Biointerface Research in Applied Chemistry
Platinum Open Access Journal (ISSN: 2069-5837)

Article
Volume 11, Issue 4, 2021, 12434 - 12446
https://doi.org/10.33263/BRIAC114.1243412446

Synthesis, Molecular Docking and Antimicrobial Activities of 5-(4-substituted-benzyl)-2-(furan/thiophen-2-ylmethylene hydrazono)thiazolidin-4-ones

Taras Chaban [1], Volodymyr Horishny [1], Mohammad Arshad [2], Zoriana Chulovska [1], Liubov Kostyshyn [1], Iryna Drapak [1], Vasyl Matiychuk [3]

1 Danylo Halytsky Lviv National Medical University, Pekarska 69, Zip Code: 79010, Lviv, Ukraine; chabantaras@ukr.net (T.C.);
2 College of Medicine, Shaqra University, Zip Code: 11911, Al-Dawadmi, Saudi Arabia; mohdarshad1985@gmail.com (M.A.);
3 Ivan Franko National University of Lviv, 6 Kyryla and Mefodia, Zip Code: 79005, Lviv, Ukraine; v_matiychuk@ukr.net (V.M.);
* Correspondence: chabantaras@ukr.net;

Scopus Author ID 55180682800
Received: 8.12.2020; Revised: 2.01.2021; Accepted: 4.01.2021; Published: 6.01.2021

Abstract: In our present work, we reported an effective synthesis, molecular docking, and antimicrobial properties of novel 5-(4-substituted-benzyl)-2-(furan/thiophen-2-ylmethylene hydrazono) thiazolidin-4-ones (6a-g) and (7a-i). The structures of the synthesized compounds (6a-g) and (7a-i) were elucidated by ^{1}H-NMR spectroscopy. The molecular docking studies were performed for all the synthesized compounds against GlcN-6P using AutoDock-tools-1.5.6 and recorded the extent of H-bonding and binding affinities. The preselected compounds *via* molecular docking were further tested for *in vitro* antimicrobial 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 antimicrobial findings exhibited that the compounds possessed significant antimicrobial potential.

Keywords: organic synthesis; thiazolidin-4-one; furan; thiophen; characterization; molecular docking; antimicrobial activity.

1. Introduction

At present, medicinal chemists' main task is to find out the effective and less-toxic drugs with low molecular weight. The search has been carried out among the various classes of compounds, in particular 4-thiazolidone derivatives. Among these compounds, various compounds have been observed as highly active agents with a wide range of biological potential. Lead compounds with antimicrobial, antitubercular, antiviral, antidiabetic, anti-inflammatory, antitumor, anticonvulsant, and other activities have been identified. Therefore, the 4-thiazolidone cycle is considered a privileged structure in medicinal chemistry [1-3].

One of the effective approaches in designing new drugs is to combine diverse structural fragments in one molecule. It is accompanied by the achievement of biosynergism [4, 5], which leads to a new pharmacological profile, potentiation of action, and reduction of toxicity of "hybrid" molecules. It was believed that there would be an enhancement in the valuable pharmacological properties of the aimed compounds, which will possess 4-thiazolidone cycle

furan and thiophene moieties. Therefore, the study aimed at creating the methods for obtaining combinatorial libraries of compounds of this type and screening their biological properties is an urgent problem today.

Among 4-thiazolidone derivatives, it was observed that 5-arylidene-4-thiazolidones are the most studied derivatives as per the reported literature [1-3]. Among these derivatives, 5-arylidene-2- (aryl-2-ylmethylenehydrazono) -thiazolidin-4-ones were reported to portray the antimicrobial [6-11], antiviral [11], antitumor [12, 13] activities and also observed to be the inhibitors of various ferments [14-16]. On the other hand, less conformationally restricted derivatives of 5-benzyl-4-thiazolidone are practically not studied.

Due to our ongoing efforts to find out some better antimicrobial agents, we recently have reported the synthesis characterization, molecular docking, and biological assessment of 1, 3-thiazolidin-4-one derivatives bearing pyrimidine moieties and 1,3-thiazolidin-4-one bearing piperonal and pyrimidine moieties [17-18]. We have performed many studies aiming at the biological heterocycles as potential antimicrobial agents [19-48].

The recent study aimed to synthesize 5-(4-substituted-benzyl)-2-(furan/thiophen-2-ylmethylenehydrazono) thiazolidin-4-ones, molecular docking, and antimicrobial assessment and believed that the fusion of the 4-thiazolidone cycle, furan and thiophene moieties would be a good effort for finding better antimicrobial agents.

2. Materials and Methods

2.1. Materials.

The reagents used for the synthesis of the target compounds were commercially available and of analytical grade. All solvents and reagents like 5-arylfurfural, heterylacetonitrile, ethanol, piperidine, dimethylformamide, ethyl acrylate, substituted aryldiazonium salts, copper bromide, thiophene-2-carboxaldehyde, furfural, glacial acetic were used without further purification.

2.2. Chemistry.

The melting points of all the compounds were recorded in an open capillary by Melt temp instrument. ^{1}H-NMR spectra were registered on a Varian Mercury 400 (400 MHz for ^{1}H) instrument with TMS or deuterated solvent as an internal reference. Chemical shifts were reported as δ (ppm). Elemental analysis was performed on a Vario MICRO cube automatic CHNS analyzer. The elemental analysis data obtained experimentally for the contents of carbon, hydrogen, and nitrogen were within ±0.3% of the theoretical values.

General procedure for the preparation of 5-(4-substitutedbenzyl)-2-(furan/thiophen-2-ylmethylenehydrazono) thiazolidin-4-ones (6a-g) and (7a-i): The 0.01 mol of 5-arylfurfural 3a-e and 0.01 mol of heterylacetonitrile 7a,b, 8 or 9 was dissolved in 20 ml of ethanol in the presence of 2 drops of piperidine. The flask was refluxed for 1 h. The precipitate formed was filtered off, washed with alcohol, and the product was purified by recrystallization from a mixture of ethanol–DMF.

2-(Furan-2-ylmethylenehydrazono)-5-(3-methylbenzyl)thiazolidin-4-one (6a). Yield 81%, mp = 209-210°C. ^{1}H-NMR (400 MHz, DMSO) δ 11.95 (s, 1H, NH), 8.19 (s, 1H, CH=), 7.83 (d, J = 1.6 Hz, 1H, furane), 7.21 (t, J = 7.5 Hz, 1H, C_6H_4), 7.10 -7.01 (m, 3H, C_6H_4), 6.93 (d, J = 3.4 Hz, 1H, furane), 6.62 (dd, J = 3.4, 1.8 Hz, 1H, furane), 4.60 (dd, J = 9.9, 4.2 Hz, 1H, CH), 3.36 (dd, J = 14.0, 4.2 Hz, 1H, CH_2), 2.94 (dd, J = 14.0, 9.9 Hz, 1H, CH_2), 2.29

(s, 3H, CH_3). Anal. Calcd. for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.45; H, 4.74; N, 13.50.

5-(4-Ethylbenzyl)-2-(furan-2-ylmethylenehydrazono)thiazolidin-4-one (6b). Yield 79%, mp = 235-236°C. ^{1}H-NMR (400 MHz, DMSO) δ 11.93 (s, 1H, NH), 8.19 (s, 1H, CH=), 7.83 (d, J = 0.9 Hz, 1H, furane), 7.18 (d, J = 8.2 Hz, 1H, C_6H_4), 7.15 (d, J = 8.3 Hz, 1H, C_6H_4), 6.93 (d, J = 3.4 Hz, 1H, furane), 6.62 (dd, J = 3.3, 1.8 Hz, 1H furane), 4.58 (dd, J = 9.7, 4.2 Hz, 1H, CH), 3.34 (dd, J = 14.1, 4.1 Hz, 1H, CH_2), 2.96 (dd, J = 14.0, 9.8 Hz, 1H, CH_2), 2.58 (q, J = 7.6 Hz, 2H, $CH_3\underline{CH_2}$), 1.17 (t, J = 7.6 Hz, 3H, $\underline{CH_3}CH_2$). Anal. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.23; N, 12.83. Found: C, 62.42; H, 5.2317; N, 12.92.

