Synthesis of Some New 1,3,4-Oxadiazole Derivatives from 4-{bis[3-(5-mercapto-1,3,4-oxadiazol-2-yl)-4-methoxy phenyl] methylene}-2-(5-mercapto-1,3,4-oxadiazol-2-yl)cyclohexa-2,5-dienone

Zaid Hassan Abood, Haitham Delol Hanoon and Ashraff Aziz Marhoon Dept. of Chemistry, College of Science, University of Kerbala

(NJC)

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Abstract

In this research new tri(1,3,4-oxadiazole) derivatives [5-10] were prepared starting from 4-{bis[3-(5-mercapto-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl]methylene}-2-(5-mercapto-1,3,4-oxadiazol-2-yl)cyclohexa-2,5-dienone [4].

The triester derivative [2] obtained from treatment of 5,5'-[(3-carboxy-4-oxocyclohexa-2,5-dienylidene)methylene]bis(2-hydroxybenzoic acid) [1] with dimethyl sulphate in presence of anhydrous sodium carbonate in dry acetone which was then converted into the trihydrazide derivative [3] by reaction with hydrazine monohydrate in absolute ethanol. Treatment of trihydrazide derivative [3] with carbon disulfide in presence of potassium hydroxide in absolute ethanol resulted in the formation of tri(1,3,4-oxadiazole) derivative [4] which was then converted into the trithioalkyl derivatives [5], [6] and [7] by reaction with benzyl chloride, n-butyl bromide and n-propyl bromide in basic medium, respectively. Treatment of trithioalkyl derivatives [5], [6] and [7] with potassium permanganate in acidic medium resulted in the formation of trisulfone derivatives [8], [9] and [10], respectively. These new synthesized compounds [2-10] probably have some biological activity.

All new compounds were characterized by melting points and were uncorrected, (C.H.N.) Elementary Analysis and FT-IR spectra.

[7] [6],[5] [4] (-3.4 1)

[7] [6],[5] [10] [9],[8]

(C.H.N.)

Introduction

The parent 1,3,4-oxadiazole compound is a liquid, b.p. 150°C. There has been a significant increase in the use of 1,3,4-oxadiazoles in diverse areas, including drug synthesis, scintillation materials and dyestuffs, therefore they comprise a large fraction of the literature⁽¹⁾.

Derivatives of 1,3,4-oxadiazole constitute an important family of heterocyclic compounds. Since many them display a remarkable biological activity, their synthesis and transformation have been received particular interest for a long time. 1,3,4-oxadiazole may be achieved by the reaction of hydrazides with carbon disulfide in the presence of potassium hvdroxide⁽²⁻⁵⁾. phosphorus oxychloride^(6,7), benzoic acid in the presence of phosphorus oxychloride⁽⁸⁾ and ethyl orthoformate in DMF⁽⁹⁾. 1,3,4-Oxadiazoles were also prepared from thiosemicarbazides carbodiimide⁽¹⁰⁾. dicyclohexyl Thioalkyl-1,3,4-oxadiazole derivatives were prepared by the reaction of 1,3,4oxadiazole-2-thiol derivatives with alkyl halides in basic medium(11-13). 2-Sulfonylalkyl-1,3,4-oxadiazole derivatives were prepared by the of 2-thioalkyl-1,3,4reaction oxadiazole derivatives with potassium permanganate in acidic medium⁽¹¹⁻¹³⁾.

1,3,4-Oxadiazole derivatives have certain biological activities and medical applications such as parasitic helminthes⁽¹⁴⁾, active against tuberculosis⁽¹⁵⁾, antimicrobial⁽¹⁶⁾, anti-

inflammatory⁽¹⁷⁾, anticonvulsant⁽¹⁸⁾ and antimalarial⁽¹⁹⁾.

Experimental

1. Materials

All materials have been used as provided from commercial suppliers except dioxan: 5,5'-[(3-carboxy-4oxocyclohexa-2,5dienylidene)methylene] bis(2hydroxybenzoic acid), Sodium carbonate (anhydrous), Ethyl acetate, Ethanol absolute, Sodium bicarbonate, Carbon disulfide, Potassium hydroxide, Dioxan, Benzyl chloride, n-Butyl bromide, Glacial acetic acid and Hydrogen peroxide (BDH), Dimethyl sulphate and Potassium permanganate Magnesium sulphate (Fluka), (anhydrous) and Acetone (Hannover), monohydrate, Hydrazine n-Propvl bromide and Hydrochloric acid [36%] (Merck).

