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Synthesis antimicrobial and antitumor activities of 2-[5-(2-R-benzyl)thiazol-2-ylimino]thiazolidin-4-ones

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ABSTRACT
By the reaction of N-(5-R-benzyl-thiazol-2-yl)-2-chloroacetamides with potassium thiocyanate were synthesized 2-[5-(2-R-benzyl)thiazol-2-ylimino]thiazolidin-4-ones. The structures of target compounds **9a-e** were confirmed by using NMR spectroscopy and elemental analysis. The antimicrobial and anticancer activity of synthesized compounds was evaluated. The compounds with high antimicrobial activity against Staphylococcus aureus ATCC 43300 were identified.
Keywords: *organic synthesis; 2-[5-(2-R-benzyl)thiazol-2-ylimino]thiazolidin-4-ones; antimicrobial activity; antitumor activity.*

1. INTRODUCTION
Every year, infectious diseases cause the deaths of many millions of people in the world. The wide variety of biological forms of pathogens, the constant emergence of new multiresistant pathogenic strains make it difficult to treat and prevent infectious diseases. On the other hand cancer is also a very dangerous disease Despite remarkable advances in modern medical sciences, cancer remains a disease difficult to treat and after heart disease, it is the second most common cause of death in the world. So development of new antimicrobial and anticancer agents is actual problem [1]. In this article, we described the synthesis and primary evolution of antimicrobial and anticancer activity of new thiazol-2-yliminothiazolidin-4-one derivatives. It should be noticed that thiazolidin-4-ones are an important class of biologically attractive compounds. They exhibit a wide range of pharmacological activity. These derivatives have also been used as sensitive analytical reagents. 4-Thiazolidone motif is considered as privileged scaffolds in medicinal chemistry and is currently the subject of extensive research [2-12].

2. MATERIALS AND METHODS
2.1. Materials.
All chemicals were of analytical grade and commercially available. All reagents and solvents were used without further purification and drying.
2.2. Chemistry.
All the melting points were determined in an open capillary and are uncorrected. NMR spectra of newly synthesized compounds in DMSO-d6 solutions were recorded on a spectrometer Varian Mercury VX-400 (400 MHz) at 298 K. Chemical shifts are reported as δ (ppm) relative to TMS as internal standard, coupling constant J is expressed in Hz. The elemental analysis experimental data on contents of sulfur and nitrogen were within ±0.3 % of the theoretical values.
General procedure for synthesis of 2-[5-(2-R-benzyl)thiazol-2-ylimino]thiazolidin-4-ones (9a-e): A mixture of 2-chloroacetamido-5-(arylmethyl)thiazole **6a-e** (0.03 mol), KSCN (6.0 g, 0.06 mol) and dry acetone (100 mL) was stirred at room temperature for 20 h and then diluted with H_2O. The solid product was filtered, washed with H_2O dried and recrystallization from EtOH .
2-[5-(2-Fluoro-benzyl)thiazol-2-ylimino]thiazolidin-4-one (9a). Yield 68%, mp 130-132 °C. ^{1}H NMR (400 MHz, DMSO): δ = 12.36 – 11.65 (br.s, 1H, NH), 7.38 – 7.25 (m, 3H, C_6H_4, thiazole), 7.21 - 7.11 (m, 2H, C_6H_4), 4.11 (s, 2H, ArCH2), 3.96 (s, 2H, C(O)CH_2). ^{13}C NMR (101 MHz, DMSO): δ = 174.45, 168.92, 162.55, 160.57 (d, J = 244.3 Hz), 137.75, 133.64, 131.28 (d, J = 4.1 Hz), 129.46 (d, J = 8.0 Hz), 127.12 (d, J = 15.7 Hz), 125.19 (d, J = 3.4 Hz), 115.87 (d, J = 21.4 Hz), 35.38, 26.36 (d, J = 2.5 Hz). Anal. Calcd. for $C_{13}H_{10}FN_3OS_2$: C, 50.80; H, 3.28; N, 13.67. Found: C, 50.67; H, 3.22; N.
2-[5-(3-Trifluoromethylbenzyl)-thiazol-2-ylimino]-thiazolidin-4-one (9b). Yield 71, mp 128-129 °C. 1H NMR (400 MHz, DMSO): δ = 12.36 – 11.86 (br.s, 1H, NH), 7.63 (s, 1H, thiazole), 7.60-7.53 (m, 3H, C_6H_4), 7.41 (s, 1H, 2H-C_6H_4), 4.22 (s, 2H, ArCH_2), 3.97 (s, 2H, C(O)CH_2). ^{13}C NMR (101 MHz, DMSO): δ = 174.4, 169.18, 162.61, 141.97, 138.02, 134.30, 133.05, 130.17, 129.76 (k, J = 31.5 Hz), 125.31 (k, J = 3.3 Hz), 123.86 (k, J = 3.7 Hz), 122.50 (k, J = 269.6 Hz), 35.40, 32.44. Anal. Calcd. for $C_{14}H_{10}F_3N_3OS_2$: C, 47.05; H, 2.82; N, 11.76. Found: C, 47.12; H, 2.73; N, 11.64.
2-[5-(3,4-Dichlorobenzyl thiazol-2-ylimino]thiazolidin-4-one (9c). Yield 73%, mp 144-145°C. ^{1}H NMR (400 MHz, DMSO): δ = 12.30 – 11.77 (br.s, 1H, NH), 7.58-7.53 (m, 2H, C_6H_4), 7.40 (s, 1H, thiazole), 7.25 (d, J = 8.1 Hz, 1H, C_6H_4), 4.11 (s, 2H, ArCH_2), 3.97 (s, 2H, C(O)CH_2). ^{13}C NMR (101 MHz, DMSO): δ = 174.46, 169.18, 162.65, 141.70, 138.08, 134.00, 131.55, 131.22, 130.82, 129.71, 129.27, 35.41, 31.78. Anal. Calcd. for $C_{13}H_9Cl_2N_3OS_2$: C, 43.58; H, 2.53; N, 11.73. Found: C, 43.62; H, 2.49; N, 11.63.
2-[5-(2,3-Dichloro-benzyl)-thiazol-2-ylimino]-thiazolidin-4-one (9d). Yield 67%, mp 123-124 °C. ^{1}H NMR (400 MHz, DMSO): δ

