ISSN 0974-3618 (Print)
0974-360X (Online)
www.rjptonline.org

RESEARCH ARTICLE

Preparation, Diagnoses of novel hetero atom compounds and Evaluation the Antibacterial Activity of them

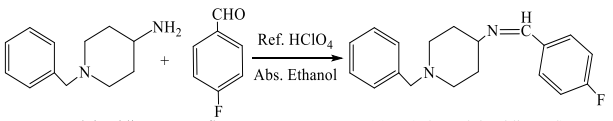
Abdulkareem Hamad Ayfan[1], Rasim Farraj Muslim[2], Marwan Mahmood Saleh[2]
[1]College of Pharmacy, University Of Anbar, Anbar, Iraq.
[2]Department of Environmental Sciences, College of Applied Sciences-Hit, University Of Anbar.
*Corresponding Author E-mail: **kareemhamad7@gmail.com, dr.rasim92hmts@uoanbar.edu.iq**

ABSTRACT:
This work included prepare of hetero atom compounds Ra_1-$Ra_5$from the interaction of prepared azomethines with anhydride compound. Azomethine compounds were prepared by condensation reaction. A number of new hetero atom compounds were prepared by acid-catalyzed Cycloaddition - reaction in anhydrous THF under reflux conditions. The formation of hetero ring has been achieved by Cycloaddition. The melting point, ^{1}H-NMR, FT-IR and ^{13}C-NMRspectroscopies technique were used to identified the final products. Biological activity of the prepared hetero compoundsRa_1-Ra_5evaluated on *E. Coli* and *S. aureus*.

KEYWORDS: Azomethine, 1,3-oxazepin, condensation reaction, cycloaddition mechanism.

1. INTRODUCTION:

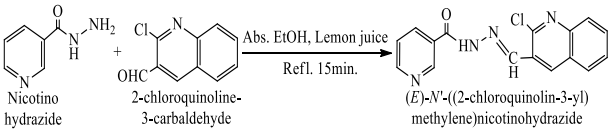
The azomethines are prepared by condensation of (-NH_2) group with (C=O) group [1]. They are versatile precursors in prepare of industrial compounds via ring closure, and they exhibit a wide range of pharmacological applications [2-4]. The reaction of 4-fluorobenzaldehyde with 1-benzylpiperidin-4-amine in presence of per chloric acid gives efficiently an imine product [5]. (Scheme 1)



1-Benzylpiperidin -4-amine | 4-fluoro benzaldehyde | (*Z*)-*N*-(1-benzylpiperidin-4-yl)-1-(4-fluorophenyl)methanimine

Scheme 1. Using $HClO_4$ as a catalyst to prepare the azomethine compound

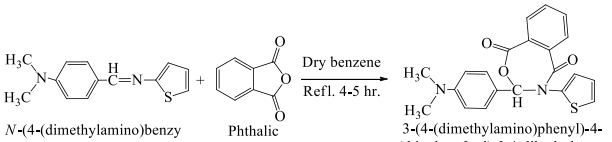
The reaction of nicotinohydrazide with 2-chloroquinoline-3-carbaldehyde lead to a good yield of the azomethine compound [6]. (Scheme 2)



Nicotino hydrazide | 2-chloroquinoline-3-carbaldehyde | (*E*)-*N*'-((2-chloroquinolin-3-yl) methylene)nicotinohydrazide

Scheme 2. Using lemon juice as a catalyst to prepare the azomethine compound

1,3-Oxazepine is unsaturated seven-membered heterocyclic consist of oxygen atom in location 1 and nitrogen atom in location 3 beside five carbon atoms [7]. Oxazepines are used as antibiotics and enzyme inhibitors. There are many studies on oxazepine in pharmacological applications [8,9]. Oxazepines have been prepared mainly by dipolar cycloaddition reaction of azomethine compoundswith five atoms cyclic anhydride [10-13], such as phthalic, succinic, maleic, and pyromellitic [14-17]. The reaction of phthalic anhydride with N-(4-(dimethylamino) benzylidene) thiophen-2-amine in dry benzene gives an 1,3-oxazepinederivatives [18]. (Scheme 3)

