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Synthesis, characterization and antibacterial evaluation of some sulfonamide Schiff base derivatives

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ABSTRACT

New series of Schiff base compounds obtained from sulfa drugs have been synthesized by the reaction of sulfonamide compounds (sulfadiazine, sulfapyridine, sulfamethazine, or sulfamerazine) with corresponding aromatic aldehydes (3-pyridinecarboxaldehyde or 4-pyridinecarboxaldehyde). The synthesized compounds were characterized by FT-IR, ESI-Mass, and ^{1}H-NMR spectroscopy to confirm the chemical structures of synthesized compounds. The purity of all synthesized compounds were verified using pre-coated TLC (MERCK) plates using dichloromethane: methanol (9:1) solvent system. The chromatographic plates were viewed under ultraviolet(UV) light at 254 nm The sulfonamide Schiff base compounds were tested for antibacterial evaluation against two pathogenic Gram-positive bacteria (*Staphylococcus aureus, Streptococcus spp.)* and two pathogenic Gram-negative bacteria (*Escherichia coli* and *Klebsiella pneumonia*). The antibacterial activity of synthesized compounds was evaluated by assessing the inhibitory concentration by measuring their inhibition zone versus certain kinds of standard antibiotics with concentrations (500, 750, and 1000) μg /ml. Most synthesized compounds at high concentration were moderately active against all tested bacteria ,compound SH7 showed best antibacterial activity for both (Gram-positive and Gram-negative) bacteria while SH8 compound exhibited moderate antibacterial activity against Gram-positive bacteria and weak activity (<10 mm) against Gram-negative bacteria and all synthesized compounds were less antibacterial activity for all tested bacterial strains than standard drugs.

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INTRODUCTION

A class of synthetic organic molecules structurally similar to PABA can inhibit bacterial growth and development named sulfonamides (sulfa drugs). Sulfonamides are molecules containing sulfur directly bound to a benzene ring in a -SO_2NH_2 moiety (Tilles, 2001). Sulfa drugs were developed and appeared in 1932 as the first effective medicines against bacterial infection at a time when death was common due to bacterial diseases like pneumonia and septicemia (Sneader, 2001). Schiff base, with a functional group of imines, is an aldehyde/ketone condensation reaction with a primary amine. It was reported at the first time about 150 years ago by Hugo Schiff (1864) and referred to his name Schiff from here on (Silva, 2011). The -C = N- imine bond plays a special role in giving these compounds various biological activities such as anti-microbial, anti-cancer, anti-inflammatory, anti-convulsion and enzymatic activity (Jesmin *et al.*,

2010; Al-Garawi *et al.*, 2012; Sahu *et al.*, 2012; Jarrahpour, 2013; Kulkarni, 2017). Sulfonamides also exhibited wider biological action as anti-bacterial, anti-viral, diuretic, and anti-cancer (Ghosh *et al.*, 2016; Husain, 2016; Reddy, 2016; Tacic, 2017). Developing resistance to antibiotics is a major issue in antibacterial therapy and needs ongoing research into new antibacterial classes (Gupta and Halve, 2015). Sulfonamide Schiff base derivative displayed promising antibacterial activity. In 2017, Ghorab, his coworkers, synthesized some novel series of 4-(4,4-dimethyl-2,6-dioxocyclohexylidene) benzene sulfonamide derivatives and reported that some synthesized compounds were found to be more potent against all bacterial strains tested compared with tetracycline (Ghorab *et al.*, 2017). The target of this research is to synthesize, characterize eight sulphonamide-derived Schiff bases, and potentially study the antibacterial activity against some Gram-positive and Gram-negative bacteria.

Aim of work

Synthesis of new sulfonamide Schiff base compounds and study the antibacterial activity to encourage the removal of anti-bacterial resistance.

MATERIALS AND METHODS

Experimental

Unless otherwise stated, all solvents and reagents were of analytical quality, and all experiments were conducted at 25 ^{o}C with deionized water resistivity (about 18.2 cm) (Bugg and Walsh, 1992).

