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SYNTHESIS OF NEW (2,4-DIOXOTHIAZOLIDIN-5-YL)ACETIC ACID DERIVATIVES WITH PIPERAZINE AND 1,2,4-TRIAZOLE SUBSTITUTES AND THEIR ANTIMICROBIAL ACTIVITY EVALUATION

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ABSTRACT

By the reaction of the acid chloride (2) with a various hydrazides (3-6), 1,2,4-triazole-3-thione derivative (7) and piperazine derivatives (8, 9) a series of novel corresponding N'-substituted-(2,4-dioxothiazolidin-5-yl)acetohydrazides (10-13), 5-[2-oxo-2-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)ethyl]thiazolidine-2,4-dione (14) or 5-[2-oxo-2-(4-substitutedpiperazin-1-yl)ethyl]thiazolidine-2,4-dione (15, 16) derivatives were obtained. All the structures were confirmed by their spectral (^{1}H NMR and ^{13}C NMR) and elemental analysis data. The new compounds were tested for their *in vitro* antimicrobial activity. Compounds 11-14 had *in vitro* activity against Gram-positive reference strains of bacteria with MIC values from 62.5 to 250 μg/ml.

Keywords: 2,4-thiazolidinedione derivatives, 1,2,4-triazoles, Piperazine derivatives, Antimicrobial activity.

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INTRODUCTION

2,4-Thiazolidinedione derivatives are well known group of compounds with wide spectrum of biological activities [1, 2]. 2,4-Thiazolidinedione ring are present in glitazones drugs (Rosiglitazone, Pioglitazone etc.), that used for the treatment of type 2 diabetes. 2,4-Thiazolidinediones lower the plasma glucose levels by acting as ligands for gamma peroxisome proliferator-activated receptors (PPARγ). In addition, this class of heterocyclic compounds possesses various other biological activities such as anticancer [3-6], anti-inflammatory [7-8], antimicrobial [9-17], aldose reductase inhibitor [18-21].

Structure activity relationship (SAR) studies on 2,4-thiazolidindiones have shown that the substituent at 5-th position of the 2,4-thiazolidinedione ring system influences the pharmacological activities [15, 22, 23]. There have been many reports in literature depicting that the present of heterocyclic moieties at fifth position in 2,4-dioxothiazolidine ring prove to be more potent and efficacious than a simple aryl group [24-27]. Such heterocyclic system might be 1,2,4-triazole and piperazine that have been a various pharmacological properties. 1,2,4-Triazole ring are known as compounds with antimicrobial [28, 29], analgesic [30], anti-inflammatory [31], antiviral [32] activities. Besides, piperazine derivatives also have a wide

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spectrum of biological activities such as anticonvulsant [33], antioxidant [34] and antimicrobial activity [35]. In addition piperazine fragment is a part of the fluorquinolones antibiotics (Ciprofloxacin, Norfloxacin, Levofloxacin etc.).

In view of the pharmacological importance 2,4-thiazolodinediones, 1,2,4-triazoles and piperazine derivatives and the continuous our previous research on biological activity of 2,4-thiazolidinedione derivatives [36-38] we modified 2,4-thiazolidinedione ring at 5-th positions with the hope to obtain the compounds with intensified activities.

MATERIALS AND METHODS

Chemistry

Melting points were determined in Fischer-Johns block (Sanyo, Japan) and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a BrukerAvance DPX 300, in DMSO-d_6, using tetramethylsilane as internal standard. Purity of all compounds was checked by TLC on aluminium oxide 60 F_{254} plates (Merck), in a $CHCl_3/C_2H_5OH$ (10:1, v/v) solvent system with UV visualization (λ=254 nm). Elemental microanalysis for C, H, N performed on AMZ 851 CHX analyser and the results were within ± 0.4% of the theoretical value.

General method for synthesis of N'-substituted-(2,4-dioxothiazolidin-5-yl)acetohydrazides (10-13), 5-[2-oxo-2-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)ethyl]thiazolidine-2,4-dione (14) and5-[2-oxo-2-(4-substitutedpiperazin-1-yl)ethyl]thiazolidine-2,4-dione (15, 16).

