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Antimicrobial and cytotoxic activities of thiazolo[4,5-*b*]pyridine derivatives

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Aim. The screening of antimicrobial and cytotoxic activities of thiazolo[4,5-*b*]pyridine derivatives was accomplished. **Methods.** The antibacterial and antifungal activities of synthesized thiazolopyridines were evaluated *in vitro* with the agar diffusion and broth microdilution methods using clinical and reference strains of Gram-positive, Gram-negative bacteria and yeasts. The structure-antibacterial/antifungal activity relationships of the screened compounds were established. The target compounds were screened for their cytotoxicity effects on HaCaT and HEK293 cells using MTT assay. **Results.** The highest antimicrobial activity was observed for compound V 2-oxo-7-thiophen-2-yl-2,3-dihydrothiazolo[4,5-*b*]pyridine-5-carboxylic acid with minimal inhibitory concentration (MIC) 12.5 μg/mL against *Candida albicans*. At the same time, the synthesized compounds were explored in the interaction with amoxicillin against multidrug resistant clinical isolates of ESβL$^+$ *Klebsiella pneumonie* and *Staphylococcus haemolyticus* (MRSH). The best synergistic activity with amoxicillin was exhibited by compound VI. HaCaT human keratinocytes and HEK293 human embryonic kidney cells demonstrated resistance to the thiazolopyridine derivatives treatment and did not reach the IC_{50} value up to 100 μM. **Conclusions.** The tested thiazolopyridines constitute an interesting background for further development of new chemotherapeutic agents.

K e y w o r d s: heterocyclic compounds, thiazolidinones, thiazolo[4,5-*b*]pyridines, antimicrobial activity, antiproliferative activity

Introduction

A wide range of infectious diseases caused by different pathogens is a main focus of the searching for new highly active and low-toxic antimicrobials in modern drug discovery. A special issue in this contest is occupied by heterocyclic compounds, due to their unique ability to mimic the structure of prokaryotic cell metabolites and to bind reversibly to diverse biotargets [1, 2]. Thus, considerable interest among antimicrobial drug-design strategies has been paid to thiazole derivatives and their structure-related analogues [3]. Noteworthy, the thiazole/thiazolidinone skeleton underlies the structure of wide antimicrobial drugs, namely, penicillins, monobactam antibiotics and sulfadrugs. Additionally, thiazolidinones have been identified as the multi-inhibitors of bacterial lactamase [4], UDP-galactopyranose mutase (UGM) [5], Sortase A (SrtA) [6], Protein mannosyl transferase 1 [5], Peptide deformylase [7], UDP-N-acetylmuramate/L-alanine ligase (MurC) [8] and MurD ligase [9]. However, the mentioned heterocycles possess wide spectra of other biological

