Tikrit Journal of Pharmaceutical Sciences 2009 5(2):169-181

Synthesis, Characterization and Study the Biological Activity of new Derivatives of 1,3- Oxazepine Containing 1,2,4-Triazoloe ring

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Received 20/10 /2009 accepted 2 /11 /2009

Abstract
Compound [1] is prepared from Esterificition of 4-Nitro benzoic acid. It has been reacted with hydrazine to get compound [2]. 3,5-bis (4-Nitro phenyl)-4-amino -1,2,4-triazole [3] has been synthesized by melting of 4-Nitro benzoic acid hydrizide to cretin temperature. The new series of Schiff bases [4a-f] have been syntheised by reacting compound [3] with different benzaldehydes., These derivatives shows ring closer reaction with phathalic anhydride to obtain 1,3- Oxazepine derivatives [5a-f]. The syntheised compound were characterized by (IR,UV) spectra, melting points the above reaction were followed by TLC. The biological activities are studied against four different kinds of bacteria .

تحضير وتشخيص ودراسة الفعالية البايولوجية لبعض مشتقات 3,1- اوكسازبين الجديدة الحاوية على حلقة 4,2,1- ترايازول

فوزي حميد جمعة سلوى عبدالستار جبار ايمان ايوب ياس

المستخلص

حضر المركب [1] من خلال أسترة 4- نايترو حامض البنزويك ومن ثم تم مفاعلته مع الهايدرازين للحصول على مركب [2]. حضر مركب3,5-بس-(4-نايتروفنيل) 4-امينوترايازول [3] من خلال صهر مركب 4-نايتروهيدرازيد البنزويك [2] وقد تم تفاعله مع مشتقات مختلفة للبنزالديهايد لتحضير سلسلة جديدة من قواعد شيف [4a-f] والتي تم غلقها من خلال تفاعلها مع انهيدريد الفثاليك للحصول على مشتقات 3,1-اوكسازبين [5a-f]، شخصت المركبات المحضرة بطيف الأشعة تحت الحمراء IR والأشعة فوق البنفسجية UV ودرجات الانصهار كما تم متابعة التفاعلات بكروموتوغرافيا الطبقية الرقيقة TLC ودرست الفعالية البايولوجية لها ضد أربعه أنواع مختلفة من الجراثيم.

Introduction

The progress achieved in the synthesis of heterocyclic compounds coutaining biological effects cause to improvement the methodological study of tested substances too. It is known that many 1,2,4-triazol derivatives have biological activity, with their antibacterial[1-4], antimycobatenal[5,6], antimycotic[7], antifungal[8,9], antideressive[10] and cardiotnic[11] action being notable .Recent research has also established for these heterocyles an analgesic[12] and anti-inflammatory activity[13-15]. In our literature of the synthesis of 1,2,4-triazole derivatives as new precursor starting material in the synthesis of some important biological active heterocyles constitute an important class of organic compounds[16]. A considerable effort has been made in recent years to further development of the synthesis of the these nucleus[17]. These derivatives are very attractive heterocyclic systems due to their extensive use in medicine, agriculture and industry[18]. Many of 4-aryl amino -4H- 1,2,4-triazole derivatives were synthesized from the treatment of 4-amino -4H-1,2,4-triazole with selected aldehyde[19]. The six- member heterocyclic ring system, 1,2-Oxazine has already been reported and thoroughly reviewed in the literature[20-23]. Maleic, arylmaleic and substituted maleic anhydride react with trimethylsilyl azide to give 4- and 5-substituted "Oxauraciles": dihydron 1,3-Oxazine-2,6-diones[24,25]. The reaction of Schiff bases withe Maleic anhydride to give 1,3-oxazine -4,6-dione[26] was also investigated.

Experimental

Materials

Chemicals employed were of analytical grade and used without further purification, melting points were determined by using a "Electro thermal" melting point apparatus and are un-corrected. The IR spectrophotometer was used Perkin-Elmer FT-IR spectrophotometer, in the 4000-400cm^{-1} rang using (KBr, disk). Electronic spectra were recorded on Jusco V-530 UV-Visible spectrophotometer S.N B213260512 in ethanol as a solvent at room temperature.

1- Preparation methyl 4-Nitrobenzoate[27] [1].

A mixture of 4-Nitrobenzoic acid (0.1mol), excess of methanol and concentrated sulphuric acid (5ml) were refluxed for 6 hrs, with stirring. After that the solvent was distilled under vacuum, the product washed by sodium bicarbonate solution then with diethyl ether (40ml) M.P= 93-96 C^0 ,yield=70%

2- preparation of 4-Nitro benzoic acid hydrazide[27] [2]

Methyl 4-Nithrobenzoate (0.1mol) was dissolved in (40ml) absolute ethanol and hydrazine hydrate 98% (0.1mol) and refluxing a mixture for 6 hrs. cooling to room temperature. The precipitate was washed, recrystallized and dried from ethanol. (M.P)= 216-218 C^0, Yield 85%.

3-Preparation of 3,5-di(4-Nitrobenzene)-4-amino 1,2,4-triazol[28] [3].

Melting (1.5)gm of 4-Nitrobenzoic acid hydrazide [2] at 200-220 C^0 for 2 hrs. Cool the reaction and added (50ml) of water with reflux the mixture for 1 hr, filtered the hot solution and dried the yellow pricipitate, recrystallization from ethanol, (M.P)= 190-191 C^0, yield=80%.

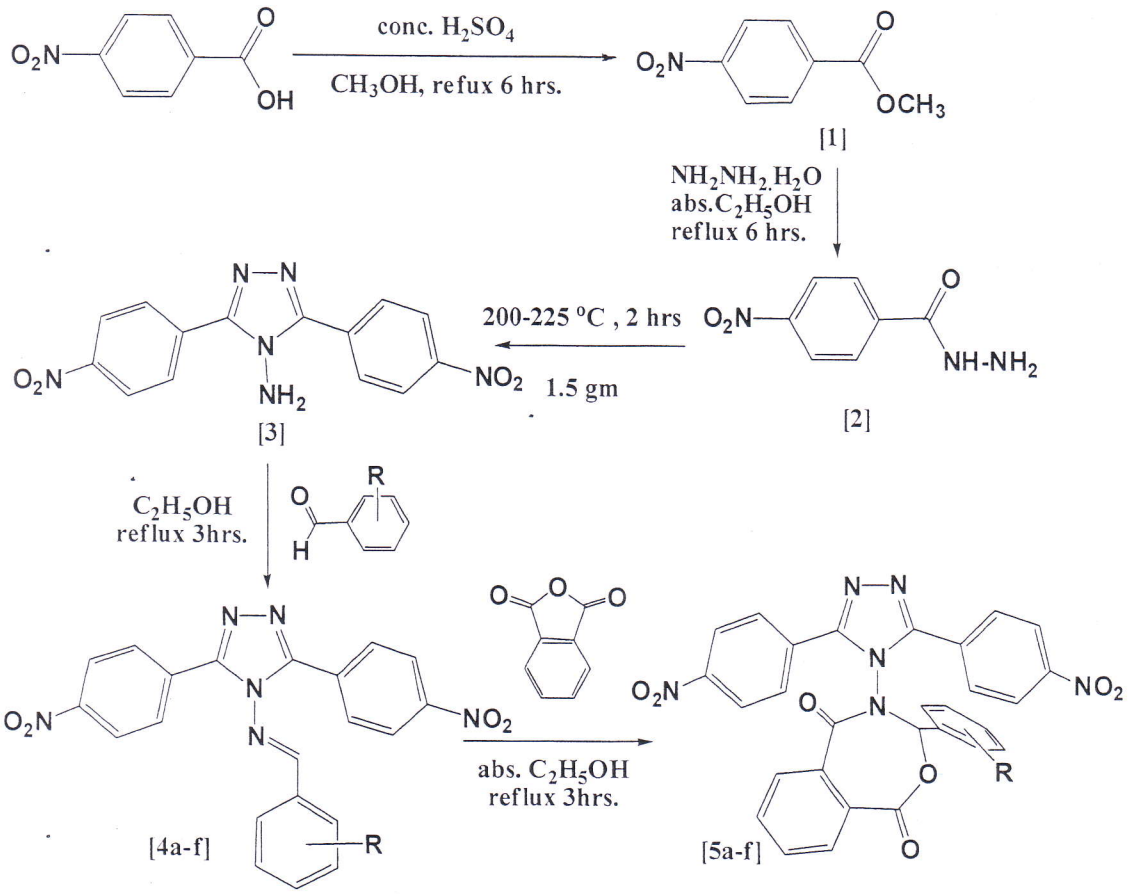
4- Preparation of 3,5-di-(4-Nitrobenzene -4-arylmethylenimino-4H-1,2,4 triazoles[19] [4a-f].

