BIRUTĖ GRYBAITĖ

SYNTHESIS AND INVESTIGATION OF FUNCTIONALIZED *N*-(4-METHYLPHENYL)- AND *N*-(4-NAPHTHALEN-1-IL)AMINOTHIAZOLE DERIVATIVES

SUMMARY OF DOCTORAL DISSERTATION

NATURAL SCIENCES, CHEMISTRY (N 003)

Kaunas
2021

KAUNAS UNIVERSITY OF TECHNOLOGY

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This doctoral dissertation was prepared at Kaunas University of Technology, Faculty of Chemical Technology, Department of Organic Chemistry, during the period of 2016–2020.

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KAUNO TECHNOLOGIJOS UNIVERSITETAS

BIRUTĖ GRYBAITĖ

FUNKCIONALIZUOTŲ *N*-(4-METILFENIL)- IR *N*-(4-NAFTALEN-1-IL)AMINOTIAZOLO DARINIŲ SINTEZĖ IR TYRIMAS

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INTRODUCTION

The growing number of various diseases and increasing severity of their forms require improvement of the existing medications. The target modifications of their structure would make a significant contribution to the development of medical science and therapy. Changing the surrounding environment causes rapid appearance of a new bacterial strain as well as the growing resistance of old ones to pharmaceuticals; therefore, the search for new biologically active drugs is particularly important. Five- and six-membered heterocyclic compounds and their derivatives possess great potential for the synthesis of new biologically active compounds. They are involved in important biochemical processes that take place in the living organisms, thus ensuring normal vital functions. Synthetic thiazole derivatives with a broad spectrum of biological activity are of particular importance. They show a broad spectrum of biological properties. Pharmaceuticals based on thiazole and its derivatives are used in medical practice for the treatment of hypertension, Alzheimer's disease, diabetes, schizophrenia, allergies; they act as anti-cancer, antimicrobial, antifungal agents. Thiazofurin is a synthetic thiazole derivative, which is used as a medication to treat cancer, and currently is being investigated for its stereoisomers, which are expected to have these properties as well [1]. In addition, many important fungicides and herbicides with aminotiazole moieties have been developed for usage in agriculture.

Many biologically active compounds contain a *β*-alanine moiety, which allows them to be used in the development of pharmaceutically important preparations. Carnosine and anserine that are found in mammals destroy free radicals. These peptides that are synthesized in mammals help them to maintain the pH of working muscles and activate the muscle myosin enzyme. One of the most important classes of pharmaceuticals containing a *β*-alanine moiety is *β*-lactam antibiotics. The antibiotic leucinostatin D is produced by *Paecilomyces marquandii*. Penicillin, one of the first and still one of the most widely used antibiotic agents, has derived from the *Penicillium* fungi. The exceedingly high bacteriostatic potency of this substance together with its low toxicity caused specific application in therapy practice and pharmacy. Recently, natural penicillins have begun to be modified under the laboratory conditions to enhance their antibiotic properties and make them active against fast adapting bacteria.

Cistothiazole A and five its methabolite Citothiazoles B-F, isolated from *Cystobacter fuscus* bacteria strain in 1998, possess high antifungal properties against *Candida albicans* [2, 3]. Trichothiazole A isolated from the cyanobacterium *Trichodesmium* show promising cytotoxic effects [4].

The synthesis and investigation of *N*-substituted amino acids, their derivatives, and heterocyclization products have been ongoing for several decades in the Department of Organic Chemistry of Kaunas University of

Technology. The investigations have shown that *N*-substituted amino acid derivatives have antimicrobial, anticancer, and plant growth-promoting properties. *N*-substituted-*β*-amino acids are widely used for the synthesis of azetidine, quinoline, imidazole, pyridine, pyrimidine, benzodiazepine derivatives.

The scientific novelty and practical value of the work

For the first time, *N*-(4-methylphenyl)-*N*-thiazolyl-*β*-alanine and *N*-(naphthalene-1-yl)-*N*-thiazolyl-*β*-alanine were used for the synthesis of compounds containing 4,5-dihydrothiazole, thiazole, and condensed thiazole system in the molecule. The chemical properties of 3-[*N*-(4-methylhenyl)-*N*-(4-oxo-4,5-dihydrothiazol-2-yl)amino]propanoic and 3-[*N*-(naphthalene-1-yl)-*N*-(4-oxo-4,5-dihydrothiazol-2-yl)amino]-2-propanoic acids were investigated, and it has been determined that the dihydrothiazolone ring is not resistant to strong alkaline media; however, it is acid resistant structure. The reaction with aromatic and heterocyclic aldehydes gives the corresponding 5-benzylidene-4,5-dihydro-4-oxothiazoles of *Z* configuration. It has been determined that hydrozinolysis of both ester groups of ethyl 2-[*N*-(4-hydroxyphenyl)-*N*-(3-methoxy-2-methyl-3-oxopropyl)amino]-4-methylthiazole-5-carboxylate proceed differently. This makes it possible to synthesize compounds of various structures using one or both hydrazine fragments. For the first time, it has been ascertained that the methane group of functionalized thiazole cycle is sufficiently reactive and participate in the condensation reactions with aldehydes to form polyfunctionalized bis(thiazol-5-yl)phenylmethanes and bis(thiazol-5-yl)methanes. Based on the research data on the biological properties of the synthesized polyfunctionalized thiazoles, new aminothiazole derivatives with bactericidal properties have been determined. 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 aim of this work:

To synthesize new variously functionalized *N*-(naphthalen-1-yl)-*N*-thiazolyl-*β*-alanines and *N*-(4-methylphenyl)-*N*-thiazolyl-*β*-alanines and their derivatives and determine the structure, chemical and biological properties of the synthesized compounds.

The objectives of this work:

1. To investigate the cyclization reactions of *N*-(4-methylphenyl)-*N*-thiocarbamoyl-*β*-alanine and *N*-(naphthalen-1-yl)-*N*-thiocarbamoyl-*β*-alanine with various *α*-halocarbonyl compounds, to investigate the condensation

reactions of newly synthesized compounds with aromatic and heterocyclic aldehydes using the reactivity of the formed methylene group.

2. To investigate the chemical properties of the heterocyclic ring of 3-[*N*-(4-methylphenyl)-*N*-(1,3-thiazol-2-yl)amino]propanoic, 3-[*N*-(naphthalen-1-yl)-*N*-(1,3-thiazol-2-yl)amino]propanoic, 3-[*N*-(4-methylphenyl)-*N*-(4-oxo-4,5-dihydrothiazol-2-yl)amino]propanoic, and 3-[*N*-(naphthalen-1-yl)-*N*-(4-oxo-4,5-dihydrothiazol-2-yl)amino]propanoic acids; to determinate the structure of the resulting products.

3. Taking advantage of the functional properties of the carboxyl group of 3-[*N*-(4-methylphenyl)-*N*-(4-arylthiazol-2-yl)amino]propanoic acids to modify them to 3-[*N*-(4-methylphenyl)-*N*-(4-arylthiazol-2-yl)amino] propanoates and 3-[*N*-(4-methylphenyl)-*N*-(4-arylthiazol-2-yl)amino]propanhydrazides; to study the condensation reactions of propanhydrazides with diketones and phenyl isothiocyanate.

4. To investigate the antibacterial and antifungal properties of some of the synthesized compounds in order to determine the dependency of the biological activity on the structure of the compound.

The main statements of the doctoral dissertation are as follows:

1. The *N*-(4-methylphenyl)-*N*-thiazolyl-*β*-alanine and *N*-(naphthalene-1-yl)-*N*-thiazolyl-*β*-alanine are convenient intermediates for the synthesis of variously functionalized thiazole heterosystems;

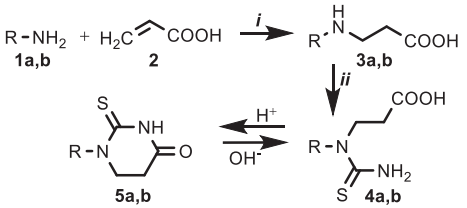
2. Taking advantage of functional properties of 3-[*N*-(4-methylphenyl)-*N*-(4-arilthiazol-2-yl)amino]propanoic and 3-[*N*-(naphthalene-1-yl)-*N*-(4-arilthiazol-2-yl)amino]propanoic acids hydrazides, the synthesis of pyrrole, pyrazole, triazole heterosystems is possible as well as the preparation of hydrazones and chalcones using acetyl group of thiazole cycle. The methine group of thiazole ring enables the synthesis of polyfunctionalized bis(thiazol-5-yl)phenylmethanes and bis(thiazol-5-yl)methanes.

3. The products of the hydrazinolysis of ethyl 2-[*N*-(4-methylphenyl)-*N*-(3-methoxy-2-methyl-3-oxopropyl)amino]-4-methylthiazole-5-carboxylate make it possible to synthesize variously functionalized structures using one or both hydrazine fragments.

RESULTS AND DISCUSSION

The synthesis of *N*-(4-methylphenyl)- and *N*-(1-naphthyl)-*N*-thiocarbamoyl-*β*-alanines

In the first stage of the work, using a well-known methodology described in 2006, the initial compounds **4a,b** [5] were prepared. The reaction of 4-methylaniline **(1a)** or 1-naphthylamine **(1b)** with acrylic acid **(2)** in acetic acid at reflux afforded intermediates *N*-(4-methylphenyl)- and *N*-(1-naphthyl)-*β*-alanine **(3a,b)** (Scheme 1), which were not isolated from the reaction mixtures. After the addition of potassium thiocyanate and glacial acetic acid, the reactions were carried out at reflux for 24 h and gave the corresponding compounds **4a,b**.



a R=4-CH_3-C_6H_4; **b** R=1-naphthyl.
i) CH_3COOH, reflux, 24 h;
ii) KSCN, CH_3COOH, reflux, 24 h.

Scheme 1.

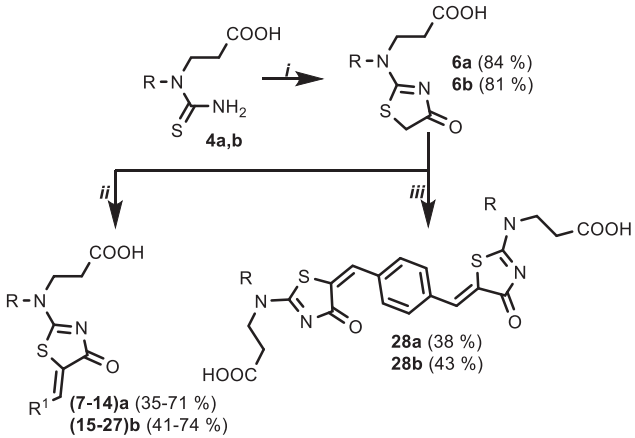
Afterwards, the mentioned compounds **4a,b** were converted to a more stable and almost insoluble in organic solvents derivatives **5a,b** by using intramolecular cyclization reaction. For this purpose, the reaction mixtures were acidified with hydrochloric acid to pH 1, refluxed for 2 h, and diluted with water. The obtained 1-(4-methylphenyl)-2-thioxotetrahydropyrimidine-4(1*H*)-one **(5a)** and 1-(1-naphthyl)-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 readily decyclize to thioureido acid derivatives, i.e., sodium salts of thioureido acids, which then are transformed into the acidic form by using acetic acid.