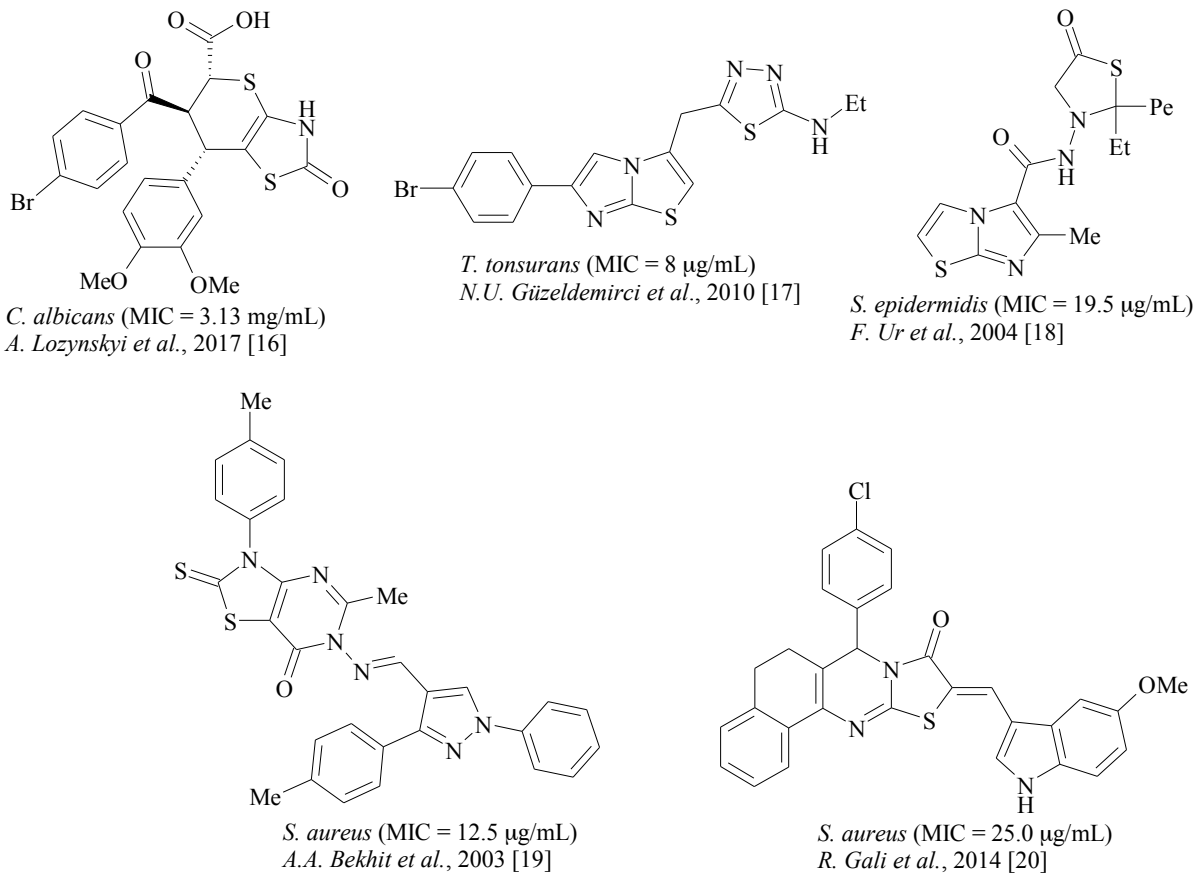

Fig. 1. Structures of fused thiazole/thiazolidinones with antimicrobial activity.

activities, especially anticancer [10, 11], antitripanosomal [12, 13], anti-inflammatory [14, 15]. Interestingly, the significant antimicrobial activity was also observed for fused thiazoles, especially thiopyrano[2,3-*d*]thiazoles [16], imidazo[2,1-*b*]thiazoles [17], azo[2,1-*b*] thiazoles [18], thiazolo[4,5-*d*]pyrimidines [19] and benzo[*h*]thiazolo[2,3-*b*]quinazolinones [20] (Figure 1). As a part of our research in the field of biologically active fused thiazoles, herein we report the antimicrobial and antiproliferative properties of some thiazolo[4,5-*b*] pyridine derivatives. Moreover, the pharmacological potential of thiazolopyridines has been associated with their affinity to various biotargets, especially the EGFR/ErbB family of protein-tyrosine kinases [21], histamine H_3-receptors [22], G-protein coupled receptors (mGluR 5) [23], fibrillar amyloid-β peptide (Aβ) [24], liver-selective glucokinase (GK) [25], 3',5'-cyclic adenosine monophosphate phosphodiesterase (PDE) III [26] *etc*. Noteworthy, we have previously established a significant antitumor activity of this class of compounds [27]. To take into account the above facts, it is promising to evaluate the biological activity of the mentioned compounds as realization of the polypharmacological strategy in the design of prospective drug-like molecules among the condensed 4-thiazolidinone derivatives.

Materials and Methods

Chemistry

The antimicrobial activity of three subtypes of thiazolopyridines, namely 5,7-diaryl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones (compounds I-II), 2-oxo-7-aryl-2,3-dihydrothiazolo[4,5-*b*] pyridine-5-carboxylic acids (compounds III–VI) and their amides (VII), was evaluated (Figure 2). A series of 5,7-diaryl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones (I-II), 2-oxo-7-aryl-2,3-dihydrothiazolo[4,5-*b*]pyridine-5-carboxylic acids (III–VI) were obtained via [3+3]-cyclization of 4-amino-5*H*-thiazol-2-one and chalcones or arylidene pyruvic acids (APAs) [28]. The target 7-(4-chlorophenyl)-2-oxo-2,3-dihydrothiazolo[4,5-*b*]pyridine-5-carboxylic acid (4-chlorophenyl)amide (VII) was synthesized from appropriate 2-oxo-7-phenyl-2,3-dihydrothiazolo[4,5-*b*]pyridine-5-carboxylic acid, which was transformed into acid chlorides and used in the acylation reaction of respective amine according to the protocol described previously [27].

