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Antimicrobial activity of some 5-aminomethylene-2-thioxo-4-thiazolidinones

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Aim. To study the antimicrobial properties of 2-thioxo-4-thiazolidinone enaminone derivatives with a L-β-phenyl-α-alanine fragment in molecule. **Methods.** Diffusion in agar; serial dilutions in agar. Clinical isolates of microorganisms: methicillin-sensitive strain of *Staphylococcus aureus* (MSSA), methicillin-resistant strain of *Staphylococcus aureus* (MRSA), methicillin-resistant strain of *Staphylococcus haemolyticus* (MRSH), *Escherichia coli*; *Pseudomonas aeruginosa*, ESβL + *Klebsiella pneumonia*, *Candida albicans*, *Candida tropicalis*. **Results.** Screening of antimicrobial activity of 13 new2-thioxo-4-thiazolidinone derivatives was carried out. The methicillin-resistant strain of *Staphylococcus aureus* (MRSA) was the most sensitive to the tested compounds. A number of derivatives exhibit synergism in combination with amoxicillin against the ESβL+ *Klebsiella pneumonia* strain. The structure-antimicrobial activity relationshipis was analyzed in detail. **Conclusions.** The tested 5-R-aminomethylene derivatives of ethyl 2-(4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropionic acid exhibit the

moderateanti microbial activity against gram-positiveand gram-negative bacteria, as well as against *Candida* fungi. The antimicrobial activity of the tested compounds depends on the structure of the enamine fragment.

K e y w o r d s: antibacterial,antifungal activity;4-thiazolidinones, enaminones

Introduction

The antimicrobial drug discovery is an actual and important area in modern bioorganic and medicinal chemistry [1,2]. The emergence of microbial cells resistance to known antimicrobial drugs is the main problem and simultaneously the main motive force for deep research in this field [3-5]. Despite the success in this process, the current antibiotic detection model does not deliver new agents at a rate sufficient to combat the current level of antibiotic resistance. A number of biological, pharmacological, chemical and sometimes philosophical approaches are proposed for the solution of this problem: a) deep understanding of the complex mechanisms of existing antibiotics action; b) hybridization and activity synergism of some substances with antimicrobial effect; c) search for narrow spectrum antiobiotics; d) screening of potential antimicrobial agents among the new classes of chemical compounds, *etc* [6-8]. The 4-thiazolidinone derivatives represent considerable interest for *de novo* design of antibacterial agents. Potential antibacterial ligands such as selective and multiinhibitors of Mur B, C, D, E, F; penicillin – binding proteins inhibitors (PBPs); inhibitors of β-lactamase A and C; inhibitors of peptide deformylase; inhibitors of mannosyl transferase 1 (PMT1) were identified among these heterocycles [9-13]. Also, in some structure – activity relationship studies (SAR analysis) it had been shown that incorporation of aromatic amino acids into organic compounds significantly improves the potency and selectivity of antibacterial activity [14]. As part of our research in the field of biologically active heterocycles [15-18], herein we report the antimicrobial properties of new 5-enamine-4-thiazolidones with L-β-phenyl-α-alanine fragment in molecules [19]. Noteworthy, we have previously established an interesting antitumor and antitrypanosomal activity of this class of compounds. Moreover, the activity type significantly depends on the structure features of enamine fragment in C5 position of 2-thioxo-4-thiazolidinone core. Taking into account the above facts, it is promising to study other types of activity of the compounds as a realization of the polypharmacological strategy in the design of potential drug-like molecules among 4-thiazolidinones [20,21].

Materials and Methods

Chemistry. Synthetic procedure and physical-chemical properties of compounds **1-13** have been described earlier [19].