2. General

- 1) Dioxan was purified.
- 2) TLC were performed on pre-coated sheets with 0.25 mm layer of Silica Gel GF254 of the Merck company, the detection was followed by coloring with iodine or H₂SO₄ in ethanol (60%) followed by heating.
- 3) Melting points (M.P.) were determined by Stuart melting point apparatus.
- 4) Elemental analysis measured on E.A.300, Euro- Vector, Italy, 2003, in AL-al-bayt University (Jordan).
- 5) FT-IR spectra were recorded on FT-IR 8400_s, Schimadzu-Spectrophotometer and using KBr discs in Kerbala University.

3. Preparation Methods Synthesis of Dimethyl 5,5'-{[3-(methoxycarbonyl)-4-oxocyclohexa-2,5-dienylidene]methylene}bis(2methoxybenzoate) [2]

5,5'-[(3-carboxy-4oxocyclohexa-2,5dienylidene)methylene]bis(2hydroxybenzoic acid) [1] (2.11g,5mmole) was dissolved in dry acetone then anhydrous (25mL)sodium carbonate (0.53g, 5mmole) was added and the mixture was left with stirring at room temperature for 20min., then dimethyl sulphate (3.15g, 25mmole) was added and the mixture was refluxed with stirring at 50°C for 24hrs., the solvent was then removed by evaporation and the product was extracted from the mixture by addition of a saturated bicarbonate solution with distilled water (60mL) and ethyl acetate (4×25mL). The organic layer was dried with anhydrous magnesium sulphate, filtered and the solvent was removed by evaporation, recrystallized from ethanol, yield 82%, M.p.=(190-192°C).

Synthesis of 5,5'-{[3-(hydrazinecarbonyl)-4oxocyclohexa-2,5-dienylidene] methylene}bis(2methoxybenzohydrazide) [3]

A mixture of triester derivative [2] (2g, 4mmole) and hydrazine hydrate (0.60g, 12mmole) in absolute ethanol (20mL) was refluxed at 75°C for 6hrs., the hydrazide was precipitate on cooling, filtered off and recrystallized from ethanol, yield 78%, M.p.= (185°C).

Synthesis of 4-{bis[3-(5-mercapto-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl] methylene}-2-(5-mercapto-1,3,4-oxadiazol-2-yl)cyclohexa-2,5-dienone [4]

To a solution of trihydrazide derivative [3] (2g, 4mmole) dissolved

in absolute ethanol (25mL), put on ice bath, potassium hydroxide (0.69g, 12mmole) and carbon disulfide (0.91g, 12mmole) were added respectively. The mixture was heated under reflux for 7hrs., the solvent was then removed by evaporation, the residue dissolved in (20mL) of cold distilled water and acidified with conc. hydrochloric acid. The precipitate was filtered and recrystallized from ethanol, yield 75%, M.p.=(216-218°C).

Synthesis of 2-(5-(benzylthio)-1,3,4-oxadiazol-2-yl)-4-{bis[3-(5-(benzylthio)-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl]methylene}cyclohex a-2,5-dienone [5]

Tri(1,3,4-oxadiazole) derivative [4] (0.5g, 0.8mmole) was dissolved in (25mL) of dry dioxan, then potassium hydroxide (0.13g,2.4mmole), dissolved in a little amount of distilled water, was added. The mixture was then refluxed with stirring at 80°C for 20min., then benzyl chloride (0.30g, 2.4mmole) was added dropwise, then the mixture was refluxed at 80°C for 2hrs., the solvent was then removed by evaporation and the product was extracted by addition of distilled water (30mL) and ethyl acetate (2×25mL). The organic layer was dried with anhydrous magnesium sulphate, filtered and the solvent was removed by evaporation, recystallized from ethanol, yield 68%, M.p.=(> 300°C).

Synthesis of 4-{bis[3-(5-(butylthio)-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl] methylene}-2-(5-(butylthio)-1,3,4-oxadiazol-2-yl)cyclohexa-2,5-dienone [6]

Compound [6] was prepared by using the same procedure which was used for the prepare of compound [5] with the following modifications: n-butyl bromide instead of benzyl chloride, recystallized from methanol, yield 61%, M.p.=(> 300°C).

Synthesis of 4-{bis[4-methoxy-3-(5-(propylthio)-1,3,4-oxadiazol-2-yl)phenyl] methylene}-2-(5-(propylthio)-1,3,4-oxadiazol-2-yl)cyclohexa-2,5-dienone [7]

Compound [7] was prepared by using the same procedure which was used for the prepare of compound [5] with the following modifications: n-propyl bromide instead of benzyl chloride, recystallized from methanol, yield 70%, M.p.=(> 300°C).