5-(2-Chlorobenzyl)-2-(furan-2-ylmethylenehydrazono)thiazolidin-4-one (6c). Yield 77%, mp = 245-246°C. ^{1}H-NMR (400 MHz, DMSO) δ 12.07 (s, 1H, NH), 8.21 (s, 1H, CH=), 7.84 (d, J = 1.5 Hz, 1H, furane), 7.49 – 7.46 (m, 1H, C_6H_4), 7.42 – 7.39 (m, 1H, C_6H_4), 7.38 – 7.29 (m, 2H, C_6H_4), 6.95 (d, J = 3.4 Hz, 1H, furane), 6.63 (dd, J = 3.4, 1.8 Hz, 1H, furane), 4.61 (dd, J = 10.2, 4.5 Hz, 1H, CH), 3.58 (dd, J = 14.2, 4.5 Hz, 1H, CH_2), 3.10 (dd, J = 14.2, 10.2 Hz, 1H, CH_2). Anal. Calcd. for $C_{15}H_{12}ClN_3O_2S$: C, 53.97; H, 3.62; N, 12.59. Found: C, 53.85; H, 3.69; N, 12.49.

5-(4-Chlorobenzyl)-2-(furan-2-ylmethylenehydrazono)thiazolidin-4-one (6d). Yield 85%, mp = 239-240°C. ^{1}H-NMR (400 MHz, DMSO) δ 11.97 (s, 1H, NH), 8.19 (s, 1H, CH=), 7.84 (d, J = 1.4 Hz, 1H, furane), 7.38 (d, J = 8.3 Hz, 2H, C_6H_4), 7.30 (d, J = 8.4 Hz, 2H, C_6H_4), 6.94 (d, J = 3.4 Hz, 1H, furane), 6.63 (dd, J = 3.4, 1.8 Hz, 1H, furane), 4.62 (dd, J = 9.1, 4.5 Hz, 1H, CH), 3.35 (dd, J = 13.3, 3.5 Hz, 1H, CH_2), 3.05 (dd, J = 14.1, 9.2 Hz, 1H, CH_2). Anal. Calcd. for $C_{15}H_{12}ClN_3O_2S$: C, 53.97; H, 3.62; N, 12.59. Found: C, 53.81; H, 3.6955; N, 12.64.

5-(2,4-Dichlorobenzyl)-2-(furan-2-ylmethylenehydrazono)thiazolidin-4-one (6e). Yield 87%, mp = 258-259°C. ^{1}H-NMR (400 MHz, DMSO) δ 12.11 (s, 1H, NH), 8.21 (s, 1H, CH=), 7.87 – 7.84 (m, 1H, furane), 7.66 – 7.63 (m, 1H, C_6H_3), 7.47 – 7.40 (m, 2H, C_6H_3), 6.95 (d, J = 3.5 Hz, 1H, furane), 6.64 (dd, J = 3.4, 1.8 Hz, 1H, furane), 4.60 (dd, J = 9.9, 4.8 Hz, 1H, CH), 3.53 (dd, J = 14.2, 4.8 Hz, 1H, CH_2), 3.13 (dd, J = 14.2, 9.9 Hz, 1H, CH_2). Anal. Calcd. for $C_{15}H_{11}Cl_2N_3O_2S$: C, 48.93; H, 3.01; N, 11.41. Found: C, 49.04; H, 2.95; N, 11.52.

5-(2,5-Dichlorobenzyl)-2-(furan-2-ylmethylene-hydrazono)thiazolidin-4-one (6f). Yield 74%, mp = 241-242°C. ^{1}H-NMR (400 MHz, DMSO) δ 12.12 (s, 1H), 8.22 (s, 1H), 7.88 – 7.83 (m, 1H, furane), 7.52 (d, J = 5.9 Hz, 1H, C_6H_3), 7.51 (s, 1H, C_6H_3), 7.41 (dd, J = 8.6, 2.6 Hz, 1H, C_6H_3), 6.96 (d, J = 3.4 Hz, 1H, furane), 6.63 (dd, J = 3.4, 1.8 Hz, 1H, furane), 4.65 (dd, J = 9.9, 4.9 Hz, 1H, CH), 3.53 (dd, J = 14.2, 4.9 Hz, 1H, CH_2), 3.15 (dd, J = 14.2, 9.9 Hz, 1H, CH_2). Anal. Calcd. for $C_{15}H_{11}Cl_2N_3O_2S$: C, 48.93; H, 3.01; N, 11.41. Found: C, 49.06; H, 3.9508; N, 11.35.

2-(Furan-2-ylmethylene-hydrazono)-5-(4-methoxy-benzyl)thiazolidin-4-one (6g). Yield 81%, mp = 224-225°C. ^{1}H-NMR (400 MHz, DMSO) δ 11.93 (s, 1H, NH), 8.18 (s, 1H, CH=), 7.84 (d, J = 1.7 Hz, 1H, furane), 7.18 (d, J = 11.8 Hz, 1H), 6.95 – 6.92 (m, 1H, furane), 6.87 (d, J = 11.7 Hz, 2H, C_6H_4), 6.63 (dd, J = 3.4, 1.8 Hz, 1H, furane), 4.56 (dd, J = 9.4, 4.3 Hz, 1H, CH), 3.73 (s, 1H, CH_3O), 3.32 – 3.27 (m, 1H, CH_2), 2.95 (dd, J = 14.1, 9.4 Hz, 1H, CH_2). Anal. Calcd. for $C_{16}H_{15}N_3O_3S$: C, 58.35; H, 4.59; N, 12.76. Found: C, 58.42; H, 4.64; N, 12.69.

5-(2-Methylbenzyl)-2-(thiophen-2-ylmethylenehydrazono)thiazolidin-4-one (7a). Yield 71%, mp = 263-264°C. ^{1}H-NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 8.53 (s, 1H), 7.65 (d, J = 5.0 Hz, 1H, thiophene), 7.48 (d, J = 3.3 Hz, 1H, C_6H_4), 7.27 – 7.10 (m, 5H, C_6H_4 +

thiophene), 4.58 (dd, J = 10.7, 4.0 Hz, 1H, CH), 3.47 (dd, J = 14.6, 3.9 Hz, 1H, CH_2), 2.97 (dd, J = 14.4, 11.0 Hz, 1H, CH_2), 2.31 (s, 3H, CH_3). Anal. Calcd. for $C_{16}H_{15}N_3OS_2$: C, 58.33; H, 4.59; N, 12.76. Found: C, 58.42; H, 4.64; N, 12.69.

5-(3-Methylbenzyl)-2-(thiophen-2-ylmethylenehydrazono)thiazolidin-4-one (7b). Yield 78%, mp = 236-237°C. ^{1}H-NMR (400 MHz, DMSO) δ 11.92 (s, 1H, NH), 8.51 (s, 1H, CH=), 7.65 (d, J = 5.0 Hz, 1H, thiophene), 7.47 (d, J = 3.4 Hz, 1H, thiophene), 7.21 (t, J = 7.5 Hz, 1H, C_6H_4), 7.13 (dd, J = 4.9, 3.7 Hz, 1H, thiophene), 7.11 – 7.04 (m, 3H, C_6H_4), 4.60 (dd, J = 9.9, 4.1 Hz, 1H, CH), 3.37 (dd, J = 14.1, 4.1 Hz, 1H, CH_2), 2.96 (dd, J = 14.1, 10.0 Hz, 1H, CH_2), 2.29 (s, 3H, CH_3). Anal. Calcd. for $C_{16}H_{15}N_3OS_2$: C, 58.33; H, 4.59; N, 12.76. Found: C, 58.27; H, 4.51; N, 12.65.

