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FULL PAPER

Synthesis, characterization, and evaluation of molecular docking and experimented antioxidant activity of some new chloro azetidine-2-one and diazetine-2-one derivatives from 2-phenyl-3-amino-quinazoline-4(3H)-one

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This research aimed to synthesize new series of β-lactam derivatives from reaction of 2-phenyl-3-amino-quinazoline-4(3H)-one(3) through several reactions. Firstly, the reaction of anthranilic acid with benzoyl chloride gives N-benzoyl anthranilic acid (1). Then, cyclization of N-benzoyl anthranilic acid with acetic anhydride to give 2-phenyl- 4H- benzo [3,1] oxazine - 4- one (2). After that, compound (2) was reacted with hydrazine hydrate to give 2-phenyl-3-amino quinazoline -4(3H)-one (3). Compound (3) was reacted with different para-substituted aromatic aldehydes to give Schiff base derivatives (4-9). Finally, cyclization of Schiff base derivatives with different reagents (chloro acetyl chloride, phenyl isocyanate, and phenyl isothiocyanate) to form a new four-membered heterocyclic ring (β-lactam and1,3- diazetine-2-one (10-15) and (16-27),respectively. The prepared compounds were characterized by FTIR, ^{1}H-NMR, and ^{13}C-NMR as well as measurements of some of its physical properties and specific tests were done. The antioxidant activity of all the prepared compounds was estimated by molecular docking studies and in an experiment.

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KEYWORDS

Quinazoline; Schiffbase; antioxidant molecular docking; β-lactam.

Introduction

Quinazoline derivatives are of great importance in biological activities, such as they exhibit antitumor [1,2], diuretic [3], anti-inflammatory [4,5], hypotensive [6,7], anticonvulsant [8], anti-allergy [9], anti-depressant [10], and into-cancer properties [11]. Several selective derivatives of quinazoline containing drugs such as lapatinib, erlotinib, and vandetanib have been approved as anticancer drugs [12] antibacterial [13]. It was also reported that thioquinazoline derivatives identified as a possible pharmacophore for anti-tubercular activity [14]. Schiff bases are an important material for inorganic chemists due to their diverse biological, pharmacological, and antitumor activities. They have gained much importance in biomimetic modeling applications, molecular magnet molecules, liquid crystals aspect, and inorganic chemistry [15,16]. Polymeric Schiff bases and coordination polymers have high thermal stability, chemical resistance, scratch resistance, and corrosive resistance [17]. The

β-lactam ring is a part of the core structure of several antibiotic families. β-lactam antibiotics are primarily classified as penicillin, cephalosporin, carbapenems, and monocyclic antibiotics based ontheir structure [18,19].

Materials and methods

All used chemicals were purchased from Fluka or Aldrich starting chemical compounds. Melting points (MP) were marked by using gallenkamp in open glass capillaries by using a Thomas capillary melting point apparatus uncorrected. FTIR spectra were recorded on SHIMAZU FTIR-8400 Fourier transform infrared spectrophotometer as KBr disc. Total primary components and reagent were pure and commercially available. ^{1}H-NMR and ^{13}C-NMR spectra were recorded by 500 MHz spectrometer. Di methyl sulfoxide solvent (DMSO- d_6) was used to record Agilent Technologies model ultra-shield nuclear magnetic resonance (NMR) spectra, and the chemical shifts are given in δ (ppm) downfield by using tetra methylsilane (TMS) as references. UV-VIS spectra were recorded by Shimadzu-spectrophotometer and apel PD-303-spectrophotometer, Japan. Schiff bases were synthesized as intermediate compounds, which were then treated with various reagents (chloro acetyl chloride, phenyl isocyanate, and phenyl isothiocyanate) and under various conditions to yield new heterocyclic compounds (azetidine and 1,3-diazetiden) bearing quinazoline-4(3H)-one core[15].

Synthesis of N-benzoyl anthranilicacid[20]

To the cold and stirred solution from anthranilic acid (1.37 g, 0.01 mol) dissolved in (5 mL) dry acetone, the solution of benzoyl chloride (1.16 mL,0.01mol.) with (0.5mL) dry pyridine was added in dropwise addition with cooling by an ice bath, the mixture was refluxed for (3 hours) in a water bath at (40-50) °C, and then cooled to room temperature and poured into ice-cold diluted HCl (5%).The solid light-yellow precipitate was filtered, washed with distilled water, and recrystallized from (ethanol-water). Physical properties of compound (1) and FTIR spectral data are represented in Table 1.

Synthesis of 2-Phenyl-4H-benzo [3,1] oxazine-4-one (2) [21]

A solution of compound (1) (2 g,0.001 mol) which dissolved in acetic anhydride (3 mL, 0.032 mol) was refluxed for (4 hours) in dry conditions. After cooling the solution to room temperature, the mixture was poured into cold petroleum ether to give crystals that were recrystallized from ethanol. Physical properties of compound (2) and FTIR spectral are demonstrated in Table 1.

Synthesis of 2-phenyl-3-amino-quinazoline-4(3H)-one (3) [22]

Compound (2)(1 g,0.001 mol) was dissolved in (8 mL) ethanol as solvent; excess of 99% hydrazine hydrate was added to the reaction mixture and reflexed for (8 hours). Finally, the reaction mixture cooled to room temperature, poured on ice-cold water, stirred, and filtered. The precipitate was recrystallized from ethanol and water. Physical properties of compounds (3) and FTIR spectral data are indicated in Table 1.

Compound (3) (0.5 g, 0.001 mol) with an equimolar amount of different para-substituted aromatic aldehydes (0.001 mol) was added, in (5 mL) absolute ethanol and (2-3) drops of a catalyst glacial acetic acid. The mixture was refluxed for (8-12) hours and recrystallized from ethanol and water to form Schiff base derivatives (4-9). Physical properties of compounds (4-9) and FTIR spectral data are shown in Table 2.

