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Design, Synthesis, And Characterization of Some New Schiff Bases Derivatives for Piperidine, 3-Amino-1,2,4-Triazole-5-Thiolate Salt and Biological Evaluation as Antibacterial Agents.

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ABSTRACT

Schiff bases (MP1-MP10) were synthesized by reacting various benzaldehyde derivatives with 3-amino-1,2,4-triazole-5-thiol in the presence of piperidine, and all compounds were identified using spectroscopy. UV, FIR, GC-Mass, and HNMR for some combinations, as well as measuring melting points. The obtained results matched the suggested structures of the newly synthesized compounds. All prepared compounds (MP1-MP10) were tested for biological activity against four types of Gram-positive and Gram-negative bacteria at seven concentrations. The study found that the compound MP1 inhibited all types of bacteria in the first four concentrations.

Keywords: *3-amino-1,2,4-triazole-5-thiol, Piperidinium salt, Schiff base, antibacterial activity*

1.INTRODUCTION

The triazole ring derivatives, in particular, are well known for their biological action against multiple cancer cells (Turky et al., 2017; Grytsai et al., 2020), fungi (Shi et al., 2020), various bacterial species (Kosikowska et al., 2020), and others; these derivatives include the well-known Schiff bases. Derivatives of the five-member ring of heterocyclic compounds are also known for their biological action against other species (Geetha et al., 2020; Nayarisseri et al., 2020; Cao et al., 2021).

The presence of the imine group, which results from the interaction of the primary amine group with the carbonyl group of various aldehydes or ketones, characterizes the chemical structure of Schiff bases, and the reaction frequently occurs in the presence of drops of glacial acetic acid or hydrochloric acid. Recent research has used basic catalysts such as piperidine instead of acidic catalysts such as glacial acetic acid or hydrochloric acid (Soliman et al., 2022; Sayed et al., 2017; Naqvi et al., 2009).

The current work is one of several that used piperidine instead of glacial acetic acid, hydrochloric acid, or other acids to create a new series of Schiff bases for the triazole ring, which has thiol and amine groups at the 5,3 positions in its structure. The change in the catalyst in this study is due to the fact that some of these reactions, when activated with known acids, do not yield a good product from the prepared derivatives, particularly the strong acids, because part of them work to form quaternary ammonium salts as a result of their interaction with the raw

material's primary amine group, preventing its transformation into Schiff bases.

The current work involved the development of a new series of Schiff bases from salts of piperidinium triazole by reacting the 3-amino-1, 2, 4-triazole-5-thole in the presence of piperidine as a catalyst with some benzaldehyde derivatives. According to two recent investigations, triazole rings with structural thiol and amine groups provide Schiff bases for piperidinium triazole salts in the above-mentioned processes (Slaihim et al., 2019; Khairuddean et al., 2020).

What distinguishes the current study from the previous two is that the structure of the new derivatives differs from the structure of the derivatives prepared in the previous two studies (Slaihim et al., 2019; Khairuddean et al., 2020) because the amino group in the previous studies is directly linked to the nitrogen atom in position No. 4, whereas the amino group in the current study is linked to a carbon atom of a triazole ring is directly at position No. 3. This structural shift is reflected negatively or positively in the biological effect and the quantitative structure-activity relationship (QSAR) for these derivatives (Aher et al., 2020; Liu et al., 2022).

In the end, the primary purpose of this research is to create new Schiff bases of piperidinium triazole salts that are promising for resistance to certain types of bacteria when compared to resistance to their equivalent forms in previous studies of breast and colon cancer cells.

2. EXPERIMENTAL

2.1. Chemicals

The following chemicals and reagents were used in this investigation of all the produced compounds: 4-Chlorobenzaldehyde (BDH); 4-Bromobenzaldehyde (BDH); 4-Methoxybenzaldehyde (BDH); 4-Methylbenzaldehyde (Fluka); 4-Dimethylaminobenzaldehyde (Merck); 4-Hydroxy-3-methoxy benzaldehyde (BDH); Absolute ethanol (Chem lab); 2,4-Dihydroxybenzaldehyde (Sigma); 2,4-Dichlorobenzaldehyde (CDH); 4-Nitrobenzaldehyde; Piperidine (BDH); Dimethyl sulfoxide (Merck); 3-Amino-1,2,4-triazole-5-thiole (Sigma).

