SYNTHESIS, IDENTIFICATION AND BIOLOGICAL ACTIVITY OF NEW HETEROCYCLIC COMPOUNDS FROM REACTION OF NEW SCHIFF-BASES WITH PHATHALIC ANHYDRI

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ABSTRACT:
Series of new Schiff bases and their derivatives (Oxazepine) have been synthesized during two steps. The first step synthesis of imines derivatives (1-10) by the condensation reaction of 1,7-diaminoheptane and 1,8-diaminooctane with different substituted aromatic aldehydes by using glacial acetic acid as catalyst. The second step includes reaction of the prepared Schiff bases derivatives with phathalic anhydride in dry benzene to obtain seven -membered heterocyclic ring derivatives (11-15). The biological activities of some prepared compounds were also studied against different kinds of bacteria. The new derivatives were confirmed by suing a range of experimental techniques including 1HNMR, 13C NMR, IR and Mass spectra.

KEYWORDS: Oxazepine, Schiff bases, 1, 7-diaminoheptane, 1, 8-diaminooctane, Antibacterial activity, Phathalic anhydride.

1. INTRODUCTION

The chemistry of the imine group is considered to be a significant part in the progress of chemistry science (Yang et al, 2002; Al-Jeboori et al, 2008). Schiff bases which characterizing by a double bond (-CH = N-) are generally prepared by condensation method of aromatic aldehyds or ketones with primary amines (Celik et al, 2009; Saeed, 2005). Schiff -bases showed different biological activities such as antibacterial, antifungal and antitubercular (Wadher et al, 2009; Mohammed et al, 2019). Many heterocyclic compounds were prepared from the Schiff bases, for example oxazepine derivative which indicate a seven membered ring involving oxygen and nitrogen atoms in addition to five carbon atoms (Khattar et al, 2004; Aljamali et al, 2014). Over the years, the synthesis of oxazepine has been studied and attested. The oxazepine is prepared from addition of Schiff bases with maleic, phthalic and succinic anhydrides (Hanoon, 2011; Abood, 2010; Sadiq, 2017; Taha, 2017; Abdul-Wahid et al, 2016; Abdullah et al, 2016; Hamak and Eissa, 2013; Abood, 2013; Abdulqahar and Jaber, 2016; Aljamali, 2013) and also by green chemistry method (Verma et al, 2015; Hameed, 2012). A vast variety of biological activities were found to show of Oxazepine derivatives such as antibacterial (Agirbas et al, 2011), antifungal (Serrano-Wu et al, 2002), hypnotic muscle relaxant (Abedel -Hahez and Abdel -Wahab, 2008), antagonistic (Hallinan et al, 1996), inflammatory (Kubota et al, 2011) and antiepileptic (Bajajt et al, 2003).

Because of the biological importance of these compounds, the aim of this work is to synthesize some new Schiff bases and oxazepine derivatives as shown in Scheme 1 and investigate their biological activities against different kinds of bacteria.

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2. EXPERIMENTAL DATA

2.1 General: Equipments, Chemical Materials and Applied Techniques

All reactions were carried out with dry in solvents under anhydrous conditions. Commercial reagents were used without purification. Ethanol was used as absolute solvent. \(^1\)H-NMR and \(^13\)C-NMR were recorded on Bruker DPX-300FT (\(\text{\textit{f}}^\text{H}: 300 \text{MHz, } \text{\textit{f}}^\text{C}: 75.5 \text{MHz})). All NMR spectra present in this work were measured in CDCl\(_3\) solution. All chemical shifts are given in ppm. The chemical shifts (\(\delta\)) is expressed in ppm. The following abbreviations were used to explain the multiplicities: \(s\) = singlet, \(d\) = doublet, \(t\) = triplet, \(q\) = quartet, \(m\) = multiplet, \(b\) = broad. High resolution mass spectra were recorded on a Micro Tof Applied Biosystems apparatus. IR spectra were recorded on a Perkin Elmer Aragon 1000 FT-IR spectrophotometer. Thin Layer Chromatography (TLC) Merck Kiese gel 60 F254 on aluminum foil from Macheray-Nagel. Melting points were determined by electrothermal apparatus and are uncorrected.