Antimicrobial activity

The antimicrobial activity of the synthesized thiazolopyridines was estimated with the agar diffusion method [29]. Nutrient agar (0.5 % peptone, 0.3 % beef extract, 1.5 % agar, 0.5 % sodium chloride, distilled water, pH ~ 6.8) was used as a nutrient medium for *in vitro* antibacterial activity. *In vitro* antifungal activity was determined by using Sabouraud Agar plates. The test cultures suspensions (in concentration 1×10^7 CFU/ml), standardized previously by the optical standard of turbidity, were uniformly sown in Petri dishes with the nutrient agar. Aliquot part (20 μL) of 0.1 % tested thiazolopyridine derivatives (concentration 1000 μg/ml) in ethanol/dimethyl sulfoxide/water (2:1:1) was placed into wells (diameter of 4.0±0.1 mm) in agar in Petri plates with test microorganisms. Antibacterial and antifungal activities were estimated by measuring the diameter of inhibition zone of microbial

growth. The plates were incubated for 24 h at 37 °C for bacteria and for 24 h at 25 °C for fungi. The inhibition zone appeared after 24 h was measured in mm around the well in each plate. The digital images of culture growth on dishes were obtained and processed with a computer program UTHSCSA ImageTool 2.0 (UT Health San Antonio, © 1995–1996) for calculation of diameters of the growth inhibition zone. Each experiment was performed by three independent researchers. The results were expressed as the means ± S.D. The experiments were carried out on the microorganism strains, which were isolated from the ambulatory patients. The following isolated clinical strains of conditionally pathogenic bacteria were used: methicillin-sensitive *Staphylococcus aureus* (MSSA); methicillin-resistant *Staphylococcus aureus* (MRSA); methicillin-resistant *Staphylococcus haemolyticus* (MRSH) (extended spectrum β-lactamase (ESβL) producing); Gram-negative bacteria *Escherichia coli*; yeasts *Candida albicans*. All clinical strains were multidrug resistant (MDR) [30] and *Candida albicans* were resistant to fluconazole and clotrimazole. All compounds were also tested against the reference strains of *Staphylococcus aureus* (ATCC 25923 (F-49)), *Escherichia coli* (ATCC 25922), *Bacillus subtilis* (ATCC 6633), *Klebsiella pneumoniae* (ATCC 700603) and *Candida albicans* (ATCC 885-653) from the culture museum. Test-cultures were identified using chemical microtests "STAPHYtest 16" and "ENTEROtest 24" (Erba Lachema, Czech Republic). Fungi cultures were identified on the basis of 40 biochemical tests using the VITEK 2 system with the VITEK® 2 YST ID card (bioMérieux Corporate, France).

The sensitivity of strains to antibiotics was determined by disc-diffusion method and serial dilutions in agar. The MICs of the com-

