KAUNAS UNIVERSITY OF TECHNOLOGY

IRMANTAS PARAŠOTAS

SYNTHESIS AND PROPERTIES OF FUNCTIONALIZED *N*-(4-HYDROXYPHENYL)-*N*-CARBOXYALKYLAMINE TIAZOLE DERIVATIVES

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

2018, Kaunas

The dissertation was carried out in Kaunas University of Technology, Faculty of Chemical Technology, Department of Organic Chemistry in the period of 2013–2017.

Scientific Supervisor:
Prof. Dr. Habil. Vytautas MICKEVIČIUS (Kaunas University of Technology, Physical Sciencies, Chemistry – 03P).

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Prof. Dr. Habil. Sigitas TUMKEVIČIUS (Vilnius University, Physical Sciencies, Chemistry – 03P).

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Address: K. Donelaičio St. 73-403, 44249 Kaunas, Lithuania.
Tel. no. (+370) 37 300 042, fax. +(370) 37 324 144, e-mail doktorantura@ktu.lt

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KAUNO TECHNOLOGIJOS UNIVERSITETAS

IRMANTAS PARAŠOTAS

FUNKCIONALIZUOTŲ *N*-(4-HIDROKSIFENIL)-*N*-KARBOKSIALKILAMINOTIAZOLO DARINIŲ SINTEZĖ IR SAVYBĖS

Daktaro disertacijos santrauka
Fiziniai mokslai, chemija (03P)

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Mokslinis vadovas:
Prof. habil. dr. Vytautas MICKEVIČIUS (Kauno technologijos universitetas, fiziniai mokslai, chemija – 03P).

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Chemijos mokslo krypties daktaro disertacijos gynimo taryba:
Prof. dr. Vytautas GETAUTIS (Kauno technologijos universitetas, fiziniai mokslai, chemija – 03P) – **tarybos pirmininkas**;
Dr. Marytė DAŠKEVIČIENĖ (Kauno technologijos universitetas, fiziniai mokslai, chemija – 03P);
Prof. dr. Vytas MARTYNAITIS (Kauno technologijos universitetas, fiziniai mokslai, chemija – 03P);
Doc. dr. Jolanta ROUSSEAU (Artua Universitetas, Prancūzija, technologijos mokslai, chemijos inžinerija – 05T);
Prof. habil.dr. Sigitas TUMKEVIČIUS (Vilniaus Universitetas, fiziniai mokslai, chemija – 03P).

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Adresas: K. Donelaičio g. 73-403, 44249 Kaunas, Lietuva.
Tel. +370 37 300042, faksas +370 37 324144, el. paštas doktorantura@ktu.lt

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INTRODUCTION

The thiazole ring, like many heterocyclic systems containing a sulfur atom, is synthesized in living organisms from the cysteine during the several steps reaction (Henkel, Beck, Westner, Meyath, Domling, 2003). Therefore, it is not surprising that compounds with heterocycles in their structure show strong biological activity. For example, penicillins that have a unique structure containing a fused thiazole fragment that is responsible for their antibacterial activity are widespread among *Penicillium* fungi, which during the evolutionary time, have adapted these compounds for their own protection against *Staphylococcus*, *Streptococcus* bacteria strains.

It is not surprising that these naturally occurring compounds found an application in pharmacy. Namely penicillins were the first antibiotics to be used to treat bacterial diseases. Recently, naturally occurring penicillins are modifiable under the laboratory conditions to enhance their antibiotic properties and make them active against fast adaptive bacteria.

The antibiotic cystothiazole A was isolated for the first time in 1998 from the myxobacterium culture broth of *Cystobacter fuscus* with another five secondary metabolites named cystothiazoles B–F (Ojika, Suzuki, Tsukamoto, Sakagami, Fudou, Yoshimura and Yamanaka, 1998; Suzuki, Ojika, Sakagami, Fudou and Yamanaka, 1998). Cystothiazole A possesses potent activity against a large range of fungi, including *Candida albicans* (MIC 0.4 μg/ml).

Thiazoles can naturally be found in a number of different food products and flavours, including peanut butter, baked potato, fried chicken. As such, thiazoles can be used to replicate these and other similar types of flavours.

Thiazoles are incredibly effective flavour ingredients at very low concentrations. They are known for having a notably nut flavour. However, depending on the type of thiazole that is being used, these flavour ingredients can have grassy properties, onion or meat flavour notes. Thiazoles may as well have flavour notes reminiscent of cocoa. For example, 2-ethyl-4-methylthiazole and 2-isopropyl-4-methylthiazole give nut smell; 2-acetylthiazole provides smell characteristic of an onion; 2,4,5-trimethylthiazole have the smell of cacao and coffee. Therefore, these compounds are used to provide depth of flavour in the food industry (http://www.adv-bio.com/thiazoles/).

Other naturally occurring or synthetically produced tiazoles exhibit a wide range of pharmacological properties: anticonvulsant, antiviral, anti-inflammatory, antifungal, anti-parkinson etc. As a result, they have recently received a lot of attention from the pharmacists.

The aim of this work: synthesis of new, variously functionalized *N*-(4-hydroxyphenyl)-*N*-thiazolyl-β-alanines, their derivatives and the investigation of the structure, chemical and biological properties of the synthesized compounds.

The scientific novelty and practical value of the work:

For the first time, *N*-(4-hydroxyphenyl)-*N*-thiazolyl-β-alanine and its α-methyl analogue were used for the synthesis of compounds containing 4,5-dihydrothiazole, thiazole and condensed thiazole cycle in the molecule. Chemical properties of 3-[(4-hydroxyphenyl)(4-oxo-4,5-dihydrothiazol-2-yl)amino]-propanoic and 3-[(4-hydroxyphenyl)(4-oxo-4,5-dihydrothiazol-2-yl)amino]-2-methylpropanoic acids were investigated, and it was determined that the dihydrothiazolone ring is not resistant to strong alkaline media; however, it is acid-resistant structure, regardless of the reaction conditions that the bromination take place both to the aromatic ring and the methylene group of dihydrothiazole cycle in the formation of 3-[(3,5-dibromo-4-hydroxyphenyl)(5,5-dibromo-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic and 3-[(3,5-dibromo-4- hydroxy-phenyl)(5,5-dibromo-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]-2-methylpro-panoic acids; the reaction with aromatic aldehydes give the corresponding 5-benzylidene-4,5-dihydro-4-oxothiazoles of *Z* configuration. It was determined that hydrozinolysis of both ester groups of ethyl 2-[(4- hydroxyphenyl)(3-methoxy-2-methyl-3-oxopropyl)amino]-4-methylthiazole-5-carboxylate is ambiguous. This makes it possible to synthesize compounds of various structures using one or both hydrazine fragments. For the first time, it was ascertained that the HC= fragment of functionalized thiazole cycle is sufficiently reactive and occurs in the condensation reactions with aldehydes in the formation of polyfunctionalized bis(thiazol-5-yl)phenylmethanes and bis(thiazol-5-yl)methanes. According to the research data of the biological properties of the synthesized polyfunctionalized thiazoles, new aminothiazole derivatives with bactericidal and strong antioxidant properties were elucidated. All the performed investigations provide a possibility to plan and broaden the area of the target synthesis of biologically active substances and a variety of reagents of the precise organic synthesis.

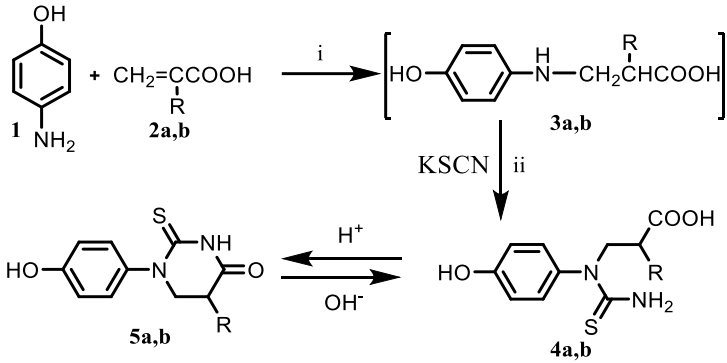
The main statements of the doctoral dissertation are as follows:

- the *N*-(4-hydroxyphenyl)-*N*-thiazolyl-β-alanine and its α-methyl analogue are convenient intermediates for the synthesis of variously functionalized thiazole heterosystems;
- taking advantage of functional properties of 3-[(4-hydroxyphenyl)(4-arilthiazol-2-yl)amino]propanoic and 3-[(4-hydroxyphenyl)(4-arilthiazol-2-yl)amino]-2-methylpropanoic acids hydrazides, the synthesis of hydrazones, pyrrole, pyrazole, oxadiazole, triazole heterosystems is possible as well as the preparation of hydrazones and chalcones using acetyl group of thiazole cycle and the synthesis of polyfunctionalized bis(thiazol-5-yl)phenylmethanes and bis(thiazol-5-yl)methanes employing the HC= fragment of the same ring;
- the products of the hydrazinolysis of ethyl 2-[(4-hydroxyphenyl)(3-methoxy-2-methyl-3-oxopropyl)amino]-4-methylthiazole-5-carboxylate can be used for the synthesis of compounds with various structures applying one or both of the hydrazine fragments.

RESULTS AND DISCUSSION

The synthesis of *N*-(4-hydroxyphenyl)-*N*-thiocarbamoyl-β-alanine and its α-methyl analogue

In the first stage of the work, by using a well-known methodology described in 1982, the initial compounds **4a, b** (Baltrušis, Beresnevičius and Mickevičius, 1982) were prepared. According to it, the reaction of 4-aminophenol **(1)** with acrylic **(2a)** or methacrylic **(2b)** acid in water at reflux affored intermediates *N*-(4-hydroxyphenyl)-β-alanine **(3a)** or *N*-(4-hydroxyphenyl)-α-methyl-β-alanine **(3b)** (Scheme 1), which were not separated from the reaction mixtures. After the addition of potassium thiocyanate and glacial acetic acid, the reactions were continued for 24 h.



i) H_2O, reflux, 12 h; **ii)** CH_3COOH, reflux, 24 h.
a) R = H, **b) R** = CH_3

Scheme 1

The thioureido acids that were formed during those reactions are easily soluble in water and acetic acid (as well as other polar solvents); therefore, the separation and purification of target products **4a, b** is complicated. Consequently, the mentioned compounds **4a, b** were converted to more stable and almost insoluble in organic solvents derivatives **5a, b** by using intramolecular cyclization reaction. For this purpose, the reaction mixture were acidified with hydrochloric acid to pH 1 and refluxed for 2 h; then, it was diluted with water. The obtained 1-(4-hydroxyphenyl)-2-thioxotetrahydropyrimidine-4(1*H*)-one **(5a)** and 1-(4-hydroxyphenyl)-5-methyl-2-thioxotetrahydropyrimidine-4(1*H*)-one **(5b)** were filtered off, washed with water, 2-propanol.

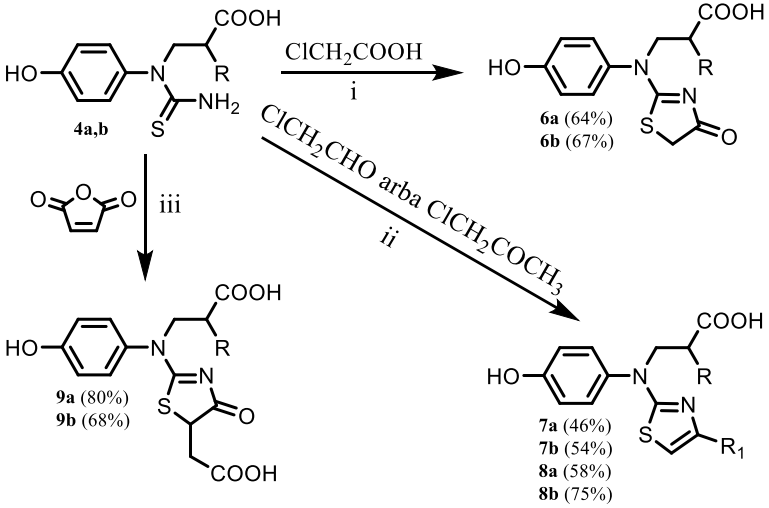
In the alkaline medium, the hydrogenated pyrimidinone derivatives easily decyclize to thioureido acids derivatives – sodium salts of thioureido acids, which

then are transformed into the acidic form by using acetic acid. The melting points of the synthesized compounds coincide with the literature data.

