ABSTRACT

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Title of Doctoral Thesis: Amaryllidaceae alkaloids of the genus *Narcissus* and their biological activity.

Narcissus pseudonarcissus cv. Carlton has been chosen for the phytochemical investigation based on the screening study. An alkaloidal extract of 485 g has been obtained from 30 kg of fresh bulbs. Repeated liquid-liquid extraction gave 187 g of concentrated crude extract, which was separated by column chromatography (CC, Al_2O_3; 5800 g), followed by repetitive CC, preparative TLC, and crystallization. Thirteen previously described Amaryllidaceae alkaloids were obtained along with four novel compounds named carltonine A, B, C, and narciabduliine. All compounds were identified and characterized by spectrometric techniques (1D and 2D NMR, CD, and HRMS) and by comparison with data from the literature. Alkaloids isolated in sufficient amounts were used for further evaluation of their inhibition activity against human acetylcholinesterase (*h*AChE), butyrylcholinesterase (*h*BuChE) and prolyloligopeptidase (POP). Carltonine A and B demonstrated promising inhibition activity against the *h*BuChE enzyme with IC_{50} values of 913 ± 20 nM and 31 ± 1 nM, respectively. Both alkaloids showed excellent selectivity profile against *h*BChE. Moreover, carltonine A showed the ability to inhibit POP (IC_{50} = 143 ± 12 μM) at the same extent as berberine. New narcikachnine-type alkaloid narciabduliine demonstrated balanced inhibition activity against *h*AChE and *h*BuChE with IC_{50} values of 3.24 ± 0.73 μM and 3.44 ± 0.02 μM, respectively.

As a part of ongoing studies, pilot series of compounds, structurally inspired by carltonine A, and B (**1**-**20**) was developed. Newly synthesized compounds were tested for their *h*AChE/*h*BuChE inhibition activity. Seven compounds (**1-4, 6, 14,** and **20**) demonstrated *h*BuChE inhibition activity with IC_{50} values lower than 1 μM. Compound **6** was the strongest *h*BuChE inhibitor with an IC_{50} value of 0.07 ± 0.01 μM. The binding mode of *h*BuChE inhibition of compound **6** was inspected by using enzyme kinetic analysis in tandem with molecular dynamic simulation. Furthermore, the CNS availability of **6** was predicted by calculating their BBB score.

Keywords: *Narcissus pseudonarcissus* cv. Carlton, Amaryllidaceae, alkaloids, biological activity, acetylcholinesterase, butyrylcholinesterase, prolyloligopeptidase.