KAUNAS UNIVERSITY OF TECHNOLOGY

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SYNTHESIS AND INVESTIGATION OF FUNCTIONALIZED FLUORO-CONTAINING AZOLES AND AZINES

Summary of Doctoral Dissertation
Physical Sciences, Chemistry (03P)

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KAUNO TECHNOLOGIJOS UNIVERSITETAS

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FLUORO TURINČIŲ FUNKCIONALIZUOTŲ AZOLŲ IR AZINŲ SINTEZĖ BEI TYRIMAS

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INTRODUCTION

Heterocyclic chemistry is a very important branch of organic chemistry and the foundation of biology and medicine. Recently, the synthesis of high nitrogen-containing heterocyclic systems has been extremely popular in pharmaceutical and agrochemical industries. The nitrogen-containing heterocycles are found in abundance in most of medicinal compounds.

Heterocyclic compounds include many of the biochemical materials essential to life. For example, nucleic acids, i.e. the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together by other types of materials. Many naturally occurring pigments, vitamins and antibiotics are heterocycles.

Azoles and azines are five- and six-membered heterocyclic compounds with one or several heteroatoms in the ring. The nitrogen, oxygen, and sulphur heterocycles are an attractive source of compounds for the identification of new biological probes.

Pyrroles are important synthons in the synthesis of natural products. Furthermore, some of these compounds are useful intermediates in the synthesis of biologically important naturally occurring alkaloids and unnatural heterocyclic derivatives. Phosphino-substituted *N*-aryl pyrroles, a novel class of sterically demanding and electron rich biaryl phosphine ligands, exhibit high turnover rates and low catalyst loadings.

The pyrazole scaffold represents a common motif in many pharmaceutical active and remarkable compounds demonstrating a wide range of pharmacological, antiproliferative, crop protection activities. A large amount of biologically active compounds containing a pyrazole fragment in the stucture have determined its leading position in the synthesis of pharmaceuticals and agrochemicals.

The triazole nucleus is one of the most important heterocycles; it is a feature of natural products and predominates among the medicinal agents. The derivatization of triazole ring is based on the phenomenon of bioisosterism in which the replacement of oxygen of the oxadiazole nucleus with a nitrogen triazole analogue occurs. Triazoles nucleus have been incorporated into a wide variety of therapeutically interesting drug candidates. They are used as optical brightening agents, as antioxidants, as corrosion inhibitors and as additives with a variety of other functions. Many dye components and pigments have contain a heterocyclic fragment.

Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum. They have also attracted interest in medicinal chemistry as surrogates (bioisosteres) for carboxylic acids, esters, and carboxamides. The ability of 1,3,4-oxadiazole heterocyclic compounds to undergo various chemical reactions has made them important for molecule planning because of their

privileged structure which has an enormous biological potential. Heterocyclic compounds bearing the 1,3,4-oxadiazole moiety have been used as a π-conjugation relay to prepare a number of donor–acceptor molecules carrying a π-electron-rich aromatic ring. Therefore, the compounds bearing 1,3,4-oxadiazole moiety may be good candidate for optical material or biologically active chemicals.

The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bioactive class of heterocycles. These molecules are also used as pharmacophores due to their favourable metabolic profile and ability to engage in hydrogen bonding. 1,3,4-oxadiazoles have proved to be useful in material science as a probe for their fluorescence and scintillation properties. In addition, oxadiazole derivatives have been widely used as the electron-conducting and hole-blocking material in molecule-based as well as polymeric light emitting devices.

The interest in 1,2,4-triazines as building blocks, reagents and chemical entities in their own right is widespread and ongoing. Triazines are common pharmacophores making them pervasive in both the pharmaceutical and agrochemical arenas. Furthermore, the specific electronic properties of the 1,2,4-triazine heteroaromatic ring impart both the reactivity and synthetic approaches of this ring system. Drugs containing a 1,2,4-triazine ring trace their origin from natural and synthetic sources as exemplified by Azaribine and Lamotrigine which have important biological activities. Encouraging results have been obtained with compounds containing a 1,2,4-triazine nucleus, and these are still in the final phases of clinical investigation. The intramolecular Diels–Alder reaction of 1,2,4-triazines is a powerful and flexible approach to a broad array of condensed heterocyclic ring systems.

The incorporation of fluorine into organic molecules can dramatically alter their reactivity, chemical and biological properties, and physiological activity. Fluorine can exert major influence on the acidity or basicity of functional groups. It may also change the molecular conformation and it generally increases the stability of hydrocarbons. For instance, fluorine substituents have been shown to affect the metabolic stability, lipophilicity, and the binding affinity of many drugs. These unique properties that fluorine substitution can produce in pharmaceuticals, agrochemicals, and materials have led to an increased interest in fluorine chemistry (Liang, Neumann, and Ritter, 2013).

The main aim of the work: synthesis of new, potentially biologically active fluorine-containing *N*-aryl-β- and β,γ-amino acids, their derivatives and cyclization products, and the investigation of the structure and characteristics of the synthesized compounds. It is known that the introduction of fluorine atoms in the molecule often increases the biological activity of the compound.

The tasks of the work:

1. To synthesize 3-[(fluorine containing phenyl)amino]propanoic and 3-[(fluorine containing phenyl)(2-carboxyethyl)amino]propanoic acids from the corresponding phenylamines, to investigate their cyclization to dihydropyrimidin-2,4(1*H*,3*H*)-dione ir 2-thioxotetrahydropyrimidin-4(1*H*)-one derivatives and perform the decyclization of the obtained heterocycles.
2. To apply the binucleophility of the thiocarbamoyl fragment of 3-[(4-fluorophenyl)carbamothioylamino]propanoic acid in order to synthesize thiazole and 4,5-dihydrothiazole heterocyclic systems with a free carboxyalkyl moiety and to investigate the chemical properties of the obtained compounds.
3. To synthesize 1-(fluorine containing phenyl)-5-oxopyrrolidine-3-carboxylic acid derivatives: hydrazides, hydrazones, variously functionalized azoles, and azines.
4. To synthesize 1-[4-fluoro or 3-(trifluoromethyl)phenyl]-5-oxopyrrolidines, containing a benzimidazole fragment in the third position of the hetero ring and to investigate the chemical properties of the synthesized compounds.
5. To investigate the antimicrobial properties of the synthesized compounds in order to find relationships between the chemical structure and the biological activity of the researched compounds**.**

The scientific novelty and practical value of the work

A series of 3-[(fluorine containing phenyl)amino]propanoic ir 3-[(fluorine containing phenyl)(2-carboxyethyl)amino]propanoic acids were synthesized and then cyclized to pyrimidinediones and their 2-thioanalogues, which were decyclized by the action of alkalis to ureido and thioureido acids.

A new approach to the synthesis of 1-substituted dihydropyrimidin-2,4(1*H*,3*H*)-diones or 2-thioxotetrahydropyrimidin-4(1*H*)-ones was proposed. The advantage of this method is the possibility to synthesize the above-mentioned heterocycles not only from pure *β*-amino acids, but also from their mixtures with 3-[(substituted phenyl)(2-carboxyethyl)amino]propanoic acids as well as from the latter compounds. For the first time 3-[(4-fluorophenyl)carbamothioylamino]propanoic acid was used for the synthesis of compounds containing thiazole, thiazole and chalkone, condensed thiazolo[4,5-*b*]quinoxalinyl and 4,9-dioxo-4,9-dihydronaphtho[2,3-*d*]thiazolyl fragments with an unchanged carboxyalkyl chain in the molecule. The biological properties of these compounds were investigated. Studies of the antimicrobial activity of the synthesized compounds revealed potentially new compounds with antibacterial activity against *Staphylococcus aureus* and *Mycobacterium luteum*. The antibacterial tests have indicated the functionalized amino thiazole derivatives to exhibit a higher activity when compared with thiazolone derivatives.

1-(4-fluoro and 3-trifluoromethylphenyl)-5-oxopyrrolidine-3-carboxylic acids were used to obtain a benzimidazole fragment at the third position of the

hetero ring. Various chemical transformations of the synthesized benzimidazoles were carried out, and a series of 1,2-substituted benzimidazole derivatives were prepared. Studies of the antimicrobial activity of the synthesized compounds were carried out.

The possibility to synthesize hydrazones, pyrrole, pyrazole, oxadiazole, aminotriazole and azine derivatives based on 1-(substituted phenyl)-5-oxopyrrolidine-3-carboxylic acid hydrazides was investigated. All the synthesized compounds provide a possibility to broaden the area of the target synthesis of biologically active substances.

The main statements of the doctoral dissertation are:

- the 3-[(fluorine containing phenyl)amino]propanoic and 3-[(fluorine containing phenyl)(2-carboxyethyl)amino]propanoic acids, depending on the reaction conditions and the nature of the substituents, can successfully be used for the synthesis of heterocyclic systems;
- both aminopropanoic and (2-carboxyethyl)aminopropanoic acids in the reaction with carbamide or potassium thiocyanate in an acidic medium compose 1-substituted dihydropyrimidine-2,4-(1*H*,3*H*)-diones or 2-thioxotetrahydropyirimidine-4(1*H*)-ones;
- variously functionalized 2-aminothiazoles can be easily prepared by the Hantzsch reaction from 3-[(4-fluorophenyl)carbamothioylamino]propanoic acid – the cleavage product of 1-(4-fluorophenyl)-2-thioxotetrahydropyrimidine-4(1*H*)-one.
- 1-(fluorine containing phenyl)-5-oxopyrrolidine-3-carboxylic acids are convenient synthons for the synthesis of hydrazides, hydrazones, variously functionalized azole and azine heterocyclic systems.

Approbation of the dissertation

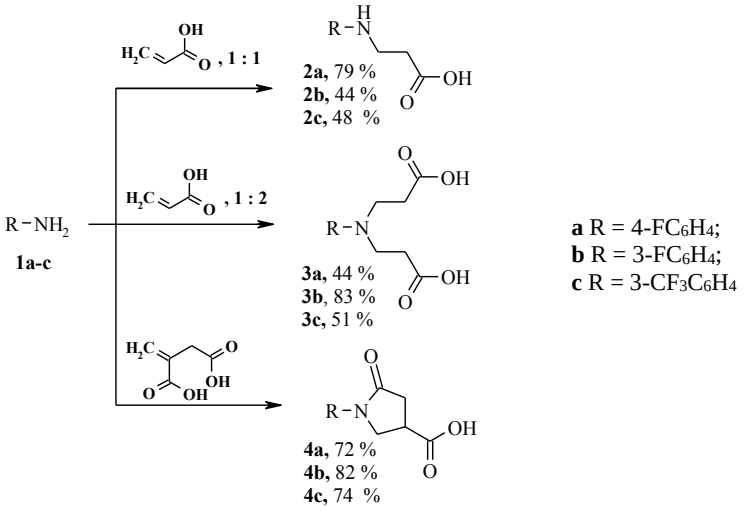
Five publications have been delivered on the theme of the dissertation in the journals included in the list of the Institute of Scientific Information (ISI), two papers were published in reviewed scientific periodical publications. The research results have been presented at ten Lithuanian national and international scientific conferences and one congress.

1. RESULTS AND DISCUSSION

1.1. The reactions of fluorine containing anilines with unsaturated acids

One of the most convenient methods for the preparation of β-aminoacids and 5-oxopyrrolidine-3-carboxylic acid is the interaction of primary amines with unsaturated acrylic and itaconic acids. The course of the reaction and the structure of the obtained products depend on the reaction conditions. The reactions of aromatic amines, which include electron-donating groups, with acrylic acid are easily accomplished, resulting in the formation of *N*-substituted and *N*,*N*-disubstituted β-amino acids.

The nucleophilic addition of fluorine-containing anilines to a stoichiometric amount of acrylic acid under the selected reaction conditions gave appropriate aminopropanoic acids **2a–c**. The double excess of acrylic acid, used in this reaction, afforded 3-[(substituted phenyl)(2-carboxyethyl)amino]propanoic acids **3a–c** (Scheme 1).



