

OPINION

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On dissertation for awarding of the educational and scientific degree „**Doctor**“

In higher education field 4. “Natural sciences, Mathematics and Informatics“

professional classification 4.2. „*Chemical Sciences*“

PhD program „*Organic chemistry*“

Author: *Yordanka Dimitrova Sapundzhieva*

Tema: „*Synthesis of Quinoline Derivatives with Potential Antibacterial Activity*“

Scientific supervisor: *Dr. Plamen Angelov Angelov, Assoc. prof. at Paisii Hilendarski University of Plovdiv*

1. General presentation of the procedure and the PhD student

According to administrative act No. RD-22-265/04.02.2025 by the Rector of Paisii Hilendarski University of Plovdiv, I have been appointed as a member of the scientific jury in the doctoral thesis defense procedure. The title of the thesis is "Synthesis of quinoline derivatives with potential antibacterial activity" for the acquisition of the educational and scientific degree "Doctor" in the field of higher education 4. "Natural Sciences, Mathematics and Informatics", professional field 4.2. "Chemical Sciences", doctoral programme "Organic Chemistry". The author of the dissertation is Yordanka Dimitrova Sapundzhieva - PhD student in full-time studies at the Department of Organic Chemistry, Faculty of Chemistry, PU with scientific supervisor Assoc. Prof. Dr. Pam Angelov.

The set of paper materials submitted by PhD student Yordanka Sapundzhieva is in accordance with Article 36 (1) of the Regulations for the Development of the Academic Staff of PU and includes the following documents::

- - a request to the Rector of PU for the disclosure of the dissertation defense procedure;
- - CV in European format;
- - the minutes of the departmental council related to the reporting of the readiness to open the procedure and the preliminary discussion of the dissertation;
- - dissertation;
- - abstract;
- - list of scientific publications on the subject of the dissertation;
- - copies of the scientific publications;
- - declaration of originality and authenticity of the attached documents;

The PhD student has attached 6 publications, and evidence of participation in 3 scientific conferences, one of which with international participation.

2. Topical relevance

In the "post-antibiotic era", the search for new bioactive substances with antimicrobial potential is more than relevant. It is a challenge linked to saving lives. Quinoline derivatives have proven antimicrobial activity, but their potential is far from exhausted. The topic posed in this

Dissertation is focused, not only on the search for such new structures, but also on the development of a new approach for their synthesis. The relevance to science is undeniable: a new method for synthesis and the opportunity to elucidate reaction mechanisms. Moreover, the results obtained have practical applicability in pharmaceuticals.

3. Knowledge of the problem

The Thesis has a distinct "Literature Review" section that includes 40 pages of detailed introduction to the problem. 155 sources are reviewed. The information is arranged in several sub-items moving from the general to the PhD student's chosen subject of study, 4-quinolones. The methods known so far for their synthesis are compared and summarized. Also, the current knowledge of the biological activity of this group of organic compounds and their applications are presented in detail.

4. Research methodology

In order to achieve the objective set in the thesis, three different approaches were investigated for the synthesis of quinoline derivatives with potential antibacterial activity from β -ketoamides as starting compounds. Several well-defined tasks have been performed, including the synthesis of the starting β -ketoamides. Each structure (starting, intermediate and final product) has been proved and characterized by several analytical methods (Thin Layer Chromatography, NMR-, Mass-, IR-spectrometry) as well as by their Tt. Moreover, data from UPLC-MS analysis were used to elucidate the mechanism of cyclization (the last step of synthesis). The PhD student Yordanka Sapundzhieva has mastered excellently the methods and laboratory techniques used, not only in the field of Organic Synthesis, but also in the field of Analytical Chemistry.

5. Characteristics and evaluation of the thesis and contributions

The dissertation is written in 144 printed pages and contains 100 diagrams, 12 tables and 45 figures. The bibliographic reference comprises 155 references. The dissertation is divided into five main sections: Introduction, Literature Review, Results and Discussion, Experimental Section and Summary. Each chapter is presented comprehensively, with a preponderance of sections devoted to own research: 78 pages out of 131 pages of main manuscript. The conclusions and contributions are summarized as follows:

Three different approaches for the preparation of quinoline derivatives from β -ketoamides, which were obtained by an original method previously developed by the research team, were investigated.