= 12.32 – 11.83 (br.s, 1H, NH), 7.54 (d, J = 7.6 Hz, 1H, C_6H_4), 7.44 – 7.24 (m, 3H, C_6H_4, thiazole), 4.25 (s, 2H, $ArCH_2$), 3.96 (s, 2H, $C(O)CH_2$). ^{13}C NMR (101 MHz, DMSO): δ = 174.46, 169.01, 162.69, 140.43, 138.35, 132.52, 132.49, 131.33, 129.90, 129.69, 128.97, 35.41, 31.72 Anal. Calcd for $C_{13}H_9Cl_2N_3OS_2$: C, 43.58; H, 2.53; N, 11.73. Found: C, 43.37; H, 2.48; N, 11.60.

2-[5-(2,3-Dichloro-benzyl)-thiazol-2-ylimino]-5-methyl-thiazolidin-4-one (9e). 56%, mp 98-99 °C. ^1H NMR (400 MHz, DMSO): δ = 12.16 – 11.76 (br.s, 1H, NH), 7.53 (d, J = 7.2 Hz, 1H, C_6H_4), 7.41 – 7.29 (m, 3H, C_6H_4, thiazole), 4.25 (br.s, 3H, $ArCH_2$, C(O)CH), 1.49 (d, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO): δ = 177.48, 168.93, 160.96, 140.44, 138.38, 132.65, 132.49, 131.33, 129.89, 129.68, 128.97, 44.32, 31.74, 18.46. Anal. Calcd. for $C_{14}H_{11}Cl_2N_3OS_2$: C, 45.17; H, 2.98; N, 11.29. Found: C, 44.95; H, 2.90; N, 11.17.

