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

molecules in cells. In our program to synthesize the bioactive nucleosides, such as AdoHcy hydrolase inhibitors and cyclic adenosine diphosphoribose(cADPR) analogues, 2'(or 3')-amino-2'(or 3')-deoxyadenosine analogues were prepared conveniently through the key intermediates, 9-(β-D-xylofuranosyl) or 9-(β-D-arabinofuranosyl) adenine, which were synthesized from readily available adenosine via conventional protocols. Compared to other precedent procedures, our synthetic strategy is convenient and versatile as well. In addition, as synthetic precursors for one of classes of AdoHcy hydrolase inhibitors, 5'-chloro-2'(or 3')-amino-deoxyadenosine analogues were prepared starting from 2'(or 3')-azido-2'(or 3')-deoxyadenosine analogues. In this poster, the versatile synthetic procedures and resulting key nucleosides will be presented.

[PD1-71] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

Culture of rabbit chondrocytes on the HA-agarose scaffold for artificial cartilage

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Emerging medical technologies for effective and lasting repair of articular cartilage include delivery of cells or cell-seeded scaffolds to a defective site to initiate de novo tissue regeneration. In this respect, the availability of an appropriate biomaterial scaffold is crucial to allow chondrocyte growth and cartilaginous matrix deposition in a three-dimensional geometry. Hyaluronic acid (HA) molecules are anchored to the chondrocyte membrane via receptors, such as CD44. Agarose is a clear, thermoreversible hydrogel but not a natural component of the cartilage matrix. However, agarose was supplemented to HA to obtain desired mechanical properties of scaffold. HA-agarose scaffold is characterized with a highly porous sponge-like structure, with average pore sizes of 200-500mm and interlinked pores. Such a structure is attractive for engineering tissues from isolated cells in vitro, as it can provide a sufficient space for seeding a large cell mass and for the reorganization of the cells into tissue-like structures. Seeding chondrocytes onto the HA-agarose scaffold was efficient due to the hydrophilic nature of the HA and agarose and the rapid wetting of the matrix by the culture medium. Consequently, the cell transport into the matrix pores was maximized, ensuring that the most of the device is uniformly cell-rich. Different techniques such as immunohistochemistry, scanning electron mircroscopy, and MTT assay were used to study the behavior, morphology, phenotype expression, and viability of the chondrocytes in the scaffold. HA-agarose scaffold is expected to be suitable as a biological matrix in three-dimensional chondrocyte cultures.

[PD1-72] [10/17/2002 (Thr) 09:30 - 12:30 / Hall C]

SYNTHESIS OF [1-FLUORO-2,2-BIS-(HYDROXYMETHYL) CYCLOPROPYLMETHYL]PURINES AS ANTIVIRAL AGENTS

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In an effort to search for the chemically and enzymatically stable carbonucleoside, we designed [1'-fluoro-2',2'-bis-(hydroxymethyl) cyclopropyl methyl]purines. The underlying concept for our design is to seek relatively conformationally-locked compound with minimal structural disturbance from acyclic carbonucleoside such as acyclovir or penciclovir. To meet such a requirement, we need to introduce cyclopropane and fluorine moiety. Due to its hybrid character of cyclic and acyclic molecules, cyclopropyl group could render the conformational rigidity to the target molecule. It has also been suggested that a fluoromethylene group is a better isostere of oxygen than the methylene. Therefore, carbocyclic and acyclic derivatives substituted by fluorine at the oxygen position in natural nucleoside are also attractive targets. Herein, we report on the design and syntheses of a series of [1'-fluoro-2',2'-bis-(hydroxymethyl) cyclopropyl methyl]purines in attempts to mimic pencyclovir by installing a fluoro group and a cyclopropyl group.