Synthesis of substitutead 1,3-Oxazepine and 1,3-Diazepine Via Schiff Bases for Selfamethoxazole drug

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Abstract

Some of aldehydeamino-N-5-methyl-3-oxazolylbenzensulfonamide (Schiff bases) were prepared by condensation of Selfamethoxazole Drug with many substituted aldehydes. These Schiff bases were found to react with maleic anhydride,to give 1,3-Oxazepine-1,3-dione derivatives were react with primary aromatic amines to give the corresponding 1,3-Diazepine-4,7-dione.

تحضير معوضات 1,3-أوكسازيبين و1,3- دايزيبين عن طريق قواعد شيف لدواء السلفاميثأوكسازول ودراسة فعاليتها البايولوجية.

ايمان أيوب ياس

الخلاصة

تم تحضير عدد من مشتقات الديهايدأمينو- ن-5- مثيل-3- أوكسازوليل بنزين سلفون أميد (قواعد شيف) بتكاثف دواء السلفاميثأوكسازول مع الألديهايدات المختلفة. فوعلت قواعد شيف مع إنهيدريد الماليك فأعطت مشتقات 1,3- أوكسازيبين وفوعلت المركبات الأخيرة مع أمين أروماتي أولي فأعطت 1,3- ثنائي آزيبين-4,7- دايون المقابل.

Introduction

Sulpha drug are also referred to as antibacterials. Sulfa drugs represent group of compounds discovered in a conscious search of antibiotics. The search on Sulfa drug with azo dye and testing with many germs lead to synthesizing and testing a number of substituted Sulfanilamide for antibacterial activity. Sulpfamethoxazole is commonly used in combination with Trimethoprim for antibacterial action[1].Sulfamethoxazole reacted with selected aldehyde and testing to give Schiff bases and its complexest improves biological activity[2]. Schiff bases react with Phthalic anhydride, Maleic anhydride and substituted phthalic anhydride to give 1,3-oxazepine-4,7-dione and test its biological activity [2-4]. oxazepine used in ASENDIN is an antidepressant of dibenzoxazepine[5]and dibenz(b,f)-1,4-oxazepine which are used as chemical weapons[5].The reaction of oxazepine with primary aromatic amine gives the corresponding 1,3-diazepine-4,7-dione(e,f).Many of the benzodiazepines and their oxides show interesting sedatives, muscie relaxant and anticonvulsant properties in animals[6,7].Since the discovery of the central nervous system,(CNS)activity of the 1,4benzodiazepines[8,9],have more importance.

Experimantale

Materials

Chemicals employed were of analytical grade and used without further purification, melting points were determined by using a "Covler" 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.

Preparation of Subtituted aldehydine amino-N-5-methyl-3-azoxazolyl benzene Sulfonamide[10] [Ia-f].

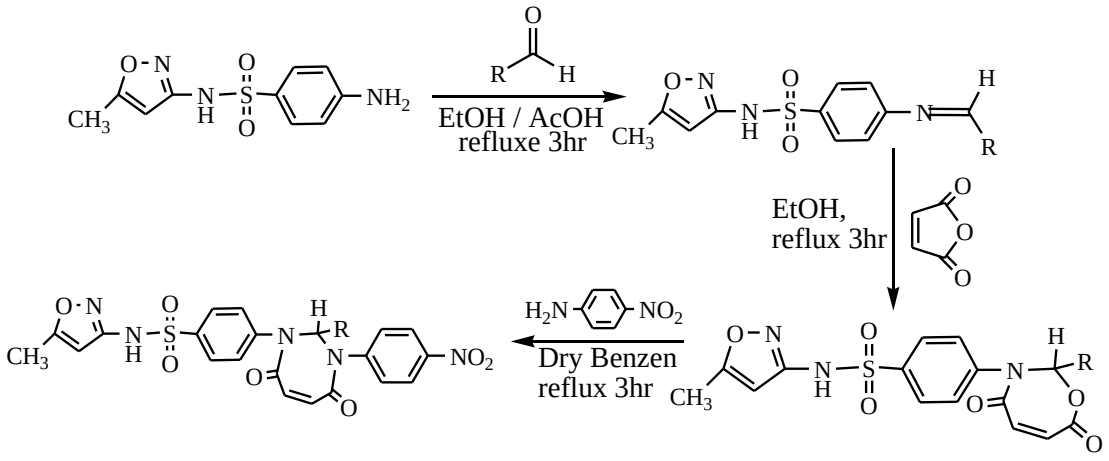
A mixture of sulfamethoxazole (0.0003mol) and substituted benzaldehydes(0.0003mol) in ethanol (25ml) was refluxed for 3 hrs. The precipitate was filtered and recrystallized from ethanol. Melting points, Yield% data are listed in Table (1).

