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Synthesis, identification and antimicrobial activity of thiazolidine-4-one and imidazolidine-4-one derived from 4,4-Methylenedianiline

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***Abstract*---**Schiff bases (M1 - M5) were produced by reacting 4,4-Methylenedianiline (MDA) with a variety of aldehydes by microwave method. Thiazolidine-4-one compounds (M6 - M10) were prepared from the reaction of the prepared Schiff bases with thioglycolic acid in equal molar ratios. Oxazolidines-4-on (M11 - M15) were prepared from Schiff bases with glycolic acids. The prepared compounds were diagnosed by spectrometric methods (FT-IR, 1H-NMR). The biological activity was tested against two types of bacteria Staphylococcus aureus + GIVe and Klebsiella pneumoniae – GIVe and compared with ciprofloxacin drug. The results proved that the prepared compounds are effective against these bacteria.

***Keywords*---**4,4-Methylenedianiline, Thiosolidine-4-one, Oxazolidines-4-on.

Introduction

Many derivatives of 4,4-Methylenedianiline have been prepared during the previous years because of their biological uses, where they are used as an antioxidant[1], and some of its derivatives act as an antiviral[2], and 4,4-Methylenedianiline derivatives can be prepared from the reaction of derivatives of carboxylic acids. With 4,4-Diaminediphenylmethane[3], 4,4'-diamino biphenyl methane was also prepared from the reaction of 4,4-Methylenedianiline with cyanate and aryl isocyanate[4], and α-diaminophosphonates were also prepared

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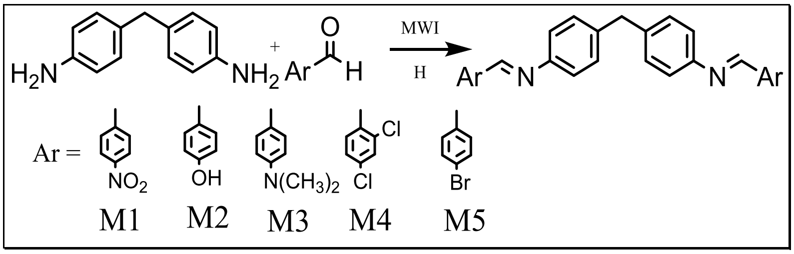
from the reaction of diphenylphosphanate with 3-bromobenzaldehyde and 4,4-methylenedianiline[5]. Schiff bases have gained the attention of chemists because of the azomethine (-C=N-) bond, which has the ability to form bonds with other compounds[6,8], and the importance of Schiff bases has increased because it has many applications, including medical applications, for example, antibacterial, anticancer, Antifungal[9]. Due to the biological importance of thiazolidine-4-on, as some of its derivatives act as an anti-cancer substance [10], anti-microbial [11] and bacteria [12]. researchers were interested in preparing may thiazolidin-4-on derivatives, as 3-(benzo[d]thiazol) was prepared -2-yl)-2-(2,4-dichlorophenyl)-2-methylthiazolidin-4-one from Schiff bases from the reaction of thiolactic acid with 2-mercaptopropanoic acid by microwave[13], and 3,3'- (ethane-1,2-diyl)bis(2-phenylthiazolidin-4-one)-3-3 from condensation of the aldehyde with diamine and mercaptoacetic acid[14]. Oxazolidin-4-one derivatives have received great interest among researchers because of their biological activity against bacteria [15], and some of its derivatives act as an antioxidant [16] He attended many of his hardships, as he prepared 4-(Hydroxymethyl)-3-phenyl Oxazolidin-2-one from the reaction of oxarin-2-ylmethanol with phenyl isocyanate in chlorobenzene[17]. New derivatives of oxazoidine-4-on were prepared from Schiff bases as a first step by reacting aldehydes and anilines and then condensing Schiff bases with glycolic acid in 4, 1- Anhydrous dioxane[18]. 4-hydroxymethyl 2-oxazolidinones was also prepared by condensation of glycidyl carbaMte derivatives with bicyclic guanidine [19].

