Synthesis and antibacterial study for some heterocyclic compounds.

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Abstract:

Some heterocyclic compounds containing S,O and N have been synthesized starting from sulfadiazine drug. The starting material has converted to Schiff bases in order to be another derivative which are oxazepines and tetrazole rings. The structures of these derivatives have characterized by using FT-IR, H-NMR spectroscopy and the melting points were recorded with the TLC to check the purity of these compounds. The antibacterial activity has studied against sta **Keywords : Heterocyclic compounds, Schiff base, oxazepines.**

Inroduction :

Heterocyclic compounds are found as construction units through several biological molecules [(1)], mostly are molecules which contain five and six membered ring [(2)].

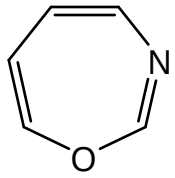
The synthesis of heterocyclic compounds is due to potential biological and industrial applications [(3-5)]. The heterocyclic compounds showed a wide range of pharmacological properties as antibacterial [(6)], antiviral [(7)] and anti-inflammatory agent [(8)], also, heterocyclic compounds play an important role in biochemical process [(9)] because the side groups of the most typical and essential constituents of living cells are based on aromatic heterocyclic compounds. Between them, sulfur and nitrogen containing heterocyclic compounds have maintained the interest of researchers through the development of organic synthesis [(10)].

.Sulfadiazine is an antibiotic. Used together with pyrimethamine it is the treat of choice for toxoplasmosis. It is a second line treatment for otitis media, prevention of rheumatic fever, chancroid, chlamydia and infections by *Haemophilus influenzae*. It is taken by mouth.

Common side effects include nausea, diarrhea, headache, fever, rash, depression, and pancreatitis. It should not be used in people who have severe liver problems, kidney problems, or porphyria.[2] If used during pregnancy it may increase the risk of kernicterus in the baby.[1] It is believed to be safe during breastfeeding if the baby is otherwise healthy. It is in the sulfonamide class of medications

Sulfadiazine was approved for medical use in the United States in 1941 It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. Sulfadiazine is available as a generic medication.

A Schiff base is nitrogen analog of aldehyde or ketone in which the carbonyl group is replaced by a (C=N) group. It is usually formed by condensation of an aldehyde or ketone with primary amine [4, 12]. 1,3-oxazepine is a seven membered ring compound with two hetero atoms oxygen atom at position (1) and nitrogen atom at position (3) . As shown in the following structure formula:



1,3-oxazepine

There are many methods for preparing of oxazepine derivatives.1,3-oxazepine synthesized from the reaction of4-(benzylamino)-N-(5-methyl-4,5-dihydro isoxazol -3-yl)benzene sulfonamide with malic anhydride in dry benzene as a solvent[13].

Instruments:

1-Melting points are recorded using hot stage Gallen Kamp melting point apparatus and are uncorrected.

2-Infrared spectra are recorded using Fourier Transform infrared SHIMADZU (8300) (F.T.IR) infrared spectrophotometer, KBr disc or thin film was performed by College of education for pure science Ibn-Al-Haitham, University of Baghdad.

3-Thin layer chromatography (TLC) was carried out using fertigfolllen precoated sheets type polygramSilg and the plate was developed with iodine vapour.

1-Preparation of Schiff bases:(2,3) [.14].

A mixture of compound [1] (0.005 mole) and 4-hydroxybenzaldehyde,4-dimethylaminobenzaldehyde(0.005mol)in absolute ethanol (18 mL) and drops of glacial acetic acid was refluxed for 4 hours, the mixture was cooled and the solid was filtered then re crystallized from ethanol and collected by filtration.

2-Synthesis o)-1,2-dihydro-phthalazin-3,8- dione ,f oxazepines:(5-8) ,1,2-dihydro-pyridazin—3,6-dione -sulffadiazine , (4)[15]: .

A mixture of Schiff base[2 or3] (0.0004 mol) with maleic or phthalic anhydride (0.0004mol) were dissolved in (15 mL) of dry benzene and then the mixture was refluxed for 6 hrs. ,then excess solvent was distilled .The solid was filtered off and re-crystallized from ethanol.

3-Synthesis of tetrazoles: (9,10) [15].