Antimicrobial activity The antimicrobial activity of the synthesized compounds was determined using a method of diffusion into agar. 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. 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. Aliquots (20 μL) of 0.1 % of the test compounds (concentration 1000 μg/ml) in EtOH/DMSO/water (2:1:1) were placed into wells (diameter of 4.0±0.1 mm) in agar in Petri dishes with test microbes. The antimicrobial activity was evaluated by measuring the diameter of inhibition zone of microbial growth. The plates were incubated for 24 h at 37 ◦C. The inhibition zone appeared after 24 h and was measured in mm around the well in each plate. Digital images of culture growth on dishes [were] obtained and processed with a computer program UTHSCSA ImageTool 2.0 (The University of Texas Health Science Center in San Antonio, ©1995-1996) for calculation of growth inhibition zone diameters. The experiments were performed in triplicate, and standard deviation was calculated. The experiments were carried out on microorganism strains, which were isolated in the laboratory of the microbiology research of the Department of Microbiology, Virology and Immunology of the Ivano-Frankivsk National Medical University from ambulatory patients. The following isolated clinical strains of conditionally pathogenic bacterial strains 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*; *Klebsiella pneumoniae*; *Pseudomonas aeruginosa*; yeasts *Candida albicans*; *Candida tropicalis*. Test-cultures were identified using chemical micro-tests "STAPHYtest 16" and "ENTEROtest 24" (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 (bioMerieux, France). Antimicrobial drug sensitivity patterns of used microbail strains are presented in Table 1.

Table 1. **Characterization of used microbial strains**

Compound	Origin	Disk diffusion antibiotic susceptibility testing, zone of inhibition (in mm) after 24 h incubation						
Staphylococci		Oxacillin, 10,0 μg	Cefazolin, 30,0 μg	Ofloxacin, 5,0 μg	Erythromycin, 15,0 μg	Gentamycin, 10,0 μg	Vancomycin, 30,0 μg	Linezolid, 30,0 μg
S. aureus MSSA	wound	23S	28 S	25 S	15	15 S	18 S	36 S
S. aureus MRSA	wound	– R	10 R	10 R	– R	– R	17 S	34 S
S. haemolyticus MRSH	wound	– R	– R	9 R	– R	– R	15 S	30 S
Gram-negative bacteria		Cefoperazone, 75,0 μg	Cefoperazone / Sulbactam, 75,0 / 30,0 μg	Ceftazidime, 30,0 μg	Imipenem, 10,0 μg	Ofloxacin, 5,0 μg	Gentamycin, 10,0 μg	Colistin, 10,0 μg
E. coli	urine	14 R	21 S	12 R	23 S	– R	18 S	11 S
K. pneumoniae	sputum	17 R	21 S	16 R	21 S	18 R	16 S	12 S
P. aeruginosa	wound	– R	14 R	– R	13 R	– R	– R	12 S
Gram-negative bacteria		Amphotericin B, 20,0 μg	Nystatin, 100U	Fluconazole, 10,0 μg	Ketoconazole, 10,0 μg	Itraconazole, 10,0 μg	Clotrimazole, 10,0 μg	Terbinafine, 30,0 μg
C. albicans	oral mucosa	9 R	14 R	30 S	25 S	15 R	23 S	– R
C. tropicalis	sputum	– R	14 R	24 S	20 S	11 R	15 R	10 R

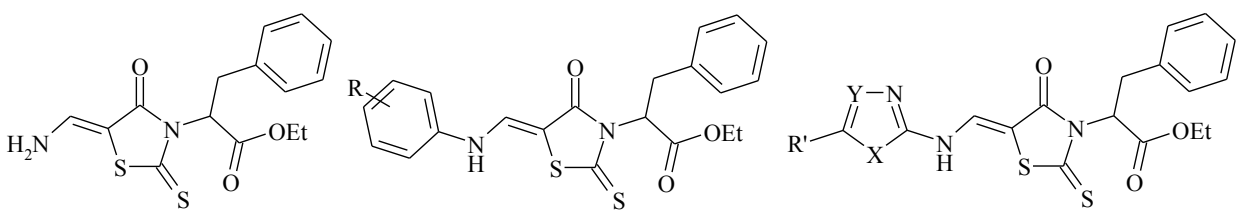
" - " – no inhibition were observed in experiment; S – sensitive and R – resistant according to EUCAST 2017 criteria.

The sensitivity of strains to antibiotics was determined by disco-diffusion method and serial dilutions in agar. The minimum inhibitory concentrations (MICs) of the compounds were determined using the microdilution susceptibility method [22]. Microorganism suspensions were inoculated to the corresponding wells. Plates were incubated at 36 ◦C for 18 h for bacteria and fungi, respectively. The presence of the microorganism growth in the bouillon (bouillon turbidity) suggested that 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 considered to be the minimum inhibitory concentration (MIC). The estimation of interaction with amoxicillin and co-amoxiclav (amoxicillin/clavulanic acid) for synthesized compounds has been performed on the growing medium with subbacteriostatic concentration of oxacillin (1/4-1/16 MIC) relative to resistant strains [23]. The following isolated clinical strains of conditionally pathogenic bacterial strains with resistance to β-lactam antibiotics were used: ESβL (β-lactamase of the extended action spectrum)-producing *Klebsiella pneumonie*; methicillin-resistant *Staphylococcus haemolyticus* (MRSH) with atypical penicillin-binding protein PBP2* and β-lactamase activities. The production of the atypical penicillin-binding protein PBP2* was determined in the latex agglutination reaction (Slidex® MRSA Detection, bioMerieux, France). The results have been processed by variation statistics methods.

