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NOVEL *β*-LACTAMS AND THIAZOLIDINONE DERIVATIVES FROM 1,4-DIHYDROQUINOXALINE SCHIFF'S BASE: SYNTHESIS, ANTIMICROBIAL ACTIVITY AND MOLECULAR DOCKING STUDIES

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Abstract. A series of novel isolated *β*-lactams **3a-c** and thiazolidinone derivatives **4a-c** were successfully synthesized from reactions of new Schiff's bases **2a-c** with chloroacetyl chloride and thioglycolic acid. The chemical structures of the new compounds were confirmed through different spectroscopic techniques including IR, ^{1}H and ^{13}C NMR, mass spectrometry and elemental analysis. The antimicrobial activity of the obtained compounds was assessed *in vitro* against gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* bacteria and *Aspergillus flavus* and *Candida albicans* fungi. All compounds exhibited good to excellent antimicrobial activity against the tested strains. Furthermore, a molecular docking study was carried out for the synthesized compounds and the results indicated that compounds **3b** and **4b** display comparable binding affinity scores as that of glutamate. These two compounds are promising candidates as antibacterial and antifungal agents that would deserve further investigations.

Keywords: heterocycle, *β*-lactam, quinoxaline, antimicrobial activity, molecular docking.

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Introduction

The *β*-lactam skeleton has attracted much attention from medicinal chemists for the past 60 years due to its numerous biological activities and the mechanism of action of its derivatives has been broadly reviewed [1-3]. As a class of organic molecules, *β*-lactams constitute more than 65% of the world antibiotics market in both human and veterinary medicine [4,5]. Since the discovery of penicillin, efforts have been devoted to synthesize various *β*-lactam derivatives bearing important biological activities [6]. Besides their antibacterial activity, *β*-lactam derivatives have shown antitumor [7,8], antiviral [9], antihyperglycemic [10], antitubercular [11], antileishmanial and other potent biological activities [12]. However, the evolution of antibiotic-resistant bacteria represents the main obstacle to broad the clinical application of *β*-lactams despite the exhaustive medicinal chemistry campaigns aiming to vary *β*-lactam antibiotics. Consequently, the need for new derivatives with efficient biological activities has increased.

During the past years, substituted quinoxaline derivatives have gained attention and have been progressively explored as a result of their broad spectrum of pharmacological properties [13-15]. Therefore, a wide variety of synthetic routes for the design of functionalized quinoxalines has been intensively studied. Quinoxaline derivatives display versatile biological activities such as antiviral [16,17], antimicrobial [18,19], anti-inflammatory [20], antitumor [21] anti-tuberculosis [22], *etc*. Diverse recent approaches were carried out to the existing drugs to minimize the microbial resistance. These, for the most part, necessitate structural modification of actual antimicrobial agents to improve the microbial intracellular concentration of the drug, and thereby to boost the antimicrobial activity. The throughout literature surveys indicate that some substituents,

particularly chlorine atoms, of structure of the bioactive organic compounds regarded as potential drug, have a promising effect on their specific biological activity. Several previous studies have pointed out that *β*-lactam derivatives possessing chlorine atoms were endued with significant biological activities [23-26]. The search for novel synthetic pathways for the design of heterocycles based on the *β*-lactam skeleton with improved biological derivatives is being actively pursued in our laboratory [27,28].

The aim of this study was to synthesize novel *β*-lactams **3a-c** and thiazolidinone derivatives **4a-c** and to evaluate *in vitro* their antibacterial and antifungal activity against several strains. Molecular docking studies were carried out to estimate the binding affinities of most active synthesized compounds on a molecular level.

Experimental

Generalities

Unless otherwise mentioned, reagents were purchased from Sigma Aldrich (Bayouni Trading Co. Ltd., Al-Khobar, Saudi Arabia) with high grade of purity and used without further purification. Reaction progress was monitored using *thin-layer chromatography* on silica gel pre-coated F254Merck plates (Darmstadt, Germany) and spots were visualized by ultraviolet irradiation. *Melting point* values of the synthesized compounds were determined using a Gallenkamp electro thermal melting point apparatus. *IR spectra* were measured as KBr pellets on a Pye-Unicam sp 1000 spectrophotometer. *^{1}H NMR spectra* were recorded in [$^2H_6$] dimethyl sulphoxide (DMSO) solution at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilan as internal reference. *^{13}C NMR spectra* were measured on a Varian MercuryVXR-300 NMR spectrometer (Palo Alto, CA) at 400 and 125 MHz using DMSO-d_6 as solvents. *Mass spectra* were obtained on a Shimadzu GCMS-QP 1000EX mass spectrometer at 70 eV. *Elemental analysis* was carried out on CE 440 Elemental Analyzer-Automatic Injector (Exeter Analytical, Inc., USA) at the Micro analytical Center of Cairo University.

