

Synthesis and Antimicrobial Properties of Naphthylamine Derivatives Having a Thiazolidinone Moiety

Vilma Petrikaitė^{1,2}, Eduardas Tarasevičius¹, Alvydas Pavilonis³

¹Department of Drug Chemistry, Medical Academy, Lithuanian University of Health Sciences,

²Department of Biothermodynamics and Drug Design, Institute of Biotechnology, Vilnius University,

³Department of Microbiology, Medical Academy, Lithuanian University of Health Sciences, Lithuania

Key words: antifungal activity; antimicrobial activity; naphthylamine; nitrofurans; thiazolidinone; synthesis of new drugs.

Summary. Objective. The aim of this study was to evaluate the influence of pharmacophores having naphthylamine and nitro groups on the antimicrobial (antibacterial and antifungal) activity of thiazolidinone derivatives.

Materials and Methods. The initial 5-substituted-2-methylmercaptothiazolidin-4-ones were subjected to S-demethylation to yield 2-amino-substituted thiazolidinones. 4-Nitro-1-naphthylamine, nitrofurans aldehydes, and nitrobenzene aldehydes were used as pharmacophoric compounds having amino or aldehyde groups. Antimicrobial (antibacterial and antifungal) activity of the new compounds was tested *in vitro* against bacterial cultures – *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Klebsiella pneumoniae* – and fungal cultures – *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida kefyr*, *Candida tropicalis*, and *Candida parapsilosis*.

Results. Microbiological analysis showed that all new thiazolidinone derivatives with nitronaphthylamine substituent possessed antibacterial and antifungal properties. New compounds 2a-b showed similar antibacterial activity *in vitro* against *S. aureus* and *B. subtilis* as aminopenicillins. The lowest antibacterial activity of all newly synthesized compounds was against capsule-forming bacteria *K. pneumoniae* and against gram-negative bacteria *E. coli* (minimum inhibitory concentration range, 500–1000 µg/mL).

Conclusions. The minimum inhibitory concentration of naphthylamine derivatives varied in the range of 0.4–1000 µg/mL, and activity of some newly synthesized compounds was similar to the activity of aminopenicillins and fluconazole, an antifungal preparation. Based on the results, it is possible to separate the perspective group of potential antimicrobial compounds.

Introduction

The incidence of fungal infections has increased over the last two decades, and *Candida* spp. have been reported as predominant mycotic pathogens (1). In recent years, because of excessive use of antibacterial antibiotics, immunosuppressors, and cytotoxins, opportunistic mycoses become prominent. To combat the increasing number of fungal pathogens and the growing burden of resistance, new antifungal compounds are required (2); therefore, new, more active or better-tolerated compounds are being developed (3–5).

Recently, there has been growing concern of rapidly increasing resistance of bacteria to the antibacterial preparations in markets. Although at present many and various drugs are used for the treatment of infections, more effective and safe preparations are still missing (6–8).

For a number of years, the Department of Drug Chemistry, the Lithuanian University of Health Sci-

ences, has investigated new thiazolidinone derivatives, which are obtained by substituting the second position with an amine moiety, such as sulfanilamides or other amines, which have antimicrobial pharmacophores (9–11). The selection of such antimicrobial pharmacophores was determined by our idea to investigate new compounds that have advantages *vis-à-vis* initial products. Nevertheless, search for a more potent antibacterial alternative is still a challenge.

Thiazole derivatives as potential drugs were taken into account at the beginning of the 20th century, and nowadays, this interest renewed again (12). The structure of rhodanine (2-thioxo-4-thiazolidinone) is convenient due to chemical properties: into different positions of thiazolidine cycle by introduction of various substituents, it is possible to get chemical compounds having different biological activity (13, 14).