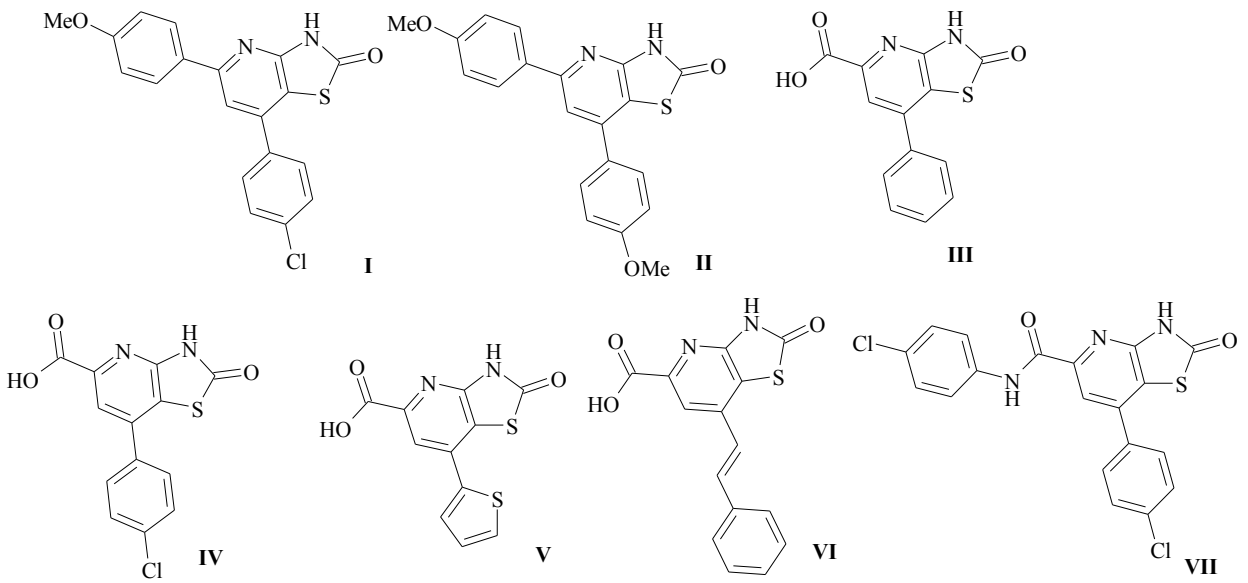

Fig. 2. Structures of tested thiazolo[4,5-*b*]pyridine derivatives **I–VII**.

pounds were determined using the microdilution methods for antimicrobial susceptibility [31, 32]. Microorganism suspensions were inoculated to the corresponding wells and incubated at 36 °C for 18 h for bacteria and at 25 °C for 24 h for fungi. The presence of the microorganism growth in the bouillon (bouillon turbidity) suggested that the concentration of the compound was insufficient to suppress its viability. The first lowest concentration of the tested compounds (from a series of dilutions), where the bacterial growth was not visually determined, was the minimum inhibitory concentration (MIC). The estimation of synergy with amoxicillin for synthesized compounds has been performed by comparison of amoxicillin MICs in the presence of compounds in subinhibitory concentrations [33]. The following bacterial strains with the resistance to β-lactam antibiotics were used: EsβL (extended spectrum β-lactamase)-producing *Klebsiella pneumonie* ATCC 700603; methicillin-resistant *Staphylococcus haemolyticus* (MRSH) with double mechanisms of β-lactam resistance included both atypical penicillin-binding protein PBP2* and β-lactamase activities. The production of the atypical penicillin-binding protein PBP2* was proved by the latex agglutination reaction (Slidex® MRSA Detection, bioMérieux Corporate, France). The results have been refined by variation statistics methods.

Antiproliferative activity

The HaCaT human keratinocites and HEK293 human embryonic kidney cells were obtained from Cell Collection of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology (Kyiv, Ukraine). The cells were cultured in Dulbecco's-modified Eagle medium (DMEM, Biowest, Nuaille, France) containing 10 % fetal bovine serum (Biowest, Nuaille, France) under standard conditions (37 °C, 5 % CO_2, 95 % humidity). The stock solution of studied compounds was prepared in DMSO and diluted with the culture medium to obtain a concentration range from 0.29 to 41.63 μg/mL. Cell viability was assessed after 72 h cultivation in the medium containing the studied compounds with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay kit (EZ4U, Biomedica, Vienna, Austria) according to the manufacturer's protocol. The optical density was measured with the Absorbance Reader BioTek ELx800 (BioTek Instruments, Inc., USA) at 490 nm with 630 nm as a reference wavelength. The percentage of the viability inhibition was calculated in comparison with the untreated control cells. The IC_{50} values (inhibition concentrations) are the compounds concentrations that inhibit the cell viability by 50 %, and were calculated by GraphPad Prism 6 software (San Diego, CA, USA) using nonlinear regression. Statistical analyses were performed using two-way ANOVA test with Dunnett's multiple comparisons test. $P < 0.05$ was considered as statistically significant.

Results and Discussion

Antimicrobial activity of the synthesized thiazolopyridines *in vitro* was evaluated with the agar diffusion method. The screening was carried out against reference and clinical strains of Gram-positive and Gram-negative bacteria and yeasts: *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Candida albicans*. Amoxicillin for bacteria and Amphotericin-B