Chemicals

1-Absolute Methanol, Chem-lab, Belgium.

2-Absolute Ethanol, Chem-lab, Belgium.

3-Glacial acetic acid, Macron fine chemical, Germany.

4-Sulfadiazine, Sigma-Aldrich, Germany.

5-Sulfapyridine, Sigma-Aldrich, Germany.

6-Sulfamethazine, Sigma-Aldrich, Germany.

7- Sulfamerazine, Sigma-Aldrich, Germany.

8-3-pyridinecarboxaldehyde, Sigma-Aldrich, Germany.

9-4-pyridinecarboxaldehyde, Sigma Aldrich, Germany.

Synthesis of the compounds

Synthesis of sulfonamide Schiff base derivatives [SH1, SH5] General procedure

A mixture of (0.01mole,2.5g) suspended sulfadiazine in 50ml boiling absolute methanol and (0.012mole,1.1ml) of corresponding aldehydes (3-pyridinecarboxaldehyde or 4-pyridinecarboxaldehyde), and refluxed by employing glacial acetic acid (2 drops) as catalyst for (8) hrs. The poor solubility of sulfadiazine in methanol is a reason for a long reaction time. Finally, the crystal powder was Filtered, washed with cold methanol, and dried at room temperature. The product is recrystallized by absolute ethanol (Krátk, 2017).

Synthesis of sulfonamide Schiff base derivatives [SH2,SH3,SH4,SH6,SH7 and SH8] General procedure

A mixture of (0.01mole) of sulfonamides (sulfapyridine, sulfamethazine, or sulfamerazine) with (0.012mole,1.1ml) of corresponding aldehydes (3-pyridinecarboxaldehyde or 4-pyridinecarboxaldehyde) dissolved in (50 ml) absolute methanol were refluxed by employing (2 drops) glacial acetic acid as catalyst for (4hrs). The precipitate crystal powder formed were filtered, washed with cold methanol, and dried at room temperature (Khubeiz, 2016).

RESULTS AND DISCUSSION

Synthesized Sulfonamide Schiff base derivatives with chemical name and physical properties, as shown in Table 1 and Table 2 respectively, were prepared from condensation reaction of different sulfonamides (sulfadiazine, sulfapyridine, sulfamethazine or sulfamerazine) with aromatic aldehydes (3-pyridinecarboxoldehyde or 4-pyridinecarboxaldehyde), as shown in Figure 1. TLC was performed to check the purity of the prepared compounds, and based on their Mass, FTIR, and 1HNMR data, the structures of the prepared compounds were assessed.

Mass spectra of the synthesized compounds (SH1 to SH8)

The mass spectra for all synthesized compounds which have chemical structures as shown in Figures 2, 3, 4, 5, 6, 7, 8 and 9 performed by electron spray ionization (ESI) technique and achieved from apex-iv detector to determine their molecular weights by $(M+H)^{+}$ ion which have peaks at m/z using chloroform and methanol as solvents at the University of Tehran, Iran.

The data from mass spectra displayed the right molecular ions as indicated by their molecular weight, as shown in Table 3.

FT-IR spectra of the synthesized compounds (SH1) to (SH8)

Table 1: ynthesized sulfonamide Schiff base compounds

No.	symbol	Chemical name
1.	SH1	(E)-N-(4-methylpyrimidin-2-yl)-4-((pyridin-4-ylmethylene) amino)- benzene sulfonamide
2.	SH2	(E)-N-(pyridin-2-yl)-4-((pyridin-3-ylmethylene) amino) benzene sulfonamide
3.	SH3	(E)-N-(4,6-dimethylpyrimidin-2-yl)-4-((pyridin-3-yl methylene) amino) benzene sulfonamide
4.	SH4	(E)-N-(4-methylpyrimidin-2-yl)-4-((pyridin-3-yl methylene) amino) benzene sulfonamide
5.	SH5	(E)-4-((pyridin-4-ylmethylene) amino)-N-(pyrimidin-2-yl) benzene sulfonamide
6.	SH6	(E)-N-(pyridin-2-yl)-4-((pyridin-4-ylmethylene) amino) benzene sulfonamide
7.	SH7	(E)-N-(4,6-dimethylpyrimidin-2-yl)-4-((pyridin-4-yl methylene) amino) benzene sulfonamide
8.	SH8	(E)-N-(4-methylpyrimidin-2-yl)-4-((pyridin-4-yl methylene) amino) benzene sulfonamide

