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New thiazolidones-4 with sulfamethizole-2 substituent as potential antifungal and antimicrobial preparations

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The growing number of semi-synthetic penicillin analogues and other antibiotics known to have the chemical structure of classic antimicrobial drugs (such as sulfonamides), as well as the increasingly pressing problem of bacterial resistance urged us to investigate new sulfanilamide derivatives. Therefore, it is of therapeutic interest to design compounds containing three or more pharmacophores in their molecule. The initial 5-substituted-2-methylmercaptothiazolidin-4-ones were subjected to S-demethylation to yield 2-aminosubstituted thiazolidinones. As pharmacophoric amino or aldehyde group containing compounds, sulfamethizole, nitrofuran aldehydes and nitrobenzene aldehydes have been used. Antimicrobial (antifungal) activity of the new compounds was screened *in vitro* in the following bacterial cultures: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Klebsiella pneumoniae* ATCC 33499 and fungal cultures: *Candida albicans ATCC* 60193, *Candida glabrata, Candida krusei, Candida kefyr* ATCC 8614, *Candida tropicalis* ATCC 8302, *Candida parapsilosis.* The results have shown that, statistically, the new compounds are significantly more effective as antimicrobial agents than the initial preparations. Their minimal inhibitory concentration (MIC) varies in the range 50–750 μg/ml and is 1.5 to 8 times higher than susceptibility of the initial compound. N-4 substituted sulfanilamide groups were not only effective against numerous gram-positive and some gram-negative bacteria, but also a spectrum of action against fungi has been discovered. The obtained results allowed to separate a promising group of potential antiinfectives possessing a higher antimicrobial and antifungal activity against some fungi and microbes than the initial compound.

Key words: antifungal agents, antimicrobial agents, sulfanilamides, nitrofurans, synthesis of new drugs, antimicrobial susceptibility, antifungal susceptibility, nitrofural, sulfamethizole

INTRODUCTION

Incidences of fungal infections have increased over the last two decades, with *Candida* as the predominant mycotic pathogen [1, 2]. Serious invasive fungal infections represent an increasing threat to human health. The species *Candida* produces a broad range of infections varying from superficial illnesses to life-threatening diseases [3]. There have been remarkable advances in medical practice during the past two decades. Medical achievements saved lives of some severely ill patients, but, on the other hand, we there appeared a population of patients with an increased risk of developing infectious diseases [1]. In the recent years, because of overzealous use of antibacterial antibiotics, the use of imunossupressors, cytotoxins, opportunistic mycoses has become prominent.

To combat the increasing number of fungal pathogens and the growing problems of resistance, new antifungal compounds are required [4].

The market of antifungal agents still continues growing due to several factors: 1) an increase in the number of people living in an immunocompromised state which makes them more susceptible to fungal infections; 2) fungi are becoming increasingly resistant to standard therapies; 3) many of the standard therapies are highly toxic and / or cause serious adverse events which require more efficacious antifungals [5–7]. For the above reasons, drug chemistry specialists and pharmacologists spare no effort to discover and investigate new biologically active antimicrobial substances. A growing number of semi-synthetic penicillin analogues and other antibiotics known to have the chemical structure of classic antimicrobial drugs (such as sulfanilamides), as well as an increasingly pressing problem of bacterial resistance urged us to investigate new sulfanilamide derivatives.

For a number of years, the Department of Pharmaceutical Chemistry of Kaunas University of Medicine has investigated new sulfanilamide compounds obtained by substituting the para-amino group with heterocycles, such as thiazole derivatives, which have antimicrobial pharmacophores [8, 9]. The selection of such antimicrobial pharmacophores rests on our idea to investigate new compounds that have advantages vis-à-vis the initial products. Nevertheless, the search for a more potent antibacterial alternatives is still a real challenge. The higher antimicrobial activity may be also related to different mechanisms of action.

