MOLDOVA STATE UNIVERSITY

DOCTORAL SCHOOL OF NATURAL SCIENCES

Consortium: Moldova State University, Institute for Information Society Development, *"Bogdan Petriceicu Hasdeu"* State University of Cahul

As a manuscript
У.Д.К.: 547.792 544.121.4
544.122.4 544.164/165
632.952

CIOBANU NATALIA

SYNTHESIS OF SUBSTITUTED DIHYDROPYRIMIDINE-5-CARBOXYLATES

143.01. ORGANIC CHEMISTRY

Summary of the doctoral thesis in chemical sciences

CHISINAU 2025

The thesis was elaborated in the Laboratory of Organic Synthesis of the Institute of Chemistry of the Moldova State University, Doctoral School of Natural Sciences at the Moldova State University.

Scientific advisor:

MACAEV Fliur	doctor habilitat chemical sciences, professor, corresponding member of the Academy of Sciences of Moldova, Institute of Chemistry, Moldova Stat University

Composition of the Doctoral Commission:

CIOCARLAN Alexandru	doctor habilitatus of chemical sciences, associate professor, Institute of Chemistry, Moldova Stat University – **President of the Doctoral Commission**
MACAEV Fliur	doctor habilitatus of chemical sciences, professor, corresponding member of the Academy of Sciences of Moldova, Institute of Chemistry, Moldova Stat University - **scientific advisor**
KULCITKI Veaceslav	doctor habilitat in chemical sciences, associate professor, Institute of Chemistry, Moldova Stat University – **reviewer**
STURZA Rodica	doctor habilitat in technical sciences, professor, corresponding member of the Academy of Sciences of Moldova, Technical University of Moldova – **reviewer**
CHEPTANARU Constantin	doctor of chemical sciences, associate professor, "*Nicolae Testemiţanu"* Moldova State University of Medicine and Pharmacy – **reviewer**

The support will take place on "October 29, 2025" at 15-00, the meeting of the doctoral thesis support of the Doctoral School of Natural Sciences of the Moldova State University, at the address: Chisinau city, Kogalniceanu street, 65 A, room 332, block 3.

The doctoral thesis and abstract can be consulted at the National Library of the Republic of Moldova, Central Library of the Republic of Moldova (MD 2009, Chisinau mun., 60, Alexei Mateevici str.) and on web page of ANACEC (http://www.anacec.md).

The abstract was submitted "September 12, 2025"

Chairman of the Doctoral Commission **CIOCARLAN Alexandru**
doctor habilitat in chemical sciences, associate professor

Scientific Director **MACAEV Fliur**
doctor habilitat in chemical sciences, professor,
corresponding member of Academy of Sciences of
Moldova

Author **CIOBANU Natalia**

TABLE OF CONTENTS

GENERAL CHARACTERISTICS OF THE WORK

Relevance and significance of the topic

Currently, considerable attention is given to the study of 4-aryl-2-thioxo(oxo)-pyrimidine-5-carboxylates, since pharmaceuticals based on these compounds exhibit cardiotropic, antiviral, and antitubercular activities and are used in medical practice. Among the important challenges in the synthesis of these substances is the development of one-pot synthetic methods employing inexpensive, regenerable catalysts, including those aimed at obtaining enantiomerically enriched 4-aryl-substituted dihydropyrimidines.

In this work on the synthesis of dihydropyrimidine-5-carboxylates, we set out to use readily available, inexpensive, and highly reactive starting materials such as ethyl acetoacetate, urea, thiourea, and aromatic benzaldehydes. Despite extensive research on substituted dihydropyrimidine-5-carboxylates, to date there have been no systematic studies on synthesis involving catalytic systems based on (+)-tartaric acid, choline chloride, imidazolium-based ionic liquids, and low-methoxylated pectin, which can influence the chemo- and stereoselectivity of the Biginelli reaction — a relevant and promising task.

The use of dihydropyrimidine-5-carboxylates for developing synthetic methods for new derivatives can be considered a convenient model for studying several theoretical problems: the mutual influence of the nature of the 4-aryl substituent and the dihydropyrimidine ring on reactivity and chemoselectivity under enolization, substitution, and addition reaction conditions, as well as investigating the relationship between biological properties and structure. This defines the relevance of the present study.

Research purpose

The objective of this work is to develop new catalytic systems based on (+)-tartaric acid, choline chloride, imidazolium ionic liquids, and low-methoxylated pectin for the development of synthetic methods for substituted dihydropyrimidine-5-carboxylates, as well as to study their structure and properties. Additionally, the synthesis of dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylates with activated methylene groups, and α,β-unsaturated compounds from the group of arylidene-3-oxo-5-aryl-3,5-dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylates, necessary for studying the dependence of biological properties on compound structure, was planned.

Research objectives

In accordance with the stated objective of the dissertation, the following tasks were established:

• Development of synthetic schemes for new eutectic mixtures based on functionalized imidazolium ionic liquids;

• Investigation of the activity, selectivity, and stability of (+)-tartaric, citric, galacturonic acids, choline chloride, and the synthesized eutectic mixtures under Biginelli reaction conditions;

• Determination of optimal conditions for the synthesis of substituted dihydropyrimidine-5-carboxylates and their use in constructing condensed heterocyclic derivatives;

• Identification of organocatalytic properties of low-methoxylated pectin for developing a synthetic method for monastrol - a mitotic kinesin Eg5 inhibitor;

• Study of one-pot reactions of substituted dihydropyrimidine-5-carboxylates with aromatic aldehydes and monochloroacetic acid;

• Evaluation of the structure–antimicrobial and antitumor activity relationships within the series of synthesized substituted dihydropyrimidine-5-carboxylates.

Research hypothesis

The research presented in this work was based on the hypothesized possibility of selectively obtaining substituted dihydropyrimidine-5-carboxylates, including enantiomerically enriched derivatives, through the use of both carboxy-functionalized eutectic mixtures and natural low- and high-molecular-weight organic acids.

A key structural feature of the studied group of compounds is the presence of a thioxo group, which upon reaction with monochloroacetic acid can lead to an S-alkylation product accompanied by intramolecular cyclization, resulting in dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylates bearing an activated methylene group. Meanwhile, the interaction of this latter group with aldehydes may yield α,β-unsaturated compounds belonging to the class of arylidene-3-oxo-5-aryl-3,5-dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylates. These compounds are promising candidates for studies evaluating the relationships between structure and antimicrobial activity as well as structure and antitumor activity, considered within a unified framework of activity manifestation.

Review and justification of the selected research methods

Throughout the course of this work, methods of fine organic synthesis were employed, guided by the objectives and tasks related both to the creation of carboxy-functionalized eutectic mixtures and the comparative study of their catalytic properties in the synthesis of substituted dihydropyrimidine-5-carboxylate derivatives, as well as to the development of one-pot synthetic methodologies for polycyclic heterosystems based on these compounds.

Research efforts focused on the development of new catalytic systems based on choline chloride, imidazolium ionic liquids, low-methoxylated pectin, and eutectic mixtures derived from natural tartaric acid, aimed at optimizing chemo- and stereoselectivity in the formation of 3,4-dihydropyrimidin-2(1*H*)-ones (thiones), as well as enabling the organocatalyzed synthesis of the enantiomerically enriched compound monastrol. Thin-layer chromatography (TLC) was utilized to monitor the progress of reactions. The synthesized substituted dihydropyrimidine-5-carboxylates and their derivatives were purified by recrystallization and column chromatography.

BRIEF DESCRIPTION OF THE WORK

The INTRODUCTION consists of a rationale for the research topic, the aim and main objectives of the study, the research hypothesis, a review and justification of the chosen research methods, and a brief description of the work.

1. ANALYSIS OF KNOWN METHODS FOR THE SYNTHESIS OF SUBSTITUTED DIHYDROPYRIMIDINE-5-CARBOXYLATES AND THEIR TRANSFORMATION PATHWAYS

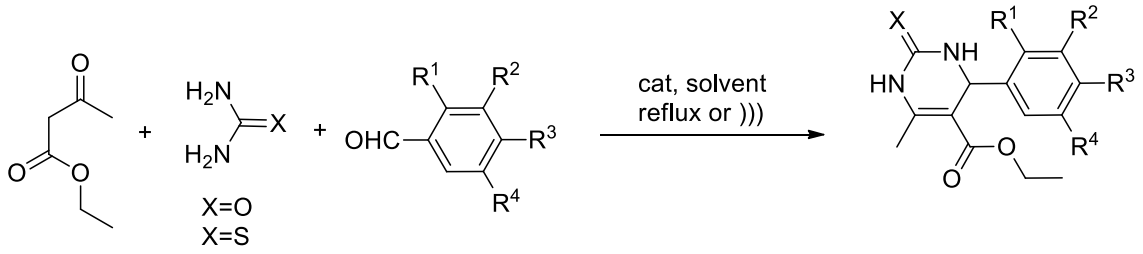
This chapter is devoted to a review of the literature data on the synthesis of substituted dihydropyrimidine-5-carboxylates and their transformation pathways. It describes the main methods for synthesizing substituted dihydropyrimidine-5-carboxylates via cyclization of precursors, as well as approaches to the preparation of polycyclic dihydropyrimidines.

2. SYNTHESIS OF FUNCTIONALIZED ETHYL DIHYDROPYRIMIDINE-5-CARBOXYLATES CATALYZED BY IONIC LIQUIDS

The detailed analysis of the data presented in the previous chapter enabled the identification of the most promising directions for the development of functionalized imidazolium salts aimed at investigating their catalytic properties in the Biginelli reaction.

2.1. Synthesis and catalytic properties of functionalized imidazolium-based ionic liquids

At the onset of our research, the literature lacked data on the ionic liquid **17-22** (Fig. 2.2) catalyzed synthesis of dihydropyrimidin-2(1*H*)-ones (thiones) **1–16** (Fig. 2.1).

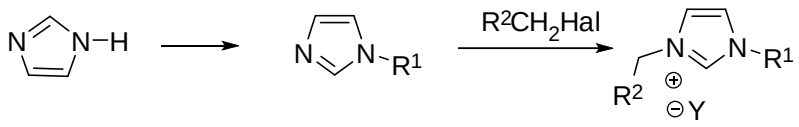


1 R^1=R^2=R^3=H, R^4=OH X=S
2 R^1=R^2=R^3=H, R^4=OH, X=O
3 R^1=R^2=R^3=R^4=H, X=S
5 R^1=R^2=R^3=R^4=H, X=O
4 R^1=R^2=R^4=H, R^3=OMe, X=S
9 R^1=F, R^2=R^3=R^4=H, X=O
6 R^1=R^2=R^4=H, R^3=F, X=S
10 R^1=R^2=R^4=H, R^3=OMe, X=O
7 R^1=R^3=R^4=H, R^2=NO_2, X=S
13 R^1=R^3=Cl, R^2=R^4=H, X=O
8 R^1=R^2=R^4=H, R^3=NO_2, X=S
15 R^1=R^4=H, R^2=R^3=OMe, X=O
11 R^1=R^2=R^4=H, R^3=Cl, X=S
12 R^1=R^2=R^4=H, R^3=NMe_2, X=S
14 R^1=R^3=Cl, R^2=R^4=H, X=S
16 R^1=R^4=H, R^2=R^3=OMe, X=S

Fig. 2.1. Catalyzed synthesis of ethyl dihydropyrimidine-5-carboxylates

As a model system, the condensation of ethyl acetoacetate, 3-hydroxybenzaldehyde, and urea or thiourea was selected. This process involves the initial interaction of the aldehyde with urea (or thiourea) to form an imine, which subsequently reacts with the enol form of ethyl

acetoacetate. Intramolecular nucleophilic attack of the carbonyl group by the amine is accompanied by the elimination of water, leading to the formation of monastrol 1 and the oxo-analog of monastrol 2, respectively. The first ionic liquid chosen for this study was 1,3-dimethylimidazolium iodide **17**, synthesized according to the reaction scheme depicted in figure 2.2.



17 R^1=Me, R^2=H, Y=I 98%
18 R^1=$(CH_2)_2CN$, R^2=$(CH_2)_2Me$, Y=Br 91%
19 R^1=$(CH_2)_2CN$, R^2=$(CH_2)_2Me$, Y=BF_4 68%
20 R^1=$(CH_2)_2CN$, R^2=$(CH_2)_2Me$, Y=PF_6 73%
21 R^1=R^2=$(CH_2)_2CN$, Y=Cl 85%
22 R^1=R^2=$(CH_2)_2CN$, Y=PF_6 73%

Fig. 2.2. Synthesis of ionic liquids

Under the selected conditions, refluxing an ethanolic solution containing 10 mol% of ionic liquid **17** with ethyl acetoacetate, 3-hydroxybenzaldehyde, and urea resulted in the formation of product **2** with a 9% yield. Increasing the yield of product **2** to 20% was achieved by performing the reaction solvent-free at 100 °C for 8 hours. The application of ultrasonic irradiation, while simultaneously halving the catalyst amount, shortened the reaction time to 4 hours and increased the yield of the target compound to 33%. When ethyl acetoacetate, 3-hydroxybenzaldehyde, and thiourea were reacted with 10 mol% of ionic liquid **17** in boiling ethanol, monastrol **1** was obtained with a yield not exceeding 13%. Under ultrasonic irradiation, the yield of the heterocyclization product increased to 35%, with the catalyst amount halved and the synthesis time reduced from 24 hours to 30 minutes.

The relatively low yields of compounds **1** and **2** are likely related to the known fact [1] that upon heating, 1,3-dimethylimidazolium iodide **17** releases methyl iodide, forming 1-methylimidazole, which does not catalyze the reaction. Previously [2–5], our laboratory described several examples of nitrile-functionalized ionic liquids used as catalysts or co-catalysts in 1,3-addition reactions of methyl vinyl ketone or acrylate esters, acrylonitrile with aromatic aldehydes, isatins, and in the synthesis of 4-substituted 2-carens; however, data on catalytic activity in the Biginelli reaction were absent.