Synthesis of 2-(5-(benzylsulfonyl)-1,3,4-oxadiazol-2-yl)-4-{bis[3-(5-(benzyl- sulfonyl)-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl]methylene}-cyclohexa-2,5-dienone [8]

Compound [5] (0.4g,0.45mmole) was dissolved in (7mL) of acetic acid at 0°C, then potassium permanganate (0.23g, 1.35mmole) dissolved in a little amount of distilled water was added dropwise. temperature was controlled at 0°C until potassium addition of permanganate was completed, then the mixture was lefte with stirring at room for 24hrs., hydrogen temperature peroxide (30%) was then added dropwise until disappearance of colour of permanganate. The product was extracted with ethyl acetate (2×25mL) and distilled water (30mL) containing little amount of sodium bicarbonate for neutralizing acetic acid. The organic layer was dried with anhydrous magnesium sulphate, filtered and the solvent was evaporated, recrystallized

from methanol, yield 66%, M.p.=(> 300°C).

Synthesis of 4-{bis[3-(5-(butylsulfonyl)-1,3,4-oxadiazol-2-yl)-4-methoxy- phenyl]methylene}-2-(5-(butylsulfonyl)-1,3,4-oxadiazol-2-yl)-cyclohexa-2,5-dienone [9]

Compound [9] was prepared by using the same procedure which was used for the prepare of compound [8] with the following modifications: compound [6] instead of compound [5], yield 58%, M.p.=(> 300°C).

Synthesis of 4-{bis[4-methoxy-3-(5-(propylsulfonyl)-1,3,4-oxadiazol-2-yl)- phenyl]methylene}-2-(5-(propylsulfonyl)-1,3,4-oxadiazol-2-yl)cyclohexa-2,5-dienone [10]

Compound [10] was prepared by using the same procedure which was used for the prepare of compound [8] with the following modifications: compound [7] instead of compound [5], yield 60%, M.p.=(> 300°C).

Table (1): Melting points, percent yields and (C.H.N.) analysis of the prepared compounds (1-10)

Comp.		M.Wt.	(M.P.) °C	Yield %	C.H.N. analysis						
	M.F.				Са	alculated	l%	Found%			
					С	Н	N	С	Н	N	
[1]	$C_{22}H_{14}O_{9}$	422	300	-	-	1	-	-	ı	-	
[2]	$C_{27}H_{24}O_9$	492	190-192	82	65.85	4.87	-	65.49	4.54	-	
[3]	$C_{24}H_{24}N_6O_6$	492	185	78	58.53	4.87	17.07	57.81	4.33	16.23	
[4]	$C_{27}H_{18}N_6O_6S_3$	618	216-218	75	52.42	2.91	13.59	51.42	2.81	13.07	
[5]	$C_{48}H_{36}N_6O_6S_3$	888	> 300	68	64.86	4.05	9.45	64.29	3.55	9.32	
[6]	$C_{39}H_{42}N_6O_6S_3$	786	> 300	61	59.54	5.34	10.68	58.89	4.57	10.07	
[7]	$C_{36}H_{36}N_6O_6S_3$	744	> 300	70	58.06	4.83	11.29	58.48	4.98	11.44	
[8]	$C_{48}H_{36}N_6O_{12}S_3$	984	> 300	66	58.53	3.65	8.53	59.04	3.38	8.11	
[9]	$C_{39}H_{42}N_6O_{12}S_3$	882	> 300	58	53.06	4.76	9.52	53.53	5.06	9.96	
[10]	$C_{36}H_{36}N_6O_{12}S_3$	840	> 300	60	51.42	4.28	10.00	50.92	4.01	9.82	

Results and Discussion

The tricarboxylic acid [1] was converted to the corresponding triester derivative [2] by reaction dimethyl sulphate. Triester derivative [2] was converted to the corresponding trihydrazide derivative [3] by reaction with hydrazine hydrate. Trihydrazide derivative [3] was converted to the corresponding tri(1,3,4-oxadiazole) derivative [4] by reaction with carbon disulfide in alcoholic potassium hydroxide solution. Thiol groups in compound [4] were converted to the corresponding trisulfide anion which was then introduced in S_N 2 reaction⁽¹³⁾ with each benzyl chloride, n-butyl bromide and n-propyl bromide,

respectively in basic medium to give tri(2-thioalkyl-1,3,4-oxadiazole) derivatives [5-7]. Tri(2-sulfonyl alkyl-1,3,4-oxadiazole) derivatives [8-10] were prepared by oxidation of tri(2thioalkyl-1,3,4-oxadiazole) derivatives respectively [5-7] with aqueous permanganate solution in acetic acid at $(0^{\circ}C)$. Mechanism of oxidation reaction of thioalkyl compound to the corresponding sulfone compound involves formation of manganese ester in the first step, then ester will be dissociated in the second step to give sulfone as shown in scheme (1)⁽¹²⁾:

