FABAD J. Pharm. Sci., 45, 3, 211-218, 2020

RESEARCH ARTICLE

Synthesis of New 2-(4-Oxothiazolidin-2-ylidene)-acetamides as Potential Antimicrobial Agents

Volodymyr HORISHNY[*], Taras CHABAN[**], Vasyl MATIYCHUK[***°]

Synthesis of New 2-(4-Oxothiazolidin-2-ylidene)-acetamides as Potential Antimicrobial Agents

SUMMARY

A series of new 2-(4-oxo-thiazolidin-2-ylidene)-acetamides was obtained from 2-cyano-3-mercapto-3-phenylaminoacrylamides. The structures of target compounds 5a-d, 7a-c, 9a-b, 11a-c were confirmed by using 1H NMR spectroscopy, mass spectroscopy and elemental analysis. The synthesized compounds have been evaluated for antimicrobal activity against five bacterial strains (Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus) and two fungal strains (Candida albicans and Cryptococcus neoformans). The 4-thiazolidinone derivatives 5a-c and 9a have high antimicrobial activity.

Key Words: *Synthesis, 2-cyano-3-mercapto-3-phenylaminoacrylamides, 2-(4-oxo-thiazolidin-2-ylidene)-acetamides, antibacterial data collection, antifungal data collection, antimicrobial activity*

Potansiyel Antimikrobiyal Ajanlar Olarak Yeni 2-(4-Oksotiyazolidin-2-iliden) -asetamidlerin Sentezi

ÖZ

2-Siyano-3-merkapto-3-fenilaminoakrilamidlerden bir seri yeni 2-(4-okso-tiyazolidin-2-iliden)-asetamid türevi elde edilmiştir. Hedef bileşikler olan 5a-d, 7a-c, 9a-b, 11a-c'nin yapıları, 1H NMR spektroskopisi, kütle spektroskopisi ve elementel analiz kullanarak doğrulanmıştır. Sentezlenen bileşikler beş bakteri suşuna (Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus) ve iki mantar suşuna (Candida albicans ve Cryptococcus neoformans) karşı antimikrobiyal aktivite açısından değerlendirilmiştir. 4-Tiyazolidinon türevleri olan 5a-c ve 9a, yüksek antimikrobiyal aktiviteye sahiptir.

Anahtar Kelimeler: *Sentez, 2-siyano-3-merkapto-3-fenilaminoakrilamidler, 2-(4-okso-tiyazolidin-2-iliden)-asetamidler, antibakteriyel veri toplama, antifungal veri toplama, antimikrobiyal aktivite.*

Received: 27.05.2020
Revised: 08.07.2020
Accepted: 09.07.2020

[*] ORCID: 0000-0002-5868-4105, Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytsky Lviv National Medical University, Ukraine
[**] ORCID: 0000-0003-0618-275X, Department of General, Bioinorganic, Physical and Colloidal Chemistry, Danylo Halytsky Lviv National Medical University, Ukraine
[***] ORCID: 00000-0001-8077-2139, Department of Organic Chemistry, Ivan Franko National University of Lviv, Ukraine

[°] Corresponding Author; Vasyl MATIYCHUK,
Tel.: +38 067 675-16-83 e-mail: v_matiychuk@ukr.net

INTRODUCTION

Despite the significant advances in the field of antimicrobial agents, infections are still the second-leading cause of death worldwide and remain an important public health problem (Payne D. *et al.,* 2007). There are various problems arising with the use of antimicrobials such as local tissue irritation, interference with wound healing process, hypersensitivity reactions, systemic toxicity, narrow antimicrobial spectrum. The primary reason for this situation is inevitable drive of evolution that leads to antimicrobial resistance and become a serious health problem (Gould I., 2010; Piddock L., 2012). So there is a need of safe, potent and novel antimicrobial agents.

4-Thiazolidinone derivatives play important role in modern organic, medical and pharmaceutical chemistry. They possess various types of biological activity (Tomasić T. *et al.,* 2009; Jain A. *et al.,* 2012; Kaminskyy D. *et al.,* 2017a; Kaminskyy D. *et al.,* 2017b) and represented in the pharmaceutical market (Tripathi K. *et al.,* 2013). The specified derivatives are also undergoing different stages of clinical trials as potential thyromimetic, antimicrobial, antiviral, anti-ischemic, cardiovascular and anticancer drugs. In this regard, the 4-thiazolidinone cycle is considered to be a privileged structure in medicinal chemistry. Among this class of organic compounds, 2-thioxo-thiazolidin-4-one (rhodanine), thiazolidin-2,4-dione, and 2-imino-thiazolidin-4-one (pseudothiohydantoine) derivatives are well studied (Tomasić T. *et al.,* 2009). At the same time, derivatives of 2-methylene-thiazolidin-4-one have been less studied, the number of methods for their synthesis is limited, biological activity has been studied only in recent years. In particular, about antitumor (George R. 2012; Ghorab M. *et al.,* 2012; Hanna M. *et al.,* 2012), antimicrobial (Rostom S. *et al.*, 2009; Nasr T.*et al.,* 2016; Salem M., 2017) and anti-inflammatory (Helal M. *et al.*, 2013; Salem M., 2017) activities was reported.