Table 2: Physical properties of the products

Comp.	Molecular formula	M.Wt. (g/mole)	color	M.P 0C	Yield%
SH1	C16H13N5O2S	339	Off white	208-211	98.82
SH2	C17H14N4O2S	338	Off white	215-218	79.88
SH3	C18H17N5O2S	367	Off white	133-135	66.75
SH4	C17H15N5O2S	353	Off white	159-161	98.86
SH5	C16H13N5O2S	339	Pale yellow	188-191	59.01
SH6	C17H14N4O2S	338	Pale yellow	198-200	86.18
SH7	C18H17N5O2S	367	Pale yellow	149-151	93.99
SH8	C17H15N5O2S	353	Pale yellow	169-171	88.92

Table 3: The mass spectral data of synthesized compounds

Comp.	M.wt	(M+H) +
SH1	339	340.2
SH2	338	339.2
SH3	367	368.2
SH4	353	354.2
SH5	339	339.9
SH6	338	339.6
SH7	367	367.8
SH8	353	354.1

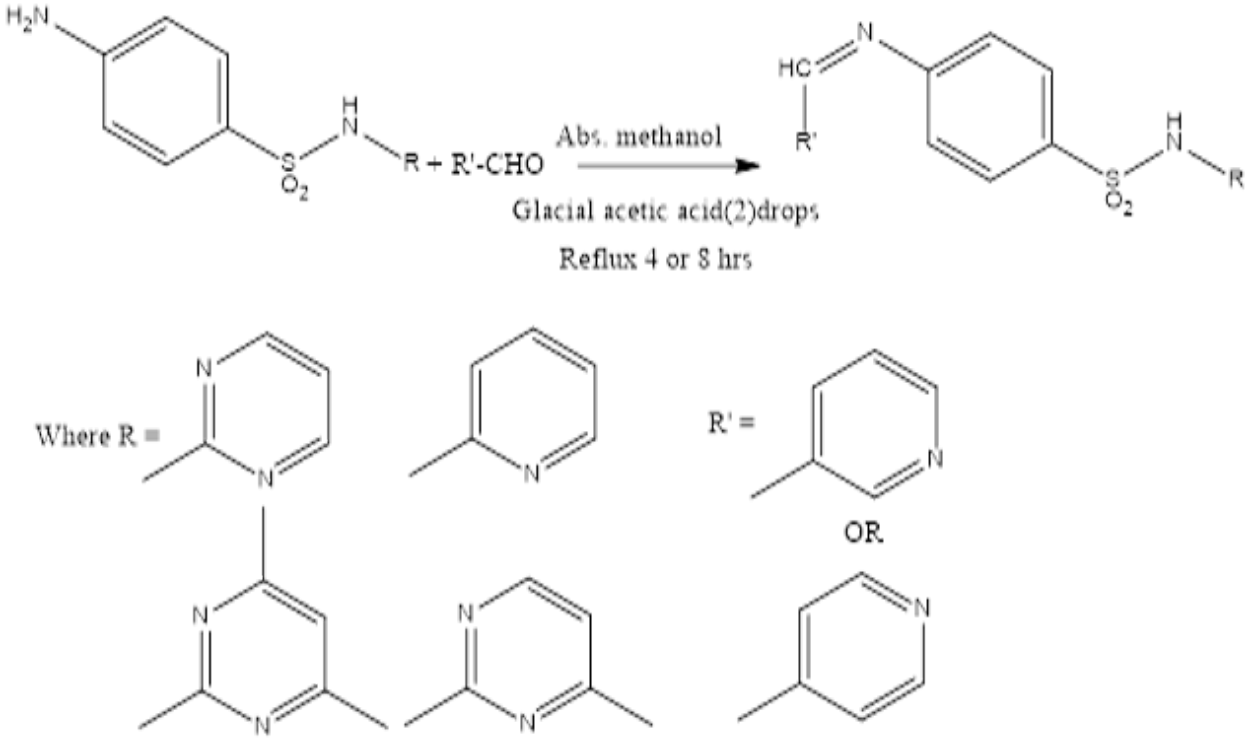

Figure 1: Synthesis of sulfonamide Schiff base derivatives SH1 to SH8

The IR spectra performed by the KBr disk method for all synthesized compounds, using FT-IR 8400S SHIMADZU (Japan) at the Pharmaceutical Chemistry Department / College of Pharmacy / University of Basrah.