Synthesis of thiazole derivatives

Products of the reactions of *N*-(4-hydroxyphenyl)-*N*-thiocarbamoyl-β-alanine and its α-methyl analogue with aliphatic α-carbonyl compounds

The reaction of thioureido acids **4a, b** with monochloroacetic acid was performed in water at reflux for 4 h and gave thiazolone derivatives **6a, b** (Scheme 2). The formed hydrogen chloride was bound using different types of bases (NaOH, Na_2CO_3, CH_3COONa). Due to the low stability of the compounds **6a, b** in the strong alkaline medium (when sodium hydroxide is used), the yields of the target products were much lower than applying other bases. However, the most suitable for this synthesis is sodium acetate, since thiazolones **6a, b** crystallize from the refluxing reaction mixtures, the filtration of which yields in pure products. The structures of the synthesized derivatives **6a, b** were approved by using data of NMR spectroscopy.



i) CH_3COOH, H_2O, reflux, 4 h; **ii)** acetone, reflux, 3 h; CH_3COONa, H_2O; **iii)** 1,4-dioxane, reflux, 6 h.

a) R = H; **b)** R = CH_3

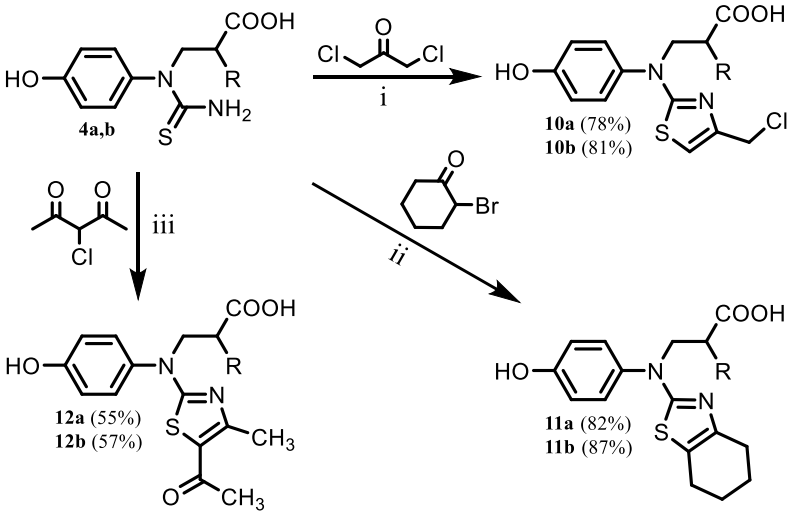
7) R_1 = H; **8)** R_1 = CH_3

Scheme 2

During the reaction of compounds **4a, b** with chloroacetaldehyde or chloroacetone at reflux 3-[(4-hydroxyphenyl)(1,3-thiazol-2-yl)amino]propanoic acid **(7a)**, its methyl derivative **7b**, 3-[(4-hydroxyphenyl)(4-methyl-1,3-thiazol-2-yl)amino]propanoic acid **(8a)** and its methyl analogue **8b** were synthesized. The use of acetone as a solvent in this reaction is convenient, because the compounds that were obtained during the reaction, i.e., hydrochlorides **7, 8a, b**, are insoluble in acetone. After filtration, the compounds were obtained as essentially pure salts, which were transferred into the base form by dissolving them in water and adding sodium acetate.

The interaction of thioureido acids **4a, b** and maleic anhydride in 1,4-dioxane gave the expected products 3-{[5-(carboxymethyl)-4,5-dihydro-4-oxo-1,3-thiazol-2-yl](4-hydroxyphenyl)amino}propanoic acid **(9a)** and its methyl analogue **9b**. In this reaction, dioxane was chosen as a solvent because of its relatively high boiling point and good solubility of maleic anhydride.

The reflux of compounds **4a, b** with 1,3-dichloroacetone in acetone (Scheme 3) afforded 4-(chloromethyl)thiazole derivatives **10a, b**. From the reaction mixtures, they were separated in the form of the hydrochlorides, which then were transferred



i) acetone, reflux, 3 h, H_2O, CH_3COONa; **ii)** 2-propanol, CH_3COONa, reflux, 3 h, **iii)** acetone, reflux, 4 h, H_2O, CH_3COONa.

a) R = H; **b)** R = CH_3

Scheme 3

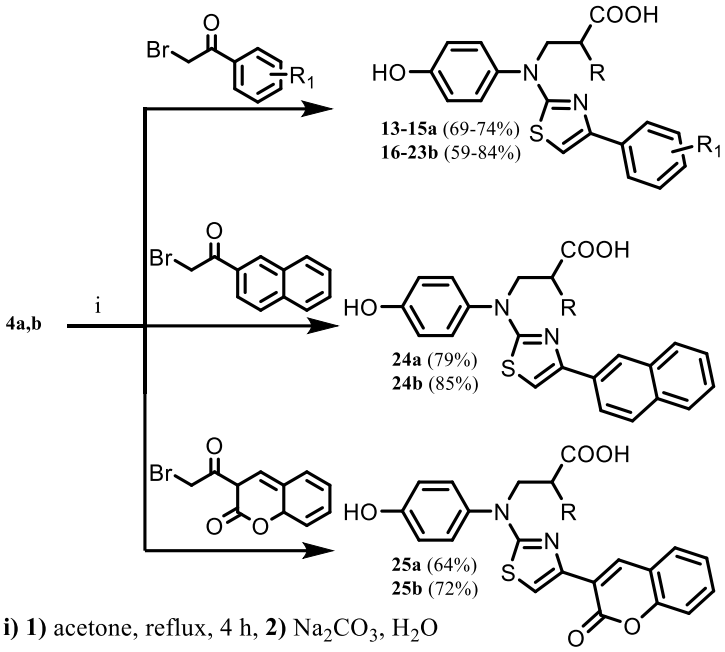
into the bases using sodium acetate. The addition of any stronger base, i.e., sodium carbonate, sodium or potassium hydroxide, decreases the yield of the target product.3-[(4-Hydroxyphenyl)(4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-yl)amino]propanoic acid **11a** and its analogue 2-methylpropanoic acid **11b** were prepared by refluxing thioureido acids **4a, b** and 2-bromocyclohexanone in 2-propanol in the present of sodium acetate. Eight protons of the cyclohexanone fragment in the ^{1}H NMR spectra of compounds **11a, b** appear in a strong magnetic field as three broad singlets.

The reaction of compounds **4a, b** with 3-chloro-2,4-pentanedione in refluxing acetone gave 3-[(5-acetyl-4-methylthiazol-2-yl)(4-hydroxyphenyl)amino]-propanoic acids **12a, b**. In order to facilitate the purification of the above-mentioned products, they were isolated from the reaction mixture in the form of hydrochlorides, which were converted into the base by treating them with an aqueous sodium acetate solution.

Products of the interaction of *N*-(4-hydroxyphenyl)-*N*-thiocarbamoyl-*β*-alanine and its *α*-methylderivative with aromatic *α*-haloketones

In this step of the work, the thiazole derivatives that are having aromatic and chromenone substituents in the 4-position of the ring were synthesized.

The condensation of compounds **4a, b** with various 2-bromoacetophenones provided derivatives **13a–23b** in good yields (Scheme 4). The interaction of **4a, b** and 2-bromo-2'-acetonaphthone or 3-(bromoacetyl)coumarin afforded 3-{(4-hydroxyphenyl)[4-(naphthalen-2-yl)thiazol-2-yl]amino}propanoic acid (**24a**) and 3-((4-hydroxyphenyl)(4-(2-oxo-3,8a-dihydro-2*H*-chromen-3-yl)thiazol-2-yl)amino)propanoic acid (**25a**) and their methylderivatives **24b** and **25b**, respectively. It is convenient to proceed these reactions in acetone, because during the reactions that are insoluble in acetone, hydrochlorides **13a–25b** are formed. After filtration and washing them with acetone, chemically pure target products were obtained. Hydrochlorides, due to their low stability in a strong alkaline medium into base form, were transferred by treating them with sodium carbonate.



i) 1) acetone, reflux, 4 h, **2)** Na_2CO_3, H_2O

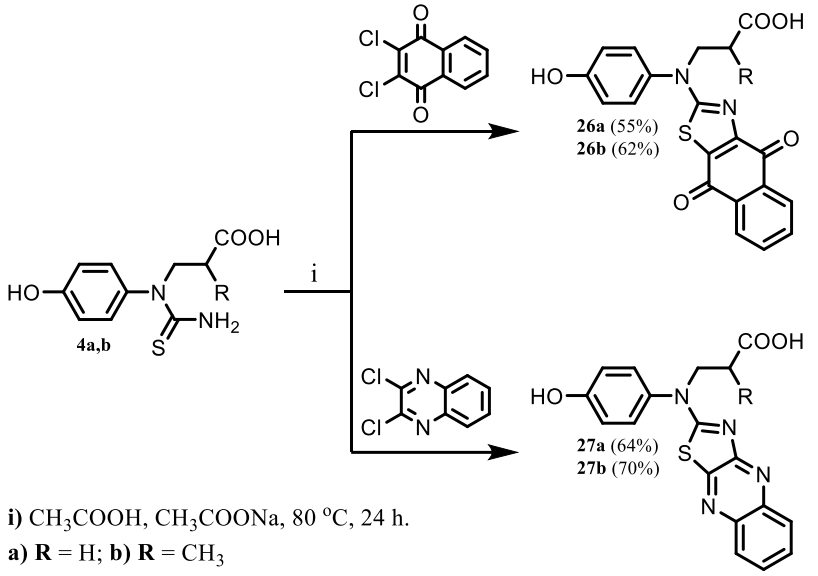
a) R = H; **b) R** = CH_3

13a) R_1 = H; **14a) R_1** = 4-F; **15a) R_1** = 4-Cl **16b) R_1** = H; **17b) R_1** = 4-F; **18b) R_1** = 3-Cl; **19b) R_1** = 4-Cl; **20b) R_1** = 3,4-Cl_2; **21b) R_1** =4-Br; **22b) R_1** = 4-CN; **23b) R_1** = 4-NO_2

Scheme 4

Synthesis of compounds containing fused thiazole system

The fused thiazole derivatives containing naphthoquinone **26a, b** or quinoxaline **27a, b** fragments (Scheme 5) in this work were synthesized from thioureido acids **4a, b** and 2,3-dichloro-1,4-naphthoquinone or 2,3-dichloroquinoxaline, respectively. The reaction was carried out in the acetic acid at 80 °C for 24 h in the presence of sodium acetate. Poor solubility of these compounds in organic solvents induced to choose purification from the alkaline solutions by acidifying them with the acetic acid. For this purpose, the formed products **26, 27a, b** were purified by dissolving them in a large amount of 10% aqueous sodium hydroxide solution, filtering and then acidifying the filtrate with acetic acid to pH 6. The obtained solid was filtered off and washed with plenty of water.



i) CH_3COOH, CH_3COONa, 80 ^oC, 24 h.

a) R = H; **b) R** = CH_3

Scheme 5

The structures of the synthesized compounds were confirmed on the basis of their spectral data and elemental analysis.

Chemical properties of 3-[(4-hydroxyphenyl)(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic acid and its 2-methyl derivatives

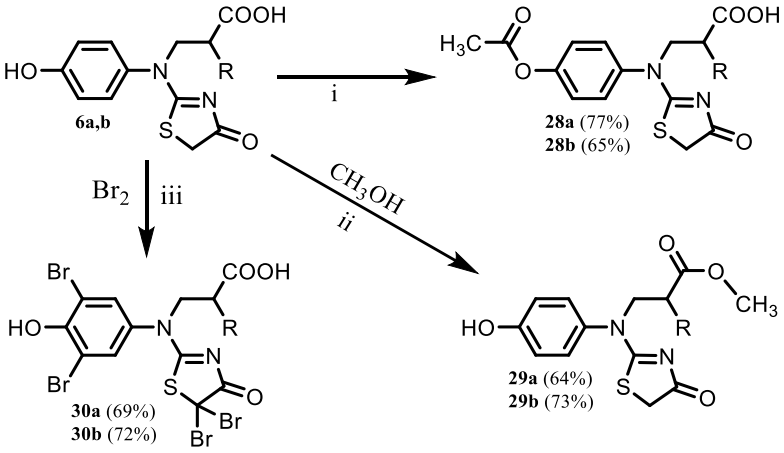
Esterification, acylation and halogenation reactions

The reaction of thiazolones **6a, b** with acetic anhydride was performed at room temperature, and acylderivatives **28a, b** (Scheme 6) were prepared. When reaction was performed at a higher temperature, hydrolysis was observed as well, in which the compounds lose the carboxyalkyl moiety.

Thiazolones **6a, b** are stable at the standard esterification reaction conditions. Therefore, the reaction in methanol in the presence of a catalytic amount of sulphuric acid was easily carried out, and methyl esters **29a, b** were synthesized. For example, in the ^1H NMR spectrum of **29b,** the methyl group proton signal appear at 3.62 ppm, while in the ^{13}C NMR spectrum, the signal of this group is observed at 52.1 ppm.