Synthesis of aminothiazole derivatives

Synthesis of hydrogenated aminothiazoles

In this work, 3-[*N*-carbamothioyl-*N*-(4-methylphenyl)amino]propanoic acid **(4a)** and 3- [*N*-carbamothioyl-*N*-(naphthalen-1-yl)amino]propanoic acid **(4b)** were used in the synthesis of aminothiazole derivatives according to the Hanthzsch reaction, which involves the condensation reaction of thioureido acids

or thioamides with α-halocarbonyl 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). Various bases have been tested to bind the formed hydrogen chloride (NaOH, Na_2CO_3, CH_3COONa). Due to the low stability of compounds **6a,b** in a strong alkaline medium (produced by sodium hydroxide), the yields of the target products were much lower than using other bases. It is worth noting that the most suitable for this synthesis appeared to be sodium carbonate. After the completion of this reaction, the cooled reaction mixture was acidified with 30 % acetic acid to pH 6, and the obtained precipitate was filtered off to give 3-[*N*-substituted -*N*-(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic acids **6a,b**. The structures of the synthesized derivatives **6a,b** were approved by using data of NMR spectroscopy.



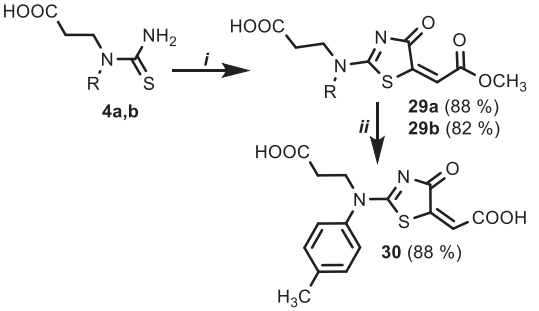
a R=4-CH_3-C_6H_4; **b** R=1-naphthyl.
i) $ClCH_2COOH$, Na_2CO_3, H_2O, reflux, 4 h, CH_3COOH pH 6;
ii, iii) R^1CHO or (OHC-C_6H_4-CHO), Na_2CO_3, H_2O, reflux, 3 h, CH_3COOH pH 6.
15b R^1=C_6H_5; **7a, 16b** R^1=4-F-C_6H_4; **17b** R^1=4-Cl-C_6H_4; **8a, 18b** R^1=4-Br-C_6H_4;
9a, 19b R^1=4-CH_3-C_6H_4; **10a, 20b** R^1=4-NO_2-C_6H_4; **21b** R^1=2-HO-C_6H_4;
11a, 22b R^1=4-HO-C_6H_4; **12a, 23b** R^1=2,4-$(HO)_2$-C_6H_3; **24b** R^1=4-$(N(CH_3)_2)$-C_6H_4;
25b R^1=-CH=CH-C_6H_5; **13a, 26b** R^1=2-thienyl; **14a, 27b** R^1=5-NO_2-thienyl.

Scheme 2.

As a part of the research program for compounds containing a thiazolyl-β-alanine moiety in their structure, the condensation reactions of 3-[*N*-(4-methylphenyl)-*N*-(4-oxo-4,5-dihidro-1,3-thiazol-2-yl)amino]propanoic **(6a)** and 3-[*N*-(naphthalene-1-yl)-*N*-(4-oxo-4,5-dihidro-1,3-thiazol-2-yl)amino]propanoic **(6b)** acids with aromatic and heterocyclic aldehydes were carried out. The reactions were performed in water in the presence of sodium carbonate at reflux and provided compounds **(7–14)a**, **(15–27)b**, **28a,b** (Scheme 2). Sodium

carbonate had several roles: water-insoluble thiazolones **6a,b** were converted to the water-soluble salts of sodium propionate, and it acted as the base catalyst. According to the data of scientific literature [6], these reactions give a single *Z* isomer.

The interaction of thioureido acids **4a,b** with dimethyl acetylenedicarboxylate afforded 5-methoxyoxoethylidenethiazolones **29a,b** (Scheme 3). In the ^{1}H NMR spectra of **29a,b**, the singlets at 3.69 ppm **(29a)** and 3.62 ppm (**29b)** ppm have confirmed the presence of the methoxy group in the molecules of the synthesized compounds.



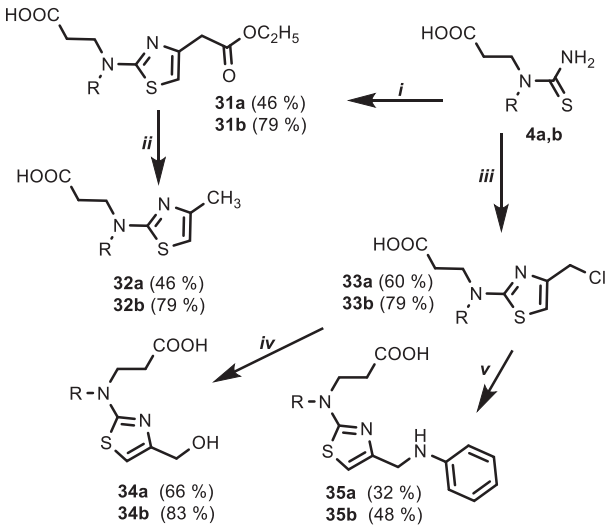
a R=4-CH_3-C_6H_4; **b** R=1-naphthyl.
i) DMAD, acetone, reflux, 24 h;
ii) HCl, H_2O, reflux, 2 h.

Scheme 3.

The hydrolysis of esters **29a,b** was successful only in the case of the compound containing *p*-tolyl substituent and resulted in the formation of dicarboxylic acid **30**. The comparison of the ^{1}H NMR spectra of compounds **29a** and **30** showed that the characteristic signal of methoxy group protons in the latter one is absent, but the signals of protons of two hydroxyl groups are visible.

Synthesis and properties of functionalized aminothiazole derivatives with aliphatic substituents

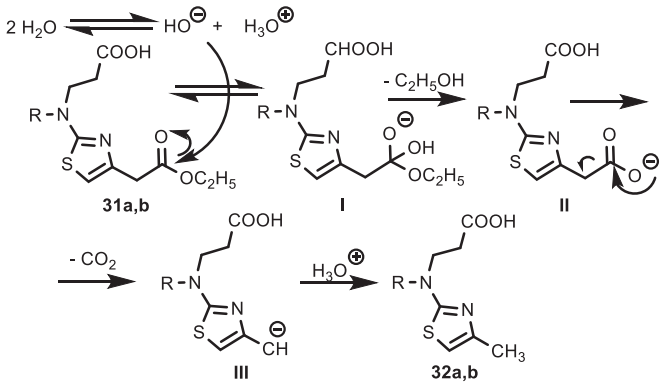
Compounds **31a,b** were prepared by the reaction of the corresponding thioureido acid **4a,b** and ethyl 4-chloroacetoacetate (Scheme 4). The attempts to hydrolyze ethoxyoxoethyl moiety in **31a,b** led to unexpected products, i.e., 4-methylthiazole derivatives **32a,b.** Based on the literature [7], a probable formation mechanism of 4-methylthiazoles **32a,b** is shown in Scheme 5. When the alkyl group of the ester **31a,b** cannot support a positive charge, it appears that a water-catalyzed nucleophilic attack occurs first, followed by the elimination of alcohol. Decarboxylation then occurs to afford an anionic intermediate **III**, which is protonated by water to yield the dealkoxycarbonylated product **32a,b**.



a R=4-CH_3-C_6H_4; **b** R=1-naphthyl.
i) $ClCH_2COCH_2CO_2C_2H_5$, 2-propanol, reflux, 4-6 h;
ii) HCl, H_2O, reflux, 3 h;
iii) $CO(CH_2Cl)_2$, acetone, reflux, 4 h, H_2O, CH_3COONa;
iv) 5% NaOH, 50 °C, 4 h, CH_3COOH pH 6;
v) aniline, DMF, 50 °C, 24 h.

Scheme 4.

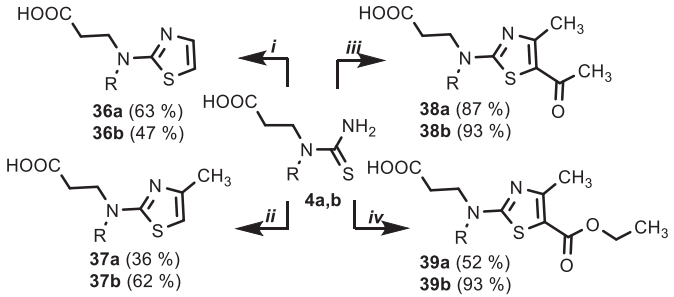
The reaction of **4a,b** with 1,3-dichloroacetone provided thiazoles **33a,b** (Scheme 4). The ^1H and ^{13}C NMR, IR spectroscopic and elemental analysis data have verified the structures of compounds **33a,b**. Under alkaline hydrolysis conditions, chloromethyl group in **33a,b** was converted to hydroxymethyl fragment in **34a,b**, whereas the reaction of **33a,b** with aniline afforded compounds **35a,b** bearing phenylaminomethyl moiety. In the ^{13}C NMR spectra of **34a,b**, the resonance at 60.1 ppm clearly indicates the formation of CH_2OH fragment; in the ^1H NMR spectra, the protons of the methylene group and the hydroxyl group of this fragment give multiplets in the range of 3.65–4.37 and 7.24–7.27 ppm for **34a** and 3.92–4.41 and 7.45–7.66 ppm for **34b**. An analogous spectral representation has been observed as well for compounds **35a,b**, in which ^{13}C NMR spectra, the resonances at 43.8 ppm (**35a** and **35b**) provide an evidence of a newly formed CH_2NHPh moiety.



a R=4-CH_3-C_6H_4; **b** R=1-naphthyl-.

Scheme 5.

