

THE SYNTHESIS AND THE STUDY OF ANTIMICROBIAL PROPERTIES OF 5-R,R'-AMINOMETHYLENE DERIVATIVES OF THIAZOLIDINE-2,4-DIONE AND 4-THIOXOTHIAZOLIDINE-2-ONE

G.O.Derkach¹, S.M.Golota^{2,3}, V.V.Zasidko¹, I.I.Soronovych³, R.V.Kutsyk¹, R.B.Lesyk²

¹Ivano-Frankivsk National Medical University

²Danylo Halytsky Lviv National Medical University

³Lviv Medical Institute

Key words: 4-thiazolidin(thi)one; 5-aminomethylene derivatives; multiresistance; antimicrobial activity

The study is devoted to the rational search of modern potential antimicrobial agents among of 4-thiazolidine(thi) ones. 5-R,R'-Enamin(thi)ones of thiazolidinone series have been tested for design and the initial screening of the antibacterial properties. The use of 5-ethoxymethylene derivatives of thiazolidine-2,4-dione and 4-thioxothiazolidin-2-one as effective "building blocks" for the synthesis of small libraries of bioactive compounds has been proposed. Nucleophilic substitution reactions between 5-ethoxymethylene derivatives and amino alcohols, the primary and secondary functionalized aromatic and heteroaromatic amines, heterocyclic amines (piperidine and substituted pyrazolines) have been studied. The pharmacological screening of the antimicrobial activity for the enamin(thi)ones synthesized on clinical isolates of staphylococci with different resistance mechanisms to protected β -lactams and multiresistance strains of *E. coli* and *Ps. Aeruginosa* has been performed. Compounds with a distinct antimicrobial effect have been identified. They can also increase the sensitivity of *S. aureus* and *S. haemolyticus* clinical strains to oxacillin, and can be used to create new combined antimicrobial chemotherapeutic agents. The "structure – antimicrobial activity" relationships for design and search for new antimicrobial agents have been analysed.

СИНТЕЗ І ДОСЛІДЖЕННЯ АНТИМІКРОБНИХ ВЛАСТИВОСТЕЙ 5-R,R'-АМІНОМЕТИЛЕНПОХІДНИХ ТІАЗОЛІДИН-2,4-ДІОНУ ТА 4-ТІОКСОТІАЗОЛІДИН-2-ОНУ

Г.О.Деркач, С.М.Голота, В.В.Засідко, І.І.Соронович, Р.В.Куцьок, Р.Б.Лесик

Ключові слова: 4-тіазолідин(ті)они; 5-амінометиленпохідні; мультирезистентність; антимікробна активність

Дослідження присвячене раціональному пошуку сучасних потенційних антимікробних агентів серед похідних 4-тіазолідин(ті)онів. Здійснено спробу дизайну та первинного скринінгу антибактеріальних препаратів на основі 5-R,R'-єнамін(ті)онів тіазолідинового ряду. Запропоновано використання 5-етоксиметилентіазолідин-2,4-діону та 4-тіоксотіазолідин-2-ону як ефективних «структурних блоків» для синтезу малих бібліотек біологічно активних сполук. Вивчені реакції нуклеофільного заміщення 5-етоксиметилентіазолідинонів з аміноспиртами, функціоналізованими первинними і вторинними ароматичними та гетероароматичними амінами, гетероциклічними амінами (піперидин та заміщені піразоліни). Проведено фармакологічний скринінг антимікробної активності синтезованих єнамінів щодо клінічних ізолятів стафілококів з різними механізмами резистентності до захищених β -лактаміє та поліантибіотикорезистентних штамів *E. coli* і *Ps. Aeruginosa*. Ідентифіковані сполуки з виразним антимікробним ефектом, здатні підвищувати чутливість клінічних штамів *S. aureus* і *S. haemolyticus* до оксациліну, що може бути використано при створенні нових комбінованих антимікробних хіміотерапевтичних засобів. Проаналізовано залежність зв'язків «структура – антимікробна активність» для спрямованого дизайну та пошуку нових антибактеріальних і протигрибкових агентів.

