Novel 3,5-Diaryl-4,5-dihydro-1H-pyrazole Derivatives: Synthesis, Antioxidant, Antimicrobial and Docking Study Against Glucosamine-6-phosphate Synthase

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Abstract

In our attempt to exploring a new class of antimicrobial and antioxidant agents, novel 4,5-dihydro-1H-pyrazole derivatives were synthesized and characterized by some spectroscopic methods such as FTIR, 1HNMR, and GCMS. The antioxidant property for all the synthesized derivatives against DPPH radical was examined using TLC autographic assay then the scavenging activity was determined using the spectroscopic method. The antimicrobial study against several bacterial species (gram +ve and gram –ve) as well as candida Albicans of the potent hits, which exhibited the highest scavenging activity, was determined using a good diffusion method. The docking approach was used to explain the binding affinity of the lead hit four inside the binding site of Glucosamine-6-phosphate Synthase, the target enzyme for the antimicrobial agents.

Keywords: Pyrazoline, antimicrobial, antioxidant, docking study

Introduction

Synthesis, design strategy and discovery of novel antioxidant agents represents one of the most interested filed for the research group wide world to reduce the effects of free-radical induced biomolecules damage such as lipids, proteins, enzymes and DNA in cells and tissues. On the other hand, the exploration of brand antibiotic agents has been attaching interest among scientist due to resistant of bacterial strains. During last decade, considerable attention has been given to 4,5-dihydro-1H-pyrazoles commonly known as 2-pyrazolines due to their continuous contribution in the field of development of active therapeutic targets [1]. The wide spectrum of activities exhibited by the 2-pyrazolines, like antioxidant [2], antimicrobial [3], anti-inflammatory [4], anti-tubercular [5], antitumor [6] motivated our group to explore novel 4,5-dihydro-1H-pyrazoles with divers aryl substituents. In this research, we exploring the synthesis of new 2-pyrazolines containing Schiff base moiety as novel antioxidant and antimicrobial agents. The new derivatives were characterized using IR, 1HNMR and GCMS techniques. The antioxidant activity was achieved for the synthesized derivatives against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical qualitatively using thin layer chromatographic technique, and quantitatively by spectrophotometric method. The potent antioxidant derivatives (1-4, 7) were in vitro screened against several bacterial species (gram positive and gram negative) as well as Candida albicans. Docking study of the most active discovered hit 4 was achieved to evaluate the binding affinity tawred the active site of glucosamine-6-phosphate synthase, the specific enzyme for the antimicrobial agents [7].

Materials and Methods

2. Methodology

2.1 Material

All chemicals and materials were used without further purification. Melting points were determined on electrothermal capillary apparatus and are uncorrected. IR measurements were recorded on a Shimadzu GCMS-QP2010 Ultra apparatus. 1HNMR spectra were gained with a Bruker spectrophotometer model ultra-shield at 400 MHz in DMSO-d6 solution with the TMS an internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP2010 Ultra apparatus.

2.2 Synthesis

2.2.1 Synthesis of (E)-1-(4-aminophenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (1)

This compound was prepared according to the method described in the published work [8]. To a solution of 4-aminoacetophenone (1 mmol) in absolute ethanol (10 mL), sodium hydroxide (40%, 1mL) was added and the mixture was stirred for 30 minutes. After that, corresponding aldehyde (1 mmol), was added and the reaction crude was stirred for 24 h. The reaction mixture was allowed to stand at room temperature. The precipitated product was dried and recrystallized from ethanol.

Yellow powder, yield 90%, m.p 123-125◦C; IR (cm-1): 3446, 3350 (NH2), 3076 (aromatic C-H), 2955, 2825 (aliphatic C-H), 1643 (C=O), 1600 (CH=CH), 1581 (aromatic C=C). 1H-NMR (300MHz, DMSO-d6) δ (ppm): 3.80 (s, 3H, OCH3), 3.85 (s, 3H, OCH3), 6.10 (s, 2H, NH2), 6.60-7.94 (m, 9H, 7 Ar-H, CH=CH). GCMS (NCI) m/z: 283 M+ For C17H17NO3, Rf = 0.72 (1:1, Hexane:Ethyl acetate).