5-(4-Ethylbenzyl)-2-(thiophen-2-ylmethylenehydrazono)thiazolidin-4-one (7c). Yield 83%, mp = 241-242°C. ^{1}H-NMR (400 MHz, DMSO) δ 11.94 (s, 1H, NH), 8.51 (s, 1H, CH=), 7.66 (d, J = 5.0 Hz, 1H, thiophene), 7.48 (d, J = 3.1 Hz, 1H, thiophene), 7.22 – 7.09 (m, 5H, C_6H_4 + thiophene), 4.59 (dd, J = 9.7, 4.1 Hz, 1H, CH), 3.35 (dd, J = 14.2, 4.1 Hz, 1H, CH_2), 2.97 (dd, J = 14.1, 9.8 Hz, 1H, CH_2), 2.58 (q, J = 7.6 Hz, 2H, $CH_3\underline{CH_2}$), 1.17 (t, J = 7.6 Hz, 3H, $\underline{CH_3}CH_2$). Anal. Calcd. for $C_{17}H_{17}N_3OS_2$: C, 59.45; H, 4.99; N, 12.23. Found: C, 59.57; H, 4.89; N, 12.31.

5-(4-Isopropylbenzyl)-2-(thiophen-2-ylmethylenehydrazono)thiazolidin-4-one (7d). Yield 85%, mp = 225-226°C. ^{1}H-NMR (400 MHz, DMSO) δ 11.95 (s, 1H, NH), 8.52 (s, 1H, CH=), 7.66 (d, J = 5.0 Hz, 1H, thiophene), 7.48 (d, J = 3.4 Hz, 1H, thiophene), 7.20 (s, 4H, C_6H_4), 7.16 – 7.11 (m, 1H, thiophene), 4.59 (dd, J = 9.9, 4.0 Hz, 1H, CH), 3.36 (dd, J = 14.2, 4.1 Hz, 1H, CH_2), 3.01 – 2.82 (m, 1H CH_2 + $(CH_3)_2\underline{CH}$), 1.19 (d, J = 6.9 Hz, 6H, $(\underline{CH_3})_2CH$). Anal. Calcd. for $C_{18}H_{19}N_3OS_2$: C, 60.48; H, 5.36; N, 11.75. Found: C, 60.53; H, 5.29; N, 11.67.

5-(3-Chlorobenzyl)-2-(thiophen-2-ylmethylenehydrazono)thiazolidin-4-one (7e). Yield 75%, mp = 224-225°C. ^{1}H-NMR (400 MHz, DMSO) δ 12.01 (s, 1H, NH), 8.52 (s, 1H, CH=), 7.48 (d, J = 2.8 Hz, 1H, thiophene), 7.40 – 7.31 (m, 4H, C_6H_4), 7.26 (d, J = 7.2 Hz, 1H, thiophene), 7.14 (dd, J = 5.0, 3.6 Hz, 1H, thiophene), 4.67 (dd, J = 9.3, 4.5 Hz, 1H, CH), 3.38 (dd, J = 14.2, 4.5 Hz, 1H, CH_2), 3.06 (dd, J = 14.2, 9.4 Hz, 1H, CH_2). Anal. Calcd. for $C_{15}H_{12}ClN_3OS_2$: C, 51.50; H, 3.46; N, 12.01. Found: C, 51.62; H, 3.51; N, 12.07.

5-(4-Chlorobenzyl)-2-(thiophen-2-ylmethylenehydrazono)thiazolidin-4-one (7f). Yield 87%, mp = 257-258°C. ^{1}H-NMR (400 MHz, DMSO) δ 11.95 (s, 1H, NH), 8.51 (s, 1H, CH=), 7.66 (d, J = 4.7 Hz, 1H, thiophene), 7.48 (d, J = 3.1 Hz, 1H, thiophene), 7.39 (d, J = 8.3 Hz, 2H, C_6H_4), 7.31 (d, J = 8.3 Hz, 2H, C_6H_4), 7.16 – 7.11 (m, 1H, thiophene), 4.62 (dd, J = 9.0, 4.3 Hz, 1H, CH), 3.36 (dd, J = 14.2, 4.4 Hz, 1H, CH_2), 3.06 (dd, J = 14.1, 9.3 Hz, 1H, CH_2). Anal. Calcd. for $C_{15}H_{12}ClN_3OS_2$: C, 51.50; H, 3.46; N, 12.01. Found: C, 51.39; H, 3.53; N, 12.09.

5-(3,4-Dichlorobenzyl)-2-(thiophen-2-ylmethylenehydrazono)thiazolidin-4-one (7g). Yield 74%, mp = 245-246°C. ^{1}H-NMR (400 MHz, DMSO) δ 12.01 (s, 1H, NH), 8.52 (s, 1H, CH=), 7.67 (d, J = 5.0 Hz, 1H, C_6H_3), 7.61 – 7.57 (m, 2H, C_6H_3), 7.50 – 7.47 (m, 1H, thiophene), 7.29 (dd, J = 8.3, 2.0 Hz, 1H, thiophene), 7.14 (dd, J = 5.0, 3.6 Hz, 1H, thiophene), 4.67 (dd, J = 8.9, 4.7 Hz, 1H, CH), 3.36 (dd, J = 14.2, 4.7 Hz, 1H, CH_2), 3.09 (dd, J = 14.2, 9.0 Hz, 1H, CH_2). Anal. Calcd. for $C_{15}H_{11}Cl_2N_3OS_2$: C, 46.88; H, 2.89; N, 10.93. Found: C, 46.97; H, 2.81; N, 10.82.

5-(4-Methoxybenzyl)-2-(thiophen-2-ylmethylenehydrazono)thiazolidin-4-one (7h). Yield 82%, mp = 221-222°C. ^{1}H-NMR (400 MHz, DMSO) δ 11.90 (s, 1H, NH), 8.51 (s, 1H, CH=), 7.66 (d, J = 5.0 Hz, 1H, thiophene), 7.47 (d, J = 3.4 Hz, 1H, thiophene), 7.19 (d, J

= 8.5 Hz, 2H, C_6H_4), 7.16 – 7.11 (m, 1H, thiophene), 6.88 (d, J = 8.5 Hz, 2H, C_6H_4), 4.56 (dd, J = 9.4, 4.2 Hz, 1H, CH), 3.73 (s, 3H), 3.31 (dd, J = 13.9, 3.9 Hz, 1H, CH_2), 2.96 (dd, J = 14.2, 9.4 Hz, 1H, CH_2). Anal. Calcd. for $C_{16}H_{15}N_3O_2S_2$: C, 55.63; H, 4.38; N, 12.16. Found: C, 55.6375; H, 4.45; N, 12.03.

2-(Thiophen-2-ylmethylenehydrazono)-5-(3-trifluoromethyl-benzyl thiazolidin-4-one (7i). Yield 77%, mp = 221-222°C. ^{1}H-NMR (400 MHz, DMSO) δ 12.02 (s, 1H, NH), 8.52 (s, 1H, CH=), 7.69 – 7.54 (m, 5H, C_6H_4 + thiophene), 7.50 – 7.46 (m, 1H, thiophene), 7.13 (dd, J = 5.0, 3.6 Hz, 1H, thiophene), 4.72 (dd, J = 9.0, 4.6 Hz, 1H, CH), 3.46 (dd, J = 14.2, 4.6 Hz, 1H, CH2), 3.19 (dd, J = 14.2, 9.1 Hz, 1H, CH_2). Anal. Calcd. for $C_{16}H_{12}F_3N_3OS_2$: C, 50.12; H, 3.15; N, 10.96. Found: C, 50.01; H, 3.1523; N, 10.87.

2.3. Molecular docking.

The molecular docking for the synthesized compounds (6a-g) and (7a-i) was performed against the receptor GlcN-6P (PDB: 2VF5) to assess the extent of H-bonding and the binding affinities. The software ChemDraw Ultra12.0 design the structures, Aautodock-tools 1.5.6 to produce PDBQTs, Autodock-vina to produce a docked file, and Pymol to produce docked images were employed in the study. The PDBs for the ligands were obtained from the online smiles translator (https://cactus.nci.nih.gov/translate/).

2.4. Pharmacology.

2.4.1. Antibacterial data collection to signify bacterial strains and growth conditions.

Inhibition of bacterial growth was determined by measuring the absorbance at 600 nm (OD600), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth inhibition was calculated for each of them, using the negative control (media only) and positive control (bacteria without inhibitors) at the same time as references.

