Synthesis of Some New Substituted 1,3,4–Oxadiazoles and the study of their Biological Activity

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Abstract

Substituted 1,3,4-oxadiazoles are well known as biological active agents. Several compounds of this group were synthesized by using coumarin derivatives as starting material The structures of the new compounds were established on bases of elemental analysis, physical and spectral data.

الخلاصة

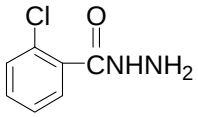
عرفت مركبات 1, 3,4- أوكسادايازول المعوضة بفعاليتها ألبايولوجية. تم في هذا البحث تحـضير عدداً من مركبات هذة المجموعة وبأستخدام مشتقات الكومارين كمواد أولية. شخـصت تراكيـب المركبـات الجديدة بالطرق الطيفية والفيزياوية.

Introduction

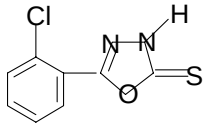
1,3,4- oxadiazoles derivatives are know to have biological, medical and industrial applications[1].

Some derivatives show antibacterial[2] fungicide[3] anti–inflammatory and hypotensive action[4].

The biological activity of these derivatives has drawn the attention of many workers and researchers who attempted to synthesize substituted oxadiazoles. When a mixture of 2-chlorobenzhydrazide (1) and carbon disulfide in the presence of potassium hydroxid in absolute ethanol was refluxed for 12 hours it offered 3-substituted-5-(2-chlorophenyl)-1,3,4-oxadiazol-2-thione[5] (2). Other oxadiazole derivatives (4) were obtained by the reaction of hydrazide (3) with cyanogen bromide[6] and also the reaction of hydrazide with carboxylic acid in the presence of phosphoric acid[7] or phosphorous oxychloride[8].

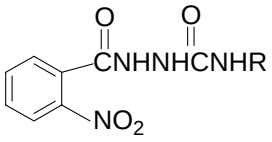


(1)

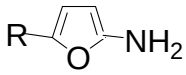


(2)

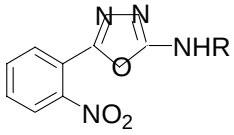
(3)



(5)



(4)



(6)

Similarly oxadiazole (6) was obtained by the treatment of (5) with lead oxide[9], mercury oxide[10] and Dicyclohexylcarbodiimide (Dcc)[11]. Phosphorous pentaoxide was also used for the synthesis of oxadiazole[12].

In this paper the synthesis of some new 1,3,4-oxadizole is reported.

Experimental

The melting points were measured on Kofler hot stage apparatus and were uncorrected. Elemental analysis measurements of C, H and N were obtained using 1106 CE Carlo-Erba.

The HNMR were recorded on Hitachi Perkin Elemer, R 248, 60 MHz instrument using DMSO-d6, as a solvent with tetramethylsilane as the internal reference. The IR spectra were recorded on a Pye-Unicam SP 1100 Infra red Spectrophotometer and U.V. spectra were carried out on shimadzu U.V.-Visible recording spectrophotometer.

4-Methyl-7-hydroxy coumarin (7):

This was prepared as mentioned in literature[13] and yielded 98% m.p. 183-185ċ (lit. m.p. 185ºC).

4-Methyl-7-O- (ethoxy carbonyl methyl) coumarin (8):

This was prepared as mentioned in liteature[14] and yielded 97% m.p. 100-102ºC (lit. m.p. 102ºC).

Ethyl coumarin-3-carboxylate (9):

This was prepared as mentioned in the litrature[15] and yielded 77% m.p. 92-90ºC (lit. m.p. 94ºC)

4-Methyl-7-coumarinloxy methyl hydrazide (10) and coumarin-3-carboxylic acid hydrazide (11)

Method 1[16]:

(0.15mol) of ester (8) or (9) and (o.15 mole, 7.26ml) of hydrazine hydrate (99%) in absolute ethanol (100ml) were refluxed for 10 hours. After the reaction mixture was concentrated, when a solid was obtained; it was filtered, washed with cold water and recrystallized from ethanol. The physical and spectral data were given in tables (1 and 2)

Method 2:

(0.05mol.) from ester (8)or(9) with (25ml) hydrazine hydrate (99%) were refluxed for 45min. The product crystallized out on cooling was washed with water, recrystallized from ethanol.See Tables (1 and 2).