General procedure for the synthesis of compounds (2a-c)

Compound **1** was prepared according to the reported method [15]. Briefly, compound **1** (0.01 mol) was treated with different aromatic aldehydes in equivalent amount in ethanol 30 mL and the reaction mixture was refluxed for 4 h. Then, the formed solid product was filtered and recrystallized from ethanol to afford the corresponding compounds **2a-c**.

Ethyl 3-(benzylideneamino)-1,4-dihydroquinoxaline-2-carboxylate ***2a***, orange crystals in 79% yield, m.p. 120-122°C. IR (KBr, cm^{-1}): 1565 (CH=N), 1730 (CO ester), 3100-3400 (NH). ^{1}H NMR: δ 1.21 (t, 3H, J= 7.52 Hz, CH_2CH_3), 4.15 (q, 2H, J= 7.51 Hz, CH_2CH_3), 7.10–8.01 (m, 9H, Ar-H), 8.3 (s, 1H, C*H*=N), 12.35 (s, 1H, N-H$_{quinox}$), 12.62 (s, 1H, N-H). ^{13}C NMR: δ 14.21 (CH_3), 61.53 (CH_2), 87.15, 119.44, 119.83, 120.35, 131.42, 137.65 (C=C), 164.24, 165.43 (*C*H=N) and (CO ester). MS (m/z, %): 307.0 (M^+, 55). Calc. for $C_{18}H_{17}N_3O_2$ (307.35): C, 70.34; H, 5.58; N, 13.67%. Found: C, 70.22; H, 5.43; N, 13.23%.

Ethyl 3-((4-chlorobenzylidene) amino)-1,4-dihydroquinoxaline-2-carboxylate ***2b***, yellow white crystals in 84% yield; m.p. 110-112°C. IR (KBr, cm^{-1}): 1568 (CH=N), 1735 (CO ester), 3100-3400 (NH). ^{1}H NMR: δ 1.25 (t, 3H, J= 7.53 Hz, CH_2CH_3), 4.18 (q, 2H, J= 7.53 Hz, CH_2CH_3), 7.10-8.01 (m, 8H, Ar-H), 8.5 (s, 1H, C*H*=N), 12.37 (s, 1H, N-H$_{quinox}$), 12.65 (s, 1H, N-H). ^{13}C NMR: δ 14.25 (CH_3), 61.57 (CH_2), 87.17, 119.44, 119.86, 120.33, 131.41, 137.64 (C=C), 164.23, 165.45 (*C*H=N) and (CO ester). MS (m/z, %): 341.0 (M^+, 45). Calc. for $C_{18}H_{16}ClN_3O_2$ (341.79): C, 63.25; H, 4.72; Cl, 10.37; N, 12.29%. Found: C, 63.17; H, 4.55; Cl, 10.40; N, 12.18%.

Ethyl 3-((4-methoxybenzylidene) amino)-1,4-dihydroquinoxaline-2-carboxylate ***2c***, red crystals in 65% yield; m.p. 135-137°C. IR (KBr, cm^{-1}): 1563 (CH=N), 1730 (CO ester), 3100-3400 (NH). ^{1}H NMR: δ 1.21 (t, 3H, J= 7.52 Hz, CH_2CH_3), 3.56 (s, 3H, OCH_3), 4.15 (q, 2H, J= 7.52 Hz, CH_2CH_3), 7.10-8.01 (m, 8H, Ar-H), 8.3 (s, 1H, C*H*=N), 12.35 (s, 1H, N-H$_{quinox}$), 12.63 (s, 1H, N-H). ^{13}C NMR: δ 14.14 (CH_3), 61.16 (CH_2), 87.15, 119.42, 119.85, 120.37, 131.44, 137.66 (C=C), 164.19, 165.28 (*C*H=N) and (CO ester). MS (m/z, %): 337.37 (M^+, 38). Calc. for $C_{19}H_{19}N_3O_3$ (337.37): C, 67.64; H, 5.68; N, 12.46%. Found: C, 67.64; H, 5.68; N, 12.46%.