2.2.2 Synthesis of 4-(5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)aniline (2)

This compound was prepared according to the modified procedure in reported reference [9]. Reaction mixture of Chalcone 1 (1 mmol) in ethanol (10 mL) and excess of hydrazine hydrate 80% (1 mL) was refluxed for 6 h. The precipitate product was recrystallized from ethanol. Orange powder, yield 42%, m.p 70-72◦C; IR (cm-1): 3323, 3288 (NH2), 3201 (NH pyrazoline), 3101 (aromatic C-H), 2931, (aliphatic C-H), 1622 (C=N),1600 (aromatic C=C). 1H-NMR (300MHz, DMSO-d6) δ (ppm): 3.80 (s, 3H, OCH3), 3.75 (s, 3H, OCH3), 2.75 (m, 1H, CH pyarazoline), 2.38 (m, 1H, CH pyarazoline), 4.65 (m, 1H, CH pyarazoline) 6.12 (s, 2H, NH2), 6.50-7.5 (m, 7H, Ar-H). GCMS (NCI) m/z: 297 M+ For C17H19N3O2, Rf = 0.25 (1:1, Hexane:Ethyl acetate).

2.2.3 Synthesis of Schiff bases (3-7)

These derivatives were obtained using modified procedure described in the reported reference [10]. To Corresponding aldehyde (1mmol) dissolved in methanol with few drops of glacial acetic acid, 2-pyrazoline (2) (1mmol) was added. The mixture was refluxed for 10 h and the reaction process was monitored by TLC using ethyl acetate:hexane system (1:1 and 3:7). The precipitate was filtered and washed with methanol, dried and recrystallized from ethanol.

4-(((4-(5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)imino)methyl)-N,N-dimethylaniline (3)

Brown powder, yield 50 %, m.p 80-82◦C; IR (cm-1):3225 (NH pyrazoline), 3060(aromatic C-H), 3000 (aliphatic C-H), 1622 (CH=N), 1611(C=N), 1522 (C=C). 1H-NMR (400MHz, DMSO-d6) δ (ppm): 3.80 (s, 3H, OCH3), 3.75 (s, 3H, OCH3), 2.75(m, 1H, CH pyarazoline), 2.38 (m, 1H, CH pyarazoline), 4.66 (m, 1H, CH pyarazoline), 6.86-7.98 (m ,11H, Ar-H), 8.5 (s ,1H, CH=N) 9.99 (s, 1H, NH pyrazoline). GCMS (NCI) m/z: 428 M+ For C26H28N4O2, Rf = 0.70 (1:1, Hexane:Ethyl acetate).

N-(4-(5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-1-(4-nitrophenyl)methanimine(4)

Orang powder, yield 77 % m.p 102-104◦C; IR (cm-1): 3200(NH pyrazoline), 3088(aromatic C-H), 2931 (aliphatic C-H), 1622 (CH=N), 1593(C=N), 1H-NMR (400MHz, DMSO-d6) δ (ppm): 3.83 (s, 3H, OCH3), 3.75 (s, 3H, OCH3), 2.75 (m, 1H, CH pyarazoline), 2.38 (m, 1H, CH pyarazoline), 4.65 (m, 1H, CH pyarazoline), , 6.86-8.5(m ,11H , Ar-H), 9 (s ,1H , CH=N), 10 (s, 1H, NH pyrazoline). GCMS (NCI) m/z: 430 M+ For C24H22N4O4, Rf = 0.70 (1:1, Hexane:Ethyl acetate).