2.2 General Procedure for Preparation N, N'- (alkane-1,7-diyl) and (alkane-1,8-diyl) bis(1-(4-substituted phenyl) methanimine (1-10)

A mixture of aromatic aldehydes (1.6 mmol, 2 eq.), 1,7-diaminoheptane, 1,8-diaminooctane (0.8 mmol, 1 eq.), and 5 drops of glacial acetic acid in 50 ml of dry ethanol were heated by reflux for (2-3) hours under dry conditions. Then ethanol was evaporated by vacuum. Finally, the solid compound was purified twice using absolute ethanol to obtain a pure product (1-10) (Ghosh et al, 2006; Aljamali, 2013) as shown in Table 1.

| Comp. No. | Substrate | Name of Compound | Color | M.P (°C) | Yield (%) | HRMS (ESI) |
|-----------|-----------|------------------|-------|----------|-----------|------------|
| 1         |          | (1\(E\),1\(E\)-N, N'- (heptane-1,7-diyl) bis(1-(4-methoxy phenyl) methanimine) | Pale-yellow | 60-63 | 78 | Calcd. 357.2307 Found 357.2307 |
| 2         |          | (1\(E\),1\(E\)-N, N'- (heptane-1,7-diyl) bis(1-p-tolylmethanimine) | Deep-yellow | 70-72 | 75 | Calcd. 389.2205 Found 389.2206 |
| 3         |          | (1\(E\),1\(E\)-N, N'- (heptane-1,7-diyl) bis(1-(nitrophenyl)methanimine) | Pale-brown | 108-110 | 79 | Calcd. 419.1695 Found 419.1697 |
| 4         |          | (1\(E\),1\(E\)-N, N'- (heptane-1,7-diyl) bis(1-(4-chlorophenyl)methanimine) | Pale-yellow | 79-80 | 77 | Calcd. 397.1214 Found 397.1212 |
| 5         |          | 4,4'-((1\(E\),1\(E\)-heptane-1,7-diyl) bis(azanylylidene)) bis(methanylylidene) dibenzonitrile | White | 81-84 | 88 | Calcd. 379.1899 Found 379.1900 |
| 6         |          | N(8-(1\(E\)-4-methoxy benzylidene amino)octyl)-1-(4(methoxyphenyl) methanimine) | Pale-brown | 110-112 | 85 | Calcd. 403.2361 Found 403.2359 |
| 7         |          | N(8-(1\(E\)-4-methyl benzylidene amino)octyl)-1-(p-tolyl)methanimine | White | 95-98 | 72 | Calcd. 371.2463 Found 371.2463 |
| 8         |          | 4-((8-((1\(E\)-4-isocyanobenzylidene amino)octyl)iminomethyl)benzonitrile | White | 75-77 | 91 | Calcd. 393.2055 Found 393.2053 |
| 9         |          | N(8-((1\(E\)-4-nitrobenzylidene amino)octyl)-1-(4-nitrophenyl) methanimine | White | 101-104 | 82 | Calcd. 433.1852 Found 433.1852 |
| 10        |          | N(8-((1\(E\)-4-chlorobenzylidene amino)octyl)-1-(4-chlorophenyl)methanimine | White | 88-90 | 71 | Calcd. 411.1371 Found 411.1369 |

