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Synthesis, Characterization and Biological Activity of heterocyclic compounds derived from Amoxcilline drug.

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Abstract

A first step in this research was to synthesize Schiff's bases(1-3)using an Amoxcilline intensification reaction with different aromatic aldehydes in absolute ethanol. In benzene and refluxing conditions,Schiff's bases were cyclized with succinic and Phthalic anhydride to give a new sequence of 1,3-oxazepine derivatives(4-6) and (7-9),respectively.The last step,cyclization reactions with sodium azide in THF solvent resulted in the formation of [10 and 11], which are supposed to be biologically significant.FT.IR, ^{1}H-NMR and ^{13}C-NMR (for compound 4,7,9, and 11),as well as melting points reported, were used to characterize these prepared compounds ,*Bacillus* (G+), *Staphylococcus* (G+), and *E.Coli* (G-)were screened against these compounds. .

To illustrate the affinity of the potent hit and the enzyme binding pocket, a docking analysis was performed using autodock pakage of compound 7 within the active location for enzyme to be targeted for antimicrobial agents L.glutamine.D.Fructose.6.phosphate amidotransferase/ glucosamine-6-phosphate synthase.

Keywords: Heterocyclic compounds; Schiff's base; Amoxcilline; 1,3-oxazepine, Tetrazole.

Introduction

The most popular heterocyclices are those that contain nitrogen, oxygen, and sulfur that act as a main component of a big number of biochemical material necessary for life, such as nucleic acids. The antibiotic amoxicillin is a semi-prepared antibiotic,acid-stable that belongs to the Penicillin family of antibiotics (lactam antibiotics). It has been shown to be effective in humans and animals versus a wide range of different kinds of bacterial infections.[2-5]. It is a congener of ampicillin (a semi-synthetic aminopenicillin) that differs only in the hydroxylation of the phenyl side chain from the parent drug [6,7].Amoxicillin is (2S,5R,6R)-6-[[(2R)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino] carboxylic acid-3,3-dimethyl-7-oxo-4-thia-1-aza-bicycyclo[3.2.0]heptanes-2 (Fig.1).It appears in some pharmacopoeias.The pharmacopoeias of the United States, the United Kingdom, and India all have an amoxicillin monograph. It's in a lot of pharmacopoeias.The monograph for amoxicillin can be found in the pharmacopoeias of the United States,the United Kingdom, and India.[8-10]

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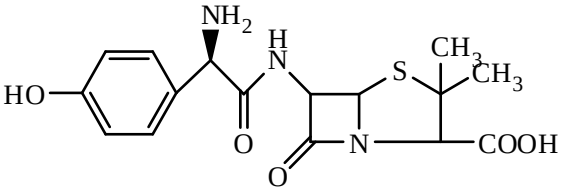


Figure 1 portrays Amoxicillin's chemical structure.

Protein–ligand docking represent one of the molecular modelling approach used to bind an organic molecule inside the binding site of target enzyme to estimate the intermolecular interactions in the active pocket which provide the biological activity[11]. The binding affinity of potent hit (compound 7) inside the active location of L.glutamine.D.Fructose.6.phosphate amidotransferase was investigated using the Autodock program.

Experimental

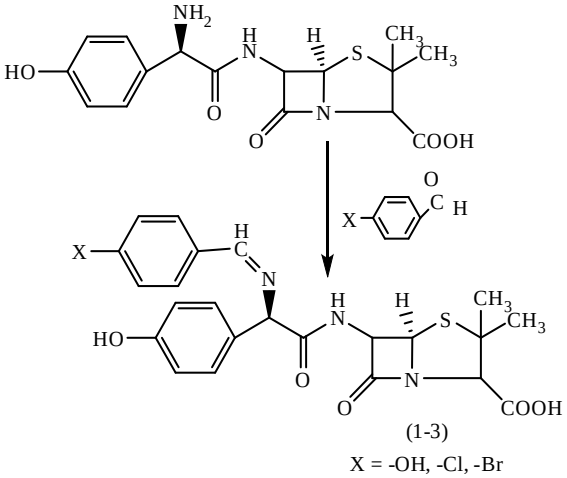
Instruments

1-Melting points are determined using an uncorrected Gallen electric melting point apparatus.
2- A spectrophotometer SHIMADZU 8300, FT.IR spectra were recorded in the range (4000-400) cm^{-1},using KBr discs measurements were made at Ibn Sina company(Baghdad –Iraq).

3- The ^{1}H.NMR and ^{13}C.NMR spectra were measured at Kashan University in Iran using a fourier transformation bruker spectrometer operating at (400MHz) with (DMSO-d^{6}).
4- The prepared compounds' biological activity was investigated in BPC Analysis Center.

preparation Schiff's bases (1-3) [12, 13]

In ethanol,a solution of substituted benzaldehydes(1.1 mmol) was combined with amoxicillin trihydrate (0.419 g,1.0 mmol) (10 mL).After magnetically mixing the solution, it was refluxed for 6 hours at boiling temperature. In cold water,the obtained brownish red solution was poured (100 mL).Before being dried in the air for two hours, the solid was filtered and washed several times with water.



