https://doi.org/10.48047/AFJBS.5.3.2023.01-08

African Journal of Biological Sciences

Open Access Research Paper

Synthesis and structural determination of piperidinium-5-amino-1, 3, 4-thiadiazole-2-thiolate and some of their Schiff bases and study of their biological activity

Noora Abdul Rhman[a], and Mukhlif Mohsin Slaihim[b*].

[a] *College of Education, University of Samarra, Iraq*

[b] *College of Applied Sciences, University of Samarra, Iraq*

*Corresponding author: mukhlif.m.s@uosamarra.edu.iq

Article Info

Volume 5, Issue 3, July 2023

Received:18 May 2023

Accepted :15 June 2023

Published: 12 July 2023

doi:10.48047/AFJBS.5.3.2023.21-31

Abstract

The study included the preparation of a series of new five-member rings represented by Schiff bases, which started with the salt of piperidinium-5-amino-1, 3, 4-thiadiazole-2-thiolate as their starting material. The new Schiff bases of piperidinium salts (S1–S10) were synthesized in one pot via compound (SP) and corresponding aldehyde in the presence of piperidine. The melting points of final products were uncorrected and these molecules were characterized by infrared spectroscopy and nuclear magnetic resonance spectroscopy. The biological activity of the prepared compounds was evaluated against four types of bacteria; (*Pseudomonas aeruginosa* and *klebcellacoccus*) as gram-negative and (*Staphylococcus Aureus* and *Streptococcus*) as Gram-positive bacteria.

Keywords: Piperidinium salts, 2-amino-1, 3, 4-thiadiazole-5-thiol, Schiff bases, biological activity.

1. Introduction

Schiff bases are a large class of organic molecules distinguished by the presence of a double bond between carbon and nitrogen atoms. Many of their compounds have a range of alkyl or aryl substituents that could be created by a number of techniques. As a result, different uses of this sort of chemical achieve different goals. This sort of organic substance may be synthesized in the laboratory and is found in nature. Schiff bases have long been an inspiration to many chemists and biochemists (Raczuk et al., 2022). Scientists have employed Schiff base in a wide range of medical applications such as antibacterial (Hwang et al., 2020; Panneerselvam et al., 2009), antifungal (Rai, & Kumar, 2013), Antitumor (Ali et al., 2020), Antiviral (Illán-Cabeza et al. 2008), anti-HIV (Kumar et al., 2010), Herbicidal (Roy et al., 2020), anticancer (Khairuddean et al., 2020), and anti-influenza virus (Illán-Cabeza et al., 2013). Several Schiff bases for the 2-amino-1, 3, 4-thiadiazole ring, including treatment of the ring with vanillin to prepare the corresponding Schiff base, were prepared by Ameen and Qasir (Ameen et al., 2012).

Since not many of the piperidinium salts with Schiff base units have been reported that indicate pharmacological properties as antibacterial agents, the research work focused on the new Schiff bases preparation of the salt of piperidinium-5-amino-1, 3, 4-thiadiazole-2-thiolate. The work on these 1,3,4-thiadiazole ring derivatives focused on four types of bacteria; (*Pseudomonas aeruginosa and klebcellacoccus*) as gram-negative and (*Staphylococcus Aureus and Streptococcus*) as Gram-positive bacteria.

2. Experimental

2.1. Chemicals

The chemicals and reagents utilized in this study of all the synthesized compounds can be as follows: Thiosemicarbazide, (ALPHA Chemika, India); Piperidine, (BDH, England); carbon disulfide CS_2, (ALPHA Chemika, India); absolute ethanol; 4-bromobenzaldehyde; 2-bromobenzaldehyde,(Fluka, brand); 4-Hydroxybenzaldehyde (Sigma, brand); 4-hydroxy-3-methoxy benzaldehyde,(BDH, England); 2,4-dihydroxy benzaldehyde,(Sigma, brand); 4-methyl benzaldehyde,(Fluka, brand); 4-nitro benzaldehyde;4-Dimethylamino benzaldehyde; 4-chloro benzaldehyde; Dimethyl sulfoxide-d_6 (DMSO), (Sigma-Aldrich, USA); TLC silica gel 60 F254, aluminum sheet, 20cm x 20cm (Merck, Germany).