Nitrofurans possess a range of positive proper-

Correspondence to V. Petrikaitė, Department of Drug Chemistry, Medical Academy, Lithuanian University of Health Sciences, A. Mickevičiaus 9, 44307 Kaunas, Lithuania
E-mail: vilma.petrikaite@med.kmu.lt

Adresas susirašinėti: V. Petrikaitė, LSMU MA Vaistų chemijos katedra, A. Mickevičiaus 9, 44307 Kaunas
El. paštas: vilma.petrikaite@med.kmu.lt

ties: they enhance phagocytosis and bacteria rarely develop resistance to these compounds, which is related to various and different mechanisms of action (15). Irrespective of all the facts mentioned above, nitrofurans are used less frequently in clinical practice because of their relatively high toxicity and a large number of side effects (16). By incorporating pharmacologically active nitrofurans and naphthylamine pharmacophores in one molecule, we expected both to preserve the advantages of antimicrobial preparations and to diminish their disadvantages.

The aim of this study was to evaluate the impact of pharmacophores having naphthylamine and nitro groups on the antimicrobial (antibacterial and antifungal) activity of thiazolidinone derivatives. Therefore, it is a therapeutic interest to develop and obtain compounds containing three or more pharmacophores in one molecule.

Materials and Methods

New naphthylamine derivatives (2a-c) were synthesized at the Department of Drug Chemistry, Lithuanian University of Health Sciences (former Kaunas University of Medicine).

Melting points were determined on a Kofler apparatus with microscope. The IR spectra were recorded in cm^{-1} for KBr pellets on a SPECORD M80 spectrophotometer. $^1\text{H-NMR}$ 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).

Chemistry

The synthesis of 5-substituted 2-methylmercaptothiazolidin-4-ones (1a-c) is shown in Fig. 1. The appropriate aldehyde (0.01 mol) was added to solution of 2-methylrhodanine (1.47 g, 0.01 mol) in concentrated acetic acid (10 mL). Ammonium acetate was used as a catalyst. The reaction mixture was stirred for 1 hour at 60°C . After cooling, the solid obtained was filtered, washed with acetic acid, then with ether, and dried. The pure product was crystallized from acetic acid.

The synthesis of 5-((5-nitrofuran-2-yl)methylene)-2-(4-nitronaphthalene-1-ylamine)thiazol-4(5H)-one (2a), 5-(3-(5-nitrofuran-2-yl)allylidene)-2-(4-nitronaphthalene-1-ylamine)thiazol-4(5H)-one (2b), and N-(5-methyl-1,3,4-thiadiazol-2-yl)-4-(5-(4-nitrobenzylidene)-4-oxo-4,5-dihydrothiazol-2-ylamino) benzenesulfonamide (2c) is shown in Fig. 2.

A mixture of 4-nitro-1-naphthylamine (2.82 g, 0.015 mol) and solution of appropriate 5-substituted 2-methylmercaptothiazolidin-4-one in acetic acid (0.01 mol) were heated for 2.5 hours at 90°C . Hot suspension was filtered, washed with acetic acid, dried, and crystallized from a mixture of 2-butanoldimethylformamide (3:2). All reactions gave a moderate yield.

In Vitro Antimicrobial Activity

Antimicrobial activity of newly synthesized compounds was determined at the Department of Microbiology, the Lithuanian University of Health Sciences (former Kaunas University of Medicine).

Antimicrobial Susceptibility Testing. Antibacterial 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 (2a-c) was tested in vitro