Equ-1: Synthesis of Schiff's bases

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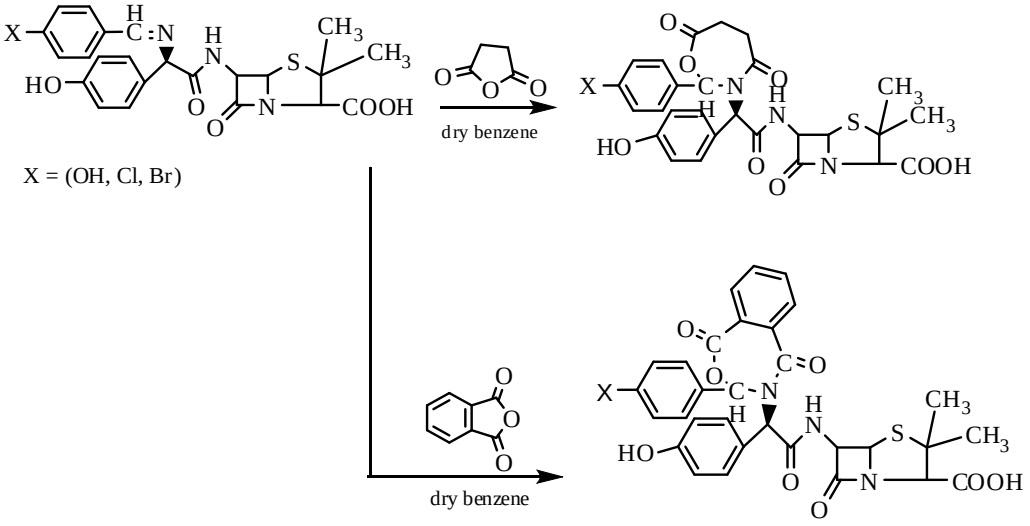
Preparation substituted 1,3-Oxazepine-4,7-dione (4-9)[14]

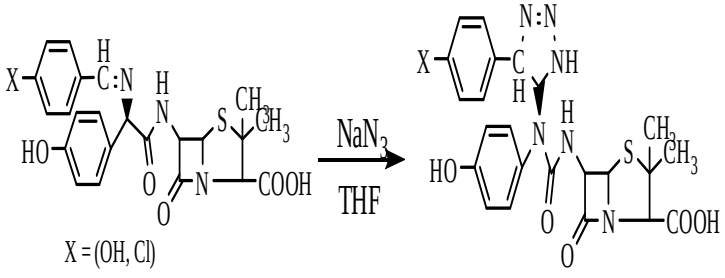
In 20 mL of dry benzene, a mixture of Schiff base (1-3) (0.01 mol) and (0.01 mol) maleic and phthaleic anhydride was refluxed along one a day, the solvent evaporated, and the precipitate was recrystallized from suitable solvents.



Scheme-1: Synthesis of 1,3-oxazepine-4,7-dione

Preparation of the derivatives (10,11)[15,16]

To Schiff's bases (1-3), (0.01 mol.) dissolved in (15 mL) tetrahydrofuran, was added drop wise of (0.01 mol) 2-mercptoacetic acid.Under reflux for 11-12 hours, the mixture was stirred.Thin layer Chromatography was used to confirm the reaction's completion, and it revealed that the starting material had vanished. The solvent was then cooled after being evaporated down to a small amount., and then the obtained reaction mixture was washed with 20% sodium bicarbonate solution to remove non-reacted acid. Solution was filtered to collect solid. The solid thus obtained was recrystallized using dioxane solvent and dried. Physical properties shown in table (1).



Equ-2: Synthesis of Tetrazole

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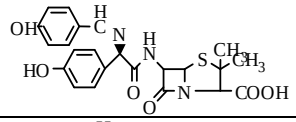
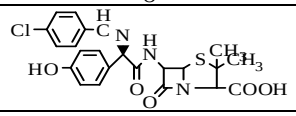
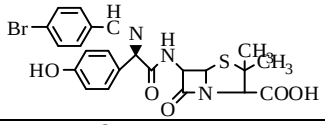
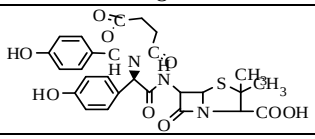
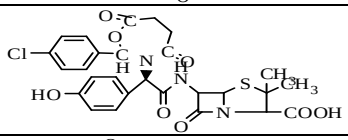
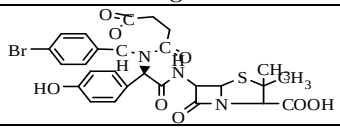
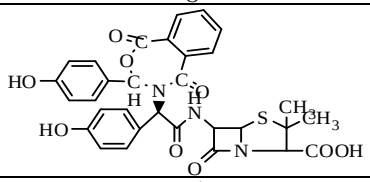
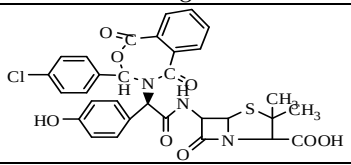
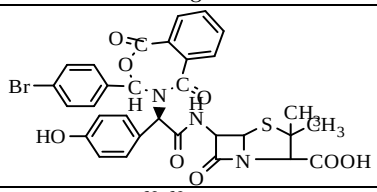
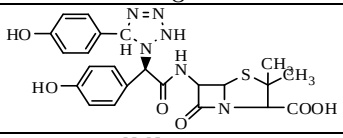
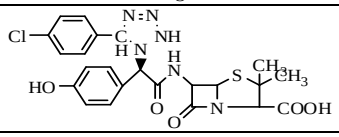
Table - 1 – The physical properties of the substances that have been prepared

No. of the comp.	Compound Structure	Formula	M.wt. gm / mol	M.P. ^{0}C	Color	Yield %
1		$C_{23}H_{23}O_6N_3S$	569	166-169	Orange	80
2		$C_{23}H_{22}O_5N_3SCl$	487	187-190	Yellow	79
3		$C_{23}H_{22}O_5N_3SBr$	532	195-198	Orange	82
4		$C_{27}H_{27}O_9N_3S$	569	140-143	Yellow	75
5		$C_{27}H_{26}O_8N_3SCl$	588	150-153	Light Yellow	70
6		$C_{27}H_{26}O_8N_3SBr$	632	183-186	Deep Yellow	73
7		$C_{31}H_{27}O_9N_3S$	617	203-206	Yellow	75
8		$C_{31}H_{26}O_8N_3SCl$	636	210-213	Light Yellow	70
9		$C_{31}H_{26}O_8N_3SBr$	680	230-233	Deep Yellow	72
10		$C_{23}H_{24}O_6N_6S$	512	-------	Gamy	69
11		$C_{23}H_{23}O_5N_6SCl$	530	-------	Gamy	70