1-(4-Methyl-7-coumarinloxy methyl carbonyl)-4-substituted thio-semicarbazide (12-14):

Method 1[17]:

An equimolecular quantity of hydrazide (10)(0.002mole, 0.496g) and (0.002mole) substituted isothiocyanate in 40ml absolute ethanol was refluxed for 6 hours. The product was crystallized out on cooling, filtered, recrystallized from ethanol. Tables (3 and 4).

Method 2[17]:

Substituted isothiocyanate (0.01mole) and sodium hydroxide (0.01mol, 0.4g as a 2N solution) were added to the solution of compound (10) 0.01 mole in ethanol 20 ml. The mixture was stirred for 24 hours and filtered. The filtrate was acidified with hydrochloric acid. The precipitate was filtered and recrystallized from ethanol-water(50:50).Tables (3and 4).

5-(4-Methyl-7-coumarinloxy methyl)-2-substituted amino-1,3,4-oxa -dizole[18] (15-16).

Dissolve (0.005mole) from any 1-(4-Methyl-7-coumarinyloxy methyl carbonyl)-4-substituted thiosemicarbazide (12-14) in methanol (50ml), then add mercury oxide (0.0055mole, 1.2g.). Refluxed the mixture for 4 hours .The precipitate formed after filtration and evaporation of the solvent is washed with water and recrystallized from ethanol, Tables (5, 6).

5-(4-Methyl-7-coumarinloxy methyl)-2-amino-1, 3, 4-oxadiazole (17) and 5-(3-coumarinloxy)-2-amino-1, 3, 4-oxadizole[4] (18)

To an ethanloic solution (50ml) of hydrazide (9 or 11)(0.005mole) add cyanogen bromide (0.0055mole, 0.6g). The reaction mixture should be refluxed for 3hours. Cool and neutralize with potassium bicarbonate solution. The solid formed after adding crushed ice is to be filtered and recrystalized from chloroform. Tables (7,8)

5-(4-Methyl-7-coumarinloxy methyl)-2-substituted-1,3,4,oxadizole (19-27) and 5-(3-Coumarinyl)-2-substituted-1,3,4,oxadizol[7] (28-33)

An appropriate aromatic carboxylic acid (0.01mole) is added gradually, with stirring for 20 minutes, to a mixture of (0.01mole) of hydrazide (10 or 11) and syrupy phosphoric acid (85%) 10ml at 120ºC. The mixture is heated with stirring at this temperature for further 1houre then poured into ice water and left overnight. The precipitate is filtered off, wash with water and with 10% sodium carbonate solution ,recrystallized from ethanol .Tables (9,10)

5-(4-Methyl-7-coumarinyloxy methyl)-1,3,4-oxadizole-2-thiol [19](34)

To a solution containing 100ml of 95% ethanol and 0.01mole of potassium hydroxide, add ((0.01mole, 2.48g.) of hydrazide (10),(0.2 mole, 12ml) of carbon disulfide .Hold the mixture was held at reflux for 4-6 hours(or until most of the hydrogen sulfide is evolved) .After the concentration of the solution to a small volume, the residue is added to ice-water (60g). Acidify with hydrochloric acid (pH =5-6), filter and recystallize the solid from ethanol .m.p. 190ºC, 60%. The spectral data is on table (24).

Analysis	**C.**	**H.**	**N.**
Calc.	53.79	3.44	9.65
Found	53.54	3.30	9.52

1-Formyl-2-(4-methyl-7-coumarinloxy methyl carbonyl) hydrazine[12] (35):

A solution of hydrazide (10) (0.025 mole, 6.2 g) in formic acid (98%) (10 ml) is refluxed for 30 minutes. The solvent is evaporated and

the residue is cooled with ice water and recrystallized from methanol. m.p. 178-180˚C, 78%.

