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Synthesis of indoline-thiazolidinone hybrids with antibacterial and antifungal activities

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Aim. Based of the Knoevenagel condensation reaction the synthesis of new rhodanine-indoline hybrid molecules for screening antibacterial and antifungal activities was accomplished. **Methods.** Organic synthesis, NMR spectroscopy, pharmacological screening. **Results.** The reaction between rhodanine-3-propanoic/ethanesulfonic acids and indolecarbaldehydes in the acetic acid provided series of 5-indolylmethylenerhodanine-3-carboxylic/sulfonic acid derivatives. Based on the esterification reaction with methanol in the presence of sulfuric acid, 5-indolylmethylenerhodanine-3-propanic acid was transformed into appropriate ester for further evaluation of antimicrobial activity. The antimicrobial activity screening allowed the identification of compounds with significant effect against *Escherichia coli*, *Staphylococcus lentus* and *Candida albicans* with MIC/MBC/MFC values in the range of 25-50 μg/mL. **Conclusions.** The synthesized 5-indolylmethylenerhodanine-3-carboxylic/sulfonic acid derivatives are a convenient platform for the development of new highly active and low-toxic agents as potential drug-like molecules with antimicrobial activity.

K e y w o r d s: synthesis, 2-thioxo-4-thiazolidinone, indolecarbaldehydes, spectral data, antimicrobial activity.

Introduction

In the era of rapidly growing number of patients suffering from various infectious diseases, the searching for novel compounds with antibiotic activity is one of the global challenges in overcoming antimicrobial resistance [1]. In this context, prominent interest belongs to heterocyclic compounds, which are one of the most valuable sources of novel chemical entities with diverse biological activity due to their unique ability to mimic the structure of peptides and to bind reversibly to diverse biotargets [2]. Among the design strategies in drug discovery, considerable interest has been paid to thiazole-based heterocycles [3–5]. Thiazole/thiazolidinone derivatives constitute an important class of therapeutic agents in medicinal chemistry including antitrypanosomal [6], antiviral [7, 8], anticancer [9–11], antioxidant [12, 13], anti-inflammatory [14–16] activities and also display a pivotal role as antimicrobial and antifungal agents [17, 18]. Thus, a thiazole ring is present in several drugs, such as penicillin, monobactam, sulfathiazole, thiabendazole and nizatidine, making this heterocyclic fragment ideal for construction more potent and safer drug candidates, especially in the therapy of infectious diseases (Fig. 1). The antimicrobial activity evaluation is also actual and promising for thiazole-based compounds. Thus, among thiazolidinones, especially rhodanines have been identified several lactamases [19], Sortase A (SrtA) [20], Peptide deformylase [21], Protein mannosyl transferase 1 [22], UDP-galactopyranose mutase (UGM) [22], UDP-N-acetylmuramate/L-alanine ligase (MurC) [23] and Dolicholphosphate mannose [24] synthase inhibitors.

It was envisaged, that the combination of thiazolidinone with other pharmacophores, especially indole fragment, would generate molecular templates with new pharmacological profile and lower toxicity [25]. Thus, among indole-based derivatives a set of potent plant hormones [26], essential amino acids [27], neurotransmitters [27], as well as a large number of commercial drugs and biologically ac-