A new method was developed for the preparation of 2-alkyl-4-quinolones, 2-alkyl-4-quinolone-3-carboxamides and their N-hydroxy derivatives, by which the two tautomeric forms of the bacterial toxin 2-nonyl-4-quinolone-N-oxide (NQNO) were isolated and characterized as individual compounds for the first time.

A method was developed for the preparation of 1,2-dialkyl-4-quinolone-3-carboxamides by intramolecular aromatic nucleophilic substitution in ortho-fluorobenzoylated enamine intermediates.

Six natural compounds of the 4-quinolone group, which are known metabolites of *P. aeruginosa* or plant alkaloids, as well as 37 new and unstudied structural analogues of these compounds were synthesized using the newly developed methods.

The behavior of γ -aminophenyl-functionalized β -ketoamides under Knorr-cyclization conditions in polyphosphoric acid was investigated, and two more types of products of competing cyclization processes were isolated along with the expected 2-quinolones.

The resulting new 4-quinolone derivatives were tested for antibacterial activity, in which several substances with potent activity against *S. aureus* and one substance with broad-spectrum activity against Gram-positive and Gram-negative bacteria were detected.

6. Assessment of publications and personal contribution of the PhD student

The experimental data in this Dissertation have been published in 5 peer-reviewed and in-designated high ranking journals, including one in a Q1 journal, one in a Q2 journal and three in a Q4 journal. A sixth article is under review and is currently available in preprint. Despite the recent years of publication (2023 and 2024), citations are also noticeable: 1 and three articles with different numbers of citations (from 1 to 4) are noticeable according to Scopus and Google-Scholar, respectively. In addition, the results were also promoted on forums with two papers and two posters.

7. Abstract

The abstract contains 32 pages and is written according to the requirements of the relevant regulations, focusing on the main results and scientific achievements of the Dissertation. It is presented as required - in the main language of the Dissertation and in English.

8. Recommendations for future use of the dissertation contributions and results

The dissertation is written in high academic language, with a very good style, concise and orderly. The material is easy to read and comprehend. Yordanka Sapun-Djieva, PhD student, developed this thesis with the support of two national projects and one international project. She worked together with scientists from the University of Alicante, Spain, colleagues from the Faculty of Biology of the Paisii Hilendarski University of Life Sciences, the University of Science and Technology in Plovdiv, as well as from the Institute of Organic Chemistry with the Centre of Phytochemistry at the Bulgarian Academy of Sciences, Sofia. The work can safely be defined as interdisciplinary, since the data were obtained not only by techniques and methods of organic synthesis, but also from the field of analytical chemistry and biological sciences, through which their great potential as biologically active substances has been proven.

I have no critical remarks. I would recommend to the PhD student Yordanka Sapundzhieva to continue her development in her chosen scientific field and to use and upgrade her competences and skills in the multidisciplinary field of bioactive substances for the benefit of human health!

CONCLUSION

The PhD thesis contains results with an original contribution to science and meet all the requirements of the Law for the Development of Academic Staff in the Republic of Bulgaria, the

Regulations for the Implementation of the law and the relevant Regulations of Paisii Hilendarski University. The dissertation work shows that the PhD student Yordanka Dimitrova Sapundzhieva possesses in-depth theoretical knowledge and professional skills in the scientific specialty "Organic Chemistry", demonstrating qualities and skills for independent scientific research.

Because of the above, I confidently give my positive assessment of the research presented in the above dissertation, abstract, results and contributions. I kindly recommend scientific jury to award the degree "Doctor" to Yordanka Dimitrova Sapundzhieva in the field of higher education. "Natural Sciences, Mathematics and Informatics", professional field 4.2 "Chemical Sciences", PhD program "Organic Chemistry".

14.03.2025 г.

Prepared by:

/Assoc. Prof. Milena Tzanova, DSc/