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Mutschler and Derendorf [10] review the development of research when it comes to the investigation of the mechanism of sulfonamide action. This mechanism explains why antibacterial activity disappears in case the aromatic amino group nitrogen (N^4) is substituted. This is because sulfonamides with a free amino function can competitively block the incorporation of *p*-aminobenzoic acid into the folic acid molecule.

Sources tell that nitrofurans, compared to sulfanilamides, possess a range of positive properties. They enhance phagocytosis and have little probability of developing bacterial resistance to these compounds because of various and different mechanisms of action [11]. Irrespective of all the facts mentioned above, the use of nitrofurans in clinical practice is becoming rarer because of their relatively high toxicity and a large number of side effects [12]. By incorporating pharmacologically active nitrofuran pharmacophores and sulfanilamide pharmacophores in one molecule we expected both to preserve the advantages of antimicrobial preparations and to diminish their disadvantages.

Our aim was to study the influence of sulfanilamides and nitrogroup-containing pharmacophores on the antimicrobial (antifungal) activity of thiazolidine derivatives. Therefore, it is of therapeutic interest to design and produce compounds containing three or more pharmacophores in one molecule.

MATERIALS AND METHODS

General

New sulfanilamide derivatives (2a, 2b, 2c, 2d, 2e) were synthesized at the Department of Pharmaceutical Chemistry of Kaunas University of Medicine.

Melting points were determined on a Kofler apparatus with a microscope. IR spectra were recorded in cm^{-1} for KBr pellets on a SPECORD M80 spectrophotometer. 1H-NMR spectra were recorded on a Bruker AM 300 spectrometer using DMSO-d^6 as a solvent and TMS as the internal reference standard. Chemical shifts are expressed in δ ppm. The purity of compounds was routinely checked by TLC using precoated silica gel plates (Kieselgel 0.25 mm, 60G F254, Merck, Germany). Spots were detected under UV (254 nm). Elemental analysis was performed at the Pharmaceutical Department of Jagiellonian University (Krakow, Poland).

Microbiological experiments were carried out at the Department of Microbiology, Kaunas University of Medicine.

Chemistry

General procedure A. *Synthesis of 5-substituted 2-methylmercaptothiazolidin-4-ones (1a-e).* To a solution of 2-methylrhodanine (1.47 g, 0.0 mol) in concentrated acetic acid (10 ml) appropriate aldehyde (0.01 mol) was added (Scheme 1). Ammonium acetate was used as a catalyst. The reaction mixture was stirred for 1 h at 60 °C. After cooling, the solid was filtered, off washed with acetic acid, then with ether and dried. The crude product was crystallized from acetic acid.