2.3 Preparation of oxazepine compounds (11-15)

Schiff base derivatives (1-10) (1.2 mmol, 1eq.) and phthalic anhydride 18 (2.5 mmol, 1eq.) were dissolved in (20 mL) dry benzene. The mixture was heated for 5 hours in water bath at (70 °C). The mixture was then allowed to cool down at room temperature; a formed precipitate was filtered and recrystallized from ethanol to obtain a pure product. (Hamak and Eissa, 2013; Al-juburi, 2012) as shown in Table 2.
primary aliphatic amines in the presence of glacial acetic acid as catalyst in absolute ethanol. The IR spectra of Schiff base compounds (1-10) appeared the medium bands at 1640-1651 cm$^{-1}$ assigned to the stretching vibration of imine group (C=N), and the disappearance of stretching band of (C=O) group. The absorption bands showed in the range of (1560-1606) cm$^{-1}$, (3020-3089) cm$^{-1}$, (2920-2935) cm$^{-1}$, related to the stretching vibrations of (C=C) aromatic, (C-H) aromatic, (C-H) aliphatic respectively as shown in Table 3. The $^1$H-NMR spectra of the Schiff bases (Figure 1) exhibited a singlet peak for the proton of CH=N group at (8.26-8.36) ppm. A triplet signal at (3.26-3.63) ppm related to methylene proton of CH=NCH$_2$ while methylene protons displayed as multiplet signal at (1.21-1.72) ppm. Aromatic protons appeared as doublet signal at the region (6.92-8.13) ppm Table 4. In the $^{13}$C-NMR spectra (Figure 2) of compounds (2, 4, 6, 7 and 10), the signal for carbon of CH=N groups of compounds showed at (166.1) ppm. A signal appeared at 59 ppm attributed to methylene carbon of CH=N-CH$_2$ while the signals of methylene carbons exhibited at (27.2-55.6) ppm. The signals of aromatic carbons exhibited at (114.2 – 184.9) ppm Table 5.

### Table 2. The physical properties of oxazepane derivatives (11-15).

| Comp. No. | Name of Compound | Color | M.P (°C) | Yield (%) |
|-----------|-----------------|-------|---------|-----------|
| 11        | 4,4’-(octane-1,8-diy)bis(3-(4-nitrophenyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione) | White | 143-145 | 80        |
| 12        | 4,4’-(heptane-1,7-diy)bis(1,5-dioxo-1,3,4,5-tetrahydrobenzo[e][1,3]oxazepine-4,3-diyl)dibenzonitrile | White | 104-107 | 78        |
| 13        | 4,4’-(heptane-1,7-diy)bis(3-(p-tolyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione) | White | 169-173 | 70        |
| 14        | 4,4’-(heptane-1,7-diy)bis(3-(4-methoxyphenyl)-3,4-dihydrobenzo[e][1,3]oxazepane-1,5-dione) | White | 171-174 | 75        |
| 15        | 4,4’-(octane-1,8-diy)bis(1,5-dioxo-1,3,4,5-tetrahydrobenzo[e][1,3]oxazepine-4,3-diyl)dibenzonitrile | White | 120-124 | 85        |

### 2.4 Preliminary Biological Study

All newly synthesized compounds were tested against two types of bacterial groups including Gram-negative, *E. coli* and Gram-positive *Staphylococcus aureus* as shown in Table 3. Of each bacterial kind a loopful was maintained in a nutrient broth and incubated at 37 °C for 14-16 hours. Finally, bacterial spread on nutrient agar using a sterilized swab. For comparison, Tetracycline, Lincomycine and Nalidixic acid were used as controls. The dishes were incubated for 18-24 hours at 37 °C. Prescott method was used to clarify the sensitivity of the studied compounds (Prescott et al, 1996). The results interpreted according to the report of W.H.O. The resistance R explains the diameter of inhibition zone < 11 mm, while the sensitive S was over 16 mm, but moderately sensitive MS was involved when the inhibition zone is 12-16 mm.