Practical part
"Experimental Materials and Physical Measurements"

All the chemicals that applied in our study are obtainable from Fluka, and Sigma aldrich]; The Melting points have been specified by Electro thermal capillary apparatus. Com-pleting of the reaction was monitored by thin layer chromatographic (TLC) using Merck silica plates and mobile phase a mixture of Toluene and ethanol (2 : 3). IR - spectra were it was received using ATR technicality Shimadzu 8400S, fourier transform IR-spectra- copy (SHIMADZU) in the range (400 – 4000cm^{-1}). The "^{1}H-NMR spectra were obtained on a Bruker, model ultra-shield" 400MHz in the laboratories of the College of Education for Pure Sciences at the University of Basra. Using tetra methyl silane "(TMS) as internal reference and DMSO-d^6 as solvent".

Synthesis of Compounds
Synthesis of Schiff bases derivatives (M1-M5)

0.001 mol of the compound 4,4-methylenedianiline was dissolved in 25ml of absolute ethanol, and 0.002 mol of the different aldehydes were added with stirring. Then to the reaction were added drops of glacial acetic acid as a catalyst. The reaction mixture was refluxed in the microwave for 12-8 minutes (425watt). The reaction was followed up using TLC technology. Yellow-orange crystals were obtained, filtered, washed with cold water, and dried. Table 1: shows some physical properties of the prepared compounds (M5-M1).



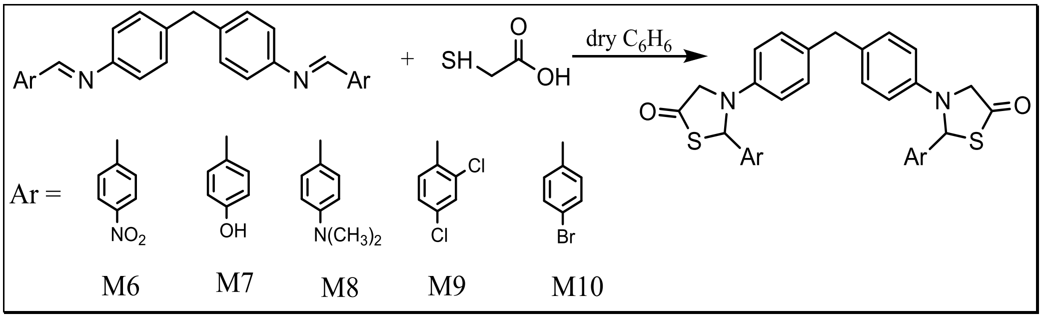
Pathway of prepared compounds (M1-M5)

Table 1
Physical properties of the prepared compounds (M5-M1)

Comp. No.	Molecular Formula	Molecular Weight	Color	M.P ^{0}C	Yield %	Rf
M1	$C_{27}H_{20}N_2O_4$	464	Dark yellow	188-191	91	0.88
M2	$C_{27}H_{22}N_2O_2$	406	Light yellow	229-232	88	0.87
M3	$C_{31}H_{32}N_4$	460	Orange	170-172	90	0.81
M4	$C_{27}H_{17}N_2Cl_4$	512	Brown	126-130	85	0.89
M5	$C_{27}H_{20}N_2Br_2$	532	Light brown	188-191	87	0.82

Synthesis of thiazolidin-4-on derivatives, compounds (M6-M10)[20]

0.001mol of Schiff bases were dissolved in 25ml of dry benzene with stirring, and 0.002 mol of thioglycolic acid was added to the reaction mixture. Heated in a microwave for (10-5 minutes) (425watt) and the reaction was followed up using TLC technology. Then after confirming the completion of the reaction, the solvent was cooled and evaporated, washed with cold water, and the solution was filtered. Table 2: some physical properties of the prepared compounds.