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Docking study

The intermolecular interactions of the potent derivatives7 with L.glutamine D.fructose.6.phosphate synthase connect location were investigated using the AutoDock 4.2 kit.The Protein Data Bank's PDB file (PDB code 1MOQ) was used as a fixed structure for the target enzyme.The ligand was removed from the protein residues, hydrogen atoms were added, and water molecules were removed.The two-dimensional structure of the tested hit was built using ChemDraw ultra 7.0 software. The free Babel 2.3.1 program was then used to convert the file to a mol formatted file.The numbers 30.5, 17.5, and 2.2 were allocated to the 62 grids in three axcis respectively, during the docking process,and dots isolated by 0.358 were created in the center of the enzyme's catalytic site.The docking study went well.[17]

Results and Discussion

In recent years, heterocyclic compounds have become of great importance because of their excellent properties in life,and medical treatment.[(18)]Substituted aromatic Schiff's bases(1-3) are obtained by reacting amoxcilline with various aromatic aldehyde[(19,20)], which were thereafter cyclized with succinic and phthaleic anhydride in dry benzene solvent to yield derivatives of Oxazepine (4-9).[(21)]

One water molecule is taken away and a nucleophilic addition to the carbonyl group occurs are needed for forming Schiff's base.[(22)]The imine group(N=CH-) identifies Schiff's bases,which is an essential compounds due to its stability and structural diversity.Absence for the primary amine's (N-H) stretching band at(3316.2asym.and 3286.7 sym.)and formation of the imino group (HC=N) is particular by the presence of a stretching band in the FT-IR spectra of Schiff's bases at (1640-1600.09) cm^{-1}[(23)] figs2 and3.Imines have been used to prepare nitrogen-containing heterocyclics effectively for many years and they are expected to play an increasingly important role in the future[(24)].

Compounds (4-9) were produced by reacting Schiff base compounds (1-3) with Succinic anhydride and phthalic anhydride in dry benzene as a solvent.These compounds were investigated and characterized using melting points,FT-IR,^{1}H-NMR spectra for compounds (4,7,and 9),^{13}C-NMR spectrum for compound(4).

The absence of the (-N=CH-)group and the presence of a new band at (1689.64-1670.35 cm^{-1}) relative to the lactone group were revealed in the FT-IR spectra of these compounds. (1616.35-1593 cm^{-1}) relative to the lactum group, and (CHAr.) at (2978.09-2931 cm^{-1}) and (2900-2865.51cm^{-1}) figs.4 and 5.

The tetrazole cycle is a promising pharmacophore fragment that's widely used in drug production.This is a reliable moiety.[(25)]The tetrazole compounds [10 and11] were synthesized by the reaction of imines (1-3) with sodium azide; these compounds were checked by TLC, ^{1}H-NMR spectrum for compound [11].

The reaction mechanism, such as [3 + 2] cyclo additions,which are taken as 1,3 -dipolar cyclo additions, was systematically investigated.[(26)]

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An unsaturated molecule is added to a 1,3-dipole molecule with positive and negative charges divided towards the 1,3-positions comparative to any other in the addition reaction.[27]The cycloaddition reaction gives a five-member ring.azides that undergo1,3 dipolar cycloadditions are the most important and prominent type of 1,3- dipoles. T.S. is involved in the 1,3- cycloaddition mechanism. Above or below the dipolarphile and its ligands, the azide is arranged in a level and in a parallel level,allowing orbitals perpendicular to the levels to overlap and take shape bonds.[28]

In the FT.IR spectra, the stretching band due to (N-H) group appears at (3325, 3235) and the stretching band due to (-N=N-) group appears at(1492.2cm^{-1}).The bands at about (1273 cm^{-1}) and (1153 cm^{-1}) were characteristic for the tetrazole cycle.This was the most telling proof of the cyclization step's progress. In addition to this the absence of imine group (C=N) stretching band at (1593cm^{-1}) is good indication of the success of this step of reaction fig 6 .

The ^{1}H-NMR spectrum of compounds [4,7,9and 11] showed the signal at (11.92,10.65, 10.02 and 9.97) ppm due to (O-H) proton of carboxylic group and signal at (9.80, 9.81, 9.39 and 9.97) ppm due to proton of phenolic (O-H), and signal at (8.32, 8.52, 8.33, and 8.41) ppm due to (N-H) proton of amide , while the other signals are listed in Table (2) as shown in Figs(7 and8), table 3.

The compound's ^{13}C-NMR spectrum 4 showed the carbon of two methyl groups at (29.33-29.46) ppm while the aromatic C-H carbon of two rings benzene are assigned at their expected location(116.32-128.92) ppm. The carbon of carbonyl group of amide is located at (163.64 -163.82) ppm while the carbons of carbonyl of oxazepine rings were appeared at 173.85 ppm and 174.12) ppm .As shown in Fig (9) .