The objective of the present work was to synthesize a series of novel 2-(4-oxo-thiazolidin-2-ylidene)-acetamides for further pharmacological screening antimicrobial activity.

MATERIALS AND METHODS

Materials. All chemicals were of analytical grade and commercially available. All reagents and solvents were used without further purification and drying.

Chemistry. All the melting points were determined in an open capillary. ^{1}H-spectra were recorded on a Varian Mercury 400 (400 MHz for ^{1}H) instrument with TMS or deuterated solvent as an internal reference. Chemical shifts are reported as δ (ppm) relative to TMS as internal standard, coupling constant *J* are expressed in *Hz*. Mass spectra were performed using Agilent 1100 series LC/MSD Agilent Technologies Inc. with an API–ES/APCI ionization mode. Satisfactory elemental analyses were obtained for new compounds (C±0.17, H±0.21, N±0.19).

*General procedure for the preparation of 2-cyano-2-[5-(R-benzyl)-4-oxo-3-phenyl-thiazolidin-2-ylidene]-acetamides **(5a-d).***

The solution 0.55 g (2.5 mmol) of 2-cyano-3-mercapto-3-phenylamino-acrylamide **1a**, 2.5 mmol ethyl 2-bromo-3-arylpropionates **4a-d** and 0.2 ml pyridine in 10 ml EtOH was refluxed for 3 hours, then allowed to cool. The obtained precipitate was filtered, washed with EtOH, dried and crystallized from EtOH-DMFA.

*2-Cyano-2-[5-(4-fluoro-benzyl)-4-oxo-3-phenylthiazolidin-2-ylidene]acetamide **(5a):***

Yield: 83%;mp 221–222 °C;^{1}H NMR: δ_H= 7.55 – 7.45 (m, 3H, ArH), 7.43 – 7.36 (m, 2H, ArH, NH), 7.36 – 7.29 (m, 2H, ArH), 7.24 – 7.16 (m, 2H, ArH), 7.13 – 7.08 (m, 1H, ArH), 6.94 (bs, 1H, NH), 4.55 (dd, *J* = 8.6, 4.7 Hz, 1H, CH), 3.38 (dd, *J* = 14.1, 4.7 Hz, 1H, CH_2), 3.18 (dd, *J* = 14.1, 8.7 Hz, 1H, CH_2); ESI-MS: m/z 368 $[M+H]^+$;anal. calcd. for $C_{19}H_{14}FN_3O_2S$: C, 62.11; H, 3.84; N, 11.44.Found: C, 62.25; H, 3.92; N, 11.39.

*2-[5-(2-Chloro-benzyl)-4-oxo-3-phenylthiazolidin-2-ylidene]-2-cyanoacetamide **(5b):***

Yield: 79%; mp 233–234 °C; ^{1}H NMR: δ_H =7.56 – 7.47 (m, 4H, ArH), 7.46 – 7.32 (m, 6H, ArH, NH), 6.98 (bs, 1H, NH), 4.57 (dd, *J* = 10.0, 5.0 Hz, 1H, CH), 3.57 (dd, *J* = 14.2, 5.0 Hz, 1H, CH_2), 3.28 (dd, *J* = 14.3, 10.0 Hz, 1H, CH_2); ESI-MS: m/z 384 $[M+H]^+$; anal. calcd. for $C_{19}H_{14}ClN_3O_2S$: C, 59.45; H, 3.68; N, 10.95. Found: C, 59.59; H, 3.74; N, 11.08.

*2-[5-(4-Chlorobenzyl)-4-oxo-3-phenylthiazolidin-2-ylidene]-2-cyanoacetamide **(5c):***

Yield: 85%; mp185–186 °C; ^{1}H NMR: δ_H =7.56 – 7.46 (m, 3H, ArH), 7.46 – 7.37 (m, 4H, ArH, NH), 7.32 (d, *J* = 8.5 Hz, 2H, ArH), 7.15 – 7.10 (m, 1H, ArH), 6.95 (bs, 1H, NH), 4.56 (dd, *J* = 8.7, 4.8 Hz, 1H, CH), 3.39 (dd, *J* = 14.0, 4.8 Hz, 1H, CH_2), 3.19 (dd, *J* = 14.1, 8.7 Hz, 1H, CH_2); ESI-MS: m/z 384 $[M+H]^+$; anal. calcd. for $C_{19}H_{14}ClN_3O_2S$: C, 59.45; H, 3.68; N, 10.95. Found: C, 59.48; H, 3.66; N, 11.14.

*2-Cyano-2-[5-(4-methoxy-benzyl)-4-oxo-3-phenyl-thiazolidin-2-ylidene]-acetamide **(5d):***

Yield: 77%; mp216–217 °C; ^{1}H NMR: δ_H =7.57 – 7.44 (m, 5H, C_6H_5), 7.39 (bs, 1H, NH), 7.21 (d, *J* = 8.5 Hz, 2H, $\underline{C_6H_4}OCH_3$), 7.09 (bs, 1H, NH), 6.92 (d, *J* =

8.5 Hz, 2H, $C_6H_4OCH_3$), 4.52 (dd, *J* = 8.7, 4.4 Hz, 1H, CH), 3.76 (s, 3H, CH_3O), 3.33 (dd, *J* = 14.1, 4.4 Hz, 1H, CH_2), 3.12 (dd, *J* = 14.1, 8.8 Hz, 1H, CH_2); ESI-MS: m/z 380 $[M+H]^+$; anal. calcd. for $C_{20}H_{17}N_3O_3S$: C, 63.31; H, 4.52; N, 11.07. Found: C, 63.15; H, 4.41; N, 11.01.

