ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

# Synthesis, Characterization and Study Biological Activity of Some New Compounds Derived From Phthalic Anhydride

**Nebras M. Jamel***

*Dept. of Chemistry/College of Education for Pure Science (Ibn Al-Haitham)/University of Baghdad/Iraq.*

***Corresponding Authors Email:** *nebras.jamel@gmail.com*

## Abstract

In this research , phthallic anhydride ring is opened with 4-methyl aniline and acetone as a solvent to results the compound [I] that reacted with dimethyl sulphate and anhydrous sodium carbonate formation to phathalate ester [II], while the acid hydrazide compound [III], was obtained from mixed the compound [II]with hydrazine hydrate, Synthesis four type of shiff bases$[IV]_{a\text{-}d}$ was synthesized from the reaction of acid hydrazide [III] with aromatic aldehyde or ketone , when reacted Shiff bases with phthalic anhydride or naphthalicanhydride,I get eight derivatives of oxazepine $[V]_{a\text{-}d}$ , $[VI]_{a\text{-}d}$. The bacterial activity of the new compounds studied by four species of bacteria: *Esherichia Coli, Enterobactecloacae* (Gram negative) and *staphylococcusaureus, Bacillus subtilis* (Gram positive). These compounds were identified by FTIR, 1HNMR and Mass (of some of them).

**Keywords**: *Schiff bass, 1, 3-oxazepine and antibacterial activity.*

## Introduction

Phthalic anhydride is starting material in synthesis many phthalate esters [1].When treated ester with hydrazine hydrate led to formation acid hydrazid[2], which was involves the preparation of many organic compounds with wide biological activity.[3,4] Schiff bases considered intermediate to get many heterocyclic compounds such as Oxazepines[5].

In addition to that Schiff base compound is known to possession antibacterial [6] antifungal, anticancer [7], and antitumor [8]. Oxazepines are seven membered heterocyclic that contains two heteroatom's (Nitrogen and Oxygen)[9,10], Oxazepine and their derivatives have some important pharmacological activities [11,12], oxazepine derivatives were synthesized by using different methods[13,15] among of these, the reaction of Schiff bases with acid anhydride[16].

### Aim the Work

Synthesis and characterization of new oxazepine compound from imine groups and Study the anti-bacterial activity for the synthesized compounds.

## Materials and Methods

### Preparation of 2-(p-tolylcarbamoyl) benzoic acid [I] [17]

A solution of Phthalic anhydride (0.218g. 0.001mole) in (15ml) acetone , a solution of 4-Methyl aniline( 0.001mole) in (15ml) acetone was added dropwise during one hour, the mixture was then left at room temperature with continuous stirring for 24 hrs , the product was then filtered off and recrystallized from acetone m.p185-187 $^0$C, yield96% .

### Preparation of methyl 2-(p-tolylcarbamoyl) benzoate [II] [18]

A mixture of compound [I](0.013mole) and anhydrous sodium carbonate ( 2.756g ,0.026 mole) were dissolved in 25ml of acetone , to this solution (0.026 mole) of dimethyl sulphate was added , after 20 min . The reaction mixture was heated (under reflux) for 4 hrs, afterword, the reaction mixture was allowed to cool down for room temperature.

The off white solid formed was filtered ,dried and recrystallized by acetone m.p198-200$^0$C, yield 52% .

### Preparation of2- (hydrazinecarbonyl)-N-(p-tolyl)benzamide [III]

A solution of ester compounds [III] (0.06 mole ) and 80% hydrazine hydrate (15ml) in 25 ml of ethanol was heated under reflux for 2 hrs ,the mixture was then cooled to room temperature[19], and the obtained solid was filtered and recrystallized from acetonem.p>290 $^0$C, yield 70%

### Synthesis of Shiff bass Derivatives [IV]$_{a-d}$

A mixture of hydrazide**[III]$_{a,b}$** (0.01 mol), different aromatic aldehyde or ketone (0.012 mol), in absolute ethanol (10 mL) and 2drops of glacial acetic acid was refluxed for 3hrs. The solvent was removed under vaccum and the residue crystallized from ethanol [20].