2-5- Preparation of 1,3-Oxazepine -4,7-dione derivatives[11] [IIa-c].

A mixture (0.0001mol) of [Ia-f] compounds and (0.0001mol) of maleic 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).

2-5- Preparation of 1,3-Diazepine -4,7-dione derivatives[12] [IIIa-f].

A mixture (0.0001mol) of oxazepin compounds and (0.0001mol) of p-nitroaniline in (30ml) of dry benzen was placed. The reaction mixture was refluxed in water bath at 78 C^0 for 3 hrs then allowed to cool to room tempreture.and separated crystalline was filterd and re-crystallized from Ethanol. Melting points, yield% data are listed in Table (3).



R=HCOH ; -CH=CH-CH_3 ; Ph ; -Ph-Br ; 4-$(CH_3)_2$-Ph ; -H

Schem(1)

Table (1): Physical properties of Subtituted aldehydine amino-N-5-methyl-3-azoxazolyl benzene Sulphonamide [Ia-f].

Comp. No.	R	Molecular Formula	M.P C^0	Color	Yield%	Solvent Crystalli.
Ia	-H	$C_{11}H_{11}N_3O_3S$	118	White	95	Ethanol
Ib	-CH=CH-CH_3	$C_{14}H_{15}N_3O_3S$	$105_{dec.}$	Brown	90	Ethanol
Ic	-Ph	$C_{17}H_{14}N_3O_3S$	170-172	White	72	Ethanol
Id	-Ph-2-OH	$C_{17}H_{15}N_3O_4SBr$	198-199	Yellow	79	Ethanol
Ie	-Ph-2-Br	$C_{17}H_{14}N_3O_3S$	Oil	Brown-red	78	Ethanol
If	-Ph-4-$N(CH_3)_2$	$C_{19}H_{20}N_4O_3S$	85	Yellow-green	88	Ethanol

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

Comp. No.	R	Molecular Formula	MP. C^0	Color	Yield%	Solvent Crystalli.
IIa	-H	$C_{15}H_{12}N_3O_5S$	150	Pink-White	79	Dioxan
IIb	-CH=CH-CH_3	$C_{18}H_{16}N_3O_6S$	115	DarkBrown	80	Dioxan
IIc	-Ph-2-OH	$C_{21}H_{16}N_3O_7S$	193	Orang	65	Dioxan

Table (3): Physical properties of Subtituted 1,3-Diazepine -4,7-dione derivatives [IIIa-f].

Comp. No.	R	Molecular Formula	M.P C^0	Color	Yield%	Solvent Crystalli.
IIIa	-H	$C_{21}H_{17}N_5O_7S$	137	Yellow	48	Ethanol
IIIb	-CH=CH-CH_3	$C_{24}H_{21}N_5O_7S$	122	Brown	30	Ethanol
IIIc	-Ph	$C_{27}H_{20}N_5O_7S$	$208_{dec.}$	Yellow-White	21	Ethanol
IIId	-Ph-2-OH	$C_{27}H_{21}N_4O_8S$	139-140	Yellow	20	Ethanol
IIIe	-Ph-2-Br	$C_{27}H_{20}N_5O_7SBr$	140	DirtyWhie	80	Ethanol
IIIf	-Ph-4-$N(CH_3)_2$	$C_{29}H_{26}N_6O_7S$	130	Broun-Red	16	Ethanol

Results and Discussion

The Schiff base compounds [Ia-f] were synthesized from the reaction of selfamethoxazole with different substituted aldehydes. 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 IR absorption bands are given in Table (4). See fig (11).

The reaction of Schiff base compounds [Ia-f] with maleic anhydride in ethanol to give 1,3-Oxazepine -4,7-dione derivatives compounds . 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 maleic 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 maleic anhydride and the LUMO orbital of (C=O) is observed for the same reason.