In order to evaluate the activity of thiazolones **6a, b** in the halogenation reaction, the above-mentioned compounds were treated with bromine in the glacial acetic acid without the use of any catalyst. The reaction was carried out at 60 °C for 1.5

hours. The analysis of the spectral data of the synthesized compounds revealed that tetrabromo-substituted derivatives **30a, b** were formed.



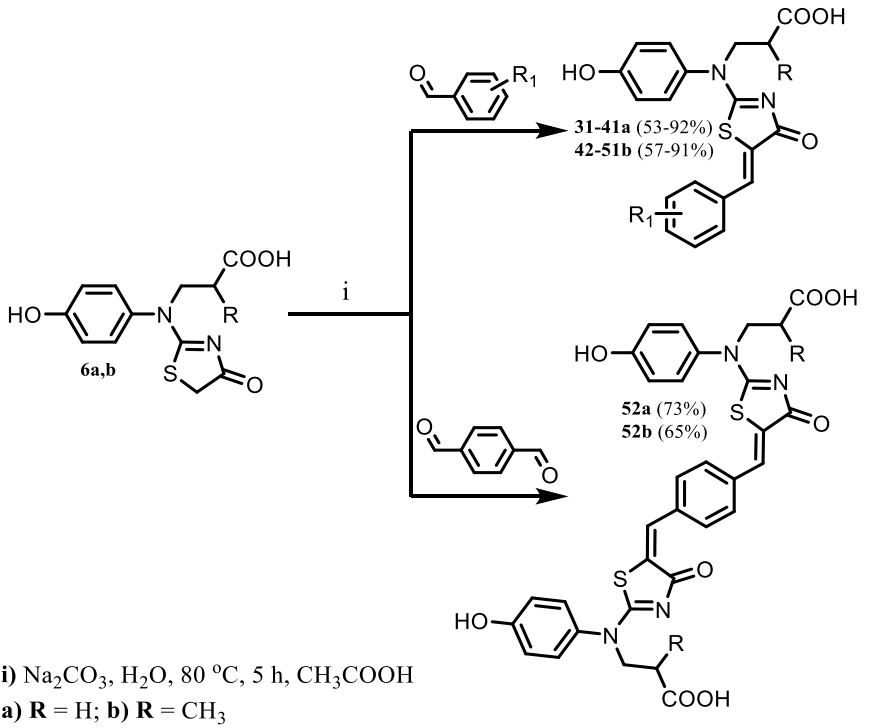
ii) CH_3OH, H_2SO_4, reflux, 5 h, **iii)** CH_3COONa, CH_3COOH, 60 ^oC, 1 h.
a) R = H; **b) R** = CH_3

Scheme 6

In order to obtain mono-, di- or tribromo-substituted derivatives, attempts to change the reaction conditions were made, but the reaction resulted in the formation of a complex mixture of the compounds, which was not further analysed.

Condensation reactions with aromatic aldehydes

In this step of investigations, the products obtained by condensing thiazolones **6a, b** with aromatic aldehydes are presented (Scheme 7). The indicated reaction was performed in water at 80 °C (the higher temperature increases water evaporation as well as distillation of aromatic aldehydes from solution with water vapour) and in the presence of sodium carbonate.



i) Na_2CO_3, H_2O, 80 °C, 5 h, CH_3COOH

a) R = H; **b) R** = CH_3

31a, 42b) R_1 = H; **32a, 43b) R_1 =** 4-F; **33a, 46b) R_1 =** 4-Cl; **34a) R_1 =** 4-Br; **35a) R_1 =** 4-CH_3; **36a) R_1 =** 4-CH_3O; **37a, 50b) R_1 =** 2,4-$(CH_3O)_2$; **38a) R_1 =** 2,5-$(CH_3O)_2$; **39a) R_1 =** 2,4,6-CH_3O; **40a) R_1 =** 4-$(CH_3)_2N$; **41a, 49b) R_1 =** 4-NO_2; **44b) R_1 =** 2-Cl; **45b) R_1 =** 3-Cl; **47b) R_1 =** 3,4-Cl_2; **48b) R_1 =** 3-NO_2; **51b) R_1 =** 2-Cl-5-NO_2

Scheme 7

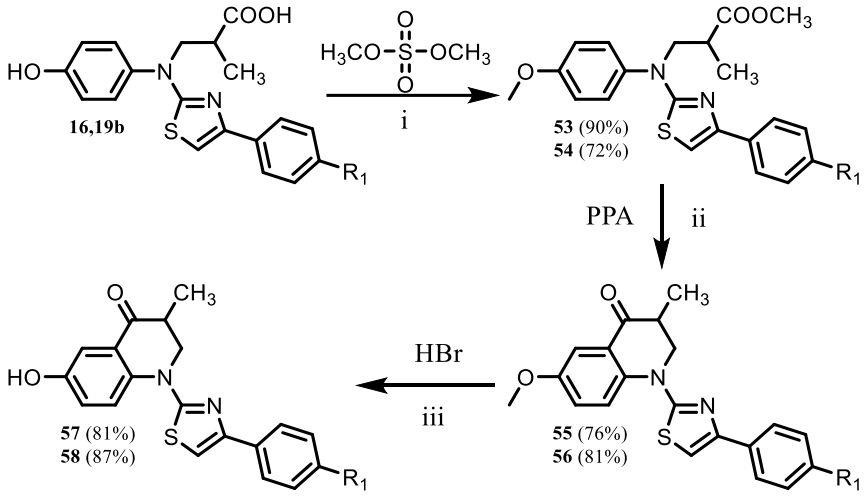
According to the data published in the scholarly literature (Chowdhry et al., 2000), these reactions give a single isomer *Z*.

Synthesis of compounds with quinolone fragment in the structure

Synthesis of 3-methyl-2,3-dihydroquinolones

The most convenient method for the preparation of quinolones is an intramolecular cyclization of *N*-substituted *β*-alanines using dehydration agents, such as polyphosphoric acid or P_2O_5 (Song, Jones et al., 2013). Compounds **13–15a**, **16–23b** for the synthesis of quinolones were selected at random. The synthesis of

desired products failed due to the interaction of the hydroxy group of these compounds with polyphosphoric acid.



i) acetone, K_2CO_3, reflux, 2 h, H_2O; **ii)** 110-120 ^oC, 12 h, H_2O; **iii)** CH_3COOH, reflux, 20 h., H_2O

53, 55, 57) R_1 = H; **54, 56, 58) R_1** = Cl.

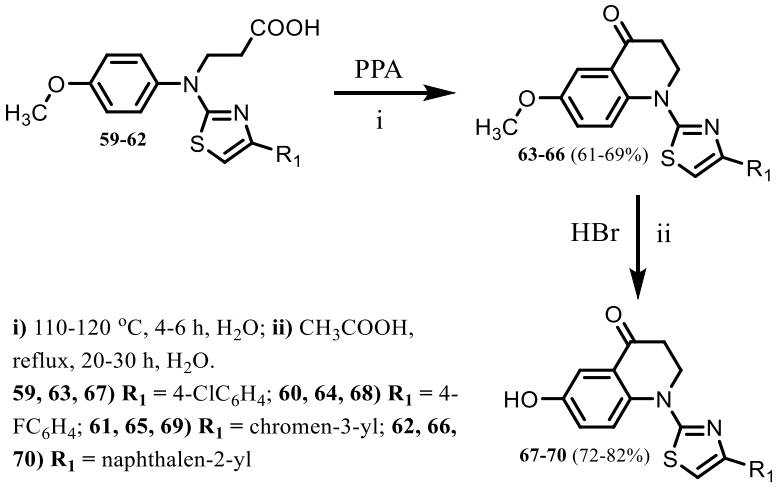
Scheme 8

In order to block the hydroxy group, the alkylation of the initial compounds with dimethyl sulphate was performed (Scheme 8). Quinolones **55, 56** were synthesized by heating compounds **53, 54** in polyphosphoric acid at 110–120 °C for 12 hours. The structures of the desired products were confirmed by the spectroscopic data. The reaction of compounds **55, 56** with hydrogen bromide in the refluxing glacial acetic acid for 5 hours broke etheric bond and resulted in the formation of the target compounds 6-hydroxy-3-methyl-1-(4-phenylthiazol-2-yl)-2,3-dihydroquinolin-4(1*H*)-ones **57, 58**.

Synthesis of 2,3-dihydroquinolones

An alternative for the synthesis method that was described earlier, skipping the alkylation with dimethyl sulphate, can be the synthesis of quinolones from 3-[(4-methoxyphenyl)(4-phenylthiazol-2-yl)amino]propanoic acids **59–62** (Parašotas, Urbonavičiūtė et al., 2017) (Scheme 9). When comparing the time of quinolone synthesis from the propanoic acid methyl esters **53, 54** and propanoic acid derivatives **59–62**, it has been observed that in reaction with methyl esters, the

reaction takes place almost twice as long as using acid derivatives. Therefore, it can be concluded that in this reaction, the acids are more active than methyl esters, and the synthesis of quinolones from acids is more effective.

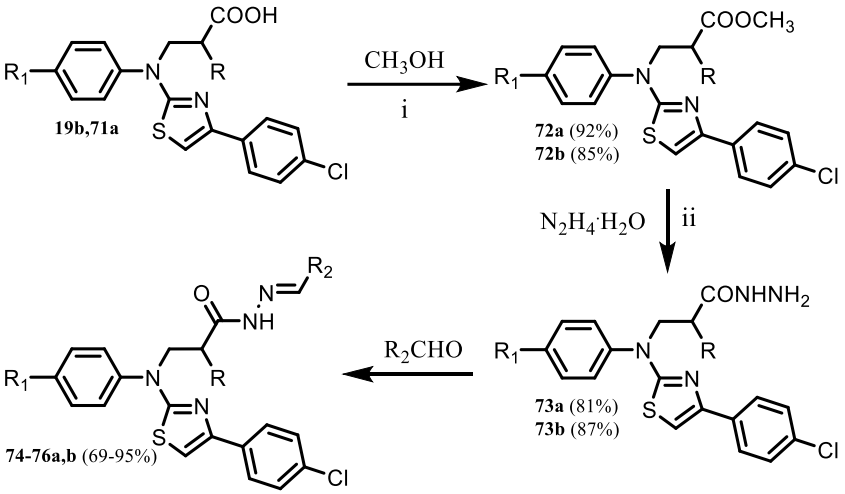


Scheme 9

The structure of the synthesized compounds **63–70** was confirmed by the instrumental analysis methods.

Synthesis of 3-{(4-[4-chlorophenyl]thiazol-2-yl)(4-methoxyphenyl)amino}propane hydrazide and its analogue

It is known that acid hydrazides can be prepared directly from acids by using toluene and xylenes as solvents or from the esters. In this case, alcohols are commonly used solvents. Due to the very poor solubility of the starting compounds in non-polar solvents, including toluene, the acids for the synthesis of hydrazides were esterified and then reacted with hydrazine monohydrate.
Acids **19b, 71a** were esterified with methanol for 20 hours in the presence of a catalytic amount of sulphur acid in the reaction mixture (Scheme 10). Methyl esters **72a**, **b** that were obtained during the reaction reacted with hydrazine monohydrate in refluxing 2-propanol, and the corresponding hydrazides **73a, b**



i) H_2SO_4, reflux, 20 h, H_2O, Na_2CO_3; **ii)** 2-propanol, reflux, 2 h, **iii)** R_2CHO, methanol, reflux, 1 h.

a) R = H, $\mathbf{R_1}$ = H_3CO; **b) R** = CH_3, $\mathbf{R_1}$ = OH

74a,b) $\mathbf{R_2}$ = 5-nitrofuran-2-yl; **75a,b)** $\mathbf{R_2}$ = 5-nitrothiophen-2-yl; **76a,b)** $\mathbf{R_2}$ = 4-$NO_2C_6H_4$

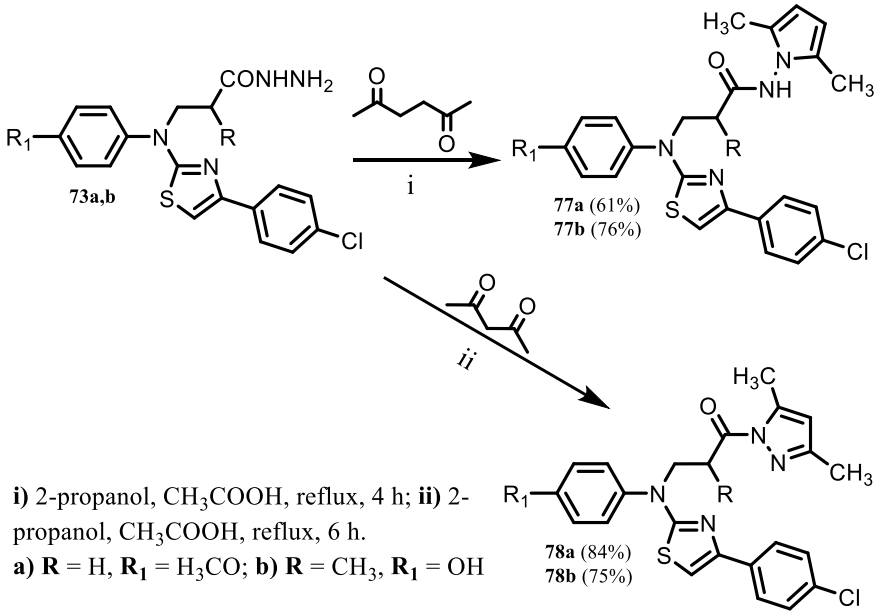
Scheme 10

were synthesized. The condensation of hydrazides **73a, b** with aromatic aldehydes afforded hydrazone type compounds **74–76a, b**, the structures of which were confirmed using various techniques of instrumental analysis.