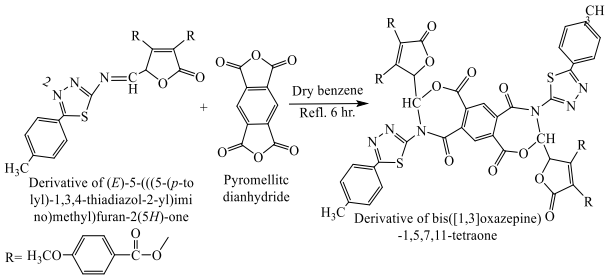


N-(4-(dimethylamino)benzy lidene)thiophen-2-amine | Phthalic anhydride | 3-(4-(dimethylamino)phenyl)-4-(thiophen-2-yl)-3,4-dihydrobenzo [*e*][1,3]oxazepine-1,5-dione

Scheme 3. Prepared 1,3-oxazepinecompound with dry benzene as solvent

Received on 13.01.2020 Modified on 18.03.2020
Accepted on 26.05.2020
Research J. Pharm. and Tech. 2021; 14(1):79-84.
DOI: 10.5958/0974-360X.2021.00015.9

The product of the reaction between pyromellitic anhydride and derivative is showed in (Scheme 4) [16].



Scheme 4. Prepared 1,3-oxazepine derivatives with double rings

This work aims to prepare azomethine compounds from the reaction between aromatic aldehyde and aromatic primary amines to produced azomethine compounds, azomethine compounds reacted with anhydride compound, this reaction produced hetero atom compounds, these derivatives are very important in the pharmaceutical and medical fields.

2. EXPERIMENTAL PART:

2. 1. Prepare of hetero atom compounds Ra_1-Ra_5

A mixture of amine (0.01mol) and aldehyde (0.02mol) with trace of glacial acetic acid dissolved in 10mL absolute ethanol was placed in a 50-mL round-bottom. The reactions are refluxing for 4 hours, the purity of the compounds were proved with Thin Lear Chromatography. The solid products were recrystallized from ethanol [19,20], after that a mixture of (0.004mol) of prepared azomethine compounds with (0.008mol) of anhydride compounds in 15mL of benzene, was refluxed for 3h, the purity of the compounds were proved with Thin Lear Chromatography. The solid products were recrystallized from ethanol. Table 1 showed the properties of the Ra_1-Ra_5 [21,22].

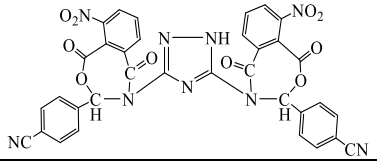
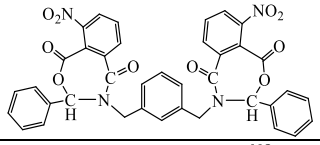
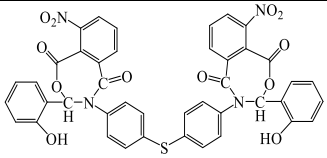
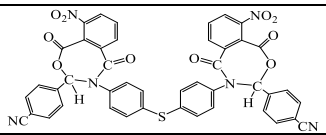
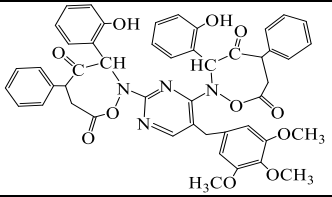
2.2. Antibacterial activity of prepared hetero atom compounds Ra_1-Ra_5

Antibacterial activity of the chemicals prepared hetero atom compounds Ra_1-Ra_5 against *E. coli* and *S. aureus*.6 µg well^{-1} of hetero atom compounds. To measure the inhibition diameter a plate method was used [23].

