# Synthesis Some Heterocyclic Compound based on 2,5–disubsituted Pyridine

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**Abstract**

The aim of the present study is to determine the useful of Schiff bases derivatives (oxazepine, tetrazole) compounds which used as drug and antimicroble the present work involved preparation starting from 2,5– diaminopyridine a variety of schiff bases and heterocyclic (oxazepine, tetrazole) have been and heterocydic (oxazepine, tetrazole) have been synthesis, all proporsed structure were supported by, FT-IR, 'H-NMR, Elemental analysis, Microbial study.

Keywords pyridine, Schiff bases, fused heterocyclic ring.

## Introduction

The development of simple synthesis route to widely used organic compounds ring, using readily available reagents is one of the main objective of organic synthesis, Nitrogen heterocycles are of a special interest because they constitute an important class of natural and non natural products, many of which exhibit useful biological activities, one–pot efficient synthesis of heterocyclic derivatives, may permit the development of novel therapies for the treatment of epilepsy, pain and other neurodegen disorder [1].

Some Schiff bases bearing aryl groups [2], or heterocyclic residues possess excellent biological activities [3], which has attracted many researcher's attention in recent year. They have been reported to used as analgesic, anthelmintic, antituberculer, plant growth regulator, antiviral, antifungal and anticancer[4]. Derivative like the other members (oxazepine, tetrazole) all the amino pyridine series have been widely applied as therapeutic agent due to their anticonvulsant, vasorelaxant and antiiflammatory properties [5].

The occurrence of the pyridine nucleus in many natural and synthetic biologically active compounds continues to contribute to the development of new synthetic methodologies to word this important heterocycle [6].

Various heterocyclic derivatives as well as known to possess an array of physiological activites, such as anticancers, muscle relexant, hypnotic, anti-inflammatory, diuretic and anti hypertertensive activities and are widely used in pharmaceticales [7], promoted by the observations of above mentioned heterocyclic rings.

## Experimental

### General

Melting point were determined on Gallenkamp melting point apparatus and were uncorrected, on a (SHIMADZU) FTIR 8300 spectra meter as KBr. disc, result were given in $cm^{-1}$, 1H-NMR and C13-NMR spectra were recorderd at 200-13 and 50.32 MHz, were reported in part permillion (ppm) down field from internal tetramethyl silane (TMS) (chemical shift in δ values). Elemental analysis were run using a Perkin-Elmer, RE2400 C.H.N analyzer, 1H-NMR; 13C-NMR; C.H.N were performed at Drug and Natural Product Department, university in Jordon.

### Synthesis of Schiff bases [1-6][8].

A series of Schiff bases were prepared from reaction (0.01mol, 1.21 ml) of 2,5-diaminopyridine with (0.02mol) of different aldehyde and ketone in 15 ml absolute. ethanol and (1-2) drop glycial acetic acid. The resulting mixture was refluxed for 4h, the solid that separated on cooling was filtered off and dried.

### Synthesis of oxazepine compounds (7-12)[9].

A mixture of schiff bases (1-6) (0.01mol) with phthalic anhydride (0.02mol, 2 gm) was heated under reflux for 5h in oil bath (60-65)C° with dry benzene (15 ml), the solid product precipitate that separated upon cooling was filtered off and recrystallized from ethanol.

**Synthesis of tetrazole compounds (13-18) [10].**

Schiff bases (1-6) about (0.01mol) with sodium azide (0.02 mol, 0.52 gm) was heated under reflux in oil bath at (50-60) C° with 15 ml (THF). The end of reaction checking by (TLC) in methanol, the solid product formed was filtered off and recrystallized from ethanol.

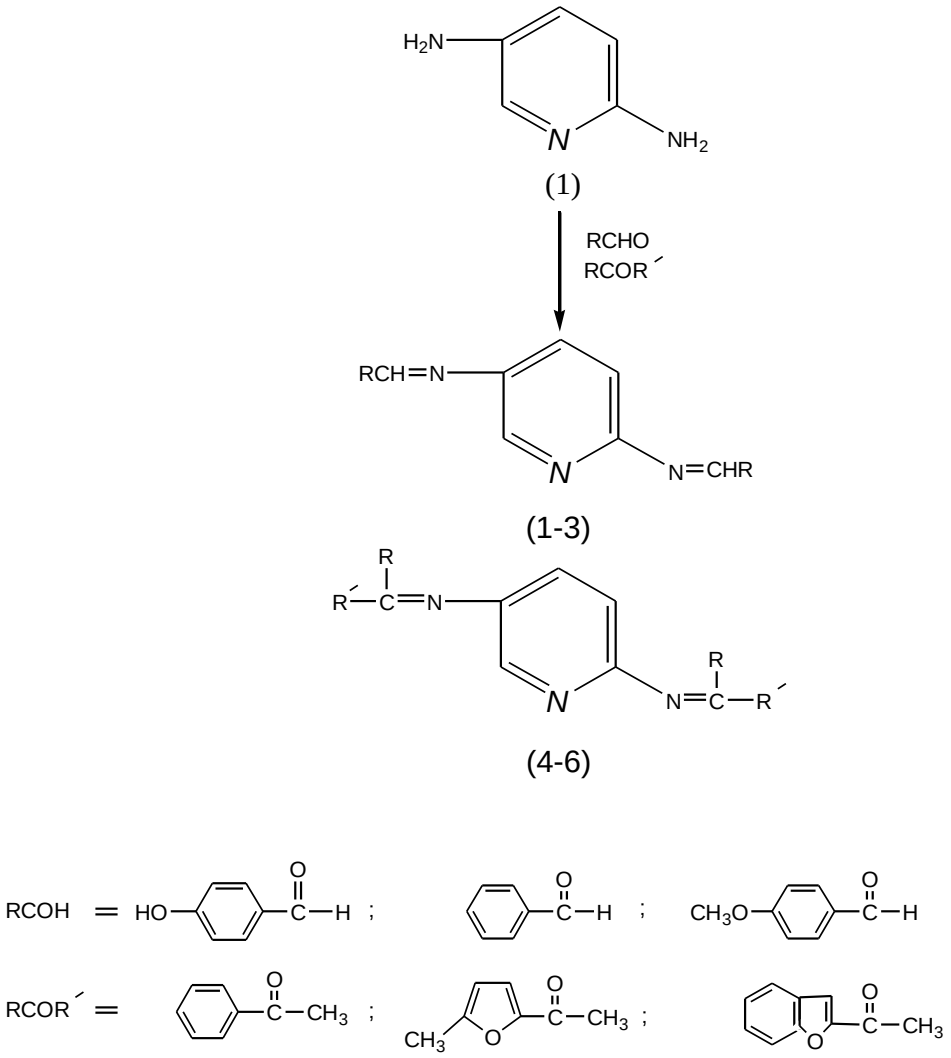
All these synthesis steps were summarized in Schemes (1-3), physical properties, FTIR, Microbial study, 1H-NMR, 13C-NMR, Elemental analysis (C.H.N) are listed in Table (1-4) respectively.

