Synthesis and Characterization of Some New 1,3-Oxazepine-4,7-dione Derivatives and Study their Antibacterial Activity

***Gazwan H. Al-Somaidaie, **Fawzi H. Al-Obaidy, ***Bushra A. Khear Allah**
*** Department of Chem., College of Science, University of Tikrit, Tikrit, Iraq**
**** Department of Chem., College of Education for women, University of Tikrit, Tikrit, Iraq**
***** Department of Chem., College of Education, University of Tikrit, Tikrit, Iraq**

Received 31/10/2010 Accepted 5/5/2011

Abstract

Symmetrical 4-amino triazole which was prepared from the fusion of phenylhydrazide was reacted with different aromatic aldehydes to product new series of Schiff bases, and the later was cyclised thermally by reaction with maleic anhydride. The prepared compounds were characterized by FT-IR, and UV spectroscopy ,the melting points were determined and the purity and reaction time were checked by TLC. The biological activity was studied against different types of bacteria.

تحضير وتشخيص بعض مشتقات ١،٣-اوكسازبين الجديدة ودراسة فعاليتها المضادة للبكتريا

غزوان حسن عبد الوهاب الصميدعي فوزي حميد جمعة العبيدي بشرى عبدالمرتاح خيرالله

المستخلص

تم تحضير ٤-امينو ترايازول المتناظر (I) من صهر مركب فنيل هيدرازيد ثم مفاعلته مع الديهايدات اروماتية مختلفة للحصول على سلسلة جديدة من قواعد شيف، وتم إجراء الحولقة الحرارية بتفاعل قواعد شيف المحضره مع انهيدريد الماليك وشخصت المركبات المحضره بطيف الاشعة تحت الحمراء(IR) والاشعة فوق البنفسجية (UV) وبقياس درجات الانصهار وتم متابعة التفاعلات بكروموتوغرافيا الطبقة الرقيقة (TLC)، درست الفعالية البايولوجية ضد انواع مختلفة من البكتريا.

Introduction

Oxazepines are important organic compounds due to their broad spectrum of applications. The biological activities of these compounds were found in the research areas as having hypnotic muscle relaxation[1], antiemetic ، antagonistic [2] and anti-inflammatory [3] effects . These compounds are also used as anxiolytics [4] antiallergic and antihistaminic agents [5], also the oxazepines with metal have shown antibacterial and antifungl activity [6], central depressant [7], analgesic [8], local anesthetic [9], anti-inflammatory [10], and antihistaminic [11] effects . Additionally , benzoxazepines have also shown the stabilizing property in photography [12]. The purpose of this study is to understand what the conditions of HOMO-LUMO condensation to product [1,3]oxazepin-3,5-dione(IIIa-e) by treating new schiff bases with malonic or maleic anhydride [13,14] (Scheme1) and reporting the complete assignments of their IR spectra.

Experimental

Materials: different substituted benzaldehydes were BDH annular grade, solvents and other chemicals used were of annular grade. Uncorrected melting points were determined using Electrothermal melting point apparatus(Electrothermal Engineering LTD S-N 10853). The IR spectra were recorded by Shimadzu FT-IR spectrophotometer as KBr disc (4000-400 cm^{-1}) range , the UV absorption spectra were measured in ethanol(95%) as a solvent by JASCOW 32 V-530, TLC-Merck Silica gel 60 F254 Plate was used, heat of formation data (H.F)was calculated by program Chem.Office 2004 .

A) Synthetic methods

1) Synthesis of methyl benzoate[15].

A mixture of benzoic acid (0.1mol), excess of methanol and concentrated sulphuric acid (5ml) was refluxed for 6 hrs with stirring. After the solvent was distilled under vacuum, the product washed by sodium bicarbonate solution then with diethyl ether (40ml) B.P= 199 °C ,yield=67%

2) Synthesis of benzoic acid hydrazide [15]

Methyl benzoate (0.1mol) and hydrazine hydrate 98% (0.1mol) mixture in absolute ethanol (40ml) was refluxed for 6 hrs, after cooling to room temperature, the precipitate was filtered, washed , recrystallized from ethanol and dried . (M.P)= 113-115 °C, Yield 75%.

3) Synthesis of 3,5-diphenyl-4-amino 1,2,4-triazole [16](I).

Phenyl hydrazide (benzoic acid hydrazide) (1.5gm) was melted at (200-225 ºC) for 2hrs,then cooled and to the reaction mixture was added 50ml of water and refluxed 1.0 hr., filtered hot, the white precipitate was recrystallized from ethanol and dried , M.P = 238-240 ºC, yield 90 %.

4) Synthesis of 3,5-diphenyl 4-arylmethylenimino-(4H) 1,2,4-triazoles[17](IIa-e).

A mixture of compound (I) (0.01 mole) and substituted benzaldehyde (0.01 mole) in ethanol 25 ml with glacial acetic acid 2 ml was refluxed for 6 hrs. The precipitate was filtered and recrystallized from ethanol. Melting Points and yields are listed in Table (1).

5) Synthesis of 1,3-oxazepin-4,7-dione derivatives [13](IIIa-e).

(0.01 mole) of compounds (IIa-e) was added to (0.01 mole) of maleic anhydride in 25 ml of absolute ethanol and refluxed for 3 hrs. to give 1,3-oxazepin-4,7-dione derivatives, These gum compounds were decanted and washed with ethanol and diethyl ether . Melting Points and yields are listed in Table (2).

B) The biological activity

The bacteria species used are listed in table (7). All strains were obtained from College of Medicine, Tikrit University. They were grown up to the stationary phase nutrient broth at 37 °C and a sample of 0.5 ml of each bacteria broth was spread over a surface of a nutrient agar plate[18].

Antibacterial assay

Disc of filter paper (6 mm diameter) were sterilized at 140 °C for 1 hr and impregnated with the germs. Absolute ethanol was used as a solvent for compounds (I),(IIa-e) and (IIIa-e), the same solvent was used for antibiotics, blank paper discs of absolute ethanol was used as control. The inoculated plates were incubated at 37 °C for 24 hrs., and the inhibition zone (mm) were measured[19]. In all experiments, the mean of each triplicate was measured[20].