Table 1. **Antimicrobial activity of thiazolopyridine derivatives.**

Compound	Zone of growth inhibition, mm*								
	S. aureus **(ATCC 25923 (F-49))**	***S. aureus*** **MSSA#**	***S. aureus*** **MRSA#**	***E. coli*** **(ATCC 25922)**	***E. coli#***	***B. subtilis*** **(ATCC 6633)**	***C. albicans*** **(ATCC 885-653)**	***C. albicans#***	
								Fungistatic	**Fungicidal**
I	4.15±0.08	4.65±0.08	7.03±0.64	0	0	0	5.43±0.21	5.91±0.22	5.58±0,14
II	5.01±0.35	4.78±0.45	4.95±0.46	0	0	0	0	0	0
III	3.71±0.21	4.76±0.29	4.47±0.41	0	0	6.74±0.45	5.12±0.22	6.21±0.36	0
IV	5.71±0.22	4.75±0.29	0	4.21±0.29	4.21±0.29	5.06±0.32	4.36±0.14	5.66±0.34	4.30±0.42
V	5.88±0.81	6.28±0.80	4.59±0.38	4.22±0.31	4.22±0.31	5.14±0.36	8.47±0,42	9.42±0,45	8.11±0.24
VI	4.35±0.22	4.20±0.27	6.18±0.83	4.74±0.29	4.74±0.29	0	6.19±0.40	6.39±0.50	5.21±0.76
VII	6.71±0.43	7.67±0.47	8.16±0.65	5.04±0.28	5.04±0.28	0	6.16±0.33	5.16±0.39	4.25±0.33
Amoxicillin	12.78±0.41	6.37±0.45	5.60±0.41	10.05±0.36	8.20±0.35	7.97±0.42	-	-	-
Amphotericin-B	-	-	-	-	-	-	11.00±0.51	9.00±0.65	-

clinical isolates

* Data are given as mean ± SD.

for fungi are taken as standard drugs. The screened compounds showed different mean zone of inhibition in the range of 00–9.42 mm against tested microorganisms (Table 1). The obtained results reveal that some of thiazolopyridine derivatives possess a moderate activity towards the tested microorganisms in the dose of 20 μg per well. Thus, antimicrobial activity assay allowed the identification of 2-oxo-7-thiophen-2-yl-2,3-dihydrothiazolo[4,5-*b*]pyridine-5-carboxylic acid **V** and 7-(4-chlorophenyl)-2-oxo-2,3-dihydrothiazolo[4,5-*b*]pyridine-5-carboxylic acid (4-chlorophenyl)amide **VII** with good growth inhibition against some tested microorganisms. The compound **V** shows the highest activity against clinical strain *Candida albicans* compared to standard drug Amphotericin-B. The compound **VII** displays a moderate antibacterial activity against *S. aureus* methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) strains. MICs for compounds **I–VII** against several microorganisms were calculated using the broth microdilution method (Table 2). The tested compounds exhibited the inhibitory activity against MSSA and MRSA *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* with MIC 12.5->50 μg/mL. Compound **V** showed a moderate activity towards *Candida albicans* with MIC 12.5 μg/mL. Compound **VII** exhibited at the same dilution inhibitory activity with MIC against MSSA and MRSA *Staphylococcus aureus* with MIC 50 μg/mL.

The derivatives **I-VII** were studied in the interaction with amoxicillin against multidrug

Table 2. **Minimum inhibitory concentration of tested compounds, μg/mL.**

Compound	***S. aureus*** **MSSA**	***S. aureus*** **MRSA**	***E. coli***	***C. albicans***
I	> 50	> 50	> 50	> 50
II	> 50	> 50	> 50	> 50
III	> 50	> 50	> 50	> 50
IV	> 50	> 50	> 50	> 50
V	> 50	> 50	> 50	12.5
VI	> 50	> 50	> 50	> 50
VII	50	50	> 50	> 50

resistant clinical isolates of ESβL+ *K. pneumonie* and MRSH (Tables 3–5). According to the preliminary results of interaction screening, the thiazolopyridine derivative with a styrene fragment in the molecule **VI** displays the promising synergistic activity with amoxicillin against ESβL + *K. pneumonie* and MRSH strains. Interestingly, in numerous literature reports, the styrene fragment combined with various heterocyclic systems exhibits a significant synergistic effect with beta-lactam antibiotics [34]. Especially it can be observed for the quinoline/quinaxoline-styrene hybrid molecules structurally related to thiazolopyridines [34, 35].

The SAR analysis showed that the antibacterial effect of compounds **I–VII** did not depend on the substituents at C5 and C7 of thiazolopyridine core. However, the thiazolo[4,5-*b*] pyridine-5-carboxylic acid **V** with thienyl substituent was the most active and demonstrated a good effect against *Candida albicans* with MIC 12.5 μg/mL. Compound **V** possessed also a slight activity on renal cancer A498 cell line (GP = 73.76 %) as described previously [28]. The antimicrobial activity of thiophene-based derivatives has already been observed in the previous systematic studies, especially for condensed benzothiophene [36], thieno[2,3-*d*] pyrimidine [37] and thieno[3,2-*c*]pyrazole derivatives [38]. Additionally, the experimental study revealed that the presence of an amide fragment in thiazolopyridine core of the compound **VII** is also favorable for antimicrobial potency. The data concerning a critical impact of electron withdrawing groups in amide fragment are also presented in our previous paper about thiazolopyridine-5-carboxylic acid amides as possible anticancer agents [27]. On the other hand, the compounds with phenyl, 4-chlorophenyl, 4-methoxyphenyl, styryl and carboxylic substituents at C5 and C7 on thiazolo[4,5-*b*]pyridine core were insufficient to show enhanced activity and didn't correlate with other types of activity typical for these compounds [27, 28] .