To a solution of 0.01 mol of corresponding hydrazides (**3-6**), 4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**7**), 1-phenylpiperazine or 1-(2-fluorphenyl)piperazine and 1 ml of triethylamine in 10 ml anhydrous dioxane was added the solution of 0.01 mol acid chloride (**2**) in 5 ml of same solvent. After 15 min, water was added and the mixture was left at room temperature at 24 h. The precipitate was filtered off and then crystallized from n-butanol. For the substance 10 acetic acid was used as the solvent for crystallization.

Spectral analysis of the synthesized compounds

2-(2,4-dioxo-1,3-thiazolidin-5-yl)-*N*'-(1*H*-1,2,4-triazol-1-ylacetyl)acetohydrazide (10)

Yield 59 %, mp = 230-232°C. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.89 (dd, 1H, CH_2,*J* = 16.8 Hz and *J* = 8.7 Hz); 3.02 (dd, 1H, CH_2,*J* = 16.8 Hz and *J* = 3.9 Hz); 4.66 (dd, 1H, CH, *J* = 8.7 Hz and *J* = 3.9 Hz,); 4.99 (s, 2H, CH_2); 7.97, 8.51 (2s, 2H, triazole); 10.27 (d, 1H, NH-NH, *J* = 3.0 Hz); 10.43 (d, 1H, NH-NH, *J* = 3.0 Hz); 11.99 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 35.4; 47.0; 47.2; 143.0; 145.7; 165.4; 168.1; 173.2; 176.3. Elemental anal. (%), Calcd for $C_9H_{10}N_6O_4S$ (298.28): C 36.24, H 3.38, N 28.18; Found: C 36.21; H 3.35; N 28.15.

2-(2,4-dioxo-1,3-thiazolidin-5-yl)-*N*'-[(5-oxo-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetyl]acetohydrazide (11)

Yield 62 %, mp = 205-207°C. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.89 (dd, 1H, CH_2,*J* = 16.5 Hz and *J* = 8.7 Hz); 3.03 (dd, 1H, CH_2,*J* = 16.5 Hz and *J* = 3.9 Hz); 4.48 (s, 2H, CH_2); 4.66 (dd, 1H, CH, *J* = 8.7 Hz and *J* = 3.9 Hz,); 7.36-7.72 (m, 5H, Ph); 8.52 (s, 1H, CH=); 10.18 (d, 1H, NH-NH, *J* = 1.5 Hz); 10.25 (d, 1H, NH-NH, *J* = 1.5 Hz); 12.00 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 35.5; 46.7; 47.2; 121.8; 127.6; 129.9; 134.5; 135.9; 152.1; 165.8; 168.2; 173.2; 176.4. Elemental anal. (%), Calcd for $C_{15}H_{14}N_6O_5S$ (390.37): C 46.15, H 3.62, N 21.53; Found: C 46.14; H 3.57; N 21.51.

2-(2,4-dioxo-1,3-thiazolidin-5-yl)-*N*'-{[5-oxo-4-phenyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetyl}acetohydrazide (12)

Yield 61 %, mp = 202-204°C. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.89 (dd, 1H, CH_2,*J* = 16.8 Hz and *J* = 8.7 Hz); 3.04 (dd, 1H, CH_2,*J* = 16.8 Hz and *J* = 3.9 Hz); 4.59 (s, 2H, CH_2); 4.66 (dd, 1H, CH, *J* = 8.7 Hz and *J* = 3.6 Hz,); 7.22-8.36 (m, 9H, Ar); 10.21, 10.32 (2s, 2H, NH-NH); 12.00 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 35.5; 47.1; 47.2; 123.6; 125.3; 127.6; 128.6; 129.3; 134.9; 137.8; 144.1; 146.3; 149.5; 153.8; 165.7; 168.2; 173.2; 176.4. Elemental anal. (%), Calcd for $C_{20}H_{17}N_7O_5S$ (467.46): C 51.39, H 3.67, N 20.97; Found: C 54.05; H 3.89; N 18.00.

