Charles University
Faculty of Pharmacy in Hradec Králové
Department of Pharmacognosy

Candidate: Iva Valachová
Supervisor: Pharm.Dr. Daniela Hulcová, Ph.D.
Title of diploma thesis: Derivatives of Amaryllidaceae alkaloids as potential drugs in the treatment of tumor diseases

Twelve aromatic derivatives were prepared. The substitutions were performed on the hydroxyl group at C-3. This was acylated with differently substituted benzoyl chlorides affording the corresponding esters. Structural identification was performed by 1D- and 2D-NMR, ESI-HRMS spectroscopic techniques and optical rotation measurement. The yield of all reactions was more than 60 %. After converting these derivatives to hydrochlorides, their biological activity was tested.

The Amaryllidaceae alkaloid vittaine itself exhibits cytotoxic activity and therefore its derivatives have been investigated in this respect. It has been tested against 9 cancerous and 1 non-cancerous cell lines. 3-*O*-(4-Chloro-3-nitrobenzoyl)vittatine showed the highest cytotoxic activity, unfortunatelly, it does not selectively affect only cancerous cells. Conversely, 3-*O*-(2-naphthoyl)vittatine has a selective effect on the HT-29 cancerous cell line (colorectal carcinoma) with a viability value of 32 ± 3 %, potentially being the subject of further studies of cytotoxicity and possible use in cancer treatment. Negative results of cytotoxic activity of cancer and mainly noncancer cells can be of benefit in the treatment of Alzheimer's disease, they can reduce the side effects.

All of these compounds were tested for acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitory activity by the Ellman method using recombinant enzymes. 3-*O*-(3-Nitrobenzoyl)vittatine and 3-*O*-(4-chloro-3-nitrobenzoyl)vittatine showed the most significant inhibitory activity against AChE with IC_{50} values 12,44 ± 0,08 μM and 17,01 ± 0,39 μM, respectively. Except 3-*O*-(4-chloro-3-nitrobenzoyl)vittatine and 3-*O*-(4-methyl-3-nitrobenzoyl)vittatine, all other derivatives, especially 3-*O*-(2-chlorobenzoyl)vittatine (IC_{50} = 5,44 ± 0,06 μM) and 3-*O*-(2-methylbenzoyl)vittatine (IC_{50} = 7,97 ± 0,02 μM), appeared to be potentially active against BuChE. These *in vitro* findings were subsequently complemented by docking studies of the most active derivatives.

Keywords: Amaryllidaceae, vittatine, semisynthetic derivatives, cytotoxicity, Alzheimer's disease