Medicinal Chemistry in the 21st Century. Lisbon, 13-14 October, 2006
Posters
P-108

Acetylcholinesterase Inhibitory Activity of Oxazole Derivatives

C. Dias[a], *M. A. Brito*[b], *A. Eleutério*[a], *J. L. Marco*[c], *D. Brites*[b], *M. C. Carreiras*[a]
[a]Centro de Estudos de Ciências Farmacêuticas and [b]Centro de Patogénese Molecular – UBMBE, Faculdade de Farmácia, Universidade de Lisboa, Av. das Forças Armadas, 1600-083 Lisboa, Portugal.
[c]Instituto de Química Orgánica General, C/ Juan de la Cierva, 3, 28006 Madrid, Espanha

Alzheimer's disease (AD) is the most common form of dementia among persons over 65 years of age. It is a brain neurodegenerative disorder characterised by loss of memory and cognition. Current treatment is symptomatic, with the major therapeutic strategy based on the "cholinergic hypothesis", specifically acetylcholinesterase (AChE) inhibition. Tacrine (THA) was the first and one of the few drugs approved in the last decade for the treatment of AD. However, due to the important adverse effects, such as hepatotoxicity, it is no longer widely used. Therefore, more potent and less aggressive THA analogues are necessary. This prompted us to evaluate the AChE inhibitory activity of new oxazole derivatives (compounds **1**-**5**), presenting a pyridine ring (compounds **2**,**3**) or a benzene ring (compounds **4**,**5**) in the molecule (1). The biological activity of the compounds was evaluated by measuring the AChE inhibitory activity by an adaptation of the method reported by Ellman et al (2). The reaction rates were compared and the percent of inhibition by the test compounds was calculated. Assays were performed in quadruplicate in at least two independent experiments, and THA was used as a reference compound. At the maximum soluble concentrations, compounds **1** and **2** inhibited AChE activity by nearly 50%, while the inhibition by the derivative **3** was only around 30%. In contrast, the oxazolo-derivatives **4** and **5** were devoid of any inhibitory activity, which we can speculate to be due to the absence of the N atom in the benzene ring in these compounds. Collectively, these preliminary findings point to a potential interest of precursor **1** and THA-derivative **2** for AD therapeutics, although structural modifications are needed to improve the solubility of the compounds, which is an essential step to enhance their activity.

Financial support: Centro de Estudos de Ciências Farmacêuticas, Centro de Patogénese Molecular – UBMBE and Instituto de Química Orgánica General – CSIC.

References:
1. Carreiras MC, Eleutério A, Marco-Contelles J, unpublished results.
2. Ellman, G. L. et al. Biochem. Pharmacol. 1961; 7: 88-95.