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Comenius University
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Evaluation review of dissertation thesis: Amaryllidaceae alkaloids of genus *Narcissus* and their biological activity

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The dissertation is written in the form of comments to existing scientific articles. In the theoretical part, the author describes the history and traditional use of Amaryllidaceae plants, important secondary metabolites mainly, alkaloids and their biosynthetic pathways, and presenting the most essential structural types.

The theoretical part continues with the genus *Narcissus*, its essential constituents – alkaloids, biological activities, and usage in folk medicine worldwide. The plant *Narcissus pseudonarcissus* cv. Carlton was chosen because this species is a rich source of alkaloids and is used for commercial isolation of therapeutically used galanthamine to treat Alzheimer's disease. Several theories and hypotheses of the etiology of the disease were described.

The work aims are clearly described in several steps, including alkaloid isolation, structural elucidation using spectroscopic methods, biological activity screening against cholinesterases, prolyl oligopeptidase, and cytotoxicity screening against different cell lines. As a result, thirteen known and three new alkaloids were isolated and described. The isolation and structural elucidation were followed by the synthetic derivation of structures with the structure-activity relationship study. According to



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published results dissertation meets all determined aims and successfully fulfilled the objectives in all respects.

Analytical methods and tools have been chosen adequately, and the interpretation of the results is also appropriate. The thesis refers to many references (242) in an acceptable way. The author's publications presented in the thesis are related and relevant to the research topic. The author builds the thesis on his results that have been published in reviewed international journals with IF. Five scientific publications were included in the dissertation (Molecules 3x, Biomolecules, and International Journal of Molecular Sciences). Additional three articles are not included in the thesis, and participation in conferences is also listed.

Comments and possible questions:

The Abstract (pages 68 and 70) does not mention prepared galanthamine derivatives and antimycobacterial activity.

Page 24 contains the statement: lycorine is an excellent anticancer candidate with high specificity to cancer cells, higher activity than paclitaxel, etc. Are there some limitations in using this compound or its derivatives in therapy? Did this compound pass some phases of clinical trials?

Page 60: blood-brain barrier score was calculated in silico for 20 newly synthesized compounds inspired by isolated alkaloids (carltonine A and B). All of them are assumed to enter the CNS area. What route of application would you expect for these compounds if we will take into account their water insolubility?

Page 62: nineteen derivatives of galanthamine were synthesized and tested in vitro against three different Mycobacterium strains. Galanthamine alone does not exhibit activity against tested strains. All of the newly synthesized compounds are aromatic esters. I would like to know your opinion about the potential activity in vivo of these compounds since, as we know, esters are very rapidly cleaved by blood esterases and are used as prodrug form for prolongation of therapeutic effect.



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Abdullah Al Mamun demonstrated his scientific quality, critical and independent thinking. The results show great skills in the laboratory, good orientation in scientific literature and data analysis. The comment above does not reduce its positive contribution.

Based on all facts and obtained results, I recommend the Ph.D. thesis for defense and acceptance for receiving the Ph.D. degree.

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Prof. PharmDr. Pavel Mučaji, Ph.D.



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