Results and Discussion

The screening of the data reveal that almost all tested compounds demonstrated a moderate antibacterial effect against both Gram-positive and Gram-negative strains (Fig. 1, Tables 2, 3).

The best levels of zone inhibition and MIC values were observed against the *MRSA*. Six compounds showed a satisfactory activity against the *MRSA* and derivatives **7** and **11** were the most active with MIC 3.12 μg/mL and 12.5 μg/mL respectively. The compounds **2**, **4**, **9**, **12** were characterized by a slightly lower inhibitory activity and their MIC for



1 **2-10** **11-13**

2. R=H; **3**. R=4-F; **4**. R=4-Cl;**5**. R=2-NO_2-4-Cl;
6. R=2-OMe-5-Cl; **7**. R=4-SO_2NH_2;
8. R=2-Me-5-(morpholine-4-sulfonyl);
9. R=4-SO_2SEt; **10**. R=4-COOEt.

11. X=S, Y=CH, R'=H;
12. X=S, Y=CH, R'=2,4-Cl_2-$C_6H_4CH_2$;
13. X=Y=N, R'=H.

Fig. 1. Structures of tested 2-(5-R-aminomethylene-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropionic acid ethyl ester derivatives **1**-**13**.

Table 2. In vitro **antimicrobial activity of compounds 1-13. Zone of growth inhibition (mm), M±S(σ)**

Compound	Zone of inhibition (in mm) at conc. 200 µg/mL after 24 h						
	In vitro antibacterial activity					*In vitro* antifungal activity	
	S. aureus MSSA	*S. aureus* MRSA	*E. coli*	*S. haemolyticus* MRSH	*P. aeruginosa*	*C. albicans*	*C. tropicalis*
1	6,03±0,77	4,85±0,33	4,50±0,10	–	–	4,96±0,24	4,33±0,57
2	–	–	–	–	4,26±0,12	4,00±0,24	–
3	–	4,57±0,31	5,22±0,44	–	–	–	4,36±0,36
4	5,20±0,38	5,71±0,23	–	–	–	5,37±0,39[a] 4,94±0,54[b]	–
5	–	–	–	–	–	–	–
6	–	–	–	–	–	4,24±0,26	–
7	7,88±0,79	6,61±0,89	–	–	–	–	–
8	4,47±0,18	–	5,65±0,22	–	–	4,38±0,32	–
9	7,79±0,56	10,15±0,80	–	–	–	8,20±0,38[a] 5,56±0,19[b]	–
10	–	–	–	–	–	–	4,95±0,36
11	5,04±0,35	–	4,35±0,26	–	–	5,91±0,77[a] 5,04±0,44[b]	-
12	6,63±0,46	6,10±0,76	–	–	–	–	–
13	5,30±0,31	5,97±0,60	4,48±0,32	–	–	6,00±0,38[a] 5,00±0,19[b]	–
Streptomycin, 10,0 µg/ml	7,59±0,49	6,92±0,53	8,45±0,74	6,42±0,35	6,60±0,42	–	–
Amphotericin-B, 10,0 µg/ml	–	–	–	–	–	6,79±0,65[a] 4,11±0,37[b]	6,13±0,65

" **-** " – no inhibition were observed in experiment; [a] – fungistatic action; [b] – fungicidal action.

