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Unmodified nucleosides exist in either S-type or N-type conformation, but due to the low energy barrier between this two dominating conformers a fast equilibrium between them exists in solution state. Therefore, many approaches to lock the puckering of the furanose ring in N-type or S-type have been made since HIV-1 reverse transcriptase is able to discriminate between two conformationally locked carbocyclic AZT triphosphate analogues. Recently, since we have found antitumor activity of 3',4'-tetrahydrofuran fused pyrimidine nucleosides locked into C1'-exo conformation, it was interesting to study the antitumor activity of the nucleosides locked into the S-the or N-type conformation. For this purpose, we synthesized the 5-azacytidine nucleoside analogues locked into the S-type or N-type conformation because 5-azacytidine derivatives like D-5-azacytidine and 2'-deoxy-D-5-azacytidine exhibited very potent anti-leukemic activity. The desired bicyclic 3'-O,5'-C-methylene-linked and 2'-O,5'-C-methylene-linked nucleosides were readily synthesized from D-glucose according to the modified Wengel's procedure and tested against several cancer cell lines. It was found that both analogues exhibited moderate anti-leukemic activity, but they did not show significant antitumor activity against lung cancer and colon cancer cells, indicating that conformationally locked nucleosides can be a good lead for the development of anticancer, not antiviral agents. Synthesis and biological activity will be presented in the meeting.

[PD1-66] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

DESIGN AND SYNTHESIS OF A3 ADENOSINE RECEPTOR LIGANDS, 3'-FLUORO ANALOGUES OF Cl-IB-MECA

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2-Chloro-N6-(3-iodobenzyl)-adenosine-5'-methylcarboxamide (2-Cl-IB-MECA) has been recognized to be one of the most selective agonists (Ki = 1.0 nM) for rat adenosine A3 receptor. On the basis of the high binding affinity of 2-Cl-IB-MECA to adenosine A3 receptor, it was interesting to find out whether 2'- and/or 3'-hydroxyl group of 2-Cl-IB-MECA is essential for the binding affinity to the receptor. Thus, we synthesized the new ligands, 2'-fluoro analogues of 2-Cl-IB-MECA to substitute the 2'-hydroxyl group of 2-Cl-IB-MECA with fluorine and evaluated them for binding affinity to adenosine A3 receptor, in which significant decrease of the binding affinity was observed, indicating 2'-hydroxyl group is essential for binding affinity. Based on this finding, it was interesting to synthesize the corresponding 3'-fluoro analogues of 2-Cl-IB-MECA and evaluated them for binding affinity to adenosine A3 receptor. In order to synthesize 3'-fluoro analogues of 2-Cl-IB-MECA, the glycosyl donor, D-3-deoxy-3-fluororibosyl acetate was first synthesized via the regioselective opening of 2,3-epoxide with fluoride anion, starting from D-xylose, condensed with silylated 2,6-dichloropurine, and then converted to the final nucleosides. The synthesized nucleosides were assayed for binding affinity to adenosine A3 receptor, in which significant correlation between 3'-hydroxyl group and 3'-fluorine atom was observed. Synthesis and binding affinity to adenosine A3 receptor will be presented in the meeting.

[PD1-67] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Asymmetric Synthesis of 12(S)-HETE

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(*S*) and (*R*) 12-HETE, endogenous eicosanoids, have recently been discovered to be implicated in a number of important biological activities. In particular, it has recently been reported by us that both the capsaicin-activated channel of sensory neurons and the cloned capsaicin receptor (VR1) are activated by the eicosanoids including these metabolites. We report herein a novel and efficient asymmetric synthesis of highly enantiomerically enriched 12(*S*)-HETE via enzymatic kinetic resolution of the key allylic alcohol synthon.

[PD1-68] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]