TABLE 1 Physicalproperties and FT-IR spectral data forpreparedcompounds (1-3)

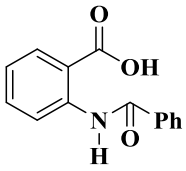
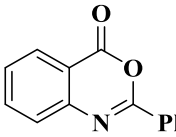
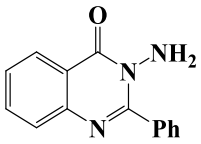
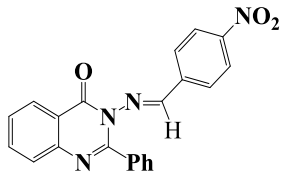
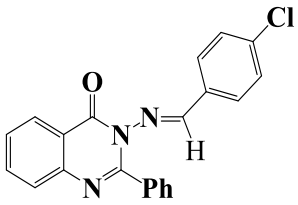
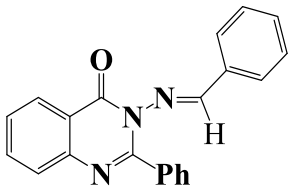
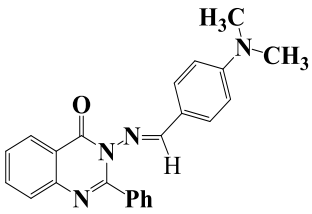
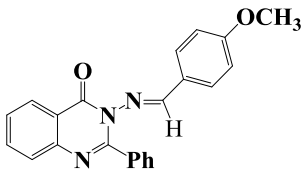
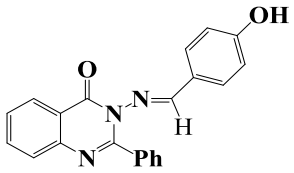
Compound	Physicalproperties				FTIR absorptionspectraldatacm^{-1}			
	Structure	M.P ^{0}C	Yield %	Color	V(C-H) Aromatic	ν (C=O)	ν(C=C) Aromatic	Other bands
1		166 - 167	75	Light yellow	3001	1710 acid 1685 amide	1544 1496	ν(OH) broad 3600-3240
2		123 - 124	85	Off white	3039	1764 lactone	1600 1573	ν(C=N) 1612 ν(C-O)1257
3		169 - 170	80	White	3039	1660	1591 1560	ν(C=N)1639ν(NH_2) asys. 3438 sym. 3309

TABLE 2 Physical properties and FT-IR spectral data cm^{-1} of prepared Schiff's base compounds (4-9)

Compound	Physicalproperties				FTIR absorptionspectraldatacm^{-1}			
	Structure	M.P ^{0}C	Yield %	Color	ν(C-H) Aromatic	ν(C=O) Amid	ν(C=N) ν(C=C)	Other bands
4		240-241	85	Yellow	3039	1681	1641 1604 1450	ν(NO_2) asys.1558sym. 1344 δp-position 815 ν(C=O) overtone ν(C=O) 3431
5		150-152	78	Pale Yellow	3039	1697	1641 1589 1452	ν (C-Cl)1093 δp-position804 ν (C=O) overtone ν (C=O) 3431
6		233-225	71	White	3037	1685	1635 1583 1527	--------
7		110-112	83	Yellow	3062	1684	164315 95 1556	ν(C=O) Overtone ν (C=O) 3431 δp-position811

8		143-145	88	Brown	3062	1685	1650 1600 1575	ν (C=O) overtone 3427 ν (C-O-C) says.1251 sym.1159 δp-position831
9		209-210	70	Yellow	3033	1680	1645 1598 1560	ν(C=O) overtone with νO-H3425 δp-position831

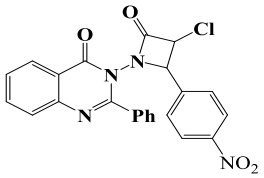
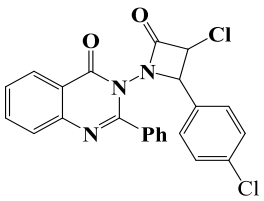
Synthesis of 3-(3-chloro-2-(4-subs. Phenyl) -4-oxo azetidin-1-yl)-2-phenyl quinazoline-4-(3H)-one (10-15) [24]

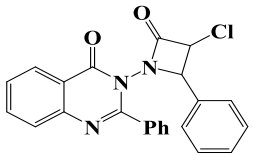
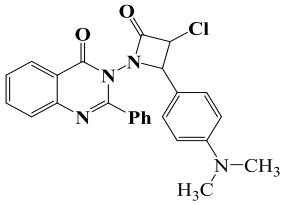
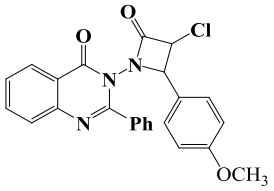
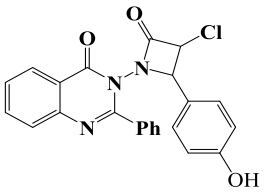
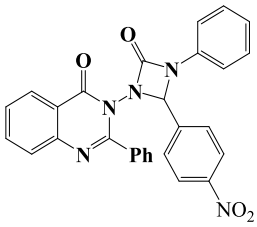
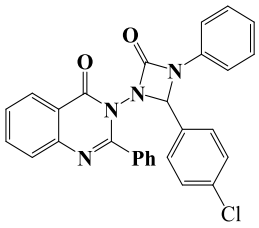
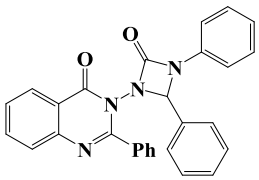
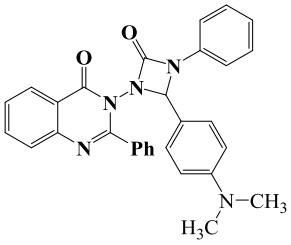
A mixture of equimolar amounts of (0.5 g, 0.001 mol) Schiff bases derivatives (3-8) in (2 mL) of dry DMF as a solvent, chloro acetyl chloride (0.2 mL, 0.001 mol), and tri ethylamine (Et_3N) (0.1mL,0.001 mol.) was added at (0-5)°C. The mixture was in reflux condition for (14-16) hoursat (45) °C. Then, it cooled at room temperature. Theproducts (10-15) were washed with cool water and recrystallization by using ethanol to form required products (10-15). Physical properties of compound (10-15) and FTIR spectral data are listed in Table 3.

