Egypt. J. Chem. **Vol. 64,** No. 5 pp. 2647 - 2652 (2021)

241

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis and characterization of some new five and seven-membered heterocyclic compounds derived from mefenamic acid

Zaidoon Jawad Kadhim [a]*, Ali Abdulkareem Raheem [a]

a Department of Chemistry, College of Science, University of Misan, Misan, Iraq

Abstract

Five and seven-membered heterocyclic compounds were prepared from mefenamic acid, which was esterified with absolute ethanol to give amino benzoate (Z1). The ester reaction with hydrazine hydrate gave benzohydrazide (Z2), then converted into Schiff base by using p-hydroxy benzaldhyde to give hydroxy benzylidene (Z3). Then the compound (Z4) gets us by reaction hydroxy benzylidene (Z3) with 2-mercoptoacetic acid. The interaction between benzohydrazide (Z2) and Cs_2 with NaOH gave salt (Z5), which was acidified with HCl to give thiol (Z6). The compound (Z6) treated with hydrazine hydrate gave hydrazine (Z7), then converted into Schiff base by using benzaldhyde towards oxadiazol (Z8), which was interaction with maleic and phthalic anhydrides to give (Z9, Z10) respectively. The compounds that attended were diagnosed with their FTIR, ^{13}C-NMR, and ^{1}H-NMR spectral data. The aim of this study is to prepare heterocyclic compounds derived from mefenamic acid that may be used in the field of the medicinal drug industry.

Keywords: mefenamic acid, heterocyclic, oxazepine.

1. Introduction

One of the important types of organic chemistry are heterocyclic compounds. The study of heterocyclic compounds is advantageous according to their electronic structure, so most studies of heterocyclic chemistry focus on unsaturated rings, therefore these compounds are used in drugs and industrial studies. It is interesting for the physiological and industrial significance of heterocyclic compounds [1]. Heterocyclic compounds containing more than two different atoms (C, N, O and S) in the ring, e.g., azetidine, thiazolidine and diazole [2]. These compounds are widely used in various ways in nature and are important in life, for example medicines containing about 68% of them are heterocyclic [3, 4]. The 7- membered heterocyclic ring such as oxazepine are unsaturated compounds which contains five carbon atoms and two hetero atoms (nitrogen and oxygen), which are used in drugs and other medicinal pharmaceutical [5], treatment of cancer diseases and schizophrenia [6]. Heterocyclic compounds played a major role in the development of antibacterial, antimicrobial [7-9], anticancer [10], and ant diabetic activities [11]. These compounds also have industrial applications such as antioxidants [12], accelerators, corrosion Inhibitors [13], copolymers and dyes [14]. Mefenamic acid is a class of non-steroidal anti-inflammatory drugs. The goal of this study is to prepare heterocyclic compounds derived from this acid that may have biological activity and use them in the field of medicinal drug industry.

Experimental

Synthesis of ethyl 2-((5, 6 dimethylcyclohexa-2, 4-dien-1-yl) amino) benzoate (Z1).

A mixture of mefenamic acid (0.01mol,2.41g) with (30mL)ethanol (absolute) was added to (1mL) of concentrated sulfuric acid, then the resulting mixture was put under reflux for (6hrs.) at 75C^0. A thin layer of chromatography was employed to check the end of the reaction. The product was isolated using water extraction [15].

*Corresponding author e-mail: zaidoonjwad@uomisan.edu.iq (Zaidoon Jawad Kadhim)
Receive Date: 13 March 2021, Revise Date: 27 March 2021, Accept Date: 30 March 2021
DOI: 10.21608/EJCHEM.2021.65196.3461

Synthesis of 2-((2, 3-dimethylphenyl) amino) benzohydrazide (Z2).

0.01 mole, (2.63g) from (Z1) in (10 mL)of absolute ethanol with (10mL) Hydrazine hydrate 80% under refluxed about (4hrs.) at 75 $C^{0.}$ Then cooling, the precipitate which formed was filtered and after that recrystallized with ethanol.

Synthesis of 2-((2, 3 dimethyl) amino)-N-(4-hydroxybenzylidene) benzohydrazide (Z3).

In round flask (50mL), (0.01mol,2.68g) of (Z2) was dissolved in (10ml) acetone, then followed by addition of (0.002mol) from p- hydroxy benzaldhide with (2mL) of acetic acid. The resulting mixture was refluxed about (6hrs.) at (40-50) ^{0}C. Then cooling, the precipitate which formed was filtered off and purified by recrystallized with ethanol [16].