2.2. Instruments

All the devices or instruments utilized for the determination structure of synthesized compounds are located at the College of Applied Sciences, University of Samarra; except for a Bruker Avance (400 MHz). The nuclear magnetic resonance, (^{1}H-NMR) spectra were measured at Basra University, College of Education, Department of Chemistry, utilizing a Bruker Avance (400 MHz) and DMSO-d_6 solvent. Infrared spectra were recorded utilizing a Fourier Transform Infrared Spectrophotometer/FTIR-8400S device supplied by Shimadzu

Japanese Company: Samples were prepared as (KBr) discs. Mass spectra were recorded utilizing a GC-MS-QP 2010 Ultra Shimadzu.

2.3 Biological assay

2.3.1 Compounds and cells

The DMSO solvent was utilized to dissolve all test compounds at the first concentration of 0.032 mg * mL^{-1} and then serially diluted for utilization in a culture medium. Four types of pathogenic bacteria were used: Two are gram-negative (Gr-ve): *Pneumonia klebsiella*, and *Pseudomonas aeruginous*. In addition, two are gram-positive (Gr+ve), which are *Staphylococcus aureus*, and *Streptococcus mutans*. The four bacterial species and the tests conducted on them were in the Microbiology Laboratory/Pathological Analysis Department/College of Applied Sciences/ University of Samarra.

2.3.2 Antibacterial assay

Test solutions for the compounds of (S1-S10) were prepared by utilizing the organic solvent DMSO and several different concentrations were prepared from it, (0.032, 0.016, 0.008, 0.004, 0.002, 0.001, 0.0005) respectively, for each compound and they were applied to the four aforementioned bacteria. The seven concentrations had distributed on two plates by the agar well diffusion method and seven holes had made with a diameter of 5 mm in the center of the agar at the circumference of each plate. Then, in each hole, 50-70 (µL) of the solutions had injected in different concentrations. A micro pipet utilization for injection of each hole and recording results have been done at a temperature of 37 °C after 18-24 hours.

2.4. Synthesis method

2.4.1 The reported method by (Yusuf et al., 2008**), was followed for the synthesis of compound PS.**

2.4.2 General procedure for the preparation of Schiff base compounds (S1-S10).

A new series of Schiff bases (S1-S10) was synthesized by mixing in one pot, an equimolar of compounds (0.001 mol) of one of the aromatic aldehyde derivatives, PS and piperidine, respectively, in (50 ml) of absolute ethanol in a round bottom flask. The contents of the reaction were refluxed with stirring for 6 hours. The mixture is concentrated and let to cool slowly. The precipitate formed was filtered, dried, and purified by appropriate methods.

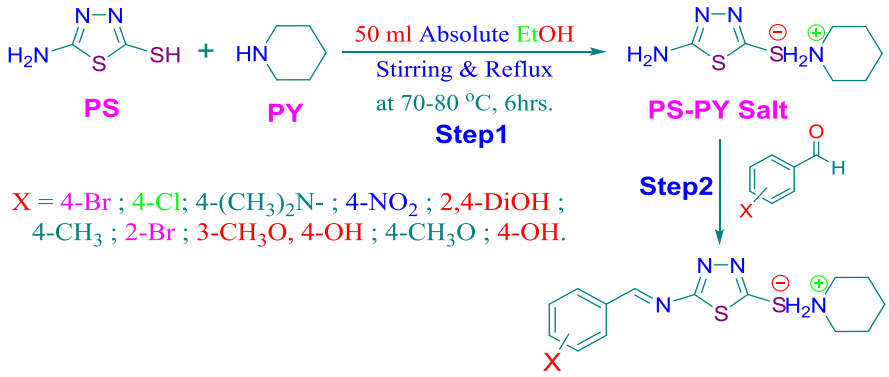
Table 1: physical properties of new Schiff base series (S1-S10).