The equation for the preparation of compounds (M6-M10)

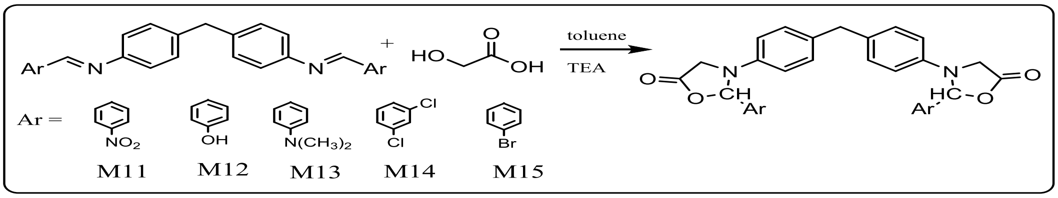
Table 2
Physical properties of the prepared compounds (M6-M10)

Comp. No.	Molecular Formula	Molecular Weight	Color	M.P ^{0}C	Yield %	Rf
M6	$C_{31}H_{24}N_4O_6S_2$	612.268	Yellow	197-198	75	0.97

M7	$C_{31}H_{26}N_2O_4S_2$	554.68	Light yellow	266-267	72	0.95
M8	$C_{35}H_{36}N_4O_2S_2$	608.82	Orange	157-160	80	0.87
M9	$C_{31}H_{22}Cl_4N_6O_2S_2$	660.45	Yellow	154-155	82	0.89
M10	$C_{31}H_{24}Br_2N_2O_2S_2$	680.47	Light yellow	Oily	83	0.92

Synthesis of Oxazolidin-4-one derivatives, compounds (M11-M15)[20]

(0.001mol) of Schiff bases were dissolved in 25ml of toluene with stirring, and after the dissolution was completed, 0.002 mol of glycolic acid was added to it, and two drops of triethylamine. The reaction mixture was refluxed in a microwave oven for 5-10 minutes, (425 watts) and the reaction was followed up using TLC. After sure of the end of the reaction, the solvent was cooled and evaporated, washed with cold water, and the solution was filtered. See Table 3.



The equation for the preparation of compounds (M11-M15)

Table 3
Physical properties of the prepared compounds (M11-M15)

Comp. No.	Molecular Formula	Molecular Weight	Color	M.P ^{0}C	Yield %	Rf
M11	$C_{31}H_{24}N_4O_8$	580.55	Dark green	132-135	78	0.98
M12	$C_{31}H_{26}N_2O_6$	522.56	Light green	214-216	84	0.96
M13	$C_{35}H_{36}N_4O_4$	576.70	Yellow	162-163	85	0.98
M14	$C_{31}H_{22}Cl_4N_2O_4$	628.33	Yellow	170-172	87	0.97
M15	$C_{31}H_{24}Br_2N_2O_4$	648.35	Light green	252-253	87	0.95

Results and Discussion

The IR of the compounds (M1 - M5) It is observed that a strong band appeared at (1649-1655 cm^{-1}) due to azomethine group (C =N) In addition, absorption bands appeared at (3058 – 3070 cm^{-1}) it reverts to the stretching of the aromatic (C-H) bond. bands appear at the range (2853- 2966 cm^{-1}) refer "to the stretching of the aliphatic (C-H) bond[21]. See Table (4).

Table 4
FTIR data of Schiff bases derivatives (M1-M5)

Comp. No.	R	ν (C-H) Arom.	ν(C-H) Aliph.	(C=N) ν	Others
M1	4-NO_2	3058	2966	1649	(-NO_2) 1504 and 1340

M2	4-OH	3089	2958	1645	OH 3316
M3	4-N(CH3)2	3104	2953	1655	-N(CH3)2 1217
M4	2,4-Cl	3070	2956	1640	C-Cl 706
M5	4-Br	3062	2902	1652	C-Br 775

^{1}H-NMR of compound (M1) shows a singlet signal at (4.02 ppm) that belongs to the aliphatic (CH_2) protons, and a multi-signal doublet of doublet in the range (7.31-8.35 ppm) which belongs to benzene rings. A single signal at (8.81 ppm), which belongs to the proton of the N=C-H [22]. Shown in Figure 1.