Synthesis of 2-((2, 3 dimethyl) amino)-N-(2-4-hydroxyphenyl)-4-oxothiazolidin-3-yl) benzamide (Z4).

0.01 mol(3.58g) of Z3 was dissolved in (20 mL) hexane and 2-mercaptoacetic acid (0.5 mL) was added. After that the solution was refluxed about (6hrs). Then cooled it, the precipitate which formed was filtered, then recrystallized it to yield product [17].

Synthesis of (Z5) and (Z6).

For solution of (Z2) (0.01mol, 2.68g) in (15mL) absolute ethanol, (2 mL) of carbon disulfide CS_2 with (0.5 gm.) NaOH was added. This mixture was refluxed in a water bath for (6hrs). gave crude (Z5), which was dissolved and acidified with a little of concentrated hydrochloric acid, then evaporated. Solid product finally filtered towards (Z6), dried and purified by recrystallized.

Synthesis of 2-(5-hydrazinyl-1,3,4-oxadiazol-2-yl)-2,3dimethylaniline (Z7).

A compound (Z6) (0.01mol,2.83g) was reacted with (10 mL) hydrazine hydrate 80% in absolute ethanol (5mL), the resulted mixture was refluxed for (8hrs), after that cooled the solution, the resulted precipitate was filtered off, dried and purified recrystallized.

Synthesis of 2-(5-(2-benzlidenehydrazinyl)-1,3,4-oxadiazol-2-yl)-2,3-dimethylaniline (Z8)

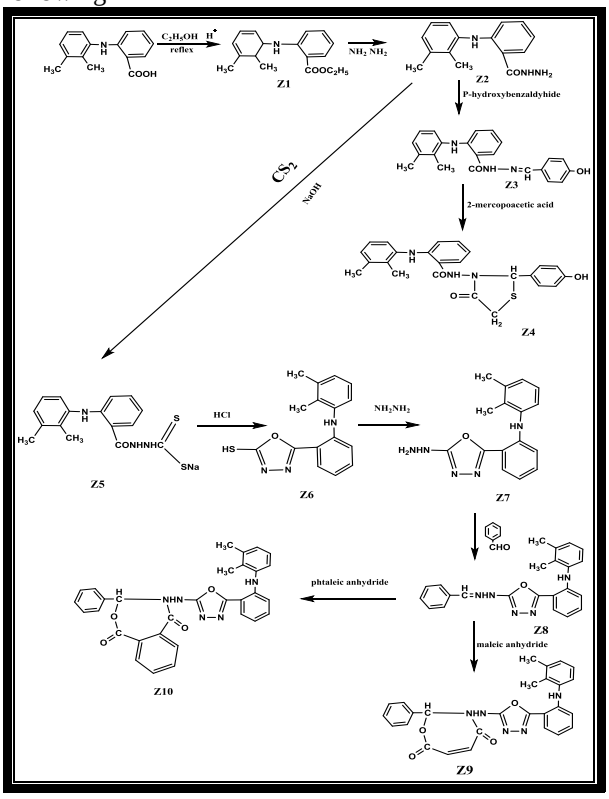
A mixture of (Z7) (0.01mol, 2.81g) in (10 mL) absolute ethanol, and (0.001mol) from benzaldehyde with (2mL) of acetic acid was refluxed about (3hrs.), the solid filtered then recrystallized by suitable solvent.

Synthesis of (Z9) and (Z10).

Equal amounts (0.01, 3.70g) of Schiff' base (Z8) with (maleic and phthalic anhydride) were dissolved in acetone sequentially, then refluxed the mixture for (5 hrs.) and removed the solvent. The solid was recrystallized afforded products (Z9, Z10) [18, 20]. The physical properties and FTIR spectrum of some compounds are shown in **Table1**.