2.2. Instruments

Except for a Bruker Avance, all of the devices or instruments used to determine the structure of produced chemicals are located at the College of Applied Sciences, Samarra University. The nuclear magnetic resonance (1H.NMR) spectra were measured using a Bruker Avance (400 MHz) and DMSO-d6 solvent at Basra University's College of Education, Department of Chemistry. Infrared spectra were recorded using a Shimadzu Japanese Company-supplied Fourier Transform Infrared Spectrophotometer/FTIR-8400S device: samples were created as (KBr) discs. Shimadzu GC-MS-QP 2010 Ultra mass spectrometer was used to collect mass spectra.

2.3. Biological assay

2.3.1. Compounds and cells

All test chemicals were dissolved in the DMSO solvent at the initial concentration of 0.032 mg * mL1 before being serially diluted for use in a culture medium. Pathogenic microorganisms of four different kinds were used: Pneumonia klebsiella and Pseudomonas aeruginosa are two that are gram-negative (Gr-ve). Additionally, Staphylococcus aureus and Streptococcus mutans are gram-positive (Gr+ve) bacteria. The University of Samarra's Microbiology Laboratory, Pathological Analysis Department, College of Applied Sciences, and the four bacterial species underwent tests there.

2.3.2. Antibacterial assay

The organic solvent DMSO was used to make test solutions for the compounds (MP1-MP10), and several various concentrations were made from it (0.032, 0.016, 0.008, 0.004, 0.002, 0.001 mg/ml respectively). These test solutions were then administered to the four aforementioned bacteria. By using the agar well diffusion method (Al-Qadsy et al., 2020), the seven concentrations were dispersed across two plates, and at the circumference of each plate, seven holes with a diameter of 5 mm were created in the center of the agar. Following that, 50–70 (µL) of the

solutions were injected into each hole at various concentrations. At a temperature of 37 °C, a micro pipet was used to inject each hole, and record the results. 18-24 hours.

2.4. Synthesis method

2.4.1 General procedure for properties of the new Schiff bases series (MP1-MP10).

An equimolar mixture of 3-amino-1,2,4-triazole-5-thiole (0.001 mol) and one of the aromatic aldehyde derivatives in presence of piperidine (0.5 mL) was combined in 50 ml of 100% ethanol to create a new series of Schiff bases (MP1-MP10). For six hours, the reaction's contents were refluxed while being stirred. It is concentrated and given time to gradually cool. By using the proper techniques, the precipitate was filtered, dried, and purified.

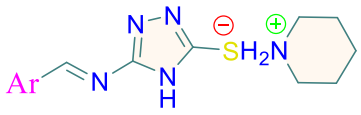
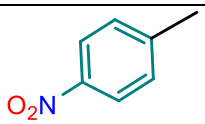
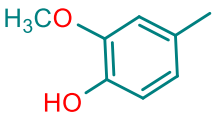
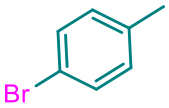
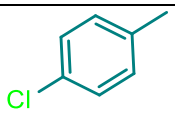
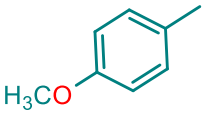
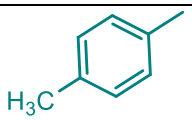
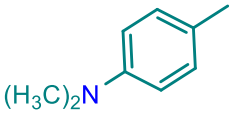
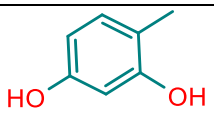
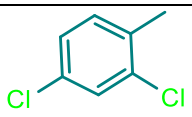
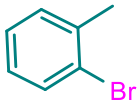


TABLE 1: The physical properties of the new Schiff bases series (MP1-MP10).