СИНТЕЗ И ИССЛЕДОВАНИЕ ПРОТИВОМИКРОБНЫХ СВОЙСТВ 5-R,R'-АМИНОМЕТИЛЕНПРОИЗВОДНЫХ ТИАЗОЛИДИН-2,4-ДИОНА И 4-ТИОКСОТИАЗОЛИДИН-2-ОНА

Г.О.Деркач, С.Н.Голота, В.В.Засидко, И.И.Соронович, Р.В.Куцьок, Р.Б.Лесык

Ключевые слова: 4-тиазолідин(ті)они; 5-амінометиленпроизводные; мультирезистентность; противомикробная активность

Исследование посвящено рациональному поиску современных потенциальных противомикробных агентов среди производных 4-тиазолідин(ті)онов. Для дизайна и первичного скрининга антибактериальных свойств апробированы 5-R,R'-єнамін(ті)они тіазолідинового ряду. Предложено использование 5-етоксиметилентіазолідин-2,4-діона и 4-тіоксотіазолідин-2-она как эффективных «структурных блоков» для синтеза малых библиотек биологически активных соединений. Изучены реакции нуклеофільного замещения 5-етоксиметилентіазолідинонів с аміноспиртами, функціоналізованими первинними и вторичными ароматическими и гетероароматическими амінами, гетероцикліческими амінами (піперидин и заміщенніє піразоліни). Проведен фармакологіческий скринінг противомикробной активности синтезированных єнаминів на клинических изолятах стафилококков с различными механизмами резистентности к защищенным β -лактамам и полиантибіотикорезистентных штаммах *E. coli* и *Ps. Aeruginosa*. Идентифицированы соединения с выразительным противомикробным эффектом, способные повышать чувствительность клинических штаммов *S. aureus* и *S. haemolyticus* к оксацилину, что может быть использовано при создании новых комбинированных противомикробных химиотерапевтических средств. Проанализирована зависимость связей «структура – противомикробное действие» для направленного дизайна и поиска новых противомикробных агентов.

The search and development of original modern antibacterial and antifungal drugs are an actual problem for medicine and pharmacy. The analysis of innovative products approved by FDA during 2011-2015 by their belonging to certain pharmacological groups shows that antimicrobial agents occupy the second position (~16% of the total number of the drugs introduced) after anti-cancer drugs (~27%) [1]. The key problem of the existing antimicrobial agents is development of resistance and appearance of new pathogenic strains [2]. The screening of potential antimicrobial agents among the new class of chemical compounds is one of the promising methods to overcome the problem of resistance [3]. 5-Ylidene derivatives of 4-thiazolidine(thi)ones are of a considerable interest for *de novo* design of antibacterial agents, among them selective and multi-inhibitors 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), etc., have been identified [4-8]. The structural modification of the 5-ylidene fragment to 5-*R,R'*-aminomethylene results in improving a number of molecular parameters, and this structure optimization strategy of drug-like molecules is promising for searching new high-affinity ligands with antimicrobial properties among derivatives of 4-thiazolidine(thi)ones [9].

The aim of this work was development of the synthetic approach to 5-*R,R'*-aminomethylene derivatives of thiazolidine-2,4-dione and 4-thioxothiazolidin-2-one, the synthesis of the series of *R,R'*-enamines, the screening

of the antimicrobial activity of the compounds synthesized and the analysis of the "structure – activity" relationships for a directed design and search of new antimicrobial agents among 4-thiazolidin(thi)ones.

To perform the planned experiment the corresponding 5-ethoxymethylene derivatives **1**, **2** were synthesized in the interaction of thiazolidine-2,4-dione and 4-thioxothiazolidin-2-one with triethyl orthoformate in the acetic anhydride medium [10] (Fig. 1), and they were used for the synthesis of the target 5-*R,R'*-aminomethylene derivatives. It was found that compounds **1**, **2** actively reacted in the ethanol or isopropanol medium with such nucleophiles as amino alcohols, the primary and secondary functionalized aromatic and heteroaromatic amines, heterocyclic amines (piperidine and pyrazolines) to form the corresponding enamines **3-17** (Fig.). The choice of nucleophilic scaffolds gives a variety of structures with satisfactory molecular properties ("Lipinski rules") for the primary screening of hit-compounds with the antimicrobial activity [11].