Table 2 Absorption bands in the FT.IR spectra of synthesized derivatives 1-11

Dert.	C-OH	N-H	C-H Arom.	C-H Aliph.	C=O	Others
1	3271	Overlap	Overlap	2831.5 , 2970.3	1670.35	υ C=N 1600.09 υ C-N 1200.06 υ C-O 1167.29
2	3437.15	3294.4	3093.8	2974.2, 2935.3	1681.93	υ C=N 1640 υ C-N 1250 υ C-O 1130.29 υ C-Cl 783.81
3	3437.66	3294.42	3066.82	2931.2, 2973.6	1662.64	υ C=N 1616.35 υ C-N 1176.58 υ C-O 1130.29 υ C-Br 682

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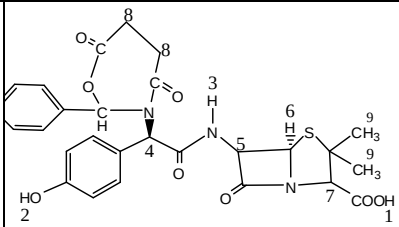
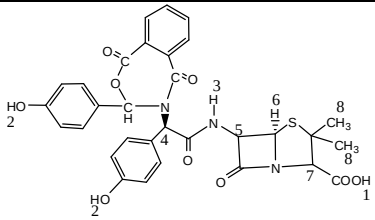
4	3420	3310	3043.67	2750.4, 2931.8	1669.64	υ C-N 1199.72 υ C-O 1161.15
5	3425	3330	3032.10	2931.6	1689.64	υ C-Cl 802.39 υ C-N 1176.58 υ C-O 1130.29
6	3406.29	3275	3039.61	2978.09, 2931.60	1689.64	υ C-Br 640.39 υ C-N 1176.58 υ C-O 1130.29
7	3456.4	3335	3078.39	2856.19, 2931	1681.93	υ C-O 1157.29 υ C-N 1157.29 υ C-O 1138
8	3425	3232.70	3070.68	2900.54, 2974.23	1685.79	υ C-Cl 798.53 υ C-N 1176.58 υ C-O 1130.29
9	3450	3290.56	3066.82	2974.23, 2931.80	1670.35	υ C-Br 636.81 υ C-O 1134.14
10	3402.43	3235	Overlap	2865.51, 2951.09	1674.21	υ C-N 1273.02 υ C-O 1153.43
11	3402.49	3325	3030	2889.37, 2958.8	1680	υ C-N 1273 υ C-O 1 126

Table -3 - : Chemical changes in ^{1}H-NMR for chosen compounds (ppm).

Der t.	Structure	Chemical shifts
4		δ11.92(S,H,OH^{1}) ; δ9.80(S,H,OH^{2}) ; δ8.27(S,H,NH^{3}); $\delta 7.79-6.71(m, H8\ Ar)$; δ5.82(S,CH-N);δ5.61(d,H,CH^{5}); δ4.89 (d,H,CH^{6}); δ4.34(S,H,CH^{7}); δ3.16(T,2H,CH$_2^{8}$); δ2.44(S,H,2CH$_3^{9}$) .
7		δ10.65(S,H,OH^{1}); δ9.81(S,H,OH^{2}); 8.52(S,H,NH^{3}); δ8.28-.6.20(m, 12H Ar); δ5.78(S,H,CH^{4});δ5.14(d, H, CH^{5}); δ4.87(d, H, CH^{6}); δ4.53(S,H,CH^{7}); δ2.40(S,H,2CH$_3^{8}$).

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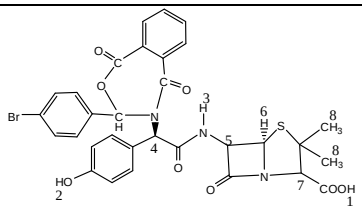
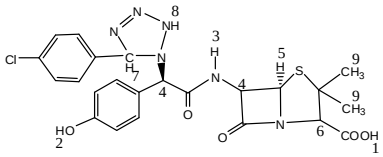
9		δ10.02(S,H,OH[1]); δ9.39(S,H,OH[2]); 8.33(S,H,NH[3]); δ8.14-.6.62(m,12H Ar); δ5.62(S,H,CH[4]);δ5.15(d,H, CH[5]); δ4.87(d, H, CH[6]); δ4.80(S,H,CH[7]); δ2.28(S,H,2CH_3[8]).
11		δ9.97(S,H,OH[1]); δ9.34(S,H,OH[2]); 8.41(S,H,NH[3]); δ7.90-.6.63(m,8H Ar); δ5.02(S,H,CH[4]);δ4.50(d,H, CH[5]); δ4.31-4.26(S,H, CH[6]); δ3.74(S,H,CH[7]); δ1.98(S,H,NH[8]) ; δ1.42(S,H,2CH_3[9]).

