SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF DIPEPTIDE ESTERS OF THE ANTI-RETROVIRAL DRUG ACYCLOVIR

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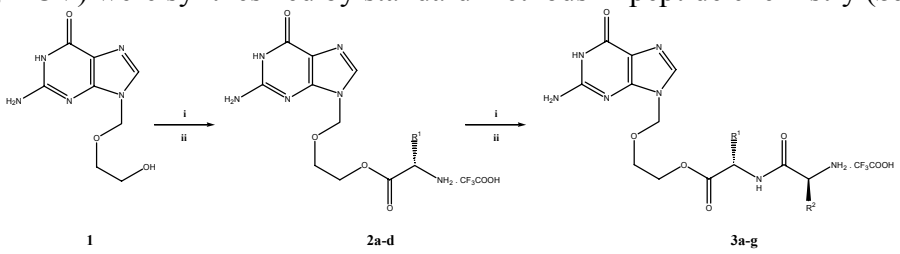
Seven dipeptide esters of the anti-retroviral drug 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir, ACV) were synthesized by standard methods in peptide chemistry (*Scheme 1*).



Scheme 1. (i) N^{α}-Boc-protected amino acid (BocAAOH), N,N'-dicyclohexylcarbodiimide (DCCI), N,N-dimethylaminopyridine (DMAP), dichloromethane (DCM); (ii) trifluoroacetic acid (TFA).

The derivatization of ACV with amino acids has been used for the development of ACV prodrugs. In fact, the valine derivative of ACV – valacyclovir – is a pro-drug of widespread use in herpes treatment. Mitra and co-workers have recently reported the synthesis and properties of novel dipeptide prodrugs of ACV, two of which are included in the present work (**3c** and **3d**) [1,2]. The compounds **3a-f** prepared were screened for their *in vitro* antimicrobial activity against Gram positive (*Bacillus cereus*, *Bacillus subtilis*) and Gram negative (*Pseudomonas aeruginosa*, *Escherichia coli*) bacteria, and also for their fungicidal activity using *Candida albicans*. The antimicrobial activities were evaluated by diameter measurement of haloes formed by growth inhibition caused by compounds **3** at different concentrations in DMSO [3]. Compounds **3** exhibited antimicrobial activity preferentially against Gram-positive bacteria and were all inactive against *Pseudomonas aeruginosa*. The minimal inhibitory concentrations (MIC) could be determined for some of the compounds in the concentration range assayed. Further dilutions are being done for MIC determination of most compounds against *B. cereus* and *B. subtilis*. The determined MIC were significantly lower than those of typical standards such as ampicilline, cloramphenicol or cyclohexamide. The parent drug, ACV, was also assayed and found to be less active than the corresponding dipeptide ester derivatives. These results suggest that compounds **3** might be activated by bacterial peptidases or actively transported through bacterial cell membrane.

References:

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[3] Isabel C.F.R. Ferreira, Ricardo C. Calhelha, Letícia M. Estevinho and Maria-João R.P. Queiroz (2004) *Bioorg. Med. Chem. Letters* **14**, 5831-5833.

Thanks are due to FCT (Portugal) for financial support to CIQUP (Oporto), CECF (Lisbon) and CIMO (Bragança), and for doctoral research grant SFRH/BD/9277/2002 (C. Santos). We also thank MEDINFAR (Portugal) for their kind gift of acyclovir.