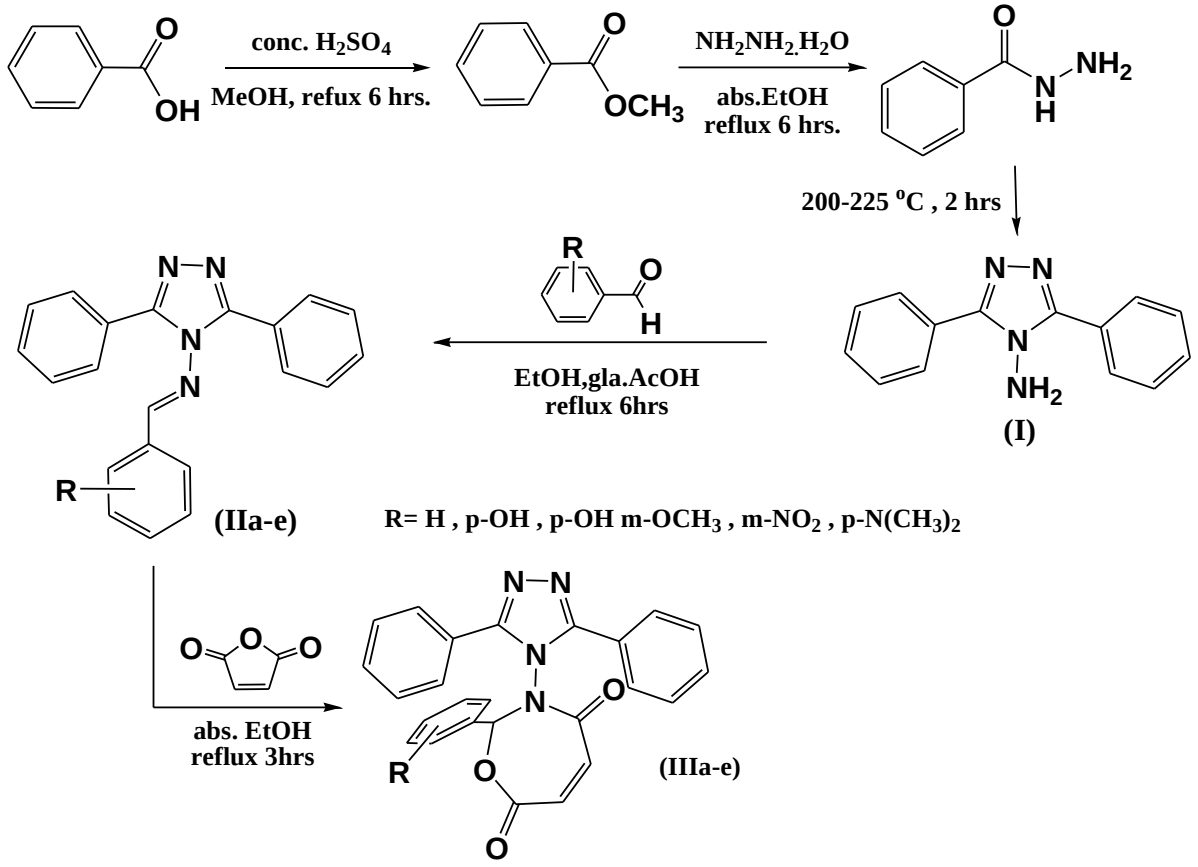
Results and Discussion

Synthesis of S-triazole and Schiff base derivatives (IIa-e). 3,5-diphenyl-4-amino 1,2,4-triazole was prepared by melting dry powder of phenylhydrazide at high temperature to give compound (1). The IR spectrum of compound (I) Fig.(11), exhibited significant two bands in the region 3205-3367cm^{-1} which could be attributed to symmetric and asymmetric stretching vibration of NH_2 group[21] besides this, a band at about 1631 cm^{-1} due to cyclic C=N, stretching is also observed. The schiff bases compounds were synthesized from 3,5-diphenyl-4-amino 1,2,4-triazole with differents substituted benzaldehyde. The synthesis of these compounds was carried out according to the steps outlined in scheme(1), and the physical properties are given in Table (1). The reaction was followed by disappearance of NH_2 absorption band at 3367 cm^{-1} and appearance of C=N absorption bond in the IR spectra of the products are give in Table(4).

Synthesis of 3-(3,5-diphenyl-1,2,4-triazol-4-yl)-2-aryl-2,3-dihydro-1,3-oxazepine-4,7-dione (IIIa-e).

The reaction of Schiff bases with maleic anhydride is asort of cycloaddition reaction. Cycloaddition is a ring formation that results from the addition of π bonds to either δ π bonds with formation of new δ bonds. This class of reaction and its reverse a compasses a large number of individual types. Huisgen[17] has formulated a useful classification of diverse cycloadditions in terms of the new δ bonds, the ring size of the product , and the number of atoms in the components taking part in the cycloaddition . this cycloaddition is classified as 5+2→7, implying a 5-atom component plus 2-atom component leading to 7-membered heterocyclic ring, but the mechanism involves addition of one δ bond COO to one π bond (C=N) to give 4- membered cyclic transition state which opens into maleic anhydride (5- membered cyclic ring)to give 7-membered cycling ring. It is obvious that N-aryl-1,2,4-triazole contains both a (C=C) function and an azomethine function (C=N) and either one or both are able to react with maleic anhydride. The reaction actually involves interaction between the HOMO orbital of maleic anhydride with LUMO orbital of (C=N), since the oxygen has higher electro negativity than nitrogen, the energy gab between its LUMO orbital and the HOMO orbital of maleic anhydride is larger than it is between the LUMO orbital of azomethine and the HOMO orbital of maleic anhydride. Energetically, the interaction between the HOMO orbital of maleic anhydride and the LUMO orbital of azomethine is more favourable. Incidentally, even in the absence of (C=N) no interaction between the HOMO orbital of maleic anhydride and the LUMO orbital of (C=C) is observed for the same reason. It is obvious that the two absorption bands at (1740-1780) cm^{-1} and at (1800-1850) cm^{-1} in the IR spectrum of pure maleic anhydride[18] have disappeared when the anhydride became part of the 7-membered heterocyclic ring. The (C=O) group of the title compounds absorbs at (1700-1734) cm^{-1}(oxazepine) and (C-O), (-O=C-O) at (1168-1172)cm^{-1} .This confirms the assigned 7-membered heterocyclic ring structure. There is a direct proportion between the decreas of

calculated heat of formation(H.F.) and the yield for Schiff bases (IIa-e) reaction products in the derivatives of oxazepins(IIIa,b,e) the heat formation is directly proportional for some, while the others (IIIc,d) is irregular and this may due to the steric effects for Ar group in the compounds, H.F. data are given in Table (6).see Fig.(1-5).



Scheme (1)

Table (1): Physical properties of 3,5-diphenyl 4-aryl methylene imino-4H-1,2,4-triazole (IIa-e).

Comp.No.	Molecular formula	M.P.°C	Color	Rf	Yield %	Recrys. solvent
IIa	$C_{21}H_{16}N_4$	200-202	Gray	0.67	60	Ethanol
IIb	$C_{21}H_{16}N_4O$	300Dec.	Milky	0.70	73	Ethanol
IIc	$C_{22}H_{18}N_4O_2$	166Dec.	Greenish	0.71	73	Ethanol
IId	$C_{21}H_{15}N_5O_2$	185-187	Dark yellow	0.55	63	Ethanol
IIe	$C_{23}H_{21}N_5$	171-173	Yellow	0.68	65	Ethanol-Methanol

Table (2): Physical properties of 1,3-Oxazepine-4,7-dione derivatives (IIIa-e).

Comp. No.	Molecular Formula	M.P.ºC	Color	Rf	Yield %	Recrys. solvent
IIIa	$C_{25}H_{18}N_4O_3$	179-181	Yellow	0.65	65	1,4-Dioxane
IIIb	$C_{25}H_{18}N_4O_4$	190-192	Yellow	0.64	71	Ethanol
IIIc	$C_{26}H_{20}N4O_5$	202-204	Brown	0.67	67	Ethanol
IIId	$C_{25}H_{17}N_5O_5$	170-172	Dark yellow	0.50	66	Ethanol
IIIe	$C_{27}H_{23}N_5O_3$	225-227	Orange	0.62	71	Ethanol-Methanol

Table (3): Uv/vis (nm) and Infra-red absorption (cm^{-1}) of 3,5-diphenyl-4-amino 1,2,4-triazole (I).

Comp.No.	UV,λmax (nm),EtOH	IR,(KBr)cm^{-1}			
		νNH_2	νC-H	νC=N in/out ring	Others
I	220 255	3367 3205	3053	1609 1631	νN-N 1120

Table (4): UV-Vis (nm) and Infra-red absorption (cm^{-1}) of 3,5-diphenyl-4-amino 1,2,4-triazole derivatives(IIa-e).

Comp. No.	UV,λmax(nm), EtOH	IR,(KBr)cm^{-1}	
		νC=N in/out ring	Others
IIa	220 224	1615/1640	δC-H Ar, o-sub., 629, 744
IIb	221 345	1631/1651	νOH, 3419, δC-H Ar, p-disub. 804
IIc	236 302	1629/1653	ν C-O-C (as.,s.) 1120,1008 νOH, 3398, νCH_3(as.,s.) 2950,2889
IId	220 285	1635/1656	νNO_2(as.,s.)1531,1409, δC-H Ar, , m-disub. 869, 806, 759
IIe	224 377	1654/1631	νCH_3(as.,s.) 2974,2896, ν C-N 1178, νC-H Ar, p-disub. 829

Table (5): Uv/vis (nm) and Infra-red absorption (cm^{-1}) of 1,3-oxazepine-4,7-dione derivatives (IIIa-e).