3. DISCUSSION AND RESULTS:

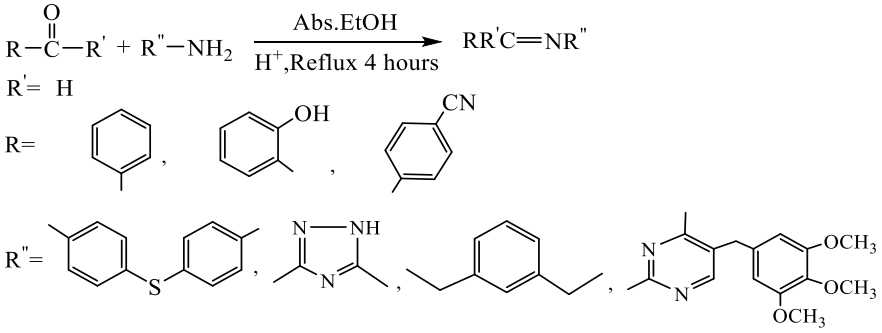
Physical properties of all prepared Ra_1-Ra_5 showed in 1 table. The higher m. p. of the prepared hetero atom compounds was for (Ra_1). The higher yield of hetero atom compounds was for Ra_4(91%).

Table 1. Physical properties of Ra_1-Ra_5

Comp.	Structural formula	Yield%	m.p. °C	Color
Ra_1		83	280-282	Red
Ra_2		81	210-212	Dark Yellow
Ra_3		77	205-207	Off White
Ra_4		91	170-171	Light Yellow
Ra_5		89	80-82	Orange

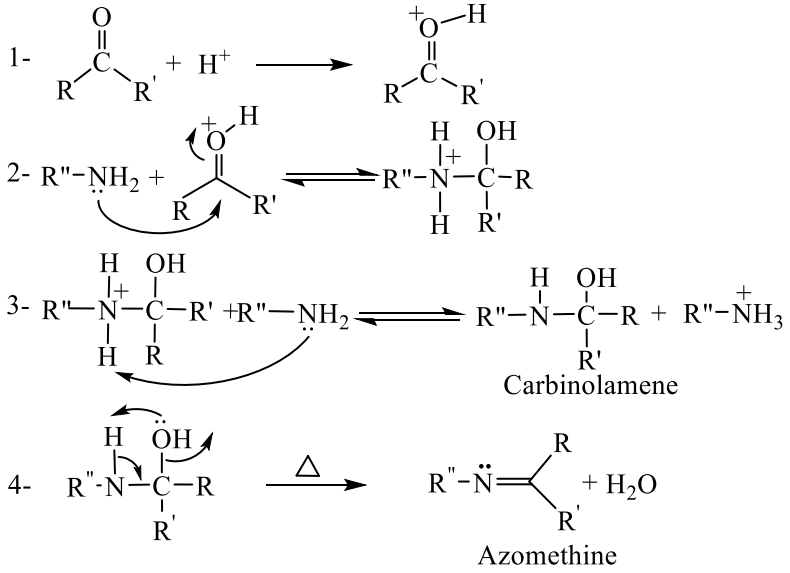
3.1. Diagnoses of prepared hetero atom compounds Ra_1-Ra_5

The general equation of prepared azomethines showed in scheme 5.



Scheme 5. The prepared azomethines

The reaction mechanism is believed to occur in (Scheme 6) [24].



Scheme 6. The azomethines formation mechanism

The FT-IR spectra was appeared the absorption at 1614-1702cm^{-1} of N-C=O, at 1718-1745cm^{-1} of O-C=O, at 1240-1282cm^{-1} of -C-O, at (1355-1381)-(1527-1584) cm^{-1} indicative of NO_2[25-27], See table 2for other absorbtion, seefigure1 and figure 2.

Table 2. IR of prepared hetero atom compounds Ra_1-Ra_5

IR, ν(cm^{-1})										
Comp.	**C-N**	**C-O**	**C=O Lactam**	**C=O Lacton**	**C=C Arom.**	**C-H Arom.**	**C≡N**	**C-H Aliph.**		**Others**
								Asym.	**Sym.**	
Ra_1	1145	1274	1703	1745	1602	3095	22 31	---	2825	NO_2:1357, 1541 N-H: 3275
Ra_2	1149	1298	1614	1718	1568	3055	---	2975	2879	NO_2:1377, 1527
Ra_3	1153	1282	1614	1730	1587	3045	---	---	2991	C-S: 700 NO_2:1381, 1584 O-H:3500b
Ra_4	1168	1278	1620	1730	1579	3062	22 23	---	2989	C-S: 688 NO_2:1355, 1560
Ra_5	1172	1240	1650	1728	1593	3064	---	2981	2939	O-H:3355b