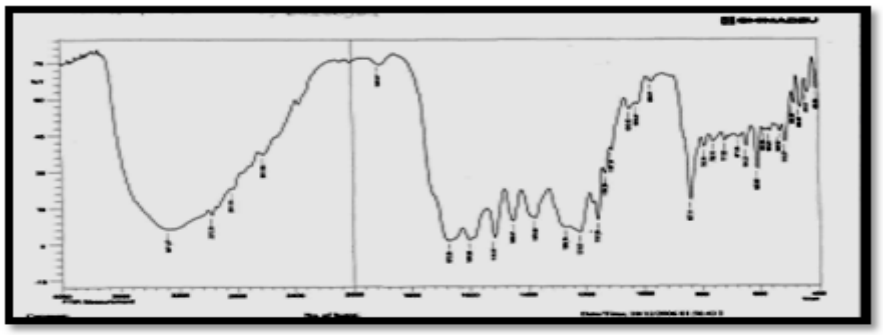


fig2Compound's FTIR 1

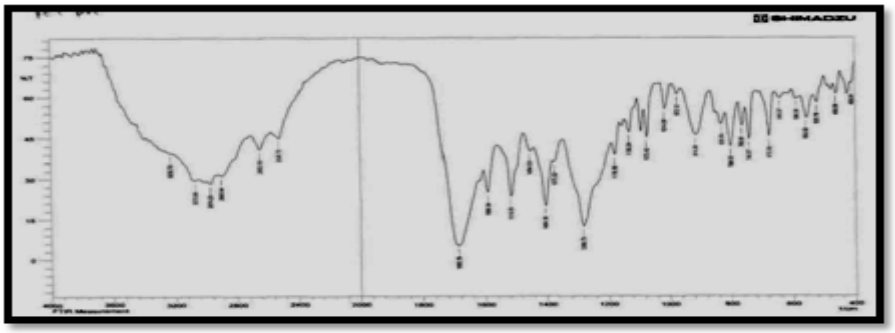


Fig3 Compound's FTIR 3

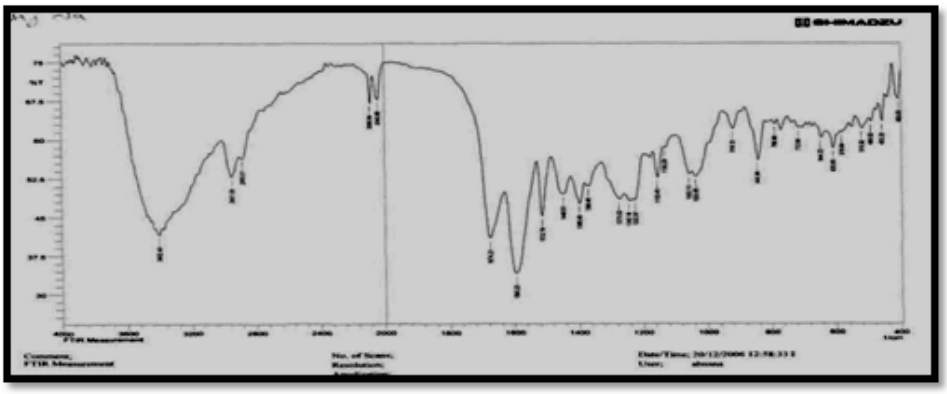


Fig4 Compound's FTIR 6

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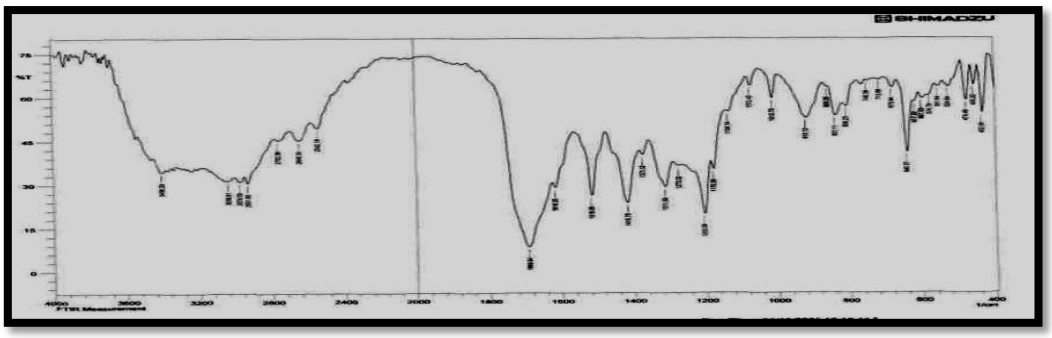