The structure of the compounds synthesized was confirmed using ^1H NMR- and mass-spectroscopy. In the ^1H NMR-spectra of the compounds synthesized the enamine fragment protons appeared as a pair of doublets or broad singlets at 8.00-8.40 ppm (proton = CH-) and 9.73-10.30 ppm (proton -NH-). The shift of ylidene proton signals in a weak field indicated formation of only *Z*-isomers [12].

In screening of the antimicrobial activity for the compounds synthesized a direct antimicrobial action

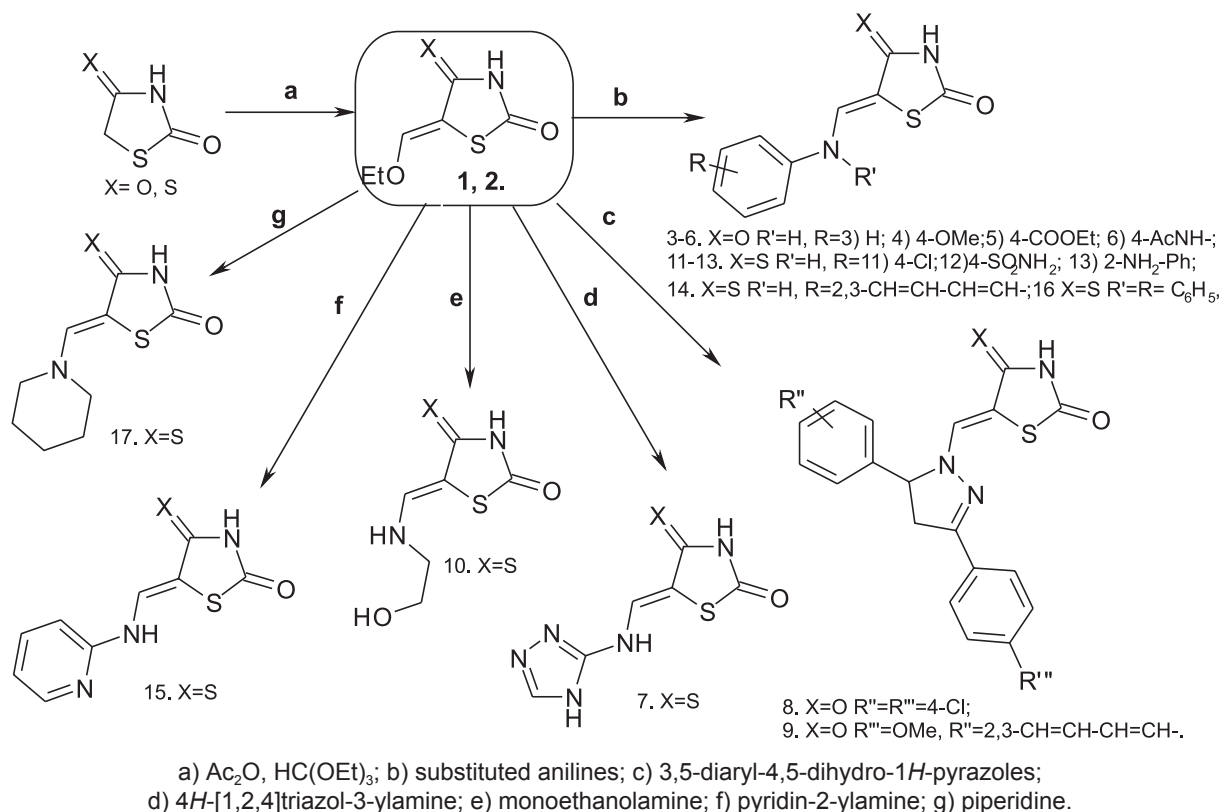


Fig. The synthesis of 5-ethoxymethylene-thiazolidine-2,4-dione (**1**), 4-thioxothiazolidin-2-one (**2**) and 5-*R,R'*-aminomethylene derivatives (**3-17**).