A mixture of compound [3] (0.01mol) and substituted benzaldehydes(0.01mol) in ethanol (25ml) was refluxed for 3 hrs. the precipitate was filtered and recrystallized from ethanol. Melting points, Yield% data are listed in Table (1).

5- Preparation of 1,3-Oxazepine -4,7-dione derivatives[29] [5a-f].

In a 100ml round bottom flask equipped with a double surface condenser fitted with calcium chloride tube, a mixture (0.01mol) of compounds [4a-f] and (0.01mol) of Phthalic anhydride in (20ml) of absolute ethanol was placed. The reaction mixture

was refluxed in water bath at 78 C^0 for 3 hrs. the solvent was then removed and the resulting solid was crystallized from 1,4-dioxane. Melting points, yield% data are listed in Table (2).



R= 4-$(CH_3)_2N$, 4-NO_2 , 4-OH , 2-OH , 3-CH_3O 4-OH , 3-NO_2

Scheme (1)

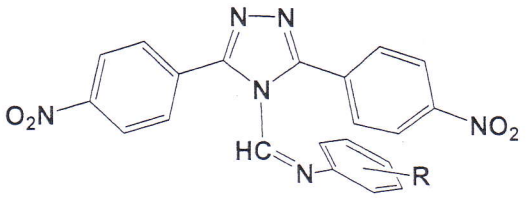


Table (1):Physical properties of 3,5-Bis (4-Nithrobenzene) -4-arylmethlenimino -4H 1,2,4- trizole [4a-f].

Comp No.	R	Molecular Formula	M.P C^0	Color	RF	Yield%	Solvent Crystalli.
4a	4-$(CH_3)_2N$	$C_{23}H_{19}N_7O_4$	69-70	Red brown	0.71	90	Ethanol
4b	4-NO_2	$C_{21}H_{13}N_7O_6$	105-106	Light brown	0.65	95	Ethanol
4c	4-OH	$C_{21}H_{14}N_6O_5$	104-105	Dark yellow	0.60	80	Ethanol
4d	2-OH	$C_{21}H_{14}N_6O_5$	116-118	Yellow	0.62	87	Ethanol

4e	3-CH_3O,4-OH	$C_{22}H_{16}N_6O_7$	120-122	Dark yellow	0.7	72	Ethanol
4f	3-NO_2	$C_{21}H_{13}N_7O_6$	150-152	Dark brown	0.74	62	Ethanol

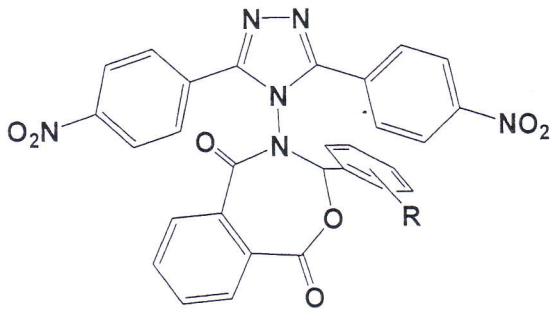


Table (2):- Physical properties of 1,3-Oxazepine-4,7- dione derivatives [5a-f]

Comp. No.	R	Molecular Formula	M.P C^0	Color	RF	Yield%	Solvent crystali.
5a	4-$(CH_3)_2N$	$C_{31}H_{23}N_7O_7$	194-196	Brown	0.8	65	Dioxane
5b	4-NO_2	$C_{29}H_{16}N_7O_9$	200Dec	Dusty	0.71	70	Dioxane
5c	4-OH	$C_{29}H_{17}N_6O_8$	285-286	Brown	0.67	61	Dioxane
5d	2-OH	$C_{29}H_{17}N_6O_8$	190-192	Brown	0.62	72	Dioxane
5e	3-CH_3O,4-OH	$C_{30}H_{19}N_6O_9$	194-194	Dusty	0.74	80	Dioxane
5f	3-NO_2	$C_{29}H_{27}N_7O_9$	192-194	Brown	0.68	67	Dioxane

Results and discussion

The compounds [1,2] were prepared according to method reported in the literature[27] while compound [3] was prepared by ting dry powder of compound [2] at high temperature, M.P (190-191 C^0). Brown, yield 70%. The IR spectrum of compound [3] Fig (1), exhibited significant of double bonds in the region (3346-3200)cm^{-1} which could be attributed to asymmetric and symmetric stretching vibration of NH_2 group besides this a band at about (1595)cm^{-1} due to C=N stretching is also observed and (1521)cm^{-1}, (1346)cm^{-1} could be attributed to asymmetric and symmetric stretching vibration of NO_2 group. The UV(nm) and IR spectra data are listed in Table (3). See fig (1,6). The Schiff base compounds [4a-f] were synthesized from the reaction of 3,5-di (4-Nitro-phenyl)-4-amino-1,2,4-triazole [3] with different substituted benzaldehydes. The synthesis of these compounds was carried out according to the steps outlined in schem (1), and the physical properties are given in Table (1). The reaction was followed by disappearance

of NH_2 absorption band at (3346)cm^{-1}, (3200)cm^{-1} and appearance of C=N absorption band in the IR spectra of the products, the UV and IR absorption bands are given in Table (4). See fig. (2,3,7,8). The reaction of Schiff base compounds [4a-f] with phthaleic anhydride in ethanol to give 1,3-Oxane -4,7-dione derivatives compounds [5a-f]. Cycloaddition is achieved by ring formation that results from the addition of π electrons either δ π bonds with formation of new δ bonds. The reaction actually in voiles interaction between the HOMO orbital of phthalic anhydride with LUMO orbital of (C=O) or (C=N), since the Oxygen has higher electro negativity than Nitrogen. Incidently, even in the absence of (C=N) no interaction between the HOMO orbital of phthalic anhydride and the LUMO orbital of (C=O) is observed for the same reason. It is obvious that the two absorption bands at (1740-1780)cm^{-1} and (1800-1850)cm^{-1} in the IR spectrum of pure phthalic anhydride has disappeared when the anhydride become Part of the 7-membered heterocyclic ring. The (C=O) group of the synthesized compounds exhibited significant double band absorption in IR spectra at (1668-1710)cm^{-1} (Oxazepine) and (C-O) at (1210-1280)cm^{-1}. This confirms the assigned 7-mempered heterocyclic ring structure. The UV and IR absorption are listed in Table (5). See fig (4,5,9,10)