The synthesis of all sulfonamide Schiff base derivatives (SH1-SH8) were indicated in their IR spectrum from the presence of azomethine (C=N)stretching vibration band appeared at range 1597-16Table 1 31 cm^{-1} combined with IR bands disappearance at range 1710-1730 cm^{-1} correlating to (C=O) aldehydes group and the doublet bands related to NH_2 sulfonamide group (Jasim, 2011; Almashal *et al.*, 2013; Chohan and Shad, 2012).

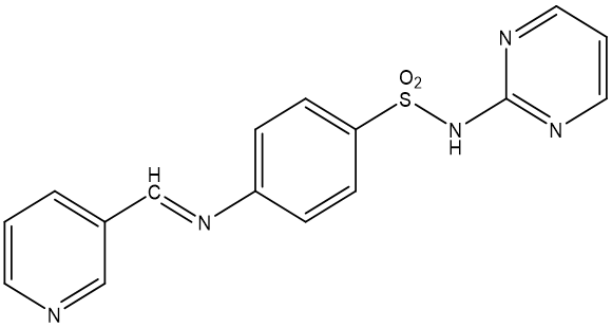

Figure 2: The structure of SH1

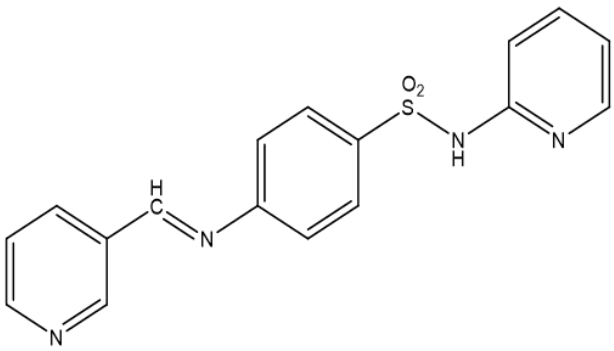

Figure 3: The structure of SH2

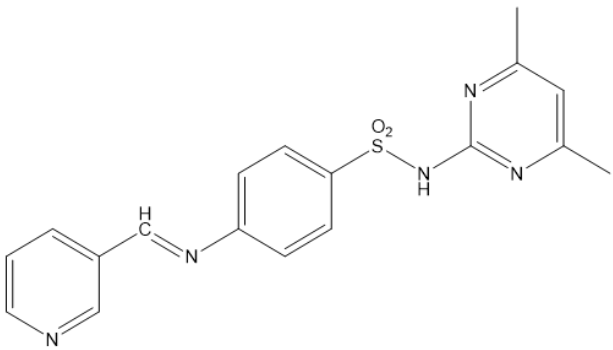

Figure 4: The structure of SH3

FT-IR spectrum of SH1

The compound (SH1) showed medium absorption band at 3255.84 cm^{-1} referred to N-H stretching of amide, the medium absorption bands at 3039.1-3086.11cm^{-1} assigned to aromatic C-H stretching vibration, the strong stretching absorption band at 1597.06 cm^{-1} related to C=N of imine, another strong absorption band at 1581.63 cm^{-1} related to

Table 4: Inhibition zone of sulfonamide Schiff base derivatives (SH1-SH8) and standard drugs against tested bacteria