Scheme 1

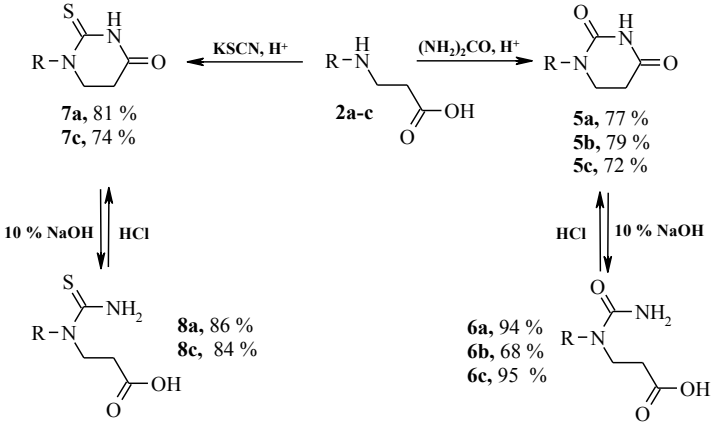
The interaction of the above-mentioned amines with itaconic acids in water at reflux for 24 h was followed by the subsequent cyclization of the formed intermediate to 5-oxopyrrolidine-3-carboxylic acids **4a–c**. The synthesis of compound **4a** using the method of heating an appropriate aniline with itaconic acid is described in the work of Watanabe et al. (1994).

These acids are chiral compounds and can exist as two enantiomers which form racemic mixtures, but they have not been studied in detail in this work.

1.2. Cyclization of β-amino acids

1.2.1. Synthesis of dihydropyrimidine-2,4-(1*H*,3*H*)-diones and their thioanalogues

Commonly, reactions of β-amino acids with carbamide or alkali metals' thiocyanates in the acidic medium result in the formation of dihydropyrimidine-2,4(1*H*,3*H*)-diones or 2-thioxotetrahydropyrimidine-4(1*H*)-ones. The condensation of β-alanines **2a–c** with urea or potassium thiocyanate in acetic acid was carried out under reflux for 24 h. The formed intermediates – ureido and thioureido acids – were cyclized *in situ* with hydrochloric acid to the more stabile and acid-resistant heterocycles: 1-(substituted phenyl)dihydropyrimidine-2,4(1*H*,3*H*)-diones **5a–c** or 1-(substituted phenyl)-2-thioxotetrahydropyrimidine-4(1*H*)-ones **7a, c**, respectively (Scheme 2).

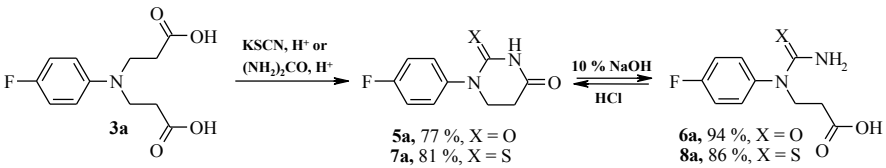


a R = 4-FC_6H_4; **b** R = 3-FC_6H_4; **c** R = 3-$CF_3C_6H_4$

Scheme 2

The investigations revealed that compounds **5a** and **7a** can be obtained by the analogous reactions from 3-[(4-fluorophenyl)(2-carboxyethyl)amino]propanoic acids **3a** (Scheme 2A).

The main advantage of this method is the possibility to synthesize heterocycles not only from pure aminopropanoic acids, but also from their mixtures with dicarboxylic acids which often form during the reaction of 4-fluoroaniline **(1a)** with acrylic acid (Anusevicius et al., 2012).



Scheme 2A

The acid-resistant compounds **5a–c** and **7a, c** are sensitive to the action of alkaline medium (10 % NaOH aqueous solution, temperature) and easily cleave to the respective sodium salts of 3-[1-(fluorine containing phenyl)carbamoylamino]propanoic **6a–c** or 3-[(fluorine containing phenyl)carbamothioylamino]propanoic **8a, c** acids. Target products **6** or **8** from the reaction mixtures were separated by the acidification of the aqueous solutions with acetic acid to pH 6.

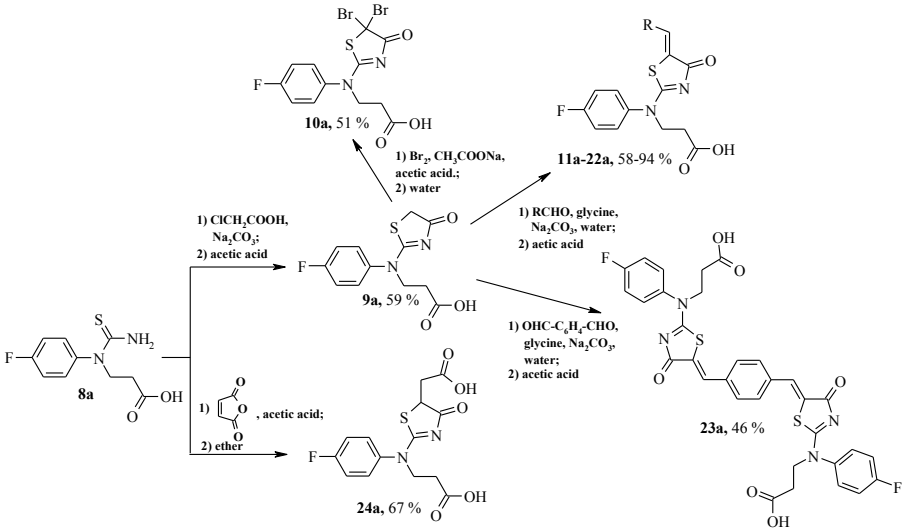
1.2.2. Synthesis of 3-[(4-fluorophenyl)(4,5-dihydro-4-oxothiazol-2-yl)amino]propanoic acid and its derivatives

It is known that compounds bearing a thiazolone moiety possess a wide variety of biological activities; therefore the development of novel compounds with thiazolone and carboxyalkyl fragments in the sturcture was part of the provided searches.

The reaction of thioureido acid **8a** with monochloroacetic acid was performed in water in the presence of sodium carbonate. The obtained 3-[(4-fluorophenyl)(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic acid **(9a)** was isolated from the reaction mixture by acidifying it with acetic acid to pH 6 (Scheme 3). The bromination of compound **9a** in acetic acid at room temperature resulted in 3-[(5,5-dibromo-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)(4-fluorophenyl)amino]propanoic acid **(10a)**. Thye condensation of **9a** with various carbaldehydes afforded a series of thiazolone derivatives **(11–22)a**. The reactions were performed in water in the presence of sodium carbonate and glycine as a bifunctional catalyst (Chowdhry et al., 2000), which gives a single isomer (*Z*). The desired products were isolated from the reaction mixtures in 58–94 % yields by acidifying them with acetic acid. In the same way, compound **23a** was synthesized from dihydrothiazolone **9a** and terephthaldehyde.

The structure of the synthesized compounds **(11–22)a** was confirmed by elemental analysis, ^{1}H, ^{13}C NMR and IR spectral data. For example, in the ^{1}H NMR spectrum of compound **16a**, the CH_2CO and NCH_2 group proton signals appear at 2.64 and 4.26 ppm, whereas aromatic and CH proton signals are observed in the range of 7.29–7.70 ppm. In the ^{13}C NMR spectrum of compound **16a**, the signals of the CH_2CO and NCH_2 groups are observed at 31.85 and

50.02 ppm, respectively, whereas aromatic, S–C=CH group carbon signals are observed in the region of 116.36–162.55 ppm. The resonances of COOH, C=O, and C=N carbon signals are observed in the range of 171.94–179.44 ppm. In the IR spectrum, the OH absorption band is observed at 3415 cm^{-1}, two C=O bands at 1725 and 1655 cm^{-1}, and a band belonging to the C=N group at 1538 cm^{-1} is also visible. The formation of isomeric structures in these reactions was not discovered.



11 R = C_6H_5; **12** R = 4-ClC_6H_4; **13** R = 4-$H_3COC_6H_4$; **14** R = 4-$(CH_3)_2NC_6H_4$; **15** R = 4-HOC_6H_4; **16** R = 4-FC_6H_4; **17** R = 4-BrC_6H_4; **18** R = 3,4-$(H_3CO)_2C_6H_3$; **19** R = 4-$O_2NC_6H_4$; **20** R = HC=CH-C_6H_5

21 R =  ; **22** R = 

Scheme 3

According to the data published in the scholarly literature, glycine used as a bifunctional catalyst gives a single isomer (*Z*).

The interaction of thioureido acid **8a** and maleic anhydride in glacial acetic acid at 80 °C for 6 h and the subsequent dilution of the reaction mixture with diethyl ether gave the expected product 3-[(4-fluorophenyl)(5-carboxymethyl-4,5-dihydro-4-oxo-1,3-thiazol-2-yl)amino]propanoic acid **(24a)**. A comparison of the ^{13}C NMR spectra of **9a** and **24a** revealed two additional resonances in the high field region (37.36 (S–CH–$\underline{C}H_2$) and 52.25 (S–$\underline{C}H$–CH_2) ppm) and four resonances in the low field region of the last-mentioned spectrum, i. e. spectral lines at 171.96, 172.39, 182.55 and 187.70 ppm, which were assigned to the COOH, S–C=N, and C=O carbons.

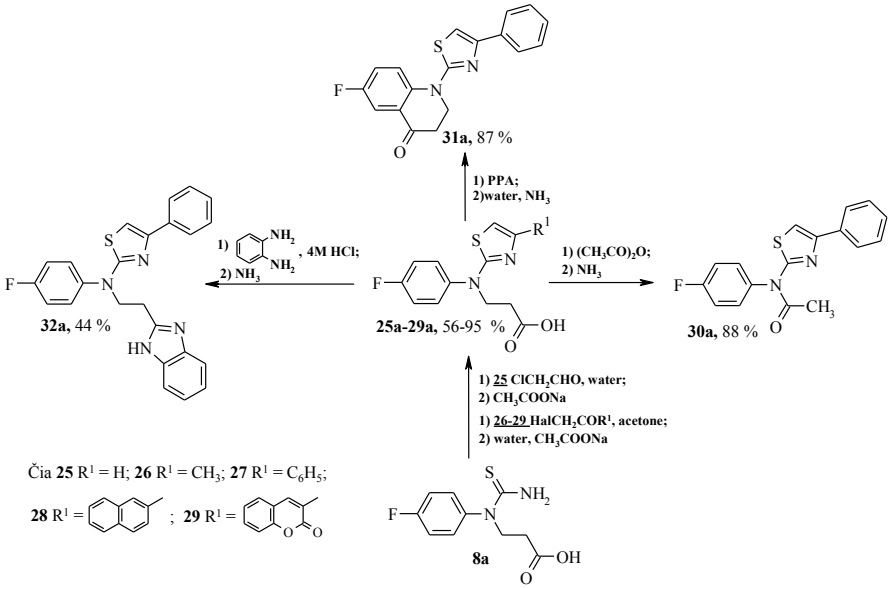
1.2.3. Synthesis of functionalized 2-aminothiazole derivatives

Previously, thioureido acids were used only as precursors for the synthesis of six-membered heterocycles. In this work, 3-[(4-fluorophenyl)carbamothioylamino]-propanoic acid **(8a)** was employed for the synthesis of a new class of compounds containing a thiazole moiety and an unchanged carboxyalkyl fragment.

One of the most convenient methods for the preparation of thiazoles is the Hantzsch synthesis, i.e. the condensation of β-halocarbonyl derivatives with thioamides or thiocarbamides. Thus, *N*,*N*-disubstituted aminothiazoles **(25–29)a** were prepared by refluxing the corresponding halocarbonyl compound with *N*-(4-phenyl)-*N*-thiocarbamoyl-β-alanine **(8a)** in water **(25a)** or acetone **(26–29)a** for 4 h (Scheme 4). The reaction provided soluble-in-water amino acid hydrochlorides which were converted into insoluble bases by diluting the reaction mixture with water and treating the solution with sodium acetate.

The structures of the synthesized compounds were confirmed on the basis of their spectral data and elemental analysis. The formation of the thiazole ring in compound **25a** has been proven by the doublets of SCH and NCH groups protons at 6.72 and 7.18 ppm, respectively, whereas the same SCH proton gave rise to singlets at 6.27–7.55 ppm in the ^{1}H NMR spectra of **(26–29)a**. In the ^{13}C NMR spectra of these compounds, the resonances ascribed to SCH group carbon are observed in the range of 102.23–109.53 ppm. The signal of NCH carbon in the ^{13}C NMR spectrum of **25a** is observed at 139.19 ppm, and the signals of N-C-R^{1} carbon of **(26–29)a** are seen in the range of 148.38-152.20 ppm. The C=N group carbon gave rise to peaks at 168.92–169.81 ppm in the spectra of thiazoles **(25–29)a**. In the IR spectrum of these compounds, the absorption band of the C=N group is observed in the range of 1506–1541 cm^{-1}.

