OPINION

By Dr. Stoyanka Nikolova Atanasova, Professor at the Paisii Hilendarski Plovdiv University

of a PhD thesis for awardinf of the educational and scientific degree "Doctor"

in: field of higher education 4. Natural Sciences, Mathematics and Informatics;

professional field 4.2. Chemical Sciences

scientific specialty: Organic Chemistry

Author: Maria Valentinova Bachvarova

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

Scientific advisor: Assoc. Prof. Dr. Stela Statkova-Abeghe

1. General description of the procedure and the doctoral candidate.

By a written order No. PD-22-1002 of 15.05.2026 of the Rector of the Paisii Hilendarski Plovdiv University I am appointed as a member of the scientific jury for ensuring a procedure for the defense of a PhD thesis on the topic "Synthetic transformations of 2-aryl thiazole and benzothiazole compounds" 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, scientific specialty Organic Chemistry. The author of the dissertation is Maria Bachvarova - a PhD student at the Department of Organic Chemistry, with scientific supervisor Assoc. Prof. Dr. Stela Statkova from the Paisii Hilendarski Plovdiv University.

The submitted thesis and all accompanying documents are in complete accordance with the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria and the internal regulations of the Plovdiv University.

2. Brief biographical data of the PhD student

PhD student Maria Bachvarova was born on January 24, 1994 in the town of Kotel. She completed her secondary education in 2013 at the Specialized High School for Teaching Western Languages "Zahariy Stoyanov" - Sliven, studying German and English languages. She completed her education at the Faculty of Chemistry of the University of Plovdiv "Paisiy Hilendarski", where in 2019 she obtained the educational and qualification degree "Bachelor" in the specialty "Medicinal Chemistry". Maria Bachvarova completed her bachelor's degree with a thesis on the topic: "Synthe-

sis of Pyrrole Derivatives - Analogues of the Phytoalexin Camalexin". During her bachelor's degree, she studied and successfully completed two postgraduate qualifications at Plovdiv University "Paisii Hilendarski" - "Chemistry Teacher" (2018–2019) and "Specialist in High-Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC)" (2019). In 2020, Maria Bachvarova acquired the educational and qualification degree "Master" in the specialty "Medicinal Chemistry". After completing her studies, PhD student Bachvarova started working as a chemist in the "Research and Development" section at "Biovet" AD - Peshtera. Since March 2021, she has been working as a senior expert chemist at the Center for Research Projects and Technology Transfer (CIPTT) at the University of Food Technologies - Plovdiv. In the period 2022–2025, she is a full-time doctoral student at the Department of Organic Chemistry, Faculty of Chemistry at the University of Plovdiv "Paisii Hilendarski", where she is developing a dissertation on the topic: "Synthetic transformations of 2-aryl thiazole and benzothiazole compounds".

During her studies, she successfully completed specialized courses at the university center Academia Iuventutis, including: English language, Methodological guidelines for developing a scientific publication; Intellectual property in academic discourse; Biofunctional heterocyclic compounds, Chemistry of narcotic substances, and last but not least, seminars on the topic: "Organic stereochemistry" with Prof. F. Alonso from the University of Alicante, organized by the Department of Organic Chemistry.

3. Relevance of the topic.

The presented dissertation work by Maria Bachvarova considers the synthesis of 2-aryl/heteroaryl thiazole and benzothiazole compounds by α-amidoalkylation reaction and some of their oxidative and reductive transformations with the aim of obtaining new functionalized analogues of natural and biologically active compounds. Research on N-acyliminium ions and their application in α-amidoalkylation is an intensively developing area, especially in connection with the development of new synthetic methods; obtaining biologically active compounds and the search for more effective, selective and scalable approaches.

The introduction of the problem is well-described and topical. The main goal of the study is clearly defined, related to the development of effective synthetic approaches for transformations of 2-aryl/heteroaryl thiazole and benzothiazole compounds and obtaining new functionalized analogues of natural and biologically active compounds. The tasks of the study are also well formulated. The tasks are expedient, as they build on previous results and fill specific gaps in the literature, such as the lack of data on amidoalkylation of ferrocene. The synthesis of compounds with the aim

of obtaining analogues of natural and biologically active compounds gives applied value to the research and confirms the relevance of the topic.