General procedure for the synthesis of ethyl 3-(3-chloro-2-oxo-4-phenylsubstituted azetidin-1-yl)-1,4-dihydroquinoxaline-2-carboxylate (3a-c)

To a solution of compounds **2a-c** (0.01 mol) in 1,4-dioxane (15 mL), chloroacetyl chloride (1.99 mL, 0.025 mol) was added drop-wise at 5-100°C in the presence of trimethylamine (3.49 mL, 0.025 mol). The mixture was stirred for 8 h, and then poured into an ice water. The obtained solid was separated by filtration and recrystallized from ethanol.

Ethyl 3-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-1, 4-dihydroquinoxaline-2-carboxylate ***3a***, reddish brown crystals in 67% yield; m.p. 150-152°C. IR (KBr, cm^{-1}): 1685 (cyclic CO), 1730 (CO ester), 3100-3400 (NH). ^{1}H NMR: δ 1.21 (t, 3H, J= 7.52 Hz, CH_2CH_3), 4.15 (q, 2H, J= 7.52 Hz, CH_2CH_3), 7.10–8.01 (m, 9H, Ar-H), 5.2 (d, 1H, J= 5.59 Hz, CH-N), 5.47 (d, 1H, J= 5.78 Hz, CHCl), 12.35 (s, 1H, N-H_{quinox}) and 12.62 (s, 1H, N-H). ^{13}C NMR: δ 14.26 (CH_3), 60.73 (CH-N), 61.5 (CH_2), 64.25 (CH-Cl), 87.14, 119.41, 119.86, 120.37, 131.45, 137.62 (C=C), 161.1(CO cyclic), 165.4 (CO ester). MS (m/z, %): 383.0 (M^+, 30). Calc. for $C_{20}H_{18}ClN_3O_3$ (383.83): C, 62.58; H, 4.73; Cl, 9.24; N, 10.95%. Found: C, 62.53; H, 4.65; Cl, 9.17; N, 10.79%.

Ethyl 3-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-1,4-dihydroquinoxaline-2-carboxylate ***3b***, green white crystals in 70% yield; m.p. 180-182°C. IR (KBr, cm^{-1}): 1690 (cyclic CO), 1732 (CO ester), 3100-3400 (NH). ^{1}H NMR: δ 1.21 (t, 3H, J= 7.53 Hz, CH_2CH_3), 4.15 (q, 2H, J= 7.53 Hz, CH_2CH_3), 7.10–8.01 (m, 8H, Ar-H), 5.2 (d, 1H, J= 5.61 Hz, CH-N), 5.47 (d, 1H, J= 5.83 Hz, CHCl), 12.35 (s, 1H, N-H_{quinox}), 12.62 (s, 1H, N-H). ^{13}C NMR: δ 14.24 (CH_3), 60.71 (CH-N), 61.55 (CH_2), 64.23 (CH-Cl), 87.16, 119.43, 119.84, 120.32, 131.45, 137.63 (C=C), 161.15 (cyclic CO), 165.46 (CO ester). MS (m/z, %): 418.0 (M^+, 42). Calc. for $C_{20}H_{17}Cl_2N_3O_3$ (418.27): C, 57.43; H, 4.10; Cl, 16.95; N, 10.05%. Found: C, 57.35; H, 4.02; Cl, 16.84; N, 10.01%.

Ethyl 3-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-1,4-dihydroquinoxaline-2-carboxylate ***3c***, violet crystals in 60% yield; m.p. 160-162°C. IR (KBr, cm^{-1}): 1685 (cyclic CO), 1732 (CO ester), 3100-3400 (NH). ^{1}H NMR: δ 1.21 (t, 3H, J= 7.52 Hz, CH_2CH_3), 3.56 (s, 3H, OCH_3), 4.15 (q, 2H, J= 7.52 Hz, CH_2CH_3), 7.10-8.01 (m, 8H, Ar-H), 5.2 (d, 1H, J= 5.59 Hz, CH-N), 5.47 (d, 1H, J= 5.78 Hz, CHCl), 12.35 (s, 1H, N-H_{quinox}), 12.62 (s, 1H, N-H). ^{13}C NMR: δ 14.25 (CH_3), 60.77 (CH-N), 61.54 (CH_2), 64.28 (CH-Cl), 87.16, 119.44, 119.86, 120.39, 131.44, 137.6 (C=C), 161.14 (CO cyclic), 165.47 (CO ester). MS (m/z, %): 413.0 (M^+, 25). Calc. for $C_{21}H_{20}ClN_3O_4$ (413.85): C, 60.95; H, 4.87; Cl, 8.57; N, 10.15%. Found: C, 60.90; H, 4.72; Cl, 8.53; N, 10.12%.

