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 CI-IB-MECA**

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2-Chloro-N6-(3-iodobenzy1)-adenosine-5′-methylcarboxamide (2-C1-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-C1-IB-MECA to adenosine A3 receptor, it was interesting to find out whether 2′- and/or 3′-hydroxyl group of 2-C1-IB-MECA is essential for the binding affinity to the receptor. Thus, we synthesized the new ligands, 2′-fluoro analogues of 2-C1-IB-MECA to substitute the 2′-hydroxyl group of 2-C1-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-C1-IB-MECA and evaluated them for binding affinity to adenosine A3 receptor. In order to synthesize 3′-fluoro analogues of 2-C1-IB-MECA, the glycosyl donor, D-3-deoxy-3-fluoronoboisyl acetate was first synthesized via the regioselective opening of 2,3-epoxide with fluoride anion, starting from D-xylene, 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 ]**
DESIGN AND SYNTHESIS OF A3 ADENOSINE RECEPTOR LIGANDS. 2′-FLUORO ANALOGUES OF CI-IB-MECA

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Since adenosine A3 receptor has been cloned from rat brain, a number of compounds have been synthesized and evaluated for the binding affinity to this receptor. Among these, 2′-chloro-N6-(3-iodobenzyl)-adenosine-5′-methylcarboxamide (2′-Cl-IB-MECA) has been found 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′-hydroxyl group of 2′-Cl-IB-MECA is essential for the binding affinity to the receptor. Thus, we designed, synthesized the new ligands to substitute the 2′-hydroxyl group of 2′-Cl-IB-MECA with fluorine, based on the biosynthetic rationale, and evaluated them for binding affinity to adenosine A3 receptor. In order to synthesize 2′-fluoro analogues of 2′-Cl-IB-MECA, the key intermediate, 2′-deoxy-2′-fluororibosyl acetate was first synthesized via direct displacement of 2′-O-triflate with tetra-n-butylammonium fluoride, starting from 2′-deoxyribose, 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 remarkable decrease of the binding affinity was observed, indicating 2′-hydroxyl group might play a crucial role as a hydrogen bonding acceptor, not a hydrogen bonding donor. Synthesis and binding affinity to adenosine A3 receptor will be presented in detail.

SYNTHESIS OF HALOGENATED 9′-(DIHYDROXYCycLOPENt-4′-ENYL) ADENINES AND THEIR INHIBITORY ACTIVITIES AGAINST S-ADENOSYLHOMOCYTEINE HYDROLASE

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S-Adenosylhomocysteine hydrolase (SAH) catalyzes the hydrolysis of S-adenosylhomocysteine to adenosine and L-homocysteine and has been an attractive target for the development of broad spectrum antiviral agents. Neplanocin A and 9′-(diacydroxyxycloponent-4′-enyl)adenine (DHCeA) have been known to inhibit SAH by cofactor (NAD+) depletion mechanism and their inhibition is reversed by the addition of NAD+ or dialysis. Since we have recently uncovered the novel irreversible mechanism of action and potent SAH-inhibitory activity of halo-neplanocin A, it was very interesting to synthesize the corresponding halo-analogues of DHCeA and to compare their SAH-inhibitory activities and mechanism of actions. The fluoro-DHCeA was synthesized via electrophilic vinyl fluorination (BuLi, N-fluorobenzensulfonylimide) and other halo-analogues were easily synthesized via halogenation of cyclopentone derivatives with halogen (Cl2, Br2 and I2), respectively. Unlike DHCeA showing irreversible inhibition, halo-DHCeA’s appear to operate by novel and irreversible mechanism of action, among which fluoro analogue was found to be slightly more potent than DHCeA against SAH. Synthesis and biological activity of halo-neplanocin A will be discussed in the meeting.

A convenient synthesis of 2′ or 3′-amino-2′(or 3′)-deoxyadenosine and 5′-chloro-2′(or 3′)-amino-deoxyadenosine analogues

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New and improved preparations of structurally modified nucleosides are important goals in synthetic organic chemistry because of the potential utility of these compounds as synthetic precursors of many biologically active