

REVIEW

BY PROFESSOR EMIL IVANOV HRISTOV, MD, PhD

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With reference to:

Public defense of a PhD Thesis "NEUROPHARMACOLOGICAL STUDY OF MYRTENAL CONJUGATES WITH AMINOADAMANTANE"

Area of higher education: 7. Healthcare and Sports

Professional field: 7.3 Pharmacy

Doctoral program (Scientific specialty): Pharmacology (incl. Pharmacokinetics and chemotherapy)

PHD STUDENT: MASTER OF PHARMACY STELA TOSHKOVA DRAGOMANOVA, PhD

SCIENTIFIC SUPERVISOR: ASSOCIATE PROF. VELICHKA ANDONOVA, PhD

SCIENTIFIC CONSULTANT: Chief Assistant NADIA HRISTOVA-AVAKUMOVA, PhD

1. GENERAL PRESENTATION OF THE PROCEDURE

The public defense **procedure of a PhD thesis: "Neuropharmacological study of myrtenal conjugates with aminoadamantane"** in doctoral program (Scientific specialty): Pharmacology (incl. Pharmacokinetics and chemotherapy), in professional field 7.3. Pharmacy, in the Area of higher education 7. Healthcare and Sports, a PhD student in an independent form of learning at the Department of Pharmacology, Pharmacotherapy and Toxicology of the Faculty of Pharmacy at Medical University "Prof. Dr. Paraskev Stoyanov" - Varna **Master of Pharmacy STELA TOSHKOVA DRAGOMANOVA, PhD**, is conducted in accordance with the Order of the Rector of Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, prof. Svetoslav Georgiev, MD, PhD, - № P-109-18/23.01.2024, based on Decisions of the Faculty Council of the Faculty of Pharmacy and Report with incoming № 108-25/18.01.2024 from prof. Petko Petkov, MD, PhD, Dean of the Faculty of Pharmacy at Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

The set of administrative and scientific documents on paper and electronic format presented for evaluation - dissertation, abstract, copies of scientific publications, a series of lists, declarations of originality, declarations of conformity and other documents, totaling 14 in number.

The analysis of the documents, as well review of the procedure so far to the public defense, show that full legal compliance with regulations is achieved, namely: Law on the Development of Academic Staff in the Republic of Bulgaria, Rules for Implementation of the Law on the Development of Academic Staff in the Republic of Bulgaria and Statutory rules for the Development of the Academic staff at the Medical University-Varna.

2. SHORT BIOGRAPHICAL DATA OF THE CANDIDATE

STELLA TOSHKOVA DRAGOMANOVA acquired the qualification "Assistant Pharmacist" in 1998 at the Semi-Higher Medical Institute - Varna. In the period 1999 - 2004, she studied Pharmacy at the Medical University - Sofia, successfully graduated and in 2004 acquired educational and qualification degree „Master of Pharmacy“.

From his graduation until 2010, she worked consecutively as a Master of Pharmacy in a pharmacy and a responsible Master of Pharmacy (manager) of a pharmacy from the so-called open type. In 2010, after a competition, she started working as an assistant professor in the Department of "Pharmacology and Clinical Pharmacology and Therapeutics", Faculty of Medicine, at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. In 2014, she moved from the Faculty of Medicine to the Faculty of Pharmacy, passed through Educational scientific section "Pharmacology and Toxicology", subsequently from 2015 until now, she has successively held the academic positions of assistant professor and chief assistant professor at the Department of "Pharmacology, Toxicology and Pharmacotherapy".

In 2020, **STELLA TOSHKOVA DRAGOMANOVA** acquired the educational and scientific degree „PhD“ in the PhD program (doctoral program) "Pharmacology" after a successfully defended dissertation work in professional field 7.1 Medicine.

In June 2023, with Order No. R-109-253/23.06.2023 of the Rector of the Medical University - Varna, she was enrolled as a PhD student in an independent form of study in the PhD program "Pharmacology, incl. pharmacokinetics and chemotherapy", in professional field 7.3. Pharmacy.

3. ASSESEMENT OF THE PhD THESIS

The structure and design of the dissertation are in full compliance with Article 61, Paragraph 3 of the Statutory rules for the Development of the Academic Staff at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, adopted in 2018, amended and supplemented on 21.11.2022, in force from 21.11.2022 (protocol No. 57/21.11.2022). The dissertation contains 220 standard typewritten pages, Illustrated with 41 figures, 7 tables and 5 appendices. The bibliographic reference includes 481 sources. The abstract adequately reflects the dissertation work.

The selected topic "Neuropharmacological study of myrtenal conjugates with aminoadamantane" is extremely interesting and is a serious challenge for scientific research and analysis, both in the context of the modern development of pharmacology, respectively pharmacy, and also in a historical aspect.

The introduction is clear, to the point, the historical development of adamantane is examined, aimed at an in-depth study of the mechanisms of action of all adamantane derivatives. **The literature review**, developed in a volume of 46 pages, is detailed, analytical, properly structured, multidirectional - all the characteristics of adamantane and myrtenal, from their industrial application to their application in pharmacy are discussed, their therapeutic application in various spheres, the possible drug delivery systems, biological properties of myrtenal, potential therapeutic properties, etc. are discussed too.