Scheme (1): Oxidation mechanism of thioalkyl to sulphonylalkyl

The structures of all synthesized compounds [1-10] were shown in scheme (2). All prepared compounds [1-10] were identified by melting points, (C.H.N.) Elementary Analysis which showed nearness between the calculated and found values for each compound as shown in Table (1), and FT-IR spectra as shown in Table (2). FT-IR spectrum of compound [1], tricarboxylic acid, showed appearance of the following characteristic absorption bands: the two weak absorption bands at 3556cm⁻ and 3425cm⁻¹ attributed to the stretching vibrations of phenolic and carboxylic acid hydroxyl groups, respectively. The absorption band at 3059cm⁻¹ attributed to the υ(C-H) aromatic of benzene ring. The two strong absorption bands at 1882cm⁻¹ and 1655cm⁻¹ attributed to the v(C=O) of ketone and carboxylic acid groups, respectively. The medium absorption band at 1438cm⁻¹ due to the v(C=C) aromatic of benzene rings. The strong absorption band at 1205cm⁻¹ attributed to the v(C-O) of phenol. The absorption band at 775cm⁻¹ due to the δ (C-H) aromatic out of plane. The absorption band at 678cm⁻¹ attributed to the $\delta(O-H)$ out of plane. FT-IR spectrum of compound [2], triester derivative, showed disappearance of the strong absorption band at 1655cm^{-1} due to the v(C=O) of carboxylic acid groups and appearance of the following characteristic

absorption bands: the absorption band at 1676cm⁻¹ attributed to the v(C=O) of ester groups. The weak absorption band at 2931cm⁻¹ due to the v(C-H) aliphatic of $(-CH_3)$ The absorption band at group. 1290cm⁻¹ attributed to the asymmetric υ(C-O) of ester group -(C=O)-O. The two absorption bands at 1217cm⁻¹ and 1116cm⁻¹ attributed to the asymmetric and symmetric v(C-O) of aromatic ether group (C-O-CH₃). The sharp strong absorption band at 1797cm⁻¹ attributed to the v(C=O) of ketone. FT-IR spectrum of compound [2] also showed appearance of another important absorption bands shown in FT-IR Table (2).spectrum compound [3], trihydrazide derivative, showed disappearance of the strong absorption band at 1676cm⁻¹ due to the v(C=O) of ester groups and appearance of strong absorption band at 1633cm^{-1} attributed to the v(C=O) of hydrazide groups. FT-IR spectrum of compound [3] also showed appearance of two absorption bands at 3553cm⁻¹ and 3491cm⁻¹ attributed to asymmetric and symmetric stretching vibrations of (-NH₂)groups. respectivly. The absorption band at 3201cm⁻¹ attributed to the v(N-H) of hydrazide groups. The absorption band at 1828cm^{-1} due to the v(C=O) of ketone. FT-IR spectrum of compound [3] also showed appearance of another important absorption bands shown in Table (2). FT-IR spectrum

compound [4], tri(1,3,4-oxadiazole)derivative, showed disappearance of the two absorption bands at 3553cm⁻¹ and 3491cm⁻¹ due to the asymmetric and symmetric stretching vibrations of (-NH₂) groups, respectively, and appearance of weak absorption band at 3160cm⁻¹ attributed to the stretching vibration of (N-H) group of thion tautomer. The strong absorption band at 1186cm^{-1} due to the v(C=S) of tautomeric thion form. The weak absorption band at 2553cm⁻¹ attributed to the v(S-H) of tautomeric thiol form. The strong absorption bands 1045cm⁻¹ and 713cm⁻¹ attributed to the v(N-N) and v(C-S), respectively, which are good evidence for the structure given to the product. FT-IR spectrum of compound [4] also showed disappearance of the strong absorption band at 1633cm^{-1} due to the v(C=O)of hydrazide groups and appearance of two sharp strong absorption bands at 1665cm⁻¹ and 1615cm⁻¹ attributed to the stretching vibrations of two different types of imine groups (C=N) endocyclic of oxadiazole rings due to the tautomerism. FT-IR spectrum of compound [4] also showed appearance of broad absorption band at 1259cm⁻¹ attributed to the $\upsilon(C\text{-O-C})$ oxadiazole ring. FT-IR spectrum of compound [4] also showed appearance of another important absorption bands shown in Table (2).

