

BRIEF REVIEW

by Prof. PhD Antoaneta Borissova Trendafilova, Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences of the Doctoral Thesis presented for awarding the degree “**Doctor of sciences**” in the field of higher education: 4. "Natural Sciences, Mathematics and Informatics"; professional field: 4.2. "Chemical Sciences"; scientific specialty: "Bioorganic chemistry, chemistry of natural and physiologically active substances"

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Topic: Phthalocyanine photosensitizers for photodynamic method towards drug resistance

1. General description of the presented materials

The documents presented by Assoc. Prof. Vanya Mantareva with respect to the thesis defence procedure are in accordance with the Regulations for the Development of the Academic Staff of the Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences (IOCCP – BAS), and meet the criteria of the Institute for obtaining the degree of “Doctor of Sciences”. Assoc. Prof. Vanya Mantareva has provided a Doctoral thesis, Abstracts in Bulgarian and English, a book chapter and 20 publications not included in the PhD thesis and published after the procedure for holding the academic position of "Associate Professor", as well as a list of 125 citations of these publications.

Assoc. Prof. Vanya Mantareva graduated from HICT-Sofia (now UCTM) in 1990 with a qualification of chemical engineer. She entered IOCCP-BAS in 1991, where she successfully defended her PhD dissertation in 1999. Over the years she has successively held the positions of specialist chemist, research assistant III, II and I degree. She was habilitated as an Associate Professor in 2014. From 1999 to 2003 she was a fellow at the Institute of Macromolecular Chemistry, the University of Bremen (Germany), the University of Luifil (USA) and the Autonomous University of Madrid (Spain).

2. Relevance of the topic

In recent decades, there has been a rapid increase in the drug resistance and a decrease in the effectiveness of the therapeutics used due to the natural evolutionary mutation of pathogenic microorganisms, as well as the improper human activity of antibiotic use, which requires the development of new photosensitizers for photodynamic therapy (PDT) as an alternative to traditional therapists. All this defines the topic of the dissertation as very interesting and relevant.

3. Knowledge of the problem

The literature review of the dissertation covers 157 literature sources, many of which have been published in the last 10 years and shows excellent knowledge of the problematics. The literature review provides a brief historical overview of the phthalocyanine chemistry and the application of photodynamic therapy, a detailed analysis of the mechanism of the method "photodynamic therapy", the importance of light as an important component for many biochemical and biological processes and PDT, the porphyrin derivatives and basic requirements for obtaining effective photosensitizers, the antimicrobial photodynamic therapy and the peculiarities of the pathogenic microorganisms, the mechanism of photosensitization, microbial resistance, as well as the achievements in the development of photosensitizers for biomedicine.

Significant place is given to phthalocyanines - structure, synthesis and mechanisms of production, basic photophysical and photochemical processes and their application in biomedicine. Guidelines for new research are outlined.

4. Research methodology

The methods applied are appropriate to the tasks set. Both classical and up-to-date methods in the field have been applied. Numerous chemical reactions have been performed to prepare the phthalocyanine compounds, some of them in an inert medium. Column chromatography was used to isolate the synthesized compounds in pure form. Various methods were applied to prove the structure of the obtained compounds, such as elemental analysis, Mass spectrometry (MALDI-TOF), IR and NMR spectroscopies. The photochemical and photophysical properties and photostability of the synthesized compounds were studied spectrophotometrically.

5. Characteristic and evaluation of dissertation thesis and contributions

The topic of the dissertation fully corresponds to the scientific specialty. The goals and objectives are clearly stated. The section "Results and discussion" contains 4 chapters set out on 108 pages and 205 references are cited. Known and new synthetic procedures for the synthesis of phthalocyanine complexes with various substituents are presented. Significant place is devoted to the study of the photochemical and photobiological properties of the obtained compounds. The relationship between molecular structure and composition and photodynamic activity in resistant pathogens is discussed. Based on the results obtained and their discussion at the end of each subchapter, the relevant more important conclusions are drawn.

The scientific contributions are clearly formulated and have both scientific and scientific-applied character. The synthesized over 40 new compounds and their studied photochemical, photophysical and photobiological properties can be defined as scientific contributions, containing novel and original information for the science. The development of a method for pharmacokinetic studies based on chemical extraction and the protocols for photobiological studies with light irradiation are contributions, both methodological and applied. They could also be used to study the photodynamic efficacy of other photosensitizers and other pathogens to determine the inactivation efficiency by photocytotoxic effect.

6. Assessment of the dissertation's publications and personal contribution

The results presented in the thesis are published in 20 scientific papers in international research journals, as well as one book chapter. Of them, 6 publications published in journals from the first quartile in the respective field (Q1), 2 – in Q2, 7 - in Q3, 3 – in Q4 and 2 – in journals with SJR. The number of the noticed citations of the publications included in the dissertation is 125. The most significant personal contribution of Assoc. Prof. Mantareva to the presented publications is obvious: she is the corresponding author of 13 out of 21 documents (publications and a bookchapter). The results of the dissertation were reported to 12 international scientific forums and were funded by 4 national and 1 international research projects. Assoc. Prof. Mantareva was the leader of two of the projects.

7. Abstract of dissertation

The abstract is in accordance with the dissertation and reflects the main results of the research. It also includes a list of publications included in the dissertation, as well as a list of projects that funded the research.

8. Critical remarks and recommendations

I have no criticisms to the dissertation. Some discrepancies have been noted between the data presented in the diagrams and figures, and in the text. For example, Ni-phthalocyanines (9,

9a, **10** and **10a**) are listed in Scheme 1.1.2 (p. 60) but not commented on in the text. Some structures of compounds are missing in the dissertation [**5** and **6** (p. 65), **4.2** (p. 111)], etc. They should present in the Results and Discussion section, not in the Experimental section. The English text appears in the text, tables and figures. It is quite confusing the presence of different compounds with the same numbers, sometimes in the same subchapter or those with acronyms only. For example, there are compounds with numbered **1**, **2** and **3** in the schemes 2.2.1 (p. 110) and 2.2.2 (p. 112), but in fact they are different compounds. With their sequential numbering in the order of appearance in the text, the dissertation would have a clearer and more complete form. I have a recommendation regarding translation of the term “derivatives” in Bulgarian.

CONCLUSION

The doctoral thesis contains substantial and significant original fundamental and applied scientific contributions, which meet all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for the implementation of the same Law and the corresponding Regulations of the IOCCP - BAS. The dissertation shows that Assoc. Prof. Mantareva has in-depth theoretical knowledge and professional skills in the scientific specialty "Bioorganic Chemistry, Chemistry of Natural and Physiologically Active Substances", demonstrating skills for conducting research with original and significant scientific contributions.

Based on the above, I give my **positive assessment** of the research presented by the dissertation, results and scientific contributions and propose to the Honourable Scientific Jury to award the degree “**Doctor of Science**” to Assoc. Prof. Vanya Mantareva, in the professional field 4.2. "Chemical Sciences"; scientific specialty "Bioorganic chemistry, chemistry of natural and physiologically active substances".

30.07. 2021 г.

Reviewer:

(Prof. Antoaneta Trendafilova, PhD)