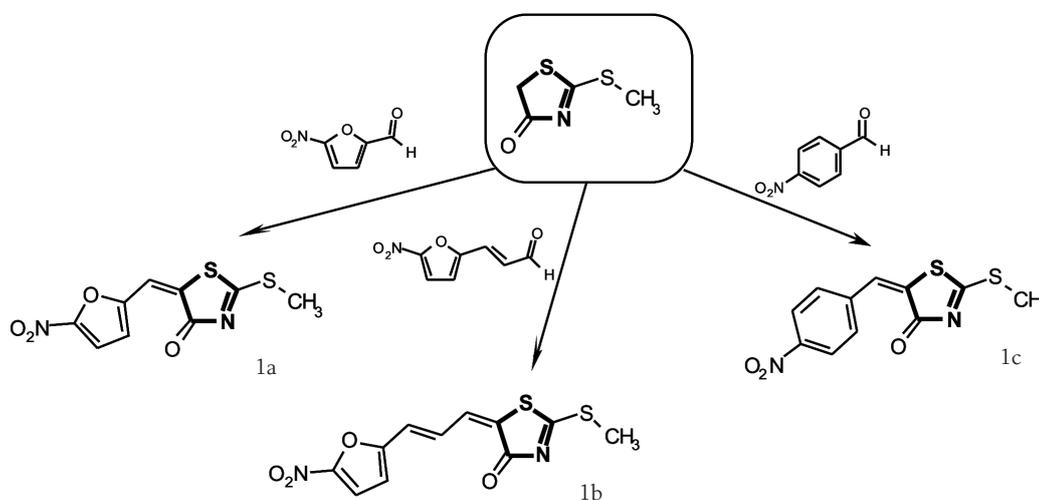


Fig. 1. Synthesis of 5-substituted 2-methylmercaptothiazolidin-4-ones

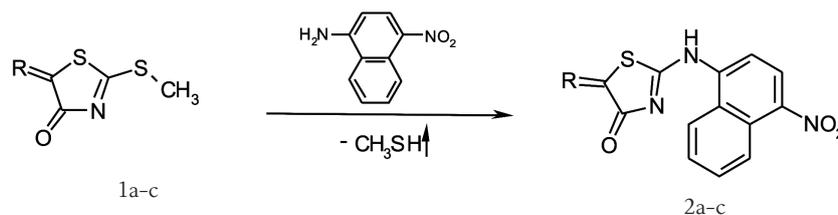


Fig. 2. Synthesis of new compounds 2a-c

in 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, and *C. parapsilosis*.

Preparation of Standard Microorganism Cultures. Standard cultures of non-spore-forming bacteria – *S. aureus*, *E. coli*, and *K. pneumoniae* – were cultivated for 20–24 hours at 35–37°C on Mueller-Hinton agar (Mueller-Hinton II agar, BBL, Cockeysville, USA). A bacterial suspension was prepared from cultivated bacterial cultures in physiological solution according to turbidity standard 0.5 McFarland.

A standard culture of spore-forming bacteria *B. subtilis* was cultivated for 7 days on Mueller-Hinton II agar at 35–37°C. After the culture of spore-forming bacteria had grown, it was washed away from the surface of the broth with sterile physiological solution, and the prepared suspension was heated for 30 minutes at 70°C and diluted to the concentration of spores in 1 mL ranging from 10×10^6 to 100×10^6 . Such suspension can be kept for a long time at temperature below 4°C.

The standard fungal cultures – *C. albicans*, *C. glabrata*, *C. krusei*, *C. kefyr*, *C. tropicalis*, and *C. parapsilosis* – were cultivated for 20–24 hours at 30°C on 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 Investigative Compounds for Microbiological Analysis. The stock solutions of new compounds (2a-c) (20 000 µg/mL) were prepared in dimethylsulfoxide. Then the dilutions of 0.4, 0.6, 1.25, 2.5, 5, 10, 15.6, 31.25, 62.5, 125, 250, 500, 750, and 1000 µg/mL were done under aseptic conditions by transferring the necessary amount of the analyzed solution using a sterile pipette to other tubes filled with 2 mL of Mueller-Hinton broth.

The minimum dilution, i.e., the lowest concentration in µg/mL of the tested and comparison compound that inhibits the growth of bacteria, was determined by the first tube in the series which inhibited visible growth – it was the minimum inhibitory concentration (MIC).

The minimum bactericidal (fungicidal) concentration, defined as the minimum concentration of antimicrobial (antifungal) compound that prevents any growth of the tested microorganisms (fungi), was determined by subculturing MIC broth tube without visible growth on Mueller-Hinton agar and incubating for 20–24 hours at temperature of 35–37°C (for bacteria) and at 30°C (for fungi).

Results

All new compounds were successfully synthesized. The structures of new compounds (2a-c) were confirmed by the elemental analysis and spectral data (IR, NMR). All characteristics of new compounds are shown in Tables 1 and 2.

For microbiological analysis of synthesized compounds, *S. aureus* (gram-positive bacterium), *E. coli* (gram-negative bacillus), *B. subtilis* (spore-forming bacterium), and *K. pneumoniae* (capsule-forming bacterium) were chosen considering their different structural characteristics.