### Synthesis of 1, 3-oxazepine Derivatives [V]$_{a-d}$, [VI] $_{a-d}$

A mixture of compound [III],[IV] or [V]$_{a,b,c}$ (0.001mole) and phthalic anhydrides or nphthalicanhydrides (0.001mol) indry benzene[21] (5mL) was heating for 6 hrs. The solvent was evaporated, the resulting colored crystalline solid recrystallized by ethanol. The physical properties for the synthesized compounds are given in Table (1).

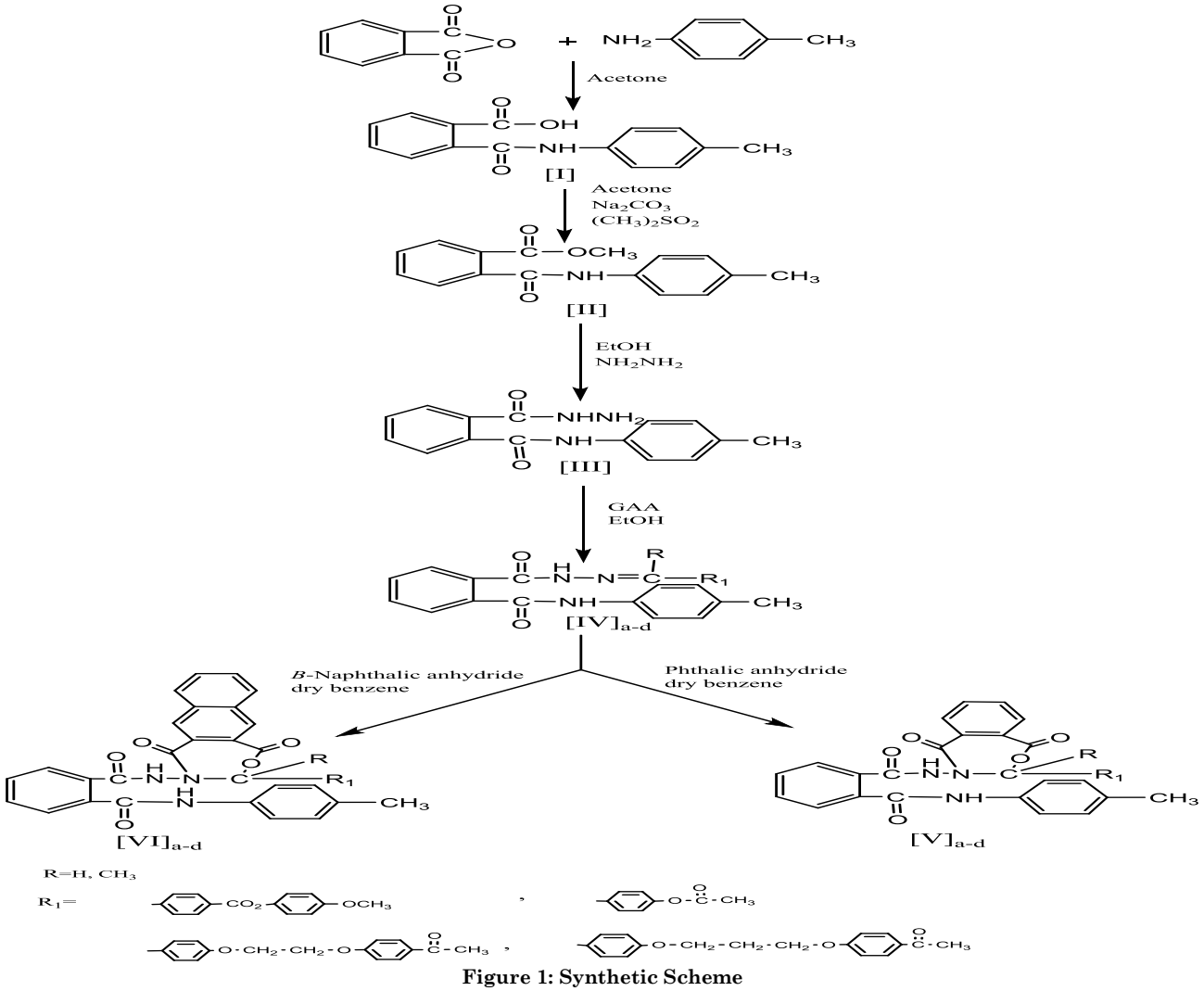



**Figure 1: Synthetic Scheme**

### Analytical Characterization

FTIR spectra were recorded by using KBr disc on a Shimadzo (Ir prestige -21) $^1$HNMR spectra were examined by company : Bruker , model: ultra shield 300 MHz, origin :Switzerland and are reported in DMSO as a solvent, ppm(δ), uses TMS as an internal standard were made at chemistry department , Gazi University, Turkey. Hot-Stage, Gallen Kamp melting point apparatus was used for determined uncorrected melting points.