General procedure for the preparation of [2-(carbamoyl-cyano-methylene)-4-oxo-3-phenyl-thiazolidin-5-ylidene]-acetates ***(7a-c).*** The solution 2.5 mmol of 2-cyano-3-mercapto-3-phenylamino-acrylamides **1a,b**, 2.5 mmol esters of acetylene dicarboxylic acid **6a,b** in 10 ml EtOH was refluxed for 3 hours, then allowed to cool. The obtained precipitate was filtered, washed with EtOH, dried and crystallized from EtOH-DMFA.

[2-(Carbamoylcyanomethylene)-4-oxo-3-phenylthiazolidin-5-ylidene]-acetic acid methyl ester ***(7a):***

Yield: 83%; mp>270ºC; ^{1}H NMR: δ_H =7.75 (bs, 1H, NH), 7.61 – 7.49 (m, 5H, C_6H_5), 7.33 (bs, 1H, NH), 6.68 (s, 1H, CH=), 3.82 (s, 3H, CH_3); ESI-MS: m/z 330 [M+H]+; anal. calcd. for $C_{15}H_{11}N_3O_4S$: C, 54.71; H, 3.37; N, 12.76. Found: C, 54.65; H, 3.40; N, 12.69.

[2-(Carbamoylcyanomethylene)-4-oxo-3-phenyl-thiazolidin-5-ylidene]-acetic acid ethyl ester ***(7b):***

Yield: 85%; mp249-250ºC; ^{1}H NMR: δ_H =7.74 (bs, 1H, NH), 7.61 – 7.47 (m, 5H, C_6H_5), 7.32 (bs, 1H, NH), 6.76 (s, 1H, CH=), 4.28 (q, *J* = 7.1 Hz, 2H, CH_2), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3); ESI-MS: m/z 344 $[M+H]^+$; anal. calcd. for $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.82; N, 12.24. Found: C, 56.08; H, 3.91; N, 12.40.

[2-(Cyanomethylcarbamoyl-methylene)-4-oxo-3-phenyl-thiazolidin-5-ylidene]-acetic acid ethyl ester ***(7c):***

Yield: 81%; mp234-235ºC; ^{1}H NMR: δ_H = 7.82 (bs, 1H, NH), 7.59 – 7.47 (m, 5H, C_6H_5), 6.73 (s, 1H, CH=), 4.26 (q, J = 7.1 Hz, 1H, CH_2), 2.64 (d, J = 4.5 Hz, 3H, CH_3N), 1.26 (t, J = 7.1 Hz, 3H, CH_3); ESI-MS: m/z 358 $[M+H]^+$; anal. calcd. for $C_{17}H_{15}N_3O_4S$: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.41; H, 4.30; N, 11.85.

General procedure for the preparation of 2-(5-arylidene-4-oxo-3-phenyl-thiazolidin-2-ylidene)-2-cyanoacetamides ***(9a, b and 11a-c).***

The solution 2.5 mmol of aldehydes **8a,b** or **10a-c**, 2.5 mmol cyano-2-(4-oxothiazolidin-2-ylidene)-acetamides **3a,b** and 0.2g anhydrous sodium acetate in 10 ml AcOH was refluxed for 3 hours, then allowed to cool. The obtained precipitate was filtered, washed with EtOH, dried and crystallized from DMFA.

2-[5-(4-Chlorobenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene]-2-cyanoacetamide ***(9a):*** Yield: 75%; mp> 270 ºC; ^{1}H NMR: δ_H =7.79 – 7.73 (m, 3H, C_6H_4Cl, CH=), 7.67 (d, *J* = 8.5 Hz, 2H, C_6H_4Cl), 7.60 – 7.50 (m, 6H, C_6H_5, NH), 7.17 (bs, 1H, NH); ESI-MS: m/z 382 $[M+H]^+$; anal. calcd. for $C_{19}H_{12}ClN_3O_2S$: C, 59.77; H, 3.17; N, 11.00. Found: C, 59.55; H, 3.25; N, 10.96.

2-Cyano-N-methyl-2-[5-(4-nitrobenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene]-acetamide ***(9b):*** Yield: 79%; mp> 270 ºC; ^{1}H NMR: δ_H =8.42 (d, *J* = 8.7 Hz, 2H, $C_6H_4NO_2$), 7.98 (d, *J* = 8.8 Hz, 2H, $C_6H_4NO_2$), 7.86 (s, 1H, CH=), 7.76 (bs, 1H, NH), 7.59 – 7.54 (m, 5H, C_6H_5). 2.69 (d, *J*= 4.3 Hz, 3H, CH_3N); ESI-MS: m/z 407 $[M+H]^+$; anal. calcd. for $C_{20}H_{14}N_4O_4S$: C, 59.11; H, 3.47; N, 13.79. Found: C, 59.25; H, 3.45; N, 13.88.

