Novel 3,5- disubstituted-2-isoxazoline derivatives; synthesis, antimicrobial evaluation, and docking study

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Abstract

One of the most significant issues confronting public health from around world today is antimicrobial resistance., generated by excess of the antimicrobial activities. To counteract the significant infection induced by these probable bacteria that are resistant to current state egent, new antimicrobial pharmaceuticals are still certainly needed. This study aimed to synthesize isoxazoline derivatives as potential antibacterial agents and to examine their early structure activity correlations (SARS). The antibacterial activity of the compounds that were tested against a wide variety of bacteria and microorganisms was determined through the use of an experiment called cup-plate agar diffusion. These infections were caused by an antifungal, a gram-negative (Escherichia coli and Pseudomonas aeruginosa), a gram-positive (Staphylococcus aureus and Bacillus subtilis), and a gram-negative (Escherichia coli and Pseudomonas aeruginosa) pathogenic (Candida albicans) . All of the most compound active were docked program into glucosamine-6-phosphate synthase (GlcN-6-P), the antibacterial drug's molecular the target enzyme via the Autodock 4.2 program. The reaction of Shiffs bases of derivatives (16 and 17) with 2-mercaptoacetic acid resulted in the synthesis of two beta lactam derivatives (21,22). The imine derivatives (16, 20) reacted with furan2,5-dione to generate oxazepine derivatives (23, 24). There is evidence to suggest that the recently synthesized heterocyclic compounds will prove to be effective trying to jump points for the studies that will lead to the development of new antibacterial therapeutics.

KeyWords: Isoxazoline ; alpha-Bta unsaturated ;Beta-lactam;Oxazepin

1. Introduction

Antibiotic-resistant pathogens present one greatest of the threats to more public health (1). New scaffold antibacterial agents are required to deal with rising antimicrobial resistance issues (2-4). Several recent articles have proposed that 2-isoxazolines and derivatives 2-pyrazolines are excellent pharmacophore the scaffolds. Several recent articles have argued that 2-isoxazolines and 2-pyrazolines are superior pharmacophore scaffolds (5).

Antioxidant [6], antimicrobial [7], antitubercular [8], anticancer [9], anti-Alzheimer [10], anti-cancer [11], also anti-inflammatory [12], and anti-HIV [13], protein tyrosine phosphatase IB [14], DNA methyltransferase I [15], and Factor Xa inhibitors [16] are only a few Uridine diphosphate N-cetylglucosamine (UDP-GlcNAc) is a componet of the enzyme glucosamine-6-phosphate synthase that who know (GlcN-6-P synthase), which used as catalyzes for the synthesis of glucosamine-6-phosphate (GlcN-6-P) from fructose-6-phosphate (Fru-6-P) and glutamine as the NH_3 source [17]. Amino sugar macromolecule units, which are involved with the formation of a microorganism's cell wall, are generated during these metabolic process cascades [18]. The following amino acids create the binding pocket for the target enzyme: Cys300, Gly301, Thr302, also Ser303, Ser347, Gln348, and Ser349, Thr352, Val399, Ser401, Ala602, and Lys603. As shown in the illustration (1), With the aforementioned bioactivity in mind, we synthesized two target molecules with heterocyclic scaffolds. It is possible to obtain 3,5-disubstituted-2-isoxazolines and 1,3,5-trisubstituted-2-pyrazoles by extracting them from the proper chalcone derivatives. The enzyme GlcN-6-P synthase serves as the molecular target for antibacterial treatment[19], so a docking study was conducted out so that the binding posture could be determined. the new antimicrobial agents and to highlight their action mechanisms. These molecules were examined against four different bacteria, two of which were gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and two that were gram-negative (*Escherichia coli* and *Proteus mirabilis*) (*Escherichia coli* and *Pseudomonas aeruginosa*)