4. Knowledge of the problem.

The literature review is comprehensive, covering 262 sources, and the reference made is interpreted with understanding. It begins with the biological activity of 2-substituted thiazole and benzothiazole derivatives. The literature review continues with the methods for the synthesis of 2-aryl/heteroaryl thiazole and benzothiazole compounds, continues with the synthesis of methoxycamalexins, benzocamalexins and ferrocene-containing hybrid molecules; it also includes synthetic approaches for C-arylation of thiazole and benzothiazole compounds. Special attention is paid to the α-amidoalkylation reaction and oxidative transformations; the reactions of formylation and introduction of a hidden formyl group are also considered.

The comprehensive literature review on the topic presented by the author demonstrates excellent information, analytical and in-depth insight into the problem. The analysis of the known synthesis methods from the scientific literature is correct, complete and up-to-date and covers a wide period, but most of them are from the last 20 years.

PhD student Bachvarova demonstrates a very good knowledge of the research problem. She clearly follows the development of the method within the scientific group. A critical analysis of known limitations (e.g. instability of adducts, limited range of nucleophiles) is made and she has demonstrated knowledge of alternative synthetic approaches. A particular strength of the literature review is the identification of unsolved problems; reasoning for the choice of reagents and conditions and explaining the relationship between structure and reactivity.

5. Research methodology

The PhD thesis uses a complex, well-structured and adequate methodology to the set goals. The methods of work include the use of a “one-pot” synthetic approach; the study of a wide range of substrates (indoles, phenols, ferrocene, etc.) and the conduct of oxidative and reductive transformations. The study includes a targeted variation of the reaction parameters – type of acyl component, heterocyclic system, solvent, temperature and molar ratio of reagents, in order to determine optimal conditions. Scaling experiments were conducted to assess the applicability of the method.

The structural characterization of the synthesized compounds was performed using modern spectral methods (^{1}H- and ^{13}C-NMR, HSQC, FTIR, HRMS), which guarantees the reliability and validity of the obtained results.

6. Characteristics and evaluation of the thesis

The PhD thesis is presented on 146 standard pages and includes 11 tables, 92 schemes and 43 figures. The bibliography covers a total of 264 literary sources. It is structured classically - Introduction; Literature review; Tasks; Results and discussion; Experimental part; Conclusions; Publications on the topic of the thesis, and literature references. The PhD thesis is very well-formed and structured, with the individual parts of the own research presented in chronological order.

The thesis is written consistently and clearly, containing original scientific research and results. Based on the extensive, orderly and very clear literature review, the research tasks in the dissertation work are correctly formulated. The task of studying the limits of application of N-acyliminium reagents obtained from various thiazoles and benzothiazole with alkyl chloroformates in α-amidoalkylation reactions is clearly set; then synthesis of new N-acylated 2-aryl/heteroarylbenzothiazolines and 2-heteroarylthiazolines, as well as oxidative and reductive transformations. The entire work is a continuation of the topic developed for years in the Department of Organic Chemistry by the doctoral student's scientific supervisor, Assoc. Prof. Statkova.

The PhD student has mastered and successfully applied in her work methods for synthesis, isolation of compounds in pure form, characterization and proof of the structure of compounds using modern analysis techniques. This allows solving the tasks set in the thesis. The precisely conducted experiment and interpretation of the methods for studying the structure of compounds make a very good impression.

An impressive volume of experimental work has been carried out. As a result of the research conducted, 43 compounds have been synthesized, of which 28 are new, not described in the literature. The experimental part of the dissertation describes in detail all the developed synthetic methods, as well as the spectral characteristics of the obtained compounds. All the obtained compounds were duly characterized by various NMR techniques, mass spectrometry, infrared spectra and melting temperature. It can be seen that the educational tasks of the doctoral program have been fulfilled.

