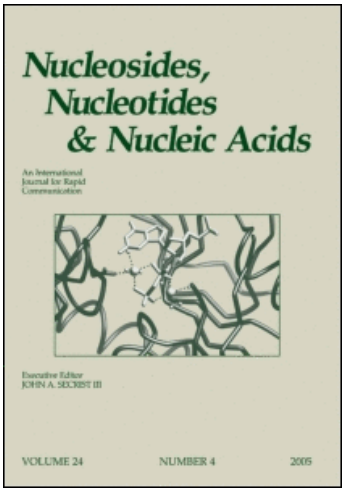

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Structure-Activity Relationships of Adenosine Deaminase Inhibitors

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STRUCTURE-ACTIVITY RELATIONSHIPS OF ADENOSINE DEAMINASE INHIBITORS

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ABSTRACT: Adenosine deaminase (ADA) is an important catabolic enzyme which converts adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. ADA exists in two different isoenzymes, namely ADA1 and ADA2, whose balance in monocytes-macrophages seems to guarantee the homeostasis of adenine nucleosides. Modifications of the purine moiety or/and substitution of the sugar moiety of adenosine with aliphatic chains led to derivatives which are good ADA inhibitors.

INTRODUCTION

Adenosine deaminase (ADA) is a key enzyme in the purine metabolism. It converts adenosine and 2'-deoxyadenosine into inosine and 2'-deoxyinosine, respectively.

ADA has a wide phylogenetic distribution and its amino acid sequence is highly conserved from bacteria to humans.[1,2] This enzyme is present in virtually all human tissues but the highest levels are found in the lymphoid system, such as lymphonodes, spleen, and thymus. In humans ADA exists as two distinct iso-enzymes, called ADA_1 and ADA_2; ADA_1 represents the majority of intracellular ADA activity, although the predominant isoenzyme in plasma and serum is ADA_2.[3]

Enzyme abnormalities, in the sense of increased levels of ADA, have been reported in acquired immunodeficiency syndrome (AIDS), in viral and bacterial infections, in autoimmune diseases, like systemic lupus erythematosus (SLE), in some cancer and, recently, in CNS degeneration, like Parkinson's disease and multiple sclerosis.

Recently it has been demonstrated that the total serum ADA activity in patients with SLE is higher than healthy controls, due to a relevant increase in ADA_2 activity.[4]

ADA INHIBITORS

The presence of high levels of adenosine deaminase in the above listed diseases and the fact that ADA inactivates a number of viral and cancer chemotherapeutic adenosine analogues stimulated our interest in the field of adenosine deaminase inhibitors.

Erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA) is a synthetic semitight inhibitor with Ki of about 0.007 μM. In order to investigate which parameters in the purine moiety of EHNA are critical for inhibitory activity and to find less toxic ADA inhibitors, we studied the role of the nitrogen atoms in the binding to the enzyme; we found that 1-deaza and 3-deazaEHNA were good inhibitors, with a Ki of 0.16 μM and 0.01 μM, respectively.[5]

Furthermore, opening the pyrimidine ring led to compounds that are still ADA inhibitors. Among them *erythro*-9-(2-hydroxy-3-nonyl)imidazole-4-carboxamide resulted to be the most active with a Ki = 0.035 μM.[6]

In order to introduce additional simplifications on the structure of these inhibitors, we have recently reported the synthesis and biological activity of a series of *erythro* and *threo*-9-(2-hydroxy-3-nonyl)azoles, the *erythro*-9-(2-hydroxy-3-nonyl)-1,2,4-triazole (Ki = 0.3 μM) being the most potent compound in the series.[7,8] On the other hand, opening the imidazole ring of EHNA resulted in pyrimidine derivatives which maintained, to some extent, the inhibitory activity with the presence of a nitrogen atom in 5 position being crucial for the activity.

In conclusion, this library of EHNA modified inhibitors of ADA could be both a useful tool to investigate the mode of binding of such inhibitors with the enzyme and a series of leads for future pharmacological applications.

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