General procedure for the synthesis of ethyl 3-(4-oxo-3-phenyl substituted 1,2,3-thiadiazolidin-2-yl)-1,4-dihydroquinoxaline-2-carboxylate (4a-c)

Thioglycolic acid (0.02 mol) was added to compounds **2a-c** (0.01 mol) and zinc chloride. The reaction mixture was heated and refluxed for 12 h. The solid product was collected and recrystallized from diethyl ether to give compounds **4a-c**.

Ethyl 3-(4-oxo-2-phenylthiazolidin-3-yl)-1,4-dihydroquinoxaline-2-carboxylate ***4a***, brown crystals in 62% yield; m.p. 215-217°C. IR (KBr, cm^{-1}): 1730 (CO ester), 1760 (CO thiazolidinone), 3100-3400 (NH). ^{1}H NMR: δ 1.21 (t, 3H, J= 7.52 Hz, CH_2CH_3), 3.96 (s, 2H, CH_2), 4.15 (q, 2H, J= 7.52 Hz, CH_2CH_3), 4.93 (s, 1H, CH), 7.10–8.01 (m, 9H, Ar-H), 8.3 (s, 1H, C*H*=N), 12.35 (s, 1H, N-H_{quinox}), 12.62 (s, 1H, N-H). ^{13}C NMR: δ 14.23 (CH_3), 61.57 (CH_2), 87.15, 119.48, 119.86, 120.37, 131.45, 137.68 (C=C), 165.45 (CO ester); MS (m/z, %): 381.0 (M^+, 55). Calc. for $C_{20}H_{19}N_3O_3S$ (381.45): C, 62.97; H, 5.02; N, 11.02; S, 8.41%. Found: C, 62.92; H, 5.00; N, 10.99; S, 8.33%.

Ethyl 3-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-1,4-dihydroquinoxaline-2-carboxylate ***4b***, brown crystals in 62% yield; m.p. 215-217°C. IR (KBr, cm^{-1}): 1730 (CO ester), 1766 (CO thiazolidinone), 3100-3400 (NH). ^{1}H NMR: δ 1.21 (t, 3H, J= 7.53 Hz, CH_2CH_3), 4.1 (s, 2H, CH_2), 4.15 (q, 2H, J= 7.53 Hz, CH_2CH_3), 4.98 (s, 1H, CH) 7.10-8.01 (m, 8H, Ar-H), 8.3 (s, 1H, C*H*=N), 12.35 (s, 1H, N-H_{quinox}), 12.62 (s, 1H, N-H). ^{13}C NMR: δ 14.22 (CH_3), 61.51 (CH_2), 87.15, 119.43, 119.86, 120.37, 131.45, 137.66 (C=C), 165.46 (CO ester). MS (m/z, %): 415.0 (M^+, 16). Calc. for $C_{20}H_{18}ClN_3O_3S$ (415.89): C, 57.76; H, 4.36; Cl, 8.52; N, 10.10; S, 7.71%. Found: C, 57.70; H, 4.23; Cl, 8.44; N, 10.5; S, 7.63%.

Ethyl 3-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-1,4-dihydroquinoxaline-2-carboxylate ***4c***, deep red crystals in 55% yield; m.p. 230-232°C. IR (KBr, cm^{-1}): 1730 (CO ester), 1762 (CO thiazolidinone), 3100-3400 (NH). ^{1}H NMR: δ 1.21 (t, 3H, J= 7.52 Hz ,CH_2CH_3), 3.94 (s, 2H, CH_2), 4.15 (q, 2H, J= 7.52 Hz, CH_2CH_3), 4.90 (s, 1H, CH), 7.10–8.01 (m, 8H, Ar-H), 8.3 (s, 1H, C*H*=N), 12.35 (s, 1H, N-H_{quinox}), 12.62 (s, 1H, N-H). ^{13}C NMR: 14.25 (CH_3), 61.58 (CH_2), 87.14, 119.46, 119.83, 120.37, 131.45, 137.67 (C=C), 165.45 (CO ester); MS (m/z, %): 411.0 (M^+, 27). Calc. for $C_{21}H_{21}N_3O_4S$ (411.47): C, 61.30; H, 5.14; N, 10.21; S, 7.79%. Found: C, 61.30; H, 5.14; N, 10.21; S, 7.79%.

