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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Several studies of terbenzimidazoles and bibenzimidazoles suggested that benzimidazoles, especially 5-nitro-2-(para-methoxyphenyl)benzimidazole, possess topoisomerase I inhibition activities. In order to find out the structure activity relationship of 5-nitro-2-phenyl-benzimidazoles, eight derivatives that are substituted at the para position of 2-phenyl moiety were selected, synthesized & evaluated considering their electronic or lipophilic parameters. Both the topoisomerase I inhibiton activities and the cytotoxicities were related neither to the electronic nor lipophilic parameters. These data suggest that their activities may be related to other parameters including steric bulk or hydrogen-bonding capacities. Further studies are on the way to investigate this relationship.

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

Asymmetric synthesis of (2S, 3R, 4E) 5-Aryl-4-pentene-1,3-diol-2-aminoueras

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(2S 3R, 4E) 5-Aryl-4-pentene-1,3-diol-2-aminoueras had been synthesized for their cytotoxic activity. Pinene was oxidized with KMnO4 to give 2-hydroxy-3-pinanone, which treated with ethyl glycinate to yield iminoglycinate and then reacted with aldehyde derivatives and titanium enolate to afford 3-hydroxy aldol compounds. These aldol compounds was hydrolyzed with HCl and reduced with NaBH4 to give 2-amino-1,3-diols, which was treated with alkyl isocyanates to yield 5-aryl-4-pentene-1,3-diol-2-aminoueras. The aldehyde derivatives was synthesized in three steps from benzelaldehydes.

[PD1-14] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

Synthesis of N-methylspiro[1,2,3,4-tetrahydro-naphthalene-1,2'-pyrrolidine]

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A pathway for synthesis of N-methylspiro[1,2,3,4-tetrahydro-naphthalene-1,2'- pyrrolidine] was developed. Formation of the imine compound from α-tetralone and methylamine using titanium tetrachloride followed by ddition of allylmagnesium bromide gave (1-allyl-1,2,3,4-tetrahydro-naphthalen-1-yl)methylamine. Protection of (1-allyl- 1,2,3,4- tetrahydro-naphthalen-1-yl)methylamine followed by substitution reaction with di-tert-butyl carbonate in 10% sodium hydroxide solution gave (1-allyl-1,2,3,4- tetrahydro- thalen-1-yl)methylcarbamic acid tert-butyl ester. Hydroboration-oxidation of (1-allyl-1,2,3,4-tetrahydro-naphthalen-1-yl) methylcarbamic acid tert-butyl ester with borane disulfide complex or borane-THF complex gave [1-(3-hydroxyypropyl-1,2,3,4- tetrahydro-naphthalen-1-yl)methylcarbamic acid tert- butyl ester and deprotection of t-Boc group in 6N hydrochloric acid solution gave 3-(1-methylamino-1,2,3,4-tetrahydro- naphthalen-1-yl)-propan-1-ol. Finally, cyclization of the amino compound in Mitsunobu conditions provided N-methylspiro[1,2,3,4-tetrahydro-naphthalene-1,2'-pyrrolidine].

[PD1-15] [04/18/2003 (Fri) 13:30 - 16:30 / Hall P]

The Synthesis of Novel Cyclobutyl Nucleoside as Potential Antiviral Agents