***Table (1)***
***Depacited physical properties of compounds (1-18).***

| *Comp. No.* | *Molecular formula* | *M.PC°* | *Colour* | *Purification solvent* | *Yield %* |
|---|---|---|---|---|---|
| 1. | $C_{19}H_{15}N_3O_2$ | 198-200 | Yellow | Ethanol | 82 |
| 2. | $C_{19}H_{15}N_3$ | 204-206 | Yellow | Ethanol | 78 |
| 3. | $C_{21}H_{19}N_3O_2$ | 220-222 | Orange | Ethanol | 60 |
| 4. | $C_{21}H_{19}N_3$ | 235-237 | Yellow | Ethanol | 70 |
| 5. | $C_{19}H_{19}N_3O_2$ | 200-202 | Orange | Ethanol | 65 |
| 6. | $C_{23}H_{19}N_3O_2$ | 205-207 | Deep- | Ethanol | 68 |
| 7. | $C_{35}H_{23}N_3O_8$ | Dec. | Deep- | Ethanol | 80 |
| 8. | $C_{35}H_{21}N_3O_6$ | 210-212 | Orange | Ethanol | 78 |
| 9. | $C_{37}H_{29}N_3O_8$ | 230-232 | Orange | Ethanol | 55 |
| 10. | $C_{37}H_{27}N_3O_6$ | 250-252 | Deep- | Ethanol | 65 |
| 11. | $C_{35}H_{27}N_3O_8$ | 262-264 | Deep- | Ethanol | 70 |
| 12. | $C_{41}H_{27}N_2O_8$ | 280-282 | Deep- | Ethanol | 55 |
| 13. | $C_{19}H_{17}N_9O_2$ | Dec | Pule-Brown | Ethanol | 70 |
| 14. | $C_{19}H_{13}N_9$ | Dec | Brown | Ethanol | 56 |
| 15. | $C_{21}H_{19}N_9O_2$ | Dec | Brown | Ethanol | 58 |
| 16. | $C_{21}H_{21}N_9$ | Dec | Brown | Ethanol | 60 |
| 17. | $C_{19}H_{21}N_9O_2$ | Dec | Brown | Ethanol | 60 |
| 18. | $C_{25}H_{21}N_9O_2$ | Dec | Brown | Ethanol | 55 |

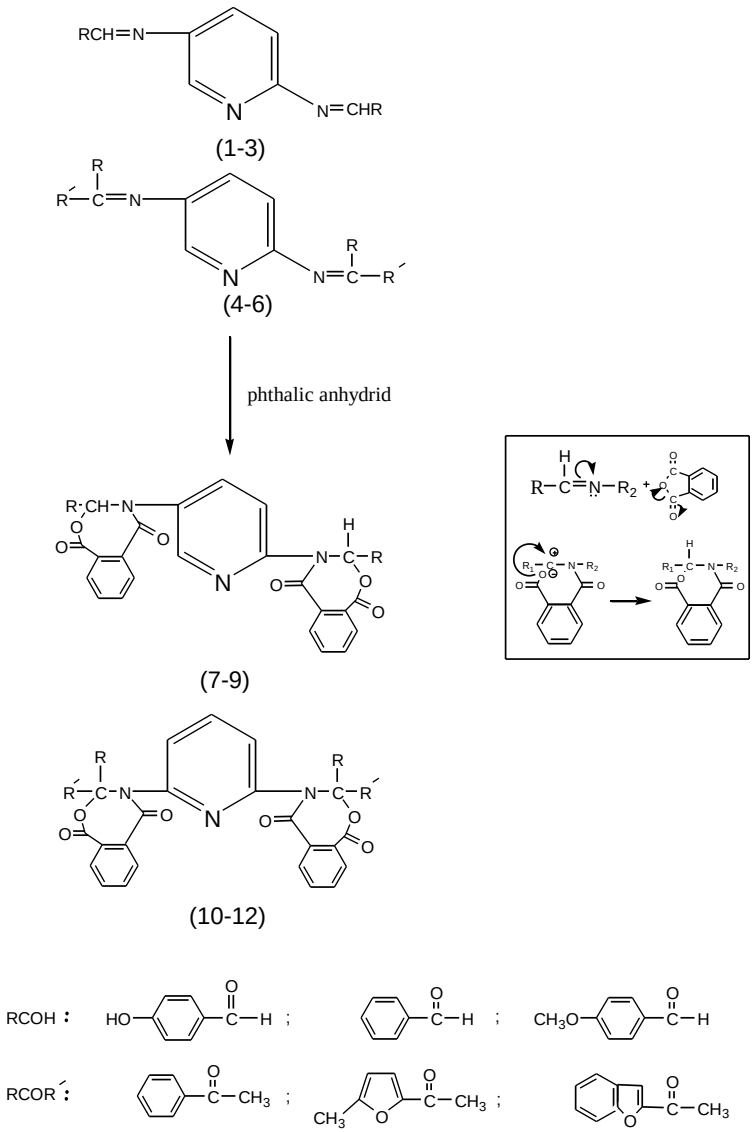
**Results and Discussion**

The synthesis starting from 2,5–diaminopyridine, amino group readily converted to Schiff bases derivatives (1–6) by heating under reflux with ethanolic solution of aldehydes and ketone, which shown in Scheme (1), Schiff bases used for synthesis of an interesting derivatives, it is a versatile key intermediate for the synthesis of some fused heterocyclic ring (7-18), good biological activity, physical properties, FT–IR; 1H–NMR, 13C–NMR, elemental analysis data were used to characterized the structure of compounds (1–18).