Table 3. The ^{1}H-NMR Spectrum of prepared hetero atom compounds (Ra_1-Ra_5) in Di Methyl Sulphoxide (DMSO)

Compound	Chemical Shift δ ppm
Ra_1	Singlet in location 4.40ppmfor N<u>H</u>, singlet in location 10.10 ppm for 2C<u>H</u>, multiplet in location 7.85-8.40 ppm for aromatic protons (14H).
Ra_2	Singlet in location 4.04 ppm for 2C<u>H</u>$_2$, singlet in location8.40 ppm for 2N-C<u>H</u>, multiplet in location7.10-7.30 ppm for aromatic protons (20H).
Ra_3	Singlet in location 8.63 ppm for2N-C<u>H</u>, singlet in location 13.22 ppm for (2O<u>H</u>), multiplet in location 6.69-7.22 ppm for aromatic protons (22H).
Ra_4	Singlet in location 10.10 ppm for 2N-C<u>H</u>, multiplet in location 6.69-8.51 ppm for aromatic protons (22H).
Ra_5	Singlet in location1.33 ppm for meta of 2O-C<u>H</u>$_3$, singlet in location2.67 ppm for para of O-C<u>H</u>$_3$, singlet in location 3.54 ppm for C<u>H</u>$_2$-Ph, doublet in location3.82 ppm for 2C<u>H</u>$_2$-C=O, triplet in 4.02 ppm for 2C<u>H</u>-C=O, singlet in location 7.90 ppm for 2N-<u>CH</u>, singlet in location9.90 ppm for 2O<u>H</u>, multiplet in location 6.33-7.40 ppm for aromatic protons and 1H of pyrimidinering (20H).

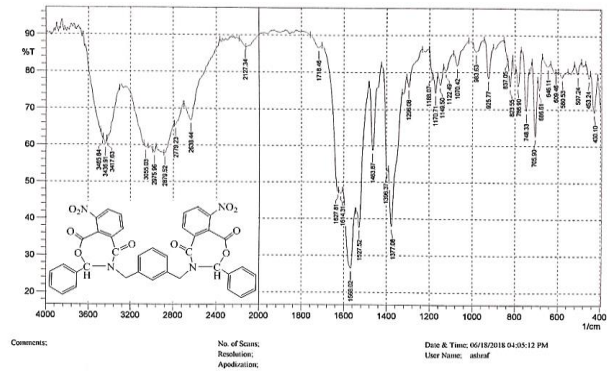


Figure 1. IR spectrum of Ra_2

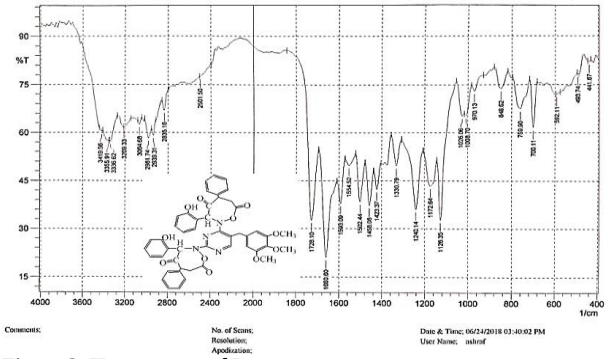


Figure 2. IR spectrum of Ra_5

^{1}H-NMR spectrum appeared DMSOthe chemical shiftsof Ra_1: Singlet in (4.40, 1H) of N<u>H</u>, singlet in (10.10, 2H) of (2C<u>H</u>), multiplet in (7.85-8.40,14H of aromatic protons)[30-34].^{1}H-NMR of Ra_1-Ra_5 showed in table 3. See figure3 and figure4.