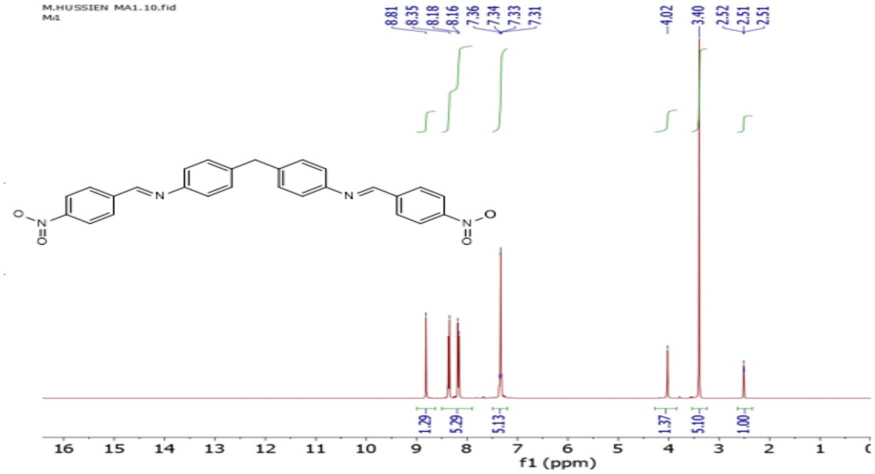


Figure 1. ^{1}H-NMR spectrum of M1

The ^{1}H-NMR spectrum of compound (M3) shows a singlet signal at (3.04 ppm) which belongs to the aliphatic C-H3 group protons. A signal in position (3.94 ppm) which belongs to the aliphatic CH2 protons and showed multiple signals in the range (6.48-7.72 ppm) which belongs to the aromatic ring proton. Signal in the position (8.40 ppm) which belongs to the proton N = C-H this is found in the literature [22]. Figure 2.

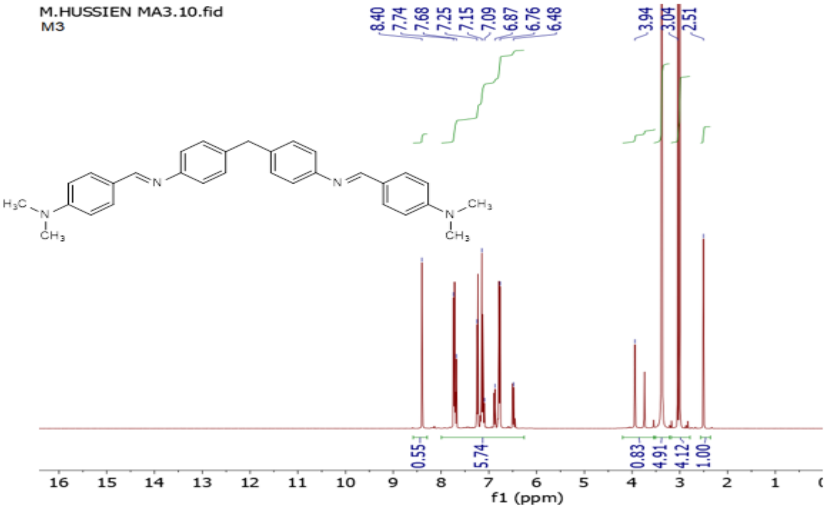


Figure 2. ^{1}H-NMR spectrum of M3

The IR spectra of the compounds [M6 – M10] observed that a strong band appeared at (1213-1219 cm-1) due to group (C-N). In addition, absorption bands appeared at (3033 – 3095 cm-1) which reverts to the stretching of the aromatic (C-H) bond. Bands appear at the range (2855- 2976 cm-1) refer "to the stretching of the aliphatic (C-H) bond and Appearance of absorption bands at the range (1716-1722 cm-1) due to the stretching of the thiazolidine carbonyl (C= O) bond[21], See Table 5.

Table 5

FT_IR data of thiazolidin-4-on derivatives (M6-A10)

Comp. No.	R	ν (C-H) Arom.	ν(C-H) Aliph.	(C-N)ν	ν(C=O) thiazolidine	Others
M6	4-NO_2	3053	2855	1217	1716	(N-O_2) 1550 1373
M7	4-OH	3033	2976	1219	1720	(O-H) 3466
M8	4-$N(CH_3)_2$	3095	2973	1215	1716	-$N(CH_3)_2$ 1217
M9	2,4-Cl	3033	2965	1219	1722	C-Cl 674
M10	4-Br	3087	2963	1213	1719	C-Br 667

The 1H-NMR spectrum of compound (M6) shows a singlet signal at (4.03 ppm) that belongs to the aliphatic CH_2 protons. A signal at (5.24 ppm) and (6.91 ppm) belongs to CH_2 and C-H protons in the thiazolidine ring. The spectrum showed multiple signals in the range (8.52-7.33 ppm) that belongs to the benzene protons[22]. See Figure 3.