Comp No	Ar	Chemical Formula	Mol. Wt	Melting Point	Color	Yield%
MP1		C14H18N6O2S	334.4	(185-187)˚C	Light Orange	71.9%
MP2		C15H21N5O2S	335	Sticky	Red	67.1%
MP3		C14H18BrN5S	368.3	(193-195)˚C	Light Yellow	95.2%
MP4		C14H18ClN5S	323.8	(203-206)˚C	Off White	57.8%
MP5		C15H21N5OS	319.4	(176-178)˚C	Light Yellow	69.8%
MP6		C15H21N5S	303.4	(167-164)˚C	Off White	61.9%
MP7		C16H24N6S	332.5	(169-172)˚C	Light Orange	73.6%
MP8		C14H19N5O2S	321.4	Sticky	Dark Brown	66.1%
MP9		C14H17Cl2N5S	358.3	(203)˚C	Light Brown	53.8%

MP10		C14H18BrN5S	368.3	(233-237)˚C	Yellow	51.7%

3. RESULTS AND DISCUSSION

3.1. Schiff bases (MP1-MP10) spectra

A new Schiff base series (MP1-MP10) were synthesized and structurally characterized with success. The following three tables, 2, 3, 4, and 5, summarize the IR, 1H-NMR, GC-MS, and MICs of the new series (MP1-MP10) data, respectively. Some organic identification techniques, such as IR, 1H-NMR, and GC-MAS spectroscopy, confirm the Schiff base unit.

The -NH2 and carbonyl groups were absent from the IR spectra, but the imine group's absorption band N=CH was present at the range (1660-1589) cm-1. The Schiff base, or imine (-N=CH-), can be seen as a singlet in the 1H-NMR spectra at 8.18-9.01 ppm. All the other important peaks and signals appeared in IR and 1H-NMR spectra. Table 3 shows characteristic data for molecular weight ions with a base peak in the mass spectrum. The following tables show characteristic data for compounds in the MP1–MP10 series.

TABLE 2: IR (ν, cm-1) characteristic bands of (MP1-MP10) series.

IR μMAX (cm-1)								
Comp No.	Max λ Nm	Aps.	ν(N-H) Ring	ν(C-H) Ar	ν(C-H) Al	ν(C=N)	ν(C=C) Ar	Others
MP1	340	3,06459	3263	3080	2966	1604	1520 1456	C-NO_2 (Ar) 1370
MP2	354	2.98000	3331	3020	2937	1653	1647 1456	C-O 1058 & O-H 3411
MP3	314	1.62169	3250	3100	2962	1597	1548 1477	C-Br688
MP4	304	2.08712	3251	3080	2962	1660	1597 1477	C-Cl 721
MP5	310	2.3853	3387	3050	2916	1645	1602 1516	
MP6	302	0.88678	3329	3005	2908	1622	1580 1475	CH3- 1400
MP7	348	3.3254	3360	3100	2939	1653	1595 1456	C-N1396& CH_3N=2883
MP8	382	2.42977	3332	3040	2935	1647	1585 1506	C-O1338
MP9	302	1.20698	3257	3100	2968	1589	1564 1463	Cl 773-C-
MP10	302	1.56092	3328	3045	2966	1635	1590 1436	C-Br 669