### Specification of Antibacterial Activity

The four kinds of bacteria were activated in a nutrient growth medium at 37$^o$C for 24 hrs.

By agar well diffusion method. Each of tested compounds was dissolved in DMSO (concentration $10^{-3}$). The zones of inhibition formed measured in millimeter [22]. The antibacterial activities examined compounds exhibited as illustrative in Table (2)

**Results and Discussion**

2-(p-tolylcarbamoyl) benzoic acid[I]was prepared by the reaction of one mole of Phthalic anhydride With one moles of 4-Mathyl aniline in acetone as a solvent FTIR spectra show the disappearance of the bands due to NH2 group and anhydride ring with appearance of new absorption stretching bands due toO-H of carboxylic moiety in the region ( 3309-3213)$cm^{-1}$, C=O(carboxylic acid) stretching at(1670 ) $cm^{-1}$ ,While a stretching band of N-H group appeared at 3140 $cm^{-1}$ C=O (amid) stretching at ( 1645 ) $cm^{-1}$[23],$CH_3$ at (2960-2839 ) $cm^{-1}$.

The ester compound [II] was prepared from reaction [I]in acetone with anhydrous sodium carbonate and add of dimethyl sulphate the FTIR spectrum for compound [II] showed the disappearance of absorption stretching bands of O-H and C=O carboxylic groups together with the appeared of a new stretching band at 1735$cm^{-1}$[24] assigned to C=O ester group the condensation of one mole of ester compound [II] with 80% hydrazinehydrate in ethanol produced the acid hydrazide [III].

The FTIR spectrum for this compound showed stretching vibration to asymmetric and symmetric bands of (N-H, NH2) groups in the region[25] (3317-3147)$cm^{-1}$ ,Also stretching absorption at 1662$cm^{-1}$ of υ C=O (amide) . The new Schiff bases (IV) a-d was synthesized of one mole of acid hydrazide (III) with one moles of different aromatic aldehyde or ketone in ethanol.

FTIR absorption-spectra which showed the disappearance of absorption bands due to NH2group with appearance of the absorption band in the region (1649-1640) $cm^{-1}$which is assigned to imine group (C=N) stretching. The other FTIR data of functional groups which are characteristic of these compounds are show in Table (1).

The $^1$HNMR spectral of Schiff base compound $(IV)_a$(in DMSO)showed the following characteristics chemical shifts: a singlet signal at δ 2.51ppm for three protons of $CH_3$ group, also a singlet signal at δ(3.9)ppm for three protons of OCH3 group and aromatic ring protons appear as multiplet in the range (δ 7.01-8.13) ppm, another singlet signal appeared atδ(8.75)ppm for a proton of imine and singlet was spotted atδ(11.64)ppm for one proton of NH group.

While$^1$HNMR spectrum (in DMSO as a solvent) of Schiff base compound $(IV)_d$, appeared singlet at δ 11,50ppm[26] that referred to the proton of NH group. Also the spectrum showed multiplet signal in the region δ (7.04-8.08) ppm for aromatic ring, a multiplet signal of two protons of $CH_2$ group appear at δ 1.25ppm and a triplet signal in δ 4.22ppm due to two protons of $CH_2O$ group and two sharp singlet signals atδ 2.51 ppm and δ 2.28 ppm impute to the$COCH_3$, $CH_3$, andCH3C=N groups, respectively.

The 1, 3-oxazepines $[V]_{a-d}$, $[VI]_{a-d}$ were formation of Schiff bases with naphthalic or phthalic anhydride in dry benzene. the FTIR-spectra of compounds$[V]_{a-d}$, $[VI]_{a-d}$ show the appearance of the absorption bands at (1775-1656) $cm^{-1}$ characteristic to (C=O) [27] and the disappearing band due to (-C=N) of Schiff bases.