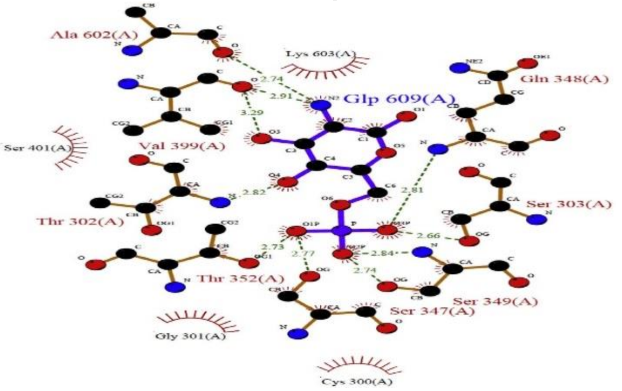

Figure (1). Binding pocket residue of the enzyme active site.[20]

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2. 2-Methods and the Material

General

We acquired all of our main components and solvents from different retailers and used them as quickly as possible. The electrothermal capillary technique was used to determine melting points, and these results have not been modified for temperature. A Shimadzu FTIR-8400S was used for the FT-IR analysis. We used a Shimadzu GCMS-QP2010 Ultra to capture the mass spectra. Substances were dissolved into deuterated solvents (DMSO-d6 or CDC solvent), and solution TMS was employed as an internal of standard for 300 MHz 'H- NMR spectra acquired with a Bruker spectrophotometer type ultra-shield. It is important to note that the signals at 3.35 and 1.56 in the 1H-NMR spectra are moisture found in the solution DMSO-d6 and CDC13, respectively, whereas the signals at 2.5 ppm and 7.26 ppm are for the solvents DMSO-d6 and CDC13.

Cemistry

Synthesis of Aryl Furfural (1-5).

The procedure for producing these chemicals is given in reference [16]. A solution of strong HCl (33.7 mL) and H2O was used to dissolve 4-substituted aniline (0.136 mol) (22.5 mL). the compound Furan-2-carboxaldehyde (15.4 g, 0.16 mol) dissolved in H_2O (50 mL) and CuCl .2H2O (5 g, 0.04 mol) in H2O (25 mL) were added, and that mixture was still stirred for 10 further minutes before being filtered. The reaction was carried out between 10 and 15 ° C The reaction after mixture was heated to 40 ° C over the course of four hours while being continuously stirred. After that the precipitate was filtered through a suction and then washed in H_2O and a 5% sodium hydrogen carbonate solution. Products were air dried at room temperature and re-crystallized from solvent ethanol.

Synthesis of 5-(4-Nitrophenyl) furan-2-carboxaldehyde (1).

orange powder colour , yield 70 %, mp. 202-205 ^{0}C; IR (KBr, cm1): C-H aromatics (3119), C-H aldehydes (2845), also C-O (1685), C-O (1602), and C=C (1519) are all included. ^{1}H-NMR (300 MHz, DMSO-d6) d (ppm) 7.57 (1H, d, H furan, j = 3.75 Hz), 7.70 (1H, d, H furan, j = 8.80 Hz), 8.33 (2H, d, H aromatic, j = 3.75 Hz), 8.12 (2H, d, H 8.80 Hz), 9.67 (s, 1H, H aldehyde). C11H7NO4 (GCMS/NCI m/z): 149 M+, R_f = 0.43 (1:1, Hexane :Ethyl acetate).

Synthesis of the chalcones derivative .

Using a previously described method with certain modification, these compounds were synthesized[21]. After allowing the mixture sit for 30 minutes, 1 mL of sodium hydroxide (40%) was added completely to a solution of acetophenone derivatives (1 mmol) in solvent of ethanol absolute (10 ml). After the reaction was mixture then mixed overnight after furfural derivatives (1 mmol) were added to it. After the elements for the reaction were combined, they were left to sit at room temperature. Ethanol was used to wash the precipitate, and then it was dried and also recrystallized.

Synthesis of (E)-1-(4-aminophenyl)-3-(5-(4-Nitrophenyl) furan-2-yl) prop-2-en-1-one(2) .