Analysis	C.	H.	N.
Calc.	56.52	4.34	10.14
Found	56.28	4.29	10.03

2- (4-Methyl -7- Coumarinyloxy methyl) -1,3,4- oxadiazle[12] (36):

To a solution of substituted 1-formyl hydrazine (35) (0.005 mole, 1.38 g) in xylene 100ml, phosphorous pentoxide (0.005 mole, 0.7 g) is added. The mixture is refluxed for 1 hour. The solvent is then evaporated and the residue is recystallized from methanol. m.p. 98-100ºC.,60%

Analysis	C.	H.	N
Calc.	60.46	3.87	10.85
Found	60.08	3.69	10.41

2,5 –bis (substituted)-1,3,4-oxadiazole (37-39):

Phosphoric acid 85% (10 ml) is added to a mixture of (0.0015 mole) hydrazides (10 or 11) and of the esters (0.0015 mole)(8 or 9). The mixture is heated at 120˚C for 1 hour Cool and add to ice water and let for 2 hours.

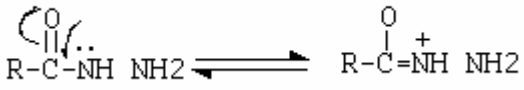
The residue is filtered and washed with water and recrystallized from ethanol, tables (11, 12).

Result and Discussion

The synthesis of new substituted 1,3,4-oxadiazoles may provide additional biologically active agents.

The ester (8) was synthesized by reaction of 4-methyl 7-hydroxy coumarin (7) with ethyl bromo acetate in the presence of anhydrous potassium carbonate, while ethyl cumarin-3-carboxylate (9) was prepared through the reaction of salicylaldehyde with diethyl malonate in the presence of 4-methyl pipyridine. These compounds were identified as mentioned in literatures [14.15]

Hydrazide (10 or 11) was obtained by refluxing the esters (8 or 9)
with 99% hydrazine hydrate in absolute ethanol. These hydrazides were identified by the appearance of the bands in the infra red spectrum in the following range: bands at 3500-3550 cm^{-1} for (N-H) stretching and also bands for carbonyl groups at (1600-1680 cm^{-1}) which is lower than the carbonyl group of ester due to the presence of resonances effect[20].



The ^{1}HNMR shows that the triplet and quartets bands for ester disappeared and instead of them new bands for (NNH2) appeared at (3.9 - 4.2) ppm and a broad band at (8.9 – 9.0) ppm for CONH which identified the hydrazide.

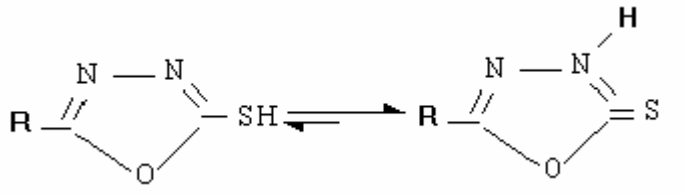
Condensation of the hydrazide (10) with suitable alkyl or aryl isothiocyante provided substituted thiosemicarbazide (12-14) which were identified by IR spectrum as following stretching bending at (1725–1760 cm^{-1}) for carbonyl group and bands at (3200-3350 cm^{-1}) for N-H stretching as well as bands at (1270-1300 cm^{-1})for thione groups (C=S). Bands for thiol disappeared and this explains the presence of these compounds in thione form in a solid state [21] . The spectrum of ^{1}HNMR gave a band between 2-4-2.5 ppm for CSNH and NHCS, also a singlet band appeared at 7.8-8.6 ppm.

for the CONH proton. Cyclization of compound (12-14) in the presence of mercury oxide in methanol offered the corresponding 5-(3- Methyl -7- coumarinloxy methyl) -2- substituted amino 1,3,4-oxadiazole (15-16). These compounds were identified by spectral data; the spectrum of IR shows the following absorbing bands, at (3150-3380 cm^{-1}) for N-H stretching banding, symmetrical stretching bands at (1230-1260 cm^{-1}) for C-O-C groups and absorption bands at (1610-1640 cm^{-1}) for C=N stretching band.