2-(2,4-dioxo-1,3-thiazolidin-5-yl)-*N*'-{[(4-phenyl-4*H*-1,2,4-triazol-3 yl)sulfanyl]acetyl}acetohydrazide (13)

Yield 57 %, mp = 176-178°C. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.87 (dd, 1H, CH_2,*J* = 16.8 Hz and *J* = 8.7 Hz); 3.01 (dd, 1H, CH_2,*J* = 16.8 Hz and *J* = 3.9 Hz); 4.03 (s, 2H, CH_2); 4.65 (dd, 1H, CH, *J* = 8.7 Hz and *J* = 3.9 Hz,); 7.51-7.61 (m, 5H, Ph); 8.85 (s, 1H, CH=); 10.21 (d, 1H, NH-NH, *J* = 3.0 Hz); 10.37 (d, 1H, NH-NH, *J* = 3.0 Hz); 11.99 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 34.8; 35.5; 47.2; 125.8; 130.0; 130.3; 133.7; 145.8; 149.1; 166.0; 168.0; 173.3; 176.5. Elemental anal. (%), Calcd for $C_{15}H_{14}N_6O_4S_2$ (406.44): C 44.33, H 3.47, N 20.68; Found: C 44.32; H 3.44; N 20.69.

5-[2-oxo-2-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)ethyl]-1,3-thiazolidine-2,4-dione (14)

Yield 58 %, mp = 212-215°C. ^{1}H NMR is

shown in [38]. ^{13}C NMR (DMSO-d_6) δ (ppm): 36.4; 46.4; 127.3; 129.8; 130.0; 134.0; 143.0; 167.8; 168.5; 173.1; 176.2. Elemental anal. (%), Calcd for $C_{13}H_{10}N_4O_3S_2$ (334.37): C 46.70, H 3.01, N 16.76; Found: C 46.68; H 2.98; N 16.75.

5-[2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]-1,3-thiazolidine-2,4-dione (15)

Yield 47 %, mp = 221-223°C. ^{1}H NMR (DMSO-d_6) δ (ppm): 3.12-3.23 (m, 1H, CH_2 and 4H, piperazine); 3.39 (dd, 1H, CH_2,*J* = 17.5 Hz and *J* = 2.5 Hz); 3.59-3.67 (m, 4H, piperazine); 4.67 (dd, 1H, CH, *J* = 10.0 Hz and *J* = 2.5 Hz); 6.84-7.32 (m, 5H, Ph); 11.91 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 36.2; 41.6; 45.0; 47.9; 48.7; 49.0; 116.4; 119.9; 129.9; 151.3; 168.1; 173.9; 176.8. Elemental anal. (%), Calcd for $C_{15}H_{17}N_3O_3S$ (319.38): C 56.41, H 5.37, N 13.16; Found: C 56.39; H 5.34; N 13.15.

5-{2-[4-(2-fluorophenyl)piperazin-1-yl]-2-oxoethyl}-1,3-thiazolidine-2,4-dione (16)

Yield 47 %, mp = 213-214°C. ^{1}H NMR (DMSO-d_6) δ (ppm): 2.96-3.04 (m, 4H, piperazine); 3.14 (dd, 1H, CH_2,*J* = 17.5 Hz and *J* = 10.0 Hz); 3.35 (dd, 1H, CH_2,*J* = 17.5 Hz and *J* = 2.5 Hz); 3.57-3.65 (m, 4H, piperazine); 4.63 (dd, 1H, CH, *J* = 10.0 Hz and *J* = 5.0 Hz); 7.00-7.22 (m, 4H, 2-F-C_6H_4); 12.03 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 36.2; 41.8; 45.3; 47.8; 50.4; 50.8; 116.4; 120.1; 123.3; 125.4; 139.9; 140.1; 168.1; 173.8; 176.7. Elemental anal. (%), Calcd for $C_{15}H_{16}FN_3O_3S$ (337.37): C 53.40, H 4.78, N 12.46; Found: C 53.40; H 4.75; N 12.44.

Microbiology

The antimicrobial activity of the tested compounds (10-16) was screened on the American Type Culture Collection (ATCC) reference strains of Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923, S*taphylococcus epidermidis* ATCC 12228, *Bacillus subtilis* ATCC 6633, *Micrococcus luteus* ATCC 10240), and of the Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Proteus mirabilis* ATCC 12453, *Pseudomonas aeruginosa* ATCC 9027).