The spectral data of FTIR for new oxazepine compounds are listed in Table(1) $^1$HNMR spectrum of compound $[V]_d$ appearing three single band at δ2.29ppm and δ2.51 ppm due to ($CH_3$cyclic),and$CH_3$ ,$COCH_3$ with appearing a quintet band of two protons of $CH_2$ group appear at δ1.24ppm and a triplet band in δ 4.22 ppm due to two protons of $CH_2O$ group in addition to that appearing multiple bands at a range of (7.04-8.08 ppm) belong to twenty aromatic protons, Finally a singlet signal appeared at δ(11.5)ppm due to NH group.

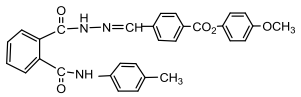
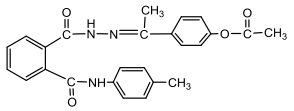
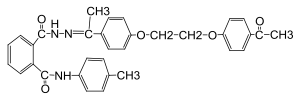
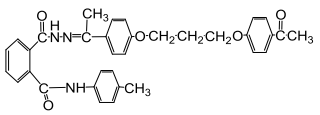
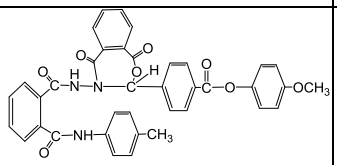
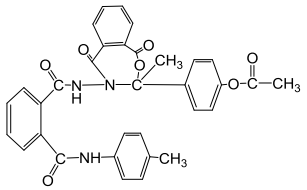
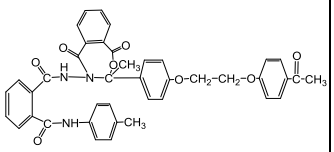
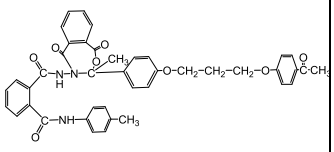
$^1$H-NMR spectra, compound $[VI]_a$ exhibited the following characteristic chemical shifts were appeared singlet band at δ(2.51ppm) attributed to $CH_3$ group ,As well appeared singlet band at δ(3.90ppm) referred to O CH3 group and multiplet band at δ(7.01-8.57)ppm that related to aromatic protons and singlet signal at δ8.78ppm for one protons of C-Hcyclic.

Furthermore, a singlet signals at δ 11.6ppm for one proton NH group. The prepared compounds were investigation against four antibacterial species, showed activity between Moderate to high with *Esherichia*

*Coli (Gram negative)* and *staphylococcus aureus, Bacillus subtilis*(Gram positive), While some compounds showed no activity against *Enterobactecloacae* (Gram negative),As illustrative in Table (2).

