occludin. Treatment of rat Ang-1 in conditionally immortalized rat brain capillary endothelial cell line TR-BBB13 for 48h induced approximately three-fold higher expression and phosphorylation of occludin in comparison with control. The upward band shift of occludin reveals the phosphorylation of occludin. Occludin phosphorylation has been implicated in the regulation of TJs function.
We show here that this is the first report of cloning and expressing the rat Ang-1 in the Bac-to-Bac baculovirus expression system. The rat Ang-1 induces the expression and phosphorylation of occludin in TR-BBB13 in vitro. Therefore, we suggest that Ang-1 regulates BBB permeability by formation of TJs.

Poster Presentations - Field D1. Medicinal Chemistry

[PD1-1] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Tumor Specific Prodrugs of O6-Benzylguanine as Inactivators of O6-Alkylguanine-DNA Alkyltransferase in Antibody-Directed Enzyme Prodrug Therapy

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In order to enhance the therapeutic effectiveness of chloroethylating anticancer drugs, O^6-benzyl-N^2-[glutamyl(carbamoyl)]guanine (1) and O^6-benzyl-9-[glutamyl(carbamoyl)]guanine (2) were synthesized and examined as tumor specific adjuvant prodrugs of O^6-benzylguanine (BG) for inactivation of O^6-alkylguanine-DNA alkyltransferase (AGT) in antibody-directed enzyme prodrug therapy (ADEPT). These compound were designed to undergo hydrolysis by carboxypeptidase G2 for the generation of BG at the tumor site, leading to improve oncotoxic selectivity in ADEPT. While compound 1 was chemically very stable under physiological aqueous buffer (pH 7.4, 37 ^{O}C), compound 2 was chemically instable. Incubation of 1 in the presence of carboxypeptidase G2, however, indicates that no BG was released. Unfortuneately, compound 1 and 2 cannot serve as prodrugs of BG.

[PD1-2] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Synthesis of benzothiazolyl compounds through cyclization of thiourea

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Benzothiazolyl moiety is a structural element of compounds having various biological activities such as potent and selective antitumor activity.
A new synthetic route for benzothiazole ring has been developed and a solid-phase synthetic procedure for construction of benzothiazole ring was investigated based on this method.
o-Aminophenol or o-hydroxyaminopyridine was reacted with phenyl isothiocyanate to yield the thiourea, which was cyclized to benzothiazolyl or pyridinothiazolyl compounds using trifluoroacetic acid. This route was simple and employable for the synthesis of substituted benzothiazoles.
This procedure was also applied to solid-phase synthesis of 5-aminomethyl-2-phenyl aminobenzothiazole. The chloroformate functionalized Wang resin was reacted with 4-aminomethyl-2-aminophenol, followed by the reaction with phenyl isothiocyanate and trifluoroacetic acid, to give the desired compound.

[PD1-3] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Studies on the Synthesis and Antibacterial Activities of 4-Pyrrolidinylthio Carbapenems: 2-Alkyl Substituents Containing Heteroaromatics Linked Via a C-N Bond

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The synthesis and biological activity of series of 2-alkyl-4-pyrrolidinylthio-β-methylcarbapenems containing a variety of heteroaromatic substituents is described. These compounds were synthesized via several step from *trans*-4-hydroxy-*L*-proline and β-methylcarbapenem by the general route. Antibacterial activities of the prepared compounds were tested.

[PD1-4] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Preparation and Application of New Friedlaender Synthon for the Synthesis of 2-Substituted Pyrido[3,2-c]acridines

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The increasing interests on pyrido[3,2-*c*]acridine and its related derivatives stem from their properties not only of showing a broad spectrum of biological properties such as antileukemic, antithrombic, and anticancer activities, but also of acting as ligands for small molecules and transition metals. The synthetic methods, however, are limited only to the Skraup reaction of 4-aminoacridine and the Friedel-Craft reaction of 7-acyl-8-arylaminoquinolines.
In connection with our interests in the design and synthesis of new polydentates and in the development of new synthetic method for the preparation of cytotoxic heterocycles, we herein described preparation of a new Friedlaender synthon, 4-aminoacridine-3-carbaldehyde and its application toward pyrido[3,2-*c*]acridines.

[PD1-5] [04/19/2002 (Fri) 10:00 - 13:00 / Hall E]

Stereoselective synthesis of novel 4'-hydroxy-carbocyclic nucleosides

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The resistance of glycosidic bond to enzymatic hydrolysis catalyzed by nucleoside phosphorylase is one of the critical points in nucleoside antiviral chemotherapy. In order to avoid such enzymatic degradation as well as to improve the antiviral activity, a great number of structural modifications have been carried out on both the sugar and the heterocycle moiety of nucleosides. One strategy has been to replace the oxygen of the furanose ring by a methylene group, which gives rise to carbocyclic nucleosides.
Recently, much attention has been paid to 4'-substituted nucleosides such as 4'-cyano-thymidine 4'-azido-thymidine, and 4'-methoxy-nucleoside as potent antiviral agents. However, only a few examples of 4'-substituted nucleosides of defined absolute stereochemistry are reported in literature. The scarcity of examples of 4'-substituted nucleosides may be due to the synthetic difficulties for elaborating a necessary tertiary carbon center. Therefore it was great important to develop efficient methodology for the synthesis of furanosyl or cyclopentane ring containing stereochemically defined tertiary carbons.
Based on promising biological activities of carbocyclic and 4'-substituted nucleosides, we designed novel 4'-hydroxy carbocyclic nucleosides from very cheap and commercially available D-lactose, which can combine the chemical and biological properties of 4'-substituted furanose nucleosides and enzyme resistant carbocyclic nucleosides.
Here, we would like to present the synthetic route of 4'-hydroxy substituted various types of novel