TABLE 3: 1H-NMR characteristic data of compounds L1-L8

Structure/Cod	Chemical Shift (δ) ppm	Signal Features	No. of Protons	Type of Protons
L1/MP1	8.50	s	1H	(CH=N-)imine
	8.29	d, J = 8.2 Hz	2H	aromatic
	8.04	d, J = 8.1 Hz	2H	aromatic
	3.02	t, J = 5.5 Hz	4H	piperidiniun
	1.60-1.62	m	4H	piperidiniun
	1.35-1.37	m	2H	piperidiniun
L2/MP3	8.35	s	1H	(CH=N-)imine
	7.80	d, J=8.0 Hz	2H	aromatic
	7.49	d, J=8.0 Hz	2H	aromatic
	3.00	t, J=5.49 Hz	4H	piperidiniun
	1.58-1.61	m	4H	piperidiniun
	1.33-1.36	m	2H	piperidiniun
L3/MP4	8.36	s	1H	(CH=N-)imine
	7.79	d, J = 8.0 Hz	2H	aromatic
	7.48	d, J = 8.0 Hz	2H	aromatic
	3.02	t, J = 5.49 Hz	4H	piperidiniun
	1.58-1.63	m	4H	piperidiniun
	1.33-1.36	m	2H	piperidiniun
L4/MP5	9.01	s	1H	(CH=N-)imine
	7.83	d, J = 8.0 Hz	2H	aromatic
	7.10	d, J = 8.0 Hz	2H	aromatic
	3.81	s	3H	-OCH3
	3.04	t, J = 5.5 Hz	4H	piperidiniun
	1.66	p, J = 5.8 Hz	4H	piperidiniun
	1.54	p, J = 5.8 Hz	2H	piperidiniun
L5/MP6	8.29	s	1H	(CH=N-)imine
	7.70	d, J = 8.0 Hz	2H	aromatic
	6.96	d, J = 8.0 Hz	2H	aromatic
	2.98	t, J = 5.49 Hz	4H	piperidiniun
	2.40	s	3H	-CH3
	1.55-1.57	m	4H	piperidiniun
	1.30-1.33	m	2H	piperidiniun
L6/MP7	8.18	s	1H	(CH=N-)imine
	7.56	d, J = 8.1 Hz	2H	aromatic
	6.70	d, J = 8.0 Hz	2H	aromatic
	3.15	s	6H	N(CH3)2
	3.00	t, J = 5.6 Hz	4H	piperidiniun
	1.56-1.60	m	4H	piperidiniun
	1.34-1.38	m	2H	piperidiniun
L7/MP9	8.64	s	1H	(CH=N-)imine
	8.03	d, J = 8.0 Hz	1H	aromatic
	7.68	s	1H	aromatic

	7.58	dd, J = 8.0 Hz	1H	aromatic
	3.06	t, J = 5.6 Hz	4H	piperidiniun
	1.62-1.66	m	4H	piperidiniun
	1.40-1.42	m	2H	piperidiniun
L8/MP10	8.62	s	1H	(CH=N-)imine
	8.00	d, J = 8.0 Hz	1H	aromatic
	7.67	dd, J = 8.0 Hz	1H	aromatic
	7.43	t, J = 8.6 Hz	2H	aromatic
	3.03	t, J = 5.5 Hz	4H	piperidiniun
	1.60-1.63	p, J = 5.7 Hz	4H	piperidiniun
	1.43-1.45	p, J = 5.8 Hz	2H	piperidiniun

TABLE 4: Molecular weight ions with a base peak in the mass spectra

Product NO.	Chemical formula	Exact Mass	Mass spectrum m\z (relative intensity) of fragments			
MP1	$C_{14}H_{18}N_6O_2S$	334.4	335(M^+,33%)	237(M^+,63%)	196(M^+,71%	151(M^+,100%)
MP4	$C_{14}H_{18}ClN_5S$	323.8	324(M^+,30%)	113(M^+,40%	85(M^+,50%)	71(M^+,100%)
MP5	$C_{15}H_{21}N_5OS$	319,4	320(M^+,35 %)	239(M^+,37 %)	135(M^+,36 %)	73 (M^+,100%)
MP6	$C_{15}H_{21}N_5S$	303.4	304(M^+,17 %)	206(M^+,60 %)	134(M^+,65%)	119(M^+,100%)
MP7	$C_{16}H_{24}N_6S$	332.5	333(M^+,30%)	266(M^+,57%)	132(M^+,38%)	99(M^+,100%)

3.2. Evaluation of the biological activity of the new Schiff bases series (MP1-MP10)

The effect of all the compounds prepared in this research on the growth of four types of bacteria was studied Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Streptococcus mutans ,These bacteria were chosen due to their importance in the medical field as they cause a number of diseases and also differ in the nature of their resistance to antibiotics and chemotherapeutic substances. The sensitivity of compounds was studied using the diffusion method. Table (2) shows that the compounds prepared in the laboratory have inhibitory activity against all the bacteria.

All of these features have something to do with the mechanism and potential of a promising antibacterial. The biological activity of all generated Schiff base derivatives is assessed against four Gram-positive and Gram-negative bacteria; the bacteria employed in this study are Staphylococcus aureus, Streptococcus mutans, Klebsiella pneumoniae, and Pseudomonas aeruginosa.