A mixture of (0.01mol) of Schiff bases [2,3] tetrahydrofuran (THF) (15ml) and sodium azide (0.01mol) was heated on a water bath, the temperature of the water bath was controlled between (50-55)°C. The end of the reaction was checked by (TLC) which showed the disappearance of the starting material.

Table (1): Physical properties of the synthesized compounds.

Comp. No.	*Molecular Formula*	*Molecular Weight (g/mole)*	*Yield (%)*	*M.P (°C)*	*Colour*	*Rf*
1	$C_{10}H_{10}N_4O_2S$	250.278	-	252-256	White	-
2	$C_{15}H_{15}N_3OS$	285.36	90	204-206	White	o.92
3	$C_{22}H_{18}BrN_3OS$	452.37	85	59-61	Pale yellow	0.88
4	$C_{24}H_{24}N_4OS$	416.54	81	96-98	Orange	0.95
5	$C_{22}H_{18}N_4O_3S$	418.47	83	173-175	Yellow	o.82
6	$C_{22}H_{18}ClN_3OS$	407.92	86	>230	Yellow	0.90

Characterization of Schiff bases[2,3]:

Compounds [2,3] were synthesized from the reaction of compound [1] with 4-hydroxy or N,N-dimethylamino in absolute ethanol afforded the imine. The condensation reaction of equimolar quantity of primary amine with the appropriate aromatic aldehydes is the major method to prepare series of Schiff bases .

The FT-IR spectrum of compound [2] indicated the appearance of (C=N) stretching band at (1664) cm^{-1} and (C-H) aliphatic at (2920, 2862) cm^{-1} and (C-H) aromatic at (3101) cm^{-1}.(C=C) at (1572\,1587) cm^{-1} [(16)].

^{1}H-NMR spectrum ,fig (1),of compound (2), shows the following characteristic chemical shifts (DMSO-d_6, ppm). The aromatic protons appeared at: δ (7.0-8.0)ppm, besides the band at δ (9.8) ppm was appeared due to (-OH) and at (6.6-7) due to NH..

^{1}H-NMR spectrum of compound [3], shows the following characteristic chemical shift, (DMSO-d_6) ppm. The aliphatic protons present at (δ 2.2,2.3,4.2), aromatic ring protons appeared at (δ 7.0 – 8.1) ppm. Furthermore, the signal at (δ 9.8) attributed to (N-H) proton[16].

Characterization of Oxazepin compounds [5-8]:

Compounds [5-8] were synthesized from the reaction of compound [2,3] with maleic or phthalic anhydride in dry benzene.

The FT-IR spectra of compounds [5-8] showed the appearance of carbonyl group band at (1629-1697,1724-1735) cm^{-1} and C-H aliphatic band at (2902,2816) cm^{-1} and C-N at (1311) cm^{-1} and (1174,1074) cm^{-1} belongs to the asymmetric and symmetric (C-O-C) band.

Characterization of tetrazoles :(9,10).

The FTIR spectrum of compound [9] indicated the appearance of (N-H) band at (3122) Cm^{-1} and appearance of aromatic (C-H) at (3057) Cm^{-1}, alph (C-H) at (2816-2812,2976-2956)Cm^{-1} and (C=C) band at (1490,1554) Cm^{-1} , the disappearance of the two bands of (N-

H) group in the region (3100) Cm^{-1} and appearance of band due to aromatic (C-H) group at the region (3039)Cm^{-1} , carbonyl groups appeared at (1688,1720)$Cm-^{1}$.

Table (2) The IR characteristic bands of compounds (9-10)

Comp. No.	Changed part(x)	IR, KBr, υ, cm^{-1}				
		(C-H) Ar.	(C-H) Aliph.	(C-N)	(C-O-C)	Others Bands
9	OH	3057	2976, 2816	1311	1172	C-OH 3310
10	$N(CH_3)_2$	3039	2914, 2870	1295	1168	$N-CH_3$ 1295

