

REVIEW

by prof. Alexander Borisov Zlatkov, DSci,
lecturer in the Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University - Sofia, appointed a member of the scientific jury on the basis 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.

Subject: dissertation for the acquisition of ONS "Doctor" in the field of higher
education 7. *Health and sports*, professional field: 7.3. *Pharmacy* and doctoral
program: *Pharmaceutical Chemistry*

Topic: "Synthesis, structure and properties of new iodine derivatives of natural
aromatic acids"

Author: Master of pharmacy Nadya Borislavova Hadzhieva, full-time doctoral
student in the doctoral program "Pharmaceutical Chemistry", enrolled by
order № R-109-42 / 01.02.2019 at the Department of Pharmaceutical
Chemistry at the Faculty of Pharmacy, MU - Varna.

Scientific supervisor: assoc. prof. Svetlana Georgieva, PhD.

I. General presentation of the procedure and the doctoral student

The presented set of materials on paper and electronic media is in accordance
with Art. 69 of the Regulations for development of the academic staff in MU - Varna
from 15.09.2020 and includes the following documents:

- ✓ Application to the Rector for opening a protection procedure;
- ✓ Curriculum vitae with the signature of the doctoral student;
- ✓ Copy of the diploma for completed higher education, educational-
qualification degree Master's degree with the appendix to it;
- ✓ Enrollment order;
- ✓ Protocol of the doctoral minimum exam;
- ✓ Protocol of Department's council with positive decision on the readiness for
defense;
- ✓ Order for deduction with the right to protection;
- ✓ Declaration of originality;
- ✓ List of publications related to the field of the dissertation (not less than 3
publications) signed by the doctoral student;
- ✓ 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

The doctoral student has attached 3 (three) scientific publications, of which 1 (one) in a journal with IF and 2 (two) in refereed scientific journals, all related to the topic of the developed dissertation.

I have no notes or comments on the documents.

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

II. Brief description of the structure of the dissertation

The presented dissertation is written on 113 pages, of which 1 page introduction, 33 pages literature review, 1 page goals and objectives, 13 pages experimental part, 48 pages results and discussion, 1 page conclusions, 1 page contributions, 8 pages literature. The work includes 14 tables and 60 figures.

III. Relevance and dissertability of the development

As is well known, iodine is an essential element involved in ensuring the functioning of the thyroid gland and a large number of metabolic reactions. In addition, it has a disinfectant and antiseptic effect, which is why it is widely used in medical practice. Its radioactive isotopes are used as radiopharmaceuticals for the treatment and diagnosis of a number of neoplastic diseases. One of the typical applications of organic iodine derivatives is their use as X-ray contrast agents. In this regard, **the topic** of the dissertation developed by the doctoral student N. Hadzhieva is relevant and dissertable, given the need to expand the number and range of activities of organic iodine derivatives

On the other hand, some derivatives such as Riodoxol show antiviral activity (against *Herpes* viruses), antifungal activity (in *Microsporum*, *Trichophyton* and candidiasis) as well as bacteriostatic activity against some acid-resistant bacteria.

In this means, the search for new derivatives with improved pharmacokinetic properties and reduced side effects by targeted production of new iodine-containing organic compounds is fully justified.

IV. Critical analysis of the dissertation

The literature review (33 pages in total) is based on 148 Latin literature sources. The literature review shows the doctoral student's good awareness of the developed problem, is written concisely and with understanding, but at the same time is thorough and reflects the theoretical aspects of the synthesis and analysis of iodine-containing organic compounds. Due attention is paid to the use of iodine and iodine-containing organic compounds and their characteristic pharmacological effects.

The aim of the dissertation, correctly determined by the literature review, is set clearly and precisely. 7 specific **goals** have been identified for its implementation, formulated precisely and in a logical sequence.

Research methodology

In the section **Experimental part**, the PhD student has presented a detailed description of the methods used in this scientific paper. Their way of presentation shows that the dissertation is developed through appropriately and correctly selected methods, allowing to achieve the set goal and obtain an adequate response to the tasks solved in the dissertation. Methodologically well-constructed synthetic, analytical (mainly spectral), microbiological methods and in vitro experiments for evaluation of the cyto- and genotoxic action of the studied derivatives have been developed and applied. The methodology is not in doubt and is a prerequisite for obtaining the correct results discussed below.