FT-IR spectra of compounds [5-7], tri(2-thioalkyl-1,3,4-oxadiazole) derivatives, showed disappearance of

the two absorption bands at 1186cm⁻¹ and 3160cm⁻¹ attributed to the v(C=S)and v(N-H) of thione tautomer, also disappearance of the weak absorption band at 2553cm^{-1} due to the v(S-H) of thiol tautomer. FT-IR spectra of compounds [5-7] showed appearance of another important absorption bands shown in Table (2). FT-IR spectra of compounds [8-10], tri(2-sulfonylalkyl-1,3,4-oxadiazole) derivatives, showed appearance of two characteristic absorption bands at 1338cm⁻¹ and 1153cm⁻¹, 1373cm⁻¹ and 1195cm⁻¹, 1373cm⁻¹ and 1139cm⁻¹, respectively, attributed to the asymmetric and symmetric stretching vibrations of sulphonyl groups (O=S=O)⁽²⁰⁾. FT-IR spectra of compounds [8-10] also showed appearance of another important absorption bands shown in Table (2).

Scheme (2): Reactions proceeding

[10]

[9]

[8]

Table(2): FT-IR Data of the prepared compounds [1-10] in cm⁻¹

Comp No.	U / O-H	U / NH ₂	U / N-H	<i>U</i> / C-H arom.	U / C-H aliph.	U / S-H	U / C=O	<i>U</i> / C=N	<i>U</i> / C=C arom.	U/SO ₂	U / C-O	U / C=S	<i>U</i> / N-N	<i>U</i> / C-S	& / C-H arom. o.o.p.
[1]	3556 (sp) 3425 (sp)			3059(w)			1882(s) ketone 1655(s) acid		1438(m)		1205(s)				775(m)
[2]				3150(w)	2931(m)		1797(s) ketone 1676(s) ester		1610(m) 1454(m)		1290(w) asym. ester 1217(m) asym. ether 1116(w) sym. ether				966(s)
[3]		3553 (m) 3491 (m)	3201 (m)	3070(w)	2950(s)		1828(m) Ketone 1633(s) hydrazide		1456(s)		1234(m) 1109(s)				813(m)
[4]			3160 (w)	3053(w)	2918(s)	2553 (w)	1770(w) ketone	1665(s) 1615(s)	1475(s)		1259(s) 1118(s)	1186 (m)	1045(s)	713(w)	900(m) 804(m)
[5]				3030(w)	2918(m)		1824(s) ketone	1631(s)	1580(m) 1448(s)		1265(s)		1047(s)	690(s)	896(m)
[6]				3060(w)	2951(m)		1825(m) ketone	1624(s)	1456(s)		1267(s)		1040(m)	700(w)	922(m) 808(m)
[7]				3140(w)	2860(w)		1930(s) ketone	1650(m)	1550(m)		1270(s)		1050(w)	600(m)	920(m)
[8]				3060(w) 3000(w)	2926(s) 2860(m)		1728(s) ketone	1604(s)	1456(s)	1153(s) 1338(s)	1095(s) 1259(s)		1028(s)	705(s) 650(s)	950(s) 880(s) 777(s)
[9]				3070(w)	2926(w) 2780(w)		1716(s) ketone	1658(s)	1602(s) 1448(s)	1195(s) 1373(s)	1263(s) 1118(s)		1030(s)	720(m) 642(s)	883(s) 840(s) 798(s)
[10]				3105(w)	2912(s) 2840(w)		1710(s) ketone	1662(s)	1564(s) 1446(s)	1139(s) 1373(s)	1205(w) 1276(s)		1028(s)	667(m) 603(m)	945(s) 891(s) 800(s)