### 2. RESULTS AND DISCUSSION

The first part in this work was the synthesis of ten Schiff bases (1-10) from the reaction of (4-substituted benzaldehydes) with primary aliphatic amines in the presence of glacial acetic acid as catalyst in absolute ethanol. The IR spectra of Schiff base compounds (1-10) appeared the medium bands at 1640-1651 cm$^{-1}$ assigned to the stretching vibration of imine group (C=N), and the disappearance of stretching band of (C=O) group. The absorption bands showed in the range of (1560-1606) cm$^{-1}$, (3020-3089) cm$^{-1}$, (2920-2935) cm$^{-1}$, related to the stretching vibrations of (C=C) aromatic, (C-H) aromatic, (C-H) aliphatic respectively as shown in Table 3. The $^1$H-NMR spectra of the Schiff bases (Figure 1) exhibited a singlet peak for the proton of CH=N group at (8.26-8.36) ppm. A triplet signal at (3.26-3.63) ppm related to methylene proton of CH=NCH$_2$ while methylene protons displayed as multiplet signal at (1.21-1.72) ppm. Aromatic protons appeared as doublet signal at the region (6.92-8.13) ppm Table 4. In the $^{13}$C-NMR spectra (Figure 2) of compounds (2, 4, 6, 7 and 10), the signal for carbon of CH=N groups of compounds showed at (166.1) ppm. A signal appeared at 59 ppm attributed to methylene carbon of CH=N-CH$_2$ while the signals of methylene carbons exhibited at (27.2-55.6) ppm. The signals of aromatic carbons exhibited at (114.2 – 184.9) ppm Table 5.

### Table 3. Spectral data (FT-IR) of N, N’-(alkane-1,7-diy) and (alkane-1,8-diyl) bis(1-(4-substituted phenyl) methanimine (1-10):

| Comp.No | FT-IR(KBr) ν cm$^{-1}$ |
|---------|-----------------------|
|         | C-H Arom. | C-H Alpha. | C=N Imine | C=C Arom. |
| 1       | 3024      | 2926       | 1649      | 1606      |
| 2       | 3020      | 2920       | 1651      | 1606      |
| 3       | 3030      | 2933       | 1643      | 1602      |
| 4       | 3049      | 2933       | 1639      | 1596      |
| 5       | 3089      | 2935       | 1643      | 1560      |
| 6       | 3047      | 2920       | 1645      | 1606      |
| 7       | 3055      | 2922       | 1647      | 1606      |
| 8       | 3055      | 2933       | 1643      | 1608      |
| 9       | 3062      | 2935       | 1643      | 1604      |
| 10      | 3053      | 2924       | 1645      | 1593      |
Table 4. Spectral data ($^1$H-NMR) of N, N'- (alkane-1,7-diyl) and (alkane-1,8-diyl) bis(1-(4-substituted phenyl) methanimine (1-10):

| Comp. No. | $^1$H-NMR δ ppm |
|-----------|-----------------|
|           | CH₃  | C=CH₂  | CH=N-CH₂ | Ar-H | OCH₃ | CH₃ |
| 1         | 1.29-1.68 m, 10H | 3.4  | t, 4H | 8.29 | s, 2H | 7.23 | d, 8H | 3.81 | s, 6H |
| 2         | 1.25-1.61 m, 10H | 3.26 | t, 4H | 8.71 | s, 2H | 7.33 | d, 8H | 2.38 | s, 6H |
| 3         | 1.21-1.68 m, 10H | 3.43 | t, 4H | 8.32 | s, 2H | 7.98 | d, 8H |
| 4         | 1.25-1.69 m, 10H | 3.44 | t, 4H | 8.33 | s, 2H | 7.42 | d, 8H |
| 5         | 1.33-1.72 m, 10H | 3.63 | t, 4H | 8.30 | s, 2H | 7.66 | d, 8H |
| 6         | 1.27-1.70 m, 12H | 3.37 | t, 4H | 8.26 | s, 2H | 7.24 | d, 8H | 3.81 | s, 6H |
| 7         | 1.28-1.70 m, 12H | 3.60 | t, 4H | 7.32 | s, 2H | 7.31 | d, 8H | 2.35 | s, 6H |
| 8         | 1.28-1.66 m, 12H | 3.51 | m, 4H | 8.36 | s, 2H | 7.64 | m, 8H |
| 9         | 1.30-1.69 m, 12H | 3.36 | t, 4H | 8.31 | s, 2H | 7.95 | d, 8H |
| 10        | 1.26-1.68 m, 12H | 3.38 | m, 4H | 8.28 | s, 2H | 7.42 | d, 8H |