2. Results and Discussion

Prepared compounds have been diagnosed by their FT-IR, ^{1}H-NMR and ^{13}C-NMR. The overall synthetic steps of these compounds shown in the following



Scheme 1: route for preparation compounds (1-10)

The FTIR spectrum of (Z1) (1) shows up absorption peak at (3234) cm^{-1}, also peak at (1731) attributed to ν (NH) and (C=O) ester sequentially. The absorption band for aromatic group ν (C-H) appeared at (3060) cm^{-1}, as well as two bands (2985) cm^{-1} and (1572) cm^{-1} have been accused to aliphatic bond ν (C-H) and aromatic bond ν (C=C) sequentially [19]. **Figure 1, Table 1.**

FTIR spectrum of (Z3) show up absorption peak at (3385) cm^{-}, attributed to ν (NH). Other peaks at (3075) cm^{-1}, (2981) cm^{-1}. attributed to aromatic bond υ (C-H) and aliphatic bond υ (C-H) respectively, also absorption band at (1680) cm^{-1} due to carbonyl group υ (C=O), as well as peaks at (1550) cm^{-}, (1610) cm^{-}, and (3420) cm^{-1}, attributed to aromatic bonds for υ(C=C), υ (C=N) and (O-H) group sequentially **Figure 2.**

Spectrum FTIR of (Z4) shows up absorption peak at (1695) cm^{-1}. As well as bands at (1585) cm^{-1}, (2995), (3065), (3378) and (3430) cm^{-1} attributed to carbonyl group, aromatic bond υ (C=C), aliphatic bond υ (CH), aromatic bond υ (C-H), υ (NH)and υ (OH) group sequentially, **Figure 3.**

The spectrum ^{1}H-NMR of (Z4), shows up at (1.73ppm,6H,CH3), also the chemical shift at (2.43ppm,H,CH), as well as signal δ= (3.47ppm,2H,CH2) ring. Chemical shift at (5.55) ppm attributed to protons for (OH) group. Moreover, multi chemical shifts (7.25-8.30 ppm,11H,CH) for protons aromatic ring, at last chemical shift at (9.55) ppm due to (NH-) proton, **Figure 4.**

Spectrum^{13}C-NMR for (Z4) shows up signals at δ = (32.24) ppm, δ = (44.80) and δ = (166.92) ppm due to (C-H), (CH_2-) and (C=O) of thiazolidine ring respectively, **Figure 5.**

For compound (Z7), FTIR spectrum show up appearance of absorptions at (3220) cm^{-1}, (3056), (2930),(1310), (1554) and (3450-3375) due to υ (NH), aromatic bond υ (C-H), aliphatic bond υ(CH), υ(C-O-C), aromatic bond υ (C=C) and υ (NH_2) sequentially, **Figure 6.**

The spectrum ^{1}H-NMR for (Z7) show up signals at (2.49-2.83ppm) attributed to protons methyl groups, signal at (6.05) ppm due to (-NH_2) protons, Chemical shifts at (7.41-8.34,ppm,7H,CH) attributed to protons for aromatic ring, at last for (N-H) appeared Chemical shift at (9.72) ppm. **Figure 7.**

For compound (Z7), ^{13}C-NMR spectrum shows up signals at δ= (11.19) ppm, δ= (155.43) ppm and at δ= (168.02) ppm belongs to (CH_3), (C=N) imine as well as (C=O) amid respectively, **Figure 8.**

The FTIR spectrum of (Z9) indicates the appearance of absorptions at (3340) cm^{-1}, (2915) cm^{-1} due to the υ (NH) group, aliphatic bond υ (C-H) sequentially. As well as appeared absorptions at (3090), (1710) and (1560) cm^{-1} due to aromatic bond υ (C-H), υ (C=O) and aromatic bond υ (C=C) sequentially.

Spectrum ^{1}H-NMR for (Z9) shows up two signals δ= (2.15, 2.29) ppm due to protons for ($2CH_3$), also appeared chemical shift at (3.36) due to proton (CH). The protons for the aromatic ring appeared at a chemical shift at (6.39-7.78) ppm. Signal at δ= (8.89) ppm attributed to (CH-N) proton, at last the proton for (NH) appeared chemical shift at (9.78) ppm the **Figure 9.**

3. Conclusions

In summary, newly heterocyclic compounds were synthesized based on mefenamic acid. The work went through several steps towards target compounds of mefenamic derivatives (Z4, Z6, Z7, Z8, Z9 and Z10). These compounds were characterized by a range of techniques including (^{1}H , ^{13}C NMR and FTIR) spectroscopy, prior to the study of their physical properties.

4. Conflicts of interest

"There are no conflicts to declare".

