PLOVDIV UNIVERSITY "PAISII HILENDARSKI"
FACULTY OF CHEMISTRY,
DEPARTMENT OF ORGANIC CHEMISTRY

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Synthetic transformations of 2-aryl thiazole and benzothiazole compounds

A B S T R A C T
of PhD thesis

for awarding the educational and scientific degree
„Doctor"

Field of higher education – 4. Natural Sciences, Mathematics and Informatics
Professional field – 4.2. Chemical Sciences
Doctoral program – Organic Chemistry

Scientific supervisor
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Plovdiv
2026

The present doctoral dissertation was developed at the Department of Organic Chemistry, Faculty of Chemistry, University of Plovdiv "Paisii Hilendarski".

The conducted research was carried out with the financial support of the European Commission (NextGenerationEU, through the National Recovery and Resilience Plan of the Republic of Bulgaria), Project DUECOS BG-RRP-2.004-0001-C01, D23-HF-001 entitled: "Preparation of Phytoalexins and Their Analogues with Potential Application in Plant Protection," led by Assoc. Prof. Dr. Stella Statkova-Abeghe, and the Competence Centre "Personalized Innovative Medicine, PERIMED-2" (BG Programme "Research, Innovation and Digitalisation for Smart Transformation" 2021–2027, co-funded by the European Union, Contract No. BG16RFPR002-1.014-0007).

The doctoral dissertation was reviewed and approved for public defense at a meeting of the Departmental Council of the Department of Organic Chemistry, Faculty of Chemistry, University of Plovdiv "Paisii Hilendarski" (Protocol №. 395/ April 22, 2026). The dissertation comprises 145 printed pages, 92 schemes, 59 figures, 11 tables, and 264 cited references.

The materials related to the defense are available to interested parties at the Central Library and the Department of Faculty Development and Doctoral Studies at Plovdiv University „Paisii Hilendarski".

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude and appreciation to my academic advisor, Associate Professor Stela Statkova-Abeghe, for the trust she has placed in me, her valuable academic guidance, her patience, and the opportunity she has provided for my research. Her support and high level of professionalism have made a significant contribution to the successful completion of this dissertation.

I am grateful for the opportunity to join the research team in which I developed my dissertation, I thank Chief Assistant Professor Dr. Yordan Stremski for the fruitful collaboration, valuable guidance and joint work.

Special thanks to the entire staff of the Department of Organic Chemistry, Faculty of Chemistry at Plovdiv University „Paisii Hilendarski“ for the supportive work environment, as well as for the guidance provided during the process of studying and developing this dissertation.

Last but not least, I would like to express my gratitude to my family and friends for their moral support, patience, and faith.

I. INTRODUCTION

Heterocyclic moieties are among the most common in a number of drugs with a wide range of therapeutic applications. Thiazole and benzothiazole are important pharmacophore nuclei in organic synthesis and medicinal chemistry [1]. The benzothiazole ring is classified as one of the „privileged moieties“ in the design and synthesis of biologically active compounds, anticancer agents, and a variety of pharmaceutical products [2]. In this context, *Camalexin*, benzocamalexin, and 2-ferrocenylbenzo[*d*]thiazole stand out as important antitumor compounds with high therapeutic potential and specific biological activity, **Figure 1** [3, 4].

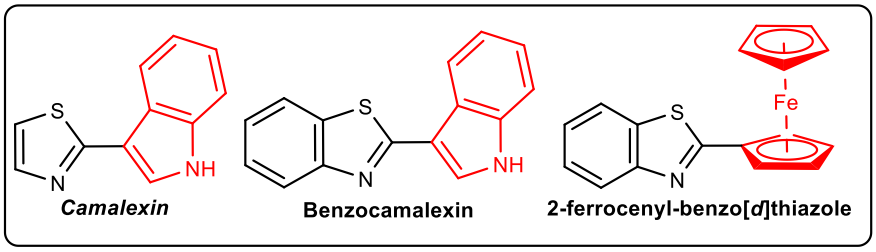


Figure 1. Compounds with antitumor activity.

Interest in natural indole phytoalexins is growing, as compounds in this group possess a wide range of biological activities: antimicrobial, antifungal, antiviral, antioxidant, anti-inflammatory, enzyme-inhibitory, antitumor, antiproliferative, and cytotoxic effects. In addition to *Camalexin*, which was isolated from *Arabidopsis thaliana* and *Camelina sativa*, other methoxylated analogues have been identified in recent years, isolated from *Capsella bursa-pastoris* and *Neslia paniculata*. Hydroxyl-containing camalexins have also been identified as key metabolites in pathogenic interactions (**Figure 2**). The significant structural diversity and biological activity of oxy-camalexins make them promising candidates for the development of new therapeutic compounds.

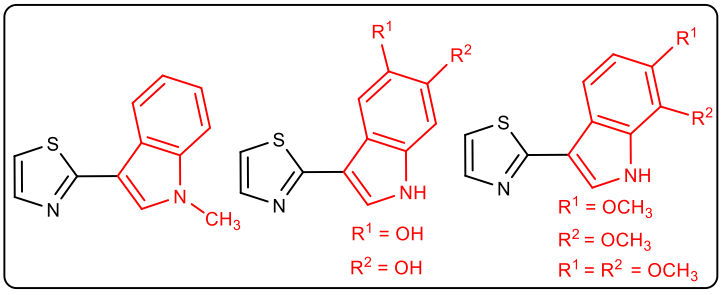


Figure 2. Natural camalexins.

In 2018, the research group proposed a new approach for the synthesis of the natural phytoalexin *Camalexin* and its analogues by introducing thiazole, imidazole, and benzothiazole into the pharmacophore indole fragment, using the *α*-amidoalkylation reaction and subsequent oxidative aromatization [5].

This work is a natural extension of these studies, broadening the scope of the *α*-amidoalkylation reaction. The main focus of the dissertation is on the synthesis of new 2-aryl/heteroaryl thiazoles and benzothiazoles, natural camalexins, and their functionalized analogues with potential biological activity.

II. PURPOSE AND OBJECTIVES OF THE DISSERTATION

The aim of this dissertation is to develop effective synthetic approaches for the transformation of 2-aryl/heteroaryl-thiazole and benzothiazole compounds to yield new functionalized analogues of natural and biologically active compounds. The following research objectives have been formulated:

1. Investigation of the application scope of *N*-acyliminium reagents derived from thiazole, 4-methylthiazole, 4,5-dimethylthiazole, benzothiazole, and alkyl chloroformates in *α*-amidoalkylation reactions of aromatic compounds;
2. Synthesis of novel *N*-acylated 2-aryl/heteroarylbenzothiazolines and 2-heteroarylthiazolines;
3. Oxidative transformations of 2-aryl/heteroarylthiazolines and benzothiazolines;
4. Aldehyde group disclosure in reductive transformations of *N*-Troc-2-(3-indolyl)-thiazolines;
5. Chromatographic purification and spectral characterization of the obtained compounds.

To achieve this objectives, variously substituted thiazoles and benzothiazoles were used, after activation as *N*-acyliminium reagents, in α-amidoalkylation reactions. Various activated aromatic compounds – ferrocene, variously substituted oxy-indoles, phenols, and others – were selected as nucleophiles, as shown in **Figure 3**.

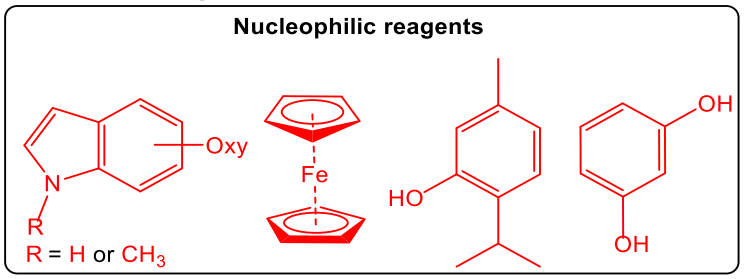
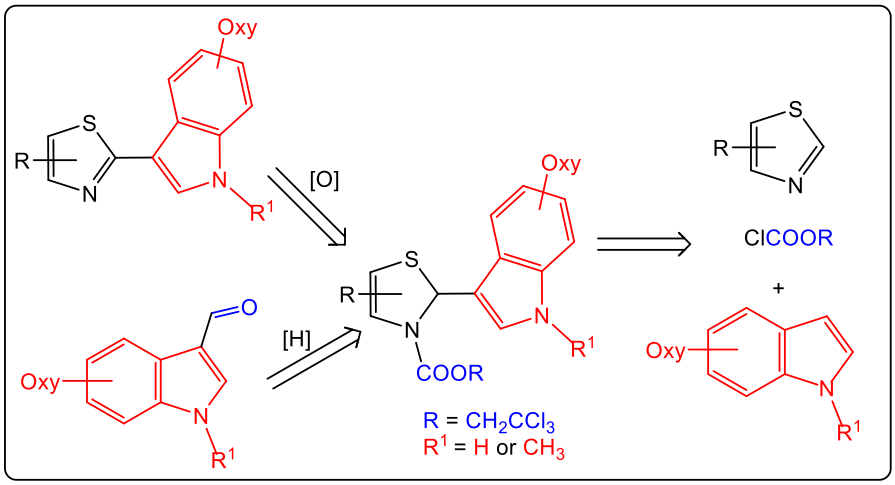


Figure 3. Selected aromatic nucleophiles.



Scheme 1. Retrosynthetic scheme for the preparation of biologically active compounds.

III. RESULTS AND DISCUSSION

III. 1. Reactions for the amidoalkylation of ferrocene with *N*-acyliminium reagents derived from benzothiazole and alkyl chloroformates.