To investigate the influence of the ionic liquid anion nature on catalytic properties in the studied reactions, bromide **18** was initially synthesized. The heterocyclization reaction of ethyl acetoacetate, benzaldehyde, and thiourea was selected as the first model to study the catalytic properties of salt **18**. It was established that the reaction of ethyl acetoacetate, 3-hydroxybenzaldehyde, and thiourea in boiling ethanol in the presence of 10 mol% ionic liquid **18**

proceeds with a 3% higher yield compared to 10 mol% ionic liquid **17**. It was shown that the reaction proceeds with similar yields when replacing ethanol with ethyl acetate as solvent or increasing the catalyst amount. Thus, the nature of the substituent in the starting aromatic aldehyde had little effect on the yields of target compounds **3** and **1**, which were obtained in 12–16% yield. The positive effect of ultrasonic irradiation on the heterocyclization reaction was observed for the synthesis of ethyl dihydropyrimidine-5-carboxylates **3** and **1**, reflected in the reduction of reaction time from 8–12 hours to 30 minutes and an increase in yields to 47% and 30%, respectively.

After stirring bromide **18** with potassium tetrafluoroborate in dry acetone at room temperature for 24 hours, crystalline product **19** was obtained. It was found that replacing the Br^- anion with BF_4^- did not affect the catalytic properties of ionic liquid **19**, as reflected in the 10% yield of product **3**. A similar trend was observed in the monastrol **1** synthesis model, where the yield did not exceed 8%. Consequently, our attention shifted to hexafluorophosphate 1-(2-ethylcarbonitrile)-3-propyl-1*H*-imidazol-3-ium **20**, which at 8 mol% catalyzed the formation of compound 3 over 15 hours with a 27% yield, twice that observed with ionic liquid **18**. Increasing the amount of catalyst **20** twofold proportionally increased the yield of the target product (46%), while prolonged reflux (20 hours) led to only a slight yield increase. It was established that salt **20** also catalyzes the reaction of ethyl acetoacetate, 3-hydroxybenzaldehyde, and thiourea in boiling ethanol. Similar to product **3**, a 26% yield of monastrol **1** was obtained by increasing the catalyst amount from 8 mol% to 15 mol% and reducing the reaction time from 15 hours to 8 hours, respectively. The efficiency of target product **1** formation increased with both catalyst loading up to 20 mol% and reaction time up to 18 hours. Replacing 3-hydroxybenzaldehyde with 4-methoxybenzaldehyde led to the formation of 4-methoxyphenyldihydropyrimidine-5-carboxylate **4**.

Additionally, it was of interest to determine how replacing thiourea with urea and ionic liquid **17** with ionic liquid **20** would affect the reaction of ethyl acetoacetate with 3-hydroxybenzaldehyde. It was established that using 10 mol% catalyst **20** resulted in a 61% yield, whereas under analogous catalytic conditions with ionic liquid **17**, the yield did not exceed 9%. Increasing the catalyst **20** loading to 15 mol% increased the target product yield by 4%.

We hypothesized that the presence of a second nitrile group in the ionic liquid molecule would enhance catalytic properties due to reversible interaction of nitriles with alcohols in the presence of acid catalysts, forming imidoester hydrohalides capable of catalyzing the reaction. To confirm this, hexafluorophosphate 1,3-bis(2-cyanoethyl)-1*H*-imidazol-3-ium **22** was synthesized from chloride **21**.

In boiling ethanol for 16 hours, ionic liquid **22** at 8 mol% catalyzed the reaction of ethyl acetoacetate, benzaldehyde, and thiourea, yielding dihydropyrimidine-5-carboxylate **3** with a 37% yield — 10% higher than with catalyst **20**. A yield of 58% was achieved upon prolonged reflux (22 hours). Increasing the catalyst amount to 15 mol% raised the product **3** yield to 43%, 49%, and 58% when the reaction was conducted for 20, 24, and 30 hours, respectively. Further increasing the catalyst loading to 25 mol% with reaction times of 18 and 22 hours afforded ethyl dihydropyrimidine-5-carboxylate **3** in 52% and 63% yields, respectively.

The dependence of catalytic activity of ionic liquid **22** on catalyst loading (10 mol%, 15 mol%, 25 mol%) was also examined using the model reaction of ethyl acetoacetate and 4-methoxybenzaldehyde with thiourea. It was found that the yield of product **4** generally depended on reaction time: at 10 mol% catalyst and 24 hours, the yield was 73%; at 15 mol% catalyst and 16 hours, 53%; and at 20 mol% catalyst and 22 hours, 68%.

The catalytic activity of 10 mol% hexafluorophosphate **22** in the model reaction of ethyl acetoacetate, 3-hydroxybenzaldehyde, and urea **2** was half that of hexafluorophosphate **20** (33% vs. 61% yield, respectively). A similar trend was observed when comparing 15 mol% loadings of **22** and **20**, with yields of 42–49% and 65%, respectively. Using 20 mol% hexafluorophosphate **22** increased the yield to 55%.

An interesting observation was made when replacing urea with thiourea in the reaction of ethyl acetoacetate, 3-hydroxybenzaldehyde in the presence of catalytic amounts of ionic liquid **22**. Comparative analysis of the activity of 15 mol% hexafluorophosphates **20** and **22** showed identical results, reflected by a 26% yield of compound **1** in both cases. This trend persisted when catalyzing with 20 mol% of either hexafluorophosphate **20** or **22** over 14 and 12 hours (yields of 33% and 36%, respectively), as well as with prolonged reaction times (yields of 57% and 55%, respectively). Further increasing catalyst **22** loading to 25 mol% and 30 mol% did not significantly improve the yield of monastrol **1**, which was 50% and 54%, respectively. A 59% yield was obtained after a 24-hour reaction using 30 mol% of catalyst **22**.

The effect of ultrasonic irradiation on the heterocyclization reaction catalyzed by ionic liquid **22** was also studied. It was found that within 30 minutes, 10 mol% catalyst **22** catalyzed the formation of compound **1** with a 64% yield. Notably, this yield is twice as high as that observed with ionic liquid **17** under similar conditions. On the other hand, replacing ethanol with ethyl acetate as solvent in the presence of 10 mol% ionic liquid **22** increased the yield of product **1** from 26% to 38%. Furthermore, the beneficial effect of the hexafluorophosphate anion in ionic liquid **22** compared to bromide **18** on monastrol **1** yield was noted, with yields of 16% and 38%, respectively. Increasing the catalyst loading to 20 mol% and the reaction time to 20 hours further increased the yield of compound **1** to 63%.

2.2. Synthesis of functionalized ethyl dihydropyrimidine-5-carboxylates catalyzed by choline chloride

To determine the scope of the described approach to 3,4-dihydropyrimidin-2(1*H*)-one **7a**, the reaction of ethyl 3-oxobutanoate with urea and benzaldehyde catalyzed by choline chloride at 1 mol%, 10 mol%, and 15 mol% was investigated at room temperature without solvent for 24 hours. In all experiments, no formation of the target product was observed. At a reaction temperature of 70–80°C, compound **5** was formed within one hour with yields of 5%, 6%, and 20% for catalysis by 1 mol%, 10 mol%, and 15 mol% choline chloride, respectively. Under the same conditions, replacing urea with thiourea resulted in an 11% lower yield of the thioanalog **3** compared to compound **5**.

Next, the influence of the substituent nature in the aromatic aldehyde on the yield of final products was studied. It was found that with 4-fluorobenzaldehyde, the target compound 6 was obtained in 52% yield. Replacing thiourea with urea and 4-fluorobenzaldehyde with its regioisomer 2-fluorobenzaldehyde enabled the synthesis of 2-fluorophenyl-substituted ethyl 6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylate **9** with a 61% yield. The reaction efficiency was also evaluated with 3-nitro- and 4-nitrobenzaldehydes. Under optimized conditions, choline chloride-catalyzed one-pot three-component reactions afforded the target compounds **8** and **7** with yields of 80% and 78%, respectively. 4-Methoxybenzaldehyde exhibited reactivity comparable to benzaldehyde, yielding compound 10 in 69%. The yield of the oxo derivative **9** was 41%. It was established that choline chloride also catalyzes the heterocyclization reaction of ethyl 3-oxobutanoate **2** with urea and 3-hydroxybenzaldehyde in boiling ethanol, producing the oxo-analog of monastrol **2** with a 74% yield. Using 4-dimethylaminobenzaldehyde in a reaction catalyzed by 25 mol% choline chloride with ethyl acetoacetate and thiourea, complete conversion was achieved within 8 hours, and the desired compound **12** was isolated with a 73% yield. 2,4-Dichlorobenzaldehyde reacted with ethyl acetoacetate, urea, or thiourea in boiling ethanol in the presence of 25 mol% choline chloride for 8 hours, affording the corresponding derivatives **13** and **14** with yields of 60% and 78%, respectively.

Within this study, it was found that 4-chlorobenzaldehyde reacts with ethyl acetoacetate and thiourea in boiling ethanol in the presence of 25 mol% choline chloride for 8 hours to form the 4-chlorophenyl-substituted compound **11**. It was shown that the reaction of ethyl acetoacetate and urea in boiling ethanol catalyzed by 25 mol% choline chloride with 3,4-dimethoxybenzaldehyde yields the target product **15** in amounts comparable to those obtained from benzaldehyde and 4-methoxybenzaldehyde under similar conditions. The thioanalog **16** was synthesized with a 63% yield.

Considering that the highest yield of 80% was obtained for compound **4** using 3-nitrobenzaldehyde, this model was selected as the standard reaction for recycling choline chloride. It was established that the catalyst could be reused up to five times with negligible loss of efficiency, although the reaction time increased to 12 hours.

2.3. Methods for synthesis and analysis of imidazolium ionic liquids and study of their catalytic properties in the Biginelli reaction

The melting point was determined using a «Boëtius» apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a "Bruker Avance III" spectrometer operating at 400,13 MHz and 100,61 MHz, respectively. IR spectra were recorded using a "Perkin Elmer Spectrum 100 FTIR Spectrometer". Elemental analysis data of the synthesized compounds were obtained on an "Elementar Vario LIII" instrument. An ultrasonic generator UZG 13-0.1/22 was used to determine the effect of ultrasound irradiation on catalytic activity. The compounds were purified by column chromatography (CPC) on silica gel 40/63 μm and 60/100 μm, and thin layer chromatography (TLC) using "Silicagel" 60 F254 and "Silufol" plates.

2.4. Conclusions of Chapter 2

1. Synthesis routes for imidazolium ionic liquids functionalized with alkyl and nitrile groups, both symmetrical and asymmetrical, have been developed. The constants of these ionic liquids have also been clarified, and their catalytic activity in the reaction of acetoacetic ester with aromatic aldehydes, urea and thiourea has been determined.

2. The results show that the efficiency of the formation of ethyl 4-(aryl)-6-methyl-2-oxo-3,4-dihydropyrimidine-5-carboxylates catalyzed by functionalized ionic liquids depends on the nature of the anion and the side-chain substituent, while the nature of the aromatic aldehyde has a minor effect. The highest catalytic activity is exhibited by imidazolium salts substituted with nitrile and hexafluorophosphate groups.

3. A positive effect of ultrasonic irradiation was demonstrated, reducing the heterocyclization reaction time from 24 hours to 30 minutes when using hexafluorophosphate 1,3-bis(2-cyanoethyl)-1*H*-imidazol-3-ium **22** in the synthesis of a practically important derivative of ethyl dihydropyrimidine-5-carboxylates **1**, which is a specific inhibitor of kinesin Eg5.

4. The influence of choline chloride quantity on the course of heterocyclization reactions involving ethyl acetoacetate, urea, thiourea, benzaldehyde, and mono- (methoxy, fluoro, chloro, nitro) and disubstituted (methoxy, chloro) benzaldehydes was revealed.

5. Testing the reaction of ethyl 3-oxobutanoate with urea and benzaldehyde showed that the reaction progress depends on the amount of choline chloride, solvent nature, temperature, and reaction time.

6. It was noted that, in most cases, the yields of ethyl 3,4-dihydropyrimidin-2(1*H*)-thiones are higher than those of their oxygen-containing analogs. It was established that choline chloride can be reused as a catalyst up to five times in the synthesis model of compound **8** without loss of activity.

3. CATALYZED BY NITRILE- AND CARBOXY-FUNCTIONALIZED EUTECTIC LIQUIDS AND PECTIN SYNTHESIS OF ETHYL DIHYDROPYRIMIDINE-5-CARBOXYLATES

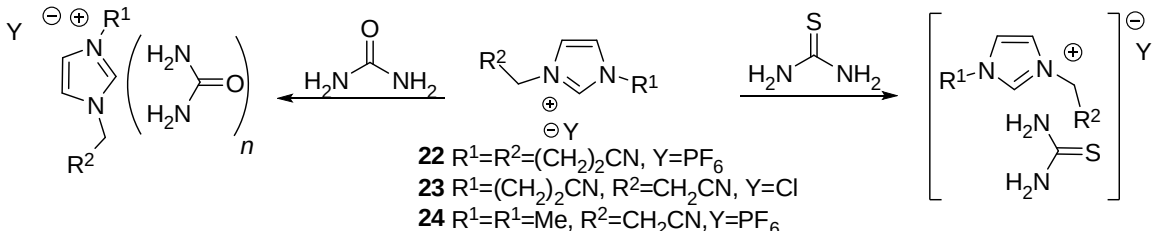
To determine the structure and assess the purity of the chemical compounds, a range of physicochemical analytical methods was employed, including infrared spectroscopy, NMR spectroscopy, and elemental analysis. In light of the promising prospects for the application of eutectic solvents, this dissertation presents a study on the synthesis of novel eutectic mixtures based on nitriles, as well as an investigation of their physicochemical and catalytic properties.

3.1. Synthesis of mono- and dinitrile-functionalized eutectic mixtures and study of their catalytic properties in the Biginelli reaction

At the beginning of our research, no data were available in the literature regarding the use of hexafluorophosphate **22** for the synthesis of eutectic solvents. During the study, two eutectic mixtures, **25** and **26**, were synthesized, and their catalytic properties were subsequently investigated.

The first eutectic liquid, compound **25**, was obtained by mixing salt **22** with urea in the absence of a solvent. It was shown that refluxing an ethanolic solution of an equimolar mixture of ethyl acetoacetate, benzaldehyde, and urea with 12 mol% of compound **25** for 8 hours resulted in the formation of ethyl dihydropyrimidin-5-carboxylate **5** in 18% yield.