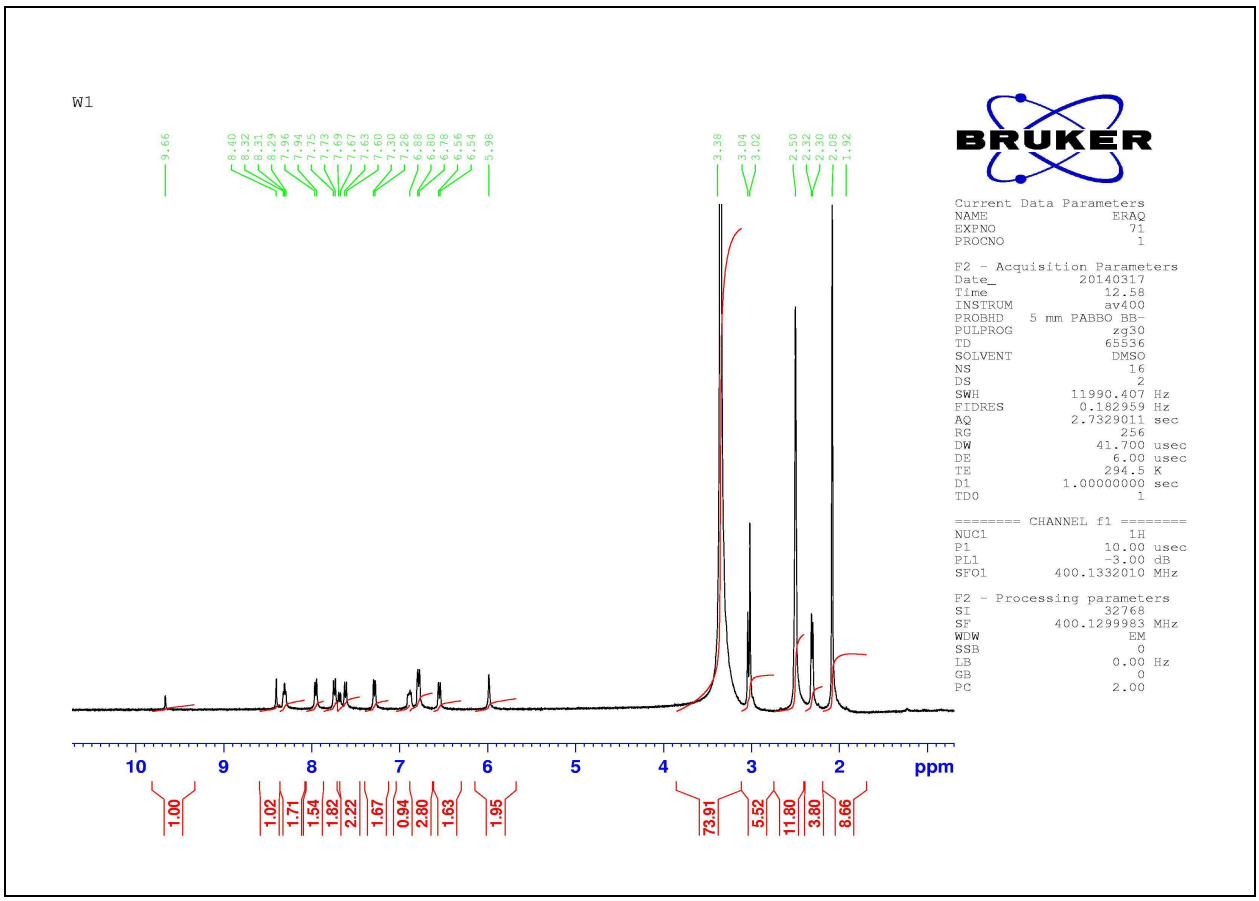


Fig.(1):H-NMR spectrum of compound (2).