Fig5Compound's FTIR 8

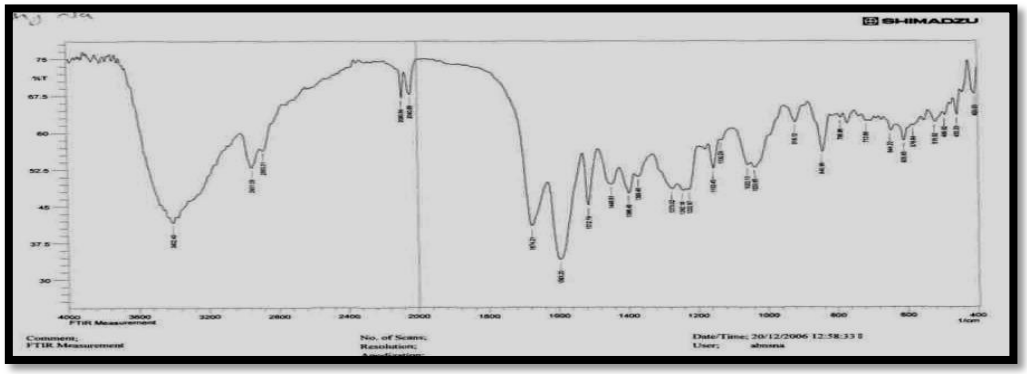

Fig6Compound's FTIR 10

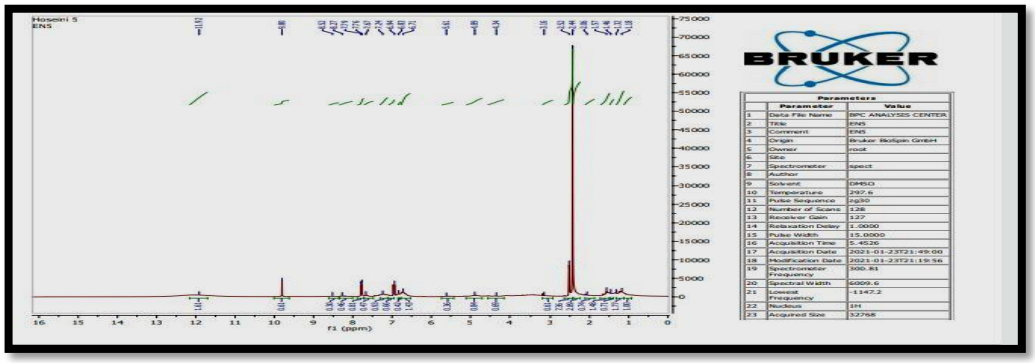

Fig7 compound's ^{1}H.NMR 4

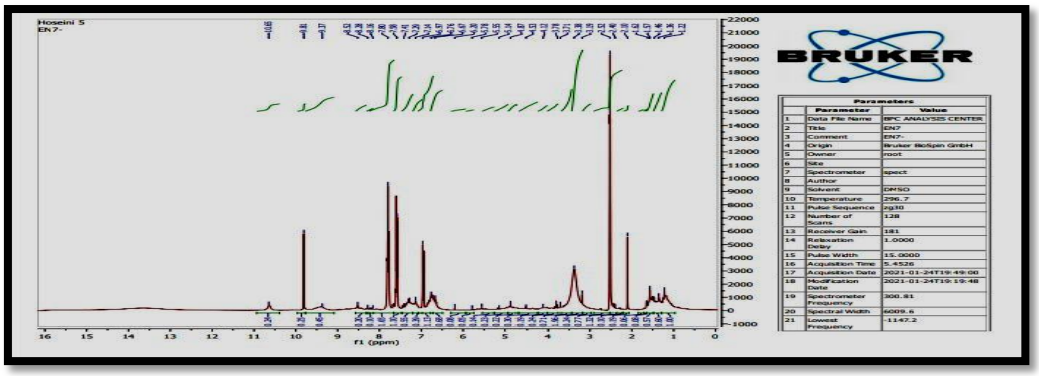

Fig8 compound's ^{1}H.NMR 7

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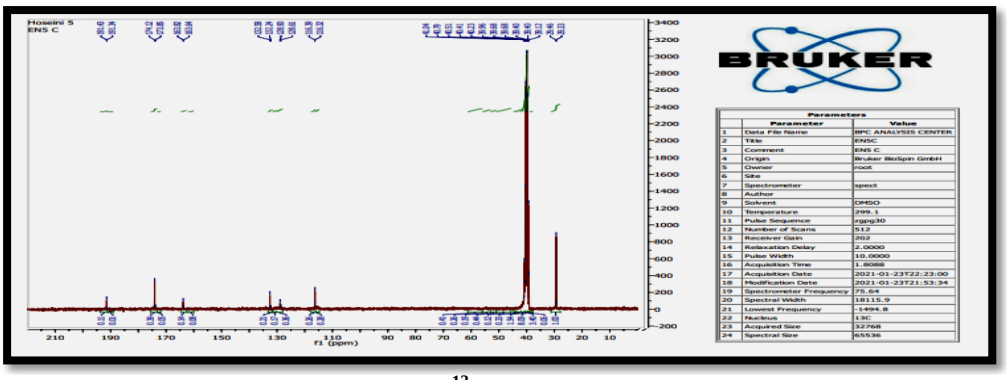

Fig9 compound's ^{13}C.NMR 4.

Antibacterial activity test (biological screening)

Antibiotic activity was assessed in vitro against Gram-negative bacteria such as Escherichia coliand Gram-positive bacteria such as Bacillus subtilis and Staphylococcus aureus using the disc deposition process.
The sterilization of the prepared agar and petridishes took 15 minutes at 121 degrees Celsius. Many of the cavities in the solidified medium were 6mm in diameter and were spaced apart accordingly 0.1 mL of prepared compounds solvated in1mL DMSO is used to fill these gaps.In the disk,DMSO was used as a control.The antibiotic Cephalexine (Keflex), which is used to treat *Salmonella*, was dissolved in the same solvent. The antibiotic cephalexine was used to equate *E. coli Klebsiella*, and *Bacillus subtilis*.Bacteria were incubated for 24 hours at 37 degrees Celsius on plates.Different compounds' inhibition areas were studied.[29]

The preliminary assay results showed that compound [eN7, eN11, eN10, eN5, eN6, eN9, and eN8] had the highest activity against *Staphylococcus aureus* and *Bacillus subtilis* (G +), whereas compound eN12 had the lowest activity against these bacteria.
Compounds[eN11, eN10, eN6, and eN12] showed Slightly activity against *E.coli*(G-).Compound [eN7, eN5, eN9 and eN8] has no effect on *E. coli.*, (table -4), figs 10, and 11.

Table -4: Antibacterial influence for some synthesized compounds

Dert.	(As seen in the image) pattern No.)	Escherichia coli (g-)	*Bacillus subtilis* (g+)	*Staphylococcus aureus* (g+)
7	eN7	-	+ + +	+ + +
6	eN11	-	+ + +	+ + +
10	eN10	-	+ ++	+ + +
4	eN5	-	+ ++	+ +
5	eN6	-	+ + +	+ + +
1	eN9	-	+ + +	+ + +

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8	**eN12**	**-**	**+**	**+**
9	**eN8**	**-**	**+ ++**	**+ + +**

Inhibition zone > 25 mm (Highly active) = +++

Inhibition zone 15-20 mm(moderately active) = ++

Inhibition zone 10-15 mm (slightly active) = +

Fig-10: Antibacterial influence for synthesized compound 7

Docking Approach

Glucosamine-6-phosphate synthase (GlcN6-P synthase) is required for the conversion of glucosamine.6.phosphate to uridine diphosphate.N-acetyl glucoseamine of (UDP-GlcNAc)(GlcN-6-P).These sequence bioformation represent vital for the cell wall buiding in a microorganism[30].The synthesis of organic molecules that bind the binding pocket and preventing enzyme biosynthetic reaction cascades represent a good strategy for discovering antimicrobial agents. The amino acid residues cys300,gly 301,thr 302,ser303,ser347,gln348,ser349,thr 352,val 399,ser 401, ala602, andlys 603 make up the active site of the enzyme, as seen in the X-ray..[31]This study using the Autodock 4.2 to study the intermolecular

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interactions between the derivative 7 and enzyme active site.The docking parameters summarized in Table(5) .