Black powder colour , yield was 75%, M.P = 163 - 165 °C its IR (cm-^{1}) spectrum includes the following rows: 3200 (OH) , 3101 for (aromatic C-H), 2820 (aliphatic C-H), also 1635 for (C=O), and 1602 for (CH=CH), 1585 (C-C). ^{1}H-NMR (300 MHz, DMSO-d6) d (ppm) 6.88 (m, 2H,Ar-H), 7.11-7.17 (m, 1Ar-H), 7.52-8.02 (m,6H, 4Ar-H, CH-CH), also 10.47 (s, 1H, OH). NCI m/z 217 $C_{19}H_{14}N_2O_4$, R_f = 0.25 (1:1, Hexane :Ethyl acetate).

Synthesis of 3,5-disubstituted isoxazoline .

The modified methodology described in reference[17] was used to produce these dreivatives. To a solution of chalcone derivatives (l) (1 mmol) in ethanol, 1.5 mmol of hydroxylamine hydrochloride dissolved in 1 mL of 40% NaOH aqueous solution was added while the reaction was stirring (10 mL). When the reaction mixture achieved 80 ℃, it was evaluated using TLC with asolvents ethyl acetate to hexane (1:1) as eluent. The reaction mixture was quenched with ice H_2O after it was complete, and the precipitate was filtered out, and washed with water, also dried in an oven, and finally recrystallized from solvent ethanol.

Synthesis of 4-(5-(5-(4-Nitrophenyl)furan-2-yl)-4,5-dihydroxazol-3-yl)aniline (11) (3).

Dark red colour and powder, yield 49%, M.P= 100-103°C, standard procedures 1600 for the (C-N), also 1558 for (C-C), 3331 (NH2), 3050 (aromatic C-H) (cm). ^{1}H-NMR ($CDC1_3$, 300 MHz) (ppm): 3.36-3.49 for the (m, 1H, Ha-isoxazoline); also 3.65-3.80 for the (m, 1H, Hb-isoxazoline); 3.96 (s. 2H, NH2); 5.82-5.95 (m, 1H, Hx-isoxazoline); 6.55-7.63 (m, 1H, Hx-isoxazoline (m, 7H, Ar CroHsN;O m/z = 233 M^{+} at the GCMS (NCI), R_f=0.23 (11 Hexane :Ethyl acetate).

Synthesis of Shiff's base (4)

After mixed (1.5 mmol) N.N dimethyl benzaldehyde with 10 ml of 1,4-dioxane and stirring for 15 minutes at the room temperature, and added two drops of concentrated H_2SO_4 to the mixture. After When the (1.5 mmol) chemical was added, the mixture was stirred for two hours. TLC with n-hexane and ethyl acetate as eluents was used to evaluate the reaction's intermediates (6:1). The revised technique described in reference [18] involves filtration and washing the solid dry result with distilled water and diethyl ether.

Synthesis of (E)-N,N-dimethyl-4-(((4-(5-(5-(4-nitrophenyl)furan-2-yl)-4,5-dihydroisoxazol-3-yl)phenyl)imino)methyl)aniline (4).

Brown colour and powder, yield 50%, m.p 132-

134 ^{0}C; IR (cm-1) values: 3059 for the (aromatic C-H), also 3001 for the (aliphatic C-H), 1626 (CH-N), 1610 (C-N), and 1521 for the (C-C). ^{1}H-NMR (CDC1$_3$, 300 MHz) (ppm) 5.71 for (s, 2H, NH2), also 3.90 for (s, 2H, NH2), 3.32-3.41 for (dd, j = 8.9, 16.5 Hz, 1H, CH-isoxazoline), 3.72-3.81 for (dd, j = 10.7, 16.4 Hz, 1H, CH-Isoxazoline compound), and 5.90 (s, 2H, NH2) (m, 1H, CH-Isoxazoline compound) 8.48 (nm, 13C, benzyl) 5.71 (m, 1H, CH-Isoxazoline) 6.85-7.93 (m, 11H, Ar-H) (s, 1H,CH-N). C28H24N4O4 (m/z) GCMS (NCI) = 373.0, R$_f$ = 0.7 (1:1, Hexane :Ethyl acetate).