Characteristics and evaluation of own research and contributions

In the section "**Results and discussion**" Hadzhieva describes in detail the obtained experimental results and at the same time presents their critical discussion.

The first part of her research is devoted to the synthesis and spectral characterization of the 2,6-diiodo-3,4,5-trimethosibenzoic acid obtained from it, as well as the preparation of several meta-terphenyl derivatives. The oscillations of the functional groups are considered in great detail.

The structural characterization of this and the other newly obtained compounds was performed correctly using modern instrumental methods. A detailed interpretation of the FTIR spectra is presented, which fully confirms the proposed structures. A comparative analysis of the spectra of 2-iodo-3,4,5-trimethosibenzoic and non-iodinated 3,4,5-trimethosibenzoic (eudesminic) acid was performed.

Modern methods were used to study the X-ray contrast properties of 2,6-diiodo-3,4,5-trimethosibenzoic acid, and it was found that it has properties comparable to those of clinically applied Urografin and Ultravist.

The total iodine content was studied by applying the method of quartz-crystal microbalance and the results were compared with those of titrimetric determination.

The comparison shows the obtaining of harmonic results. However, the proposed QCM method is far from routine application due to experimental difficulty.

The chemical part of the dissertation's own research ends with research on the production of cocrystals of 2,6-diiodo-3,4,5-trimethoxybenzoic acid with two antibacterial drugs - Nitrofurantoin and Metronidazole. The obtained products were characterized by radiographs and ATR-FTIR spectra. I find the conducted research to be an end in itself, aimed only at the theoretical study of the crystal structure of the obtained cocrystals, and in this sense devoid of applicability.

The last part of the research of the dissertation reflects the results of the research on the potential genotoxicity and cytotoxicity by testing the roots of *Allium cepa* L. The antimicrobial activity of the newly obtained compounds against strains of *St. aureus* and *E. coli*, as well as antifungal activity against *Candida albicans* was also studied. The results show a dose-dependent cytotoxic effect of the 2,6-diiodo-3,4,5-trimethoxybenzoic acid and no genotoxicity.

From the presented results for antibacterial and antifungal activity it is necessary to conclude that the tested compounds have minimal antibacterial activity compared to the used strains *St. aureus* and *E. coli* (MIC 0.375 mg / ml and 0.75 mg / ml, respectively). At MIC = 3.00 mg / ml in my opinion there can be no talk of antifungal activity against *Candida albicans*.

Conclusions (8 in number) are adequate and correctly reflect the results of the research.

V. Assessment of the publications and personal contribution of the doctoral student

In connection with the dissertation, 3 scientific articles have been published, and in one of the publications master-Pharm. Hadzhieva is a leading author. There are no data that parts of the dissertation have been presented at national and international scientific forums..

Regarding these scientometric indicators, the dissertation covers the requirements for awarding the educational and scientific degree "Doctor", laid down in the Regulations of MU - Varna.

VI. Extended abstract

The extended abstract (total volume of 60 pages) is made according to the requirements and accurately and sufficiently reflects the content of the dissertation.

CONCLUSION

The work is written in good scientific language, there are almost no typographical and grammatical errors in the text. In general, the dissertation deals

with a topical issue from a theoretical point of view. The set goals and tasks have been successfully fulfilled, and the doctoral student has mastered and used a number of modern synthetic, analytical and microbiological methods.

The dissertation contains mainly scientific and theoretical results, which represent an original contribution to research on the spectral behavior of iodine-containing aromatic derivatives and meet the requirements of the Academic Staff Development Act in the Republic of Bulgaria (RASRB), MU - Varna. The presented materials and dissertation results correspond to the specific requirements adopted in connection with the Regulations of MU - Varna for application of ZRASRB.

The dissertation shows that the doctoral student Nadya Borislavova Hadzhieva has the necessary theoretical knowledge and professional skills and demonstrates qualities and skills for independent research.

In view of the above, I give my *positive assessment* of the research presented by the above peer-reviewed dissertation, abstract, results and contributions, and I *propose to the esteemed scientific jury to award the educational and scientific degree "Doctor"* to master- pharmacist Nadya Borislavova Hadzhieva in a doctoral program in Pharmaceutical Chemistry.

Sofia.

30 May 2022

Reviewer:

(prof. Al. Zlatkov, DSci)