During the reaction of compounds **4a,b** with 50 % chloroacetaldehyde solution in water in the presence of sodium carbonate at reflux, 3-[*N*-(4-methylphenyl)-*N*-(1,3-thiazol-2-yl)amino]propanoic acid (**36a**) and 3-[*N*-(naphthalene-1-yl)-*N*-(1,3-thiazol-2-yl)amino]propanoic acid (**36b**) were synthesized. The target products **36a,b** were isolated from the reaction mixtures in 63 % and 47 % yields, respectively, by acidifying them with acetic acid to pH 6. The doublets at 6.36 and 6.73 ppm in the ^{1}H NMR spectra for compounds **36a,b** were assigned to the S-CH and N-CH group protons, respectively. The reaction of 3-[*N*-carbamothioyl-*N*-(4-methylphenyl)amino]propanoic acid **(4a)** or 3- [*N*-carbamothioyl-*N*-(naphthalene-1-yl)amino]propanoic acid **(4b)** with chloroacetone in water provided 3-[*N*-(4-methyl-1,3-thiazol-2-yl)-*N*-(4-methylphenyl)amino]propanoic acid **(37a)** or 3-[*N*-(4-methyl-1,3-thiazol-2-yl)-*N*-(naphthalene-1-yl)amino]propanoic acid **(37b)** (Scheme 6). The reaction was carried out at reflux for 4 h. Afterwards, the reaction mixture was cooled down to room temperature, acidified with acetic acid to pH 6 to give the products **37a, b**.



a R=4-CH_3-C_6H_4; **b** R=1-naphthyl.

i, ii) $ClCH_2CHO$ ($ClCH_2COCH_3$), Na_2CO_3, H_2O, reflux, 4 h, CH_3COOH pH 6;

iii) $ClCH(COCH_3)_2$, acetone, reflux, 4 h, H_2O, CH_3COONa;

iv) $CH_3COCHClCO_2C_2H_5$, CH_3COONa, H_2O, reflux, 6 h.

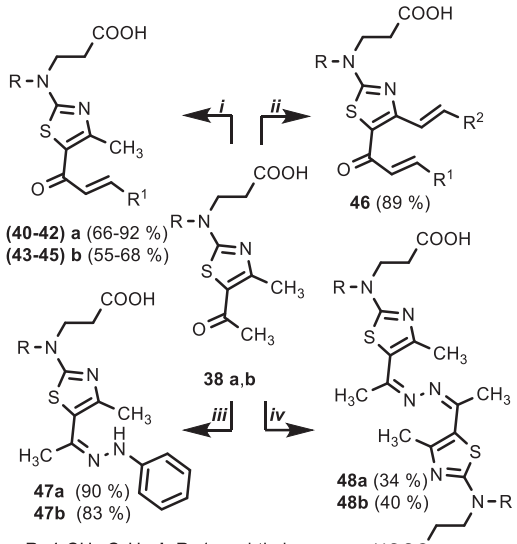
Scheme 6.

The reaction of compounds **4a,b** with 3-chloro-2,4-pentanedione in refluxing acetone gave 3-[*N*-(5-acetyl-4-methylthiazol-2-yl)-*N*-(4-hydroxyphenyl)amino]propanoic acids **38a,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 then were converted into the base by treating them with an aqueous sodium acetate solution. In the ^1H NMR spectrum of compound, **38a** singlets at 2.30 and 2.36 ppm have been attributed to the CH_3CO- and CH_3- groups protons.

The reaction of **4a,b** with ethyl 2-chloroacetoacetate afforded 5-ethoxycarbonyl-4-methyl thiazole derivatives **39a,b**.

In the next step of the work, the compounds synthesized from 5-acetyl-4-methylthiazole derivatives **38a,b** and aromatic aldehydes, hydrazine monohydrate and phenylhydrazine, are discussed (Scheme 7).

The acetyl groups of compounds **38a,b** readily participate in the well-known classic Claisen-Schmidt aldol condensation and in the reaction with aromatic aldehydes in the presence of a base catalyst form compounds **(40–42)a**, **(43–45)b**, **46**, 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 [8].



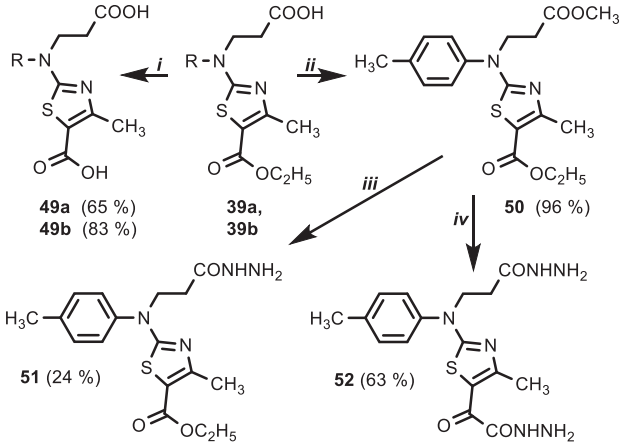
a R=4-CH_3-C_6H_4; **b** R=1-naphthyl.
i) 1. R^1CHO, 30 % KOH, 80 °C, 2 h, 2. CH3COOH pH 5;
ii) C_6H_5CHO, 2-propanol, 10 % NaOH, reflux, 4 h;
iii) $C_6H_5NHNH_2$, CH_3OH, CH_3COOH, reflux, 4 h;
iv) $N_2H_4 \cdot H_2O$, CH_3OH, CH_3COOH, reflux, 5 h.
40a, 43b $R^1=C_6H_5$; **41a, 44b** R^1=4-F-C_6H_4;
42a, 45b R^1=4-Cl-C_6H_4; **46** R^1,$R^2=C_6H_5$.

Scheme 7.

The interaction of compounds **38a,b** with phenylhydrazine yielded (*E*)-3-/*N*-{4-methyl-5-[1-(2-phenylhidyrazon)ethyl]thiazol-2-yl}-*N*-(4-methylphenyl)amino/propanoic acid **(47a)** and (*E*)-3-/*N*-{4-methyl-5-[1-(2-phenylhydrazon)ethyl]thiazol-2-yl}-*N*-(naphthalene-1-yl)amino/propanoic acid **(47b)**, while in the reaction with hydrazine hydrate, the acetyl fragment of the thiazole derivatives **38a,b** gave an molecular dimer –-3,3'-hydrazine-1,2-diylidenebis{*N*-[(ethan-1-yl-1-ylidene)-4-methyl-1,3-thiazole-5,2-diyl]-*N*-(4-methylphenyl)amino}propanoic acid **(48a)** and 3,3'-hydrazine-1,2-diylidenebis{*N*-[(ethan-1-yl-1-ylidene)-4-methyl-1,3-thiazole-5,2-diyl]-*N*-(naphthalene-1-yl)amino}propanoic acid **(48b)**. In the ^{1}H NMR spectrum of **48a**, twelve methyl protons gave two singlets at 2.20 and 2.42 ppm. The spectrum as well showed two triplets at 2.56 and 4.07 ppm (J = 7.3 Hz), which were assigned to four methylene groups of alkyl fragments, and the resonance of the hydroxyl protons appeared as a broad singlet at 12.25 ppm. The double intensities of all

carbon resonances in the ^{13}C NMR spectrum of **48a** proved the formation of the expected structure.

Some chemical properties of previously synthesized compounds **39a,b** were investigated. Under alkaline hydrolysis conditions, 5-ethoxycarbonyl-4-methyl thiazole derivatives **39a,b** were converted to dicarboxylic acids **49a,b** (Scheme 8). The esterification reaction of **39a** with methanol in the presence of concentrated sulfuric acid as a catalyst provided methyl ester **50**, which was transformed to acid hydrazide **51** and dihydrazide **52** depending on the hydrazinolysis conditions.



a R=4-CH_3-C_6H_4; **b** R=1-naphthyl.
i) 5 % NaOH, 100 °C, 1 h, CH_3COOH pH 6;
ii) CH_3OH, H_2SO_4, reflux, 4 h;
iii) $N_2H_4 \cdot H_2O$, 2-propanol, reflux, 48 h;
iv) $N_2H_4 \cdot H_2O$, 100 °C, 24 h.

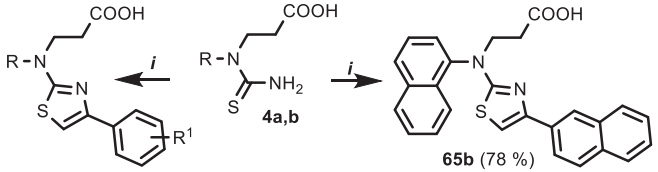
Scheme 8.

It has been found that the hydrazinolysis of each ester group proceeds differently, and mono- or dihydrazide can be selectively obtained from compound **50**. In this reaction, the methyl ester was characterized by a higher reaction rate; therefore, the interaction of **50** with three equivalents of hydrazine monohydrate in 2-propanol at reflux for 48 hours gave monohydrazide **51**. The ester group directly attached to the thiazole ring did not react under these conditions. However, the reaction of compound **50** in pure hydrazine monohydrate at 100 °C for 24 hours resulted in the formation of dihydrazide **52** in 62 % yield. In the ^1H NMR spectrum for **52**, a broad singlet integrated for four protons (4.20 ppm) and two singlets (8.82 and 9.03 ppm), each integrated for one

proton, have been attributed to the NH_2 and NH groups of two hydrazide fragments, respectively.

Synthesis and properties of functionalized aminothiazole derivatives with aromatic substituents

In this step of the work, the condensation of compounds **4a,b** with various 2-bromoacetophenones provided derivatives **(53–57)a** and **(58–64)b** in excellent and good yields (Scheme 9). The interaction of **4b** and 2-bromo-2'-acetonaphthone afforded 3-{*N*-[4-(naphthalene-2-yl)-1,3-thiazole-2-yl]-*N*-(naphthalene-1-yl)amino}propanoic acid **(65b)**. These reactions are conveniently carried out in acetone, because during the reactions, the insoluble chemically pure hydrobromides **(53–57)a** and **(58–64)b** are formed. Hydrobromides, due to their low stability in a strong alkaline medium, were easily transferred into the base form by treating them with sodium carbonate.

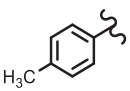


(53-57)a (85-99 %)
(58-64)b (57-92 %)

i) 1) $R^1C_6H_4COCH_2Br$ arba 2-bromo-2'-acetonaphthone **(65b)**, acetone, reflux, 3 h, 2) CH_3COONa, H_2O, reflux, 5 min

Scheme 9.