Table 5. Spectral data ($^{13}$C-NMR) of N, N'- (alkane-1,7-diyl) and (alkane-1,8-diyl) bis (1-(4-substituted phenyl) methanimine:

| Comp. No. | $^{13}$C-NMR δ ppm |
|-----------|--------------------|
|           | CH₂ | CH=N-CH₂ | Ar-H | CH=N | OCH₃ | CH₃ |
| 2         | 27.2-31.0 5C | 59.0 | 2C | 128.9-142.5 12C | 166.1 | 2C |
| 3         | 27.2-31.0 5C | 59.0 | 2C | 124.7-151.2 12C | 166.1 | 2C |
| 4         | 27.2-31.0 5C | 59.0 | 2C | 129.4-137.1 12C | 166.1 | 2C |
| 6         | 27.2-55.6 6C | 59.0 | 2C | 114.2-184.9 12C | 166.1 | 2C | 56.0 | 2C |
| 7         | 27.2-31.0 6C | 59.0 | 2C | 128.9-142.5 12C | 166.1 | 2C |
| 10        | 27.2-31.0 6C | 59.0 | 2C | 129.4-137.1 12C | 166.1 | 2C |

Figure 1. $^1$H-NMR spectrum of the Schiff base (1E,1'E)-N, N'- (heptane-1,7-diyl)bis(1-p-tolylmethanimine) (1)

Figure 2. $^{13}$C-NMR spectrum of the Schiff base (1E,1'E)-N, N'- (heptane-1,7-diyl)bis(1-p-tolylmethanimine) (1)
The second part focused on the synthesis of five oxazepine derivatives (11-15) by reaction between imine groups of Schiff bases (1-10) and cyclic acid anhydride [phthalic anhydride] in dry benzene as shown in the Scheme 2. The general feature of the IR spectra of oxazepine derivatives showed the band at (1705-1782) cm⁻¹ belongs to (C=O) groups in oxazepane structure and disappearance of (C=N) group. Also appeared a strong band which belongs to the formation of (C=O-C) at 1280-1185 cm⁻¹, this evidence confirmed the formation of the described products Table 6.

The ¹H-NMR spectra for oxazepine compounds (11-15) observed a triplet signal of methylene proton attached to nitrogen atom at (3.09) ppm and showed the proton of the CH-N group with protons of aromatic ring as multiplet signals at (6.90-8.23) ppm, which is a good evidence of obtaining the products Table 7. Furthermore, the appearance of the new extra different carbon peaks in the aromatic at δ (109.5-160.2) and carbonyl groups at (166.4 and 170.6) ppm regions in the ¹³C-NMR spectra, provided further support to the structures of the oxazepine products Table 8.

Table 7. Spectral data (¹H-NMR) of oxazepane compounds (11-15):

| Comp. No. | CH₃ | C-N-CH₂ | Ar-H & C-H | OCH₂ | CH₂ |
|-----------|-----|--------|------------|------|-----|
| 11        | 1.28-1.66 m, 12H | 3.70 t, 4H | 7.55-8.23 m, 18H | - | - |
| 12        | 1.23-1.63 m, 10H | 3.55 t, 4H | 7.45-8.06 m, 18H | - | - |
| 13        | 1.23-1.59 m, 10H | 3.69 t, 4H | 7.17-8.06 m, 18H | - | 2.34 s, 6H |
| 14        | 1.37-1.70 m, 10H | 3.78 m, 4H | 6.90-8.05 m, 18H | 3.42 s, 6H | - |
| 15        | 1.21-1.64 m, 12H | 3.57 t, 4H | 7.47-8.07 m, 18H | - | - |