2.4.2. Antifungal data collection.

The growth inhibition of *C. albicans* was determined by measuring the absorbance at 530 nm (OD530), while the growth inhibition of *C. neoformans* was determined by 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 of them, using the negative control (media only) and positive control (fungal without inhibitors) at the same time as references.

2.4.3. Inhibition.

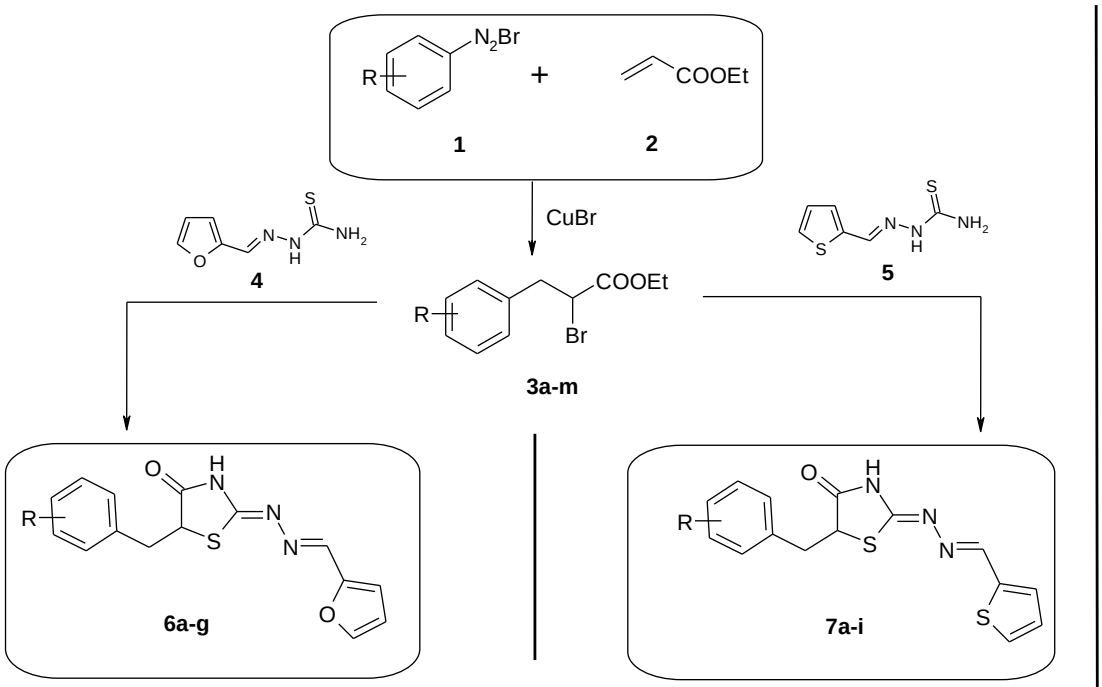
The percentage of growth inhibition of an individual sample was based on the negative controls (media only) and positive controls (bacterial/fungal media without inhibitors). Negative inhibition values indicated that the growth rate (or OD600) is higher than the negative control (Bacteria/fungi only, set to 0% inhibition). The growth rates for all the bacteria and fungi have a variation of -/+ 10%, which is within the reported normal distribution of bacterial/fungal growth (https://www.co-add.org).

3. Results and Discussion

3.1. Synthesis of 5-(4-substituted-benzyl)-2-(furan/thiophen-2-ylmethylene-hydrazono) thiazolidin-4-ones.

The starting reagents for the preparation of target compounds were ethyl 2-bromo-3-aryl propanates 3a-m, which were synthesized by bromarylation of ethyl acrylate 2 using aryldiazonium salts 1 respective to the procedure described in [49]. It was found that on refluxing 3a-m in ethanol with thiosemicarbazones of furfural 4 and thiophene-2-carbaldehyde 5 yielded the 5-(4-R-benzyl)-2-(furan / thiophen-2-ylmethylenehydrazono) thiazolidine-4 - they are 6a-i and 7a-i (Scheme 1).

The structures of the obtained compounds were confirmed by ^{1}H-NMR spectroscopy and elemental analysis. In ^{1}H-NMR spectra, signals for all the structural units' protons were observed in their characteristic ranges. In the region of a strong magnetic field, we observed three doublets of doublets, which is the characteristic of the ABX spin-spin system.



1, 3: R = 2-CH_3(**a**), 3-CH_3(**b**), 4-C_2H_5(**c**), 4-$(CH_3)_2CH$(**d**), 2-Cl(**e**), 3-Cl(**f**), 4-Cl(**g**), 2,4-Cl_2(**h**), 2,5-Cl_2(**i**) 3,4-Cl_2(**j**), 4-CH_3O(**k**), 3-CF_3(**m**)

6: R = 3-CH_3(**a**), 4-C_2H_5(**b**), 2-Cl(**c**), 4-Cl(**d**), 2,4-Cl_2(**e**), 2,5-Cl_2(**f**), 4-CH_3O(**g**)

7: R = 2-CH_3(**a**), 3-CH_3(**b**), 4-C_2H_5(**c**), 4-$(CH_3)_2CH$(**d**), 3-Cl(**e**), 4-Cl(**f**), 3,4-Cl_2(**g**), 4-CH_3O(**h**), 3-CF_3(**i**)

Scheme 1. Synthesis of 5-(4-substituted-benzyl)-2-(furan/thiophen-2-ylmethylene-hydrazono) thiazolidin-4-ones.

3.2. Molecular docking.

The synthesized compounds (6a-g) and (7a-i) were subjected to molecular docking assessment using Aautodock-tools 1.5.6 tools against GlcN-6P as per the procedure mentioned [50-51]. The molecular docking findings revealed that some ligands have been observed to represent similar H-bonding with the amino acid residues like ASN522 (6a, 6b, 6e, 6f), ASP474 (6a, 6b), SER316 (6d, 6e), ASN261 (7b, 7e, 7f, 7g, 7h) SER328 (7c, 7d). The ligands (6a-g) and (7a-i) represented the significant binding affinities in the range -6.9 to -5.5 kcal/mole and

-7.0 to -5.2 kcal/mole, respectively. While comparing the molecular docking findings and antimicrobial assessment, it was observed that there is strong agreement in both the findings.