The research is based on a newly developed "*one-pot*" synthetic approach, in which a wide range of aromatic nucleophiles are successfully amidoalkylated using *in situ* generated *N*-acyliminium reagents derived from azole or benzazole heterocyclic compounds. In recent years, the scope of this approach has been expanded, and the methodology has been successfully applied to the gram-scale synthesis of the biologically active compounds *Camalexin* and benzocamalexin via multicomponent indole amidoalkylation reactions followed by oxidative aromatization [5]. This approach has also been used to successfully synthesize new *Quercetin*, *Thymol*, and *Carvacrol* hybrid molecules. The synthesized compounds contain a pharmacophore with antitumor activity, which highlights the method's potential practical application in medicinal chemistry. In this context, we focused our attention on investigating ferrocene as a nucleophile in *α*-amidoalkylation reactions using *N*-acyliminium reagents derived from thiazole, 4,5-dimethylthiazole, imidazole, and benzothiazole. There are no data on the *α*-amidoalkylation of ferrocene using *N*-acyliminium reagents derived from variously substituted azole and benzazole compounds.

Building on the synthetic experience of our research group and the approaches published in the literature for the synthesis of ferrocene-substituted heterocyclic compounds, our focus was on investigating the possibility of applying a new approach based on „*one-pot*" *α*-amidoalkylation. Initially, the ferroocene amidoalkylation reaction was tested using thiazole and 2,2,2-trichloroethyl chloroformate (Troc-Cl) in 1,2-dichloroethane ($C_2H_4Cl_2$). When the reaction was carried out at room temperature for 24 hours, no interaction was observed. This necessitated a search for suitable reaction conditions. When the reaction mixture was boiled for 2 hours, no difference in the reaction progress was observed. The same reaction conditions were also tested with the addition of imidazole, but this also failed to yield a result.

In attempts to replace the alkyl chloroformate (Troc-Cl) used with acid chlorides, such as acetyl- and benzoyl chloride, no reaction was observed. Only upon the use of anhydrous $AlCl_3$, as a Lewis acid, was a reaction observed. Spectral data of the isolated product showed that under these conditions, the acylation reaction proceeds via the Friedel–Crafts mechanism, without the participation of thiazole. Using 4,5-dimethylthiazole (**1c**), acetylferrocene (**3a**) (62 %) and benzoylferrocene (**3b**) (72 %) were obtained in good yields (**Scheme 2**).

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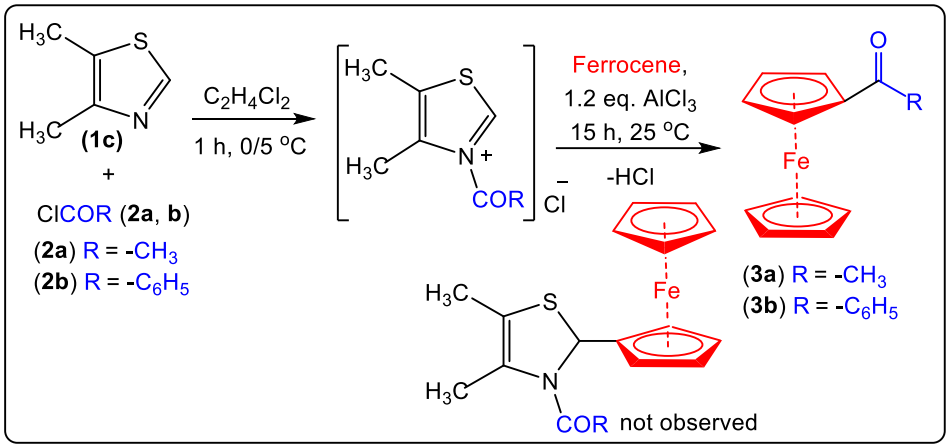
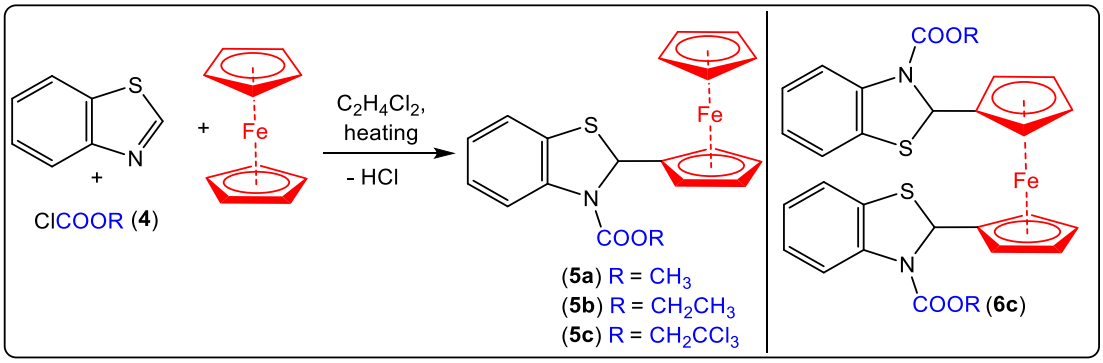


Scheme 2. The attempts to perform the amidoalkylation of ferrocene in the presence of anhydrous $AlCl_3$.

We continued our experiments on the amidoalkylation of ferrocene with *N*-acyl iminium reagents generated in situ from benzothiazole. We investigated the reactivity of *N*-acyliminium ions derived from benzothiazole and the following acid chlorides: acetyl chloride, benzoyl chloride, and selected alkyl chloroformates–methyl chloroformate, ethyl chloroformate, and 2,2,2-trichloroethyl chloroformate (Troc-Cl). We found that *N*-acyliminium reagents prepared using alkyl chloroformates are more effective for the amidoalkylation of ferrocene upon boiling in 1,2-dichloroethane. In the other cases, the reaction does not proceed (**Scheme 3**). When using equimolar amounts of the reactants under these conditions, two products are observed, one of which is basic. The reaction conditions are presented in **Table 1**.



Scheme 3. *α*-Amidoalkylation of ferrocene and preparation of products (**5a**–**c**).

The different reaction conditions are presented as Methods **A** and **B**. Under reaction conditions A: with a 1:1 molar ratio and a reaction time of 6 hours, compounds **5a**–**c** were obtained after isolation and chromatographic purification in yields ranging from 49 % to 63 %. To direct the reaction toward the formation of monosubstituted products, a twofold excess of benzothiazole and the

corresponding alkyl chloroformate was used. The reaction time was also extended to 12 hours. Under these conditions, the expected increase in yields for compounds **5a** (66 %) and **5b** (65 %) was observed, while compound **5c** was obtained in a yield of only 41 %. Here, a significant amount of the di-substituted product with ferrocene **6c** was observed.

Table 1. Yields for compounds (**5a–c**).

Product (**5a-c**)	**R**	**Yield, % Method A**	**Yield, % Method B**	**Temperature range, t_r, °C**
a	CH_3	49	66	119–121
b	CH_2CH_3	56	65	129–131
c	CH_2CCl_3	63	41	130–132

A: Ratio benzothiazole + ClCOOR : ferrocene = 1:1, reaction time 6 hours.
B: Ratio benzothiazole + ClCOOR : ferrocene = 2:1, reaction time 12 hours.

After the α-amidoalkylation reactions, single crystals of compound **5c** (2,2,2-trichloroethyl 2-ferrocenyl-benzothiazole-3(2*H*)-carboxylate) were obtained, and single crystal X-ray diffraction was performed. The results confirmed the formation of a racemic mixture in the amidoalkylation reaction, which was also observed in previous studies. The structures of the two stereoisomers are shown in **Figure 4**.

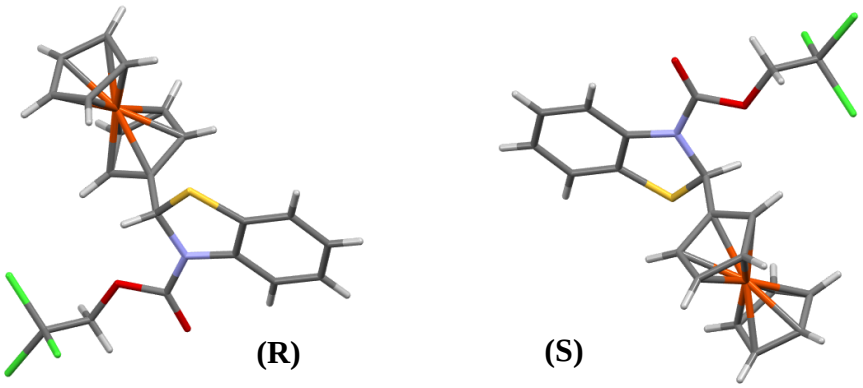


Figure 4. Racemic mixture, confirmed by X-ray diffraction analysis.

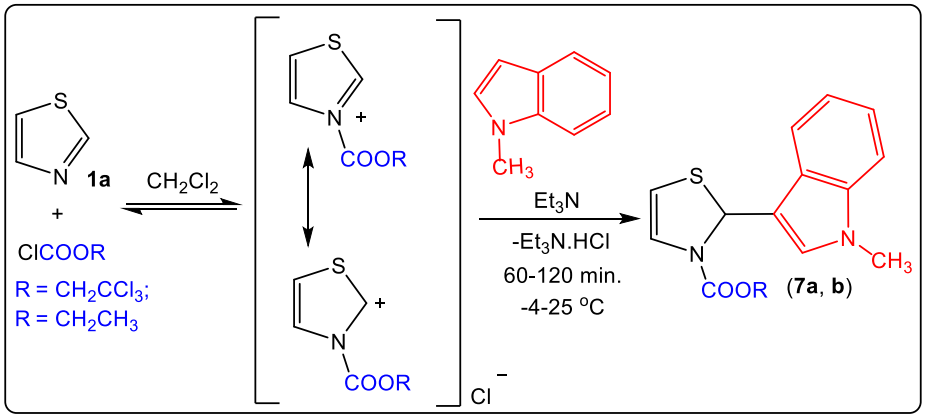
The proposed reactions in **Scheme 3**, involving the amidoalkylation of ferrocene, represent a new strategy for the preparation of *N*-alkoxycarbonyl-2-ferrocenyl-benzothiazoline compounds (**5a**–**c**). The type of acylating reagent used is key to their generation. The results show that, among the alkyl chloroformates tested, 2,2,2-trichloroethyl chloroformate generates the most reactive *N*-acyliminium ion. When using an excess of the reagents (**Table 1**, reaction conditions – **B**), due to its high reactivity, a decrease in the yield of compound **5c** is observed, with the formation of the diastereomeric product **6c**. The di-substituted product was identified by HPLC-MS analysis, but directing the reaction toward the formation of diastereoisomers, investigating the stereochemical course, and determining the yield are the subject of future studies. We can conclude that when acetyl and benzoyl chlorides are used in the presence of a Lewis acid catalyst, ketones are primarily formed, with the highest yields observed in reactions with 4,5-dimethylthiazole, while alkyl chloroformates are

more effective for the preparation of *N*-acylated 2-ferrocenylbenzothiazolines. When acetyl and benzoyl chloride are used, regardless of whether the heterocyclic system is 4,5-dimethylthiazole or benzothiazole, the main reaction product in both cases is a ketone (**3a**, **3b**). Under these conditions, no formation of amidoalkylated ferrocene is observed. In contrast to the unsuccessful attempts with ferrocene, previous studies by our synthetic group have shown that *N*-acyliminium reagents derived from benzothiazole, benzothiazole, and acid chlorides (acetyl and benzoyl chloride) successfully amidoalkylate indole, pyrrole, and others [5].