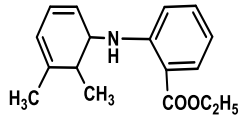
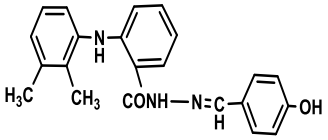
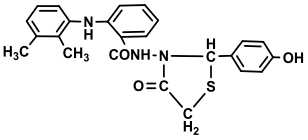
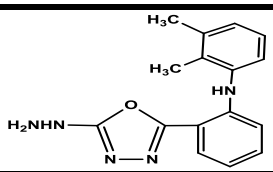
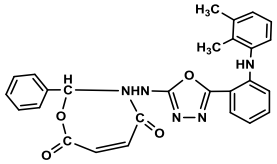
5. Formatting of funding sources

Self

6. Acknowledgments

Authors thankfully Acknowledge the University of Misan, Department of Chemistry for supporting this work.

Table 1:FTIR spectral data and physical properties for some compounds

Compound No.	Physical properties				Major FTIR Absorption cm^{-1}				
	Compound structure	Colour	Yield %	Melting Point	ν(N-H)	ν(Ar-H)	ν(C-H)	ν(C=O)	Others
Z1		White	76	232-234	3244	3063	2989	1733	1598 ν(C=C) aromatic
Z3		White	64	249-251	3391	3070	2973	1685	1604 ν(C=N) aromatic 3421 ν(OH)
Z4		Pale yellow	48	260-262	3388	3060	2998	1695	1595 ν(C=C) aromatic 3421 ν(OH)
Z7		White	52	293-295	3218	3046	2929	-	3453-3363 $ν(NH_2)$ 1310 υ(C-O-C)
Z9		White	57	284-286	3344	3092	2912	1706	1655 ν(C=C)

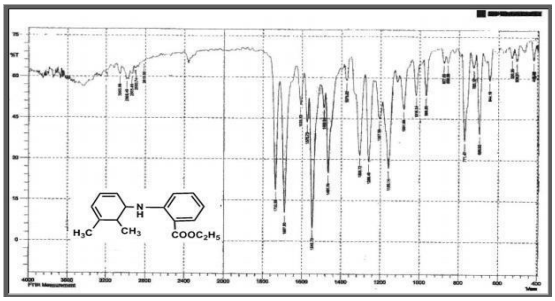


Figure 1: FTIR spectrum for (Z1)

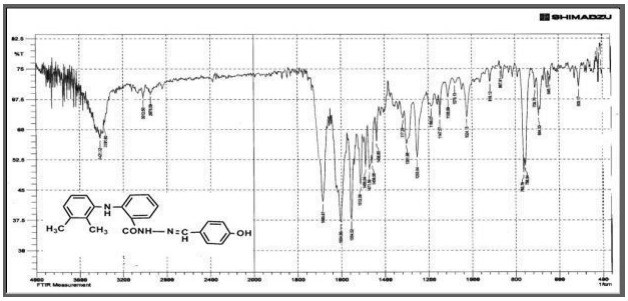


Figure 2: FTIR spectrum for (Z3)

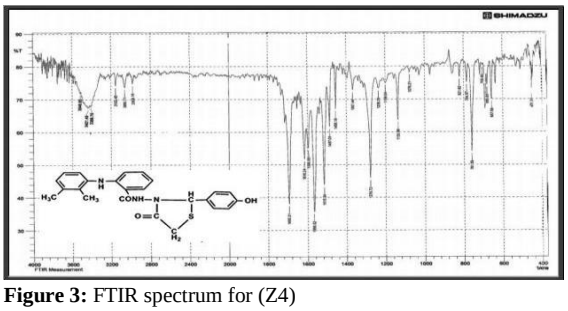


Figure 3: FTIR spectrum for (Z4)

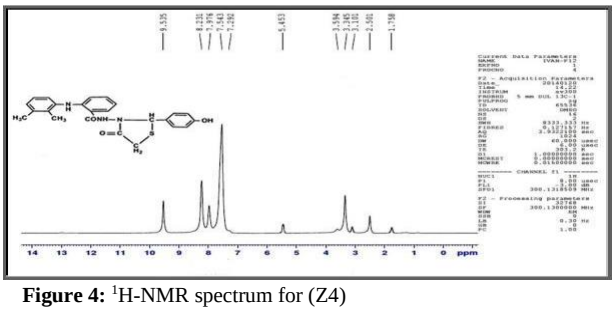


Figure 4: ^{1}H-NMR spectrum for (Z4)