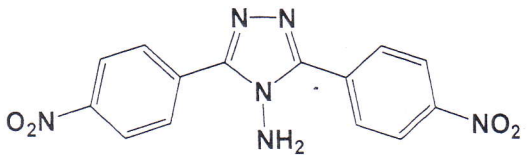


Table (3):- UV-Visible (nm) and IR absorption (cm^{-1}) of 3,5-di(4-Nitrobenzene)-4-amino-1,2,4-triazole [3]

Comp. No.	UV(nm) $\Lambda_1$max , $\lambda_2$max	υNH_2 As. s.	υCH Aro.	υC=N	υC=C Aro.	υC-N	υNO_2 As. s.
3	204,246	2346 3200	3020	1595	1595 1467	1106	1521 1346

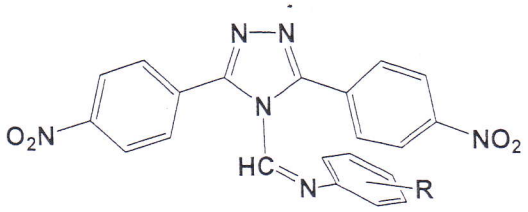


Table (4): UV-Visible (nm) and major IR absorption (cm^{-1}) of Schiff bases [4a-f]

Comp. No.	UV(nm) $\lambda_1$max , $\lambda_2$max	υC=N In /out ring	Others
4a	241, 338	1660/1664	υCH_3 as./s.2910/2815. 4-sub. 835 ,υC-N 1163
4b	263, 398	1650/1670	υNO_2 as./s. 1520/1348,4-sub. 840 σCH Ar. 954,780,750.
4c	221, 284	1660/1675	υOH 3201,σCHAr. 4-sub.825
4d	267, 396	1650/1662	υOH 3200, σCHAr. 2.sub. 642,740
4e	231, 305	1650/1660	νCOC as./s 1271/1108 υOH 3199, υCH_3 as./s. 2954/2854
4f	260, 397	1640/1654	υNO_2 as./s.1515/1348, 1,3-disub.740,730 σCHAr. 101, 821, 711

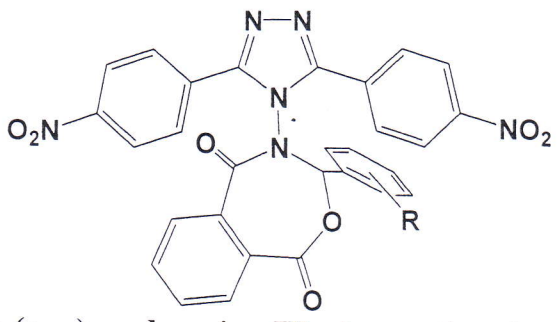


Table (5):-UV –Visibie (nm) and major IR absorption (cm^{-1}) of Oxazepine derivative [5a-f]

Comp. No.	UV (nm) $\lambda_1$max, $\lambda_2$max	υC=O	υC-O	Sub.	Other
5a	205,265	1710	1210	630,750	υCH_3 as-/s. 2921/2850
5b	220,300	1706	1216	640,740	υNO_2 as-/s. 1517/1340
5c	265,396	1668	1284	601,709	υOH 3199
5d	270,380	1680	1210	625,720	υOH 3210
5e	210,366	1668	1267	632,711	υOH 3197 υCOC as-/s. 1267/1157
5f	215,242	1710	1271	614,741	υNO_2 as-/s. 1550/1340

Biological activity

The antimicrobial activity of the synthesized compounds[3],(4a-f) and (5a-f) were examined by the agar diffusion method[30] using four different bacterial species *Escherichia Coli, Staphylococcus Aurous, Salmonella Typhi* and *Pseudomonas Aeruginosa.* In the sulfide media (Nutrient agar), suitable spaced apart holes were made (6mm in diameter), suitable spaced apart holes were filled with (0.1ml) of prepared compounds concentration that dissolve in ethanol beffer 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 hole was observed and measured in mm and were represented by (+),(++) and (-) depending upon the diameter and clarity , the results are given in Table (6). The results indicate that all the synthized compounds showed an microbial activity against the tested organisms up to 3.2 mg/disk. Among this group of organism *stap aurous* and *E. Coli* showed higher sensitivity to ward the mentioned compounds.

Table(6):- the antimicrobial activity of the tasted compounds

Comp. No.	*Staph. Aureus*	*E. Coli*	*Sal. typh*	*Ps. Aeruginosa*
3	++	±	+	-
4a	±	+	-	-
4b	+	++	±	-
4c	++	+	-	+
4d	++	±	-	-
4e	+ -	+	±	-
4f	++	±.	±	-
5a	+	±	+	-
5b	++	++	±	-
5c	±	+	-	+
5d	+	±	+	-
5e	±	±	-	-
5f	++	+	-	-

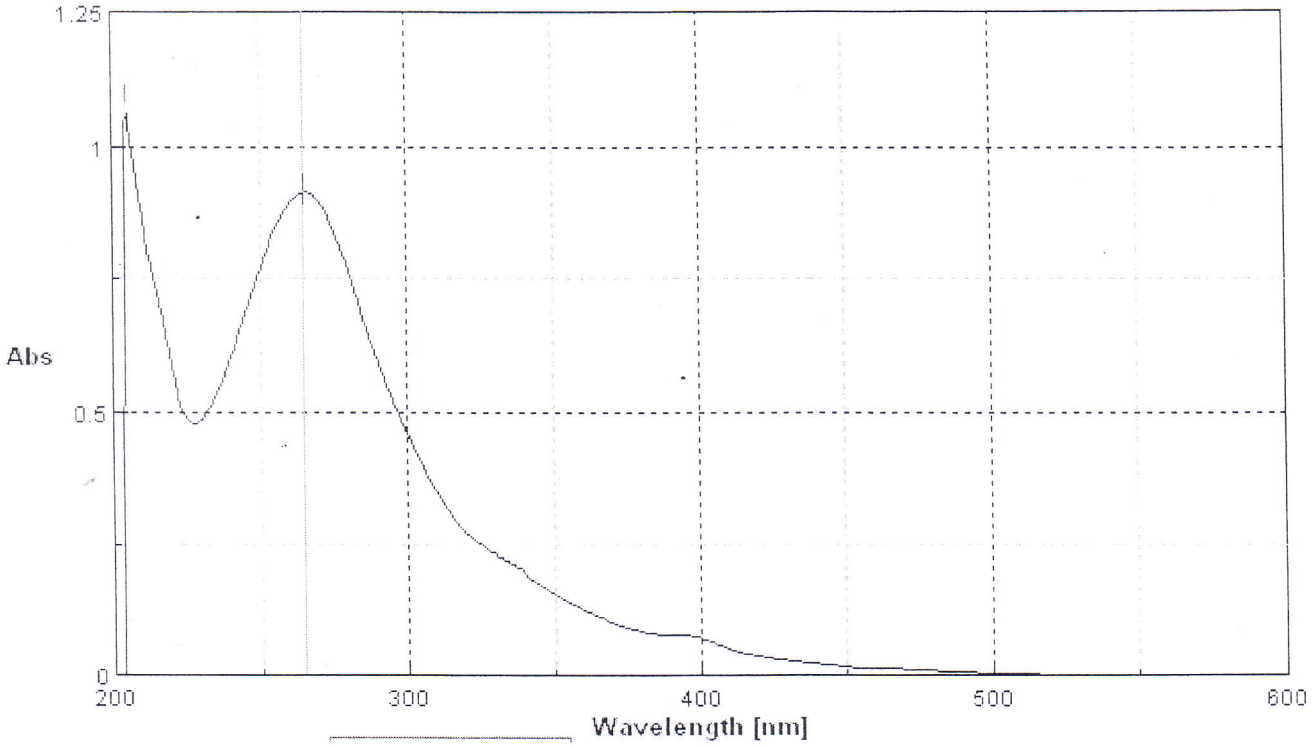


Fig.(1): UV spectrum of the compound [3]