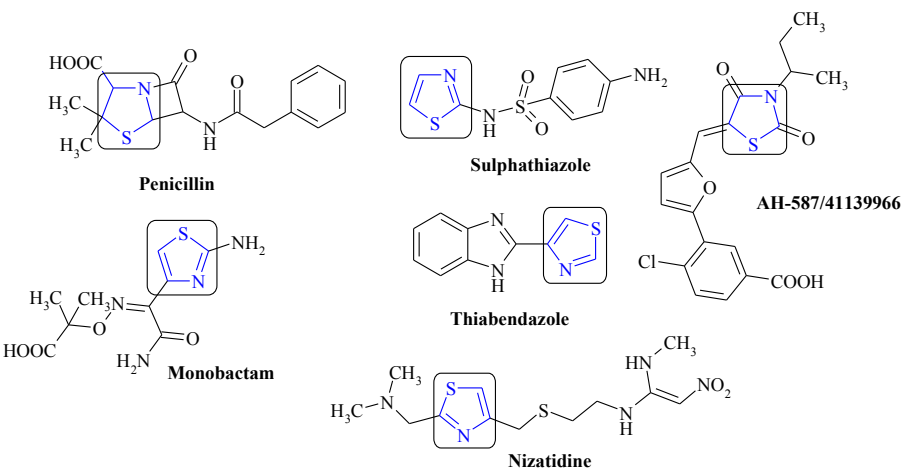


Fig. 1. Structures of thiazole-containing drugs.

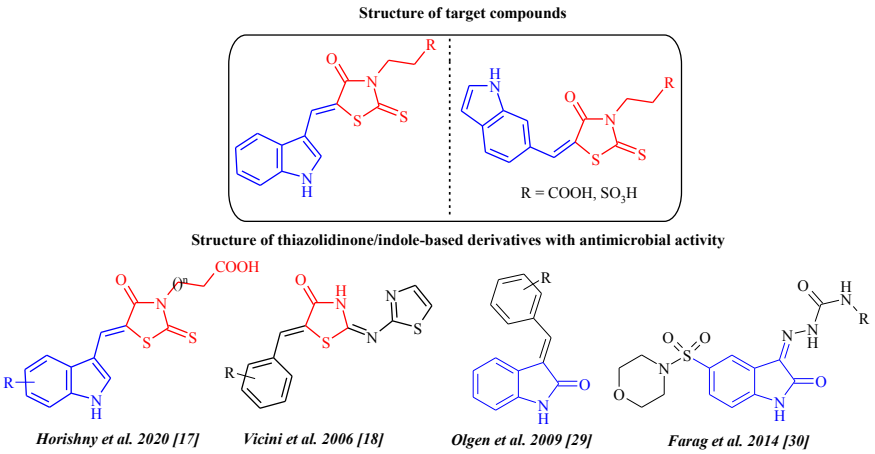


Fig. 2. Background for target compounds synthesis.

tive molecules have been identified [28–30]. In continuation of this theme, we designed and synthesized new non condensed heterocyclic compounds containing 4-oxo-2-thioxothiazolidine (rhodanine), and pharmacologically attractive indole moieties (Fig. 2). The evaluation of their antimicrobial and antifungal activity *in vitro* against several reference and clinical strains was carried out.

Materials and Methods

Chemistry

The starting rhodanine-3-propanoic/ethanesulfonic acids 1,2 were obtained according to the known synthetic methods [17,31].

Melting points were measured in open capillary tubes and were uncorrected. The elemental analyses were performed using the Perkin–Elmer 2400 CHN analyzer. The analyses indicated by the symbols of the elements or functions were within ±0.4 % of the theoretical values. The ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini (^{1}H at 400 and ^{13}C at 100 MHz) instrument in DMSO-d_6 using tetramethylsilane as an internal standard. Chemical shifts are reported in ppm units with use of δ scale. Mass spectra were obtained using electrospray (ES) ionization techniques on an Agilent 1100 Series LCMS.

General procedure for the synthesis of 5-indolylmethylene rhodanine-3-propanoic/ethanesulfonic acids (3, 5, 6). A mixture of rhodanine-3-propanoic/ethanesulfonic acid (5 mmol), sodium acetate (5 mmol), and appropriate indolecarbaldehyde (5.5 mmol) was refluxed for 2 h in 10 mL of acetic acid. A solid product that precipitated out was filtered, dried, and recrystallized from acetic acid (10–15 mL).

