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Docking and Synthesis of Some 2-Aminothiazole Derivatives as Antimicrobial Agents

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Abstract

The 2- aminothiazole compounds are medicinally important agents due to their broad spectrum of biological activities. This study aims to design new 2-aminothiazole derivatives, docking, and synthesis via several steps and identified using physical and spectroscopic techniques. The bioactivities of the synthesized compounds were evaluated concerning their antimicrobial activities against were screened against five bacterial strains, *Enterobact aerogenes*, *Escherichia coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and two types of fungal strain *Candida albicans* and *Cryptococcus neoformans var. grubii*.

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eywords*: 2-aminothiazole, E.coli, antimicrobial activities, C. albicans.*

1. Introduction

The 2-aminothiazole agents are associated with a broad spectrum of biological properties, including anticonvulsant [1], antiviral [2], antimicrobial [3], antituberculous [4], antimalarial [5], anticancer [6], and hypertension [7], are just a few of the biological features related with 2-aminothiazole compounds. Cefdinir is a semi-synthetic broad-spectrum antibiotic 3rd generation cephalosporin [8], and several marketed medicines for various diseases contain 2-aminothiazole moieties as illustrated in Figure 1. In this study, we devised a simple and efficient technique for synthesizing five-membered ring-2-aminothiazole derivatives, which we tested for antibacterial activity against five bacterial species,.*Enterobacter , aerogenes*, *Escherichia coli*, *Enterococcu faecalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and a fungal strain *Candida albicans*, *C. neoformans* respectively.

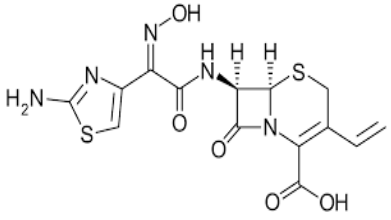

Figure 1: Chemical structure of Cefdinir

2. Experimental

All chemicals and solvents are purchased from Fluka & BDH Companies (Germany). Melting points were recorded in open capillaries using electrothermal digital 9200 melting point apparatus and were uncorrected. The infrared spectra were `recorded on Shimadzu FT-IR spectrophotometer (Japan). ^{1}H NMR spectra were measured on a Bruker 400 MHz spectrometer (Turkey) in deuterated dimethyl sulfoxide (DMSO-d_6) as a solvent and tetramethylsilane (TMS) as an internal standard. For *in silico* protein-ligand docking simulation, Mcule docking online. Antimicrobial screening tests were done according to CO-ADD protocols (Queensland University, Australia).

Molecular docking studies

Using the Mcule online program, the novel 2-aminothiazole derivatives were docked in the chosen active site of enzymes. The 3-D structure of 2-aminothiazole derivatives (ligand) was molecular docked to comprehend the binding sites with a particular enzyme (receptor) as ligand-receptor complex intermolecular interactions. The standard procedure for docking was used [9]. The 3-D structure of 2-aminothiazole derivatives (ligand) was molecular docked to comprehend the binding sites with a particular enzyme (receptor) as ligand-receptor

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complex intermolecular interactions. The usual technique and default parameters of molecular docking Mcule online were used to perform the docking. In online dock tools, only polar hydrogens were added to the protein file, and all water molecules were deleted. The ligands were presumed to be flexible molecules in the docking technique, and the docking program was permitted to rotate all rotatable bonds of the ligands to find the best and most optimal conformer of the ligands within the enzyme's active site. 2-aminothiazole derivatives, the natural ligand, was redocked to the binding site.

For DNA gyrase, the grid box was centered at x = 19.259, y = 29.159, and z = 42.461. Grid box dimensions were 46 46 46, with a grid point spacing of 0.375. A cluster analysis was performed at the end of the 200-run docking experiment. The binding free energy was used to rank the conformations, which were clustered using a 2.0 root mean square deviation tolerance[10]. The conformation with the best-scored pose and the lowest binding energy was chosen for this ligand among the numerous conformations produced through the docking procedure [10].

Chemistry

General procedure of the preparation of Ethyl thiazole-2-ylglycinate (1)[11].

The 2-aminothiazole (2g, 10mmol) and bromoethyl acetate (3.34ml, 20 mmol) and (3g) sodium bicarbonate were refluxed for 8 hours in abs.ethanol. The reaction mixture was poured into 100 mL of cold water, filtered, dried, the crude oil was added to the ice then extracted by ether to yield ethyl 2- (thiazole-2-ylamino) acetate (1). Yield 95%; oily; IR (KBr) broadband at 3320 cm^{-1}(NH), 3070 cm^{-1}(CH. Aromatic), 2958 cm^{-1}(CH. Aliphatic), 1756 cm^{-1}(C=O).