1-(4-bromophenyl)-N-(4-(5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)methanimine(5)

Brown powder, yield 45 % m.p 94-96◦C; IR (cm-1): 3219 (NH pyrazoline), 3088(aromatic C-H), 2931 (aliphatic C-H), 1626 (CH=N), 1587(C=N), 1566(C=C). 1H-NMR (400MHz, DMSO-d6) δ (ppm): 3.83 (s, 3H, OCH3) , 3.75 (s, 3H, OCH3) , 2.75 (m, 1H, CH pyarazoline), 2.38 (m, 1H, CH pyarazoline), 4.65 (m, 1H, CH pyarazoline), 6.5-8. (m ,11H, Ar-H), 8.7 (s ,1H, CH=N) 10 (s, 1H, NH pyrazoline), GCMS (NCI) m/z: 464 M+ For C24H22N3O2Br, Rf = 0.60 (1:1, Hexane:Ethyl acetate).

1-(4-chlorophenyl)-N-(4-(5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)methanimine(6)

yellow powder, yield 40 % m.p 88-90◦C; IR (cm-1): 3200 (NH pyrazoline), 3080(aromatic C-H) , 2960 (aliphatic C-H) , 1624 (CH=N), 1593 (C=N), 1522 (C=C) 1H-NMR (400MHz, DMSO-d6) δ (ppm): 3.83 (s, 3H, OCH3) , 3.75 (s, 3H, OCH3) , 2.75 (m, 1H, CH pyarazoline), 2.38 (m, 1H, CH pyarazoline), 4.65 (m, 1H, CH pyarazoline), 6.50-8.00 (m ,11H , Ar-H) , 8.70 (s ,1H , CH=N), 10.00 (s, 1H, NH pyrazoline), GCMS (NCI) m/z: 419 M+ For C24H22N3O2Cl, Rf = 0.70 (1:1, Hexane:Ethyl acetate).

N-(4-(5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-1-(thiophen-2-yl)methanimine(7)

Orange powder, yield 70 %, m.p128-130◦C; IR (cm-1): 3217 (NH pyrazoline), 3076 (aromatic C-H) , 2935 (aliphatic C-H) , 1612 (CH=N), 1589(C=N), 1512(C=C) 1H-NMR (400MHz, DMSO-d6) δ (ppm): 3.83 (s, 3H, OCH3) , 3.75 (s, 3H, OCH3) , 2.75 (m, 1H, CH pyarazoline), 2.38 (m, 1H, CH pyarazoline), 4.65 (m, 1H, CH pyarazoline), 6.50-7.80 (m ,10H, Ar-H), 8.80 (s ,1H , CH=N) 10.00 (s,1H,NH pyrazoline), GCMS (NCI) m/z: 391 M+ For C22H21N3O2S, Rf = 0.70 (1:1, Hexane:Ethyl acetate).

2.3 Determination of scavenging activity

2.3.1 Qualitative method using Thin layer chromatography

Few milligrams of synthesized derivative (3-7) and Gallic acid (as a standard) dissolved in methanol were added to the TLC plate by extremely small capillary. After drying, TLC plates were sprayed with methanolic solution of 0.2 % DPPH. The plates were examined after 30 min of spraying under UV light. Active compounds appear as yellow or blue spots against a purple background [11].

2.3.2 Quantitative determination using spectroscopic method

At first, the tested derivatives and Gallic acid (as a standard) at concentration of 5, ,25, 50, 100 and 200 µg/mL were taken separately then added to 0.25 mL of methanolic DPPH solution (0.13 mg DPPH/mL) then the volume was complete to 1.5 mL with methanol. The reaction mixture was left to stand for 30 min in dark place. The control contained all reagents without the sample. The DPPH radical scavenging activity was determined by measuring the absorbance at 517 nm against the blank. The capability to scavenge the DPPH radical was calculated using the following equation: DPPH scavenging (%) = (A0 – A1/A0)×100, where A0 is the absorbance of the control reaction and A1 is the absorbance in the presence of the samples or standards. The results of DPPH scavenging (%) were plotted against scavenger concentration to calculate IC50 9-10.

