Synthesis and study the Biological Activity of some new bis Maleimide derivatives containing 1 ,3 ,4- Oxadiazole ring

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Key word: 1 ,3 ,4-Oxadiazole ,Maleimide, Biological activity .

Abstract :

This paper contains the synthesis of some new bis heterocyclic compounds starting from the esters of bis carboxylic acid which then converted to its hydrazide [1-5] then to bis1,3,4-Oxadiazole derivatives [6-10] beside bis maleamic acid derivatives [11-15] and finally with bis maleimides [16-20] .

Preparing of bis ester by usual esterification of substituted bis aliphatic carboxylic acid with absolute ethanol in acidic medium , then has converted to its substituted bis aliphatic carboxylic acid hydrazide by reacting it with hydrazine hydrate . The derivatives bis-1,3,4-Oxadiazole have synthesized by cyclization of bis aliphatic carboxylic acid hydrazide with 4- amino benzoic acid in presence of phosphoric acid 85% .

So ,the bis- maleamic acids have been synthesized by the reaction of compounds [6-10] with maleic anhydride in diethyl ether. Also bis maleimides are synthesized by cyclization of bis maleamic acids derivatives by using acetic acid anhydride and anhydrous sodium acetate. The synthesized compounds were identified by spectral methods UV,FT-IR and H^1-NMR beside melting point and the purity was determined by using (TLC) and some of its physical properties were measured . Some of these compounds are tested against four strains of bacteria *(Staph. aurease , E. coli ,Sal. thph and Ps. aeruginosa)*

تحضيرودراسة الفعالية البايولوجية لبعض مشتقات ثنائى المالئيمايد الجديدة الحاوية على حلقة-4,3,1 اوكسادايازول

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الكلمات المفتاحية: 4,3,1-اوكسادايازول , المالئيمايد, الفعالية البايولوجية

المستخلص:

تضمن هذا البحث تحضير بعض المركبات الحلقية غير المتجانسة ابتداء من أسترات الأحماض الكاربوكسيلية ومرورا بالهيدرازيدات [1-5] ثم مشتقات 4,3,1-اوكسادايازول [6-10] ومشتقات حامض الماليماميك [11-15] وانتهاء بالمالئيمايدات المقابلة [16-20].

حضرت معوضات أسترات الأحماض الكاربوكسيلية الاليفاتية الثنائية بعملية الاسترة الاعتيادية لمشتقات الأحماض الكاربوكسيلية الاليفاتية الثنائية مع الايثانول المطلق في وسط حامضي والتي تم تحويلها إلى مشتقات الهيدرازيدات المقابلة [1-5] من خلال تفاعلها مع الهيدرازين المائي.

حضرت مركبات 2-(4-امينو فنيل) -5-(فنيل/ أريل) 4,3,1-اوكسادايازول [6-10] من خلال الغلق الحلقي لهيدرازيدات حامض البنزويك الاحادية الاروماتية مع 4-امينو حامض البنزويك بوجود حامض الفسفوريك 85٪.

حضرت مركباتN-[4-(5- فنيل /أريل) 4,3,1-اوكسادايازول -2-يل] فنيل حامض الماليماميك [11-15] من خلال معاملة المركبات [6-10] مع حامض الماليك اللامائي في ثنائي اثيل ايثر.

اما المركبات N- [4-(5-فنيل /اريل) 4,3,1-اوكسادايازول -2- يل] فنيل مالئيمايد [16-20] فقد حضرت من خلال الغلق الحلقي لمشتقات حامض الماليماميك بوجود حامض الخليك اللامائي وخلات الصوديوم.

شخصت المركبات المحضرة باستخدام التقنيات الطيفية (طيف الاشعة فوق البنفسجية- المرئيةUV-Vis) وطيف ا لاشعة تحت الحمراء FT-IR وطيف الرنين النووي المغناطيسي للبروتون H^1-NMR وباستخدام مذيب-DMSO d^6إضافة الى درجات الانصهار ومتابعة سير تفاعلات المركبات باستخدام (TLC).

درست الفعالية البايولوجية لبعض المشتقات المحضرة ضد أربعة أنواع من الجراثيم المرضية المعروفة بمقاومتها للمضادات الحيوية وهي المكورات العنقودية الذهبية *Staphylococcus auras* الموجبة لصيغة كرام واشر يشيا القولون *Escherichia coli* وسيدوموناس ايروجينوزا *Pseudomonas aeruginosa* وسالمونيلا التايفوئيد *salmonella typhi* السالبة لصيغة كرام.

Introduction:

The chemistry of azoles derived *N*-bridged heterocycles has received considerable attention in recent years due to their usefulness in different areas of biological activities and as industrial intermediates.In that respect oxadiazole plays a significant role among other heterocycles. From the literature survey Oxadiazole was found to be having diverse activities like anti-inflammatory, antimicrobial, antifungal, antiviral, analgesic, anti-mycobacterial,antidepressent and anticancer etc. So it was plannedto synthesize a novel series of 1,3,4 oxadiazole derivatives and to check their activity as antimicrobial and antifungal agent [(1-7)].

This interesting group of compounds possess diverse biological activities such as anticonvulsant[(8)], antimicrobial[(8,9)], antitubercular[(10)] and anticancer[(11)].

Maleimides are widely known as active electrophilic reagents to readily react with a variety of dienes and 1,3-dipoles including azomethine ylide, carbonyl ylide and, nitorenes,leading to various heterocycles[(12)]. We have explored the abundant synthetic potential of the new functionalized maleimides which can effectively be converted to fused pyridazine derivatives[(13)] and polymethine dyes[(14,15)] .

The N-substituted maleimides and their derivatives were important high performance engineering plastic[16]. Recently, we have shown that maleimide derivatives of the anticancer drugs doxorubicin to the cystene-34 position of circulating albumin after intravenous administration[17-19].

Experimental part:

Materials :

All chemicals which have been used of reagent grad supplied by (Merck, Fluka, BDH and Aldrich). The melting point are determined by Electro thermal melting Apparatus 9300 in open capillary tubes that are un corrected. Thin layer chromatography (TLC)was used for monitory the reaction and to check purity. The FT-IR spectra in the rang (400-4000) cm^{-1} are recorded as KBr disk on FT-IR 8300 Shimadzu spectrophotometer . The UV-Visible spectra are measured in ethanol using Shimadzu UV propel version 1.11 in range (200-400) nm. H^1-NMR Spectra are recorded on Bruker 400 MH_z instrument in DMSO-d6 with TMS as internal standard .

A) Synthesis Methods :

1) Synthesis of substituted bis aliphatic carboxylic acid esters [20].

A mixture of substituted bis aliphatic carboxylic acid (0.1 mol) excess of absolute ethanol and concentrated sulfuric acid (5ml) was refluxed for 6 hrs. , after that the solvent was distilled under vacuum , the product washed by sodium bicarbonate solution then with diethyl ether (40 ml) .

2)Synthesis of substituted bis aliphatic carboxylic acid hydrazides [20] [1-5].

Dissolved substituted bis aliphatic carboxylic acid esters (0.1mol) and hydrazine hydrate 98% (0.2mol) mixture in absolute ethanol (40ml) and refluxed for 6hrs., after cooling to room temperature , the precipitate was filtered ,washed , recrystallized from ethanol and dried .The physical properties of these derivatives are given in Table (1).

3) Synthesis of bis-1,3,4-Oxadiazole derivatives [21] [6-10].