Compound (1) was combined with hydrazine hydrate (1: 6 mmol), then refluxed for 6 hours. To make 2-(thiazol-2-ylamino) acetohydrazide(2), the reaction was emptied in cold water, the precipitate was filtered, dried, and crystalized from ethanol (2.). 85 present yield; m.p. 189-190 °C; white crystals; IR (KBr) broadband at 3299, 3189cm^{-1}(NH), 3084 cm^{-1}(CH. Aromatic), 2984 cm^{-1}(CH. Aliphatic), 1632 cm^{-1}(C=O).

5-[(thiazol-2yl)ethylamino)methyl] -1,3,4-oxadiazole-2-thiol [12].

A mixture of (0.005 mol, 0.86g) 2-(thiazol-2-ylamino) acetohydrazide (compound 2) and (0.01 mol, 0.56 g of KOH in 100 ml of ethanol) was adding (0.2 mol , 16ml) of carbon disulphide, then reflux for 24hours . The contents were poured into ice-cold water and acidified with dil.HCl to give the desired product, which was recrystallized from ethanol. The percentage yield of the final product (3) is 98 %, m. p. 116-118ºC.

5-[(thiazol-2ylamino)methyl]1,3,4 thiadiazole-2-thiol(4)[12].

To dry and pure product of hydrazide salt (0.001mol) and cold conc.H_2SO_4 (10ml). At 5 ºC , the reaction mixture was stirred at room temperature for about 5-6 hours. The reaction mixture was then poured into crushed ice and vigorously stirred for 5-10 minutes. The resulting product is filtered, washed in cold water, and dried. Yield 60%; m.p. 220-222 ^{0}C. ; IR (KBr). Band at 1404 cm^{-1}(N-N=C), 1095 cm^{-1}(N-N), 1109 cm^{-1}(C=S), 717 cm^{-1}(C-S-C).

4-amino-5-[(thiazol-2-ylamino)methyl]-4*H*-1,2,4,-triazole-3-thiol (5)[13].

A mixture of hydrazide salt (0.01 mol), hydrazine hydrate (0.02 mol), and water (15 ml) was refluxed for 2 hours, the hydrogen sulphide gas was evolved. The contents were diluted with 100 mL of cold water and acidified with hydrochloric acid; the resulting product was filtered, washed with cold water, and recrystallized from aqueous ethanol to yield (5). Yield 64%; m.p. 118-120 ^{0}C. ; IR (KBr). band at 3244,3140 cm^{-1}(NH_2), 1404 cm^{-1}(N-N=C), 1083 cm^{-1}(N-N), 1240 cm^{-1}(C=S).

Synthesis of hydrazone derivatives (6-15) [14].

With stirring, hydrazide (2) (0.0011 mol) in ethanol (20 ml) was added to the substituted benzaldehyde mixture (0.001mol), and the mixture was refluxed for 2-4 hours. After cooling, the reaction mixture was kept for 24 hours. The corresponding Schiff base products were obtained by filtering, drying, and recrystallizing the crystals found in abs. ethanol (6-15) show Table 4.

N((4-oxo-2-arylthiazolidin-3-yl)-2-(thiazol-2-ylamino) acetamide (16-20) [15].

The mixture was refluxed for 24 hours after a solution of hydrazone derivatives (6,11,13,14, 15) (0.005 mol) in 40ml dry benzene was added, followed by thioglycolic acid (0.0041mol) in zinc chloride 0.2g as catalyst. The reaction was reflux with stirring for 24 hours, then evaporate the benzene, wash the crud product with sodium bicarbonate. The precipitate was crystallized from ethanol, the crystals were filtered, dried, The physical and infrared data were listed in Table(5).

N-((3-chloro-2-oxo-4-arylazetidin-1-yl)-2-thiazol-2-ylamino) acetamide (21-27) [16].

Chloroacetyl chloride (0.01 mol) was added dropwise with cooling to the corresponding hydrazones (6, 8,9,11,12,13, 15) (0.005mol) in a (0.01 mol) triethylamine in 40 ml of dioxane with stirring at room temperature for 20 minutes, then the mixture was refluxed for 8 hours. The reaction mixture was concentrated then poured into ice water; crude compounds were isolated, filtered, dried, and recrystallized from absolute ethanol, physical, and IR data for compounds (21-27) Table (5).