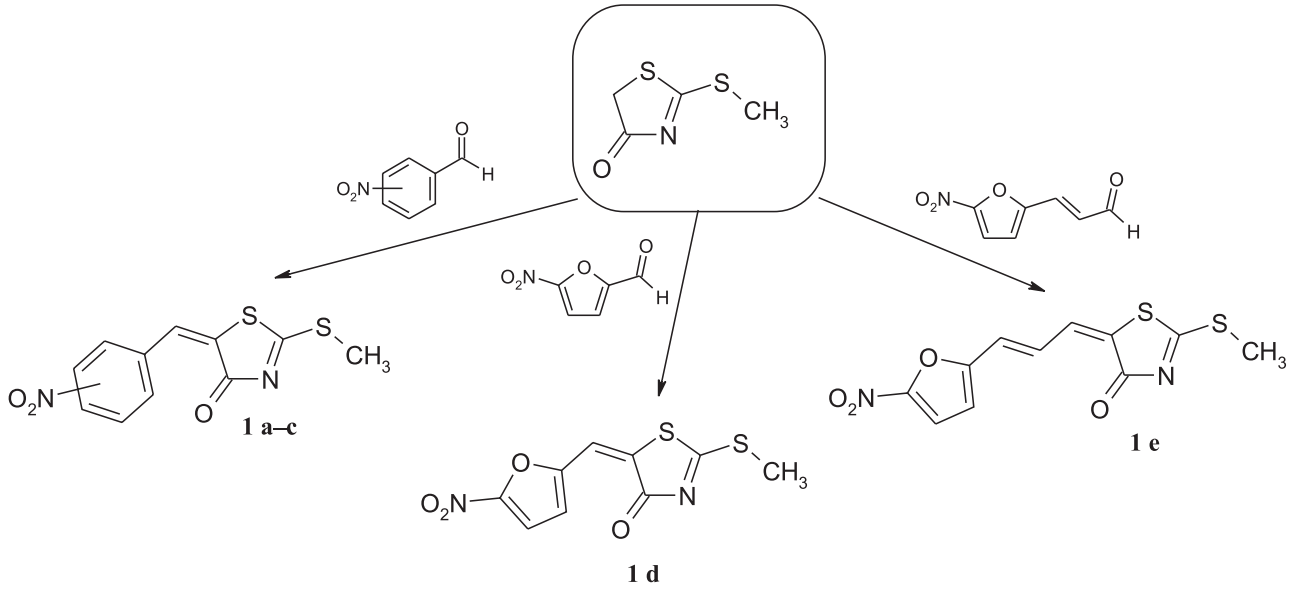
General procedure B (Scheme 2). A mixture of sulfamethizole (0.01 mol) and solution of appropriate 5-substituted 2-methylmercaptothiazolidin-4-one in acetic acid (2b, 2d) or 1-butanol (2a, 2e) or a mixture of 1-butanol and dimethylsulfoxide (2c) was heated at 90 °C from 1 h to 5 h. The hot suspension was filtered and recrystallized. All reactions proceeded smoothly with a good yield.

Synthesis of N-(5-methyl-1,3,4-thiadiazol-2-yl)-4-{[5-(2-nitrobenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino}benzenesulfonamide (2a)

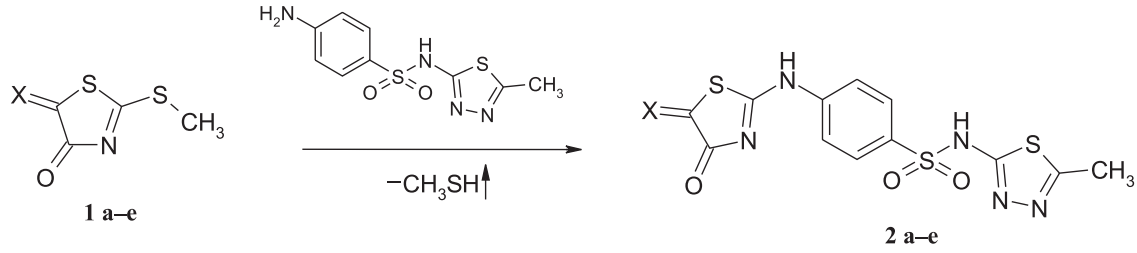
A mixture of sulfamethizole (2.7 g, 0.01 mol) and a solution of 1a (1.4 g, 0.005 mol) in 1-butanol (30 ml) was heated for 2 h at 90 °C. The solid obtained was filtered off, washed with ethanol, dried and crystallized from a mixture of acetic acid-dimethylsulfoxide (4:1).

Synthesis of N-(5-methyl-1,3,4-thiadiazol-2-yl)-4-{[(5-(3-nitrobenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino}benzenesulfonamide (2b)

A mixture of sulfamethizole (2.7 g, 0.01 mol) and a solution of 1b (1.4 g, 0.005 mol) in acetic acid (30 ml) was heated for 1.5 h



Scheme 1. Synthesis of 5-substituted 2-methylmercaptothiazolidin-4-ones



Scheme 2. Synthesis of new compounds 2 a–e

at 90 °C. The solid obtained was filtered, washed with acetic acid and ether, dried and crystallized from a mixture of 2-butanol-dimethylformamide (5:3).