2.4 Antimicrobial study using well diffusion method

The agar well-diffusion method was used to estimate the antimicrobial activity for the synthesized derivatives against various bacterial species Staphylococcus epidermidis, Staphylococcus aureus (gram positive), Escherichia coli, Klebsiella species (gram negative), as well as Candida albicans (yeast). These isolates were obtained from department of Biology/College of Science / Mustansiriyah University. The concentrations for each compound was 1000 µg/ml. Plates were prepared by spreading approximately 105 CFU/ml culture broth of each indicator bacterial isolates on Muller Hinton agar surface using sterile cotton swabs. The agar plates were left for about 10 min before aseptically dispensing the 50µl of each compound into the agar wells already bored in the agar plates. The plates were then incubated at 37°C for 24 h. Zones of inhibition were measured and recorded in millimeter diameter. The Dimethyl sulfoxide was used as control [12].

2.5. Docking study

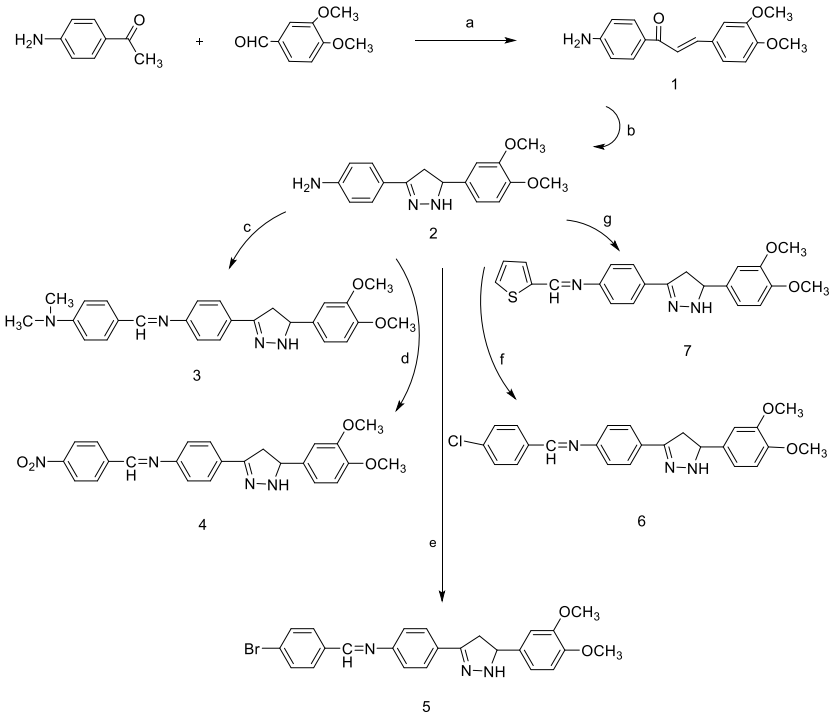
AutoDock 4.2 package software was selected to explore the binding of compound 4 inside the active site of GlcN-6-P synthase as described by the reported reference [13-14]. The pdb file format (PDB code 1MOQ) of receptor was obtained from the Protein Data Bank (RCSB) and applied as a rigid molecule. All the water molecules were eliminated then the hydrogen atoms were added to the amino acid residues. ChemDraw ultra 7.0 tool was used to constructed the mol file of the docked compound, while the open Babel 2.3.1 software was used to build the pdb file. In order to achieve the docking study, grid dimensions of 30.5, 17.5 and -2.2, were

applied. On the other hand, Lamarckian Genetic algorithm was employed with 10 runs, 150 population size, 2,500,000 maximum number of energy evaluations and 27,000 maximum number of generations.

3. Results and discussion

3.1 Organic Synthesis

Chalcone derivative (1) and the pyrazoline compound (2) were prepared and characterized as described by previous work 8. Schiff bases (3-7) were obtained from the reaction of 2-pyrazoline derivative (2) with different aromatic aldehydes in methanol using glacial acetic acid as a catalyst (Scheme 1).

