

# REVIEW

by

prof. Maya Boyanova Georgieva, PhD, Faculty of Pharmacy, Medical University – Sofia, designated as a member of a scientific jury on the basis of Art. 4, paras 1 and 2, ZRASRB, Decision of the Faculty Council of the Faculty of Pharmacy at the Medical University of Varna and order of the Rector No. R-109-545/05.12.2023.

for the acquisition of an educational and scientific degree "**doctor**" in the *Higher Education Region: 7. Health care and sports; Professional direction: 7.3. Pharmacy; Doctoral program: Pharmaceutical Chemistry*

from M.Sc. Pharm. Tanya Nedelcheva Dimova, full-time doctoral student in the "Pharmaceutical Chemistry" doctoral program, enrolled by order No. R-109-385/08.10.2020 at the Department of Pharmaceutical Chemistry at the Faculty of Pharmacy, MU - Varna with the topic: "**New aromatic iodine derivatives - synthesis, structure, properties**" with scientific supervisors assoc. prof. Svetlana Fotkova Georgieva, Ph.D. and assoc. prof. Iliyan Nikolov Kolev, Ph.D.

## **Procedural data:**

The necessary set of materials presented by the doctoral student in paper and electronic media is in accordance with Art. 69 of the Regulations for the Development of the Academic Staff at the MU - Varna dated 21.11.2022, including: Dissertation work; Abstract in Bulgarian and English; Application to the Rector for the disclosure of a protection procedure; Autobiography; A copy of a diploma for a completed higher education educational-qualification degree OKS "Master" with its annex; Enrollment order; Minutes of an exam held for the doctoral minimum; Minutes of a language exam; Minutes from the CC with a positive decision on the readiness for protection; Deduction Order with Right of Defense; Declaration of originality; List of publications related to the topic of the dissertation; A copy of the publications related to the topic of the dissertation; Declaration of authenticity of the submitted documents; Declaration for registration of profiles in scientific databases; Similarity Reference; Evidence of an up-to-date scientific profile in Google Scholar and ORCID; Certificate of recognized specialization in Drug Technology with Biopharmacy.

## **Biographical data:**

Tanya Nedelcheva Dimova was born on 23.03.1982. The training passed successively through the acquisition of the OKS "bachelor" with the professional qualification "biologist" in 2006 from Sofia University "St. Kliment Ohridski", after which in 2010 she obtained a bachelor's degree from the UCTM - Sofia with the professional qualification "chemical engineer". In 2010, she completed her higher education in the specialty "pharmacy" with a master's degree in the Faculty of Pharmacy of MU-Sofia. In addition, in 2019 she acquired the educational and scientific degree "doctor" in scientific specialty 5.10. Chemical Technology (Composite Materials Technology), and 2020 majored in Drug Technology with

Biopharmaceutics. By Order No. R-109-385/08.10.2020 of the Rector of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna is enrolled as a full-time doctoral student in the doctoral program "Pharmaceutical Chemistry" in the field of higher education 7. Health care and sports, professional direction 7.3 Pharmacy, with the topic of the dissertation work: "New aromatic iodine derivatives - synthesis, structure, properties" and scientific supervisors – assoc. prof. Svetlana Fotkova Georgieva, Ph.D. and assoc. prof. Iliyan Nikolov Kolev, Ph.D.. With Order No. R-109-545/05.12.2023. is charged with the right of defence.

The work experience of the doctoral student began in 2011, when she was appointed to the academic position of "assistant" in Pharmaceutical Chemistry and Pharmaceutical Analysis in the Department of "Pharmaceutical Sciences and Pharmaceutical Management" of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, and from 2019 to the present she holds the position of AD "chief assistant" at the same University.

**The Dissertation** complies with the requirements laid down in the Regulations for the terms and conditions for acquiring scientific degrees and for holding academic positions in the Medical University - Varna in its part concerning the conditions for acquiring the educational and scientific degree "doctor" and its essence corresponds to a professional direction 7.3. Pharmacy ("Pharmaceutical Chemistry").

The PhD thesis is written on 101 standard pages and includes the following main elements: Introduction, Theoretical part, Aim and tasks, Experimental part, Results and discussion; Conclusions, Contributions, Publication of results and References. The work contains 29 figures, 75 diagrams and 10 tables. 213 titles were cited.

The presented dissertation covers research aimed at the synthesis and detailed structural characterization of new iodo-, bromo- and mixed halogen-substituted aromatic compounds characterized by potential in the field of pharmaceutical synthesis and also in imaging diagnostics. In addition, emphasis is placed on methods for growing single crystals of each compound obtained, with the aim of unambiguously proving the structure of the compounds obtained. In addition, the toxicity of some of the obtained derivatives was determined, and the possibility of making real physical phantoms of them with application in contrast-enhanced mammography was separately evaluated..

The developed dissertation is located in an up-to-date scientific field related to the assessment of the possibilities of applying the obtained new iodo-, bromo- and mixed halogen-substituted aromatic compounds as radio-contrast substances in the diagnostic analysis.