Some chemical transformations were carried out with a chosen thiazole derivative – 3-[(4-fluorophenyl)(4-phenyl-1,3-thiazol-2-yl)amino]propanoic acid **(27a)**. Under the action of an excess of acetic anhydride at reflux and the following dilution with aqueous ammonia, the desired cyclic product was not obtained. The NMR spectra showed the formation of *N*-acyl derivative **30a**: the spectral lines at 2.01 (^{1}H NMR) and 23.76 (^{13}C NMR) ppm show the presence of a CH_3 group, the chemical shifts assignable to N=C–S and C=O fragments in **30a** appear at a higher field (159.80 and 169.78 ppm, respectively) than for those in **27a** (169.00 and 172.59 ppm, respectively). Attempts to prepare a cyclic product by using polyphosphoric acid were successful and led to the formation of derivative **31a** containing a quinolinone fragment.



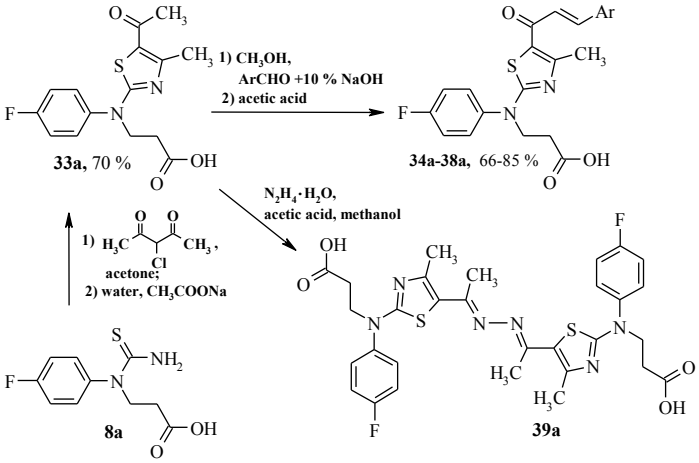
Scheme 4

The formation of the cyclic structure is clearly demonstrated by chemical shifts in the ^{13}C NMR spectrum, i. e. signals at 37.36 (CH_2CO), 49.29 (NCH_2), and 192.02 (C=O) which differ from the signals of the same functional groups of the initial compound. The heating of 3-[(4-fluorophenyl)(4-phenyl-1,3-thiazol-2-yl)amino]propanoic acid **(27a)** in 4 M hydrochloric acid with the subsequent neutralization of the reaction mixture with a 10 % sodium carbonate solution afforded compound **32a**.

1.2.4. Synthesis of 3-[(5-acetyl-4-methylthiazol-2-yl)(4-fluorophenyl)amino]-propanoic acid and products of its chemical modification

3-[(5-Acetyl-4-methylthiazol-2-yl)(4-fluorophenyl)amino]propanoic acid **(33a)** was synthesized from thioureido acid **8a** and 3-chloropentane-2,4-dione in acetone at reflux. Sodium acetate was used to transfer the formed aminothiazolium chloride into the base. The synthesis of the target chalcones **(34–38)a** was accomplished by Claisen–Schmidt condensation of 5-acetyl-4-methylthiazole **33a** with various aromatic aldehydes, in methanol, and 10% aqueous sodium hydroxide (Liaras et al., 2011) (Scheme 5). The reactions proceeded smoothly and with good yields (66–85%). All the new structures of compounds **(34–38)a** were satisfactorily confirmed by the methods of IR, ^1H and ^{13}C NMR spectroscopy and elemental analysis. IR spectra showed absorptions at 1728–1630 cm^{-1} (C=O) and

sharp bands at 3421–3438 cm^{-1} (OH). In the ^1H NMR spectra, chalcones showed peaks at ~2.61 (CH_3) in the region of 7.18–7.39 (CO–CH=) and 7.50–7.61 (=CH–Ar) ppm. The



34a Ar = C_6H_5; **35a** Ar = 4-FC_6H_4; **36a** Ar = 4-ClC_6H_4; **37a** Ar = 4-BrC_6H_4; **38a** Ar = 4-$NO_2C_6H_4$

Scheme 5

CH=CH double bond in the enone moiety of chalcones can potentially adopt either a *Z* or an *E* configuration. The ^1H NMR spectrum of each compound exhibited CH=CH protons around 7.18–7.61 ppm, with J >15. Thus, it would be suggested that the compounds were produced with the (*E*) configuration (Eliel and Wilen, 1994).

In order to perform a more detailed investigation of the structure of the synthesized chalkones, the X-ray analysis of **35a** was carried out. A molecular structure with atomic labels of the compound **35a** is shown in Figure 1. Figure 2 illustrates a projection of the crystal structure along the crystallographic axis ***a***. In the crystal structure, there are strong intermolecular hydrogen bonds of OH···N type between the carboxyl group and the nitrogen atom of thiazole.

The parameters of the hydrogen bonds are the following:

O···N = 2.787(5)Å,

H···N = 1.89 Å,

O–H···N =162º.

By means of these bonds, molecules of the compound are associated in centrosymmetrical dimers.

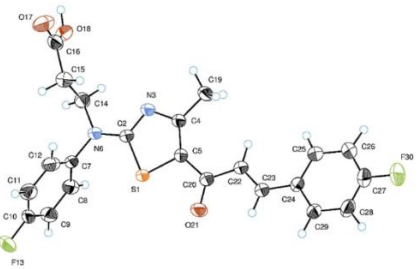


Fig. 1. ORTEP molecular structure of **35a**

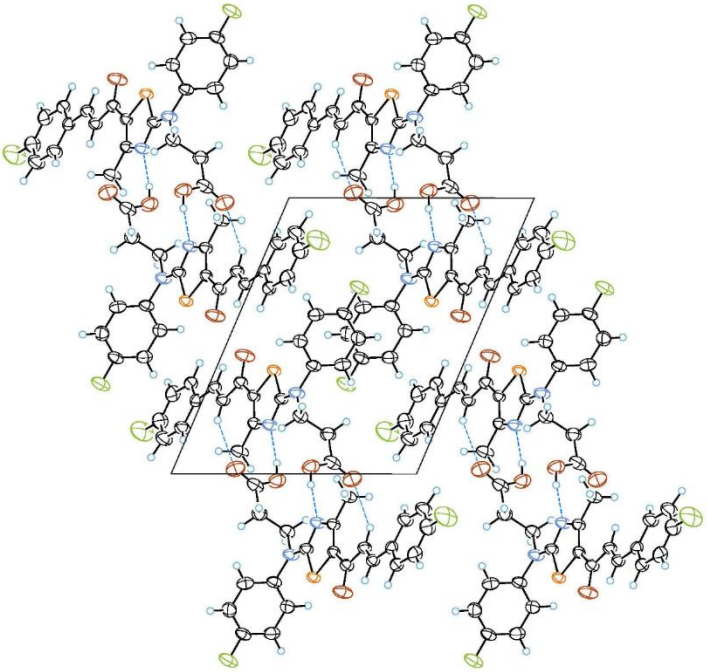


Fig. 2. Projection of the crystal structure of **35a** along the crystallographic axis ***a***

The intermolecular contact between carbonyl oxygen of the carboxyl group and one of olefin hydrogens (2.68 Å) can be described as a very weak CH···O type of hydrogen bonds with the C···O length of 3.337(6)Å (angle C–H···O is equal to 126º).

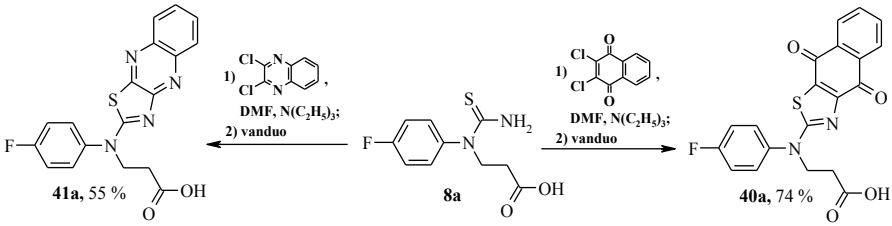
Crystallographic data for the analyzed compound is as follows: monoclinic; a = 7.2935(2), b = 11.0615(3), c = 13.5361(4) Å, α = 66.671(1), β = 85.083(1) γ =

84.500(1)°; V = 996.79(5) Å^3, Z = 2, D_{calc} = 1.428 g·cm^{-1}; the space group is P-1. The final R-factor is 0.068.

On reaction with hydrazine hydrate, the carboxyalkyl fragment containing the thiazole derivative **33a** gave an unexpected molecular dimer – 3-[(5-{1-[(1-{2-[(2-carboxyethyl)(4-fluorophenyl)amino]-4-methylthiazol-5-yl}ethylidene)-hydrazono]ethyl}-4-methylthiazol-2-yl)(4-fluorophenyl)amino]propanoic acid **(39a)**. In the ^{1}H NMR spectrum of this compound, the twelve methyl protons gave two singlets at 2.21 and 2.42 ppm. The spectrum also showed two triplets at 2.58 and 4.07 ppm (J = 7.2 Hz) which were assigned to four methylene groups of alkyl fragments, and the resonance of hydroxyl protons appeared as a broad singlet at 12.21 ppm. The double intensities of all carbon resonances in the ^{13}C NMR spectrum of **39a** proved the formation of the structure under consideration.

1.2.5. Synthesis of fused thiazole derivatives

Cyclic compounds – 2,3-dichloro-1,4-naphthoquinone and 2,3-dichloroquinoxaline – are interesting both for their chemical properties and practical uses. Various assays showed that derivatives containing naphthoquinone or quinoxaline moieties are characterized by a broad spectrum of biological activities (Nasr and Nasr, 2002; Wu, 2015). 3-[(4,9-Dioxo-4,9-dihydronaphtho[2,3-d]thiazol-2-yl)(4-fluorophenyl)amino]propanoic acid **(40a)** and 3-[(4-fluorophenyl)-(thiazol[4,5-b]quinoxalin-2-yl)amino]propanoic acid **(41a)** in this work were synthesized from 3-[(4-fluorophenyl)carbamothioylamino]propanoic acid **(8a)** and 2,3-dichloro-1,4-naphthoquinone or 2,3-dichloroquinoxaline, respectively (Scheme 6). The reaction was carried out in dimethylformamide at 85 °C for 30 h in the presence of a double excess of a base – triethylamine. Then the mixture was cooled and diluted with water. The formed products **40a** or **41a** were purified by dissolving them in 5 % aqueous sodium hydroxide or sodium carbonate solution, filtering, and then acidifying the filtrate with acetic acid to pH 6.

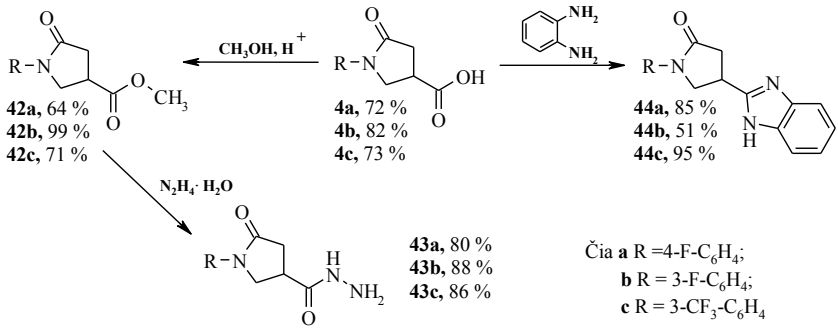


Scheme 6

The exhaustive spectral data of the synthesized derivatives **40a** and **41a** is presented in the experimental section.

1.3. Products of the reactions of 1-substituted-5-oxopyrrolidine-3-carboxylic acids and their esters with diamines

In this work, methyl 1-(substituted phenyl)-5-oxopyrrolidine-3-carboxylates **42a, c** were synthesized, and **42b** resynthesized (CAS Registry Number: 133747-62-3) by the esterification of carboxylic acids **4a–c** with excess methanol under reflux in the presence of a catalytic amount of sulfuric acid. The reaction of esters **42** with hydrazine hydrate in 2-propanol under reflux gave 5-oxopyrrolidine-3-carbohydrazides **43a–c** which were crystallized from the reaction mixture after cooling (Scheme 7). ^{1}H NMR spectra are most suitable for the confirmation of the structures of **43**. The narrow singlets at ~3.70 ppm characteristic of OCH_3 protons of **42a–c,** are absent in the ^{1}H NMR spectra of **43a–c**. The broadened singlets at ~4.30 ppm assigned to the protons of the NH_2 group and signals at ~9.29 ppm assigned to the protons of the CONH fragment of **43a–c** prove the presence of a hydrazide fragment in these compounds. The IR spectra of these hydrazides showed $NHNH_2$ absorption at 3323–3170 cm^{-1}.