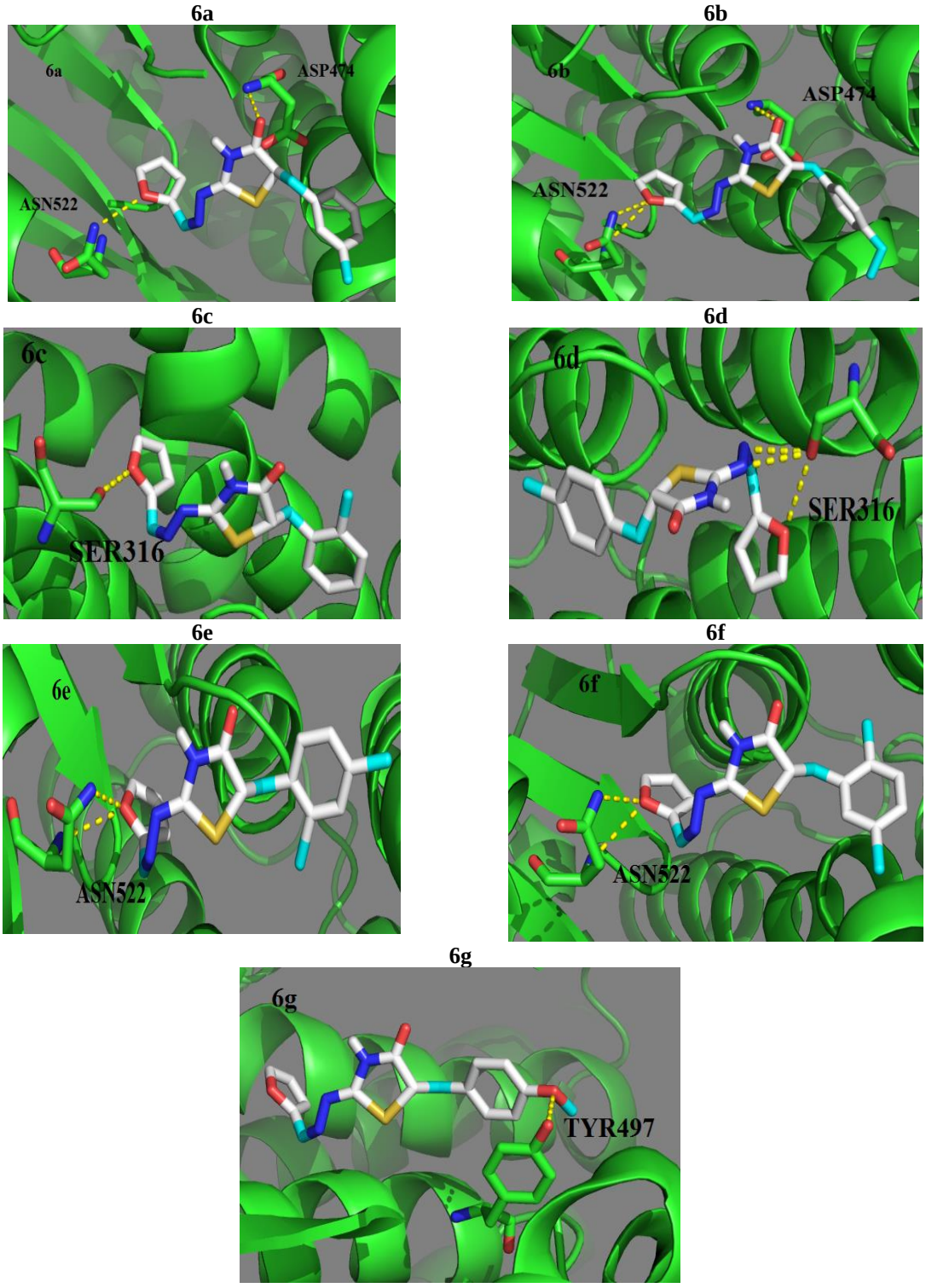


Figure 1. The docked images of the compounds (6a-g) against the receptor GlcN-6P (PDB: 2VF5).

7a **7b** **7c**

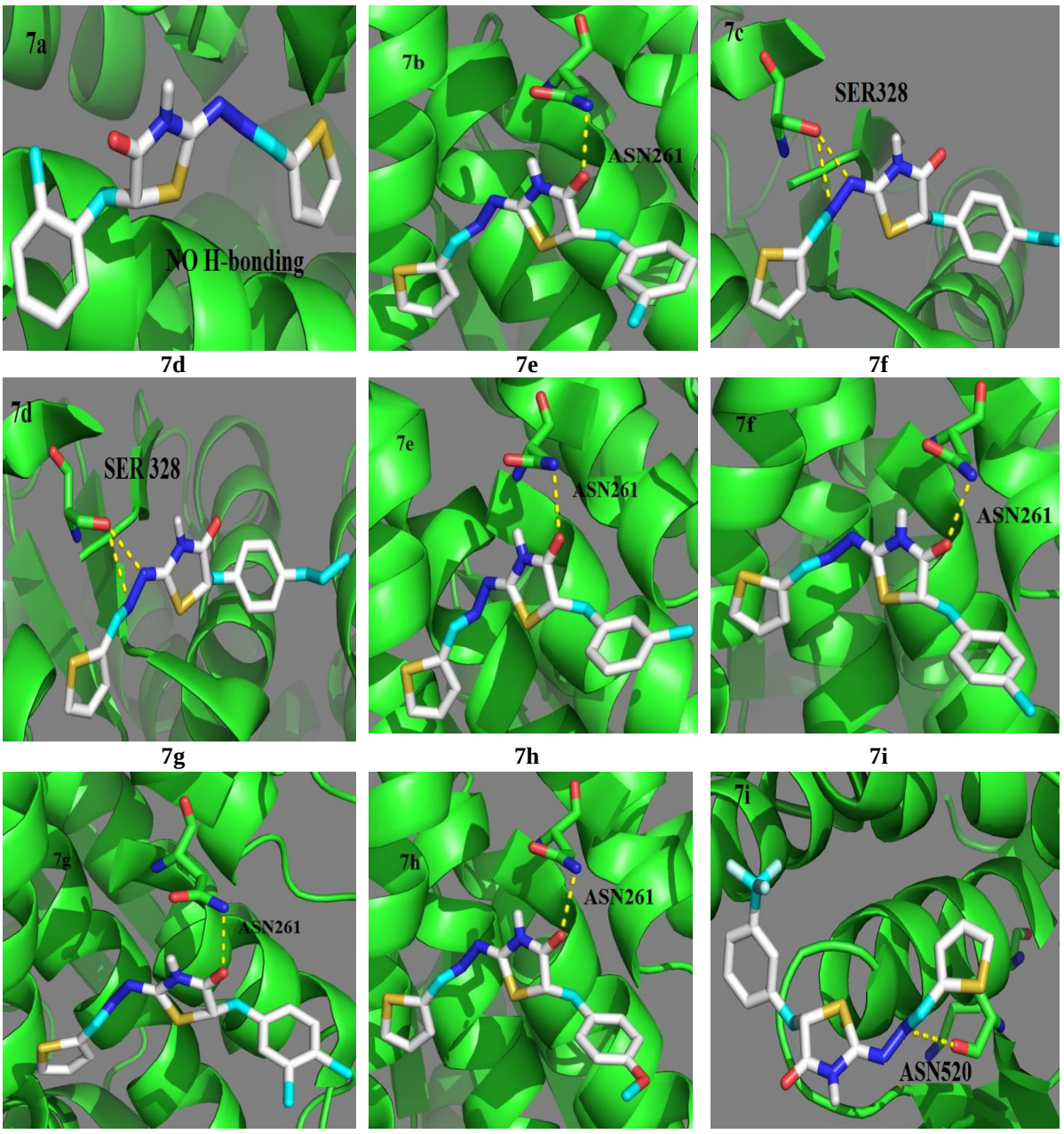


Figure 2. The docked images of the compouds (7a-i) against the receptor GlcN-6P (PDB: 2VF5).

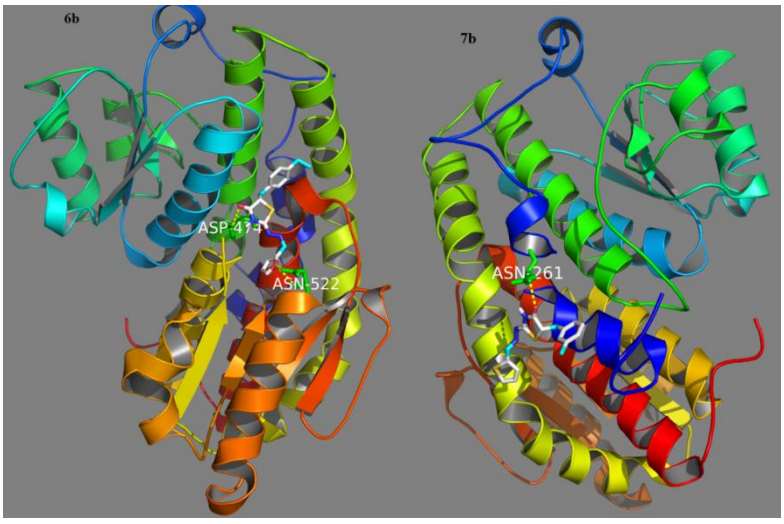


Figure 3. The docked images of the compounds (6b & 7b) against the receptor GlcN-6P (PDB: 2VF5).

The compounds 6e, 6f, 7g, and 7f have been found to exhibit significant antibacterial effects against *S. aureus*; simultaneously, these compounds were reported to represent the significant H-bonding. On the other hand, the compounds 6a, 6e, 6f, 7d, and 7g have been observed to possess significant antifungal potential against *C. albicans, and C. neoformans* and at the same time represented the significant *H-bonding.* The detailed docked images and the binding affinities are represented in Figure 1, Figure 2, Figure 3 Table 1.