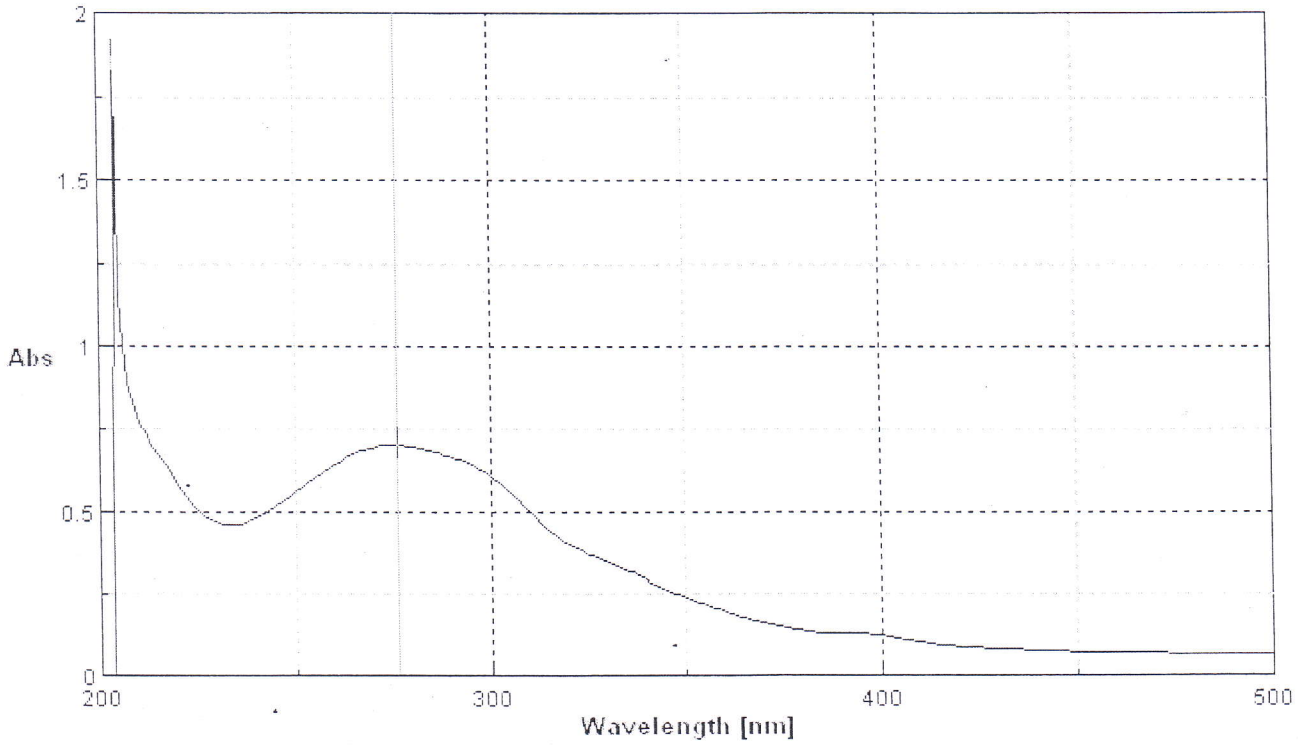


Fig.(2): UV spectrum of the compound [4b]

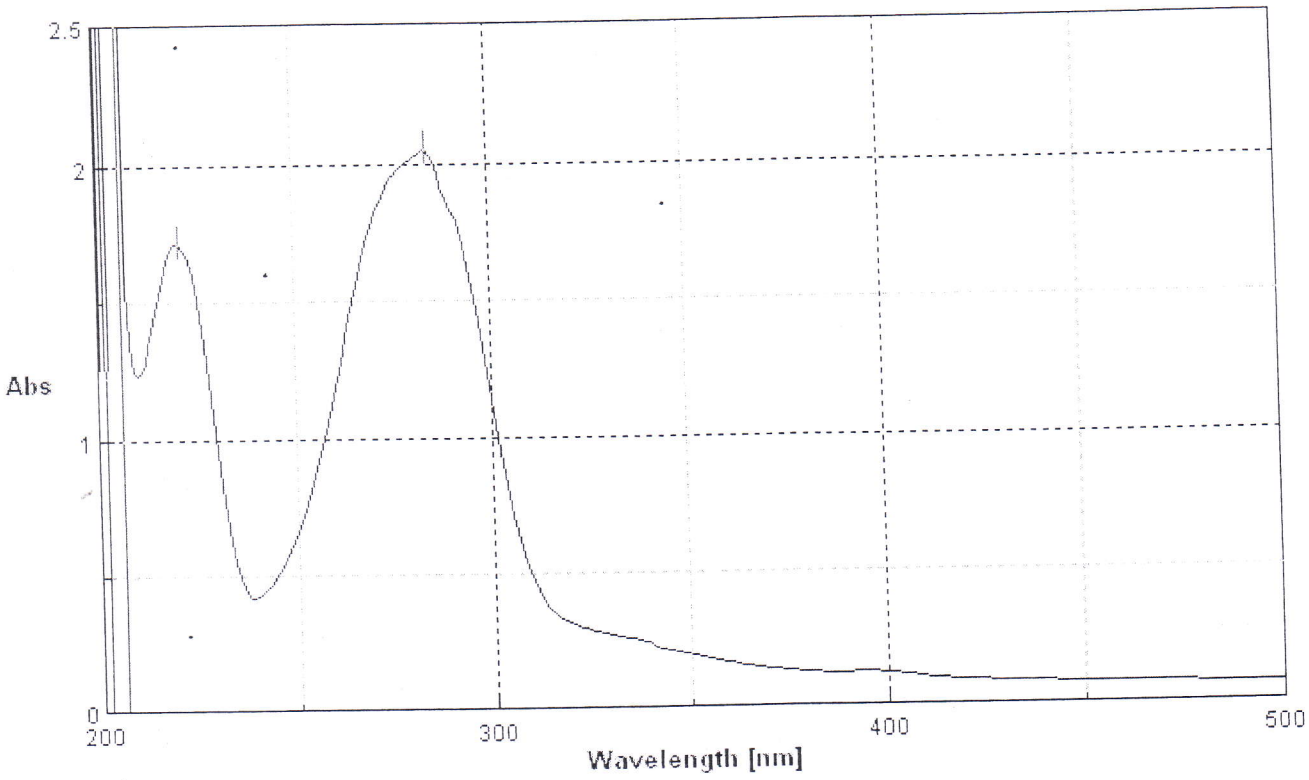


Fig.(3): UV spectrum of the compound [4c]