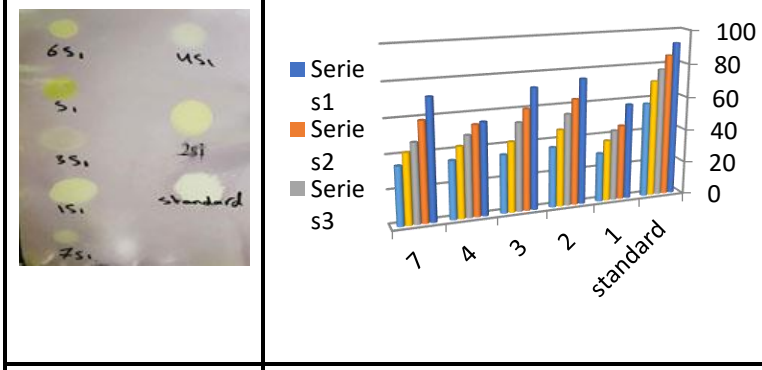


Scheme (1): Schematic representation for the synthesized derivatives: (a) NaOH, EtOH, (b) hydrazine hydrate, EtOH, (c) 4-N,N-dimethylbenzylaldehyde, AcOH, MeOH (d) p-nitrobenzaldehyde, AcOH, MeOH (e) p-bromobenzaldehyde, AcOH, MeOH (f) p-chlorobenzaldehyde, AcOH, MeOH (g) 2-thiophenecarboxaldehyde, AcOH, MeOH .

The synthesized derivatives were characterized by spectral analysis. The FT- IR spectra of compounds (3-7) showed absorption bands at 1612-1624 cm-1 and 1611-1587 cm-1 regions due to the stretching vibrations of the CH=N and C=N, respectively. The disappearance of the NH2 stretching frequencies strongly enhances the elucidation of synthesized compounds. The HNMR spectra of the synthesized compounds (3-7) showed singlet at the 8.50-9.00 ppm regions due to CH=N protons with the absent of the singlet signal at 6.12 related to NH2 group in compound 2. Mass analysis for the synthesized derivatives strongly confirming the structure elucidation.

3.2 Antioxidant scavenging activity:

Thin layer autographic assay (TLC) were used to evaluate the scavenging properties of all the synthesized derivatives (1-7) (S1,1S1, 2S1, 4S1, 3S1,7S1,6S1) against DPPH radical as shown in Figure 1(a). The synthesized compounds dissolved in methanol were distributed on TLC plate using spotting capillary. After drying and spraying the DPPH solution, the most active compounds (1-4, 7) appeared as yellow or blue spots with purple background. The scavenging activity of the lead derivatives (1-4, 7) was determined using spectroscopic method as described in the experimental section. The IC50 was calculated from the plotting of DPPH scavenging activity against different concentrations of each tested compound (5, 25, 50, 100 and 200 µg/ml) as shown in Figure 1 (b) and depicted in Table 1.



a **b**

Figure 1: (a) TLC assay for the synthesized compounds (1-7) (S1, 1S1, 2S1, 4S1, 3S1, 7S1, 6S1). (b) Comparison of DPPH scavenging assay of potent compounds (1-4, 7) against Gallic acid

Compounds	IC50 µg/ml
Gallic Acid	3
1	136
2	45
3	68
4	112
7	73

Table 1: IC50 of the synthesized derivatives

3.3 Antimicrobial activity

The in vitro assay of the synthesized compounds (1-4, 7) which exhibited the potent antioxidant activities, against different pathogenic bacteria and yeast were achieved using 1000 µg/ml concentration as illustrated by Table 2. The activity of compounds was evaluated against Staphylococcus Epidermidis, Staphylococcus aureus (gram positive bacteria), Escherichia coli , Klebsiella species (gram negative bacteria), and Candida albicans (yeast). Compound 4 revealed promising activity against the different species at applied concentration.

Table 2: In Vitro antimicrobial inhibition zone (mm) of the synthesized compounds

Compound	**Gram positive**		**Gram Negative**		**Fungi**
	Staphylococcus epidermidis	Staphylococcus aureus	Escherichia coli	Klebsiella species	Candida albicans
1	-	-	14	-	-
2	-	-	10	10	-
3	-	-	13	11	-
4	-	10	20	-	-

7	-	-	13	17	-
Amoxicillin (Control)	33	21	20	15	-

3.4 Docking study

The docking approach of the potent active 2-pyrazoline derivative 4 inside the binding pocket of glucosamine-6-phosphate synthase, the potential target for antibacterial and antifungal agents was achieved. The grid box was constructed to include all the binding residues of enzyme (Cys 300, Gly 301, Thr 302, Ser 303, Ser 347, Gln 348, Ser 349, Thr 352, Val 399, Ser 401, Ala 602 and Lys 603) as indicated by the X-ray study (Figure 2) [15].

