STANDPOINT

By Assoc. Prof. Velichka Yordanova Andonova, Ph.D.

Head of the Department of Pharmaceutical Technologies, Vice Dean "Educational Affairs, Accreditation and Quality" at the Faculty of Pharmacy, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna

Appointed as an internal member of the Scientific Jury by order № P-109-119 / 18.03.2022 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov "- Varna

Subject: *Ph.D. dissertation to acquire the educational and scientific degree "Doctor."*

Field of higher education: *7. Health and sports*

Professional field: *7.3. Pharmacy*

Doctoral program: *Pharmaceutical Chemistry*

Title: *Synthesis, structure and properties of new iodine derivatives of natural aromatic acids*

Author: *Nadya Borislavova Hadzhieva*

Form of doctoral studies: *Full-time Ph.D. student, enrolled by order № P-109- 42 / 01.02.2019 of the Rector of the Medical University" Prof. Dr. Paraskev Stoyanov "- Varna*

Scientific supervisor: *Assoc. Prof. Svetlana Georgieva, Ph.D.*

Department: *"Pharmaceutical Chemistry" at the Faculty of Pharmacy of the Medical University "Prof. Dr. Paraskev Stoyanov "- Varna*

General presentation of the procedure

The set of materials presented by the Ph.D. student Nadya Borislavova Hadzhieva is under Art. 69 of the Regulations on academic staff development at Medical University Prof. Dr. Paraskev Stoyanov - Varna (MU-Varna).

She is a full-time Ph.D. student in the Department of Pharmaceutical Chemistry at the Faculty of Pharmacy at MU-Varna with scientific supervisor Assoc. Prof. Svetlana Georgieva, PhD (Order № P-109-42 / 01.02.2019). During her preparation, she strictly followed the procedure regarding the requirements of full-time doctoral studies, as evident from the submitted documents. Therefore,

Nadya Borislavova Hadzhieva has the right to defend the dissertation by Order № P-109-119 / 18.03.2022.

The Ph.D. student has submitted 3 (three) scientific publications, of which 1 (one) in a journal with IF, all related to the dissertation's topic.

Brief biographical data about the Ph.D. student

Nadia Borislavova Hadjieva was born on February 25, 1968. She completed her higher education in Pharmacy with a Master's degree in 2018 at the Faculty of Pharmacy at MU-Varna. By Order № P-109- 62 / 01.02.2019, she was enrolled as a full-time Ph.D. student in the Field of higher education 7. Health and sports, Professional field 7.3. Pharmacy in the doctoral program: "Pharmaceutical Chemistry" with scientific supervisor Assoc. Prof. Svetlana Georgieva, Ph.D. at the Department of Pharmaceutical Chemistry of the Faculty of Pharmacy at MU-Varna. With Order № P-109-120 / 21.03.2022, she is deducted with the right to the dissertation defense. From June 2020 to the present, Nadia Hadjieva has worked as a Master Pharmacist at Pharma Dynamics Ltd.

Structure and sections of the dissertation

The dissertation is 113 standard pages long and includes the following main elements: Introduction; Theoretical part (33 pages); Goals and objectives (1 page); Experimental part (13 pages); Results and discussion (48 pages); Conclusions (1 page); Contributions (1 page); List of publications related to the dissertation (1 page); References (8 pages) and Appendices. The work contains 60 figures and 14 tables. One hundred forty-eight literature sources are cited. The dissertation structure follows the procedure for acquiring the educational and scientific degree "Doctor" and the Regulations at MU-Varna.

Relevance of the topic and practicality of the set goal and tasks

The synthesis of new iodine-containing organic compounds with potential applicability in pharmaceutical practice is of undeniable interest given their known properties, which determine their wide application as antiseptics and disinfectants. Furthermore, developing new radiopharmaceutical products for diagnosis and treatment of the needs of nuclear medicine is again of great importance. In this regard, expanding the number and spectrum of activities of organic iodine derivatives is a topical issue, and the topic is strictly dissertable.

The dissertation aims to synthesize and study the structural features and some of the biological properties of a series of new organoiodic substances and evaluate their potential in the synthesis of other substances. To achieve the set goal, 7 specific tasks have been formulated accurately and logically.