This method provides an alternative route for the preparation of the antitumor agent 2-ferrocenyl-benzo[*d*]thiazole (**11**), previously synthesized via a condensation reaction between an aromatic aldehyde and 2-aminothiophenol, as described in the literature review. The synthetic approach now proposed allows for molecular hybridization and the direct formation of carbon-carbon (C-C) bonds via in situ generated *N*-acyliminium ions, which is one of the advantages of the approach.

III. 2. Synthesis of precursors for the preparation of *N-methylcamalexin* and oxy-camalexins.

Interest in camalexins, due to their physiological properties, has led to a search for accessible routes for their synthesis. The success of the group's previously proposed approach for the preparation of *Camalexin*, benzocamalexin, and azacamalexin [5], suggests an extension involving the use of variously substituted oxy-indoles to obtain natural camalexins and their analogues, which are inaccessible by other methods. Building on these experiments, as well as our current work with ferrocene, we selected acyliminium reagents prepared *in situ* from thiazole, 2,2,2-trichloroethyl chloroformate (Troc-Cl), and ethyl chloroformate for the *α*-amidoalkylation of *N*-methylindole (**Scheme 4**).



Scheme 4. *α*-Amidoalkylation reaction of *N*-methylindole to yield precursors of *N*-methylcamalexin.

The reactions proceed under mild reaction conditions. The *α*-amidoalkylation reaction has been successfully demonstrated using the more economical ethyl chloroformate for the synthesis of compound **7b**, which was obtained in 78 % yield. To determine the feasibility of the two-step approach,

experiments were conducted to scale up the reaction and produce the precursor in gram quantities. For this purpose, we selected the target product 2,2,2-trichloroethyl 2-(1-methyl-1*H*-indol-3-yl)thiazole-3 (2*H*)-carboxylate **7a**, due to the high reactivity of Troc-Cl and the reaction duration of 1 hour at temperatures ranging from -4 to 0 °C (**Table 2**).

Table 2. Reaction conditions and yields of compounds (**7a**, **b**) obtained according to **Scheme 4**.

Product (7)	R	Reaction conditions, T, h	Yield, %	t_r, °C
a	CH_2CCl_3	-4–0 °C, 1	72*	137–139
b	CH_2CH_3	0–25 °C, 2	78	115–116

* Compound **7a** was obtained on a gram scale (2.256 g) with a 72 % yield.

Attempts to isolate a pure product after recrystallization resulted in losses and low yield, which is why column chromatography using a stationary phase of neutral alumina (Al_2O_3) was employed, confirming the effectiveness of the *α*-amidoalkylation reaction on a gram scale. Previous studies conducted by our synthetic group have shown that *N*-acylthiazole reagents used in *α*-amidoalkylation reactions of indole lead to the rapid release of hydrogen chloride. This is one of the reasons why the target products decompose. That is why controlling the acidity of the reaction is crucial. To achieve optimal conditions and the synthesis of the target products, triethylamine (Et_3N), acting as a hydrogen acceptor and previously dissolved in CH_2Cl_2, is added dropwise. Conducting the reactions in the absence of Et_3N leads to the formation of triindolylmethane as the main product [5].

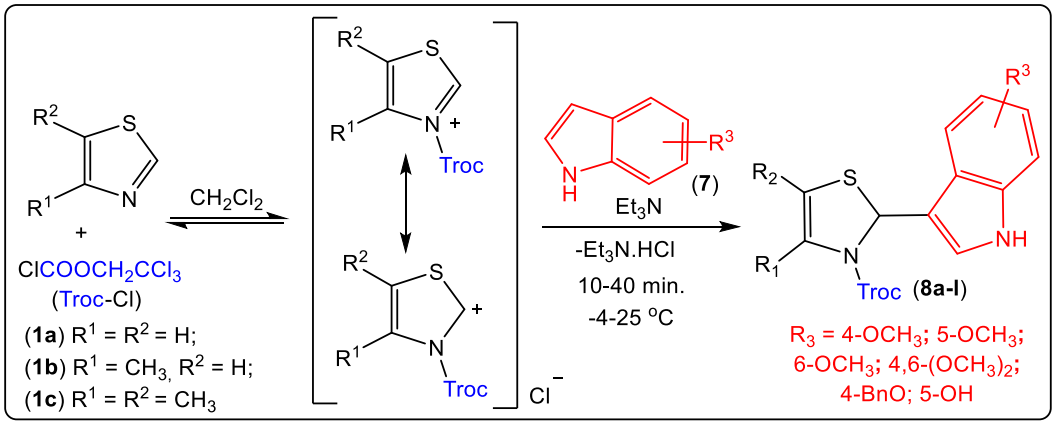
These same previous studies found that the acquisition of ^{1}H-NMR spectra of *N*-alkoxycarbonyl products at room temperature in deuterated dimethyl sulfoxide (DMSO-d_6) resulted in the detection of highly broadened signals, making their correct integration and subsequent interpretation impossible. In carbon $^{13}C\{^1H\}$-NMR spectra recorded under the same conditions show an absence of significant characteristic signals for the molecules. This is due to rotameric transformations in the alkoxycarbonyl group at room temperature. Optimal conditions were established for the acquisition of proton ^{1}H- and carbon $^{13}C\{^1H\}$-NMR spectra, with the aim of increasing the rate of rotamer transitions and averaging the recorded signals. The appropriate conditions for their measurement have been determined to be spectral measurements at 80 °C in deuterated DMSO-d_6 [5].

The main objective was the structural identification of the compounds obtained (**7a**, **b**). In the proton ^{1}H-NMR spectra of the analysed compounds, characteristic singlets are observed in the range δ = 6.87–7.19 ppm, corresponding to the proton bonded to the symmetric sp^3 - C_2 carbon atom in the thiazoline ring. The isolation of new oxy-camalexins from other plants in 2021 [6] also set the

direction for future research. In order to broaden the scope of the *α*-amidoalkylation reaction, we specifically replaced the nucleophilic reagent with variously substituted commercial oxy-indoles. As noted in the literature review, known synthetic methods do not allow for the preparation of camalexins containing two methoxyl groups in their structure. The failure to obtain them is due to the increased nucleophilicity of the aromatic benzene ring in the indole and the occurrence of competing side reactions [7].

The choice of Troc-Cl as an alkyl chloroformate is due to its high reactivity and its ability to generate variously substituted *N*-acylthiazolium intermediates. The electron-accepting character of the trichloroethyl group increases electrophilicity and facilitates the formation of reactive *N*-acylthiazolium salts, which participate in *α*-amidoalkylation reactions of variously substituted oxyindoles as nucleophilic reagents, (**Scheme 5**). As a result, a higher reaction rate and better yields of the target products are observed compared to other alkyl chloroformates, such as ethyl chloroformate.

In the reactions studied, *N*-acylthiazolium reagents prepared *in situ* by mixing thiazole/4-methylthiazole/4,5-dimethylthiazole (**1a**–**c**) with 2,2,2-trichloroethyl chloroformate (Troc-Cl) were successfully employed. The use of 2,2,2-trichloroethyl chloroformate was preferred due to the faster reaction rate and higher yields of the target products compared to ethyl chloroformate.

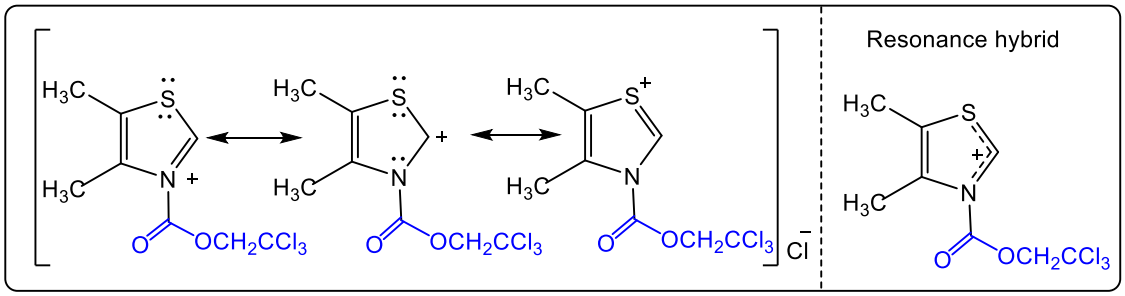


Scheme 5. Synthesis of precursors for the preparation of oxy-camalexins.