Also the spectrum of ^{1}HNMR gave results conforming to expectation, as in table (6). Refluxing hydrazide (10-11) with cyanogen bromide in ethanolic solution gives 5-(4-Methyl-7-coumarinyloxy methyl)-2-amino-1, 3, 4-oxadiazole (17) and 5-(3-coumarinyl)-2-amino- 1,3,4-oxadiazole (18) which were identified by I.R. spectrum through the disappearance of carbonyl band (C=O) for hydrazide and the appearance of band at (1100 cm^{-1})for symmetrical group C-O-C. Aband at (1650 cm^{-1}) for (C=N) stretching group, and bands at (3450-3500 cm^{-1}) were noticed for streching banding of N-H group. The ^{1}HNMR spectrum showed bands at (3.0-3.2 ppm) for the absorption of proton NH_2 groups substituted at oxadiazole ring and other bands appeared at the expected positions as shown in table (8)

Reaction of hydrazide (10 or 11) with different carboxylic acid in the presence of phosphoric acid (85%) at 120C°;offered 5-(4-Methyl -7-coumaringloxy methyl) -2- substituted -1,3,4- oxadiazole (19-27)and 5-(3-coumarinyl)-2-substituted–1,3,4 oxadiazoles(28-33)which were identified by I.R. spectrum which showed bands at (1090-1180 cm^{-1}) for streching band of (C-O-C) group. Other bands between (1600-1650 cm^{-1}) for streching (C=N)group were also noticed. ^{1}HNMR spectrum showed results as expected. See table (9)

In addition refluxing the hydrazide (10) with carbon disulfide in alcoholic potassium hydroxide gave 5-(4-Methyl 7- coumarinloxy methyl)-1,3,4-oxadiazole -2 thiol (34).This compound was identified by the appearance of streching band at(1060 cm^{-1}) for (C-O-C) group and the disappearance of streching band for carbonyl group of hydrazide. Absorption ban at((1640-1650 cm^{-1})for(C=N) and absorption band for (C=S) group appeared at (1200 cm^{-1}) and this confirms the presence of resonance form [20]

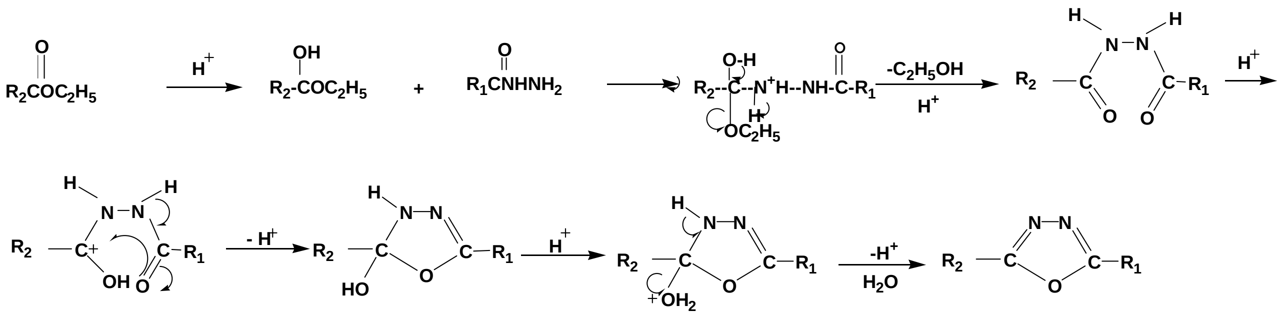


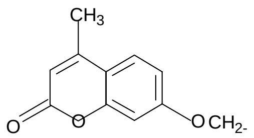
1-Formyl -2- (4-methyl -7-coumarinyloxy methyl carbonyl) hydrazide (35) was obtained by refluxing the hydrazide (10) with formic acid. This compound was identified by IR spectrum which showed a band at (1685 cm^{-1})for stretching banding of carbonyl group (C=O) for aldehyde and a band at(1730 cm^{-1}) for carbonyl group of hydrazide. Another band appeared at (3400 cm^{-1}) for N-H streching band. Cyclization of compound (35) with phosphorous pentoxide in xylene liquid led to the formation 2-(4-Methyl -7-coumarinloxy methyl)-1,3,4- oxdiazole

(36) which was identified by IR Spectrum by the disappearance of the streching band for carbonyl group of aldehyde and carbonyl group of hydrazide as well as (N-H) group. On the other hand a new band for streching banding for C=N group appeared at (1100 cm^{-1}) for (C-O-C) group streching banding.