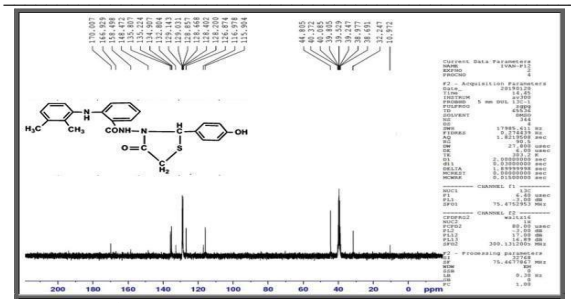


Figure 5: ^{13}C-NMR spectrum for (Z4)

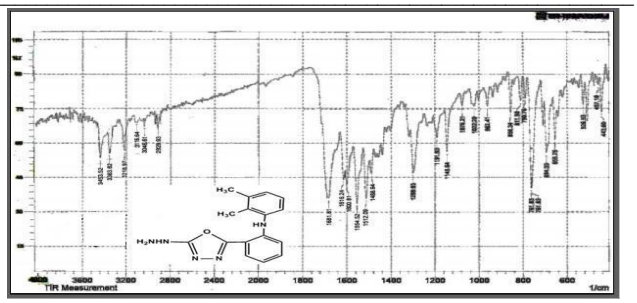


Figure 6: FTIR spectrum for (Z7)

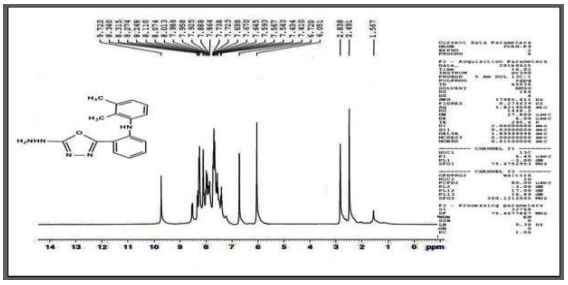


Figure 7: ^{1}H-NMR spectrum for (Z7)

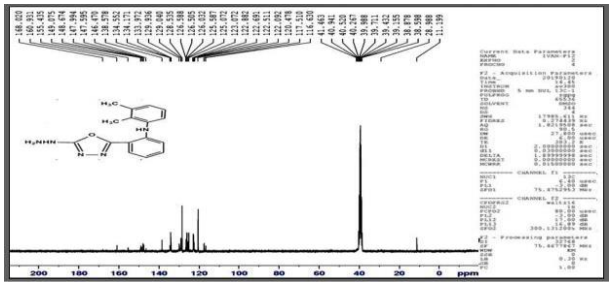


Figure 8: ^{13}C-NMR spectrum for (Z7)

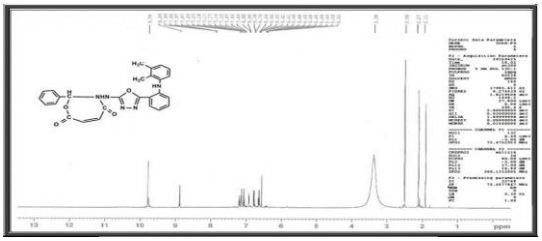


Figure 9: ^{1}H-NMR spectrum for (Z9)

References

1. Eicher, T., Hauptmann, S., and Speicher, A. *The chemistry of heterocycles: Structures, reactions, synthesis, and applications*. John Wiley and Sons (2013).

2. El-Gaby, M., A Ammar, Y., IH El-Qaliei, M., M Ali, A., F Hussein, M., and A Faraghally, F. Sulfonamides: Synthesis and the recent applications in Medicinal Chemistry. *Egyptian Journal of Chemistry*, *63*(12), 5289-5327(2020).

3. Chand, S., Tyagi, M., Tyagi, P., Chandra, S., and Sharma, D. Synthesis, characterization, DFT of novel, symmetrical, N/O-donor tetradentate Schiff's base, its Co (II), Ni (II), Cu (II), Zn (II) complexes and their in-vitro human pathogenic antibacterial activity. *Egyptian Journal of Chemistry*, *62*(2), 291-310 (2019).

4. Dahiya, R., Kumar, A., and Yadav, R. Synthesis and biological activity of peptide derivatives of iodoquinazolinones/nitroimidazoles. *Molecules*, *13*(4), 958-976 (2008).

5. Mohamed, S. U. M., and El-Hady, H. A. 15 Synthesis and mass spectra of some new heterocyclic compounds containing thiophene moiety. *Egyptian Journal of Chemistry*, *49*(2), 209-224 (2006).

