NOVEL HIGHLY POTENT ADENOSINE DEAMINASE INHIBITORS CONTAINING THE PYRAZOLO[3,4-*d*]PYRIMIDINE RING SYSTEM. SYNTHESIS, STRUCTURE-ACTIVITY RELATIONSHIPS AND MOLECULAR MODELING STUDIES

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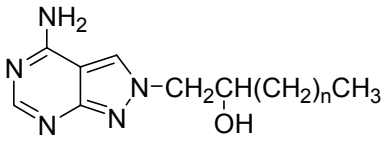
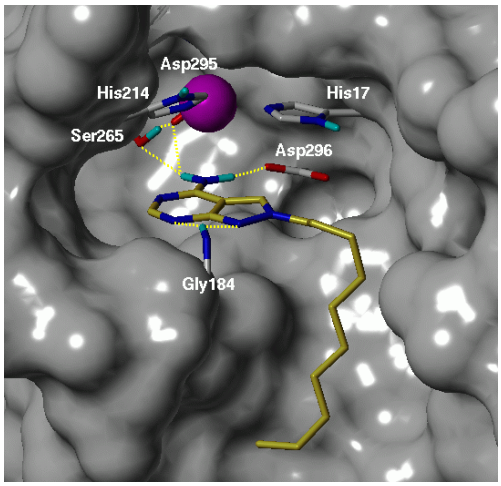
Adenosine deaminase (ADA) is a key enzyme in purine metabolism, playing a central role in controlling the effects of adenosine in a variety of system and a critical function in the development of the immune system. ADA inhibitors represent therefore an useful tool to potentiate the level of endogenous extracellular adenosine as well as an effective pharmacological approach towards the treatment of limphoproliferative disorders [1]. This study reports the synthesis of a number of 1- and 2-alkyl derivatives of the 4-aminopyrazolo[3,4-*d*]pyrimidine (APP) nucleus and their evaluation as inhibitors of ADA from bovine spleen. The 2-substituted APP compounds proved to be potent inhibitors, most of them exhibiting K_i values in the nanomolar/subnanomolar range. In this series, the inhibitory activity enhances with the increasing of the length of the alkyl chain, reaching its maximum with the *n*-decyl substituent. Insertion of a 2'-hydroxy group in the *n*-decyl chain gave 4-amino-2-(β-hydroxydecyl)pyrazolo[3,4-*d*]pyrimidine **1**, whose (*R*)-isomer displayed the highest inhibitory potency of the series (K_i = 0.053), showing an efficacy two order of magnitude higher than that of (+)-EHNA (K_i 1.14) [2]. Thus, docking simulations of the most potent APP inhibitors into the ADA binding site were performed, in order to rationalize the SARs observed and to guide, perspectively, the design of new analogues.



1 n = 7



[1] Cristalli, G.; Costanzi, S.; Lambertucci, C.; Lupidi, G.; Vittori, S.; Volpini, R.; Campioni, E. Adenosine Deaminase: Functional Implications and Different Classes of Inhibitors. *Med. Res. Rev.* **2001**, *21*, 105-128.

[2] Schaeffer, H. J.; Schwender, C. F. Enzyme Inhibitors. 26. Bridging Hydrophobic and Hydrophilic Regions on Adenosine Deaminase with Some 9-(2-hydroxy-3-alkyl)adenines. *J. Med. Chem.* **1974**, *17*, 6-8.