Antimicrobial Screening Tests

Antibacterial assay [17].

All bacteria, *S. aureus* (Strain ATCC 43300, MRSA), *E. coli* (Strain ATCC 25922, FDA control strain), *K. pneumoniae* (Strain ATCC 700603, MDR), *A. baumannii* (Strain ATCC 19606, Type strain), *P. aeruginosa* (Strain ATCC 27853, Quality control strain), were cultured in Cation-adjusted Mueller Hinton broth (CAMHB) at 37 °C overnight. A sample of each culture was then diluted 40-fold in fresh broth and incubated at 37 °C for 1.5–3 hours. The resultant mid-log phase cultures were diluted (CFU/mL measured by OD_{600}), then added to each well of the compound containing plates, giving a cell density of 5×10^5 CFU/mL and a total volume of 50 µL. All the plates were covered and incubated at 37 °C for 18 hours without shaking.

Antifungal Assay [18].

Fungi strains *C. albicans* (Strain ATCC 90028, CLSI reference) and *C. neoformans* (Strain ATCC 208821, H99 Type strain), were cultured for 3 days on Yeast Extract-Peptone Dextrose (YPD) agar at 30 °C. A yeast suspension of 1×10^6 to 5×10^6 CFU/mL (as determined by OD_{530}) was prepared from five colonies. The suspension was subsequently diluted and added to each well of the compound-containing plates giving a final cell density of fungi suspension of 2.5×10^3 CFU/mL and a total volume of 50 µL.

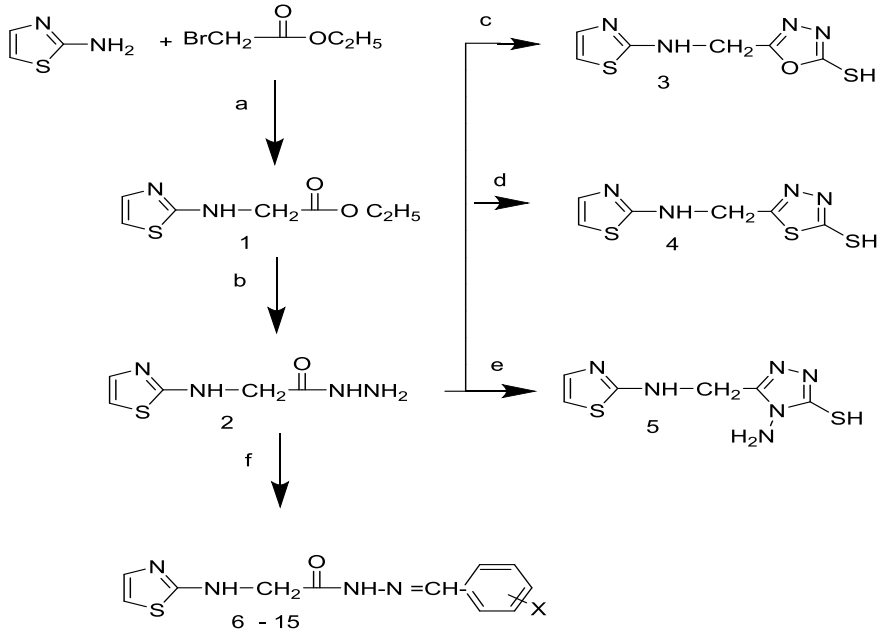
3. Results and Discussion

3.1. Chemistry

Several new 2-aminothiazole derivatives were synthesized in this study using various procedures [11-17], as shown in Schemes 1&2.

Table 1: Antimicrobial Screening Tests (CO-ADD protocols) Abbreviations, code, name, description and type of strain.

Abbrev.	Code	Name	Description	Strain
Sa	Gp_020	*Staphylococcus aureus*	MRSA	ATCC 43300
Ec	GN_001	*Escherichia coli*	FDA Control	ATCC 25922
Kp	GN_003	*Klebsiella pneumoniae*	MDR	ATCC 70060
Ab	GN_034	*Acinetobacter baumannii*	Type strain	ATCC 19606
Pa	GN_042	*Pseudomonas aeruginosa*	Type strain	ATCC 27853
Ca	FN_001	*Candida albicans*	CLSI reference	ATCC 90028
Cn	FG_002	*Cryptococcus neoformans var. grubii*	Type strain	H99; ATCC 208821