An appropriate bis aliphatic carboxylic acid hydrazide (0.01mol)was added gradually with stirring for 20 minutes, to a mixture(0.02mol)of 4-amino benzoic acid and syrupy phosphoric acid 85% (20ml) at 120°C . The mixture was heated with stirring at this temperature for further 2 hrs. then poured into ice water and left overnight. The precipitated was filtered off, washed with water and 10% sodium carbonate solution and recrystallized from ethanol. The physical properties of these derivatives are given in Table (2).

4) Synthesis of bis- maleamic acid derivatives [22] [11-15].

A Solution of maleic anhydride (0.02mol) in dioxane was added drop wise with stirring to a suspension of(0.01mol) compound [6-10] in dioxane. The mixture was stirred overnight

at room temperature. The precipitated was filtered, washed with water and recrystallized from ethanol. The physical properties of these derivatives are given in Table (3)

5)) Synthesis of bis- maleimide derivatives [23,24][16-20].

(0.01mol)of compounds [11-15] was dissolved in acetic anhydride (10-20%)from the weight of acid sodium acetate anhydrous was added then reflux until to changed the color of solution ,then was cooled and added ice after strongly stirring , precipitated maleimide derivatives which was filtered , washed with water then by dilute sodium bicarbonate and finally by ethanol and recrystallized from Ethanol + Acetone . The physical properties of these derivatives are given in Table (4).

B) The biological activity[25].

The bacteria species used are listed in tables (9-12). All strains were obtained from College of Medicine, Tikrit University. They were grown up to the stationary phase nutrient bath at 37 °C and a sample of 0.5 ml of each bacteria was spread over a surface of a nutrient agar plate.

Antibacterial assay[26].

Disc of filter paper (6 mm diameter) is sterilized at 140°C for 1hr., and impregnated with the germs. Absolute ethanol was used as a solvent for compounds [6-10], [11-15] and[16-20]. The same solvent was used for antibiotics. Blank paper discs of absolute ethanol was used as control. The inoculated plates are incubated at $37C^0$ for 24 hrs., and the inhibition zone (mm) were measured[27]. In all experiments the mean of each triplicate was measured[28].

Results and Discussion:

1- Characterization of Bis oxadiazol derivatives [6-10].

The reaction of phosphoric acid 85% with 4-aminobenzoic acid in presence of substituted bis aliphatic carboxylic acid hydrazide to give Bis oxadiazole derivatives.

The FT-IR spectra of these compounds in general have exhibited the significant two bands in the region (3423-3461)cm^{-1}, which could be attributed to asymmetric (3330-3373)cm^{-1}, and symmetric stretching vibration of NH_2 group. In addition to a band at about (1652-1664)cm^{-1} due to cyclic (C=N) stretching is also observed. Also spectra have displayed an asymmetrical (C-O-C) aromatic stretching band at (1230-1290) cm^{-1}, with symmetrical near (1030-1072)cm^{-1}, in addition to a peak at (1010-1072) cm^{-1} duet to (N-N) group, besides UV spectrum show the transions $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ which confirmed the presence of the un-bonded pair electrons on Nitrogen, Oxygen atoms and aromatic system. (double bond). UV and IR absorbance spectra are given in Table(6). See fig(8) and H^1NMR

spectrum of compound [7] is given in Fig(11) .The steric conformation of compound [6] is given in fig (2).

2- Characterization of Bis maleamic acid derivatives [11-15].

Maleamic acid derivatives have synthesized from the reaction of compounds [6-10] with maleic anhydride. The FT-IR spectra of Maleamic acid derivatives in general showed disappearance of (NH_2) absorption of primary amine and appearances of (NH) absorption band in (3209-3272)cm^{-1}. Besides bands in (1700-1720)cm^{-1}, (1660-1670)cm^{-1} are due to (C=O) acid and (C=O) amide, and band at (3410-3446)cm^{-1} due to (OH) acid.

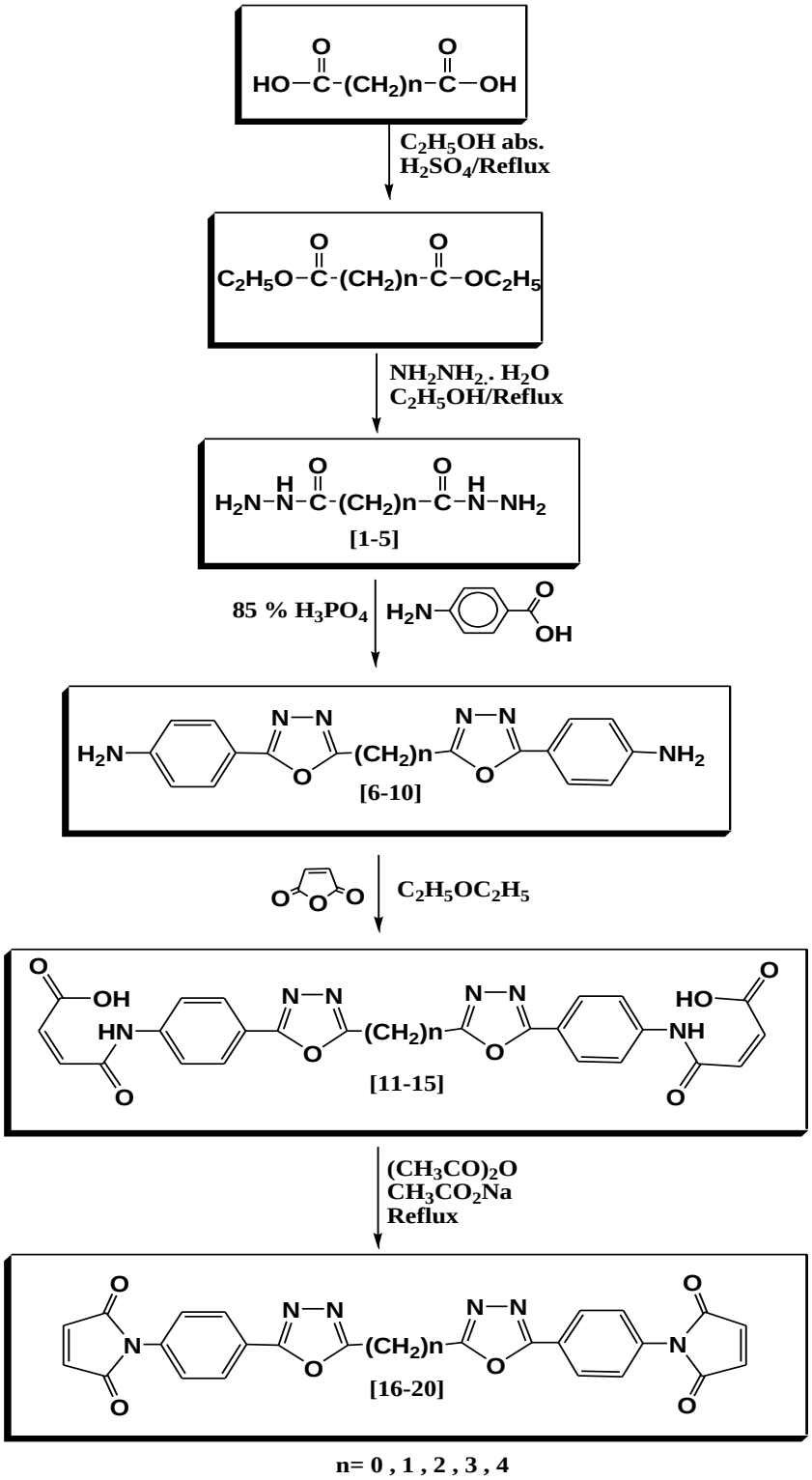
Beside UV spectra show the transions $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ which have confirmed the presences of the un-bonded pair electrons on Nitrogen, Oxygen atoms and aromatic system (double bond). UV and IR absorbance spectra are given in Table (7) see Fig (5) and (9). So H^1NMR spectrum of compound [11] is given in Fig(12) .The steric conformation of compound [12] is given in fig (3).

