

STATEMENT

by Assoc. Prof. Elisaveta Georgieva Apostolova, PharmD, PhD

Department of Pharmacology, Toxicology and Pharmacotherapy,

Faculty of Pharmacy, Medical University - Plovdiv

regarding a Ph.D. thesis for awarding the educational and scientific degree 'doctor'

professional direction 7.3. "Pharmacy",

Ph.D. program "Pharmacology, including Pharmacokinetics and Chemotherapy".

Author: Stela Toshkova Dragomanova

Form of doctoral program: independent preparation

Department: Pharmacology, Toxicology and Pharmacotherapy

Topic: „Neuropharmacological investigation of myrtenal conjugates with aminoadamantane"

Scientific supervisors:

Assoc. Prof. Velichka Andonova, PhD

Scientific consultant :

Prof. Ljubka Tancheva, PhD

1. General presentation of the procedure and the doctoral student

I received a set of materials on an electronic medium, which is in accordance with the Regulations for the development of the academic staff at MU-Varna and includes the following documents: application to the Rector of the MU-Varna, curriculum vitae, copy of a higher education diploma, orders of enrollment and termination of the doctoral studies, a protocol for passing the exams "Doctoral minimum in the specialty" and "Doctoral minimum in foreign language", Ph.D. thesis, abstract, list and copies of scientific publications on the topic of the dissertation, list of participations in scientific forums, declaration of originality and authenticity of documents, declaration for registration of profiles in scientific databases. The Ph.D. student has attached a list of 7 publications, of which 2 are full-text articles in refereed journals (in *Scopus* and *Web of Science* databases) and 5 are abstracts from scientific conferences.

The documents meet the requirements of the regulations for starting a dissertation defense procedure.

Stela Toshkova Dragomanova graduated from PMI-Varna in 1998 with the professional qualification "assistant pharmacist" and the Faculty of Pharmacy of the Medical University - Sofia in 2004 with the professional qualification "master of pharmacy". During the period 2000 – 2005, she worked as a pharmacist, and during the period 2005 - 2010 - as a manager in an open type of pharmacy. Stela Dragomanova began her academic career in 2010 when she was appointed as an assistant at the Department of Pharmacology and Clinical Pharmacology at the Faculty of Medicine of the Medical University - Varna. During the period 2015 – 2024, the doctoral student worked successively as an assistant and chief assistant at the Department "Pharmacology, Toxicology and Pharmacotherapy" of the Faculty of Pharmacy of MU-Varna. She teaches pharmacology and toxicology practicals to pharmacy students. Chief Assistant Dragomanova has a defended dissertation on the topic "Pharmacological, toxicological and neurobiological studies of myrtenal - a bicyclic monoterpenoid of natural origin" in the scientific specialty of pharmacology. She has acquired a post-graduate specialty "Clinical Pharmacy" in the health care system, and participates in 4 research projects, 2 of which are national. The doctoral student has 20 publications in the period 2013-2023.

2. Relevance of the topic

Neurodegenerative diseases represent a significant problem in clinical practice and their frequency among the population of developed countries is constantly increasing. Alzheimer's disease is one of the most common neurodegenerative diseases with a prevalence of 22% in the age group over 50 according to 2023 data. The multifactorial etiology of the disease determines the need to discover new pharmacological agents with a complex mechanism of action. Thus, the study of new compounds containing conjugates of components of plant origin and amino adamantane is particularly promising. Revealing the neuropharmacological effects and the mechanisms of the neuroprotective effect of these complexes would have significant scientific and scientific-applied importance.

3. Knowledge of the problem

The literature review represents an in-depth study of the problem and lays the theoretical background for the experiments performed. It includes a detailed description of adamantane, its areas of application, and its potential as a pharmacophore for the development of new pharmacotherapeutic agents. The possibilities for including adamantane in pharmaceutical forms for selective drug delivery (liposomes, dendrimers, cyclodextrin complexes) are also presented. The plant terpenoid myrtenal and its therapeutic potential are the subject of a separate section in the literature review. The literature review shows knowledge of the problem and testifies to the doctoral student's abilities to creatively evaluate literary material.