Chemical Symbol	M. w	°C M.P	Color	Yield%
S1	385.3	184-186	Orange	**52.0**
S2	340.9	168-170	Yellow	**70.5**
S3	349	228-230	Orange	**43.5**
S4	351.4	180-182	Somber Orange	**14.3**

S5	338.4	158-160	Yellow	**77.33**
S6	320.5	172-174	Brawn	**53.13**
S7	385.3	155-157	Vivid Orange	**38.9**
S8	352.10	Sticky	Chocolate	**44.7**
S9	336.5	145-143	Yellow	**66.9**
S10	322.4	Sticky	Mustard	**90.4**

3. Results and Discussion

Slaihim et al., (2019), described a new method for synthesizing a new series of Schiff bases. In this work, we created a new series of Schiff bases (S1-S10) by refluxing a one-pot reaction of (PS-PY) salt in 100% ethanol and a few drops of piperidine before adding a series of substituted benzaldehyde (Scheme 1).



Scheme 1: Synthesis pathway of piperidinium-5-amino-1, 3, 4-thiadiazole-2-thiolate derivatives with Schiff base moiety.

A new Schiff base series (S1-S10) was successfully synthesized and structurally determined. The next five tables, 1, 2, 3, 4, and 5, include the summaries of physical properties, ^{1}H-NMR, IR, GC-MS, and MICs of the new series (S1-S10) data, respectively. The Schiff base unit is confirmed by some techniques of organic identification such as IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy. The -NH_2 and carbonyl groups were absent in the IR spectra, but the absorption band N=CH (of the imine group) was present. The Schiff base, or imine (-N=CH-), can be observed in the ^{1}H NMR spectra as a singlet at 9.60–10.30 ppm and a peak at 152.30-164.20 ppm in the ^{13}CNMR spectra. This group (-N=CH-) is an important group due to its flexibility and structural similarities with SAR (the structure-activity relationship). All these properties relate to the mechanism and potential of a promising antibacterial. The biological activity of all prepared Schiff base derivatives is evaluated against four types of Gram-positive and Gram-negative bacteria; the four types of bacteria used in the current study are Staphylococcus aureus, Streptococcus mutans, Klebsiella pneumoniae, and Pseudomonas aeruginosa. All the new compounds tested showed inhibitory activity against one or more of the four bacterial species selected in this

study; this activity ranged from moderate to strong. As the study showed, compound S1 did not show any inhibitory activity at all the concentrations used. As for the rest of the tested materials, they showed a clear and, for the most part, medium inhibitory effect, and the values of the minimum inhibitory concentration (MIC), according to the results, were as follows: Compound S2 showed an inhibitory effect against Staphylococcus aureus with effect diameters of 15 mm at the lowest concentration used in the study (0.0005 mg/ml). As for the compounds S9, S8, S4, and S10, they showed an inhibitory effect against Streptococcus mutans with an effective diameter of 15–20 mm, respectively.