*3-[5-(1H-Indol-3-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]-propanoic acid (**3**)*. Yield 96 %, mp 256-257 ºC (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.63 (t, 2H, J = 7.8 Hz, CH_2), 4.24 (t, 2H, J = 7.8 Hz, CH_2), 7.20-7.29 (m, 2H, arom.), 7.51 (d, 1H, J = 7.8 Hz, arom.), 7.89 (s, 1H, arom.), 7.75 (d, 1H, J = 7.7 Hz, arom.), 8.08 (s, 1H, =CH), 12.38 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 42.9, 45.5, 111.3, 113.5, 114.7, 118.9, 122.1, 123.1, 125.4, 126.7, 130.3, 136.9, 166.7, 191.3. ESI-MS m/z 334 $(M+H)^+$. Anal. Calcd for

$C_{15}H_{13}N_2O_3S_2$: C, 54.04; H, 3.93; N, 8.40. Found: C, 54.08; H, 3.85; N, 8.51.

*2-[5-(1H-Indol-3-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]-ethanesulfonic acid (**5**).* Yield 71 %, mp > 260ºC (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.72 (t, 2H, *J* = 7.6 Hz, CH_2), 4.27 (t, 2H, *J* = 7.5 Hz, CH_2), 7.20-7.29 (m, 2H, arom.), 7.51 (d, 1H, *J* = 7.8 Hz, arom.), 7.91 (s, 1H, arom.), 7.96 (d, 1H, *J* = 7.6 Hz, arom.), 8.09 (s, 1H, =CH), 12.38 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.7, 51.6, 110.0, 112.5, 114.2, 118.4, 121.5, 123.3, 126.3, 126.7, 130.6, 136.3, 166.3, 170.6, 192.1. ESI-MS m/z 369 $(M+H)^+$. Anal. Calcd for $C_{14}H_{12}N_2O_4S_3$: C, 45.64; H, 3.28; N, 7.60. Found: C, 45.58; H, 3.22; N, 7.54.

*3-[5-(1H-Indol-6-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]-propanoic acid (**6**).* Yield 74 %, mp > 260ºC (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (t, 2H, *J* = 7.0 Hz, CH_2), 4.27 (t, 2H, *J* = 7.0 Hz, CH_2), 6.54 (s, 1H, arom.), 7.27 (d, 1H, *J* = 7.7 Hz, arom.), 7.59 (m, 1H, arom.), 7.70 (d, 1H, *J* = 7.6 Hz, arom.), 7.76 (m, 1H, arom.), 7.93 (s, 1H, =CH), 11.46 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 30.8, 40.4, 101.9, 115.2, 118.1, 121.0, 121.6, 125.6, 129.8, 130.1, 135.6, 136.0, 166.7, 171.7, 193.1. ESI-MS m/z 333 $(M+H)^+$. Anal. Calcd for $C_{15}H_{12}N_2O_3S_2$: C, 54.20; H, 3.64; N, 8.43. Found: C, 54.28; H, 3.55; N, 8.40.

Synthesis of 3-[5-(1H-indol-3-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]-propanoic acid methyl ester (**4**). The 3-[5-(1*H*-indol-3-ylmethylene)-4-oxo-2-thioxothiazolidin-3-yl]-propanoic acid (**3**) was refluxed for 1h with methanol (15 mL) in the presence of sulfuric acid (2 mL) as catalyst. The resulting solid was collected by filtration, washed with methanol and diethyl ether, dried and recrystallized from methanol (20 mL). Yield 81 %, mp 245–247 ºC (MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.53 (s, 3H, CH_3), 2.77 (t, 2H, *J* = 8.1 Hz, CH_2), 4.30 (t, 2H, *J* = 8.2 Hz, CH_2), 7.20-7.29 (m, 2H, arom.), 7.51 (d, 1H, *J* = 7.9 Hz, arom.), 7.88 (s, 1H, arom.), 7.96 (d, 1H, *J* = 7.7 Hz, arom.), 8.07 (s, 1H, =CH) 12.31 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 41.1, 47.3, 54.5, 110.0, 112.5, 114.6, 118.5, 121.4, 123.3, 125.9, 126.7, 130.4, 136.3, 166.4, 192.0. ESI-MS m/z 347 $(M+H)^+$. Anal. Calcd for $C_{16}H_{14}N_2O_3S_2$: C, 55.47; H, 4.07; N, 8.09. Found: C, 55.38; H, 4.12; N, 8.14.