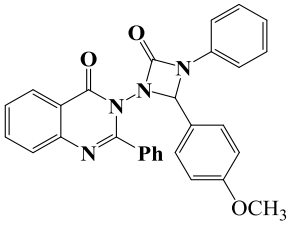
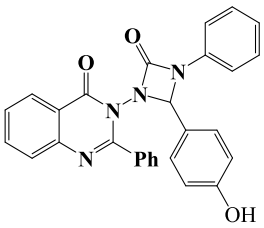
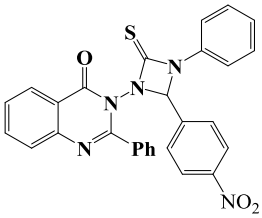
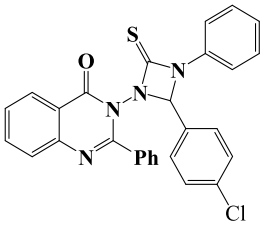
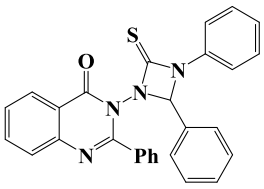
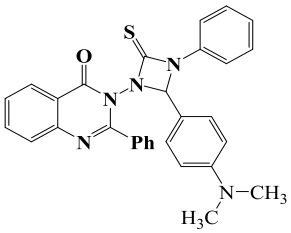
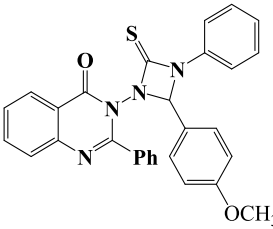
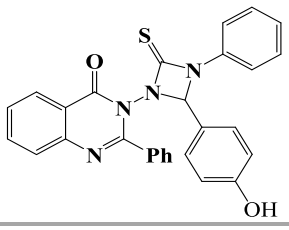
Synthesis of 3-[2-(4-subs. Phenyl)-4-oxo -3-phenyl-1,3-diazietidin-1-yl)-2-phenyl quinazoline-4-(3H)-one (16-21).and 3-[2-(4-sub. Phenyl)-4-thioxo-3-phenyl-1,3-diazetttidin-1-yl]-2-phenyl quinazoline-4-(3H)-one(22-27)[25]

A solution of (0.0016 mol) Schiff bases (4-9), phenyl isocyanate, and phenyl iso thio cyanate (0.1 mL, 0.001 mol) in (5 mL) ethanol were added in a round-bottomed flask with continuous stirring in addition to the reaction mixture was heated at room temperature, and then heated under reflux condition for (5-6) hours. The products (16-27) were washed with cool water and recrystallization by using ethanol to form the required products (16-27). Physical properties of compound (16-27) and FTIR spectral data are shown in Table 3.

TABLE 3 Physical properties of compounds (10-27)

Compound	Physical properties Structures	M.p.°C	Yield %	Color
10		180-182	88	Deep brown
11		160-162	82	Pale white

12		214-216	83	White
13		236-238	80	Yellow
14		160-162	85	Peggy
15		210	70	Brown
16		118-120	83	yellow
17		236-238	75	White
18		160-162	80	White
19		164-166	85	Brown

20		212-214	78	White
21		190-192	82	Pale brown
22		230-232	83	Deep yellow
23		160-162	80	Yellow
24		130-132	82	Peggy
25		158-159	85	Brown
26		156-158	78	Brown
27		250-252	75	Pale white

Antioxidant activity (DPPH radical scavenging assay)[26]

The antioxidant activity of compounds (3-27) was assessed by using the stable DPPH free radical according to a known procedure. A variety of concentrations of (50,100, and 150) mg/mL of the synthesized compounds (3-27) were mixed with methanol solution (up to 3 mL) including 0.0001 mg/mL of DPPH radical. The absorbance of the reaction mixture was measured at 517 nm after incubation for 30 min at room temperature by using a spectrophotometer. Ascorbic acid was used as the positive control at the same concentrations of the tested compounds. Percentage inhibitions of compounds (3-27) and that of ascorbic acid were calculated by using the following formula:

DPPH inhibition effect (%) = ((Ac-As)/Ac) *100
Ac=Absorbance reading of the control, As=Absorbance reading of the sample

In silico studies

Ligand preparation

Molecular docking studies were performed with Small Drug Discovery Suites package (Schrodinger 2020-3, LLC). Two dimensional structures of the synthesized compounds were sketched, and then converted into 3D structures by using the LigPrep module in maestro 12.5. To prepare ligands for the docking process, the ligands were set to the physiological pH and by using the OPLS-2005 force field performed energy minimization. The epik option was used for keeping the ligand in the correct protonation state.

Protein processing and binding site identification

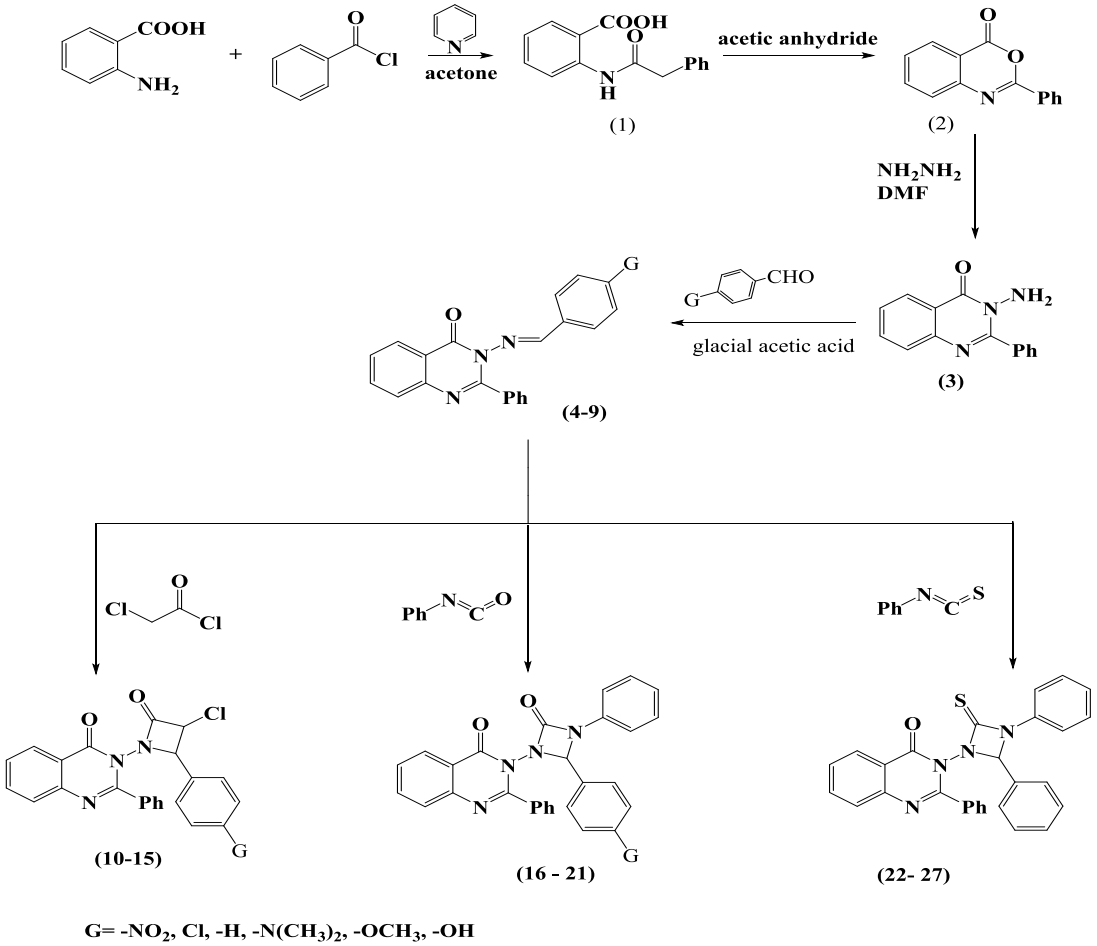
The 3D crystal structures of the (3-27) enzyme were obtained from RCSB Protein Data Bank (PDB ID: 3pp0). The 3D crystal structure was repaired and prepared via protein preparation wizard in maestro 12.5. All water molecules were initially removed from the crystal structure. Bond orders and charges were assigned, and then all missing hydrogen atoms were added to the protein structure. Amino acids were ionized by setting physiological pH byPropka software. Finally, the restrained minimization step has also been performed by using the OPLC force field. This minimized structure was the best structure to utilize for molecular docking. After protein preparation, top-ranked potential protein binding sites were identified to determine the most suitable binding site of proteins by using the glide grid tool of maestro 12.5.