As *Candida* spp. are considered predominant mycotic pathogens (1), the activity of synthesized compounds was investigated against several *Candida* species: *C. albicans*, *C. glabrata*, *C. kefyr*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*.

Antifungal and antibacterial activities of new compounds (2a-c) are presented in Table 3.

Microbiological analysis showed that all new thiazolidinone derivatives with nitronaphthylamine substituent possessed antibacterial and antifungal properties. New compounds 2a-b showed similar antibacterial activity in vitro against *S. aureus* and *B. subtilis* as antibiotics aminopenicillins, but they were less active against gram-negative bacteria *E. coli* (MIC of aminopenicillins is 0.12–8 µg/mL against *S. aureus*, 1.25–12.5 µg/mL against *E. coli*, and 0.03–0.25 µg/mL against spore-forming bacterium *Bacillus anthracis*) (17).

Discussion

Aldehydes react with 2-methylrhodanine upon heating in acetic acid at 60°C. Boiling makes reactions go faster but yields of products are lower, most likely because 2-methylrhodanine is decomposed. Ammonium acetate was used as a catalyst as higher yields are obtained in this case.

Table 1. Physicochemical Data of Compounds 2a-c

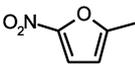
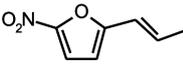
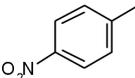
Compound	R	Yield %	Melting Point °C	Molecular Formula (M _r)	Elemental Analysis Calculated/found (%)			
					C	H	N	S
2a		64	234–236	C ₁₈ H ₁₀ N ₄ O ₆ S (410.37)	52.68 52.72	2.46 2.52	13.65 13.65	7.81 7.80
2b		53	216–219	C ₂₀ H ₁₂ N ₄ O ₆ S (436.41)	55.05 54.98	2.77 2.74	12.84 11.96	7.35 7.17
2c		68	206–208	C ₂₀ H ₁₂ N ₄ O ₅ S (420.41)	57.14 56.71	2.88 2.83	13.33 13.21	7.63 7.95

Table 2. Spectral Characteristics of Compounds 2a-c

Compound	IR (KBr) (cm ⁻¹)	¹ H BMR (DMSO-d ₆ , δ ppm)
2a	NH 3140 C=O 1720 NO ₂ 1588, 1520	7.24 (d, 4 Hz, 1H, Ar-H), 7.32 (d, 9 Hz, 1H, Ar-H), 7.60 (s, 1H, =CH), 7.68–7.80 (m, 2H, Ar-H), 7.86 (t, 9 Hz, 1H, Ar-H), 8.16 (dd, 2 and 9 Hz, 1H, Ar-H), 8.44 (dd, 2 and 9 Hz, 1H, Ar-H), 8.57 (d, 9 Hz, 1H, Ar-H)
2b	NH 3144 C=O 1700 NO ₂ 1592, 1508	6.94 (dd, 9 and 12 Hz, 1H, =CH), 7.16 (d, 9 Hz, 1H, =CH), 7.20 (d, 9 Hz, 1H, Ar-H), 7.29 (d, 9 Hz, 1H, Ar-H), 7.42 (d, 12 Hz, 1H, =CH), 7.67 (d, 9 Hz, 1H, Ar-H), 7.70 (d, 2 and 9 Hz, 1H, Ar-H), 7.85 (d, 2 and 9 Hz, 1H, Ar-H), 8.14 (dd, 2 and 9 Hz, 1H, Ar-H), 8.41 (d, 9 Hz, 1H, Ar-H), 8.54 (d, 9 Hz, 1H, Ar-H), 12.45 (br s, NH)
2c	NH 3252 C=O 1740 NO ₂ 1592, 1568	7.34 (dd, 2 and 9 Hz, 1H, Ar-H), 7.69–7.91 (m, 5H, Ar-H, =CH), 8.15 (dd, 2 and 9 Hz, 1H, Ar-H), 8.22 (dd, 2 and 9 Hz, 2H, Ar-H), 8.41 (d, 2 and 9 Hz, 1H, Ar-H), 8.52 (d, 9 Hz, 1H, Ar-H)