Besides, the methicillin-resistant *Staphylococcus aureus* (MRSA) Microbank 14.001 from the collection of National Medicines Institute in Warsaw was used. All stock solutions of the tested compounds were dissolved in dimethyl sulfoxide (DMSO). Microbial suspensions were prepared in sterile saline (0.85% NaCl) with an optical density of 0.5 McFarland standard - 150 x 10^6 CFU/mL (CFU - colony forming units). The medium with dimethyl sulfoxide at the final concentration and without the tested compounds served as a negative control. Cefuroxime was used as reference antibiotic. The antibacterial potency of tested compounds was screened using the agar dilution method on the basis of the growth inhibition on the Mueller-Hinton agar to which the tested compounds at concentrations 1000 μg/mL were added.

Then the antibacterial activity of the compounds with inhibitory effect was determined by broth microdilution technique using 96-well microplates with series of twofold dilution of the tested compounds, according to described earlier [41].

The activity was expressed as the minimal concentration of the compound that inhibits the visible growth of the bacteria (MIC). The MBC (minimal bactericidal concentration), defined as the lowest concentration of each compound that resulted in >99.9% reduction in CFU of the initial inoculum, was also determined. MBC was determined by a broth microdilution technique by plating out the contents of wells (5 μL) that showed no visible growth of bacteria, onto Mueller-Hinton agar plates and incubating at 35°C for 18 h.

RESULTS AND DISCUSSION

Chemistry

In a present research as a starting material was used (2,4-dioxothiazolidin-5-yl)acetic acid (1). This acid was synthesized by the reaction of cyclocondensation of thiourea with maleic anhydride in presence of concentrated hydrochloric acid [39]. (2,4-Dioxothiazolidin-5-yl)acetic acid by the reaction with thionyl chloride provided to (2,4-dioxothiazolidin-5-yl)acetyl chloride (2), which is a good synth on for modifying of 2,4-dioxothiazolidine rin g (Scheme 1).

New N'-substituted-(2,4-dioxothiazolidin-5-yl) acetohydrazides (10-13), 5-[2-oxo-2-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl) ethyl] thiazolidine-2,4-dione (14) or 5-[2-oxo-2-(4-substitutedpiperazin-1-yl)ethyl]thiazolidine-2,4-dione (15, 16) derivatives were obtained by the reaction of the acid chloride (2) with a various hydrazides (3-6), 4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (7), 1-phenylpiperazine (8) and 1-(2-fluorphenyl) piperazine (9) corresponding. The reaction proceeded according to the Scheme 2.

2,4-Thiazolidinedione-5-acetic acid and their derivatives contain diastereotopic protons of methylene group. That is why the fragment $CH^AH^BCH^X$ is presented in ^{1}H NMR spectra as ABX spin system, which appears as doublet of doublets at 2.87-3.14 ppm and 3.01-3.39 ppm, and 4.63-4.67 ppm with coupling constants J_{AB} = 16.5-18.9 Hz, J_{AX} = 8.7-10.0 Hz, J_{BX} = 2.5-3.9 Hz. For the compound 14doublet of doublets appears at 3.73 ppm, 4.06 ppm

and 4.86 ppm, respectively. High value of J_{AB} agreed with the data of Takahashi ("carbonyl effect") for structurally related 2-thioxo-4-thiazolidine-5-acetic acids [40]. Chemical shifts of NH-NH group of compounds (10, 11 and 13) in the ^{1}H NMR spectra were observed as doublets at 10.18-10.27 ppm and 10.25-10.43 ppm with coupling constants J = 1.5-3.0 Hz. But, signal of NH-NH group for compound 12 appears as two singlets at 10.21 and 10.32 ppm. All compounds (10-16) showed proton signals in the range 11.91-12.13 ppm typical for the NH group of the 2,4-thiazolidinedione ring. In the ^{1}H NMR spectra compounds 10, 11 and 13, 14 showed proton signal typical for CH group of 1,2,4-triazole ring in the range of 7.97-8.93 ppm.

In the ^{13}C NMR δ values of the carbons of the all 2,4-dioxothiazolidine derivatives (10-16) showed the carbon signals of two C=O groups in the range 173.09-176.83 ppm.