sp=sharp, w=weak, m=medium, s=strong, o.o.p.= out of plane

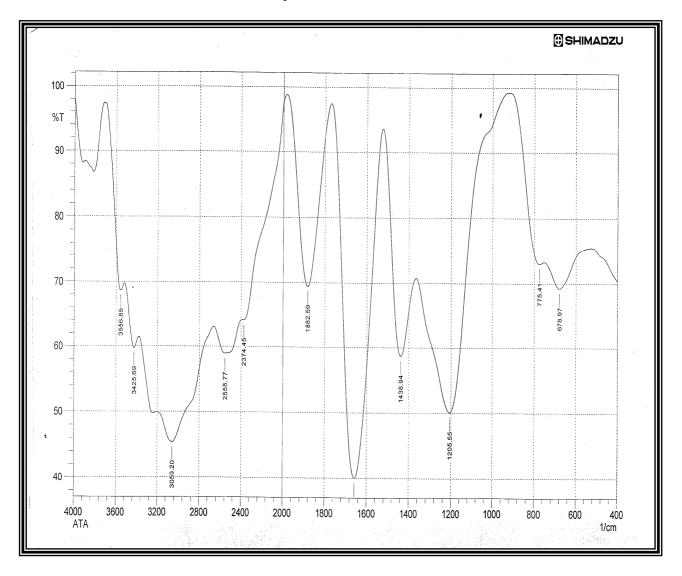


Fig.(1): FT-IR spectrum of compound [1]

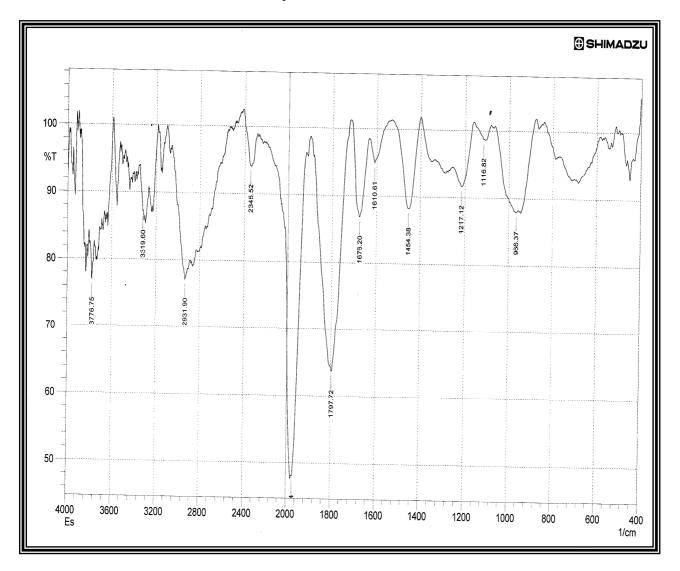


Fig.(2): FT-IR spectrum of compound [2]

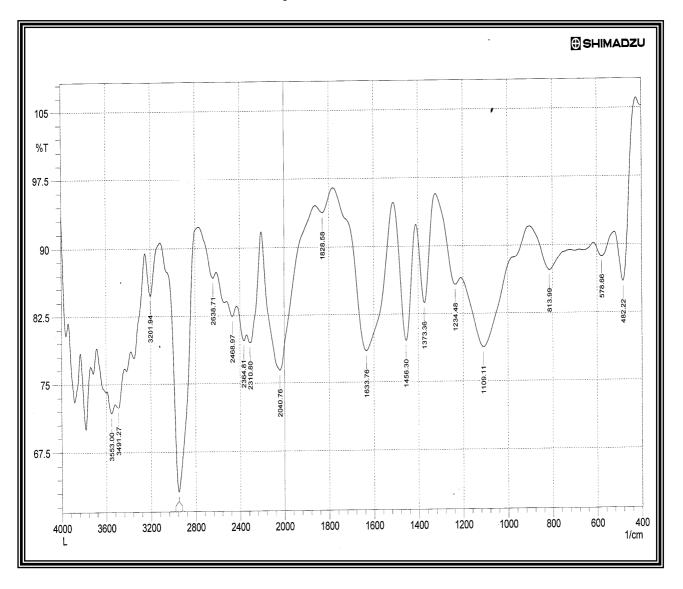


Fig.(3): FT-IR spectrum of compound [3]

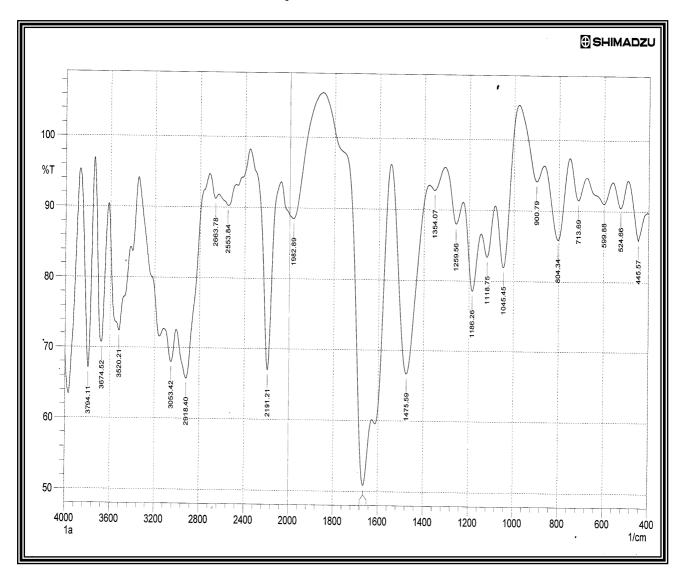


Fig.(4): FT-IR spectrum of compound [4]