Table 3. **MIC, MBC, MFC of compounds 1-13, µg/mL**

Compounds	MIC (MBC/MFC)					
	S. aureus MSSA	*S. aureus* MRSA	*E. coli*	*Ps. aeruginosa*	*C. albicans*	*C. tropicalis*
1	>100 (>100)	50 (>100)	100 (>100)	25 (50)	50 (100)	100 (>100)
2	50 (50)	25 (>100)	50 (>100)	50 (100)	50 (>100)	25 (50)
3	>100 (>100)	>100 (>100)	25 (>100)	6,25 (50)	50 (100)	50 (100)
4	6,25 (50)	25 (>100)	12,5 (100)	50 (100)	50 (100)	25 (100)
5	100 (>100)	50 (100)	50 (100)	50 (>100)	25 (100)	100 (>100)
6	>100 (>100)	100 (100)	50 (100)	50 (50)	50 (100)	50 (50)
7	>100 (>100)	3,12 (6,25)	100 (100)	50 (100)	25 (100)	100 (100)
8	>100 (>100)	>100 (>100)	50 (>100)	12,5 (50)	25 (25)	50 (50)
9	25 (25)	25 (25)	25 (50)	50 (>100)	25 (25)	25 (50)
10	>100 (>100)	50 (>100)	50 (50)	25 (50)	>100 (>100)	100 (100)
11	>100 (>100)	12,5 (>100)	3,12 (100)	25 (50)	12,5 (100)	25 (100)
12	>100 (>100)	25 (50)	50 (50)	50 (100)	25 (100)	100 (100)
13	>100 (>100)	>100 (>100)	>100 (>100)	25 (50)	25 (25)	25 (100)

MRSA strain was 25 μg/mL. The similar pattern of activity was observed against *Ps. aeruginosa*. The derivatives **3** and **8** display good activity level with MIC 6.5 μg/mL and 12.5 μg/mL respectively. The compounds **1**, **10**, **11**, **13** were exhibited slightly lower inhibitory activity with MIC against *Ps. Aeruginosa* 25 μg/mL. The activity of the tested compounds against *E. coli* was somewhat lower compared to activity against *MRSA* and *Ps. aeruginosa*. The derivatives **11** and **4** were the most active with MIC 3,12 μg/mL and 12,5 μg/mL respectively. The compounds **2**, **3**, **5**, **6**, **8**, **9**, **10**, **12** exhibited inhibitory activity against *E. coli* with MIC 25-50 μg/mL. Interestingly, however, that almost all the compounds were practically inactive to the strain *MSSA*. Only derivatives **4** and **9** were active with MIC 6,25 μg/mL and 25 μg/mL respectively. No significant activity for the tested compounds in individual form against *MRSH* was observed.

The derivatives **4**, **9**, **11** and **13** were estimated in the interaction with amoxicillin and co-amoxiclav (amoxicillin/clavulanic acid) against multidrug resistant clinical isolates of ESβL$^+$ *K. pneumonie* and *MRSH* (Tables 4,5).

According to the preliminary interaction screening results, the derivative **13** displays promising synergistic activity with amoxicillin against ESβL$^+$ *K. pneumonie* strain. The similar results were obtained for derivatives **4** and **9** with amoxicillin against *MRSH*. However, any positive activity changes in the combinations of tested compounds with co-amoxiclav were not observed against both ESβL$^+$ *K. pneumonie* and *MRSH*.

The antifungal activity screening results have shown that tested compounds display potent activity against *C. albicans* (Tables 2, 3). The derivative **11** was the most active with MIC 12.5 μg/mL and the compounds **1-9**, **12**, **13** exhibited inhibitory activity against *C. albicans* with MIC 25-50 μg/mL. The antifungal activity against *C. tropicalis* was a slightly lower and derivatives **2**, **3**, **4**, **6**, **8**, **9**, **11**, **13** were the most active with MIC 25-50 μg/mL.

The SAR analysis showed that the antibacterial effect of compounds **1-13** depends on the structure features of the enamine fragment. The compound **1** with unsubstituted NH_2-group displayed the equivalent activity level to compound **2** with phenyl group. However, the activity level of these compounds was not satisfactory. Introduction of halogen atoms (F, Cl) into position 4 of benzene ring improved the activity (compounds **3**, **4**), but additional NO_2 – or MeO-groups and change [in the] halogen position (compounds **5**, **6**) provoke a decrease in the activity. The derivative **9** with 4-ethylsulfanylthiosulfonylphenyl substituent was the most active and demonstrated a good effect against all tested microorganisms with MIC 25 μg/mL. The change of 4-EtS-group in **9** to 4-NH_2-group (compound **7**) provides an increasing selectivity against *MRSA* (MIC 3.12 μg/mL) but generally decreasing activity. The similar pattern of activity decreasing was observed for the transformation of the sulfonyl-group into position 2 of benzene ring and the additional introduction of CH_3-group and morpholine cycle (compound **8**). Also, compound **10** with isosteric COOEt-group showed a lower activity than **9**. The derivative with unsubstituted thiazole rings (**11**) displayed good level of activity against *E. coli* (MIC 3.12 μg/mL) and *MRSA* (MIC 25 μg/mL), but introduction of 2,4-dichlorobenzyl-fragment into thiazole ring (compound **12**) provides a lower