Compound	Concentration (μg/ml)	(Gm+ve) Bacteria Inhibition zone (mm)		(Gm-ve) Bacteria Inhibition zone (mm)	
		S. aureus	*Str. spp.*	*K. pneumonia*	*E. coli*
SH1	1000	14	14	12	12
	750	-	8	8	-
	500	-	8	8	-
SH2	1000	14	15	10	12
	750	-	8	10	10
	500	-	8	-	-
SH3	1000	10	13	14	13
	750	8	10	14	13
	500	-	10	-	-
SH4	1000	12	12	16	15
	750	-	-	-	-
	500	8	-	-	-
SH5	1000	13	16	15	12
	750	12	8	15	12
	500	-	-	10	-
SH6	1000	14	12	14	13
	750	-	8	14	-
	500	-	-	12	-
SH7	1000	15	15	15	16
	750	15	10	14	14
	500	-	10	14	14
SH8	1000	14	10	8	8
	750	14	-	8	8
	500	10	-	-	8
MethoprimÒ	1000	28	28	28	25
	750	12	24	28	22
	500	10	16	17	18
Ceftriaxone	1000	20	31	30	33
	750	19	25	30	20
	500	16	19	19	16
DMSO	PURE	-	-	-	-

S. aureus: Staphylococcus aureus. *Str. spp.:* Streptococcus spp.
K. pneumonia: Klebsiella pneumonia. *E. coli:* Escherichia coli.
Methoprim: Trade name drug of Sulfamethoxazole + Trimethoprim.

C=N of pyridine and pyrimidine rings, the strong bands at 1342.46 and 1157.29 cm^{-1} correlated to asymmetric and symmetric stretching vibration of S=O respectively, another strong medium stretching bands reported at 1535.34 cm^{-1} and 1485.19 cm^{-1} were the feature of C=C bonds.

FT-IR spectrum of SH2

The compound (SH2) showed medium absorption band at 3244.27 cm^{-1} referred to N-H stretching of amide, aromatic C-H showed medium stretching band at 3059.1 cm^{-1}, C=N(imine) exhibited strong stretching absorption band at 1627.92 cm^{-1} , another strong stretching band at 1608.63 cm^{-1} correlated to C=N of pyridine rings, while asymmetric and symmetric vibration of S=O showed strong absorption stretching band at 1384.89 and 1138 cm^{-1} respectively, aromatic C=C bonds showed strong medium stretching bands at 1535.34-1485.18 cm^{-1}.