The effect of substituents on the thiazole ring on the stability of *N*-acyliminium reagents was investigated. The experimental results presented in **Table 3** show a difference in reaction rate depending on the thiazole used (**1a**–**c**). Reactions with 4,5-dimethylthiazole generally proceed more rapidly, within 10 to 30 minutes. This is likely due to the presence of electron-donating methyl groups, which increase the nucleophilicity of the nitrogen atom in the thiazole and stabilize the *N*-acyliminium ions, facilitating their formation.

The resulting cationic intermediate is stabilized by the delocalization of the positive charge across the variously substituted thiazolium ring. The methyl groups at positions C_4 and C_5 exhibit an electron-donating inductive (+I) effect, which further stabilizes the system and facilitates the *α*-amidoalkylation reaction.

The canonical forms of the *N*-acylthiazolium cation derived from 4,5-dimethylthiazole and (Troc-Cl) are presented in **Scheme 6**.



Scheme 6. Canonical forms of *N*-acylthiazolium cation derived from 4,5-dimethylthiazole and (Troc-Cl).

The position of the methoxy group in indole does not significantly affect the reaction time or the yield of the final products. The presence of a second methoxy substituent in 4,6-dimethoxyindole resulted in a faster reaction. In the amidoalkylation of 5-hydroxyindole, a secondary product is observed, leading to a decrease in the yield of product **8l** (77 %). A competitive reaction likely occurs in the benzene ring of 5-hydroxyindole, similar to other reactions involving phenolic compounds.

Table 3. Reaction times and yields of compounds (**8a–l**) according to **Scheme 5.**

Product (**8**)	R^1	R^2	R^3	Reaction time, min.	Yield, %	t_r, °C
a	CH_3	H	4-OCH_3	30	98	175–177
b	CH_3	CH_3	4-OCH_3	20	97	191–193
c	H	H	5-OCH_3	40	93	162–164 [8]
d	CH_3	H	5-OCH_3	30	96	122–124
e	CH_3	CH_3	5-OCH_3	20	98*	143–145
f	H	H	6-OCH_3	30	96	Oil
g	CH_3	CH_3	6-OCH_3	20	93	66–68
h	CH_3	H	4,6-$(OCH_3)_2$	10	92	171–173
i	CH_3	CH_3	4,6-$(OCH_3)_2$	10	96	183–185
j	H	H	4-BnO	30	97	54–56
k	CH_3	CH_3	4-BnO	30	93	141–143
l	CH_3	CH_3	5-OH	10	77	Oil

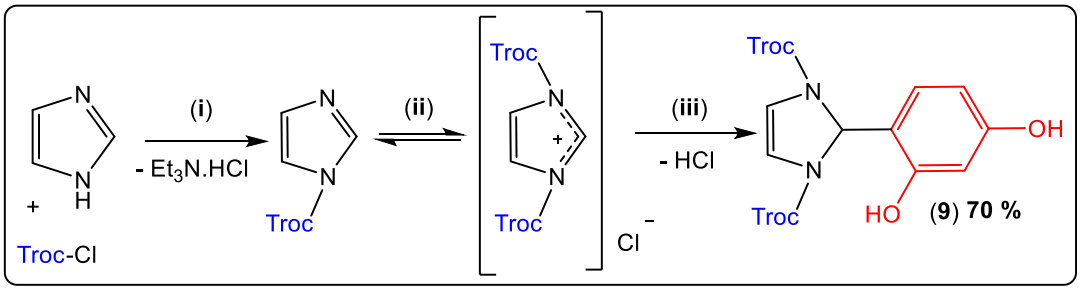
* Compound **8e** was obtained in gram quantities (1.255 g) with a 96 % yield.

To determine the scope and applicability of this method, it was necessary to scale up the synthesis to gram quantities. For this purpose, we selected a target product - 2,2,2-trichloroethyl-2-(5-methoxy-1*H*-indol-3-yl)-4,5-dimethylthiazole-3(2*H*)-carboxylate (**8e**), a precursor for the preparation of an analogue of 2-(5-methoxy-1*H*-indol-3-yl)thiazole (**13c**), which has proven fungicidal activity.

In this case, the reaction was successfully scaled up, yielding compound (**8e**) in a high yield of 96 % (1.255 g). During this scale-up, conditions were

identified for isolating the product via recrystallization rather than column chromatography, which once again confirmed the method's effectiveness on a gram scale.

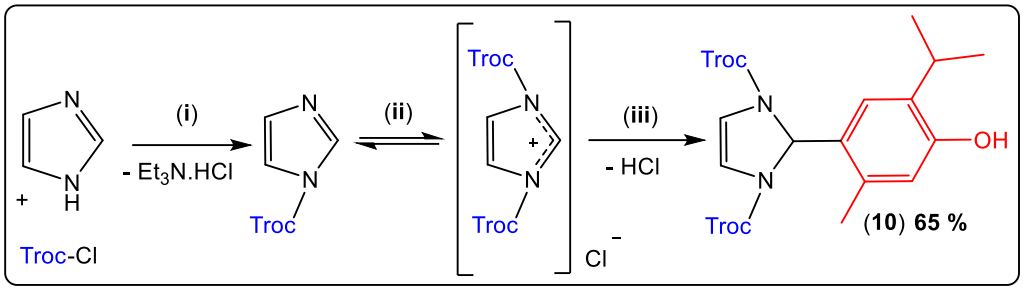
In addition to hydroxy- and methoxy-substituted indoles found in natural compounds or their analogues, this dissertation also includes 4-benzyloxyindole. The introduction of a benzyloxy group aims to expand the structural diversity of the studied substrates and to evaluate the influence of bulky substituents on the reaction mechanism. With this expansion of the scope of the approach, the applicability of the method to other nucleophilic reagents, including phenols and phenolic natural monoterpenoids, can be evaluated. The approach was also tested for phenolic nucleophilic reagents, such as resorcinol and thymol. Despite experiments conducted under various reaction conditions, the *N*-acylthiazoline reagents did not lead to the successful amidoalkylation of phenolic compounds. The probable reason for this is the lower reactivity and the inability to generate a stable *N*-acyliminium reagents derived from thiazoles. To overcome these limitations, the thiazoles were replaced with another heterocycle - imidazole. The imidazole ring is more basic and has a greater ability to stabilize the cationic intermediate by delocalizing the positive charge, generating more stable 1,3-diacyliminium reagents. It also exhibits the ability to stabilize the cationic intermediate, making it more suitable for generating more reactive electrophilic 1,3-diacyliminium reagents (**Scheme 7**).



Scheme 7. Synthesis of bis(2,2,2-trichloroethyl)-2-(2,4-dihydroxyphenyl)-1*H*-imidazole-1,3(2*H*)-dicarboxylate (**9**) via an *α*-amidoalkylation reaction; (**i**) imidazole (2 mmol), dissolved in 10 mL CH_2Cl_2, Et_3N (2 mmol), 0–4 °C, Troc-Cl (2 mmol), 20 min; (**ii**) Troc-Cl (2 mmol), 0–4 °C, 20 min; (**iii**) resorcinol (1.5 mmol), 0–4 °C, 2 h.

Following the successful application of the *α*-amidoalkylation reaction to resorcinol, the synthetic approach has been extended to other natural phenolic nucleophilic reagents. In a manner analogous to the methodology described above, the imidazole is initially activated via nitrogen acylation with Troc-Cl. In the next step, the natural monoterpenoid thymol participates in the reaction via electrophilic aromatic substitution, and the generated 1,3-diacyliminium reagent successfully amidoalkylates thymol. The amidoalkylation reaction proceeded under conditions similar to those applied to resorcinol, demonstrating the method's applicability to a variety of phenolic nucleophiles. The compound bis(2,2,2-trichloroethyl)-2-(4-hydroxy-5-isopropyl-2-methylphenyl)-1*H*-

imidazole-1,3(2*H*)-dicarboxylate (**10**) is successfully obtained in 65 % yield, as shown in **Scheme 8**.



Scheme 8. Synthesis of bis(2,2,2-trichloroethyl)-2-(4-hydroxy-5-isopropyl-2-methylphenyl)-1*H*-imidazole-1,3(2*H*)-dicarboxylate (**10**) via an α-amidoalkylation reaction; (**i**) imidazole (4 mmol), dissolved in 12 mL CH_2Cl_2, Et_3N (4 mmol), 0–4 °C, Troc-Cl (4 mmol), 20 min; (**ii**) Troc-Cl (4 mmol), 0–4 °C, 20 min; (**iii**) thymol (2 mmol), 25 °C, 24 h.

Experiments to isolate products from the amidoalkylation of resorcinol and thymol with variously substituted thiazoles were unsuccessful, whereas the use of imidazole and optimization of the conditions led to the successful isolation of compounds (**9**, 70 %; **10**, 65 %) in good yields.

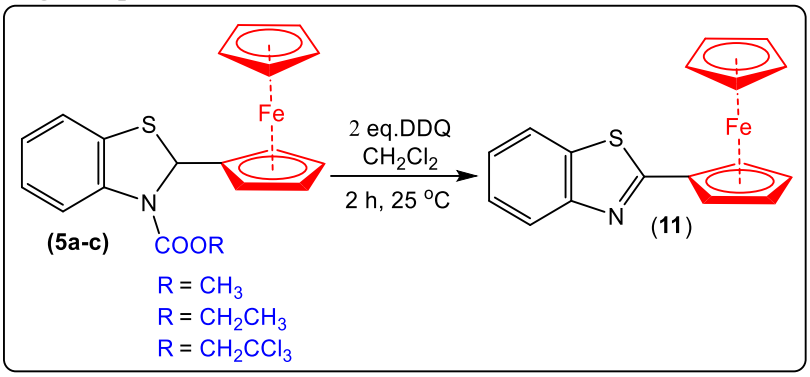
The structures of all target products obtained were characterized by their ^{1}H-proton and ^{13}C{^{1}H}-carbon NMR spectra, using two-dimensional HSQC-NMR techniques, Fourier transform infrared spectroscopy (FTIR), and high-resolution mass spectrometry (HRMS).