Pharmacology

Antimicrobial and antifungal activities in vitro (agar diffusion method)

The antimicrobial activity of the synthesized compounds was studied by the method of diffusion into agar. Aliquots (50 μL) of 0.1 % tested compound solution in the mixture of EtOH : DMSO : water (2:1:1) were placed into wells in agar in Petri dishes with test microbes. The antimicrobial activity was evaluated by measuring the diameter of the zone of inhibition of microbial growth. The plates were incubated for 24 h at 37 ˚C. The inhibition zone that appeared after 24 h around the well in each plate was measured in mm. Experiments were in triplicates and standard deviation was calculated. All compounds were tested against six Gram-negative (reference strains *Pseudomonas aeruginosa* (ATCC 27853 (F-51)), *Escherichia coli* (ATCC 25922); clinical multi-drug resistante strains (MDR) *Pseudomonas aeruginosa*, *Escherichia coli*; rarely found clinical strains *Raoultella terrigena* and *Brevundimonas ve-*

sicularis), five Gram-positive (reference strains *Staphylococcus aureus* (ATCC 25923 (F-49)), *Bacillus licheniformis* (ВКПМ-7038); clinical MDR strain *Staphylococcus aureus*; rarely found clinical strains *Staphylococcus lentus* and *Staphylococcus lugnuniensis*) bacterial strains, according to the literature protocol [32]. Clinical strains were isolated from patient with nosocomial infections. *In vitro* antibacterial activity was determined by using Mueller Hinton Agar plates. The antifungal screening of all compounds was carried out against reference strain of yeast *Candida albicans* (ATCC 885–653); clinical MDR strains *Candida dubliniensis*, *Candida albicans*; and reference strain of mold *Aspergillus niger*, s according to the literature protocol [33, 34]. *In vitro* antifungal activity was determined by using Sabouraud Agar plates. All results were compared with those of the DMSO.

The MICs of the compound assays were carried out using the microdilution susceptibility method. The microorganism suspensions were inoculated to the corresponding wells. The plates were incubated at 36 ºC for 18 h for bacteria and fungi, respectively. The minimum inhibitory concentrations of the compounds were recorded as the lowest concentration of each compound in the tubes with no turbidity (i.e. no growth) of inoculated bacteria/fungi.

