inhibitors of AdoHcy hydrolase via the coupling sugar-modified adenosine analogues with L-homocysteine sodium salt.

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S-adenosyl-L-homocysteine(AdoHcy) is the product of all biological methylation in which S-adenosyl-L-methionine (AdoMet) is utilized as a methyl donor and is reversibly hydrolyzed to L-homocysteine and adenosine by AdoHcy hydrolase physiologically. Inhibition of this enzyme results in intracelluar accumulation of AdoHcy leading to a feedback inhibition of AdoMet-dependent methylation reactions which are essential for viral replication. Therefore AdoHcy hydrolase has become an attractive target for the molecular design of broad-spectrum antiviral agents. While the majority of the synthetic efforts has been focused on the Neplanocine A or aristeromycin-derived nucleosides, there has been very few studies on the AdoHcy analogues and evaluation of their activities. So, it was interesting to us to synthesize sugar-modified AdoHcy analogues and to investigate the role of amino acid portion of AdoHcy and the effect of functionality in sugar moiety on their inhibitory activity. A series of sugar-modified nucleosides were synthesized from adenosine via conventional protocols and converted to 5'-chloroadenosine analogues. The required L-homocyteine sodium salt was prepared via Birch reduction of L-methionine. Finally, AdoHcy analogues were prepared in moderate yields via the coupling 5'-chloroadenosine analogues with L-homocysteine sodium salt. The activity test against some kind of viral species is in progress. The synthetic details will be discussed in the meeting.

[PD1-11] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

A Novel Photonuclease; Bromofluoroacetophenone-Pyrrolecarboxamides

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Bromofluoroacetophenone derivatives which produce fluorine substituted phenyl radicals that cleave DNA upon excitation were investigated as a novel photonuclease. Pyrrolecarboxamide-conjugated bromofluoroacetophenones; 4'-bromo-2'-fluoroacetophenone and 2'-bromo-4'-fluoroacetophenone were synthesized and their DNA cleaving activities and sequence selectivities were determined. Bromofluoroacetophenone-pyrrolecarboxamide conjugates were found to be effective DNA cleaving agent upon irradiation in concentration dependent manner based on plasma relaxation assay. The DNA cleaving activities of 2'-bromo-4'-fluoroacetophenone derivatives were larger than those of 4'-bromo-2'-fluoroacetophenone derivatives.

[PD1-12] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Topoisomerase I inhibition of 2-substituted 5-nitrobenzimidazoles

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