3-Characterization of Bis maleimide derivatives [16-20].

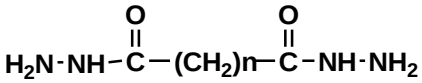
Maleimide derivatives have synthesized by dehydration of compounds [11-15] using acetic anhydride with sodium acetate anhydrous. The FT-IR spectrum of Maleimide derivatives showed disappearance of (OH) acid and (NH) amide absorption bands and appearance of (C=O) imide at (1705-1718)cm^{-1}. Beside UV spectra show the transions $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ which has confirmed the presence of the un-bonded pair of electrons on Nitrogen, Oxygen and aromatic system (double bond). UV and IR Absorbance spectra are given in Table(8). See Fig(6) ,(10). The steric conformation of compound [17] is given in fig (4).

B) Biological activity[28]:

The antimicrobial activity of the synthesized compounds[6-10],[11-15]and[16-20] were examined by the agar diffusion method by using four different bacterial species *Escherichia coli, Staphylococcus aurous, Salmonella typhi* and *Pseudomonas aeruginosa.* The results indicated that all the assayed compounds showed an weak microbial activity against the tested organisms up to 3.2 mg/disk. Among this group of organism *Staph aurous* and *E. coli* showed higher sensitivity toward the mentioned compounds.

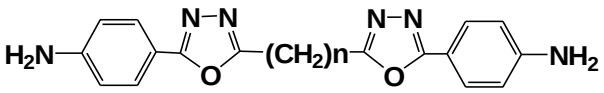

HO–C–(CH2)n–C–OH
C2H5OH abs.
H2SO4/Reflux
C2H5O–C–(CH2)n–C–OC2H5
NH2NH2. H2O
C2H5OH/Reflux
H2N–N–C–(CH2)n–C–N–NH2
[1-5]
85 % H3PO4
H2N
OH
[6-10]
C2H5OC2H5
[11-15]
(CH3CO)2O
CH3CO2Na
Reflux
[16-20]

n= 0 , 1 , 2 , 3 , 4



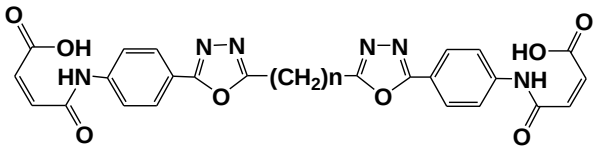
Table(1) physical properties of bis aliphatic carboxylic acid hydrazide [1-5].

Compd. No.	n	Molecular Formula	Color	M.P °C	Yield %	Rf	Crystallization Solvent
1	-	$C_2H_6N_4O_2$	White	146-148	70	0.72	Ethanol
2	1	$C_3H_8N_4O_2$	White	150-152	74	0.71	Ethanol
3	2	$C_4H_{10}N_4O_2$	White	187-189	67	0.65	Ethanol
4	3	$C_5H_{12}N_4O_2$	White	135-137	79	0.74	Ethanol
5	4	$C_6H_{14}N_4O_2$	White	180-182	63	0.78	Ethanol



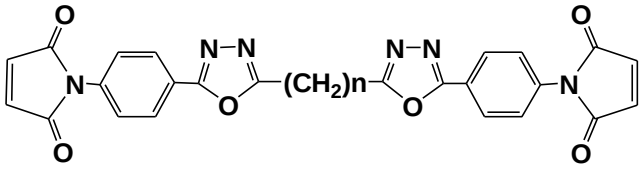
Table(2) physical properties of bis-1,3,4-Oxadiazole derivatives [6-10].

Compd. NO.	n	Molecular Formula	Color	M.P °C	Yield %	Rf	Crystallization Solvent
6	-	$C_{16}H_{12}N_6O_2$	White	195-197	70	0.58	Ethanol
7	1	$C_{17}H_{14}N_6O_2$	White	210-212	67	0.52	Ethanol
8	2	$C_{18}H_{16}N_6O_2$	White	215-217	74	0.65	Ethanol
9	3	$C_{19}H_{18}N_6O_2$	White	225-227	78	0.70	Ethanol
10	4	$C_{20}H_{20}N_6O_2$	Light Yellow	200-202	70	0.65	Ethanol



Table(3) physical properties of bis- maleamic acid derivatives [11-15] .

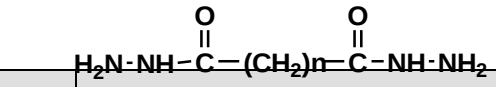
Compd. No.	n	Molecular Formula	Color	M.P ^{o}C	Yield %	Rf	Crystallization Solvent
11	-	$C_{24}H_{16}N_6O_8$	Light Yellow	212-213	77	0.72	Ethanol
12	1	$C_{25}H_{18}N_6O_8$	Yellow	224-226	70	0.78	Ethanol
13	2	$C_{26}H_{20}N_6O_8$	Yellow	230-232	85	0.88	Ethanol
14	3	$C_{27}H_{22}N_6O_8$	Dark Yellow	215-217	80	0.90	Ethanol
15	4	$C_{28}H_{24}N_6O_8$	Yellow	240-242	82	0.83	Ethanol



Table(4) physical properties of bis- maleimide derivatives [16-20] .

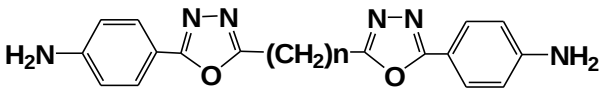
Compd. No.	n	Molecular Formula	Color	M.P ^{o}C	Yield %	Rf	Crystallization Solvent
16	-	$C_{24}H_{12}N_6O_6$	Yellow	160-162	70	0.67	Ethanol+Dioxane
17	1	$C_{25}H_{14}N_6O_6$	Yellow	130-132	72	0.75	Ethanol+ Acetone
18	2	$C_{26}H_{16}N_6O_6$	Yellow	175-177	68	0.73	Ethanol+ Acetone
19	3	$C_{27}H_{18}N_6O_6$	Yellow	150-152	80	0.60	Ethanol+ Acetone
20	4	$C_{28}H_{20}N_6O_6$	Yellow	180-182	70	0.64	Ethanol+ Acetone

Table (5): UV-Vis (nm) and Infra-red absorption (cm^{-1}) of bis aliphatic carboxylic acid hydrazide [1-5]



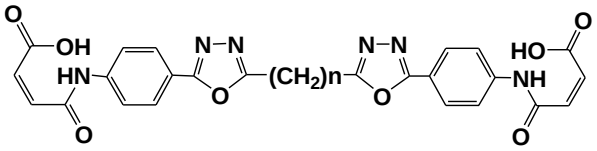
Comp. No.	n	UV,λmax (nm),EtOH	IR,(KBr)cm^{-1}						
		λmax.1 λmax.2	ν(NH_2) asy. sy.	ν (NH)	ν(CH_2) asy. sy.	Amide I	Amide II	Amide III	ν (C-C)
1	-	240 290	3390 3290	3137	-----	1681	1640	1260	-----
2	1	240 290	3301 3201	3132	2968 2879	1666	1620	1249	-----
3	2	230 280	3311 3199	3100	2918 2862	1660	1625	1240	985
4	3	207 225	3390 3220	3140	2925 2852	1677	1630	1230	927
5	4	250 356	3315 3280	3147	2925 2862	1689	1638	1223	985