**Table 1: Analytical characterization of synthesized compounds**

| Comp.No. | Structural formula | Mel. Point (0C) | Yield% | IR Spectral Study |
|---|---|---|---|---|
| $[IV]_a$ |  | 290-292 | 70 | 3250,3170cm$^{-1}$NH, 3012cm$^{-1}$C-$H_{aromatic}$, 2972-2845 cm$^{-1}$ C-$H_{aliphatic}$, 1726,1683 cm$^{-1}$ C=O1649 cm$^{-1}$ C=N,1602 cm$^{-1}$C=C<br>1253 cm$^{-1}$ (ether)1282 cm$^{-1}$ (ester)C-O |
| $[IV]_b$ |  | 275-277 | 40 | 3325,3165cm$^{-1}$NH, 3008cm$^{-1}$C-$H_{aromatic}$, 2958-2856 cm$^{-1}$ C-$H_{aliphatic}$, 1739,1660 cm$^{-1}$ C=O1640 cm$^{-1}$ C=N,1604 cm$^{-1}$C=C<br>1257 cm$^{-1}$C-O |
| $[IV]_c$ |  | >290 | 100 | 3329,3180cm$^{-1}$NH,3043cm$^{-1}$C-$H_{aromatic}$, 2924-2881 cm$^{-1}$ C-$H_{aliphatic}$, 1666cm$^{-1}$ C=O1645 cm$^{-1}$ C=N,1580 cm$^{-1}$C=C<br>1242 cm$^{-1}$C-O |
| $[IV]_d$ |  | 225-227 | 86 | 3250,3190cm$^{-1}$NH,3050cm$^{-1}$C-$H_{aromatic}$, 2922-2873 cm$^{-1}$ C-$H_{aliphatic}$, 1664cm$^{-1}$ C=O1654 cm$^{-1}$ C=N,1597cm$^{-1}$C=C,<br>1249 cm$^{-1}$C-O |
| $[V]_a$ |  | >290 | 75 | 3190cm$^{-1}$NH,3014cm$^{-1}$C-$H_{aromatic}$, 2922-2854 cm$^{-1}$ C-$H_{aliphatic}$, 1762,1724,1700,1666cm$^{-1}$ C=O,1600cm$^{-1}$C=C,1257 cm$^{-1}$C-O |
| $[V]_b$ |  | >290 | 75 | 3161cm$^{-1}$NH,3008cm$^{-1}$C-$H_{aromatic}$, 2958-2891cm$^{-1}$ C-$H_{aliphatic}$, 1775,1739,1700,1658cm$^{-1}$ C=O,1597cm$^{-1}$C=C,1261 cm$^{-1}$C-O |
| $[V]_c$ |  | >290 | 100 | 3195cm$^{-1}$NH,3008cm$^{-1}$C-$H_{aromatic}$, 2926-2890 cm$^{-1}$ C-$H_{aliphatic}$, 1770,1730,1695,1668cm$^{-1}$ C=O,1597cm$^{-1}$C=C,1244 cm$^{-1}$C-O |
| $[V]_d$ |  | >290 | 80 | 3190cm$^{-1}$NH,3050cm$^{-1}$C-$H_{aromatic}$, 2922-2877cm$^{-1}$ C-$H_{aliphatic}$, 1772,1735,1695,1668cm$^{-1}$ C=O,1598cm$^{-1}$C=C,1249 cm$^{-1}$C-O |

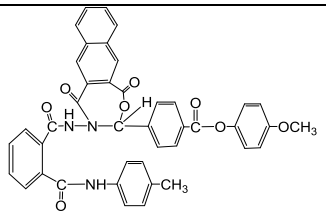
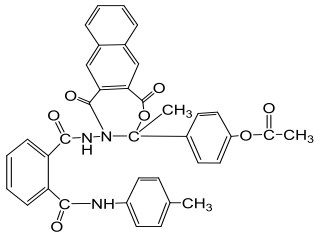
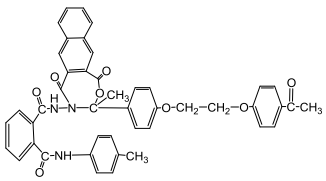
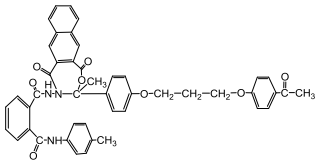
| | | | | |
|---|---|---|---|---|
| $[VI]_a$ |  | 223-225 | 100 | 3192cm$^{-1}$NH,3014cm$^{-1}$C-$H_{aromatic}$, 2962-2841cm$^{-1}$ C-$H_{aliphatic}$, 1772,1724,1700,1656cm$^{-1}$ C=O,1650cm$^{-1}$C=C,1257 cm$^{-1}$C-O |
| $[VI]_b$ |  | >290 | 75 | 3161cm$^{-1}$NH,3008cm$^{-1}$C-$H_{aromatic}$, 2920-2852cm$^{-1}$ C-$H_{aliphatic}$, 1768,1735,1710,1660cm$^{-1}$ C=O,1595cm$^{-1}$C=C,1261 cm$^{-1}$C-O |
| $[VI]_c$ |  | >290 | 100 | 3210cm$^{-1}$NH,3050cm$^{-1}$C-$H_{aromatic}$, 2926-2870cm$^{-1}$ C-$H_{aliphatic}$, 1772,1734,1690,1666cm$^{-1}$ C=O,1600cm$^{-1}$C=C,1246 cm$^{-1}$C-O |
| $[VI]_d$ |  | >290 | 100 | 3195cm$^{-1}$NH,3050cm$^{-1}$C-$H_{aromatic}$, 2922-2873cm$^{-1}$ C-$H_{aliphatic}$, 1770,1734,1695,1664cm$^{-1}$ C=O,1598cm$^{-1}$C=C,1249 cm$^{-1}$C-O |