Comp.No.	UV,λmax (nm),EtOH	IR,(KBr)cm^{-1}			
		Olefin, νC=C νC-H	νC=O	νC-O	Others
IIIa	244 257	1580 3056	1700 1734	1171	----
IIIb	230 380	1577 3056	1700 1733	1170	νOH, 3180
IIIc	223 356	1633 3010	1731 1718	1172	νOH, 3392, νCH Ar, 3153
IIId	221 332	1577 3053	1708 1728	1170	νNO_2(as.,s.)1577,1353
IIIe	220 340	1577 3051	1706 1726	1168	νCH_3(as.,s.) 2927,2858

Table (6): Heat of formation Kcal/mol of synthesized compounds (IIa-e,IIIa-e)

Comp. No.	Heat of Formation	Comp. No.	Heat of Formation
IIa	204.93518 kcal	IIIa	131.57081 kcal
IIb	162.57525 kcal	IIIb	108.00542 kcal
IIc	119.80375 kcal	IIIc	056.70623 kcal
IId	206.87886 kcal	IIId	141.45780 kcal
IIe	214.67274 kcal	IIIe	141.09057 kcal

Colors of steric conformation

Atoms	C	O	N	H
Color	Black	Red	Blue	Gray

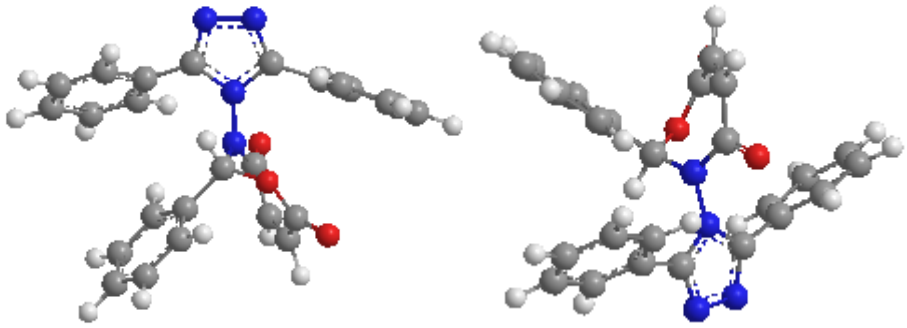


Fig. (1): Steric conformation of compound (IIIa)

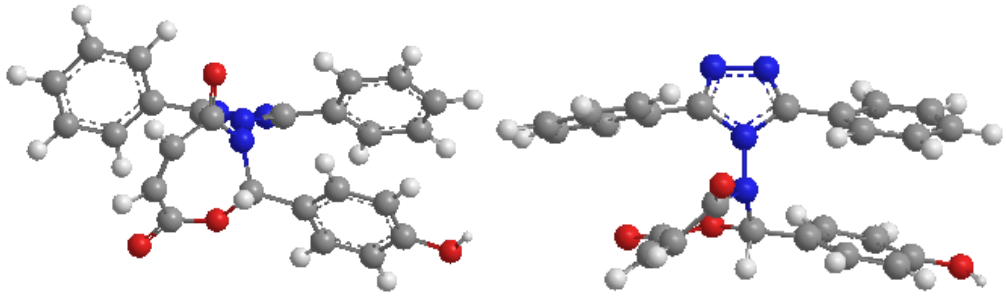


Fig. (2): Steric conformation of compound (IIIb)

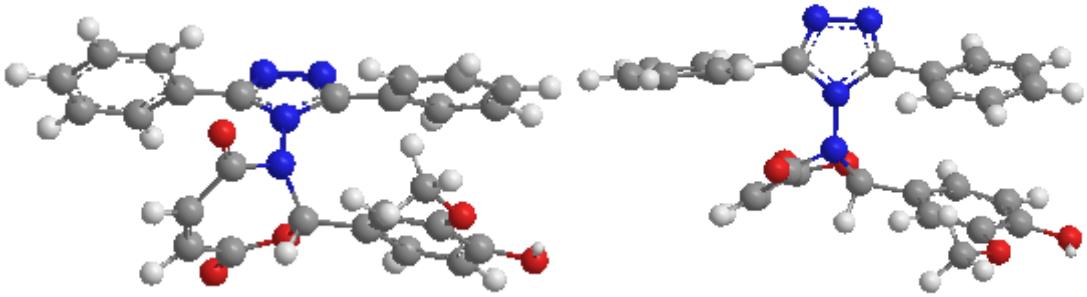


Fig. (3): Steric conformation of compound (IIIc)

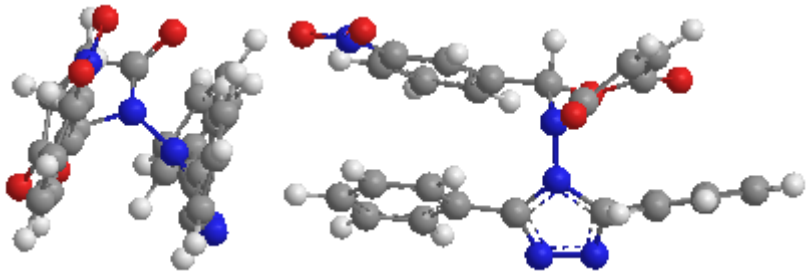


Fig. (4): Steric conformation of compound (IIId)

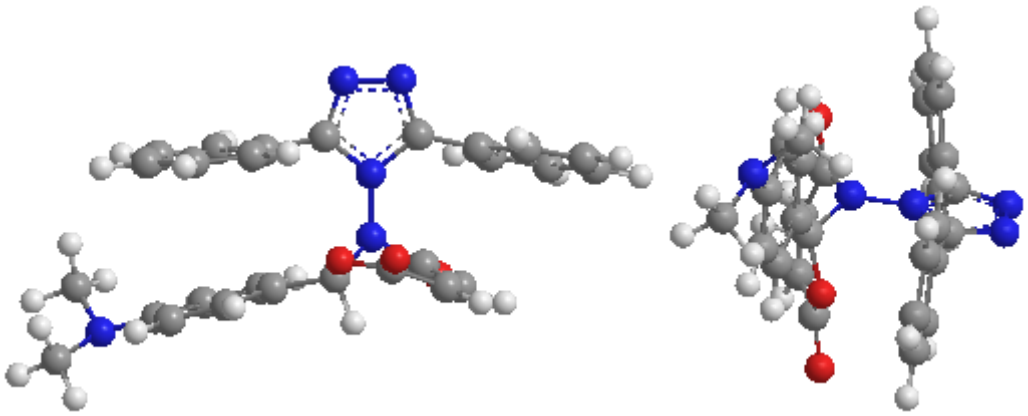


Fig. (5): Steric conformation of compound (IIIe)

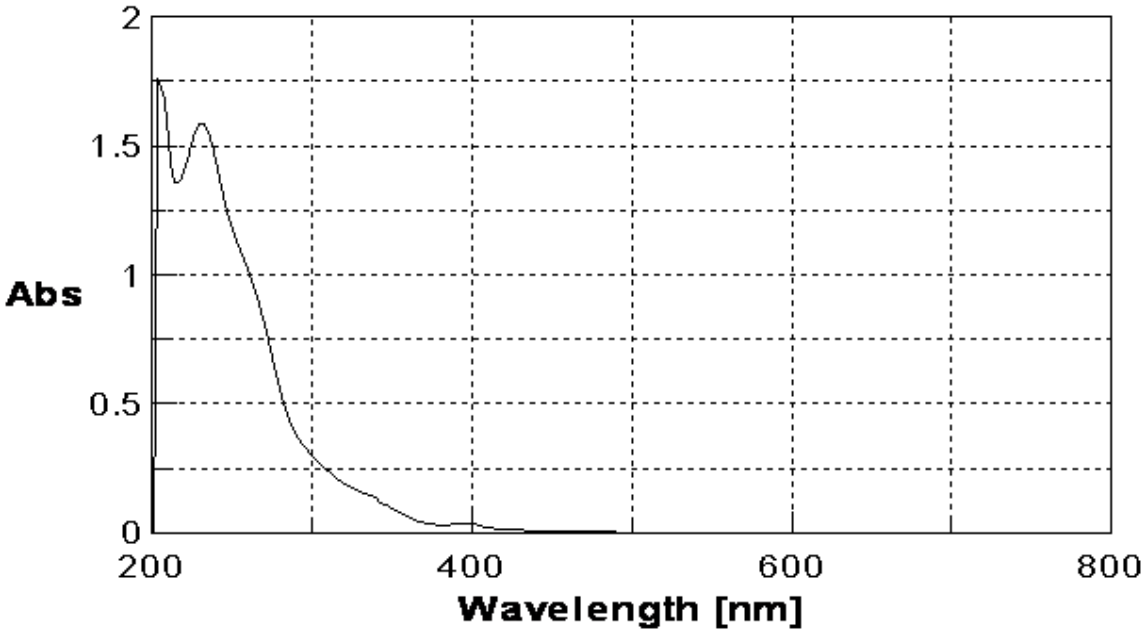


Fig.(6): UV spectrum of compound (I)