4. Research methodology

The formulated tasks correspond to the set aim. The chosen research methodology allows achieving the aim and obtaining an adequate answer to the tasks solved in the dissertation work.

The "Materials and Methods" section contains a detailed description of the experimental settings and allows reproduction of the performed studies. The statistical methods are appropriately selected.

5. Characterization and evaluation of the dissertation work and contributions

The dissertation is written on 219 standard pages and contains an introduction – 3 pages, literature review – 47 pages, aim and tasks – 2 pages, material and methods – 13 pages, results and discussion – 63 pages, conclusions – 2 pp., contributions - 1 pp., bibliography - 46 pp. and appendices - 29 pp. The dissertation work is illustrated with 41 figures, 7 tables, and 5 appendices. The literature review includes 482 sources, of which 40 are from the last 5 years.

The literature review demonstrates knowledge of the literature and provides a theoretical background for the chosen research methods. The aim is clearly formulated, and the tasks are logically related to the set aim. The "Materials and Methods" section contains a detailed description of the experimental settings and they are appropriately selected according to the tasks set. Statistical methods guarantee a correct assessment of the reliability of the obtained experimental data. The results include data from *in silico* analyses showing potential binding targets of the investigated MAC-197 and MAC-198 complexes in rat and human, as well as an investigation of the physical stability of their solutions and myrtenal emulsion. The choice of experimental models is well justified. A comparison was made between the obtained results of the *in silico* analysis, the results of the *in vivo* experiments, and the changes in certain biochemical parameters. The conclusions are supported by the obtained results and fully meet the set aim and tasks. Five contributions of important scientific and scientific-practical importance have been formulated. The use of a complex of methods including *in silico* and *in vivo* settings and biochemical studies, allowing complete characterization of the conjugates, is of great applied importance. The two synthetic conjugates of myrtenal show the potential to be developed as drug molecules.

6. Evaluation of the publications and personal contribution of the doctoral student

The presented list of 7 publications related to the dissertation includes 2 full-text articles and 5 abstracts in scientific conference proceedings. Two of the full-text statistics are in journals referenced in the Scopus and Web of Science databases. Chief Assistant Drahomanova is the first author in all 7 publications. The scientific production of the doctoral student fully covers the quantitative criteria specified in the Regulations of the MU - Varna.

Based on the presented declaration of originality and credibility and the pictures presented in the attachments, I consider that the doctoral student participated in the conduct of the experiments described in the dissertation, and the results obtained and formulated conclusions and contributions are her personal credit.

7. Abstract

The submitted abstract contains 68 pages and meets the requirements of the regulations for its preparation. It includes a description of the materials and methods used, and reflects the main results, conclusions, and contributions of the dissertation work.

8. Critical remarks and recommendations

I have no critical remarks about the doctoral student. I recommend her to increase her publication activity in refereed journals.

CONCLUSION

The dissertation **contains scientific, scientific-applied, and applied results**, which represent an **original contribution** to science and **meet all the requirements** of the Law for the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of LDASRB and the Regulations of the MU - Varna. The presented materials and dissertation results fully correspond to the specific requirements included in the Regulations of the MU - Varna for the application of the LDASRB.

The dissertation shows that the doctoral student Stela Toshkova Dragomanova possesses in-depth theoretical knowledge and professional skills in the scientific specialty "Pharmacology, including Pharmacokinetics and Chemotherapy", demonstrating qualities and skills for independent conduction of scientific research.

Due to the above, **I confidently give my positive assessment** of the conducted research, presented by the above-reviewed dissertation work, abstract, achieved results, and contributions, and I propose to the honorable scientific jury **to award** the educational and scientific degree "doctor" to Stela Toshkova Dragomanova in a doctoral program in pharmacology.

19.02.2024

Prepared by:

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
2016/679

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