Next, we used the MTT assay to investigate cytotoxicity of the thiazolopyridine derivatives towards the pseudo-normal cell line (HaCaT human keratinocytes and HEK293 human em-

Table 3. **The synergistic interaction of thiazolopyridine derivatives with amoxicillin against ESβL$^+$ *Klebsiella pneumonie* ATCC 700603, zone of growth inhibition (mm), M±S(σ), MIC amoxicillin 250 μg/mL.**

Compounds	Control (medium without amoxicillin)	Media with amoxicillin			
		1/8 MIC (32 μg/mL)	1/16 MIC (16 μg/mL)	1/32 MIC (8 μg/mL)	1/64 MIC (4 μg/mL)
EtOH+DMSO	2.86±0.21	2.75±0.52	2.63±0.21	3.38±0.71	3.06±0.33
I	3.85±0.51	4.37±0.48	3.85±0.46	3.14±0.17	2.91±0.32
II	3.28±0.59	3.47±0.61	3.25±0.43	3.20±0.07	3.24±0.43
III	3.31±0.33	3.75±0.22	5.18±1.14	3.47±0.44	4.30±0.60
IV	3,46±0,57	2,95±0,39	2,95±0,17	4,70±0,39	2,66±0,14
V	3.03±0.43	4.04±0.65	3.16±0.45	3.05±0.19	2.67±0.36
VI	6.02±0.48 [12.73±0.83]	8.37±1.38 [13.20±1.05]	6.27±0,29 [11.06±1.25]	6.03±0,58 [15.47±2.16]	5.90±0.66 -
VII	3.25±0.37	2.34±0.16	[4.04±0.81]	[8.83±1.02]	3.79±0.68

in brackets — zones of partial inhibition of the bacterial growth (bacteriostatic effect).

Table 4. **The synergistic interaction of thiazolopyridine derivatives with amoxicillin against MRSH, zone of growth inhibition (mm), M±S(σ), MIC amoxicillin 4000 μg/mL.**

Compounds	Control (medium without amoxicillin)	Media with amoxicillin			
		1/8 MIC (500 μg/mL)	1/250 MIC (16 μg/mL)	1/500 MIC (8 μg/mL)	1/1000 MIC (4 μg/mL)
EtOH+DMSO	2.83±0.57	2.94±0.27	4.22±0.07	4.99±0.44	3.91±0.36
I	2.92±0.12	2.85±0.44	2.69±0.49	5.29±0.59	3.08±0.19
II	4.11±0.27	3.42±0.31	[11.31±0.24]	[11.03±0.29]	3.35±0.53
III	4.78±1.01	5.55±0.56	5.98±0.64	4.14±0,61	5.05±1.03
IV	2.92±0.25	3.25±0.47	3.17±0.32	3.97±0.87	3.15±0.11
V	3.28±0.56	3.75±0.40	4.77±0.44	6.29±0.31	8.51±2.55
VI	7.34±0.36 [13.66±0.72]	14.28±0.53 -	13.69±0.57 -	- [13.53±0.77]	- [13.07±0.32]
VII	3.52±0.65	3.18±0.11	4.44±0.68	2.83±0.43	7.51±1.32

in brackets — zones of partial inhibition of the bacterial growth (bacteriostatic effect).