Products of condensation of 3-{(4-[4-chlorophenyl]thiazol-2-yl)(4-methoxyphenyll)amino}propane hydrazide and its analogue with diketones

The condensation of hydrazides **73a, b** with 2,5-hexanedione (Scheme 11) in boiling 2-propanol in the presence of a catalytic amount of acetic acid in the mixture led to the formation of dimethylpyrrole derivatives **77a, b**, and the condensation of the above mentioned hydrazides **73a, b** with 2,4-pentanedione afforded the compounds **78a, b** containing dimethylpyrazole cycle in the structure. In the ^{1}H NMR spectra of compounds **77a, b**, the singlets of protons of the pyrrole ring, due to the restricted rotation around the amide CO-NH bond, are observed by a set of two singlets with the intensity ratio of 0.9 : 0.1. The NMR spectra of the above-mentioned compounds displayed the characteristic signals of the suggested structures. For example, the intense singlets at 1.98, 2.03 and 5.65, 5.73 ppm attributed to the CH_3 and CH groups of the pyrrole ring were present in the

^{1}H NMR spectrum of compound **77a**. The protons of the amide fragment gave two singlets at 10.15 and 10.62 ppm. The absorption band of this fragment in the IR spectrum was observed at 3255 cm^{-1}.



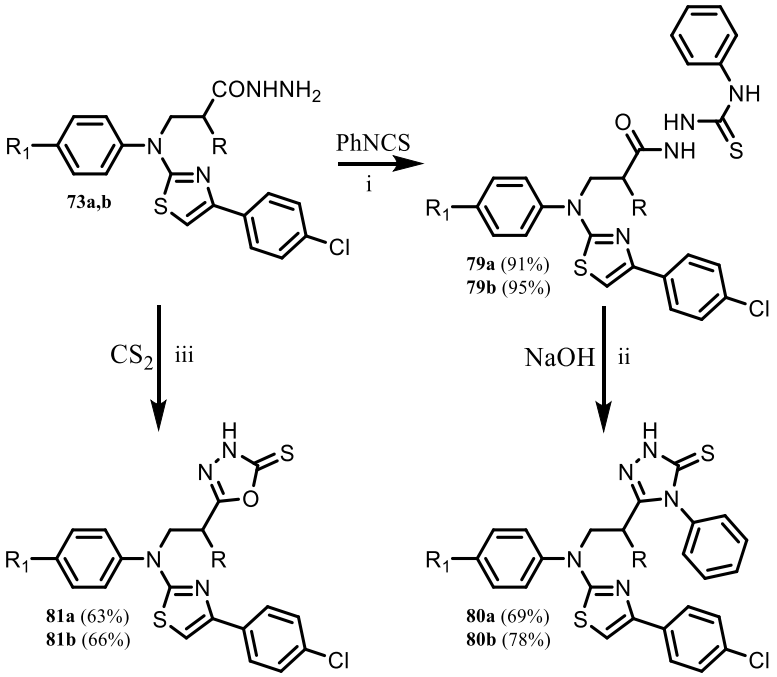
i) 2-propanol, CH_3COOH, reflux, 4 h; **ii)** 2-propanol, CH_3COOH, reflux, 6 h.
a) R = H, $\mathbf{R_1}$ = H_3CO; **b) R** = CH_3, $\mathbf{R_1}$ = OH

Scheme 11

When comparing the ^{1}H NMR spectra of the starting compounds **73a, b** with the spectra of newly synthesized compounds **78a, b,** the latter showed additional peaks characteristic to the dimethyl pyrazole cycle. Two peaks at 2.04 and 2.63 ppm (2×CH_3) and singlet at 6.12 ppm (CH) were observed in the ^{1}H NMR spectrum of derivative **78a**.

Synthesis and cyclization of semicarbazides and thiosemicarbazides

The reaction of hydrazides **73a, b** and phenylisothiocyanate provided 2-{3-([4-(4-chlorophenyl)thiazol-2-yl](4-methoxyphenyl)amino)propanoyl}-*N*-phenylhydrazine-1-carbothioamide (**79a**) and its methyl analogue **79b** (Scheme 12). The thiosemicarbazides **79a, b** in the alkaline medium, during the intra-condensation reaction, were cyclized to 4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione derivatives **80a b**.



i) methanol, reflux, 3 h, **ii)** 10% NaOH, H_2O, reflux, 8 h, HCl; **iii)** KOH, 2-propanol, reflux, 20 h.

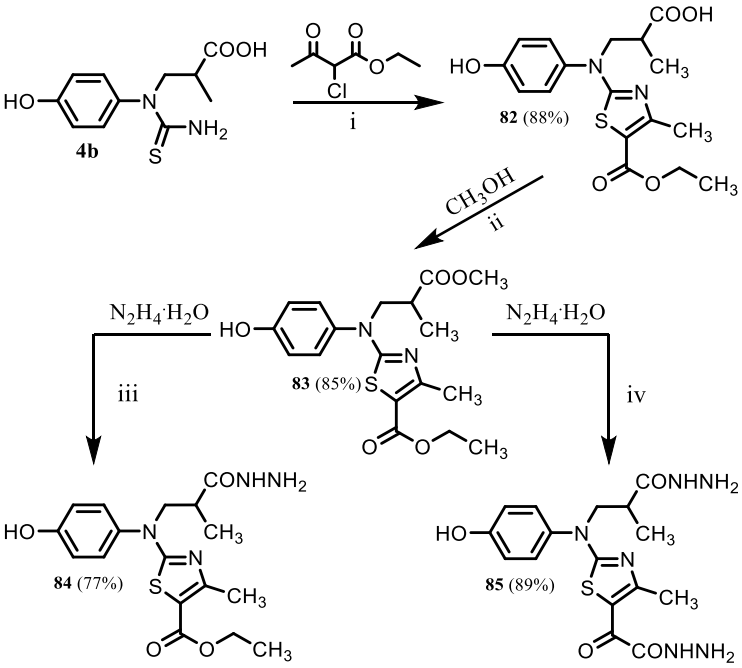
a) R = H, $\mathbf{R_1}$ = H_3CO; **b) R** = CH_3, $\mathbf{R_1}$ = OH

Scheme 12

One of the methods to prepare the oxadiazole heterosystems is their synthesis from hydrazides using carbon disulphide. In this investigation, 1,3,4-oxadiazoles **81a, b** were synthesized by refluxing the corresponding hydrazide **73** with carbon disulphide in ethanol in the alkaline medium. The resonance line of the C=N group of the newly synthesized heterocyclic fragment in the ^{13}C NMR spectrum of compound **81a** was observed at 164.2 ppm, and the peak of the S=C group was seen at 169.7 ppm.

Synthesis and hydrazinolysis of ethyl 2-[(4-hydroxyphenyl)(3-metohoxy-2-methyl-3-oxopropyl)amino]-4-methylthiazole-5-carboxylate

The reaction of thioureido acid **4b** with ethyl 2-chloroacetoacetate in water in the presence of sodium acetate in the mixture gave compound **82** (Scheme 13) in 88% yield. The esterification of carboxylic group was carried out in refluxing methanol in the presence of a catalytic amount of sulphuric acid.



i) H_2O, CH_3COONa, reflux, 5 h.; **ii)** methanol, H_2SO_4, reflux, 13 h., Na_2CO_3, H_2O; **iii)** 2-propanol, reflux, 30 h.; **iv)** $N_2H_4 \cdot H_2O$, 70 ^oC, 1 h., 2-propanol.

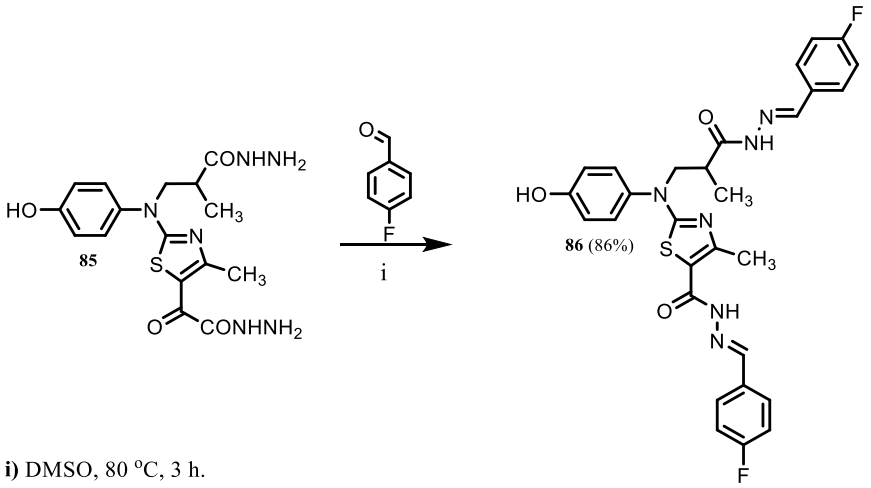
Scheme 13

It has been observed that the hydrazinolysis of each ester group proceed differently, and mono- or dihydrazide can be selectively obtained from compound **83**. In this reaction, the methyl ester was characterized by a higher reaction rate; therefore, the interaction of **83** with eight equivalents of hydrazine monohydrate in 2-propanol at reflux for 30 hours gave monohydrazide **84**.

The second ester group did not react under these conditions. However, the reaction of compound **83** in pure hydrazine monohydrate at 70 °C for 1 hour resulted in dihydrazide **85** in 89% yield.

Products of condensation of 2-[(3-hydrazinyl-2-methyl-3-oxopropyl)(4-hydroxyphenyl)amino]-4-methylthiazole-5-carbohydrazide with aromatic aldehydes

Acid dihydrazide **85** readily involves in the condensation reaction with aromatic aldehyde, during which dihydrazone **86** was synthesized in a high yield (Scheme 14).



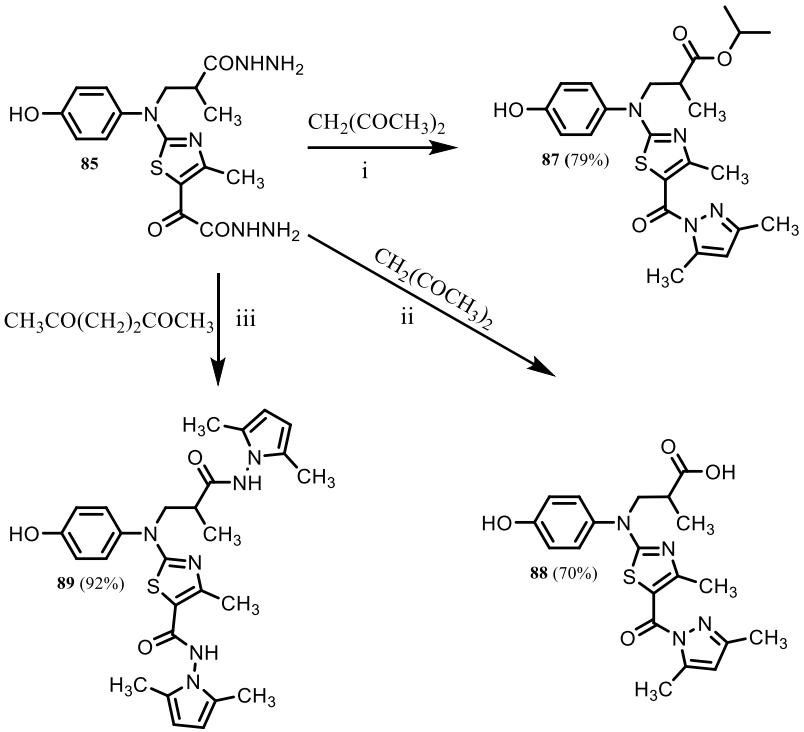
i) DMSO, 80 °C, 3 h.

Scheme 14

The structure of the synthesized compound **86** was proved by ^{1}H and ^{13}C NMR, IR spectroscopy. In the ^{1}H NMR spectrum of **86**, fourteen signals of aromatic protons (three *p*-substituted aromatic rings and two CH groups) are observed.