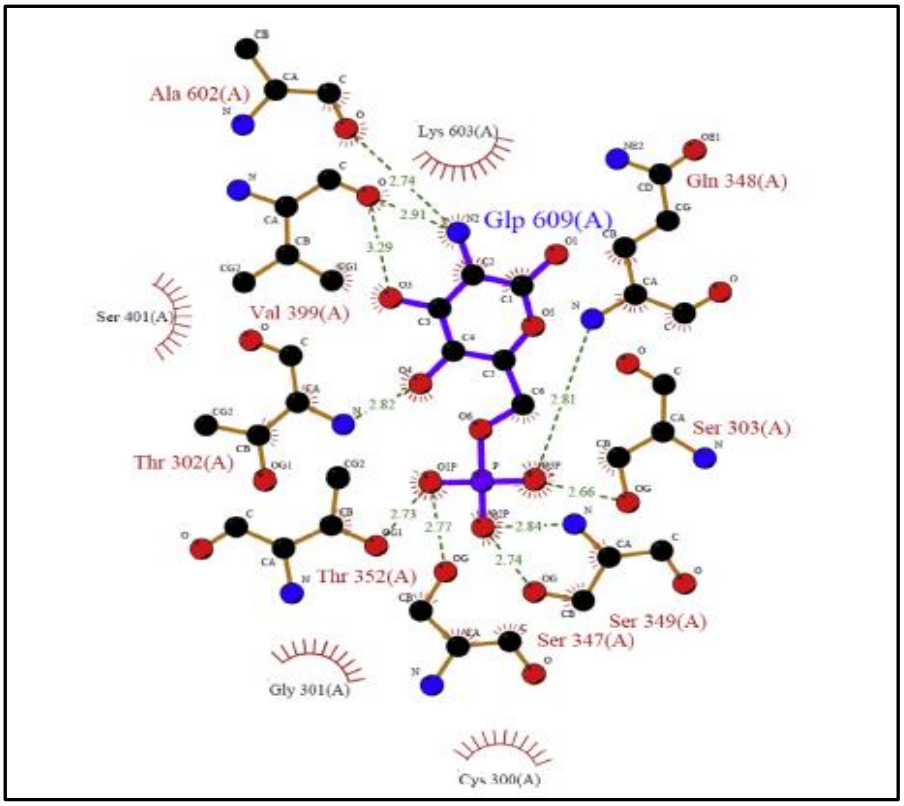


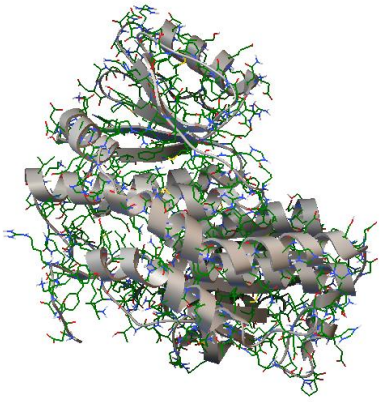
Figure 2: Ligplot of GlcN-6-P: Binding of glucosamine-6-phosphate within the active pocket of target enzyme.

The docking parameters for the ten generated conformers by the Autodock 4.2 are illustrated in Table 3. The binding energy of the best generated conformer is -8.73 Kcal mol-1 with -10.82 Kcal mol-1 intermolecular energy. The calculated inhibition constant (Ki) was 3.96x10-2 μM as determined by the docking approach. The best conformer bonds the enzyme pocket with two hydrogen bonding, the first one with SER349 while the second with the ALA602 residue as shown in Figure 3.