Table 8. Spectral data (¹³C-NMR) of oxazepane compounds (11-15):

| Comp. No. | CH₂ | C-N-CH₂ | Ar-H & C-H | C=O | OCH₂ | CH₂ | CN |
|-----------|-----|--------|------------|-----|------|-----|----|
| 11        | 27.5-29.0 6C | 42.1 2C | 123.7-147.2 26C | 166.4,170.6 4C | - | - | - |
| 12        | 27.5-29.0 5C | 42.1 2C | 109.5-142.9 26C | 166.4,170.6 4C | - | - | 119.5 2C |
| 13        | 27.5-29.0 5C | 42.1 2C | 126.1-139.2 26C | 166.4,177.6 4C | - | 21.1 2C | - |
| 14        | 27.5-29.0 5C | 42.1 2C | 112.9-160.2 26C | 166.4,170.6 4C | 56.0 2C | - | - |
| 15        | 27.5-29.0 6C | 42.1 2C | 126.1-147.2 24C | 166.4,170.6 4C | - | - | 123.7 2C |

Figure 3. ¹H-NMR spectrum of the oxazepine 4,4’-(heptane-1,7-diyl)bis (3-(p-tolyl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione)
The results of such preliminary biological study exhibited that most of new compounds have good antibacterial activity Table 9. The compounds 1, 3, 5, 6, 8, 9, 11, 12 and were sensitive against *Escherichia Coli* bacteria which represent Gram-negative type. Inhibition of these compounds was similar to that one in Tetracycline and Nalidixic acid. While the compounds 3, 5, 7, 9, 11, 14 and 15 showed sensitive against the type of bacteria. Other compounds 2, 4 and 13 have resistant against the *Staphylococcus aureus* bacteria which represent Gram-positive type and this inhibition were the same as Lincomycine. Furthermore, the compounds 3, 5, 7, 9, 11, 14 and 15 showed sensitive against these bacteria and the result was agreed with that one in Tetracycline and Nalidixic acid. While the compounds 1, 6, 8, 10 and 14 were moderately sensitive with this kind of bacteria.

| Compound no. | Test organism | E. coli | GIZ in mm | Mode | Sta. aureus | GIZ in mm | Mode |
|--------------|---------------|---------|-----------|-------|-------------|-----------|-------|
| 1            |               | 23      | S         | 15    | MS          |           |       |
| 2            |               | 11      | R         | 11    | R           |           |       |
| 3            |               | 22      | S         | 20    | S           |           |       |
| 4            |               | 15      | MS        | 10    | R           |           |       |
| 5            |               | 23      | S         | 21    | S           |           |       |
| 6            |               | 23      | S         | 16    | MS          |           |       |
| 7            |               | 10      | R         | 20    | S           |           |       |
| 8            |               | 21      | S         | 14    | MS          |           |       |
| 9            |               | 22      | S         | 21    | S           |           |       |
| 10           |               | 13      | MS        | 16    | MS          |           |       |
| 11           |               | 21      | S         | 19    | S           |           |       |
| 12           |               | 22      | S         | 20    | S           |           |       |
| 13           |               | 10      | R         | 9     | R           |           |       |
| 14           |               | 15      | MS        | 14    | MS          |           |       |
| 15           |               | 22      | S         | 20    | S           |           |       |
| Control     | Tetracycline  | 25      | S         | 26    | S           |           |       |
|             | Lincomycine   | 11      | R         | 24    | S           |           |       |
|             | Nalidix acid  | 22      | S         | 10    | R           |           |       |

4. Conclusion

A series of new Schiff bases and 1,3-oxazepine derivatives containing imine group were synthesized successfully using pericycliccyclo addition of Schiff bases with phthalic anhydrides, besides using a small amount of solvents, shorter reaction times and good yield. Some of these compounds shown good antibacterial activity against the bacterial pathogens.

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