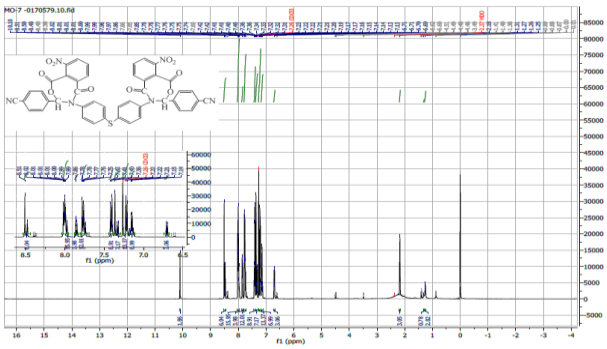


Figure3. The^{1}H-NMR spectrum ofRa_4

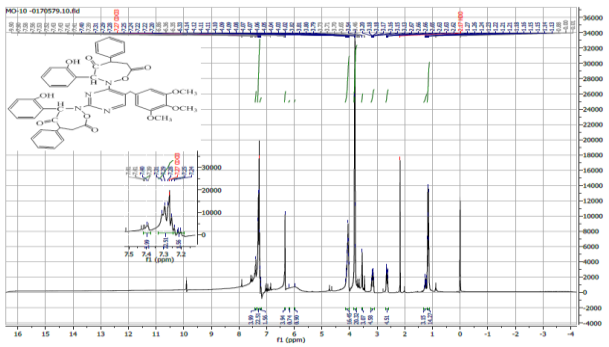


Figure 4. The^{1}H-NMR spectrum ofRa_5

The resonance spectra of ^{13}C-NMR was taken for three derivatives (Ra_3-Ra_5), Ra_3 showed the signals: 147 indicated to presence 2 groups of N-<u>C</u>H, 160 indicated to presence 2 lactam groups of N-<u>C</u>=O, 163 indicated to presence 2 lactone groups of O-<u>C</u>=O, 116-133 indicated to presence aromatic carbons [35-41]. See table 4, figure5 and figure 6.

Table 4. The ^{13}C-NMR Spectra of 1,3-oxazepin-5(1*H*)-one derivatives (Ra_3-Ra_5) in Di Methyl Sulphoxide (DMSO)

Compound	Chemical Shift δ ppm
Ra_3	147ppmindicated to presence 2 lactone groups of N-<u>C</u>H, 160 ppm indicated to presence 2 lactone groups of N-<u>C</u>=O, 163 ppm indicated to presence 2 lactone groups of O-<u>C</u>=O, 116-133 ppm for aromatic carbons.
Ra_4	150 ppm indicated to presence 2 lactone groups of N-<u>C</u>H, 156 ppm indicated to presence 2 lactone groups of N-<u>C</u>=O, 157 ppm indicated to presence 2 lactone groups of O-<u>C</u>=O, 190 ppm indicated to presence 2 lactone groups of cyanide <u>C</u>N, 114-136 ppm for aromatic carbons.
Ra_5	14 **ppm** for two meta (O-C<u>H</u>$_3$) group, 38 ppm for one para (O-C<u>H</u>$_3$)group, 56 ppm indicated to presence 2 lactone groups of C<u>H</u>$_2$-Ph, 61 ppm for (C<u>H</u>$_2$-C=O), 172 ppm indicated to presence 2 lactone groups of <u>C</u>H-C=O, 173 ppm indicated to presence 2 lactone groups of 2N-<u>C</u>H), 176 ppm indicated to presence 2 lactone groups of N-<u>C</u>=O, 178 ppm indicated to presence 2 lactone groups of O-<u>C</u>=O, 117-153 ppm for aromatic carbons pyrimidine ring carbons.