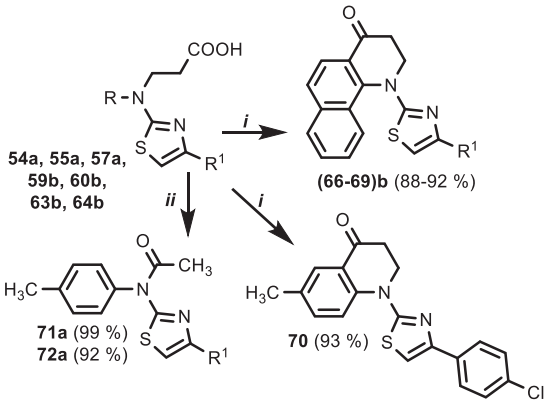
Table 1. Data of yield

No.	R	R^1	Yield
53a		4-H	89 %
54a		4-F	87 %
55a		4-Cl	99 %
56a		4-CN	85 %
57a		4-NO_2	89 %
58b		4-H	86 %
59b		4-F	79 %
60b		4-Cl	90 %
61b		4-Br	54 %
62b		2,4-Cl	60 %
63b		4-CN	92 %
64b		4-NO_2	77 %

The structures of compounds **(53–57)a** and **(58–64)b** were confirmed by spectral data. For example, the IR spectrum of compound **53a** revealed a strong

absorption bands at 1721 and 1510 cm^{-1}, characteristic to C=O and C=N functional groups, respectively. Its' ^{1}H and ^{13}C NMR spectra showed signals at 7.10 and 102.4 ppm, respectively, assigned to CH protons of the thiazole ring.

It is known that quinolone-type compounds can be obtained by heating *N*-aryl-*β*-alanines with strong dehydrators, i.e., polyphosphoric acid or phosphorus pentoxide [9]. In this work, compounds **(66–69)b** and **70** were obtained by heating the starting materials **55a**, **59b**, **60b**, **63b**, **64b** in polyphosphoric acid at 100 °C (Scheme 10). Afterwards, the reaction mixtures were cooled down to room temperature, diluted with water, and neutralized with aqueous ammonia solution to pH 6. The formed crystals were filtered off and washed with water. Acids **54a** and **57a** were treated with acetic anhydride to give acylated compounds at 5-position of the thiazole ring. However, this acylation to the 5-position of the heterocyclic ring did not take place. Under these conditions, the carboxyalkyl fragment was replaced by an acetyl group to give only the *N*-acyl derivatives **71a** and **72a**. The ^{1}H and ^{13}C NMR, IR spectroscopic, and elemental analysis data have verified the structures of compounds. The formation of the cyclic structure **70** is clearly demonstrated by chemical shifts in the ^{13}C NMR spectrum, i.e., the chemical shifts of the CH_2CO, NCH_2, and C=O group signals (37.65, 49.05, 192.88 ppm) are markedly different from the signals of the same functional groups of the initial compound.



a R=4-CH_3-C_6H_4; b R=1-naphthyl.

i) PPA, 100 °C, 1 h, NaOH pH 8; ***ii)*** $(CH_3CO)_2O$, reflux, 24 h.

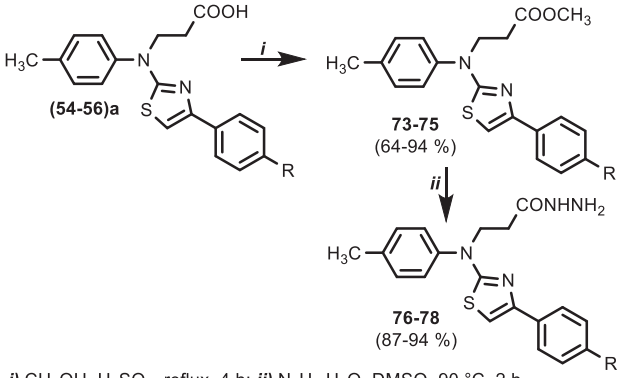
66b R^1 =4-F-C_6H_4; **67b** R^1 =4-Cl-C_6H_4; **68b** R^1 =4-CN-C_6H_4;

69b R^1 =4-NO_2-C_6H_4; **71a** R^1=4-F-C_6H_4; **72a** R^1=4-NO_2-C_6H_4.

Scheme 10.

Synthesis and cyclization of 3-{*N*-[4-(4-substituted phenyl)thiazol-2-yl]-*N*-(4-methylphenyl)amino}propane hydrazides

It is known that acid hydrazides can be prepared directly from carboxylic 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.

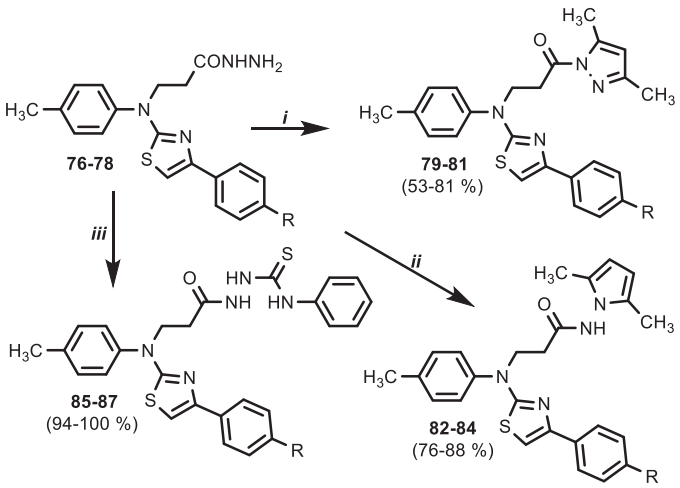


i) CH_3OH, H_2SO_4, reflux, 4 h; ***ii)*** $N_2H_4 \cdot H_2O$, DMSO, 90 °C, 2 h.
73, 76 R =F; **74, 77** R=Cl; **75, 78** R=CN.

Scheme 11.

Acids **(54–56)a** were esterified with methanol for 4 hours in the presence of a catalytic amount of sulfur acid in the reaction mixture (Scheme 11). The obtained methyl esters **73–75** reacted with hydrazine monohydrate in dimethyl sulfoxide at 90 °C temperature, and the corresponding hydrazides **76–78** were synthesized.

The next step of the work was the condensation of hydrazides **76–78** with diketones, 2,4-pentane-dione and 2,5-hexanedione. These reactions resulted in the formation of 3-{[4-(4-substituted phenyl)thiazol-2-yl]-*p*-tolylamino}-1-(3,5-dimethylpyrazol-1-yl)propan-1-one **79–81** and 3-{[4-(4-substituted phenyl)thiazol-2-yl]-*p*-tolylamino}-*N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)propanamide **82–84**. The ^{13}C NMR spectrum of compound **80** exhibited three resonance lines at 111.2, 143.1, and 151.4 ppm, which were attributed to the carbons of the pyrazole moiety. The proton signals of the two methyl groups and the C-CH=C fragment resonated in the expected field of the ^{1}H NMR spectrum and as well approved the presence of the pyrazole ring.

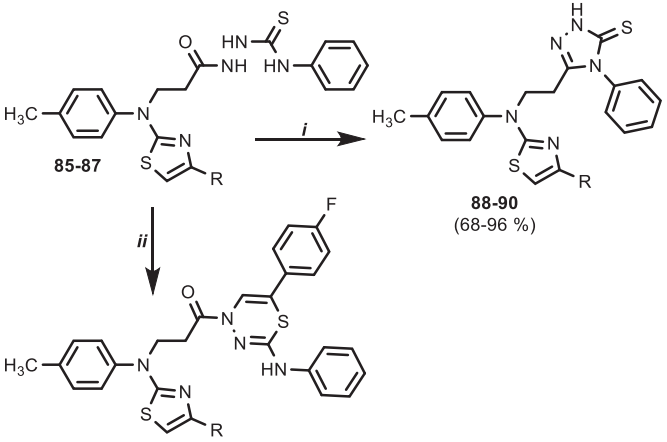


i) $CH_2(COCH_3)_2$, dioxane, reflux, 24 h; ***ii)*** $CH_2CH_2(COCH_3)_2$, 2-propanol, CH_3COOH reflux, 3 h; ***iii)*** C_6H_5NCS, CH_3OH, reflux, 2 h.
79, 82, 85 R =F; **80, 83, 86** R=Cl; **81, 84, 87** R=CN.

Scheme 12.

The ^{1}H NMR spectrum of the pyrrole derivative **83** exhibited characteristic signals of the desired structures: intense singlets at 1.92 and 5.60 ppm were assigned to CH_3 and CH groups of the pyrrole fragment. The double intensity resonances at 10.9, 102.9, and 126.7 ppm in the ^{13}C NMR spectrum demonstrate the existence of the pyrrole moiety. Despite the presence of the NH–CO fragment in the molecule, only the *s-cis* isomer with traces of the *s-trans* isomer is visible in the ^{1}H and ^{13}C NMR spectra of compound **83** in DMSO-d_6 solutions. The interaction of carbohydrazide **76–78** with phenyl isothiocyanate in methanol at reflux gave thiosemicarbazides **85–87**. The precipitate has already been formed during the reaction. In the ^{1}H NMR spectrum of compound **86**, one intense singlet at 9.53 ppm integrated for two protons and other less intense at 9.97 ppm, integrated for one proton, show the presence of three NH groups. The formation of the C(O)-NH-NH-C(S)-NHPh fragment finally approves the resonances at 170.0 and 180.9 ppm assigned to C=O and C=S groups and additional spectral lines in the aromatic region in the ^{13}C NMR spectrum.

The last step of the study was ring closure reactions when the thiosemicarbazides **85–87** were heated at reflux in aqueous sodium hydroxide solution or reacted with 2-bromo-4′-fluoroacetophenone in acetone. The first reaction afforded 3-substituted 1,2,4-triazole-5-thione derivatives **88–90**, and the other one resulted in the formation of the thiadiazine cycle in the molecule and gave derivative **91** (Scheme 13).



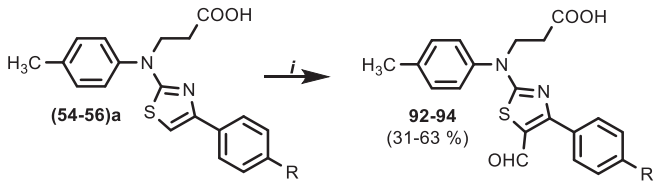
i) 4% NaOH, reflux, 5 h, conc. HCl pH 4; ***ii)*** 4-F-$C_6H_4COCH_2Br$, acetone, reflux, 16 h.
88 R =4-F-C_6H_4; **89, 91** R =4-Cl-C_6H_4; **90** R =4-CN-C_6H_4.

Scheme 13.

A characteristic singlet at 13.75 (NH, ^{1}H NMR) and a resonance line at 167.7 (C=S, ^{13}C NMR) ppm in the NMR spectra of compound **87** show the formation of the 1,2,4-triazole-5-thione moiety. The absorption band at 1267 cm^{-1} in the IR spectrum proves the existence of the thiocarbonyl group formation. The absence of the proton signal of the SH group in the strong field of the ^{1}H NMR spectrum ensures the presence of the thione form. The structure of compound **91** was proved by spectroscopic techniques.