The binding energy of high ranking generated conformer (ten by default) was -8.33 with - 11.01 (kcalmol-1) intermolecular energy. the 3D structure of the target illustrated in 12 fig. enzyme and all the generated conformers inside the active site 21. The best conformer (the first generated as shown in figure 13) fit the binding site with four hydrogen bonds through two hydroxy hydrogens with the enzyme residue (LIG:H:ASP354:OD2;LIG:H:ASN600:O);while the other interactions were between the carbonyl oxygen (ALA602:HN:LIG:O) and the carboxyl oxygen of compound 7 (SER401:HG:LIG:O)

Table -5: Docking parameters of compound 7 ranked by energy

Generated Conformer	Energy that binds (Kcal (mol-1	Constant of inhibition (μM)	Intermolecular energy (kcalmol^{-1})	Hydrogen-bonds	Creating a bond
1	-8.33	0.783	- 11.01	4	LIG - H - ASP354 - OD2 ALA602-HN-LIG-O SER401-HG-LIG-O LIG-H-ASN600-O
2	-8.11	1.14	- 10.79	3	THR302-HN-LIG-O LYS603-HZ3-LIG-O GLN348-HE21-LIG-OXT
3	-8.01	1.35	- 10.69	2	SER401-HG-LIG-O LYS603-HZ3-LIG-O
4	-7.98	1.41	- 10.67	4	THR302-HN-LIG-O GLN348-HE21-LIG-OXT VAL605-HN- LIG-O SER349-HN-LIG-O
5	-7.94	1.51	- 10.63	4	THR302-HN-LIG -O GLN348-HE21-LIG-OXT VAL605-HN-LIG-O SER349-HN- LIG-O
6	-7.82	1.85	- 10.51	4	SER303-HG - LIG-O VAL605-HN-LIG- O SER349- H- LIG- OXT LIG- H - GLU488- OE2
7	-7.73	2.16	- 10.41	3	SER401-HG - LIG- OXT SER328- HG- LIG- O LIG- H- ASP354- OD2
8	-7.58	2.76	- 10.27	4	SER349-HN- LIG- O GLN348 -HE21-LIG-OXT VAL605-HN- LIG- O THR302- HN- LIG-O
9	-7.45	3.45	- 10.14	5	LIG-H-GLU488-OE2 VAL605 – HN – LIG- O LIG- H- ASN600- O GLN348- HE21- LIG- OXT GLN348-HN- LIG-O

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10	-7.45	3.47	- 10.13	1	ALA602-HN-LIG-O