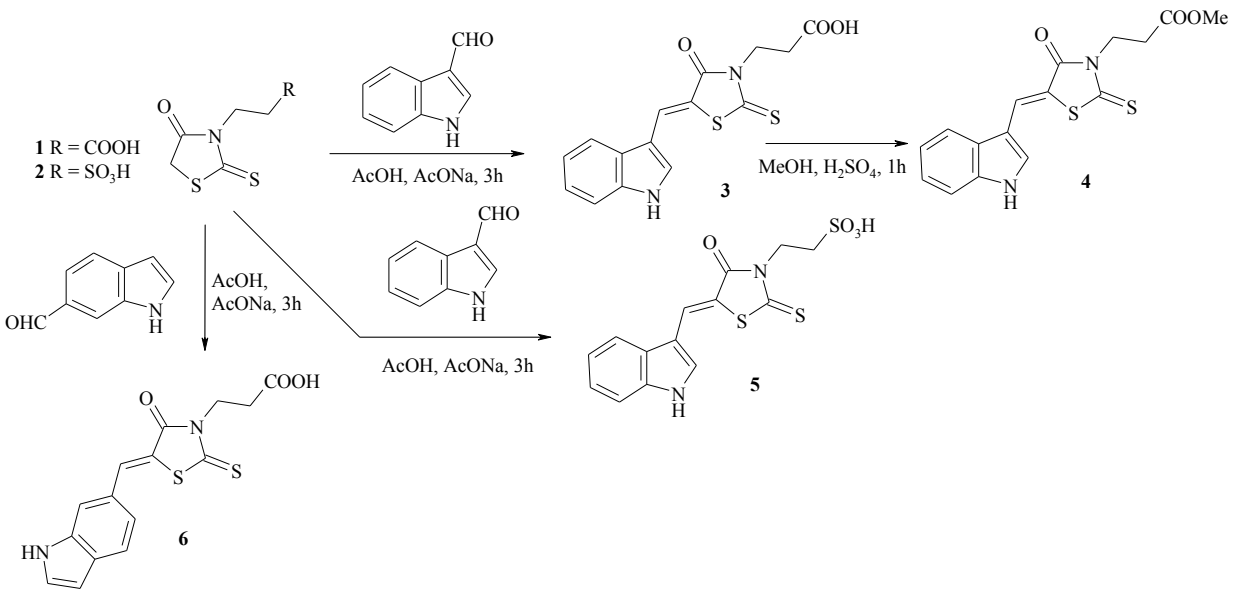
Acute toxicity

The experiments were conducted on white male mice weighing 23–25 g. Compounds were dissolved in saline solution (0.9 % NaCl) with l-2 drops of Polysorbate 80 (Tween-80®). After dissolution they were administered to mice by the oral route. The LD_{50} was evaluated for 4 or 5 different doses each on 6 animals and calculated by the Litchfield-Wilcoxon method [35, 36].

Results and Discussion

Chemistry

The general methods for synthesis of target indoline substituted rhodanines are depicted in Scheme 1. The starting rhodanine-3-propanoic/ethanesulfonic acids were synthesized per the procedure reported previously [17, 31]. The target 5-indolylmethylene-3-substituted rhodanines were obtained by the Knoevenagel reaction in the medium of acetic acid in the presence of sodium acetate. Additionally, 5-indolylmethylenerhodanine-3-propanoic acid **3** was transformed into corresponding ester **4** via heating with alcohols in the presence of an acid as a catalyst. The structures of synthesized compounds were elucidated by the spectral data (^{1}H and ^{13}C NMR). The ^{1}H NMR spectra of compounds (**3**-**6**) CH_2 protons of the alkyl fragment in position N-3 appear as a triplet at δ 2.63–2.77 and 4.24–4.30 ppm, respectively. The chemical shift of the methylene group (=CH) of synthesized 5-indolidenederivatives is insignificantly displaced in the weak magnetic field, δ 7.93–8.09 ppm, and clearly indicated that only *Z*-isomers were obtained in the Knoevenagel reaction of rhodanines with indole-carbaldehydes. The signals of NH group of indole fragment appeared as single-proton singlets displaced in the weak magnetic field at δ 11.46–12.41 ppm. In the ^{13}C NMR spectra the characteristic signals of (thio)carbonyl carbons at δ ~166.3–193.1 ppm and the signals of methylene group (130.3–135.6 ppm) are observed.



Scheme 1. Synthesis of rhodanine-3-propionic/ethanesulfonic acids derivatives 3-6

Biological activity

The synthesized compounds were screened for their *in vitro* antibacterial and antifungal activities using the agar diffusion method [32]. A total of 15 microorganisms which consisted of eleven bacteria, three yeasts and one mold fungi were tested. Clinical and rarely found clinical strains were multidrug resistant [37] and isolated from patient with health-care-associated infections. All the synthesized compounds exhibited varying degree of inhibitory effect on the growth of different tested strains at a dose of 50 μg per well (Table 1 and Fig. 3). The synthesized compounds showed different mean zone of inhibition in the range of 00-19.4 mm against tested microorganisms. DMSO was used as control. Compounds **3** and **4** show good antifungal activity against *Candida albicans*, *Candida dubliniensis*, *Aspergillus niger* and did not possess significant antibacterial activity. Compound **5** showed the highest activity against *Escherichia coli*, *Bacillus licheniformis*, *Staphylococcus aureus*, *Staphylococcus lugnuniensis*. Compound **6** displayed moderate activity against *Raoultella terrigena*. No significant antifungal activity was observed for compounds **5** and **6**.