2.3. Antimicrobial activity.

2.3.1. Methodology for the research of the antibacterial activity.

All bacteria were cultured in Cation-Adjusted Mueller-Hinton Broth (CAMHB) at 37 °C overnight. Each sample was diluted 40 times in a fresh medium and then, incubated at 37 °C for 1.5-3 hours. The samples of the mean logarithmic phase were diluted ($4.5^{-5} \times 10^5$ CFU/ ml, measured by 600 nm (OD600)). Then, the compounds containing the plates were added to each well, yielding a cell density of 5×10^5 CFU/ml and a total volume of 50 µl. All plates were coated and incubated at 37 °C for 18 hours without shaking. Inhibition of growth of all bacteria 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 reference.

2.3.2. Methodology of research of the antifungal activity.

The fungi strain was cultivated for 3 days on YPD at 30 °C. A suspension of yeast from 1×10^6 to 5×10^6 CFU / ml (as defined by OD530) was prepared from five colonies. The suspension was then diluted and added to each well of the plates containing the compound, which gave the final density of fungi cells suspension of 2.5×10^3 CFU / ml and a total volume of 50 µl. All plates were coated and incubated at 35 °C for 36 hours without shaking. The growth inhibition of *C. albicans* was determined measuring absorbance at 530 nm (OD530). 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 hours. The absorbance was measured using Biotek Synergy HTX Microplate Reader. The percentage of growth inhibition was calculated for each well, using negative control (media only) and positive control (fungi without inhibitors) on one plate. The percentage of growth inhibition of an individual sample is calculated based on negative controls (media only) and positive controls (bacterial/fungal media without inhibitors). The 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 has a variation of — + 10 %, which is within the reported normal distribution of bacterial/fungal growth.

2.4. Anticancer activity.

A primary anticancer assay was performed on a panel of approximately 60 human tumor cell lines derived from nine neoplastic diseases, following the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda. The tested compounds were added to the culture at a single concentration (10^{-5} M) and the cultures were incubated for 48 h. Endpoint determinations were made with a protein binding dye, sulforhodamine B (SRB). Results for each tested compound were reported as the percent growth of the treated cells when compared to the untreated control cells. The percent growth was evaluated spectrophotometrically versus controls not treated with the test agents. The cytotoxic and/or growth inhibitory effects of the most active selected compounds were tested *in vitro* against the full panel of about 60 human tumor cell lines at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8}M. The 48-h continuous drug exposure protocol was followed and an SRB protein assay was used to estimate cell viability or growth.

Using the seven absorbance measurements [time zero, (Tz), control growth in the absence of drug, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percent growth was calculated at each of the drug concentrations levels. Percent growth inhibition was calculated as:

$[(Ti - Tz)/(C - Tz)] \times 100$ for concentrations for which $Ti \geq Tz$.

$[(Ti - Tz)/Tz] \times 100$ for concentrations for which $Ti < Tz$.

Three dose-response parameters were calculated for each compound. Growth inhibition of 50% (GI50) was calculated from $[(Ti - Tz)/(C - Tz)] \times 100 - 50$, which is the drug concentration resulting in a 50% lower net protein increase in the treated cells (measured by SRB staining) as compared to the net protein increase seen in the control cells. The drug concentration resulting in total growth inhibition (TGI) was calculated from Ti = Tz. The LC50 (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment was calculated from $[(Ti - Tz)/Tz] \times 100 = -50$. Values were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the value for that parameter was expressed as more or less than the maximum or minimum concentration was tested.

3. RESULTS

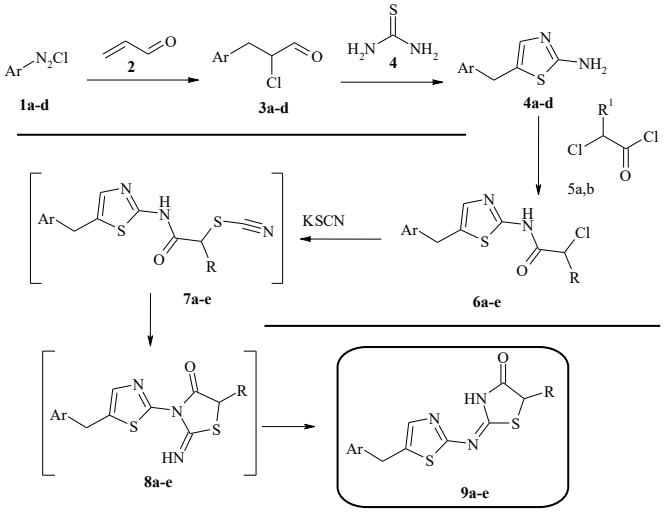
3.1. Synthesis of some 2-[5-(2-R-benzyl)thiazol-2-ylimino]thiazolidin-4-ones.