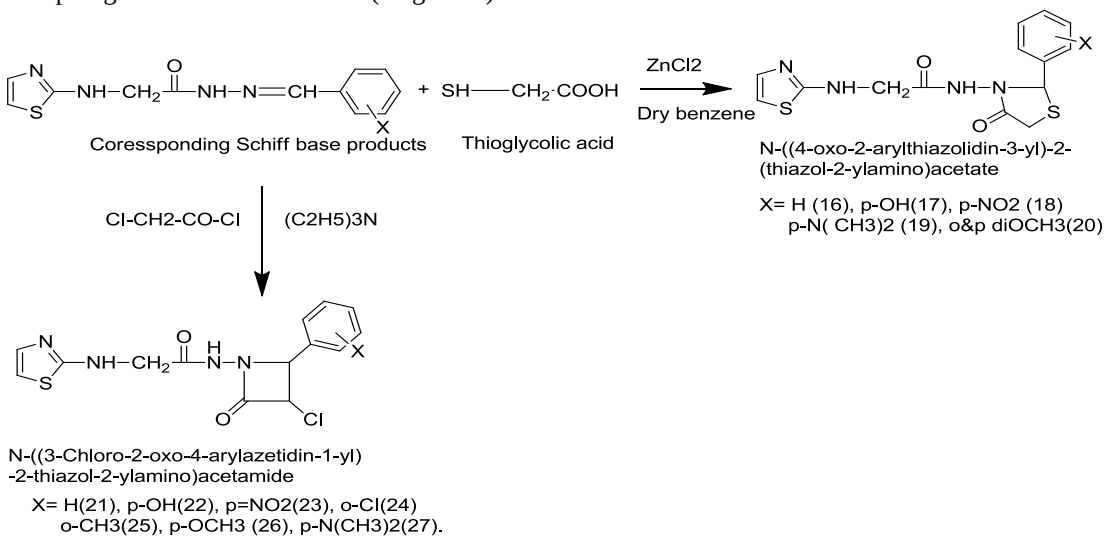
Scheme 1: The route of the synthesis oxadiazole, thiadizole and triazole -2-thiol derivatives and Schiff-bases products.

a- NaHCO3,abs. Ethanol./Reflux; b- N2H4.H2O/ Reflux; c- CS2/ KOH/ 24h Reflux
d- conc. H2SO4/ Stirring; e-N2H4.H2O/ Reflux; f-Ethanol/ Substituted benzaldehyde. Reflux.

Table 2: Predicted physicochemical parameters of the 2- aminothiazole derivatives.

X	M.F	MW	logP	H $_{Don}$	H $_{Acc}$	Routable bonds	TPSA A^2
3	$C_6H_6N_4OS_2$	214.2	1.17	1	4	3	130.88
4	$C_6H_6N_4S_3$	230.3	1.96	2	7	4	145.88
5	$C_6H_8N_6S_2$	228.3	0.3	2	3	3	148.64
6	$C_{12}H_{12}N_4OS$	260.3	1.84	2	3	6	94.62
7	$C_{12}H_{13}N_5OS$	275.3	1.29	3	3	6	120.64
8	$C_{13}H_{14}N_4OS$	290.3	1.88	2	4	7	103.85
9	$C_{12}H_{11}ClN_4OS$	294.7	2.29	2	3	6	94.62
10	$C_{12}H_{11}BrN_4OS$	339.4	2.97	2	3	6	94.62
11	$C_{12}H_{12}N_4O_2S$	276.3	1.44	3	4	6	114.85
12	$C_{13}H_{14}N_4OS$	290.3	1.88	2	4	7	103.85
13	$C_{12}H_{11}N_5O_3S$	305.3	1.24	2	5	7	144.44
14	$C_{14}H_{17}N_5OS$	303.4	1.86	2	3	7	97.86
15	$C_{14}H_{16}N_4O_3S$	320.4	1.90	2	5	8	113.08

H $_{Don}$: Hydrogen atom donor; H $_{Acc}$: Hydrogen atom acceptor; P: Partition coefficient
TPSA: Topological Polar Surface Area (Angstrom).



Scheme 2: The route of the synthesis new heterocyclic 2-thiazole-2-ylamino acetamide derivatives

Table 3: Predicted physicochemical parameters of the new heterocyclic 2- thiazole-2-ylaminoacetamide derivatives.

