MULTIPOWER DRUGS WITH CHOLINERGIC AND NEUROPROTECTIVE PROPERTIES FOR THE TREATMENT OF ALZHEIMER’S AND NEURONAL VASCULAR DISEASES

C. Figueiredo¹, D.B. Silva¹, E. Mendes¹, M.C. Carreiras¹, M. Chioua², M.L. Jimeno², R. Léon³, C. de los Rios⁴, M. Bartolini⁴, V. Andrisano⁴, A. Romero³, A. Sàmadi², M. Villarroya³, M. López³, J. Marco-Contelles⁵

¹Fac. Pharmacy, Univ. Lisbon, Lisbon, Portugal, ²Instituto de Química Orgánica General, CSIC, ³Instituto Teófilo Hernando, Fac. Medicina, UAM, Madrid, Spain, ⁴Department of Pharmaceutical Sciences, Alma Mater Studiorum, Bologna University, Bologna, Italy

Introduction: The synthesis and pharmacological analyses of a number of pyrazolo[3,4-b]quinoline, benzo[b]pyrazolo[4,3-g][1,8]naphthyridine, furo[2,3-b]quinoline, and pyrrolo[2,3-b]quinoline derivatives are reported.

Aims: A series of new compounds were synthesized to look for both selective AChE and BuChE inhibitors, endowed with neuroprotective and antioxidant properties.

Methods: The Friedländer reaction of different aminonitrile precursors with cyclohexanone, under the usual experimental conditions afforded the target compounds.

The inhibitory activity against both cholinesterases was assessed following the spectrophotometric method of Ellman.

Lactate dehydrogenase activity was evaluated, as well as neuroprotection experiments with rotenone/oligomycin A. To determine cell viability, the MTT formazan probe was used. Neuroprotection experiments with okadaic acid were also carried out.

Results: Some pyrazolotacrines were potent and selective AChE inhibitors, the most interesting inhibitor is compound 5 [IC₅₀ (EeAChE) = 69±6 nM, and IC₅₀ (eqBuChE) = 6.3± 0.6 µM]. Kinetic studies on compound 5 proved this compound is a mixed-type inhibitor for EeAChE, showing a Kᵢ of 155 nM. Compound 5 indicated a 45% neuroprotection value against rotenone/oligomycin A-induced cell death, but it was unable to improve cell viability of SH-SY5Y cells damaged with OA.

Furanotacrines 19-29, and pyrrolotacrine 31 are potent, in the micromolar range, and highly selective inhibitors of BuChE.

Pyrrolotacrines 30 and 32 proved to be moderately equipotent for both cholinesterases and pyrrolotacrine 30 was the most potent for the inhibition of both enzymes.

Conclusions: Among all these compounds, pyrazolotacrine 5, and pyrrolotacrine 30 can be considered attractive compounds for the potential treatment of Alzheimer’s and cerebrovascular diseases.