Antimicrobial activity

Antimicrobial activity (antibacterial and antifungal) of the tested samples was assessed following a modified Kirby–Bauer disk diffusion method [29]. Plates impregnated with filamentous fungi like *Aspergillus flavus* at 25°C for 48 h;

gram-positive bacteria as *Staphylococcus aureus*; gram-negative bacteria as *Escherichia coli*, were incubated at 35-37°C for 24-48 h and *Candida albicans* and *Aspergillus flavus* fungi were incubated at 30°C for a period varying between 24 and 48 h. The standard disks of ampicillin (an antibacterial agent) and amphotericin B (an antifungal agent) served as positive control for antimicrobial activity and filter disks impregnated with 10 µL of solvent (distilled water, chloroform and DMSO) were used as negative controls. All experiments were repeated and carried out in triplicate in the case of a significant difference in the results and the average inhibition diameters were measured in mm/mg sample.

Molecular docking

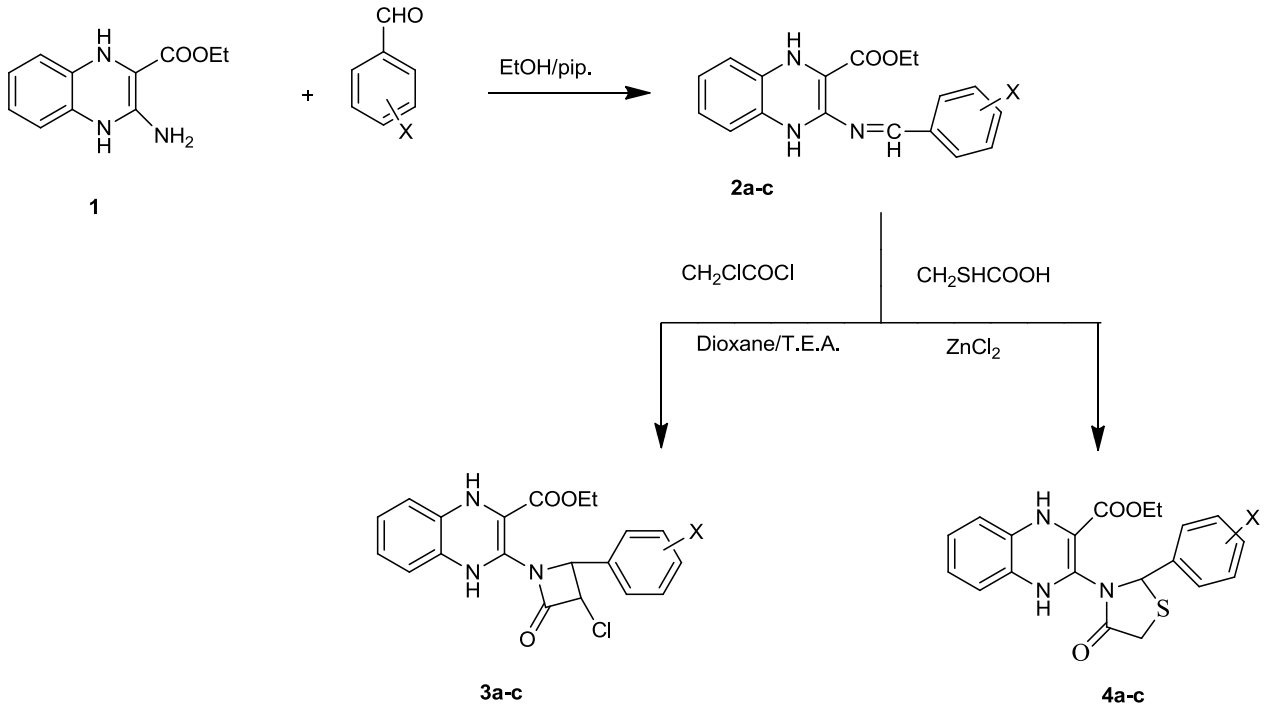
In this study, molecular simulation and modelling were performed using Molecular Operating Environment software (MOE, Version 2010.08, Canada). Glucosamine-6-phosphate synthase enzyme (GlcN-6-P) (PDB: ID 1gdo) was downloaded from RCSB Protein Data Bank [30]. The novel synthesized compounds **3a-c** and **4a-c** were subjected to molecular docking *via* their 2D and 3D structures. Before docking, adequate steps were performed including running conformational analysis using systemic search, 2D protonation of the structures, selecting the least energetic conformer and applying the protocol.