2-{5-[5-(3-Chlorophenyl)-furan-2-ylmethylene]-4-oxo-3-phenylthiazolidin-2-ylidene}-2-cyanoacetamide ***(11a):*** Yield: 86%; mp> 270 ºC; ^{1}H NMR: δ_H =7.97 (s, 1H, C_6H_4Cl), 7.85 (d, *J* = 7.8 Hz, 1H, C_6H_4Cl), 7.63 (s, 1H, CH=), 7.61 – 7.47 (m, 8H, ArH, NH), 7.45 (d, *J* = 3.8 Hz, 1H, furan), 7.28 (d, *J* = 3.7 Hz, 1H, furan), 7.13 (bs, 1H, NH); 7.13 (bs, 1H, NH); ESI-MS: m/z 448 $[M+H]^+$; anal. calcd. for $C_{23}H_{14}ClN_3O_3S$: C, 61.68; H, 3.15; N, 9.38. Found: C, 61.59; H, 3.24; N, 9.42.

2-Cyano-N-methyl-2-{5-[5-(2-nitrophenyl)-furan-2-ylmethylene]-4-oxo-3-phenylthiazolidin-2-ylidene}-acetamide ***(11b):***

Yield: 83%; mp> 270 ºC; ^{1}H NMR: δ_H =8.07 (d, *J* = 8.0 Hz, 1H, $C_6H_4NO_2$), 7.97 (d, *J* = 7.8 Hz, 1H, $C_6H_4NO_2$), 7.86 (t, *J* = 7.6 Hz, 1H, $C_6H_4NO_2$), 7.72 (t, *J* = 7.8 Hz, 1H, $C_6H_4NO_2$), 7.63 (bs, 1H, NH), 7.60 (s, 1H, CH=), 7.58 – 7.49 (m, 5H, C_6H_5), 7.28 (d, *J* = 3.7 Hz, 1H, furan), 7.11 (d, *J* = 3.7 Hz, 1H, furan), 2.68 (d, *J* = 4.4 Hz, 3H, CH_3N); ESI-MS: m/z 474 $[M+H]^+$; anal. calcd. for $C_{24}H_{16}N_4O_5S$: C, 61.01; H, 3.41; N, 11.86. Found: C, 60.85; H, 3.48; N, 11.77.

2-Cyano-N-methyl-2-{5-[5-(4-nitro-phenyl)-furan-2-ylmethylene]-4-oxo-3-phenyl-thiazolidin-2-ylidene}-acetamide ***(11c):***

Yield: 90%; mp> 270 ºC; ^{1}H NMR: δ_H = 8.32 (d, *J* = 8.9 Hz, 2H, $C_6H_4NO_2$), 8.10 (d, *J* = 8.5 Hz, 2H, $C_6H_4NO_2$), 7.61 (s, 1H, CH=), 7.59 – 7.48 (m, 7H, C_6H_5, furan, NH), 7.29 (d, *J* = 3.7 Hz, 1H, furan), 2.76 (d, *J* = 2.8 Hz, 3H, CH_3N); ESI-MS: m/z 474 $[M+H]^+$; anal. calcd. for $C_{24}H_{16}N_4O_5S$: C, 61.01; H, 3.41; N, 11.86. Found: C, 61.15; H, 3.36; N, 11.80.

Antibacterial data collection. Inhibition of bacterial growth was determined measuring absorbance at 600 nm (OD600), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth

inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references.

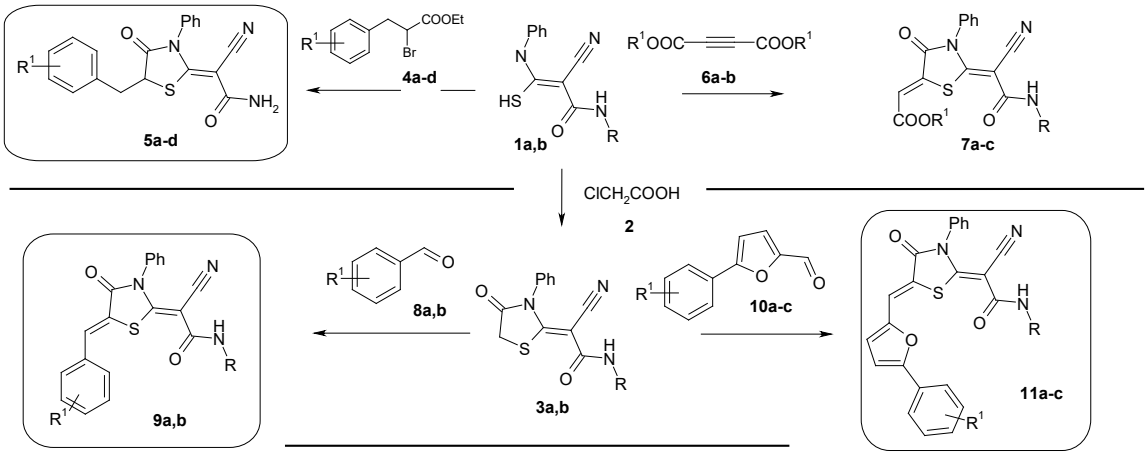
Antifungal data collection. Growth inhibition of *C. albicans* was determined measuring absorbance at 530 nm (OD530), while the growth inhibition of *C. neoformans* was determined measuring the difference in absorbance between 600 and 570 nm (OD600-570), after the addition of resazurin (0.001% final concentration) and incubation at 35°C for additional 2 h. The absorbance was measured using a Biotek Synergy HTX plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references.