Table 1

A direct antimicrobial activity of the compounds (diameters of growth inhibition zones, mm)

Microorganism/ Compound	<i>S. aureus</i> "Ivanyshyn" (MSSA)	<i>S. aureus</i> ICA-5 (MRSA)	<i>S. haemolyticus</i> "Buhryn" (MRSH)	<i>S. haemolyticus</i> "Beley" BSSH (β -Lac ⁺)	<i>E. coli</i>	<i>Ps. Aeruginosa</i>
3	3.90±0.26	3.79±0.35	3.58±0.19	n/t	3.73±0.34	3.82±0.19
4	4.62±0.28	3.66±0.26	3.57±0.17	n/t	3.84±0.16	3.73±0.28
5	4.04±0.35	4.04±0.46	5.38±0.43	n/t	3.50±0.13	3.67±0.15
6	4.00±0.20	3.77±0.32	3.56±0.27	n/t	3.59±0.09	3.67±0.14
7	5.10 ± 0.46	5.17±0.26	3.60±0.27	n/t	4.00±0.34	4.22±0.25
8	0	0	5.50±0.42	0	n/t	n/t
9	0	0	0	0	n/t	n/t
10	0	[20.73±1.11]	5.00±0.17	0	n/t	n/t
11	21.91±0.60	0	4.94±0.32	0	n/t	n/t
12	0	0	0	0	n/t	n/t
13	0	0	5.35±0.25	0	n/t	n/t
14	0	0	5.87±0.49	0	n/t	n/t
15	8.90±0.26	11.85±0.43	6.06±0.50	7.53±0.14	n/t	n/t
16	26.00±0.59	6.05±0.25	5.31±0.39	[11.67±0.16]	n/t	n/t
17	0	0	0	0	n/t	n/t
Control	3.63±0.23	3.57±0.34	3.42±0.29	3.62±0.21	3.36±0.4	3.51±0.3

Notes: in brackets there are diameters of zones of the growth partial inhibition of cultures (bacteriostatic effect);
n/t – the compound was not tested in the given experiment.

was studied, and the synergetic interaction with oxacillin was assessed. [13]. The methicillin-sensitive strain of *S. aureus* "Ivanyshyn" (MSSA), methicillin-resistance strains of *S. aureus* ICA-5 (MRSA) and *S. haemolyticus* (MRSH) "Buhryn"; boundary methicillin-sensitive (BSSH) *S. haemolyticus* "Beley" characterized with a high resistance to β -lactam antibiotics, but with absolutely different resistance mechanisms and antibiotic-sensitive strains of *E. Coli* and *Ps. Aeruginosa* were used as the main test objects. The test-cultures were identified using "STAPHYtest 16" biochemical microtests (Lachema, Czech Republic). The sensitivity of strains to antibiotics was determined by the disc-diffusion method and serial dilutions in agar. The antimicrobial activity of the compounds synthesized was studied by agar diffusion. Suspensions of test-cultures standardized according to the optical turbidity standard (the concentration of $1 \cdot 10^7$ CFU/mL) were put uniformly on the surface of the nutrient agar in Petri dishes. About 20 μ L of solutions with the test compounds in the concentration of 1000 μ g/ml in the solution of alcohol/DMSO/water (2:1:1) were placed in agar wells with the diameter of 4.0 ± 0.1 mm. Diameters of zones of the growth inhibition of test-cultures were determined after incubation for 24-48 h. Digital images of the culture growth on dishes were obtained and processed with a UTHSCSA ImageTool 2.0

computer program (the University of Texas Health Science Center in San Antonio, ©1995-1996). The results obtained were processed by the methods of variation statistics. The pure solvent was put in control wells. To assess the synergistic interaction with oxacillin the similar experiments were performed on the media containing the subbacteriostatic concentrations of oxacillin ($1/4$ - $1/16$ IPC) in relation to each of the resistant strains. The summarized results of the antimicrobial activity screening of compounds **3-17** are presented in Tab. 1, 2.