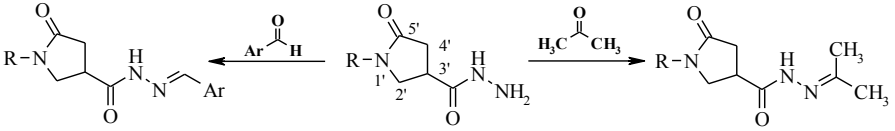


Scheme 7

One of the methods of the synthesis of a benzimidazole heterosystem is the condensation of carboxylic acids with 1,2-diaminobenzene. Target compounds **44a, c** were synthesized by melting a mixture of the corresponding 3-carboxy-5-oxopyrrolidines **4a, c** with 1,2-diaminobenzene at 170 °C, and then at 230 °C. Products **44a, b** were obtained from **4a, b** by applying the Phillips method (heating of both reagents in 4 M hydrochloric acid). It is evident that the melting method is more efficient because of a higher yield of products. The formed bezimidazole derivatives **44a–c** were confirmed by the methods of NMR and IR spectroscopy. The NH signal clearly appeared at 9.77 **(a)** and 12.49 **(b, c)** ppm in ^{1}H NMR, and N=C–NH carbon was observed at ~154.89 ppm in ^{13}C NMR as expected.

1.4. Products of the condensation reaction of hydrazides with monocarbonyl compounds

The structure of hydrazides **43a–c** was also verified by their reaction with carbonyl compounds. The condensation of compounds **43** with aromatic aldehydes gave N′-benzylidene-1-(3-substituted phenyl)-5-oxopyrrolidine-3-carbohydrazides **45–51**. The reaction was carried out under reflux in 2-propanol or 1,4-dioxane for 1 h **(a)** or 3 h **(b, c)** (Scheme 8). A detailed analysis of the ^{1}H and ^{13}C NMR spectra of hydrazones **45–51** having different substitution patterns in the benzene ring was carried out. Considerable interest was focused on the ability to reveal the geometrical isomers originating from the azomethine group and on rotamer formation because of the restricted rotation of the amide group. NMR did not yield conclusive information about the conformations mentioned above, consequently, molecular modeling data was also used. The total steric energies were obtained for all models of the available isomers of **45–51** by using the MM2 and AM1 methods. The dominant isomers were ascertained by a comparison of the variations of tendencies of the obtained total steric energy values and the distribution of the intensities of NH signals in the ^{1}H NMR spectra. The results of the comparison led us to conclude that *s-cis/(Z)* and *s-trans/(E)* (*s-cis* and *s-trans* – amide rotamers, *(Z)* and *(E)* – azomethine geometrical isomers) isomers are favored in DMSO-d_6 solutions of **45–51**. The presence of isomers was noticeable in the ^{1}H and ^{13}C NMR spectra for atoms separated by a few bonds from the center of isomerism.



46a, (48-50)a, 92-96 %
(45-51)b, 69-91 %
(45-51)c, 64-99 %

43a-c

52a, 88 %
52b, 77 %
52c, 34 %

a R = 4-F-C_6H_4; **b** R = 3-F-C_6H_4; **c** R = 3-CF_3-C_6H_4
45b, c Ar = C_6H_5; **46a–c** Ar = 4-F-C_6H_4; **47b, c** Ar = 4-Cl-C_6H_4; **48a–c** Ar = 4-Br-C_6H_4; **49a–c** Ar = 4-$(H_3C)_2$N-C_6H_4; **50a–c** Ar = 4-H_3CO-C_6H_4; **51b, c** Ar = 4-O_2N-C_6H_4

Scheme 8

The most informative signals for the study of the isomers of **45–51** were the NH group singlets which resonated at ~11.49 and 11.56 **(a)**, ~11.64 and 11.70 **(b, c)** ppm with the intensity ratio of 0.6:0.4 and 0.7:0.3, respectively, indicating the existence of *s-cis/s-trans* rotamers. The resonances of the N=CH fragments and CH groups of the pyrrolidinone ring with the same intensity ratio also showed the presence of the isomers. The ^{13}C NMR spectra of **45–51** exhibited double sets of resonances of CO, N=CH, pyrrolidinone ring carbons, and even some carbons

(C-1, 2, 6) of the *N*-phenyl ring because of restricted rotation around the CO–NH bond. The decay of the differences of the corresponding averaged chemical shifts of 4.97 ppm, 3.36 ppm (CO, N=CH), 1.97 ppm (C-3′), 0.73 ppm (C-4′), 0.48 ppm (C-2′), and 0.18 ppm (C-5′) demonstrates with certainty the presence of the center of isomerism. Such decay was not observed for the differences of the chemical shifts for carbons (C-1, 2, 6) of the *N*-phenyl ring.

The reaction of carbohydrazides **43a–c** with acetone under reflux was facile and provided corresponding *N′*-isopropylidene hydrazides **52a–c**. The magnetic nonequivalence observed for both of the methyl groups was caused by the presence of a lone pair of electrons of the nitrogen atom in the azomethine group, and the restricted rotation around the amide bond influenced the formation of a mixture of geometric and conformational isomers.

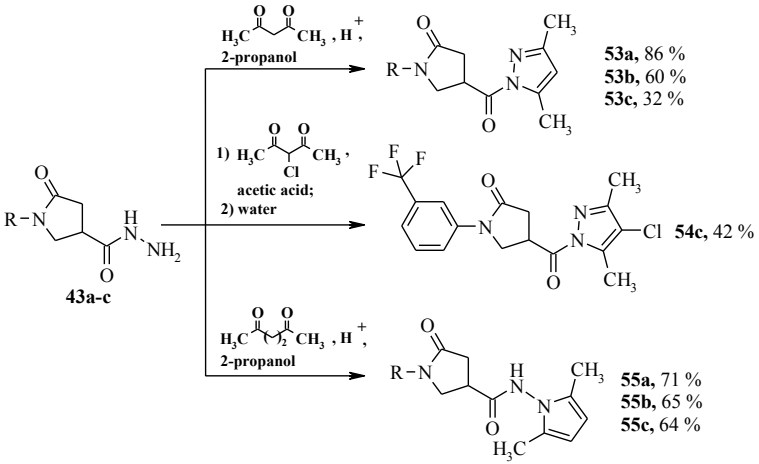
1.5. Products of the condensation reaction of hydrazides with dicarbonyl compounds

The reaction of acid hydrazides with β- and γ-diketones usually provides cyclic compounds. The condensation of hydrazides **43a–c** with 2,4-pentanedione in 2-propanol in the presence of a catalytic amount of hydrochloric acid resulted in the formation of pyrazoles **53a–c** (Scheme 9). The ^{13}C NMR spectra of these compounds exhibited three resonances at ~111.62, ~143.90, and ~152.17 ppm, assigned to the pyrazole ring. The protons of CH and CH_3 groups resonated in the expected region of the ^{1}H NMR spectra and thus also confirmed the presence of the pyrazole moiety. A characteristic spin–spin coupling (^4J = 0.6 Hz) between the CH and CH_3 ($CH{=}CCH_3$) groups was observed.

The treatment of **43a–c** with an excess amount of 3-chloro-2,4-pentanedione in acetic acid afforded only one expected compound, namely, **54c**. In the other cases (**a** and **b**), resin multicomponent products were obtained. A comparison of the ^{1}H NMR spectrum of **53c** with **54c** showed in the last-mentioned case the absence of a singlet signal assignable for the CH proton of the five-membered heterocycle, and the ^{13}C NMR spectrum of **54c** exhibited resonances at 113.76, 139.48 and 149.15 ppm attributed to the pyrazole cycle. This data proved the formation of 4-[(4-chloro-3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]-1-[3-(trifluoromethyl)phenyl]pyrrolidine-2-one **(54c)**.

The condensation of hydrazides **43a–c** with 2,5-hexanedione in 2-propanol in the presence of a catalytic amount of acetic acid resulted in the formation of *N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1-(3-substituted phenyl)-5-oxopyrrolidine-3-carboxamides **55a–c**. When hydrochloric acid was used as a catalyst, the reaction mixture darkened, and resinification occurred (Mickevičius and Vaickelionienė, 2008). The NMR spectra of the above-mentioned compounds displayed the characteristic signals of the suggested structures. The intense singlets at 2.00 and 5.65 ppm **(a–c)**, attributed to the CH_3 and CH groups of the pyrrole ring, were

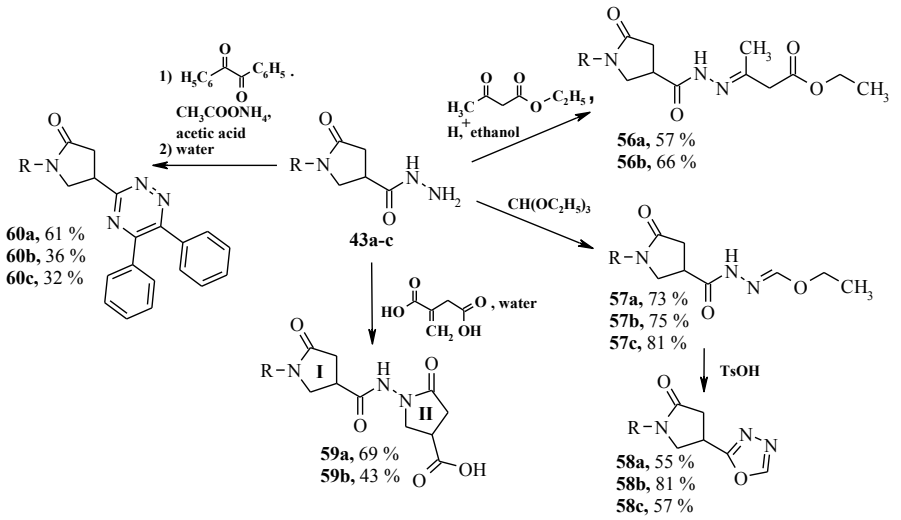
present in the ^{1}H NMR spectra. The double intensity resonances at ~10.87, ~103.00, and ~126.62 ppm in the ^{13}C NMR spectra pointed to the existence of a pyrrole ring.



a R = 4-FC_6H_4; **b** R = 3-FC_6H_4; **c** R = 3-$CF_3C_6H_4$

Scheme 9

Despite the presence of the amide fragment, only the *s-cis* isomer with traces of the *s-trans* isomer were observed in the ^{1}H and ^{13}C NMR spectra of **55a–c** in DMSO-d_6 solutions. The specific conformational behavior of **55b, c** of rotation around the CO–NH bond was investigated by using molecular modeling techniques. The rotation barriers computed for model **55b** were 117.50 kJ/mol (*s-cis*) and 62.37 kJ/mol (*s-trans*), and those for **55c** were 174.18 kJ/mol (*s-cis*) and 64.16 kJ/mol (*s-trans*). This allowed the conclusion that rotation around the CO–NH bond is highly restricted by the voluminous 2,5-dimethylpyrrole ring.



Scheme 10

Some chemical transformations of acid hydrazides were carried out during this research. The condensation of hydrazides **43** with ethyl acetoacetate gave 3-[2-[[5-oxo-1-phenylpyrrolidin-3-yl]carbonyl]hydrazinylidene]butanoates **56a, b** (in the case of **56c** the resinification of the product occurred) (Scheme 10). The NMR spectra of compounds **56a, b** are complicated due to additional sets of resonances. The origin of such resonances is determined by isomers of different spatial structure. This fact was revealed on the grounds of the optimized molecular models of each isomer. It should be noted that the molecules of the study compounds in the solutions apparently were in the dynamic equilibrium characterized by the equilibrium portion of each structure. NMR did not provide conclusive information about separate conformations of the molecules studied but still gave a time-averaged spectral view from all of the structures existing in the solution. Two sets of resonances observed in ^{13}C NMR spectra **(56a)** may be attributed to *E* (7.15 kJ/mol)/*Z* (9.46 kJ/mol) rotamers. The more sensitive ^{1}H NMR spectra showed two intensively and four less intensively resolved resonances in the CH_3 and NH spectral regions.

The refluxing of hydrazides **43** in the excess of triethyl orthoformate, in the presence of *p*-toluenesulfonic acid gave 2-substituted oxadiazoles **58a–c**. The observed resonances at ~154.9 ppm (OCH=N) at ~166.3 ppm (O-C=N) in ^{13}C NMR spectra and at ~9.25 ppm (O-CH=N) in ^{1}H NMR spectra confirmed the successful formation of the oxadiazole ring. The shortening of the reaction time to 5 minutes allowed us to isolate the hydrazone-type intermediates **57a–c** containing amide, azomethine, and ether fragments. The presence of the mentioned fragments

determines the specific features of compounds **57**. The NMR spectra of these compounds exhibited four sets of resonances; therefore, four different spatial states may exist in the DMSO-d_6 solution (Intaitė et al., 2012).

The investigation of the reactions of hydrazides **43** with itaconic acid revealed that they as primary amines form compounds containing a fragment of γ-amino acid which undergoes closure of the 5-membered pyrrolidinone cycle already during the reaction, and compounds with two pyrrolidine rings **59a, b** are obtained.