It is an obviously that the PhD student has serious knowledge in the field, has analytical abilities, knows the methodology of medical research projects and based on this she has structured and conducted in an original way all the necessary preliminary studies.

The aim of the PhD thesis is to study in vivo the potential neuropharmacological effects of synthetic myrtenal conjugates with aminoadamantane and to reveal their main neuroprotective mechanisms on an experimental model of dementia of the Alzheimer type in rats.

The tasks of the PhD Thesis are accurately and clearly described, several scientific hypotheses are formulated, numerous directions in scientific research and analyzes are specified. 4 main groups of tasks were formulated, grouped and structured in 10 sub-directions - study of the physico-chemical parameters of myrtenal conjugates with aminoadamantane; neuropharmacological effects; biochemical mechanisms of influence in brain structures; neuroprotective action; neuromodulatory properties and others.

The PhD thesis offers us a variety of **materials and methods** corresponding to the aims and tasks. Starting from the selection of the experimental animals and medicinal substances, the

software studies, the physical stability of the myrtenal emulsions, the planning of the behavioral tests of the experimental animals, the biochemical studies and the selection of the statistical packages, it can be definitively concluded that all the materials and methods have been selected adequately and objectively ensure the scientific value of the obtained results.

The PhD student and his supervisor significantly demonstrate an excellent taste for perfectionism and comprehensiveness in the selection and arrangement of materials and methods.

4. RESULTS ANALYSIS

The results are structured in 6 directions: 1. Physicochemical characteristics of myrtenal conjugates; 2. Predicting the potential targets of myrtenal conjugates with aminoadamantane using SwissADME software; 3. Physical stability of myrtenal emulsion and MAC-197 and MAC-198 solutions for intraperitoneal administration; 4. Experiments on intact rats; 5. Experiments with rats with induced dementia; 6. Comparing the effects of myrtenal derivatives.

The presented results are reliable and correspond to the set aims and objectives. Their comprehensiveness is impressive, they are presented in extreme detail, shown for the most part in tabular and graphic form, which guarantees clarity, traceability and credibility. The statistical analyzes are impressive – they are done professionally, easy to read and presented comprehensibly.

5. CONTRIBUTIONS AND SIGNIFICANCE OF THE DEVELOPMENT

The author derives and formulates conclusions in 7 fields with a scientific-theoretical and scientific-applied nature.

1.The physicochemical properties of synthetic myrtenal conjugates with aminoadamantane (MAC-197 and MAC-198) favor their passage through the blood-brain barrier, have the ability to connect with structures in the CNS and thus influence various neurotransmitter systems and regulatory processes. **2.**The multiple intraperitoneal administration of myrtenal conjugates with aminoadamantane did not cause negative effects on memory processes in intact rats, no general toxic effects was found and no macroscopic damage to the internal organs was recorded. **3.**Molecular modeling indicates that brain AChE is a plausible target for aminoadamantane conjugates of myrtenal. **4.**Myrtenal analogs demonstrate pronounced neuromodulatory properties. **5.**Myrtenal analogues have pronounced antioxidant properties and correct oxidative stress. **6.**Myrtenal conjugates with aminoadamantane have more distinct anticholinesterase, antioxidant and neuromodulatory properties compared to the

natural referent. 7. Complex neuroprotective mechanisms of the two studied substances are established.

In conclusion, the author formulate and brings out contributions in 5 directions, which I fully accept!

1. The neuropharmacological effects of newly synthesized conjugates of myrtenal with aminoadamantane have been studied for the first time.
2. The neuroprotective potential of aminoadamantane derivatives was established for the first time.
3. The potential of the newly synthesized substances to influence diseases associated with an imbalance of noradrenergic and serotonergic neurotransmission has been revealed.
4. The synthetic conjugates were found to possess specific neuroprotective properties that were more pronounced in memory-impaired rodents than in healthy ones.
5. The original data obtained for the first time in this study reveal the greater effectiveness of synthetic conjugates of myrtenal with aminoadamantane, compared to the starting natural product, which is a basis for their future development as neuroprotective agents in memory disorders.

6. EVALUATION OF SCIENTIFIC PUBLICATIONS

The PhD student presents 2 scientific publications and 5 participations in national and foreign scientific forums. The presented scientific production corresponds to the PhD thesis and meets the requirements for this type of indicators.

CONCLUSION:

MASTER OF PHARMACY STELA TOSKOVA DRAGOMANOVA, PhD is completed highly qualified pharmacist and pharmacologist. A broad pharmaceutical competence of the PhD student is evident, which accounts for the demonstrated ease of entering the depths of medical knowledge, evident in all sections of PhD thesis submitted for review! I admire this scientific work, and due recognition must be given to both the PhD student and his supervisor and scientific consultant!

I POSITIVELY EVALUATE the PhD thesis on the topic: "NEUROPHARMACOLOGICAL STUDY OF MYRTENAL CONJUGATES WITH AMINOADAMANTANE"!

I will vote **"FOR"** the award of the Educational and Scientific Degree **"PHILOSOPHY DOCTOR"** of **Master of Pharmacy STELA TOSHKOVA DRAGOMANOVA, PhD!**

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

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