Synthesis of Beta lactam derivative .

In order to synthesis these products, we used the procedure described in reference [19]. Add Schiff base (16,18) (0.0009 mol) and triethylamine to DMF (10) mL. (3 drops) After the mixture was stirred for 30 minutes at room temperature and after drops of chloroacetyl chloride (0.0018 mol) were added drop by drop. In order to keep a watch on the reaction of the mixture while it was being heated under the refluxing for 8 hours, TLC was utilized. Immediately following the completion of the reaction, refrigerate the item for a full 24 hours in ice cold H$_2$O. finally The precipitate was filtered off, also washed with water, and air-dried, then recrystallized from solvent ethyl acetate.

Synthesis of 2-(4-(dimethylamino) phenyl)-1-(4-(3-(3-(4-nitrophenyl)furan-2-yl)-4,5-dihydroisoxazol-3-ylphenyDazetidin-3-one (5) .

Brown colour and powder, yield 50%, m.p 270-273 ^{0}C; C-H (at 3061 nm), C-H (at 2955 nm), C-O (1703 nm), C-O (1595 nm), C-C (1564 nm), and the 1504-1340 nm band in the infrared (5 cm-1) (N-0) IH-NMR (300MHz, DMSO-d6) (300MHz, DMSO-d6) 1.21(d, 1H, CH-CI), 4.46(d, 1H, CH-N), 7.57-7.98(m, SH, Ar-H. GCMS (NCI) m/z: 480 M$^+$ for the CH$_2$N$_4$OS, R$_f$= 0.25 (1:1, Hexane: Ethyl acetate).

2.2.4 - Synthesis Oxazepine derivative

To a solution of (2 mmol) acceptable anhydride compound in (10 mL) benzene, (0.365 g, Immol) compound was added, then that mixture was heated at a reflux for 10 hours . The yield of the reaction was measured by thin-layer chromatography (TLC) with dichloromethane and methanol (2% each) as eluents. Once the solid is isolated, it is dried with benzene and finally crystallized from chloroform once more[20].

Synthesis of 2-(4-(dimethylamino)phenyl)-3-(4-(5-(5-(4-nitrophenyl)furan-2-yl)-4,5-dihydroisoxazol-3-yl)phenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione (6) .

Gray colour and powder, yield 73 %, and M.P= 254-256 °C; IR (at 5 cm^{-1}): 3088 for the (aromatic C-H), also 2937 for (aliphatic C-H), 2893 for (aliphatic C-O), 1604 (C-N), and 1516 (aromatic C=C). ^{1}H-NMR (300 MHz, DMSO-d6) 8 (ppm): 6.33-6.45 for (m, 2H, Ar-H, CH-Oxazepane); 6.57-6.98 (m, 2H, Ar-H, CHb-Oxazepane); 7.11-7.53 (m, 8H, Ar-H, CH-Oxazepane); finally 7.60-7.84 for (m, 3H, Ar-H). For $C_{32}H_{26}N_4O_7$, the molar masses are 374, 264, and 110 M-, with a relative refractive index of 0.84. (1:2.5, Hexane: Ethyl acetate).

Antimicrobial Activities

The microbiological activity of the synthesized isoxazoline derivatives was evaluated against *Escherichia coli*. Using the well diffusion methodology, we were able to recognize between *Pseudomonas aeruginosa* (gram-negative), *Staphylococcus aureus*, *Streptococcus SPP* (gram-positive), and *Candida albicans* (Table 1) [21]. Amoxicillin was employed as a reference medication, and DMSO as a solvent was applied as a control in good diffusion tests. The tests were run at a concentration of 2 mg/ml in DMSO solvent. The concentrations of 10 and 100 mg/mL were used, and the average of three measurements was obtained for each experiment. The average of three values for each experiment was recorded [22].