Synthesis and properties of thiazoles-5-carboxaldehydes

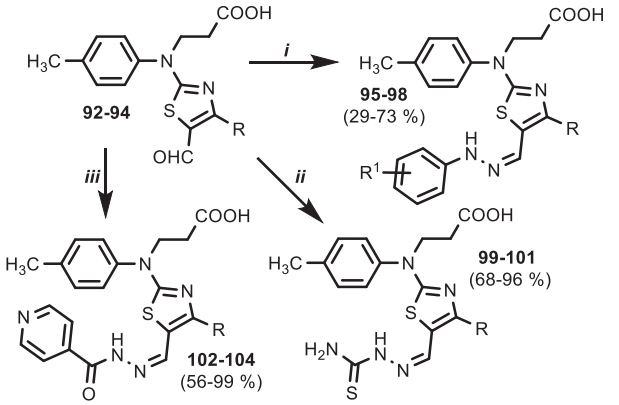
The previously synthesized compounds **(54–56)a** were used for the preparation of derivatives **92–94** (Scheme 14). The ^{1}H and ^{13}C NMR, IR spectroscopic, and elemental analysis data have verified the structures of compounds **92–94**. The characteristic proton signal of the aldehyde group of compound **92** was observed as a singlet at 9.60 ppm.



i) $POCl_3$, DMF, 100 °C, 20 min.
92 R =F; **93** R =Cl; **94** R =CN.

Scheme 14.

Compounds **92–94** reacted with the excess of the different hydrazine, i.e., phenylhydrazine, 2,4-dinitrophenylhydrazine, or thiosemicarbazide, or isoniazid, to form the corresponding hydrazone-type compounds **95–98**, **99–101**, and **102–104** (Scheme 15). The comparison of ^{1}H NMR spectra of the aldehydes **92–94** with the ones for compounds **95–104** has revealed that proton singlets of aldehyde group at 9.60–9.63 ppm in the spectra of **92–94** have been replaced by the singlets of the CH group protons in the range of 7.68–8.58 ppm in the spectra of **95–104**. The obtained polysubstituted thiazoles containing reactive functional groups can be used for different further chemical transformations and preparation of a diverse library of biologically active thiazole derivatives.

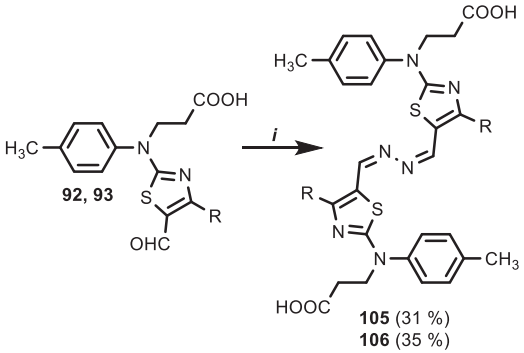


i) $C_6H_5NHNH_2$ **(95-97)** or 2,4-$(NO_2)_2C_6H_3NHNH_2$ **(98)**, CH_3OH, reflux, 3 h;
ii) $H_2NCSNHNH_2$, C_2H_5OH, reflux, 24 h; ***iii)*** isoniazid, C_2H_5OH, reflux, 24 h.
95, 99, 102 R =4-F-C_6H_4; **96, 98, 100, 103** R =4-Cl-C_6H_4;
97, 101, 104 R =4-CN-C_6H_4; **95-97** R^1 =H; **98** R^1 =2,4-NO_2.

Scheme 15.

In the next step of the work, symmetric hydrazine derivatives **105** and **106** were synthesized by the reaction of aldehydes **92** and **93** with hydrazine hydrate

in methanol (Scheme 16). The structure of the mentioned compounds was confirmed by the methods of ^{1}H NMR, IR, and mass spectrometry. For example, in the ^{1}H NMR spectrum of compound **105**, the proton signals of the two C<u>H</u> = N groups are observed as an intense singlet at 8.36 ppm. When comparing the ^{1}H NMR spectra of the starting compounds **92** with the spectra of newly synthesized compounds **105**, the latter one showed an increase of aromatic peaks. Based on the mass spectrometry analysis, the monoisotopic mass of compound **105** was determined to be 765.2125, and the calculated value is [M + H] + 765.2051.



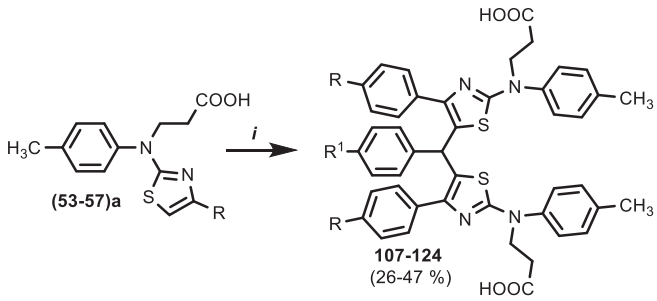
i) $N_2H_4 \cdot H_2O$, CH_3OH, 100 °C, 24 h.
105 R =4-F-C_6H_4;
106 R =4-Cl-C_6H_4.

Scheme 16.

Products of the reactions of 3-[*N*-(4-methylphenyl)-*N*-(4-arylthiazol-2-yl)amino]propanoic acid with aldehydes

Synthesis of bis(thiazol-5-yl)phenylmethanes

The reactions of thiazole derivatives **(53–57)a** with aromatic aldehydes in a 2:1 molar ratio and in the presence of a catalytic amount of concentrated hydrochloric acid afforded bis(thiazol-5-yl)phenylmethanes **107–124** (Scheme 17), which have already been crystallized in the reaction mixture.



i) 1) R^1CHO, acetone, HCl reflux, 18 h.
2) CH_3COONa, H_2O, reflux, 5 min.

Scheme 17.

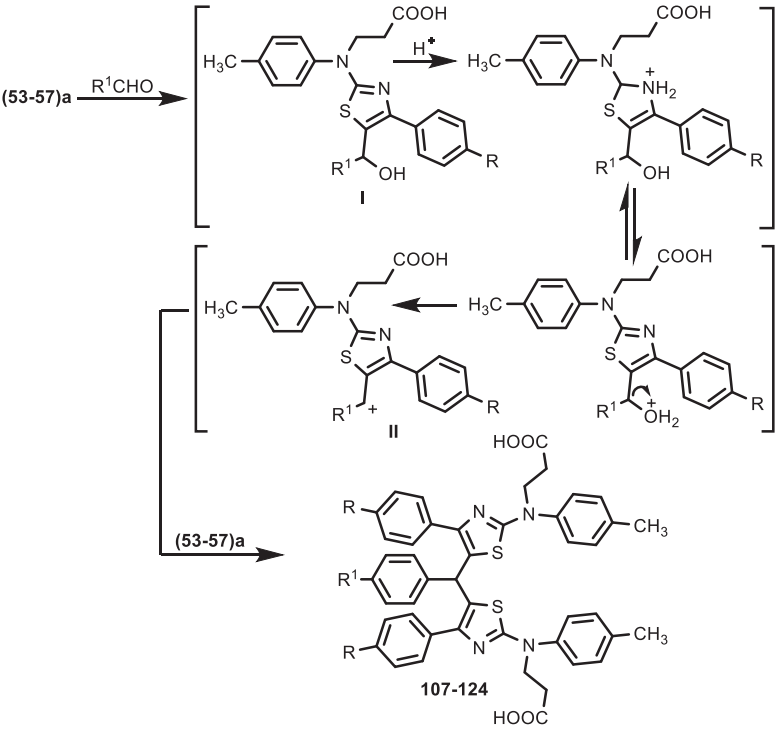
Table 2. Data of yield

No.	R	R^1	Yield
107	-H	-F	44 %
108	-Cl		26 %
109	$-NO_2$		39 %
110	-H	-Cl	47 %
111	-Cl		28 %
112	-CN		41 %
113	$-NO_2$		42 %
114	-H	-Br	42 %
115	-Cl		47 %
116	$-NO_2$		38 %
117	-H	$-NO_2$	47 %
118	-F		40 %
119	-Cl		43 %
120	$-NO_2$		37 %
121	-H	$-N(CH_3)_2$	47 %
122	-F		35 %
123	-Cl		37 %
124	$-NO_2$		41 %

The formed crystalline product was filtered off, washed with plenty of acetone, and boiled in 4 % aqueous sodium acetate solution for 5 min. The obtained appropriate product was filtered off, washed with water, and dried. The products were elucidated based on their IR, NMR, and mass spectroscopy data. The analysis of the ^1H NMR spectra of compounds **107–124** revealed a singlet at approx. 5.74 ppm, ascribed to the newly formed C-CH-C fragment, which is clearly confirmed by the resonance line at approx. 40.8 ppm in the ^{13}C NMR

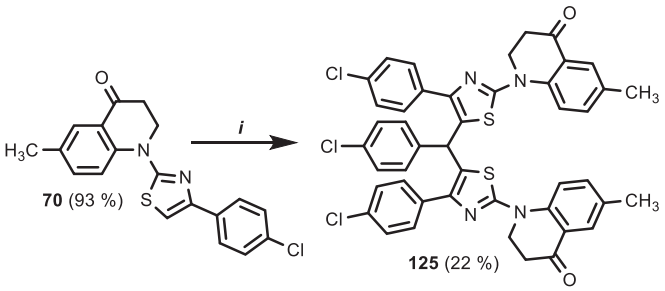
spectra. Both spectra displayed an increased abundance of the aromatic signals as well.

Based on the literature [10], a supposed mechanism for the preparation of compounds **107–124** is presented in Scheme 18. First of all, during the reaction between thiazoles **53–57a** and aromatic aldehyde 3-{*N*-[4-(4-substituted phenyl)-1,3-thiazole-2-yl]-*N*-(4-methylphenyl)amino}propanoic acid, derivative **I** is formed. Under the action of acidic medium, the obtained compound **I** transforms to the carbenium ion intermediate **II**, reaction of which with another thiazole derivative **53–57a** results in the formation of bis(thiazol-5-yl)phenylmethanes **107–124**.



Scheme 18.

Under the same conditions as for the synthesis of bis(thiazol-5-yl)phenyl methanes **107-124**, 1,1'-[(4-chlorophenyl)methylylidene]bis[4-(4-chlorophenyl)-1,3-tiazole-5,2-diyl]bis(6-methyl-2,3-dihydrochinoline-4(1*H*))-one **(125)** was obtained. The reaction was carried out between quinolone **70** and 4-chlorobenzaldehyde in a molar ratio of 2:1 (Scheme 19).