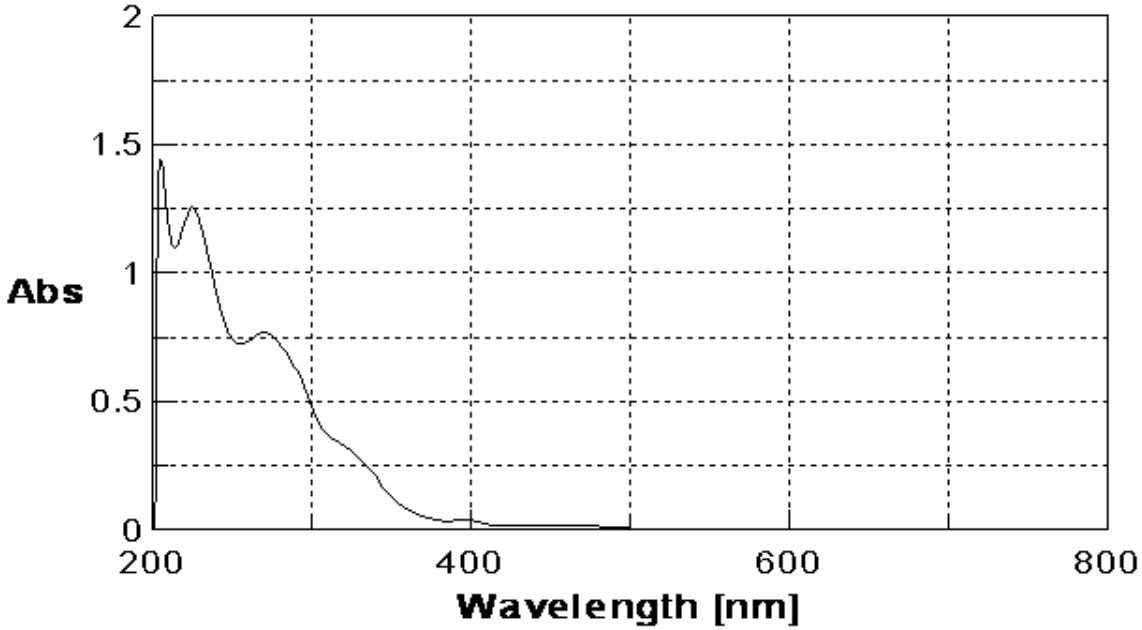


Fig.(7): UV spectrum of compound (IIb)

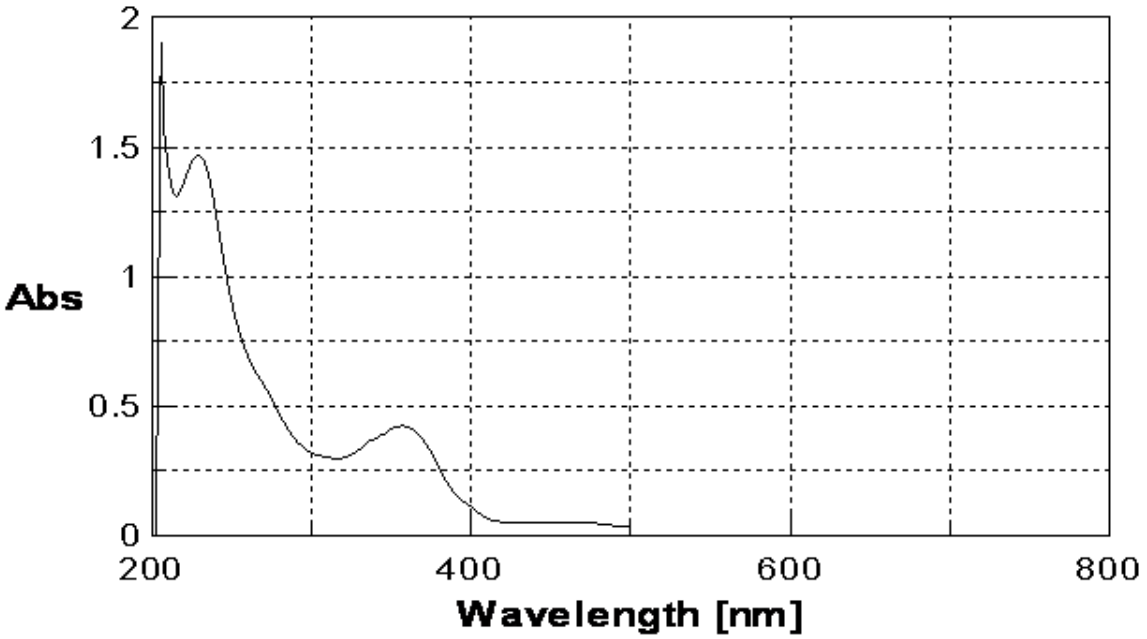


Fig.(8): UV spectrum of compound (IIIb)

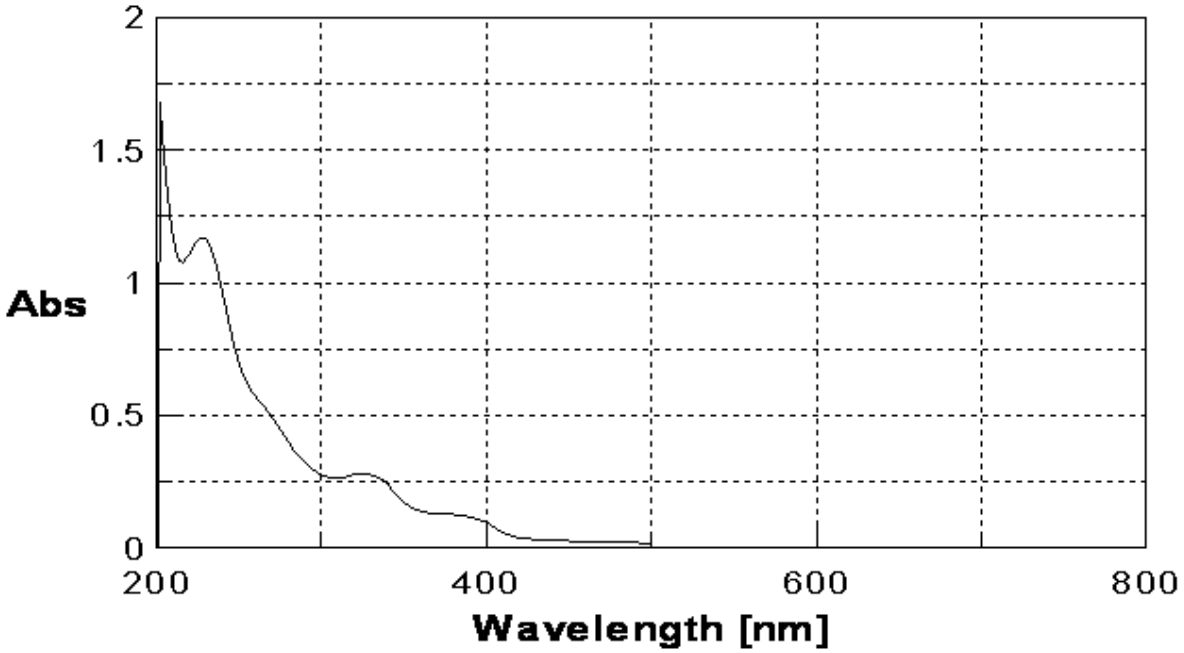


Fig.(9): UV spectrum of compound (IIe)