Inhibition. Percentage growth inhibition of an individual sample is calculated based on Negative controls (media only) and Positive Controls (bacterial/fungal media without inhibitors). Negative inhibition values indicate that the growth rate (or OD600) is higher compared to the Negative Control (Bacteria/fungi only, set to 0% inhibition). The growth rate for all bacteria and fungi have a variation of -/+ 10%, which is within the reported normal distribution of bacterial/fungal growth.

RESULTS AND DISCUSSION

Chemistry. As part of our continuous efforts to design new biological active heterocycles (Tsyalkovsky V. *et al.*, 2005; Zimenkovskii B. *et al.*, 2006; Obushak N. *et al.*, 2008; Pokhodylo N. *et al.*, 2009a; Pokhodylo N. *et al.*, 2009b; Pokhodylo N. *et al.*, 2010; Zubkov S. *et al.*, 2010; Lozynska L. *et al.*, 2015; Zelisko N. *et al.*, 2015; Chaban T. *et al.*, 2016; Chaban T. *et al.*, 2017; Klenina O. *et al.*, 2017; Chaban T. *et al.*, 2018; Tupys A. *et al.*, 2018; Chaban T. *et al.*, 2019; Chaban T. *et al.*, 2020) we report about synthesis and antimicrobial activities of novel 2-cyano-2-(4-oxo-thiazolidin-2-ylidene)-acetamides. A combinatorial library of these compounds was obtained from 2-cyano-3-mercapto-3-phenylaminoacrylamides **1a, b** which are synthesized by the reaction of phenylisothiocyanate with cyanacetamide according procedure described in (Shaoyong K. *et al.,* 2016). **1a, b** were used in various [3+2] cyclocondensation reactions. By the reaction of **1a, b** with chloroacetic acid **2**cyano-2-(4-oxo-thiazolidin-2-ylidene)-acetamides **3a, b** were prepared. The methylene group in the position 5 of these compounds is active and reacts with aldehydes to form 5-arylidene derivatives **9a, b** and **11a-c**. In this reaction, aromatic aldehydes **8a, b** and arylfurfurals **10a-c** were used. Aldehydes **10 a-c** were prepared by arylation of furfural with diazonium salts under the conditions of the Meervein reaction (Obushak N. *et al.,* 2009) according procedure were prepared via described protocol (Obushak N. *et al.,* 2008).

In order to obtain conformationally not restricted compounds, we also studied the reaction of **1a** with 2-bromo-3-arylpropionates **4a-d**. It was found that refluxing of these reagents in alcohol in the presence of a base leads to formation of 5-benzyl derivatives **5a-d** in good yields. 4-Thiazolidinone derivatives **7a-c** were prepared by the reaction of **1a, b** with esters of acetylene dicarboxylic acid (Figure 1).



1, 3: R = H(**a**); R = CH_3(**b**);
4, 5 a,d: R^1 = 4-F(**a**); R^1 = 2-Cl(**b**); R^1 = 4-Cl(**c**); R^1 = 4-CH_3O(**d**);
6a,b: R^1 = CH_3(**a**); R^1 = C_2H_5(**b**);
7: R = H, R^1 = CH_3(**a**); R = H, R^1 = C_2H_5(**b**); R = CH_3, R^1 = C_2H_5(**c**);
8, 9: R = H, R^1 = 4-Cl(**a**); R = CH_3, R^1 = 4-NO_2(**b**);
10: R = 3-Cl(**a**); R = 2-NO_2(**b**), R = 4-NO_2(**c**);
11; R = H, R^1 = 3-Cl(**a**); R = CH_3, R^1 = 2-NO_2(**b**); R = CH_3, R^1 = 4-NO_2(**c**);

Figure 1. The scheme for the synthesis of 2-(4-oxo-thiazolidin-2-ylidene)-acetamides.

The structures of the obtained compounds were confirmed by ^{1}H, mass spectroscopy and elemental analysis. All these new compounds gave spectroscopic data in accordance with the proposed structures.

Antimicrobial activity. The antimicrobial study was performed by CO-ADD (The Community for Antimicrobial Drug Discovery), funded by the Wellcome Trust (UK) and The University of Queensland Australia (https://www.co-add.org). Evaluation of all synthesized compounds for their antimicrobial activity against five pathogenic bacteria, *methicillin-resistant Staphylococcus aureus* (ATCC 43300) as Gram-positive bacteria, *Escherichia coli* (ATCC 25922), *Klebsiella pneumonia* (ATCC 700603), *Acinetobacter baumannii* (ATCC 19606) and *Pseudomonas aeruginosa* (ATCC 27853) as Gram-negative bacteria and antifungal activity against two pathogenic fungal strains *Candida albicans* (ATCC 90028) and *Cryptococcus neoformans var. Grubii* (H99; ATCC 208821).

Results revealed (Table 1) that 4-thiazolidinone derivatives **5d, 9b** and **11a-c** have moderate antibacterial activity against Gram-positive *Staphylococcus aureus* with growth inhibition of 41.3–63.85%, while the derivatives **5a-c,** and **9a** have high antibacterial activity against this bacteria with growth inhibition ranged from 85.3 to 97.9%. All compounds do not possess antibacterial activity against tested Gram-negative bacteria (Table 1) and have weak or moderate antifungal activity against *C. neoformans var. Grubii* (Table 2).