**The theoretical part** of the dissertation examines in detail the pharmaceutical application, both of iodine and its salts and isotopes, and of a set of iodoarenes.

The advantages and disadvantages of a wide range of synthetic approaches used to prepare iodoarenes based on the inclusion of a wide variety of catalysts, polarizing the iodine molecule or activating reagents favoring the preparation of highly reactive electrophilic  $I^+$  forms are discussed in detail.

A substantial part of the review is directed to the methods for the synthesis of *ortho*-diiodo substituted aromatic acids.

In addition, the possibility of applying the organoiodine compounds as tissue-imitating and diagnostic materials in contrast diagnostics is briefly presented..

Despite its spaciousness and good structure, the theoretical part does not define clearly enough the objective of the dissertation, obtaining bromine-containing analogues. A brief comparison of the advantages and disadvantages of the two types of halogens would be a good conclusion to the overview.

**The purpose of the dissertation submitted to me for review** is the synthesis of new iodo-substituted compounds and their bromine-containing analogues, and the evaluation of their structural characteristics, toxicity and X-ray contrast properties. To achieve it, 5 specific **tasks** have been set.

Here I would say that for greater clarity of the purpose it would be useful to specifically define the type of iodo- and bromo-substituted derivatives. The goal thus set seems to me too broad.

**The experimental part** is divided into 4 sections, each of which describes in detail the methods and equipment used in the synthesis of the target iodo- and bromo-derivatives, as well as the approach to evaluating a new material based on "iodine" as the main tool on contrast-enhanced X-ray imaging.

In the **results and discussion part**, the doctoral student has characterized in detail, including the very useful X-ray structural analysis, 2 mono- and diiodo derivatives of 3,4,5-dimethoxybenzoic acid, of 2-iodo-3,4,5-trimethoxybenzaldehyde, as well as the corresponding mono- and di-bromo-3,4,5-trimethoxy benzoic acids.

It is worth noting the achieved optimization of the iodination and bromination methods of the starting polysubstituted aromatic acids, especially since the modifications proposed in the dissertation increase the eco-friendliness of the synthetic protocol.

However, the question remains puzzling to me as to why the newly obtained 2 compounds are so briefly mentioned at the end of the section. In my opinion, a detailed examination of precisely their synthesis and subsequent characterization would contribute to emphasizing the innovativeness of the work performed.

In conclusion, I believe that the addition of X-ray structural analysis of the newly obtained 2-(2-iodo-3,4,5-trimethoxyphenyl)acetic acid will confirm the successful synthesis and highlight the scientific value of the work.

#### **Critical notes and questions:**

I believe that when writing the dissertation work, there is a blurring and incorrect placement of information more suitable for the theoretical part, at the expense of a discussion element in the results and discussion part.

As a main note to the doctoral student, the insignificant characterization of her newly obtained compounds (her contribution) is formed at the expense of the detailed development of already published molecules.

I have the following questions for the PhD student:

1. Was the *in vitro* photoinduced toxicity of the two new compounds investigated?
2. Has the potential of the new compounds been explored to construct real physical phantoms designed for contrast-enhanced mammography?

The results of the conducted research are summarized in 7 well-defined **conclusions** reflecting the results of the conducted research.

**The Abstract** is prepared on 59 pages in accordance with the established requirements and correctly reflects the main results and contributions of the dissertation work.

### **Dissemination of the results**

The results of scientific research in the PhD thesis of the doctoral student are reflected in 4 scientific publications, in two of which the doctoral student is the first/last author, distributed as follows: 1 of the scientific reports in a journal with IF, 1 in an edition referenced and indexed in world-renowned databases with scientific information and 2 in non-refereed peer-reviewed publications. The absence of one of the scientific supervisors in the author collectives of the scientific publications accompanying the dissertation work is puzzling. The works presented logically reflect the results obtained by the doctoral student.

Parts of the dissertation work were financed through the participation of the doctoral student in a scientific project on the theme "Synthesis and structural analysis of new organo-iodine compounds - potential X-ray contrast agents" with supervisor assoc. prof. Iliyan Nikolov Kolev, Ph.D. and financed through the "Science" Fund at the MU - Varna.

### **Conclusion**

The dissertation is devoted to a current problem. The research was conducted at a 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 the educational and scientific degree "**doctor**". The scientific parameters are in accordance with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Rules for its Implementation and the Rules of the MU - Varna.

This gives me the reason to give a **positive assessment** of the dissertation work on the topic: "New aromatic iodine derivatives - synthesis, structure, properties" and to recommend to the respected members of the Scientific Jury to vote positively for the awarding of the educational and scientific degree "**doctor**" in the *Professional direction: 7.3. Pharmacy in Doctoral Program: Pharmaceutical Chemistry of M.Sc. Pharm. Tanya Nedelcheva Dimova*, according to the Law on the Development of the Academic Staff in the Republic of Bulgaria

Sofia

01.02.2024

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/prof. Maya Georgieva, PhD/