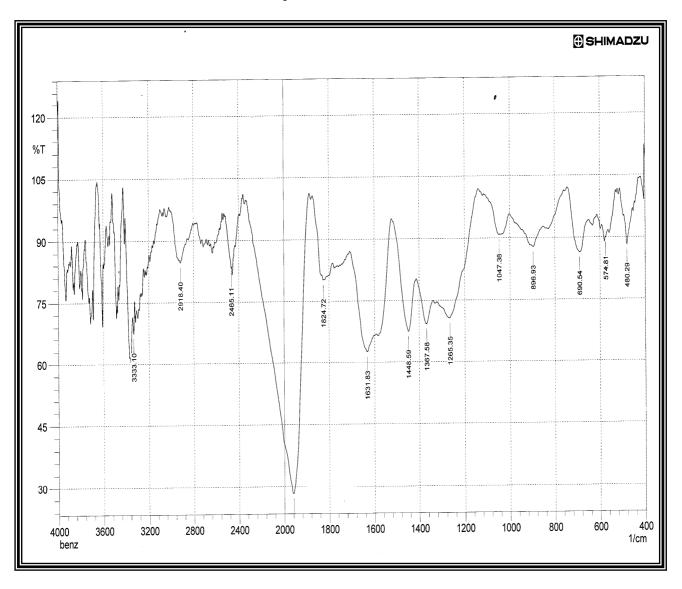


Fig.(5): FT-IR spectrum of compound [5]

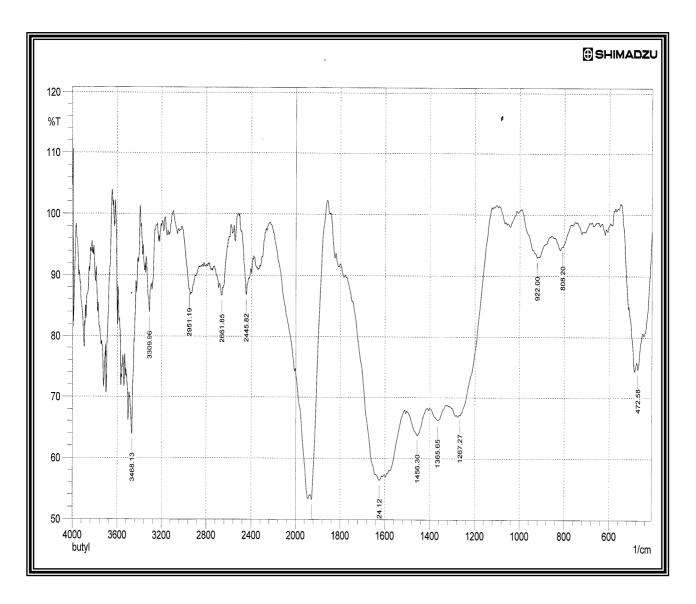


Fig.(6): FT-IR spectrum of compound [6]

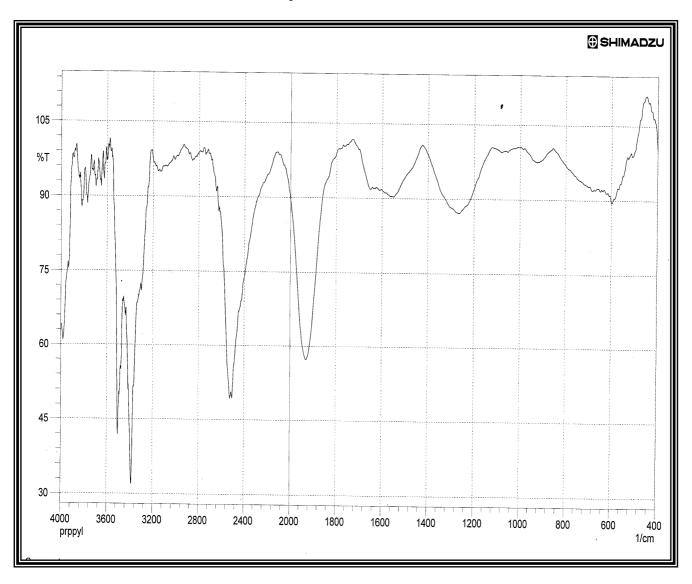


Fig.(7): FT-IR spectrum of compound [7]