Table 2: ^{1}H-NMR characteristic data of compounds **L1-L6**

Structure/Cod	Chemical Shift (δ) ppm	Signal Features	No. of Protons	Type of Protons
L1/S3	**8.42**	**s**	**1H**	**(CH=N-)imine**
	7.80	**d, *J* = 8.8 Hz**	**2H**	**aromatic**
	6.81	**d, *J* = 8.8 Hz**	**2H**	**aromatic**
	3.07	**s**	**6H**	**-N(CH_3)$_2$**
	2.97	**t, *J* = 5.7 Hz**	**4H**	**piperidiniun**
	1.65	**p, *J* = 5.5 Hz**	**4H**	**piperidiniun**
	1.53	**p, J = 5.6 Hz**	**2H**	**piperidiniun**
L2/S4	**8.50**	**s**	**1H**	**(CH=N-)imine**
	8.04	**d, *J*=8.1 Hz**	**2H**	**aromatic**
	8.29	**d, *J*=8.2 Hz**	**2H**	**aromatic**
	3.02	**t, *J*=5.51 Hz**	**4H**	**piperidiniun**
	1.60- 1.62	**m**	**4H**	**piperidiniun**
	1.35-1.37	**m**	**2H**	**piperidiniun**
L3/S5	**8.53**	**s**	**1H**	**4-OH-Ph**
	8.25	**s**	**1H**	**(CH=N-)imine**
	7.86	**d, *J* = 8.7 Hz**	**1H**	**aromatic**
	7.58	**s**	**1H**	**aromatic**
	6.85	**d, *J* = 8.5 Hz**	**1H**	**aromatic**
	3.57	**s**	**1H**	**2-OH-Ph**
	2.99	**t, *J* = 4.5Hz**	**4H**	**piperidiniun**
	1.67	**p, *J* = 5.6 H**	**4H**	**piperidiniun**
	1.55	**p, J = 5.5Hz**	**2H**	**piperidiniun**
L4/S7	**8.74**	**s**	**1H**	**(CH=N-)imine**
	7.93	**dd, *J* = 8.0 Hz**	**1H**	**aromatic**
	7.86	**d, *J* = 8.7 Hz**	**1H**	**aromatic**
	7.81	**t, *J* = 8.0 Hz**	**1H**	**aromatic**
	7.70	**dd, *J* = 8.0 Hz**	**1H**	**aromatic**

	2.99	**t, *J* = 4.0 Hz**	**4H**	**piperidiniun**
	1.68	**p, *J* = 5.8 Hz**	**4H**	**piperidiniun**
	1.56	**p, J = 5.8 Hz**	**2H**	**piperidiniun**
L5/9	**8.65**	**s**	**1H**	**(CH=N-)imine**
	7.98	**d, *J* = 8 Hz**	**2H**	**aromatic**
	7.02	**d, *J* = 8 Hz**	**2H**	**aromatic**
	3.87	**s**	**3H**	**-OCH_3**
	2.99	**t, *J* = 5.7 Hz**	**4H**	**piperidiniun**
	1.67	**p, *J* = 5.5 Hz**	**4H**	**piperidiniun**
	1.56	**p, J = 5.6 Hz**	**2H**	**piperidiniun**
L6/S10	**8.53**	**s**	**1H**	**(CH=N-)imine**
	7.59	**d, *J* = 8.6 Hz**	**2H**	**aromatic**
	6.84	**d, *J* = 8.6 Hz**	**2H**	**aromatic**
	2.99	**t, *J* = 5.7 Hz**	**4H**	**piperidiniun**
	1.67	**p, *J* = 5.7 Hz**	**4H**	**piperidiniun**
	1.55	**p, *J* = 5.8 Hz**	**2H**	**piperidiniun**

Table 3: IR (ν, cm^{-1}) characteristic bands of (S1–S10) series.

No.	ν(C-H) Ar	ν (C-H)Al	ν (CH=N)	ν (C=C) Ar	Others
S1	3016	2935	1610	1589,1558	**C-Br 698**
S2	3118	2951	1645	1560,1645	**C-Cl 784**
S3	3082	2893	1600	1533,1508	**C-CH_3 1369**
S4	3020	2900	1601	1521,1562	**C-NO_2 1348**
S5	3132	2926	1604	1577,1604	**3414-3650**
S6	3124	2929	1610	1485,1508	**C-CH_3 1363**
S7	3101	2927 4	1608	1558,1508	**C-Br 669**
S8	3020	2947	1668	1456,1516	**O-H 3385**
S9	3110	2947	1668	1516,1560	**O-H 3590.07** **O -$CH_3$1456**
S10	3022.	2927	1600	1456,1517	**O-H 3590**