Results and discussion

The series of the reactions that were carried out to prepare the new chloro azetidine-2-one,1,3-diazetiden-2-one,and 1,3diazetidne -2- thione derivative with 2-phenyl-quinazoline -4(3H)-one derivatives is displayed in Scheme 1.

The FTIR spectrum for compound (1) indicated characteristic broad absorption bands at ν(3600-3240)cm^{-1}duetoν(O-H),(3396)cm^{-1}forν (N-H),(3001)cm^{-1}dueto ν(C-H) aromatic, and two bands that appeared at (1710) cm^{-1} and (1685) cm^{-1}belonged to ν(C=O acid) and ν(C=O amide), respectively, also, at (1544,1496) cm^{-1} for ν(C=C) aromatic. Compound(2) was prepared by cyclization reaction of compound (1) in the presences of acetic anhydride. Disappearing bands of carbonyl group of amid NH group of compound (1) in the FTIR spectrum of compound (2) was a good evidence for the formation of this compound (2). Conversion of compound (2)into 2-phenyl-3-amino-quinazoline-4(3H)-one compound (3) was performed in the presences of hydrazine hydrate. The FTIR spectrum of this compound showed a strong absorption band at (asys. 3438 and sym. 3309) cm^{-1} for (NH_2) group and (3039) cm^{-1}

due to ν(C-H) aromatic, (1660) $cm^{-1}$for stretching band due to (C=O amide). While1H-NMR spectrum of compound (3) is depicted in Table 5,^{13}C-NMR spectrum data of this compound (3) demonstrated in Table 5, it was subjected to condensation reaction with para-substituted aromatic aldehydes to form Schiff bases derivatives (4-9). The FTIR spectra of these compounds showed absorption bands at -1635-1650) cm^{-1} due to ν (C=N). ^{1}H-NMR spectrum of compound (7) was shown in Table 5. ^{13}C-NMR spectra data of these compounds (7 and 8) were listed in Table 5. Schiff base derivatives (4-9) were subjected to cyclization reaction with different reagents (chloro acetyl chloride, phenyl isocyanate and phenyl iso thio cyanate) to form 4-oxoazetidin derivatives (10-15),4-oxo-1,3-diazetidin derivatives (16-21) and 4- thioxo-1,3-diazetidin derivatives (22-27), respectively.



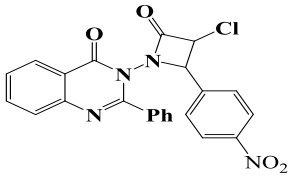
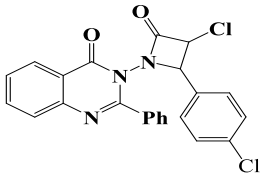
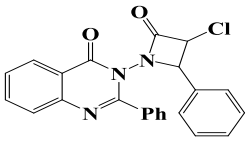
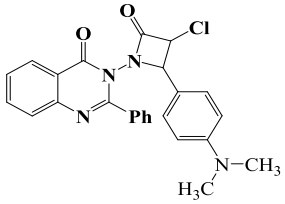
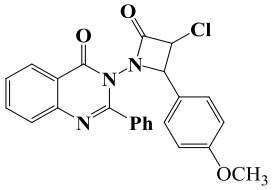
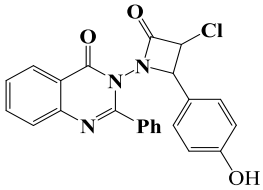
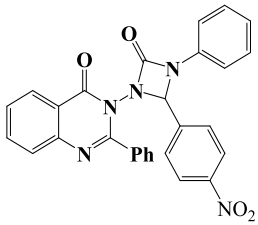
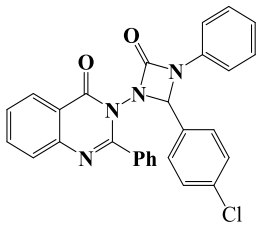
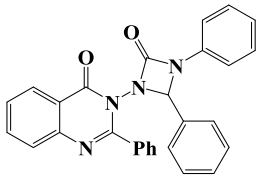
SCHEME 1 Synthesis of compounds (10-27)

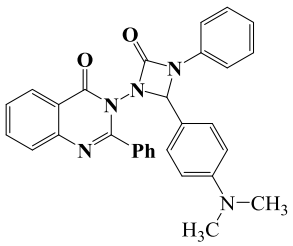
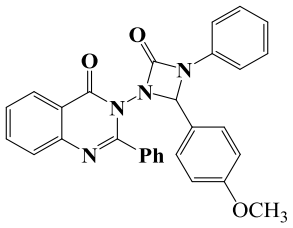
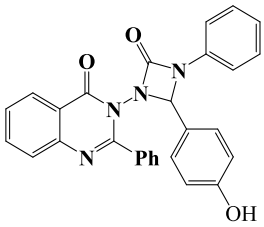
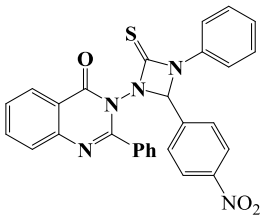
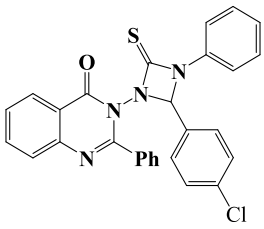
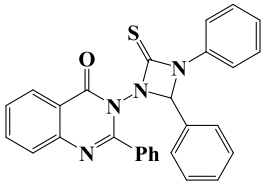
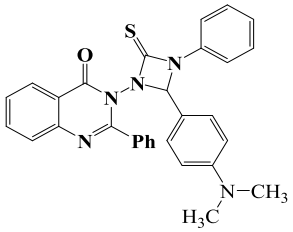
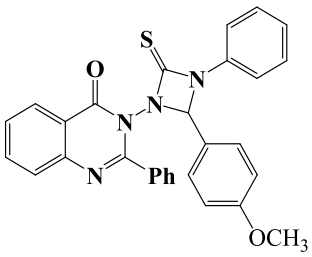
The FTIR spectra (Table 3) of 4-oxoazetidin derivatives (10-15) revealed new bands at (1658-1701) cm^{-1} owing to (C=O lactam ring).^{1}H-NMR spectra were depicted in Table 6; ^{13}C-NMR spectra data of these compounds (13 and 15)was listed in Table 5.