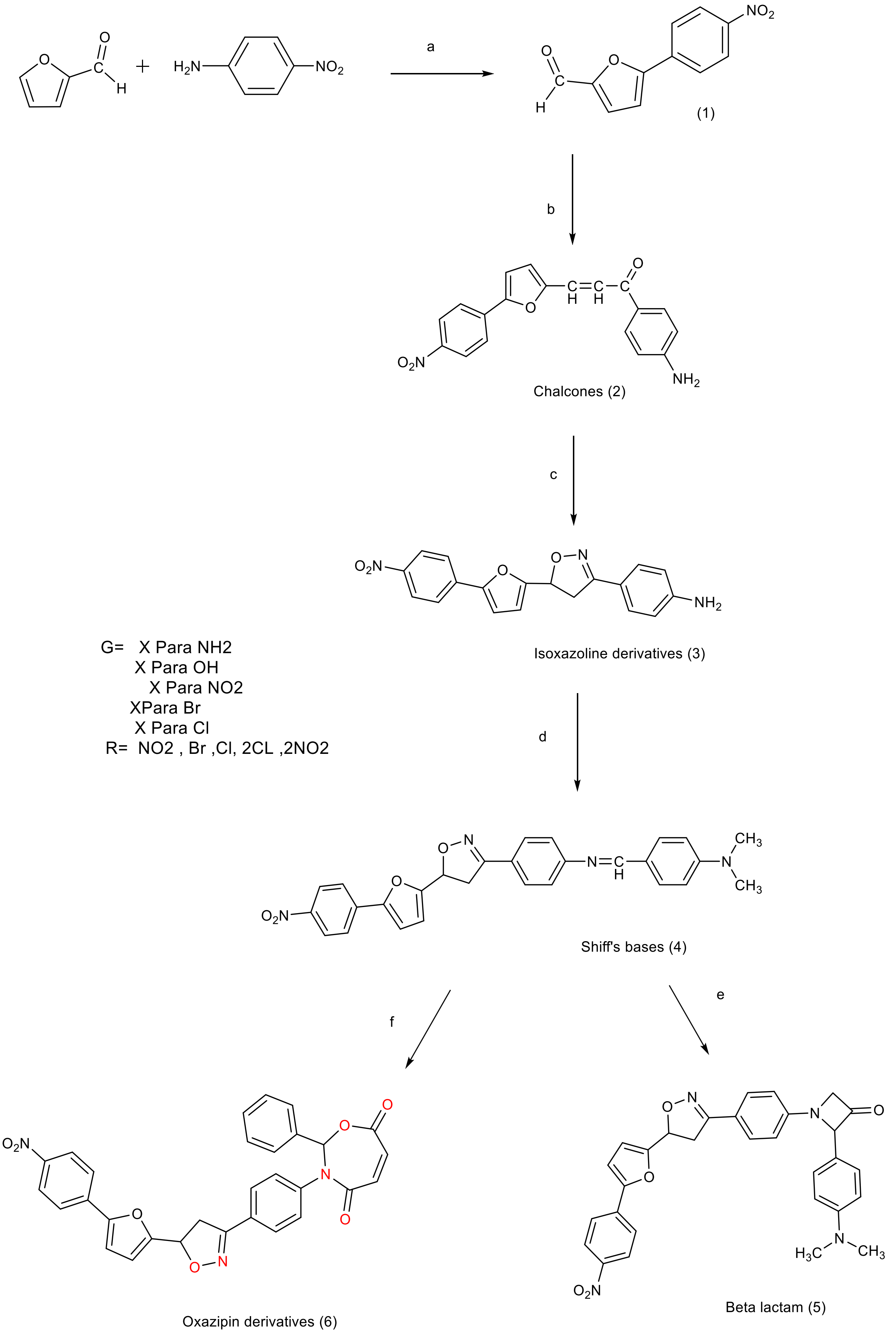
Docking Study

Researcher applied the AutoDock 42 package program to investigating into the reported affinity of the substrate isoxazoline derivatives for the binding pocket that known as GlcN-6-P synthase. The enzyme's pdb file (PDB code: IMOQ) was acquired from the Bank of Protein Data and employed in a fixed-model simulation. Then As a result of the elimination of water molecules, the protein residues have been modified by the addition of hydrogen atoms[23. After generating two-dimensional structures of the test findings in ChemDraw ultra 7.0, the data was converted to a mol format file with the help of the free program Babel 2.3.1. The enzyme catalytic site was positioned in the middle of a 62 A grid with X=30.5, Y=17.5, and Z=-2.2, with a 0.358 A spacing between grid points. The Lamarckian genetics algorithm was being used, and the standard settings of ten cycles and 150 population sizes were used. The docking analysis was conducted with grid sizes of 30, 17, and -2.2 cells. We used a docking technique based on Lamarckian genetics, with parameters including 10 iterations, 150-person populations, a maximum of the number 2,500,000 energy evaluations, also the number 27,000 generations. By default, there could be no more than 27103 generations and no more than 2.5105 energy classes[24].

3. Disscussion and the Result

Organic synthesis

The chalcone derivative (2) also the isoxazoline compound (3) were synthesized and characterized as described in previous projects 8. Schiff bases compound (4) were synthesized by reacting isoxazoline derivative (3) with



various aromatic aldehydes in methanol with glacial acetic acid as a catalyst. Scheme (2) .