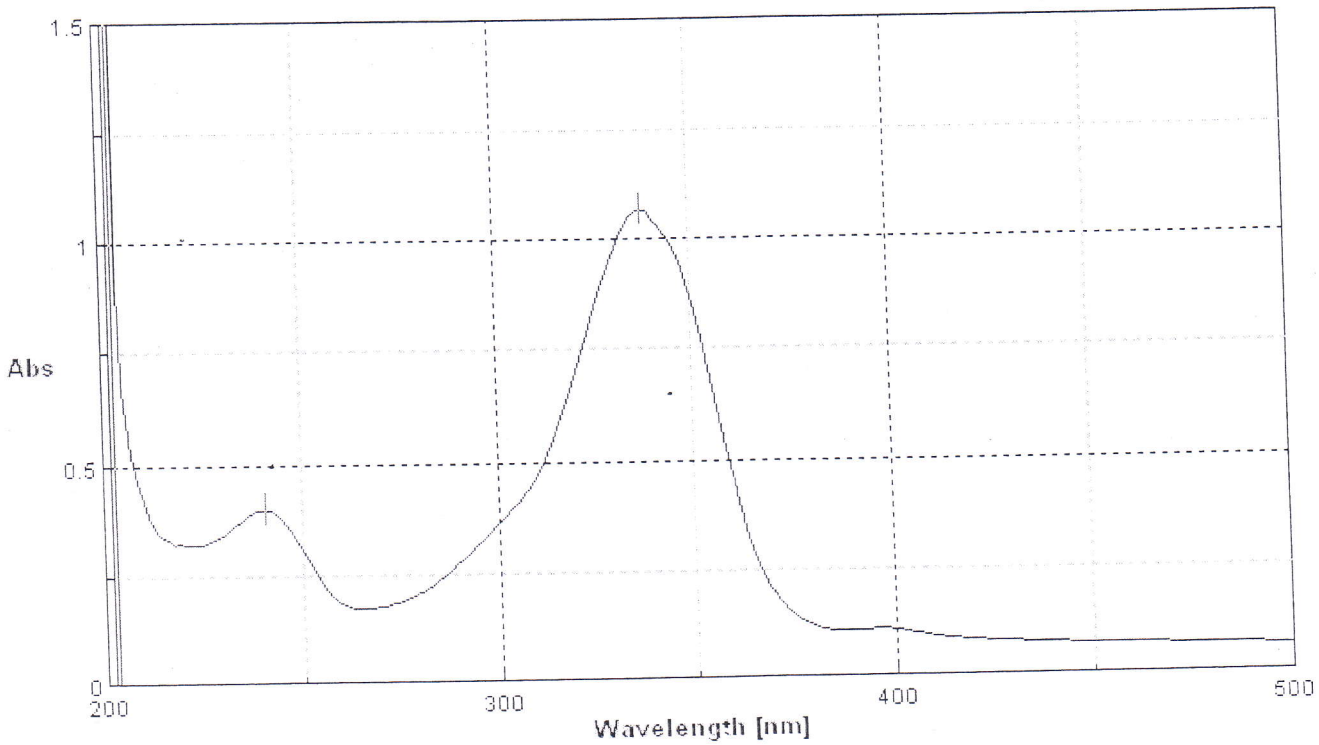


Fig.(4): UV spectrum of the compound [5b]

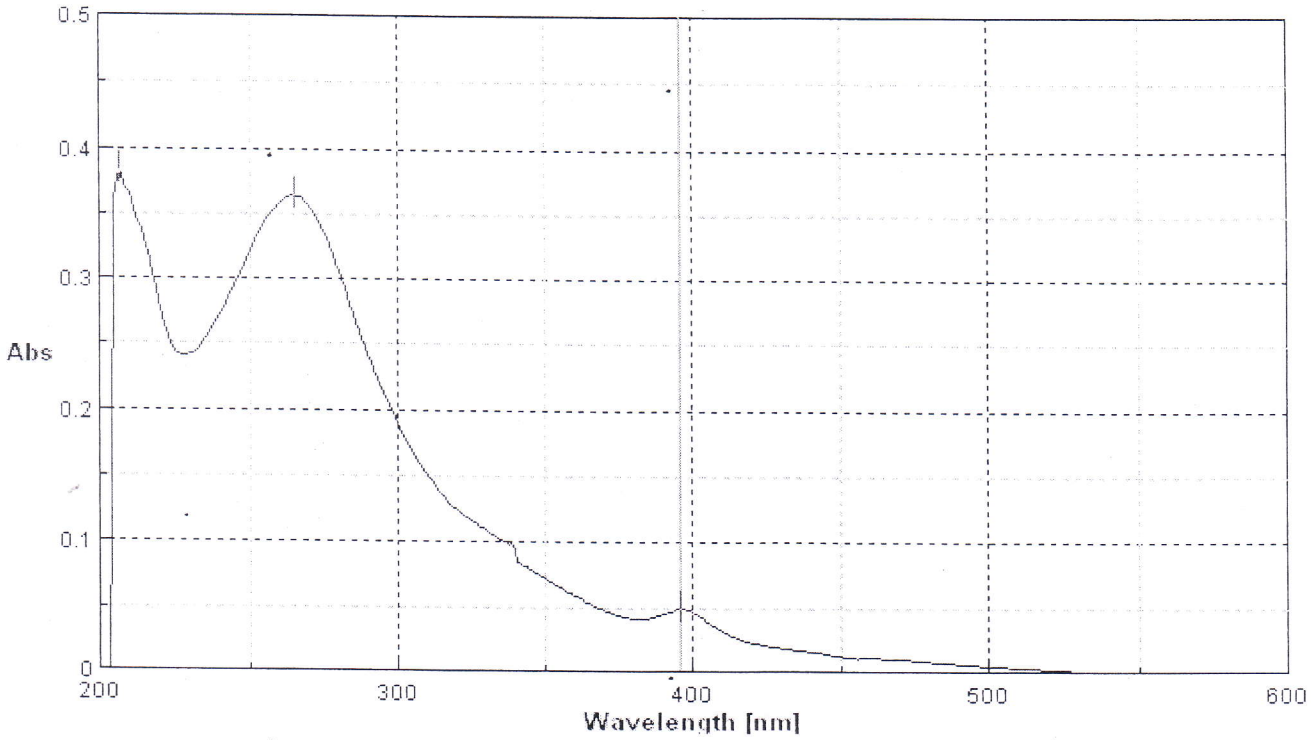


Fig.(5): UV spectrum of the compound [5f]