The FTIR spectra of 4-oxo-1,3-diazetidin derivatives (16-21) illustrated bands at (1668-1699) cm^{-1} for (C=O lactam). ^{1}H-NMR spectra of compounds (19, 20) were presented in Table 6; ^{13}C-NMR spectra data of these compounds (19,20) was listed in Table 5.

The FTIR spectra (Table 3) of 4-thioxo-1,3-diazetidin derivatives (22-27) showed new bands at (1438-1477) cm^{-1} for (C=S) group. ^{1}H-NMR spectra of compounds (22-27) were illustrated in Table 6. ^{13}C-NMR spectra data of these compounds (22 and 27) was listed in Table 4.

TABLE 4 FTIR spectral data cm^{-1} of compounds (10-27)

No.	Structures	Major FTIR Absorption cm^{-1}			
		ν(C-H) Arom.	ν(C=O)	ν(C=C) Arom.	Other bands
10		3001	1679 lactam 1649 quinazoline	1573 1475	ν(NO_2) asym. 1573 sym. 1342 δp-position802 ν (C-Cl) 923
11		3068	1683 lactam 1649 quinazoline	1556 1475	ν (C-Cl) 923 δp-position 761
12		3039	1680 lactam 1651 quinazoline	1558 1477	ν(C-Cl) 923
13		3065	1683 Lactam 1651 quinazoline	1591 1477	δp-position806 ν (C- Cl) 923
14		3055	1683 lactam 1652 quinazoline	1577 1492	δp-position825 ν (C-Cl) 921
15		3064	1680 Lactam 1650 quinazoline	1554 1475	ν(OH) 3433 ν (C-Cl) 921 δp-position831
16		3060	1686 lactam 1650 quinazoline	1539 1442	ν(NO_2) asym. 1539 and sym. 1317 δp-position827
17		3055	1683 lactam 1654 quinazoline	1577 1450	ν (C-Cl) 1014 δp-position 825
18		3056	1686 lactam 1649 quinazoline	1577 1442	

19		3047	1679 Lactam 1653 quinazoline	1565 1445	ν(aliph. CH) 2981, 2804 δp-position815
20		3001	1679 lactam 1650 quinazoline	1573 1475	δp-position 802
21		3062	1680 lactam 1650 quinazoline	1583 1448	ν(OH) 3463 δp-position 827 ν(C-O)1276
22		3058	1680 Lactam 1652 quinazoline	1575 1448	ν(C=S) 1448, ν(NO_2) asym. 1519 sym. 1338 δ*p*-position831
23		3058	1683 Lactam 1652 quinazoline	1591 1494	ν(C=S) 1450 δ*p*-position825 ν (C-Cl) 1091
24		3050	1683 Lactam 1650 quinazoline	1589 1413	ν(C=S) 1452
25		3065	1685 Lactam 1650 quinazoline	1591 1494	ν(C=S)1444 δ*p*-position815
26		3055	1683 Lactam 1654 quinazoline	1591 1492	ν(C=S) 1448 δ*p*-position 806

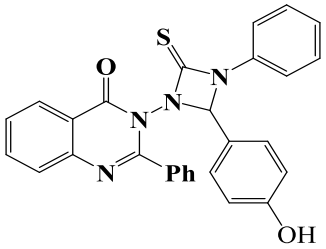
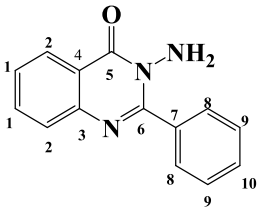
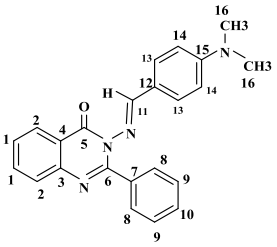
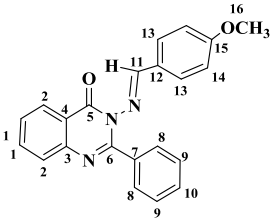
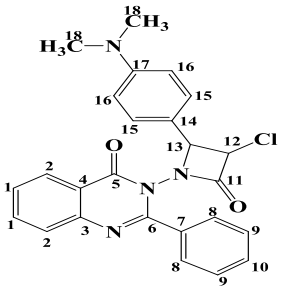
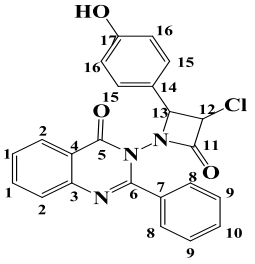
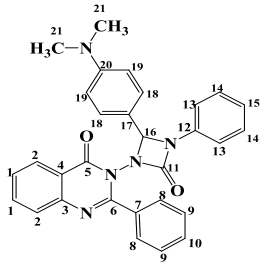
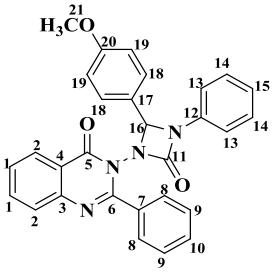
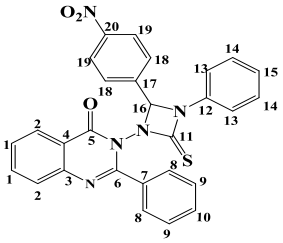
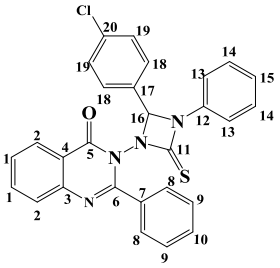
27		3029	1683 Lactam 1654 quinazoline	1556 1477	ν(OH) 3444 ν(C=S) 1413 δ*p*-position825