III. 3. Oxidative aromatization of *N*-acyl-2-(1-ferrocenyl)benzothiazolines.

A review of the literature shows that the oxidative aromatization of 2-substituted *N*-acylated heterocyclic compounds depends primarily on the type of heterocycle, but also on the acyl group and the substituent at the 2-position. There are no data in the literature on similar oxidative transformations with ferrocenyl-benzothiazolines, but a wide range of methods for other synthetic transformations of ferrocene-containing heterocyclic compounds has been described. The studies found in the literature focus on the synthesis of new 4-ferrocenyl-1,2,3,4-tetrahydroquinolines and 4-ferrocenylquinolines. These compounds are important because the quinoline core and its derivatives possess significant biological activity (antimalarial, antibacterial) and antioxidant properties, and the presence of a ferrocene moiety often enhances their pharmacological potential. The method described in the literature is a versatile and highly efficient approach for the synthesis of new 4-ferrocenyl-1,2,3,4-tetrahydroquinolines and 4-ferrocenylquinolines. Using 2 equivalents of the oxidizing agent DDQ in toluene, the aromatization of the tetrahydroquinolines proceeds successfully, with the approach yielding high yields of the target products up to 93 %. [9].

Following the successful *α*-amidoalkylation of ferrocene and the synthesis of new *N*-acylated benzothiazolines, the next step involved synthetic

transformations through their oxidative aromatization. In the search for suitable conditions, the use of DDQ as a strong oxidizing agent for ferrocene-containing *N*-acylated heterocyclic compounds was tested for the first time. It was found that oxidative reactions proceed even at room temperature in $C_2H_4Cl_2$ solvent and at an equimolar ratio of the reactants, but even after 24 hours, unreacted *N*-alkoxycarbonyl-2-ferrocenylbenzothiazoline remains. The yields of the target compound (**11**) (which has demonstrated antitumor activity) remain low even after boiling the reaction mixture. Therefore, the reactions were carried out with a twofold excess of the oxidizing agent DDQ. Thus, maximum yields were obtained by conducting the oxidation reactions at room temperature in $C_2H_4Cl_2$ for 2 hours using 2 equivalents of DDQ.



Scheme 9. Oxidative transformations of *N*-acyl-2-ferrocenylbenzothiazolines (**5a**–**c**).

Table 4. Yields of 2-ferrocenylbenzo[*d*]thiazole (**11**), as shown in **Scheme 9.**

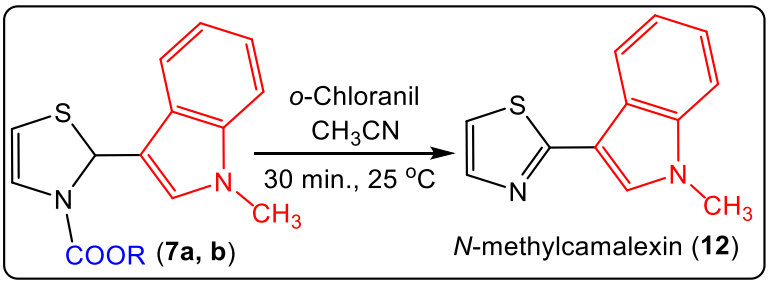
Starting material (5)	Yield (11), %	t_r, °C
a	73	
b	66	120 – 122
c	81	

The resulting precursors (5a–c) were successfully converted into the target 2-ferrocenylbenzo[*d*]thiazole (**11**) in high yields ranging from 66 % to 81 % (**Scheme 3**, **Table 1**). As previously observed by other authors, the acyl group influences the reaction, the rate of which depends on its leaving ability. The results presented show that the yield of the target product (**11**) varies depending on the alkyl chloroformate used. Unlike the methyl and ethyl groups, the presence of electron-accepting Troc-Cl atoms likely facilitates oxidative aromatization. The subsequent oxidative transformation yields higher yields compared to the oxidative conversion of compounds **5a** and **5b**. The ethoxycarbonyl group in compound **5b** is more difficult to cleave, and this may lead to side reactions during oxidative aromatization, which explains the lower yield of 66 %.

The products obtained were purified by column chromatography and spectrally characterized by ^{1}H-NMR, ^{13}C-NMR, IR, and MS analyses.

III. 4. Oxidative transformations of 2-indolylthiazolines. Synthesis of the natural phytoalexin *N-methylcamalexin* and oxy-camalexins.

The reactivity of 2-substituted *N*-acylthiazolines in oxidative aromatization reactions is significantly higher than that of similarly substituted benzothiazolines. In the oxidative aromatization to yield the phytoalexin *N-methylcamalexin*, the previously established and published conditions were initially applied. The reaction conditions for oxidative aromatization were successfully optimized by varying the temperature, the ratio of reactants, and the type of oxidizing agent (**Table 5**). The oxidizing agent *o*-Chloranil was preferred due to environmental considerations and its potential for effective chromatographic purification and isolation of the desired camalexins. The starting precursors, *N*-acylated compounds **7a**–**b**, were successfully oxidized with an equivalent amount of *o*-Chloranil (**Scheme 10**). The phytoalexin *N-methylcamalexin* was obtained in quantitative yield.



Scheme 10. Oxidative aromatization to yield *N-methylcamalexin* (**12**).

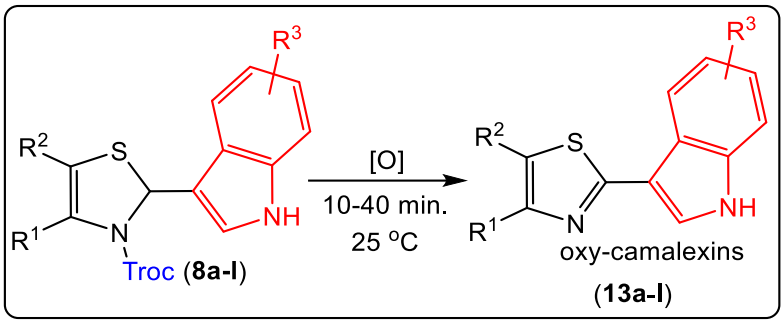
Table 5. Yields for the natural *N-methylcamalexin* (**12**), as shown in **Scheme 4**.

Starting material (7)	*o*-Chloranil	
	Yield (12), %	t_T, °C
a	86* [8]	58–60
b	99	

* The natural compound *N-methylcamalexin* (**12**) was synthesized on a gram scale (1.014 g) with a yield of 86 %.

Optimizing the reaction conditions for the synthesis of the natural compound *N-methylcamalexin* (**12**) also involves changing the type and amount of the solvent. The following conditions have been determined as optimal for oxidative aromatization: Oxidizing agent *o*-Chloranil; Solvent acetonitrile; Room temperature; Reaction time – 30 minutes. The phytoalexin *N-methylcamalexin* (**12**) was obtained in gram quantities from compound (**7a**) with a yield of 86 % (1.014 g, **Scheme 4**). The structure of the resulting aromatic compound (**12**) was confirmed by spectroscopic analysis. Following these successful oxidative rearomatizations, we proceeded to optimize the conditions and carry out further oxidative transformations for the synthesis of various oxy-camalexins. A series of experiments were conducted using equivalent amounts of the oxidizing agents *o*-Chloranil and DDQ. Optimization of the reaction conditions for the synthesis of

oxy-camalexins involves changing the type and amount of solvent, as well as using different oxidizing reagents. The reaction conditions for oxidative rearomatization are presented in **Scheme 11**.



Scheme 11. Oxidation reactions for the preparation of oxy-camalexins (**13a**–**l**).

The oxidation reaction with *o*-Chloranil was carried out in acetonitrile at room temperature for 10 to 40 minutes. Ten new oxy-camalexins were obtained in high yields ranging from 62 % to 98 %, as shown in **Scheme 11**. For some of the reactions, oxidative aromatization was also tested with DDQ. The synthetic transformations of precursors (**8b**) and (**8i**) were carried out at room temperature in CH_2Cl_2, using an equimolar amount of the oxidizing agent. From the oxidation reactions conducted, we can conclude that the oxidizing agent influences the reaction time. Oxidation reactions with *o*-Chloranil proceed within a time range of 15–40 minutes, depending on the different substituents on the indole moiety. The electronic effects of the substituent on the indole fragment play a role; compound (**13c**) undergoes complete aromatization within 15 minutes. In contrast, for compound (**13l**), which contains a hydroxyl group, the reaction takes the longest time, 40 minutes. In contrast, reactions using DDQ significantly shorten the reaction time to 10 minutes. The resulting products (**13b** and **13i**) were isolated with approximately a 10 % higher yield compared to the reactions conducted with *o*-Chloranil (**Table 6**).

Table 6. Reaction conditions and yields of the compounds obtained (**13a**–**l**), as shown in **Scheme 11**.

Product (13a-l)	R^1	R^2	R^3	Reaction time, min.	Yield, %	$t_т$, °C
a	CH_3	H	4-OCH_3	30	86	180–181
b	CH_3	CH_3	4-OCH_3	30	80(93)*	212–214
c	H	H	5-OCH_3	15	98	112–114 [8, 10]
d	CH_3	H	5-OCH_3	30	90	Oil
e	CH_3	CH_3	5-OCH_3	30	91	169–170
f	H	H	6-OCH_3	30	78	161–163 [10]
g	CH_3	CH_3	6-OCH_3	20	91	163–165
h	CH_3	H	4,6-$(OCH_3)_2$	30	68	167–169
i	CH_3	CH_3	4,6-$(OCH_3)_2$	30	70(80)*	188–190
j	H	H	4-BnO	30	82	166–168
k	CH_3	CH_3	4-BnO	30	90	168–170

l	CH_3	CH_3	5-OH	40	62	233–235

* With DDQ as the oxidizing agent in dichloromethane (CH_2Cl_2) for 10 minutes at room temperature.