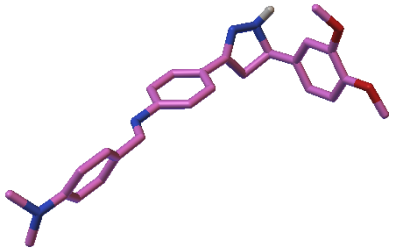
Table 3: docking parameters of 2-pyrazoline derivative 4

Compound 4	**Binding Energy (Kcal mol^{-1})**	**Inhibition constant (μM)**	**Intermolecular energy (kcalmol^{-1})**	**H-bonds**	**Bonding**
1	-8.73	3.96x10-2	-10.82	2	SER349:HN:LIG:O ALA602:HN:LIG:N

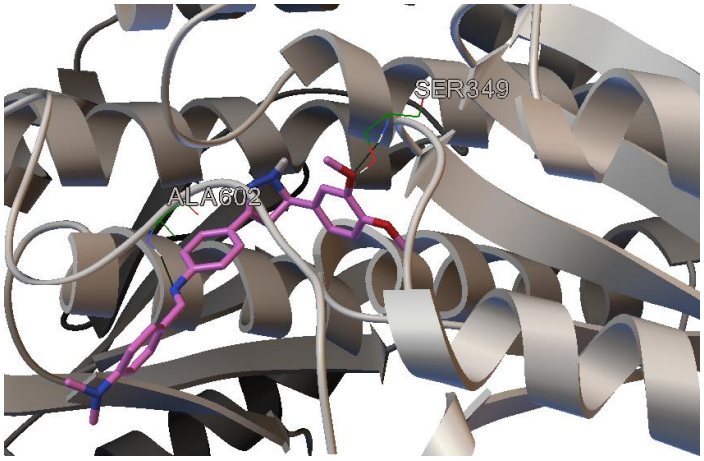
2	-8.73	3.95x10-2	-10.82	3	SER349:HN:LIG:O ALA602:HN:LIG:N THR352:HG1:LIG:O
3	-8.15	1.07	-10.23	2	ALA602:HN:LIG:N GLN348:HN:LIG:O
4	-8.12	1.12	-10.21	3	ALA602:HN:LIG:N GLN348:HN:LIG:O SER303:HG: LIG:O
5	-7.91	1.59	-10.00	2	ALA602:HN:LIG:N GLN348:HN:LIG:O
6	-7.83	1.82	-9.92	3	ALA602:HN:LIG:N GLN348:HN:LIG:O SER303:HG: LIG:O
7	-7.58	2.79	-9.67	2	GLN348:HN:LIG:O ALA602:HN:LIG:N
8	-7.46	3.43	-9.54	2	ALA602:HN:LIG:N THR352:HG1:LIG:O
9	-7.35	4.08	-9.44	2	THR352:HG1:LIG:O ALA602:HN:LIG:N
10	-6.63	13.85	-8.72	2	LIG:N:VAL399:O SER349:HN:LIG:O



3D structure of GlcN-6-P



Structure of compound 4



Best generated conformer inside the binding site of GlcN-6-P

Figure 3: Docking of the best generated conformer of compound 4 inside the binding pocket of L-Glutamine: D-fructose-6-phosphate amidotransferase (GlcN-6-P).

The docking results of generated conformers within the binding pocket strongly related to the antibacterial activities and enhancing the discovered hit (compound 4) as promising antimicrobial agents at lower concentration.

Conclusion

The present research summarized the synthesis of novel 3,5-disubstituted-4,5-dihydro-1H-pyrazoles derivatives containing imine moiety. The antioxidant activity for all the derivatives were determined by using DPPH radical. The discovered hits which exhibited promising antioxidant results were screened against several bacterial species as well as Candida Albicans to explore the antimicrobial activity of the novel derivatives. On the other hand, docking approach using Autodock 4.2 was achieved to illustrate the binding state of the potent hit inside the glucosamine-6-phosphate synthase.

Acknowledgment

The authors would like to thank, Mustansiriyah University (www.uomustansiriyah.edu.iq) Baghdad, Iraq for its support in the present work.

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