The minimum inhibitory concentrations (MIC) for the most active compounds **3-6** against several microorganisms were calculated using the broth microdilution method (Resazurin Reduction-Based Assay) [33,34] (Table 2). The tested compounds exhibited the inhibitory activity against clinical strains *Escherichia coli*, *Staphylococcus lentus* and *Candida albicans* with MIC 00-50 μg/mL. Two compounds showed a moderate activity (dilution 1:4) against *Candida albicans* (compound **3**), *Escherichia coli* and *Staphylococcus lentus* (compound **5**) with MIC 25.0 μg/mL respectivel. Compound **4** exhibited at the same dilution a slightly lower

inhibitory activity with MIC 50 μg/mL against *Candida albicans*. Compound **6** was inactive against tested microorganisms. Interestingly, the tested compounds at dilution 1:1 possessed a slight inhibitory activity with MIC 50.0 μg/mL.

The SAR analysis showed that the antibacterial effect of compounds **3**-**6** depends on the substituents at C-5 and N-3 positions of 2-thioxo-1,3-thiazolidin-4-one (rhodanine) core. The 5-enerhodanine-3-propanoic acid **3** with indol-3-ylmethylene fragment in the mol-

Table 1. **Antibacterial and antifungal activities of the synthesized compounds.**

№	Type of species		Species of bacteria and fungi	Diameter of inhibitory zones (mm ± SE)				
				Compd 3	Compd 4	Compd 5	Compd 6	DMSO
1	Gram-negative bacteria	reference strains	*Pseudomonas aeruginosa* (ATCC 27853 (F-51))	7.2 ± 0.3	00	8.5 ± 0.5	00	00
2			*Escherichia coli* (ATCC 25922)	00	00	15.2 ± 0.4	00	00
3		clinical strains	*Pseudomonas aeruginosa* № 7 (n=4)	7.0 ± 0.3	00	7.5 ± 0.5	00	00
4			*Escherichia coli* № 5 (n=4)	7.0 ± 0.2	7.0 ± 0.2	15.4 ± 0.6	7.0 ± 0.2	7.0 ± 0.2
5		rarely found clinical strains	*Raoultella terrigena* № 1 (n=4)	00	00	6.6 ± 0.2	8.0 ± 0.3	00
6			*Brevundimonas vesicularis* № 111 (n=4)	00	00	00	00	00
7	Gram-positive bacteria	reference strains	*Staphylococcus aureus* (ATCC 25923 (F-49))	7.0 ± 0.2	7.0 ± 0.2	6.8 ± 0.4	6.8 ± 0.4	6.8 ± 0.4
8			*Bacillus licheniformis* (ВКПМ-7038)	7.0 ± 0.3	00	9.5 ± 0.5	00	00
9		clinical strains	*Staphylococcus aureus* 120 (n=4)	00	00	12.2 ± 0.4	00	00
10		rarely found clinical strains	*Staphylococcus lentus* № 21 (n=4)	00	00	10.3 ± 0.5	00	00
11			*Staphylococcus lugnuniensis* 142	00	00	9.5 ± 0.5	00	00
12	Fungi	reference strains of yeast	*Candida. albicans* (ATCC 885-653)	19.4 ± 0.5	15.4 ± 0.6	7.2 ± 0.2	7.2 ± 0.2	7.2 ± 0.2
13		clinical strains of yeast	*Candida dubliniensis* № 67 (n=4)	14.5 ± 0.6	10.5 ± 0.6	00	00	00
14			*Candida albicans* № 60 (n=4)	12.5 ± 0.6	11.5 ± 0.6	00	00	00
15		reference strain of mold	*Aspergillus niger* № 162	15.5 ± 0.5	14.5 ± 0.5	00	00	00

00: no activity; diameter of zone of inhibition (mm) including the well diameter of 6 mm; data are presented as mean ±SD (n = 3)