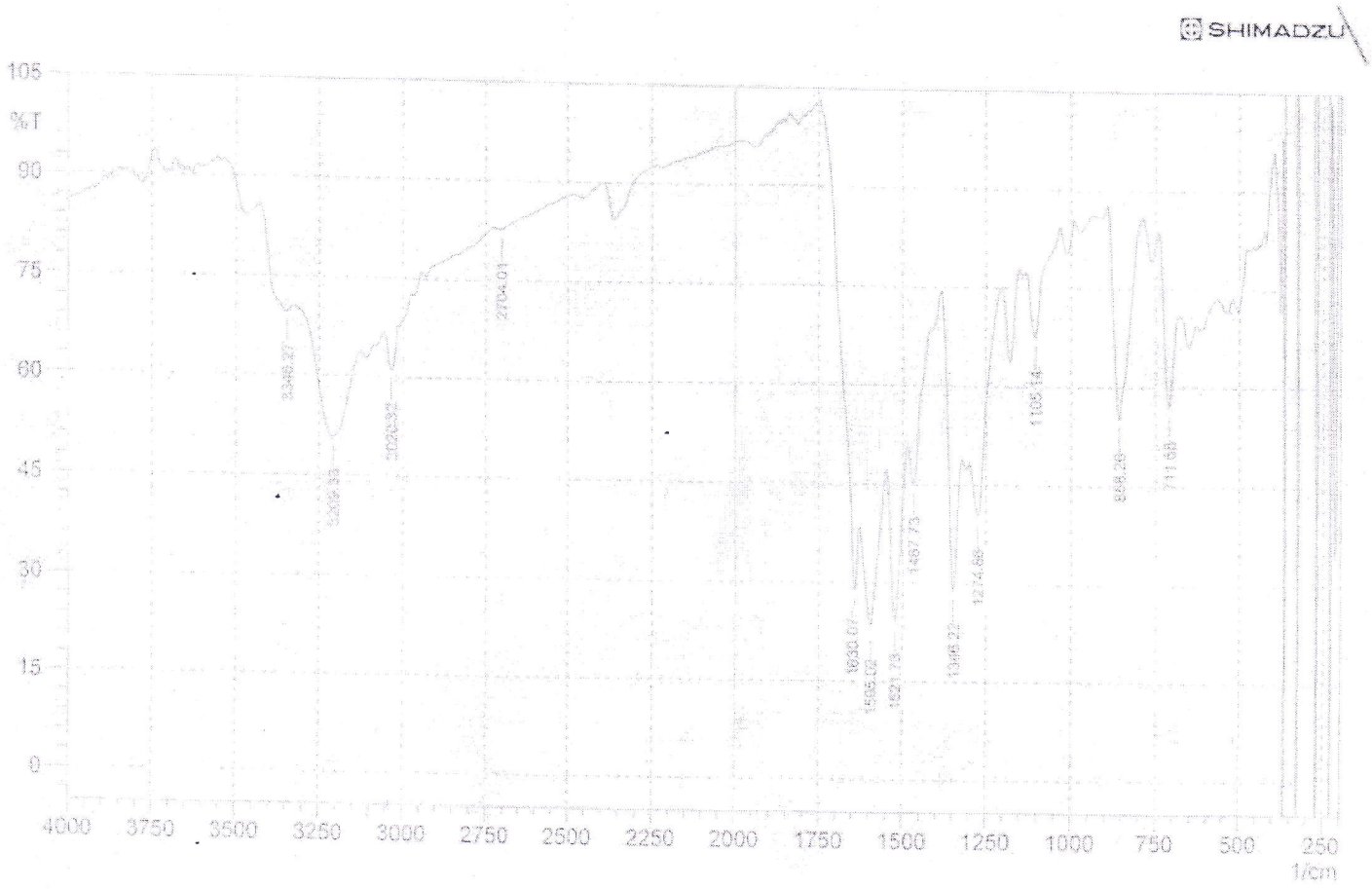


Fig.(6): IR spectrum of the compound (3)

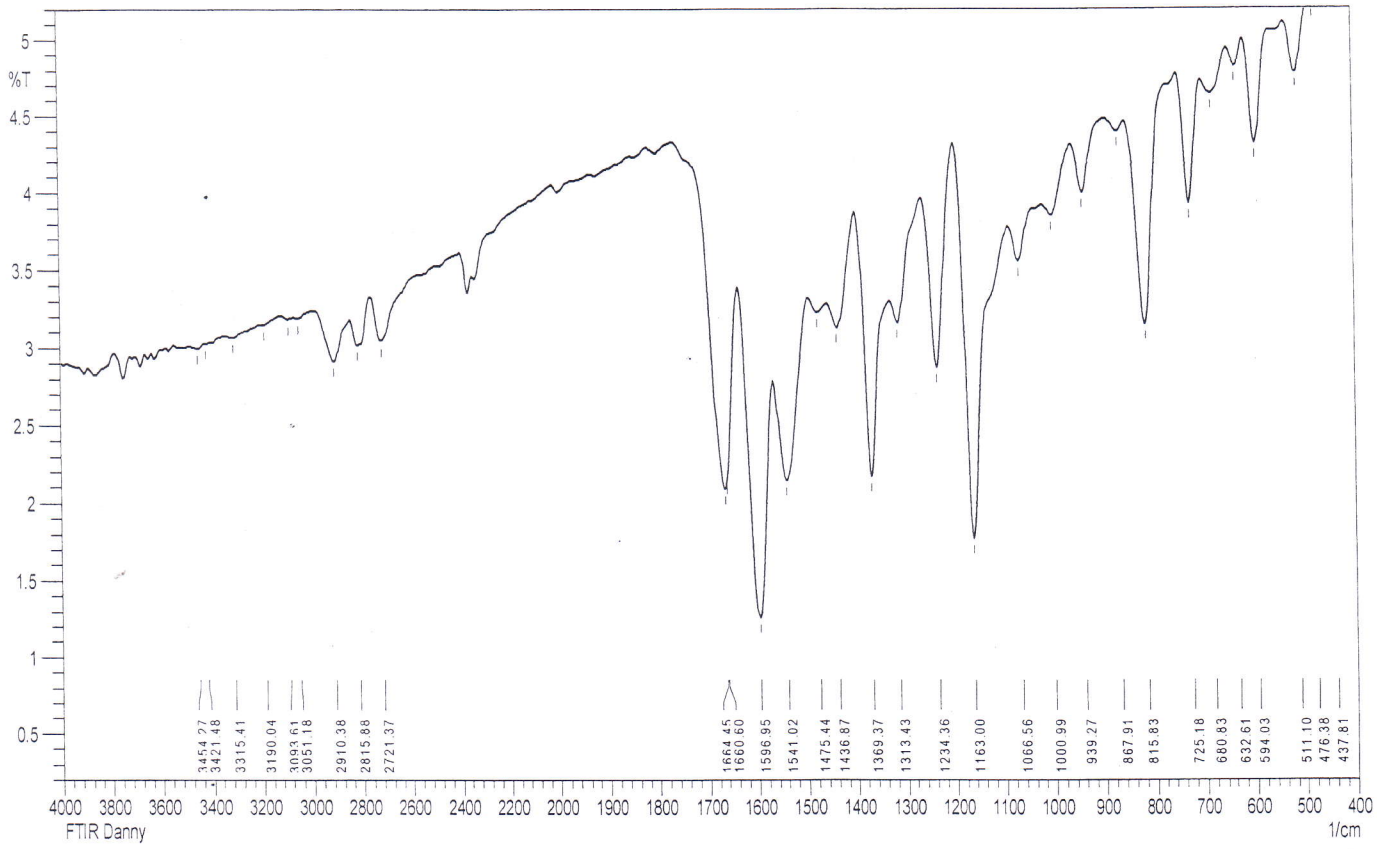


Fig.(7): IR spectrum of the compound [4a]