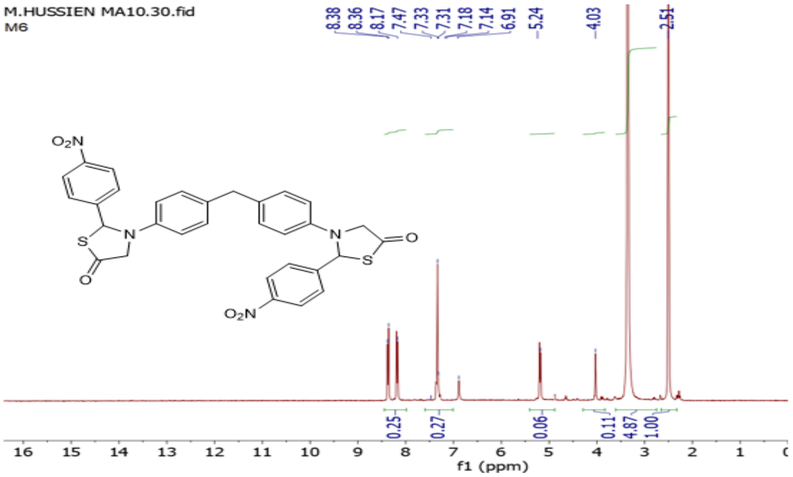


Figure 3. ^{1}H-NMR spectrum of M6

The IR spectra of the compounds [M11 – M15] It is observed that a strong band appeared at (1216-1219 cm^{-1}) due to group (C-N) In addition, absorption bands appeared at the scope (3020 – 3066 cm^{-1}) it reverts to the stretching of the aromatic (C-H) bond. bands appear at the range (2873- 2920 cm^{-1}) refer "to the stretching of the aliphatic (C-H) bond. Appearance of absorption bands at the range (1721-1726 cm^{-1}) due to the stretching of the Oxazolidin ring (C=O) bond, Appearance of absorption bands at the range (1188-1218 cm^{-1}) due to the stretching of the aster[21], See Table 6.

Table 6
FT_IR data of Oxazolidin-4-one derivatives (M11-M15)

Comp. No.	R	(C-H)ν Arom.	ν(C-H) Aliph.	(C-N)ν	ν (C=O) Oxazolidin	(C-O)ν	Others
M11	4-NO_2	3020	2889	1216	1722	1212	NO_2 asy 1553 sy 1374
M12	4-OH	3022	2881	1218	1725	1210	O-H 3463
M13	4-$N(CH_3)_2$	3038	2873	1217	1721	1215	-$N(CH_3)_2$ 1220
M14	2,4-Cl	3045	2920	1216	1726	1218	C-Cl 670
M15	4Br	3066	2911	1219	1722	1188	C-Br 666

^{1}H-NMR of compound (M12) shows a signal at (3.95 ppm) that belongs to the proton of the CH_2 group and it shows a signal in the position (4.83 ppm) that belongs to the proton of the C-H group in oxazolidine ring. a signal in the position (4.89 ppm), which belongs to the proton of oxazolidine ring C-H_2 group, and the multiple signals in the range (6.44- 8.45ppm) which belong to the protons of benzene. Which is close to what was found in the literature [22]. Show Figure 4.