Table 1. Antibacterial activity of synthesized compounds.

Compound	*S. aureus ATCC 43300*	*E. coli ATCC 25922*	*K. pneumoniae ATCC 700603*	*P. aeruginosa ATCC 27853*	*A. baumannii ATCC 19606*
5a	*91.3; 96.1*	*-0.7; 1.8*	*2.3; 3.0*	*-3.2; 1.2*	*3.5; 9.2*
5b	*85.3; 85.4*	*-1.1; -1.6*	*5.2; 6.4*	*0.0; 5.3*	*10.9; 4.6*
5c	*98.2; 84.7*	*3.3; 7.4*	*-4.9; 3.5*	*2.5; 6.7*	*-11.6; -7.9*
5d	*60.2; 43.5*	*-1.1; 0.3*	*0.5; 3.5*	*-0.9; 7.2*	*-10.7; -6.5*
7a	*-16.8; -8.2*	*-2.7; 5.8*	*-5.9; 8.3*	*2.7; 4.8*	*-10.8; -3.3*
7b	*11.8; 27.2*	*-2.6; 0.1*	*-1.6; -6.7*	*1.0; 8.4*	*-4.0; 7.3*
7c	*2.6; 3.6*	*1.7; 4.2*	*-5.3; 1.9*	*-0.1; 10.6*	*11.8; 14.7*
9a	*94.0; 97.9*	*-0.7; 5.4*	*31.9; 35.2*	*4.1; 5.5*	*17.7; 5.9*
9b	*41.3; 51.5*	*-8.9; -9.9*	*-6.7; 5.9*	*4.9; 5.0*	*-2.1; 5.5*
11a	*63.8; 53.6*	*0.5; 7.2*	*-8.2; 3.0*	*-0.3; 1.9*	*-1.0; 0.6*
11b	*44.6; 35.6*	*-0.3; -0.8*	*-1.7; -1.7*	*1.2; 10.7*	*-2.1; -5.8*
11c	*45.6; 49.7*	*-5.2; 7.4*	*-3.4; 6.2*	*0.4; 3.2*	*-0.9; 8.7*

Table 2. Antifungal activity of synthesized compounds.

Compound	*C.albicans ATCC 90028*	*C. neoformans ATCC 208821*	***Compound***	*C. albicans ATCC 90028*	*C. neoformans ATCC 208821*
5a	1.0; 5.6	31.3; 38.6	**7c**	6.6; 8.6	71.0; 47.7
5b	1.4; 1.9	42.0; 32.7	**9a**	-1.6; 2.5	38.2; 40.9
5c	7.4; 8.2	52.8; 23.3	**9b**	3.8; 5.5	42.1; 24.5
5d	12.9; 3.0	38.1; 48.3	**11a**	0.8; 7.4	38.1; 34.4
7a	1.4; 2.5	66.7; 75.2	**11b**	0.8; 6.5	38.2; 49.6
7b	10.8; 16.4	51.2; 64.2	**11c**	1.3; 5.0	28.6; 37.7

The minimal inhibitory concentration (MIC μg/mL) measurements were performed for compounds with significant microbial growth inhibition (**5a-c** and **9a)** using ceftriaxone as a reference drug. As shown in Table 3, **5a-c,** and **9a** have best antibacterial activity comparable to that of ceftriaxone.

Table 3. Antibacterial activity of compounds 5a-c and 9a against *S. aureus ATCC 43300* and cytotoxicity against human embryonic kidney cells and erythrocytes (μg/mL).

Compound	***MIC***	***Hk*** CC_{50}	***Hm*** HC_{10}
5a	4; 4	>32; >32	>32; >32
5b	8; 16	>32; >32	>32; >32
5c	16; 16	>32; >32	>32; >32
9a	4; 8	>32; >32	>32; >32
Ceftriaxone	32	Not tested	Not tested

The safety margin for the active compounds toward human cells was determined through cytotoxicity against human embryonic kidney cell line and hemolysis of human red blood cells. The tested compounds were tolerated and non-toxic for human cells as the cytotoxic and hemolytic dose was higher than the therapeutic dose (Table 3).

CONCLUSION

In our present work, we presented an efficient synthesis and antimicrobial activity evaluation of some 2-(4-oxo-thiazolidin-2-ylidene)-acetamides. We have shown that the proposed approaches provide the possibility to design thiazolidines diversity with a considerable chemical novelty. Firstly found antimicrobial activity among the tested compounds was identified. Further optimization of the structure to improve their activities is currently in progress.

ACKNOWLEDGEMENTS

We are grateful CO-ADD (the Community for Antimicrobial Drug Discovery) for screening antimicrobial activity.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

REFERENCES

Chaban, T., Klenina, O., Zimenkovsky, B., Chaban, I., Ogurtsov,V., & Shelepeten L. (2016). Synthesis of novel thiazolo[4,5-*b*]pyridines as potential biologically active substances. *Der Pharma Chemica, 8*(19), 534-542.