All of the new compounds tested exhibited inhibitory action against one or more of the four bacterial species chosen for this investigation, ranging from moderate to strong according to the results in a table (5), as well as the values of the minimum inhibitory concentration (MIC).

TABLE 5: MICs of the new series (MP1-MP10) against gram-negative and gram-positive bacterial strains.

Comp No.	Conce.	Staphylococcus aureus	Streptococcus mutans	Klebsiella pneumoniae	Pseudomonas aeruginosa
MP1	0.032	28	18	19	31
	0.016	22	14	17	26
	0.008	16	11	12	24
	0.004	_	11	12	22
	0.002	_	_	_	_
	0.001	_	_	_	_
	0.0005	_	_	_	_
MP2	0.032	11	__	__	12
	0.016	__	__	__	__
	0.008	__	__	__	__
	0.004	__	__	__	__
	0.002	__	__	__	__
	0.001	__	__	__	__
	0.0005	__	__	__	__
MP3	0.032	28	__	__	__
	0.016	12	__	__	__
	0.008	11	__	__	__
	0.004	11	__	__	__
	0.002	__	__	__	__
	0.001	__	__	__	__
	0.0005	__	__	__	__
MP4	0.032	__	21	__	
	0.016	__	__	__	__
	0.008	__	__	__	__
	0.004	__	__	__	__
	0.002	__	__	__	__
	0.001	__	__	__	__
	0.0005	__	__	__	__
MP5	0.032	__	23	__	21
	0.016	__	18	__	18
	0.008	__	15	__	13
	0.004	__	15	__	__
	0.002	__	__	__	__
	0.001	__	__	__	__
	0.0005	__	__	__	__
MP6	0.032	__	__	__	__
	0.016	__	__	__	__
	0.008	__	__	__	__
	0.004	__	__	__	__
	0.002	__	__	__	__
	0.001	__	__	__	__

	0.0005	__	__	__	__
MP7	0.032	__	__	__	15
	0.016	__	__	__	__
	0.008	__	__	__	__
	0.004	__	__	__	__
	0.002	__	__	__	__
	0.001	__	__	__	__
	0.0005	__	__	__	__
MP8	0.032	20	17	__	__
	0.016	__	15	__	__
	0.008	__	__	__	__
	0.004	__	__	__	__
	0.002	__	__	__	__
	0.001	__	__	__	__
	0.0005	__	__	__	__
MP9	0.032	25	__	35	15
	0.016	17	__	33	12
	0.008	13	__	22	10
	0.004	12	__	18	__
	0.002	12	__	__	__
	0.001	12	__	__	__
	0.0005	12	__	__	__
MP10	0.032	__	__	__	16
	0.016	__	__	__	__
	0.008	__	__	__	__
	0.004	__	__	__	__
	0.002	__	__	__	__
	0.001	__	__	__	__
	0.0005	__	__	__	__