The presence of two pyrrolidinone rings and four carbonyl groups in the molecules of the study compounds made the NMR spectra of **59a, b** intricate for interpretation. Nevertheless, the NMR spectra of compounds **59a, b** were elucidated, and their resonances were unambiguously assigned on the basis of general considerations of NMR properties, spectral data of structurally related compounds, and the computer molecular modeling. Molecules of **59a, b** compounds can exist as a mixture of *E/Z* rotamers through the amide bond. Experimental NMR data exhibited only one isomer in the DMSO-d_6 solution. The information derived from MM2 calculations allowed us to conclude that, for example, compound **59a** existed as a *Z* rotamer, because the total sterical energy for rotamer *E* is 31.31 kJ/mol and for *Z* it is 17.92 kJ/mol. The chemical shift values of resonances of pyrrolidinone rings and carbonyl group carbons have been paralleled with the Extended Hückel partial charges computed for each atom of *Z* isomer of compound **59a.** The carbons of pyrrolidinone ring II were found to be more shielded than those of the ring I, whereas, in the sequence of carbonyl group carbons, the CONH group carbon was the most shielded while the COOH carbon the least shielded.

It must be mentioned that compounds **59** contain two chiral centers. Each chiral carbon can exist in either the *R* or the *S* configuration. Four stereoisomers are therefore possible: *R,R*, *S,S*, *S,R*, and *R,S*. Unfortunately, the growing of crystals suitable for the X-ray analysis was unsuccessful, hence we could not determine the position of the substituents in the molecule.

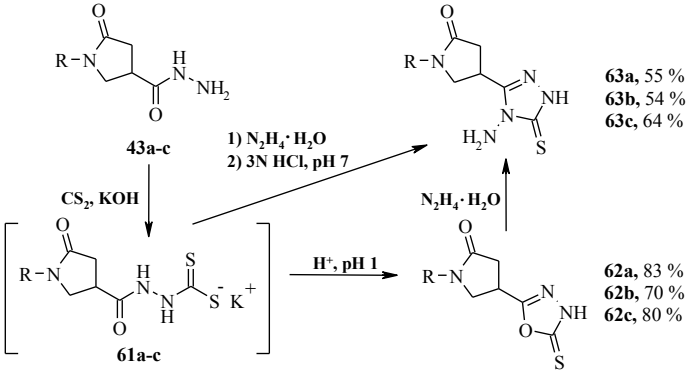
In the final stage of this part of the work, 4-(5,6-diphenyl-1,2,4-triazin-3-yl)-1-phenylpyrrolidin-2-ones **60a–c** were synthesized from hydrazides **43** via a three-component reaction. The expected structure of triazines **60a–c** indicated resonances at ~166.8 ppm (N=C-N), ~156.0, and ~ 156.2 ppm (N-C=C-N); additional resonances of two benzene rings in ^{13}C NMR spectra and the aromatic multiplets integrated to 14 protons in ^{1}H NMR spectra confirmed the formation of **60a–c** containing 5,6-diphenyl-1,2,4-triazine fragments.

1.6. Synthesis of 1,3,4-oxadiazoles and 4-amino-1,2,4-triazoles

For the synthesis of oxadiazole and triazole derivatives, hydrazides **43a–c**, obtained by the method described in (Vaickelioniene and Mickevicius, 2006),

were heated with carbon disulfide in 2-propanol in the presence of potassium hydroxide. Upon refluxing, the formed potassium dithiocarbazates **61a–c** were dissolved in water and acidified with diluted hydrochloric acid to pH 1. The formation of the oxadiazolethione ring in compounds **62a–c** (Scheme 11) was proven by signals at ~163.8 ppm (O-C=N) and ~178 ppm (C=S) in ^{13}C NMR spectra and by the broad singlet centered at ~14.48 ppm (NH) in ^{1}H NMR spectra. A characteristic absorption band of the NH group of compounds **62** was observed at ~3107 cm^{-1} in the IR spectrum. The absorption band at ~1685 cm^{-1} was ascribed to the C=O group of the pyrrolidinone ring.

The corresponding aminotriazoles **63a–c** were obtained by heating potassium dithiocarbazates **61a–c** with hydrazine hydrate in water. Another way for the synthesis of aminotriazoles **63a–c** is the treatment of corresponding 1,3,4-oxadiazoles **62a–c** with hydrazine hydrate in ethanol (Farghaly, Haider, and Lee, 2012). The resonances at ~152.6 ppm (N-C=N) and at ~167.3 ppm (C=S) in ^{13}C NMR spectra as well as the resonances at 5.57 ppm (NH_2) and at ~13.64 **(a, b)** and 9.67 **(c)** ppm (NH/SH) in ^{1}H NMR spectra revealed the formation of 5-membered triazole derivatives **63a–c**. Absorption bands in characteristic regions of NH, NH_2, and C=O functional groups in IR spectra proved the structure of the synthesized compounds.

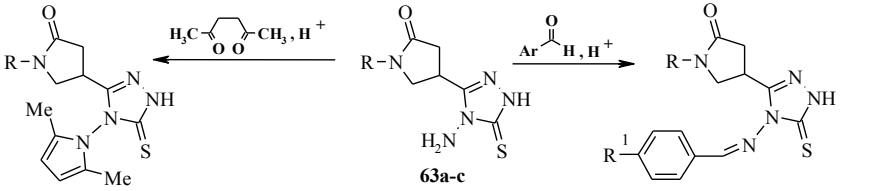


Scheme 11

It should be noted that such compounds as **62** and **63** in DMSO-d_6 solutions can exist in thiole and thione tautomeric forms (El Ashry et al., 2006; Cretu et al., 2010; Holla et al., 2006; Karakuş et al., 2010; Pîrnău et al., 2009; Socea et al., 2012). In the light of the above-mentioned works, the simultaneous presence of thione and thiole tautomers in the DMSO-d_6 solution may be assumed. The theoretical chemical shift for hydrogen bonded to N is 14.35 ppm, the thiole tautomer SH proton chemical shift being 4.12 ppm (Pîrnău et al., 2009). Considering the observed values of ~14.48 ppm and 13.63 ppm of the chemical

shift of the NH proton for the study compounds **62a** and **63a,** it can be manitained that the thione form may be concluded to be the dominant form.

During reactions of 4-amino-1,2,4-triazoles **63a–c** with 2,5-hexanedione, performed in the refluxing 2-propanol in the presence of a catalytic amount of hydrochloric acid, *N*-substituted pyrrole derivatives **64a–c** were synthesized. The formation of a 2,5-dimethylpyrrole ring included into the **64a–c** composition is displayed by the double intensity resonances of CH at ~105.79 ppm, =C at ~127.40 and ~127.52 ppm, and CH_3 at ~10.93 and ~11.0 ppm in ^{13}C NMR spectra, and singlets at ~2.0 ppm (CH_3), ~5.93 ppm (=CH) in ^{1}H NMR spectra.



64a, 87 %
64b, 82 %
64c, 80 %

65a, 55 %, **65b,** 72 %, **65c,** 59 %, **R¹ = H**
66a, 86 %, **66b,** 97 %, **66c,** 95 %, **R¹ = Cl**

Scheme 12

The condensation of aminotriazoles **63a–c** with aromatic aldehydes (benzaldehyde and 4-chlorobenzaldehyde) was carried out, and the corresponding Schiff bases **65a–c** and **66a–c** were obtained (Scheme 12). Due to the above-mentioned condensation reaction, the resonances of protons of the NH_2 group (5.57 ppm) disappeared in ^{1}H NMR spectra of compounds **65a–c** and **66a–c**. Characteristic changes of the chemical shift of resonances of the triazole moiety were observed because of the changed influence of the substituent at C-N-CS. In this case, the C=S atom resonated at ~162.04 ppm, and the N-C=N atom at ~151.42 ppm in ^{13}C NMR spectra. Additional spectral lines were observed in the aromatic region and were assigned to the carbon atoms of the other benzene ring and the azomethine group. The value of the latter chemical shifts depends on the nature of the substituent in the benzene ring and was manifested in the range of ~161–163 ppm. The ^{1}H NMR spectra of compounds **65a–c** and **66a–c** showed characteristic resonances at ~14 ppm (NH/SH), at ~10.15 ppm attributed to the azomethine group proton and the multiplet of the benzene ring integrated for 9 **(65a–c)** or 8 **(66a–c)** protons.

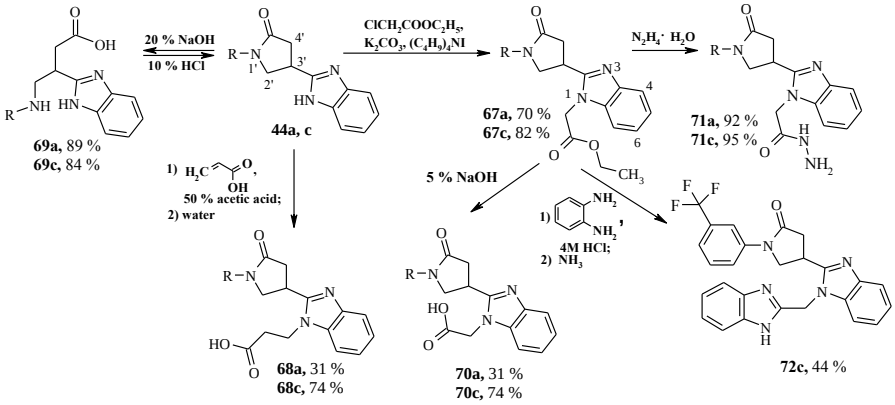
1.7. Synthesis of 1-substituted and 1,2-disubstituted benzimidazole derivatives

Substituted benzimidazole derivatives **67a, c** were synthesized by alkylation of 1-aryl-3-(1*H*-benzimidazol-2-yl)-5-oxopyrrolidines **44a, c** with ethyl

chloroacetate in toluene in the presence of potassium carbonate and a catalytic amount of tetrabutylammonium iodide as a phase tranfer catalyst. Hydrolysis of resulting products **67** with 5 % sodium hydroxide solution liberated the sodium salts of the substituted acids, which were converted to respective pure acids **70a, c** by acidifying the alkaline solution with acetic acid up to pH 6. The IR, ^{1}H, and ^{13}C NMR were in agreement with the suggested structures of compounds **67** and **70** (Scheme 13).

The possibility of alkylation of benzimidazoles **44** with *α,β*-unsaturated acrylic acid was investigated. The reaction was carried out in refluxing 50 % acetic acid for 24 **(a)** and 36 **(c)** hours. The obtained compounds **68a, c** were purified by dissolving them in alkaline solution, filtrating the solution, and acidifying the filtrate with acetic acid up to pH 6. The structure of all the synthesized compounds has been confirmed by the methods of ^{1}H, ^{13}C NMR, IR spectroscopy and elemental analysis.

It is known that the 5-oxopyrrolidine cycle is not resistant to alkaline hydrolysis (Mickevicius et al., 2006; Miller et al., 1990). In the present work, sodium salts of *γ*-amino acids **69** were obtained by decomposition of the pyrrolidinone cycle of 1-aryl-3-(1*H*-benzimidazol-2-yl)-5-oxopyrrolidines **44a, c** in refluxing 20 % solution of sodium hydroxide. Acidification of the aqueous solutions of these salts with acetic acid up to pH 6 gave stable 3-(1*H*-benzimidazol-2-yl)-4-arylaminobutanoic acids **69a, c** (Scheme 13). They were purified by a double precipitation from alkaline solution with acetic acid.



Scheme 13

The opposite reaction of cyclization of the open-chain **69a, c** compounds to **44a, c** was also carried out by boiling *γ*-amino acids **69a, c** in diluted hydrochloric acid and subsequently neutralizing the reaction mixture with aqueous ammonia. Cyclic compounds **44** were obtained in 79 **(a)** and 95 **(c)** % yields. The structural

changes of series **69** compounds have been revealed by comparison of their ^{13}C NMR spectra with those of corresponding compounds **44** containing a pyrrolidinone ring. The resonances at 174.52 **(a)** and 173.14 **(c)** ppm clearly show the presence of an open-chain compound. The ^{1}H NMR spectrum of the same products revealed a broad singlet of NH at 5.81 **(a)** and 6.35 **(c)** ppm attributable to the alkyl chain compounds. The broad absorption band characteristic of the NH and OH groups is observed in the region 2840–3430 cm^{-1} in the IR spectra of these compounds. It partially overlaps the absorbtion bands of the aromatic system.

Acid hydrazides **71a, c** were obtained by the reaction of ethyl esters **67a, c** with hydrazine hydrate in refluxing 2-propanol.