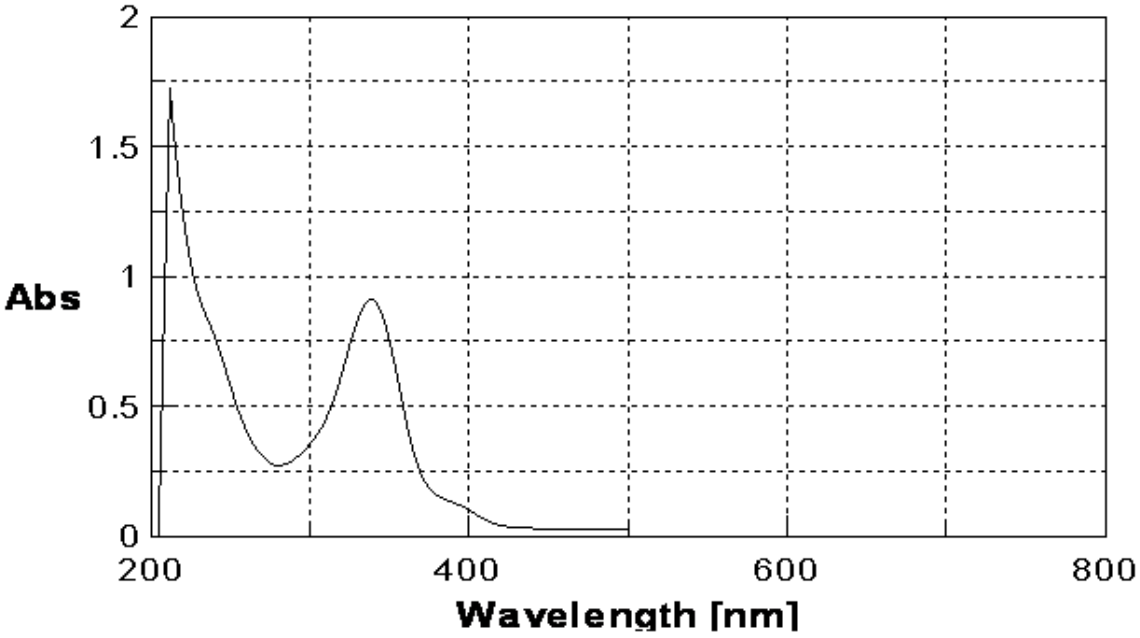


Fig.(10): UV spectrum of e compound (IIIe)

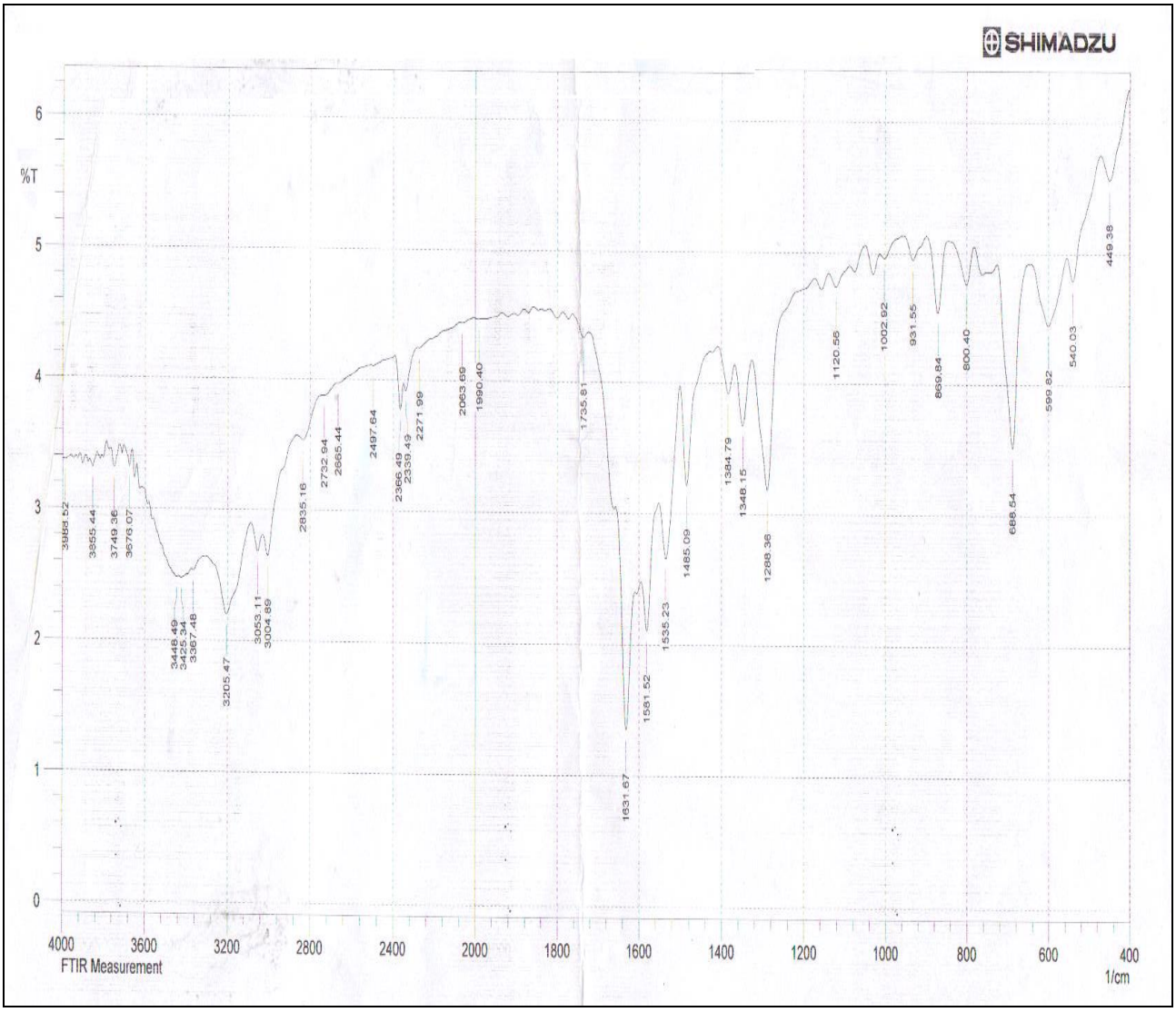


Fig.(11): IR spectrum of compound (I)

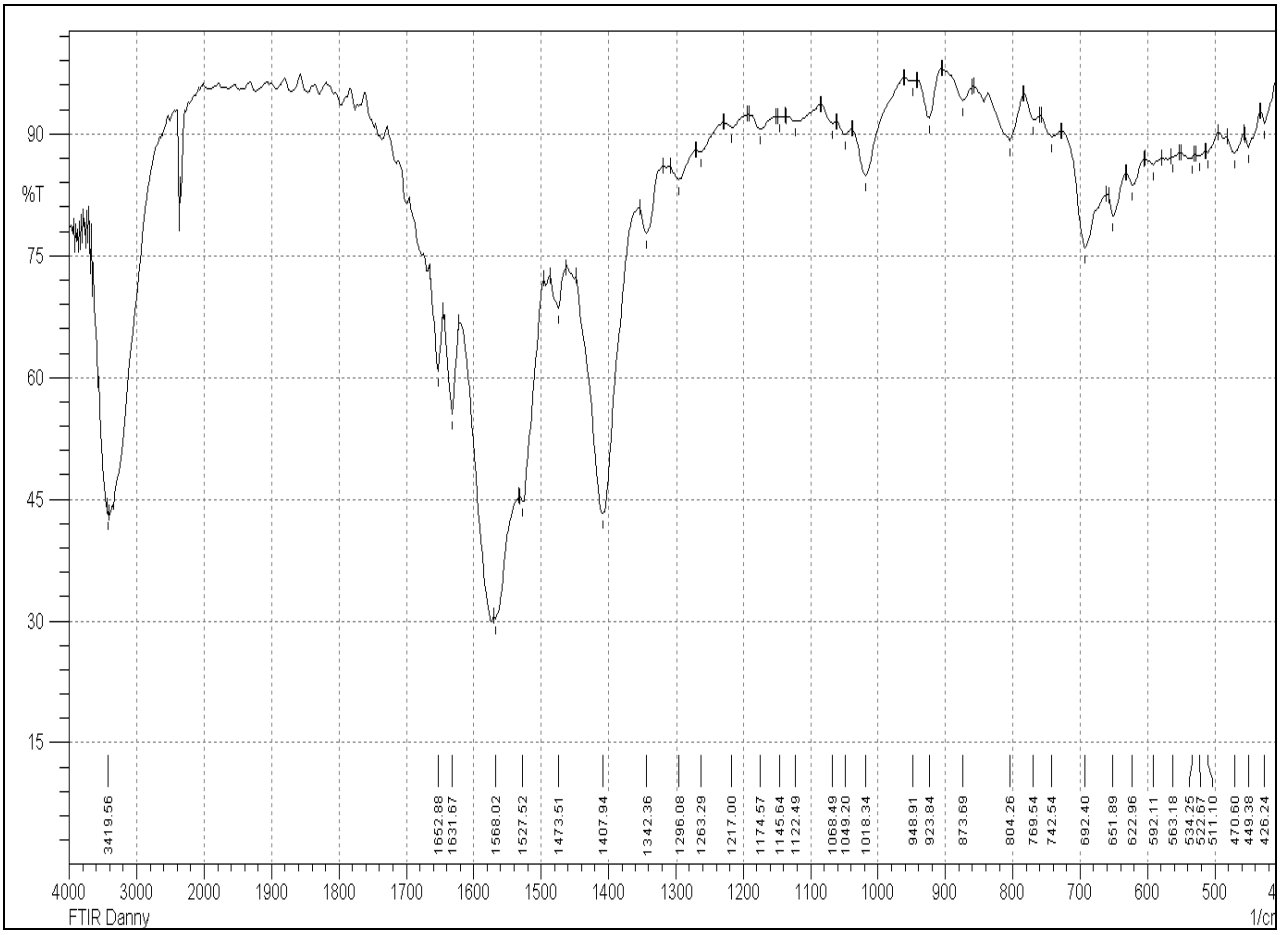


Fig.(12): IR spectrum of compound (IIb)