TABLE 5 ^{1}H-NMRand^{13}C-NMR spectral data (ppm) compounds (3, 7, 8, 13, 15, 19, 20, 22, and 23)

Compound	Structure	^{1}H-NMRspectral data (δppm)	^{13}C-NMRspectraldata (δppm)
3		3.37(s,2H,NH2); 7.21-8.73(m,9H,Ar-H)	117.41 (C10); 120.31 (C2); 127.39 (C4); 128.27 (C8); 128.53 (C7); 129.48 (C9); 130.49 (C1); 146.72 (C3); 156.86 (C6); 167.78 (C5).
7		3.47(s,6H,N-(C<u>H</u>$_3$)$_2$; 6.67(s,1H,-N=CH-);8.32-8.60 (m,13H, Ar-<u>H</u>);	40.50 (C16); 121.27 - 139.74 (C3, C4, C7,C12); 127.48-129.21 (C$_1$,C2,C8, C9, C10,C13); 150.57 (C15);152.18(C6, C11); 164.96 (C5).
8		3.38 (s, 3H, OC<u>H</u>$_3$); 7.35(s, 1H, -N=CH-). 7.37-8.58 (m, 13H, Ar-<u>H</u>);	40.06 (C16); 120.90-129.50 (C1,C2,C8,C9,C10,C13);132.16-140.37 (C3,C4,C7,C$_{12}$); 143.81 (C15); 151.47 (C6,C11); 165.38 (C5) .
13		2.98(d,1H,CH-Cl azetidine ring); 3.04 (s,6H,N(CH$_3$)$_2$);3.35 (s,1H, CH diazetidin ring), ;6.75-8.62(m,13H,Ar-H).	43.01(C18);63.11(C12);65.31 (C13); 150.55-121.61(C1, C2,C3,C4,C7,C8,C9,C10,C14,C15 ,C16,C17); 152.19 (C6) ; 164.91(C5) ;168.91 (C11).
15		2.88(d,1H,CH-Cl azetidin ring);3.36(S,1H,CH di azetidine ring); 6.85-8.8 (m,13H,Ar-H), 10.34 (S,1H,OH).	60 (C12);70(C13); 128.11-116.24 (C1,C2,C3,C4,C7,C8,C9,C10,C14, C15,C16, C17); 153.61(C6);165.16 (C5);169.99(C11).

19		3.38(s,6H,2CH_3); 4.14(s,1H,CHdi azetidine ring);6.75-8.71 (m,17H,Ar-H).	40.59(C21); 60.56(C16); C12(60);140.19-121.61 (C1,C2,C3,C4,C7,C8,C9, C10,C13,C14,C15,C17, C18,C19,C20);154.01(C6);1616 0.29(C5);164.92 (C11).
20		3.35(s,3H,CH_3) ; 4.13 (s,1H, CH di azetidine ring); 6.98-8.59 (m,18H,Ar-H).	52.42(C21);60.55(C16);140.35-118.6 (C1,C2,C3,C4,C7,C8,C9,C10,C12, C13,C14,C15,C17,C18, C19,C20);154(C6);164.92(C5), 165.38(C11).
22		3.37(s,1H, CH di azetidine ring);7.14-8.56(m,18H,Ar-H).	67.16(C16);140.79-121.07 (C1,C2 C3,C4,C7,C8,C9,C10,C12,C13,C1 4,C15,C17,C18,C19, C20);148.47 (C6);165.7 (C11); 165.08(C5).
23		3.36(s,1H,CHdiazetidine ring);7.15-8.72 (m,18H,Ar-H).	65.31(C16);139.78-120.97 (C1,C2,C3,C4,C7,C8,C9, C10,C12,C13,C14,C15, C17,C18,C19,C20);148.13 (C6);165.5(C5);166.93 (C11).

Antioxidant activity

Antioxidants can stop the oxidative stress by binding with free radicals and neutralizing their harmful effects through several chemical mechanisms created by natural active [26]. Oxidative degradation of organic materials, including biological molecules such as lipids, proteins, foods, and cosmetics, like any other radical chain reaction, autoxidation is composed of three steps: initiation, propagation, and termination [27].

DPPH scavenging activity

All the compounds (3-27) and starting 2-phenyl-3-amino-quinazoline-4(3H)-one showed comparable or slight less activity than the standard (ascorbic acid). It was predestined by DPPH (2,2- diphenyl-1-picrylhydrazyl) assay method at various concentrations (50,100, and 150 µg/mL). The result depending on the reaction characterized by a change in its deep violet color (DPPH) or Decolourization is stoichiometric concerning several captured electrons. Compounds (3-27) exhibited the best results among all compounds. Some compounds (4, 11, 17, and 22) bearing a nitro group (electron-withdrawing group) at a para-position showed high antioxidant activity when compared with some compounds (8, 14, 20, and 26) that have methoxylgroup (electron-donating group).

Compounds (5, 11, 17, and 23) substituted with halogen groups-Cl (electron-withdrawing group) exhibits a good antioxidant activity. These Compounds (6, 8, 12, 14, and 20) appear to be the antioxidant activity that is decreased. These compounds possessed good reducing power ability at a concentration of (150 µg/mL) among other compounds and exhibited close or higher antioxidant activity than the standard solution (ascorbic acid). Figure 1 displays the DPPH scavenging activity of the newly synthesized compound, as shown in Table 7.