Scheme 2: Schematic representation for the synthesized derivatives:(a) NaNO2,HCL,CuC12, C (b)NaOH, Xpara benzaldehyde (e)Hydroxyl amine hydrochloride NaOH 40% (d) N,N-dimethylbenzylaldehyde, AcOH, MeOH (e) 2-Mercaptoacetic acid, 1,4- dioxan (f)furan-2,4-dione, Benzen.

The synthetic derivatives were characterized using spectral analysis. Absorption bands were seen in the spectra of FT-IR compounds (1-6) at 1612-1624 cm-1 and 1611-1587 cm^{-1}, corresponding to the stretching vibrations of the CH-N and C-N. Incorporating NH2 stretching frequencies greatly enhances our comprehension of the produced compounds. The singlet signal from CH-N protons was observed around 8.50-9.00 ppm in the HNMR spectra of the generated compounds (1-24), while the NH2-group in compound 2 produced a singlet at 6.12 ppm. The structure is confirmed by a mass analysis of the derived products.

3.2 Antimicrobial Study

We evaluated the synthesized compounds (1-6) for their antimicrobial activities against a diverse range of organisms, including two bacteria of gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) also two bacteria of gram-positive (*Escherichia coli* and *Pseudomonas*) and *Candida albicans* , The compounds were evaluated in solvent of DMSO at two concentrations (10 and 100 mg/ml) as part of the in vitro technique that involved diffusion[25]. Commonly, antibiotics like amoxicillin would be prescribed.

Table 1: shows how the prepared compounds inhibit a selection of microbial species

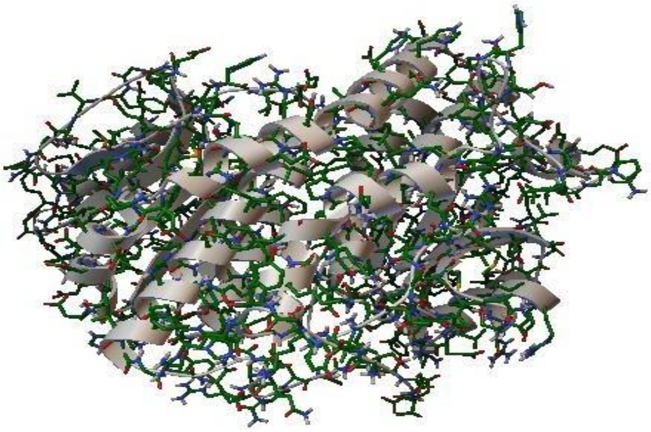
	Inhabition Zone (mm) on 10 or 100* mg\ml				
Compound	Gram negative		Gram Posative		Fungie
	E.colie	P.areuginasa	S.aureus	B.subitilis	C.albicacans
1	-	-	12	11	12
2	11	11	12	-	-
3	-	12	12	10	11
4	-	-	12	11	12
5	11	20(11)*	21(17)*	12	20(11)*
6	-	-	13	12	17
Amoxicilin	17	12	16	17	21