The 2-fluoro-substituted analog **9** can be obtained via the reaction of 2-fluorobenzaldehyde with urea and ethyl acetoacetate in boiling ethanol, catalyzed by 15 mol% and 25 mol% of eutectic mixture **25**, over 12 and 18 hours, with yields of 22% and 31%, respectively. The maximum yield of 47% was achieved by refluxing the reactants in water in the presence of 25 mol% of eutectic mixture **25**.



22 $R^1=R^2=(CH_2)_2CN$, $Y=PF_6$
23 $R^1=(CH_2)_2CN$, $R^2=CH_2CN$, $Y=Cl$
24 $R^1=R^1=Me$, $R^2=CH_2CN$, $Y=PF_6$

25 $R^1=R^2=(CH_2)_2CN$, $Y=PF_6$, $n=1$ 82%
28 $R^1=R^1=Me$, $R^2=CH_2CN$, $Y=PF_6$, $n=1$ 93%
29 $R^1=R^1=Me$, $R^2=CH_2CN$, $Y=PF_6$, $n=2$ 70%

26 $R^1=R^2=(CH_2)_2CN$, $Y=PF_6$ 88%
27 $R^1=(CH_2)_2CN$, $R^2=CH_2CN$, $Y=Cl$ 75%

Fig. 3.1. Synthesis of eutectic mixtures based on 1*H*-imidazolium hexafluorophosphate derivatives

Under similar conditions, using anisaldehyde, ethyl 4-methoxyphenyl dihydropyrimidine-5-carboxylate **10** was synthesized with yields of 9%, 26%, and 31% in the presence of 15 mol% and 20 mol% of catalyst **25**. The formation of the oxo-analog of monastrol **2** through the reaction of urea with ethyl acetoacetate and 3-hydroxybenzaldehyde, catalyzed by 15 mol% of eutectic mixture **25**, proceeded in boiling ethanol or ethyl acetate with yields of 22% and 28%, respectively.

Thus, a positive effect was observed when ethanol was replaced with ethyl acetate in the Biginelli reaction catalyzed by a eutectic mixture based on hexafluorophosphate **22** and urea. The product yield remained nearly unchanged with an extended reaction time up to 12 hours. Replacing ethanol with ethyl acetate and doubling the catalyst loading led to an increase in the yield of compound **5** to 25%. The thio-analog **26** of eutectic mixture **25** was used as a catalyst in the reaction of ethyl acetoacetate with benzaldehyde and thiourea in boiling ethanol and ethyl acetate. In the presence of 15 mol% of the eutectic mixture for 12 hours, the product was obtained with a yield of 41%. Increasing the catalyst amount by 5 mol% and the reaction time to 16 hours led to an improved yield of 53%. At the same catalyst loading, after 20 and 22 hours, the product yields were 69% and 81%, respectively. Increasing the catalyst loading to 25 mol% did not significantly affect the reaction outcome (yield 65%).

In order to investigate the effect of solvent nature on the formation of the target compound **3**, model reactions were carried out in ethyl acetate. When using 15 mol%, 20 mol%, and 25 mol% of the catalyst, the product yield of compound **3** was higher by 42%, 11%, and 30%, respectively. A similar effect was observed in the synthesis of the 2-fluoro derivative **6** with 15 mol% of the eutectic mixture, where the yield in ethanol was 42% lower compared to the reaction in boiling ethyl acetate (yield 61%). A comparable yield (68%) was recorded for the synthesis of the 4-methoxy derivative **4** when the reaction was carried out in boiling ethanol in the presence of 20 mol% of eutectic mixture **26**.

The investigation of the influence of the amount of eutectic mixture **26**, solvent, and reaction time on the formation of monastrol **1** was initiated using ethanol, 10 mol% catalyst, and a reaction time of 15 hours (yield: 18%). When the catalyst loading was increased to 15 mol% and the reaction time was reduced to 10 hours, the yield increased to 31%, whereas with 20 mol% of catalyst and a 12-hour reaction, the yield reached 49%. Using the same amount of eutectic mixture **22**, a further increase in reaction time by 4 and 8 hours led to yields of 59% and 66%, respectively. A maximum yield of 78% was achieved with 25 mol% catalyst over 22 hours. Replacing ethanol with ethyl acetate had no significant impact on the formation of compound **1** when catalyzed by 12 mol% and 15 mol% of the eutectic mixture (yields: 27% and 52%, respectively). However, when using 20 mol% of catalyst over 12 hours, the highest yield of 83% was obtained.

The formation of the 4-nitro derivative **8** with a yield of 10% was observed upon refluxing an equimolar mixture of ethyl acetoacetate **2**, 4-nitrobenzaldehyde, and thiourea in the presence of 10 mol% of eutectic mixture **26**. A trend of increasing yield was noted, reaching 19%, 21%, and 59% after 12, 15, and 21 hours, respectively, when using 15 mol% of catalyst. This trend persisted when 20 mol% of the catalyst was employed for 10 and 16 hours, resulting in yields of 63% and 79%, respectively. As in the case of monastrol synthesis, replacing ethanol with ethyl acetate did not significantly affect the formation of the target product **8**, as indicated by yields of 49% (15 mol% catalyst, 24 hours), 58% (20 mol% catalyst, 16 hours), and 68% (25 mol% catalyst, 22 hours). The application of ultrasonic irradiation allowed for a reduction in catalyst loading to 5 mol% and a drastic decrease in reaction time to 30 minutes, affording the product in yields of 80% in ethanol and 89% in ethyl acetate.

To investigate the effect of catalyst nature on the formation of ethyl dihydropyrimidine-5-carboxylates, a third eutectic mixture, compound **27**, was selected. It was prepared by mixing an equimolar amount of the known chloride **23** [5,6] with thiourea under solvent-free conditions. In the synthesis of the 4-methoxy derivative **4**, eutectic mixture **27** was less effective compared to eutectic mixture **26**. Increasing the amount of eutectic mixture **27** to 25 mol% resulted in a yield of 63%, and no significant improvement was observed when the heterocyclization reaction was carried out in ethyl acetate instead of ethanol. The yields of product **1** in ethyl acetate with 15 mol%, 20 mol%, and 25 mol% catalyst were higher than in ethanol by 22%, 3%, and 1%, respectively, also indicating no direct correlation between catalyst loading and efficiency of product formation.

Eutectic mixtures **28** and **29** were synthesized by heating the previously described hexafluorophosphate of 3-(cyanomethyl)-1-methyl-1*H*-imidazol-3-ium **24** with urea and thiourea, respectively. In the heterocyclization reaction conducted in boiling ethanol for 8–12 hours, product **5** was obtained in yields of 18% and 19% with 15 mol% of eutectic mixture **28**. A slight increase in yield up to 25% was observed when the catalyst loading was raised to 25 mol% and the reaction time extended to 16 hours. A comparable yield (25%) was obtained in 8 hours when using 8 mol% of eutectic mixture **29**. Conducting the reaction in boiling ethyl acetate allowed the yield of compound **5** to be increased to 53% within 8 hours using 8 mol% of eutectic mixture **29**.

For the synthesis of the thio-analog **3**, compound **30** was used as a catalyst in amounts of 15 mol%, 20 mol%, and 30 mol% in boiling ethanol and ethyl acetate. The reaction between thiourea, benzaldehyde, and ethyl acetoacetate proceeded more efficiently in ethanol (yield 74%) than in ethyl acetate (yield 63%) in all experiments, even with increased reaction time and catalyst amount.

An inverse correlation between the solvent nature and the efficiency of formation of the practically important compound monastrol **1** was observed. Using 10 mol% of the catalyst for 8 hours resulted in yields of 15% in ethanol and 18% in ethyl acetate; with 15 mol% catalyst under the same conditions, yields were 17% in ethanol and 20% in ethyl acetate. At 20 mol% catalyst for 12 hours, the yield reached 42% in ethanol but only 20% in ethyl acetate. When 25 mol% of the catalyst was used for 24 hours, the product yield was 65% in ethanol and 26% in ethyl acetate. Finally, with 30 mol% catalyst over 24 hours, the yield was 75% in ethanol and 63% in ethyl acetate. A similar trend was observed in the synthesis of the 4-methoxy derivative **16**, catalyzed by eutectic mixture **30**.

3.2. Synthesis of carboxy-functionalized eutectic mixtures and comparison of their catalytic properties with pectin in the Biginelli reaction

Previous studies in our laboratory demonstrated that carboxy-functionalized quaternization products of N-methylimidazole catalyze the Biginelli reaction, whereas data on the synthesis of eutectic solvents were not available. On the other hand, it was also of interest to compare the catalytic activity of mono- and dibasic carboxy-functionalized eutectic mixtures, natural monobasic galacturonic acid, tribasic citric acid, and multibasic low-methoxylated pectin.

As starting compounds, the well-known chlorides 3-carboxymethyl-1-methyl-1*H*-imidazol-3-ium salts **30** and **31** [5,6] (Fig. 3.2) were used.

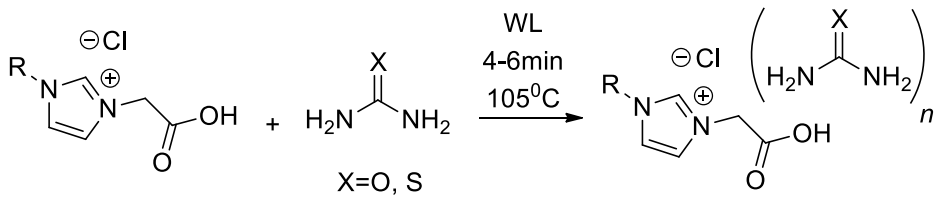


Fig. 3.2. Synthesis of eutectic mixtures based on 3-carboxymethyl-1-methyl-1*H*-imidazol-3-ium chloride

The synthesis of eutectic liquids **32** and **33** involved mixing imidazolium salts **30** and **31** with thiourea in various proportions. When the reagents were mixed in a 1:2 ratio, eutectic mixture **33** was synthesized. On the other hand, it was of interest to determine how replacing the methyl group with a vinyl group would affect both the yield and the physicochemical properties of eutectic mixtures **32–36**. It was found that the yields of the target mixtures increased with the amount of starting thiourea, reaching 66%, 73% and 77%, whereas the melting points, which ranged from 80–120°C, 115–145°C, and 95–125°C, respectively, did not show a clear correlation.

After synthesizing the above-mentioned eutectic mixtures, we proceeded to investigate the possibility of synthesizing a molecular hybrid of *N*-methylimidazole with optically active tartaric acid and thiourea according to the scheme shown in figure 3.3.

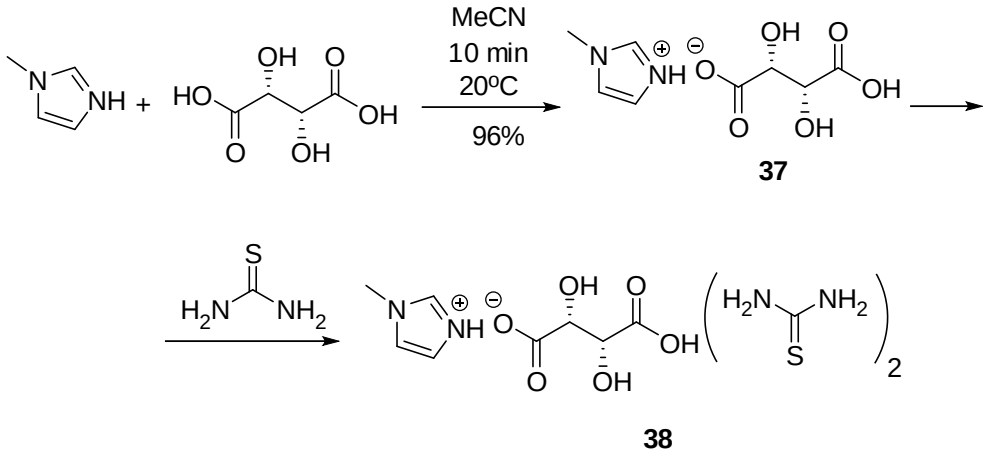
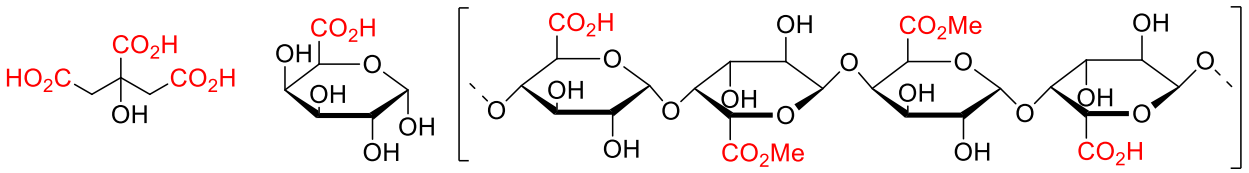


Fig. 3.3. Synthesis of the eutectic mixture based on *N*-methylimidazole and tartaric acid

N-Methylimidazole, under the action of a solution of (+)-tartaric acid in MeCN at room temperature for 10 minutes, is converted into compound **37**. A mixture of salt **37** and thiourea in a 1:2 ratio was stirred for one hour at 85–95°C until it transformed into the colorless liquid **38**.

It was established that the synthesized eutectic mixtures **32–36** catalyze the heterocyclization reaction of ethyl acetoacetate with urea or thiourea in the presence of benzaldehyde, 2-fluorobenzaldehyde, 4-nitrobenzaldehyde, anisaldehyde, 3-hydroxybenzaldehyde, 4-dimethylaminobenzaldehyde and 2,4-dichlorobenzaldehyde, producing ethyl dihydropyrimidin-5-carboxylates with the following yields: compound **3**: 12–88%; compound **6**: 29–34%; compound **8**: 5–71%; compound **4**: 22–59%; compound **2**: 14–56%; compound **12**: 22–57%; compound **14**: 27–55%.

pe baza sării de acid tartric natural și acid citric.