Chaban, T.I., Klenina, O.V., Harkov, S, Ogurtsov, V.V., Chaban, I, & Nektegaev, I. (2017). Synthesis of some new N*3* substituted 6-phenylazo-3H-thiazolo[4,5-*b*]pyridin-2-ones as possible anti-inflammatory agents. *Pharmacia, 64*(4), 16-30.

Chaban, T., Klenina, O., Chaban, I., Ogurtsov, V., Harkov, S, & Lelyukh M. (2018). Thiazolo[5,4-d] pyrimidines and thiazolo[4,5-*d*]pyrimidines: A review on synthesis and Pharmacological importance of their derivatives. *Pharmacia, 65*(2), 54-70.

Chaban, T., Ogurtsov. V., Matiychuk, V., Chaban, I., Demchuk, I., & Nektegayev, I. (2019). Synthesis, anti-inflammatory and antioxidant activities of novel 3*H*-thiazolo[4,5-*b*]pyridines. *Acta Chimica Slovenica, 66*(1), 103–111. doi: https://doi.org/10.17344/acsi.2018.4570

Chaban, T., Matiychuk, V., Mahlovanyy, A., Chaban, I., Ogurtsov, V., & Lelyukh, M. (2020). Antitumor properties of thiazolo[4,5-b]pyridin-2-one derivatives. *Biointerface Research in Applied Chemistry, 10*(4), 5944-5950. doi:10.33263/BRIAC104.944950

George, R. (2012). Stereoselective synthesis and QSAR study of cytotoxic 2-(4-oxo-thiazolidin-2-ylidene)-2-cyano-*N*-arylacetamides. *European Journal of Medicinal Chemistry, 47*(1), 377-386. doi:10.1016/j.ejmech.2011.11.006

Ghorab, M., Al-Said Y., & Nissan, M. (2012). Dapson in Heterocyclic Chemistry Part VI: Synthesis and Molecular Docking of Some Novel Sulfonebis compounds of Expected Anticancer Activity. *Arzneimittel for Schung*, *62*(11), 497–507. doi:10.1055/s-0032-1323660

Gould, I. (2010). Coping with antibiotic resistance: The impending crisis. *International Journal of Antimicrobial Agents, 36*(3), S1–S2. doi:10.1016/S0924-8579(10)00497-8

Hanna, M., & George, R. (2012). Facile Synthesis and Quantitative Structure–Activity Relationship Study of Antitumor Active 2-(4-Oxo-thiazolidin-2-ylidene)-3-oxo-propionitriles. *Chemical and Pharmaceutical Bulletin*, *60*(9), 1195–1206. doi:10.1248/cpb.c12-00498

Helal, M., Salem, M., .El-Gaby, M., & Aljahdalif, M. (2013). Synthesis and biological evaluation of some novel thiazole compounds as potential anti-inflammatory agents. *European Journal of Medicinal Chemistry*, *65*(7), 517-526. doi:10.1016/j.ejmech.2013.04.005

Jain, A, Vaidya,F.; Ravichandran, V., Kashawa, S., & Agrawal, R. (2012). Recent developments and biological activities of thiazolidinone derivatives: A review *Bioorganic & Medicinal Chemistry, 20*(11), 3378-3395. doi:10.1016/j.bmc.2012.03.069

Kaminskyy, D., Kryshchyshyn, A., & Lesyk, R. (2017a). Recent developments with rhodanine as a scaffold for drug discovery. *Expert Opinion on Drug Discovery*, *12*(12), 1233-1252. doi:10.1080/17460441.2017.1388370

Kaminskyy, D., Kryshchyshyn, A., & Lesyk, R. (2017b). 5-Ene-4-thiazolidinones. An efficient tool in medicinal chemistry. *European Journal of Medicinal Chemistry*, *140*(10), 542-594. doi:10.1016/j.ejmech.2017.09.031

Klenina, O., Chaban, T., Zimenkovsky, B., Harkov, S., Ogurtsov, V., Chaban, I., & Myrko, I. (2017). Qsar modeling for antioxidant activity of novel N^3 substituted 5,7-dimethyl-3H-thiazolo[4,5-*b*]pyridin-2-ones. *Pharmacia*, *64*(4), 49-71.

Lozynska, L.; Tymoshuk, O.; & Chaban, T. (2015). Spectrophotometric studies of 4-[*N*'-(4-imino-2-oxo-thiazolidin-5-ylidene)-hydrazino]-benzenesulfonic acid as a reagent for the determination of Palladium. *Acta Chimica Slovenica, 62*(1), 159-167. doi:10.17344/acsi.2014.866.

Nasr, T., Bondock, S., & Eid, S. (2016). Design, synthesis, antimicrobial evaluation and molecular docking studies of some new 2,3-dihydrothiazoles and 4-thiazolidinones containing sulfisoxazole. *Journal of Enzyme Inhibition and Medicinal Chemistry, 31*(2), 236-246. doi:10.3109/14756366.2015.1016514

Obushak, N., Gorak, Yu., Matiichuk, V., & Lytvyn, R. (2008). Synthesis of heterocycles based on arylation products of unsaturated compounds: XVII. Arylation of 2-acetylfuran and synthesis of 3-R-6-(5-aryl-2-furyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines. *Russian Journal of Organic Chemistry, 44*(11), 1689-1694. doi:10.1134/S1070428008110213

Obushak, N., Lesyuk, A., Gorak, Y., & Matiichuk, V. (2009). Mechanism of Meerwein arylation of furan derivatives. *Russian Journal of Organic Chemistry, 45*(9), 1375-1381. doi:10.1134/S1070428009090103

Open-access antimicrobial screening program (https://www.co-add.org).