Table 1. Representing the Aminoacid residues of GlcN-6 involved in H-bonding, binding affinities, rmsd values of the compounds (6a-g) and (7a-i).

S. No.	Amino acid residues involved in H-bonding	Binding Affinity (9 Modes of binding) Kcal/mole	Distance from rmsd (l. b)	Distance from rmsd (u. b)
6a	ASN522, ASP474	-6.6 to -6.1	0 to 27.861	0 to 29.449
6b	ASN522 (2 Bonds), ASP474	-6.9 to -6.1	0 to 29.795	0 to 31.019
6c	SER316	-6.4 to -5.5	0 to 29.953	0 to 31.984
6d	ASN522 (2 Bonds)	-6.7 to -5.5	0 to 28.430	0 to 30.404
6e	SER316 (3 Bonds)	-6.4 to -5.8	0 to 32.950	0 to 34.903
6f	ASN522 (2 Bonds)	-6.4 to -5.8	0 to 29.383	0 to 31.961
6g	TYR497	-6.2 to -5.7	0 to 29.921	0 to 31.167
7a	No Bonds	-6.4 to -5.7	0 to 28.171	0 to 29.070
7b	ASN261	-6.3 to -5.5	0 to 29.146	0 to 32.788
7c	SER328 (2 Bonds)	-6.3 to -5.7	0 to 29.450	0 to 31.480
7d	SER328 (2 Bonds)	-6.7 to -5.6	0 to 30.289	0 to 31.125
7e	ASN261	-6.1 to -5.5	0 to 32.683	0 to 34.644
7f	ASN261	-6.2 to -5.6	0 to 32.134	0 to 33.710
7g	ASN261	-6.3 to -5.6	0 to 31.959	0 to 33.609
7h	ASN261	-6.1 to -5.2	0 to 34.427	0 to 36.129
7i	ALA 520	-7.0 to -6.0	0 to 26.824	0 to 28.108

Table 2. Antimicrobial activity of compounds 6a-i and 7a-i.

Compounds	*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*
6a	2.5	9.1	11.3	8.2	15.4	33.7	14.5
6b	6.3	12.5	13.7	14.3	-4.7	24.5	17.9
6c	34.5	15.7	28.5	-5.7	11.8	6.5	11.4
6d	32.3	15.3	-5.6	14.5	14.4	13.5	13.3
6e	53.3	-11.1	10.4	-0.3	11.4	15.20	34.5
6f	72.4	13.9	15.4	14.5	23.7	11.6	41.4
6g	23.1	4.7	0.5	6.7	-1.0	2.9	-0.8
7a	10.4;	13.2	14.5	15.3	13.3	24.3	25.1
7b	10.6	1.5	5.4	7.1	5.0	26.9	2.7
7c	7.5	-5.6	-4.3	-0.4	23.7	25.6	-5.7
7d	12.4	2.6	5.8	11.4	-11.2	31.3	7.5
7e	31.0	9.2	9.2	5.0	10.3	7.1	-4.7
7f	43.1	22.43	-6.1	5.5	7.3	7.5	12.4
7g	64.4	21.5	11.3	12.4	31.2	7.5	33.7
7h	23.3	-10.5	-8.3	-23.5	5.6	3.7	21.4
7i	-4.9	-5.1	5.2	-1.7	-3.4	4.0	-3.5

3.3. Evaluation of the antimicrobial activities.

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) [52]. 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 the screening was 32 mg/mL in DMSO. The observed *in vitro* antimicrobial activities of our synthesized products 6a-i and 7a-i are tabulated in Table 2.

Analysis of the antimicrobial data revealed that the bacteria *Staphylococcus aureus (ATCC 43300)* were sensitive to a lesser extent than the fungi *Candida albicans ATCC 90028* and *Cryptococcus neoformans ATCC 208821* that were found to be more sensitive to the compounds of the analyzed group. Compound 6a,b, 7b,c,d with methyl, ethyl, isopropyl groups contribute to the emergence of activity against *Candida albicans (ATCC 90028*) (GI in the range of 24.5 - 33.7%), while electron-withdrawing substituents (chlorine and dichloro-, compounds 6e, f, 7g) caused the enhancement in the sensitivity to fungus *Cryptococcus neoformans (ATCC 208821)* to these substances (GI in the range of 33.7 - 41.4%). More active compounds and their higher activity were observed in relation to gram-positive bacteria Staphylococcus aureus (ATCC 43300). This applied only to halogen-substituted benzyl derivatives (compounds 6c, d, e, f, 7e, f, g with GI values within 31.0 - 72.4%). Dichloro-substituted 6e, f, 7g, GI = 53.3, 72.4, and 64.4%, respectively, differ especially against this background. It should be noted that the substance 7g is also characterized by a broader spectrum of activity, involving in its active action on *E. Coli ATCC 25922* (GI = 21.5%), *A. Baumanii ATCC 19606* (GI = 31.2%) *C. neoformans ATCC 208821* (GI = 33.7%), while the highest rates were in compounds 6f (GI = 72.4% relative to *Staphylococcus aureus (ATCC 43300)* and GI = 41.4% relative to *Cryptococcus neoformans (ATCC 208821*).

4. Conclusions

In conclusion, we have displayed that the suggested synthetic protocols provided the opportunity to design of series of new 5-(4-substituted-benzyl)-2-(furan/thiophen-2-ylmethylene hydrazono) thiazolidin-4-ones. The structures of aimed substances were reaffirmed by using ^{1}H-NMR spectroscopy and elemental analysis. The molecular docking study reported the significant H-bonding of the synthesized substances as ligands with the amino acid residues of the receptor GlcN-6P. The performed biological activity evaluation results suggested the synthesized compounds as a promising structure in antimicrobial drug development. Further optimization of the structure to improve biological activity is currently in progress.

Funding

This research received no external funding.