Reaction of hydrazide (10 or 11) with ester (8 or 9)in the presence of phosphoric acid (85%) at 120˚c gave 2,5-disubsituted -1,3,4-oxadiazole (37-39) and the suggested mechanism for these reaction is as follows;

These compounds were identified by spectrum methods: the IR spectrum showed the disappearance of the following stretching bands for carbonyl ester hydrazide as well as the stretching banding of(C=N) group of hydrazide Bands at (1640-1650 cm^{-1}) for the stretching (C=N) group and bands at (1050-1130 cm^{-1}) for symmetrical stretching band of (C-O-C) group also appeared.



R1= 

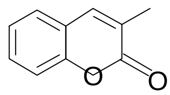
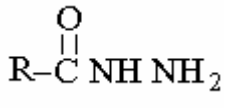
R2= 

Table (1): physical data for substituted hydrazide



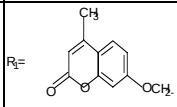
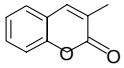
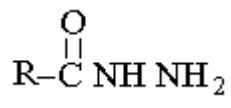
Compd. No.	R	M.p. C°	Yield %	Color	Analysis Calc./ Found C. H. N.
10		204-206	94	White	58.06 4.8 3 11.29 57.88 4.78 11.13
11		205-206	85	Yellow	58.82 3.92 13.72 58.46 4.01 13.58

Table (2): spectral data for substituted hydrazide



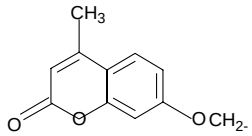
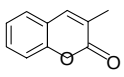
Compd. No.	R	U.V λmax nm EtoH	I.R V cm^{-1}		^{1}HNMR ς(ppm) Solv. DMSO-d6
			N-H	C=O	
10		248	3500	1680	2.2(s,3H) CH3 4.2(b,2H)NH3 5.1(s,2H)OCH2 6.12-7.5(m,4H)CH, Ar-H 9.0(b,1H)CONH
11		310	3550	1660	4.0(b,2H)NNH2 7.2-7.63(m,4H)Ar-H 8.9(b,1H)CONH 8.72(s,1H)CH

Table (3): Physical data for 1-(4-methyl-7-coumarinloxy methyl carbonyl)-4-substituted thiosemicarbazide

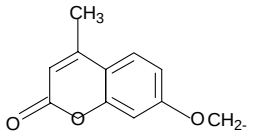
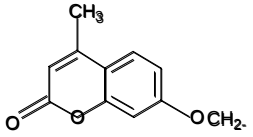
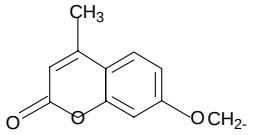
Compd. No.	R1	R2	M.P °C	Yield %	color	Analysis Calc./ Found C.	H.	N.
12			178-0	78	White	59.53 59.28	4.43 4.38	10.96 10.79
13		CH3CH2	224-5	60	White	53.73 53.28	5.07 4.97	12.53 12.42
14		CH3	170-2	75	White	52.23 51.98	4.67 4.73	13.08 12.96

Table (4) : Spectral data for 1-(4-methyl-7-coumarinloxy methyl carbonyl)-4-substituted thiosemicarbazide.