Table 4. **The synergistic interaction of 4, 9, 11, 13 with amoxicillin against ESβL$^+$ *Klebsiella pneumonie* and *MRSH* (zone of growth inhibition (mm), M±S(σ))**

Mediums with amoxicillin	EtOH+DMSO	Compounds			
		4	**9**	**11**	**13**
ESβL$^+$ *Klebsiella pneumonie* (MIC amoxicillin 250 μg/mL)					
Control (medium without amoxicillin)	–	–	4,88±0,52	–	–
1/8 MIC (32 μg/mL)	–	4,26±0,04	–	–	–
1/16 MIC (16 μg/mL)	–	–	–	–	4,58±0,50
1/32 MIC (8 μg/mL)	–	–	–	–	5,09±0,46
1/64 MIC (4 μg/mL)	–	–	–	–	4,07±0,87
MRSH *Staphylococcus haemolyticus* (MIC amoxicillin 4000 μg/mL)					
Control (medium without amoxicillin)	–	4,24±0,87	10,05±0,20	–	4,01±0,22
1/8 MIC (500 μg/mL)	–	–	6,83±0,22	–	4,17±0,58
1/250 MIC (16 μg/mL)	4,22±0,07	6,19±0,16	5,42±0,15	–	4,23±0,18
1/500 MIC (8 μg/mL)	4,99±0,44	5,76±0,82	–	–	–
1/1000 MIC (4 μg/mL)	–	–	–	4,15±0,50	5,27±0,34

" **-** " – no inhibition were observed in experiment.

Table 5. **The synergistic interaction of 4, 9, 11, 13 with co-amoxiclav (amoxicillin/clavulanic acid) against ESβL$^+$ *Klebsiella pneumonie* and *MRSH* (zone of growth inhibition (mm), M±S(σ))**

Mediums with co-amoxiclav	EtOH+DMSO	Compounds			
		4	**9**	**11**	**13**
ESβL$^+$ *Klebsiella pneumonie* (MIC co-amoxiclav 8/1,6 μg/mL)					
Control (medium without co-amoxiclav)	–	–	[8,32±0,90]	–	5,00±0,94
1/4 MIC (2/0,4 μg/mL)	4,28±0,56	[8,38±1,50]	[12,38±1,18]	12,41±0,27	–
1/8 MIC (1/0,2 μg/mL)	4,39±0,78	–	[8,00±0,84]	–	–
1/16 MIC (0,5/0,1 μg/mL)	5,27±1,13	–	[10,27±2,09]	[6,62±0,64]	[5,55±1,55]
MRSH *Staphylococcus haemolyticus* (MIC co-amoxiclav 64/12,5 μg/mL)					
Control (medium without co-amoxiclav)	–	–	–	4,17±0,52	5,02±0,38
1/8 MIC (8/1,6 μg/mL)	–	4,44±0,46	4,45±0,48	14,66±2,31	–
1/16 MIC (4/0,8 μg/mL)	–	2,82±0,40	–	–	–

#in brackets - zones of partial inhibition of the bacterial growth (bacteriostatic effect)

activity. The presence of 4*H*-[1.2.4]-triazol-3-ylamine-subtituent (**13**) was good, especially for antifungal activity. So, from the SAR viewpoint it was not established clear dependence of the influence of electron-donating or electron-withdrawing groups on the activity realization.

Noteworthy, the tested 5-enamine-rhodanines **1-13** possess a higher antimicrobial activity than unsubstituted in N3 position thiazolidin-2,4-dione [15] and 2-thioxo-4-thiazolidinone [16] analogs. This indicates the positive impact of introducing the amino acid fragments into the 4-thiazolidinone scaffold

for the design of antimicrobial agents. In addition to increasing activity, the presence of the phenylalanine moiety promotes a higher selectivity of the tested compounds to MRSA (Tables 2,3). But the tested compounds **1-13** are less active compared with unsubstituted in N3 position 4-thioxo-2-thiazolidinone analogs [15].