**Table 2: Result of bacterial activity**

| Compound | *Esherichia Coli* | *Enterobacter cloacae* | *Staphylococcus aureus* | *Bacillus subtilis* |
|---|---|---|---|---|
| **$[IV]_a$** | **17** | **-** | **17** | **10** |
| **$[IV]_b$** | **11** | **-** | **19** | **11** |
| **$[IV]_c$** | **10** | **-** | **15** | **11** |
| **$[IV]_d$** | **17** | **-** | **16** | **10** |
| **$[V]_a$** | **12** | **12** | **12** | **12** |
| **$[V]_b$** | **16** | **-** | **12** | **11** |
| **$[V]_c$** | **11** | **12** | **15** | **11** |
| **$[V]_d$** | **11** | **-** | **18** | **10** |
| **$[VI]_a$** | **17** | **-** | **11** | **10** |
| **$[VI]_b$** | **11** | **11** | **19** | **14** |
| **$[VI]_c$** | **19** | **-** | **17** | **14** |
| **$[VI]_d$** | **11** | **12** | **12** | **12** |

## Conclusions

In general, synthesis eight derivatives oxazepine from four type of Schiff bass, And examined were antibacterial activity where the result All the Compounds moderate antibacterial activity against *Esherichia Coli* ,*Staphylococcus aureus and Bacillus subtilis* while evidence some of them antibacterial activity towards *Enterobacter cloacae*.

## Acknowledgements

I would like to express thanks my to Assit. Prof. Dr. Jumbad H. Tomma for the supporting this work by chemical material and scientific consultations.