According to the results of the direct antimicrobial action screening it was found that compounds **3-17** demonstrated a moderate multilevel antimicrobial activity. When analyzing the "structure – activity" relationships it was found that the nature of the substituents in the enamine fragment influenced on the effect, and the presence of *p*-OMe- (**4**) and *p*-COOEt-phenylamine (**5**), diphenylamine (**16**), 4*H*-[1.2.4]-triazol-3-ylamine (**7**) and pyridine-2-ylamine substituents (**15**) were optimal. It should be also noted that 4-thioxothiazolidin-2-one derivatives were characterized by a higher general level of activity compared to the oxygen-containing analogues. When studying the synergistic interaction of the derivatives synthesized with oxacillin compounds **12** and **15** exhibiting the ability to improve significantly the sensitivity of

Table 2

The synergistic interaction of compounds 8-17 with oxacillin in relation to MRSH, BSSH (β -Lac⁺) and MRSA (diameters of growth inhibition zones, mm)

	8	9	10	11	12	13	14	15	16	17	Control
MRSH "Buhryn"	5.50±0.42	0	5.00±0.17	4.94±0.32	0	5.35±0.25	5.87±0.49	6.06±0.50	5.31±0.39	0	5.24±0.54
+ Oxacillin 500 mkg/ml	4.96±0.14	0	5.36±0.37	5.90±0.15	5.65±0.29	4.89±0.14	5.28±0.31	6.21±0.20	5.13±0.12	4.92±0.29	4.87±0.28
+ Oxacillin 250 mkg/ml	0	4.97±0.26	[7.98±0.31]	5.35±0.42	8.14±0.41	[6.41±0.12]	[6.22±0.47]	6.27±0.19	5.19±0.31	5.17±0.19	0
+ Oxacillin 125 mkg/ml	[4.91±0.21]	0	[8.45±0.28]	6.76±0.61	[6.83±0.29]	[6.67±0.68]	[7.05±0.32]	7.84±0.60	[7.27±0.35]	[6.28±0.34]	[4.84±0.13]
BSSH (β -Lac ⁺) "Beley"	0	0	0	0	0	0	0	7.53±0.14	[11.67±0.16]	0	0
+ Oxacillin 125 mkg/ml	0	0	11.84±0.88	5.36±0.32	12.61±0.63	[5.42±0.27]	0	7.61±0.61	[6.42±0.33]	0	4.92±0.44
+ Oxacillin 62,5 mkg/ml	0	0	[4.68±0.31]	6.15±0.20	12.11±0.26	0	0	0	[5.86±0.44]	0	5.02±0.48
MRSA «ICA-5»	0	0	20.73±1.11	0	0	0	0	11.85±0.43	6.05±0.25	0	0
+ Oxacillin 125 mkg/ml	6.39±0.19	0	0	0	0	0	0	5.29±0.66	0	0	0
+ Oxacillin 62,5 mkg/ml	0	0	0	0	7.06±0.47	[5.70±0.81]	0	5.24±0.29	0	0	7.11±0.79
+ Oxacillin 31,25 mkg/ml	0	0	0	0	9.51±1.31	0	0	9.75±0.56	0	0	0

Note: in brackets there are diameters of zones of the growth partial inhibition of cultures (bacteriostatic effect).

clinical strains of *S. aureus* and *S. haemolyticus* to oxacillin were identified. It can be used to develop new combined antimicrobial chemotherapeutic agents.

Experimental Part

Melting points were measured in open capillary tubes on a BÜCHI B-545 melting point apparatus and were uncorrected. The elemental analysis (C, H, N) was performed using a Perkin-Elmer 2400 CHN analyzer, and it was within $\pm 0.4\%$ of the theoretical values. The $^1\text{H-NMR}$ -spectra were recorded on a Varian Gemini spectrometer at 400 MHz using the mixture of DMSO- d_6 + CCl_4 as a solvent and TMS as an internal standard. Chemical shift values were reported in ppm units with the use of δ scale.

The general procedure for the synthesis of 5-*R,R'*-aminomethylene derivatives 3-17. Reflux the mixture of compound **1** or **2** (10 mmol) and the corresponding amine (10 mmol) for 2 h in ethanol or isopropanol (5 ml). Filter the mixture obtained, wash with ethanol or isopropanol and recrystallize from the corresponding solvent.

