

STANDPOINT

from

assoc. prof. Maya Boyanova Georgieva, PhD, Faculty of Pharmacy, Medical University – Sofia, appointed a member of a scientific jury on the grounds of Art. 4, para 1 and 2, ZRASRB, Decision of the Faculty Council of the Faculty of Pharmacy at MU - Varna and order of the Rector № P-109-119 / 18.03.2022.

for obtaining the educational and scientific degree "Doctor" in the field of higher education: 7. Health and sports: 7.3. Pharmacy; scientific specialty: Pharmaceutical Chemistry

from master of pharmacy Nadya Borislavova Hadzhieva, PhD student under the doctoral program "Pharmaceutical Chemistry", enrolled by order № P-109-42 / 01.02.2019 at the Department of Pharmaceutical Chemistry at the Faculty of Pharmacy, MU - Varna with the topic: „**Synthesis, structure and properties of new iodine derivatives of natural aromatic acids**“ with supervisor assoc. prof. Svetlana Georgieva, PhD.

Biographical data:

Nadya Borislavova Hadzhieva was born on February 25, 1968. In 2018 she graduated with a Master's degree in Pharmacy from the Faculty of Pharmacy at the Medical University of Varna. By Order № P-109-42 / 01.02.2019 she was enrolled as a full-time PhD student at the Department of Pharmaceutical Chemistry at the Faculty of Pharmacy at MU-Varna in the field of Higher Education “7. Healthcare and sports”, professional field: “7.3. Pharmacy”, doctoral program: “Pharmaceutical Chemistry” with supervisor assoc. prof. Svetlana Georgieva, PhD. With Order № P-109-119 / 18.03.2022 was expelled with the right to protection for up to one year.

The presented dissertation covers research in an interesting scientific field related to the participation in the development of new drugs including in its structure one or more halogen elements. Research in the field of organoiodic substances and their structure will be useful for organic and medicinal chemistry by providing opportunities for the application of the described synthetic methods in the production of useful products for radiopharmaceuticals in order to expand the number and range of activities of organic iodine derivatives.

The dissertation is written on 113 standard pages and includes the following main elements: Introduction, Theoretical part, Goals and objectives, Experimental part, Results and discussion; Conclusions, Contributions, List of publications related to the dissertation, References and Appendices. The work contains 60 figures and 14 tables. 148 references are cited.

The aim of the dissertation submitted for my opinion is synthesis and study of the structural features and some of the biological manifestations of a series of new organoiodic substances and assessment of their potential in the synthesis of other substances. To achieve it, 7 specific goals have been set, formulated accurately and in a logical sequence.

For realization of the set goals an appropriate method for preparation of a series of tri- and tetraiodosubstituted aromatic acids, derivatives of *Amidotrizoic acid*, as well as for the synthesis of the new 2,6-diiodo-3,4,5-trimethoxybenzoic acid and several *meta*-terphenyl derivatives. In

addition, a correct and detailed structural characterization of the synthesized compounds was performed using modern instrumental methods, and the presented interpretation of the obtained FTIR spectra fully confirms the proposed structures. The chemical part of the dissertation ends with research on the production of cocrystals of 2,6-diiodo-3,4,5-trimethoxybenzoic acid (DITMBA) with two antibacterial drugs - Nitrofurantoin and Metronidazole. The obtained products were characterized by radiographs and ATR-FTIR spectra.

The next step was to evaluate the potential genotoxicity and cytotoxicity of the obtained DITMBA using the *Allium cepa* test, and the results showed a dose-dependent cytotoxic effect of the 2,6-diiodo-3,4,5-trimethoxybenzoic acid and no genotoxicity.

The results of studies on antimicrobial activity against *St. aureus* and *E. coli*, as well as on antifungal activity against *Candida albicans* 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. The value of MIC = 3.00 mg / ml obtained in the antifungal activity study, in my opinion, could not be considered as a manifestation of antifungal activity against *Candida albicans*.

The dissertation presented for my opinion is characterized by the following contributions, defined by its authors:

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

The extended abstract is prepared on 60 pages in accordance with the established requirements and reflects the most significant moments of the dissertation. The extended abstract correctly reflects the main applications and scientific-applied contributions of the dissertation.

The dissertation is in accordance with the requirements set out in the Regulations on the terms and conditions for obtaining scientific degrees and for holding academic positions at MU - Varna in its part concerning the conditions for obtaining the educational and scientific degree "Doctor" and its essence corresponds to professional field 7.3. Pharmacy ("Pharmaceutical Chemistry").

The results of the scientific research in the field of the dissertation are reflected in 3 scientific publications, one of which in a journal with IF. There are no data that parts of the dissertation have been presented at national and international scientific forums. The presented papers logically reflect the results obtained by the dissertation.

Questions:

After reading the dissertation the following questions arose:

1. Why the 3,4,5-trimethoxybenzoic acid was selected as the starting product?
2. Has the cytotoxic and genotoxic effects of the parent 3,4,5-trimethoxybenzoic acid been studied?
3. Has the antibacterial and antifungal activity of the parent 3,4,5-trimethoxybenzoic acid been studied?
4. What is the application of the obtained organic cocrystals?

I would like to note that the observed inaccuracies are of a technical nature and do not reduce the achievements of the doctoral student and the scientific value of the research.

Conclusion:

The dissertation is dedicated to a topical issue. The research has been conducted at the scientific level and the results are of scientific and applied orientation. In terms of volume, overall design and scientific publications in connection with it, the dissertation meets the requirements for obtaining an educational and scientific degree "Doctor". The scientometric parameters are in accordance with the requirements of the Law for the development of the academic staff in the Republic of Bulgaria, the Regulations for its implementation and the Regulations of MU - Varna.

This gives me reason to give a **positive assessment** of the dissertation on " Synthesis, structure and properties of new iodine derivatives of natural aromatic acids" and to recommend to the distinguished members of the Scientific Jury to vote positively for the award of mag. farm. **Nadya Borislavova Hadzhieva** of the educational and scientific degree "**Doctor**" in the professional field: 7.3. Pharmacy; scientific specialty: Pharmaceutical Chemistry, according to the Law for development of the academic staff in the Republic of Bulgaria.

Sofia
08.06.2022 г.


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/assoc. prof. Maya Georgieva, PhD/