Table (6): UV-Vis (nm) and Infra-red absorption (cm^{-1}) of bis1,3,4-Oxadiazole derivatives [6-10]



Comp. No.	n	UV,λmax (nm),EtOH	IR,(KBr)cm^{-1}							
		λmax.1 λmax.2	ν(NH_2) asy. sy.	ν(=CH) δ (NH)	ν(CH_2) asy. sy.	ν(C=N) ν(C-N)	ν(C=C) Ar	ν(C-O-C) asy. sy.	ν(N-N) ν (C-C)	δ (=C-H) in plan bending
6	-	240 320	3428 3330	3068 1579	----- -----	1652 1310	1570 1460	1236 1030	1010 -----	-----
7	1	230 310	3423 3373	3072 1610	2983 2889	1660 1301	1575 1475	1240 1040	1012 -----	1114
8	2	232 294	3461 3363	3060 1629	2977 2866	1664 1319	1600 1470	1290 1072	1072 1012	1172
9	3	240 280	3444 3366	3070 1570	2999 2860	1654 1326	1579 1482	1230 1060	1010 1070	1070
10	4	235 296	3441 3328	3068 1656	2916 2823	1656 1326	1581 1470	1236 1050	1010 1068	1068

Table (7): UV-Vis (nm) and Infra-red absorption (cm^{-1}) of bis- maleamic acid derivatives [11-15].



Comp. No.	N	UV,λmax (nm),EtOH	IR,(KBr)cm^{-1}							
		λmax.1 λmax.2	ν(OH) δ(OH)	ν(NH) δ (NH)	ν(CH_2) asy. sy.	ν(C=O) acid ν(C=O) amide	ν(C=N) ν(C=C) olefin	ν(C-N) ν(=C-H) olefin	ν(C=C)Ar ν(=C-H)Ar	ν(C-O-C) asy. sy.
11	-	250 340	3418 920	3272 1539	----- -----	1715 1668	1620 1630	1319 3020	1573 1480 3076	1288 1012
12	1	280 340	3410 920	3211 1541	2958 2894	1700 1670	1640 1600	1321 3030	1581 1470 3106	1230 1030
13	2	240 335	3421 940	3271 1539	2929 2858	1710 1660	1640 1560	1320 3020	1571 1480 3080	1260 1040
14	3	270 350	3446 945	3209 1542	2960 2877	1715 1670	1620 1602	1313 3020	1579 1475 3070	1260 1035
15	4	274 360	3426 930	3209 1540	2995 2858	1720 1665	1620 1620	1321 3010	1581 1470 3105	1268 1050

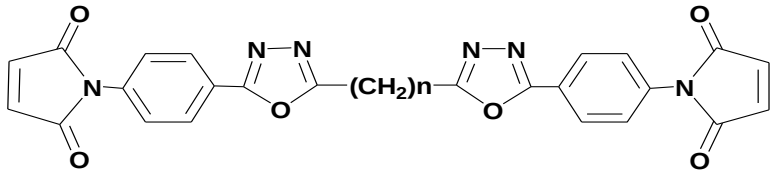


Table (8): UV-Vis (nm) and Infra-red absorption (cm^{-1}) of bis- maleimide derivatives

Comp. No.	N	UV,λmax (nm),EtOH	IR,(KBr)cm^{-1}						
		λmax.1 λmax.2	ν(=C-H)Ar ν(=C-H) olefinic	ν(CH_2) asy. sy.	ν(C=O) Imide	ν(C=C) olefin ν(C=N)	ν(C=C) Ar	ν(C-O-C) asy. sy.	ν (C-N) ν (N-N)
16	-	240 325	3070 3020	----- -----	1710	1654 1612	1579 1456	1215 1012	1326 1068
17	1	215 300	3120 3020	2937 2890	1710	1633 1620	1571 1460	1240 1040	1320 1045
18	2	222 390	3101 2024	2923 2855	1718	1632 1624	1552 1470	1270 1045	1327 1064
19	3	224 315	3105 3010	2927 2856	1710	1672 1640	1591 1470	1270 1070	1321 1034
20	4	230 318	3115 3020	2937 2860	1705	1640 1610	1571 1472	1267 1060	1315 1050

Table (9) Antibacterial activity of bis 1,3,4- Oxadiazole derivatives.[6-10]

Comp. No.	*St. aureus*	*E. coli*	*Sal. typhi*	*Ps . aeruginosa*
6	+	±	-	-
7	+	±	-	-
8	+	+	-	-
9	±	+	±	-
10	+	±	-	-

Note: (-) = (No Inhibition) , (+) = (5-10)mm , (++) = (10-20)mm , (+++) = (More than 20)mm .

Table (10) Antibacterial activity of bis - maleamic acid derivatives.[11-15]

Comp. No.	*St. aureus*	*E. coli*	*Sal. typhi*	*Ps . aeruginosa*
11	++	+	±	±
12	±	+	±	-
13	+	++	±	±
14	+	+	+	±
15	±	+	+	-

Table (11) Antibacterial activity of bis- maleimide derivatives.[16-20]

Comp. No.	*St. aureus*	*E. coli*	*Sal. typhi*	*Ps . aeruginosa*
16	+	-	-	-
17	±	±	-	-
18	+	±	-	-
19	±	±	±	-
20	±	±	-	-

Table (12) Antibacterial activity of control samples.

Comp. No.	*St. aureus*	*E. coli*	*Sal. typhi*	*Ps . aeruginosa*
C_1	±	+	-	-
C_2	±	±	±	-
C_3	+	±	-	-
blank disk	-	-	-	-

C_1: Ampicillin C_2:Erythromycin C_3:Cloxacilin

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Colors of steric conformation

