SYNTHESIS, CHARACTERIZATION, AND STUDY THE BIOLOGICAL ACTIVITY OF SOME SCHIFF'S BASES, AND 1,3 - OXAZEPINE COMPOUNDS DERIVED FROM SULFAMETHOXAZOLE DRUG

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ABSTRACT
This study including synthesis of some new Schiff bases compounds [1-6] from the reaction of Sulfamethoxazole drug with some aromatic aldehydes in classical Schiff base method then treatment Schiff bases with succinic anhydride to get oxazepines rings [7-11]. These derivatives were characterized by melting point, FT-IR, 1H NMR and mass spectra. Some of synthesized compounds were evaluated in vitro for their antibacterial activities against three kinds of pathogenic strains Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosaby agar diffusion disk method, and against the fungal species (Candida). The results showed that some of these derivatives have good antibacterial activities compared to biological activity of parent drug.

Keywords: Sulfamethoxazole, Schiff base, 1,3-Oxazepine, antibacterial activity.
INTRODUCTION

4-Amino-N-5-methyl-3-isoxazolylbenzenesulfonamide is the common name of Sulfamethoxazole, but N1-5-Methyl-3-isoxazolyl sulfanilamide, is the IUPAC name(Figure 1). This drug was considered by previous working groups (Lyon, 1980; Lyon, 1987). Sulfamethoxazole is an antibiotic that has been used since the 1990s to treat various general injuries in humans and different species. There was more use in the treatment of acute infections of the urinary tract. Also, sulfamethoxazole is used against gonorrhea, meningitis, respiratory infections and prevention of poor meningococcal meningitis. Given the relatively unfavorable, pattern of tissue delivery, antibacterial medication that is widely used to treat various systemic infections worldwide with trimethoprim or pyrimethamine. With methoprim, the mixture is used mainly to treat the device's inflammation. Sulfamethoxazole of chloroquineresistant plasmodium falciparum malaria (Lyon, 1980; Gennaro, 1995; Elggellal& Alshadly, 2014).

Researches on complexes of sulfamethoxazole have a lot of physiological and pharmacological due to complexes of sulfa drugs have been discovered to be more bacteriostatic than the medication themselves (Alias et al., 2015; Al-Khodir, 2015).

Figure (1): The structure of Sulfamethoxazole.
MATERIALS AND METHODE
Materials and measurements of physical
Both reactants and solvents used in this study were reagent grade and are available from companies such as Sigma-Aldrich, BDH and Fluka. Sulfamethoxazole was obtained from Samara, Iraq.

Melting points have been registered and are uncorrected using a hot stage Gallen Kamp melting point apparatus. SHIMADZU model FT-IR-8400S was used to receive the FT-IR spectrum. On the BRUKER model Ultra shield 300MHz spectrophotometer. \(^1\)H-NMR spectra were obtained in the DMSO-d6 solution with the TMS as the internal standard. Mass spectra were recorded using Mass Spectrometer, Agilent Technology (HP) at Tehran University, Central Lab, Iran.

Common technique of preparing of Schiff bases (1-6)
For 6-8 hrs, a mixture of Sulfamethoxazole (0.0039 mole, 1 g), and various aromatic aldehydes (0.0039 mol) in absolute ethanol (15 mL) and 3 drops of glacial acetic acid were refluxed (Jassim & Ali, 2018; Abdullah et al., 2013). The mixture was cooled and the solid was purified after the end of the reaction, checked with TLC ethanol: benzene (1:1), then recrystallized from ethanol and collected by filtration, as shown in (Scheme 1) (Table 1) describes the physical properties of these compounds.

Preparation 1,3-oxazepin-4,7-dione derivatives (7-11)
In 15 mL of dry benzene, Schiff base (1,2,3,5-6) (0.0005 mol) was combined with phthalic anhydride (0.0005 mol) and then refluxed for 18-20 hrs, evaporating the excess solvent. The solid product was washed with distilled water and then purified and recrystallized, as illustrated in (Scheme 2) (Table 2) lists the physical properties (Tawfiq et al., 2012; Muhsen et al., 2017; Sallal & Ghanem, 2018).