5-Phenylaminomethylenethiazolidine-2,4-dione (3). Yield – 68%. M. p. – 244-247°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 6.80-7.60 m (5H, C_6H_5), 8.30 d (1H, -CH=), 10.20 d (1H, NH), 13.40 bs (1H, NH). ESI-MS: *m/z* 221 $[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 54.53; H, 3.66; N, 12.70. $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2\text{S}$. Found, %: C, 54.70; H, 3.80; N, 12.90.

5-[(4-Methoxyphenylamino)methylene]thiazolidine-2,4-dione (4). Yield – 71%. M. p. – 258-261°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 1.75 s (3H, CH_3), 6.99 d, (*J* = 8.4 Hz), 7.39 d, (*J* = 8.4 Hz), (4H, C_6H_4), 8.10 d (1H, -CH=), 10.00 d (1H, NH), 12.30 bs (1H, NH). ESI-MS: *m/z* 251 $[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 52.79; H, 4.03; N, 11.19. $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$. Found, %: C, 52.90; H, 4.30; N, 11.40.

4-[(2,4-Dioxothiazolidin-5-ylidenemethyl)amino]benzoic acid ethyl ester (5). Yield – 80%. M. p. – 231-233°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 1.30 t (3H, CH_3), 4.30 q (2H, CH_2), 7.70 d, (*J* = 7.9 Hz), 7.90 d, (*J* = 7.9 Hz), (4H, C_6H_4), 8.20 d (1H, -CH=), 10.10 d (1H, NH), 12.20 bs (1H, NH). ESI-MS: *m/z* 293 $[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 53.42; H, 4.14; N, 9.58. $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_4\text{S}$. Found, %: C, 53.60; H, 4.30; N, 9.80.

N-{4-[(2,4-Dioxothiazolidin-5-ylidenemethyl)amino]phenyl}acetamide (6). Yield – 82%. M. p. – 264-267°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 1.80 s (3H, CH_3), 7.50 d, (*J* = 8.1 Hz), 7.80 d, (*J* = 8.1 Hz), (4H, C_6H_4), 8.20 d (1H, -CH=), 9.20 s (1H, NH), 10.00 d (1H, NH), 12.00 bs (1H, NH). ESI-MS: *m/z* 278 $[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 51.98; H, 4.00; N, 15.15. $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_3\text{S}$. Found, %: C, 52.10; H, 4.20; N, 15.30.

5-[(4H-[1,2,4]Triazol-3-ylamino)methylene]thiazolidine-2,4-dione (7). Yield – 61%. M. p. – 227-229°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 8.30 d (1H, -CH=), 8.50 s (1H, -CH=, triazole), 10.30 d (1H, NH), 12.50 bs (1H, NH), 14.20 s (1H, NH, triazole). ESI-MS: *m/z* 213

$[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 34.12; H, 2.39; N, 33.16. $\text{C}_6\text{H}_5\text{N}_5\text{O}_2\text{S}$. Found, %: C, 34.20; H, 2.40; N, 33.30.

5-[3,5-Bis-(4-chlorophenyl)-4,5-dihydropyrazol-1-ylmethylene]thiazolidine-2,4-dione (8). Yield – 83%. M. p. – 274-277°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 3.40 dd (*J* = 17.8, 10.6 Hz), (1H, CH_2), 4.10 dd (*J* = 18.0, 10.7 Hz), (1H, CH_2), 5.70 dd (*J* = 12.4, 3.8 Hz), (1H, CH), 7.05 d (*J* = 8.0 Hz), 7.20 d (*J* = 8.0 Hz), (4H, C_6H_4), 7.15 d (*J* = 8.3 Hz), 7.30 d (*J* = 8.3 Hz), (4H, C_6H_4), 8.20 s (1H, -CH=), 12.50 bs (1H, NH). ESI-MS: *m/z* 419 $[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 54.56; H, 3.13; N, 10.05. $\text{C}_{19}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_2\text{S}$. Found, %: C, 54.70; H, 3.40; N, 10.30.