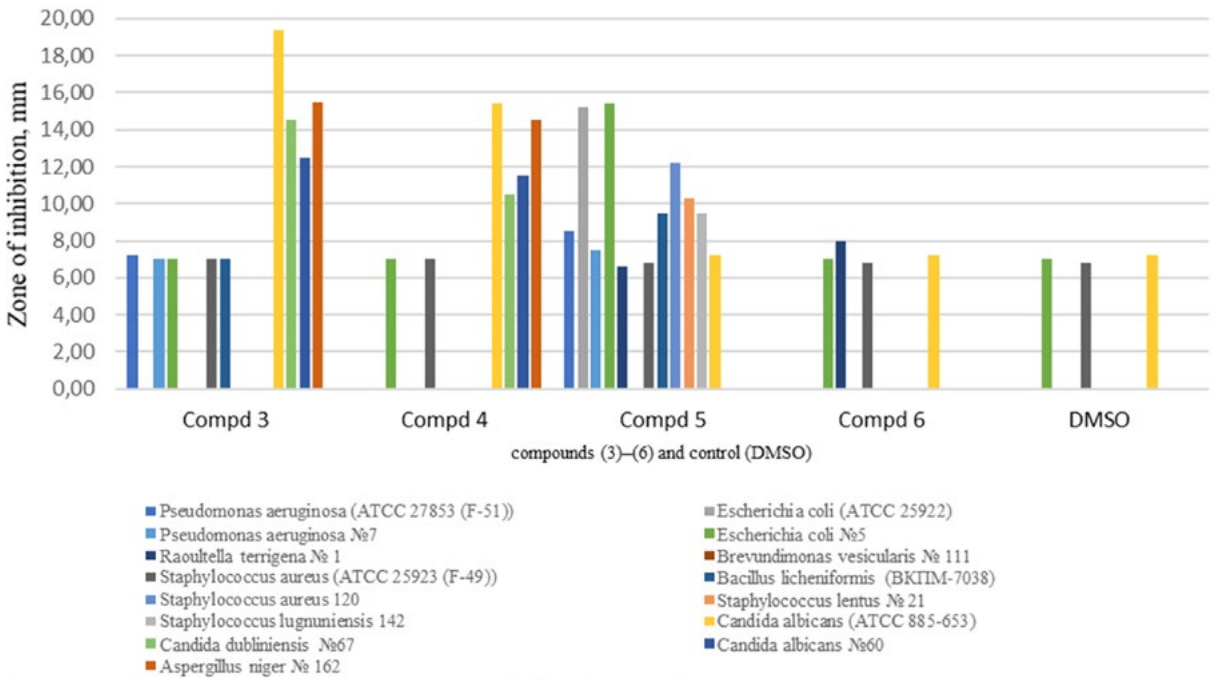


Fig. 3. Comparison of antibacterial and antifungal activities of compounds **3-6**.

Table 2. **Minimum Inhibitory (MIC) and Bactericidal/Fungicidal Concentration (MBC/MFC)**

№	Type of species	Species of bacteria and fungi	Minimum Inhibitory (MIC) and Bactericidal /Fungicidal Concentration (MBC/MFC)							
			Compd 3		**Compd 4**		**Compd 5**		**Compd 6**	
			MIC (μg/mL)	MBC / MFC (μg/mL)	MIC (μg/mL)	MBC / MFC (μg/mL)	MIC (μg/mL)	MBC / MFC (μg/mL)	MIC (μg/mL)	MBC / MFC (μg/mL)
1	Gram-negative bacteria	*Escherichia coli* №5	0	0	0	0	1:4 (25 μg/mL)	1:1 (50 μg/mL)	0	0
2	Gram-positive bacteria	*Staphylococcus lentus* № 21	0	0	0	0	(1:4 25 μg/mL)	(1:1 50 μg/mL)	0	0
3	Fungi	*Candida albicans* №60	1:4 (25 μg/mL)	1:1 (50 μg/mL)	1:1 (50 μg/mL)	1:1 (50 μg/mL)	0	0	0	0

ecule displayed the equivalent antimicrobial activity to its ester **4**. The derivative **5** with ethanesulfonic acids substituent of rhodanine core at N-3 and indol-3-ylmethylene fragment at C-5 was the most active and demonstrated a good effect against all tested bacteria with

MIC 25 μg/mL. The introduction of indol-6-ylmethylene fragment at C-5 position of rhodanine-3-propanoic acid provides the loss of antibacterial and antifungal activities.

