

REVIEW
by Prof. Mariana Dimitrova Argirova, DSc

of the dissertation for the award of the educational and scientific degree doctor (PhD) in the field of higher education 4. Natural Sciences, Mathematics and Informatics, professional field 4.2. Chemical Sciences, doctoral program "Organic Chemistry"

Author: Maria Valentinova Bachvarova – full-time doctoral student at the Department of Organic Chemistry, Faculty of Chemistry, Plovdiv University Paisii Hilendarski

Topic: Synthetic transformations of 2-aryl thiazole and benzothiazole compounds

Scientific supervisor: Assoc. Prof. Stella Mironova Statkova-Abeghe, PhD

1. General description of the procedure and the materials presented

By order No. RD-22-1002 of 15.05.2026 of the Rector of Plovdiv University "Paisii Hilendarski" (PU), I have been appointed as a member of the scientific jury in the procedure for the defense of a dissertation on the topic "Synthetic transformations of 2-aryl thiazole and benzothiazole compounds", presented by the doctoral student Maria Bachvarova for the acquisition of the educational and scientific degree "doctor". At the first meeting of the scientific jury, held on 19.05.2026, I was assigned to prepare a review of the dissertation. I received all the materials necessary for the preparation of this review in electronic format. They are in accordance with Art. 36 (1) of the Regulations for the Development of the Academic Staff of PU. The doctoral student has submitted a declaration of originality and authenticity of the documents presented, as well as a declaration that the results included in the dissertation are original and have not been copied from research and publications in which she has no participation.

2. Brief biographical data

Doctoral student Maria Bachvarova is a graduate of the Paisii Hilendarski University, where in 2019 she graduated as a bachelor with a degree in Medicinal Chemistry, and in 2020 she received a master's degree in the same specialty. She also has two postgraduate qualifications as a chemistry teacher and a specialist in chromatographic methods. She was enrolled as a full-time doctoral student in the doctoral program "Organic Chemistry" on 13.07.2022 till 15.07.2025 with the right to defend her thesis. She is currently a research chemist at the University of Food Technology – Plovdiv, Center for Research Projects and Technology Transfer (CIPTT), and, she is involved in the work on the project "Personalized Innovative Medicine" (PERIMED-2)

As a student and doctoral student, Maria Bachvarova participated in several theoretical and practical courses and seminars. She is a co-author of 11 scientific papers published in respected international journals. She is a member of the working teams of 5 national projects.

3. Goals and objectives of the dissertation and their implementation

The dissertation work, presented by the doctoral student Maria Bachvarova, further extends a traditional topic developed at the Department of Organic Chemistry – formation of a new carbon-carbon bond through amidoalkylation reactions. This method allows, by selecting appropriate nucleophiles, to obtain both known natural compounds and their analogues with potential biological activity. The advantages of this method are that most often it does not require isolation of intermediates (the so-called one-pot method) and under relatively mild conditions to obtain products with high yields.

The goal of the dissertation work is to develop effective synthetic approaches for transformations of 2-aryl/heteroaryl thiazole and benzothiazole compounds with the preparation of new functionalized analogues of natural and biologically active compounds. Five specific tasks have been formulated to achieve this goal. The results of the doctoral student's experimental work show that the set goal has been successfully achieved. Over 40 compounds were synthesized, including 3 new ferrocene-containing hybrid molecules, 13 new N-acylated precursors of the natural phytoalexin camalexin, 2 new imidazoline derivatives containing a phenolic fragment and 10 new oxy-camalexins. The structures of all products obtained were characterized by their proton ¹H- and carbon ¹³C-NMR spectra, application of two-dimensional techniques HSQC-NMR, Fourier transform infrared spectroscopy (FTIR) and high-resolution mass spectrometry (HRMS).

4. General characteristics and evaluation of the dissertation work

The content of the dissertation covers 145 pages. The literature review, written on 45 pages, outlines the known data on the biological activity of 2-substituted thiazole and benzothiazole compounds, methods used for the synthesis of 2-aryl/heteroaryl thiazole and benzothiazole compounds, applied oxidative transformations of heterocyclic compounds and formylation reactions. I find the literature review unnecessarily extensive (about 40% of the main content of the dissertation), especially when it comes to the biological properties of camalexin – its biotransformation from pathogenic, the tabular data on IC₅₀ of camalexin and its derivatives against various tumor cell lines, etc. This information would be more logical to use in future biological tests of the newly synthesized compounds.

It is quite appropriate that the doctoral student combines the results and their discussion in one chapter, since in this way the diversity of methods and results is logically linked to their meaning and significance. The experimental part describes in detail the synthetic procedures, and the spectral characteristics of the products obtained are also presented. The bibliography includes 264 sources.

Among the impressive merits of the peer-reviewed dissertation, I would like to mention:

- The impeccable graphic design, very informative reaction schemes;
- The doctoral student does not spare unsuccessful experiments;
- Verification of the applicability of the proposed synthetic approaches with a large number of substrates;
- Many of the methods used have been rescaled to larger amounts of starting reactants, which leads to the preparation of gram quantities of the desired products in good yield

and allows for future studies on the biological activity of the newly obtained compounds.