Atoms	C	O	N	H	Cl
Color	Black	Red	Blue	Gray	Green

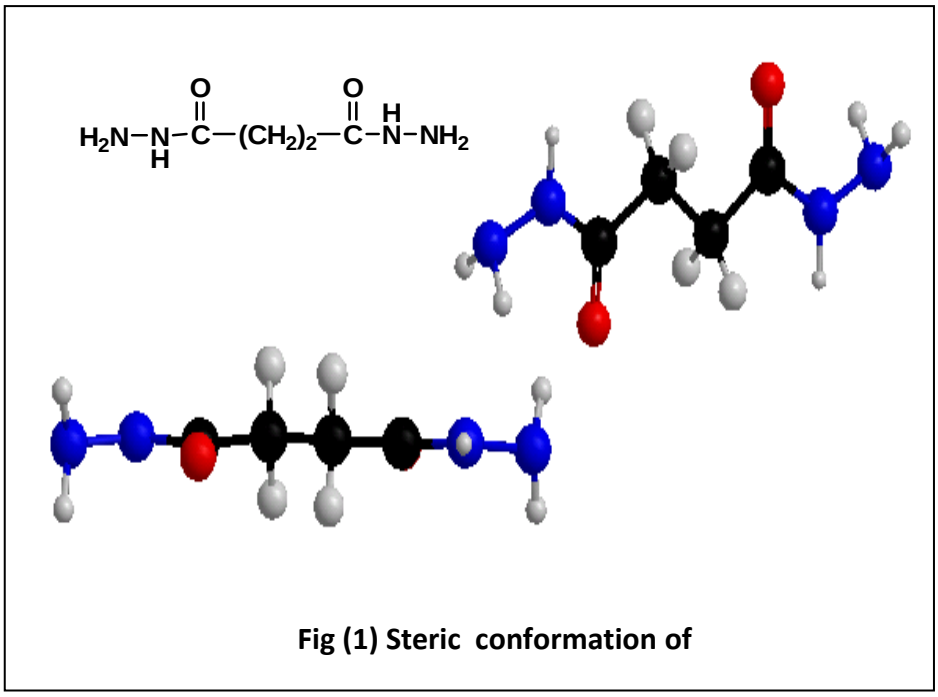

Fig (1) Steric conformation of

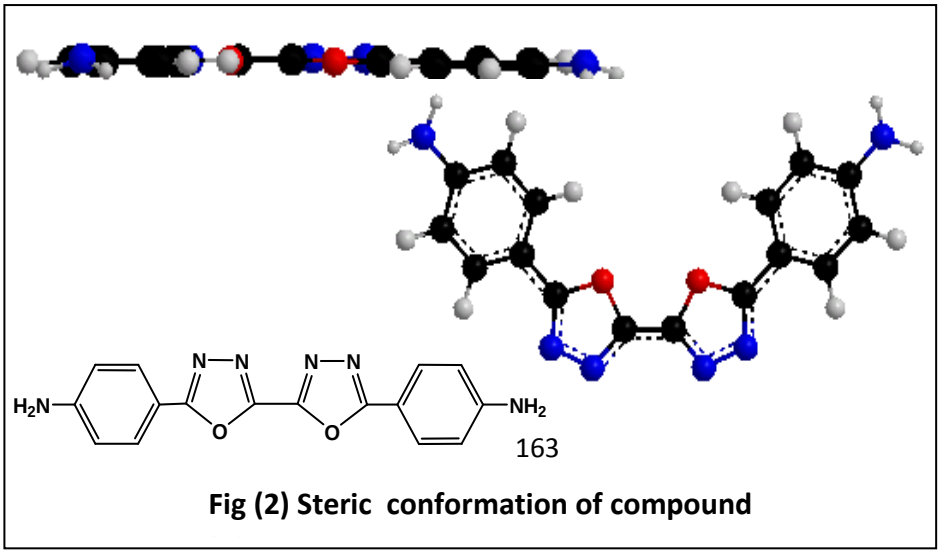

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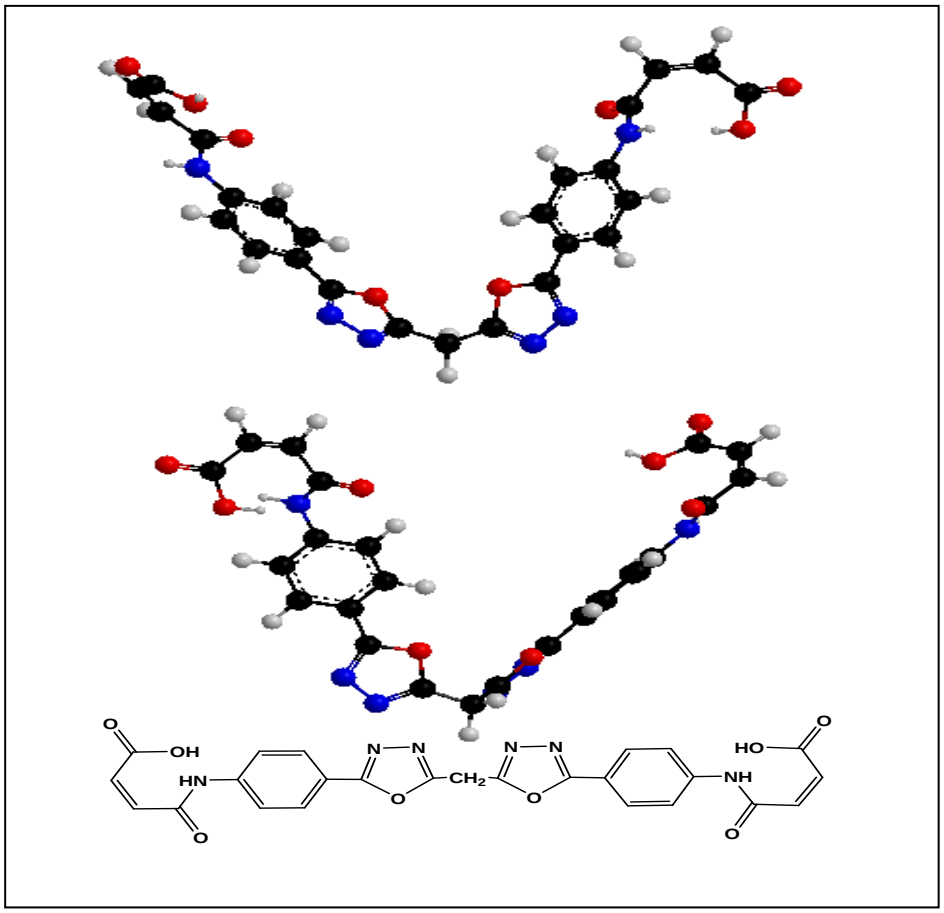
Fig (2) Steric conformation of compound



Fig(3) steric conformation of compound [12]