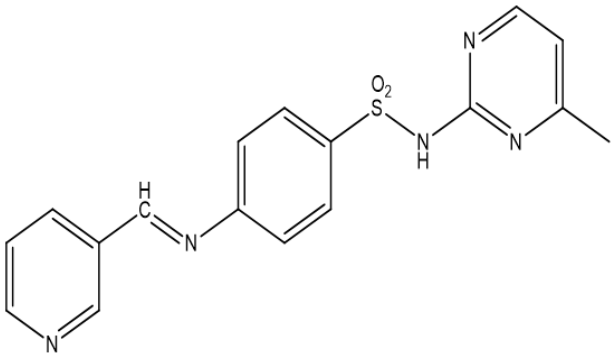

Figure 5: The structure of SH4

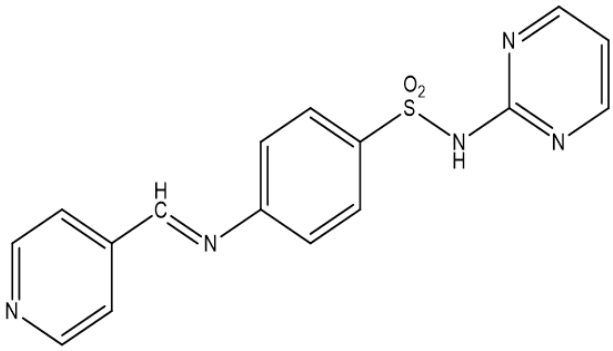

Figure 6: The structure of SH5

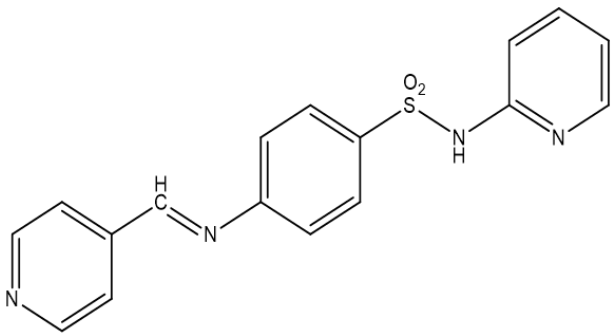

Figure 7: The structure of SH6

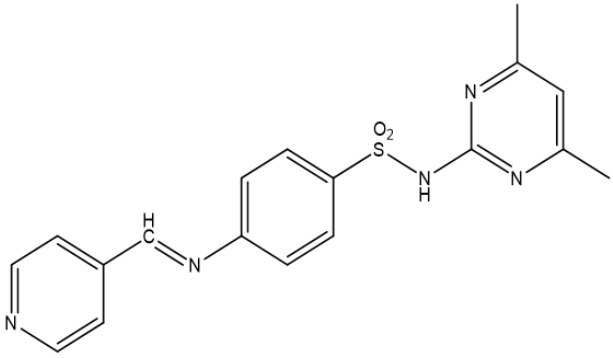

Figure 8: The structure of SH7

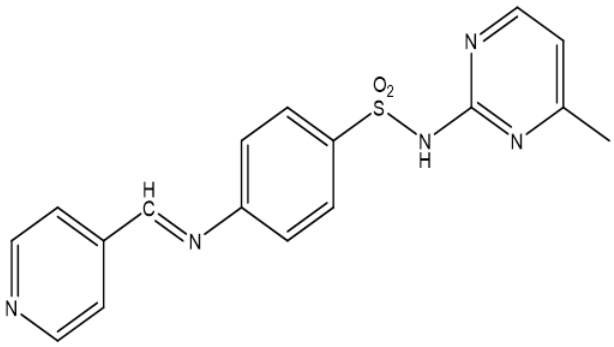

Figure 9: The structure of SH8

FT-IR spectrum of SH3

The compound (SH3) showed medium absorption band at 3259.7 cm^{-1} referred to N-H stretching of amide, the weak absorption bands at 3059-3086 cm^{-1} correlated to aromatic C-H stretching vibration while aliphatic C-H showed weak absorption band at 2935.6 cm^{-1} related to methyl group, C=N(imine) displayed strong stretching absorption band at 1597.06 cm^{-1} while C=N of pyridine and pyrimidine rings displayed strong stretching at 1558.48 cm^{-1}, the strong bands at 1323.17 and 1153.43 cm^{-1} related to asymmetric and symmetric stretching vibration of S=O respectively, while C=C bonds exhibited medium stretching bands at 1500-1531 cm^{-1}.

FT-IR spectrum of SH4

The compound (SH4) showed strong absorption band at 3251.98 cm^{-1} referred to N-H stretching of amide, aromatic C-H exhibited medium stretching band at 3039.81 cm^{-1} while aliphatic C-H exhibited medium stretching band at 2935.6 cm^{-1} related to methyl group, the strong stretching band at 1597 cm^{-1} related to C=N of imine, another strong stretching band at 1566 cm^{-1} related to C=N of pyridine and pyrimidine rings, the strong bands at 1342.46 and 1157.29 cm^{-1} related to asymmetric and symmetric stretching vibration of S=O respectively, C=C bonds showed stretching absorption bands at 1446-1527 cm^{-1}.

FT-IR spectrum of SH5

The compound (SH5) was described by medium absorption band at 3340.71 cm^{-1} attributed to N-H stretching vibration of amide, the medium absorption bands at 3039.81-3086.11 cm^{-1} assigned to aromatic C-H stretching vibration, the stretching band at 1597.06 cm^{-1} related to C=N of imine, another strong band at 1581.63 cm^{-1} related to C=N of pyridine and pyrimidine rings, the strong absorption bands at 1334.74 and 1153.43 cm^{-1} correlated to asymmetric and symmetric stretching vibration of S=O respectively, the strong stretching bands at

1438-1496 cm^{-11} were the feature of C=C bonds.