Synthesis of N-(5-methyl-1,3,4-thiadiazol-2-yl)-4-(5-(4-nitrobenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)benzenesulfonamide (2c)

A mixture of sulfamethizole (2.7 g, 0.01 mol) and a solution of 1c (1.4 g, 0.005 mol) in a mixture of 1-butanol and dimethylsulfoxide (50 ml, 4:1) was heated for 5 h at 90 °C. The solid obtained was filtered off, washed with ethanol, dried and crystallized from a mixture of acetic acid and dimethylsulfoxide (4:1).

Synthesis of N-(5-methyl-1,3,4-thiadiazol-2-yl)-4-(5-((5-nitrofuran-2-yl)methylene)-4-oxo-4,5-dihydrothiazol-2-ylamino)benzenesulfonamide (2d)

A solution of sulfamethizole (2.7 g, 0.01 mol) and 1d (1.35 g, 0.005 mol) in acetic acid (35 ml) was heated for 1 h at 90 °C. The solid obtained was filtered off, washed with acetic acid, ether, dried and crystallized from acetic acid.

Synthesis of N-(5-methyl-1,3,4-thiadiazol-2-yl)-4-((E)-5-(3-(5-nitrofuran-2-yl)allylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino)benzenesulfonamide (2e)

A mixture of sulfamethizole (5.4 g, 0.02 mol) and a solution of 1e (1.5 g, 0.005 mol) in 1-butanol (40 ml) was heated for 1 h at 90 °C. The solid obtained was filtered off, washed with ethanol, dried and crystallized from a mixture of acetic acid-dimethylsulfoxide (4:1).

Antimicrobial activity

Microbiological experiments were conducted with both new and comparison preparations (antimicrobial compound – sulfamethizole). The antimicrobial activity of the nitrofuran derivative – nitrofural (furacilin) – was determined at the Department of Microbiology of Kaunas University of Medicine in our previous research [9].

Antimicrobial susceptibility tests. Antimicrobial and antifungal susceptibility was tested *in vitro* using a serial broth dilution technique (in Mueller–Hinton broth II, BBL, Cockeysville, USA). Antimicrobial activity of new compounds (2 a–e) and sulfanilamide (sulfamethizole) was tested *in vitro* in the standard bacterial cultures *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Klebsiella pneumoniae* ATCC 33499 and fungal cultures *Candida albicans* ATCC 60193, *C. glabrata, C. krusei, C. kefyr* ATCC 8614, *C. tropicalis* ATCC 8302, *C. parapsilosis.*

Preparation of standard microorganism cultures. Standard cultures of the nonsporic bacteria *Staphylococcus aureus, Escherichia coli* and *Klebsiella pneumoniae* were cultivated for 20–24 hours at a temperature of 35–37 °C in Mueller–Hinton Agar (Mueller-Hinton II Agar, BBL, Cockeysville, USA). A bacterial suspension was prepared from cultivated bacterial cultures in physiological solution according to the 0.5 McFarland turbidity standard.

The standard culture of sporic bacteria *Bacillus cereus* was cultivated for 7 days at a temperature of 35–37 °C in Mueller–Hinton II Agar. After the sporic bacteria culture had grown, it was washed away from the surface of the broth with sterile physiological solution, and the prepared suspension was heated for 30 min at a temperature of 70 °C and diluted till the concentration of spores in 1 ml ranged from 10×10^6 to 100×10^6. Sporic suspension can be kept for a long time at a temperature below 4 °C.

The standard fungal cultures: *Candida albicans, C. glabrata, C. krusei, C. kefyr, C. tropicalis* and *C. parapsilosis* were cultivated for 20–24 hours at 30 °C in Mueller-Hinton Agar (Mueller-Hinton II Agar, BBL, Cockeysville, USA). A fungal suspension was prepared from cultivated fungal cultures in physiological solution according to the turbidity standard 0.5 McFarland.