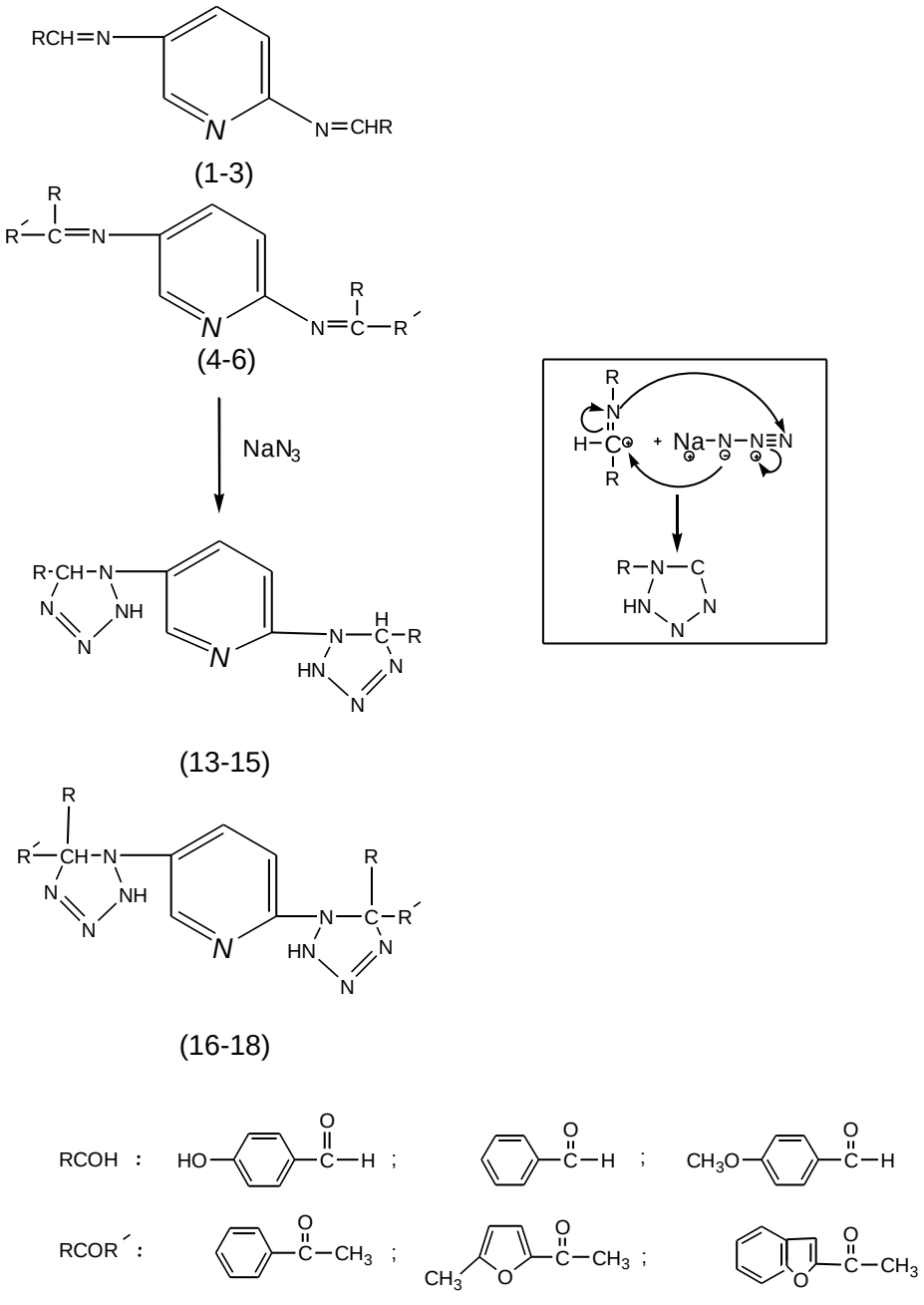

***Scheme (1) Synthetic path ways for preparation of compounds (1-6).***

FTIR spectra of Schiff bases for compound [1] showed clear absorption bands at (3440-3200) $cm^{-1}$ for (OH), (1601) cm-1 for (C=N), (3008) $cm^{-1}$ for aromatic (CH), (1250) $cm^{-1}$ for phenolic (C-O); 1H-NMR (DMSO- d6)δ: (7.73-7.95) ppm due to (Ar-H), (10.4-10.85) ppm due to 13C-NMR (DMSO-d6) δ: (164.6-165.8) ppm due to pyridine, (133.13-134.03) for (C=N) (128.1- 129.6) aromatic carbons, FTIR spectrum of Schiff bases for compound [4] show absorption bands at (1627) $cm^{-1}$ for (C=N), (2885) $cm^{-1}$ for aliphatic (CH2), (1166) $cm^{-1}$ for (C-O-C); 1H-NMR (DMSO- d6) δ: (6.1-6.9) ppm due to (Ar-H), (2.10- 1.25) ppm due to (3H, CH); 13C-NMR (DMSO-d6) δ: (133-133.9) ppm due to (C=N), (2.95-3-H) ppm for (C, CH3), (165.9-166.6) ppm for pyridine ring, (130.2-131.1) ppm for aromatic carbons.




