SYNTHESIS OF DIPEPTIDE ESTERS OF AZT AND THEIR INTERACTION WITH THE hPEPT1 PEPTIDE TRANSPORTER[1]

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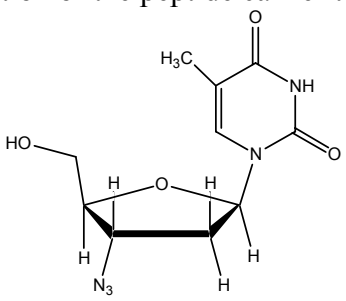
In the last decades, the acquired immunodeficiency syndrome – AIDS – has been a major health problem worldwide. The disease is caused by a retrovirus, the human immunodeficiency virus – HIV – and much research has been devoted to the development of efficient anti-retroviral agents, lethal to HIV while innocuous for the patient. Zidovudine, best known as AZT (**1**), has become the most widely employed drug in AIDS chemotherapy. However, AZT is associated with many adverse effects such as anaemia and leucopoenia [1]. Further, AZT is insoluble in the cerebrospinal fluid and does not penetrate into the brain tissue, and therefore may not prevent viral replication in the brain [1]. Thus, pro-drugs of AZT appear as a possible means to obviate the problems posed by the employment of AZT to treat AIDS. We have been working on drug derivatization with dipeptides, in order to obtain potential pro-drugs that could be activated by intramolecular cyclization of the peptide carrier to a 2,5-diketopiperazine [2,3].



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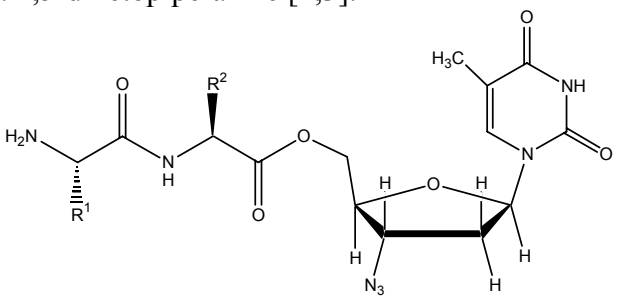

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We have recently published quite promising results regarding the application of this strategy to the phenolic analgesic paracetamol [3], which makes this approach potentially applicable to other hydroxyl-containing drugs such as AZT. Thus, we now wish to present the synthesis of dipeptide esters of AZT (**2**) as well as preliminary results on their interactions with the intestinal oligopeptide transporter hPEPT1. Out of eight different prodrugs tested, the Val-Ala and Val-Gly prodrugs were seen to have highest affinity (IC50 < 0.5 mM) for hPEPT1.

References:

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[2] P. Gomes, J. R. B. Gomes, M. Rodrigues and R. Moreira (2003) *Tetrahedron* **59**, 7473-7480.
[3] C. Santos, M. L. Mateus, A. P. dos Santos, R. Moreira, E. Oliveira and P. Gomes (2005) *Bioorg. Med. Chem. Lett.*, accepted for publication.

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