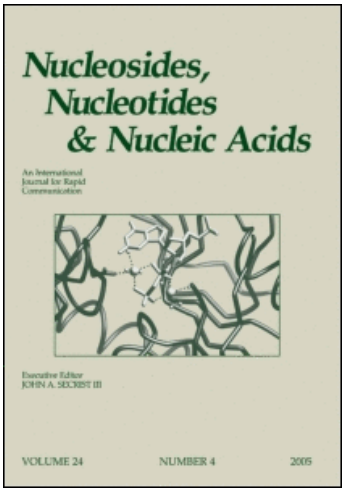

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Strategically Functionalized Adenosines: Agonists for Adenosine Receptors

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STRATEGICALLY FUNCTIONALIZED ADENOSINES: AGONISTS FOR ADENOSINE RECEPTORS

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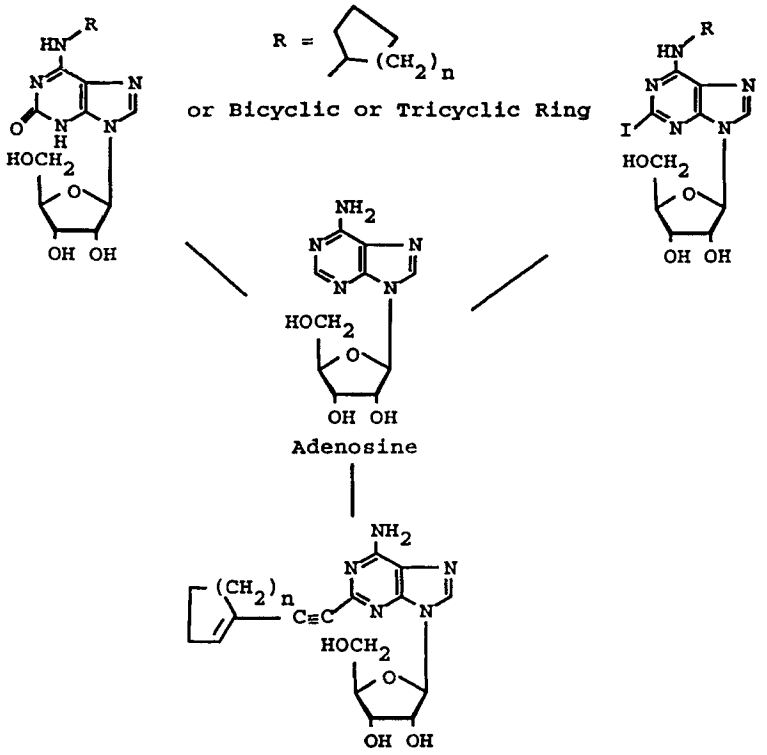
Abstract: The syntheses of three classes of adenosine analogues involving cyclo-substitution at the 6-position and functionalization at the 2-position are reported. The target molecules synthesized are stable with respect to hydrolytic deamination by mammalian adenosine deaminase, and, because of major structural changes at the 2- and 6-positions, these compounds are expected to be poor phosphorylation substrates for the kinases. Adenosine receptor binding data reveal that several of the compounds synthesized show excellent A_1 receptor affinity and A_2/A_1 selectivity.

The biochemical basis for the physiological effects of natural adenosine has been the subject of numerous studies in recent years. These studies have revealed that some of the biological activities of adenosine may be mediated through the involvement of extracellular purinergic receptors, termed A_1, A_2, A_3 (and others) which appear to be distributed in a wide variety of tissues in the human system.[1,2] There is considerable interest in the development of adenosine analogues and derivatives that mimic the pharmacological properties of adenosine but with much higher receptor specificity and with resistance toward rapid metabolic degradation.[3-6] This paper will report on the synthesis of metabolically stable adenosine analogues with interesting adenosine receptor activity.

The molecular design of target compounds incorporated strategic changes in the adenine ring of adenosine and included cyclosubstitution at the nitrogen of the 6-position and functionalization at the 2-position, both modifications in the parent molecule intended to increase receptor affinity and selectivity through hydrophobic, H-bonding and other interactions. Three representative classes of compounds that were studied are shown in Scheme 1.

Synthesis of the 2-halogenated N^6-cyclosubstituted compounds were approached from 2,6-dihalogenated precursors using methodologies previously described by us.[7,8] Approaches to the preparation of N^6-cyclosubstituted isoguanosines were from the



Scheme 1

corresponding 2-sulfones by nucleophilic displacement reactions also utilizing procedures previously developed in our laboratory.[9,10] The development of potential selective A_2 binding compounds[11,12] utilized palladium-mediated methodologies[11-16] to introduce cycloalkenylalkynyl groups at the 2-position of adenosine. The key step involved the use of triflic enolates in palladium-catalyzed cross-coupling with 2-ethynyladenosine.

The target molecules synthesized are stable with respect to hydrolytic deamination by mammalian adenosine deaminase, and, because of major changes at the 2- and 6-positions, these compounds are expected to be poor phosphorylation substrates for the kinases. Adenosine receptor binding data[17] of many compounds synthesized in this project, reveal that several of these show excellent A_1 receptor affinity and selectivity. In particular, 2-iodo-N^6-cyclopentyladenosine showed A_1 receptor binding at 20 nM and A_2/A_1 selectivity of 2000 and N^6-(endo-2-norbornyl)isoguanosine showed A_1 receptor binding at 35 nM and A_2/A_1 selectivity of 2300. Further biological studies are in progress.

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