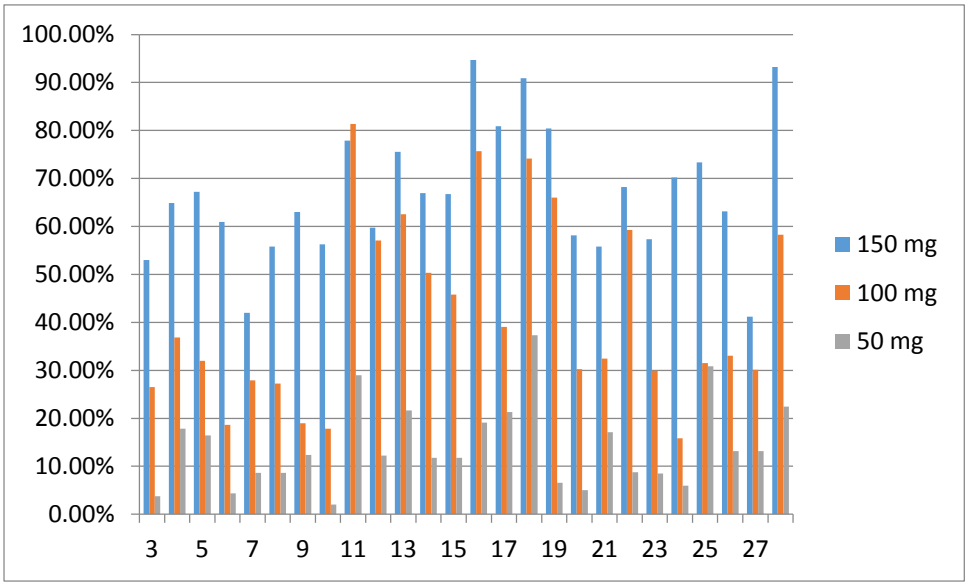


FIGURE 1 DPPH scavenging activity of the newly synthesized compound

Total antioxidant capacity

The total antioxidant capacity of the synthesized compounds was evaluated by the phosphomolybdenum method. A different concentrations (50, 100, and150 mg/mL) of an aliquot compound solutions was combined with (1 mL) of reagent (0.6 M) sulfuric acid, (28 mM) sodium phosphate, and (4 mM) ammonium molybdate. All test tubes containing the reaction solution for the tested compounds were capped and incubated at 95 °C for 90 min. Next, the tubes were cooled to room temperature, and then the absorbance of each tube was measured by using a spectrophotometer at 695 nm against blank. The total antioxidant activity is expressed as the number of grams equivalent to ascorbic acid. Different concentrations (10, 20, 30, 50, 70, 90, 120, 180, and 200 µg/mL) of ascorbic acid with DW where it is used to plot the calibration curve,as depicted in Figure 2.

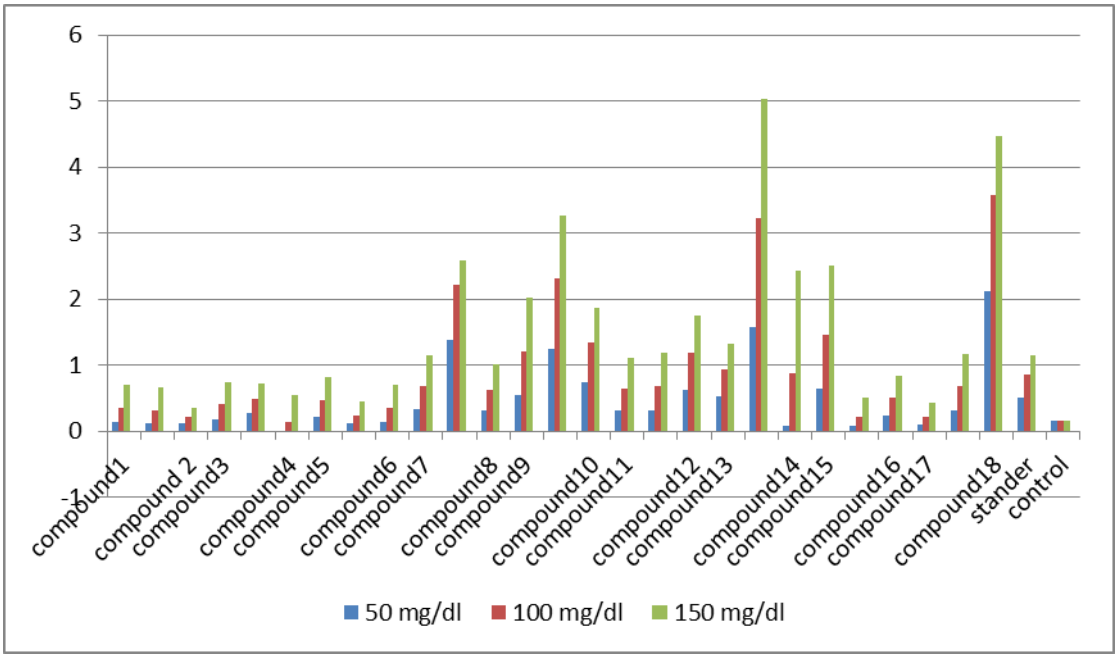


FIGURE 2 Total antioxidant capacity for compound

Molecular docking studies [28]

Ligand docking was performed for the prediction of the best poses and binding energies of ligands at binding sites identified by glide grid tool on the receptor. All ligands were initially docked on the receptors by using Glide docking module in Maestro 12.5. Briefly, grid box was generated around the selected co-crystalized ligand at the binding site by using the receptor grid generation platform. Then rigid receptor docking simulations were performed by the extra precision options in maestro 12.5. Finally, both visualizing poses and results analyses were performed by using maestro 12.5 work space visualizer, as illustrated in Figure 2.

TABLE 6 The molecular docking of compounds (1-22)

Compound	Types of residues	Types of interaction	Docking score	Glide Energy	Glidermsd	Glideposenum
2		Hydrophobic	-7.63096	-50.3906	32.8306	2
3	MET 801	Hydrophobic	-7.61815	-47.646	33.48688	4
4		Hydrophobic	-7.35403	-34.7349	34.87986	3
5	ASP 808	Hydrophobic	-7.18914	-45.9591	32.63256	10
6		Hydrophobic	-6.80809	-43.9367	33.45379	2
7		polar	-5.85965	-38.1529	34.99858	1
8	LYS 753	polar	-5.83351	-44.4437	33.14897	9
9	ARG 849	Charge positive	-4.40299	-23.9661	34.99762	3
10		Charge positive, negative	-2.74401	-41.2674	33.18349	2
	ARG 849	H-bond				
11	ARG 811	Pi-cation	-2.61187	-41.8032	34.10098	28
	SER728	Halogen bond				
12	ASP 863	Hydrophobic	-2.02553	-34.5091	33.28576	9
13	----------	Charge negative	-1.94687	-34.3469	33.50194	7
14	Glycin	Charge negative	-1.93338	-33.672	33.25601	24
15	SER 728	H-bond	-1.88123	-36.547	32.80697	1
16			-1.74724	-39.0748	33.46274	3

17	---------- -	Hydrophobic	-1.68242	-28.7082	32.75414	2
18		Hydrophobic	-1.50985	-33.9516	33.51797	3
19	LYS 724	Pi-cation	-1.37096	-29.4818	33.02363	1
20	ARG 849 CYS 805	Hydrophobic	-1.04894	-31.8322	33.69674	10
21	CYS 805	Hydrophobic	-0.77708	-24.1768	32.04859	15
22	ARG 849 CYS 805	Hydrophobic	-0.77708	-24.1768	32.32675	15
	CYS 805	H-bond	-0.33853	-32.8685	32.7587	1