***Scheme (2) Synthetic path ways for preparation for compounds (7-12).***

The FTIR spectrum (Oxaizepine) derivatives compound [7]: displayed the strong bands (1693) $cm^{-1}$ for (C=O) combined with disappearance of (C=N) bands, (827-895) $cm^{-1}$ (aromatic, P-Substitute) (1550) cm-1 for (C=C), (3360) $cm^{-1}$ for (OH); 1H-NMR (DMSO-d6) δ : (7.73- 7.95) ppm for (Ar-H), (7.00) for (d, 4H), (9.78- 9.81) for (H, OH); 13C-NMR (DMSO- d6) δ: (128,130.5, 134.8) ppm (aromatic carbon), (160-164.2) ppm for (C=O); compound [10]: displayed (1739) $cm^{-1}$ for (C=O) combined with disappearance of (C=N) bands, (1570) $cm^{-1}$ for (C-C), (2927) cm-1 for (CH2): 1H-NMR (DMSO-d6 ) δ: (7.92- 7.97) ppm for (Ar-H), (5.93-5.10) ppm due to (d, 5H); 13C-NMR (DMSO-d6) δ: (2.95- 2.88) ppm due to (CH3); (130.3, 130.5, 134.3, 134.4) ppm (aromatic carbon), (163.2-163.8) ppm for pyridine ring; Compound [1-6] similarly react with Sodium azide afforded tetrazol [13-18] compounds:




***Scheme (3) Synthetic path ways for preparation of compound (13-18).***

The FTIR spectrum tetrazole derivatives compound [13] displayed strong bands (1448) $cm^{-1}$ for (N=N) combined with disappearance (C=N), (3210) $cm^{-1}$ for (NH), (1230) $cm^{-1}$ for (C-N); (1250) for (C-O) 1H-NMR (DMSO-d6) δ: (7.92- 8.20) ppm due to (Ar- H), (5.83) ppm due to (s, H, NH), (9.88- 9.80) ppm for (H, OH); 13C-NMR (DMSO-d6) δ: (128.2- 129.3) ppm for (aromatic carbons), (163.9- 164.1) ppm for pyridine ring; compound [16]: displayed strong bands (1485) $cm^{-1}$ for (N=N), (3197) $cm^{-1}$ for (NH), (1225) cm-1 for (C-N); 1H-NMR (DMSO-d6) δ: (7.79-7.45) ppmdue to (Ar-H), (5.92) ppm due to (s, H, NH); 13C-NMR (DMSO4-d6) δ: (126.4-128.2) ppm (aromatic carbon), (162.8- 164.8) ppm for pyridine ring.

That's data give further evidence for the formation of (Oxazepine, tetrazole) compounds.

***Table (2)***
***FTIR spectral data of compounds (1-18).***

| Comp No. | VC=N | Vc=c | VoH | VcH aromatic | VcH Alpha | Others | Comp No. | VC-N | VC=C | VoH | VcH aromat | VcH alpha | Others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | 1600 | 1597<br>1550 | 3440 | 3100 | _ | V(c-o)1250 | 10. | _ | 1570 | _ | 3075 | 2927 | V(c-o-c) 1106<br>V(c=o)1739 |
| 2. | 1607 | 1570 | _ | 3016 | _ | _ | 11. | _ | 1575 | _ | 3110 | 2902 | V(c-o-c) 1127<br>V(c=o) 1717 |
| 3. | 1610 | 1556 | _ | 3010 | 2980 | V(c-o-c) 1180 | 12. | - | 1585 | - | 3016 | 2881 | V(c-o-c) 1122<br>V(c=o)1740 |
| 4. | 1627 | 1575 | - | 3050 | 2885 | V (C-O-C) 1166 | 13. | 1230 | 1590 | 3290 | 3035 | 2880 | V(NH)3210<br>V(N=N)1454 |
| 5. | 1623 | 1548 | - | 3065 | 2995 | V(c-o-c) 1117 | 14. | 1225 | 1591 | - | 3060 | 2900 | V(NH)3200<br>V(N=N)1448 |
| 6. | 1617 | 1603 | _ | 3120 | 2940 | V(c-o)1250 | 15. | 1235 | 1589 | _ | 3065 | 2901 | V(NH)3200<br>V(N=N)1445 |
| 7. | _ | 1550 | 3360 | 3032 | 2877 | V(c=o)1693 | 16. | 1225 | 1597 | _ | 3044 | 2889 | V(NH)3197<br>V(N=N)1485 |
| 8. | _ | 1565 | _ | 3009 | 2885 | V(c=o)1720 | 17. | 1200 | 1595 | _ | 3027 | 2875 | V(NH)3201<br>V(N=N)1456 |
| 9. | _ | 1580 | _ | 3030 | 2890 | V(c=o)1723 | 18. | 1220 | 1596 | _ | 3090 | 2885 | V(NH)3199<br>V(N=N)1458 |

***Table (3)***
***Depacited Elemental Analysis (C.H.N) of Some Compounds.***

| Comp No. | C.H.N Analysis% calculated (Found) | | |
|---|---|---|---|
| | %C | %H | %N |
| 1 | 71.92(72.40) | 4.73(5.53) | 13.25(13.20) |
| 4 | (81.5) 80.51 (81.05) | 6.07(6.35) | 13.14(13.90) |
| 7 | 79.10(79.60) | 3.96(4.50) | 7.41(8.41) |
| 10 | 72.91(73.70) | 4.43(5.51) | 6.90(7.50) |
| 13 | 56.58(57.20) | 4.22(4.50) | 31.27(32.40) |
| 16 | 63.16(64.10) | 5.26(6.30) | 31.58(32.50) |