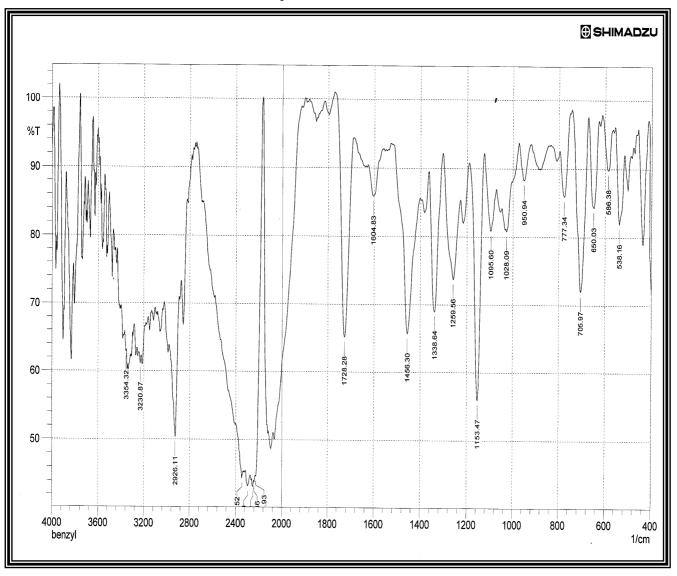


Fig.(8): FT-IR spectrum of compound [8]

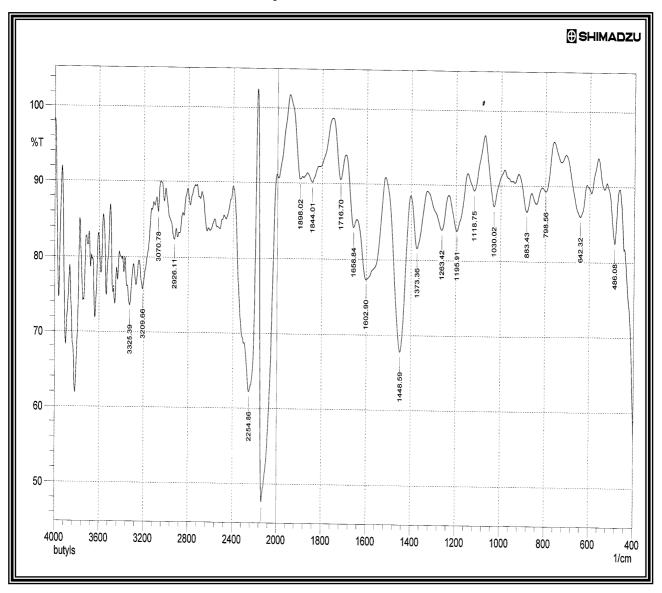


Fig.(9): FT-IR spectrum of compound [9]

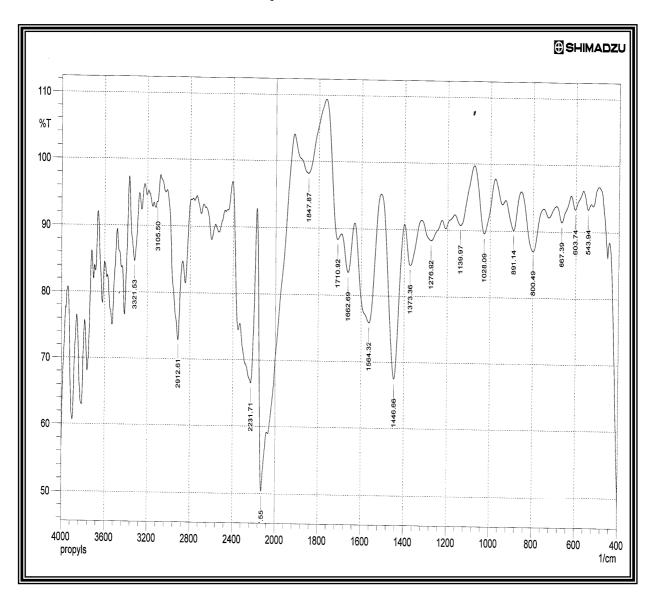


Fig.(10): FT-IR spectrum of compound [10]

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