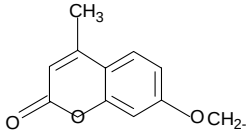
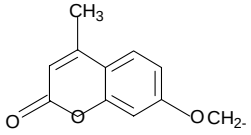
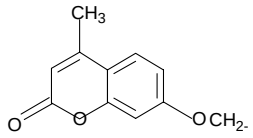
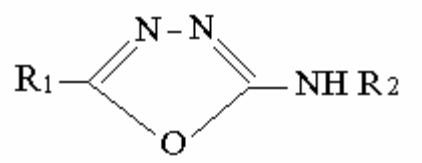
Compd . No.	R1	R2	U.V λMax nm EtOH	I.R Vcm^{-1} N-H C=O C=S	^{1}HNMR ς(ppm) Solv. DMSO-d6
12			324	3350 1725 1280	2.4(s,3H) CH3 3.0(s,1H) CSNH 3.9(s,1H)NHCS 4.7(s,2H)OCH2 6.0(s,1H)C-H 6.7(m,8H)Ar-H 8.7(b,1H)CONH
13		C2H5	330	3200 1730 1270	1.2(t,3m)CH3 2.3(s,3H)CH3 2.5(s,1H)CSNH 2.8(s,1H)NHCS 3.0(q,2H)CH2 5.0(s,2H)OCH2 6.7-7.5(m,4H)CH,Ar-H 8.7 (b,1H)CONH
14		CH3	333	3300 1760 1300	2.4(s,3H)CH3 2.6(s,3H)CH3 2.7(s,1H)CSNH 2.9(s,1H)NHCS 4.9(s,2H)OCH2 6.1(s,1H)CH 6.7-7.8(m,3H)Ar-H 8.8 (b,1H)CONH

Table (5): Physical data for 5-(4-methyl-7-coumarinloxy methyl) 2-subistituted amino-1,3,4-oxadiazole



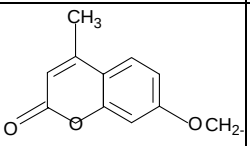
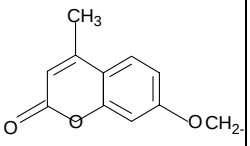
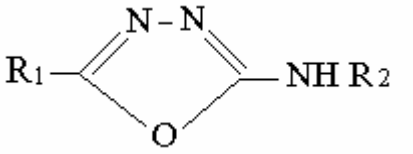
Compd. No.	R1	R2	M.p C°	Yield %	Color	Analysis Calc.*1* Found C. H. N.
15			188-0	57	Yellow	65.32 4.29 12.03 64.9 7 4.19 11.94
16		CH3 CH2	231-3	63	white	59.80 4.98 13.95 59.55 5.03 13.82

Table (6) : Spectral data for 5(methyl-7-coumarinyloxy methyl) 2-substituted amino 1,3,4 oxadiazole



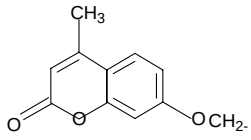
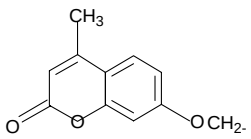
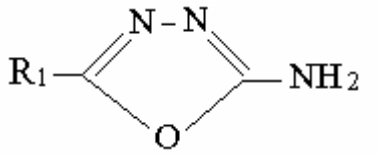
Compd. No.	R1	R2	U.V λmax nm EOH	IR Vcm^{-1} N-H C=N C-O-C	^{1}HNMR ς(ppm) solv. DMSO-d6
15			302	3380 1640 1230	2.3(S,3H)CH3 2.5(b,1H)NH 4.8(S,2H)OCH2 6.4-8.1(m,9H)Ar-H,CH
16		CH3CH2	348	3150 1610 1260	1.2(t,3H)CH3 2.4(s,3H)CH3 3.3(q,2H)CH2 4.1(b,1H)NH 4.9(s,2H)OCH2 6.6-9.1(m,4H)Ar-H,CH

Table (7): Physical data for 5-substituted 2-amino -1,3,4- oxadiazole



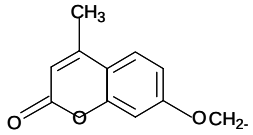
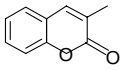
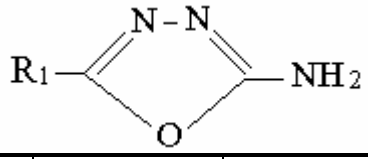
Compd. No.	R1	M.P C°	Yield%	Color	Analysis Calc.*1*Found C. H. N.
17		220-2	73	Pale yellow	57.14 4.02 15.38 56.89 3.98 15.22
18		178-0	50	Brown	57.64 3.05 18.34 57.41 3.00 18.24