***Table (4)***
***Microbial Study of Some Compounds.***

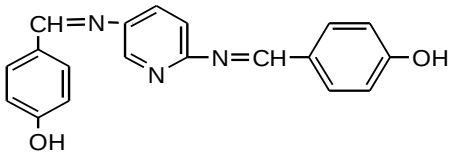
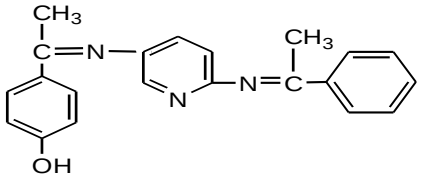
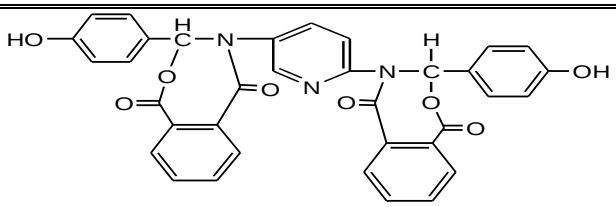
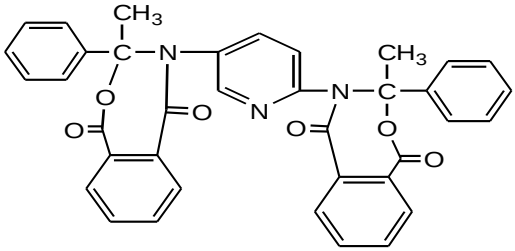
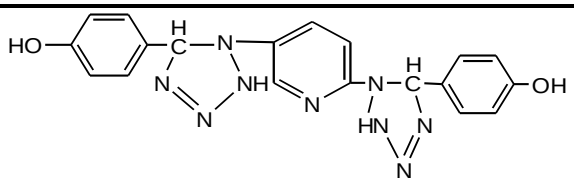
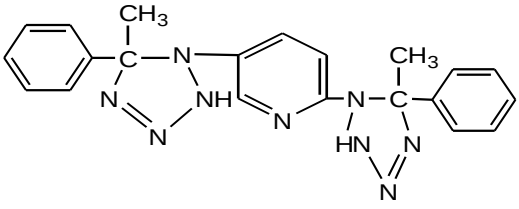
| Comp No. | Activity against $G^+$Ve bacteria* | Activity against $G^-$Ve bacteria** | Activity against Fungicide*** |
|---|---|---|---|
| | Stap, aurea, Bacillus Subtillis | Escher. Coli, Kleb.spp,salm.spp.Pseu.spp | A spring in ussb |
| 1 | 6.1 | Nill | Nill |
| 4 | 2.3 | Nill | Nill |
| 7 | 10.1 | Nill | 10 |
| 10 | 7.9 | Nill | 11 |
| 13 | 18.1 | Nill | 12 |
| 16 | 16.0 | Nill | 10 |

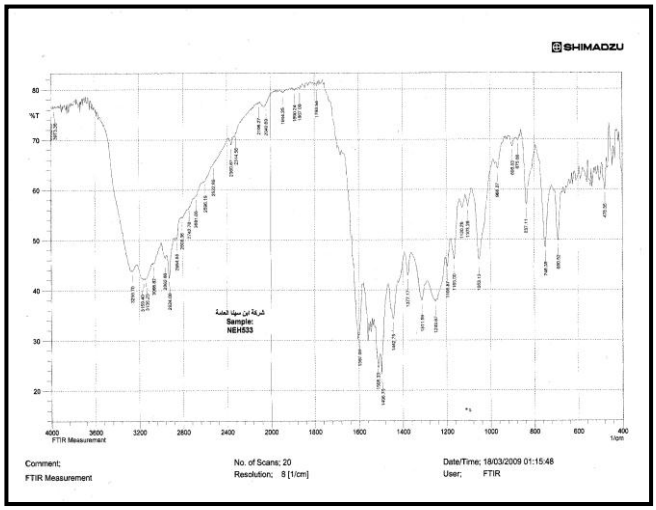
****$G^+$ Ve bacteria = (staphylococcus, aurea and Bacillus Subtilis) respectively.***
*****$G^-$ Ve bacteria = (Escherichia Coli, Klebsilla Spp, Salmonella spp, pseudomonas spp).***
******fungicide = (A spring in ussb).***
***Note = A diameter around 6mm disc impregnated with the all prepared compounds.***

## Microbial Study

Microbial study of (1–18) compounds were evaluated against representive (staphylococcus aureus) bacteria $G^{+}Ve$, (Klebsiella pneumonia) bacteria $G^{-}Ve$ bacteria and fungicide according to agar plate method". All the solutions were prepared freshly by dissolving in (DMSO) solvent to obtain a final concentration (0.5 mg/ ml). The diameter of inhibition zone in (mm unit) including a disc diameter was measured for each treatment. The compounds (13–18) showed a moderate antimicrobial (staphylococcus, aureus and Bacillus subtilis). All the compounds (1-6) have not any antimicrobial activity against $G^{-}Ve$ bacteria (ES cherichia coli, Klebsiella SPP, Salmonella SPP and Pendomonas SPP). All the compounds (1–18) showed a moderate microbial activity against fungicide (Aspiring in Ussb) [11].

