Abstract

Charles University, Faculty of Pharmacy in Hradec Králové
Department of Pharmacognosy and Pharmaceutical Botany

Candidate:	Mgr. Filip Pidaný
Supervisor:	Prof. Ing. Lucie Cahlíková, Ph.D.
Consultant:	Assoc. Prof. Jan Korábečný, Ph.D.
Title of Doctoral Thesis:	The structure of minor alkaloids of the Amaryllidaceae family as inspiration for the synthesis of compounds with biological activity targeting Alzheimer's disease

The theoretical part of this dissertation provides a basic overview of the Amaryllidaceae family known for its rich occurrence of structurally diverse alkaloids. These substances exhibit a wide range of pharmacological effects, with our studies focusing on their potential therapeutic use in the treatment of Alzheimer's disease (AD). It is the most common form of dementia, which is characterized by progressive neurodegeneration. As the life expectancy of the population increases, the global prevalence of AD is also rising. This trend presents not only economic but also social challenges for healthcare systems, and society as a whole. The thesis provides detailed descriptions of the most well-known hypotheses of AD development and the characteristics of clinically used medications. Attention is given to the decline in levels of acetylcholinesterase, the dominant enzyme in a healthy brain, as well as the gradual increase in levels of the compensatory enzyme butyrylcholinesterase (BChE).

The experimental part of the thesis focuses on researching new potential selective inhibitors of BChE. The study extends the knowledge gained from previous isolation efforts on new alkaloids from *Narcissus pseudonarcissus* cv. Carlton, with particular focus on the alkaloids named Carltonine A-E. Carltonine A and B demonstrated particularly significant inhibition of human butyrylcholinesterase (*h*BChE) with IC_{50} = 0.91 ± 0.02 μM and IC_{50} = 0.031 ± 0.001 μM, respectively.

In the follow-up first synthetic series, we identified the most potent inhibitor of *h*BChE, designated as molecule **I-6**, with an IC_{50} = 0.07 ± 0.01 μM. Subsequently, in the second series, two molecules, **II-87**, and **II-88**, exhibited even more significant *h*BChE inhibitory activity, with IC_{50} = 0.0038 ± 0.0002 μM and IC_{50} = 0.0057 ± 0.0015 μM, respectively. In parallel with the second series, the preparation of the third series was carried out, where compounds **III-28** and **III-33** were identified as the most active derivatives, with IC_{50} values = 0.171 ± 0.063 μM and IC_{50} = 0.167 ± 0.018 μM, respectively.

In this thesis, I discuss the experimental data related to the design, synthesis, and evaluation of the biological activity of the prepared derivatives and analyze in detail the structure-activity relationship (SAR). The most effective compounds were specifically evaluated in terms of their ability to cross the blood-brain barrier, cytotoxicity profile, microsomal and plasma stability, and in a selected case, water solubility. The data obtained were supported by *in silico* studies and a crystallographic study of the most potent molecule **II-87** with *h*BChE. Our research has identified a range of promising compounds with potential use in the treatment of diseases associated with cholinergic dysfunction.

Key words: natural products, drugs, alkaloids, neurodegenerative diseases, Alzheimer's disease