Results and discussion

Synthesis and characterization

The chemical synthesis of the compounds is illustrated in Scheme 1. The synthesis of new Schiff's bases derived from ethyl 3-amino-1,4-dihydroquinoxaline-2-carboxylate **1** is the fundamental key in the synthesis of the conforming isolated *β*-lactams **3a-c** and thiazolidinone **4a-c** derivatives. Thus, the reaction of compound **1** with different aromatic aldehydes in ethanol (30 mL) under reflux for about 4 h [27,31-33] led to the formation of the corresponding Schiff's bases **2a-c** in 65-84% yield.

Subsequent cyclocondensation of Schiff's bases **2a-c** with chloroacetyl chloride in 1,4-dioxane and trimethylamine [27,31-33] afforded the corresponding *β*-lactam derivatives **3a-c** respectively in 60-70% yield. Similarly, cyclization of Schiff's bases with thioglycolic acid and 1,4-dioxane solvents [27,31-33] gave the corresponding thiazolidinones derivatives **4a-c** in 55-62% yield. The chemical structures of products **3a-c** and **4a-c** were determined based on ^{1}H and ^{13}C NMR, IR spectroscopy as well as mass spectrometry data.



Scheme 1. Synthesis of the novel *β*-lactams (3a-c) and thiazolidinone derivatives (4a-c).

The IR spectra of compounds **3a-c** revealed a N-H stretching band at about 3100-3400 cm^{-1} and absorption bands at 1685-1690 cm^{-1} and 1730-1732 cm^{-1} corresponding to cyclic CO and CO ester, respectively. On the other hand, the IR spectrum of compounds **4a-c** exhibited absorption bands at 1760-1766 cm^{-1} corresponding to CO related to thiazolidinones. The ^1H NMR spectrum of compounds **3a-c** displayed a singlet resonate at 12.35 ppm assignable to N-H quinoxaline; the spectrum of compound **3c** showed a singlet at 3.56 ppm corresponding to (3H, for OCH_3). Moreover, the ^1H NMR spectrum of compounds **3a-c** exhibited a doublet at 5.2 ppm corresponding to -CH-N.

Antimicrobial activity

The synthesized compounds (**1**, **2a-c**, **3a-c** and **4a-c**) were evaluated for their antimicrobial activity against strains of gram-positive *Staphylococcus aureus*, gram-negative *Escherichia coli*, *Aspergillus flavus* and *Candida albicans* fungi. The initial screening results of *in vitro* antibacterial and antifungal activity are presented in Table 1. All tested compounds showed a comparatively promising activity towards gram-negative bacteria than gram-positive bacteria. Moreover, the highest activity of the designed compounds was recorded against the *Candia albicans* fungi. Thus, the obtained results show that compound **3b** exhibited the highest activity against *Escherichia coli* and *Staphylococcus aureus* bacteria. By comparing the *β*-lactam derivatives **3a-c** to their corresponding Schiff bases **2a-c**, the *β*-lactam derivatives exhibited better activity and higher growth inhibition for the tested strains including bacteria and fungi.

Structure-activity relationship studies were carried out to better understand the effect of benzene substitution operation on antimicrobial activity. Considering gram-negative bacteria (*Escherichia coli*) testing results, it is obvious that Schiff base **2b** and *β*-lactam derivative **3b** with electron-withdrawing chlorine atoms showed better antibacterial activity than all other tested compounds. Schiff base derivative **2a** without substituent on the benzene ring showed good antibacterial activity against *Escherichia coli*. It is worth noting that all thiazolidinones derivatives exhibited low activity against *Escherichia coli* compared to the Schiff base parents **2a-c**.

Besides, all compounds displaying an electron donating methoxy group on the benzene ring showed the lowest activity against gram-positive and gram-negative bacteria. It can be initially concluded that the presence of chlorine atom as a substituent on the benzene moiety withdraw electrons by induction and give electrons by resonance convey higher antibacterial and antifungal activity to Schiff's base **2b**, *β*-lactam **3b** and thiazolidinones derivatives **4b**. Whereas, the presence of the methoxy group as a substituent on the benzene ring (**2c**, **3c**, and **4c)** donates electrons by induction and reduces the antimicrobial activity of the synthesized compounds against the tested bacterial strains.