Preparation of compounds for microbiological analysis. The main solution of the new compounds (VIL-1, VIL-2, VIL-3) and the comparison compound (sulfamethizole) (20000 μg/ml) was prepared in dimethylsulfoxide because of its slight solubility in other solvents. Then 0.6, 1.25, 2.5, 5, 10, 15.6, 31.25, 62.5, 125, 250, 500, 750, 1000 μg/ml dilutions were carried out under aseptic conditions by transferring the necessary amount of a solution with a sterile pipette into other tubes filled with 2 ml of Mueller–Hinton broth.

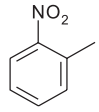
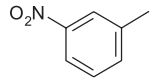
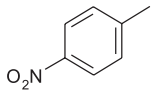
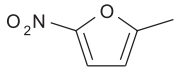
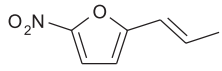
The minimal dilution, i. e. the lowest concentration of the investigative and the comparison compounds that inhibit the growth of bacteria, was determined by the first tube in a series that inhibited the visible growth, – it was the minimal inhibitory concentration (MIC).

The minimal bactericidal (fungicidal) concentration, defined as the minimal concentration of antimicrobial (antifungal) compound that prevented any growth of the test microorganisms (fungi), was determined by subculturing a MIC broth tube without visible growth to Mueller–Hinton agar and incubating for 20–24 h at 35–37 °C (for bacteria) and 30 °C (for fungi).

RESULTS AND DISCUSSION

All the new compounds were successfully synthesized. The structure of the new compounds (2 a–e) were confirmed by elemental analysis and spectral data (IR, NMR). All characterisation data on the new compounds are presented in Table 1.

Table 1. **Characterization data of compounds 2 a–e**

Compd No.	X	M. p. (°C)	Mol. formula (Mr)	Elemental analysis Calcd. / found (%)				Spectral data	
				C	H	N	S	1H NMR (DMSO-d^6, δ ppm)	IR (KBr) (cm^{-1})
2a		297–298	$C_{19}H_{14}N_6O_5S_3$ (502.55)	45.41 44.99	2.81 2.90	16.72 16.22	19.14 19.28	2.48 (s, 3H, CH_3), 7.10–7.25 (m, 1H, ArH), 7.60–7.95 (m, 7H, ArH, =CH), 8.16 (dd, 2 and 9Hz, 1H, ArH), 12.70 (br s, 1H, NH), 13.90 (br s, 1H, NH)	3236 (NH), 1676 (C = O), 1596, 1548 (NO_2)
2b		286–287	$C_{19}H_{14}N_6O_5S_3$ (502.55)	45.41 45.47	2.81 2.92	16.72 16.62	19.14 19.32	2.47 (s, 3H, CH_3), 7.10–7.53 (m, 1H, ArH), 7.71–8.02 (m, 6H, ArH), 8.23–8.48 (m, 2H, ArH), 12.58–13.70 (m, 2H, NH)	3259, 3201 (NH), 1670 (C = O), 1594, 1505 (NO_2)
2c		274–276	$C_{19}H_{14}N_6O_5S_3$ (502.55)	45.41 45.52	2.81 2.77	16.72 16.72	19.14 19.69	2.48 (s, 3H, CH_3), 7.10–7.31 (m, 1H, ArH), 7.69–8.01 (m, 6H, ArH), 8.27–8.45 (m, 2H, ArH), 12.6–13.6 (m, 2H, NH)	3417, 3146 (NH), 1673 (C = O), 1589, 1555 (NO_2)
2d		298–300	$C_{17}H_{12}N_6O_6S_3$ (492.51)	41.46 41.48	2.46 2.79	17.06 16.87	19.53 19.78	2.46 (s, 3H, CH_3), 7.18–7.29 (m, 3H, ArH), 7.56–7.64 (m, 1H, ArH), 7.74 (s, 1H, =CH), 7.80 (dd, 2 and 9Hz, 2H, ArH), 7.91 (br s, NH)	3268, 3200 (NH), 1676 (C = O)
2e		324–326	$C_{19}H_{14}N_6O_6S_3$ (519.55)	44.01 43.97	2.72 2.82	16.21 15.98	18.55 19.02	2.47 (s, 3H, CH_3), 6.95–7.27 (m, 5H, ArH, =CH), 7.43 (d, 12Hz, 1H, =CH), 7.73 (d, 4Hz, 1H, ArH), 7.84 (dd, 2 and 9Hz, 2H, ArH)	3144 (NH), 1672 (C = O), 1588, 1544 (NO_2)

Aldehydes react with 2-methylrhodanine upon heating in acetic acid at 60 °C. Boiling made reactions go faster but the yields of products were lower, most likely because 2-methylrhodanine decomposed. As a catalyst, ammonium acetate was used because higher yields were obtained in this case.