47 **48** **49**

Fig. 3.4. Structure of low-methoxylated pectin 49, *D*-galacturonic acid 48, and citric acid 47

Within the scope of this work, a comparison was conducted of the catalytic activity of natural monobasic galacturonic acid **48**, tribasic citric acid **47**, and multibasic low-methoxylated

pectin **49** with the synthesized dibasic carboxy-functionalized eutectic mixture **38**, obtained based on the salt of natural tartaric acid.

As in previous syntheses of ethyl dihydropyrimidin-5-carboxylates, the new eutectic mixtures catalyze the heterocyclization reaction of ethyl acetoacetate with thiourea and 3-hydroxybenzaldehyde, leading to the formation of ethyl dihydropyrimidin-5-carboxylate **3** with yields ranging from 7% to 72%. It was found that conducting the reaction under ultrasonic irradiation in the presence of eutectic mixture **38** reduces the reaction time to 30 minutes with a product yield of 55%. Similar to the nitrile-functionalized eutectic mixtures, good results were obtained in refluxing ethanol using 25 mol% of catalyst **32** (yield 39%), 30 mol% of catalyst **34** (yield 51%), 20 mol% of catalyst **35** (yield 61%), 20 mol% of catalyst **36** (yield 42%), and 10 mol% of catalyst **38** (yield 67%).

It should be noted that in the last case, asymmetric induction was also observed, as evidenced by the specific rotation of $[\alpha]_D^{20}$+0.832 (c 0.0133, MeOH). According to literature data [7], the specific rotation of the *S*-enantiomer of monastrol is $[\alpha]_D^{20}$+1.1 (c 0.007, MeOH), indicating that the optical purity of our product was 76%.

It was demonstrated that when the reaction is conducted in refluxing ethyl acetate, the yields of monastrol **1** are as follows: 71% with 25 mol% catalyst **33**, 29% using 20 mol% catalyst **34**, 53% using 30 mol% catalyst **35** and 72% with 25 mol% catalyst **36**. It was established that 20 mol% citric acid catalyzes the model reaction in refluxing ethanol with a yield of 61%. For catalyst **35**, the yield can be increased from 23% to 81% under ultrasonic irradiation conditions, simultaneously reducing the reaction time from 18 hours to 30 minutes.

Under ultrasonic irradiation of an ethanolic solution of ethyl acetoacetate, thiourea, and 3-hydroxybenzaldehyde with *D*-galacturonic acid, the target product **1** was formed with a yield of 8%. When the reaction was carried out in refluxing ethanol, the yield did not exceed 28% and replacing ethanol with ethyl acetate also did not lead to an increase in yield. The low product yields are likely due to the known instability of *D*-galacturonic acid [8].

Our attention was drawn to commercially available low-methoxylated pectin, which in some cases is a by-product of pectin production. Studies were conducted under reflux using ethyl acetate and ethanol as solvents and 2% pectin as the catalyst. Under optimized conditions, the yield of the target product **1** increased to 72% and 79%, respectively. Moreover, the catalyst can be reused up to five times.

3.3. Methodology for synthesis and analysis of nitrile-functionalized eutectic mixtures and study of their catalytic properties in the Biginelli reaction

Melting points were determined using a Boëtius apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a “Bruker Avance III” spectrometer operating at 400,13 MHz and 100,61 MHz,

respectively. IR spectra were measured using a “Perkin Elmer Spectrum 100 FTIR” spectrometer. Elemental analysis data of the synthesized compounds were obtained using an “Elementar Vario LIII” analyzer. For ultrasonic irradiation in the study of catalytic activity, an ultrasonic generator UZG 13-0.1/22 was used. In the work, silica gel with indices of 40/63 μm and 60/100 μm was used to purify the obtained compounds, and “Silicagel” 60 F254 plates and “Silufol” plates were used in thin-layer chromatography.

3.4. Conclusions of Chapter 3

1. The synthesis and catalytic activity of mono- and dinitril-functionalized eutectic mixtures in the heterocyclization reaction of ethyl acetoacetate with urea, thiourea, benzaldehyde, 3-hydroxybenzaldehyde, 2-fluorobenzaldehyde, 4-fluorobenzaldehyde, 4-methoxybenzaldehyde, and 4-dimethylaminobenzaldehyde were successfully realized and investigated. A dependence of the reaction time on the composition, amount of eutectic mixtures, and nature of the solvent was established. The best results (yields up to 83%) were generally obtained when the reaction was conducted in boiling ethyl acetate catalyzed by the symmetrical dinitril-functionalized eutectic mixture **22**.

2. Comparative testing of the catalytic activity of eutectic mixtures **28** and **29**, differing only in the amount of urea in their composition, demonstrated the promise of such substances, leading to a reduction in the reaction time of ethyl acetoacetate with urea and benzaldehyde, along with an increase in the yield of the target product **5.**

3. It was shown that the yields of the practically important monastrol **1** were, in most cases, higher when the reaction was conducted in ethanol compared to ethyl acetate. It was established that the asymmetric dinitril-functionalized eutectic mixture **27** is less catalytically active than both the symmetrical dinitril-functionalized eutectic mixture **26** and the mononitril-functionalized eutectic mixture **30**.

4. The synthesis and comparative testing of the catalytic activity of mono-, di-, tri-, and polybasic carboxy-functionalized substances in the Biginelli reaction were carried out.

5. It was found that *N*-methyl-substituted eutectic mixtures catalyze the heterocyclization reaction less efficiently than the corresponding *N*-vinyl-substituted analogues. An increase in the amount of thiourea in the *N*-methyl-substituted eutectic mixture positively affected the reaction product yield, which was not observed in the case of the *N*-vinyl-substituted eutectic mixture.

6. A comparison was made of the catalytic activity of monobasic galacturonic acid, tribasic citric acid, and polybasic low-methoxylated pectin with the synthesized dibasic carboxy-functionalized eutectic mixture **38** based on natural tartaric acid. The yield of monastrol **1** was generally higher when the reaction was conducted in ethanol than in ethyl acetate, including under ultrasonic irradiation conditions.

7. It was established that the dibasic carboxy-functionalized eutectic mixture **38** acts as an asymmetrizing agent, whereas in other catalyses involving natural chiral acids, the reaction product was racemic. The possibility of reusing low-methoxylated pectin up to five cycles was demonstrated.

4. HETEROCYCLIZATION OF MONASTROL

The modification of known pharmaceutical agents is one of the key strategies in medicinal chemistry for the discovery of new biologically active compounds, which may incorporate, in addition to carbon, one or more atoms of other elements. The ethyl 4-(aryl)-6-methyl-2-thioxo-3,4-dihydropyrimidine-5-carboxylates synthesized in the previous chapters are multifunctional compounds, and the construction of polycyclic systems based on them can be achieved either through the interaction of an electrophilic reagent with a nucleophilic fragment of the molecule - leading to the formation of an adduct - or by elimination of small molecules such as water, hydrogen sulfide, or others, resulting in the formation of new cycles.

Monastrol **1** is an aromatic compound in which the hydroxyl group is bound to a carbon atom of the aromatic ring and can potentially undergo a Pechmann condensation to form a coumarin according to the method described in [9].

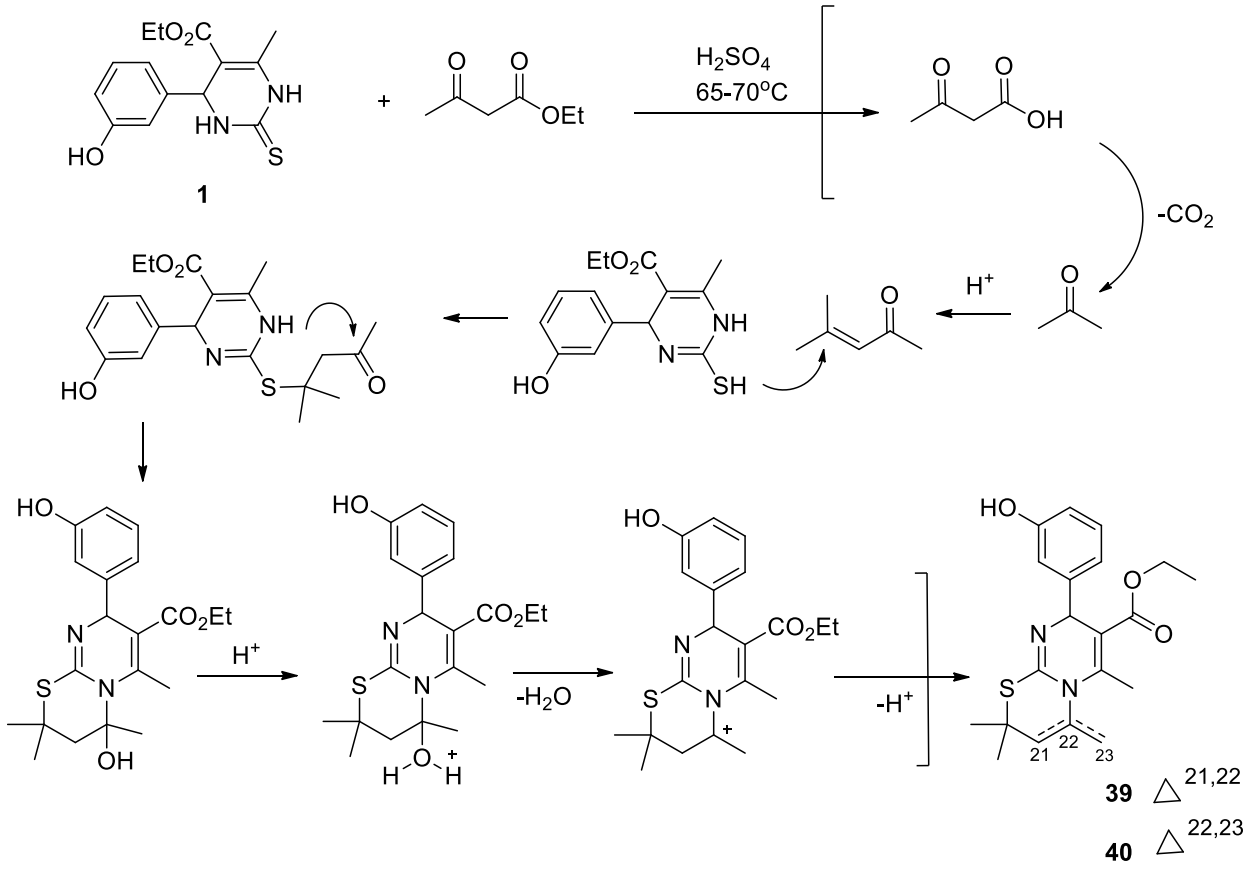


Fig. 4.1. Proposed mechanism for the formation of tetrahydropyrimidothiazine-7-carboxylates

It was found that heating a mixture of ethyl acetoacetate with ethyl dihydropyrimidinethione **1** in concentrated sulfuric acid leads to the formation of a mixture of

two major products, which could not be separated. The fact that the reaction product consists of a mixture of two compounds is also supported by the data from the ^{13}C NMR spectrum.

A possible mechanism for the formation of the isomeric compounds **39** and **40** is presented in figure 4.1. Initially, under the action of concentrated sulfuric acid, an acid-catalyzed cleavage of the β-keto acid occurs. Then, the product of crotonic condensation of acetone, mesityl oxide, reacts with the thiol form of monastrol to form an adduct, which undergoes a series of transformations leading to the formation of bicyclic products with endo- and exocyclic C=C double bonds, **39** and **40**.

It was of interest to carry out a heterocyclization reaction of monastrol **1** with monochloroacetic acid, which contains a highly reactive C–Cl bond and a carboxyl group. These functional groups are required for S-alkylation as well as for intramolecular cyclization involving the N-8 atom, resulting in the formation of a product with an activated methylene moiety. This, in turn, can undergo condensation with aromatic aldehydes via the Knoevenagel reaction, yielding α,β-unsaturated compounds.

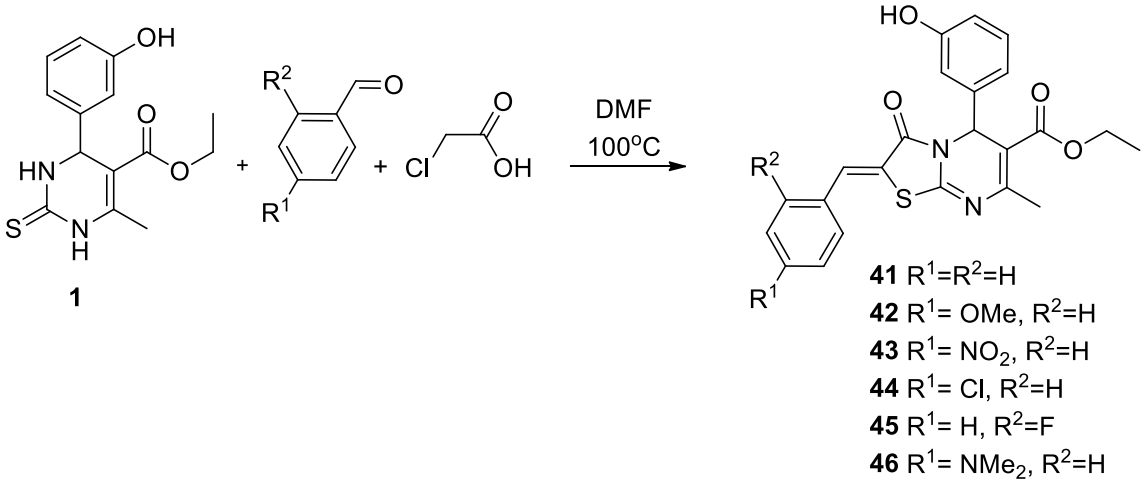


Fig. 4.2. Synthesis of heterocyclization products of monastrol 1

Upon refluxing an equimolar mixture of monastrol **1**, monochloroacetic acid, and benzaldehyde in dimethylformamide (DMF), ethyl 2-benzylidene-5-(3-hydroxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate **41** was obtained in 46% yield. It was found that replacing benzaldehyde with anisaldehyde did not significantly affect the course of the reaction, as reflected by a comparable yield (43%) of the methoxy-substituted product **42**. It was shown that the nitro- and chloro-substituted derivatives **43** and **44** can also be synthesized by refluxing equimolar mixtures of 4-nitrobenzaldehyde or 4-chlorobenzaldehyde with monastrol and monochloroacetic acid in DMF, resulting in yields of 8% and 15%, respectively. Within the framework of this research, the 2-fluorinated compound **45** was synthesized, yielding 21%. Under similar conditions, the synthesis of the dimethylamino-

substituted product **46** was carried out using dimethylaminobenzaldehyde, resulting in a 58% yield.