Despite the higher yield and shorter reaction time, the oxidizing agent *o*-Chloranil was chosen for environmental reasons and because it allows for more efficient chromatographic separation and isolation of the resulting oxy-camalexins. **Scheme 12** proposes putative a mechanism for the oxidative reaction with DDQ.

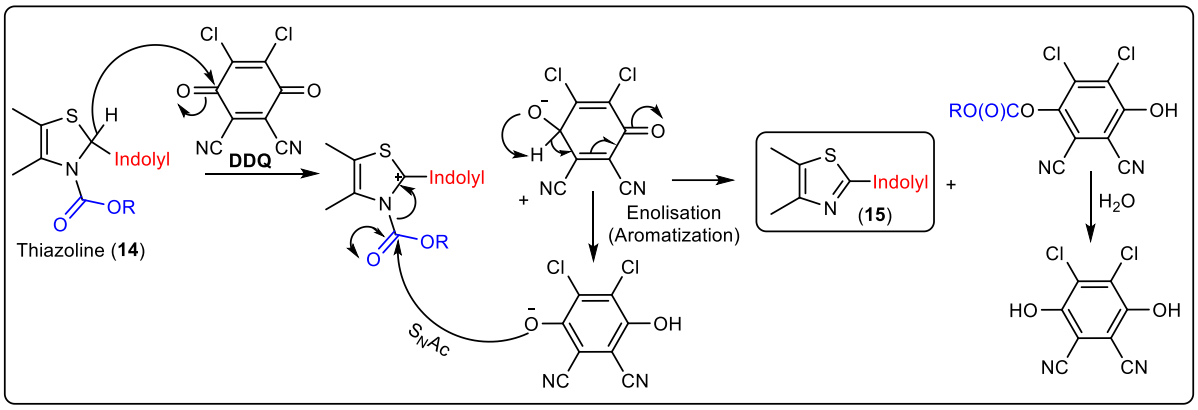


Figure 12. Proposed putative mechanism for oxidative aromatization with DDQ.

The proposed mechanism of oxidative aromatization involves the use of the oxidizing agent DDQ, which abstracts a hydride anion from the C-atom at the 2-position of the thiazoline ring (**14**), generating an iminium-type thiazoline cation, and the oxidizing agent is converted to its reduced hydroquinone form ($DDQH_2$). The next key step is deacylation, in which the protecting group is removed from the *N*-atom via nucleophilic acyl substitution (S_NAc), followed by enolization, which allows for the rearomatization of the ring. In this type of oxidative aromatization, thiazoline compounds are transformed into stable aromatic products, successfully yielding oxy-camalexins.

The method has also proven effective when scaled up for synthesis in gram quantities. For this purpose, we selected compound **8e**, 2,2,2-trichloroethyl 5-methoxy-3-(thiazol-2-yl)-1*H*-indole-1-carboxylate. By performing oxidative aromatization of **8e**, the final target product, 2-(5-methoxy-1*H*-indol-3-yl)-4,5-dimethylthiazole (**13e**), was synthesized with a 90 % yield (0.6975 g).

In conclusion, we can state that the main advantages of the developed two-step approach for the synthesis of oxy-camalexins are its high efficiency, the use of readily available starting materials, and the high yields of the resulting compounds, ranging from 62 % to 98 %. Unlike the published approaches presented in the literature review, such as the Suzuki reaction, the synthetic approach we propose for the preparation of oxy-camalexins does not require the use of expensive catalysts. The method allows for scaling up and obtaining the quantities of target products required for subsequent studies. The approach has proven successful in yielding compounds that are inaccessible using methods reported in the literature, such as the Ayer method and the Hantzsch reaction. One

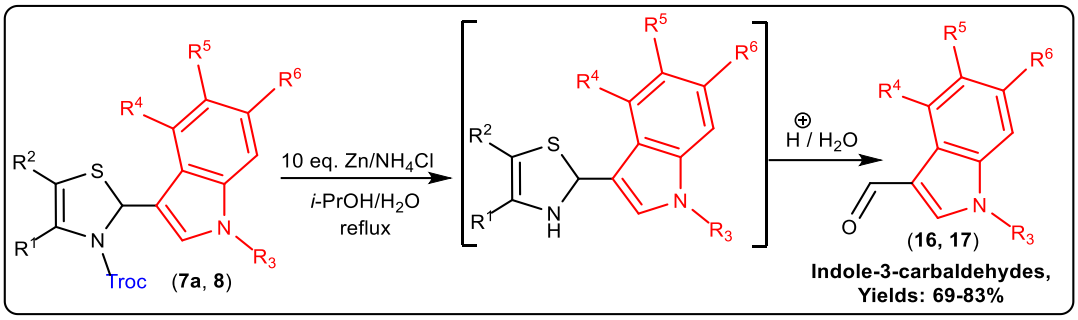
of the advantages and successes of the present work is the application of our proposed approach for the synthesis of *N-methylcamalexin* and hardly accessible analogues of *Camalexin*. We successfully obtained for the first time two 4,6-dimethoxy camalexins-(2-(4,6-dimethoxy-1*H*-indol-3-yl)-4-methylthiazole and 2-(4,6-dimethoxy-1*H*-indol-3-yl)-4,5-dimethylthiazole), for which no conditions for preparation have been found using the methods published in the literature.

III. 5. Aldehyde group disclosure in reductive transformations of *N*-Troc-2-(3-indolyl)-thiazolines.

In 2018, a new approach for the synthesis of indole-3-carboxaldehydes [5], based on the use of *N*-Troc-2-(3-indolyl)-thiazolines and 1,3-diacylimidazoline intermediates as „masked formyl equivalents". This type of reaction involves the reductive elimination of the acyl group (2,2,2-trichloroethoxycarbonyl) using activated zinc (Zn) and ammonium chloride (NH_4Cl). For thiazoline compounds, the reaction proceeds upon heating in a mixture of methanol and water ($MeOH/H_2O$) for 3 hours, yielding yields in the range of 70 % – 74 %. Reductive transformations involving 1,3-diacylimidazoline compounds lead to an increase in yields up to 82 %. These studies have shown that the imidazoline ring is more stable and less prone to hydrolysis than its thiazoline analogues. This approach has the potential to be expanded and scaled up to yield a variety of formulated compounds containing reactive groups and electron-donating substituents in their structures, while avoiding the use of expensive catalysts or organometallic reagents.

That is why, in this dissertation, our focus was on building upon the proposed approach for the formation of indoles; here, we successfully further develop the concept of using the *N*-Troc-thiazoline moiety as a masked formyl equivalent. In the present studies, we expanded the scope of the approach by investigating the reactivity of the previously obtained precursors for the synthesis of oxy-camalexins, *N-methylcamalexin*, as well as 1,3-diacylimidazolines containing a phenolic moiety in their structure. The investigated reductive transformations proceeded in the presence of activated Zn and NH_4Cl, and the reaction conditions were optimized. The initially used $MeOH/H_2O$ mixture was replaced with an isopropanol and water system ($i\text{-}PrOH/H_2O$), which allowed the reaction to be carried out at a higher temperature, reaching the boiling point of the reaction mixture, which in turn increased the yields of the target products.

The reductive transformations of the *N*-Troc-thiazoline moiety are shown in **Scheme 13**, and the reaction conditions and yields are shown in **Table 7**.



Scheme 13. Aldehyde group disclosure in reductive transformations of *N*-Troc-2-(3-indolyl)-thiazolines.

Table 7. Conditions for the synthesis and yields of variously substituted indole-3-carbaldehydes.

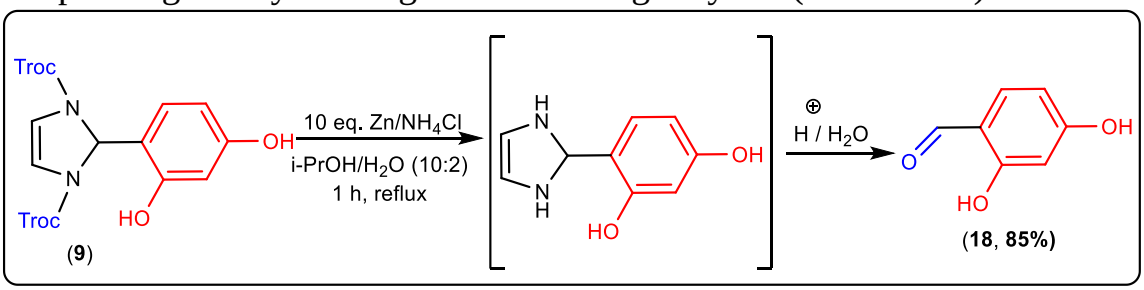
Starting material (8)	R^1	R^2	R^3	R^4	R^5	R^6	Yield (16/17), %	$t_т$, °C
l	CH_3	CH_3	H	H	OH	H	**a** 73	239–241
c	H	H	H	H	OCH_3	H	**b** 77	177–179
d	CH_3	H	H	H	OCH_3	H	**b** 83	
i	CH_3	CH_3	H	OCH_3	H	OCH_3	**c** 77	140–142
a	CH_3	H	H	OCH_3	H	H	**d** 69	153–155
k	CH_3	CH_3	H	BnO	H	H	**e** 72	179–181
7a	H	H	CH	H	H	H	75	Oil

The reaction conditions for the preparation of indole-3-carbaldehydes are: 2 hours of boiling in i-PrOH/H_2O (10:2).

To determine the scope of the method, variously substituted *N*-Troc-2-indolylthiazolines containing electron-donating substituents - hydroxy (-OH), methoxy (-OCH_3), benzyloxy (-BnO), and an *N*-methyl group were used. The results obtained show that the method is applicable for the synthesis of variously substituted indole-3-carbaldehydes, including compounds containing sensitive functional groups, along with *N*-methylindole-3-carbaldehyde and, in particular, 4,6-dimethoxy-1*H*-indole-3-carbaldehyde, which is obtained in trace amounts by the methods known to date. Pedras reports that the formation of 4,6-dimethoxyindole yields the expected 4,6-dimethoxy-1*H*-indole-3-carbaldehyde (33 %), as well as an additional product of substitution with a formyl group at the C_7 position (59 %). Similarly, the formylation of 5,7-dimethoxyindole led to the corresponding 5,7-dimethoxy-1*H*-indole-3-carbaldehyde (45 %), plus an additional product of substitution with a formyl group at the C_4 position (30 %) [7]. The selective preparation of hardly accessible aldehydes is one of the main advantages of this synthetic transformation.