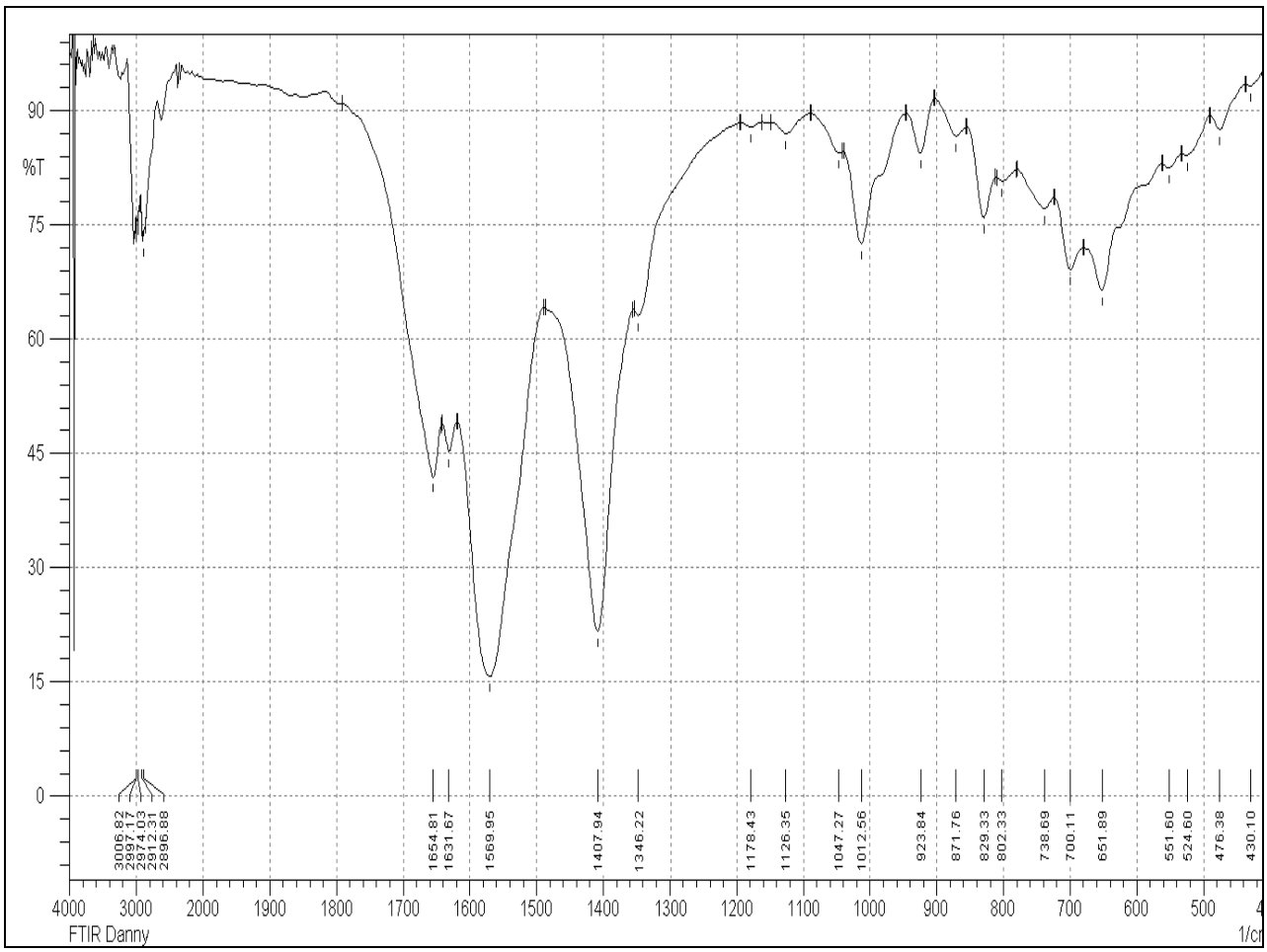


Fig.(13): IR spectrum of compound (IIe)

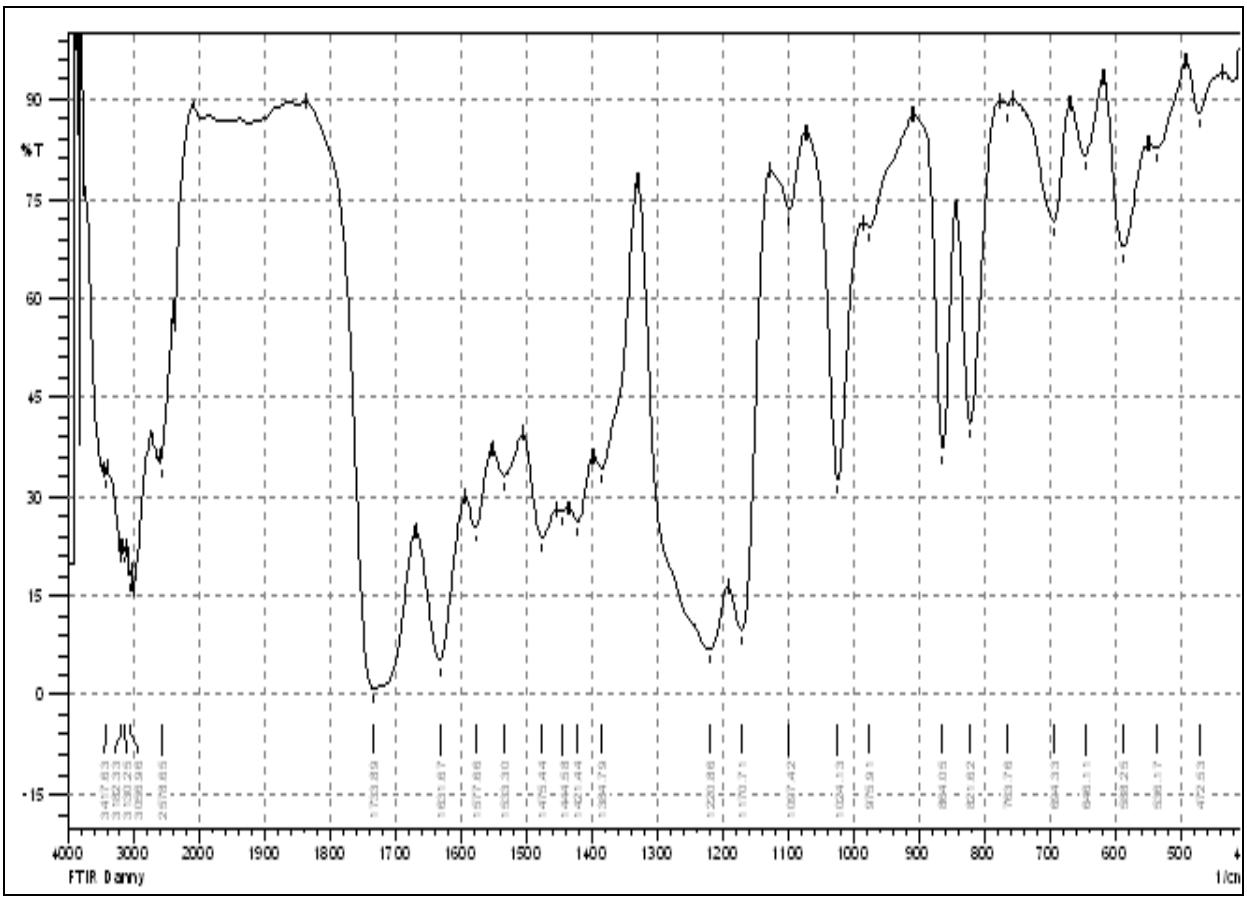


Fig.(14): IR spectrum of compound (IIIa)