Products of condensation of 2-[(3-hydrazinyl-2-methyl-3-oxopropyl)(4-hydroxyphenyl)amino]-4-methylthiazole-5-carbohydrazide with diketones

The attempts to synthesize compounds containing two 3,5-dimethylpyrazole or 2,5-dimethylpyrrole cycles in the molecule succeeded only in pyrrole case, and derivative **89** was obtained (Scheme 15). In the reaction with 2,4-pentanedione, depending on the used solvent, compounds **87** or **88** were isolated.



i) 2-propanol, CH_3COOH, reflux, 9 h; **ii)** 1,4-dioxane, CH_3COOH, reflux, 7 h; **iii)** 2-propanol, CH_3COOH, reflux, 10 h.

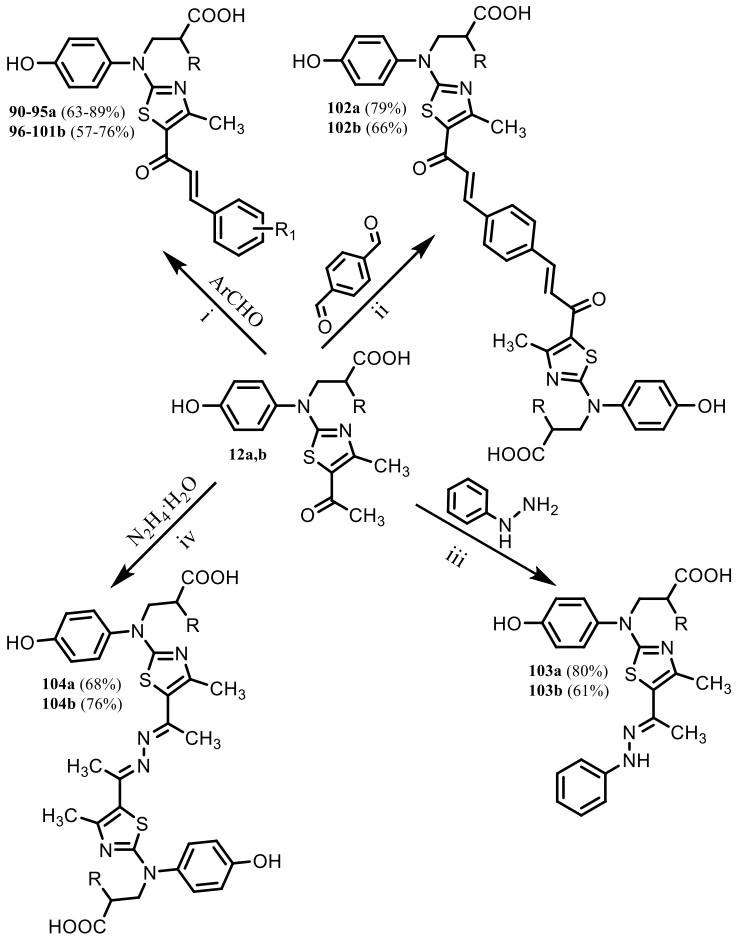
Scheme 15

The analysis of the ^1H NMR spectrum of derivative **87** showed spectral lines that are characteristic of 3,5-dimethylpyrazole ring as well as a set of signals attributed to the isopropyl fragment. Consequently, the spectral data showed only one pyrazole fragment in the molecule, the other desirable fragment did not form. The other hydrazide group was esterified to isopropyl moiety.

For reliable interpretation of the NMR spectra, bidimentional correlation spectrum H,H-COSY was registered, and heteronuclear correlation technique H,C-HMBC was used. The detailed analysis confirmed the formation of compound **87**. The replacement of the solvent 2-propanol with 1,4-dioxane in this reaction led to the isolation of compound **88**. The reaction of thiazole derivative **85** with 2,5-hexanedione in the presence of a catalytic amount of acetic acid provided pyrrole **89.** The structure of the synthesized compound was proved using data of the instrumental analysis.

Products of the reactions of 3-[(5-acetyl-4-methyl-1,3-thiazol-2-yl)(4-hydroxyphenyl)amino]propanoic acid and its 2-methyl derivative with aromatic aldehydes, hydrazine monohydrate and phenylhydrazine

In this step of the work, the compounds synthesized from 5-acetyl-4-methylthiazole derivatives **12a, b** and aromatic aldehydes, hydrazine monohydrate



i) methanol, H_2O, 10% NaOH, r.t, 24 h; **ii)** methanol, H_2O, 10% NaOH, r.t., 30 h; **iii)** methanol, CH_3COOH, reflux, 22 h; **iv)** methanol, CH_3COOH, reflux, 24 h; **a) R** = H; **b) R** = CH_3; **90a, 96b) R_1** = H; **91a, 97b) R_1** = 4-F; **92a, 98b) R_1** = 3-Cl; **93a, 99b) R_1** = 4-Cl; **94a, 100b) R_1** = 4-Br; **95a, 101b) R_1** = 4-NO_2.

Scheme 16

and phenylhydrazine, are discussed (Scheme 16).

The acetyl groups of compounds **12a, b** participate in the well-known classic aldol condensation (Claisen-Schmidt condensation) with aromatic aldehydes (or terephthalaldehyde in case of **102a, b**) in the presence of the base catalyst and form compounds containing chalcone functional group in the structure, which theoretically can exist in *Z* or *E* configurations. However, the coupling constant of protons of the enone COCH=CH fragment is more than 15 Hz ($J > 15$ Hz), and this indicates that the compound exists only in the form of *E* isomer (Eliel and Wilen, 1994).

In order to perform a more detailed investigation of the structure of the synthesized chalcones, the X-ray analysis of **98b** was carried out. The analysis showed that due to the asymmetric carbon atom, compound exists in two conformations.

The value of the torsion angle N6-C7-C8-C10 of the prevailing conformation (g-factor = 0.75) is 62.3(5)°; the torsion angle of the other conformation (g-factor = 0.25) is -93,4(9)°. The molecular structure with atomic labels of the compound **98b** is shown in **Figure 1**. This figure confirms the above-mentioned statement that chalcone fragment exists only in *E* configuration.

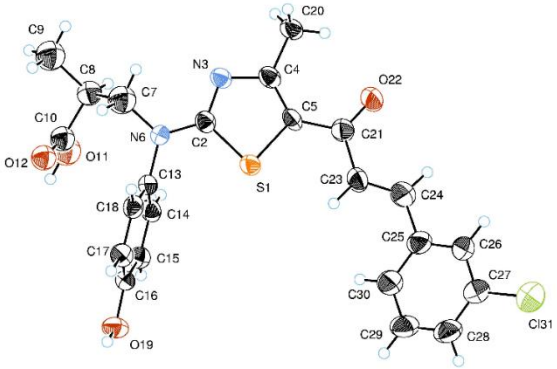


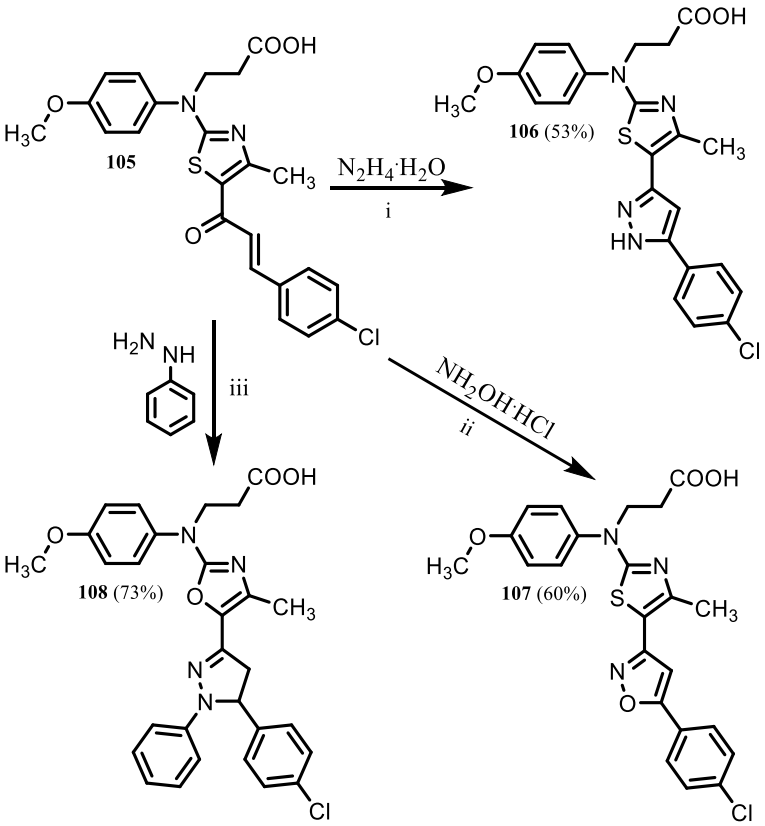
Figure 1. The ORTEP diagram of compound **98b**

The interaction of thiazoles **12a, b** with phenylhydrazine or hydrazine monohydrate (in this case in ratio 2:1) provided compounds **103a, b** or **104a, b**, respectively.

Cyclization reactions of (*E*)-3-((5-(3-(4-chlorophenyl)acryloyl)-4-methylthiazol-2-yl)(4-methoxyphenyl)amino)propanoic acid

The action of chalcone **105** (Parašotas, Urbonavičiūtė et al., 2017) with hydrazine monohydrate in refluxing 2-propanol in the presence of potassium hydroxide in

the reaction mixture resulted in the formation of compound **106** (Scheme 17); meanwhile, the reaction of chalcone with hydroxylamine hydrochloride gave compound **107** containing an isoxazole cycle in the structure.



i) 2-propanol, KOH, 70 °C, 24 h; **ii)** 1,4-dioxane, reflux, 40 h, 10% K_2CO_3, CH_3COOH; **iii)** 2-propanol, KOH, 70 °C, 6 h, CH_3COOH.

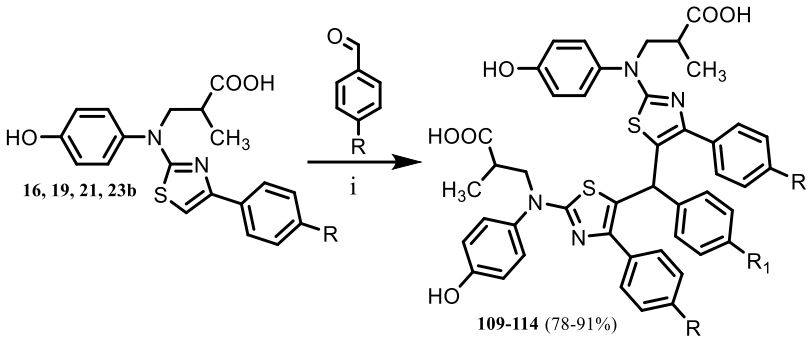
Scheme 17

Using phenylhydrazine instead of the hydrazine monohydrate, compound **108** with a dihydropyrazole moiety in the molecule was obtained.

Products of the reactions of 3-[(4-hydroxyphenyl)(4-arylthiazol-2-yl)amino]-2-methylpropanoic acid with aldehydes

Synthesis of bis(thiazol-5-yl))phenylmethanes

The reactions of thiazole derivatives **16, 19, 21, 23b** with aromatic aldehydes in molar ratio 2:1 and in the presence of a catalytic amount of concentrated hydrochloric acid afforded bis(thiazol-5-yl))phenylmethanes **109–114** (Scheme 18). The reaction products from the reaction mixtures crystallize from acetone in the form of the insoluble hydrochlorides.



i) acetone, HCl, reflux, 17 h, 5% Na_2CO_3 H_2O, CH_3COOH
109) R = 4-Cl, $\mathbf{R_1}$ = 4-$(CH_3)_2N$; **110) R** = 4-Br, $\mathbf{R_1}$ = 4-$(CH_3)_2N$; **111) R** = 4-NO_2, $\mathbf{R_1}$ = 4-$(CH_3)_2N$.
112) R = H, $\mathbf{R_1}$ = 4-NO_2; **113) R** = 4-Cl, $\mathbf{R_1}$ = 4-NO_2; **114) R** = 4-Br, $\mathbf{R_1}$ = 4-NO_2.