Duration of reaction depended on the nature of the aldehyde. Reactions with nitrofuran derivatives were going faster (by forming compounds 1d and 1e); it was enough to heat these compounds with 2-methylrhodanine for 0.5 h. Reactions with nitrobenzaldehydes were going slower (with forming 1 a–c); in these cases the reaction mix had to be heated for 1 h. The latter compounds are better soluble in acetic acid compared to compounds having a nitrofuran cycle in their structure, so the reaction mixture of compounds 1 a–c was cooled in an ice bath for a longer time (4 h). Reaction yields also differed (76–91%) depending on the nature of the aldehyde. The yield of reaction between 2-nitrobenzaldehyde and 2-methylrhodanine was the lowest (76%).

Reactions of sulfamethizole derivatives were going in 1-butanol, acetic acid or 1-butanol and dimethylsulfoxide mixture. A solvent was chosen according to the solubility of the initial compounds 1 a–e. The reaction mixture was heated at a constant 90 °C temperature because at a higher temperature the reaction products decomposed. The process of reaction was monitored using a lead acetate indicator. Reaction yields of all sulfamethizole derivatives were rather high, especially of those having nitrofuran aldehyde moiety in the fifth position of thiazolidine cycle (80–91%). Reaction duration depended on 5-substituted 2-(methylthio)thiazol-4(5*H*)-one used for synthesis and ranged within 1–5 h. Upon taking a double excess of sulfamethizole, the reaction was going faster, but the excretion of the reaction product was more complicated.

For microbiological analysis of the synthesized compounds, bacteria *Staphylococcus aureus* (gram-positive bacterium), *Escherichia coli* (gram-negative bacillus), *Bacillus subtilis* (sporic bacterium) and *Kl. pneumoniae* (capsule-forming bacterium) were chosen considering their different structural peculiarities.

According to the literature, *Candida* are predominant mycotic pathogens [1], so the activity of the synthesized