(-): no inhibition; sources: B. subtilis (nonclinical: food), C. Albicans (clinical: vaginal inhibition zone (mm) at 10 mg/mL test drug concentration), E. coli (clinical: urinary tract infection), P. aeruginosa (clinical: burn infection), S. aureus (clinical: skin infection).

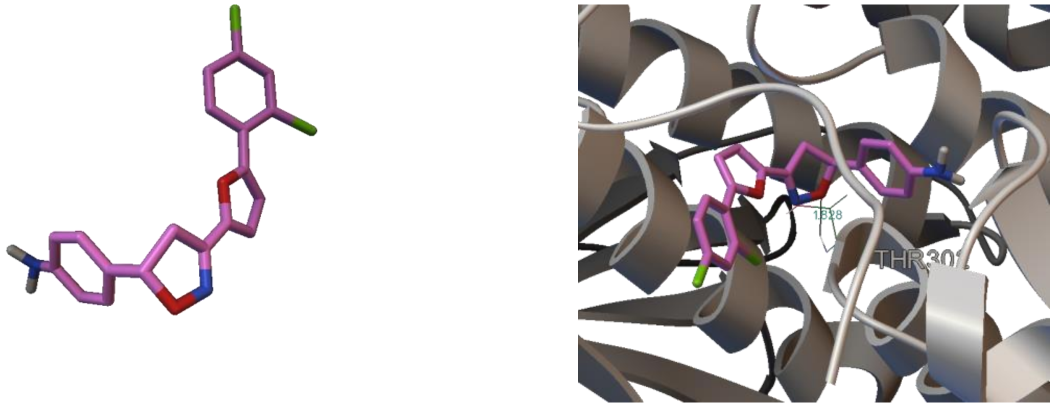
The antimicrobial properties of compound 5 were demonstrated against both gram-becteria negative and also gram bacteria-positive , as well as against the fungal *Candida albicans*. To the contrary, compound 5 was very active even at relatively low doses (10 mg/ml) (entries 3, 4 and 5, Table 1). Compound 5 when used at a high proportion (100 mg/mL), was more effective than the standard treatment medicine (amoxicillin), which is commonly used to treat various microbial infection. Interesting, we found that some chemicals are selective against given species. Compound 1 showed selectivity against bacteria gram-negative and fungies, while the compounds 2 and compound 3 showed solely fungal selectivity (entries 1, 2, 3, and 4, table 1). Compound 3 was shown to be selective against bacteria gram-positive , while compound 2 was found to be selective against bacteria gram-negative (entries 2 and 3, Table 1). Compound 5 was also said to have selective activity against E. coli (entry 4, Table 1).

3.3- Docking study

Among the many methodologies used to calculate the affinity of a minor compound's binding to bindind protein pocket with 3D structure is docking. The binding affinity of the refer derivative (5) inside of the binding site of synthase glucosamine-6-phosphate , the specific target of antibacterial and antifungal therapeutics, was measured by docking analysis. One technique employed for docking was the Lamarckian Genetic Algorithm that known as (LGA) [26]. The X-ray structure of the enzyme shows that residues of Cys300, Gly301, Thr302, Ser303, Ser347, also Gln348/49, Thr352/49, Val399, then Ser401, Ala602/603, and Lys603 all compensate its binding pocket. The molecular docking parameters[27] show that substance 5 has a binding energy of 7.89 kcal mol-1 within the target enzyme, with a corresponding intermolecular energy of -9.68 kcal^{-}1. We determined that the inhibition constant was 1.65 micro molar. As shown in Table 2, the appropriately produced conformer forms five hydrogen bonds with the target enzyme. In addition, Compound 5 highest-scoring produced conformer has an intermolecular energy of 10.72 kcal mol1 when linked to the binding site. Table 2 shows the results of our calculations for the inhibition constant Ki and hydrogen bonds for each of the produced conformers.