Acknowledgments

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

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Tomasić, T.; Masic L. Rhodanine as a privileged scaffold in drug discovery. *Current Medicinal Chemistry* **2009**, *16*, 1596–1629, https://doi.org/10.2174/092986709788186200.
2. Kaminskyy, D.; Kryshchyshyn, A.; Lesyk, R. 5-Ene-4-thiazolidinones – An efficient tool in medicinal chemistry. *European Journal of Medicinal Chemistry* **2017**, *140*, 542–594, https://doi.org/10.1016/j.ejmech.2017.09.031.
3. Kaminskyy, D.; Kryshchyshyn, A.; Lesyk, R. Recent developments with rhodanine as a scaffold for drug discovery. *Expert Opinion on Drug Discovery* **2017**, *12*, 1233–1252, https://doi.org/10.1080/17460441.2017.1388370.
4. Fortin, S.; Berube, G.; Advances in the development of hybrid anticancer drugs. *Expert Opinion on Drug Discovery* **2007**, *8*, 1547–1577, https://doi.org/10.1517/17460441.2013.798296.
5. Havrylyuk, D.; Roman, O.; Lesyk, R. Synthetic approaches, structure activity relationship and biological applications for pharmacologically attractive pyrazole / pyrazoline–thiazolidine–based hybrids. *European Journal of Medicinal Chemistry* **2016**, *113*, 145–166, https://doi.org/10.1016/j.ejmech.2016.02.030.
6. De Monte,C; Carradori, S.; Bizzarri, B.; Bolasco, A.; Caprara, F.; Mollica, A.; Rivanera, D.; Mari, E.; Zicari, A.; Akdemi, A.; Secci, D. Anti-Candida activity and cytotoxicity of a large library of new N-substituted-1,3-thiazolidin-4-one derivatives. *European Journal of Medicinal Chemistry* **2016**, *107*, 82-96, https://doi.org/10.1016/j.ejmech.2015.10.048.
7. El-Sayed, W.; Abdel-Monem, Y.; Yousif, N.; Tawfek, N.; Shaaban, M.; Abdel-Rahman, A. Antimicrobial activity of new 2,4-disubstituted thiazolidinone derivatives. *Zeitschrift fuer Naturforschung, C: Journal of Biosciences* **2009**, *64*, 785-789, https://doi.org/10.1515/znc-2009-11-1205.
8. Oniga, O.; Thierry Ndongo, O.; Moldovan, C.; Tiperciuc, B.; Oniga, S.; Pîrnău, A.; Vlase, L.; Verité, P. Synthesis and antimicrobial activity of some new 2-hydrazone-thiazoline-4-ones. *Farmacia* **2012**, *60*, 785-797.
9. Belwal, C.; Joshi, K. Synthesis and antimicrobial screening of 2-[(5,6-dimethoxy-2,3-dihydro-1H-inden-1-ylidene)hydrazinylidine]-1,3-thiazolidin-4-one and its 5-Arylidine derivatives. *Heterocyclic Letters* **2014**, *4*, 65-71.
10. Hassan, A.; Mohamed, S.; Nasr, M.; El Shaieb, K.; Abdel-Azis, M.; Abdel-Azis, A. Synthesis and antibacterial activity of new substituted ethylidenehydrazinylidene-1,3-thiazol-4-ones. *Journal of Chemical Research* **2014**, *38*, 673-678, https://doi.org/10.3184/174751914X14138794305033.
11. Goudreau, N.; Hucke, O.; Faucher, A.M.; Grand-Maître, C.; Lepage, O.; Bonneau, PR.; Mason, SW.; Titolo, S. Discovery and Structural Characterization of a New Inhibitor Series of HIV-1 Nucleocapsid Function: NMR Solution Structure Determination of a Ternary Complex Involving a 2:1 Inhibitor/NC Stoichiometry. *Journal of Molecular Biology* **2013**, *425*, 1982-1998, https://doi.org/10.1016/j.jmb.2013.02.022.
12. Abbas, E.; Gomha, S.; Farghaly, T.; Abdalla, M. Synthesis of New Thiazole Derivatives as Antitumor Agents. *Current Organic Synthesis* **2016**, *13*, 456-465, https://doi.org/10.2174/1570179412666150828195202.
13. El-Mekabat, A.; Habib, O. Efficient and convenient route to the synthesis of some novel sulfonate ester-based heterocycles as antitumor agents. *Heterocycles* **2018**, *96*, 677-689, https://doi.org/10.3987/COM-18-13870.
14. Khan, A.; Diwan, A.; Thabet, H.; Imran, M.; Bakht, M. Discovery of novel pyridazine-based cyclooxygenase-2 inhibitors with a promising gastric safety profile. *Molecules* **2020**, *25*, https://doi.org/10.3390/molecules25092002.
15. Khan, A.; Diwan, A.; Thabet, H.; Imran, M. Synthesis of novel N-substitutedphenyl-6-oxo- 3-phenylpyridazine derivatives as cyclooxygenase-2 inhibitors. *Drug Development Research* **2020**, *81*, 573-584, https://doi.org/10.1002/ddr.21655.
16. Channar, P.A.; Saeed, A.; Larik, F.A.; Rafiq, M.; Ashraf, Z.; Jabeen, F.; Fattah, T.A. Synthesis, computational studies and enzyme inhibitory kinetics of substituted methyl [2-((4-dimethylamino-benzylidene)-hydrazono)-4-oxo-thiazolidin-5-ylidene]acetates as mushroom tyrosinase inhibitors. *Bioorganic & Medicinal Chemistry* **2017**, *25*, 5929-5938, https://doi.org/10.1016/j.bmc.2017.09.009.
17. Arshad, M.; Ahmad, D.; Akhter, R. 1, 3-thiazolidin-4-one derivatives bearing pyrimidine moieties: Design, computational studies, synthesis, characterization, antimicrobial, MTT assessment and molecular docking assessment. *Chemical Data Collections* **2020**, *28*, https://doi.org/10.1016/j.cdc.2020.100405.
18. Arshad, M. Design, Drug-Likeness, Synthesis, Characterization, Antimicrobial Activity, Molecular Docking, and MTT Assessment of 1,3-Thiazolidin-4-one Bearing Piperonal and Pyrimidine Moieties. *Russian Journal of Bioorganic Chemistry* **2020**, *46*, 599–611, https://doi.org/10.1134/S1068162020040056.
19. Chaban, T.; Matiychuk, V.; Mahlovanyy, A.; Chaban, I.; Ogurtsov, V.; Lelyukh, M. Antitumor properties of thiazolo[4,5-*b*]pyridin-2-one derivatives. *Biointerface Research in Applied Chemistry* **2020**, *10*, 5944-5950, https://doi.org/10.33263/BRIAC104.944950.
20. Tupys, A.; Kalembkiewicz, J.; Ostapiuk, Y.; Matiichuk, V.; Tymoshuk, O.; Woźnicka, E.; Byczyński, Ł. 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* **2017**, *127*, 2233-2242, https://doi.org/10.1007/s10973-016-5784-0.
21. Chaban, T.I.; Ogurtsov, V.V.; Matiychuk, V.S.; Chaban, I.G.; Demchuk, I.L.; Nektegayev, I.A. Synthesis, anti-inflammatory and antioxidant activities of novel 3*H*-thiazolo[4,5-*b*]pyridines. *Acta Chimica Slovenica* **2019**, *66*, 103–111, https://doi.org/10.17344/acsi.2018.4570.
22. Pokhodylo, N.T.; Matiychuk, V.S. Synthesis of new 1,2,3-triazolo[1,5-a]quinazolinones. *Journal of Heterocyclic Chemistry* **2010,** *47*, 415-420, https://doi.org/10.1002/jhet.321.
23. Chaban, T.; Klenina, O.; Chaban, I.; Ogurtsov, V.; Harkov, S.; Lelyukh, M. Thiazolo[5,4-*d*]pyrimidines and thiazolo[4,5-*d*] pyrimidines: A review on synthesis and Pharmacological importance of their derivatives. *Pharmacia* **2018**, *65*, 54-70.
24. Obushak, N.D.; Gorak, Yu.I.; Matiichuk, V.S.; Lytvyn, R.Z. 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)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines. *Russian Journal of Organic Chemistry* **2008**, *44*, 1689-1694, https://doi.org/10.1134/S1070428008110213.
25. Chaban, T.; Matiychuk, V.; Ogurtsov, V.; Chaban, I.; Harkov, S.; Nektegaev, I. Synthesis and biological activity of some novel derivatives 5,7-dimethyl-6-phenylazo-3*H*-thiazolo[4,5-*b*]pyridine-2-one. *Pharmacia* **2018**, *65*, 51-62.
26. Bazel, Y.; Tupys, A.; Ostapiuk, Y.; Tymoshuk, O.; Matiychuk, V. A green cloud-point microextraction method for spectrophotometric determination of Ni(II) ions with 1-[(5-benzyl-1,3-thiazol-2-yl)diazenyl]naphthalene-2-ol. *Journal of Molecular Liquids* **2017**, *242*, 471-477, https://doi.org/10.1016/j.molliq.2017.07.047.
27. Chaban, Z.; Harkov, S.; Chaban, T.; Klenina, O.; Ogurtsov, V.; Chaban, I. Recent advances in synthesis and biological activity evaluation of condensed thiazoloquinazolines: A review. *Pharmacia* **2017**, *64*, 52-66.
28. Pokhodylo, N.T.; Teslenko, Y.O.; Matiychuk, V.S.; Obushak, M.D. Synthesis of 2,1-benzisoxazoles by nucleophilic substitution of hydrogen in nitroarenes activated by the azole ring. *Synthesis* **2009**, *16*, 2741-2748, https://doi.org/10.1055/s-0029-1216875.
29. Chaban, T.; Ogurtsov, V.; Chaban, I.; Myrko, I.; Harkov, S.; Leluykh, M. Synthesis of some new 4-iminothiazolidine-2-ones as possible antioxidants agents. *Pharmacia* **2019**, *66*, 27-32, https://doi.org/10.3897/pharmacia.66.e35131.
30. Lozynska, L.; Tymoshuk, O.; Chaban, T. 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* **2015**, *62*, 159-167.
31. Pokhodylo, N.T.; Matiychuk, V.S.; Obushak, N.D. Synthesis of 1H-1,2,3-triazole derivatives by the cyclization of aryl azides with 2-benzothiazolylacetonone, 1,3-benzo-thiazol-2-ylacetonitrile, and (4-aryl-1,3-thiazol-2-yl)acetonitriles. *Chemistry of Heterocyclic Compounds* **2009**, *45*, 483-488, https://doi.org/10.1007/s10593-009-0287-6.
32. Chaban, T.I.; Matiichuk, Y.E.; Horishny, V.Y.; Chaban, I.G.; Matiychuk, V.S. Synthesis and Anticancer Activity of 2-aryl-3-methylbenzofuro[3,2-*B*]pyrazolo[4,3-*E*]azepine-4,11(2*H*,10*H*)-dione and 2-Aryl-3,7,9-trimethylpyrido[3',2':4,5]thieno[3,2-*b*]pyrazolo[4,3-*E*]azepine-4,11(2*H*,10*H*)-diones. *Russian Journal of Organic Chemistry* **2020,** *56*, 813-818, https://doi.org/10.1134/S1070428020050139.
33. Matiichuk, Y.; Ogurtsov, V.; Ostapiuk, Y.; Chaban, T.; Matiychuk, V. Synthesis, anti-inflammatory activity and molecular docking of 2-methyl-3-furamides. *Biointerface Research in Applied Chemistry* **2020**, *10*, 5809-5814, https://doi.org/10.33263/BRIAC104.809814.
34. Tymoshuk, O.; Oleksiv, L.; Rydchuk, P.; Chaban, T.; Tymoshuk, S.; Matiychuk, V. Spectrophotometric Study of the Interaction of Platinum(IV) with New Derivatives of Azolidones. *Chemistry and Chemical Technology* **2020**, *14*, 139-145, https://doi.org/10.23939/chcht14.02.
35. Chaban, T.; Klenina, O.; Harkov, S.; Ogurtsov, V.; Chaban, I.; Nektegaev I. Synthesis of some new N^3 substituted 6-phenylazo-3*H*-thiazolo[4,5-*b*]pyridin-2-ones as possible anti-inflammatory agents. *Pharmacia* **2017**, *64*, 16-30.
36. Pokhodylo, N.T.; Matiychuk, V.S.; Obushak, N.D. Synthesis of 1H-1,2,3-triazole derivatives by the cyclization of aryl azides with 2-benzothiazolylacetonone, 1,3-benzo-thiazol-2-ylacetonitrile, and (4-aryl-1,3-thiazol-2-yl)acetonitriles. *Chemistry of Heterocyclic Compounds* **2009**, *45*, 483-488, https://doi.org/10.1007/s10593-009-0287-6.
37. Chaban, T.I.; Matiychuk, V.S. Synthesis of 2-Aryl-5-oxo-5H-thiopyrano[4,3-b]pyridine-7-carboxylic Acids as the First Representatives of a New Heterocyclic System. *Russian Journal of General Chemistry* **2020**, *90*, 1578–1580, https://doi.org/10.1134/S1070363220080290.
38. Tymoshuk, O.; Oleksiv, L.; Khvalbota, L.; Chaban, T.; Patsay, I. Spectrophotometric determination of ru(iv) using 5-hydroxyimino-4-imino-1,3-thiazolidin-2-one as a novel analytical reagent. *Acta Chimica Slovenica* **2019**, *66*, 62–69, https://doi.org/10.17344/acsi.2018.4448.
39. Chaban, T.; Ogurtsov, V.; Mahlovanyy, A.; Sukhodolska, N.; Chaban, I.; Harkov, S.; Matiychuk, V. Antioxidant properties of some novel derivatives thiazolo[4,5-*b*]pyridine. *Pharmacia* **2019**, *66*, 171-180, https://doi.org/10.3897/pharmacia.66.e36764.

