ABSTRACT

Charles University

Faculty of Pharmacy in Hradec Králové

Department of Organic And Bioorganic Chemistry

Student: Lucia Pokrievková

Supervisor: doc. PharmDr. Jaroslav Roh, Ph.D.

Supervisor specialist: RNDr. Eva Mezeiová, Ph.D., PharmDr. Jan Korábečný, Ph.D.

Title of Diploma thesis: Synthesis of novel huprine derivatives as potential cholinesterase inhibitors

Alzheimer's disease (AD) is a complex neurodegenerative disease that is manifested by the gradual loss of short-term and, at more advanced stages, also of long-term memory. The characteristic histopathological features of AD is the presence of neuritic plaques and neurofibrillary tangles in affected brain regions. Cholinergic neurotransmission is also one of the key pathological findings in AD. Only two drug groups are used in AD therapy. The first group consists of acetylcholinesterase inhibitors (AChEIs). Memantine, which is a glutamate receptors antagonist, belongs to the second one. The aim of the diploma thesis was the synthesis of a new group of drugs acting as multipotent ligands (multi-target directed ligands, MTDLs) derived from huprines. The new compounds were designed to be able to interact with both anionic sites of acetylcholinesterase (AChE), thereby exaggerating the enzyme-inhibiting effect. In the experimental part of the diploma thesis two structural types of huprines were designed and prepared. The heterodimers based on huprine-L-tryptophan (HupY-L-Trp) with different side chain lengths were the first type. The aim of the second synthesis was the design and preparation of a 2-methoxyhuprine. The inhibitory activity of the new derivatives against cholinesterase (ChE) was determined by method of Ellman and obtained results are expressed as the IC_{50} value. These measurements were carried out by the staff of the Department of Toxicology and Military Pharmacy in Hradec Králové (Faculty of Military Health Sciences, University of Defense, Brno). The biological results of the new compounds were compared with the reference drugs (tacrine, 6-chlorotacrine and 7-methoxytacrine). The rate of

permeability of new derivatives through the blood-brain barrier was determined by using parallel artificial membrane permeability assay (PAMPA). This determination was carried out by the staff of the Centre of Biomedical Research (Faculty Hospital Hradec Králové). The biological results of the new compounds were compared with the references. All newly emerged compounds demonstrated inhibitory activity against both ChE subtypes in micromolar to nanomolar IC_{50} values with presumed CNS availability.