Table 3. Antibacterial and Antifungal Activity of New Compounds

Antibacterial and Antifungal Activity		Compound		
		2a	2b	2c
MIC, µg/mL	Antibacterial data			
	<i>Staphylococcus aureus</i> ATCC 25923	0.4±0.1	0.5±0.1	500.0±48.7
	<i>Escherichia coli</i> ATCC 25922	750.0±58.8	500.0±41.2	1000.0±90.7
	<i>Bacillus subtilis</i> ATCC 6633	0.5±0.1	0.5±0.1	125.0±12.1
	<i>Klebsiella pneumoniae</i> ATCC 33499	500.0±44.6	500.0±41.5	1000.0±89.8
	Antifungal data			
	<i>Candida albicans</i>	1.3±0.1	31.3±2.3	62.5±5.7
	<i>Candida glabrata</i>	1.0±0.1	12.5±9.8	31.3±24.4
	<i>Candida krusei</i>	1.3±0.1	62.5±5.5	31.23±22.1
	<i>Candida kefyr</i> ATCC 8614	12.5±1.7	10.0±0.8	31.25±24.0
<i>Candida tropicalis</i> ATCC 8302	10.0±0.6	31.3±2.8	61.5±5.7	
<i>Candida parapsilosis</i>	1.0±0.1	4.1±0.3	250.0±18.5	
MBC, µg/mL	Antibacterial data			
	<i>Staphylococcus aureus</i> ATCC 25923	125.0±12.2	125.0±11.8	>1000.0
	<i>Escherichia coli</i> ATCC 25922	>1000.0	1000.0±83.9	>1000.0
	<i>Bacillus subtilis</i> ATCC 6633	125.0±12.3	62.5±5.9	500.0±41.4
	<i>Klebsiella pneumoniae</i> ATCC 33499	>1000.0	1000.0±80.9	>1000.0
	Antifungal data			
	<i>Candida albicans</i>	62.5±5.2	125.0±10.4	250.0±22.9
	<i>Candida glabrata</i>	125.0±11.3	125.0±11.8	208.0±16.7
	<i>Candida krusei</i>	125.0±12.8	250.0±18.8	125.0±12.3
	<i>Candida kefyr</i> ATCC 8614	208.0±19.3	125.0±11.2	125.0±10.8
<i>Candida tropicalis</i> ATCC 8302	125.0±11.6	333.0±27.7	250.0±23.1	
<i>Candida parapsilosis</i>	62.5±5.7	62.5±5.7	750.0±66.7	

The duration of reaction depends on nature of aldehyde. Reactions with nitrofurans derivatives go faster (by forming compounds 1a and 1b); it is enough to heat these compounds with 2-methylrhodanine for 0.5 hour. Reactions with nitrobenzaldehyde go slower (by forming 1c); in this case, the reaction mixture has to be heated for 1 hour. The last-mentioned compound is better soluble in acetic acid compared to compounds having nitrofurans cycle in their structure so reaction mixture of compound 1c is cooled in an ice bath for longer time (for 4 hours). Reaction yields also differ (82%–91%), depending on the nature of aldehyde. Yield of reaction between 3-nitrobenzaldehyde and 2-methylrhodanine is the lowest (82%).

Reactions of intermediate compounds with 4-nitro-1-naphthylamine were carried out in acetic acid. A solvent was chosen according to the solubility of initial compounds 1a-c. Reaction mixture was heated at constant temperature of 90°C because reaction products are decomposed at higher temperature. Reaction process was monitored using a lead acetate indicator. Reaction yields of all newly synthesized compounds were moderate ranging from 53% to 68%. Upon taking double excess of 4-nitro-1-naphthylamine reaction is going faster but separation of reaction product is more complicated.