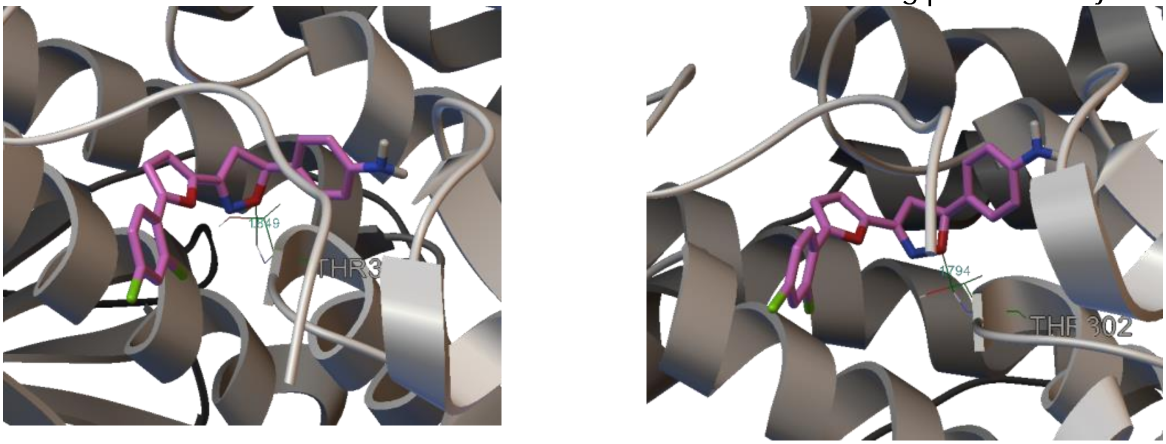


3D structure of (GLcN-6_P) that known glucosamine-6-phosphate synthase



Structure of compound 5

The first generated conformer of compound 5 inside the bending pocket of enzyme



The second generated conformer of 5 compound that inside the bending pocket of enzyme

The third generated conformer of 5 compound that inside the bending pocket of enzyme

Figure 3: The docking program of the best-generated conformes of the potenet discovered hits (5) that Inside of the binding pocket of glucosamine-6-phosphate synthase (GLcN-6-P).

Table 2 : Docking parameters of compound (1-6) compounds

Conformers	Binding Energy (Kcal mol^{-1})	Inhibition constant (,uM)	Intermole cular energy (Kcalmo^{-1})	H-bonds	Bonding
1	- 9.78	0.503	-8.59	1	THR302:HN:LIG:N,O
2	- 9.33	1.090	-8.13	2	SER401:HN:LIG:N SER401:HG:LIG:O
3	-8.93	0.284	- 10.72	1	LIG: N:GLU:488:OE2
4	-8.57	0.524	- 10.36	1	LIG: N:GLU:488:OE2
5	-8.56	0.532	- 10.35	1	LIG: N:GLU:488:OE2
6	-7.31	4.38	- 9.10	-	-

4. Conclusion

Spectral analysis was used in the synthesis and characterization of new antimicrobial agents, such as isoxazoline and pyrazoline derivatives. In the first scheme, we see how the new chalcone derivatives served as progenitors to the appropriate heterocyclic derivatives. Multiple microbiological species, including *bacteria Escherichia coli*, *Pseudomonas aeruginosa*, also bacteria *Staphylococcus aureus*, *Bacillus subtilis*, and *Candida albicans*, were used to the test of antimicrobial properties of the synthetic derivatives. When compared to amoxicillin, the potential activity of the compound (5) showed great promise. Autodock was used as a docking method to investigate the orientations of the lead derivatives within the GlcN-6-P synthase binding pocket and characterize the affinities of the potent hits (5).

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