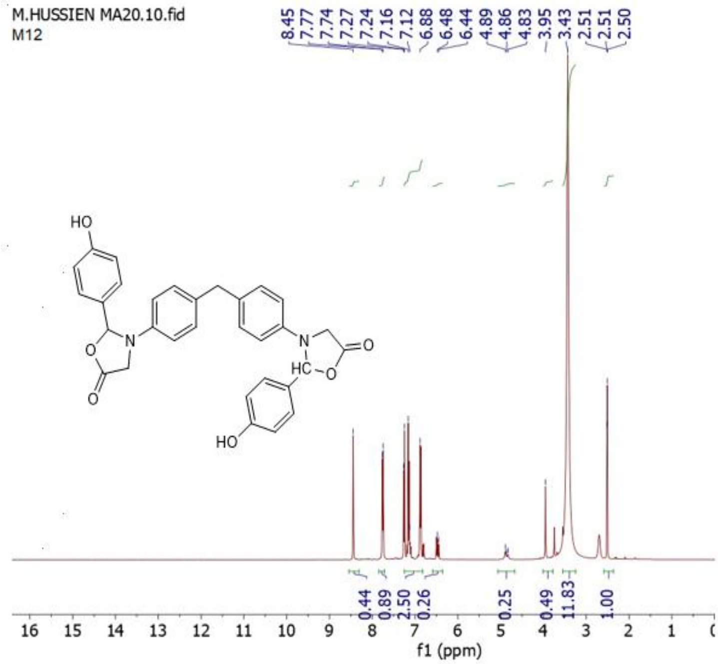


Figure 4. ^{1}H-NMR spectrum of M12

^{1}H-NMR of compound (M13) shows a signal at (3 ppm) that belongs to the proton of the C-H_3 group, and a signal at (3.38 ppm) that belongs to the proton of the C-H_2 group in the oxazolidine ring. The appearance of a signal at (4.89 ppm) that belongs to the C-H proton in the oxazolidine ring ,and appearance of signals In the range (6.45-7.73 ppm), which belongs to the protons of the benzene ring[22]. Shown in Figure 5.

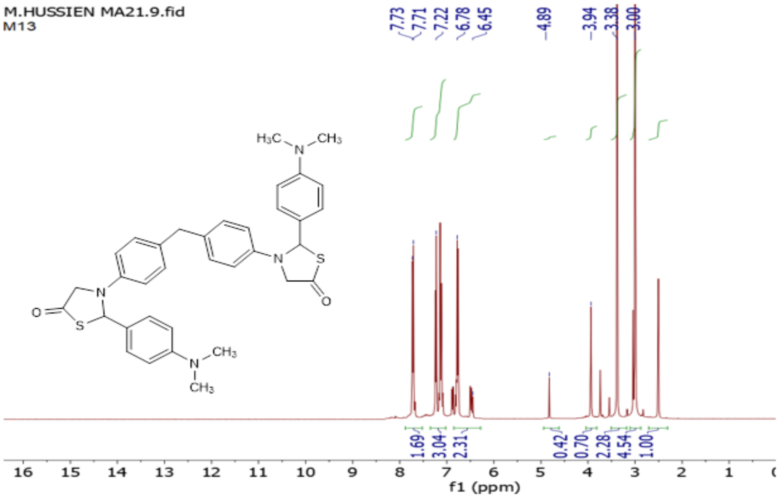


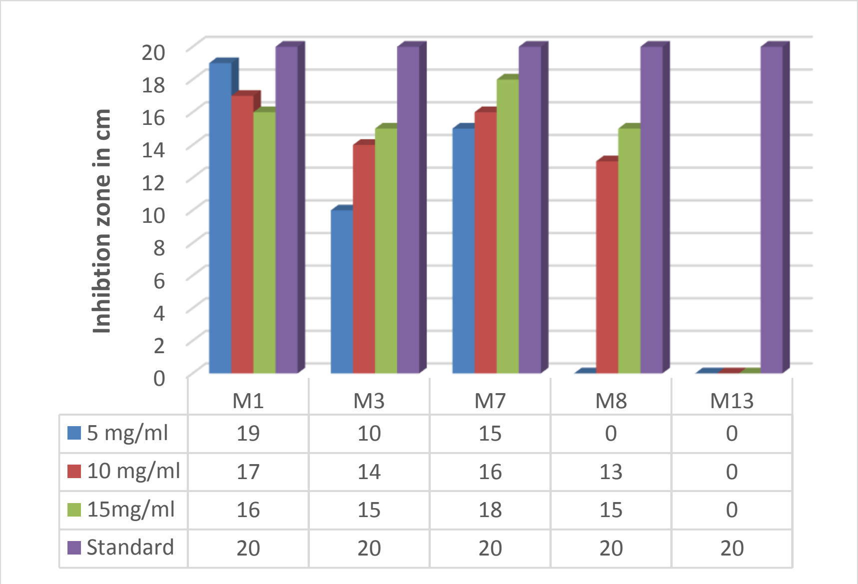
Figure 5. ^{1}H-NMR spectrum of M13

Test the inhibitory activity of some prepared compounds [23-25]