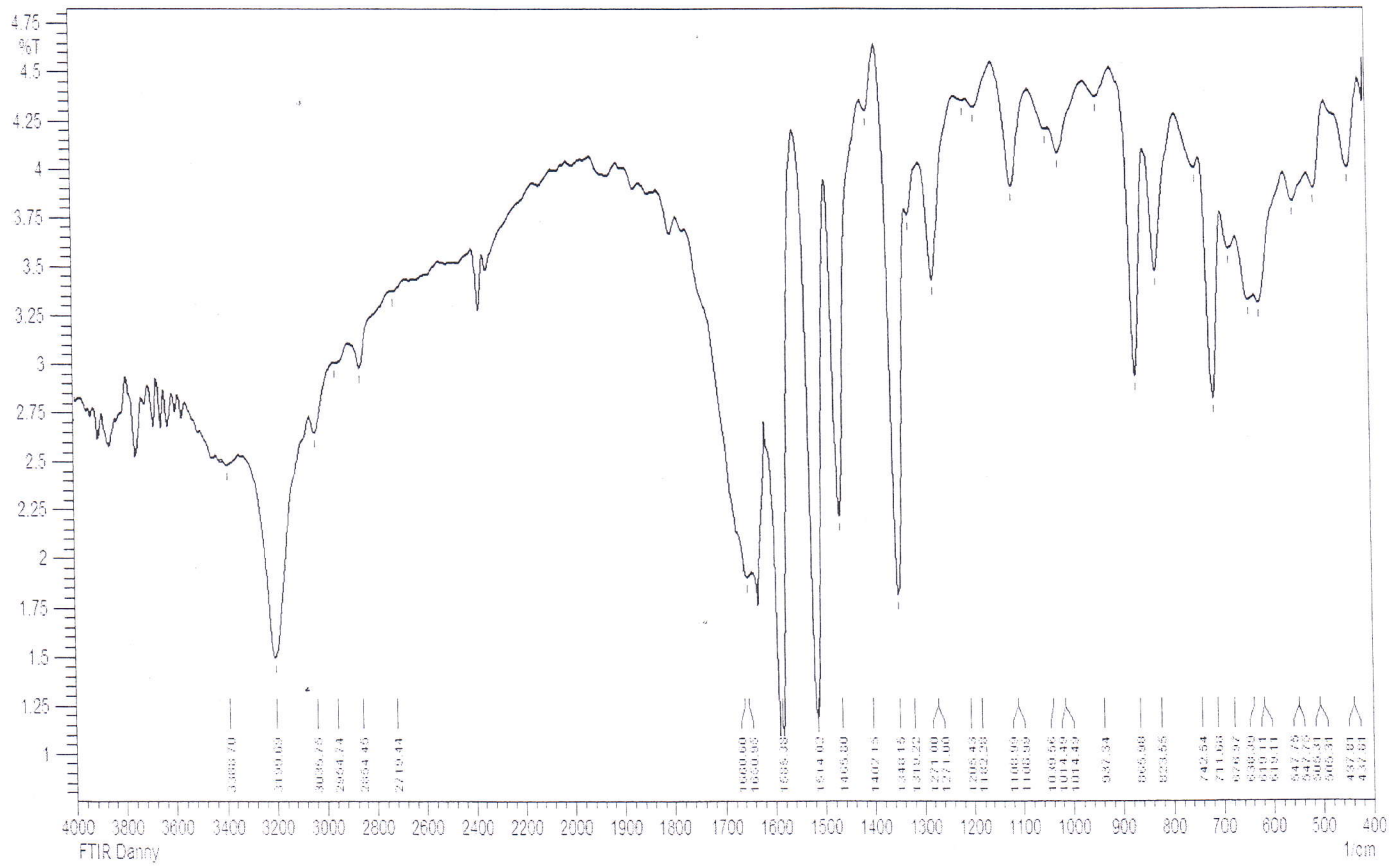


Fig.(8): IR spectrum of the compound [4e]

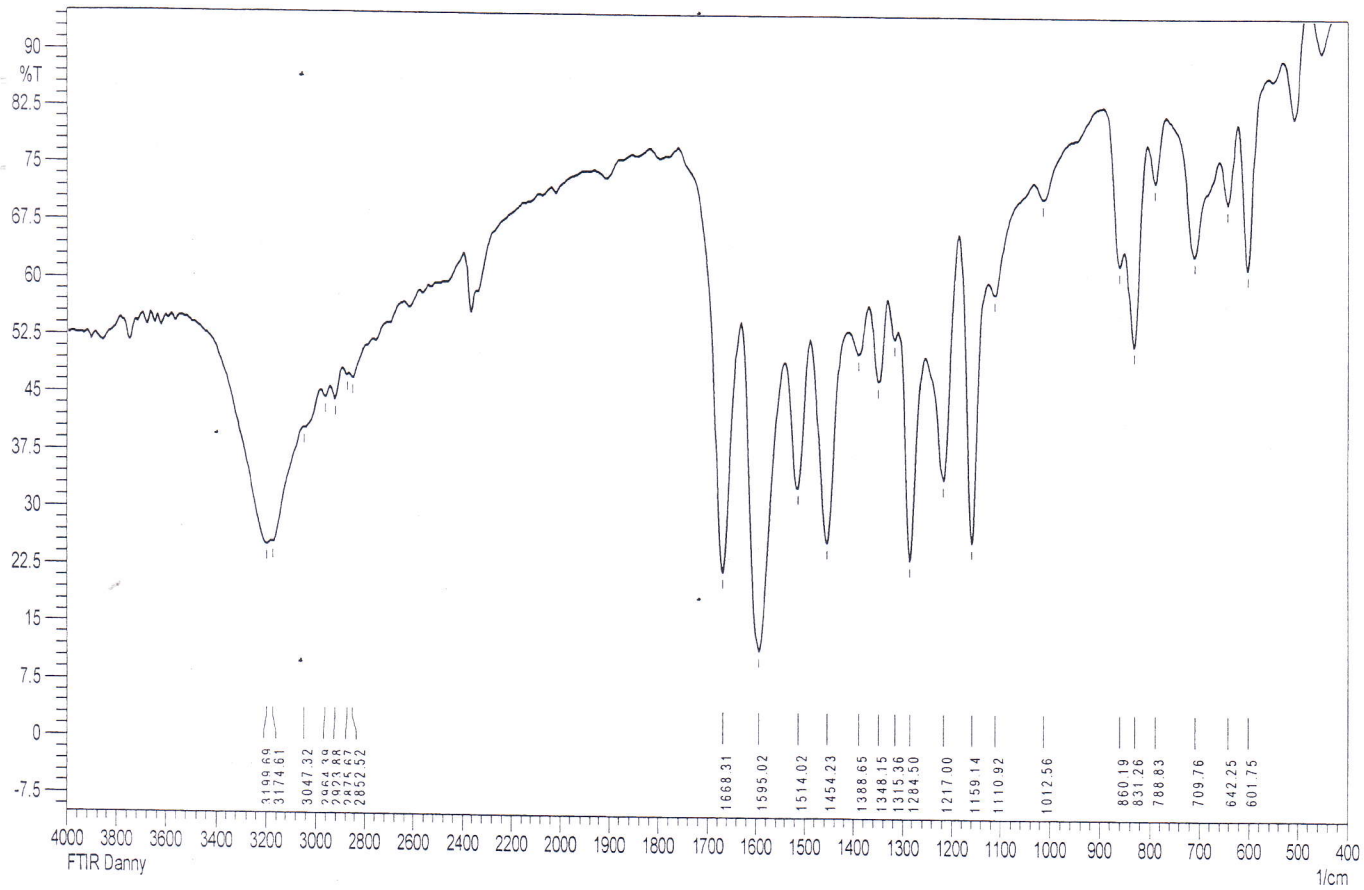


Fig.(9): IR spectrum of the compound[5c]