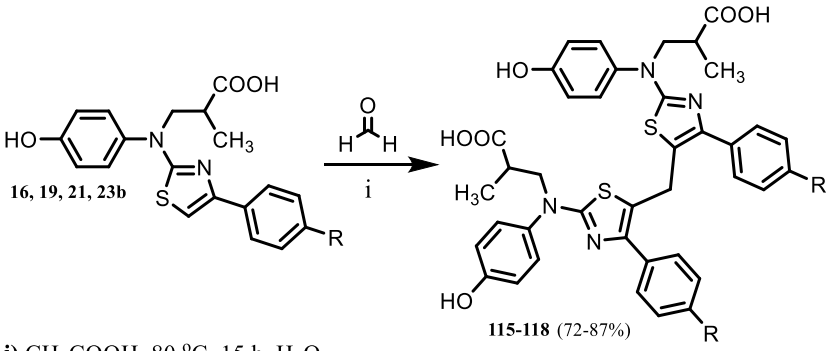
Scheme 18

These salts were converted into the bases by dissolving them in 5% aqueous sodium carbonate solution, filtering and acidifying the filtrate with acetic acid to pH 6.

Synthesis of bis(thiazol-5-yl))methanes

Using an aqueous formaldehyde solution instead of the aromatic aldehydes and replacing acetone with acetic acid, di(thiazol-2-yl)substituted methane derivatives **115–118** were synthesized. Two thiazole cycles in the molecules of these compounds are connected through methylene fragment (Scheme 19). In the ^1H NMR spectra of compounds **115–118**, the protons of the methylene group are

observed at approx. 4.14 ppm (the precise values are presented in the experimental part of the work).



i) CH_3COOH, 80 ^oC, 15 h, H_2O.

115) R = H; **116) R** = 4-Cl; **117) R** = 4-Br; **118) R** = 4-NO_2

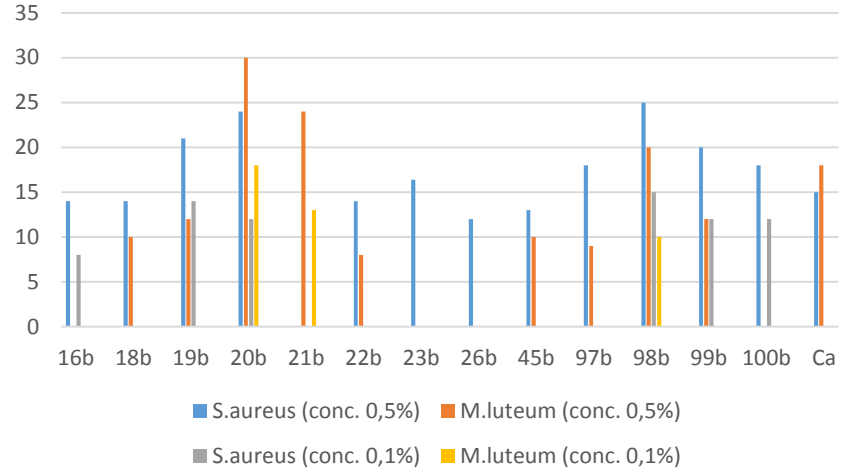
Scheme 19

BIOLOGICAL TESTS

Investigation of antimicrobial activity

A part of newly synthesized compounds containing 4-oxo-4,5-dihydrothiazol-2-yl (**6b**), 4-methylthiazol-2-yl (**8b**), 4-(chloromethyl)thiazol-2-yl (**10b**), 5-acetyl-4-methyl-1,3-thiazol-2-yl (**12b**), 4-phenyl substituted 1,3-thiazol-2-yl (**16b, 18b, 19b, 20b, 21b, 22b, 23b**), naphthoquinone (**26b**), 5,5-dibromo-4-oxo-4,5-dihydro-1,3-thiazol-2-yl (**30b**), 5-(benzylidene substituted)-4-oxo-4,5-dihydrothiazol-2-yl (**42b, 43b, 44b, 45b, 49b, 51b**), 5-[(2*E*)-3-phenyl substituted)prop-2-enoyl]-4-methyl-1,3-thiazol-2-yl (**97b, 98b, 99b, 100b**) fragments were evaluated for their antimicrobial 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*) by the diffusion technique (Villanova, 1990) and the serial dilution technique (determination of minimal inhibition concentrations MIC) (Wayne, 1998). Their activities were compared with those of the already known antibacterial agent vancomycin. The evaluation was performed at the Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology of Lviv Polytechnic National University (Ukraine).

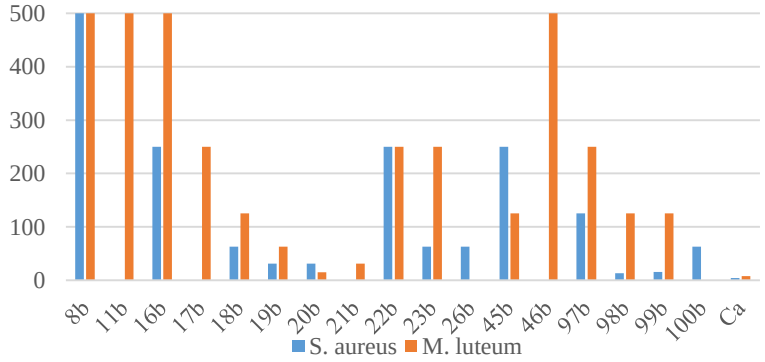
Figure 2. Antibacterial activity of compounds accomplished by the diffusion technique



[Ca] Vancomycin

Test-cultures of *E. coli* appeared to be not sensitive to the tested compounds **8b–104b**, investigated using both diffusion and serial dilution techniques. *S. aureus* and *M. luteum* were highly sensitive to compound **20b** (**Figure 2.**). Compounds **16b, 23b, 100b** showed selective antibacterial activity against *S.*

Figure 3. Antibacterial activity of compounds accomplished by the serial dilution technique



[Ca] Vancomycin

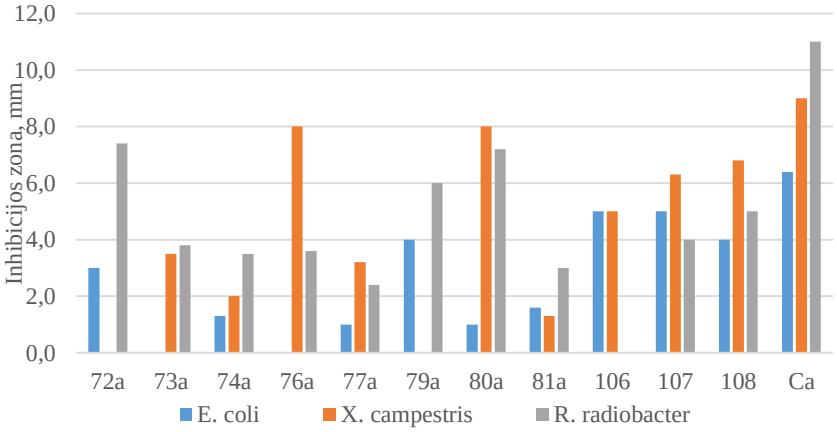
S. aureus and compound **21b** containing the 4-bromophenyl fragment showed selective activity against *M. luteum* strain. Only one compound **45b** (with a 3-chlorobenzylidene moiety in structure) out of six that were studied, containing 5-(benzylidene substituted)-4-oxo-4,5-dihydrothiazol-2-yl fragment, was active against *S. aureus* and *M. luteum* strains. In the class of chalcone-group compounds, derivative **98b** with a 3-chlorophenyl substituet in the molecule has the strongest antibacterial properties.

The synthesized compounds **6b**, **10b**, **12b**, **30b**, **42b**, **43b**, **44b**, **45b**, **49b** and **51b** had no inhibitory effect at the studied concentrations against *S. aureus* and *M. luteum*, and compounds **8b**, **11b**, **16b**, **17b**, **22b**, **45b**, **46b**, **97b** showed only low antibacterial action against both strains of bacteria (MIC varied in the interval 125–500 μg/mL) (**Fig. 3.**). Compound **20b** can be concluded as the most active in the group of the compounds containing 4-phenyl substituted 1,3-thiazol-2-yl moiety. Compound **26b** was active only against *S. aureus* bacteria strain. Among the chalcones, the most effective appeared to be derivative **98b**. The MIC of **98b** was observed at 13.2 μg/mL against *S. aureus*.

Based on the data obtained, it can be argued that the best antibacterial properties had compounds containing chlorophenyl or dichlorophenyl ring in their structure, and the most promising compounds are **20b** and **98b**, which would be expedient for further studies to increase their antibacterial activity.

Some of the synthesized compounds **(72a**, **73a**, **74a**, **76a**, **77a**, **79a**, **80a**, **81a**, **106**, **107**, **108)** that were studied as well have been evaluated for their antimicrobial

Figure 4. The inhibition zone diameters of compounds at MIC 1000 μg/mL

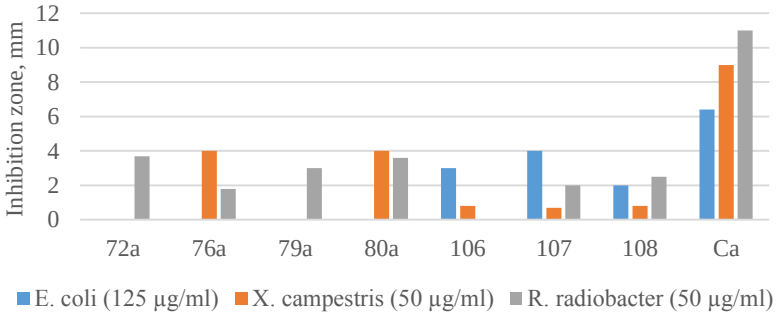


[Ca] Ampicillin (50 μg/mL)

activity against strains of *R. radiobacter*, *X. campestris* and *E. coli* by the diffusion technique. Their activities were compared with those of the already known

antibacterial agent Ampicillin. The evaluation was performed at the Department of Organic Chemistry of Kaunas University of Technology (Dr. Ilona Jonuškienė, Kaunas, Lithuania).
The activity of compounds was initially evaluated at the concentration of 1000 μg/mL (**Fig. 4.**). The most active against *E. coli* appeared to be compounds **106**, **107**, while compounds **76a** and **80a** were the most effective against *X. campestris*. *R. radiobacter* strain was the most affected by compound **72a**.
Using the lower concentrations of the test compound (125 μg/m against the strain of *E. coli* and 50 μg/mL against *X. campestris* and *R. radiobacter*), the isoaxazole **107** (**Fig. 5.**) was observed to have the best antibacterial properties against *E. coli*. Replacing the proton of the amino group of the pyrazole ring with a benzene ring (compound **108**), the activity of the compound against *E. coli* decreased. Hydrazone **76a** and thiazole-3-thione derivative **80a** showed the strongest antibacterial properties against *X. campestris*.

Figure 5. The inhibition zone diameters of compounds at MIC 125 and 50 μg/mL



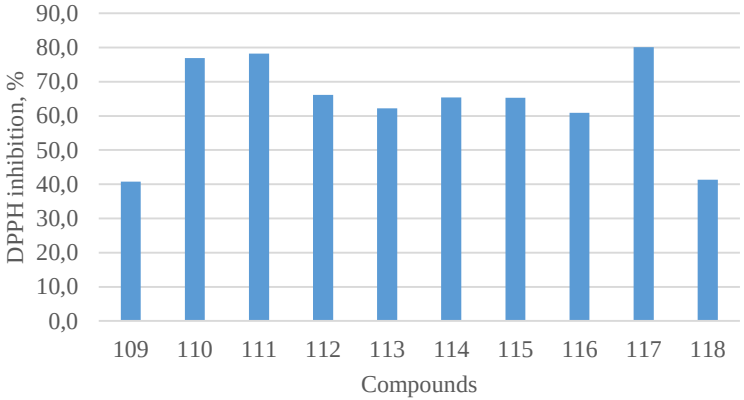
[Ca] Ampicillin

Compounds **72a, 76a, 79a, 80a** were not active against the strain of *E. coli*. *X. campestris* bacteria was resistant to the action of compounds **72a** and **79a**; meanwhile, only the pyrazole derivative **106** was ineffective against *R. radiobacter* at a concentration of 50 μg/mL.

Evaluation of antioxidant properties

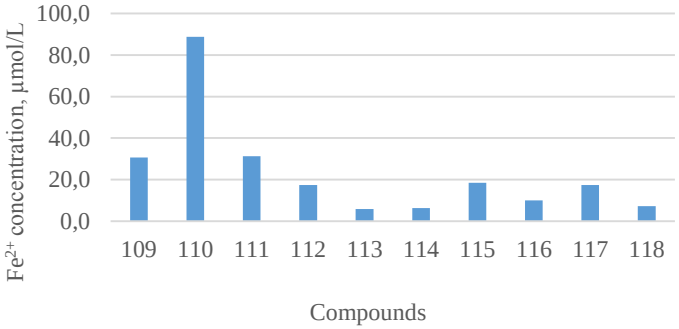
The next step of biological tests was the evaluation of the antioxidant properties of some synthesized compounds. Antioxidant properties of bis(thiazol-5-yl)phenylmethanes **109–114** and bis(thiazol-5-yl)methanes **115–118** were investigated. The evaluation was performed at the Department of Organic Chemistry of Kaunas University of Technology (Dr. Ilona Jonuškienė, Kaunas, Lithuania).