Scheme (1): The synthesis of Schiff’s bases compounds from Sulfamethoxazole drug.

Scheme (2): The synthesis of 1,3-oxazepin-4,7-dione derivatives (7-11) by reaction Schiff’s bases compounds with succinic anhydride
Table (1): Physical properties of compounds of the Schiff base(1-6).

| Comp. No. | Structure of Compounds | Molecular Formula | Molecular Weight (g/mole) | Yield (%) | M.P. (°C) | Colour | Rf |
|-----------|------------------------|-------------------|---------------------------|-----------|-----------|--------|----|
| 1         | ![Structure 1](image1)  | C_{18}H_{17}N_{3}O_{5}S | 387.40                   | 76        | 172-174   | Dark yellow | 0.74 |
| 2         | ![Structure 2](image2)  | C_{17}H_{15}N_{3}O_{4}S | 420.28                   | 81        | 192-194   | Pale yellow | 0.76 |
| 3         | ![Structure 3](image3)  | C_{17}H_{14}N_{3}O_{3}SBr | 420.28                   | 81        | 196-198   | Pale yellow | 0.76 |
| 4         | ![Structure 4](image4)  | C_{18}H_{14}N_{3}O_{5}S | 386.28                   | 83        | 88-90     | Yellow    | 0.77 |
| 5         | ![Structure 5](image5)  | C_{17}H_{14}N_{3}O_{3}SCl | 375.78                   | 86        | 137-139   | Pale Yellow | 0.81 |
| 6         | ![Structure 6](image6)  | C_{20}H_{24}N_{6}O_{5}S | 604.56                   | 85        | > 250(dec) | Orange    | 0.58 |
RESULTS AND DISCUSSION

The Schiff’s bases compounds of sulfamethoxazole (1-6) were synthesized in good percentage from the reaction of sulfamethoxazole with different aromatic aldehydes in absolute ethanol as a solvent. These compounds have been synthesized according to the steps described in (Scheme 1).

The physical properties described in (Table 1) and spectral methods, such as FT-IR and some of them by $^1$H-NMR, verified the structures of (1-6) compounds, spectra of compounds (1-6) displayed, characteristic absorption bands at 1614-1627 cm$^{-1}$, 2976-2993 cm$^{-1}$, 2839-2891 cm$^{-1}$, 3066-3086 cm$^{-1}$ and 1465-1593 cm$^{-1}$ due to stretching vibrations for (C=N)-asymmetrical, (C-H) aliphatic, symmetrical (C-H) aliphatic, (C-H) aromatic and (C=O) aromatic. These and other bands as shown in (Figures 2, 3 and 4).

At 1735-1774 cm$^{-1}$, 2854-2997 cm$^{-1}$ and 1265-1267 cm$^{-1}$, 1693-1706 cm$^{-1}$ and 1157-1161 cm$^{-1}$ to stretch vibrations (C = O) lactone (C=O), lactame, (C-H) aliphatic, (C-N) and (C-O-C) band, the FT-IR spectra of oxazepine compounds (7-11) displayed characteristic absorption bands. These and other bands are shown in (Table 4), as shown in (Figure 5).

Table 2: The physical properties of 1,3-oxazepin derivatives (7-11).

| comp. no. | Structure of Compounds | Molecular Formula | Molecular Weight (g/mole) | Yield (%) | M.P. (°C) | Colour | Rf |
|-----------|------------------------|-------------------|---------------------------|-----------|-----------|--------|----|
| 7         |                        | C$_{22}$H$_{21}$N$_3$O$_5$S | 487.98 | 74 | 165-167 | Yellow | 0.76 |
| 8         |                        | C$_{22}$H$_{19}$N$_3$O$_5$S | 457.40 | 75 | 135-137 | Dark yellow | 0.90 |
| 9         |                        | C$_{22}$H$_{18}$N$_3$O$_5$SBr | 520.28 | 73 | 154-156 | Orange | 0.82 |
| 10        |                        | C$_{22}$H$_{18}$N$_3$O$_5$SCl | 475.78 | 74 | 140-142 | Yellow | 0.94 |
| 11        |                        | C$_{30}$H$_{12}$N$_6$O$_2$S$_2$ | 704.56 | 73 | 210-212 | Orange | 0.77 |
The $^1$H-NMR spectra of compounds (1, 3 and 6) showed the signal at 2.24, 2.25 and 2.31 ppm due to proton of (CH$_3$) group and the singlet signal at 6.11, 6.05 and 6.08 ppm due to proton of isoxazol ring, the multiplet signals at $\delta$[(7.30-7.83),(7.33-7.85),(7.44-7.47)]ppm, the singlet signal appeared at $\delta$ (8.40, 8.58, 8.73) ppm which could be assigned to proton of (N=CH) group that could be assigned to protons of benzene rings, and the singlet signal at $\delta$ (10.92, 11.42, 10.91) ppm suggested the attribution of the proton of (NH) group of sulfonamides shown in (Figures 6, 7 and 8).