4.1. General methodology for synthesis and analysis of monastrol heterocyclization poducts

The melting points were determined using a "Boëtius" apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on a "Bruker Avance III" spectrometer operating at 400,13 and 100,61 MHz, respectively. IR spectra were recorded using a "Perkin Elmer Spectrum 100 FTIR spectrometer". Elemental analysis data of the synthesized compounds were obtained using an "Elementar Vario LIII" analyzer. Silica gel with particle sizes of 40/63 μm and 60/100 μm, as well as "Silicagel" 60 F_{254} and "Silufol" plates, were used in the experimental work.

4.2. Conclusions of Chapter 4

1. Synthetic routes for the heterocyclic derivatives of monastrol containing pyrimidothiazine-7-carboxylate and thiazolopyrimidine-6-carboxylate fragments have been proposed.

2. For the first time, the synthesis of bicyclic products bearing endo- and exocyclic C=C double bonds in pyrimidothiazine-7-carboxylates has been achieved. The experimentally established reaction pathway indicates selective bond formation between atoms N-8 and C-22, with no interaction involving the phenolic group of the starting monastrol.

3. One-pot synthetic approaches have been developed for the preparation of ethyl 5-(3-hydroxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylates bearing a 2-benzylidene fragment, starting from benzaldehyde, anisaldehyde, and 4-nitro-, 4-chloro-, 4-dimethylamino-, and 2-fluoro-substituted benzaldehydes, under reflux in a polar aprotic solvent.

5. BIOLOGICAL ACTIVITY OF THE OBTAINED COMPOUNDS

As part of this study, a structure–biological activity relationship assessment was conducted for a series of substituted ethyl dihydropyrimidine-5-carboxylates, in collaboration with the research group of professor Athenia Geronikaki from Aristotle University of Thessaloniki, Greece, and the research team led by professor Steven De Jonghe from the Catholic University of Leuven, Belgium.

5.1. Evaluation of antimicrobial activity

The synthesized compounds **1–16** were evaluated for their antibacterial activity against *Streptococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa* (*P. aeruginosa*), as well as their resistant strains: Methicillin-resistant *Staphylococcus aureus* (MRSA), resistant *Escherichia coli*, and resistant *Pseudomonas aeruginosa*. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) ranged from 0,42 to 8,0 μg/mL and 0,50 to 8,0 μg/mL, respectively. The MIC values decreased in the following order: **2→9→5→10→6→9→1=16→7→15→14→3→12→8→13→11.** Taking into

account the combined MIC and MBC values, the overall activity order was as follows: **10**>**5**>**9**>**2**>**6**>**4**>**15**>**1**=**16**>**7**>**3**>**14**>**12**>**8**>**13**>**11**. Among all the tested compounds, compound **10** exhibited the highest activity, with MIC/MBC values ranging from 0,75–4,0 µg/mL and 1,0–8,0 µg/mL, respectively.

The results indicate that *P. aeruginosa* is the most sensitive strain to the tested compounds. Specifically, compounds **1, 4, 6, 8** and **11** showed the best activity against *P. aeruginosa* (MIC = 0,4 µg/mL), whereas compounds **2** and **11** demonstrated the lowest activity, with MIC values expressed in µM. Compounds **7, 14** and **16** showed good activity against this strain, with their MIC values reported in µg/mL. Meanwhile, compounds **3, 5, 9** and **10** had MIC values expressed in µM.

Compound **9** showed similar activity against *S. aureus* (MIC = 0,75 µg/mL), which appeared to be the most resistant strain among those tested. Sensitivity to the compounds varied across bacterial strains. For the most sensitive bacteria, the order of activity was: **1**=**12**=**4**=**6**=**8**>**16**=**7**=**14**>**5**=**3**=**10**=**9**>**15**=**13**>**2**=**11**, whereas for *S. aureus*, the activity order was: **9**>**2**>**12**>**5**=**3**=**1**=**10**=**4**=**15**=**16**=**7**=**13**=**14**=**6**=**8**>**11**. The two most active analogs, compounds **5** and **10**, are cyclic urea derivatives.

The "*structure–activity"* relationship (SAR) study revealed that the presence of a fluorine atom in the 2-position of the phenyl ring (compound **9**) enhances antibacterial activity against non-resistant strains. The absence of fluorine in the phenyl moiety (compound **5**) slightly decreased the antibacterial activity, making it comparable to that of the 2,4-dichlorophenyl-substituted derivative (compound **13**). Replacement of the urea fragment with its analog, thiourea, in the 3,4-dihydropyrimidinone ring further reduced the biological activity of the tested compound.

The compounds were also tested against three resistant bacterial strains: Methicillin-resistant *S. aureus* (MRSA), resistant *Escherichia coli* (*E. coli*), and resistant *Pseudomonas aeruginosa* (*P. aeruginosa*). It is noteworthy that the compounds exhibited greater activity against resistant strains compared to non-resistant ones. The order of activity against the resistant strains can be represented as: **2**>**6**>**10**>**4**>**5**>**16**>**3**=**15**=**7**>**1**>**12**=**14**=**8**=**11**>**9**>**13**. Compound **2** demonstrated the highest activity against resistant strains with MIC values ranging from 0,4 to 2,0 µg/mL, followed by compounds **6** and **10**. Comparison of the activity against non-resistant and resistant strains showed that compound **10** was the only one to exhibit nearly the same level of activity across all tested strains. When comparing the activity of the compounds against both non-resistant and resistant strains, compound **10** was the most active in both cases, whereas compounds **8** and **11** showed lower activity.

Structure-activity relationship studies revealed that the presence of a phenolic group in the ethyl 6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate scaffold favors

antibacterial activity against resistant strains. Introduction of fluorine at the 4-position of the phenyl ring and replacement of the carbonyl group with a thiocarbonyl fragment (compound **6**) led to a decrease in antibacterial activity. Replacement of fluorine (compound **6**) with a methoxy group in the benzene ring (compound **4**) also reduced the desired activity, as was the case for the 2,4-dichlorophenyl derivative (compound **14**).

5.2. Evaluation of fungicidal activity

The synthesized compounds were tested against fungal strains: *Aspergillus fumigatus* (*A. fumigatus*), *Aspergillus niger* (*A. niger*), *Penicillium funiculosum* (*P. funiculosum*) and *Candida albicans* (*C. albicans*) using ketoconazole as a reference drug for determining the minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC). The activity level decreased in the following order: **2→1→10→6→15→7→16→12→3→5→9→4=14→11→8→13**. Compound **2** exhibited the best antifungal activity among all tested compounds, with MIC values ranging from 0,65 to 2,0 µg/mL and MFC values from 1,0 to 4,0 µg/mL. It was found that among the most dangerous fungi, *Candida albicans* along with *Aspergillus fumigatus* were the most sensitive to the action of the investigated compounds. Compounds **1, 2, 4, 6, 7, 9, 11, 13,** and **15** showed good activity against *C. albicans* with an MIC of 0,75 µg/mL. Compound **2** also demonstrated similarly good activity against *Aspergillus niger*. Compounds **1, 3, 4, 5, 6, 7**, and **14** exhibited good activity against *A. niger*, while compounds **2, 3, 4**, and **6** were effective against *Penicillium funiculosum* with an MIC of 1,0 µg/mL. However, none of the compounds surpassed the activity of ketoconazole. It is worth noting that *A. fumigatus* was the most resistant strain to the tested compounds.

Structure-activity relationship studies showed that the presence of a phenolic group in ethyl dihydropyrimidin-5-carboxylate 2 favors antifungal activity. Replacement of the urea fragment with thiourea in the 3,4-dihydropyrimidine ring, as in monastrol 1, led to decreased antifungal activity. Similarly, the 4-methoxy derivative 10 ranked third in activity, showing reduced efficacy. Substitution of the hydroxyl group in monastrol 1 with fluorine in compound 6 further diminished antifungal activity. The oxo- and thio-analogues 5 and 3 exhibited similar activity, indicating that the nature of the heteroatom does not significantly affect activity. Thus, antifungal activity mainly depends on the nature and position of substituents on the phenyl ring. A common observation is that compound 2 showed the highest activity against resistant strains as well as in antifungal assays, while compounds 8 and 11 were the least active as both antibacterial and antifungal agents.

Regarding biofilm inhibition, this process is aimed at preventing or reducing the formation of a protective bacterial biofilm. Compound 10 exhibited a stronger antibiofilm effect, inhibiting the formation of *Pseudomonas aeruginosa* biofilm by 70,22%, compared to 54,67% for compound 6. At sub-inhibitory concentrations (0,25 µg/mL), compounds 6 and 10 inhibited

biofilm formation by 33,33% and 59,11%, respectively. Both compounds demonstrated significant antibiofilm potential compared to the control.

5.3. Molecular docking

To predict the potential mechanisms of action of the synthesized compounds, molecular docking was carried out on various biological targets, with a focus on enzymes typically associated with antibacterial mechanisms of action, such as: *E. coli* DNA gyrase, *S. aureus* thymidylate kinase, *E. coli* primase, as well as the MurA and MurB enzymes of *E. coli*. Docking results indicate that the most probable mechanism of action is the inhibition of the *E. coli* MurB enzyme, as suggested by the binding scores, which correlate well with the observed biological activity. The most active compound **9**, formed three hydrogen bonds: between the oxygen atom of its carboxyl group and the Ser229 residue (O•••H, 1.57 Å), the same oxygen atom and Gln120 (O•••H, 2.74 Å), and between the oxygen atom of the second carbonyl group and Arg327 (O•••H, 2.45 Å). Additionally, docking studies were performed for all tested compounds, as well as the reference drug ketoconazole, on the enzyme lanosterol 14α-demethylase (*C. albicans*) and DNA topoisomerase IV to investigate their potential antifungal mechanism of action. The results show that compound **2** is the most active, exhibiting strong binding to the enzyme's active site through its carboxyl group, which interacts with the Fe atom of the heme group. A strong coordination (iron) bond and a hydrogen bond (H•••N, 2.74 Å) were formed between the compound and the enzyme. Furthermore, hydrophobic interactions were observed with several residues, including Tyr118, Tyr122, Ile131, Tyr132, Leu376 and Met508. Ketoconazole also interacts with the heme group via hydrophobic and aromatic interactions involving its benzene ring. However, due to the stronger coordination of compound **2** with the iron atom in the heme group, it forms a more stable complex with the enzyme. This suggests that compound **2** may serve as a promising inhibitor of lanosterol 14α-demethylase (CYP51A1).

5.4. Evaluation of cytotoxicity of the compounds

The cytotoxic activity of the synthesized compounds was evaluated against pancreatic adenocarcinoma (Capan-1), colorectal carcinoma (HCT-116), glioblastoma (LN229), lung carcinoma (NCI-H460), acute lymphoblastic leukemia (DND-41), acute myeloid leukemia (HL-60), chronic myeloid leukemia (K562), and non-Hodgkin lymphoma (Z138) cell lines, in comparison with the reference drugs etoposide (a DNA topoisomerase II inhibitor) and nocodazole (a tubulin polymerization inhibitor). The testing revealed significant differences in cytotoxicity among the compounds, as some exhibited promising activity, while others showed minimal or no effect at the tested concentrations.

Compounds **3, 5, 7, 12, 13** and **15** did not exhibit significant cytotoxicity ($IC_{50} > 100$ μM) against any of the tested cell lines, indicating a lack of anticancer potential within the studied concentration range. Similarly, compound **9**, which displayed the best antibacterial activity

among all tested compounds, was inactive against all cancer cell lines. In contrast, compounds **4, 8, 11** and **16** demonstrated notable cytotoxic effects. Compound **4** exhibited moderate activity against most cell lines, with IC_{50} values ranging from 7,2 μM (Capan-1) to 59,4 μM (LN229). Compound **16** showed cytotoxicity with IC_{50} values between approximately 30 and 88 μM across all tested lines. Compound **8** demonstrated appreciable activity, particularly against hematological cancer cell lines such as Z138 (IC_{50} = 7.9 μM) and HL-60 (IC_{50} = 9.0 μM), and was also effective against solid tumors such as Capan-1 (IC_{50} = 11.0 μM).

Compound **11** proved to be one of the most active molecules, with IC_{50} values below 10 μM for nearly all cell lines tested, including LN229 (IC_{50} = 6.3 μM), HL-60 (IC_{50} = 5.6 μM) and Z138 (IC_{50} = 5.9 μM), suggesting a strong cytotoxic effect comparable to that of standard anticancer agents etoposide and nocodazole.

5.5. Conclusions of Chapter 5

1**.** Antibacterial activity of the synthesized compounds was observed against *S. aureus, E. coli* and *P. aeruginosa*, including their resistant strains. Compounds **9b** and **32d** demonstrated significant antibiofilm potential against *P. aeruginosa* biofilm formation compared to the control, including at sub-inhibitory concentrations (0,25 × MIC). The compounds exhibited higher activity against resistant strains than against non-resistant ones.

2. The fungicidal activity of the compounds was evaluated against fungal strains *Aspergillus fumigatus, Aspergillus niger, Penicillium funiculosum* and *Candida albicans*. It was established that the activity largely depends on the nature and position of the substituents in the benzene ring.

3. Among the tested compounds, compound **10** was identified as a lead structure, active against resistant bacterial strains and exhibiting antifungal activity. Based on the *in silico* data, it is suggested that the strong interaction of the compound with iron in the heme group results in the formation of a more stable complex, making it a promising inhibitor of lanosterol 14α-demethylase (CYP51A1).