It is obvious that the two absorption bands at (1691-1710) cm^{-1} and (1800-1850) cm^{-1} in the IR spectrum of pure maleic 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 (1668-1720) cm^{-1} (Oxazepine) and (C-O) at (1280-1286) cm^{-1}. This confirms the assigned 7-mempered heterocyclic ring structure. The IR absorption are listed in Table (5). See fig (12).

The structure of oxazepine subestituted is a combination of both lactone and lactam in a 7-membered heterocyclic ring. This is indicated by the appearance of the characterastic (C-N lactone/ C-N lactam) absorption band at (1172-1182) cm^{-1} in their IR spectra. The lactone group (cyclic ester) can be converted into lactam group (cyclic amide) by reaction with aromatic primary amines. This permits conversion of [1,3]-oxazepine-4,7-dione ring into [1,3]-diazepine-4,7-dione ring via tetrahedral mechanism[(14)].

The IR absorption are listed in Table (5). See fig (13). The UV. spectra gave absorption band at different wave lengths for the resulted Schiff bases, oxazepine and diazepine (in %95 EtOH), due to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition and all these transition are listed in Table(4,5,6). See fig (5,6,7,8,9,10).

Table(4):FT-IR and UV./Vis. spectral data for compounds [Ia-b].

Comp. No.	UV(nm) $\lambda_1$max , $\lambda_2$max	νC=N In/Out ring	Others
Ia	268	1600\1650	-C-H $_{Olef.}$ 2981
Ib	280	1610\1660	-CH=CH $_{Olef.}$ 2972
Ic	272	1623\1660	
Id	274	1616\1645	-OH 3442
Ie	268	1600\1640	-Br 550
If	340	1602\1658	Tri amine 3286

Table(5):FT-IR and UV./Vis. spectral data for compounds[IIa-c].

Comp. No.	UV(nm) $\lambda_1$max , $\lambda_2$max	νC=O	νC-H Olef,	ν O=C-O and C-O
IIa	274	1695	3000	1163\1280
IIb	228,376	1704	3030	1164\1286
IIc	268	1710	3082	1161\1338

Table(6):FT-IR and UV./Vis. spectral data for compounds[IIIa-b].

Comp. No.	UV(nm) $\lambda_1$max , $\lambda_2$max	νC-N	ν 4-NO_2 as.\s.
IIIa	228,376	1181	1506\1326
IIIb	272	1180	1500\1326
IIIc	374	1172	1500\1320
IIId	228,374	1182	1475\1301
IIIe	228,374	1180	1475\1299
IIIf	228,376	1180	1465\1328

Biological Activity

The antimicrobial activity of the synthesized compounds (Ia-f),(IIa-c) and (IIIa-f) were examined by the agar diffusion method[15] using two different bacterial species , *Staphylococcus Aurous*, *Klebsiella pneumoniae*. (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: water 50:50 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 of diameter and clarity , the results are given in Table (7).

The results indicate that all the synthized compounds showed a microbial activity against the tested organisms up to 3.2 mg/disk. Among this group of organism *stap. aurous* and showed higher sensitivity toward the mentioned compounds see fig(1,2,3,4).

Table(6): the antimicrobial activity of the tasted compounds after 24 hrs.

Comp. No.	*Staph. Aureus*	*Kleps. pneumoniae*	Comp. No.	*Staph. Aureus*	*Kleps. Pneumoniae*
Ia	+++	++	IIIa	+	+
Ib	++	±	IIIb	+	+
Ic	+++	++	IIIc	++	+
IIa	+++	+	IIId	+	+
IIb	+	±	IIIf	++	+
IIc	+++	±	Ampicillin	++	++
			Erythromycin	++	++

Table(6) the antimicrobial activity of the tasted compounds after 72 hrs.

Comp. No.	*Staph. Aureus*	*Kleps. pneumoniae*	Comp. No.	*Staph. Aureus*	*Kleps. Pneumoniae*
Ia	+++	+	IIIa	++	+
Ib	++	+	IIIb	-	-
Ic	+++	+	IIIc	++	+
IIa	+++	+	IIId	++	+
IIb	+	+	IIIf	++	+
IIc	+++	±	Ampicillin	++	++
			Erythromycin	++	++

Key to asymbols (-) = no inhibition, (±)= 6-10mm, (+) = 11-20mm, (++)=21-29mm,(+++)=30-38mm.