For the synthesized compounds, the acute toxicity in mice was studied and their medium lethal doses (LD_{50} value) were determined. The stock solutions of the compounds used in this study were prepared immediately before usage and increasing amounts of substances (100–1000 mg/kg) were injected intraperitoneally. The LD_{50} values were calculated according to Litchfield and Wilcoxon. The synthesized compounds showed low acute toxicity in mice with the LD_{50} values within the range of 300–350 mg/kg (Table 3).

Table 3. **Acute toxicity of the target compounds.**

Compound	LD_{50}, mg/kg
3	960.0 ± 64.5
4	1005.0 ± 67.0
5	1050.6 ± 67.5
6	900.0 ± 57.0

Conclusions

The new 5-indolylmethylenerhodanine-3-propanoic/ethanesulfonic acids derivatives **3**–**6** were synthesized via the Knoevenagel reaction from appropriate rhodanine-3-propanoic/ethanesulfonic acids and indolecarbaldehydes. The antimicrobial screening of synthesized compounds against reference and clinical strains bacteria and fungi was performed. It was found that some derivatives have potential antimicrobial activity against *Escherichia coli*, *Staphylococcus lentus* and *Candida albicans* and are attractive as a novel template for the design of new synthetic antibacterial/antifungal agents.

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Синтез індолін-тіазолідинонових гібридних молекул з протимікробною та протигрибковою активностями

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Мета. На основі конденсації Кньовенагеля здійснити синтез нових роданін-індолінових гібридних молекул для скринінгу антибактеріальної та протигрибкової активності. **Методи.** Органічний синтез, спектроскопія ЯМР, фармакологічний скринінг. **Результати.** Взаємодією роданін-3-пропанової/етансульфонової кислоти з індолкарбальдегідами в середовищі оцтової кислоти синтезовано ряд 5-індолілметиленроданін-3-карбонових/сульфонових кислот. В умовах реакції естерифікації метанолом у присутності сульфатної кислоти 5-індолілметиленроданін-3-пропанова кислота трансформована у відповідний естер для подальшого вивчення протимікробної дії. Скринінг протимікробної активності дозволив ідентифікувати сполуки, які відзначаються помітним ефектом відносно *Escherichia coli*, *Staphylococcus lentus* та *Candida albicans* із значеннями MIC/MBC/MFC 25-50 μg/mL. **Висновки.** Синтезовані 5-індолілметилен роданін-3-карбонові/сульфонові кислоти є зручною платформою для розроблення нових високоактивних та малотоксичних агентів як потенційних лікоподібних молекул з антимікробною активністю.

Ключові слова: синтез, 2-тіоксо-4-тіазолідинон, індолкарбальдегіди, спектральні характеристики, протимікробна активність

Синтез индолин-тазолидиновых гибридных молекул с противомикробной активностью

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Цель. На основе конденсации Кнёвенагеля осуществить синтез новых роданин-индолиновых гибридных молекул для скрининга антибактериальной и противогрибковой активности. **Методы.** Органический синтез, спектроскопия ЯМР, фармакологический скрининг. **Результаты.** Взаимодействием роданин-3-пропановой/етансульфоновой кислоты с индол-карбальдегидами в среде уксусной кислоты синтезирован ряд 5-индолилметиленроданин-3-карбоновых/сульфоновых кислот. В условиях реакции этерификации метанолом в присутствии серной кислоты 5-индолилметиленроданин-3-пропановая кислота была трансформирована в соответствующий сложный эфир для дальнейшего изучения противомикробной активности. Скрининг противомикробной активности позволил идентифицировать соединения, отличающиеся заметным эффектом в отношении *Escherichia coli*, *Staphylococcus lentus* и *Candida albicans* со значениями MIC/MBC/MFC 25-50 μg/mL. **Выводы.** Синтезированные 5-индолилметиленроданин-3-карбоновые/сульфоновые кислоты являются удобной платформой для разработки новых высокоактивных и малотоксичных агентов как потенциальных лекарственных средств с антимикробной активностью.

Ключевые слова: синтез, 2-тиоксо-4-тиазолидинон, индолкарбальдегиды, спектральные характеристики, противомикробная активность.

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