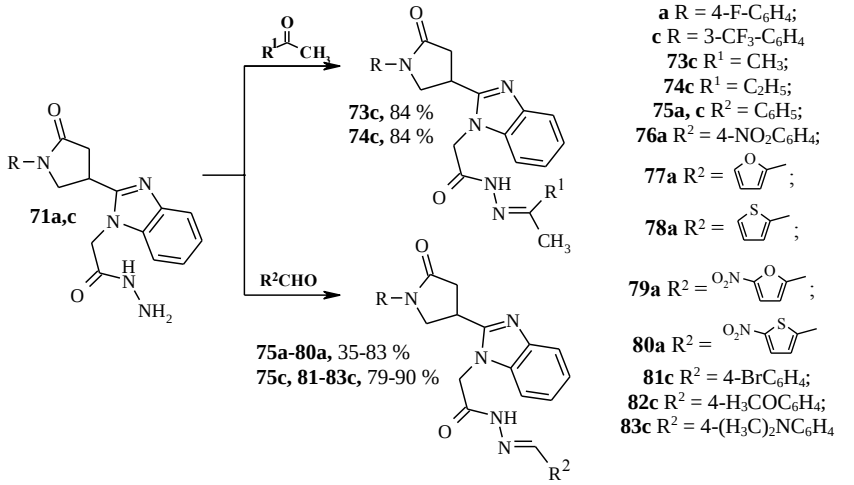
The attempt to synthesize compounds containing two benzimidazole fragments was successful only in one case. By conducting the reaction of methyl 2-{2-[5-oxo-1-[3-(trifluoromethyl)phenyl)-3-pyrrolidinyl]-1*H*-benzimidazol-1-yl}acetate **67c** with 1,2-benzenediamine under conditions of the Philips method (heating the reagents in the 4 M HCI solution) and subsequently treating the reaction mixtures with aqueous ammonia, corresponding compound **72c**, containing two benzimidazole fragments, was synthesized. The structure of the formed 4-[1-(1*H*-benzimidazol-2-ylmethyl)-1*H*-benzimidazol-2-yl]-1-[3-(trifluoromethyl)phenyl]-2-pyrrolidinone **(72c)** was confirmed by elemental analysis and spectroscopic data.

1.8. Condensation products of 2-{2-[5-oxo-1-(substituted phenyl)-3-pyrrolidinyl]-1*H*-benzimidazol-1-yl}acetohydrazides and monocarbonyl compounds

By employing the most general and oldest method for the synthesis of hydrazone-type compounds, i.e. the reaction of hydrazides with carbonyl compounds (Brehme et al., 2007; Enders, 1967), hydrazones **73-83** were synthesized. Condensation of acid hydrazides **71a, c** with acetone and ethylmethylketone afforded products **73c** and **74c**, condensation with carbaldehydes gave hydrazone-type derivatives **(75–80)a** and **(75, 81–83)c** (Scheme 14). Molecules of compounds **75–83** consist of azomethine and amide fragments which may be a reason for the existence of isomers.

Taking into account that dimethylsulfoxide as a polar solvent with donor sites is capable of forming hydrogen bonds, it can be assumed that some stabilization of structural fragment NHCO has happened. An important distinguishing feature of the ^{1}H NMR spectra of these compounds is the resolution of spectral lines of aliphatic CH_2 and NH groups as well as the methyl proton signal of **73c**. This is due to the restricted rotation around the C–N amide bond and the formation of *s-cis-* ir *s-trans* conformers. The existing C=N double bond in the molecules determines geometric *Z-* and *E*-isomers. A large aromatic substituent attached to this bond presumably is the reason for the formation of the *E*-isomer. Geometrical isomerism is clearly impossible in **73c** because of the presence of two

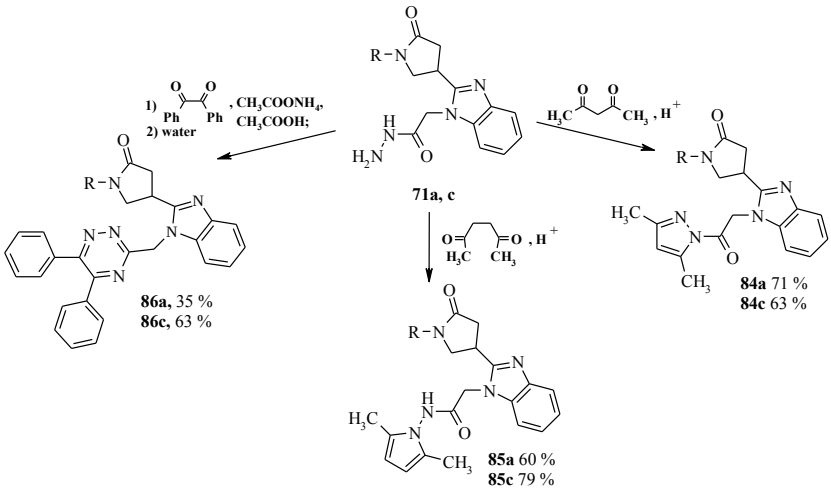
equal terminal substituents; therefore, only a mixture of conformers is observed. It is known that the *cis*-conformation is characteristic of amides (Cordier et al., 2004; Hermecz et al., 1991; Mickevičius, 2009; Rodios et al., 1988; Илиел и др., 2007), thereby the more intensive signals of NH protons and aliphatic CH_2 groups can be ascribed to the *cis*-isomer.



Scheme 14

In the ^{1}H NMR spectrum of *N*-(2-buthylidene)hydrazide **74c**, four singlets for each of NH, N=CCH_2CH_3 ir N=CCH_3 fragments probably show the formation of a mixture of *s-cis*- and *s-trans* conformers and geometric *Z*- and *E*-isomers with the prevalent spatial less restricted *E*-isomer .

During reactions of hydrazides **71a, c** with 2,4-pentanedione or 2,5-hexanedione performed in refluxing 2-propanol in the presence of a catalytic amount of hydrochloric or acetic acid, respectively, the *N*-substituted pyrazole **84a, c** or pyrrole **85a, c** derivatives were synthesized (Scheme 15). The structure of these compounds authenticates the spectral data. For example, the formation of a 2,5-dimethylpyrrole ring included in **85a** composition is displayed by the double-intensity resonances at 103.27 (CH) ppm, at 126.78 (=C–CH_3) ppm, at 11.08 (CH_3) ppm in the ^{13}C NMR spectrum, and intensive singlets at 2.00 (CH_3) and 5.64 (CH) ppm in the ^{1}H NMR spectrum.



a R = 4-FC_6H_4; **c** R = 3-$CF_3C_6H_4$

Scheme 15

The interaction of **71a, c** with diketone – 1,2-diphenylethane-1,2-dione in refluxing acetic acid, in the presence of a large excess of ammonium acetate, afforded 1,2-disubstituted benzimidazole derivatives **86 a, c** with a 1,2,4-triazine ring in the structure. For example, peaks at 156.23, 156.79, and 162.08 ppm in the ^{13}C NMR spectrum of **86c** show the formed six-membered heterocycle.

2. BIOLOGICAL TESTS

2.1. Investigation of antimicrobial properties of the synthesized thiazole derivatives

Synthesized compounds **(9–22)a, (25–29)a, 30a, 31a,** and **(33–38)a** were evaluated for their antibacterial and antifungal activity against strains of *Escherichia coli B-906, Staphylococcus aureus 209-P, Mycobacterium luteum B-917* (as a nonpathogenic test bacteria culture representative of the genus *Mycobacterium*), *Candida tenuis VKM Y-70*, and *Aspergillus niger VKM F-1119* by the diffusion technique and by the serial dilution technique (determination of minimal inhibition concentrations MIC). Their activities were compared with those of the already known antibacterial agent vancomicine and the antifungal agent nistatine (control C). The evaluation was performed at the Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology of Lviv Polytechnic National University (Ukraine).

Test-cultures of *E. coli* appeared not to be sensitive to all the tested compounds investigated by the diffusion technique at concentrations of 0.1 and 0.5%. *S. aureus* was highly sensitive to compounds **10a, 28a** and **29a** at a concentration of 0.5% and low-sensitive to compounds **12a, 27a** and **33a** at the same concentration. Other compounds were not active against this strain of bacteria. The *M. luteum* strain was moderately sensitive to compounds **28a** and **29a** at a concentration of 0.5% (the diameter of the inhibition zone was 15.4 and 16.0 mm, respectively).

Compounds **10a** and **27a** were found to exhibit low antibacterial activity against this strain in comparison with the control evaluated by the diffusion method.

The biological characteristics of the compounds obtained when using the serial dilution technique were classified as follows: the antibacterial activity was considered significant when the MIC was 100 μg/mL or less, moderate when the MIC was 100–500 μg/mL, weak when the MIC was 500–1000 μg/mL, and inactive when the MIC was above 1000 μg/mL. All the synthesized compounds, except for **18a** (MIC 500 μg/ml) and **19a** (MIC 250 μg/ml), had no inhibitory effect at the studied concentrations against *E. coli*. The evaluation of the antibacterial activity of these compounds showed that **10a, 28a,** and **29a** have MIC 125 μg/mL, **12a, 18a, 27a** – 500 μg/mL against the test-culture *S. aureus*. The MIC of **28a, 29a** was observed at 31.2 μg/mL, **37a** – at 62.5 μg/mL, **27a, 34a, 35a** – at 125 μg/mL, **10a** – at 250 μg/mL, and **11a, 20a** – at 500 μg/mL against the test-culture *M. luteum*. The growth of the bacteria *S. aureus* and *M. luteum* was observed for other compounds.

The evaluation of the antifungal activity of the synthesized compounds showed that the strain of *Candida tenuis* was low-sensitive (fungistatic action) to compounds **12a** and **26a** at a concentration of 0.5% (the diameter of the inhibition

zone was 13.0 and 10.0 mm, respectively). The MIC of **11a** and **27a** was observed at 125 μg/mL, of **12a, 19a, 25a** – at 250 μg/mL, of **33a** – at 500 μg/mL.

Compounds **12a** and **17a** showed low fungistatic action against *Aspergillus niger* cultures at 0.5% concentrations (the diameter of the inhibition zone was 7.0 mm). *A. niger* was moderately sensitive to compounds **16a** and **26a** (the diameter of the inhibition zone was 13.7 and 14.0 mm, respectively). The MIC of **10a** and **27a** was observed at 125 μg/mL against *A. niger*. The growth of the fungi *Candida tenuis* and *Aspergillus niger* was observed for other compounds.

In summary, *N*,*N*-disubstituted aminothiazole derivatives with carboxyethyl moiety can be easily synthesized from *N*-aryl-*N*-thiocarbamoyl-β-alanines and α-halocarbonyl compounds by the Hantzsch method. Studies of antimicrobial activity of synthesized compounds **(9–22)a, (25–29)a, 30a, 31a** and **(33–38)a** revealed potentially new compounds with antibacterial activity against *S. aureus* (**10a, 28a, 29a**) and against *M. luteum* (**28a** and **29a**). The antibacterial tests have indicated the functionalized amino thiazole derivatives to exhibit a higher activity if compared with thiazolone derivatives. The evaluation of the antifungal activity of the synthesized compounds showed them to be low-sensitive.

A comparison of the antibacterial properties of the synthesized compounds containing the fluorosubstituted phenyl cycle to those one with an unsubstituted phenyl ring (Mickevičius et al., 2013) showed that the introduction of the fluorine atom to the para-position increased the biological activity of the compounds.

The evaluation of the antibacterial properties of 6-fluoro-1-(4-phenylthiazol-2-yl)-2,3-dihydroquinolin-4(1*H*)-one **(31a)** revealed that the gram-negative rods *Salmonella enteritidis* (ATCC 8739), *Pseudomonas aeruginosa* (NCTC6750), and the gram-positive coccus *Staphylococcus aureus* (ATCC 9144) were highly-sensitive to this compound. The MIC of **31a** was observed at 62.5 μg/ml, the MBC (minimal bactericidal concentration) was 125 μg/ml. However, quinolinone derivative **31a** exhibited no action against methicillin-resistant *S. aureus* (MASA) and coagulase-negative staphylococcus (CoNS).