Figure 6. Antioxidant activity of compounds established by DPPH method



As seen from the results presented in **Figure 6.**, compound **117** possesses a very high DPPH radical scavenging ability with a value of 80.12%. Compounds **110** and **111** should be mentioned as well. Their values of 2,2-diphenyl-1-picrylhydrazyl radical scavenging ability was 76.9% and 78.2%, respectively.

Figure 7. The antioxidant activity of compounds established by FRAP method



The FRAP method is based on the reduction of a ferroin analog, the Fe^{3+} complex of tripyridyltriazine $Fe(TPTZ)^{3+}$, to the intensely blue coloured Fe^{2+} complex $Fe(TPTZ)^{2+}$ by antioxidants in an acidic medium. The results are obtained as the absorbance increases at 593 nm and can be expressed as a Fe^{2+} μmol/L concentration.

The results revealed (**Fig. 7.**) that compound **110** showed the highest antioxidant activity evaluated by the FRAP method.

RESULTS AND CONCLUSIONS

1. *N*-(4-hydroxyphenyl)-*N*-thiocarbamoyl-β-alanine and its α-methyl analogue were resynthesized, and their reactions with α-halocarbonyl compounds were investigated. It has been determined that
   1.1. in the reaction with monochloroacetic acid, 3-[(4-hydroxyphenyl)(4-oxo-4,5-dihydrothiazol-2-yl)amino]propanoic and 3-[(4-hydroxyphenyl)(4-oxo-4,5-dihydrothiazol-2-yl)amino]-2-methylpropanoic acids are formed, and in the reaction with chloroacetaldehyde, 3-[(4-hydroxyphenyl)(thiazol-2-yl)amino]propanoic and 3-[(4-hydroxyphenyl)(thiazol-2-yl)amino]-2-methylpropanoic acids are obtained;
   1.2. in the reactions with α-halogketones, corresponding 3-[(4-hydroxyphenyl)(4-alkyl-, aryl- or heterocyclylthiazol-2-yl)amino]propanoic and 3-[(4-hydroxyphenyll)(4-alkyl-, aryl- or heterocyclylthiazol-2-yl)amino]-2-methylpropanoic acids are formed;
   1.3. in reaction of *N*-(4-hydroxyphenyll)-*N*-thiocarbamoyl-β-alanine and its methyl analogue with 2,3-dichloronaphthoquinone and 2,3-dichloroquinoxaline, both chloro atoms participate in the reaction, and 3-[(4,9-dioxo-4,9-dihydronaphtho[2,3-*d*]thiazol-2-yl)(4-hydroxyphenyl)amino]propanoic and 3-[(4-hydroxyphenyl)(thiazol[4,5-*b*]quinoxalin-2-y)amino]propanoic acids and their methyl analogues are formed.
2. The chemical properties of 3-[(4-hydroxyphenyl)(thiazol-2-yl)amino]propanoic and 3-[(4-hydroxyphenyl)(thiazol-2-yl)amino]-2-methylpropanoic acids were investigated, and it has been determined that
   2.1. dihydrothiazolone cycle is not resistant to the strong alkaline medium, but it is resistant to acids; the carboxy group existing in the molecule can be esterified, and hydroxy group can be acetylated without touching the heterocyclic ring;
   2.2. regardless of the reaction conditions, the bromination occur both in the aromatic cycle and the methylene group of dihydrothiazole ring, resulting in the formation of 3-[(3,5-dibromo-4-hydroxyphenyl)(5,5-dibromo-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic and 3-[(3,5-dibromo-4-hydroxyphenyl)(5,5-dibromo-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]-2-methylpropanoic acids;
   2.3. in the reaction of the methylene group of heterocyclic ring with aromatic aldehydes, 5-benzylidene-4,5-dihydro-4-oxothiazoles of *Z* configuration are formed.
3. Chemical properties of functionalized 3-[(4-hydroxyphenyl)(1,3-thiazol-2-yl)amino]propanoic and 3-[(4-hydroxyphenyl)(1,3-thiazol-2-yl)amino]-2-methylpropanoic acids were investigated, and it has been determined that

3.1. using the functional properties of 3-[(4-hydroxyphenyl)(4-arylthiazol-2-yl)amino]propanoic and 3-[(4-hydroxyphenyl)(4-arylthiazol-2-yl)amino]-2-methylpropanoic acids hydrazides, it is possible to synthesize hydrazones, pyrrole, pyrazole, oxadiazole, triazole heterocyclic systems as well as to obtain hydrazones and chalcones employing the acetyl group of thiazole cycle as shown.

3.2. the hydrazinolysis of each ester group of ethyl 2-[(4-hydroxyphenyl)(3-methoxy-2-methyl-3-oxopropyl)amino]-4-methylthiazole-5-carboxylate proceed differently. In this reaction, the methyl ester is characterized by a higher reaction rate; therefore, the reaction proceeds in 2-propanol; meanwhile, the ethyl ester group reacts only in pure hydrazine monohydrate.

3.3. the HC= fragment of the functionalized thiazole cycle is enough reactive to participate in the condensation reactions with aldehyde. In the reaction of thiazole derivatives with aromatic aldehydes in 2:1 molar ratio, functionalized bis(thiazol-5-yl)phenylmethanes are synthesized in good yields; the replacement of aromatic aldehydes with formaldehyde afford the symmetric structure compounds containing two thiazole rings connected with the methylene moiety.

4. Antibacterial and antioxidant properties of some synthesized compounds were investigated, and it has been determined that

4.1. *Mycobacterium luteum* have been found to be sensitive to 3-{(4-[3,4-dichlorophenyl]thiazol-2-yl)(4-hydroxyphenyl)amino}-2-methylpropanoic (**20b**) and 3-[{5-[(2*E*)-3-(3-chlorophenyl)prop-2-enoyl]-4-methyl-1,3-thiazol-2-yl}(4-hydroxyphenyl)amino]-2-methylpropanoic (**98b**) acids. It has been ascertained that the lowest value (13.2 μg/mL) of minimum inhibition concentration (MIC) against *S. aureaus* has compound 3-[{5-[(2*E*)-3-(3-chlorophenyl)prop-2-enoyl]-4-methyl-1,3-thiazol-2-yl}(4-hydroxyphenyl)amino]-2-methylpropanoic acid (**98b**); the minimum value against the strain of *M. luteum* shows 3-{(4-[3,4-dichlorophenyl]thiazol-2-yl)(4-hydroxyphenyll)amino}-2-methylpropanoic acid (**20b**) with the MIC value of 14.9 μg/mL.

4.2. the best antibacterial properties against *E. coli* showed isoxazole **(107)** (125 μg/mL) as well as pyrazole derivative **(106)**. The introduction of benzene cycle to the amino group of the pyrazole ring decreased the effectivity of 3-([5-{5-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}-4-methylthiazol-2-yl][4-methoxyphenyl]-amino)propanoic acid **(108)** against the *E. coli* strain. Thiazole derivative 5-{2-([4-(4-chlorophenyl)thiazol-2-yl][4-methoxyphenyll]-amino)ethyl}-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **(80a)** and hydrazine **(76a)** containing the 4-nitrobenzene substituent demonstrated the strongest antibacterial properties against *X. campestris* bacteria strain (50 μg/mL).

The most active against the *R. radiobacter* strain was methyl 3-{(4-[4-chlorophenyl]thiazol-2-yl)(4-methoxy-phenyl)amino}propionate **(72a)**.

4.3. antioxidant properties of some of the synthesyzed compounds by the FRAP method revealed that 3,3'-{([(4-(dimethylamino)phenyl)-methylene]-bis[4-(4-bromophenyl)thiazole-5,2-diyl]}bis((4-hydroxy-phenyl)azane-diyl))bis(2-methylpropanoic acid) **(110)** was the most active, and the test by DPPH method indicated that 3,3'-{(methylenbis[4-(4-bromophenyl)thiazole-5,2-diyl])bis[(4-hydroxy-phenyl)azanediyl]}-bis(2-methylpropanoic acid) **(117)** was the most potent.

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CURRICULUM VITAE

Surname, name	Parašotas Irmantas
Birth date and place	01 March 1987, Kaunas
Education:	
2013–2017	Doctoral studies at the Department of Organic Chemistry, Kaunas University of Technology.
2011–2013	Master's Degree of Applied Chemistry at the Department of Organic Chemistry, Kaunas University of Technology
2006–2011	Bachelor's Degree of Applied Chemistry at the Department of Organic Chemistry, Kaunas University of Technology.
2002–2006	Kėdainių Šviesioji gymnasium.
1994–2002	Mikalojus Daukša Primary School in Kėdainiai.
Email	irmantas.parasotas@yahoo.com

REZIUMĖ

Tiazolo žiedas, kaip ir daugelis heterociklinių sistemų, turinčiu sieros atomą yra sintetinami gyvuosiuose organizmuose. Pastarasis biologinių proceso metu sintetinamas iš cisteino keliu pakopų reakcijos metu (Henkel, Beck, Westner, Mejat, Domling, 2003). Todėl nenuostabu, kad junginiai, savo struktūroje turintys šiuos heterociklus pasižymi stipriu biologinių aktyvumu. Pavyzdžiui gamtoje aptinkami penicilinai, junginiai turintis kondencuotos stuktūros tiazolo žiedo fragmentą plačiai paplitę tarp grybų *Penicillium*, kurie šiuos junginius per milijonus metų trukusia evoliucija pritaikė apsisaugojimui nuo *Staphylococcus*, *Streptococcus* bakterijų. Nenuostabu, kad šie natūraliai gamtoje aptinkami junginiai surado pritaikymą ir farmacijoje. Būtent penicilinai buvo pirmieji antibiotikai pradėti naudoti bakterijų sukeliamoms ligoms gydyti. Pastaruoju metu, gamtoje aptinkami penicilinai yra modifikuojami laboratorinėmis sąlygomis, siekiant sustiprinti šių vaistų antibiotines savybes, bet padaryti juos aktyvius prieš vis labiau prisitaikančias prie antibiotikų bakterijas. 1998 m. iš *Cystobacter fuscus* bakterijos buvo išskirtas cistotiazolas A ir jo penki metabolitai vadinami cistotiazolas B-F (Ojika, Suzuki, Tsukamoto, Sakagami, Fudou, Yoshimura ir Yamanaka, 1998; Suzuki, Ojika, Sakagami, Fudou ir Yamanaka, 1998), cistotiazolas A kaip nustatyta pasižymi plačiu priešgrybeliniu poveikiu, tame tarpe ir prieš *Candida albicans* (MIC 0,4 μg/ml).

Kai kurie tiazolo dariniai natūraliai aptinkami riešutiniame svieste, keptoje vištienoje ar keptose bulvėse jiems suteikia būdinga kvapą. Net ir labai maži tiazolo darinių kiekiai suteikia maistui būdingą aromatą, dažniausiai riešutų. Tačiau priklausomai nuo to, koks tiazolo darinys naudojamas, galima išgauti svogūno, žolelių, mėsos ar net kakavos aromatą. Kaip pavyzdį galima paminėti 2-etil-4-metiltiazolą, 2-izopropil-4-metiltiazolą, kurie suteikia riešutų kvapą, 2-acetiltiazolas suteikia svogūnui būdingą kvapą, 2,4,5-trimetiltiazolas – kakavos, kavos kvapą. Todėl šie junginiai pritaikomi maisto pramonėje kvapui sustiprinti (http://www.adv-bio.com/thiazoles/).

Kiti natūraliai aptinkami arba sintetiniu keliu gaunami tiazolai pasižymi plačiomis farmakologinėmis savybėmis: antikonvulsinėmis, antivirusinėmis, priešuždegiminėmis, priešgrybelinėmis, antiparkinsoninėmis ir kitomis. Todėl pastaruoju metu jie susilaukia didelio farmacininkų dėmesio.

Darbo tikslas

Susintetinti naujus įvairiai funkcionalizuotus *N*-(4-hidroksifenil)-*N*-tiazolil-*β*-alaninus, jų darinius, ištirti susintetintų junginių struktūrą, chemines ir biologines savybes.

Tikslui pasiekti buvo iškelti šie uždaviniai:

1. Ištirti *N*-(4-hidroksifenil)-*N*-tiokarbomoil-*β*-alanino ir jo *α*-metilanalogo ciklizacijos reakcijas su įvairiais α-halogenkarboniliniais junginiais, 2,3-dichlor-1,4-naftochinonu ir 2,3-dichlorchinoksalinu;
2. Ištirti 3-[(4-hidroksifenil)(4-okso-4,5-dihidrotiazol-2-il)amino]propano rūgšties ir jos 2-metilanalogo chemines savybes, nustatyti susidarančių junginių struktūrą;
3. Ištirti įvairiai funkcionalizuotų 3-[(4-hidroksifenil)(1,3-tiazol-2-il)amino]-propano rūgščių ir jų 2-metilanalogų chemines savybes, nustatyti susidarančių produktų struktūrą;
4. Ištirti dalies susintetintų junginių antibakterines ir antioksidacines savybes, siekiant nustatyti biologinio aktyvumo priklausomybę nuo junginio struktūros.