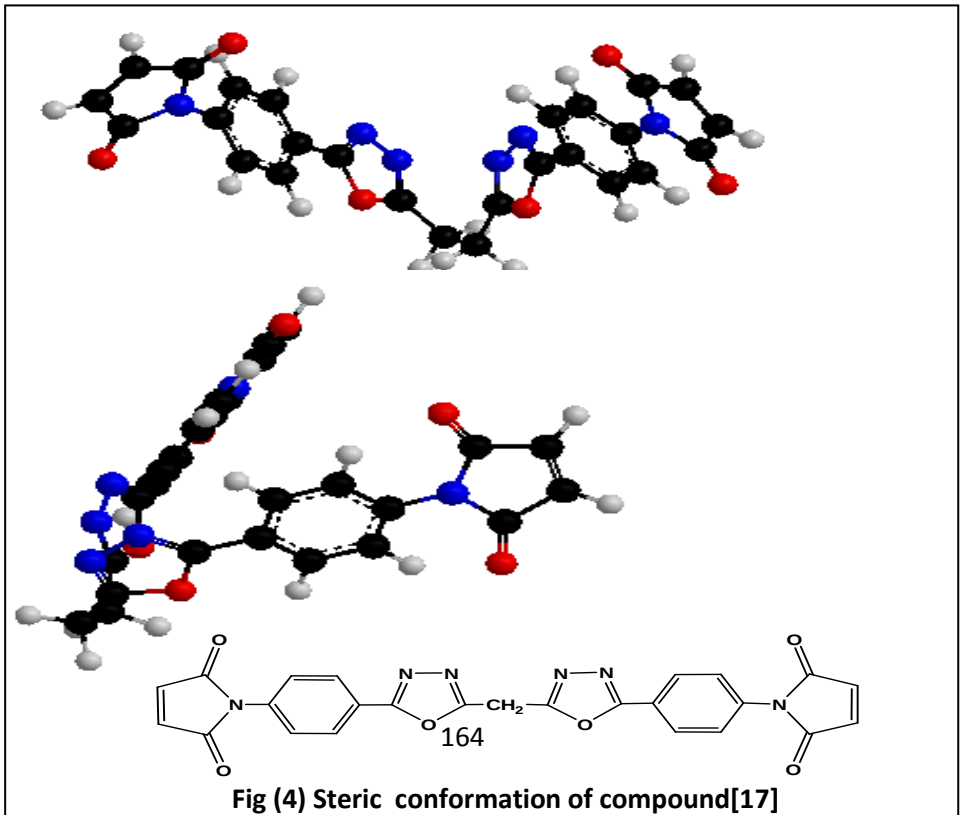
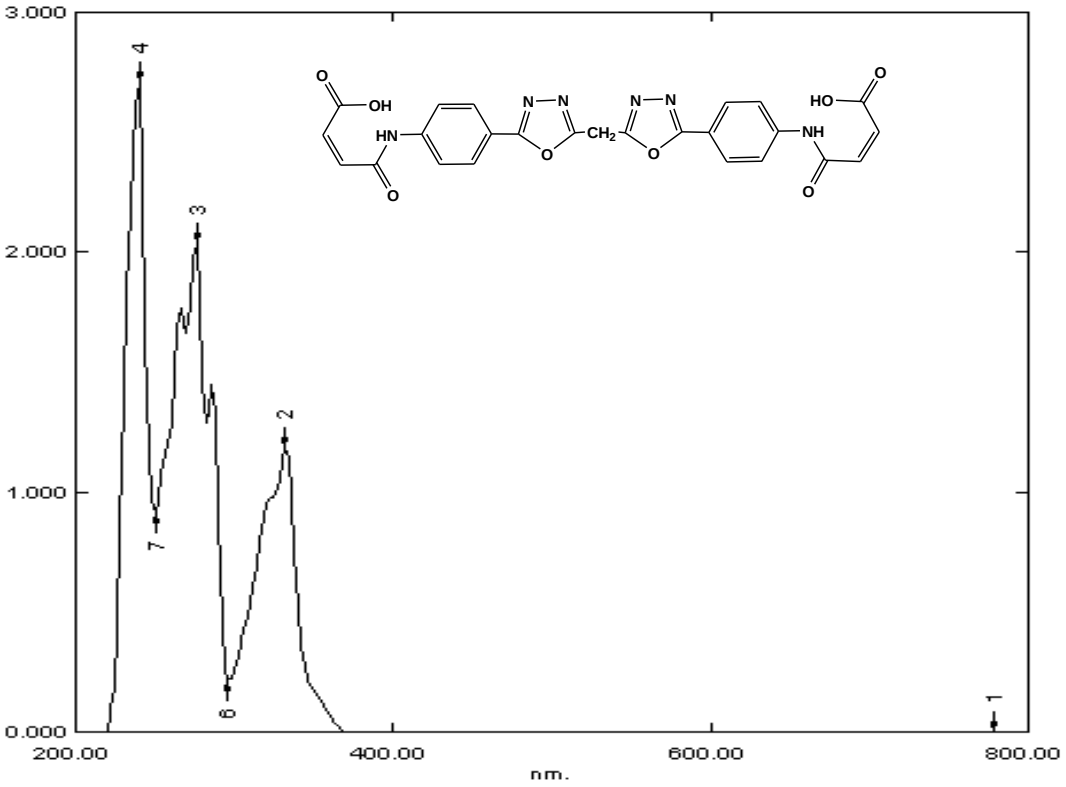
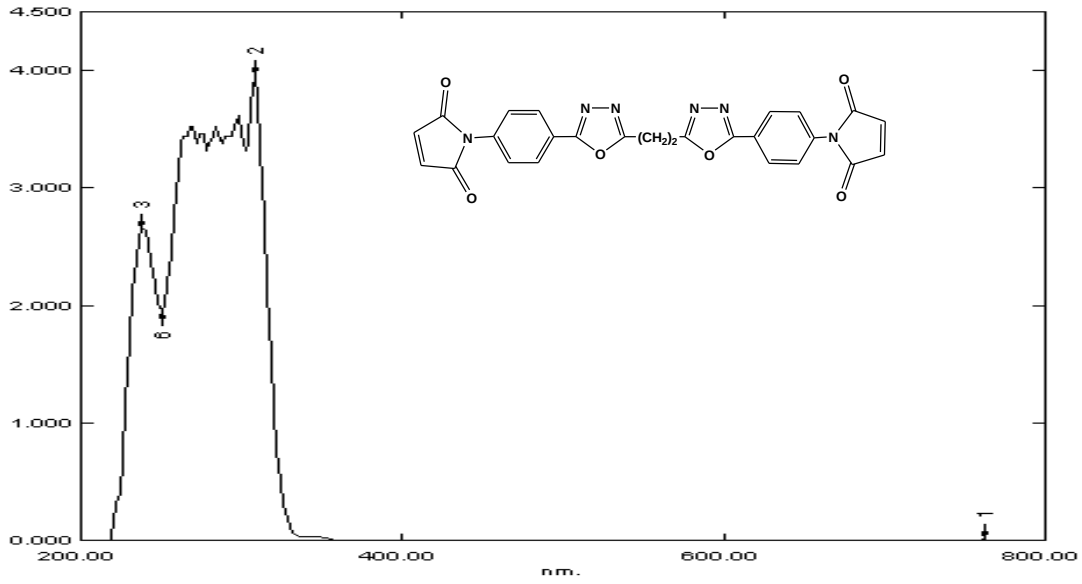


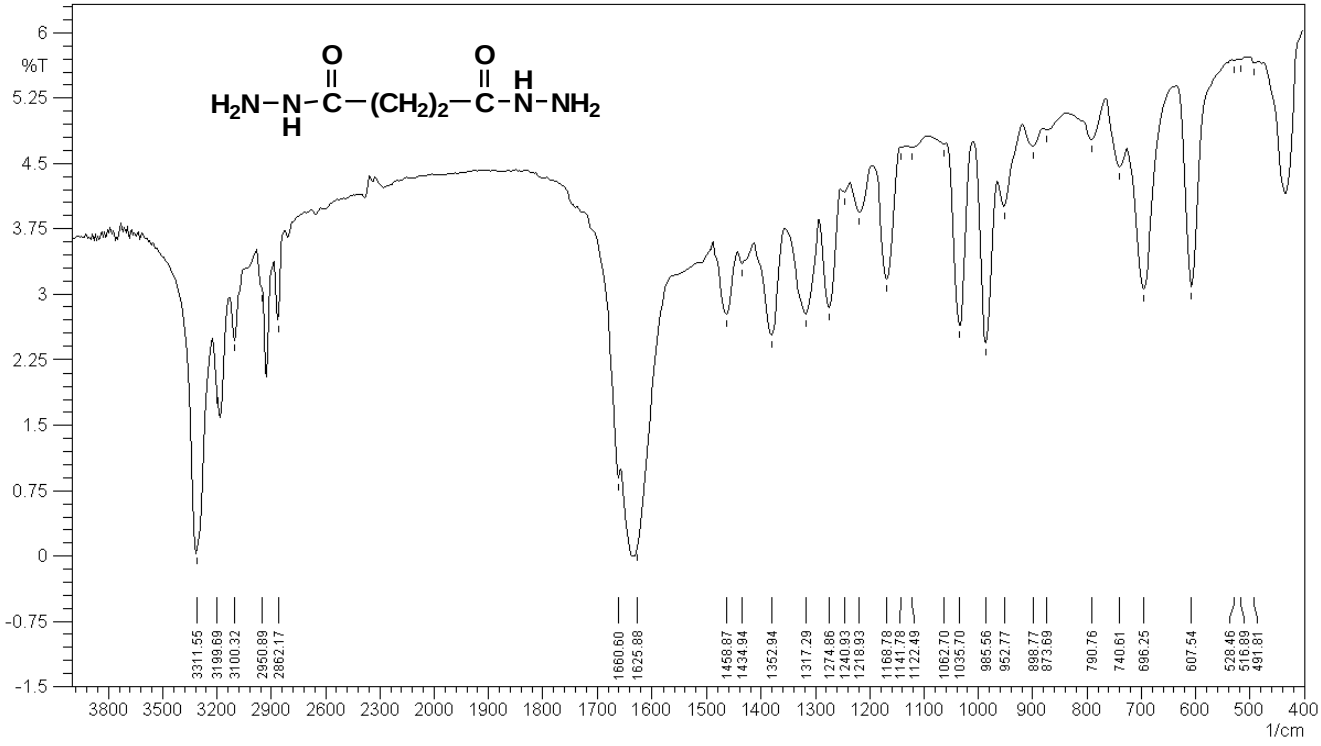
Fig (4) Steric conformation of compound[17]