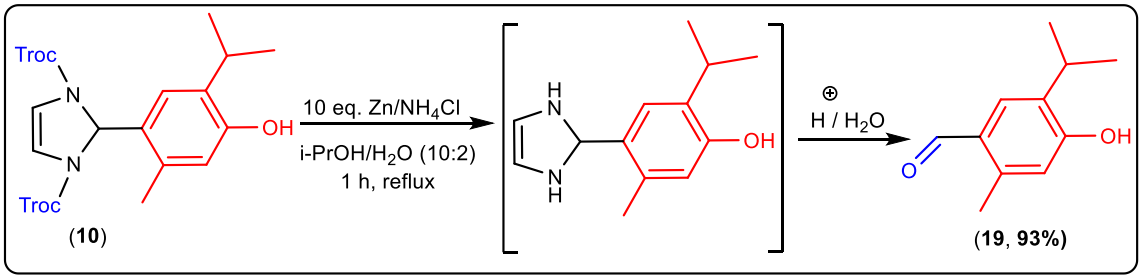
III. 5.1. Aldehyde group disclosure in reductive transformations of 1,3-bis(2,2,2-trichloroethoxycarbonyl)-2-phenyl-imidazolines.

Following the successful application of the method for the synthesis of variously substituted indole-3-carbaldehydes, the possibility of transforming 1,3-diacylated imidazolines containing phenolic moieties in their structure was also investigated. For this purpose, compounds (**9**, **10**) containing resorcinol and thymol in their structures, shown in **Schemes 14** and **15**, were selected. The transformations of such compounds are of particular interest due to the presence of hydroxyl groups, which may participate in additional reactions or lead to undesirable side reactions. The elimination of the formyl group in this case proceeds significantly more easily compared to thiazolines, with the corresponding aldehyde being obtained in higher yield (**Scheme 14**).



Scheme 14. Aldehyde group disclosure in reductive transformations of bis(2,2,2-trichloroethyl)-2-(2,4-dihydroxyphenyl)-1*H*-imidazole-1,3(2*H*)-dicarboxylate.

Similarly, in compound (**10**), which contains a thymol moiety, the reaction proceeds efficiently, and 4-hydroxy-5-isopropyl-2-methylbenzaldehyde (**19**) is successfully obtained in a 93 % yield.



Scheme 15. Aldehyde group disclosure in reductive transformations of bis(2,2,2-trichloroethyl)-2-(4-hydroxy-5-isopropyl-2-methylphenyl)-1*H*-imidazole-1,3(2*H*)-dicarboxylate.

Table 8 presents the reaction conditions and yields for the synthesis of the target arylcarbaldehydes. The reactions proceed with good yields, indicating that the method is applicable to other substrates, such as the selected activated arenes containing two hydroxyl groups in their structure. Compound (**19**) is obtained in a higher yield of 93 %, in contrast to compound (**18**); the likely reason is the better solubility of the starting precursor.

Table 8. Yields of the aryl carbaldehydes obtained (**18**, **19**).

Starting material	Product	Yield, %	t_r, °C
9	**18**	85	136–138
10	**19**	93	131–133

In conclusion, we can summarize that this study has expanded the synthetic potential of the method proposed by Stremski et al. [5]. The method demonstrates good functionality, allowing the preparation of a variety of aldehydes containing electron-donating substituents - hydroxy, methoxy, benzyloxy, and *N*-methyl groups in their structures. It has been demonstrated that the developed approach is also applicable to synthetic transformations of precursors containing phenolic moieties, such as the obtained derivatives of resorcinol and thymol. The results obtained expand the synthetic potential of the method previously proposed by our synthetic group and confirm its applicability as a scalable approach for the synthesis of functionalized indole-3-carbaldehydes. Some of these represent important precursors for the preparation of biologically active heterocyclic compounds. A significant advantage in terms of its applicability is the production of 4,6-dimethoxyindole-3-carbaldehyde. The production of hard-to-obtain aldehydes both natural ones and those with important biological activity highlights the effectiveness and practical value of this approach. A major limitation of the method is the α-amidoalkylation reaction and the preparation of precursors for reductive transformations. Only a small portion of the successful experiments is presented in the dissertation. To date, amidoalkylation has proceeded successfully with activated arenes - hydroxybenzenes, phenolic terpenoids, *N*,*N*-dimethylaniline, and other variously substituted indoles and pyrroles. This significantly limits the scope of its applicability and necessitates the selection of starting nucleophilic reagents, as well as the optimization of reaction conditions. As a result, the scope of the method's applicability remains limited. A subject for future research is the conduct of α-amidoalkylation reactions with other nucleophilic reagents that can undergo reductive transformations.

All of the aldehydes obtained in this dissertation, presented in **Figure 5**, are known compounds described in the scientific literature. They are also commercially available from specialized suppliers of chemical reagents, which confirms their place among the known organic compounds.

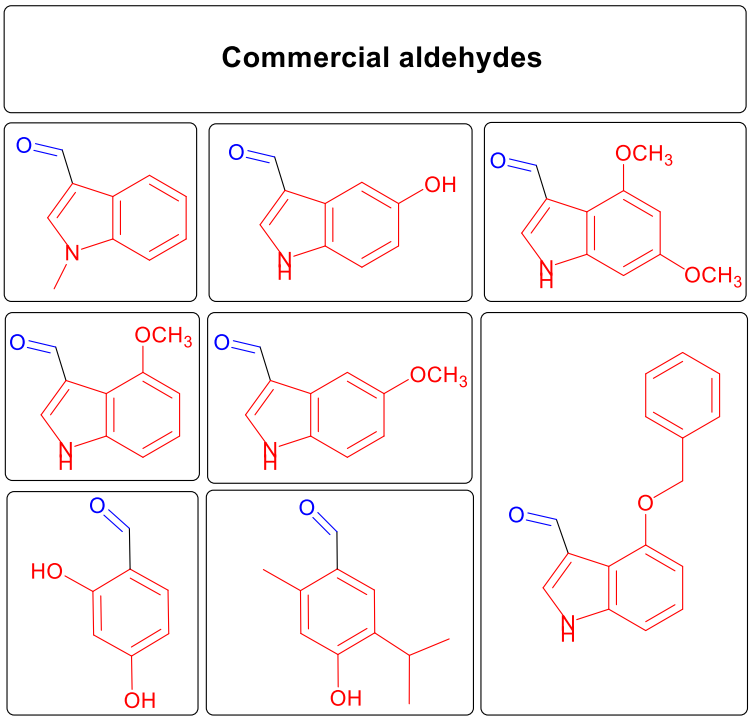


Figure 5. Commercial aldehydes obtained.

The structures and purity of all obtained compounds were confirmed by spectral methods. Unpublished spectral data are described in the dissertation, the signals for the proton ^{1}H-NMR and carbon ^{13}C-NMR spectra are reported and are presented in the experimental section. For the published compounds, all proton ^{1}H- and carbon ^{13}C{1H}-NMR spectra, two-dimensional HSQC-NMR techniques, IR and HPLC-MS spectra are available in scientific publications and accompanying supplementary materials, which are open access.

IV. SUMMARY OF RESULTS AND CONCLUSIONS

• For the first time, *α*-amidoalkylation reactions of ferrocene with *N*-acyliminium reagents derived from benzothiazole and alkyl chloroformates were carried out. **3 novel** (SciFinder, Reaxys) ferrocene-containing hybrid molecules were successfully synthesized;

• The appropriate conditions for oxidative aromatization of *N*-acyl-2-(1-ferrocenyl)benzothiazolines were established, with the preparation of the antitumor agent – 2-ferrocenyl-benzo[*d*]thiazole in yields of 66 % – 81 %;

• The appropriate conditions for *α*-amidoalkylation of hydroxy-, methoxy-, *N*-methyl- and benzyloxyindoles with *N*-acyliminium reagents derived from thiazole/methyl thiazoles and alkyl chloroformates were established. **13 novel** (SciFinder, Reaxys) *N*-acylated precursors of camalexins were synthesized;

• For the first time, the appropriate conditions for *α*-amidoalkylation of resorcinol and thymol with 1,3-diacyliminium reagents derived from imidazole and Troc-Cl have been established. **2 novel** (SciFinder, Reaxys) imidazoline derivatives containing a phenolic fragment have been obtained;

• After oxidative aromatization of the corresponding thiazolines, **10 novel** (SciFinder, Reaxys) oxy-camalexins have been obtained, including analogues of the difficult-to-access 2-(4,6-dimethoxy-1*H*-indol-3-yl)thiazole. The two-step synthetic approach is distinguished by high efficiency, use of available reagents and the possibility of scaling up;

• For the first time, an approach for the synthesis of natural *N-methylcamalexin* in gram quantities has been proposed;

• The appropriate conditions for purification and isolation of all obtained products with preparative column chromatography on neutral alumina Al_2O_3 or silica gel have been found;

• Various 1*H*-indole-3-carbaldehydes were synthesized by revealing an aldehyde group during reductive transformations of *N*-Troc-2-(3-indolyl)-thiazolines with different substituents in the indole fragment. **6 differently** substituted 1*H*-indole-3-carbaldehydes were obtained with high yields in the range of 69 % – 83 %, among which the natural one - 5-hydroxy-1*H*-indole-3-carbaldehyde with important biological activity;

• The method was extended by revealing an aldehyde group during reductive transformations of 1,3-diacylimidazolines containing a phenol fragment in their

structure, allowing for the selective preparation of aromatic aldehydes with different substituents and sensitive functional groups;

• The scope of applicability of the method remains limited with respect to the α-amidoalkylation reaction;

• As a result of the conducted research, **43 compounds** were synthesized, of which **28 are new** and not described in the literature (SciFinder, Reaxys);

• All newly synthesized compounds were spectrally characterized and structurally proven by – ^{1}H-, ^{13}C-NMR, FTIR spectra, HSQC-NMR and mass spectrometry (HRMS). Melting points were determined for solids.