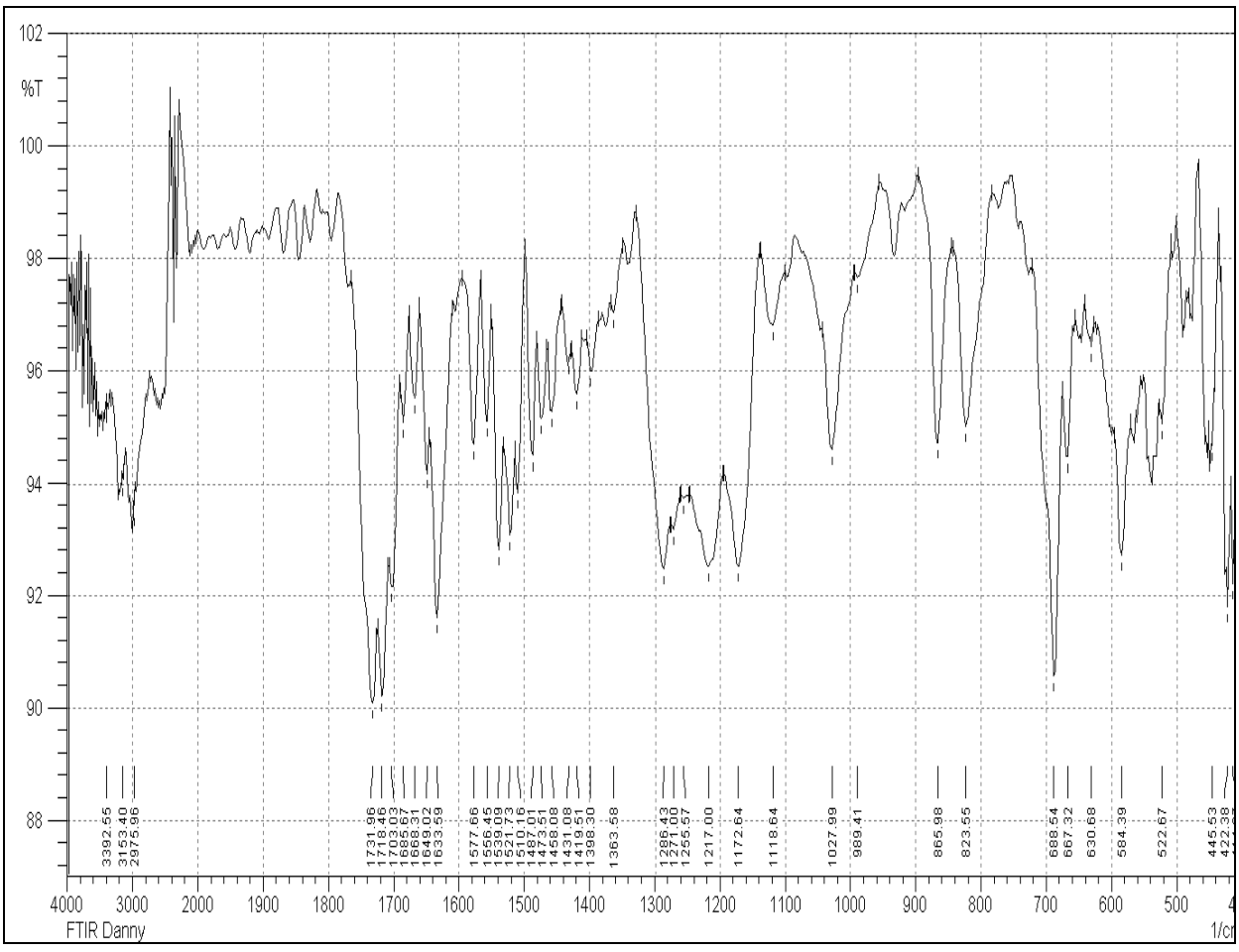


Fig.(15): IR spectrum of compound (IIIc)

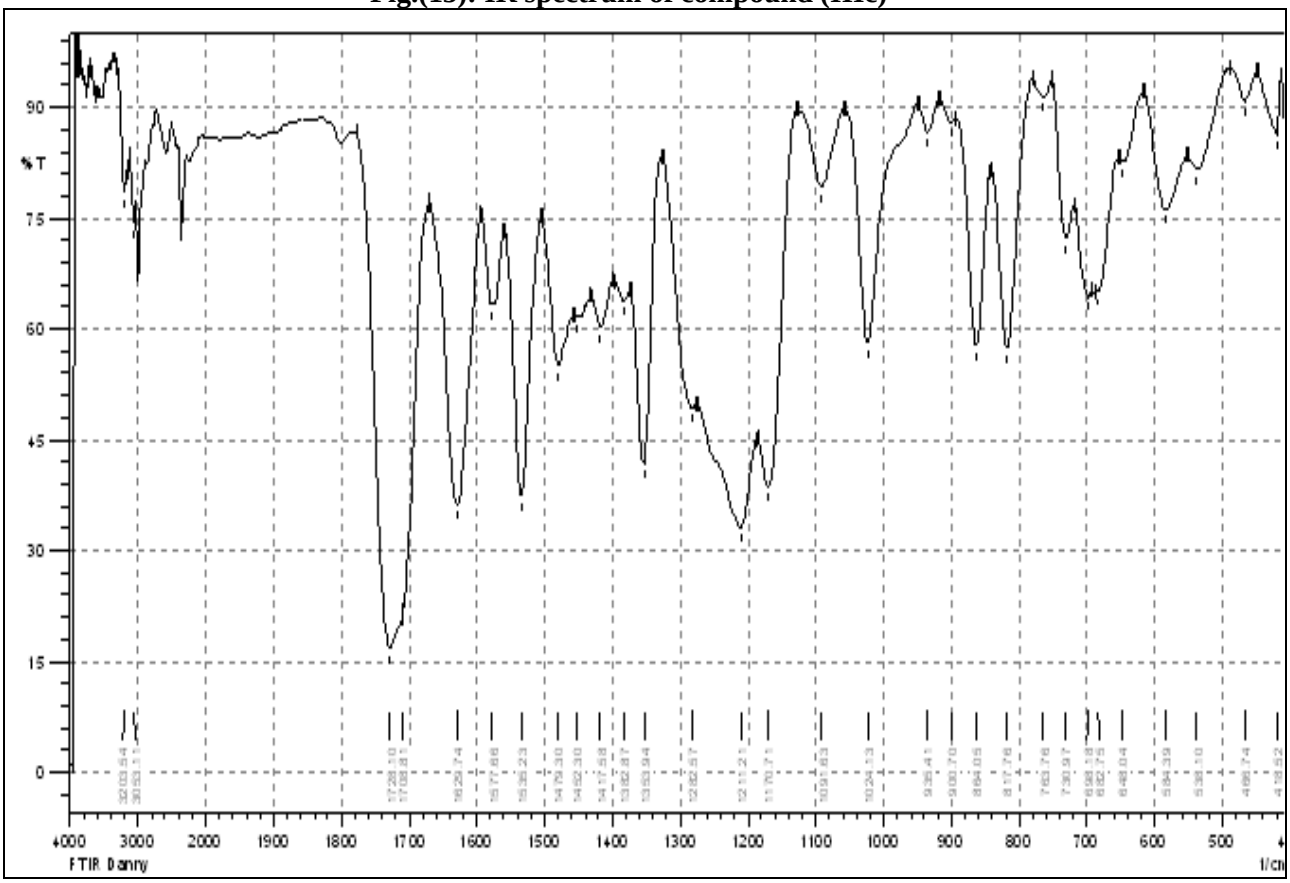


Fig.(16): IR spectrum of compound (IIId)