Payne, D., Gwynn, M., Holmes, D., & Pompliano, D. (2007). Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nature Reviews Drug Discovery, 6*(1), 29-40. doi: 10.1038/nrd2201

Piddock, L. (2012). The crisis of no new antibiotics—What is the way forward? *The Lancet Infectious Diseases, 12*(3), 249–253. doi:10.1016/S1473-3099(11)70316-4

Pokhodylo, N., Matiychuk, V., & Obushak, N. (2009a). A convenient method for the synthesis of thiopyrano[4,3-*c*]quinoline, a new heterocyclic system. *Chemistry of Heterocyclic Compounds, 45*(1), 121-122. doi:10.1007/s10593-009-0238-2.

Pokhodylo, N., Savka, R., Matiichuk, V., & Obushak, N. (2009b). Synthesis and selected transformations of 1-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl) ethanones and 1-[4-(4-R-5-methyl-1*H*-1,2,3-triazol-1-yl)phenyl]ethanones. *Russian Journal of General Chemistry*, *79*(2), 309-314. doi:10.1134/S1070363209020248.

Pokhodylo, N., & Matiychuk, V. (2010). Synthesis of new 1,2,3-triazolo[1,5-*a*]quinazolinones. *Journal of Heterocyclic Chemistry, 47*(2), 415-420. doi:10.1002/jhet.321.

Rostom, S., El-Ashmawy, I., Abd el Razikm, H., Badr, M., & Absour, H. (2009). Design and synthesis of some thiazolyl and thiadiazolyl derivatives of antipyrine as potential non-acidic anti-inflammatory, analgesicand antimicrobial agents. *Bioorganic & Medicinal Chemistry, 17*(2), 882–895. doi:10.1016/j.bmc.2008.11.035.

Salem M. (2017). Synthesis of New Thiazole, Bithiazolidinone and Pyrano[2,3-d]thiazole Derivatives as Potential Antimicrobial Agents. *Croatica Chemica Acta, 90*(1), 7–15. doi:10.5562/cca2955.

Shaoyong, K. (2016). Convenient Structural Diversity-Guided Synthesis of Functionalized Sulfur-Containing Heterocycles via α-Substituted Cyanoacetamides. *Journal of Heterocyclic Chemistry, 54*(3), 1957-1962. doi:10.1002/jhet.2792.

Tomasić, T., & Masic, L.(2009). Rhodanine as a privileged scaffold in drug discovery. *Current Medicinal Chemistry, 16*(13), 1596–1629. doi:10.2174/092986709788186200.

Tripathi, K.D. (2013). *Pharmacological Classification of Drugs with Doses and Preparations*. New Delhi, India: Jaypee Brothers Medical Publishers.

Tsyalkovsky, V., Kutsyk, R., Matiychuk, V., Obushak, N., & Klyufinskaya, T. (2005). Synthesis and antimicrobial activity of 5-(R1-benzyl)-2-(R 2-benzylidenehydrazono)-3-(2-furylmethyl)thiazolidin-4-ones. *Pharmaceutical Chemistry Journal, 39*(5), 245-247. doi:10.1007/s11094-005-0126-8.

Tupys, A., Kalembkiewicz, J., Ostapiuk, Y., Matiichuk, V., Tymoshuk, O., Woźnicka, E., & Byczyński, Ł. (2018). Synthesis, structural characterization and thermal studies of a novel reagent 1-[(5-benzyl-1,3-thiazol-2-yl)diazenyl]naphthalene-2-ol. *Journal of Thermal Analysis and Calorimetry*, *127*(3), 2233-2242. doi:10.1007/s10973-016-5784-0.

Zelisko, N., Atamanyuk, D., Ostapiuk, Y., Bryhas, A., Matiychuk, V., Gzella, A., & Lesyk, R. (2015). Synthesis of fused thiopyrano[2,3-*d*][1,3]thiazoles *via* hetero-Diels-Alder reaction related tandem and domino processes. *Tetrahedron, 71*(50), 9501-9508. doi:10.1016/j.tet.2015.10.019.

Zimenkovskii, B, Kutsyk, R., Lesyk, R., Matyichuk, V., Obushak, N., & Klyufinska, T. (2006). Synthesis and antimicrobial activity of 2,4-dioxothiazolidine-5-acetic acid amides. *Pharmaceutical Chemistry Journal, 40*(6), 303-306. doi:10.1007/s11094-006-0115-6.

Zubkov, F., Ershova, J., Zaytsev, V., Obushak, M., Matiychuk, V., Sokolova, E., … Varlamov, A. (2010). The first example of an intramolecular Diels-Alder furan (IMDAF) reaction of iminium salts and its application in a short and simple synthesis of the isoindolo[1, 2-*a*]isoquinoline core of the jamtine and hirsutine alkaloids. *Tetrahedron Letters, 51*(52), 6822-6824. doi:10.1016/j.tetlet.2010.10.046.