The detailed results of ^{1}H NMR and ^{13}C NMR spectra are presented in the experimental part.

MICROBIOLOGY

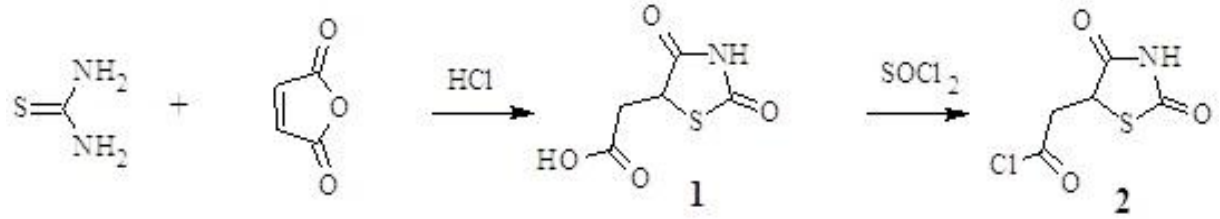
Using the agar dilution method, it was shown that compound 11, 12, 13 and 14 had *in vitro* potential activity against Gram-positive reference strains (Table 1). The tested derivatives were active against *Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* ATCC 6633 and *Micrococcus luteus* ATCC 10240 with MIC values from 62.5 to 250 μg/mL, with almost none activity against methicillin-resistant *S. aureus* Microbank 14.001 (MIC = 500 – ≥ 1000 μg/mL. On the basis of MBC/MIC ratio, it was found that tested compounds have bacteriostatic effect (MBC/MIC> 4) towards the sensitive Gram-positive strains. None of the tested compound had significant effect against the growth of Gram-negative bacteria.

Table 1. The influence of compounds (11-14) on the growth of Gram-positive reference strains of bacteria on the basis of MIC (μg/mL) and MBC (μg/mL) values determined by broth microdilution method.

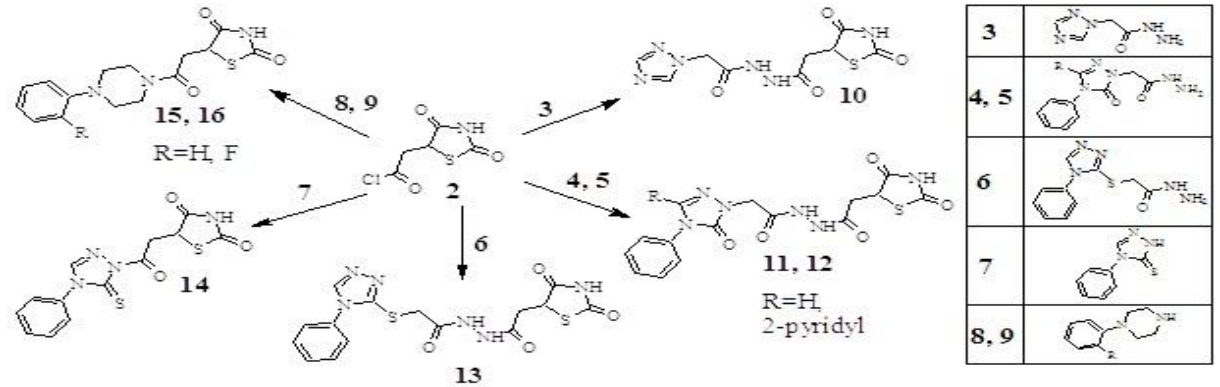
	Sa25923		Sa14001		Se12228		Bs6633		Ml102240	
Compound	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**
11	62.5	>1000	1000	>1000	125	>1000	62.5	62.5	62.5	500
12	62.5	>1000	>1000	>1000	125	>1000	62.5	250	62.5	>1000
13	62.5	>1000	1000	>1000	250	>1000	62.5	62.5	62.5	500
14	250	>1000	500	>1000	250	1000	62.5	62.5	125	500
Cefuroxime	0.49	-	nt	-	0.24	-	15.63	-	0.98	-

Abbreviations: Sa25923 - *Staphylococcus aureus* ATCC 25923, Sa14001 - *Staphylococcus aureus*Microbank 14.001, Se12228 - *Staphylococcus epidermidis* ATCC 12228, Bs6633 - *Bacillus subtilis* ATCC 6633, Ml10240 - *Micrococcus luteus* ATCC 10240, nt- not tested.