Table 5. **The synergistic interaction of thiazolopyridine derivatives (50 μg/mL) with amoxicillin against β-lactamase producing bacteria.**

Compounds	*Klebsiella pneumonie* ATCC 700603		*Staphylococcus haemolyticus* # MRSH	
	Amoxicillin MIC	Fold reductions	Amoxicillin MIC	Fold reductions
Amoxicillin	256		4096	
+ Clavulanate	8	32	64	64
+I	256	1	4096	1
+II	256	1	1024	4
+III	256	1	2048	2
+IV	256	1	4096	1
+V	256	1	2048	2
+VI	32	8	128	32
+VII	256	1	4096	1

clinical isolate with both atypical penicillin-binding protein PBP2* and β-lactamase activities

bryonic kidney cells). We found that HaCaT and HEK293 demonstrated resistance to the thiazolopyridine derivatives treatment and did not reach the IC_{50} value at 28.73–41.63 μg/mL (Figure 3). Compound **I** at 36.88 μg/mL inhibited the growth of HaCaT cells by 30.2 %, HEK293 cells — by 42.8 %. Compound **IV** at 30.67 μg/mL inhibited the growth of HaCaT cells by 24.1 %, HEK293 cells — by 33.0 %. Compound **V** at 28.73 μg/mL reduced the viability of HaCaT cells by 14.3 %, of HEK293 cells — by 31.3 %. Compound **VI** reduced the viability of HaCaT cells by 7.0 %, of HEK293 cells — by 15.8 %. Under compound **VII** treatment at 41.63 μg/mL, we found 26.3 % of HaCaT cells growth inhibition, and 26.5 % of HEK293 cells growth inhibition (Figure 3).

Conclusions

The various subtypes of thiazolopyridines **I**–**VII** were evaluated for *in vitro* antibacterial activity against *Staphylococcus aureus*,

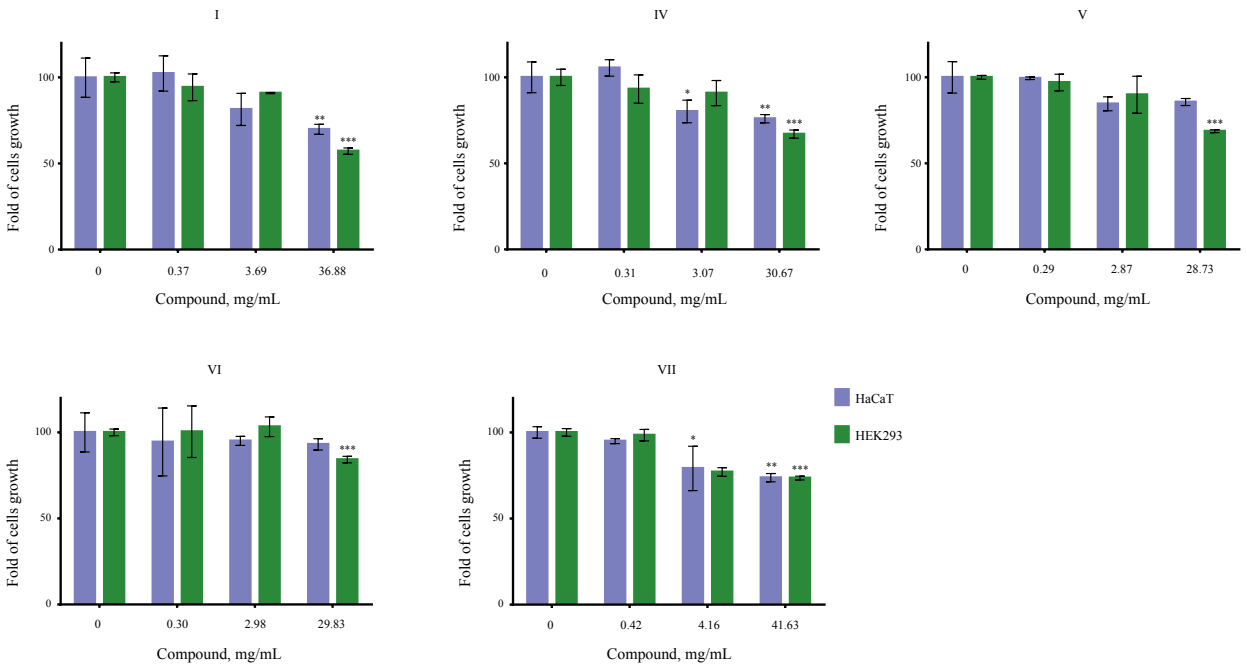

Fig. 3. Cytotoxic action of thiazolopyridine derivatives **I–VII** towards HaCaT human keratinocytes and HEK293 human embryonic kidney cells. The effect was measured by the MTT assay after 72 h of cells exposure. Data are presented as the mean ± SD. * – $P < 0.05$; ** – $P < 0.01$; *** – $P < 0.001$ compared with control (non-treated) cells.