40. Rydchuk, P.V.; Tymoshuk, O.S.; Oleksiv, L.V.; Chaban, T.I.; Matiychuk, V.S. Voltammetric determination of pt(Iv) using 5-hydroxyimino-4-imino-1,3-thiazolidine-2-one. *Methods and Objects of Chemical Analysis* **2019**, *14*, 130-139, https://doi.org/10.17721/moca.2019.130-139.
41. Matiichuk, Y.; Ostapiuk, Y.; Chaban, T.; Ogurtsov, V.; Matiychuk, V. Synthesis and anticancer properties of n-(5-r-benzyl-1,3-thiazol-2-yl)-2,5-dimethyl-3-furamides. *Biopolymers and Cell* **2020**, *36*, 74-83, http://dx.doi.org/10.7124/bc.000A22.
42. Horishny, V.; Chaban, T.; Matiychuk, V. Synthesis and Primary Antitumor Screening of 5-Ylidene Derivatives of 3-(Morpholin-4-yl)-2-sulfanylidene-1,3-thiazolidin-4-one. *Russian Journal of Organic Chemistry* **2020,** *56*, 454-457, https://doi.org/10.1134/S1070428020030148.
43. Chaban, T.I.; Matiichuk, Y.E.; Matiychuk, V.S. Synthesis of 2*H*-thiopirano[3,4-*c*]pyrazol-7-one derivatives as the first example a new heterocyclic system. *Russian Journal of General Chemistry* **2020**, *90*, 1357-1361, https://doi.org/10.1134/S1070363220070257.
44. Chulovska, Z.; Chaban, T.; Drapak, I.; Chaban, I.; Nektegaev I. Synthesis of some C^5 substituted 4-phenylimino-thiazolidin-2-ones as possible anti-inflammatory agents. *Biointerface Research in Applied Chemistry* **2021**, *11*, 8009-8017, https://doi.org/10.33263/BRIAC111.80098017.
45. Drapak, I.; Foliush, V.; Chaban, T.; Matiychuk, V. Synthesis antimicrobial and antitumor activities of 2-[5-(2-R-benzyl)thiazol-2-ylimino]thiazolidin-4-ones. *Biointerface Research in Applied Chemistry* **2020**, *10*, 5507-5511, https://doi.org/10.33263/BRIAC103.507511.
46. Chaban, T.I.; Matiychuk, V.S.; Ogurtsov, V.V.; Chaban, I.G.; Nektegayev, I.A. Development of effective anti-inflammatory drug candidates among novel thiazolopyridines. *Ukrainian Biochemical Journal* **2020**, *92*, 132-139, https://doi.org/10.15407/ubj92.02.132.
47. Klenina, O.; Chaban, T.; Zimenkovsky, B.; Harkov, S.; Ogurtsov, V.; Chaban, I.; Myrko, I. Qsar modeling for antioxidant activity of novel N^3substituted 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones. *Pharmacia* **2017**, *64*, 49-71.
48. Ostapiuk, Y.V., Chaban, T.I., Matiychuk, V.S. Thiazolidine-2,4-dithione in the Knoevenagel/Hetero Diels–Alder Domino Reaction. *Russian Journal of Organic Chemistry* **2020,** *56*, 1495-1497, https://doi.org/10.1134/S1070428020080242.
49. Obushak, N.D.; Matiichuk, V.S.; Ganushchak, N.I.; Burlak, Y.É. Synthesis of heterocycles from products of the anion arylation of unsaturated compounds. 3. 2-Arylimino-5-arylmethyl-4-thiazolidones. *Chemistry of Heterocyclic Compounds* **1998**, *34*, 492–496, https://doi.org/10.1007/BF02290893.
50. Mouilleron, S.; Badet-Denisot, M.A.; Golinelli-Pimpaneau, B. Ordering of C-terminal loop and glutaminase domains of glucosamine-6-phosphate synthase promotes sugar ring opening and formation of the ammonia channel. *Journal of Molecular Biology* **2008**, *377*, 1174-1185, https://doi.org/10.1016/j.jmb.2008.01.077.
51. Trott, O.; Olson, A. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. *Journal of Computational Chemistry* **2010**, *31*, 455-461, https://doi.org/10.1002/jcc.21334.
52. Open-access antimicrobial screening program: https://www.co-add.org/.