X	M.F	MW	logP	H $_{Don}$	H $_{Acc}$	Rotable bonds	TPSA A^2
16	$C_{14}H_{14}N_4O_2S_2$	334.4	1.61	2	3	6	127.87
17	$C_{14}H_{14}N_4O_3S_2$	350.4	1.26	3	4	6	148.10
18	$C_{14}H_{13}N_5O_4S_2$	379.4	1.00	2	5	7	173.69
19	$C_{17}H_{12}N_5OS_2$	375.5	2.47	2	2	7	114.04
20	$C_{16}H_{18}N_4O_4S_2$	394.5	1.66	2	5	8	146.33
21	$C_{14}H_{13}ClN_4O_2S$	336.8	1.68	2	3	6	102.57
22	$C_{14}H_{13}ClN_4O_3S$	352.8	1.35	3	4	5	122.80
23	$C_{14}H_{12}ClN_5O_4S$	381.8	1.15	2	5	7	148.39
24	$C_{14}H_{12}Cl_2N_4O_2S$	371.3	2.26	2	3	6	102.57
25	$C_{15}H_{15}ClN_4O_2S$	350.8	2.04	2	3	6	102.57
26	$C_{15}H_{15}ClN_4O_3S$	366.8	1.74	2	4	7	111.80
27	$C_{16}H_{18}ClN_5O_2S$	379.9	1.76	2	3	7	105.81

Table 4. The physical and IR spectra data of compounds (6-15)

Compd.	Yield %	m.p. °C	Color	IR(ν,cm^{-1}) C=N C=O(amid) NH C-S-C Ar.C=C Others
6	50	179-180	White	1637, 1666, 3311, 756, 1496
7	87	180-182	Yellow	1637, 1666, 3311,3460 , 742, 1489
8	76	176-178	White	1637,1666,3311,756,1498,
9	53	194-196	Fait yellow	1651,1681,3205,700,1502, 590(C-Cl)
10	60	169-171	Fait Yellow	1649,1666,3313,752,1496, 682(C-Br)
11	50	180-182	White Yellowish	1608,1657,3307,825,1450, 3570 (OH)
12	52	194-195	White yellowish	1637,1666,3311,770,1498, 1076 Sy(C-O-C) 1130 Asy(C-O-C)
13	87	208-209	Yellow- reddish	1603,1669,3230,744,1393, 1334Sy(C-NO_2) 1507 Asy(C-NO_2)
14	83	197-199	Yellow	1600,1630,3313,760,1440, 3100 N(CH_3)$_2$
15	60	166-167	White-yellowish	1629,1668,3298,750,1508 1049 Sy(C-O-C) 1199 Asy(C-O-C)

Table 5. The physical and IR spectra data of compounds (16-27) .

Compd. No.	Yield %	m.p. °C	Color	IR(ν,cm^{-1}) NH C=O CONH Others
16	42	173-175	White	3224 1695 1575 -
17	66	175-177	Fait brown	3398 1743 1629 3446(OH)
18	64	172-173	Yellow	3221 1697 1597 1344Sy C-NO_2 1517 Asy C-NO_2
19	61	217-218	Reddish orange	3214 1675 1601 2913 N(CH_3)$_2$
20	72	246-247	Greenish yellow	3406 1751 1604 (C-O-C) Sy 1161 (C-O-C) Asy
21	63	190-192	Yellowish-brown	3232 1695 1608 -
22	65	203-205	Yellow	3251 1683 1604 3429 (OH)
23	52	148-150	Brown	3220 1700 1597 1344Sy C-NO_2 1519Asy C-NO_2
24	70	Oily	Orange	3352 1734 1620 680 C-Cl
25	50	80-81	Pink	3335 1695 1604 -
26	45	101-103	Orange	3215 1683 1602 1068 Sy (C-O-C) 1118 Asy(C-O-C)
27	-	-	-	Fail

Table 6: Preliminary antimicrobial screening for selected synthetic compounds.

Compd No.	Sel	Act	Sa	Ec	Kp	Pa	Ab	Ca	Cn
3	2	2	**89.61 S**	-4.15	21.59	6.37	-12.88	**85.3 S**	**85.08 S**
23	0	0	28	-10.18	5.08	-0.5	-16.59	**74.54 P**	-23.84
13	0	0	29.16	-5.64	35.32	9.07	3.26	38.51	68.38

Concentration 32µg/ml. S : Sensitive ; P partial active.

Tables 2 and 3 show the predicted absorption, distribution, metabolism, and excretion (ADME) parameters of the indicated 2- aminothiazole derivatives. The Lipinski rule (R_o^5) is applied to all compounds[18]. The ^{1}H-NMR spectrum of compound 3, δ (ppm): 3.35 SH, 5.19 (CH_2), 8.25(CH=CH) thiazole ring, 7.24- 7.28 (m, 4H) Ar-H, 5.19 (s, 1H) NH.