2.2. Investigation of the antibacterial activity of the synthesized benzimidazole derivatives

The antibacterial activity of synthesized 4-(1*H*-benzimidazol-2-yl)-1-(4-fluorophenyl)-2-pyrrolidinone derivatives **44a, (67–71)a, 72c, (75–80)a, (84-86)a** and **86c** was determined by testing different concentrations against gram-negative rods *Salmonella enteritidis* (ATCC 8739), *Pseudomonas aeruginosa* (NCTC6750), gram-positive coccus *Staphylococcus aureus* (ATCC 9144), meticillin-resistant *Staphylococcus aureus* ATCC (33592) (MRSA) and meticillin-resistant coagulase negative staphylococcus (CoNS) isolated from nasal cavities of humans and dogs by the serial dilution and pour plate methods (Approved Standard, 2012; Wiegand, 2008). The evaluation was performed at the

Veterinary Academy of LUHS under the supervision of Prof. J. Šiugždaitė. The growth of bacteria and the antibacterial activity were determined by using two nutrition media: tryptone soya agar (TSA) and tryptone soya broth (TSB) (Oxoid, Great Britain).

All the test bacteria were streaked out on TSA plates and incubated at 37 °C for 24 h. A representative colony was placed in 5 ml of TSB and incubated at 37 °C for 24 h. *S. enteritidis*, *P.aeruginosa*, *S. aureus*, MRSA and CoNS cultures containing 10^8 CFU/ml (colony-forming units corresponding to McFarland's) were prepared by dilution with TSB and used for antibacterial tests. The following concetrations of solutions in dimethyl sulfoxide were prepared: 1000, 500, 250, 125 and 62.5 μg/ml. The test organisms (100 μl) were added to each tube and incubated at 37 °C for 24 h. After the incubation period, a small amount of the diluted mixture from each tube was spread on TSA and incubated at 37 °C for 48 h. The growth of bacterial cells was noted on agar plates. The lowest concentration of the bacterial material at which no growth was observed was determined as the minimum bactericidal concentration (MBC) value.

The data showed a number of the investigated compounds to have antibacterial properties. The minimum inhibition concentration (MIC) and MBC of **44a, (67–71)a, 72c, (75–80)a, 84a, 85a, 86a, 86c** were determined.

All the synthesized compounds showed moderate activity against *S. enteritidis* and *P. aeruginosa* bacteria strains. The MIC value was 250 μg/ml and MBC 500 μg/ml. The most active against the *S. aureus* strain was hydrazone **80a** containing a 5-nitrothiophene fragment. Its MIC value was 125 μg/ml and MBC measured 250 μg/ml. The meticillin-resistant *S. aureus* (MRSA) bacteria were revealed to be sensitive to benzimidazole derivatives having carboxy alkyl **(68a)**, hydrazine **(71a)** and hydrazone **(78a** and **79a)** fragments (MIC – 125 μg/ml, and MBC – 250 μg/ml). The tests of coagulase negative and meticillin-resistant staphylococci isolated from human nasal cavity showed that the most effective against this strain were 3-(1*H*-benzimidazol-2-yl)-4-[(4-fluorophenyl)amino]butanoic acid **(69a)** and {2-[1-(4-fluorophenyl)-5-oxopyrrolidin-3-yl]-1*H*-benzimidazol-1-yl}acetic acid **(70a)**; their minimum inhibitory and minimum bactericidal concentrations were 125 μg/ml and 250 μg/ml, respectively. The other tested compounds had a weaker influence on the strain. Interestingly, the evaluation of coagulase negative and meticillin-resistant staphylococci isolated from dog nasal cavity appeared to be especially sensitive to the 3-{2-[1-(4-fluorophenyl)-5-oxopyrrolidin-3-yl]-1*H*-benzimidazol-1-yl}propanoic **(68a)** and {2-[1-(4-fluorophenyl)-5-oxopyrrolidin-3-yl]-1*H*-benzimidazol-1-yl}acetic **(70a)** acids and also to 2-{2-[5-oxo-1-(4-fluorophenyl)-3-pyrrolidinyl]-1*H*-benzimidazol-1-yl}acetohydrazide **(71a)**. The MIC of the above-mentioned compounds was 125 μg/ml, and MBC 250 μg/ml showed bactericidal action.

RESULTS AND CONCLUSIONS

1. Synthesis of *N*-phenyl substituted *β*- and *β,γ*-amino acids from fluorine-containing anilines and acrylic or itaconic acids and their cyclization were carried out, and an investigation of the properties of the obtained products was performed.
2. A new method for synthesis of dihydropyrimidine-2,4-(1*H*,3*H*)-diones and their thioanalogues from *N*-aryl-*N*-carboxyethyl-*β*-alanines was suggested. The advantage of this method is the possibility to obtain dihydropyrimidine-2,4-(1*H*,3*H*)-diones or 2-thioxotetrahydropyrimidine-4(1*H*)-ones not only from pure *β*-amino acids but also from their mixtures with dicarboxylic acids which usually form in the interaction of aromatic amines and acrylic acid.
3. The condensation of *N*-phenyl substituted *β*-amino acids with carbamide or potassium thiocyanate afforded *N*-phenyl-*N*-carbamoyl(thyocarbamoyl)-*β*-alanines which, under the action of hydrochloric acid, were transformed to 1-substituted dihydro-2,4(1*H*,3*H*)pyrimidinediones or their 2-thioanalogues. For the first time, *N*-(4-fluorophenyl)-*N*-thiocarbamoyl-*β*-alanine was used in the Hantzsch synthesis of variously functionalized 2-aminothiazole derivatives.
4. Employing the functional properties of the carboxylic group of 3-[(4-fluorophenyl)(4-phenylthiazol-2-yl)amino]propanoic acid, the possibility to synthesize benzimidazole and quinolone heterocyclic systems was shown. The acetyl group of 3-[(5-acetyl-4-methylthiazol-2-yl)(4-fluorophenyl)amino]propanoic acid was used for the synthesis of important organic intermediates – chalkones.
5. Fluorine-containing 1-phenyl substituted 5-oxopyrrolidin-3-carboxylic acid hydrazides were synthesized, and their condensation with mono- and dicarbonyl compounds was investigated; it has been determined that:
   - in the reaction with aromatic aldehides, hydrazone-type compounds are formed which in DMSO-d_6 solutions due to the presence of an amide fragment and the restricted rotation around the CO-NH bond exist as a mixture of *E/Z* isomers' with the prevailing *Z* form, while in the reaction with acetone, the obtained hydrazones exist as a mixture of geometric and conformational isomers;
   - in the reaction with dicarbonyl compounds, five- and six-membered heterocycles are formed; their structure is determined by the position of the carbonyl groups in the molecule of the used dicarbonyl compound.
6. Fluorine-containing 1-phenyl substituted 4-(1*H*-benzimidazol-2-yl)-2-pyrrolidinones were synthesized, and their properties were studied; it has been determined that alkylation of the benzimidazole ring with ethylchloroacetate or acrylic acid proceeds easily and results in the

formation of *N*-alkyl products, and the alkaline hydrolysis of the pyrrolidinone cycle decomposes it to (1*H*-benzimidazol-2-yl)-4-phenylaminobutanoic acid sodium salts which, under the action of acetic acid, are converted into 3-(1*H*-benzimidazol-2-yl)-4-arylaminobutanoic acids.

7. The chemical properties of ethyl-[2-(1-phenyl substituted 5-oxopyrolidin-3-yl)-1*H*-benzimidazolyl]ethanoates were researched, and it was determined that the action of hydrochloric acid induces the hydrolysis of the ester group, and heating with hydrazine leads to the formation of carboxylic acid hydrazides; their condensation with aromatic aldehydes and ketones produces hydrazones, which in the DMSO-d_6 solution exist as a mixture of *E/Z* conformational isomers whereas the reaction of hydrazides with α-, β- ir γ-diketones provides triazine, pyrazole, and pyrrole heterocycles.
8. The antibacterial and antifungal activities of the compounds containing thiazole and thiazolone moieties against the strains of *Escherichia coli B-906, Staphylococcus aureus 209-P, Mycobacterium luteum B-917, Candida tenuis VKM Y-70,* and *Aspergillus niger VKM F-1119* was screened, and two microorganism strains, i.e. *Staphylococcus aureus* and *Mycobacterium luteum*, have been found to be sensitive to 3-{(4-fluorophenyl)[4-(2-naphthyl)-1,3-thiazol-2-yl]amino}propanoic and 3-{(4-fluorophenyl)[4-(2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-2-yl]amino}-propanoic acids. The antibacterial evaluation of benzimidazole derivatives against *Salmonella enteritidis* (ATCC 8739), *Pseudomonas aeruginosa* (NCTC6750), gram-positive coccus *Staphylococcus aureus* (ATCC 9144), meticillin-resistant *Staphylococcus aureus* ATCC (33592) (MRSA) and meticillin-resistant coagulase negative staphylococcus (CoNS), isolated from nasal cavities of humans and dogs, have revealed the moderate activity of the test compounds against all the employed microorganism strains. It also has been determined that 6-fluoro-1-(4-phenylthiazol-2-yl)-2,3-dihydroquinolin-4(1*H*)-one appears to be more effective at inhibiting the above mentioned bacteria rods and cocci than benimidazoles.

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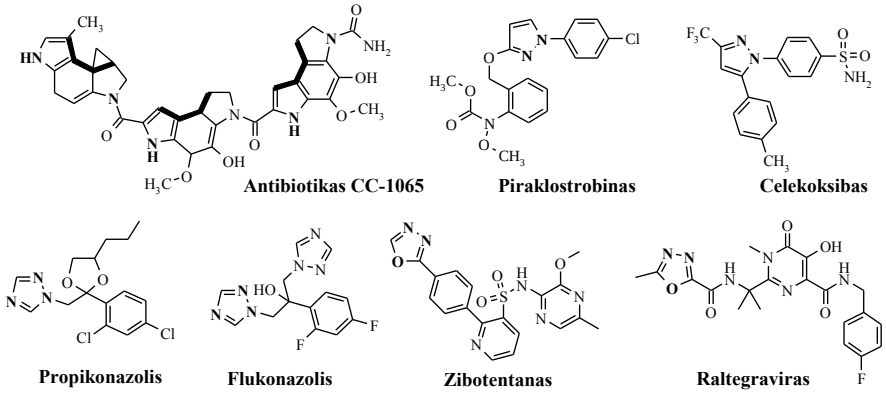
REZIUMĖ

Heterocikliniai junginiai sudaro didžiulę organinių junginių grupę, pasižyminčią biologinių savybių įvairove. Azolai ir azinai – penkianariai ir šešianariai heterocikliniai junginiai, savo struktūroje turintys vieną ar kelis azoto atomus, biologiniu požiūriu yra svarbios organinių junginių klasės. Pirolai labai plačiai paplitę gyvajame pasaulyje. Jų struktūrinis fragmentas aptinkamas alkaloiduose, didelėje azoto turinčių junginių klasėje, kuriuos sintetina augalai. Pirolo žiedas yra daugelio biologiškai aktyvių junginių, pavyzdžiui, fermento katalazės, bilirubino pigmento, molio pigmento prodigiosino sudedamoji dalis, taip pat svarbus chlorofilo – šviesą sugeriančio pigmento žaliuosiuose augaluose ir kituose fotosintezėje dalyvaujančiuose organizmuose, ir hemo, deguonį pernešančiame hemoglobine bei mioglobine, vitamino B_{12} (kobalamino) fragmentas. Kai kurie pirolo dariniai gana plačiai naudojami kietafazėje sintezėje kaip terminalinių aminų apsauginė grupė.



1.1 pav. Azolų klasės vaistinių preparatų pavyzdžiai

Kiti azolų klasės dariniai – pirazolai – jau ganėtinai seniai naudojami žemės ūkyje ir farmacijos pramonėje veiksmingiems preparatams gaminti. Pavyzdžiui, pirazolo fragmentas yra piraklostrobino – plataus spektro strobilurinų klasės fungicido, celekoksibo, naudojamo kaip analgetikas (1.1 pav.), sudėtyje.

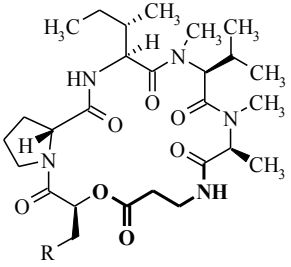
Triazolo dariniai yra daugelio vaistinių preparatų sudėtinė dalis, jie naudojami šviestukams gaminti, kaip antioksidatoriai, korozijos inhibitoriai, įeina į dažų ir pigmentų sudėtį. Žemės ūkyje apsaugoti augalus nuo grybelių sukeltų ligų naudojamas ypač efektyvus propikonazolis, medicinoje – vaistas flukonazolis (1.1 pav.), kuris yra ir balkšvagrybių (*Candida*) infekcijos profilaktikos priemonė.