It is important to note that the activities of newly synthesized compounds were different. The compounds containing a nitrofuryl fragment in their structure (2a-b) were more active against tested bacteria and fungi than that having a nitrobenzyl fragment. The lowest antibacterial activity of all newly synthesized compounds was against capsule-forming bacteria *K. pneumoniae* and against *E. coli* (MIC is in range 500–1000 µg/mL). The similar principles of structure-activity relationship were observed in our previous studies (9, 11). However, the compound 2b having an additional double bond in nitrofurans substituent was similarly active against bacteria as compared with the compound 2a, but it was up to 60 times less active against all fungi except *C. kefyr*. The compound having a nitrobenzene moiety in its structure (2c) possessed the lowest activity against bacteria and fungi as compared with thiazolidinone derivatives having a nitrofurans frag-

ment (2a-b). Our presumption regarding the introduction of nitrofurans component to achieve higher antimicrobial activity was proved for this time.

However, similar principles could be applied for the estimation of structure-antifungal activity of tested compounds 2a-c. Compound 2a was found to be most active against tested *Candida* spp. It should be noted that the compound without an additional double bond in nitrofurans component (2a) was more active against *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*, but less active against *C. kefyr* as compared with the compound containing a nitrofurylallylidene fragment in its structure (2b). It can be presumed that the introduction of these different nitrofurans substituents into the fifth position of thiazolidinone ring has a different impact on antifungal activity against different fungi. Nevertheless, more detailed experiments should be carried out to confirm this. Compound 2a possessed similar anticandidal activity as fluconazole – the most popular antifungal preparation nowadays (18).

New compounds were found to be bacteriostatic and fungistatic at lower concentrations, but bactericidal and fungicidal at higher concentrations. The findings of this study could further help to develop more active antimicrobial compounds having a thiazolidinone ring in their structure.

Conclusions

Newly synthesized compounds 2a-c having a 4-nitro-1-naphthylamine substituent in their structure showed antifungal and antibacterial activities. Naphthylamine derivatives with nitrofuryl and nitrofurylallylidene moieties in the fifth position of a thiazolidinone ring had similar antibacterial activity in vitro against *S. aureus* and *B. subtilis* as aminopenicillins. The compound with a nitrofuryl fragment in the fifth position of a thiazolidinone ring possessed higher activity against some *Candida* spp. than fluconazole. The results indicate that naphthylamine derivatives having a thiazolidinone and especially nitrofuryl fragment in one molecule could be potential antimicrobial compounds.

Statement of Conflict of Interest

The authors state no conflict of interest.

Naftilamino darinių, turinčių tiazolidinono ciklą, sintezė ir antimikrobinis aktyvumas

Vilma Petrikaitė^{1,2}, Eduardas Tarasevičius¹, Alvydas Pavilionis³

¹Lietuvos sveikatos mokslų universiteto Medicinos akademijos Vaistų chemijos katedra,

²Vilniaus universiteto Biotechnologijos instituto Biotermodinamikos ir vaistų tyrimo skyrius,

³Lietuvos sveikatos mokslų universiteto Medicinos akademijos Mikrobiologijos laboratorija, Lietuva

Raktažodžiai: priešgrybelinis aktyvumas, antimikrobinis aktyvumas, naftilaminas, nitrofuranai, tazolidinonas, naujų vaistų sintezė.

Santrauka. *Tyrimo tikslas.* Ištirti naftilamino liekanos ir nitrogrupę turinčių fragmentų įtaką antimikrobiniam (antibakteriniam ir priešgrybeliniam) tiazolidinono darinių aktyvumui.

Tyrimo medžiaga ir metodai. Pradiniai junginiai – 5-pakeisti 2-metillmerkaptotiazolidin-4-onai buvo S-demetilinti ir susintetinti 2-amino pakeisti tiazolidinonai. Kaip farmakoforai, turintys amino ar aldehido grupę, naudoti 4-nitro-1-naftilaminas, nitrofurano ir nitrobenzeno aldehydai. Antimikrobinis (antibakterinis ir priešgrybelinis) naujų junginių aktyvumas nustatytas *in vitro* su šiomis mikroorganizmų kultūromis: *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Candida albicans*, *C. glabrata*, *C. krusei*, *C. kefyr*, *C. tropicalis*, *C. parapsilosis*.