***Table (5)***
***1H-NMR and 13C_NMR spectral data for some compounds.***

| *Comp No.* | *Compound structure* | *1H-NMR spectra data* | *13C_NMR spectra data* |
|---|---|---|---|
| 1 |  | δ =7.73-7.95(Ar-H)<br>δ:10.46-10.85 (H,OH) | δ=115.1-117.2(2C, =CH-)<br>δ=128.1-129.6(aromatic carbon)<br>δ=164.6-165.8 (pyridine)<br>δ=133.13-134.03 (C=N) |
| 4 |  | δ = 6.1-6.9 (Ar-H) | δ = 3.11-2.95(CH3)<br>δ=130.2-131.1(aromatic carbon)<br>δ=165.9-166.6 (pyridine)<br>δ=133-133.9 (C=N) |
| 7 |  | δ =7.73-7.95(Ar-H)<br>δ = 9.98- 9.81 (H, OH)<br>δ:7.0 (d, 4H) | δ=128,130.5,134.4,134.8 (aromatic carbon)<br>δ =1.92-1.99 (C-O)<br>δ: 160- 164 (C=O) |
| 10 |  | δ: 7.92- 9.97 (Ar-H)<br>δ: 5.93- 5.19 (d, 5H) | δ = 2.95-2.88(CH3)<br>δ =130.3,130.5,134.3,134.4 (aromatic carbon)<br>δ=163.2-163.8 (pyridine) |
| 13 |  | δ =7.92- 8.20 (Ar-H)<br>δ = 9.88- 9.80 (H, OH)<br>δ: 5.83 (s, H, NH) | δ=161.8-162.2(Ar-C-N)<br>δ=128.2-129.3(aromatic carbon)<br>δ=163.9-164.1 (pyridine) |
| 16 |  | δ=7.79-7.45 (Ar-H)<br>δ: 5.92 (s, H, NH) | δ=126.4-128.2(aromatic carbon)<br>δ =162.8-164.8 (pyridine) |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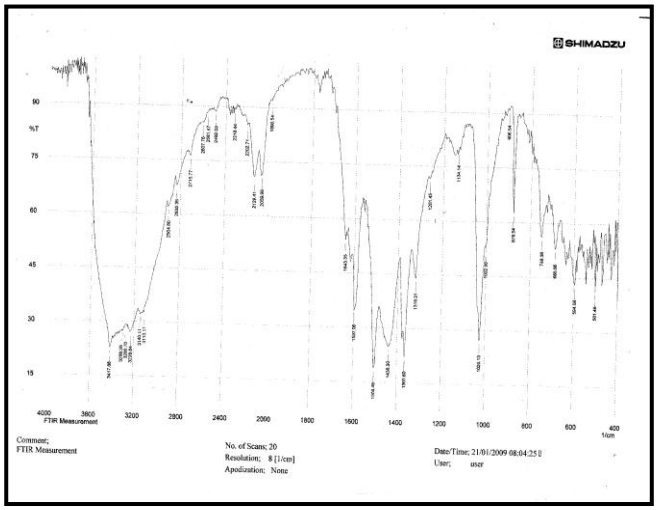
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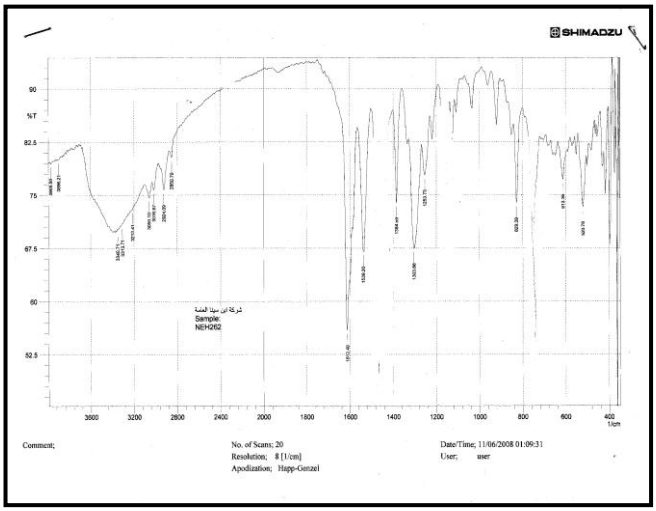
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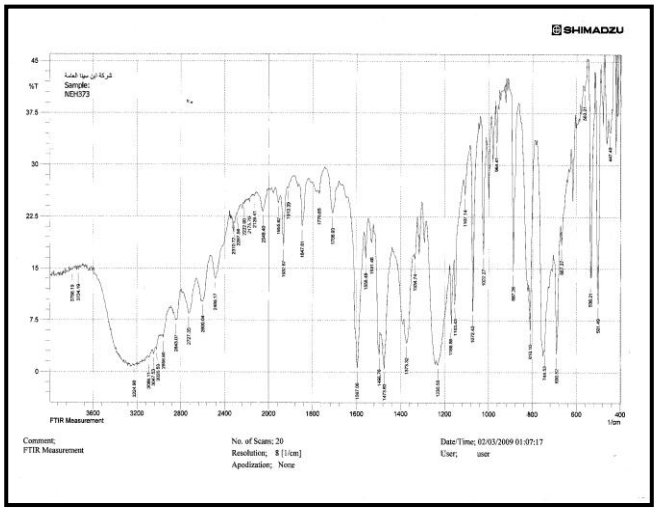
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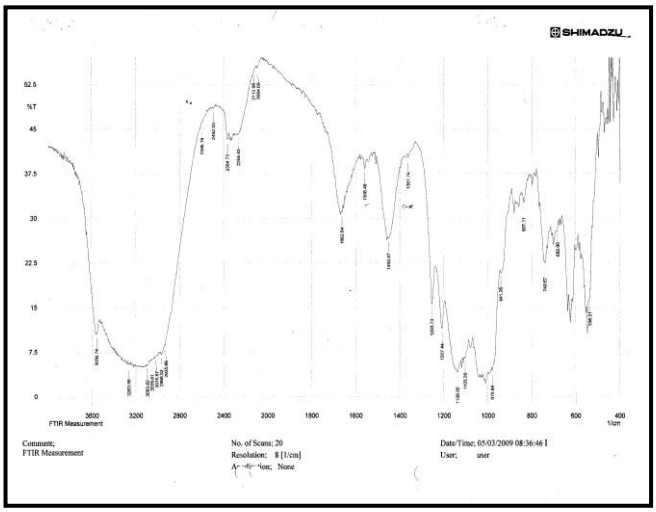
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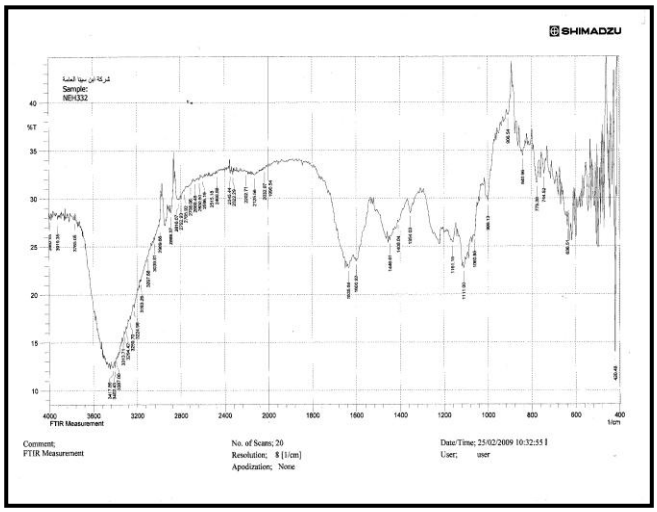
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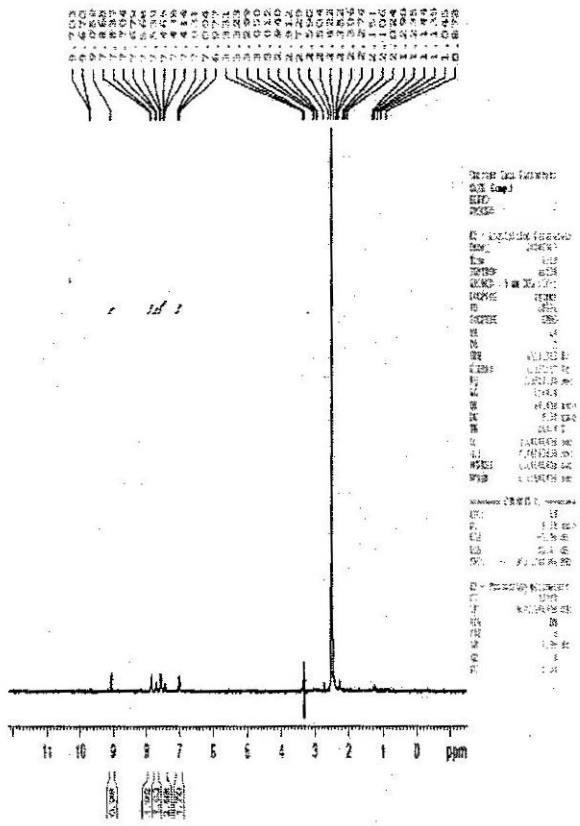