Molecular docking study

The most biologically active derivatives **3a-c** and **4a-c** were subjected to molecular docking study to predict their binding modes on a molecular level. Glucosamine-6-phosphate synthase enzyme (GlcN-6-P), a potential target for antibacterial and antifungal agents, was the enzyme of choice for performing the docking study.

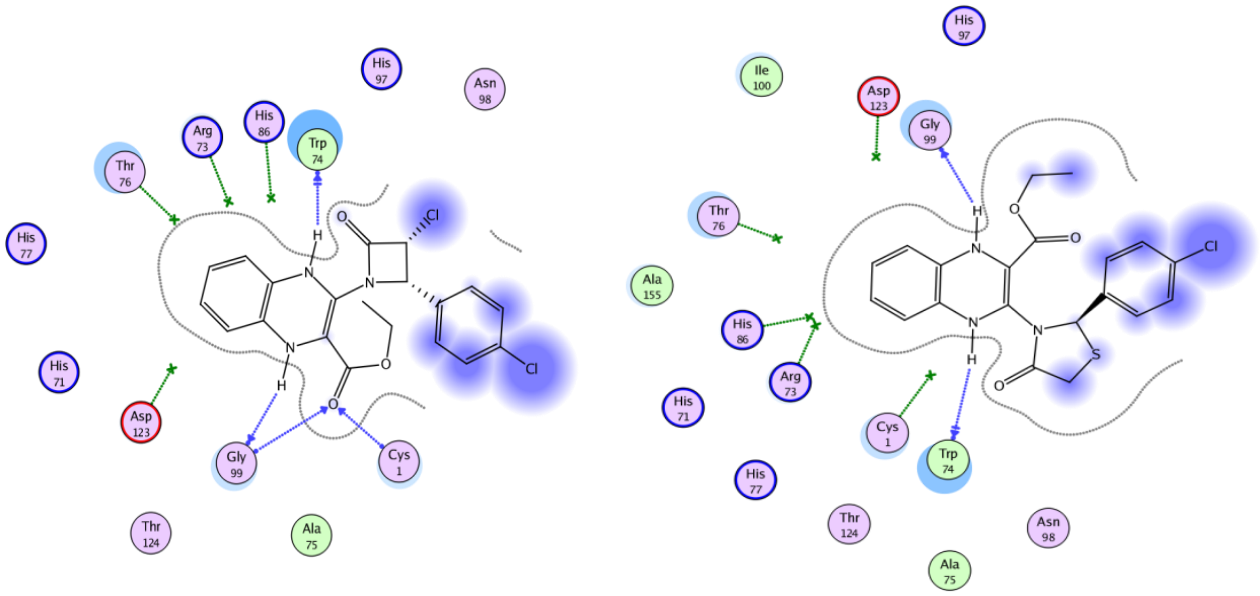
Table 1

Antimicrobial evaluation of the new synthesized compounds[*].

Compound no.	*Bacteria*		*Fungi*	
	Staphylococcus aureus	*Escherichia coli*	*Aspergillus flavus*	*Candida albicans*
Control (DMSO)	0	0	0	0
Ampicillin	23	28	-	-
Amphotericin B	-	-	14	20
1	19	21	8	12
2a	20	23	9	13
2b	22	24	10	14
2c	18	20	8	11
3a	21	24	13	17
3b	25	26	15	22
3c	20	20	12	15
4a	19	17	11	12
4b	24	19	13	13
4c	18	16	11	10

[*]*Mean inhibition zone diameter (mm/mg sample) (n=3).*

The target derivatives were re-docked into the binding site of GlcN-6-P enzyme (PDB: ID 1gdo). To do so, first, glutamate was re-docked into GlcN-6-P with a root mean standard deviation (RMSD) of 1.25, the ligand showed score binding energy (S) of -15.11 kcal/mol and hydrogen bonding with Gly99, Trp74, Cys1, His86, Arg73, Thr76, Asp123 (Figure 1). The data of this study including the energy associated with intermolecular interactions (affinity in kcal/mol) of the target compounds **3a-c** and **4a-c** and hydrogen bonding interactions are presented in Table 2.



(a) *(b)*

Figure 1. The 2D predicted binding mode from docking simulation of compound 3b *(a)* and compound 4b *(b)* into the active site of GlcN-6-P synthase.