V. PUBLICATIONS RELATED TO THE DISSERTATION

1. Stremski, Y.; **Bachvarova, M**.; Statkova-Abeghe, S.; Angelov, P.; Ivanov, I.; Ahmedova, A.; Dołęga, A. Synthesis and Crystal Structure of Ferrocenyl Benzothiazole Derivatives. *Journal of Organometallic Chemistry*, 1001, **2023**. https://doi.org/10.1016/j.jorganchem.2023.122871

Cited Articles:

Yang, H.; Zhang, D.; Song, Y.; Shi, J.; Yang, L.; Zhang, D.; Liang, R.; Liu, A. Molecular Dynamic Study of Heterocyclic Compounds and Carbon Nanotube. *Applied Physics A*, 130(6), **2024**. https://doi.org/10.1007/s00339-024-07555-y

2. **Bachvarova, M**.; Stremski, Y.; Ganchev, D.; Statkova-Abeghe, S.; Angelov, P.; Ivanov, I. An Efficient Method for the Synthesis and *In Silico* Study of Novel Oxy-Camalexins. *Molecules*, 30(9), 2049, **2025**. https://doi.org/10.3390/molecules30092049

Publication 1	Publication 2
IF_{2023} = 2.4, (Q2 - Scopus, Web of Science)	IF_{2025} = 4.6, (Q1 - Scopus, Web of Science)

VI. PARTICIPATION IN CONFERENCES

● **October 7–8, 2022** – Sixth Scientific Conference for Students and PhD Candidates "Challenges in Chemistry," Faculty of Chemistry, Paisii Hilendarski University of Plovdiv. Presentation: Synthesis of New Halogen-Containing Analogues of the Phytoalexin Camalexin. Authors: **M. Bachvarova**, Y. Stremski, S. Statkova-Abeghe, P. Angelov, I. Ivanov;

● **May 19, 2023** – XXI National Chemistry Conference for Students and PhD Candidates, Faculty of Chemistry and Pharmacy, St. Kliment Ohridski University of Sofia. Presentation: Synthesis and Radical-Scavenging Activity of Benzazoles Containing a Resorcinol Fragment. Authors: E. Suyleyman, **M. Bachvarova**, Y. Stremski, S. Statkova-Abeghe, D. Kirkova, M. Docheva. Presentation: Synthesis and Antimicrobial Activity of Halogenated Camalexins. Authors: **M. Bachvarova**, Y. Stremski, B. Goranov, Z. Denkova, S. Statkova-Abeghe, P. Angelov, I. Ivanov;

● **August 17–20, 2023** – Oral presentation in English at the 25th International Conference "Materials, Methods & Technologies," Bulgaria, Burgas, Bulgaria. "The Synthesis and Radical Scavenging Activity of New Benzazole-Resorcinol Hybrids." Authors: **M. Bachvarova**, E. Suyleyman, D. Kirkova, Y. Stremski, S. Statkova-Abeghe, M. Docheva;

● **October 13–14, 2023** – Two poster presentations at the 12th Scientific Conference in Chemistry with International Participation, Park Hotel Saint Petersburg, Plovdiv, organized by the Faculty of Chemistry at Paisii Hilendarski University of Plovdiv. „Novel analogues of Azacamalexin". Автори: Y. Stremski, **M. Bachvarova**, D. Kirkova, S. Statkova-Abeghe and „Synthesis, structure and activity of benzazole-based hybrids". Автори: **M. Bachvarova**, E. Suyleyman, D. Kirkova, Y. Stremski, S. Statkova-Abeghe, M. Docheva;

● **November 17–19, 2023** – Jubilee Conference dedicated to the 20th Anniversary of the Pharmacy Program, Medical University of Plovdiv. Presentation: Antimicrobial Activity of Natural and Synthetic Camalexins. Authors: **M. Bachvarova**, Y. Stremski, B. Goranov, Z. Denkova, S. Statkova-Abeghe, P. Angelov, I. Ivanov;

● **June 5–6, 2024** – Two poster presentations at the International Seminar: Instrumental Techniques and Methods for Chemical Analysis – Challenges and New Solutions, Plovdiv. Poster: "Application of Thyme Essential Oil for the Preparation of Biologically Active Substances." Authors: **M. Bachvarova**, S. Bobova, A. Hristozova, Y. Stremski, S. Statkova-Abeghe. Poster: "Synthesis and Spectral Characterization of Novel Indole-Containing Tris-Heterocycles."

Authors: E. Milinova, Y. Stremski, **M. Bachvarova**, D. Kirkova, S. Statkova-Abeghe;

● **June 20–23, 2024** – Xth International Scientific Conference of Young Researchers – Plovdiv 2024, organized by the Young Researchers' Club at the Union of Scientists in Bulgaria – Plovdiv. Poster: "Study of the Spectral Properties of Benzocamalexin." Authors: **Maria Bachvarova**, Mina Todorova, Ivan Popov, Yordan Stremski, Stela Statkova-Abeghe;

● **March 5–7, 2024** – Scientific Forum for Students and PhD Candidates "Revolutions and Evolutions," Paisii Hilendarski University of Plovdiv. Presentation: Application of Thyme Essential Oil for the Preparation of Biologically Active Substances. Authors: St. Bobova, **M. Bachvarova**, Y. Stremski, S. Statkova-Abeghe;

● **May 16–17, 2024** – XXII National Chemistry Conference for Students and PhD Candidates 2024, Faculty of Chemistry and Pharmacy, St. Kliment Ohridski University of Sofia. Presentation: "Properties of Multifunctional Molecules with Potential Applications in Cosmetics." Authors: St. Bobova, **M. Bachvarova**, Y. Stremski, M. Todorova, S. Statkova-Abeghe. Presentation: "Synthesis of New Benzocamalexin Analogues." Authors: E. Milinova, Y. Stremski, **M. Bachvarova**, D. Kirkova, S. Statkova-Abeghe;

● **June 5, 2024** – International Seminar "Instrumental Techniques and Methods for Chemical Analysis – Challenges and New Solutions," organized by ACM_2, Paisii Hilendarski University of Plovdiv, and Thermo Fisher Scientific. Poster: "Synthesis and Spectral Study of Benzocamalexins." Authors: **M. Bachvarova**, Y. Stremski, I. Popov, M. Todorova, S. Statkova-Abeghe;

● **October 18–19, 2024** – Seventh Scientific Conference for Students and PhD Candidates "Challenges in Chemistry," Faculty of Chemistry, Paisii Hilendarski University of Plovdiv. Presentation: "Reductive Transformations of 2-Substituted Thiazolines." Authors: **M. Bachvarova**, Y. Stremski, S. Statkova-Abeghe, P. Angelov, I. Ivanov;

● **May 16–17, 2025** – 2nd International Scientific Conference – Plovdiv 2025, The Second International Conference on Medicinal, Aromatic, and Edible Plants (MAEPs) and Their By-Products. Oral Presentation: "Application of Thyme Essential Oil for the Synthesis of 2-Substituted Benzimidazolines." Authors: **M. Bachvarova**, D. Kirkova, Y. Stremski, S. Statkova-Abeghe, M. Docheva. Poster: "Antioxidant Activity of Various Extracts from Medicinal Plants and Tobacco." Authors: Desislava Kirkova, **M. Bachvarova**, Y. Stremski, M. Docheva, S. Statkova-Abeghe;

● **July 3, 2025** – Conference “Digital Sustainable Ecosystems – Technological Solutions and Social Models for Ecosystem Sustainability – DUEcoS,” Paisii Hilendarski University of Plovdiv. Presentation: Synthesis and In Silico Analysis of New (Aza)Camalexin Analogues. Authors: Y. Stremski, **M. Bachvarova**, S. Statkova-Abeghe, D. Gunchev;

VII. PARTICIPATION IN RESEARCH PROJECTS

1. **2022–2024** – National project under contract No. KP-06-M69/4, funded by the Research Fund, Ministry of Education and Science, on the topic: "Investigation of Activity and Derivatization of Biologically Active Compounds in Tobacco (Nicotiana tabacum) and Wild Medicinal Plants in Bulgaria," supervised by Assoc. Prof. Dr. Desislava Kirkova, ITTI;

2. **2023–2024** – Project under the Student Research Program of Paisii Hilendarski University of Plovdiv, contract No. MU-PD23-CF-003, on the topic: "Synthesis and Properties of New Multifunctional Molecules with Potential Applications in Cosmetics," supervised by Assoc. Prof. Dr. Stela Statkova-Abeghe;

3. **2023–2024** – Project under contract No. FP23-CF-005 on the topic: "Synthesis, Application, In Silico and In Vitro Biological Evaluation of New Biofunctional Molecules," supervised by Prof. Dr. Iliyan Ivanov;

4. **2023–2025** – National project No. BG-RRP-2.004-0001-C01, funded by the European Union – NextGeneration EU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, "Digital Sustainable Ecosystems – Technological Solutions and Social Models for Ecosystem Sustainability" (DUEcoS), contract D23-CF-001 on the topic: "Production of Phytoalexins and Their Analogues with Potential Applications in Plant Protection," supervised by Assoc. Prof. Dr. Stela Statkova-Abeghe;

5. **2025–2027** – National project No. BG16RFPR002-1.014-0007, Competence Center "Personalized Innovative Medicine (PERIMED-2)," funded under the "Research, Innovation and Digitalization for Smart Transformation" Program, co-financed by the European Union.

VIII. REFERENCES

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