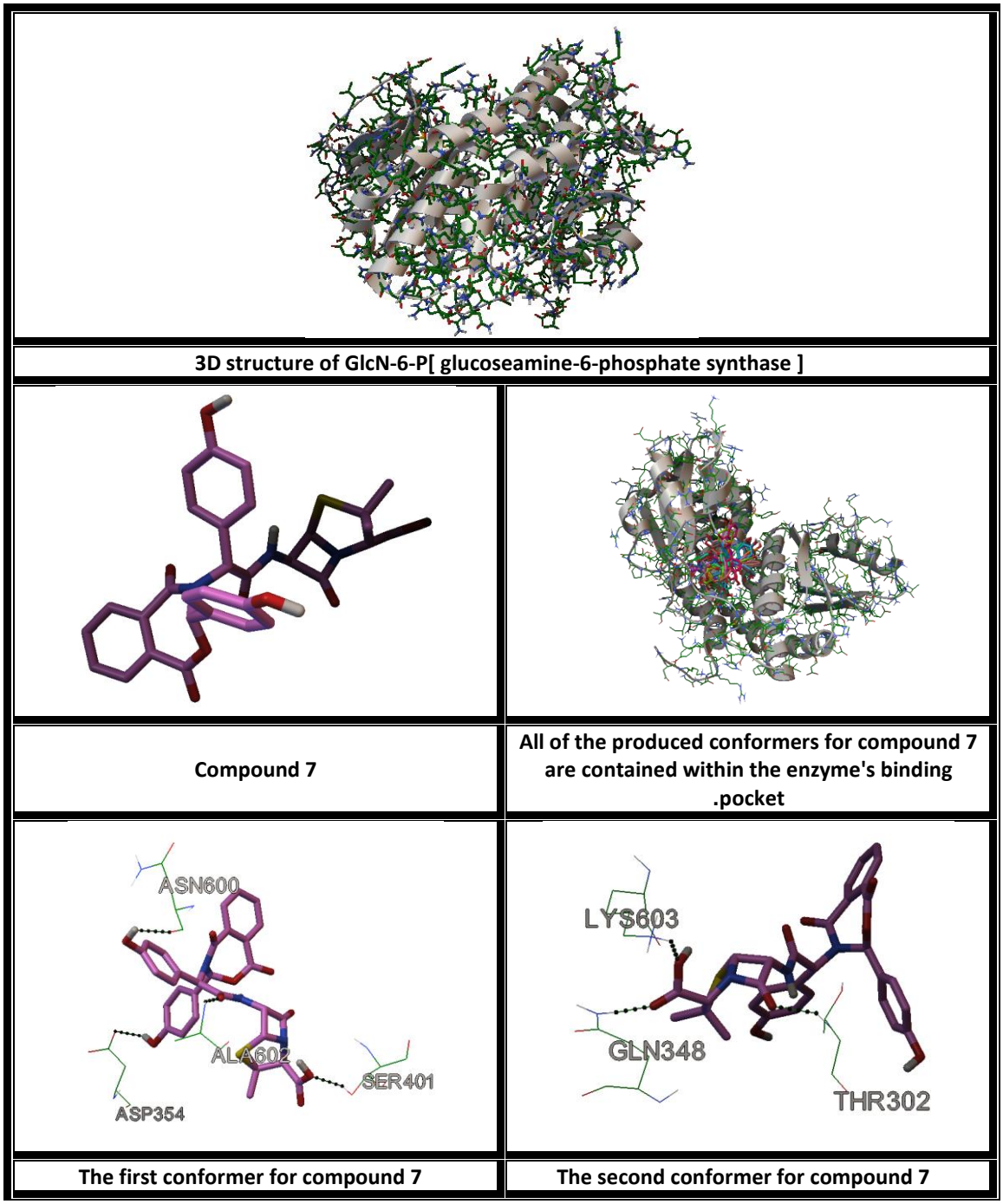

Fig- 12: The most potent newly detected hit 7 conformers were docked into the binding pocket for glucoseamine-6-phosphate synthase

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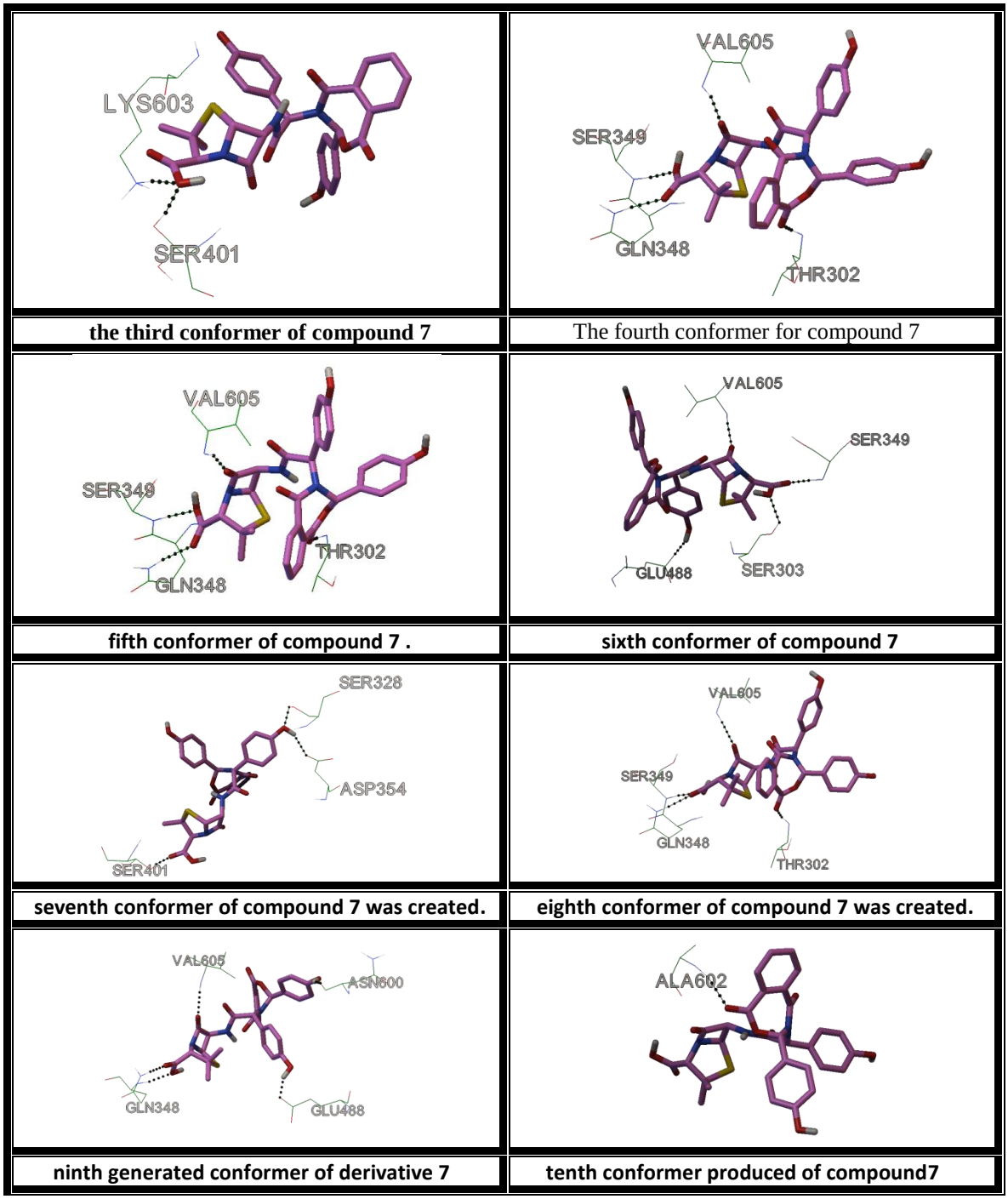

the third conformer of compound 7	The fourth conformer for compound 7
fifth conformer of compound 7 .	**sixth conformer of compound 7**
seventh conformer of compound 7 was created.	**eighth conformer of compound 7 was created.**
ninth generated conformer of derivative 7	**tenth conformer produced of compound7**

Fig- 13: Continue with docking of the most effective conformers.

Conclusion

Many bioactive heterocyclic compounds contain 1,3 oxazepine and tetrazole derivatives, which have a wide range of biological, pharmaceutical, therapy, and clinical applications. Tetrazoles with the most promising structure forms for use as anticancer drugs have been identified.The docking study of the discovered hit 7 inside the active site of target enzyme strongly enhanced the antimicrobial activity.

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