Table (8) : Spectral data for 5-substituted 2-amino 1,3,4-oxadiazole



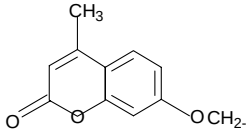
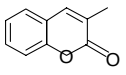
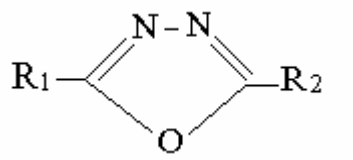
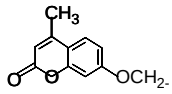
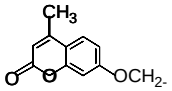
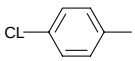
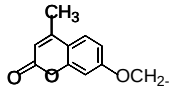
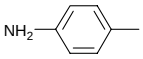
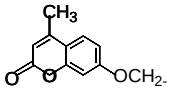
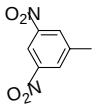
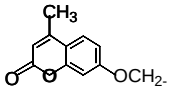
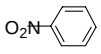
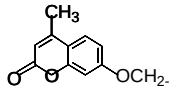
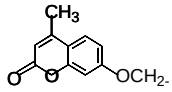
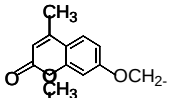
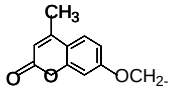
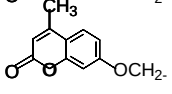
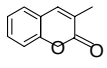
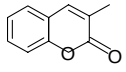
Compd. No.	R	U.V λMax nm EtOH	I.R Vcm^{-1} N-H,C=H C-O-C	'HNMR S(ppm) Solv. DMSO-d6
17		259	3500 1650 1100	2.3(s,3H)CH3 3.0(b,2H)NH2 4.8(s,2H)OCH2 6.1(s,1H)CH 6.7-8.0(m,3H)Ar-H
18		305	3450 1650 1100	

Table (9) : Physical data for 2,5 disubstituted 1,3,4- oxadiazole



Compd. No.	R1	R2	M.P °C	Yield %	color	Analysis Calc./ Found C. H. N.
19			188-0	70	White	68.26 4.19 8.38 67.26 4.23 8.24
20			173-5	2	White	61.87 3.52 7.59 61.59 3.60 7.43
21			180-2	91	Pale yellow	65.32 4.29 12.03 64.99 4.32 11.88
22			170-1	85	Pale yellow	53.77 2.83 13.20 53.28 2.95 13.08
23			218-0	83 [	White	60.15 3.43 11.08 59.79 3.35 10.96
24			193-5	60	White	60.15 3.43 11.08 59.88 3.38 10.08
25		$CLCH_2$--	225-7	53	Yellow	54.81 3.58 9.13 54.33 3.65 9.08
26			177-9	94	White	64.58 4.03 6.27 64.21 3.98 6.18
27			140-2	85	White	65.67 3.48 6.96 65.34 3.41 6.79
28			198-0	62	Yellow Pale brown	70.34 3.44 9.65 69.98 3.35 9.49 62.86 2.77 8.26

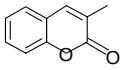
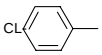
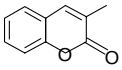
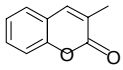
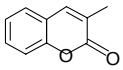
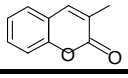
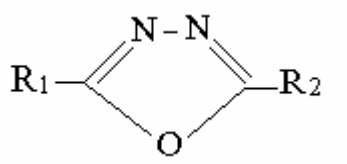
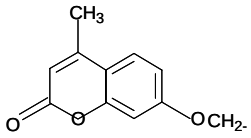
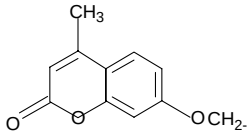
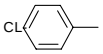
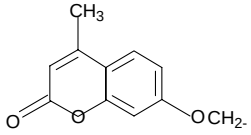
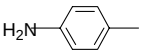
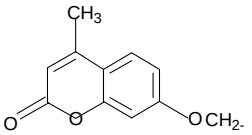
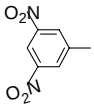
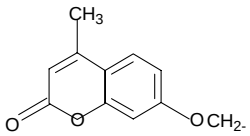
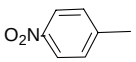
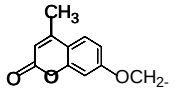
29			190-2 207-9	59 87	Brown	62.55 2.70 8.59 66.88 3.60 13.77 66.64 3.55 13.70
30						
31		CL_3C--	210-2	62	Brown	43.43 1.50 8.44 43.21 1.42 8.33
32		$CLCH_2$--	218-0	75	Pale Yellow	54.85 2.66 10.66 54.54 2.71 10.51
33		H_2N-CH_2--	217-9	80	Pale yellow	59.25 3.70 17.28 58.89 3.64 17.17