The biological activity of some prepared compounds (M1, M3, M7, M8, M13) was evaluated on two types of bacterial isolates namely *Staphylococcus aureus* + GIVe and *Klebsiella pneumoniae* - GIVe .The results showed the inhibitory activity of the prepared compounds against bacteria and the results were compared with the antibacterial ciprofloxacin. The results indicated that the prepared compouds had the ability to inhibit bacteria using different concentrations of the compounds (5 mg/ml), (10 mg/ml) and (15 mg/ml). Especially compound M7, which showed high efficacy at concentrations (15 mg/ml) compared to the standard antibiotic. See Table 7 and Figure 6 and 7.

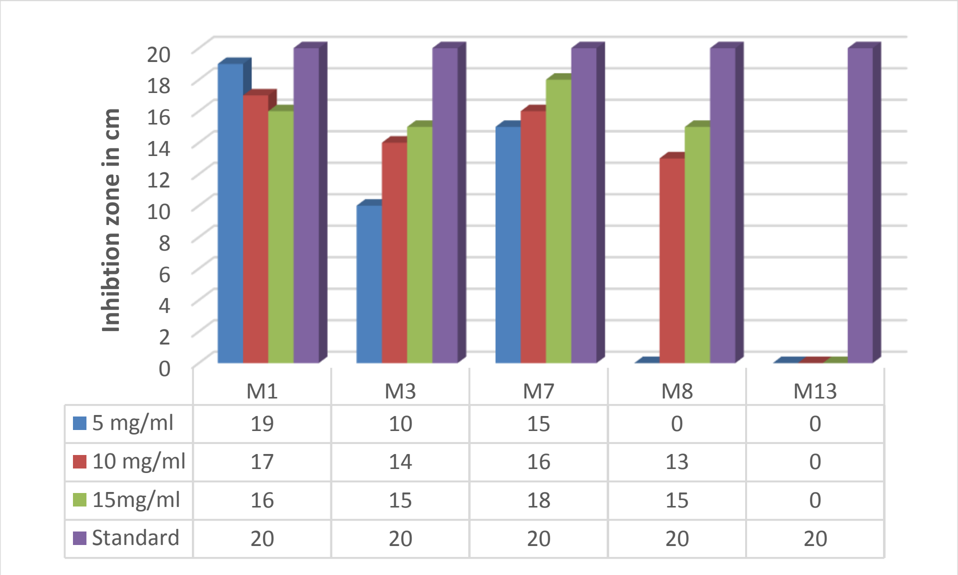
Table 7
Anti-bacterial activity data for some prepared compounds measured in millimeters

Comp. No.	*Staphylococcus aureus*			*Klebsiella pneumoniae*		
	5 mg/ml	10 mg/ml	15 mg/ml	5 mg/ml	10 mg/ml	15 mg/ml
M1	19	17	16	0	0	0
M3	10	14	15	8	10	12
M7	15	16	18	12	13	15
M8	0	13	15	0	0	0
M13	0	0	0	0	0	0
Standard 10mg/m	20	20	20	20	20	20



	M1	M3	M7	M8	M13
🟦 5 mg/ml	19	10	15	0	0
🟥 10 mg/ml	17	14	16	13	0
🟩 15mg/ml	16	15	18	15	0
🟪 Standard	20	20	20	20	20

Figure 6. the effectiveness of some prepared compounds (M1, M3, M7, M8, M13) against *Staphylococcus aureus* + GIVe



	M1	M3	M7	M8	M13
🟦 5 mg/ml	19	10	15	0	0
🟥 10 mg/ml	17	14	16	13	0
🟩 15mg/ml	16	15	18	15	0
🟪 Standard	20	20	20	20	20

Figure 7. The effectiveness of some prepared compounds (M1, M3, M7, M8, M13) against the bacteria *Klebsiella pneumoniae* – GIVe

The following pictures show the inhibition areas of the prepared compounds against two types of bacteria used. See Figure 8 and 9.