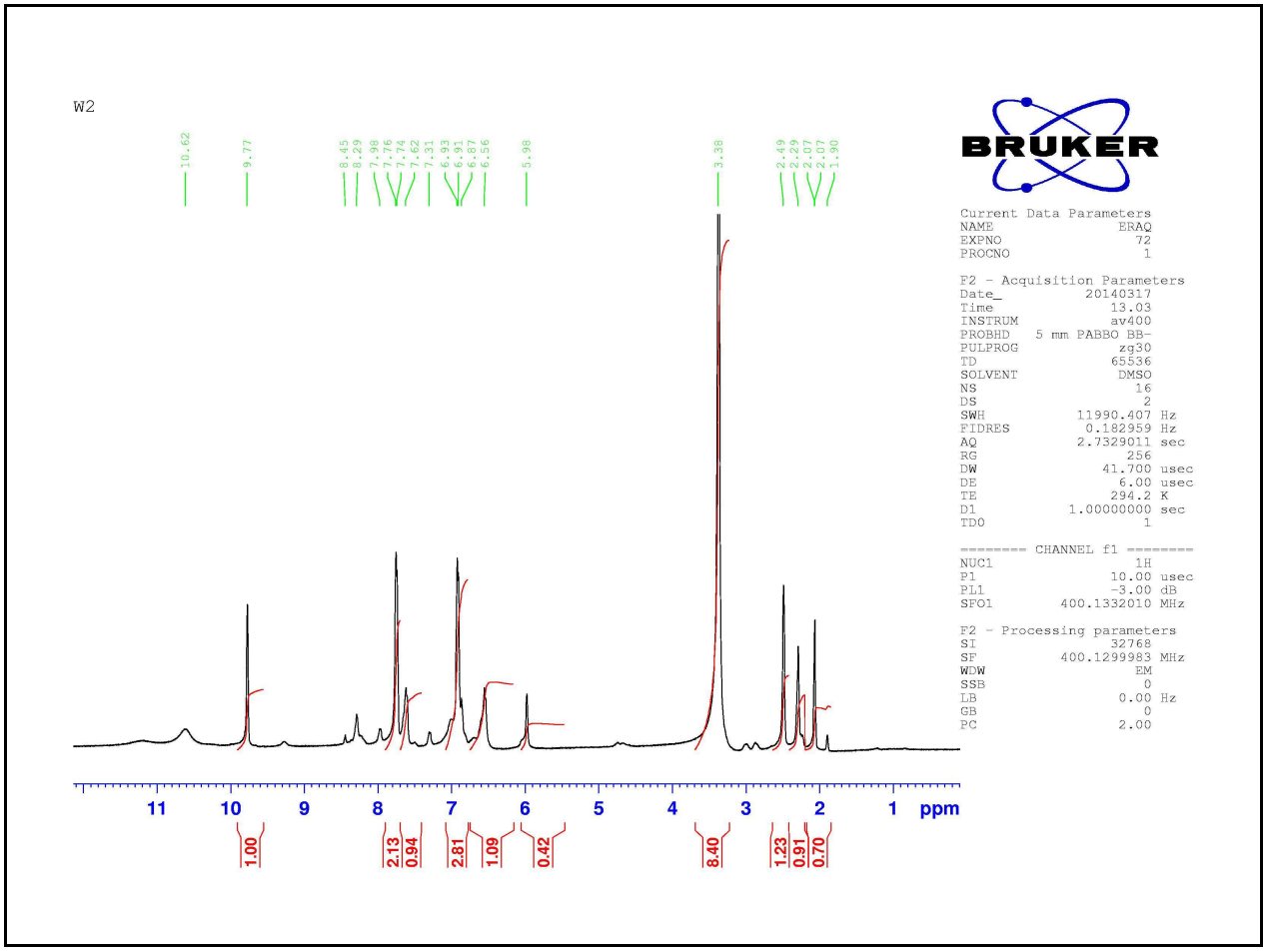


Fig.(2): H-NMR spectrum of compound 3.

Antibacterial activity:

A few pathogenic species are known to be almost sensitive to certain antimicrobial agents, although in some parts of the world the situation is changing. As strains of pathogenic organism differ from one to another within their species in their antibiotic sensitivities, sensitivity tests are required as a routine.

In this work, the antibacterial test was performed according to the disc diffusion method [17]. Compounds (2,3,4,5,7,9) were assayed for their antimicrobial activity in *vitro* against one strain of Gram negative bacteria (**E.coli**) and one strain of Gram positive bacteria (**Staphylococcus aureus**).

The previous bacteria were activated in a Nutrient Growth medium at 37 ºC for 24 hour. The prepared agar and Petri dishes were sterilized by autoclaving for 15min at 121ºC. The agar was surface inoculated uniformly from the broth culture of the tested microorganisms.

Conclusions:

1- Compounds [4] showed moderately active on *E.coli* and on, *Staphylococcus*.

2- Compounds [3] showed moderately active on *E.coli*.

3- Compounds [2] showed no effect on *Staphylococcus*.

4- Compounds [7] showed high effect on *E.Coli*.

Table (2): Antibacterial activities of the prepared compounds.