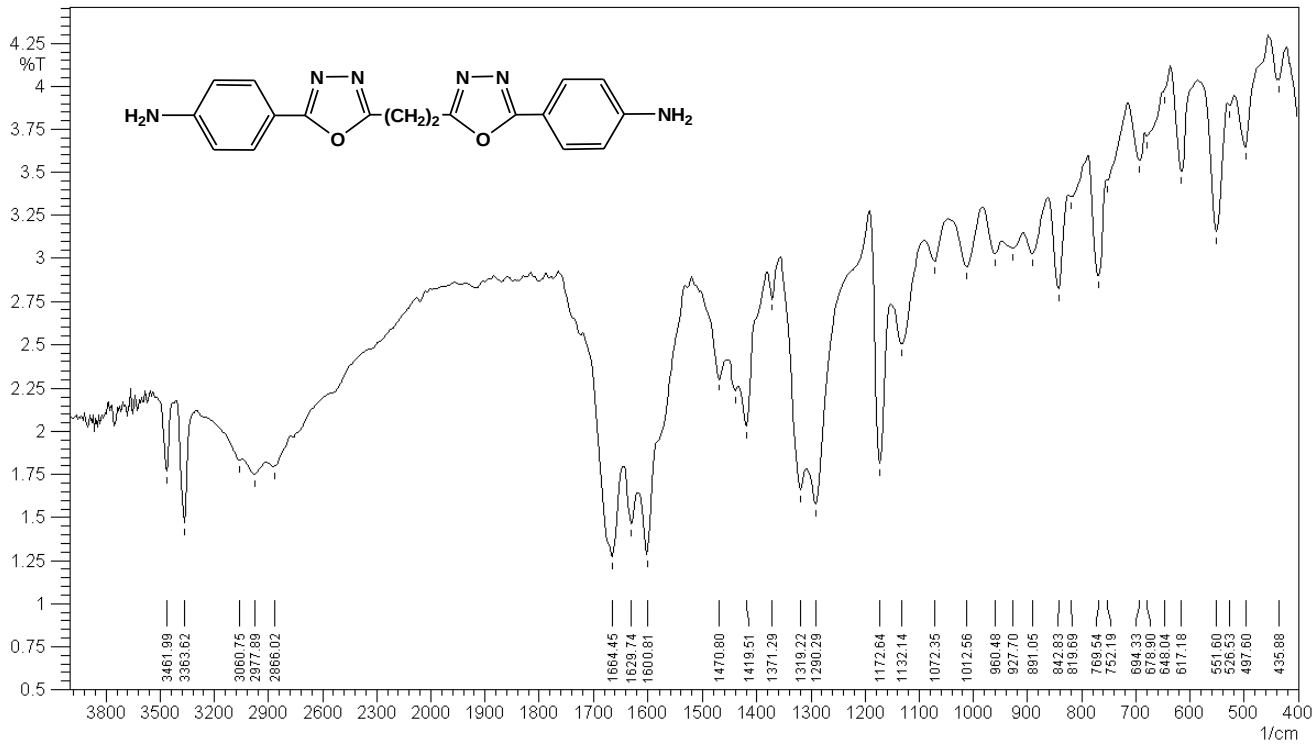
Fig(5) UV spectrum of compound [12].



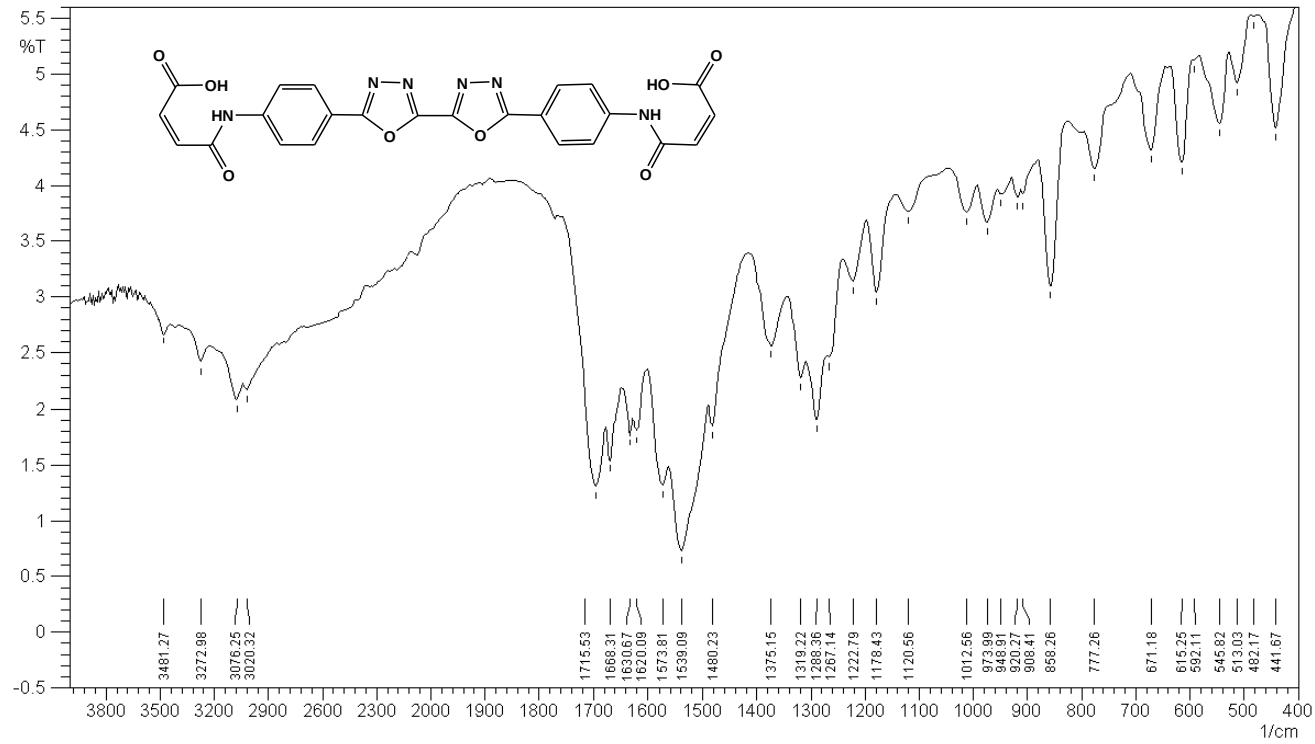
Fig(6) UV spectrum of compound [18].



