[PD1-11] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

Synthesis of 1,4-Dioxane Ring-fused Quinazoline Derivatives as an EGFR Tyrosine Kinase Inhibitor

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Protein tyrosine kinases (PTKs) catalyze the selective transfer of phosphate group from ATP to a tyrosine hydroxyl residue of a substrate protein. Tyrosine phosphorylation is critical event in growth factor mediated signal transduction and PTKs are key components of this process. The aberrant overexpression of receptor PTKs or their cognate ligands has been implicated in the pathogenesis of proliferative diseases. Therefore, the inhibition of tyrosine kinase-mediated signal transduction pathways represents a therapeutic approach to the intervention of proliferative diseases such as cancer. In this study, we synthesized a novel series of 1,4-dioxane ring-fused quinazoline derivatives and tested on the EGFR tyrosine kinase activity in vitro.

[PD1-12] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

Synthesis of Novel 1,2-Substituted Pyrrolidine Derivatives for COX-2 Inhibitors

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The recent discovery of the inducible form of cyclooxygenase (COX-2) that is associated with inflammation has provided the pharmaceutical industry with a target for development of nonsteroidal antiinflammatory drugs (NSAIDs). This study reports on design and synthesis of novel selective cyclooxygenase-2 inhibitors with greatly reduced gastrointestinal or renal toxicity. The 5-membered ring heterocycle such as thiazole, thiadiazole, pyrrole, oxazole, isoxazole, imidazole, pyrazole, furan, furanone were replaced on the thiophene ring of Dup 697. A series of pyrrolidine-based inhibitor were designed and synthesized in this study. The N, 4-alkoxy- 1-(4-methylphenylsulfonyl)- 2-phenyl carboxamidyl- L-prolines were synthesized through N-tosylation, esterification, O-alkylation, base-hydrolysis, amination from 4-hydroxy-L-proline.

[PD1-13] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

Synthesis and β-lactamase inhibitory activities of 2-conjugated alkenyl penam sulfones II

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The β-lactamases cause the bacterial drug resistance and the β-lactamase inhibitors show high efficacy of synergistic effect in the combination of β-lactam group antibiotics. As a search for new broad-spectrum β-lactamase inhibitors, we prepared 2β-conjugated alkenyl penam sulfones which contains amide, aldehyde, or cyanide functional group, and their activities against β-lactamase were

evaluated in vitro. The key intermediate 2β-formyl penam ester was obtained by multistep synthesis starting from 6-amino penicillanic acid. The wittig reaction of 2β-formyl penam ester with various phosphonium ylide containing double bond resulted in conjugated double bond at 2 position. The β-lactamase inhibitory activity of the prepared compounds was determined by microiodometric assay using the β-lactamase type I, III, IV, and E.coli TEM.

[PD1-14] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

Synthesis of Pyridine, Thiophene and Furane-containing Compounds and their Antitumor Activities

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Terpyridine has been extensively studied as a ligand in a wide range of metal complexes and DNA binding agents. In our research program for the discovery and development of novel antitumor agents, a series of terpyridine derivatives containing pyridine, thiophene and furane moiety were synthesized and their cytotoxicity against several human solid tumor cell lines were evaluated. Selective cytotoxicity were also investigated. Some of the terpyridine derivatives showed high antitumor cytotoxicity with GI_{50} values in the range of 10^{-5} - 10^{-7} μg/ml while the GI_{50} value of Doxorubycin was larger than 10^{-3} μg/ml. The structure-activity relationships of these new antitumor agents would be further discussed.

[PD1-15] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

SYNTHESIS AND HIV-1 INTEGRASE INHIBITORY ACTIVITIES OF CAFFEOYLGLUCOSIDES

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Human immunodeficiency virus type 1 (HIV-1) is the probable causative agent of acquired immune deficiency syndrome (AIDS). The recent understanding of life cycle of this virus has afforded targets for anti-HIV-1 therapy, one of which is HIV-1 Integrase (IN). HIV-1 integrase is an enzyme that mediates the integration of HIV-1 DNA into a host chromosome and is essential to replication of the virus. This enzyme inhibitor is therefore thought to be a suitable drug for chemotherpeutic agent. In an effort to identify new structural leads for anti-HIV-1 agent, caffeoylglucosides were synthesized from methyl D-glucosides and their anti-HIV-1 activities were tested. Among them, a few of dicaffeoylglucosides showed HIV-1 integrase inhibitory activity as potent as chicoric acid.

[PD1-16] [04/21/2000 (Fri) 14:50 - 15:50 / [1st Fl, Bldg 3]]

Synthesis of Thienopyrimidines as Potential NMDA Receptor Antagonists

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2-substituted quinoline derivatives, represented by L-695902 and L-701324, are one of the most important class of compounds for NMDA glycine binding site antagonists. The characteristic feature