While the physical properties and infrared data of the synthetic compounds (16-27) were listed in Table.5. The ^{1}H-NMR of the corresponding hydrazone compounds (6-15) show the following peaks δ (ppm):

3.55 (s, 1H) NH, 3.79 (m, 2H) CH_2, 8.51 (s, 1H) NHCO, 7.73-7.82 (dd, 4H) Ar-H, 7.93-8.08 (d,2H) CH=CH thiazole ring, 7.18 (s, 1H) HC=N imine. While the ^{1}H-NMR spectrum of the monolactam compound 23 gives the corresponding peaks, δ (ppm): 4.75(s, 2H) CH_2, 3.25 (m, 1H) CHCl, 8.38 (m, 1H) -NCH-Ar, 7.98- 8.04 (dd, 4H) Ar-H, 8.15-8.18 (m, 2H) CH=CH thiazole ring, 4.27(1H, s) NHCO.

3.2. Antimicrobial activity

In this study, the newly synthesized 2-amino thiazole compounds were subjected to antimicrobial activities evaluation on bacteria and fungi according to the community for antimicrobial drug discovery, Australia.

3.2.1.Antibacterial Assay [19].

Using a Tecan M1000 Pro monochromator plate reader, the inhibition of bacterial growth was evaluated by measuring absorbance at 600 nm (OD_{600}). For each well, the percentage of growth inhibition was estimated using the negative control (media only) and positive control (bacteria without inhibitors) as references on the same plate. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate. The minimum inhibitory concentration (MIC) was defined as the lowest concentration at which growth was completely inhibited, defined by an inhibition ≥80%.

3.2.2.Antifungal Assay [20].

The Growth inhibition of *C. albicans* was determined by measuring absorbance at 630 nm (OD_{630}), while the growth inhibition of *C. neoformans* was determined by measuring the difference in absorbance between 600 and 570 nm ($OD_{600–570}$), after the addition of resazurin (0.001% final concentration) and incubation at 35 °C for 2 hours. The absorbance was measured using a Biotek Multiflo Synergy HTX plate reader. In both cases, the percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (fungi without inhibitors) on the same plate. The MIC was determined as the lowest concentration at which the growth was fully inhibited.

Using the negative control (media only) and positive control (fungi without inhibitors) on the same plate, the percentage of growth inhibition was computed for each well. The minimum inhibitory concentration (MIC) was defined as the lowest concentration at which growth was completely inhibited. defined by an inhibition ≥80% for *C. albicans* and an inhibition ≥70% for *C. neoformans*. Due to a higher variance in growth and inhibition, a lower threshold was applied to the data for *C. neoformans* [20].

The molecular docking results were in good agreement with the bioassay results, the order of antimicrobial activity shows compound 3> compound 23> compound 13. In other words, the compound (3) 1,3,4 oxadiazole -2 thiol derivative has the highest antimicrobial activity.

Our aim after the synthesis is to investigate their antimicrobial activity against various types of bacteria and fungi species. The antibacterial activity order was compound 3> compound 23> compound 13 in the molecular docking data, which were in good accord with the bioassay data. In other words, the antibacterial activity of compound (3) 1,3,4 oxadiazole -2 thiol derivative is the highest. Following the synthesis, we plan to test their antibacterial efficacy against a variety of bacteria and fungi [20,21]. The antibacterial potency of these substances has been determined. The results revealed that derivatives with component (3) had high activity that outperformed the commonly used antibiotics. Table 4 lists the physical characteristics and infrared data of the compounds (6-15).

Antimicrobial activity was assayed for the selected synthetic compounds 3, 13, &23 against five types of bacteria and two types of fungal species as shown in Table 6 [22-25]. The oxadiazole derivative compound 3 showed the highest antibacterial Sa (89.61) against G(-)ve bacteria and active against two types of fungal species Ca & Cn respectively[23]. We found that the Compound (6-15) hydrazone derivatives showed non-active against bacteria or fungi. The monolactam ring of the 2-amino thiazole derivative compound 23 showed partial activity against Ca fungal species. Further studies of the 2-aminothiazole derivatives as anticancer activity [26].

4. Conclusion

The synthetic program was focused on the development of three novel 2- aminothiazole derivatives, which were identified. The compounds were evaluated for antibacterial activity against five types of bacteria and two types of fungi.

5. Conflicts of interest

There are no conflicts to declare.

6. Formatting of funding sources

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