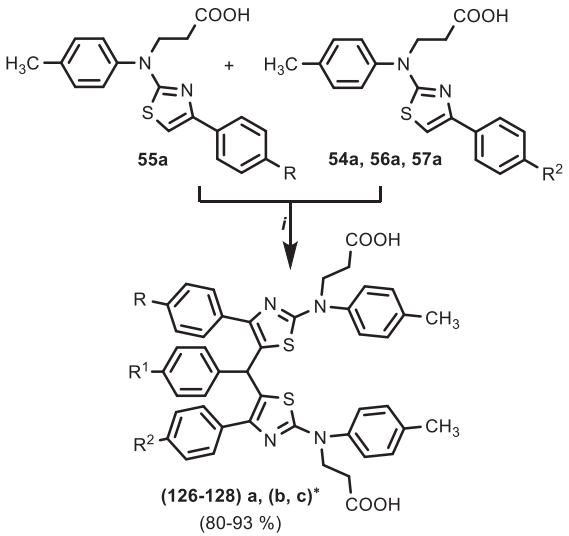
i) 4-Cl-C_6H_4CHO, acetone, HCl, 85 °C, 24 h.

Scheme 19.

In the ^{1}H NMR spectrum of this compound, the singlet at 5.96 ppm is assigned to the proton of the SC-CH-CS fragment of the molecule. Based on the mass spectrometry analysis, the monoisotopic mass of compound **125** was determined to be 833.1159, and the calculated value is [M + H] + 833.1111.

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

The reaction of two different thiazole derivatives **(54–57)a** with aromatic aldehydes was not successful. In reaction, the mixtures of three compounds **(126–128)a, b*, c*** were formed (Scheme 20). These reactions were performed in acetone at reflux using concentrated hydrochloric acid as a catalyst. The structure of the synthesized compounds **(126–128)a, b*, c*** is confirmed by the ^{1}H NMR data, where the three singlets at 5.55, 5.65, 5.75 ppm was assigned to the protons of the -SC-CH-CS- fragment (the exact values are presented in the experimental part of the work).



i) 1) R^1CHO, acetone, HCl, reflux, 16 h, 2) CH_3COONa, H_2O, reflux, 5 min.

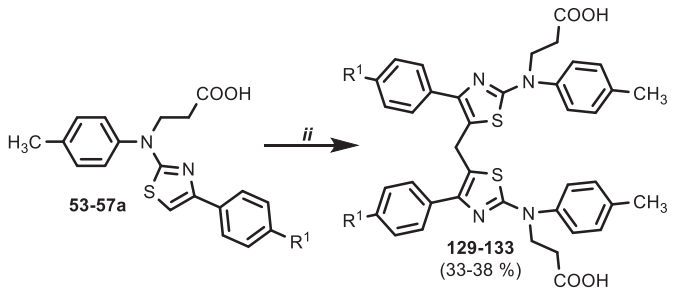
Scheme 20.

Table 3. Data of yield

No.	R	R^1	R^2	Yield
126a	-Cl	-Cl	-F	48 %
126b*	-F	-Cl	-F	20 %
126c*	-Cl	-Cl	-Cl	32 %
127a	-Cl	-Cl	-CN	45 %
127b*	-Cl	-Cl	-Cl	24 %
127c*	-CN	-Cl	-CN	29 %
128a	-Cl	$-N(CH_3)_2$	$-NO_2$	41 %
128b*	-Cl	$-N(CH_3)_2$	-Cl	29 %
128c*	$-NO_2$	$-N(CH_3)_2$	$-NO_2$	30 %

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

Using an aqueous formaldehyde solution instead of the aromatic aldehydes and replacing acetone with acetic acid, diyl(thiazole-2-yl)substituted methane derivatives **129–133** were synthesized. Two thiazole cycles in the molecules of these compounds are connected through methylene fragment (Scheme 21). In the ^1H NMR spectra of compounds **129–133**, 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).



ii) HCHO, CH_3COOH, reflux, 16 h.
129 R^1 = -H; **130** R^1 = -F; **131** R^1 = -Cl; **132** R^1 = -CN; **133** R^1 = $-NO_2$.

Scheme 21.

BIOLOGICAL TESTS

Investigation of antimicrobial activity

A part of newly synthesized thiazoles and bisthiazoles **53–57a**, **74**, **77**, **80**, **83**, **86**, **89**, **91**, **107–124**, **126–128**, **129–133** were evaluated for their antimicrobial activity against strains of *Escherichia coli* B-906, *Staphylococcus aureus* 209-P, *Mycobacterium luteum* B-917, *Candida tenuis* VKM Y-70, *Aspergillus niger* VKM F-1119 by the diffusion technique [11] and serial dilution technique (determination of minimal inhibition concentrations MIC) [12]. 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).

E. coli, *C. tenuis* and *A. niger* appeared to be not sensitive to the tested compounds **53–57a**, **74**, **77**, **80**, **83**, **86**, **89**, **90**, **107–124**, **126–128**, **129–133**, investigated using both diffusion and serial dilution techniques. *S. aureus* were sensitive to three compounds **54a, 55a**, and **57a** (Figure 1) containing a 4-phenyl substituted-1,3-thiazol-2-yl moiety. The most active against *A. niger* strain was compound **55a** containing a 4-chlorophenyl-1,3-thiazol-2-yl fragment. *E. coli* bacteria strain is most sensitive to compound **54a**. Compound **57a** containing the 4-nitrophenyl fragment showed selective activity against *S. aureus* strain. Compound **112** can be concluded as the most active in the group of the compounds containing bis(thiazol-5-yl)phenylmetanes moiety, and the *M. luteum* strain showed the highest sensitivity to the action of these compounds.

The investigation of the antibacterial activity of the synthesized compounds by the serial dilution method showed that none of the tested compounds had an inhibitory effect on the studied concentrations against *E. coli* and *S. tenuis* strains. Compounds **54a**, **55a**, **57a**, **121**, **126**, **127**, **128** showed

promising antibacterial activity against *S. aureus*, and compounds **54a**, **55a**, **57a**, **112**, **120**, **121**, **126**–**128** affected *M. luteum* bacteria strain. *M. luteum* strain was highly sensitive to compound **54a**, **57a**, **112** with MIC value of 7.8 μg/mL containing 4-phenyl substituted-1,3-thiazol-2-yl or bis(thiazol-5-yl)phenylmetane fragments. Only compounds **126**–**128** having different bis(thiazol-5-yl)phenyl methane fragments showed antifungal activity against *A. niger* with the MIC of 31.2–500 μg/mL. Surprisingly, the modification of the carboxyalkyl chain by incorporation of various heterocyclic moieties did not yield any positive antimicrobial effect. Thus, derivatives **74**, **77**, **80**, **83**, **86**, **89**, **91** of compound **55a** appeared completely inactive against all the tested bacterial and fungal strains.

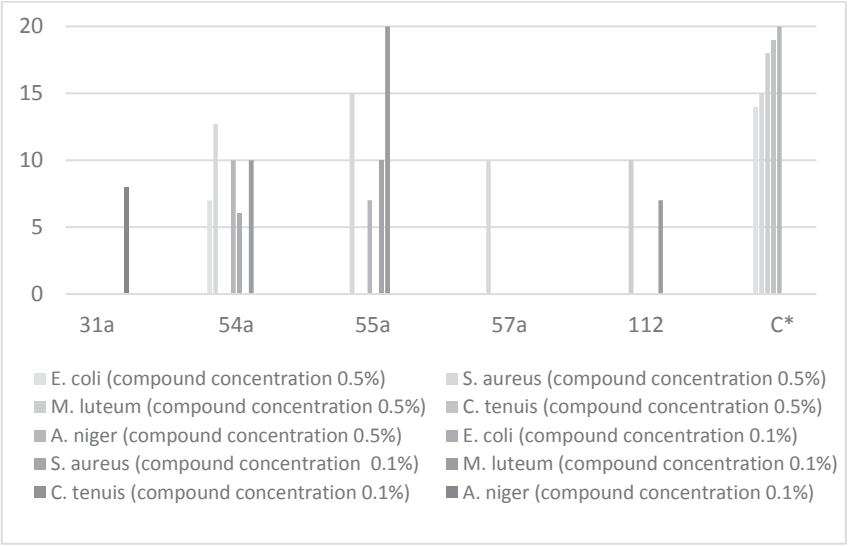


Fig. 1. Antibacterial activity of compounds accomplished by diffusion technique

The evaluation data affirmed that thiazoles **(53–57)a**, bis(thiazole-5-yl) phenylmethanes **107**–**124**, and different bis(thiazole-5-yl-)phenylmethanes **126**–**128** were completely inactive or had very low antifungal activity against *C. tenuis* and *A. niger*. The replacement of the nitro group with a halogen atom in thiazoles **54a**, **55a** increase their antibacterial activity against *M. luteum* strain. The comparison of thiazoles **(53–57)a** with bis(thiazole-5-yl)phenylmethanes **107**–**124**, different bis(thiazol-5-yl)phenylmethanes **126**–**128** or bis(thiazole-5-yl-)methanes **129**–**133**, revealed that the incorporation of an additional thiazol-5-yl fragment in the molecules does not broaden the antimicrobial activity against the tested bacterial and fungi strain. The results of the investigation affirmed that

the compounds with a 4-phenyl substituted 1,3-thiazol-2-yl moiety had the best antibacterial properties. The most promising of the tested compounds are derivatives **(54a–57)a**, which would be used for further studies to increase their antibacterial activity.

The activity of compounds **29a**, **31a,b**, **33a**, **34b**, **35a,b**, **39b**, **49a**, **50–52**, **99**, **101**, **102**, **104** was evaluated by diffusion techniques. All tested compounds showed antifungal activity against test-culture *A. niger* (diameter of the inhibition zone 8–13 mm). *A. niger*, as highly sensitive to compound **31a**, is the only one who acted against this bacterium (at 0.1 % concentration).

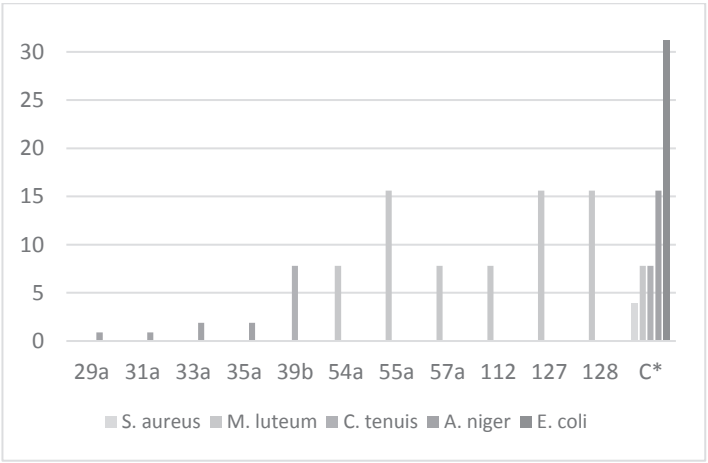


Fig. 2. Antibacterial activity of compounds accomplished by serial dilution technique

Some of the synthesized compounds **29a,b**, **30**, **31a,b**, **33a,b**, **34a,b**, **35a,b**, **39a,b**, **49a,b**, **50–52**, **92–104** were evaluated for their antimicrobial activity by the serial dilution method (Fig. 2). Compounds **29a**, **31a**, having 5-(2-methoxy-2-oxoethylidene)-4-oxo-4,5-dihydrothiazol-2-yl and 4-(2-ethoxy-2-oxoethyl)thiazol-2-yl moieties, demonstrated an excellent antifungal activity against the *A. niger* strain, at MIC of 0.9 μg/mL, which is more than eight times lower than that of the control. *A. niger* was as well highly sensitive to the compounds **33a**, **35a** containing 4-(chloromethyl)thiazol-2-yl and 4-[*N*-(phenylamino)methyl]thiazol-2-yl fragments in the structure. Their MIC value appeared to be 1.9 μg/mL, and this is significantly lower than that of the control (MIC 7.8 μg/mL).