Continuing systematic study of various derivatives of thiazolidine as potential drug candidates we represented synthesis, antimicrobial and anticancer properties evaluation of some 2-[5-(2-R-benzyl)thiazol-2-ylimino]thiazolidin-4-ones. Previously we have successfully demonstrated the use of diazonium salts in the synthesis of biologically active heterocycles such as furane [13, 14], thiazole [15-17] and triazole [18, 19]. Various combinatorial libraries of condensed compounds were also prepared [13, 14, 18, 21-32]. Thus, the research to explore different chemical modifications avenues of diazonium salts to obtain novel active compounds should be continued.

At first stage diazonium salts **1a-e** react with acroleine **2** in Meerwein reaction condition [33] to form 3-aryl-2-chloropropanales **3a-e** [17]. These aldehydes were converted into

N-(5-R-benzyl-thiazol-2-yl)-2-chloroacetamides **6a-e** in two stages according to the previously reported synthetic protocols [13].

One of the methods of their synthesis is the cyclization of chloracetamides under the action of thiocyanate [7]. Using this method, we performed the synthesis of thiazol-2-yliminothiazolidin-4-one **9a-e**. The process begins as a nucleophilic substitution of chlorine by thiocyanate group with the formation of intermediate **7a-e**. Then there is a spontaneous cyclization in **8a-e**, followed by the migration of the thiazole substituent from the cyclic nitrogen atom to the exocyclic one **(Scheme 1)**. This reaction can be carried out in a wide range of solvents (methanol and ethanol, acetonitrile, acetone, DMF, DMSO, etc.). The yields and purity of the products are practically unaffected by the nature of the solvent.



Scheme 1. Synthesis of some 2-[5-(2-R-benzyl)thiazol-2-ylimino]thiazolidin-4-ones.

Table 1. Antimicrobial activity compounds **9a-e**.

Compound	S. aureus ATCC 43300	E. coli ATCC ATCC 25922	K. pneumoniae ATCC 700603	P. Aeruginosa ATCC 27853	A. Baumannii ATCC 19606	C.albicans ATCC 90028	C. Neofor-mans ATCC 208821
9a	103.5; 89.6	-0.8; -1.0	2.3; 9.9	1.4; 2.3	0.1; 1.9	14.6; 6.8	-18.5; -3.5
9b	101.3; 77.3	3.0; 3.3	3.9; 5.2	5.4; 8.1	-1.5; 4.8	16.9; 46.8	-3.2; -5.2
9c	104.3; 104.5	4.3; 5.8	5.1; 6.3	4.4; 6.1	-2.8; 6.4	11.3; 11.6	-15.8; -8.6
9d	34.6; 46.8	3.4; 6.0	10.6; 14.1	3.6; 4.1	11.6; 19.3	2.7; 7.8	-0.6; -2.5
9e	57.0; 66.7	7.1; 9.0	-3.2; 11.6	1.6; 2.5	-5.3; 4.3	3.9; 4.4	-9.4; -9.5

The obtained compounds **9a-e** are white powders, soluble in DMF, DMSO, acetic acid, acetonitrile, alcohols, insoluble in water and ether. The structures of the obtained compounds were confirmed by ^{1}H, ^{13}C NMR and elemental analysis. All these new compounds gave spectroscopic data in accordance with the proposed structures.

3.2. Evaluation of the antimicrobial activity.

The antimicrobial screening was performed by CO-ADD (the Community for Antimicrobial Drug Discovery) funded by the Wellcome Trust (UK) and the University of Queensland (Australia) [34]. The growth inhibition was measured against five bacterial strains (*Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Staphylococcus aureus*) and two fungal strains (*Candida albicans* and *Cryptococcus neoformans*). The standard concentration employed for screening was 32 mg/mL in DMSO. The observed in vitro antimicrobial activities of our synthesized products **9a-e** are tabulated in Table 1.