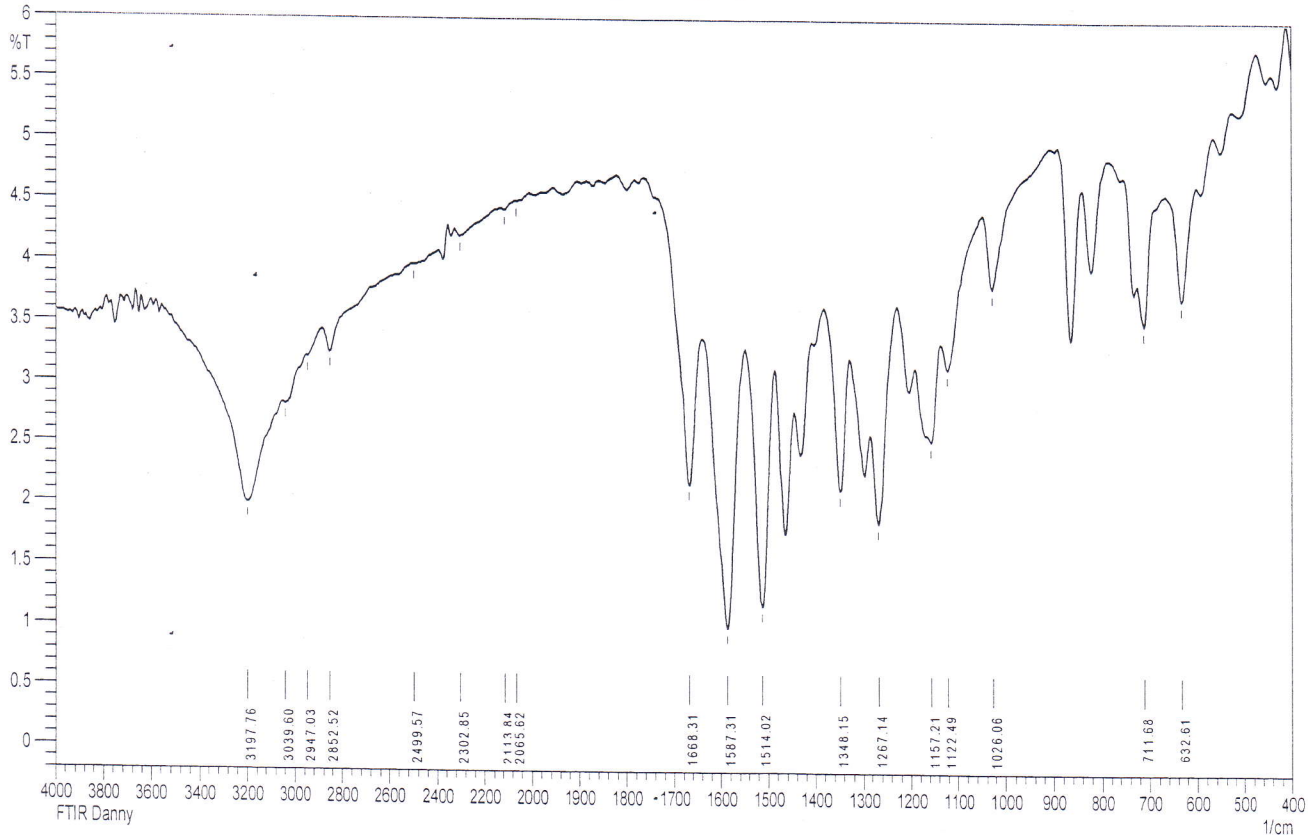


Fig.(10): IR spectrum of the compound [5e]

References

1- M. Gokce, B. Cakir, K. Earl and M. Sahin, ***Arch. Pharm***. (2001), 334, 279-83.

2- O.Pintilie, L. Profire, V. Soon, M. Popa and A. Pui, ***Molecules,*** (2007), 12, 103-13.

3- R.El-Sayed, ***Grasas Acteites***, (2006), 57,2,180-88.

4- A. Faroumadi, M. Mirzaei and A. Shafiee, ***Pharmazie*** (2001), 56, 610-12.

5- M.G. Mammals, V. Falagiani, D. Zanpier, L.Vio and F.Banfi, ***Farmaco*** (2001), 56, 587-92.

6- K. Zamani, K. Faghif, I. Tefighi and R. sharlatzadeh, ***Turk, J. Chem***.. (2004), 28, 95-01.

7- X. I. Zan, L. H. Lai, G. Y. jin and Z. X. Zhong, ***J. Agric. Food Chem***. (2002), 50, 3757-60.

8- H. Chem., Z. Li and Y. Han, ***J. Agric. Food Chem***. (2000), 48, 5312-15.

9- F. Clerici, D. Pocar, M. Guido, A. Loche, V. Perlini and M. Brufoni, ***J. Med. Chem.***. (2001), 44, 931-36.

10- T. Onkol, B. Cakir and M. F. Sahin, ***Turk. J. Chem.***. (2004), 28, 461-66.

11- S. Shenone, O. Bruno, A. Ranise, W. Bondavalli, G. Falcone, L. Giordano and M. Vitelli, ***Bioorg. Med. Chem***. (2001), 9, 2149-53.

12- L. Labanauskas, V. Kalcas, E. Uderenaite, P. Gaidelis A. Brukstus and V. Dauksas, ***Pharmazie*** (2001), 56, 617-19.

13- E. Palaska, G. Sahin, P. Kelincen, N. T. Durlu and G. Altionax, ***Farmaco*** (2002), 57, 101-07.

14- M. Mihaela, S. Valeria, P. Lenuta, P. Marcel, D. Jacques and P, Cristion, ***Molecules*** (2009), 14, 2621-31.

15- A. A. Taysser, A.D Manal and M. H. Hamdi, ***Molecules*** (2002), 7, 494-00.

16- M. A. Boshar, A. S. Ferwanah, a. M. Awadallah and N. M. El-halabi, ***Asian J. Chem***.. (2002), 14, 1235-40.

17- H. Xin-Ping, D. Heng-Shan, X. Peng-Fei, Z. Zhang, W. Qin and G. Yan-Ni, ***J. Chinese Chem. Sos***. (2000), 47, 1115-19.

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

19- A. I. Mayer "***Heterocyclic in Organic System***". John-Wiley and Sons, New York, (1974), P.P 201.

20- J. D. Waren, J. Macmillan, and S. S. Washburen, ***J. Org. Chem***.. (1975), 40, 6, 743.

21- J. C. Robert and Diketene, ***Chem.. Rev***. (1986), 1,2,241.

22- M. W. Steven and M. S. Paul, ***Chem.. Rev***. (1989), 89,7, 1525.

23- J. Macmillan and S. Washburen, ***J. Heterocyclic Chem***.. (1975), 1,6, 1215.

24- J. H. Macmillan, ***Int***. (1977), 9,2, 87.

25- O. H. Abid, ***National J. Chem***.. (2002), 7,1, 446-60.

26- I. A. Vogel, "***Tex Book of Practical Organic Chemistry***" (1974), 3ed, Longman Group ltd. London.

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

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

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