DESIGN AND SYNTHESIS OF A3 ADENOSINE RECEPTOR LIGANDS, 2'-FLUORO ANALOGUES OF Cl-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 bioisosteric 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, D-2-deoxy-2-fluororibosyl acetate was first synthesized via direct displacement of 2-O-triflate with tetra-butylammonium fluoride, starting from D-arabinose, 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.

[PD1-69] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

SYNTHESIS OF HALOGENATED 9-(DIHYDROXYCYCLOPENT-4'-ENYL) ADENINES AND THEIR INHIBITORY ACTIVITIES AGAINST S-ADENOSYLHOMOCYSTEINE 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-(dihydroxycyclopent-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 (n-BuLi, N-fluorobenzenesulfonimide) and other halo-analogues were easily synthesized via halogenation of cyclopentenone derivatives with halogen (Cl2, Br2 and I2), respectively. Unlike DHCeA showing reversible 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.

[PD1-70] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

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