Table 2. **Antimicrobial and antifungal activity of new compounds**

		Compound	2a	2b	2c	2d	2e	Sulfamethizole
MIC, µg/ml	Antibacterial data	*Staphylococcus aureus* ATCC 25923	250.0 ± 19.6	250.0 ± 20.0	500.0 ± 48.8	125.0 ± 8.9	62.5 ± 4.7	500.0 ± 48.9
		Escherichia coli ATCC 25922	500.0 ± 42.1	500.0 ± 49.2	500.0 ± 46.8	250.0 ± 19,1	125.0 ± 9.0	1000.0 ± 90.4
		Bacillus subtilis ATCC 6633	250.0 ± 18.1	250.0 ± 20.0	500.0 ± 45.4	125.0 ± 9.1	62.5 ± 5.0	100.0 ± 9.3
		Klebsiella pneumoniae ATCC 33499	750.0 ± 70.7	750.0 ± 66.4	500.0 ± 48.9	750.0 ± 65.4	500.0 ± 49.1	1000.0 ± 89.1
	Antifungal data	Candida albicans	50.0 ± 4.0	62.5 ± 4.8	62.5 ± 4.9	62.5 ± 4.6	50.0 ± 2.5	250.0 ± 18.3
		Candida glabrata	62.5 ± 4.8	125.0 ± 8.6	125.0 ± 8.1	62.5 ± 4.8	125.0 ± 8.4	250.0 ± 19.7
		Candida krusei	62.5 ± 5.0	125.0 ± 8.6	125.0 ± 10.0	62.5 ± 4.7	125.0 ± 7.4	500.0 ± 49.7
		Candida kefyr ATCC 8614	62.5 ± 4.4	125.0 ± 8.8	125.0 ± 8.1	62.5 ± 5.0	125.0 ± 3.8	250.0 ± 19.1
		Candida tropicalis ATCC 8302	62.5 ± 5.1	62.5 ± 4.7	62.5 ± 4.9	125 ± 8.5	125.0 ± 8.2	250.0 ± 19.1
		Candida parapsilosis	250.0 ± 18.6	250.0 ± 19.4	125.0 ± 9.0	250.0 ± 17.4	50.0 ± 4.3	250.0 ± 18.5
MBC, µg/ml	Antibacterial data	Staphylococcus aureus ATCC 25923	1000.0 ± 86.7	1000.0 ± 85.0	1000.0 ± 86.0	1000.0 ± 88.7	1000.0 ± 92.8	1000.0 ± 90.0
		Escherichia coli ATCC 25922	1000.0 ± 95.9	1000.0 ± 88.7	1000.0 ± 91.3	1000.0 ± 90.0	1000.0 ± 90.6	1000.0 ± 95.2
		Bacillus subtilis ATCC 6633	1000.0 ± 90.4	1000.0 ± 85.0	1000.0 ± 92.0	1000.0 ± 90.4	1000.0 ± 90.0	1000.0 ± 91.4
		Klebsiella pneumoniae ATCC 33499	1000.0 ± 88.2	1000.0 ± 88.8	1000.0 ±90.5	1000.0 ± 89.1	1000.0 ± 84.4	1000.0 ± 89.0
	Antifungal data	Candida albicans	500.0 ± 48.5	250.0 ± 18.0	1000.0 ± 94.8	500.0 ± 48.6	500.0 ± 42.9	1000.0 ± 86.7
		Candida glabrata	125.0 ± 8.4	250.0 ± 17.8	500.0 ± 46.5	62.5 ± 4.8	125.0 ± 8.4	1000.0 ± 94.5
		Candida krusei	500.0 ± 47.4	500.0 ± 49.0	750.0 ± 62.8	62.5 ± 4.7	125.0 ± 7.4	1000.0 ± 49.8
		Candida kefyr ATCC 8614	500.0 ± 47.0	1000.0 ± 93.8	500.0 ± 44.5	62.5 ± 5.0	750.0 ± 64.7	1000.0 ± 97.5
		Candida tropicalis ATCC 8302	500.0 ± 45.5	500.0 ± 48.4	500.0 ± 47.3	500.0 ± 48.5	125.0 ± 8.2	1000.0 ± 95.6
		Candida parapsilosis	1000.0 ± 93.7	1000.0 ± 93.6	1000.0 ± 98.5	500.0 ± 47.3	125.0 ± 7.5	500.0 ± 48.9

compounds was investigated against several *Candida* species: *Candida albicans, C. glabrata, C. kefyr, C. krusei, C. parapsilosis* and *C. tropicalis*.

Data on the antifungal and antimicrobial activity of the new compounds (2 a–e) are presented in Table 2.

Statistical analysis of the results showed that the antifungal and antimicrobial properties of compounds 2a–e were significantly more effective than those of the initial preparation sulfamethizole. All the new compounds, except 2e, demonstrated a lower activity against sporic bacteria (*Bacillus subtilis*) in comparison with sulfamethizole. It is important to note that the activity of the new sulfamethizole derivatives was different. A compound that contains a nitrofurilalilidene group in its structure (2e) is more active than others against bacteria. The same principle of the structure–activity relationship was observed in our previous research [9]. Considering this fact, it can be presumed that an additional double bond in the above-mentioned group enhances antibacterial properties. Compounds containing a nitrofuran component in their structure (2d and 2e) were more active against bacteria as compared with nitrobenzene substituent containing derivatives (2 a–c). 2e was the most active of all new sulfanilamide derivatives. *In vitro,* its effect on the test microorganisms was 2 to 8 times higher in comparison to the initial compound (sulfamethizole). The minimal activity was shown by the new compound 2c.