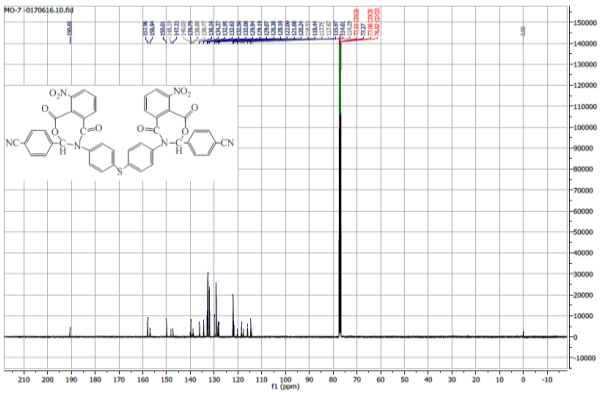


Figure5. ^{13}**C-NMR spectrum of**Ra_4

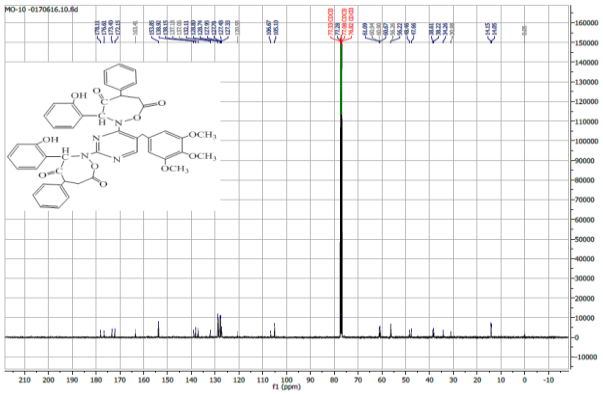
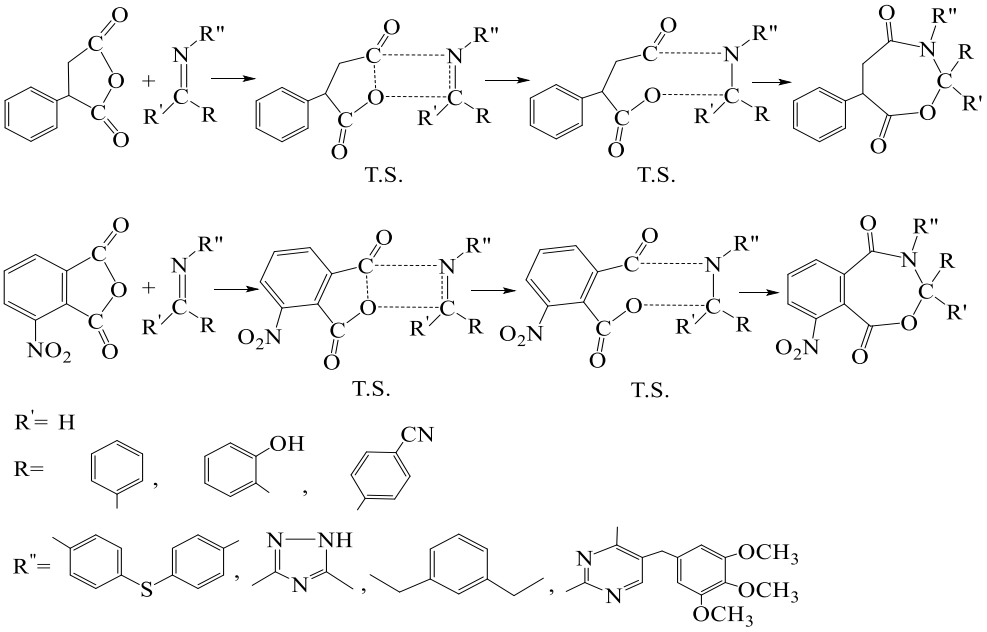


Figure6. ^{13}**C-NMR spectrum of** Ra_5

The reaction included many transition state formed from the bond of O-C=O of the anhydride with the C=N of Azomethine [27-30]. See (Scheme 7)



Scheme 7. Mechanism of prepared hetero atom compounds formation

3.2. The biological activityof prepared hetero atom compoundsRa_1-Ra_5

Tables 5 and 6 appeared the comparison between the drug in table 5 and the prepared hetero atom compounds in table 6.

Table 8 appeared that the best result of inhibition was 20mm for (45%) concentration, 25mm (50%), 28mm (75%) concentration and 32mm (100%) concentration against ***S. aureus*** by Ra_5compounds.Maybe the composite of the prepared hetero atom compounds destroyed the wall of microbes [41,42].