FT-IR spectrum of SH6

The compound (SH6) was described by medium absorption band at 3390.86 cm^{-1} referred to N-H stretching of amide, aromatic C-H showed medium stretching band at 3032.1 cm^{-1}, C=N(imine) exhibited strong stretching absorption band at 1631.78 cm^{-1}, another strong stretching band at 1593.2 cm^{-1} correlated to C=N of pyridine rings, while asymmetric and symmetric vibration of S=O showed strong absorption stretching band at 1388.75 and 1134.14cm^{-1} respectively, aromatic C=C bonds showed strong medium stretching bands at 1512.91-1527.62 cm^{-1}.

FT-IR spectrum of SH7

The compound (SH7) was described by strong absorption band at 3383.14 cm^{-1}referred to N-H stretching of amide, the medium absorption band at 3035.96 cm^{-1} assigned to aromatic C-H stretching vibration while aliphatic C-H showed medium absorption band at 2924.09 cm^{-1} related to methyl group, C=N(imine) displayed strong stretching absorption band at 1597.06 cm^{-1}while C=N of pyridine and pyrimidine rings displayed strong stretching at 1562.34 cm^{-1}, the strong bands at 1311.59 and 1154.72 cm^{-1}related to asymmetric and symmetric stretching vibration of S=O respectively, while C=C bonds exhibited strong stretching bands at 1438.9-1519.91 cm^{-1}.

FT-IR spectrum of SH8

The compound (SH8) showed strong absorption band at 3387 cm^{-1} referred to N-H stretching of amide, aromatic C-H exhibited medium stretching band at 3051.9-3086.1 cm^{-1} while aliphatic C-H exhibited medium stretching band at 2924.09 cm^{-1} related to methyl group, the strong stretching band at 1597.06 cm^{-1} related to C=N of imine ,another strong stretching band at 1562.34 cm^{-1} related to C=N of pyridine and pyrimidine rings, the strong bands at 1319.31 and1153.43 cm^{-1}correlated to asymmetric and symmetric stretching vibration of S=O respectively, C=C bonds showed stretching absorption bands at 1454.3-1519.91cm^{-1}.

^{1} H-NMR spectra of the synthesized compounds (SH1) to (SH8)

1HNMR bands (solvent DMSO-d6) were reported using a 500 MHZ spectrometer.500MHz NMR (INOVA Switzerland) with TMS as an internal standard, performed by the University of Tehran / College of Science / Chemistry Department. All spectra had a peak of 2.5 ppm due to DMSO solvent, and some spectra had a sharp peak of 3.3 ppm owing to DMSO water solution (Silverstein *et al.*, 1981).

^{1} H-NMR spectrum of SH1

The compound (SH1) showed distinct multiplet signals at 6.56-9.08 ppm related to eleven aromatic protons, singlet signal at 8.7 ppm attributed to azomethine group, and the -NH signal proton appeared at 11.5 ppm due to the neighboring SO_2 deshielding effect.

^{1} H-NMR spectrum of SH2

The compound (SH2) displayed multiplet signals assigned to twelve aromatic protons at 6.54-9.06 ppm, while the singlet signal of azomethine observed at 8.7 ppm, and the singlet signal that appeared at 11.61ppm assigned to -NH group.

^{1} H-NMR spectrum of SH3

The spectrum of (SH3) compound, singlet signal displayed at 2.26 ppm attributed to six protons of two methyl group, the multiplet signals for nine aromatic protons observed at 6.54-9.09 ppm, the azomethine proton singlet signal showed at 8.71 ppm and the -NH singlet signal appeared at 11.5 ppm.

^{1} H-NMR spectrum of SH4

The (SH4) compound spectrum showed a singlet signal at 2.23 ppm related to -CH3 group, the eleven aromatic protons displayed at 6.56-9.06 ppm, while the singlet signal proton of (-CH=N) observed at 8.71 ppm, and the -NH proton signal showed at 11.22 ppm.