Conclusion

The compounds Ia,Ic,IIa showed more activity agains *Staphylococcus Aurous* than other compounds. In compounds IIIf some resistant isolates grown within the inhibition zone appeared that may be as aresult of mutation.

After 72hrs.some compounds showed more inhibition aginst bacteria or the inhibition effect is over such as compound IIIb, and others in wich no changing diameter of inhibition zone appeared

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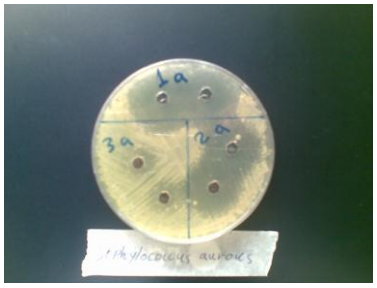


Fig(1):for compounds [Ia,IIa,IIIa].

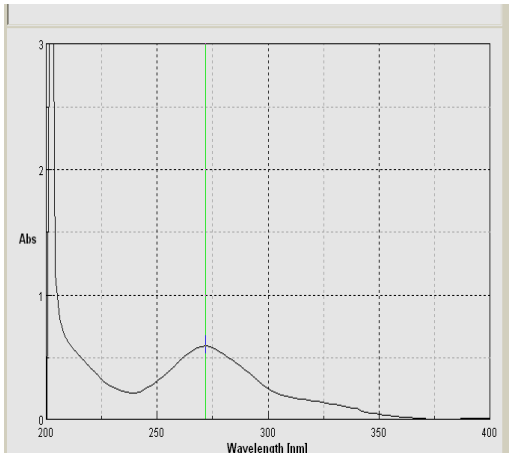
Fig(3):for compounds [Ia,IIa,IIIa].

Fig(2):for compounds [Ic,IIc,IIIc].

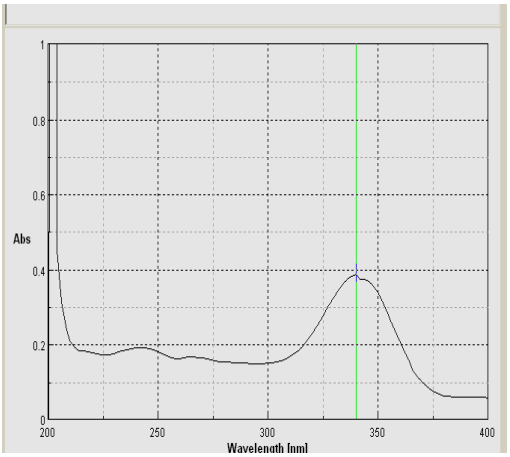
Fig(4):for compounds [Ic,IIc,IIIc].

Fig(1,2) agains *Staph.Aureus.*

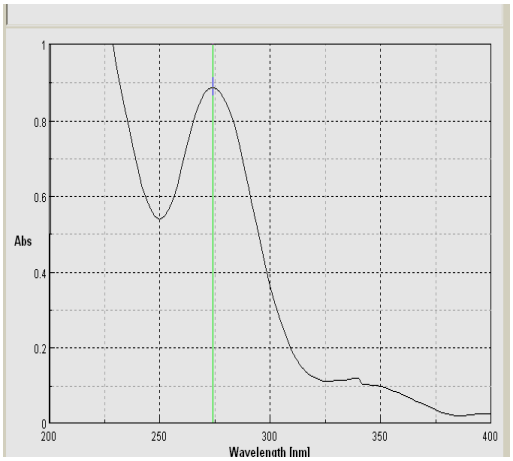
Fig(3,4) agains *Kleps. Pneumoniae.*



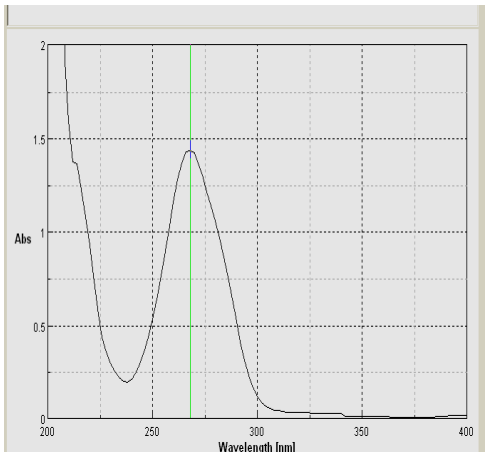
Fig(5):UV spectrum of the compound[Ic].