The evaluation of the antifungal activity of compounds **50–52** showed that the replacement of one or two ester groups in the diester molecule with the hydrazide groups reduces the biological activity of these compounds. The substitution of the aldehyde group of compounds **92–94** with 5-[(2-

phenylhydrazone)methyl] or 5-(2-isonicotinoylhydrazone) moiety in compounds **95**–**97** and **102**–**104** increases their antibacterial activity against *M .luteum* strain. Moreover, it could be affirmed that the insertion of a 5-(2-isonicotinoylhydrazone) moiety in the molecule containing fluorine **102**, and in particular chlorine **103** atoms, broadens the spectrum of biological activity. Among these compounds, derivative 103 is the leading inhibitor of all bacterial and fungal strains that were tested.

CONCLUSIONS

1. The reactions of *N*-(4-methylphenyl)-*N*-thiocarbamoyl-*β*-alanine **4a** and *N*-(naphthalene-1-yl)-*N*-thiocarbamoyl-*β*-alanine **4b** with *α*-halocarbonyl compounds were investigated. It has been determined that in the reaction with monochloroacetic acid, 3-[*N*-(4-methylphenyl)-*N*-(4-oxo-4,5-dihydrothiazol-2-yl)amino]propanoic **(6a)** and 3-[*N*-(naphthalene-1-yl)-*N*-(4-oxo-4,5-dihydrothiazol-2-yl)amino]-2-propanoic **(6b)** acids are formed. Meanwhile, in the reaction with *α*-haloketones, 3-[*N*-(4-methylphenyl)-*N*-(4-alkyl- or arylthiazole-2-yl)amino]propanoic **29a**, **30**, **31a**, **33a**, **(36–39)a**, **(53–57)a** and 3-[*N*-(naphthalene-1-yl)-*N*-(4-alkyl- or arylthiazole-2-yl)amino]-2-propanoic **29b**, **31b**, **33b**, **(36–39)b**, **(58–65)b** acids are obtained.
2. The chemical properties of 3-[*N*-(4-methylphenyl)-*N*-(4-oxo-4,5-dihydrothiazol-2-yl)amino]propanoic **(6a)** and 3-[*N*-(naphthalene-1-yl)-*N*-(4-oxo-4,5-dihydrothiazol-2-yl)amino]-2-propanoic **(6b)** acids were investigated, and it has been determined:

- dihydrothiazolone cycle is not resistant to the strong alkaline medium, but it is resistant to acids;
- in the reaction of the methylene group of the heterocyclic ring with aromatic and heterocyclic aldehydes, 5-benzylidene-4,5-dihydro-4-oxothiazoles of Z configuration are formed.

3. The chemical properties of functionalized 3-[*N*-(4-methylphenyl)-*N*-(1,3-thiazol-2-yl)amino]propanoic **38a**, **(53–57)a** and 3-[*N*-(naphthalene-1-yl)-*N*-(1,3-thiazol-2-yl)amino]-2-propanoic **38b**, **(58–64)b** acids were investigated, and it has been determined:

- using the functional properties of 3-[*N*-(4-methylphenyl)-*N*-(4-arylthiazol-2-yl)amino]propanoic acids hydrazides **76–78**, it is possible to synthesize pyrrole, pyrazole, triazole heterocyclic systems;
- employing the acetyl group of thiazole cycle enables the synthesis of hydrazone and chalcone derivatives;
- the hydrazinolysis of each ester group of ethyl 2-[*N*-(4-hydroxyphenyl)-*N*-(3-methoxy-2-methyl-3-oxopropyl)amino]-4-methylthiazole-5-carboxylate **(50)** proceeds differently. In this reaction, the methyl ester group is characterized by a higher reaction rate, comparing with ethyl ester moiety attached to the heterocyclic ring;
- the methine group of the functionalized thiazole cycle is sufficiently reactive to participate in the condensation reactions with formaldehyde or aromatics aldehydes for the formation of functionalized bis(thiazol-5-yl)methanes **129–133** or bis(thiazol-5-yl)phenylmethanes **107–124**, **(126–128)a**.

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

- *Mycobacterium luteum* have been found to be sensitive to thiazole and bis(thiazol-5-yl)phenylmethane derivatives. The most active of them were 3-{*N*-(4-[4-fluorophenyl]thiazol-2-yl)-*N*-(4-methylphenyl)amino}propanoic acid **(54a)**, 3-{*N*-(4-[4-nitrophenyl]thiazol-2-yl)-*N*-(4-methylphenyl)amino}propanoic acid **(57a)**, and 3,3'-[(4-chlorophenyl)methylene]bis{*N*-[4-(4-cianophenyl)-1,3-thiazole-5,2-diyl]-*N*-(4-methylphenyl)amino}propanoic acid **(112)**;
- the best antifungal properties against *S. tenuis* showed thiazolone and thiazole derivatives 3-{*N*-[5-(2-methoxy-2-oxoethylidene)-4-oxo-4,5-dihidrothiazol-2-yl]-*N*-(4-methylphenyl)amino}propanoic acid **(29a)**, 3-{*N*-[4-(2-ethoxy-2-oxoethyl)thiazol-2-yl]-*N*-(4-methylphenyl)amino}propanoic acid **(31a)**, 3-{*N*-[4-(chloromethyl)thiazol-2-yl]-*N*-(4-methylphenyl)amino}propanoic acid **(33a)**, and 3-{*N*-[4-(phenylaminomethyl)thiazol-2-yl]-*N*-(4-methylphenil)amino}propanoic acid **(35a)**;
- the introduction of the (2-isonicotinylhydrazone)methyl moiety at the 5th position of the thiazole ring containing 4-(4-chlorophenyl) substituent greatly increases the spectrum of biological activity of 2,4,5-trisubstututed thiazole derivatives.

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REZIUMĖ

Dabartiniu metu didėja sergamumas įvairiomis ligomis, vis dažniau sergama sunkesnėmis jų formomis, taigi būtinas esamų vaistų tobulinimas modifikuojant jų struktūrą. Šioje srityje itin didelį potencialą turi penkianariai ir šešianariai heterocikliniai junginiai ir jų dariniai. Jie dalyvauja svarbiuose biocheminiuose procesuose, vykstančiuose gyvuosiuose organizmuose, taip užtikrindami normalias gyvybines funkcijas. Ypač didelės reikšmės turi sintetiniai tiazolo dariniai, pasižymintis plačiu biologinio veikimo spektru. Jų pagrindu sukurti vaistai naudojami medicininėje praktikoje gydant hipertenziją, Alzheimerio ligą, diabetą, šizofreniją, alergijas, vėžinius, bakterinius susirgimus. Tiazofurinas – sintetinis tiazolo darinys, naudojamas kaip vaistas vėžiui gydyti; šiuo metu tyriami jo stereoizomerai, galintys pasižymėti minėtu aktyvumu [1]. Be to sukurta daug svarbių žemės ūkio sektoriuje naudojamų fungicidų ir herbicidų, kurių struktūroje yra aminotiazolo fragmentai.

Daug biologiškai aktyvių junginių turi *β*-alanino fragmentą ir tai leidžia juos panaudoti farmacijoje svarbiems preparatams kurti. Žinduoliuose aptinkami karnozinas ir anserinas naikina laisvuosius radikalus. Tai peptidai, sintetinami žinduolių organizmuose, padedantys palaikyti pastovų dirbančių raumenų pH ir aktyvinti raumenų miozino fermentą. Viena svarbiausių vaistinių preparatų klasių, turinčių *β*-alanino fragmentą, yra *β*-laktaminiai antibiotikai. Grybuose *Paecilomyces marquandii* sintetinamas antibiotikas leucinostatinas D. Penicilinas, vienas pirmųjų ir iki dabar plačiai naudojamų antibiotikų, yra kilęs iš *Penicillium* pelėsių. Išskirtinai didelė bakteriostatinė šios medžiagos geba ir mažas toksiškumas neatsitiktinai randa itin platų pritaikymą medicininėje praktikoje ir farmacijoje. Pastaruoju metu gamtoje atrasti penicilinai yra modifikuojami laboratorinėmis sąlygomis, siekiant sustiprinti jų antibiotines savybes ir padidinti aktyvumą prieš vis labiau prie antibiotikų prisitaikančių bakterijų. 1998 m. iš *Cystobacter fuscus* bakterijos buvo išskirtas cistotiazolas A ir jo penki metabolitai, vadinami Cistotiazolais B-F, kurie pasižymi stipriu poveikiu prieš grybelius *Candida albicans* [2, 3]. Trichotiazolas A išskirtas iš cianobakterijos *Trichodesmium*, pasižymėjo citotoksiniu poveikiu [4].

Jau keli dešimtmečiai Kauno technologijos universiteto, Organinės chemijos katedroje, vykdomi *N*-pakeistų aminorūgščių ir jų darinių, jų heterociklizacijos produktų sintezė ir tyrimai. Nustatyta, kad *N*-pakeistų aminorūgščių dariniai pasižymi antimikrobiniu, priešvėžiniu ir augalų augimą skatinančiu poveikiu. *N*-pakeistosios-*β*-aminorūgštys panaudojamos sintetinant azetidino, chinolino, imidazolo, piridino, pirimidino, benzodiazepino darinių.

Darbo tikslas

Susintetinti naujus įvairiai funkcionalizuotus *N*-(naftalen-1-il)-*N*-tiazolil-*β*-alaninus ir *N*-(4-metilfenil)-*N*-tiazolil-*β*-alaninus, bei jų darinius, nustatyti susintetintų junginių struktūrą, chemines ir biologines savybes.

Tikslui pasiekti buvo iškelti šie uždaviniai:

1. Ištirti *N*-(4-metilfenil)-*N*-tiokarbomoil-*β*-alanino ir *N*-(naftalen-1-il)-*N*-tiokarbomoil-*β*-alanino ciklizacijos reakcijas su įvairiais *α*-halogenkarboniliniais junginiais, ir, pasinaudojus gautos metileninės grupės reaktyvumu, ištirti gautų naujų junginių kondensacijos reakcijas su aromatiniais ir heterocikliniais aldehidais.
2. Ištirti 3-[*N*-(4-metilfenil)-*N*-(1,3-tiazol-2-il)amino]propano rūgščių ir 3-[*N*-(naftalen-1-il)-*N*-(1,3-tiazol-2-il)amino]propano rūgščių bei 3-[*N*-(4-metilfenil)-*N*-(4-okso-4,5-dihidrotiazol-2-il)amino]propano rūgščių ir 3-[*N*-(naftalen-1-il)-*N*-(4-okso-4,5-dihidrotiazol-2-il)amino]propano rūgščių heterociklinio žiedo chemines savybes, nustatyti susidarančių produktų struktūrą.
3. Pasinaudojus 3-[*N*-(4-metilfenil)-*N*-(4-ariltiazol-2-il)amino]propano rūgščių karboksigrupės funkcinėmis savybėmis, atlikti jų modifikaciją ir susintetinti 3-[*N*-(4-metilfenil)-*N*-(4-ariltiazol-2-il)amino]propanoatus bei 3-[*N*-(4-metilfenil)-*N*-(4-ariltiazol-2-il)amino]propanhidrazidus, ištirti jų kondensacijos reakcijas su diketonais ir fenilizotiocianatu.
4. Ištirti dalies susintetintų junginių antibakterines ir priešgrybelines savybes, siekiant nustatyti biologinio aktyvumo priklausomybę nuo junginio struktūros.

Darbo mokslinis naujumas ir praktinė reikšmė

Pirmą kartą *N*-(4-metilfenil)-*N*-tiokarbamoil-*β*-alaninas ir *N*-(naftalen-1-il)-*N*-tiokarbamoil-*β*-alaninas panaudotas 4,5-dihidrotiazolo, tiazolo, kondensuotų tiazolo ciklą molekulėje turinčių junginių sintezėje. Ištirtos 3-[*N*-(4-metilfenil)-*N*-(4-okso-4,5-dihidrotiazol-2-il)amino]propano ir 3-[*N*-(naftalen-1-il)-*N*-(4-okso-4,5-dihidrotiazol-2-il)amino]propano rūgščių cheminės savybės ir nustatyta, kad dihidrotiazolono žiedas neatsparus stipriai šarminei terpei, tačiau atsparus rūgštims, o su aromatiniais ir heterocikliniais aldehidais sudaro *Z* konfigūracijos atitinkamus 5-benziliden-4,5-dihidro-4-oksotiazolus. Nustatyta, kad, vykdant etil- 2-[*N*-(4-metilfenil)-*N*-(3-metoksi-2-metil-3-oksopropil)amino]-4-metiltiazol-5-karboksilato hidrazinolizę, kiekvienos esterinės grupės hidrazinolizė vyksta nevienareikšmiai. Ir iš etil 2-[*N*-(4-metilfenil)-*N*-(3-metoksi-2-metil-3-oksopropil)amino]-4-metiltiazol-5-karboksilato galima selektyviai gauti mono- ar dihidrazidą. Tai sudaro galimybę sintetinti įvairios struktūros junginius, išnaudojant vieną ar abu hidrazininius fragmentus. Pasinaudojus metino grupės, esančios tiazolo cikle, reaktyvumu ir

vykdant kondensacijos reakcijas su aldehidais, gauti polifunkcionalizuoti bis(tiazol-5-il)fenilmetanai ir bis(tiazol-5-il)metanai. Remiantis susintetintų aminotiazolų antibakterinių tyrimų duomenimis, nustatyti nauji aminotiazolo dariniai, pasižymintys ryškiu baktericidiniu aktyvumu. Atlikti darbai sudaro galimybę planuoti ir praplėsti biologiškai veiklių medžiagų tikslinės sintezės metodologiją, išplėsti tiksliosios organinės sintezės reagentų įvairovę.

Ginamieji teiginiai:

1. *N*-(4-metilfenil)-*N*-tiokarbamoil-*β*-alaninas ir *N*-(naftalen-1-il)-*N*-tiokarb-amoil-*β*-alaninas yra patogūs tarpiniai junginiai įvairiai funkcionalizuotoms tiazolo heterosistemoms sintetinti.

2. Pasinaudojus 3-[*N*-(4-metilfenil)-*N*-(4-ariltiazol-2-il)amino]propano rūgščių hidrazidų funkcinėmis savybėmis, parodyta galimybė sintetinti hidrazonus, pirolo, pirazolo, triazolo heterociklines sistemas, tiazolo žiede esančią acetilgrupę panaudoti hidrazonams bei chalkonams sintetinti, o tiazolo cikle esančią metino grupę – polifunkcionalizuotų bis(tiazol-5-il)fenilmetanų ir bis(tiazol-5-il)metanų sintezėje.

3. Etil-2-[*N*-(4-metilfenil)-*N*-(3-metoksi-2-metil-3-oksopropil)amino]-4-metil-tiazol-5-karboksilato hidrazinolizės produktai suteikia galimybę sintetinti įvairios struktūros junginius, panaudojant vieną ar abu hidrazininius fragmentus.

IŠVADOS

1. Ištirtos *N*-(4-metilfenil)-*N*-tiokarbamoil-*β*-alanino **4a** ir *N*-(naftalen-1-il)-*N*-tiokarbamoil-*β*-alanino **4b** reakcijos su *α*-halogenkarbonilinias junginiais ir nustatyta, kad reakcijoje su monochloracto rūgštimi susidaro 3-[*N*-(4-metilfenil)-*N*-(4-okso-4,5-dihidro-1,3-tiazol-2-il)amino]propano **(6a)** ir 3-[*N*-(naftalen-1-il)-*N*-(4-okso-4,5-dihidro-1,3-tiazol-2-il)amino]propano **(6b)** rūgštys. Tuo tarpu reakcijose su *α*-halogenketonais susidaro atitinkamos 3-[*N*-(4-metilfenil)-*N*-(4-alkil- ar ariltiazol-2-il)amino]propano **29a**, **30**, **31a**, **33a**, **(36–39)a**, **(53–57)a** ir 3[*N*-(nafalen-1-il)-*N*-(4-alkil- ar ariltiazol-2-il)amino]propano rūgštys **29b**, **31b**, **33b**, **(36–39)b**, **(58–65)b**.

2. Ištirus 3-[*N*-(4-metilfenil)-*N*-(4-okso-4,5-dihidro-1,3-tiazol-2-il)amino]propano **(6a)** ir 3-[*N*-(naftalen-1-il)-*N*-(4-okso-4,5-dihidrotiazol-2-il)amino]propano **(6b)** rūgščių chemines savybes nustatyta, kad:

- dihidrotiazolono žiedas neatsparus stipriai šarminei terpei, tačiau atsparus mineralinėms rūgštims.
- reaguojant heterociklinio žiedo metileninei grupei su aromatiniais ir heterocikliniais aldehidais, susidaro *Z* konfigūracijos 5-benziliden-4,5-dihidro-4-oksotiazolai.

3. Ištirtos įvairiai funkcionalizuotų 3-[*N*-(4-metilfenil)-*N*-(1,3-tiazol-2-il)amino]propano 38a, **(53–57)a** ir 3-[*N*-(naftalen-1-il)-*N*-(1,3-tiazol-2-il)amino]propano rūgščių 38b, **(58–64)b** bei jų darinių cheminės savybės ir nustatyta, kad:

- 3-[*N*-(4-metilfenil)-*N*-(4-ariltiazol-2-il)amino]propano rūgščių hidrazidai **76–78** yra patogūs sintonai pirolo, pirazolo, triazolo heterociklinių sistemų formavimui.
- tiazolo žiede esanti acetilgrupė sudaro galimybę sintetinti hidrazonų ir chalkonų klasės junginius.
- vykdant etil-2-{*N*-[3-metoksi-2-metil-3-oksopropil]-*N*-(4-metilfenil)amino}-4-metil-1,3-tiazol-5-karboksilato **(50)** hidrazinolizę, kiekvienos esterinės grupės hidrazinolizė vyksta nevienareikšmiai. Aminorūgšties metilesteris pasižymi didesniu reaktingumu lyginant su etilesterine grupe esančią heterocikliniame žiede;
- funkcionalizuoto tiazolo cikle esanti reaktyvi metino grupė dalyvauja kondensacijos reakcijose su formaldehidu ir aromatiniais aldehidais, atitinkamai susidarant funkcionalizuotiems bis(tiazol-5-il)metanams **129–133** arba bis(tiazol-5-il)fenilmetanams **107–124**, **(126–128)a**.

4. Ištirtos dalies susintetintų junginių antibakterinės savybės ir nustatyta, kad:

- antibakteriniu aktyvumu prieš *M. luteum* pasižymėjo tiazolo bei bis(tiazol-5-il)fenilmetano dariniai. Aktyviausi iš jų – 3-{*N*-[4-(4-fluorfenil)-1,3-tiazol-2-il]-*N*-(4-metilfenil)amino}propano rūgštis **(54a)**, 3-{*N*-[4-(4-nitrofenil)-1,3-tiazol-2-il]-*N*-(4-metilfenil)amino}propano rūgšti**s (57a)** ir 3,3'-[(4-chlorfenil)metilen]bis{*N*-[4-(4-cianofenil)-1,3-tiazol-5,2-diil]-*N*-(4-metilfenil)amino}propano rūgštis **(112)**.
- geriausiu priešgrybeliniu poveikiu prieš *S. tenuis* pasižymėjo tiazolono bei tiazolo dariniai –3-{*N*-[5-(2-metoksi-2-oksoetiliden)-4-okso-4,5-dihidro-1,3-tiazol-2-il]-*N*-(4-metilfenil)amino}propano rūgštis **(29a)**, 3-{*N*-[4-(2-etoksi-2-oksoetil)-1,3-tiazol-2-il]-*N*-(4-metilfenil)amino}propano rūgštis **(31a)**, 3-{*N*-[4-(chlormetil)-1,3-tiazol-2-il]-*N*-(4-metilfenil)amino}propano rūgštis **(33a)** ir 3-{*N*-[4-(fenilaminometil)-1,3-tiazol-2-il]-*N*-(4-metilfenil)amino}propano rūgštis **(35a)**.
- Į tiazolo žiedo, turinčio 4-(4-chlorfenil) pakaitą, 5-padėtį įvedus (2-izonikotinoilhidrazon)metil fragmentą, stipriai išplėčiamas 2,4,5-tripakeistų tiazolo darinių biologinio aktyvumo spektras.

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