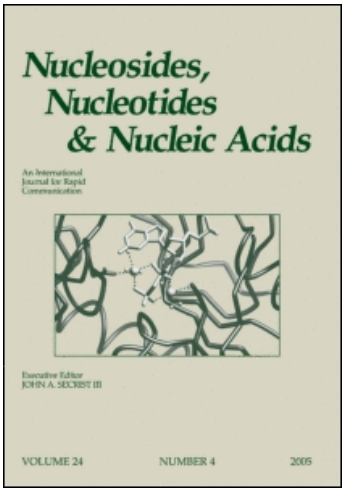

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Cristalli, G. , Grifantini, M. , Vittori, S. , Balduini, W. and Cattabeni, F.(1985) 'Deaza-analogues of Adenosine and 2-Chloroadenosine as Agonists of Adenosine Receptors', Nucleosides, Nucleotides and Nucleic Acids, 4: 1, 237
To link to this Article: DOI: 10.1080/07328318508077868
URL: http://dx.doi.org/10.1080/07328318508077868

NUCLEOSIDES & NUCLEOTIDES, 4(1&2), 237 (1985)

DEAZA-ANALOGUES OF ADENOSINE AND 2-CHLOROADENOSINE AS AGONISTS OF ADENOSINE RECEPTORS

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A variety of adenosine analogues have been recently evaluated in order to find more potent and selective agonists on adenosine receptors. The most potent adenosine analogues acting on A_1 receptor, a high affinity receptor inhibitory to adenylate cyclase, are N^6-substituted compounds. So N^6-cyclohexyladenosine (CHA) and N^6-L-phenylisopropyladenosine (L-PIA) are extremely potent agonists on A_1 receptor, whereas they are relatively weak agonists on A_2 receptor, a lower affinity receptor which is stimulatory to cyclase, and they have no effect on the adenosine P site.

Recently we found that in a series of adenosine deaza-analogues the 1-deazaadenosine showed the highest affinity for adenosine receptors. We therefore have synthesized some N^6-substituted 1-deaza-analogues of adenosine and 2-chloroadenosine and measured the IC_{50} on [^{3}H]N^6-cyclohexyladenosine (^{3}H-CHA) and [^{3}H]adenosine 5'-ethylcarboxamide (^{3}H-NECA) binding selective for A_1 and A_2 receptors respectively. Binding assays were performed utilizing rat brain membranes. From the data obtained it was observed that also in the case of 1-deazaadenosine a cyclohexyl or a L-phenylisopropyl moicty at the N^6 position increases both the affinity and the specificity for A_1 receptor. The N^6-L-phenylisopropyl-1-deazaadenosine showed the highest affinity for A_1 receptor in the series of 1-deaza-analogues so far examined, being three times less active than L-PIA. A chlorine atom at C^2 position increases binding affinity for A_1 receptor only in those analogues that are not substituted with other groups.

0732-8311/85/0401-0237$3.50/0