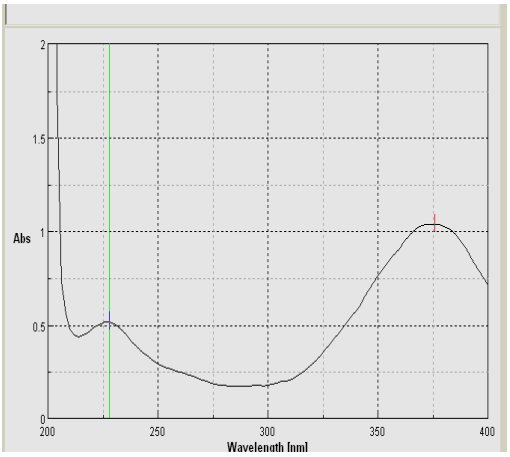
Fig(6):UV spectrum of the compound[If].



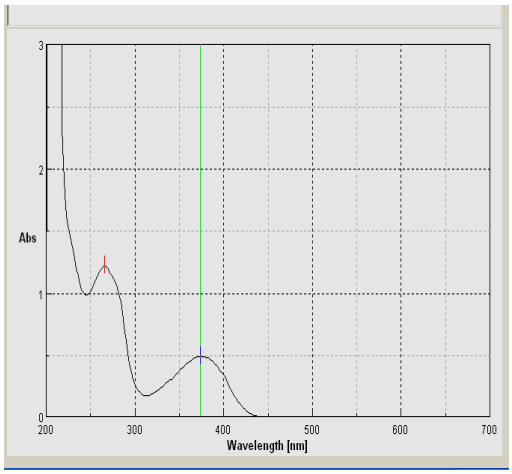
Fig(7):UV spectrum of the compound[IIa].



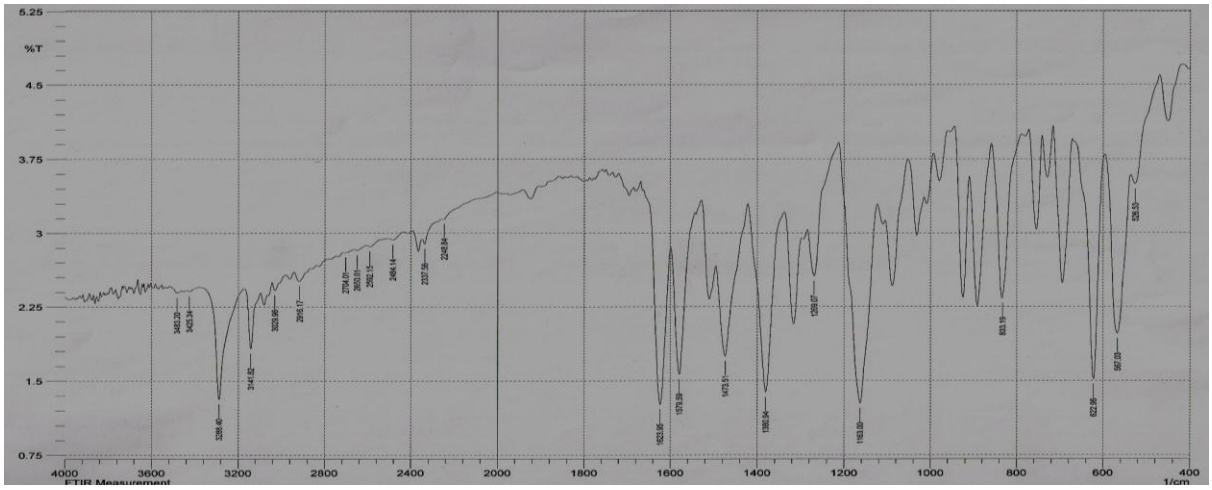
Fig(8):UV spectrum of the compound[IIc].