5-[5-(4-Chlorophenyl)-3-naphthalen-1-yl-4,5-dihydropyrazol-1-ylmethylene]thiazolidine-2,4-dione (9). Yield – 75%. M. p. – 271-273°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 1.80 s (3H, CH_3), 3.30 dd (*J* = 17.6, 10.2 Hz), (1H, CH_2), 4.00 dd (*J* = 17.8, 10.5 Hz), (1H, CH_2), 5.50 dd (*J* = 12.5, 3.9 Hz), (1H, CH), 6.90 d (*J* = 7.8 Hz), 7.10 d (*J* = 7.8 Hz), (4H, C_6H_4), 7.15 – 7.75 m (7H, C_{10}H_7), 8.10 s (1H, -CH=), 12.40 bs (1H, NH). ESI-MS: *m/z* 430 $[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 67.12; H, 4.46; N, 9.78. $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$. Found, %: C, 67.40; H, 4.50; N, 10.00.

5-[(2-Hydroxyethylamino)methylene]-4-thioxothiazolidin-2-one (10). Yield – 75%. M. p. – 271-273°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 3.56 bs (4H, $(\text{CH}_2)_2$), 4.92 t (1H, OH), 8.00 d (1H, -CH=), 9.90 t (1H, NH), 12.90 bs (1H, NH). ESI-MS: *m/z* 205 $[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 35.28; H, 3.95; N, 13.71. $\text{C}_6\text{H}_8\text{N}_2\text{O}_2\text{S}_2$. Found, %: C, 35.40; H, 4.00; N, 14.00.

5-[(4-Chlorophenylamino)methylene]-4-thioxothiazolidin-2-one (11). Yield – 78%. M. p. – 239-242°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 7.20 d (*J* = 7.9 Hz), 7.40 d (*J* = 7.9 Hz), (4H, C_6H_4), 8.20 d (1H, -CH=), 10.30 t (1H, NH), 12.80 bs (1H, NH). ESI-MS: *m/z* 271 $[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 44.36; H, 2.61; N, 10.35. $\text{C}_{10}\text{H}_7\text{ClN}_2\text{OS}_2$. Found, %: C, 44.40; H, 2.80; N, 10.50.

4-[(2-Oxo-4-thioxothiazolidin-5-ylidenemethyl)amino]benzenesulfonamide (12). Yield – 64%. M. p. – 271-272°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 7.30 d (*J* = 7.6 Hz), 7.50 d (*J* = 7.6 Hz), (4H, C_6H_4), 8.40 d (1H, -CH=), 10.20 t (1H, NH), 10.40 s (2H, NH_2), 13.00 bs (1H, NH). ESI-MS: *m/z* 316 $[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 38.08; H, 2.88; N, 13.32. $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_3\text{S}_3$. Found, %: C, 38.30; H, 3.00; N, 13.60.

5-[(2-Aminophenylamino)methylene]-4-thioxothiazolidin-2-one (13). Yield – 78%. M. p. – 224-226°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 4.92 s (2H, NH_2), 6.71 t (*J* = 8.1 Hz), 6.87 d (*J* = 7.5 Hz), 6.96 t (*J* = 8.1 Hz) (4H, C_6H_4), 7.27 d (*J* = 7.5 Hz), 8.33 d (1H, -CH=), 9.73 d (1H, NH), 13.10 bs (1H, NH). ESI-MS: *m/z* 252 $[\text{M}+\text{H}]^+$ (100%). Calculated, %: C, 47.79; H, 3.61; N, 16.72. $\text{C}_{10}\text{H}_9\text{N}_3\text{OS}_2$. Found, %: C, 47.80; H, 3.80; N, 16.90.

5-(Naphthalen-1-ylaminomethylene)-4-thioxothiazolidin-2-one (14). Yield – 73%. M. p. – 268-271°C. $^1\text{H NMR}$, δ , ppm, (*J*, Hz): 7.20-7.90 m (7H, C_{10}H_7), 8.15 d (1H, -CH=), 10.10 d (1H, NH), 12.90 bs (1H, NH). ESI-MS:

m/z 289 $[M+H]^+$ (100%). Calculated, %: C, 58.72; H, 3.52; N, 9.78. $C_{10}H_9N_3OS_2$. Found, %: C, 58.80; H, 3.80; N, 9.90.

