

BRIEF REVIEW

By Prof. DSc Pavlinka Aleksandrova Dolashka, Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences

for PhD of Doctoral Thesis in the field of higher education: 4. "Natural Sciences, Mathematics and Informatics"; professional area: : 4.2. "Chemical Sciences"; scientific specialty "Bioorganic chemistry, chemistry of natural and physiologically active substances", 01.05.10.

Applicant: Assoc. Prof. Vanya Nikolova Mantareva, PhD, Chem. Ing., Lab. "Chemistry and Biophysics of the Proteins and Enzymes", Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences (IOCCP-BAS).

Title of the thesis: „PHTHALOCYANINE PHOTSENSITIZERS FOR PHOTODYNAMIC METHOD TOWARDS DRUG RESISTANCE”.

I. Biographical information

Dr. Vanya Mantareva has diploma from the High Institute of Chemical Technology – Sofia since the year 1990, and a diploma for PhD since 1999 r. after defense of the doctoral thesis in the Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences. Since 2014 she is appointed as Associate Professor in the Laboratory "Chemistry and Biophysics of Proteins and Enzymes", IOCCP-BAS.

II. An overview of the thesis

The files presented by the applicant as hard copies and on the electronic carrier, all are prepared according to the law on scientific development in Republic of Bulgaria, the Rules for the law application and the specific criteria in the IOCCP-BAS for the scientific degree "Doctor of Sciences".

The scientific topic of the thesis is original and very up-to-date because of the acceleration of the drug and multidrug resistance of pathogens towards the presently in usage chemotherapeutics. The thesis presents a well-developed method for tumors, such as Photodynamic therapy (PDT) with characteristics of non-specific and local action to the targets, with fast effect after a single application and without development of resistance as a result of the mechanism of the photosensitization process. The investigations have scientific contributions in several research fields, namely the development of new photosensitizers on the basis of the phthalocyanine macromolecule, which involves the synthetic schemes and the procedure as well as investigations of the new derivatives with chemical analyses and physicochemical methods.

The features and evaluation of the thesis

The thesis is an overview of twenty scientific papers which have 128 citations till April, 2021. The thesis contains 221 pages, 25 Tables and 83 Figures, Conclusions and Contributions. The thesis is well assembled, illustrated with plenty of graphical material. Each part finishes with a summary of the collected results and conclusions.

Introduction – the thesis starts with a short introduction about the topic of the research. The used References are written on 14 pages and consist 205 scientific papers and books, more of them are published after the year 2010.

Aim and Tasks – the main goal of the thesis is the development and studies of functionalized phthalocyanine complexes with metal and semimetal ions, and with substituents of chromophores and biologically-active compounds, and inhibitors with antibacterial properties, by following the new and the well-known synthetic procedures. The new derivatives are evaluated as photosensitizers for the PDT method as an actual and alternative therapy for resistant pathogens. This goal together with the formulated four research tasks are evidently realized.

Materials, Methods and Instrumental techniques – this part is properly described.

The materials are the solids, solvents and substances for synthesis and chemical characterization of phthalocyanine derivatives as complexes and as bioconjugates with sterols, galactopyranose, amino acids and inhibitor such as different parabens. The structure of the newly synthesized compounds are characterized with the modern analytical techniques with high resolution such as infrared spectroscopy (FT-IR), MALDI-TOF spectrometry, NMR, fluorescence spectroscopy and others.

The studies of photodynamic activity of the photosensitizers were carried out on the pathogenic bacterial strains of Gram (+) *Staphylococcus aureus* 1337, methicillin-resistant strain (MRSA); *A. actinomycetemcomitans*, *Streptococcus mutans* 20523 и *P. intermedia* 20706, as well as the fungus strain *Candida albicans* 74; Gram (+) *Enterococcus faecalis* and Gram (-) *Pseudomonas aeruginosa* 1390

Results and Discussion

The results included in the thesis are part of 20 scientific papers which described new complexes of phthalocyanines as photosensitizers for the PDT method with application towards resistant pathogenic species associated with acute infections.

1. The new phthalocyanine derivatives as complexes of the traditional ions for PDT photosensitizers such as zinc Zn(II) and silicon Si(IV), as well as the new ions which are not approved for PDT applications such as Lu(III), Sn(IV), Pd(II) and Ni(II).

2. The new original synthetic schemes are developed on the basis of the well-known from organic chemistry reactions, but with new reaction conditions to be used for phthalocyanine chemistry. The bioconjugates of phthalocyanines as complexes of Zn(II) are substituted with functional groups of amino acids linked with aminophenoxy group and amino bond to the main molecule; carbohydrates and parabens chemically linked through ether bond and the steroid linked through azidoethoxy group and triazole ring.
3. The studied physicochemical properties of the new phthalocyanine derivatives are presented. The photophysical characteristics of absorption and fluorescence, and the photochemical features concerning the singlet oxygen generation and the photostability are in agreement for the valuable potential photosensitizers for biomedicine.
4. The new method for pharmacokinetic and uptake studies was developed for the phthalocyanine dyes which involves a procedure of chemical extraction of the compound and the fluorescence measurements for quantitative evaluation of the amount of compound in pathogenic cells as well in tumors and normal tissues and cells.
5. The new derivatives characterized with relative high uptake behavior in the resistant Gram (+) and Gram (–) pathogenic bacteria and fungus *Candida albicans*, as well as for the early-stage biofilms.
6. The well-developed by this study, new approach in photobiology can be applied as the methodology for other photosensitizers beyond phthalocyanines and for other photogenic strains under research interest.

Contributions and significance of the results for the science and the practice

The conclusions and the contributions are formulated clearly. The presented conclusions and contributions have novelty and originality for the fundamental science and can be in use for the further invention in the clinical practice. The summary of the thesis is in both Bulgarian and English is according to the main contents.

III. Personal impressions

I know the applicant with her scientific achievements and the publications on this research topic. Nevertheless, more of the presented publications are in collaborations with different scientific groups local and from abroad, the leadership of the applicant is visible as a leader author.

IV. Conclusion

The theses for a scientific degree “Doctor of Sciences” presents a summary of the scientific achievements on research and development of phthalocyanine derivatives for the method Photodynamic therapy. The main physicochemical properties, cellular

uptakes and photodynamic activity are presented. The thesis is written shortly but the contribution to the science are well described. Assoc. Prof. Vanya Mantareva possess theoretical and practical knowledge in bioorganic and photochemistry, with qualities and expertise, and fully complies with the requirements of the Law for Scientific Development in Bulgaria, the Rules of its Application and the Regulations for its implementation, as well as the Internal Rules for the implementation of the Law at IOCCP-BAS.

In view of the above, I fully believe in my positive assessment of the research presented by the dissertation, abstracts, results and contributions reviewed above, and propose to the Honorable Scientific Jury to award the degree of Doctor of Science to Assoc. Prof. Dr. Vanq Mantareva, PhD in Higher Education: 4. "Natural Sciences, Mathematics and Informatics, Professional, area 4.2. "Chemical Sciences"; scientific specialty "Bioorganic chemistry, chemistry of natural and physiologically active substances", 01.05.10.

10.07. 2021 г.
Sofia

Reviewer :
(Prof. DSc P. Dolashka)