Darbo mokslinis naujumas ir praktinė reikšmė

Pirmą kartą *N*-(4-hidroksifenil)-*N*-tiokarbamoil-*β*-alaninas ir jo α-metilanalogas panaudotas 4,5-dihidrotiazolo, tiazolo, kondensuotų tiazolo ciklą molekulėje turinčių junginių sintezėje. Ištirtos 3-[(4-hidroksifenil)(4-okso-4,5-dihidrotiazol-2-il)amino]propano ir 3-[(4-hidroksifenil)(4-okso-4,5-dihidrotiazol -2-il)amino]-2-metilpropano rūgščių cheminės savybės ir nustatyta, kad dihidrotiazolono žiedas neatsparus stipriai šarminei terpei, tačiau atsparus rūgštims, brominant nepriklausomai nuo reakcijų sąlygų brominasi tiek aromatinis žiedas, tiek ir dihidrotiazolo žiedo metileninė grupė susidarant 3-[(3,5-dibrom-4-hidroksifenil)(5,5-dibromo-4-okso-4,5-dihidro-1,3-tiazol-2-il)amino]propano ir 3-[(3,5-dibrom-4-hidroksifenil)(5,5-dibromo-4-okso-4,5-dihidro-1,3-tiazol-2-il)amino]-2-metilpropano rūgštims, o su aromatiniais aldehidais sudaro *Z* konfigūracijos atitinkamus 5-benziliden-4,5-dihidro-4-oksotiazolus. Nustatyta, kad vykdant etil 2-[(4-hidroksifenil)(3-metoksi-2-metil-3-oksopropil)amino]-4-metiltiazol-5-karboksilato hidrazinolizę, kiekvienos esterinės grupės hidrazinolizė vyksta nevienareikšmiai. Tai sudaro galimybę sintetinti įvairios struktūros junginius išnaudojant vieną ar abu hidrazininius fragmentus. Pirmą katrą konstatuota, kad funkcionalizuoto tiazolo cikle esantis HC= fragmentas yra pakankamai reaktyvus ir dalyvauja kondensacijos reakcijose su aldehidais sudarydami polifunkcionalizuotus bis(tiazol-5-il)fenilmetanus ar bis(tiazol-5-il)metanus. Remiantis susintetintų funkcionalizuotų tiazolų antibakterinių tyrimų duomenimis nustatyti nauji aminotiazolo dariniai, pasižymintys ryškiu baktericidiniu ir stipriu antioksidaciniu aktyvumu. Atlikti darbai sudaro galimybę planuoti ir praplėsti biologiškai aktyvių medžiagų tikslinės sintezės metodologiją, išplėsti tiksliosios organinės sintezės reagentų įvairovę.

Ginamieji teiginiai:

1. *N*-(4-hidroksifenil)-*N*-tiokarbamoil-β-alaninas ir jo α-metilanalogas yra patogūs tarpiniai junginiai įvairiai funkcionalizuotoms tiazolo heterosistemos sintetinti.

2. Pasinaudojus 3-[(4-hidroksifenil)(4-ariltiazol-2-il)amino]propano ir 3-[(4-hidroksifenil)(4-ariltiazol-2-il)amino]-2-metilpropano rūgščių hidrazidų funkcinėmis savybėmis parodyta galimybė sintetinti hidrazonus, pirolo, pirazolo, oksadiazolo, triazolo heterociklines sistemas, tiazolo cikle esačią acetilgrupę panaudoti hidrazonų bei chalkonų sintezei, o tiazolo cikle esantį HC= fragmentą - polifunkcionalizuotų bis(tiazol-5-il)fenilmetanų ir bis(tiazol-5-il)metanų sintezėje.

3. Pasinaudojus etil 2-[(4-hidroksifenil)(3-metoksi-2-metil-3-oksopropil)-amino]-4-metiltiazol-5-karboksilato hidrazinolizės produktais parodyta galimybė sintetinti įvairios struktūros junginius panaudojant vieną ar abu hidrazininius fragmentus.

REZULTATAI IR IŠVADOS

1. Resintezuotas *N*-(4-hidroksifenil)-*N*-tiokarbamoil-β-alaninas, jo α-metilanalogas, ištirtos jų reakcijos su α-halogenkarbonilinias junginiais ir nustatyta, kad;

1.1. reakcijoje su monochloracto rūgštimi susidaro 3-[(4-hidroksifenil)(4-okso-4,5-dihidrotiazol-2-il)amino]propano ir 3-[(4-hidroksifenil)(4-okso-4,5-dihidrotiazol-2-il)amino]-2-metilpropano rūgštys, o reakcijoje su chloracetaldehidu - 3-[(4-hidroksifenil)(tiazol-2-il)amino]propano ir 3-[(4-hidroksifenil)(tiazol-2-il)amino]-2-metilpropano rūgštys;

1.2. reakcijose α-halogenketonais susidaro atitinkamos 3-[(4-hidroksifenil)(4-alkil-, aril- ar heterociklil tiazol-2-il)amino]propano ir 3-[(4-hidroksifenil)(4-alkil-, aril- ar heterociklil tiazol-2-il)amino]-2-metilpropano rūgštys.

1.3. reakcijose su 2,3-dichlornaftochinonu bei 2,3-dichlorchinoksalinu dalyvauja abu chloro atomai ir susidaro kondensuotieji tiazolo dariniai - 3-[(4,9-diokso-4,9-dihidronafto[2,3-*d*]tiazol-2-il)(4-hidroksifenil)ami-no]propano ir 3-[(4-hidroksifenil)(tiazol[4,5-*b*]chinoksalin-2-il)ami-no]propano rūgštys bei jų metilanalogai.

2. Ištirtos 3-[(4-hidroksifenil)(4-okso-4,5-dihidrotiazol-2-il)amino]propano ir 3-[(4-hidroksifenil)(4-okso-4,5-dihidrotiazol-2-il)amino]-2-metilpropano rūgščių cheminės savybės ir nustatyta, kad;

2.1. dihidrotiazolono žiedas neatsparus stipriai šarminei terpei, tačiau atsparus rūgštims, molekulės struktūroje esančią karboksigrupę

galima esterinti, o esančią molekulės struktūroje hidroksigrupę galima acetilinti, nepaliečiant heterociklinio žiedo;

2.2. brominant, nepriklausomai nuo reakcijų sąlygų, brominasi tiek aromatinis žiedas, tiek ir dihidrotiazolo žiedo metileninė grupė susidarant 3-[(3,5-dibrom-4-hidroksifenil)(5,5-dibrom-4-okso-4,5-dihidro-1,3-tiazol-2-il)amino]propano ir 3-[(3,5-dibrom-4-hidroksifenil)(5,5-dibrom-4-okso-4,5-dihidro-1,3-tiazol-2-il)amino]-2-metilpropano rūgštims;

2.3. reaguojant heterociklinio žiedo metileninei grupei su aromatiniais aldehidais susidaro *Z* konfigūracijos 5-benziliden-4,5-dihidro-4-oksotiazolai.

3. Ištirtos įvairiai funkcionalizuotų 3-[(4-hidroksifenil)(1,3-tiazol-2-il)amino]propano rūgščių ir jų 2-metilanalogų chemines savybes ir nustatyta, kad;

3.1. pasinaudojus 3-[(4-hidroksifenil)(4-ariltiazol-2-il)amino]propano ir 3-[(4-hidroksifenil)(4-ariltiazol-2-il)amino]-2-metilpropano rūgščių hidrazidų funkcinėmis savybėmis galima sintetinti hidrazonus, pirolo, pirazolo, oksadiazolo, triazolo heterociklines sistemas, o tiazolo cikle esačią acetilgrupę panaudoti hidrazonų bei chalkonų sintezei.

3.2. vykdant etil 2-[(4-hidroksifenil)(3-metoksi-2-metil-3-oksopropil)ami-no]-4-metiltiazol-5-karboksilato hidrazinolizę, kiekvienos esterinės grupės hidrazinolizė vyksta nevienareikšmiai. Metilesteris pasižymi didesniu reaktingumu – reakcija vyksta 2-propanolyje, tuo tarpu etilesterinė grupė su hidrazinu reaguoja tik gryname hidrazinhidrate.

3.3. funkcionalizuoto tiazolo cikle esantis HC= fragmentas yra pakankamai reaktyvus ir dalyvauja kondensacijos reakcijose su aldehidais. Reaguojant tiazolo dariniams su aromatiniais aldehidais moliniu santykiu 2:1, gera išeiga susintetinti funkcionalizuoti bis(tiazol-5-il)fenilmetanai, o vietoje aromatinių aldehidų panaudojus formaldehidą, gauti simetrinės struktūros junginiai, metileniniu fragmentu jungiantys du tiazolo žiedus.

4. Ištirtos dalies susintetintų junginių antibakterinės ir antioksidacinės savybes ir nustatyta, kad;

4.1. *Mycobacterium luteum* bakterijų padermė yra jautriausia junginio 3-{(4-[3,4-dichlorfenil]tiazol-2-il)(4-hidroksifenil)amino}-2-metilpropano rūgštis (**20b**) ir 3-[{5-[(2*E*)-3-(3-chlorfenil)prop-2-enoil]-4-metil-1,3-tiazol-2-il}(4-hidroksifenil)amino]-2-metilpropano rūgšties (**98b**) poveikiui. Tiriant junginius praskiedimo metodu nustatyta, kad minimalia inhibicijos koncentracijos verte (MIC) prieš *S. aureus* pasižymejo junginys 3-[{5-[(2*E*)-3-(3-chlorfenil)prop-2-enoil]-4-metil-1,3-tiazol-2-il}(4-hidroksifenil)amino]-2-metilpropano rūgštis (**98b**) – 13,2 μg/ml. O

prieš *M. luteum* padermę 3-{(4-[3,4-dichlorfenil]tiazol-2-il)(4-hidroksifenil)amino}-2-metilpropano rūgštis (**20b**), kurio MIC – 14,9 μg/ml.

4.2. geriausiomis antibakterinėmis savybėmis prieš *E. coli* pasižymėjo izoksazolas 3-([5-{5-(4-chlorfenil)izoksazol-3-il}-4-metiltiazol-2-il][4-metoksifenil]amino)propano rūgštis (**107**) (125 μg/ml). Taip pat aktyvus buvo pirazolo darinys 3-([5-{5-(4-chlorfenil)-1*H*-pirazol-3-il}-4-metiltiazol-2-il][4-metoksifenil]amino)propano rūgštis (**106**). Pakeitus pirazolo žiedo amino grupės protoną benzeno žiedu, gauto junginio 3-([5-{5-(4-chlorfenil)-1-fenil-4,5-dihidro-1*H*-pirazol-3-il}-4-metiltiazol-2-il][4-metoksifenil]amino)propano rūgštis (**108**) aktyvumas prieš *E. coli* sumažėjo. Tiazolo darinys 5-{2-([4-(4-chlorfenil)tiazol-2-il][4-metoksifenil]amino)etil}-4-fenil-2,4-dihidro-3*H*-1,2,4-triazol-3-tionas (**80a**) ir hidrazonas **(***E/Z*)-3-{(4-[4-chlorfenil]tiazol-2-il)(4-metoksifenil)amino}-*N'*-(4-nitrobenziliden)propanhidrazidas (**76a**), turintis 4-nitrobenzeno pakaitą pasižymėjo stipriausiomis priešbakterinėmis savybėmis prieš *X. campestris* (50 μg/ml). Prieš *R. radiobacter* padermę aktyviausias junginys buvo metil 3-{(4-[4-chlorfenil]tiazol-2-il)(4-metoksifenil)amino}propionatas (**72a**).

4.3. geriausiomis antioksidacinėmis savybėmis, tiriant FRAP metodu, pasižymėjo 3,3'-{([(4-(dimetilamino)fenil)-metilen]bis[4-(4-bromfenil)-tiazol-5,2-diil]}bis((4-hidroksifenil)azanediil))-bis(2-metilpropano rūgštis) (**110**), o tiriant DPPH metodu aktyviausia buvo 3,3'-{(metilenbis[4-(4-bromfenil)tiazol-5,2-diil])bis[(4-hidroksifenil)-azanediil]}bis(2-metilpropano rūgštis) (**117**).

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Išleido Kauno technologijos universitetas, K. Donelaičio g. 73, 44249 Kaunas
Spausdino leidyklos „Technologija“ spaustuvė, Studentų g. 54, 51424 Kaunas