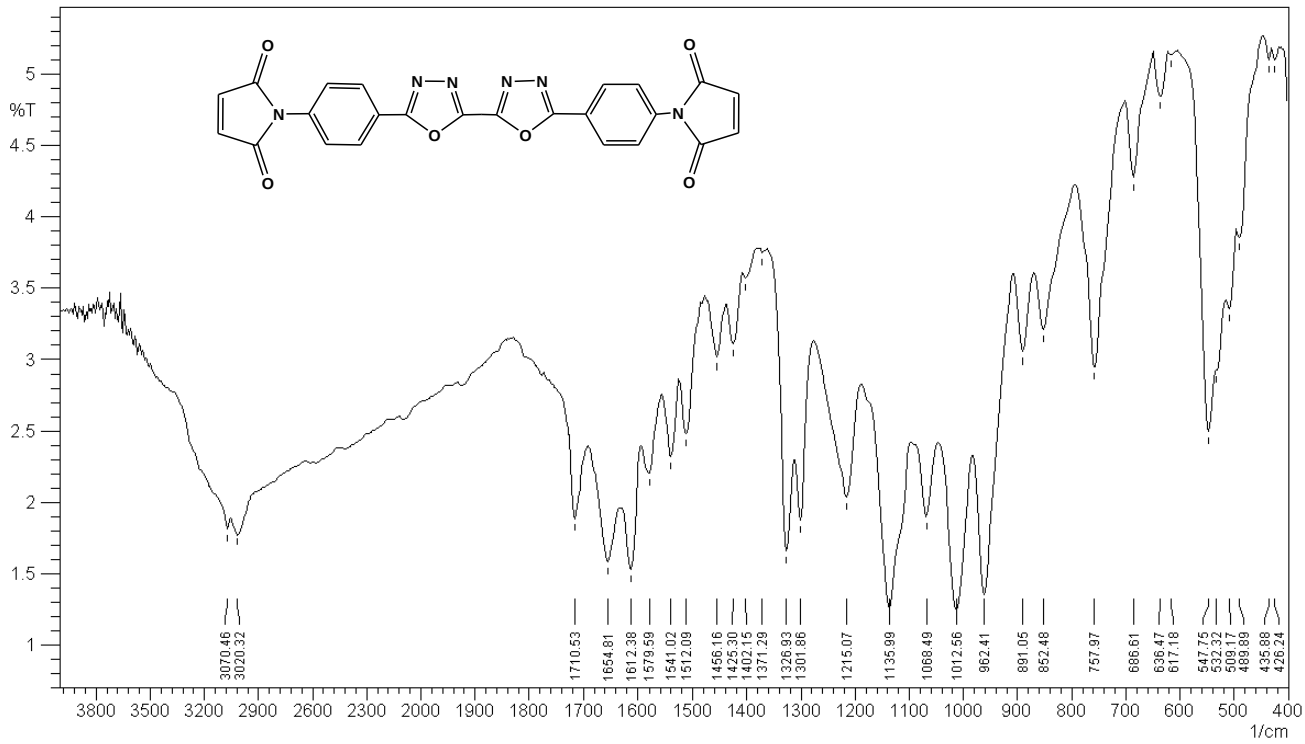
Fig(7) IR spectrum of compound [3].



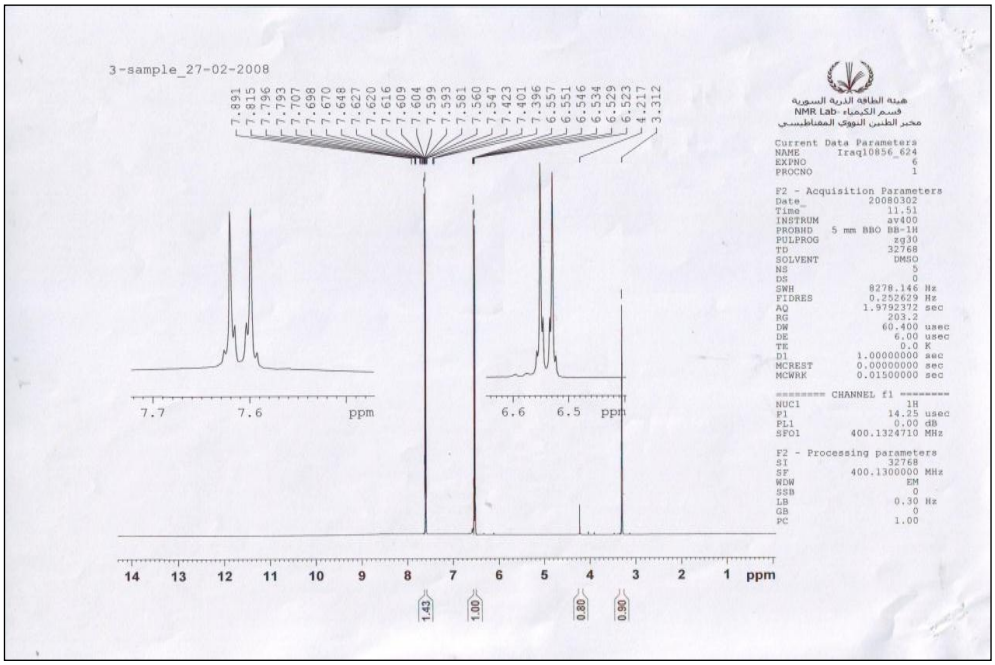
Fig(8) IR spectrum of compound [8].



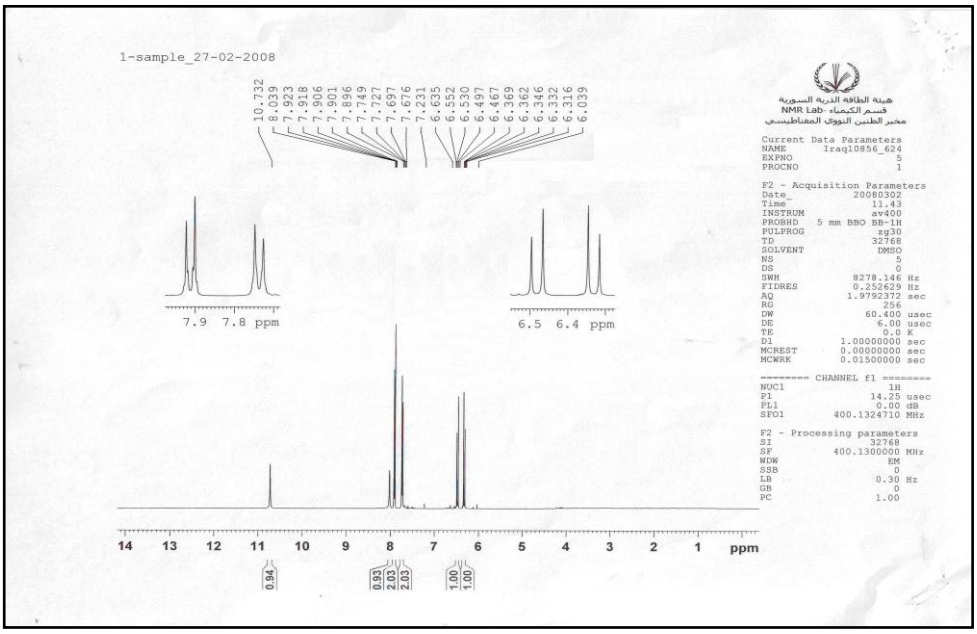
Fig(9) IR spectrum of compound [11].



Fig(10) IR spectrum of compound [16].



Fig(11) H-NMR spectrum of compound [7].



Fig(12) H-NMR spectrum of compound [11]

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