Scheme 1. Synthesis of (2,4-dioxothiazolidin-5-yl)acetyl chloride.



Scheme 2. Synthesis of (2,4-dioxothiazolidin-5-yl)acetic acid derivatives with piperazine and 1,2,4-triazoles substitutes.



CONCLUSION

In conclusion, we report the synthesis and antimicrobial evaluation of new (2,4-dioxothiazolidin-5-yl)acetic acid derivatives with piperazine and 1,2,4-triazole substitutes. The results of antimicrobial evaluation showed that only (2,4-dioxothiazolidin-5-yl)acetic acid derivatives with 1,2,4-triazole substitutes (compounds 11-14) have bacteriostatic effect (MBC/MIC>4) against sensitive Gram-positive strains.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

REFERENCES

1. Lesyk RB, Zimenkovsky BS. 4-Thiazolidones: Centenarian history, current status and perspectives for modern organic and medicinal chemistry. *Curr. Org. Chem.*, 8, 2004, 1547-1577.
2. Malik S, Upadhyaya PK, Miglani S. Thiazolidinediones: a plethro of biological load. *Int. J. Pharm. Tech. Res.*, 3, 2011, 62-75.
3. Kaminsky DV, Lesyk RB. Structure–anticancer activity relationships among 4-azolidinone-3-carboxylic acids derivatives. *Biopolymers and Cell*, 26, 2010, 136-145.
4. Kaminsky D, Zimenkovsky B, Lesyk R. Synthesis and *in vitro* anticancer activity of 2,4-azolidinedione-acetic acids derivatives. *Eur. J. Med. Chem.*, 44, 2009, 3627-3636.
5. Alegaon SG, Alagawadi KR. New thiazolidinedione-5-acetic acid amide derivatives: synthesis, characterization and investigation of antimicrobial and cytotoxic properties. *Med. Chem. Res.*, 21, 2012, 816-824.
6. Havrylyuk DY, Lesyk RB, Zimenkovsky BS, PachovskyVYu. Synthesis and anticancer activity studying of 4-(2,4-thiazolidinedione-5-acetoxy)benzylidenehydrazones of benzazol-3-thioacetic acids. *Farm. Zh. (Kyiv)*, 2, 2006, 53-58.
7. Dandona P, Aljada AA, Chaudhuri A. Vascular reactivity and thiazolidinediones. *Am. J. Med.*, 115, 2003, 81-86.
8. Santos LC, Uchoa FT, Canas ARPA, Sousa IA, Moura RO, Lima MCA, Galdino SL, Pitta IR, Barbe J. Synthesis and anti-inflammatory activity of new thiazolidine-2,4-diones, 4-thioxothiazolidinones and 2-thioxoimidazolidinones. *Heterocycl. Comm.*, 11, 2005, 121-128.
9. Heerding DA, Christmann LT, Clark TJ, Holmes DJ, Rittenhouse SF, Takata DT, Veslavsky JW. New benzylidenethiazolidinediones as antibacterial agents. *Bioorg. Med. Chem. Lett.*, 13, 2003, 3771-3773.