*Fig. (1) HNMR spectrum of compound (1).*

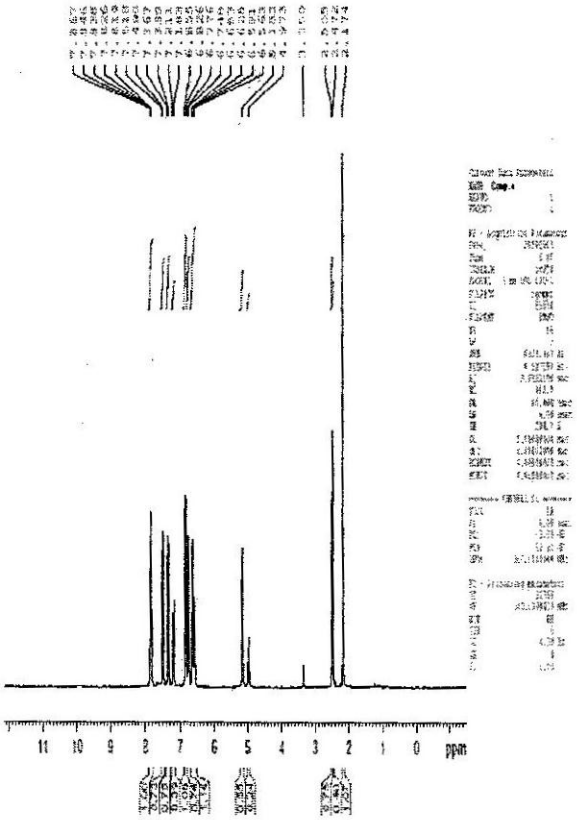

*Fig. (2) HNMR spectrum of compound (4).*

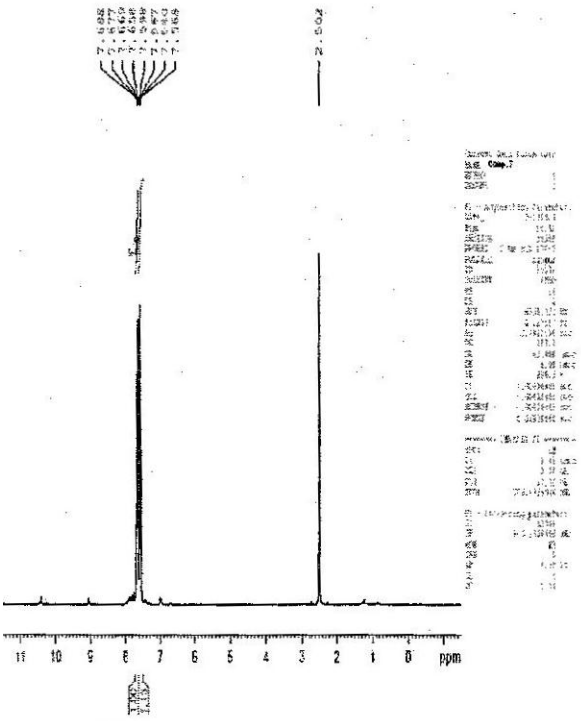

*Fig. (3) HNMR spectrum of compound (7).*

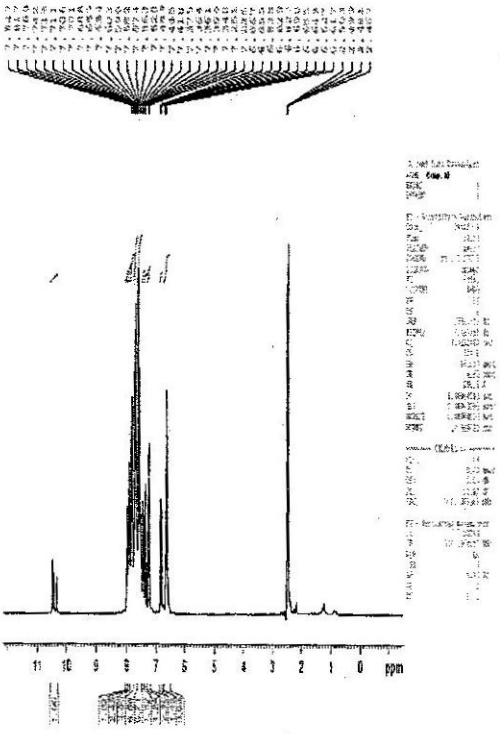

*Fig. (4) HNMR spectrum of compound (10).*

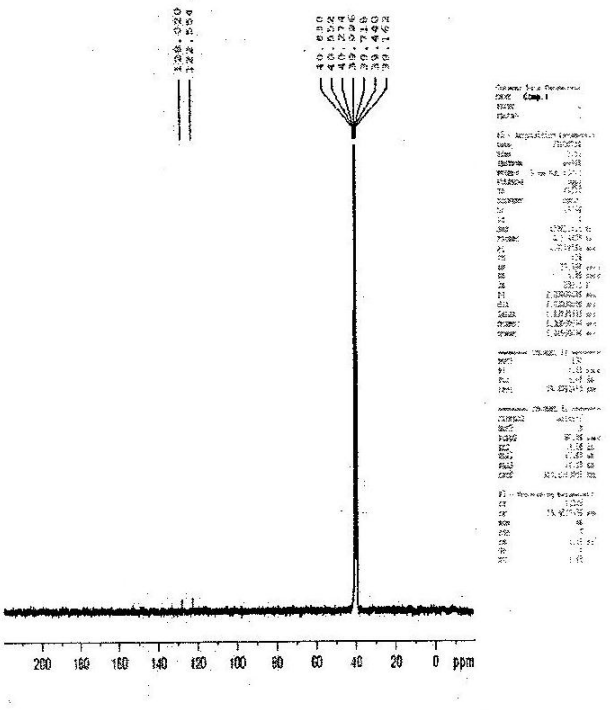

*Fig.(5) $^{13}$CNMR spectrum of compound (1).*

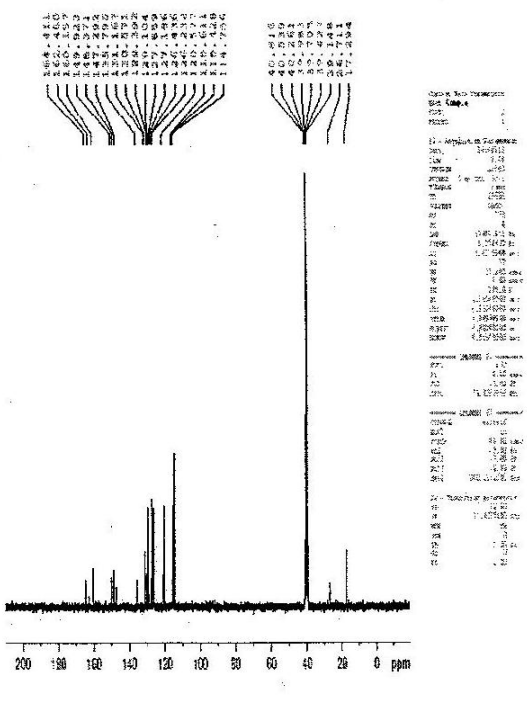

*Fig.(6) $^{13}$CNMR spectrum of compound (4).*

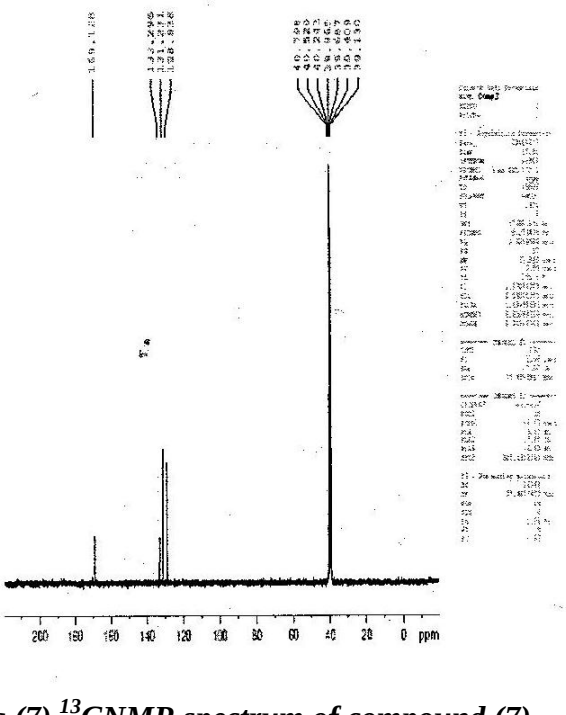

*Fig.(7) $^{13}$CNMR spectrum of compound (7).*

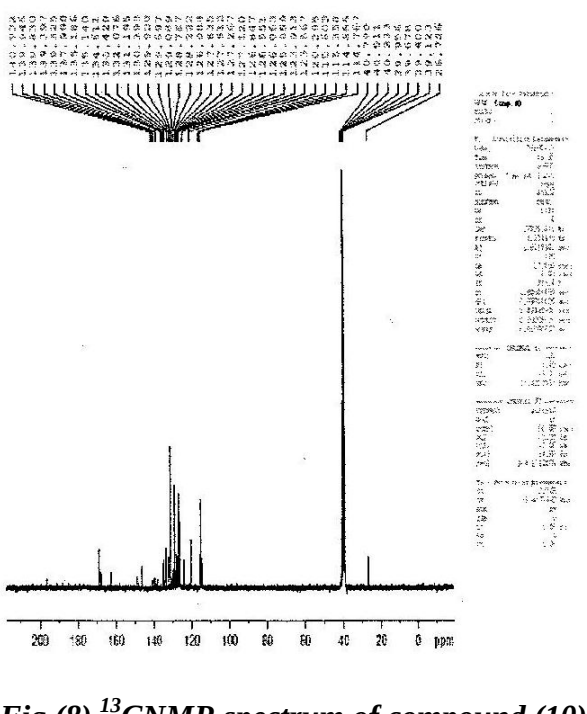

*Fig.(8) $^{13}$CNMR spectrum of compound (10).*

**الخلاصة**

الغرض من الدراسة تحضير مشتقات (الاوكسوفين والتترازول) المشتقة من قواعد شيف لمركب (2,5– ثنائي أمين البريديين) من خلال تكثيفة مع بعض الالديهايدات و الكيتونات للحصول على قواعد شيف (١ – ٦). ثم تحضير ستة من مشتقات الأوكسوفين (٧ – ١٢) حلقات سباعية غير متجانسة من خلال تفاعل قواعد شيف (١–٦) مع انهدريد الفثاليك ثم تحضير مركبات التترازول وذلك من تفاعل قواعد شيف (١– ٦) مع أزيد الصوديوم في محلول (THF) للحصول على حلقات خماسية غير متجانسة. وتم تشخيص هذه المشتقات بمطيافية الأشعة تحت الحمراء و(1H-NMR; C13-NMR) والتحليل الدقيق للعناصر C.H.N. اضافة إلى دراسة الفعالية البايولوجية والخواص الفيزياوية وقد اظهرت غالبية هذه المركبات فعالية بايولوجية ضد البكتريا الموجبة والبكتريا السالبة والفطريات.

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