Comp.no.	*Staph.*	*E.Coli.*
2	–	+
3	+	+
4	++	++
5	+	+
7	++	+++
9	+	+

Key to symbols:

Highly active = +++ (inhibition zone > 20 mm).

Moderately active = ++ (inhibition zone 11-20 mm).

Slightly active = + (inhibition zone 5-10 mm).

Inactive = - (inhibition zone <5 mm

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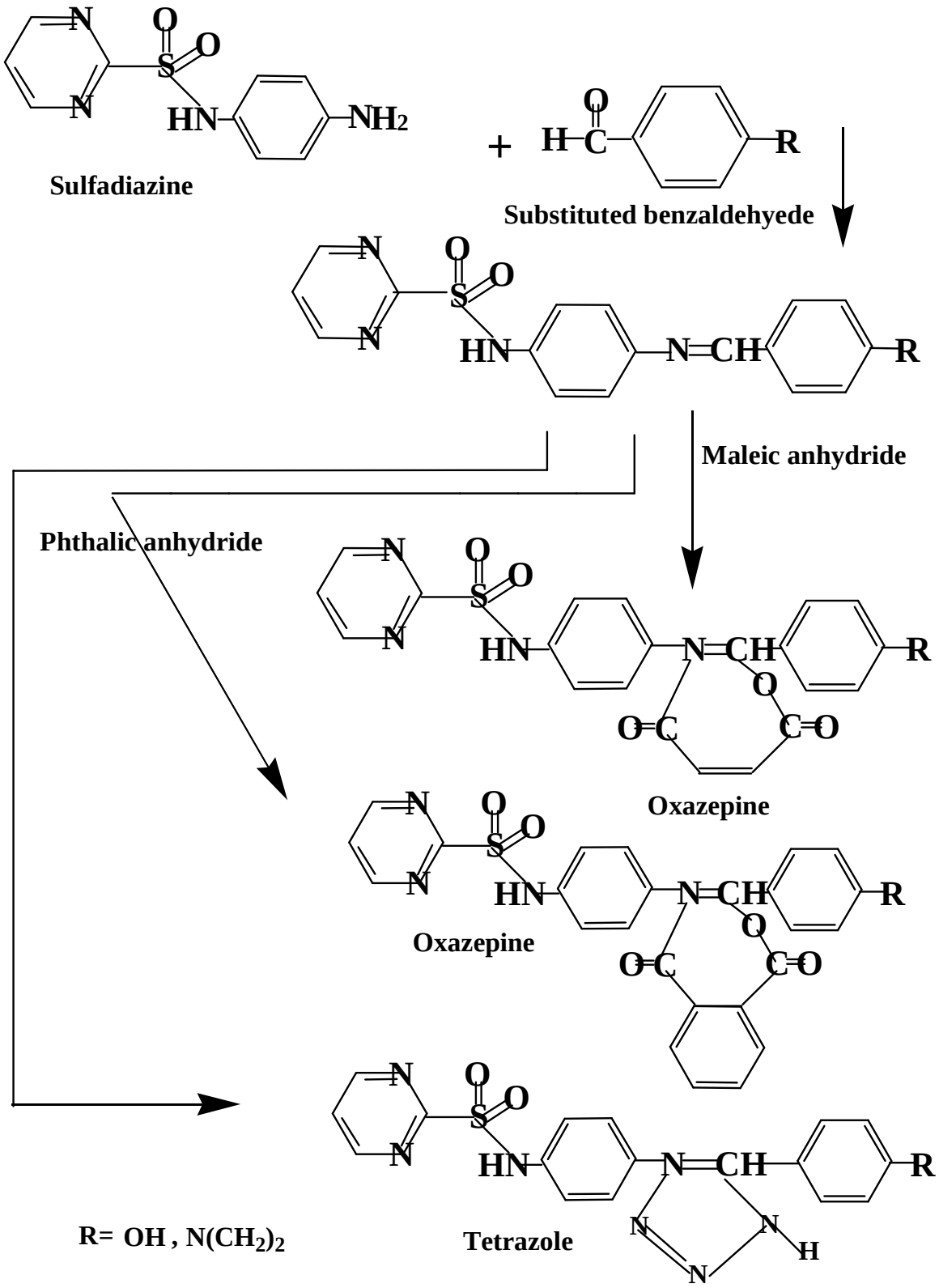

Scheme for the prepared compounds.