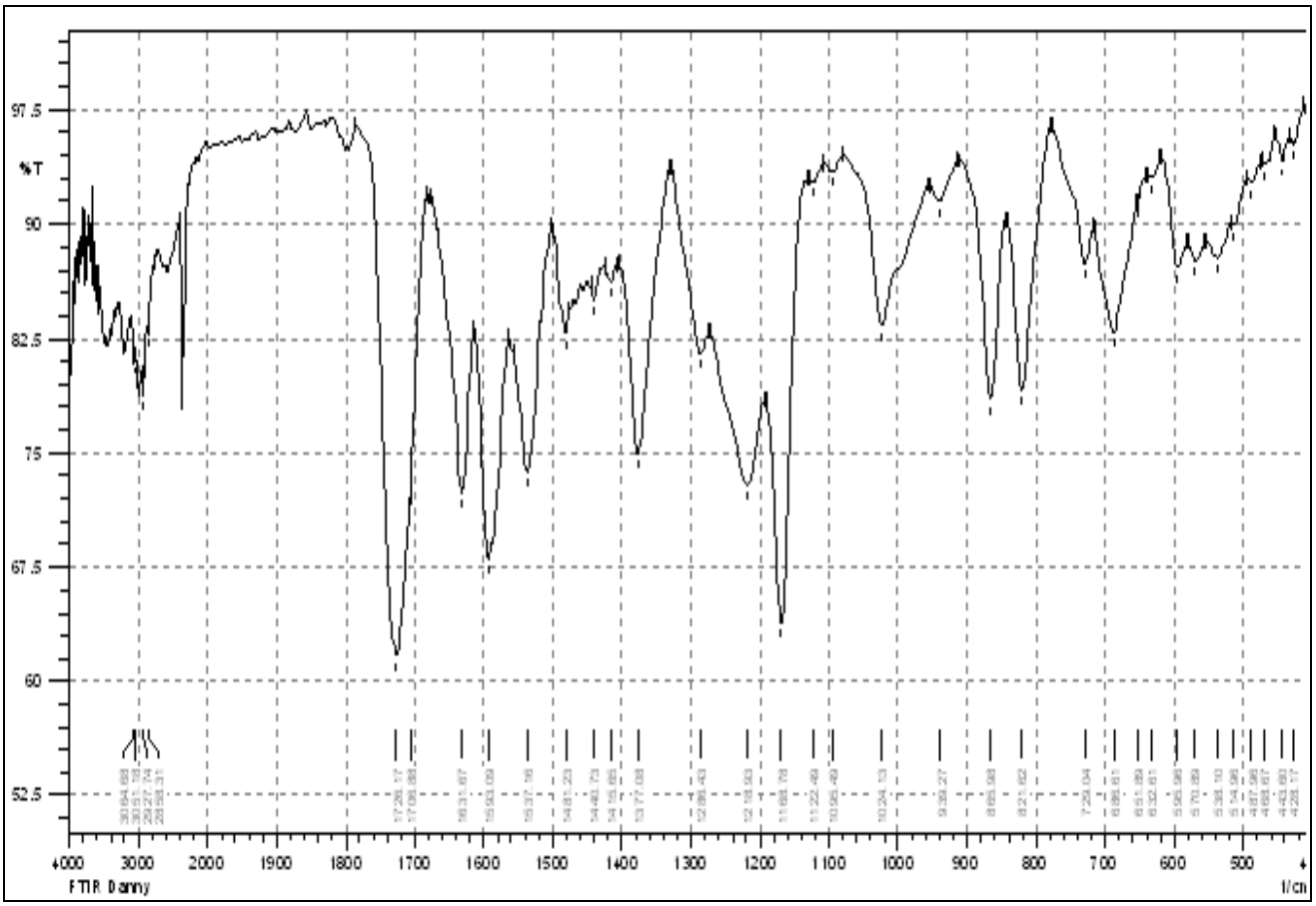


Fig.(17): IR spectrum of compound (IIIe)

Biological activity

The antimicrobial activity of the synthesized compounds(1),(IIa-e) and (IIIa-e) were examined by the agar diffusion method[20] using four different bacterial species *Escherichia coli*, *Staphylococcus aurous*, *Salmonella typhi* and *Pseudomonas aeruginosa.* In the Nutrient agar, prepared discs were distribute offer spread the bacteria on agar. These plates were incubated at 37 C^0 for 24 hr, the zone of inhibition of bacteria growth around the disc was observed and measured in mm and were represented by (+), (++),(+ -) and (-) depending upon the diameter and clarity , the results are given in Table (7). The results indicated that all the assayed compounds showed an week microbial activity against the tasted organisms up to 3.2 mg/disk. Among this group of organism *Staph aurous* and *E. coli* showed higher sensitivity to ward the mentioned compounds.

Table (7): Antibacterial activity of synthesized compounds(I ,IIa-e, IIIa-e)

Comp.No.	*Staph.aureus*	*E.coli*	*Sal. typhi*	*Ps. aeruginosa*
I	++	-	+	-
IIa	+	+	+-	-
IIb	+	++	-	+
IIc	++	++	-	-
IId	+	+	+	-
IIIe	++	++	-	+
IIIa	-	+	+-	-
IIIb	+	++	-	-
IIIc	-	-	-	+
IIId	+	+	+	-
IIIe	++	+	+	-

Notesno(-) = inhibition) , (+_) =6-9 mm , (+) =10 – 14 mm , (++) = 15-20 mm .

References

1- T. Hirohashi, T. Izumi and H. Yamamoto, ***Ger. Offen.***, 2, 014, 223 (Cl, C07d) (1970)

2- F. Okada, Y. Torii, H. Saito and N. Matsuki, ***Jpn. J. Pharmacol.*** 2, 64, 109 (1994).

3-R.A. Mueller, ***Ger. Offen,*** 2, 700, 091 (Cl. CO7D413/12)(1977).

4- R. C. Effland, G.C. Helsley and J. J. Tegeler, ***J. Heterocyclic. Chem.,*** 537(1982).

5- A. D. Cale, B. V. Franko and C. A. Leonard, ***Eur. Pat. Appl.,*** EP107, 930(Cl. CO7D267/14)(1984).

6- B. Basavaraju, H. S. B. Naik and M. C. Prabhakara, ***Bioinorg. Chem. Application*** , 1, doi:10.1155/42587(2007).

7- J. Himizu, A. Ishida and K. Yoshikawa, ***Japan J.,*** 72, 48,380(Cl. CO7cd, A61k)(1970).

8- K. Schenker, ***Swiss,*** 505, 850 (Cl. CO7d)(1968).

9- J. Nichimizu, A. Ishida, K. Yoshikawa and T. Tokada, ***Japan J.,*** 75, 06, 531 (Cl. CO7D, a61K)(1975).

10- D. R. Schridhar, C. R. Sarma R. R. Krishna, ***Indian J. Chem***., Sect. B. 17B , 2, 155(1979).

11- A. D. Cale and A. H. Robins, ***U.S. ,*** US 4,705, 853(Cl. 540-490; CO7D281/08)(1987).

12- Y. Kaneko, ***Jpn. Kokai Tokyo Koho,*** Jp 63 95, 442[88 95,442](Cl. GO3C7/38)(1988).

13- A. A. Mohammed , ***University of Sharjah Journal of pure and Applied Sciences,*** 3 , 3 , 25-45 (2006).

14- K. J. Ibtisam , A. O. Khalida and H. A. Gazwan, ***Tikrit Journal of Pure Scinces ,*** 13 , 2 , 230-7(2008).

15- I. A. Vogel, **"Tex Book of Practical Organic Chemistry"** 3rd Ed, Longman Group ltd. London 781, 395(1974).

16- A. Kh. Ahmed and A. O. M. Obaid, ***J. Edu. Sci.,*** 16,3(2004).

17- R. Huisgen, ***Angew Chem. Internat. Edit.***, 7, 321(1968).

18- B. Olcay , K. Bahittin and k. Murat, ***Turk J. Chem. ,*** 30, 29-40 (2006).

19- G.H. Collins, P.M. Lyne and J.M. Grange **"Microbiological Methods"** 6th Ed., Butter Worths (1989).

20- A. W. Bauer, W. A. M. Kirby, J. S. Sherris and M. Turk, ***Amer. J. Clin. Patho.***, 45, 493-96 (1966).

21- R. M. Silverstein and G. C. Basser **"Spectrometric Identification of Organic Compounds"** 2nd Ed. , John Wiley and Sonc Ltd. (1979).