Particularly valuable is the contribution related to expanding the applicability of α-amidoalkylation to various nucleophilic systems, as well as the development of effective conditions for subsequent oxidative and reductive transformations. The possibility of synthesizing new and difficult-to-access compounds, including biologically active molecules such as camalexin analogues, has been demonstrated. The work has both fundamental and applied nature, offering methods that are relatively economical, scalable and with potential for use in medicinal chemistry

and pharmacy. The PhD student shows a skill for critical analysis, clearly outlining the limitations of the method and directions for future research.

Overall, the dissertation is characterized by high scientific value, originality of approaches, and a significant contribution to the development of synthetic organic chemistry.

7. Contributions and significance of the thesis.

The contributions of the doctoral student's dissertation work are undeniable, and we can include: **scientific** - an effective synthetic approach for α-amidoalkylation involving N-acyliminium reagents generated in situ was developed and systematically studied, which contributes to expanding the fundamental knowledge of this reaction; regularities related to the influence of electronic and steric factors on the reactivity of various nucleophiles (indoles, phenols, ferrocene derivatives) were studied; 28 new compounds were synthesized; and **scientific and applied** - the application of the α-amidoalkylation reaction was expanded, practically applicable "one-pot" synthetic procedures were developed and reaction conditions suitable for scaling were optimized; the possibility of subsequent functionalization (oxidative and reductive transformations) was demonstrated, which increases the synthetic flexibility of the developed approaches; methods for the synthesis of biologically active compounds with potential application in medicinal chemistry and pharmacy have been proposed; a basis has been created for the future application of the developed methods in the synthesis of pharmacologically significant molecules and materials with functional properties.

The contributions of the development are significant both in theoretical and practical aspects. They not only expand the existing scientific knowledge, but also offer real opportunities for application in modern synthetic and medicinal chemistry.

8. Publications in connection with the thesis and personal contribution of the PhD student

The list of publications of PhD student Bachvarova in connection with the dissertation work presents 2 articles in specialized journals. One of the articles is in a journal with Q1, the other one is in Q2. The personal participation of the PhD student in the indicated scientific works is illustrated by the fact that in the publications she is in the first or second position. The attached articles fully correspond to the results presented in the dissertation. One of the articles has already been cited. The results of the conducted research were reported at 13 scientific sessions with nine oral presentations and seven posters.

9. Remarks and recommendations

I have no major remarks or recommendations.

10. Personal opinion.

I have known PhD candidate Bachvarova as my student since her studies in the specialty "Medicinal Chemistry", and later as a PhD student in the department. The impression I have of her is of a very hardworking and inquisitive young researcher, who I hope will develop her potential in the future.

11. Recommendations for future use of the thesis contributions and results

The research conducted is in a relevant and interesting area of modern knowledge and in particular in the search for new, more effective medicinal substances to combat socially significant diseases. Simultaneously with the accumulation of useful information, the PhD student has also carried out a huge amount and quality of experimental work, which could provide her with a basis for further continuation of research and growth in her scientific career.

CONCLUSION

The PhD thesis contains both scientific and applied scientific results that represent an original contribution to science and meet all the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for the Implementation of the Law, and the relevant Regulations of the Paisii Hilendarski Plovdiv University.

The thesis shows that the PhD student Maria Bachvarova possesses in-depth theoretical knowledge and professional skills in the scientific specialty of Organic Chemistry, demonstrating qualities and skills for independent conduct of scientific research.

Considering the relevance and significance of the topic of the dissertation, the abstract, the fulfillment of the set goal, the scientific and applied scientific results contained therein, which represent an original contribution to science, I kindly recommend to the scientific jury to award the educational and scientific degree "doctor" to Maria Bachvarova in the field of higher education: 4. Natural Sciences, Mathematics and Informatics, professional field 4.2. Chemical Sciences, scientific specialty "Organic Chemistry".

09.06.2026 г. …….....

(Prof. Stoyanka Nikolova, PhD)