4. A number of compounds from the ethyl dihydropyrimidine-5-carboxylate series demonstrated promising cytotoxic activity, while others showed minimal effects against Capan-1, HCT-116, LN-229, NCI-H460, DND-41, HL-60, K562 and Z138 cell lines. Compound **11** was among the most active molecules, with IC_{50} values below 10 μM for nearly all tested cell lines, including LN229 (IC_{50} = 6.3 μM), HL-60 (IC_{50} = 5.6 μM), and Z138 (IC_{50} = 5.9 μM), indicating a strong cytotoxic effect comparable to that of standard anticancer agents such as etoposide and nocodazole.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

1. Based on functionalized imidazolium-based ionic liquids, synthetic schemes for new eutectic mixtures were developed, and a comparative study was conducted on the catalytic

activity of choline chloride, galacturonic acid, citric acid, and low-methoxylated pectin in the synthesis of substituted ethyl dihydropyrimidine-5-carboxylates under ultrasonic irradiation or refluxing conditions in water, ethyl acetate, or ethanol.

2. It was established that the dicarboxy-functionalized eutectic mixture **38**, derived from natural tartaric acid, acts as an asymmetrizing agent in the studied reaction, whereas in other catalytic systems involving natural chiral acids, the reaction products were racemic. The possibility of reusing both low-methoxylated pectin and eutectic mixture **38** was demonstrated (up to five cycles).

3. New synthetic schemes were developed for the Eg5 mitotic kinesin inhibitor monastrol, and condensed heterocyclic derivatives were synthesized based on its structure.

4. For the first time, the synthesis of bicyclic products with endo- and exocyclic C=C double bonds of pyrimidothiazine-7-carboxylates was achieved in concentrated sulfuric acid. The experimentally established reaction pathway indicates the selectivity of bond formation between atoms N-8 and C-22, and the absence of interaction with the phenolic group of the starting monastrol.

5. An efficient one-pot synthetic approach was developed for the preparation of ethyl 5-(3-hydroxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylates containing a 2-benzylidene fragment, based on the reaction of monastrol with monochloroacetic acid and aromatic aldehydes under reflux in a polar aprotic solvent.

6. It was found that the antibacterial activity of the synthesized compounds against *S. aureus*, *E. coli*, and *P. aeruginosa* was lower than their activity against resistant strains, including Methicillin-resistant *S. aureus* (MRSA), resistant *Escherichia coli* and resistant *Pseudomonas aeruginosa*.

7. The fungicidal activity of the compounds was investigated against fungal strains *Aspergillus fumigatus*, *Aspergillus niger, Penicillium funiculosum*, *Candida albicans* and it was established that the activity strongly depends on the nature and position of substituents in the benzene ring.

The obtained data allowed for the formulation of the following **recommendations**:

1. The identified patterns of the newly catalyzed synthesis of ethyl dihydropyrimidine-5-carboxylates open up possibilities for structural modification of substituted derivatives and expand the theoretical understanding of the chemical and catalytic properties of functionalized ionic liquids and novel imidazolium-based deep eutectic mixtures, as well as choline chloride, galacturonic and citric acids, and low-methoxylated pectin.

2. The newly obtained data on the asymmetric synthesis of monastrol complement theoretical knowledge on the Biginelli reaction.

3. The developed methods formed the basis for the selective synthesis of a series of heterocyclic compounds. Lead compounds were identified that are active against bacterial strains with antifungal properties and exhibit significant antibiofilm potential against *P. aeruginosa* biofilms.

BIBLIOGRAPHY

1. Ricciardi, F., Romanchick, W.A., Joullie, M.M. 1,3-Dialkylimidazolium salts as latent catalysts in the curing of epoxy-resins. In: *Journal of Polymer Science: Polymer Letters Edition*. 1983, 21, pp. 633-638. https://doi.org/10.1002/pol.1982.130200209
2. Macaev, F., Stângaci, E., Radul, O., Şargorovschi, V., Pogrebnoi, S., Sucman, N. Catalizator pentru sinteza derivaţilor 2-pirol-3-iloxindolului. Brevet de invenţie MD 4233. Publicat 03.02.2012.
3. Sucman, N., Macaev, F. Procedeu de obţinere a derivaţilor carbonitrilici ai spiro[ciclopropan-oxindolilor]. Brevet de invenţie MD 4201. Publicat 21.03.2012.
4. Sucman, N., Macaev, F. Procedeu de obţinere a derivaţilor carbometoxi ai spiro[ciclopropan-oxindolilor]. Brevet de invenţie MD 4202. Publicat 21.03.2012.
5. Macaev, F., Gavrilov, K., Muntianu, V., Styngach, E., Vlad, L., Bets, L., Pogrebnoi, S., Barba, A. Synthesis of 4-substituted 2-carenes in novel imidazolium ionic liquids. In: *Chemistry of Natural Compounds*, 2007, 43, pp. 136-139.
6. Munteanu, V., Stingaci, E., Barba, A., Pogrebnoi, S., Macaev, F. New room temperature liquids: Synthesis and characterization. In: *Chemistry Journal of Moldova*. 2007, 2, pp. 119-122.
7. Kappe, O., Shishkin, O., Uraya, G., Verdinoa, P. X-Ray Structure, Conformational Analysis, Enantioseparation, and Determination of Absolute Configuration of the Mitotic Kinesin Eg5 Inhibitor Monastrol. În: *Tetrahedron*. 2000, 56(13), pp. 1859–1862.
8. Bornik, M.A., Kroh, L.W. D-Galacturonic Acid as a Highly Reactive Compound in Nonenzymatic Browning. Formation of Browning Active Degradation Products. In: *Journal of Agricultural and Food Chemistry*. 2013, 61, pp. 3494−3500. DOI: 10.1021/jf303855s.
9. Шокол, Т.В., Абдуллаев, Э.Н., Горбуленко, Н.В., Фрасинюк, М.С., Хиля, В.П.. В: *Химия природных соединений*. 2018, 3, с. 373-376.
10. Gondru, R., Peddi, S.R., Manga, V., Khanapur, M., Gali, R., Sirassu, N., Bavantula, R. One-pot synthesis, biological evaluation and molecular docking studies of fused thiazolo[2,3-b]pyrimidinone-pyrazolylcoumarin hybrids. In: *Molecular Diversity*. 2018, 22, pp. 943–956.

AUTHOR'S PUBLICATIONS ON THE DISSERTATION TOPIC

2. Articles in scientific journals

2.2. in journals from other databases accepted by ANACEC

1. **CIOBANU, N.**, SUCMAN, N., PETROU, A., GORINCIOI, E., VALICA, V., UNCU, L., FESATIDOU, M., GLAMOČLIJ, J., IVANOV, M., PERSOONS, L., SCHOLS, D., DE JONGHE, S., GERONIKAKI, A., MACAEV, F. Biological and Computational Study of the Dual Antimicrobial and Anticancer Potential of 3,4-Dihydropyrimidin-2(1*H*)-ones and Thiones. In: *ChemistrySelect.* 2025, 10, e02768, (IF 2,0). DOI: 10.1002/slct.202502768. https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/slct.20250276

2. **CIOBANU, N.**, GORINCIOI, E., SUCMAN, N., VALICA, V., UNCU, L., MACAEV, F. Novel Insight into Sustainable Synthesis of (±)-Monastrol: Utilizing Biginelli Multicomponent Reaction with Low Methoxyl Pectin as Catalyst. In: *Chemicke Listy*. 2025, 119(6), pp. 340-344. ISSN 1213-7103 (on-line), 0009-2770, (IF 0,6).
DOI: 10.54779/chl20250340. http://www.chemicke-listy.cz

3. **CIOBANU, N.**, MACAEV, F. New opportunities in the synthesis of monastrol. In: *Journal of Pharmaceutical Research and Reports.* 2025, 6(2), pp. 1-3. ISSN: 2754-5008. SRC/JPRSR-196. DOI: 10.47363/JPRSR/2025(6)172.

4. **CIOBANU, N.,** GORINCIOI, E., OKOPNAYA, N., OZOL, L. Selectarea metodei optimale pentru sinteza dihidropirimidin-2-onelor(thione) folosind diversi catalizitori. In: *Kenkyu Journal of Pharmacology*. 2025, 8(1), pp. 1-2. ISSN: 2455-9237.

5. МАКАЕВ, Ф.З., **ЧОБАНУ, Н.Г**. Эвтектические растворы на основе 3-(карбоксиметил)-1-винил-1*H*-имидазол-3-иум хлорида и тиомочевины для получения монастрола. В: *Вестник Башкирского государственного медицинского университета*. 2021, 26(2), с. 384-387. УДК: 547.31; 547.729.9; 547.781.1. ISSN 1998-4812.
DOI: 10.33184/bulletin-bsu-2021.2.19.

2.3. in journals from the National Register of specialized journals

1. **CIOBANU, N.**, STINGACI, E., MACAEV, F. Cercetarea proprietăților catalitice ale amestecurilor eutectice pe baza 1-metilimidazolului pentru sinteza 3,4-dihidropirimidin-2(1H)-tionelor. In: *Ştiinţe chimice. Akademos*. 2025, 1(76), pp. 31-36. CZU: 634.8:632.632.952.
DOI: 10.52673/18570461.25.1-76.02.
http://academia/conf.2025/articulAkademos202025/20pdf/201.pdf

2. **CIOBANU, N.,** MACAEV, F. Фармакологические аспекты некоторых продуктов дигидропиримидинового ряда. In: *EcoSoEn, Scientific Journal Economics, Social and Engineering Sciences.* 2021, 3/4, pp. 213-217. UDC: 669.715. ISSN 2587-344X.
https://ULIM2015.10.21//Ecosoen//p.213-217/Ecosoen-3-4-2021Final.pdf

3. Articles in the proceedings of conferences and other scientific events

3.2. in the proceedings of scientific events included in other databases accepted by ANACEC

1. **CIOBANU, N**., STYNGACH, E., BARBA, A., MACAEV, F. Unusual heterocyclization of monastrol under the conditions of the Pechmann reaction. In: *Сборник материалов Международной конференции, посвященной 60-летию фармацевтического факультета учреждения образования "Витебский государственный ордена Дружбы народов медицинский университет", "Современные достижения фармацевтической науки и практики".* 31 октября, 2019, Витебск, Республика Беларусь, с. 40.
ISBN 978-985-466-971-7. УДК 615:[001:371.38] "60"(06). ББК 52.82я431.

2. **ЧОБАНУ, Н.Г.,** СТЫНГАЧ, Е.П., МАКАЕВ, Ф.З. Новый синтез монострола с применением катализатора эвтектической природы. В: *Сборник материалов V Всероссийской молодежной конференции "Достижения молодых ученых: химические науки".* 16-19 мая, 2020, Уфа, Россия, с. 164-166. ISBN978-5-7477-5082-1.

3. **ЧОБАНУ, Н.Г.**, АРМАШУ, С.А., ТЕРТЯК, Д.Д., ЧЕБАНУ, В.А., МАКАЕВ, Ф.З. Синтез и активность монострола против вирусов бронзовости томатов и табачной мозаики. В*: Сборник материалов V Всероссийской молодежной конференции "Достижения молодых ученых: химические науки".* 16-19 мая, 2020, Уфа, Россия, с. 166-167. ISBN978-5-7477-5082-1.

4. **ЧОБАНУ, Н.Г.**, СТЫНГАЧ, Е.П., МАКАЕВ, Ф.З. Некоторые аспекты синтеза дигидропиримидинов. В: *IV Международная научно-практическая конференция „Лекарства - человеку. Современные проблемы фармакотерапии и назначения лекарственных средств".* 12-13 марта, 2020, Харьков, Украина, с. 618. ISSN: 2412-0456.

5. **ЧОБАНУ, Н**. Синтез монастрола с применением экологических катализаторов. В: *Самарская международная медицинская научная конференция (SIMS 2020).* 14 октября, 2020, Самара, Россия, с. 416. https://drive.google.com/file/d/Samara

6. **ЧОБАНУ, Н.**, ТЕРТЯК, Д., АРМАШУ, Д., ЧЕБАНУ, В., МАКАЕВ, Ф. 1,3-бис(2-цианоэтил)-1*H*-имидазол-3-иум гексафторфосфат мочевиной катализируемый синтез оксимонострола и активность против вирусов бронзовости томатов и табачной мозаики. В: *VII Международная молодежная научно-практическая конференция "Актуальные вопросы современного материаловедения".* 29-30 октября, 2020, Уфа, Россия, с. 165.
ISBN 978-5-7477-5165-1.

7. **ЧОБАНУ, Н.**, МАКАЕВ, Ф. Синтез и активность монострола против вирусов бронзовости томатов и табачной мозаики. В: *IV Всероссийской молодежной конференции "Проблемы и достижения химии кислород- и азотсодержащих биологически активных соединений".* 18-21 ноября, 2020, Уфа, Россия, с. 102. ISBN 978-5-7477-5182-8.

8. **CIOBANU, N**. Synthesis and activity 3,4-dihydropyrimidin-2-ones (thion). In: *International Medical Congress of Silesia*. 12-14 mai, 2021, Katowikachi, Poland, p. 37. ISBN 978-83-950834-4-0.

9. **CIOBANU, N.**, MACAEV, F. Eco-favorable catalytic conditions in the synthesis of some dihydropyrimidine derivatives. In: *MOSA CONFERENCE 2021 „Bio-medical innovation and emerging technoques in digital health”.* 21-23 iunie, 2021, Maastricht University, the Netherlands, Hasselt University, Belgium. http://[/Biomedical%20innovation/conference.%20Belgium/23.06.2021.pdf

10. **CIOBANU, N.** Eco-favorable catalytic conditions in the synthesis of some dihydropyrimidine derivatives. In: *XXVII Symposium on Bioinformatics and Computer-Aided Drug*. 5-8 aprilie, 2021, Moscow, Russia, p. 22. ISBN 978-5-900760-17-9.

11. **ЧОБАНУ, Н.**, МАКАЕВ, Ф. Синтез и активность 3,4-дигидропиримидин-2-онов(тионов) с применением различных органических катализаторов. В: Вестник Башкирского государственного медицинского университета. 16-17 мая, 2022, Уфа, Россия, 5, с. 191-195. ISSN 2309-7183.