Rezultatai. Mikrobiologinio tyrimo rezultatai parodė, kad visi nauji tiazolidinono dariniai su nitronaftilamino pakaitu turi antibakterinių ir priešgrybelinių savybių. Junginių 2a-b antibakterinis aktyvumas *in vitro* prieš *S. aureus* ir *B. subtilis* yra panašus į antibiotikų aminopenicilinų aktyvumą. Visi nauji junginiai mažiau- siai aktyvūs prieš kapsulę sudarančią bakteriją ir gramneigiamą bakteriją *E. coli* (MSK yra 500–1000 µg/ml).

Išvados. Mažiausia susintetintų naftilamino darinių slopinamoji koncentracija (MIK) yra 0,4–1000 µg/ml, o kai kurių jaunų junginių aktyvumas panašus kaip aminopenicilinų ir priešgrybelinio junginio flukonazolo. Remiantis šio tyrimo duomenimis, būtų galima išskirti perspektyvią antimikrobinių junginių grupę.

References

- Klepser ME. Future candidates in the search for new antifungal agents. *Curr Opt Infect Dis* 2003;5:489-94.
- de Pauw B. Is there a need for new antifungal agents? *Clin Microbiol Infect* 2000;6:23-8.
- Beale JM. Antifungals. In: Block JH, Beale JM, editors. *Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry*. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2004, p. 230-47.
- Maertens JA. History of the development of azole derivatives. *Clin Microbiol Infect* 2004;10:1-10.
- Tremolieres F, Garraffo R, Lortholary O. Need for alternative approaches in the evaluation of new antibacterial antibiotics. *Med Mal Infect* 2005;35:229-35.
- Livermore DM. The need for new antibiotics. *Clin Microbiol Infect* 2004;10:1-9.
- Meyer AL. Prospects and challenges of developing new agents for tough Gram-negatives. *Curr Opin Pharmacol* 2005;5:490-4.
- Theuretzbacher U, Toney JH. Nature's clarion call of antibacterial resistance: are we listening? *Curr Opin Investig Drugs* 2006;7:158-66.
- Petrikaitė V, Tarasevičius E, Pavilionis A. New ethacridine derivatives as the potential antifungal and antibacterial preparations. *Medicina (Kaunas)* 2007;43:657-63.
- Petrikaitė V, Tarasevičius E, Pavilionis A. New thiazolidinones-4 with sulfamethizole-2 substituent as the potential antifungal and antimicrobial preparations. *Biologija* 2007; 18:45-50.
- Tarasevičius E, Akramas L, Petrikaitė V, Pavilionis A. Antimicrobial properties of new sulfanilamide derivatives. *Medicinos teorija ir praktika* 2003;3:185-7.
- Lesyk R, Zimenkovsky B. 4-Thiazolidones: centenarian history, current status and perspectives for modern organic and medicinal chemistry. *Curr Org Chem* 2004;8:1547-77.
- Shah V, Pant CK, Joshi PC. Synthesis and antifungal activity of some bis (2-arylimino-3-ylthiazolidinones) and bis (1-aryl-3-ylthiohydantoin). *Asian J Chem* 1993;5:83-8.
- Vicini P, Geronikaki A, Anastasia K, Incerti M, Zani F. Synthesis and antimicrobial activity of novel 2-thiazolylimino-5-arylidene thiazolidinones. *Bioorg Med Chem* 2006; 14:3859-65.
- Bryan GT. Nitrofurans: chemistry, metabolism, mutagenesis and carcinogenesis. New York: Raven Press; 1978. p. 171-233.
- Mitscher LA. Antibiotics and antimicrobial agents. In: Foye WO, Lemke TL, Williams DA, editors. *Principles of medicinal chemistry*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 819-67.
- AHFS Drug Information. American Society of Health-System Pharmacists, American Hospital Formulary Service; 2001. p. 365-6.
- Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TE, et al. Practice guidelines for the treatment of candidiasis. *Clin Infect Dis* 2004;38:161-89.

Received 1 October 2010, accepted 23 June 2011
 Straipsnis gautas 2010 10 01, priimtas 2011 06 23