Kartu su piridino, pirimidino dariniais, tiazolai yra labai svarbūs heterociklinių junginių chemijoje, nes jų struktūros elementai įeina į gamtinių

biologiškai aktyvių junginių, pavyzdžiui, vitaminas B_1 (tiaminas), penicilinas ir kt. sudėtį. Tačiau ir sintetiniai tiazolo dariniai yra biologiškai aktyvios medžiagos, kurioms būdingos įvairiausios gydomosios savybės, jie naudojami funkcinių dažų sintezėje, žemės ūkio chemijoje.

Junginiai, turintys 1,3,4-oksadiazolo konstrukcinio fragmento, geba dalyvauti įvairiose reakcijose. Tai suteikia jiems išskirtinę molekulės planavimo galimybę bei milžinišką biologinį potencialą. Raltegraviras, priešvirusinis vaistas, ir zibotentanas, priešvėžinis preparatas (1.1 pav.), – tai tik du šiuo metu naudojamų vaistinių preparatų, kurių sudėtyje yra 1,3,4-oksadiazolo fragmento, pavyzdžiai.

Gamtoje *β*-aminorūgštys aptinkamos kaip laisvosios aminorūgštys ir peptiduose bei alkaloiduose. Daug natūralių *β*-aminorūgščių gauta iš2,3-aminomutazių, fermentų, esančių bakterijose, augaluose ir grybuose. Daugybė natūralių junginių, sudėtyje turinčių *β*-alanino fragmento, pasižymi biologiniu aktyvumu. Vienas iš pavyzdžių yra destruksinai A ir B (1.2 pav.), išgaunami iš entomopatogeninių *Metarrhizium anisopliae* padermės grybų.



Destruksinas A, R = $CH{=}CH_2$
Destruksinas B, R = $CH(CH_3)_2$

1.2 pav. Destruksinai A ir B

N-Pakeistosios aminorūgštys, jų dariniai – tai puikūs tarpiniai junginiai azetidino, pirolo, imidazolo, oksadiazolo, tiadiazolo, triazolo, pirimidino, chinolino, diazepino ir kitokioms heterociklinėms sistemoms, turinčioms vertingų praktinių savybių, sintetinti.

Azolų ir azinų, savo struktūroje turinčių fluoro atomą, sintezės pasirinkimą lemia galimybė susintetinti naujas biologiškai aktyvias medžiagas.

Šio darbo tikslas – susintetinti naujas, potencialiai biologiškai aktyvias fluoro turinčias *N*-aril-*β*- ir *β,γ*-aminorūgštis, jų darinius ir ciklizacijos produktus, ištirti susintetintų junginių struktūrą bei savybes. Yra žinoma, kad fluoro atomo įvedimas į molekulę neretai padidina junginio biologinį aktyvumą.

Tikslui pasiekti buvo iškelti šie **uždaviniai**:

1. Iš atitinkamų fluoro turinčių anilinų susintetinti 3-[(fluoro turinčias fenil)amino]propanoir3-[(fluoro turinčias fenil)(2-karboksietil)amino]-propano rūgštis, jas ciklizuoti į dihidropirimidin-2,4(1*H*,3*H*)-diono ir 2-tioksotetrahidropirimidin-4(1*H*)-ono darinius bei atlikti pastarųjų produktų deciklizaciją.
2. Pasinaudojus 3-[(4-fluorfenil)karbamotioilamino]propano rūgštyje esančio tiokarbamoilinio fragmento binukleofiliškumu susintetinti tiazolo ir 4,5-dihidrotiazolo heterociklines sistemas, išlaikant laisvą karboksialkilinį fragmentą, ištirti gautų junginių chemines savybes.

3. Susintetinti 1-(fluor- ir trifluormetil- pakeistųjų fenil)-5-oksopirolidin-3-karboksirūgščių darinius – hidrazidus, hidrazonus, įvairiai funkcionalizuotus azolus bei triazino darinius.
4. Susintetinti 1-aril-5-oksopirolidinus, 3-ioje heterožiedo padėtyje turinčius benzimidazolo fragmento, ištirti susintetintų junginių chemines savybes.
5. Ištirti dalies susintetintų junginių antimikrobines savybes, siekiant nustatyti biologinio aktyvumo priklausomybę nuo junginio struktūros.

Darbo mokslinis naujumas ir praktinė reikšmė

Pasiūlytas naujas metodas 1-(fluoro turintiems fenil)dihidropirimidin-2,4-(1*H*,3*H*)-dionams ir 2-tioksotetrahidropirimidin-4(1*H*)-onams gauti. Šio metodo privalumas – minėtų junginių sintezė ne tik iš atitinkamų aminopropano rūgščių, bet ir iš jų mišinių su (2-karboksietil)aminopropano rūgštimis bei iš grynų (2-karboksietil)aminopropano rūgščių. Pirmą kartą 3-[(4-fluorfenil)karbamotioil-amino]propano rūgštis panaudota tiazolo ir 4-okso-4,5-dihidrotiazolo fragmentų turinčių darinių sintezėje. Susintetinta daugybė naujų benzimidazolo darinių, molekulėje turinčių fluoro arba trifluometilpakaitų. Atlikti sintezės darbai sudaro galimybę praplėsti biologiškai aktyvių medžiagų tikslinės sintezės metodologiją. Susintetintųjų 2-aminotiazolo ir benzimidazolo darinių antimikrobiniai tyrimai atskleidė naujus junginius, pasižyminčius baktericidinėmis savybėmis.

Ginamieji teiginiai:

1. 3-[(Fluoro turinčiosios fenil)amino]propano ir 3-[(fluoro turinčiosios fenil)(2-karboksietil)amino]propano rūgštys, priklausomai nuo pakaitų prigimties ir reakcijos sąlygų, sėkmingai gali būti panaudotos heterociklinių sistemų sintezėje:
   - tiek aminopropano, tiek (2-karboksietil)aminopropano rūgštys reakcijose su karbamidu arba kalio tiocianatu rūgštinėje terpėje sudaro 1-pakeistuosius dihidropirimidin-2,4-(1*H*,3*H*)-dionus arba 2-tioksotetrahidropirimidin-4(1*H*)-onus;
   - funkcionalizuotieji 2-aminotiazolo dariniai lengvai gaunami iš 1-(4-fluorfenil)-2-tioksotetrahidropirimidin-4(1*H*)-ono deciklizacijos produkto – 3-[(4-fluorfenil)karbamotioilamino]propano rūgšties, pasinaudojus Hanthsch metodu.
2. Iš 4-(1*H*-Benzimidazol-2-il)-1-[4-fluor arba 3-(trifluormetil)fenil]-2-pirolidinonų, įvairių cheminių transformacijų metu, priklausomai nuo sąlygų, gaunami bezimidazolo dariniai, savo struktūroje turintys 4-fluor, 3-trifluormetilfenil, 2-pirolidinono ir karboksialkilinį, hidrazido, hidrazono, azolų arba triazino fragmentų.

REZULTATAI IR IŠVADOS

1. Fluoro turinčių anilinų reakcijų su akrilo, itakono rūgštimis metu susintetintos *N*-fenilpakeistos *β*- ir *β,γ*-aminorūgštys, atlikta jų ciklizacija, ištirtos gautų produktų savybės.
2. Kondensuojant *N*-fenilpakeistąsias-*β*-aminorūgštis su karbamidu arba kalio tiocianatu acto rūgštyje, gauti *N*-fenil-*N*-karbamoil(tiokarbamoil)-*β*-alaninai, kurie dėl druskos rūgšties poveikio trasformuoti į 1-pakeistus dihidro-2,4(1*H*,3*H*)pirimidindionus ar jų 2-tioanalogus. Pirmą kartą *N*-(4-fluorfenil)-*N*-tiokarbamoil-*β*-alaninas panaudotas įvairiai funkcionalizuotų 2-aminotiazolo darinių sintezėje Hantzsch metodu.
3. Nustatyta, kad *N*-aril-*N*-karboksietil-*β*-alaninus taip pat galima panaudoti dihidropirimidin-2,4(1*H*,3*H*)-dionų ir jų 2-tioanalogų sintezei. Minėto metodo privalumas – galimybė dihidropirimidin-2,4(1*H*,3*H*)-dionus arba 2-tioksotetrahidropirimidin-4(1*H*)-onus sintetinti ne tik iš *β*-aminorūgščių, bet ir iš jų mišinių su dikarboksirūgštimis, kurie gana dažnai gaunami aromatinius aminus veikiant akrilo rūgštimi.
4. Pasitelkus 3-[(4-fluorfenil)(4-feniltiazol-2-il)amino]propano rūgšties karboksigrupės funkcines savybes parodyta galimybė sintetinti bezimidazolo, chinolono heterociklines sistemas, o 3-[(5-acetil-4-metiltiazol-2-il)(4-fluorfenil)amino]propano rūgšties struktūroje esančią acetilinę grupę panaudoti svarbių tarpinių organinių junginių – chalkonų – sintezėje.
5. Susintetinti fluoro turintys 1-fenilpakeisti-5-oksopirolidin-3-karboksirūgščių hidrazidai, ištirta jų kondensacija su mono- bei dikarboniliniais junginiais ir nustatyta, kad:
   - reaguojant su aromatiniais aldehidais susidaro hidrazonai, kurie, DMSO-d_6 tirpaluose dėl fragmento CO-NH buvimo molekulėse ir suvaržyto sukimosi apie CO-NH ryšį, egzistuoja *E/Z* izomerų mišinių, kuriuose vyrauja *Z* izomeras, pavidalu. Reaguodami su acetonu sudaro hidrazonus, kuriems būdinga padėties ir posūkio *E/Z* izomerija;
   - reaguojant su dikarboniliniais junginiais susidaro penkianariai ar šešianariai heterocikliniai junginiai, kurių struktūrą lemia panaudoto dikarbonilinio junginio karbonilinių grupių padėtis molekulėje.
6. Susintetinti fluoro turintys 1-fenilpakeisti 4-(1*H*-benzimidazol-2-il)-2-pirolidinonai, ištirtos jų savybės ir nustatyta, kad benzimidazolo ciklas yra lengvai alkilinamas etilchloracetatu, akrilo rūgštimi, susidarant *N*-alkilintiesiems produktams, o šarminės hidrolizės metu pirolidinono ciklas suyra iki 3-(1*H*-benzimidazol-2-il)-4-fenilaminobutano rūgšties druskų, kurias paveikus acto rūgštimi gaunamos 3-(1*H*-benzimidazol-2-il)-4-arilaminobutano rūgštys.

7. Ištirtos etil-[2-(1-fenilpakeistųjų 5-oksopirolidinil-3-il)-1*H*-benzimidazolil]etanoatų cheminės savybės ir nustatyta, kad dėl druskos rūgšties poveikio vyksta esterinės grupės hidrolizė, o šildant juos su hidrazinu susidaro karboksirūgščių hidrazidai, kurie, vykstant reakcijoms su aromatiniais aldehidais ir ketonais, virsta hidrazonais, DMSO-d_6 tirpaluose egzistuojančiais *E*/*Z* posūkio izomerų pavidalu. Reakcijose su α-, *β*- ir *γ*-diketonais hidrazidai sudaro triazino, pirazolo ar pirolo heterociklines sistemas.

Ištirtas antibakterinis ir priešgrybelinis susintetintųjų tiazolų ir tiazolonų poveikis *Escherichia coli B-906, Staphylococcus aureus 209-P, Mycobacterium luteum B-917* bakterijų padermėms ir *Candida tenuis VKM Y-70* bei *Aspergillus niger VKM F-1119* grybams. Nustatyta, kad dvi bakterijų padermės, t. y. *Staphylococcus aureus* ir *Mycobacterium luteum*, yra itin jautrios 3-{(4-fluorfenil)[4-(2-naftil)-1,3-tiazol-2-il]amino}propano ir 3-{(4-fluorfenil)[4-(2-okso-2*H*-chromen-3-il)-1,3-tiazol-2-il]amino}propano rūgščių poveikiui. Antibakteriniai benzimidazolo darinių tyrimai naudojant gramneigiamų bakterijų kultūras *Salmonella enteritidis* (ATCC 8739), *Pseudomonas aeruginosa* (NCTC6750), *Staphylococcus aureus* (ATCC 9144), meticilinui atsparią *Staphylococcus aureus* ATCC (33592) (MRSA) ir meticilinui atsparų koagulazei neigiamą stafilokoką (KNS), išskirtą iš žmogaus ir šuns nosies ertmės, parodė, kad minėtieji junginiai tik vidutiniškai veikė naudotas mikroorganizmų padermes. Efektyviausiai baktericidiškai gramneigiamas lazdeles *Salmonella enteritidis*, *Pseudomonas aeruginosa* ir gramteigiamus kokus *Staphylococcus aureus* veikė heterociklinis darinys 6-fluor-1-(4-feniltiazol-2-il)-2,3-dihidrochinolin-4(1*H*)-onas.

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