12. **ЧОБАНУ, Н**. Использование эвтектических смесей на основе 3-(карбоксиметил)-1-винил-1*H*-имидазол-3-иум хлорида и тиомочевины при получении монастрола. В: *II Всероссийская молодежная научно-практическая конференция “Вершины науки – покорять молодым! Современные достижения химии в работах молодых ученых”.* 25-28 мая, 2021, Уфа, Россия, 26(2), с. 86-87. ISBN 978-5-88185-500-0.

13. **CIOBANU, N.** Conditions for the synthesis of some dihydropyrimidine derivatives. In: *III Всеукраїнської науково-практичної конференції з міжнародною участю “YOUTH PHARMACY SCIENCE”.* 7 september, 2022, Harcov, Ucraine, pp. 14-15. http:\\yps_materiali-konferencii_2022.pdf

14. **CIOBANU, N.** New catalytic conditions in the synthesis of dihydropyrimidine derivatives. In: *International conference modern problems of theoretical and experimental chemistry devoted to the 90th anniversary of academician Rafiga Aliyeva*. 29-30 september, 2022, Baku, Azerbaijan, p. 301. ISBN: 978-9952-546-73-6.

15. **ЧОБАНУ, Н.,** МАКАЕВ, Ф. Синтез и активность 3,4-дигидропиримидин-2-онов(тионов). In: *XXVIII Symposium on Bioinformatics and Computer-Aided Drug Discovery (BCADD-2022)*. 20 апреля-26 мая, 2022, Москва, Россия, с. 104. ISBN: 978-5-900760-18-6. eLIBRARY ID: 48534772. DOI: 10.18097/BCADD2022.

16. **ЧОБАНУ, Н.** Синтез некоторых биологически активных производных дигидропиримидинов. В: *XXVIII Всероссийская конференция молодых учёных с международным участием “Актуальные проблемы биомедицины – 2022”.* 24-26 марта, 2022, Москва, Россия, с. 396-397. ISBN 978-5-88999-775-7.

17. **ЧОБАНУ, Н.**, МАКАЕВ, Ф. Биологическая активность некоторых производных дигидропиримидинов. В: *Достижения молодых ученых: химические науки VII Всероссийской (заочной) молодежной конференции*. 19–20 мая, 2022, Уфа, Россия, с. 142-143. ISBN 978-5-7477-5473-7.

18. **CIOBANU, N.**, MACAEV, F., OZOL, L., OCOPNAIA, N. New opportunities in the synthesis of monastrol. In: *XXIX Symposium on Bioinformatics and Computer-Aided Drug Discovery*. 26 aprilie, 2023, Moscow, Russia, p. 100. DOI: 10.18097/BCADD2023. ISBN: 978-5-900760-19-3.

19. **CIOBANU, N**. Eco-favorable catalytic conditions in the synthesis of some dihydropyrimidine derivatives. В: *VIII Междисциплинарной конференции "Молекулярные и Биологические аспекты Химии, Фармацевтики и Фармакологии".* 24-27 апреля, 2023, Санкт-Петербург, Россия, с.153. ISBN 978-5-00218-187-2.

20. **CIOBANU, N**., MACAEV, F., OCOPNAIA, N., OZOL, L. Some details in the synthesis of dihydropyrimidines. In: *RSU, Research Week 2023*. 29-31 martie, 2023, Riga, Latvia, p. 507. ISSN 1648-9233.

21. **CIOBANU, N.**, MACAEV, F., OCOPNAIA, N., OZOL, L. New opportunities in the synthesis of monastrol. In: *l4th International conference on biological and medical sciences, ICBMS23*. 15-16 iulie, 2023, Budapest, Hungary, p. 59. ISBN: 978-622-94710-8-1.

22. **ЧОБАНУ, Н.**, ОЗОЛ, Л. Биоактивность и особенности синтеза производных ряда 3,4-дигидропиримидин-2-(ти)онов. В: *Конференция с международным участием "Актуальные вопросы экспериментальной и клинической медицины – 2023".* 1-28 апреля, 2023, Санкт-Петербург, Россия, с. 155. ISBN 978-5-88999-879-2.

23. **CIOBANU, N.**, MACAEV, F. Synthesis and activity of 3,4-dihydropyrimidin-2-ones(thiones) using various organic catalysts. In: *XXX Sympozium BCADD-2024*. 31 July, 2024, Moscow, Russia, p. 24. http://conf.2024/Symp.Bio/e-page.pdf

24. **CIOBANU, N**., MACAEV, F. Synthesis of substituted dihydropyrimidine-5-carboxylates. In: *VIII-lea Târg Internațional de Inovare și Educație creativă pentru tineret (ICE-USV)*. 31 mai-2 iunie, 2024, Suceava, România, p. 77. http:\\Suceava\31.05-02.06.2024 p.77\VOLUM ICE - USV 2024.pdf

25. **ЧОБАНУ, Н.Г**., ОКОПНАЯ, Н.Т., ОЗОЛ, Л.Д. Выбор оптимального метода синтеза дигидропиримидин-2-онов(тионов) с применением различных катализаторов. В: *XIII Всероссийская научная конференция с международным участием и школа молодых ученых "Химия и технология растительных веществ*". 28 мая-1 июня, 2024, Сыктывкар, Россия, с. 245. ISBN 978–5–498–01074–8. DOI: 10.19110/978-5-498-01074-8.

26. **CIOBANU, N.**, MACAEV, F. Eco-favorable catalytic conditions in the synthesis of some dihydropyrimidine derivatives. In: *MOSA CONFERENCE 2021 „Bio-medical innovation and emerging technoques in digital health”.* 21-23 iunie, 2021, Maastricht University, the Netherlands, Hasselt University, Belgium.
https://share.medall.org/posters/0cebff56-11e3-47ea-b1fb-e06d883ab557

27. **ЧОБАНУ, Н.Г**. Использование эвтектических смесей на основе 3-(карбоксиметил)-1-винил-1*H*-имидазол-3-иум хлорида и тиомочевины при получении монастрола. In: *II Science and Technology Center in Ukraine (STCU). „How has human transformed science”. Webinar series to Promote Responsible Science*. 1-29 June, 2021, Azerbaijan & Georgia, постер. https:\\conf.2021\seminar STCU Azerbadgan 1-8-22-29.06.2021 poster.pdf

28. **CIOBANU, N.** Synthesis and biological activity of monastrol. In: *IX-a ediție a Târgului Internațional de Inovare și Educație Creativă pentru Tineret (ICE-USV)*. 23-25 mai, 2025, Suceava, România, pp. 40-45.
https://academia/conf.2025/conf.Suceava.p.39+%20art.2%20p.44.pdf

29. **CIOBANU, N.**, MACAEV, F. Bioactivity of 3,4-dihydropyrimidine-2-(ti)s. In: *IX-a ediție a Târgului Internațional de Inovare și Educație Creativă pentru Tineret (ICE-USV)*. 23-25 mai, 2025, Suceava, România, pp. 45-46. https://academia/conf.2025/conf.Suceava.p.39art.20p.44.pdf

30. **ЧОБАНУ, Н**. Новые возможности синтеза продуктов дегидропиримидинового ряда. В: *Международный конкурс для научно-педагогических работников “Лучший педагог СНГ – 2023”, Общенациональное движение Бабек*. 10 мая, 2023, Астана, Казахстан, устный доклад. http://astana/bobec/%202%20medal

31. VERDEŞ, A., **CIOBANU, N.**, GORINCIOI, E., DRAGALIN, I., MACAEV, F. Sustainable Synthesis of (±)-Monastrol: Utilizing Biginelli Multicomponent Reaction with Ethanol and *D*-Glucuronic Acid as Ecofriendly Reactants. In: *"Yesterday's cultural heritage – contribution to the development of tomorrow's sustainable society*". 8-9 februarie, 2024, Iași, Romania, 9, pp. 299-300. ISSN 2558 – 894X. https://ibn.idsi.md/vizualizare_articol/204302

32. **ЧОБАНУ, Н.Г.** Биоактивность 3,4-дигидропиримидин-2-(ти)ов. В: *Конкурс ежегодный “ЛУЧШИЙ НАУЧНЫЙ СОТРУДНИК – 2023” содружества независимых государств*. 3 ноября, 2023, Астана, Казахстан, устный доклад. http://academia/conf.2023

3.3. in the works of scientific events included in the Register of materials published on the basis of scientific events organized in the Republic of Moldova

1. **CIOBANU, N**. Metode de sinteza derivațiilor dihidropirimidinelor. In: *Conferința științifică cu participare internațională „UNIVERSITAS EUROPAEA: spre o societate a cunoaşterii prin europenizare şi globalizare”*. 7-8 noiembrie, 2019, ULIM, Chișinău, Moldova, raport oral.
https://egbahdxjiaz.exactdn.com/wp-content/uploads/2019/10/Program-Conf_ULIM_2019.pdf

2. **CIOBANU, N.**, MACAEV, F., STINGACI, E., BARBA, A. Unusual heterocyclization of monastrol under the conditions of the pechmann reaction**.** In: *International Conference achievements and perspectives of modern chemistry dedicated to the 60th anniversary from the foundation of the Institute of Chemistry*. 9-10 octombrie, 2019, Chisinau, Moldova, raport oral. http:\Conference_Program\10.10.2019 In.chim.pdf

3. **CIOBANU, N.**, MACAEV, F. Sinteză și bioactivitate 3,4-dihidropirimidin-2-ones (thion). In: *Conferința științifico-practică cu participare internațională cu genericul: „Perspective în cercetarea produselor farmaceutice de origine sintetică și naturală”. Revista Farmaceutică a Moldovei*. 2021, 45(2), p. 38. ISSN 1812-5077.

4. **CIOBANU, N.**, MACAEV, F. Synthesis and bioactivity 3,4-dihydropyrimidin-2-ones (thion). In: *Conferința științifico-practică cu participare internațională cu genericul: „Perspective în cercetarea produselor farmaceutice de origine sintetică și naturală” Revista Farmaceutică a Moldovei*. 2021, 45(2), p. 39. ISSN 1812-5077.

5**. CIOBANU, N**. Sinteza și activitatea unor derivați de dihidropirimidină cu folosire diverți catalizitori organici. In: *Conferința științifică studențească cu participare internațională.* 20 aprilie, 2022, Chisinau, Moldova, LXXI, p. 405**.** ISBN 978-9975-76-394-3.

6**. ЧОБАНУ, Н.**, МАКАЕВ, Ф. Materiale biodegradabile si regenerabile in sinteza mijloacelor profilactice împotriva diferitelor virusuri ale plantelor agricole. В: *Международная научно-практическая конференция “Наука. Образование. Культура”, “Ştiinţă. Educaţie. Cultură”, посвященная 31-ой годовщине КОМРАТСКОГО ГОСУДАРСТВЕННОГО УНИВЕРСИТЕТА.* 11 февраля, 2022, Комрат, Молдова, с. 215-218.
ISBN 978-9975-83-176-5.

7. **ЧОБАНУ, Н.**, МАКАЕВ, Ф. Синтез и применение дигидропиримидинов в качестве химических средств защиты растений. В: *Международная научно-практическая конференция “Наука. Образование. Культура”, “Ştiinţă. Educaţie. Cultură”, посвященная 31-ой годовщине КОМРАТСКОГО ГОСУДАРСТВЕННОГО УНИВЕРСИТЕТА.* 11 февраля, 2022, Комрат, Молдова, с. 311-313.
ISBN 978-9975-83-176-5.

8. **CIOBANU, N.**, MACAEV, F., OCOPNAIA, N., OZOL, L. Sinteza si activitatea biologica dihidropirimidinelor. In: *Universitas Europaea: Towards a knowledge-based society through europianisation and globalization*. 17-20 octomber, 2022, ULIM, Chisinau, Moldova, raport oral. http:\\PROGRAM-conferinta-aniversara-ULIM-1.pdf

9. **CIOBANU, N.**, MACAEV, F., OCOPNAIA, N., OZOL, L. Sinteza si activitatea biologica dihidropirimidinelor. In: *Conferinţa ştiinţifică naţională cu participare internaţională "Integrare prin Cercetare şi Inovare", dedicată Zilei Internaționale a Științei pentru Pace și Dezvoltare*. 9-10 noiembrie, 2023, USM, Chisinau, Moldova, p. 593. ISBN 978-9975-62-687-3.
ISBN 978-9975-62-690-3.

10. **CIOBANU, N.**, MACAEV, F. Perspective pentru sinteza dihidropirimidinelor. In: *Conferința științifico-practică internațională "Instruire prin cercetare pentru o societate prosperă".* 18-19 martie, 2023, UPS, Chisinau, Moldova, X, pp. 296-298.
ISBN 978-9975-46-716-2.

11. **ЧОБАНУ, Н.**, МАКАЕВ, Ф., ОКОПНАЯ, Н. Условия получения некоторых производных дигидропиримидинов. В: *Международная научно-практическая конференция "Наука. Образование. Культура", посвященная 32-ой годовщине Комратского государственного университета*. 10 февраля, 2023, КГУ, Комрат, Молдова, с. 438. ISBN 978-9975-83-254-0.

12. GORINCIOI, E., **CIOBANU, N**. Complete assignments of the ^{1}H, ^{13}C and ^{15}N spectra for(±)-monastrol by ^{1}D and ^{2}D HR NMR techniques. In: *Conferinţa ştiinţifică naţională cu participare internaţională „Integrare prin Cercetare şi Inovare*". 7-8 noiembrie, 2024, USM, Chisinau, Moldova, p. 577.
https://cercetare.usm.md/wp-content/uploads/Programa-Conferintei-1.pdf

13. **CIOBANU, N.**, MACAEV, F. Selectarea metodei optimale pentru sinteza dihidropirimidin-2-onelor(thione) folosind diversi biocatalizitori. In: *Congresul internațional cercetare-inovare-antreprenoriat inovativ*. 17-18 mai, 2024, Chisinau, Moldova, pp. 264-266.
ISBN 978-9975-46-964-7.