Table 5. The zoneinhibition of the drug and Di Methyl Sulphoxide (DMSO)

Type of bacteria	**Inhibition** (mm)	
	The drug (Gentamycin) 50 µg/well	**DMSO** 50 µg/well
E. coli	24	0
S. aureus	28	0

Table 6. Biological activity (mm) of the prepared hetero atom compounds Ra_1-Ra_5

Compound	Isolated	5%	10%	15%	20%	25%	30%	35%	40%	45%	50%	75%	100%
Ra_1	*E. coli*	-ve	-ve	ve	-ve	ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Ra_1	*S.aureus*	-ve	-ve	ve	-ve	ve	-ve	5mm	8mm	8mm	10mm	11mm	12mm
Ra_2	*E. coli*	-ve	-ve	ve	-ve	ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Ra_2	*S.aureus*	-ve	-ve	ve	-ve	ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Ra_3	*E. coli*	-ve	-ve	ve	-ve	ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Ra_3	*S.aureus*	-ve	-ve	ve	-ve	ve	-ve	-ve	-ve	-ve	7mm	8mm	10mm
Ra_4	*E. coli*	-ve	-ve	ve	-ve	ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Ra_4	*S.aureus*	-ve	-ve	ve	-ve	ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Ra_5	*E. coli*	-ve	-ve	ve	-ve	ve	-ve	7mm	7mm	9mm	11mm	11mm	13mm
Ra_5	*S.aureus*	-ve	-ve	7mm	7mm	10mm	13mm	15mm	17mm	20mm	25mm	28mm	32mm

4. CONCLUSIONS:

DerivativeRa_5showed the best zone of inhibition against *S. aureus*, this result helpful the other researchers to applied the concentration of the active prepared hetero atom compounds against pathogenic bacteria *in vivo* such a rats or rabbits.

5. ACKNOWLEDGEMENTS:

Thankful to the College of Applied Sciences –Hit, College of Sciences and College of Pharmacy/ University of Anbar for their kind support to carry out this project.