6. McElligott, A. M., Maginn, E. N., Greene, L. M., McGuckin, S., Hayat, A., Browne, P. V., Butini, S., Campiani, G., Catherwood, M. A., Vandenberghe, E., Williams, D. C., Zisterer , D. M. and Lawler, M. The novel tubulin-targeting agent pyrrolo-1, 5-benzoxazepine-15 induces apoptosis in poor prognostic subgroups of chronic lymphocytic leukemia. Cancer research, 69(21), 8366-8375(2009).

7. Gatadi, S., Madhavi, Y. V., Chopra, S., and Nanduri, S. Promising antibacterial agents against multidrug resistant Staphylococcus aureus. *Bioorganic chemistry*, *92*, 103252 (2019).

8. Mishra, V. R., Ghanavatkar, C. W., Mali, S. N., Qureshi, S. I., Chaudhari, H. K., and Sekar, N. Design, synthesis, antimicrobial activity and

computational studies of novel azo linked substituted benzimidazole, benzoxazole and benzothiazole derivatives. *Computational biology and chemistry*, *78*, 330-337 (2019).

9. Song, D., & Ma, S. Recent development of benzimidazole- containing antibacterial agents. *ChemMedChem*, *11*(7), 646-659(2016).
10. Goud, N. S., Ghouse, S. M., Vishnu, J., Komal, D., Talla, V., Alvala, R., Pranay, J., Kumar, J., Qureshi, I. A., and Alvala, M. Synthesis of 1-benzyl-1H-benzimidazoles as galectin-1 mediated anticancer agents. Bioorganic chemistry, 89, 103016(2019).
11. Chaurasia, M., Tomar, D., and Chandra, S. BSA Binding Studies of Co (II), Ni (II) and Cu (II) Metal Complexes of Schiff base Derived from 2-hydroxy-4-methoxybenzaldehyde and 2-amino-6-methylbenzothiazole. *Egyptian Journal of Chemistry*, *62*(2), 357-372(2019).
12. Malki, F., Touati, A., and Moulay, S. Antioxidant Activity of Two Mesomeric Heterocyclic Betaines Containing a Pyrimidine Moiety. *Pertanika Journal of Tropical Agricultural Science*, *36*(4)(2013).
13. A Negm, N., A Yousef, M., and M Tawfik, S. Impact of synthesized and natural compounds in corrosion inhibition of carbon steel and aluminium in acidic media. *Recent Patents on Corrosion Science*, *3*(1), 58-68(2013).
14. Coelho, P. J., Sousa, C. M., Castro, M. C. R., Fonseca, A. M. C., and Raposo, M. M. M. Fast thermal cis–trans isomerization of heterocyclic azo dyes in PMMA polymers. *Optical Materials*, *35*(6), 1167-1172(2013).
15. Al-Mathkuri, T., Al-Hilfi, J., and Al-Jubori, H. Identification and investigation of the chelating activity of some phenolic polymers derived from mefenamic acid. *Egyptian Journal of Chemistry*, *63*(1), 155-169(2020).
16. Al-Majidi, S. M., Ahmad, M. R., and Khan, A. K. Synthesis and characterization of novel 1, 8-Naphthalimide derivatives containing 1, 3-oxazoles, 1, 3-thiazoles, 1, 2, 4-triazoles as antimicrobial agents. *Al-Nahrain Journal of Science*, *16*(4), 55-66(2013).
17. Čačić, M., Molnar, M., Šarkanj, B., Has-Schön, E., and Rajković, V. Synthesis and antioxidant activity of some new coumarinyl-1, 3-thiazolidine-4-ones. *Molecules*, *15*(10), 6795-6809(2010).
18. Sallal, Z. A., and Ghanem, H. T. Synthesis and Identification of New Oxazepine Derivatives bearing Azo group in their structures. *Iraqi Journal of Science*, 59(1A), 1-8 (2018).
19. Silverstein, R. M., Bassler, G. C., and Morril, T. C. Spectroscopic Identification of Organic Compounds 4 John Wiley and Sons Inc. *New York*(1981).
20. Ramesh, L. S., Mahesh, S. M., Jyoti, B. W., and Wadekar, B. Synthesis and antimicrobial activity of Schiff Bases of 1, 3- oxazines. *International Journal of PharmTech Research*, *4*(4), 1653-1659 (2012).