The $^1$H-NMR spectra of compounds (7 and 10) showed the signal at 2.26 and 2.29 ppm due to proton of (CH$_3$) group and signal at 2.06-2.79 ppm due to the protons of oxazepine ring (CH$_3$), while the other signals are listed in as shown in (Figures 9 and 10).

The compound 1 mass spectrum (Figure 11), shows the molecular ion at m/z = 387.4, and the compound 3 mass spectrum (Figure 12), shows the molecular ion at m/z = 420.28.

### Table (3): The FT-IR distinguishing bands of Derivatives (1-6).

| Deriv. No. | Molecular Formula | $\nu$ (C-H) Ar. | $\nu$ (C-H) Aliph. | $\nu$ (C=O) lactame | $\nu$ (C=N) | $\nu$ (C-O-C) | other bands |
|------------|-------------------|----------------|-------------------|---------------------|------------|---------------|--------------|
| 1          | C$_{18}$H$_{17}$N$_{3}$O$_{3}$S | 3084 | 2993,2891 | 1618 | 1467-1593 | (1265,1029) P-OH(3588) |             |
| 2          | C$_{17}$H$_{15}$N$_{2}$O$_{2}$S | 3066 | 2981,2854 | 1618 | 1465-1593 | (1265,1029) P-OH(3589) | P-Br 684 |
| 3          | C$_{17}$H$_{14}$N$_{2}$O$_{2}$S | 3086 | 2987,2848 | 1627 | 1473-1579 | (1265,1029) P-OH(3589) | P-Br 684 |
| 4          | C$_{18}$H$_{14}$N$_{2}$O$_{2}$S | 3086 | 2976,2875 | 1616 | 1465-1593 | (1265,1029) P-OH(3589) | P-Br 684 |
| 5          | C$_{18}$H$_{14}$N$_{2}$O$_{2}$S | 3088 | 2991,2839 | 1616 | 1467-1593 | (1265,1029) P-OH(3589) | P-Cl 786 |
| 6          | C$_{20}$H$_{24}$N$_{2}$O$_{2}$S | 3086 | 2991,2879 | 1614 | 1469-1581 | (1265,1029) P-OH(3589) |             |

### Table (4): The FT-IR distinguishing bands of derivatives (7-11).

| Comp.No. | Molecular Formula | $\nu$ (C-H) aromatic | $\nu$ (C-H) aliphatic | $\nu$ (C=O) lactame | $\nu$ (C=O) lactame | $\nu$ (C-N) | $\nu$ (C-O-C) | Other Bands |
|----------|-------------------|----------------------|----------------------|---------------------|---------------------|------------|---------------|--------------|
| 7        | C$_{22}$H$_{15}$N$_{2}$O$_{2}$S | 3078 | 2987,2893 | 1745 | 1701 | 1161 | 1267 | p-OH3550 |
| 8        | C$_{18}$H$_{16}$N$_{2}$O$_{2}$S | 3092 | 2931,2854 | Overlap with C=O lactame | 1705 | 1157 | 1265 | p-OH3464 |
| 9        | C$_{21}$H$_{15}$N$_{2}$O$_{2}$S | 3093 | 2997,2897 | Overlap with C=O lactame | 1705 | 1161 | 1265 | p-Br686 |
| 10       | C$_{18}$H$_{15}$N$_{2}$O$_{2}$S | 3093 | 2926,2854 | 1735 | 1693 | 1157 | 1265 | p-C792 |
| 11       | C$_{18}$H$_{15}$N$_{2}$O$_{2}$S | 3095 | 2922 | 1774 | 1706 | 1161 | 1265 | ------ |