6. REFERENCES:

1. H. Tawfeeq, R. Muslim, O. Abid, M. Owaid. Acta Chim. Slov. 2019, 66, 1-8.
2. R. Muslim, M. Saleh, S. Saleh, Revista Aus. 2019, 26, 129-135.
3. W. Qin, S. Long, M. Panunzio, S. Biondi, Molecules.2013, 18, 12264-12289.
4. A. Ayfan, R. Muslim, N. Noori, Research J. Pharm. and Tech.2019, 12, 1008-1016
5. P. Mayavel, K. Thirumurthy, S. Dineshkumar, G. Thirunarayanan, Umcschem. 2014, lxix, 159-179.
6. V. Desai, R. Shinde, Int J Pharm. 2015,5, pp. 930-935.
7. A. Yasir, H. Mohammed, Int. J. Adv. Res,2016, 5, 170-175
8. J. Bucher, J. Haseman, R. Herbert, M. Hejtmancik, M. Ryan, Toxycological,1998,42, 1-12.
9. G. Yeap, T. Mohammad, H. Osman, J. of Molecular structure.2011, 982, 33-44.
10. P. Verma, S. Gupta, V. Yadav, Der Chemica- Sinica.2015,6, 86-89.
11. N. Al-Jamali, M. Jameel, A. Al-Haidari, Innovare Journal of Science.2013, 1, 13-15.
12. R. Muslim, S. Saleh, Orient. J. Chem. 2019, 35, 1360-1367.
13. T. Helal, G. Abbas, F. Mohammed, IJMRD.2014, 1, 41-45.
14. A. Kareem, H. Ghanim, Journal of Applied, Physical and Biochemistry Research.2015, 5, 45-56.
15. R. Haiwal, Scientific Journal of Kerbala University. 2011,9, 96-111.
16. A. Mukhlus, M. Al-Rawi, J. Tomma, A. Al-Dujaili, Ibn Al-Haitham Journal for Pure and Applied Science.2012,25, 1-14.
17. A. Khan, I. Raoof, H. Essa, Journal of Natural Sciences Research. 2015, 5, 69-80.
18. N. Aljamali, International Journal of Current Research in Science and Technology. 2015, 1,9-15.
19. H. Sabah, Der Pharma Chemica. 2014,6,38-41.
20. H. M. Tawfeeq, R. F. Muslim, O. H. Abid, M. N. Owaid, Acta Pharm. Sci.2019, 57,45-63.
21. O. H. Abid, H. M. Tawfeeq, R. F. Muslim, Acta Pharm. Sci.2017,55, 43-55.
22. R. F. Muslim, H. M. Tawfeeq, M. N. Owaid, O. H. Abid, Acta Pharm. Sci.2018, 56, 39-57.
23. M. Owaid, J. Raman, H. Lakshmanan, S. Al-Saeedi, V. Sabaratnam, I. Al-Assaffii, Mater. Lett.2015, 153, 186-190.
24. J. Simek, Organic Chemistry, Inc., New York, 2013.
25. R. Silverstein, F. Webster, D. Kiemle, Spectrometric identification of organic compounds, John Wiley and sons, Inc., New York, 2005.
26. B. Mistry, A Handbook of spectroscopic Data chemistry, Oxford Book Company Jaipur India, Mehra Offset Printers, Delhi, 2009.
27. R. Al-Bayati, A. Al-Amiery, Y. Al-Majedy, African Journal of Pure and Applied Chemistry. 2010, 4, 74-86.
28. A. Samir, R. Rumez, H. Fadhil, International Journal of Applied Chemistry, 2017,13, 393-407.
29. G. McDonnell, A. Russell, Clinic. L Microbio.Rev.1999, 12,147-179.
30. M. Owaid, R. Muslim, H. Hamad, JJBS.2018, 11, 401-405.
31. A. Samir, R. Rumez and H. Fadhil, International Journal of Applied Chemistry. Vol. 13, 393-407, (2017).
32. Puttaraj C., Chetan M. Bhalgat, Sandeep K. Chitale, B. Ramesh, Research Journal of Pharmacy and Technology. Vol. 4 Pages: 972-975 (2011).
33. B. R. Thorat, M. Mustapha, D. Khandekar, Swati Lele, P. Kamat, S. Sawant, R. Jadhav, D. Shelke, Shivaji Kolekar, R. G. Atram, R. Yamgar, Research Journal of Pharmacy and Technology. Vol. 5, Pages: 369-375(2012).
34. Vandana S. Bhavnani, Padmanabh B. Deshpande, Santosh V. Gandhi, Prajakta Pawar, Ashish K. Gaikwad, Research Journal of Pharmacy and Technology. Vol. 5, Pages: 1461-1464(2012).
35. Nagham Mahmood Aljamali, Intisar O. Alfatlawi, Research Journal of Pharmacy and Technology. Vol.8, Pages: 1225-1242(2015).
36. Shetha. F. Al-Zubiady, Zainab. H. Kadhim Al-Khafaji, Iman. M. Mohamed, Research Journal of Pharmacy and Technology. Vol. 11, 0974-3618 (2018).
37. WD Sam Solomon, Rahul A Kumar, PR Vijai Anand, R Venkatnarayanan, Asian Journal of Research in Chemistry. Vol. 3, 0974-4169(2010).
38. Valli G., Ramu K., Mareeswari P., Asian Journal of Research in Chemistry, Vol. 5,0974-4169(2012).
39. Valli G., Ramu K., Mareeswari P., Thanga Thirupathi A., Asian Journal of Research in Chemistry. Vol. 5, 0974-4169 (2012).
40. Mahendrasinh M. Raj, Hemul V. Patel, Lata M. Raj, Naynika K. Patel, Asian Journal of Research in Chemistry. Vol. 6, 0974-4169 (2013).
41. Varsha A. Dighe, Rohini R. Pujari, Asian Journal of Pharmaceutical Research. Vol. 7, 2231-5683 (2017).
42. C. J. Patil, Manisha C. Patil, Mrunmayee C. Patil, Research Journal of Science and Technology. Vol. 10, 0975-4393 (2018).