

# **R E C E N S I O N**

**From**

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**Member of the scientific jury on the basis of order R-109-119/18.03.2022 of the  
Rector of the Medical University-Varna and appointed for preparation of an opinion  
according to protocol 1/22.03.2022.**

**SUBJECT:** Public defense of the dissertation of Nadia Borislavova Hadjieva for obtaining the educational and scientific degree "Doctor" in the field of higher education 7. Health and Sports, 7.3. Pharmacy and doctoral program "Pharmaceutical Chemistry" with the topic of the dissertation: "Synthesis, structure and properties of new iodine derivatives of natural aromatic acids". Scientific supervisor of the dissertation is: Assoc. Prof. Svetlana Fotkova Georgieva, Ph.D.

For the preparation of the review I was given the dissertation and the abstract to the dissertation of the candidate.

## **Biographical data of the candidate**

Nadia Borislavova Hadjieva was born on February 25, 1968. In 2018 she graduated as a "Master Pharmacist" at the Faculty of Pharmacy at MU-Varna with excellent results.

In 2019, by Order of the Rector of MU-Varna (№ P-109-42 / 01.02.2019) she was enrolled as a full-time doctoral student at the Department of Pharmaceutical Chemistry at the Faculty of Pharmacy at MU-Varna in the field of Higher Education 7 "Health and Sports", professional field: 7.3. "Pharmacy", doctoral program: "Pharmaceutical Chemistry" with supervisor Assoc. Prof. Svetlana Fotkova Georgieva, Ph.D. In 2022 with Order № P-109-119 / 18.03.2022. was expelled with the right to protection for up to one year.

### **Structure of the dissertation**

The dissertation is described on 113 standard pages, including the following chapters: Introduction, Theoretical part, Aims and objectives, Results and discussion, Conclusions, Contributions, List of publications related to the dissertation, References and Appendices. A total of 60 figures and 14 tables are included to illustrate the scientific work and 148 literature sources are cited. I have no remarks about the structure of the dissertation.

### **Relevance of the dissertation**

Organohalogen and in particular organoiodine derivatives are of interest to science due to their wide range of applications in medicine. X-ray contrast iodine-containing substances have become established as a standard in diagnostics. The development of new such compounds, the preparation of protocols for their detailed analysis and the determination of their biological behavior will contribute to the enrichment of knowledge in this field. Therefore, I believe that the topic under consideration is relevant with a scientific and applied focus.

## **Purpose and tasks**

The goal is clearly and precisely formulated and is the synthesis and study of structural features and some of the biological manifestations of a series of new organoiodic substances and evaluation of their potential in the synthesis of other compounds. The main tasks set by the dissertation are seven, and they follow the original goal and could be summarized as follows:

- Synthesis of tri- and tetraiod substituted aromatic acids derived from amidotriazoic acid
- Study of the effectiveness of various iodizing agents for the synthesis of 2,6-diiodo-3,4,5-trimethoxybenzoic acid (DITMBA), structural characterization of DITMBA by FTIR and NMR, as well as its antimicrobial, gene- and cytotoxic activity
- Conduction of synthesis of meta-terphenyl derivatives
- Synthesis of organic co-crystals with DITMBA

## **Materials and methods used**

The experimental part lists the materials and methods used in great detail. The dissertation shows that she has mastered a wide range of analytical methods used - IR, MRI, HPLC, etc., as well as the main synthetic methods for obtaining organohalogen substances. Methods for assessing the antimicrobial potential, gene and cytotoxicity of the obtained compounds have been applied.

It is extremely important for the acquisition of this scientific title is the mastery of the largest possible set of methodologies that can be applied to contribute to the proof of a thesis. The task that the PhD student handle with.

## Results, discussion, conclusions and contributions

The results, following the pre-set tasks, are visually presented using a number of figures, tables, diagrams and photographs, which show that the dissertation is able to present the necessary evidence for his dissertation work. The more important results could be summarized as follows:

- Synthesis of a new organoiodic compound - 2,6-diiodo-3,4,5-trimethoxybenzoic acid (DITMBA) was performed with optimization of the conditions in order to increase the yield and purity
- The unique spectral behavior of DITMBA has been established in order to study the molecular structure in detail
- The antibacterial potential of DITMBA was established, while low genotoxicity was reported using the *Allium cepa* test.
- The co-crystallizing ability of DITMBA was determined with two antibacterial drugs - Nitrofurantoin and Metronidazole. The obtained products were characterized by radiographs and ATR-FTIR spectra.
- A new approach for the synthesis of triiodosubstituted aromatic acids, analogues of the pharmacopoeial amidotriazoic acid, has been proposed.
- Synthesis of two new meta-terphenyl derivatives with a central 3,4,5-trimethoxybenzoic carboxyl motif was performed.

The discussion is united in the chapter with the presented results. Mixing the two generally reduces the possibility of a more detailed discussion on the results obtained to show the mastery of this part of the dissertation. In some parts, such as testing for biological activity, there is a lack of in-depth discussion, comparison of the results with those of other authors and seeking explanations for the observed effects. The literature sources used are not uniform and a relatively small part is from the last five years.

The conclusions that have been made are 8 in number. Four contributions were presented without specifying whether they were of original scientific, scientific-applied or confirmatory nature. What is striking is that some of the conclusions overlap with those of the contributions.

### **Publishing activity**

The dissertation has presented three publications in connection with the dissertation, one of which is in an international journal with IF 3.196 (Journal of Molecular Structure), which meets the requirements for the acquisition of PhD.

### **Conclusion**

The dissertation covers a current topic and meets the necessary criteria. It fully complies with the Law on the Development of the Academic Staff in the Republic of Bulgaria, both the Regulations for its implementation and the PRAS of MU-Varna for the acquisition of ONS "Doctor". Based on this, I give a **POSITIVE EVALUATION** and suggest the esteemed members of the Scientific Jury to vote for the award of the educational and scientific degree "Doctor" in the field of higher education. 7. Health and sports, professional field 7.3. Pharmacy and scientific specialty "Pharmaceutical Chemistry" by Nadia Borislavova Hadjieva.

Varna

10.06.2022

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Assoc. Prof. Kaloyan Georgiev, PhD, DSc