10. Tomasic T, Zidar N, Rupnik V, Kovac A, Blanot D, Gobec S, Kikelj D, Masic LP. Synthesis and biological evaluation of new glutamic acid-based inhibitors of MurD ligase. *Bioorg. Med. Chem. Lett.*, 19, 2009, 153-157.
11. Zvarec O, Polyak SW, Tieu W, Kuan K, Dai H, Pedersen DS, Morona R, Zhang L, Booker GW, Abell AD. 5-Benzylidenerhodanine and 5-benzylidene-2,4-thiazolidinedione based antibacterials. *Bioorg. Med. Chem. Lett.*, 22, 2012, 2720-2722.
12. Aneja DK, Lohan P, Arona S, Sharma C, Aneja KR, Prakash O. Synthesis of new pyrazolyl-2,4-thiazolidinediones as antibacterial and antifungal agents. *Org. Med. Chem. Lett.*, 1:15, 2011.
13. Purohit SS, Alman A, Shewale J. Synthesis & antimicrobial activity of a new series of 3, 5-disubstituted thiazolidine-2,4-diones. *Int. J. Pharm. Pharm. Sci.*, 4, 2012, 273-276.
14. Juddhawala K, Parekh NM, Rawal BM. Synthesis and antibacterial activities of N-chloro aryl acetamide substituted thiazole and 2,4-thiazolidinedione derivatives. *Arch. Appl. Sci. Res.*, 3, 2011, 540-548.
15. Jawale DV, Pratap UR, Mane RA. Synthetic route for new (Z)-5-[4-(2-chloroquinolin-3-yl)methoxy]benzylidinethiazolidine-2,4-diones. *Bull. Korean Chem. Soc.*, 32, 2011, 2171-2177.
16. Pattan S, Kedar M, Pattan J, Dengale S, Sanap M, Gharate U, Shinde P, Kadam S. Synthesis and evaluation of some novel 2,4-thiazolidinedione derivatives for antibacterial, antitubercular and antidiabetic activities. *Indian J. Chem.*, 51B, 2012, 1421-1425.
17. Zimenkovskii BS, Kutsyk RV, Lesyk RB, Matyichuk VS, Obushak ND, Klyufinska TI. Synthesis and antimicrobial activity of 2,4-dioxothiazolidine-5-acetic acid amides. *Pharm. Chem. J.*, 40, 2006, 303-306.
18. Bruno G, Costantino L, Curinga C, Maccari R, Monforte F, Nicolo F, Ottana R, Vigorita MG. Synthesis and aldose reductase inhibitory activity of 5-arylidene-2,4-thiazolidinediones. *Bioorg. Med. Chem.*, 10, 2002, 1077-1084.
19. Rakowitz D, Maccari R, Ottana R, Vigorita MG. *In vitro* aldose reductase inhibitory activity of 5-benzyl-2,4-thiazolidinediones. *Bioorg. Med. Chem.*, 14, 2006, 567-574.
20. Maccari R, Del Corso A, Giglio M, Moschini R, Mura U, Ottana R. *In vitro* evaluation of 5-arylidene-2-thioxo-4-thiazolidinones active as aldose reductase inhibitors. *Bioorg. Med. Chem. Lett.*, 21, 2011, 200-203.