Though nitrobenzene substituent containing compounds show a similar activity against bacteria *in vitro*, a nitro group in the ortho or meta position of the benzene ring enhances activity of such compounds.

However, different principles could be applied to structure–antifungal activity of the test compounds 2 a–e. Compound 2a was most active against the *Candida* spp tested. It should be

noted that compounds without an additional double bond in the nitrofuran component (2d) is more active against *C. glabrata, C. krusei* and *C. kefyr* but less active against *C. albicans* and *C. parasilosis* compared to compounds containing a nitrofurilalilidene group in its structure (2e). It can be presumed that introduction of these different nitrofuran substituents into the fifth position of thiazolidine ring exerts a different influence on antifungal activity against different fungi. Nevertheless, more detailed experiments are required in this case.

It should be noted that the nitro group in ortho position of the benzene ring in nitrobenzene substituent remarkably enhances activity of sulfamethizole derivatives against all the tested *Candida* species *in vitro*.

The new compounds are bacteriostatic and fungistatic at lower concentrations, but bactericidal and fungicidal at higher concentrations.

The obtained results could contribute to designing more active antimicrobial compounds having a thiazole cycle in their structure.

CONCLUSIONS

• New compounds 2 a–e are characterised by a higher antifungal and antimicrobial activity *in vitro* than the initial sulphanilamide preparation.

• New sulphanilamide derivatives (2 a–e) are 1.5 to 8 times more effective against standard gram-positive and gram-negative bacteria *in vitro*.

• New sulphanilamide derivatives (2 a–e) are 2 to 8 times more effective against *Candida* species *in vitro.*

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SULFAMETIZOLIO PAKAITĄ TURINTYS NAUJI TIAZOLIDONAI-4 – POTENCIALŪS PRIEŠGRYBELINIAI IR ANTIMIKROBINIAI VAISTAI

Santrauka

Augantis pusiau sintetinių penicilinų ir kitų antibiotikų, turinčių „klasikinių" priešmikrobinių junginių struktūrinių elementų, skaičius, taip pat vis didėjanti bakterinio rezistentiškumo problema paskatino mus kurti naujus sulfanilamidų darinius. Be to, siekėme sintezuoti junginius, kurių struktūroje yra trys ir daugiau farmakoforų. Pradiniai junginiai – 5-substituoti-2-metilmerkaptotiazolidin-4-onai – buvo S-demetilinti ir sintezuoti 2-aminosubstituoti tiazolidonai. Kaip farmakoforai, turintys amino ar aldehido grupę, panaudoti sulfametizolis, nitrofurano ir nitrobenzeno aldehidai. Antimikrobinis (priešgrybelinis) naujų junginių aktyvumas nustatytas *in vitro* su šiomis mikroorganizmų kultūromis: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Klebsiella pneumoniae* ATCC 33499, taip pat grybelių kultūromis: *Candida albicans* ATCC 60193, *Candida glabrata, Candida krusei, Candida kefyr* ATCC 8614, *Candida tropicalis* ATCC 8302, *Candida parapsilosis*. Nustatyta, kad naujų junginių priešmikrobinis aktyvumas yra statistiškai patikimai didesnis, palyginus su pradiniais junginiais. Minimali inhibicinė koncentracija (MIC) svyruoja 50–750 μg/ml ir yra nuo 1,5 iki 8 kartų mažesnė už pradinių medžiagų. N-4 substituoti sulfanilamidai buvo aktyvesni ne tik prieš gramteigiamas ir gramneigiamas bakterijas, bet ir prieš grybelius. Remiantis gautais rezultatais būtų galima išskirti perspektyvią potencialių antiinfekcinių junginių grupę, pasižyminčią didesniu priešmikrobiniu ir priešgrybeliniu aktyvumu.