### Table 5: $^1$H-NMR parameters (ppm) $\delta$-H

| Deriv.No. | Derivative Structure | $^1$H-NMR parameters (ppm) $\delta$-H |
|-----------|---------------------|-------------------------------------|
| 7         | ![Derivative Structure](image1) | $\delta$(2.26)(s,3H,CH$_3$);$\delta$(3.81)(s,3H,CH$_3$);$\delta$(2.06 – 2.39)(t,4H,2CH$_2$);$\delta$(6.07)(s,1H,isoxazol ring); (6.54 – 8.58)(m,8H,for both two benzene ring);$\delta$(11.32)(s,1H,NH) |
| 10        | ![Derivative Structure](image2) | $\delta$(2.29)(s,3H,CH$_3$);$\delta$(2.54-2.79)(t,4H,2CH$_2$);$\delta$(6.08)(s,1H,isoxazol ring);7.40(s,1H,CH of oxazepin ring);7.44-7.96(m,8H,for both two benzene ring);10.95(s,1H,NH) |
Figure (2): FT-IR Spectrum of compound 1.

Figure (3): FT-IR Spectrum of derivative 3.

Figure (4): FT-IR Spectrum of derivative 6.
Figure (5): FT-IR Spectrum of derivative 11.

Figure (6): $^1$H-NMR chart for derivative 1

Figure (7): $^1$H-NMR chart for derivative 3
Figure (8): $^1$H-NMR chart for derivative 6.

Figure (9): $^1$H-NMR chart of derivative 7.

Figure (10): $^1$H-NMR chart of derivative 10.
BIOLOGICAL ACTIVITY

Anti-bacterial activity

Three forms of pathogenic strains (S. aureus, E. coli, and P. aeruginosawere used to test the antimicrobial activity of the synthesized compounds (2, 4, 7, 10 and 11) using the agar diffusion process. Appropriate spaced separate holes were created by Muelle Hinton agar (6mm in diameter) appropriate spaced separate holes were filled with 0.1mL concentration of prepared compounds that dissolve in DMSO before spreading the bacteria on agar. These plates were incubated for 24 hr at 37°C, the bacteria growth inhibition zone around the hole observed and measured in millimeter of diameter (Entesar & Enaam, 2017; Saleh & Ali, 2020). Results and clarification are given in (Table 6).

Anti-fungal activity

The antifungal activity was tested against the fungal species, C. albicans at 10mg/mL concentration of some prepared compounds using DMSO as solvent. The results were reported as zone of inhibition compared to standard Nystatin as antifungal drugs. The results obtained showed that some of these derivatives showed commensurable activity like exhibited by (Table, 7).
**Table (6):** Antimicrobial Activities of several prepared derivatives.

| Deriv. No. | Sample No. | *Staphylococcus aureus* | *Escherichia coli* | *Pseudomonas aeruginosa* |
|------------|-------------|--------------------------|-------------------|--------------------------|
| 2          | 9           | ++                       | +                 | +                        |
| 4          | 8           | +++                      | +                 | +                        |
| 7          | 3           | ++                       | +                 | +                        |
| 10         | 10          | +++                      | +                 | ----                     |
| 11         | 15          | +++                      | +                 | ----                     |

(++) = 18- 24mm, (+++) = 28-33mm.

**Table (7):** Anti-fungicide activity for the prepared derivatives(6,7,and8).

| Deriv. No | Candida albicans |
|-----------|------------------|
| 6         | S                |
| 7         | R                |
| 8         | S                |
| Nystatine | S                |

S: Sensitive, R: Resistance.

**CONCLUSION**

The results indicate that the synthesized compounds (2, 4, 7,10 and 11) have a microbial activity against the tested organisms up to 3.2mg/ disk. These derivatives showed higher effect against *S. aureus* and moderately activity against *E. coli* and *P. aeruginosa*. The fungal species, *Candida albicans* showed higher sensitivity toward the compounds 6 and 8 more than compound 7.

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