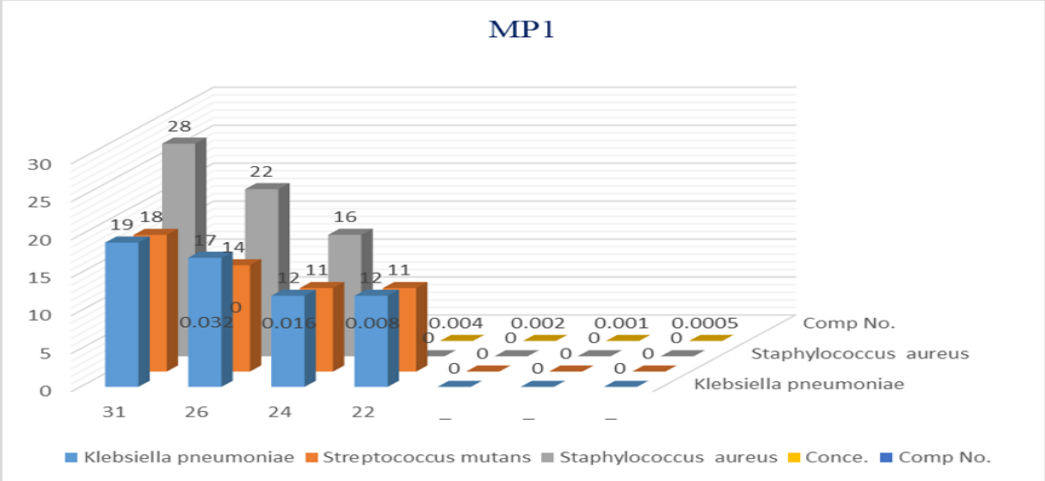


FIGURE 1: The effect of varying MP1 concentrations on the four bacterial species

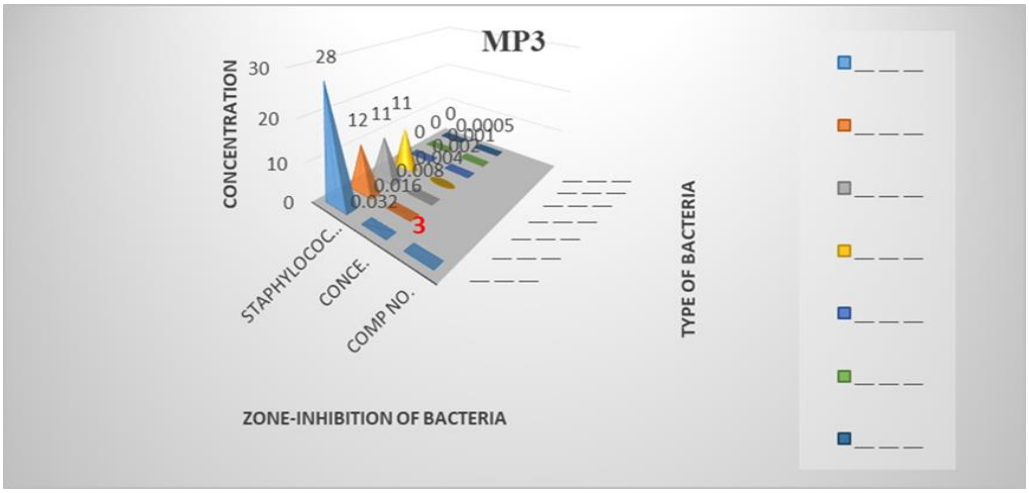


FIGURE 2: The effect of varying MP1 concentrations on the four bacterial species

FIGURE 3: Some MP1 and MP4 concentrations show different inhibition diameters for Klebsiella pneumoniae and Streptococcus mutans bacteria.

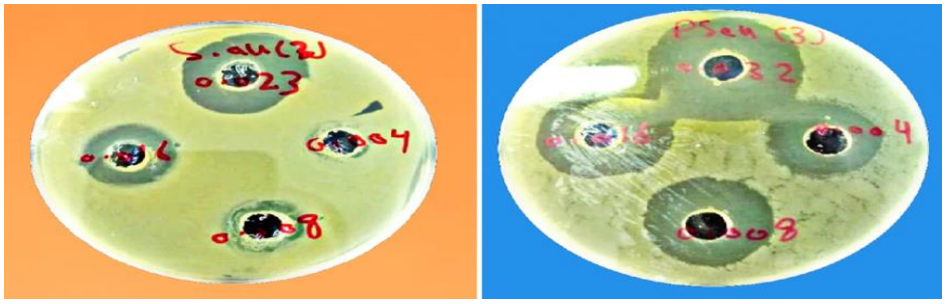


FIGURE 4: Some MP3 concentrations show different inhibition diameters for Pseudomonas aeruginosa and Staphylococcus aureus

4. CONCLUSION

All new Schiff bases (MP1-MP10) were characterized and their biological activity was examined in this work. It also featured the development of new forms of organic salts including various amines with aliphatic ring structures: 1-piperidinium-5-amino-1,2,4-triazole-3-thiolate.

On the other hand, it should be mentioned that when compared to the results of peer studies in the same field, all of the current work's results could be considered keys to future studies that indicate the importance of piperidinium triazole salts for different Schiff bases.

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