Research methodology and results analysis

To fulfill the set tasks, an appropriate method for preparing a series of tri- and tetraiodosubstituted aromatic acids, derivatives of Amidotrizoic acid, and synthesis of the new 2,6-diiodo-3,4,5-trimethosibenzoic acid (DITMBA), and several meta-terphenyl derivatives have been formulated and implemented. Correct and detailed structural characterization of the synthesized compounds was performed using modern instrumental methods (^{1}H NMR, ^{13}C NMR). The presented interpretation of the obtained FTIR spectra confirms the proposed structures. In addition, modern techniques have been used to study the X-ray properties of DITMBA. It has been found to have properties comparable to those of clinically administered Urografin and Ultravist. The method of the quartz-crystalline microbalance for the study of the total iodine content was also applied, and the results were compared with those of titrimetric determination.

The Ph.D. student completed the chemical part of her research with those on the production of DITMBA cocrystals with two antibacterial drugs – Nitrofural and Metronidazole. The obtained products were characterized by X-ray and ATR-FTIR spectra.

The potential gene- and cytotoxicity of newly derived DITMBA were assessed using the *Allium cepa* test. The results obtained indicate the presence of a dose-dependent cytotoxic effect for DITMBA and a lack of genotoxicity.

The results of studies on antimicrobial activity against *St. aureus* and *E. Coli* lead to the observation of minimal antibacterial activity against selected strains of *St. aureus* and *E. coli* with MICs of 0.375 mg / mL and 0.75 mg / mL, respectively. Therefore, the MIC value = 3.00 mg / mL obtained in the study could not be considered a manifestation of antifungal activity against *Candida albicans*.

Conclusions, contributions, and significance of development for science and practice

8 conclusions correctly reflect the results of the work

The dissertation is characterized by the following contributions defined by the author:

1. A new organoiodic acid, 2,6-diiodo-3,4,5-trimethoxybenzoic acid (DITMBA), has been synthesized and studied in detail.
2. The influence of ortho-positioned iodine atoms on the structural and spectral behavior of the carboxyl DITMBA functional has been established.
3. Two new meta-terphenyl acids have been synthesized.
4. A new, effective microbiological method for testing poorly soluble organoiodic compounds has been developed.
5. Allium cepa test applied for the first time on an organoiiodic substance.

My detailed acquaintance with the dissertation of Nadya Borislavova Hadjieva showed that there are both scientific-theoretical and scientifically-applicable contributions, which are original and are defended in the presented work.

Evaluation of the publications on the dissertation

In connection with the dissertation, 3 scientific articles have been published, one of which is in a journal with IF. There are no data that parts of the dissertation have been presented at national and international scientific forums. The proposed works logically reflect the results obtained by the dissertation.

Personal contribution of the Ph.D. student in the dissertation research

The personal contribution of the Ph.D. student in the review of the problem, formulation of the goals and tasks, conducting the experimental research, analysis of the results, and the derived contributions is available. An in-depth understanding of the specific subject and free terminology in the dissertation is evident. In addition, there is the ability to present and describe the scientific results and the supervisor's support.

Extended abstract

The abstract is prepared on 60 pages, according to the requirements. It includes the purpose, tasks, and a description of the materials and methods used. The presented research and discussion fully reflect the main results achieved in the dissertation. The obtained results are illustrated with a sufficient number of figures and tables. The conclusions coincide with those in the dissertation. Scientific contributions and a list of publications in connection with the dissertation are included. Getting acquainted with the abstract allows one to understand the developed problem, the research conducted, and the interpretation of the results.

Critical remarks and recommendations

After my acquaintance with the dissertation, I would like to ask the Ph.D. student the following question: How do you assess the application of the co-crystallizing ability of DITMBA that you have identified to these four N-containing pharmacopoeial agents?

I want to point out that the observed inaccuracies are technical and do not reduce the achievements of the Ph.D. student and the scientific value of the research performed.

CONCLUSION

The dissertation of Nadya Borislavova Hadzhieva contains original scientific and applied results, which are a contribution to science and meet all the requirements of the Higher Education Act, the Act on Development of the Academic Staff in the Republic of Bulgaria, Regulations on the implementation of the Development of Academic Staff in the Republic of Bulgaria Act, and the Regulations on Academic Staff Development at Medical University Prof. Dr. P. Stoyanov - Varna.

Due to the above, **I confidently give my positive assessment of the research presented by the above peer-reviewed dissertation, abstract, results, and contributions. Therefore, I invite the esteemed Scientific Jury to award the educational and scientific degree "Doctor" of Nadya Borislavova Hadzhieva in the doctoral program in "Pharmaceutical Chemistry," Professional field 7.3 "Pharmacy," field of higher education 7. Health and sports.**

10.06. 2022

Varna

Reviewer: .....

(Assoc. Prof. Velichka Andonova, Ph.D.)