Conclusions

The antimicrobial screening of 13 new 2-thioxo-4-thiazolidinones against Gram-positive, Gram-negative microorganisms and *Candida* fungi was performed and the results are described in this paper. It was found that some derivatives have potential antimicrobial activity against *S. aureus* methicillin-resistant (MRSA) strain, *Ps. aeruginosa*, *C. albicans* and are attractive as a novel template for the design of new synthetic antibacterial/antifungal agents. Some derivatives displayed promising synergistic activity with amoxicillin against multiresistant strain of clinical isolates of ESβL$^+$ *K. pneumonie* and *MRSH* and can be used for the development of new combined antimicrobial chemotherapeutic agents.

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Особливості антимікробної активності деяких 5-амінометилен-2-тіоксо-4-тіазолідинонів

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Мета. Вивчення протимікробних властивостей єнамінових похідних 2-тіоксо-4-тіазолідинону з фрагментом L-β-феніл-α-аланіну в молекулі. **Методи.** Мікрометод дифузії в агар; мікрометод серійних розведень в агарі. Тест-об'єкти – клінічні ізоляти мікроорганізмів: метіцилінчутливий штам *Staphylococcus aureus* (MSSA), метіцилінрезистентний штам *Staphylococcus aureus* (MRSA), метіцилінрезистентний штам *Staphylococcus haemolyticus* (MRSH), *Escherichia coli*; *Pseudomonas aeruginosa*, ESβL$^+$ *Klebsiella pneumonie*, *Candida albicans*, *Candida tropicalis*. **Результати.** Проведено скринінг протимікробної активності 13 нових похідних 2-тіоксо-4-тіазолідинону. Встановлено, що найбільш чутливим до досліджуваних виявився метіцилінрезистентний штам *Staphylococcus aureus* (MRSA). Ряд 2-тіоксо-4-тіазолідинонів проявляють синергізм при комбінованому застосуванні з амоксициліном по відношенню до штаму ESβL$^+$ *Klebsiella pneumonie*. Детально проаналізовано взаємозв'язок "структура-протимікробна активність". **Висновки.** Тестовані 5-*R*-амінометилен-похідні етилового естеру 2-(4-оксо-2-тіоксотіазолідин-3-іл)-3-фенілпропіонової кислоти проявляють помірну протимікробну активність по відношенню грам-позитивних та грам-негативних бактерій, а також грибів роду *Candida*. Протимікробна активність тестованих сполук залежить від структурних особливостей в єнамінового фрагменту.

Ключові слова: антибактеріальна, протигрибкова активність; 4-тіазолідинони; єнамінони

Особенности противомикробной активностинекоторых 5-аминометилен-2-тиоксо-4-тиазолидинонов

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Цель. Изучение противомикробных свойств енаминовых производных2-тиоксо-4-тиазолидинонас фрагментом L-β-фенил-α-аланина в молекуле. **Методы.** Микрометод диффузиив агар; микрометод серийных разведений вагаре. Тест-объекты — клинические изоляты микроорганизмов: метициллинчуствительный штамм *Staphylococcus aureus* (MSSA), метициллинрезистентний штамм *Staphylococcus aureus* (MRSA), метициллинрезистентний штамм *Staphylococcus haemolyticus* (MRSH), Escherichia coli; *Pseudomonas aeruginosa*, ESβL+*Klebsiella pneumonie*, *Candida albicans*, *Candida tropicalis*. **Результаты.** Проведён скринингпротивомикробной активности 13 новых производных 2-тиоксо-4-тиазолидинона. Установлено, что наиболее чувствительным к исследуемым соединениям является метициллинрезистентный штамм *Staphylococcus aureus* (MRSA). Ряд производных проявляют синергизм при одновременном применении с амоксициллинлом по отношению к штамму ESβL+*Klebsiella pneumonie*. Подробно проанализирована взаимосвязь «структура-противомикробное активность». **Выводы.** Тестированные 5-R-аминометилен производные этилового эфира 2-(4-оксо-2-тиоксотиазолидин-3-ил)-3-фенилпропионовой кислоты проявляют умеренную противомикробную активность по отношению к грамположительными грамотрицательным бактериям, а также грибам рода *Candida*. Противомикробная активность исследованы соединений зависит от особенностей структуры енаминового фрагмента.

Ключевые слова: антибактериальная, противогрибковая активность; 4-тиазолидиноны; енаминоны

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