Bacillus subtilis and *Escherichia coli* as well as for antifungal activity against *Candida albicans* using the agar diffusion and microbroth dilution methods. The antimicrobial screening led to the identification of the active compound **V** with the highest activity against *Candida albicans* (MIC = 12.5 μg/mL). The synergism of action with amoxicillin allowed the distinguishing of the most active compound **VI** with good antimicrobial activity against ESβL + *K. pneumonie* and *Staphylococcus haemolyticus* (MRSH) strains. Compounds **I**, **IV–VII** in concentrations of 0–41.63 μg/mL demonstrated low cytotoxicity against HaCaT human keratinocytes and HEK293 human embryonic kidney cell lines. Considering the above, the thiazolopyridine derivatives are justified as a fruitful template for the development of a new class of chemotherapeutic agents in the modern drug discovery.

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Антимікробна та цитотоксична активність похідних тіазоло[4,5-*b*]піридину

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Мета. Здійснити скринінг протимікробної та цитотоксичної активності похідних тіазоло[4,5-*b*]піридину. **Методи.** Вивчення антибактеріальної та протигрибкової активностей синтезованих сполук проведено *in vitro* методом дифузії в агар та мікрометодом серійних розведень в агарі відносно клінічних та музейних штамів грампозитивних, грамнегативних бактерій та дріжджів. Встановлено взаємозв'язок структура-антибактеріальна/протигрибкова активність для досліджуваних сполук. Проведено оцінку цитотоксичності цільових сполук відносно клітинних ліній HaCaT та HEK293 (МТТ-тест). **Результати.** Найвища антимікробна активність спостерігалася для 2-оксо-7-тіофен-2-іл-2,3-дигідротіазоло[4,5-*b*]піридин-5-карбонової кислоти (сполука V) із значенням мінімальної інгібуючої концентрації (МІК) 12.5 μg/mL відносно *Candida albicans*. Одночасно для синтезованих сполук досліджувався синергізм взаємодії з амоксициліном відносно мультирезистентних клінічних ізолятів ESβL$^+$ *Klebsiella pneumonie* та *Staphylococcus haemolyticus* (MRSH). Найкращий синергізм взаємодії з амоксициліном спостерігався для сполуки VI. Кератиноцити людини лінії HaCaT та клітини ембріональної нирки людини HEK293 продемонстрували стійкість до дії на них похідних тіазолопіридину із значенням IC_{50} менше 100 μM. **Висновки.** Досліджувані похідні тіазолопіридину становлять цікаву платформу для подальшої розробки нових хіміотерапевтичних лікарських засобів.

Ключові слова: гетероциклічні сполуки, тіазолідинони, тіазоло[4,5-*b*]піридини, протимікробна активність, антипроліферативна активність

Антимикробная и цитотоксическая активность производных тиазоло[4,5-*b*]пиридина

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Цель. Осуществить скрининг противомикробной и цитотоксической активности производных тиазоло[4,5-*b*]пиридина. **Методы.** Изучение антибактериальной и противогрибковой активности синтезированных соединений проведено *in vitro* методом диффузии в агар и микрометодом серийных разведений в агаре относительно клинических и музейных штаммов грамположительных, грамотрицательных бактерий и дрожжей. Установлена взаимосвязь структура-антибактериальная/противогрибковая активность для исследуемых соединений. Проведена оценка цитотоксичности целевых соединений относительно клеточных линий HaCaT и HEK293 (МТТ-тест). **Результаты.** Наивысшая антимикробная активность наблюдалась для 2-оксо-7-тиофен-2-ил-2,3-дигидротиазоло[4,5-*b*]пиридин-5-карбоновой кислоты (соединение V) со значением минимальной ингибирующей концентрации (МИК) 12.5 μg/mL относительно *Candida albicans*. Одновременно для синтезированных соединений исследовался синергизм взаимодействия с амоксициллином относительно мультирезистентных клинических изолятов ESβL$^+$ *Klebsiella pneumonie* и *Staphylococcus haemolyticus* (MRSH). Лучший синергизм взаимодействия с амоксициллином наблюдался для соединения VI. Кератиноциты человека линии HaCaT и клетки эмбриональной почки человека HEK293 продемонстрировали устойчивость к действию на них производных тиазолопиридина со значением IC_{50} менее 100 μM. **Выводы.** Исследуемые производные тиазолопиридина составляют интересную платформу для дальнейшей разработки новых химиотерапевтических лекарственных средств.

Ключевые слова: гетероциклические соединения, тиазолидиноны, тиазоло[4,5-*b*]пиридины, противомикробная активность, антипролиферативная активность.

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