The tested compounds **9a-e** were found to have a significant antimicrobial effect against *S. aureus* ATCC 43300 with GI = 34.6-104.5 %. To other tested microorganisms, the mentioned substances did not show activity. It should also be noted that compounds containing 2,3-dichloro substituents in the benzyl radical exhibited significantly less activity than other compounds.

For compounds, **9a-c** MIC and cytotoxicity to Human embryonic kidney and Human red blood cells were also investigated. They demonstrated significant activity (MIC = 4^{-16} ug/mL) and low cytotoxicity to Human red blood cells. The most active were the compounds **9a** and **9b** containing a fluorine substituent in the arene ring, for which the MIC was 4 ug/ml.

The selectivity indexes were also calculated. They were above 2 for the tested compounds (table 2) which make the perspective of this class of compounds for further studies as potential antimicrobial agents.

Table 2. Antimicrobial activity and cytotoxicity to Human embryonic kidney Human red blood cells compounds **9a-c.**

Compound	MIC	Hk CC_{50}	Hm HC_{10}	SI = MIC/HC_{10}
9a	4; 4	6.52; 9.31	>32; >32	> 8
9b	4; 4	7.68; 8.61	>32; >32	> 4
9c	16; 16	6.51; 7.96	>32; >32	> 2

3.3. Evaluation of the antitumor activity.

Among all newly synthesized compounds substances **9a-e** were selected by the National Cancer Institute (NCI) Developmental Therapeutic Program for the *in vitro* cell line screening to investigate their antitumor activity. The human tumor cell lines were derived from nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. Primary anticancer assays were performed according to the US NCI protocol, which was described elsewhere [35-38]. The results of the primary screening are reported as the percent cancer cell line growth (GP %) and are presented in Table 3. The range of growth % shows the lowest and the highest growth % found among the different cancer cell lines.

The synthesized compounds displayed moderate activity *in vitro* screening on the tested cell lines. The most active compounds were **9c** with mean GP = 77.38% The most sensitive cell line was CCRF-CEM (Leukemia) (GP = 44.38%).

Table 3. Cytotoxic activity of the tested compounds **9a-e** in the concentration 10^{-5} M against 60 cancer cell lines.

Test compounds	Average growth, %	Range of growth, %	Most sensitive cell line (cancer line/type) GP, %
9a	102.34	85.88 – 114.84	*SNB-75 (CNS Cancer)* **85.88**.
9b	94.74	71.34 – 122.78	*CCRF-CEM (Leukemia)* **74.76;** *MOLT-4 (Leukemia)* **76.57**; *NCI-H460 (Non-Small Cell Lung Cancer)* **76.87;** *LOX IMVI (Melanoma)* **71.34;** *MALME-3M (Melanoma)* **76.91.**
9c	77.38	35.49 – 117.26	*CCRF-CEM (Leukemia)* **44.38;** *K-562 (Leukemia)* **57.03;** *NCI-H460 (Non-Small Cell Lung Cancer)* **35.49;** *NCI/ADR-RES (Ovarian Cancer)* **57.56;** *T-47D (Breast Cancer)* **59.20.**
9d	101.25	79.32 – 135.54	*UO-31 (Renal Cancer)* **79.32.**
9e	100.25	75.83 – 123.97	*CCRF-CEM (Leukemia)* **75.83.**

4. CONCLUSIONS

In our present work, we presented an eficient synthesis, antimicrobial activity and antitumor activities evaluation of some 2-[5-(2-R-benzyl)thiazol-2-ylimino]thiazolidin-4-ones. We have shown that the proposed approaches provide the possibility to design thiazol-2-yliminothiazolidin-4-one derivatives diversity with a considerable chemical novelty. The structures of target compounds **9a-e** were confirmed by using ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. The synthesized compounds have been evaluated for antimicrobal activity against five bacterial strains and two fungal strains. According to the antimicrobial activity results, tested compounds were found to be active against *Staphylococcus aureus*. The synthesized compounds were selected by the National Cancer Institute (NCI) Developmental Therapeutic Program for the in vitro cell line screening to investigate their anticancer activity. The tested compounds displayed moderate activity in vitro screening on the tested cell lines. Further optimization of the structure to improve their activities is currently in progress.

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