14. **CIOBANU, N.**, MACAEV, F. Каталитический характер эвтектических смесей в синтезе дигидропиримидинов. В: *Conferinţa ştiinţifică naţională cu participare internaţională „Integrare prin Cercetare şi Inovare".* 7-8 noiembrie, 2024, USM, Chisinau, Moldova, с. 689.
https://cercetare.usm.md/wp-content/uploads/Programa-Conferintei-1.pdf

15. **CIOBANU, N**. Detectarea metodelor de sinteza a derivaților de dihidropirimidine. In: *Conferința științifică cu participare internațională „Obținerea și cercetarea farmaceutică a unor noi molecule și produse farmaceutice cu potențial terapeutic"*. 31 ianuarie, 2020, Chisinau, Moldova, raport oral. https://drive.google.com/file/d/1ZMMK

16. **CIOBANU, N**. Synthesis of monastrol using ecological catalysts. In: *Conferința științifică a doctoranzilor Tendințe contemporane ale dezvoltării științei: viziuni ale tinerilor cercetători.* 10 iunie, 2019, Chisinau, Moldova, VIII, pp. 38-43.
http:///Conf./USDC//10/06/2019//p,38-43.pdf

17. **CIOBANU, N**. Sinteza și activitatea biologică a monastrolului. In: *Conferința științifică a studenților-doctoranzi Tendințe comtemparane ale dezvoltării științei: viziuni ale tinerilor cercetători.* 10 iunie, 2020, Universitatea "Dumitru Cantemir", Chisinau, Moldova, pp. 82-87. http:\\conf.\USDC 10.06.2020 p.\82-86\.pdf

18. **CIOBANU, N**. Environmental safety of catalytic conditions in the synthesis of dihydropyrimidine products. In: *Natural sciences in the dialogue of Generations, The National Conference with international participation.* 14-15 septembrie, 2023, Chisinau, Moldova, VI, p. 205. ISBN 978-9975-3430-9-1.

19. **CIOBANU, N.**, MACAEV, F. Environmental conditions in the synthesis of monastrol. In: *Scientific seminar: Advanced materials to reduce the impact of toxic chemicals on the environment and health*. 23 septembrie, 2023, Chisinau, Moldova, pp. 34-37.
UDC: 547.781.1:502.5.

20. **CIOBANU, N.**, MACAEV, F. Selection of the optimal method for synthesis of dihydropyrimidin-2-ones(thiones) using various catalysts. In: *Natural sciences in the dialogue of generations.* 12-13 septembrie, 2024, Chisinau, Moldova, VII, p. 33.
ISBN 978-9975-62-756-6.

21. **CIOBANU, N.**, MACAEV, F. Synthesis and activity of 3,4-dihydropyrimidin-2-ones (thiones) using various organic catalysts. In: *10th International Conference on Materials Science and Condensed Matter Physics MSCMP-2024*. 1 octombrie, 2024, Chisinau, Moldova, p.100. ISBN 78-9975-62-763-4.

22. GORINCIOI, E., **CIOBANU, N.**, MACAEV, F. Low-ester pectin as recyclable green catalyst for eco-friendly synthesis of (±)-monastrol. In*: Natural sciences in the dialogue of generations.* 12-13 septembrie, 2024, Chisinau, Moldova, VII, p. 58.
ISBN 978-9975-62-756-6.

23. **CIOBANU, N**. Metode noi de sinteza derivațiilor dihidropirimidinelor. In: *Conferinţă ştiinţifică cu participare internaţională "Universitas europaea: towards a knowledge-based society through europeanisation and globalization"*. 16 octombrie, 2020, ULIM, Chișinău, Moldova, raport oral. http:\\academia\conf.2020\ULIM 16.10.20.pdf

АННОТАЦИЯ

Диссертация **«Синтез замещенных дигидропиримидин-5-карбоксилатов»**, представленная кандидатом - **Чобану Наталья**, на соискание степени доктора химических наук по специальности – **143.01. Органическая химия**.

Кишинэу, 2025

Структура диссертации: диссертация написана на русском языке и состоит из введения, пяти глав, общих выводов и рекомендаций, библиографии из 196 названий и 2 приложений. Диссертация содержит 129 страниц основного текста, 21 таблицы 40 рисунков. Полученные результаты опубликованы в 62 научных работах.

Ключевые слова: дигидропиримидин-5-карбоксилат, тетрагидропиримидотиазин-7-карбоксилат, 2-бензилиден-3,5-дигидро-2*H*-тиазоло[3,2-a]пиримидин-6-карбоксилат, конденсация, ионная жидкость, эвтектическая смесь.

Цель научной работы: создание новых катализируемых систем синтеза замещенных дигидропиримидин-5-карбоксилатов и разработки селективных методов их трансформации в органические гетероатомные продукты, необходимых для изучения зависимости свойств от структуры веществ.

Задачи исследования: определение оптимальных условий получения этил дигидропиримидин-5-карбоксилатов и использование последних для построения связи углерод-гетероатом циклических производных; определение оптимальных условий получения непредельных соединений из группы тиазоло[3,2-a]пиримидин-6-карбоксилатов и пиримидотиазин-7-карбоксилатов, оценка взаимосвязи «*структура-биоактивность*» в ряду синтезированных замещенных дигидропиримидин-5-карбоксилатов.

Новизна и научная оригинальность работы – выявление эффективности синтеза препарата монастрола и аналогично построенных этил дигидропиримидин-5-карбоксилатов при использовании каталитических количеств хиральных агентов на основе (+)-винной, галактуроновой, лимонной кислот и низкометоксилированного пектина. Разработан региоселективный метод синтеза бициклических производных ряда пиримидотиазин-7-карбоксилатов в условиях реакции Пехмана.

Решённая важная научная проблема - разработан подход к серии ранее неизвестных ионногенных материалов имидазолиевого ряда и установлены каталитические свойства при получении практически важных веществ из группы этил дигидропиримидин-5-карбоксилатов.

Теоретическая значимость работы - Разработанный новый эффективный метод однореакторного получения этил 5-(3-гидроксифенил)-7-метил-3-оксо-3,5-дигидро-2*H*-тиазоло[3,2-a]пиримидин-6-карбоксилатов с 2-бензилиденовым фрагментом является существенным вкладом в развитие основ органической химии.

Прикладная значимость работы - разработанные методы легли в основу селективного синтеза серии производных этил дигидропиримидин-5-карбоксилатов. Анализ зависимости «структура-свойство» показал, что синтезированные вещества обладают цитотоксичностью, антибактериальной и фунгицидной активностью сопоставимый со стандартными средствами, что, представляет практический интерес для углубленных исследований.

Внедрение научных результатов. Методы селективного получения производных дигидропиримидин-5-карбоксилатов нашли применение в научно-исследовательской деятельности Лаборатории Органического Синтеза Института Химии, Государственного Университета Молдовы, Школы Фармации Университета Аристотеля Салонники, Греция. Данные по биоактивности выявили перспективные вещества для дальнейших углубленных исследований в Центре Исследования Медицинских Препаратов Университета Медицины и Фармации *«Николае Тестемицану».*

ADNOTARE

La teza cu titlul **”Sinteza dihidropirimidin-5-carboxilaților substituiți”,** înaintată de către candidatul – **Ciobanu Natalia**, pentru conferirea titlului științific de doctor în științe chimice la specialitatea **-143.01. Chimie organică**.

Chișinău, 2025

Structura tezei: teza este scrisă în limba rusă și constă din introducere, cinci capitole, concluzii generale și recomandări, bibliografie 196 de titluri și 2 anexe. Teza conține 129 de pagini de text de bază, 40 figuri și 21 tabele. Rezultatele obținute sunt publicate în 62 lucrări științifice.

Cuvinte-cheie: dihidropirimidin-5-carboxilat, tetrahidropirimidotiazin-7-carboxilat, 2-benziliden-3,5-dihidro-2*H*-tiazolo[3,2-a]pirimidin-6-carboxilat, condensare, lichid ionic, amestec eutectic.

Scopul lucrării: crearea de noi sisteme catalizate pentru sinteza dihidropirimidin-5-carboxilaților substituiți și dezvoltarea de metode selective pentru transformarea acestora în produse organice heteroatomice necesare pentru studierea dependenței proprietăților de structura substanțelor.

Obiectivele cercetării: determinarea condițiilor optime pentru obținerea dihidropirimidin-5-carboxilaților de etil și utilizarea acestora pentru construirea legăturilor carbon-heteroatom ale derivaților ciclici; determinarea condițiilor optime pentru obținerea compușilor nesaturați din grupul tiazolo[3,2-a]pirimidin-6-carboxilaților și pirimidotiazin-7-carboxilaților, evaluarea relației structură-bioactivitate într-o serie de dihidropirimidin-5-carboxilați substituiți sintetizați.

Noutatea și originalitatea științifică: dezvăluind eficiența sintezei medicamentului monastrol și a dihidropirimidin-5-carboxilați de etil construiți similar, utilizând cantități catalitice de agenți chirali pe bază de acizi (+)-tartaric, galacturonic, citric și pectin slab metoxilată. A fost dezvoltată o metodă regioselectivă pentru sinteza derivaților biciclici ai unei serii de pirimidotiazin-7-carboxilați în condițiile reacției Pechman.

Problema științifică soluționată: a fost dezvoltată o abordare a unei serii de materiale ionogene necunoscute anterior din seria imidazoliu și au fost stabilite proprietăți catalitice în producerea de substanțe importante din gruparea etil dihidropirimidin-5-carboxilat.

Semnificația teoretică. Noua metodă eficientă dezvoltată pentru prepararea într-un singur pas a 5-(3-hidroxifenil)-7-metil-3-oxo-3,5-dihidro-2*H*-tiazolo[3,2-a]pirimidin-6-carboxilaților de etil cu un fragment de 2-benziliden reprezintă o contribuție semnificativă la dezvoltarea fundamentelor chimiei organice.

Valoarea aplicativă. Metodele dezvoltate au stat la baza sintezei selective a unei serii de derivați de etil dihidropirimidin-5-carboxilat. Analiza relației „*structură-actiune”* a arătat că substanțele sintetizate posedă citotoxicitate, activitate antibacteriană și fungicidă comparabile cu agenții standard, ceea ce prezintă interes practic pentru studii aprofundate.

Implementarea rezultatelor științifice: metodele de preparare selectivă a derivaților de dihidropirimidină-5-carboxilat și-au găsit aplicații în activitățile de cercetare ale Laboratorului de Sinteză Organică al Institutului de Chimie al Universității de Stat din Moldova și Facultatea de Farmacie a Universității Aristotel din Salonic, Grecia. Datele de bioactivitate au identificat substanțe promițătoare pentru studii aprofundate ulterioare la Centrul de Cercetare a Preparatelor Medicale al Universității de Medicină și Farmacie „*Nicolae Testemițanu*”.

ANNOTATION

Of the thesis entitled **"Synthesis of substituted dihydropyrimidine-5-carboxylates".** Presented by the candidate **Ciobanu Natalia**, for obtaining the degree of Doctor of Chemical Sciences with specialty – **143.01. Organic Chemistry.**

Chisinau, 2025

Structure of the thesis: the thesis is written in russian and consists of an introduction, five chapters, general conclusions and recommendations, a bibliography of 196 titles and 2 appendices. The thesis contains 129 pages of basic text, 40 figures and 21 tables. The obtained results were published in 62 papers.

Keywords: dihydropyrimidine-5-carboxylate, tetrahydropyrimidothiazine-7-carboxylate, 2-benzylidene-3,5-dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate, condensation, ionic liquid, eutectic mixture.

Research purpose: creation of new catalyzed systems for the synthesis of substituted dihydropyrimidine-5-carboxylates and development of selective methods for their transformation into organic heteroatomic products necessary for studying the dependence of properties on the structure of substances.

Research objectives: determination of optimal conditions for obtaining ethyl dihydropyrimidine-5-carboxylates and the use of the latter to construct carbon-heteroatom bonds of cyclic derivatives; determination of optimal conditions for obtaining unsaturated compounds from the group of thiazolo[3,2-a]pyrimidine-6-carboxylates and pyrimidothiazine-7-carboxylates, assessment of the "structure-bioactivity" relationship in a series of synthesized substituted dihydropyrimidine-5-carboxylates.

Scientific novelty and originality: revealing the efficiency of the synthesis of the drug monastrol and similarly constructed ethyl dihydropyrimidine-5-carboxylates using catalytic amounts of chiral agents based on (+)-tartaric, galacturonic, citric acids and low-methoxylated pectin. A regioselective method for the synthesis of bicyclic derivatives of a series of pyrimidothiazine-7-carboxylates under the conditions of the Pechman reaction has been developed.

The result obtained. An approach to a series of previously unknown ionogenic materials of the imidazolium series was developed and catalytic properties were established in the production of practically important substances from the ethyl dihydropyrimidine-5-carboxylate group.

The theoretical significance. The developed new efficient method for the one-pot preparation of ethyl 5-(3-hydroxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2*H*-thiazolo[3,2-a]pyrimidine-6-carboxylates with a 2-benzylidene fragment is a significant contribution to the development of the fundamentals of organic chemistry.

The applicative value: the developed methods formed the basis for the selective synthesis of a series of ethyl dihydropyrimidine-5-carboxylate derivatives. Analysis of the "structure-property" relationship showed that the synthesized substances possess cytotoxicity, antibacterial and fungicidal activity comparable to standard agents, which has a practical importance in the cours of in-depth research.

Implementation of the results. Methods for the selective preparation of dihydropyrimidine-5-carboxylate derivatives have found application in the research activities of the Laboratory of Organic Synthesis of the Institute of Chemistry, State University of Moldova, School of Pharmacy of the Aristotle University of Thessaloniki, Greece. Bioactivity data have identified promising substances for further in-depth studies at the Center for Research of Medical Preparations of the University of Medicine and Pharmacy "*Nicolae Testemitanu"*.

CIOBANU NATALIA

SYNTHESIS OF SUBSTITUTED DIHYDROPYRIMIDINE-5-CARBOXYLATES

143.01. ORGANIC CHEMISTRY

Summary of the doctoral thesis in chemical sciences

Approved for printing: 10-09-2025
Offset paper.
Printed sheets: 2,5

Paper size: 60x84 1/16
Print run: 35 ex.
Order number: 10-09/2025

"Tipocart-Print" S.R.L.
Republic of Moldova, Chisinau, Pushkin, Str., 22, of. 523