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

Products NO .	Chemical formula	Exact Mass	Mass spectrum m\z (relative intensity) of fragments			
S2	$C_{14}H_{15}CLN_4S_2$	340	341[M⁺,24 %]	111[M⁺,26%]	84[M⁺,73%]	**57[M⁺,100%]**
S5	$C_{13}H_{16}N_4O_3S_2$	338	339[M⁺20 %]	248[M⁺,11%]	130[M⁺20%]	**73[M⁺,100%]**
S6	$C_{15}H_{20}N_4S_2$	320	321[M⁺,2 %]	285[M⁺,5%]	222[M⁺,6%]	**102[M⁺,100 %]**
S9	$C_{15}H_{20}N_4OS_2$	336	337[M⁺,10 %]	294[M⁺15%]	224 [M⁺,17%]	**117 [M⁺,100%]**
S10	$C_{14}H_{18}N_4OS_2$	322	323[M⁺,22 %]	264 [M⁺,2%]	235 [M⁺,20%]	**207[M⁺,100 %]**
TH	$S_2H_3N_3S_2$	131	132 [M⁺,20%]	101[M ⁺ ,4 6%]	73[M⁺,100%]	----------

Table 5: MICs of the new series (S1-S10) against gram-negative and gram-positive bacterial strains.

COMPOUND: (S2)	**s.aurus**	**Strepto**	**Klepcella**	**Pseudomonas**
0.032	26	22	26	25
0.016	30.3	21	25	24
0.008	27	21	23	18
0.004	22	20	22	24
0.002	24	19	0	22
0.001	22	18	0	12
0.0005	20	18	0	16
COMPOUND: (S3)				
0.032	0	18	23	**18**
0.016	0	18	20	**15**
0.008	0	17	18	**14**
0.004	0	16	15	**11**
0.002	0	0	15	**0**
0.001	0	0	15	**0**
0.0005	0	0	14	**0**

COMPOUND: (S4).				
0.032	29	20	14	**16**
0.016	24	20	13	**20**
0.008	21	15	14	**25**
0.004	18	16	0	**29**
0.002	15	16	0	**0**
0.001	14	16	0	**0**
0.0005	13	17	0	**0**
COMPOUND: (S5)				
0.032	19	25	20	**20**
0.016	14	30	20	**15**
0.008	15	25	13	**13**
0.004	13	16	12	**11**
0.002	15	15	10	**0**
0.001	15	0	0	**0**
0.0005	11	0	0	**0**
COMPOUND: (S6)				
0.032	25	30	21	**15**
0.016	13	27	23	**18**
0.008	20	24	20	**16**
0.004	20	23	12	**11**
0.002	17	20	11	**18**
0.001	0	13	0	**16**
0.0005	0	0	0	
COMPOUND: (S7)	s.aureus	Strpto	Klepcella	**Klebsiella**
0.032	25	22	16	**17**
0.016	20	22	16	**13**
0.008	20	19	11	**13**
0.004	22	19	0	**12**
0.002	15	17	0	**0**
0.001	14	12	0	**0**
0.0005	12	0	0	**0**
COMPOUND: (S8)				
0.032	25.5	21	0	**18**
0.016	15	20	0	**15**
0.008	15	17	0	**14**
0.004	15	17	0	**11**
0.002	0	17	0	**0**

0.001	0	17	0	**0**
0.0005	0	15	0	**0**
COMPOUND: (S9)				
0.032	20	35	18	**20**
0.016	19	35	18	**15**
0.008	17	31	16	**15**
0.004	0	25	14	**11**
0.002	15	22	0	**14**
0.001	0	19	0	**11**
0.0005	0	18	0	**11**
COMPOUND: (S10)				
0.032	23	28	16	**20**
0.016	18	27	13	**11**
0.008	17	24	11	**0**
0.004	14	20	10	**0**
0.002	11	17	0	**0**
0.001	0	17	0	**0**
0.0005	0	15	0	**0**

4. Conclusion

The present study included the preparation, characterization, and study of the biological activity of all new Schiff bases (S1–S10). It also included the preparation of new types of organic salts bearing in their composition different types of amines with aliphatic ring structures: 1-piperidinium-5-amino-4,3,1-thiadiazole-2-thiolate (piperidine-1-ium 5-salt).

Acknowledgment

The authors would mind thanking the college of Applied Sciences, Samarra University /Iraq for providing the lab facilities.

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Cite this article as: **Noor Ghazi saab (2023).**
Inter-canine distance for gender determination in adolescence
Noor Ghazi saab, African Journal of Biological Sciences. 5(3),21-27. doi: 10.33472/AFJBS.5.3.2023.21-31