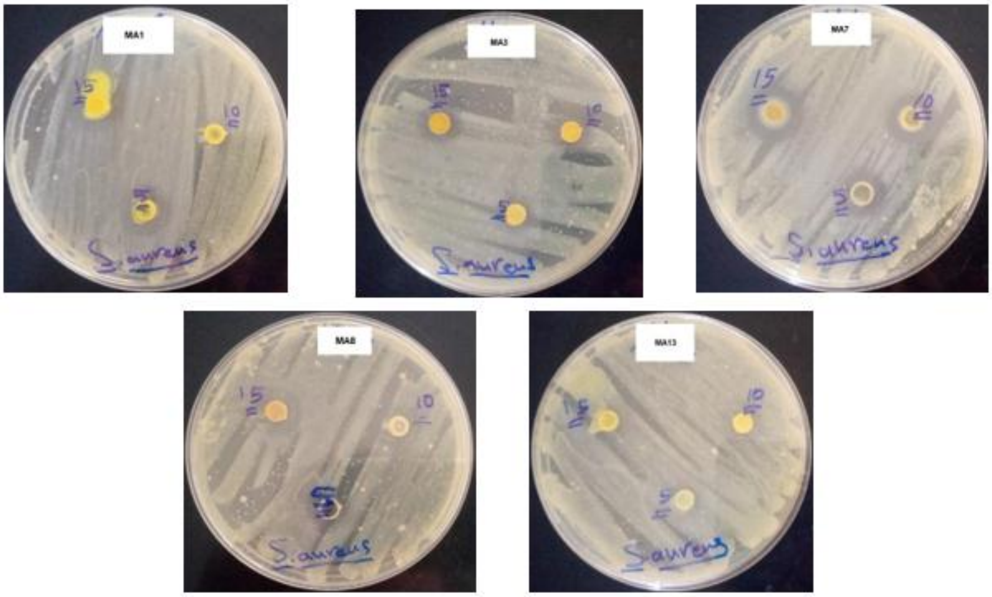


Figure 8. Inhibition zone diameter (mm) on *Staphylococcus aureus* + GIVe

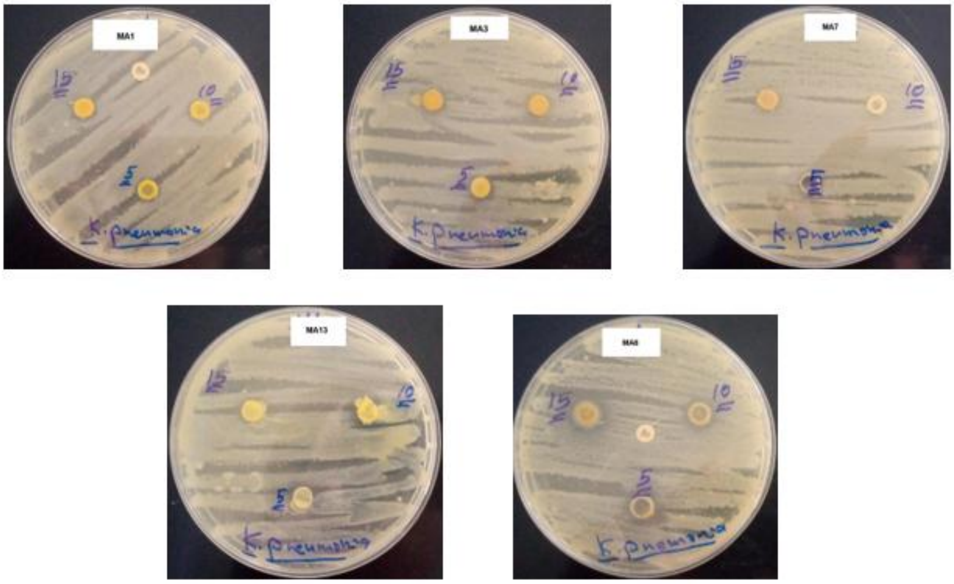


Figure 9. Inhibition zone diameter (mm) on *Klebsiella pneumoniae* – GIVe

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