5-(Pyridin-2-ylaminomethylene)-4-thioxothiazolidin-2-one (15). Yield – 84%. M. p. – 286-288°C. 1H NMR, δ , ppm, (J , Hz): 7.00 t, 7.20 t, 7.40 d, 7.60 d (4H, pyridine), 8.40 d (1H, -CH=), 10.30 d (1H, NH), 13.10 bs (1H, NH). ESI-MS: m/z 238 $[M+H]^+$ (100%). Calculated, %: C, 45.55; H, 2.97; N, 17.71. $C_9H_7N_3OS_2$. Found, %: C, 45.80; H, 3.00; N, 17.90.

5-[(Diphenylamino)methylene]-4-thioxothiazolidin-2-one (16). Yield – 54%. M. p. – 259-261°C. 1H NMR, δ , ppm, (J , Hz): 7.10 – 7.50 m (10H, $2^*C_6H_5$), 8.55 s (1H, -CH=), 12.66 bs (1H, NH). ESI-MS: m/z 313 $[M+H]^+$ (100%). Calculated, %: C, 61.51; H, 3.87; N, 8.97. $C_{16}H_{12}N_2OS_2$. Found, %: C, 61.80; H, 4.00; N, 9.00.

5-Piperidin-1-ylmethylene-4-thioxothiazolidin-2-one (17). Yield – 72%. M. p. – 243-245°C. 1H NMR, δ , ppm, (J , Hz): 1.72 bs, 3.63 bs (10H, piperidine), 8.17 s (1H, -CH=), 12.26 bs (1H, NH). ESI-MS: m/z 229 $[M+H]^+$ (100%). Calculated, %: C, 47.34; H, 5.30; N, 12.27. $C_9H_{12}N_2OS_2$. Found, %: C, 47.50; H, 5.50; N, 12.40.

References

1. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm>
2. Chen L. F., Chopra T., Kaye K. S. *Med. Clin. N. Am.*, 2011, Vol. 95, pp.647-676.
3. Payne D. J. *Nature Reviews. Drug Discovery*, 2006, pp.29-40.
4. Zervosen A. *Antimicrob. Agents Chemother.*, 2004, Vol. 48, pp.961-969.
5. Sim M. M. *Bioorg. Med. Chem. Lett.*, 2002, Vol. 12, pp.697-699.
6. Orchard M. D. *Bioorg. Med. Chem. Lett.*, 2004, Vol. 14, pp.3975-3978.
7. Grant B. E. *Bioorg. Med. Chem. Lett.*, 2000, Vol. 10, pp.2179-2182.
8. Gualtieri M. J. *Antimicrob. Chemother.*, 2006, Vol. 58, pp.778-783.
9. Golota S. *Modern Directons in Chemistry, Biology, Pharmacy and Biotechnology, Lviv*, 2015, pp.71-75.
10. Ead H. A. *Arch. Pharm. (Weinheim)*, 1987, Vol. 320, pp.1227-1231.
11. Chopra I. *Expert Opin. Investig. Drugs*, 1997, Vol. 6, pp.1019-1024.
12. Momose Y. *Chem Pharm Bull.*, 1991, Vol. 39(6), pp.1440-1445.
13. Mounyr B., Sadiki M., Ibsouda S.-K. *J. Pharm. Analysis*, 2016, Vol. 6, No.2, pp.71-79.

Надійшла до редакції 05.08.2016 р.

Conclusions

1. A synthetic approach to the pharmacologically attractive 5-*R,R'*-aminomethylene-4-thiazolidine(thi)ones based on the interaction of the corresponding 5-ethoxymethylene-4-thiazolidine(thi)ones and some nucleophiles has been proposed.

2. Based on the traditional pharmacological screening of 5-*R,R'*-aminomethylene-4-thiazolidine(thi)ones it has been determined that they possess the antimicrobial activity, and the 5-*R,R'*-aminomethylene fragment is a promising scaffold for the directed synthesis of 4-thiazolidinone derivatives as potential antimicrobial agents.

3. In the combination study of the direct antimicrobial action and the synergistic interaction with oxacillin compounds **12** and **15** that exhibit the ability to increase the sensitivity of clinical strains of *S. aureus* and *S. haemolyticus* to oxacillin have been identified. These compounds can be used to optimize the structure and develop of new combined antimicrobial chemotherapeutic agents.