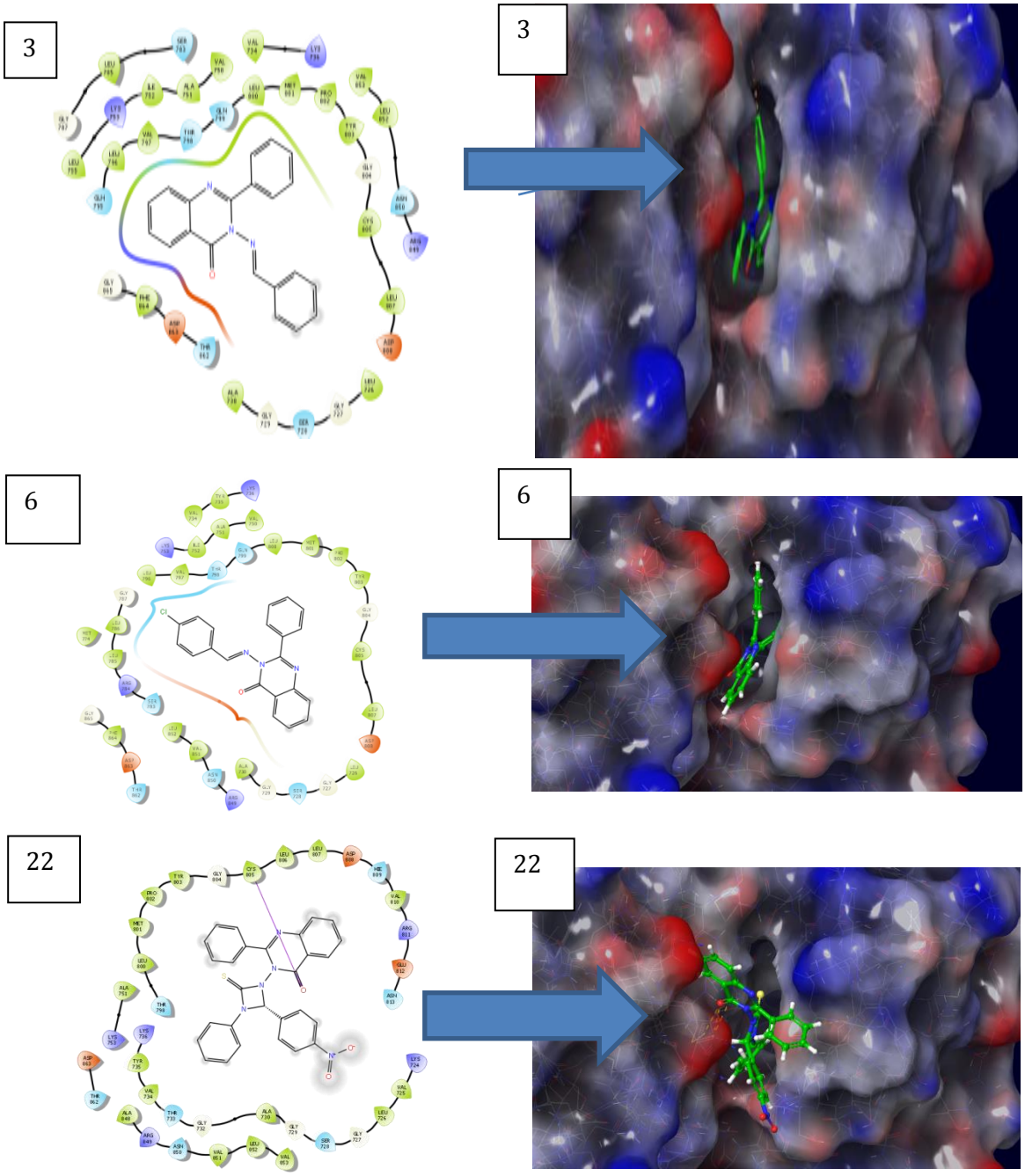


FIGURE 3 The best and stable conformations of all the synthesized molecules

The best result was related to compounds (1, 2, 3, and 4) for docking score ranging from [(-7.630)-(-7.189)] and RMSD score ranging from (32.8306- 32.7587), as indicated in Figure 3.

The compounds (5, 6, 7, and 8) for docking scores range from ranging from [(-6.80809)-(-4.402)] and RMSD score ranging from (33.45379-34.99762) as showed in Figure 3.
On other hand, the lowest results for compounds (9-22) for docking score ranging from [(-2.744)-(0.338)] and RMSD score ranging from (33.18349-32.7587), as demonstrated in Figure 3.

The docking was perfect for compounds (1-4).the best interaction was with the target protein for compound (2). The type of residues was (MET) at (801) where a type of interaction was (hydrophobic). This combination gives the best grove pose and affinity for the protein, this situation was shown in less form for the compounds (5-8) as the residue (LYS) at (753), (ARG) at (849), and type of interaction was (polar).

The situation was less appropriate for compounds (5-8) because this compound have lower interaction with the target protein. For compound (6), the types of residues and the type of interaction were (polar). This combination gives the lower grove pose and affinity for the protein. Finally, the worst result was for compounds (9-22). This gives less interaction with the target protein, this may be for the reasonthat the residues and interaction were very weak as it has (CYS) at position (805) with (H-bond) interaction, this gives a low affinity and makes interaction as nearly impossible. According to this results we can state that this value can give a good prediction for the protein-compound interaction, this prediction will consume less time and costs, our results show the best compound is 3that can be used for laboratory experiment and gives us the desired effect without using any form of compounds (9-22) that will consume our efforts.

Conclusion

Various derivatives of new β-lactam were synthesized from Schiff bases derivatives and different reagents (chloro acetyl chloride, phenyl isocyanate, and phenyl isothiocyanate). These derivatives were identified with FT-IR, ^{1}HNMR, ^{13}CNMR, and physical properties. All synthesized derivatives were studied in-vitro antioxidant activity. The results revealed a good biological property. We used molecular docking and chemical synthesis to study the structure activity relationships of synthesized compounds as inhibitors for TEM-class β-lactamase.

In the last study [29],new β-lactams were synthesized from N-carbazole derivatives. Physical and chemical properties and identified for all synthesized compounds of (tetra hydro carbazole and N-carbazole) derivatives and they studied in-vitro antioxidant activity for the prepared compounds. The results showed that a test had been a good ant-biological activity. In this study, we synthesized, characterized, evaluated molecular docking, and experimented them with antioxidant activity of some new chloro azetidine-2-one and diazepine-2-one derivatives from 2-phenyl-3-amino-quinazoline-4(3H)-one in addition to newly application for this group from organic compounds.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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