The dissertation was developed at the Department of Organic Chemistry at the Faculty of Chemistry of the University of Plovdiv – a reputable scientific center, where proven specialists in the field of organic synthesis work, which does not cast doubt on the reliability of the results obtained and their discussion.

The results of the doctoral student are a good basis on which to continue further studies on the biological and/or pharmacological activity of the synthesized compounds.

5. Contributions and significance of the dissertation for science and practice

The value of a dissertation in the field of organic synthesis is most often assessed by the new compounds obtained and the proposed new, more rational synthetic approaches. According to these criteria, the dissertation work is undoubtedly of high value.

A total of 43 compounds were synthesized, of which 28 were new. All of them were structurally characterized with appropriate instrumental methods. The entire strategy of the work – proven pharmacophores such as thiazole and benzothiazole to be chemically modified or used to obtain new bioactive compounds, was invariably followed in all experiments.

With regard to the synthetic approaches used, the scientific achievements and scientific contributions of the dissertation can be summarized into the following main areas:

- For the first time, α -amidoalkylation reactions of ferrocene with N-acyliminium reagents derived from benzothiazole and alkyl chloroformates have been carried out;
- The appropriate conditions for α -amidoalkylation of hydroxy-, methoxy-, N-methyl- and benzyloxyindoles with N-acyliminium reagents derived from thiazole/methylthiazoles and alkyl chloroformates have been established;
- The appropriate conditions for α -amidoalkylation of resorcinol and thymol with 1,3-diacyliminium reagents derived from imidazole have been established for the first time;
- Optimization of the method with the disclosure of an aldehyde group during reductive transformations of 1,3-diacylimidazolines containing a phenol fragment in their structure allows the selective preparation of aromatic aldehydes with various substituents and sensitive other functional groups.

In conclusion, Maria Bachvarova's dissertation is fundamental in the field of organic synthesis with potential for practical application.

6. Assessment of dissertation publications

The vast part of the dissertation content is included in 2 scientific articles published in international journals, referenced in international databases for scientific literature WoS and/or Scopus. The doctoral student is the first author of one of them, and the second author of the other. The first article, published in 2023 in the Journal of Organometallic Chemistry (Q2), includes the preparation of ferrocenyl benzothiazole derivatives and has already been cited by one foreign author. The second article, published in the journal Molecules (Q1) in 2025, includes the synthesis and structural characterization of oxygen-containing derivatives of camalexin.

Regarding the points required by the Regulations for the Implementation of the Development of the Academic Staff in the Republic of Bulgaria Act (DASRBA), the doctoral student fully covers the 30 points of publications set by Regulations, with the published articles on the dissertation totaling 45 points.

The results included in the dissertation have received publicity from the scientific community not only through publications in international journals, but also through presentation at 13 scientific forums.

7. Abstract

The abstract is 32 pages long and includes the content of the dissertation in a condensed but comprehensive form. A large number of the schemes from the dissertation are included, which are individually numbered, as well as the summarized results and conclusions. A bibliographic reference for publications on the dissertation and participation in scientific forums is also attached. In this form, the abstract is fully informative for presentation in subsequent procedures for scientific and academic degrees.

8. Critical notes, recommendations and questions

The dissertation is written in a very good scientific language, follows the logical sequence of the experiments and their interpretation, and this makes it very convincing. It impresses with the many methods used and a large amount of data, graphically presented in 92 schemes, 59 figures, 11 tables. Some terms could be replaced with more modern ones, e.g. resorcinol instead of resorcin, resonance instead of canonical structures. On page 9 line 5, the relationship is most likely the opposite – phytoalexins affect signaling pathways that lead to apoptosis of pathogen cells.

The review of the dissertation also raised some questions to which the doctoral student can probably give a reasonable answer:

- Are there any advantages to using o-chloranyl over p-chloranyl, which is the most commonly used oxidant in the Hantzsch synthesis of the pyridine ring (scheme 88 shows the mechanism of oxidation with p-chloranyl)?
- Figure 43 shows some of the compounds that are known commercial products, but they were synthesized by new and more rational synthetic approaches. Have their characteristics (melting point, spectral data) been compared with literature data or data from the manufacturers?

- In the structure of a number of secondary plant metabolites (phytoalexins, alkaloids, flavonoids, carotenoids, etc.) a methoxy group is very often found. Is there any special reason why nature “loves” this group?

CONCLUSION

According to the DASRBA, “doctor” is an educational and scientific degree. The content of the dissertation convincingly shows that the doctoral student Maria Bachvarova has not only built on the knowledge obtained in the master's degree and has covered the educational component of the “doctor” degree but has also mastered several synthetic and instrumental methods. She can critically discuss the results obtained and present them in written form. The dissertation submitted for review, in terms of its scientific value, meets the requirements of the DASRBA, the Regulations for its implementation and the corresponding Regulations of the “Paisii Hilendarski” University.

Based on the analysis of the significance of the research conducted, the presented dissertation and publications, **I confidently give my positive assessment and recommend to the esteemed members of the scientific jury to award the educational and scientific degree "doctor" to Maria Valentinova Bachvarova** in the scientific field 4. Natural Sciences, Mathematics and Informatics, professional field 4.2. Chemical Sciences, doctoral program "Organic Chemistry".

June 8, 2026,
Plovdiv

Reviewer: