Synthesis and Antimicrobial Activity of New 3-Allyl-1,3-Thiazolidin-4-Ones

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Key words: *synthesis; thiazolidin-4-one; antibacterial activity; antifungal activity.*

Summary. *Background and Objective. Heterocycles are one of the most important compounds in organic chemistry. Growing attention has been paid to the derivatives of thiazole, which are biologically important compounds and are useful antimicrobial and antifungal agents. Because of the structure of 1,3-thiazolidin-4-one, it is possible to obtain new biologically active compounds by introducing substitutes at various positions of 1,3-thiazolidin-4-one ring. By incorporating nitrofuran as a pharmacophore into 5 position of 4-thiazolidone ring and allyl group into 3 position, new compounds having antimicrobial activity were expected to be designed.*

Material and Methods. New compounds were synthesized in several steps: synthesis of 4-allylthiosemicarbazide, then addition of aldehyde to obtain semicarbazone, and synthesis of 3-allyl-1,3-thiazolidin-4-one ring. Furaldehyde, 5-nitrofuraldehyde, and 5-nitro-2-furylacroleine was used as pharmacophores. Antimicrobial (antifungal) activity was tested in vitro in Mueller-Hinton agar against standard bacteria cultures – Staphylococcus aureus ATCC 25923, Enterococcus faecalis ATCC 29212, Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853, Klebsiella pneumoniae ATCC 33499, Proteus mirabilis ATCC 12459, Bacillus subtilis ATCC 6633, and Bacillus cereus ATCC 8035 – and standard fungal culture – Candida albicans ATCC 60193.

Results. The results of microbial activity showed that all new compounds could be characterized as antimicrobial and antifungal agents. None of the tested compounds showed activity against Pseudomonas aeruginosa. The minimum bactericidal concentration varied in the range of 1–250 μg/mL. The compounds with the nitro group in their structure showed a higher antimicrobial and antifungal activity.

Conclusion. Five new derivatives of 3-allyl-1,3-thiazolidin-4-one with antimicrobial and antifungal activity were synthesized.

Introduction

Heterocycles are one the most important compounds in organic chemistry. Among them, sulfur- and nitrogen-containing heterocyclic compounds have been the focus of interest among researchers because of their biological activities (1–5). Many heterocyclic compounds are natural compounds that can also be formed by biosynthesis. In the important group of heterocyclic compounds, a growing interest is given to the thiazole derivatives, especially after the identification thiazole ring in the structures of some active compounds. The derivatives of thiazolidine are biologically important compounds and are useful antimicrobial and antifungal agents (6–8). Since the beginning of the 20th century, people have been interested in them as potential drugs (9–13). The structure of 1,3-thiazolidin-4-one allows obtaining new biologically active compounds by introducing substitutes into various positions of 1,3-thiazolidin-4-one ring. The most reactive positions of 4-thiazolidone molecule are 2, 3, and 5, which determine the major directions of heterocycle modification (6, 14). The methylene group at 5-position of 4-thiazolidones is active enough; therefore, most of modification reactions of the 4-thiazolidone ring are carried out at this position. After substitution of the carbonyl group to 5-position of 4-thiazolidones, it is possible to obtain bioactive compounds (15–19). Nitrofurans are active agents against gram-negative and gram-positive bacteria, including *Salmonella*. Their activity against bacteria that are resistant to sulfanylamides and other antibiotics is well known.

The derivatives of nitrofurans have broad-spectrum antimicrobial and antifungal activities and slow growing microbial resistance (2, 15, 20, 21), but their application in clinical practice is becoming more rare because of their high toxicity and a

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large number of side effects (20). Allyl isothiocyanate comes from the seeds of black mustard (*Brassica nigra*); it serves the plant as a defense against herbivores. Synthetic allyl isothiocyanate is used as an insecticide, bactericide, and nematocide (21). By incorporating nitrofuran as a pharmacophore into 5-position of 4-thiazolidone ring and allyl group into 3-position, new compounds having antimicrobial activity were expected to be designed.

The aim of this study was to synthesize the new derivatives of 3-allyl-1,3-thiazolidin-4-one, having 2-furaldehyde and its derivatives, to analyze their structure, and to determine their antimicrobial activity.

Materials and Methods

Equipment

New compounds were synthesized at the Department of Drug Chemistry, Lithuanian University of Health Sciences. All reactions were monitored by the thin layer chromatography (Merck Kieselgel 60 F254). Melting points were determined with a Kofler melting point apparatus. Elemental analyses were performed using a Gerhardt Vapodest 20 (nitrogen) analyzer and by the Schoniger method. Infrared (IR) spectra were recorded on a Spektrum 100 FT-IR (PerkinElmer) spectrometer. Purity was checked at the Department of Analytical and Toxicological Chemistry, Lithuanian University of Health Sciences, by high-performance liquid chromatography (HPLC) with the separation system Waters 2695 and photodiode array detector Waters 996.

Synthesis

The method of synthesis and structure of new compounds was chosen according to literature data (16, 22–27).

General Procedure A. Synthesis of the intermediate compounds (1a-c) – 1-(furan-2-ylmethylidene) amino-3-(prop-2-en-1-yl)thiourea (1a), 1-((5-nitrofuran-2-yl)methylidene)amino-3-(prop-2-en-1-yl)thiourea (1b), and 1-(3-(5-nitrofuran-2-yl)prop-2-en-1-ylidene)amino-3-(prop-2-en-1-yl)thiourea (1c) – is shown in Fig. 1. Hydrazine hydrate (2 mol) was dissolved in anhydrous ethanol (200 mL), and allyl isothiocyanate (2 mol), dissolved in anhydrous ethanol (100 mL), was added into the solution by slow stirring. Reaction temperature was 0°C–5°C. After some time, a white precipitate appeared. The corresponding pure compounds were obtained by filtration. 4-Allylthiosemicarbazide was dissolved in anhydrous ethanol (50 mL) by heating and stirring, and the appropriate aldehyde (0.125 mol) dissolved in anhydrous ethanol (50–100 mL) was added into the solution by slow stirring. After being refluxed for 30 min, the reaction mixture was cooled to room temperature, and then the precipitate appeared. The corresponding pure compounds were obtained by filtration. For some special cases, the target compounds were purified by recrystallization from n-propanol.

General Procedure B. Synthesis of the 3-allyl-1,3-thiazolidin-4-ones (2a-e) – (2-[2-(furan-2-ylmethylidene) hydrazin-1-ylidene]-3-(prop-2-en-1-yl)-1,3-thiazolidin-4-one (2a), 5-(furan-2-ylmethylidene)-2-[2-(furan-2-ylmethylidene)hydrazin-1-ylidene]-3-(prop-2-en-1-yl)-1,3-thiazolidin-4-one (2b), 2-[2-[(5-nitrofuran-2-ylmethylidene] hydrazin-1-ylidene]-3-(prop-2-en-1-yl)-1,3-thiazolidin-4-one (2c), 5-[(5-nitrofuran-2-yl) methylidene]-2-[2-[(5-nitrofuran-2-yl)methylidene]hydrazin-1-ylidene]-3-(prop-2-en-1-yl)-1,3-thiazolidin-4-one (2d), and 2-[2-[3-(5-nitrofuran-2-yl) prop-2-en-1-ylide-ne]hydrazin-1-ylidene]-3-(prop-2-en-1-yl)-1,3-thiazolidin-4-one (2e)) is shown in Fig. 2. The appropriate semicarbazone (0.01 mol), chloracetic acid (0.02 mol), and anhydrous potassium acetate (0.03 mol) were dissolved in methanol (5–10 mL) or n-propanol (30 mL) or n-butanol (30 mL).

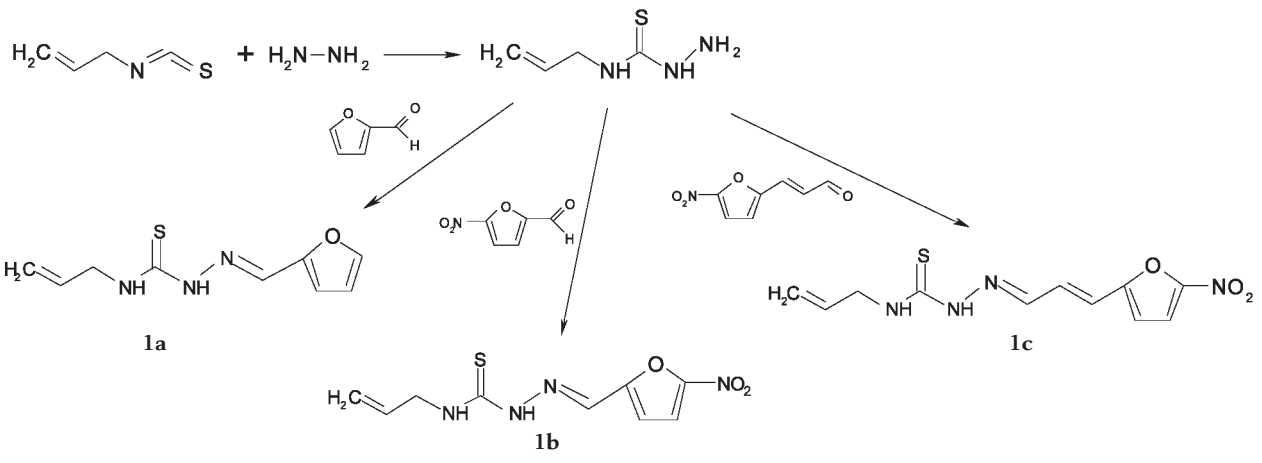


Fig. 1. Synthesis of the intermediate compounds

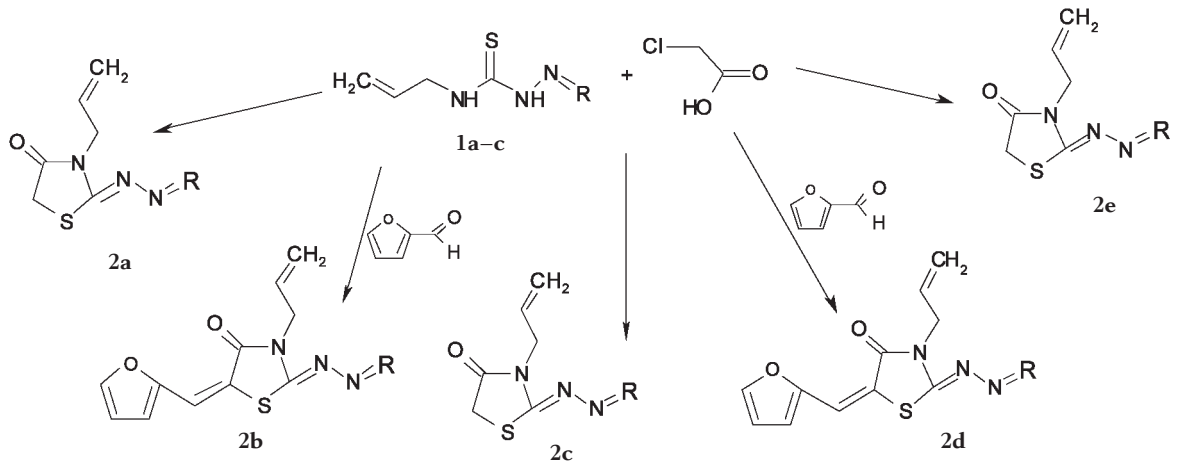


Fig. 2. Synthesis of the new derivatives of 3-allyl-1,3-thiazolidin-4-ones

After heating for 1.5–2 hours, the aldehyde was added, and reaction mixture was refluxed for 1.5 hours. After this, the mixture was filtrated and cooled to room temperature, and then the appearance of precipitate was documented. The corresponding pure compounds (derivatives of 3-allyl-1,3-thiazolidin-4-one) were obtained by filtration.

Determination of Antimicrobial Activity

Experiments on antimicrobial activity were carried out at the Department of Microbiology, Lithuanian University of Health Sciences.

Antimicrobial Susceptibility Testing. Antimicrobial activity was tested in vitro in Mueller-Hinton agar (Mueller-Hinton II agar, BBL, Cockeysville, USA). Antimicrobial activity of new compounds (2a-e) was tested against standard bacteria cultures – *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 33499, *Proteus mirabilis* ATCC 12459, *Bacillus subtilis* ATCC 6633, and *Bacillus cereus* ATCC 8035 – and standard fungal culture – *Candida albicans* ATCC 60193.

Preparation of Standard Microorganism Cultures. Standard bacteria and fungal cultures were cultivated for 20–24 h on Mueller-Hinton agar at 35°C–37°C. Bacterial and fungal suspensions were prepared from the cultures cultivated in physiological solution adjusted to the turbidity of a 0.5 McFarland standard.

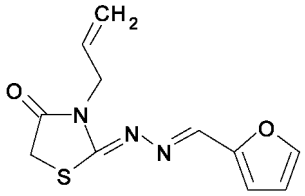
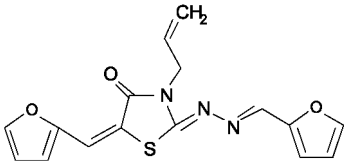
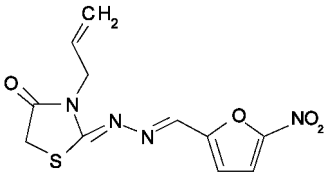
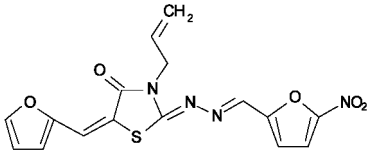
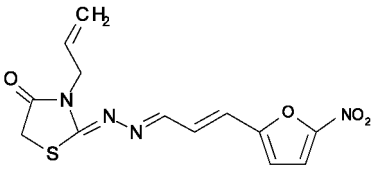
Preparation of Solutions of Test Compounds. The test compounds were dissolved in dimethyl sulfoxide (20 mg/mL) and then diluted to obtain the final concentration ranging from 1 to 1000 μg. The diluted solutions were mixed with 10 mL of Mueller-Hinton agar. Petri plates were incubated for 20–24 hours at 35°C–37°C. The minimum concentration of antimicrobial (antifungal) compound that prevents any growth of tested bacteria (fungi) was indicated as minimum bactericidal (fungicidal) concentration (MBC).

Results

All new compounds were successfully synthesized. The structures of new compounds were confirmed by elemental analysis (quantity of nitrogen and sulfur in each compound was determined) and IR spectra (wave numbers of some specific groups were indicated). All characteristic data (formula, yield, melting point, quantity of nitrogen and sulfur) are shown in Table 1; the data for structure confirmation (wave numbers) are shown in Table 2.

Synthesis of the intermediate compounds was performed in two steps: synthesis of 4-allylthiosemicarbazide and synthesis of allylsemicarbazone. First, 4-allylthiosemicarbazide was obtained. The compound was purified from ethanol by recrystallization. The yield of this reaction was 75%–77%. The melting point of 97°C–98°C was determined (ethanol). The appropriate semicarbazones were obtained by refluxing the mixture of 4-allylthiosemicarbazide and appreciate aldehyde for 30 min. The yield of products ranged from 74% to 91%. The highest yield was obtained for the compound 1c containing 5-nitro-2-furylacrylaldehyde (91.4%). The compounds with the nitro group (1b, 1c) had higher melting points (1b, 180°C–182°C; 1c, 185°C–187°C). Synthesis of the derivatives of 3-allyl-1,3-thiazolidin-4-one was carried out in alcohols. The reaction mixture was heated at constant temperature of 80°C. For the synthesis of compounds 2a, 2c, and 2e, all the components were heated for 1.5–2 hours. For the synthesis of compounds 2b and 2d, all the components, except aldehyde, were heated for 1.5 hours, and then aldehyde was added and refluxed for 1.5 hours.

Table 1. Characteristics of New Compounds

Compound		Yield %	Melting Point °C	Elemental Analysis Calculated/ Found, %	
No.	Formula			N	S
2a		92.2	86–88 (hexane)	16.86/16.82	12.86/12.85
2b		68.2	85–90 (hexane)	12.84/12.82	9.80/9.78
2c		85	155–156 (n-propanol)	19.04/19.00	10.90/10.91
2d		59.1	158–160 (n-propanol)	15.05/15.02	8.61/8.59
2e		87.5	158–160 (n-propanol)	17.49/17.52	10.01/10.05

The results of microbial activity showed that all new compounds could be characterized as antimicrobial and antifungal agents. The data on antibacterial and antifungal activity are shown in Table 3.

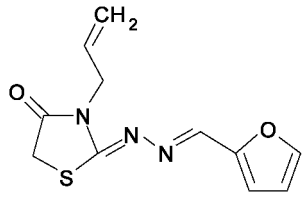
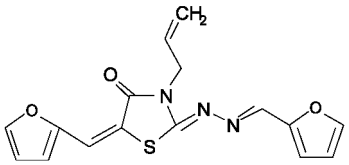
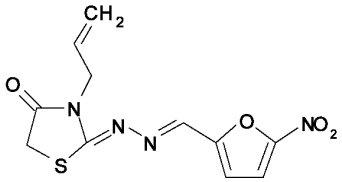
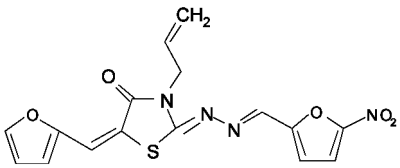
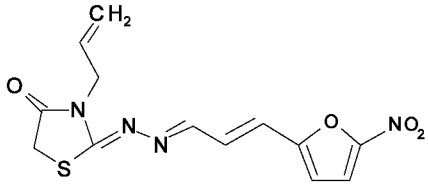
Compounds with the nitro group in their structure showed a higher antimicrobial and antifungal activity. None of the tested compounds showed activity against *Pseudomonas aeruginosa* (MBC, >1000 μg/mL), and only one compound (2e) showed low activity against *Klebsiella pneumoniae* (MBC, 800 μg/mL). The compounds 2c, 2d, and 2e showed high activity against *Staphylococcus aureus* (MBC, <1 μg/mL), *Escherichia coli* (MBC, <1 μg/mL), *Enterococcus faecalis* (MBC, 1–50 μg/mL), and *Candida albicans* (MBC, 1–25 μg/mL).

Structure-Activity Relationship. It should be noted that the compound 2e was found to be the most active of test compounds against the microbial cultures tested. The compound 2e having an additional double bond in the side chain of a molecule was more active against *Enterococcus faecalis* up to 50 times, but had the same antifungal activity against *Candida albicans* as the compound 2c. The compounds with the nitro group in their structure (2c, 2d, and 2e) showed a higher antimicrobial and antifungal activity. Comparison of the structure and activity of compounds 2a and 2c revealed that by incorporating the nitro group into the structure (2c), activity against bacteria was 2 (*Bacteria subtilis*) to 500 (*Staphylococcus aureus*) times higher.

Discussion

Synthesis of the intermediate and final compounds was performed according to literature data (16, 22–27). 4-Allylthiosemicarbazide is chemically classified as a derivative of thiourea (6) and can be synthesized by condensation reaction, using alcohol as a solvent (6, 14, 15, 27). Our experiments showed that the use of ethanol was optimal because of solubility of initial products and better yields

Table 2. Data of Spectral Analysis

Compound	Wave Number, cm^{-1}				
	C=O Group	C=N Group	CH_2 Group	–CH= Group	NO_2 Group
	1715	1545	2933	701	–
	1716	1544	–	880	–
	1720	1542	2925	710	1569
	1720	1542	–	890	1568
	1715	1543	–	901	1558

of final products. As the reaction is exothermic, components were dissolved separately and mixed by slow stirring. The reaction was carried out at 0°C–5°C temperature (other authors recommended 0°C±5°C temperature) (2). For the synthesis of semicarbazones, it is recommended in the literature to use alcohol as a solvent and refluxing for 15–30 min (6, 10, 11, 15, 27). Our results showed that refluxing the mixture of 4-allylthiosemicarbazide and appreciate aldehyde for 30 min, a yield of not less than 70% may be achieved. The amount of solvent (ethanol) depends on nature of aldehyde. The solubility of furaldehyde is better than that of 5-nitro-2-furaldehyde and 5-nitro-2-furylacrylaldehyde; therefore, the amount of solvent was 50 mL and 100 mL, respectively. Synthesis of the derivatives of 3-allyl-1,3-thiazolidin-4-one was carried out in alcohols. The solvents and amount of them were chosen according to the solubility of initial compounds (1a-c), nature of aldehydes, and better yields of final products. For the synthesis of compounds 2a, 2c, and 2e, all components were heated for 1.5–2 hours. For synthesis of compounds 2b and 2d, all components, except aldehyde, were heated for 1.5 hours, and then aldehyde was added and refluxed for 1.5 hours. According to the literature data, after addition of aldehyde, it is recommended to heat for 15–30 min (2, 3, 9, 22, 24), but our experiment showed that heating for 1.5–2 hours was optimal for getting better yield and purer final compound.

For microbiological analysis of synthesized compounds, various microorganisms were chosen considering their different structural features. Since *Candida* species are predominant mycotic pathogens, the activity of synthesized compounds was

Table 3. Data of Antibacterial and Antifungal Activity

	Microorganism	Compound				
		2a	2b	2c	2d	2e
Minimum bactericidal/fungicidal concentration, μg/mL	*Staphylococcus aureus* ATCC 25923	>500	250	<1	<1	<1
	Enterococcus faecalis ATCC 29212	>500	>500	50	50	<1
	Escherichia coli ATCC 25922	150	200	<1	<1	<1
	Klebsiella pneumoniae ATCC 27853	>500	>500	>500	>500	>500
	Pseudomonas aeruginosa ATCC 27853	>500	>500	>500	>500	>500
	Bacillus cereus ATCC 8035	500	250	250	200	250
	Bacillus subtilis ATCC 6633	250	>500	100	250	250
	Proteus mirabilis ATCC 12459	250	250	250	300	250
	Candida albicans ATCC 60193	250	250	<1	25	<1

tested against the standard *Candida albicans* culture. According to the literature data, antimicrobial activity requires the 5-nitro group, while substitutions may be made in aldehydes at the 2 position (28). Our results have shown that addition of the nitro group (compound 2c) increased antimicrobial activity, but compounds without the 5-nitro group (2a, 2b) showed antimicrobial activity as well. Comparison of our compounds with the earlier synthesized and known derivatives of nitrofurans revealed their higher activity against *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae* than it was reported in previous similar investigations (28).

Conclusions

Five new derivatives of 3-allyl-1,3-thiazolidin-4-one were synthesized. Structure of all the compounds was confirmed by determination of elemental composition and infrared spectra. All synthesized compounds showed antimicrobial and antifungal activity; the compounds containing a nitro group (2c, 2d, and 2e) showed higher activity. The compound 2e showed the highest activity against the tested microorganisms compared with other synthesized and known compounds.

Statement of Conflict of Interest

The authors state no conflict of interest.

Naujų 3-alil-1,3-tiazolidin-4-ono darinių sintezė ir antimikrobinis aktyvumas

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Raktažodžiai: sintezė, tiazolidin-4-onas, antibakterinis aktyvumas, priešgrybelinis aktyvumas.

Santrauka. *Įvadas.* Heterociklai yra vieni svarbiausių junginių organinėje chemijoje. Iš heterociklinių junginių labiausiai domimasi tiazolo dariniais, kurie yra biologiškai aktyvūs ir vartojami kaip antimikrobiniai ir priešgrybeliniai vaistai. Dėl dėkingos 1,3-tiazolidin-4-ono struktūros, įterpiant skirtingus pakaitus į įvairias padėtis, galima gauti naujų biologiškai veiklių junginių. Įterpdami nitrofurano darinius, kaip farmakoforus, į tiazolidin-4-ono ciklo 5 padėtį ir alilo grupę į 3 padėtį, tikėjomės gauti naujus antimikrobinius junginius.

Tyrimo medžiaga ir metodai. Nauji junginiai sintezuoti keliais etapais: 4-aliltiosemikarbazido sintezė ir aldehido prijungimas; 3-alil-1,3-tiazolidin-4-ono žiedo sintezė. Furfurolas, 5-nitrofurfurolas ir 5-nitro-2-furilakroleinas buvo naudojami kaip farmakoforai. Antimikrobinis (priešgrybelinis) aktyvumas buvo tiriamas *in vitro* Mueller-Hinton agare su standartinėmis bakterijų kultūromis: *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 33499, *Proteus mirabilis* ATCC 12459, *Bacillus subtilis* ATCC 6633, *Bacillus cereus* ATCC 8035 ir standartine grybų kultūra: *Candida albicans* ATCC 60193.

Rezultatai. Antimikrobinis tyrimas parodė, kad visi nauji junginiai gali būti charakterizuojami kaip antimikrobiniai ir priešgrybeliniai junginiai. Nė vienas iš tirtų junginių nebuvo aktyvus prieš *Pseudomonas aeruginosa*. Nustatyta minimali baktericidinė koncentracija yra 1–250 μg/ml. Junginiai, kurių struktūroje buvo nitro grupė, pasižymėjo didesniu antimikrobiniu ir priešgrybeliniu aktyvumu.

Išvada. Susintezuoti penki nauji 3-alil-1,3-thiazolidin-4-ono dariniai, turintys antimikrobinį ir priešgrybelinį aktyvumą.

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