## References


1. National Cancer Institute (1979) Bioassay of Phthalic Anhydride for Possible Carcinogenicity. Technical Report159. Public Health Service, Bethesda, MD,.
2. Abdel-AzizHa, Elsaman Ti, Attia Mo, Alanazi Am (2013) The Reaction of Ethyl 2-oxo-2H-chromene-3-carboxylate with Hydrazine Hydrate.Molecules,18: 2084-2095.
3. Fang G, Li Y, Shen F, Huang Y, Li J, Lin Y, Cui H, Liu L (2011) Protein chemical synthesis by ligation of peptide hydrazides. Angew. Chem. Int. Ed., 50: 7645-7649.
4. Tabanca N, Ali A, Bernier UR (2013) Biting deterrence and insecticidal activity of hydrazide – hydrazones and their corresponding 3- acetyl – b3 , 5-disubstituted– 2, 3 – dihydro – 1,3,4 – oxxa-diozoles against Aedes aegypti. Pest Manag Sci., 69 (6): 703-708
5. Sadiq Ha (2017) Synthesis and Characterization of Novel 1,3-Oxazepine Derivatives from Aminopyrazine. World Journal of Pharmacy and Pharmaceutical Sciences,6(5): 186-198.
6. Abu Talip Ru, Tay Me, Hashim Ha (2017) Synthesis, Characterization and Antibacterial Activities of Hydrazone Schiff Base Compouns and Its Derivatives. Malaysian Journal of Analytical Sciences, 21 (5): 1168-1175
7. Abdullah As, Salman Kh (2010) Synthesis and Anti-Bacterial Activities of Some Novel Schiff Bases Derived from Aminophenazone. Molecules, 15: 6850-6858.
8. Mohareb Ra, Fleita Da, Sakka Ol (2011) Novel Synthesis of Hydrazide-Hydrazone Derivatives and Their Utilization in the Synthesis of Coumarin, Pyridine, Thiazole and Thiophene Derivativeswith Antitumor Activity. Molecules, 16: 16-27.
9. Hikmet A, Berat K, Fatma B (2013) Synthesis and structure antibacterial activity relationship studies of 4-substituted phenyl-4, 5-Dihidrobenzo[f][1,4]oxazepin-3(2H)-thiones.*Medicinal Chemistry Res*earch, 20: 1170-1180
10. Ledeti L, Alexa A, Bercean V, Vlase G, Vlase T, Suta M Fulias A (2015) Synthesis and Degradation of Schiff Bases Containing Heterocyclic Pharmacophore. *Int. J. Mol. Sci.,* 16: 1711-1727
11. Ramesh L, Mahesh S, Jyoti B (2012) Anticoagulant potential of schiff bases of 1, 3-oxazines. International Journal of Pharmacy and Pharmaceutical Sciences, 4(4): 320-323.
12. Iman K, Naeem Ezzat, H Zimam (2017) Synthesis, Characterization and Study Antibacterial Activity of some New 1,3-oxazepine and 1,3-diazepine Derivatives. Der Pharma Chemica, 9(21):86-93
13. Al-Jamali NM, (2008) "Synthesis, Characterization of New 1,3-Oxazepine, Diazepine, Thiazepine derivatives and Open Ring of Thio Compounds", Ph.D. Thesis, College of Education Ibn-Al Haitham , University of Baghdad.
14. Tawfiq MT (2004) Synthesis of Substituted 1,3-Oxazepines and 1,3-Diazepines Via Schiff Bases, Ph.D. Thesis, College of Education Ibn Al Haitham, University of Baghdad.
15. Tomma J, Ali E, Tomi I, Al-Witry Z, Hassan H (2011) Synthesis and Characterization of New Heterocyclic compound" ,Mustansiriyah Journal of Science, 22(2):35-44.
16. Matsuzaki H, Takuchi I, Hamad Y, Hatano K (2000) Studies on the 1,4-oxazepine ring formation reaction using the molecular orbital method, Chem. pharm. Bull, Chem., 48(5): 755-756.
17. E Ali, K AL-Aliawy, J Tomma (2011) Synthesis and Characterization of New Symmetrical Pyromellitdiimide Derivatives and Their Amic Acids Ibn AL-Haitham J. forpure& Appl. SCI., 24 (3),110-121.
18. Z Al-Rwbaiy (1998) M.Sc thesis, college of Education –Ibn –Al Haitham, Baghdad University.
19. Tomma J, karam N, Al-Dujaili A (2006) Synthesis a new series of compounds containing oxadiazole rings. National Journal of Chemistry,21:63-72
20. Tomma J, Khazaal M, Al-Dujaili A (2014) Synthesis and characterization of novel Schiff bases containing pyrimidine unit, Arabian Journal of Chemistry, 7:157-163.

21. Muhsen T, Tomma J, Mukhlus AJ (2012) Synthesis and Characterization of Novel Compounds Containing of Imidazolidinone and Oxazepine Rings, Ibn Al-Haitham Journal for Pure and Applied Science, 3(25): 276-283

22. Mcmurry J (2008) Organic Chemistry. Thomson Learning Academic Resource Center, 6ed.

23. Al-Azzawi Ahlam, Abd Al-Razzak Marwa (2013) Synthesis Characterization and Antibacterial Screening of New Schiff bases Linked to Phthalimide, IJRPC, 3(3):682-690.

24. Abdel Gawaad Mohamed (2008) Synthesis and Cyclization Reactions with Pyrazolopyrimidinyl Keto-esters and their Enzymaic Activity, Acta Chim. Slov., 55: 492-501.

25. Hayder Ghanim Chfat, Hasan Thamer Ghanim (2017) Synthesis and Characterization of Some Heterocyclic Compounds from Salicylic Acid, Journal of Chemical and Pharmaceutical Research, 9(1):93-99.

ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

26.Rafat M. Mohareb, Daisy H. Fleita and Ola K. Sakka,(2011), Novel Synthesis of Hydrazide-Hydrazone Derivatives and Their Utilization in the Synthesis of Coumarin, Pyridine, Thiazole and Thiophene Derivatives with Antitumor Activity,Molecules, 16, 16-27.

27.Saued Shaimaa , Tomma Jumbad and Ali Emad. (2014) Synthesis and Characterization of Novel 1,3-Oxazepines Derived from Diamic Acid : N,N¯-Bis-(4-methyl phenyl ) pyromellitamic Diacid, Ibn Al-Haitham Jour. for Pure & Appl. Sci., ( 3) 7,381-392.