^{1} H-NMR spectrum of SH5

The compound (SH5) showed multiplet signals for eleven aromatic protons at 6.55-8.78 ppm, the (-CH=N) singlet signal proton observed at 8.51, while the SO_2NH singlet signal appeared at 11.44 ppm.

^{1} H-NMR spectrum of SH6

The spectrum of (SH6) compound exhibited distinct multiplet of their twelve aromatic protons at 6.82-8.07 ppm and singlet of their azomethine proton at 8.59 ppm while the proton signal of SO_2NH group was found to be at 11.21 ppm.

^{1} H-NMR spectrum of SH7

the (SH7) compound showed the characteristic of singlet signal at 2.23 ppm related to six protons of two (-CH_3) groups, the nine aromatic protons appeared at 6.74-7.75 ppm, the signal at 8.6 ppm related to azomethine singlet proton and the signal at 11.28 ppm assigned to (SO_2NH) group.

^{1} H-NMR spectrum of SH8

The singlet signals of the compound (SH8) at (2.33, 8.69, and 11.49) ppm were attributed to (-CH_3, -

CH=N and SO_2NH) respectively while the eleven aromatic protons appeared at 6.82-8.89 ppm.

Antibacterial activity

All synthesized compounds were checked in University of Basrah/College of Veterinary Medicine for their antibacterial activity against two Gram-positive bacteria (*Staphylococcus aureus, Streptococcus spp.*) and two Gram-negative bacteria (Escherichia *coli* and *Klebsiella pneumonia*)) using the diffusion technique of filter paper disc, For such a filter paper disk (6 mm), impregnated with specified concentrations (500 μg / mL,750μg / mL and 1000 μg / mL), synthetic compounds were placed on the Petri dishes under investigation. Similar plates for the standard drugs were prepared. The nutrient agar media was clinically activated and retained to check antibacterial activity, measuring the diameter of the inhibition area after 24 hours at 37^0c. Methoprim and ceftriaxone were used as standard drugs. The preliminary result showed that all compounds had varying degrees of inhibitory effect on the progression of various bacterial strains tested in Table 4. It was noticed from the results that the zone of inhibition increased with increase in concentration, so for high concentration (1000 μg/ml) , the compounds (SH1-SH7) showed moderate antibacterial activity (^{3}10 mm) against all tested Gram-positive and Gram-negative bacteria while compound (SH8) showed moderate antibacterial activity against Gram-positive bacteria and weak activity (<10 mm) against Gram-negative bacteria. All synthesized compounds showed less inhibition zone

comparable to standard drugs against tested bacteria. The inhibition zone depends on the nature of the bacterial strain, the solvent, and the compound structure. All the azomethine derivatives have the same basic moiety with different inside chain, thus side chains play a significant role in inhibition for a specific effect (Gupta and Halve, 2015), for that reason compound (SH7) showed best anti-bacterial-activity(^{3}15mm) from all synthesized compounds against both Gram-positive and Gram-negative bacteria which may be due to presence of two electron-donating substitution (CH_3) on aromatic structure and para position of nitrogen atom of pyridine ring (Bauer, 1996).

CONCLUSION

The synthesized sulfonamide Schiff base compounds were tested against two Gram-positive bacteria (*staphylococcus aureus, streptococcus spp.)* and two Gram-negative bacteria (*Escherichia coli* and *klebsiella pneumonia*). The result displayed that the compound (SH7) was highly active against all tested bacteria. All compounds except (SH8) were moderately active against all bacterial species, while (SH8) was moderate anti-bacterial activity against Gram-positive and weak activity against Gram-negative bacteria.

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Contribution of authors

We consider that the authors named in this article have done this work, and the authors will carry all liabilities relating to the article content. The research was conceived and designed by Mustafa M. Al-Hakiem. Rita S. Elias designed the experiment and revised the manuscript. The experiments were carried out, documented, and analyzed by Munther A. Mohammed-Ali.

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