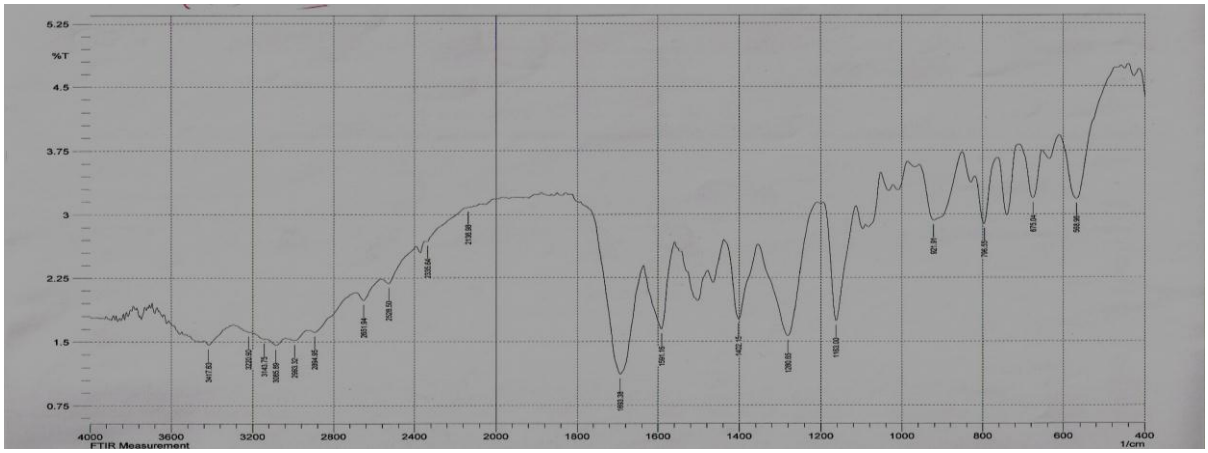
Fig(9):UV spectrum of the compound [IIIc].



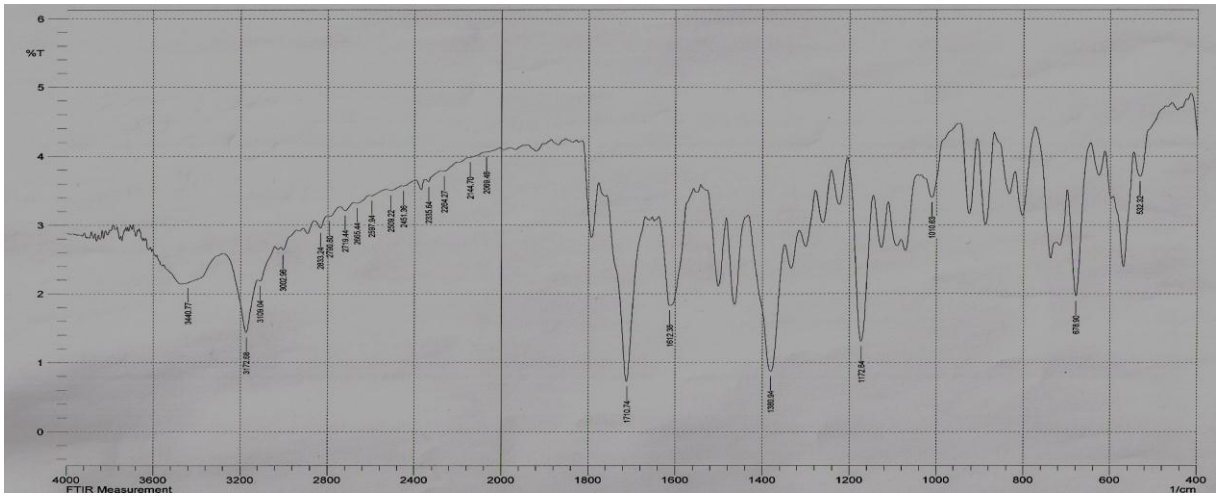
Fig(10):UV spectrum of the compound [IIIf].



Fig(11):FT-IR spectrum of the compound[Ic].



Fig(12):FT-IR spectrum of the compound[IIc].



Fig(13):FT-IR spectrum of the compound[IIIc].

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