21. Soni LK, Gupta AK, Kaskhedikar SG. QSAR study of 5-arylidene-2,4-thiazolidinediones as aldose reductase inhibitors. *Med. Chem. Res.*, 17, 2008, 258-266.
22. Maccari R, Ottana R, Curinga C, Vigorita MG, Rakowitz D, Steindl T, Langer T. Structure–activity relationships and molecular modelling of 5-arylidene-2,4-thiazolidinediones active as aldose reductase inhibitors. *Bioorg. Med. Chem.*, 13, 2005, 2809-2823.
23. Maccari R, Ottana R, Ciurleo R, Rakowitz D, Matuszczak B, Laggner C, Langer T. Synthesis, induced-fit docking investigations, and *in vitro* aldose reductase inhibitory activity of non-carboxylic acid containing 2,4-thiazolidinedione derivatives. *Bioorg. Med. Chem.*, 16, 2008, 5840-5852.
24. Bozda DO, Evranos B, Daş EN, Sarıkaya M, Ertan R. Synthesis and aldose reductase inhibitory activity of some new chromonyl-2,4-thiazolidinediones. *Eur. J. Med. Chem.*, 43, 2008, 2412-2417.
25. Tunçbilek M, *et al.* Synthesis and hypoglycemic activity of some substituted flavonyl thiazolidinedione derivatives - fifth communication: flavonyl benzyl substituted 2,4-thiazolidinediones. *Farmaco*, 58, 2003, 78-83.
26. Bozdag DO, Ozgen O, Menteşe A, Altanlar N, Atli O, Kendi E, Ertan R. Synthesis and antimicrobial activity of some new thiazolyl thiazolidine-2,4-dione derivatives. *Bioorg. Med. Chem.*, 15, 2007, 6012-6017.
27. Brooke EW, Davies SG, Mulvaney AW, Okada M, Pompeo F, Sim E, Vickers RJ, Westwood IM. Synthesis and *in vitro* evaluation of novel small molecule inhibitors of bacterial arylamine*N*-acetyltransferases (NATs). *Bioorg. Med. Chem. Lett.*, 13, 2003, 2527-2530.
28. Bayrak H, Demirbas A, Karaoglu SA, Demirbas N. Synthesis of some new 1,2,4-triazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities. *Eur. J. Med. Chem.*, 44, 2009, 1057-1066.
29. Almajan GL, Barbuceanu S-F, Almajan E-R, Draghici C, Saramet G. Synthesis, characterization and antibacterial activity of some triazoleMannich bases carrying diphenylsulfone moieties. *Eur. J. Med. Chem.*, 44, 2009, 3083-3089.
30. Tozkoparan B, Küpeli E, Yeşilada E, Ertan M. Preparation of 5-aryl-3-alkylthio-l,2,4-triazoles and corresponding sulfones with antiinflammatory–analgesic activity. *Bioorg. Med. Chem.*, 15, 2007, 1808-1814.
31. Kumar H, Javed SA, Khan SA, Amir M. 1,3,4-Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid: Synthesis and preliminary evaluation of biological properties. *Eur. J. Med. Chem.*, 43, 2008, 2688-2698.
32. Kritsanida M, Mouroutsou A, Marakos P, Pouli N, Papakonstantinou-Garoufalias S, Pannecouque C, Witvrouw M, De Clerq E. Synthesis and antiviral activity evaluation of some new 6-substituted 3-(1-adamantyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles. *Farmaco*, 57, 2002, 253-257.
33. Marona H, Korona R, Szneler E. Synthesis and anticonvulsant activity of some piperazine derivatives. *Boll. Chim. Farm.*, 143, 2004, 329-335.
34. Pietrzycka A, Stępniewski M, Waszkielewicz AM, Marona H. Preliminary evaluation of antioxidant activity of some 1-(phenoxyethyl)-piperazine derivatives. *Acta Pol. Pharm.*, 63, 2006, 19-24.
35. Chaudhary P, Kumar R, Verma AK, Singh D, Yadav V, Chhillar AK, Sharma GL, Chandra R. Synthesis and antimicrobial activity of N-alkyl and N-aryl piperazine derivatives. *Bioorg. Med. Chem.*, 14, 2006, 1819-1826.
36. Trotsko N, Dobosz M, Lukianchuk V. Synthesis of amides of 5-arylidene-2,4-dioxothiazolidine-3-acetic acid with 1,2,4-triazole system.*Acta Pol. Pharm.*, 63, 2006, 47-52.
37. Trotsko N, Dobosz M, Jagiełło-Wójtowicz E. Cyclization of thiosemicarbazide derivatives of 5-arylidene-2,4-dioxothiazolidine-3-acetic acids to 1,3,4-thiadiazoles and their pharmacological properties.*Acta Pol. Pharm.*, 64, 2007, 227-231.
38. Trotsko N, Dobosz M, Chodkowska A, Jagiełło-Wójtowicz E. Synthesis of amides of 2,4-dioxothiazolidin-5-yl acetic acid with 1,2,4-triazole substituents.*Acta Pol. Pharm.*, 65, 2008, 217-221.
39. Lesyk RB, Zimenkovsky BS, Golota S, Leb'yak MM. Synthesis of 2,4-dioxothiazolidine-5-acetic acid and its amides - perspective synthons for obtaining combinatorial libraries of biologically active substances. *Farm. Zh. (Kyiv)*, 5, 2001, 57-62.
40. Takahashi T. Spin-spin coupling constants for methylene groups adjacent to carbonyl groups.*Tetrahedron Lett.*, 5, 1964, 565-572.
41. Trotsko N, Król J, Siwek A, Wujec M, Kosikowska U, Malm A. Synthesis and antimicrobial evaluation of new 1-{[4-(4-halogenophenyl)-4*H*-1,2,4-triazol-3-yl]sulfanyl}acetyl-4-substituted thiosemicarbazides and products of their cyclization. *Heteroatom Chem.*, 23, 2012, 117-121.

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