Table 2

Molecular modeling data for compounds 3a-c and 4a-c in the active site of glucosamine-6-phosphate synthase enzyme (PDB: ID 1gdo).

Compound	*Affinity, Kcal/mol*	*Number of hydrogen bonds*	*Distance from main residue, Å*		*Functional group*
3a	-16.67	4	Trp74	2.93	NH
			Gly99	2.12	NH
			Gly99	2.93	C=O
			Cys1	3.11	C=O
3b	-18.95	4	Trp74	2.95	NH
			Gly99	2.00	NH
			Gly99	2.89	C=O
			Cys1	3.16	C=O
3c	-16.00	4	Thr124	2.23	OCH_3
			Arg73	2.15	OCH_3
			His86	3.19	OCH_3
			Ser176	2.64	C=O
4a	-15.50	2	Thr76	2.99	NH
			Cys1	2.67	C=O
4b	-18.50	2	Thr76	3.12	NH
			Trp74	2.98	NH
4c	-13.22	1	Cys1	2.79	OCH_3

Continuation of Table 2

Compound	*Affinity, Kcal/mol*	*Number of hydrogen bonds*	*Distance from main residue, Å*		*Functional group*
Glutamate	-15.11	10	Gly99	2.02	C=O
			Trp74	2.06	CO-
			Cys1	2.54	CO-
			His86	1.77	CO-
			Arg73	2.70	CO-
			Arg73	3.05	C=O
			Thr76	2.70	C=O
			Asp123	3.05	NH
			Thr76	2.70	NH
			Gly99	3.07	NH

Docking results on the compounds **3a-c** and **4a-c** revealed moderate to strong binding affinity varying from -13.22 to -18.75 kJ/mol compared to -15.11 kJ/mol for the reference drug glutamate, which exhibited ten hydrogen-bonding interactions with the amino acid series Gly99, Trp74, Cys1, His86, Arg73, Thr76, Asp123, respectively (Table 2). Compound **3a** recorded the energy docking of -16.67 kcal/mol, and it showed four bonding as following: i) Trp74 with NH, ii) Gly99 with NH, iii) Gly99 with C=O, iv) Cys1 with C=O. Besides, compound **3b** registered a docking energy value of -18.95 kcal/mole and was found to perform four hydrogen-bonding interactions: i) Trp74 with NH, ii) Gly99 with NH, iii) Gly99 with C=O, iv) Cys1 with C=O. Moreover, the candidate **3c** recorded a docking energy value of -16.00 kcal/mol and four hydrogen-bonding interactions: i) Thr124 with OCH3, ii) Arg73 with OCH3, iii) His86 with OCH3, and iv) Ser176 with C=O. In addition, the target compound **4a** displayed two hydrogen bonds with Thr76 and Cys1 *via* binding with NH and C=O groups. On the other hand, the candidate **4b** showed a high docking energy value of -18.50 kcal/mol and two hydrogen-bonding interactions with Thr76 and Trp74. Finally, compound **4c** demonstrated the least docking energy score of -13.22 kcal/mol with only one hydrogen bonding interaction with Cys1 amino acid.

It can be concluded that the most active compounds are **3b** and **4b** since they showed comparable binding affinity scores as that of glutamate. These results are considered in agreement with the experimental results.

Conclusions

Substituted *β*-lactams **3a-c** and thiazolidinone derivatives **4a-c** were successfully synthesized from the reaction of new Schiff's bases **2a-c** with chloroacetyl chloride and thioglycolic acid. All reactions were prepared with satisfactory yields and spectral data (IR, ^{1}H and ^{13}C NMR) of the obtained compounds (**3a-c**, **4a-c**) were in full agreement with the proposed structures.

All newly synthesized compounds were evaluated *in vitro* for their antimicrobial activity against gram-positive and gram-negative bacteria and fungi. All compounds displayed moderate to excellent antimicrobial activity against the tested strains. The biological screening proved compound **3b** to be the most active compound against all tested bacteria and fungi. Furthermore, compound **4b** showed good antibacterial activity when tested against *Staphylococcus aureus* bacteria. This behaviour was ascribed to the presence of chlorine withdrawing atom as a substituent on the benzene moiety.

It was found that all compounds carrying an electrodonating methoxy group as a substituent on the benzene ring displayed the least biological activity. Furthermore, the results from the biological testing were in agreement with the molecular docking studies. Therefore, compounds **3b** and **4b** represent promising candidates as antibacterial and antifungal agents that would deserve further investigations.

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