Table (10) : Spectral data for 2,5-disubstituted oxadiazole



Compd No.	R1	R2	U.V λmax nm EtoH	IR Vcm^{-1} N-H C=N C=S C-O-C	^{1}HNMR ς(ppm) Solv.DMSO-d6
19			350	___,1650 ___,1100	2.2(s,3H)CH3 4.4(s,2H)OCH2 6.0(s,1H)CH 6.0-7.6(m,8H)Ar-H
20			348	___,1640 __,1090	2.4(s,3H)CH3 5.1(s,2H)OCH2 6.1(s,1H)CH 6.6-7.8(m,7H) Ar-H
21			254	3350,1660 1095	4.1(b,2H)NH2 2.2(s,3H)CH3 4.7(s,2H)OCH2 6.2(s,1H)CH 6.5-7.6(m,7H)Ar-H
22			261	___,1640 ___,1105	2.2(s,3H)CH3 4.6(s,2H)OCH2 5.9(s,1H)CH 6.6-8.5(m,6H)Ar-H
23			349	___,1620 ___,1120	2.2(s,3H)CH3 4.6(s,2H)OCH2 6.0(s,1H)CH 6.6-8.4(m,7H)Ar-H
24			346	___,1620 ___,1120	2.2(s,3H)CH3 4.6(s,2H)OCH2 6.0(s,1H)CH 6.6-8.4(m,7H)Ar-H

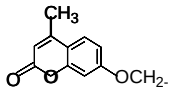
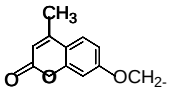
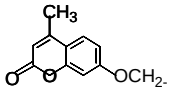
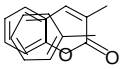
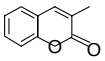
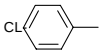
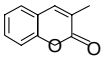
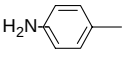
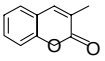
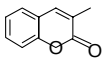
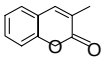
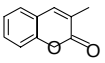
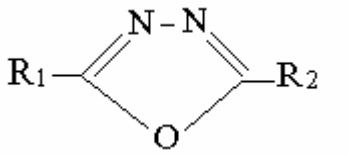
25		CL CH_2-	327	_ __,1650 ___,1110	
26		R_1--	329	___,1630 ___,1120	
27			265 245	___,1640 ___,1120	
28			248	___,1640 ___,1110	
29			296	__,1640 ___,1100	
30		CL_3C--	310	3300,1620 ___,1090	
31		$CLCH_2$--	346	_ __,1600 ___,1150	
32		H_2N-CH_2--	309	___,1610 ___,1180	
33				3250,1635 ---,1110	

Table (11) :physical data for 2,5-bis(substituted)-1,3,4-oxadiazole



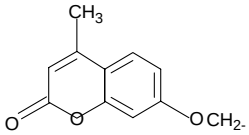
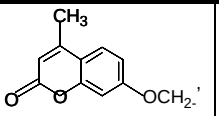
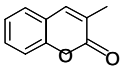
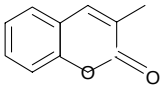
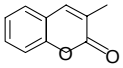
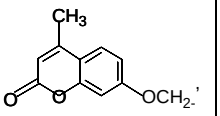
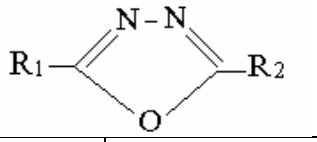
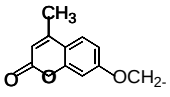
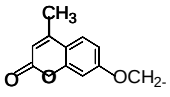
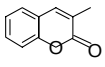
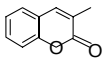
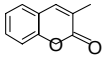
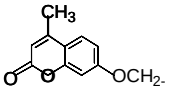
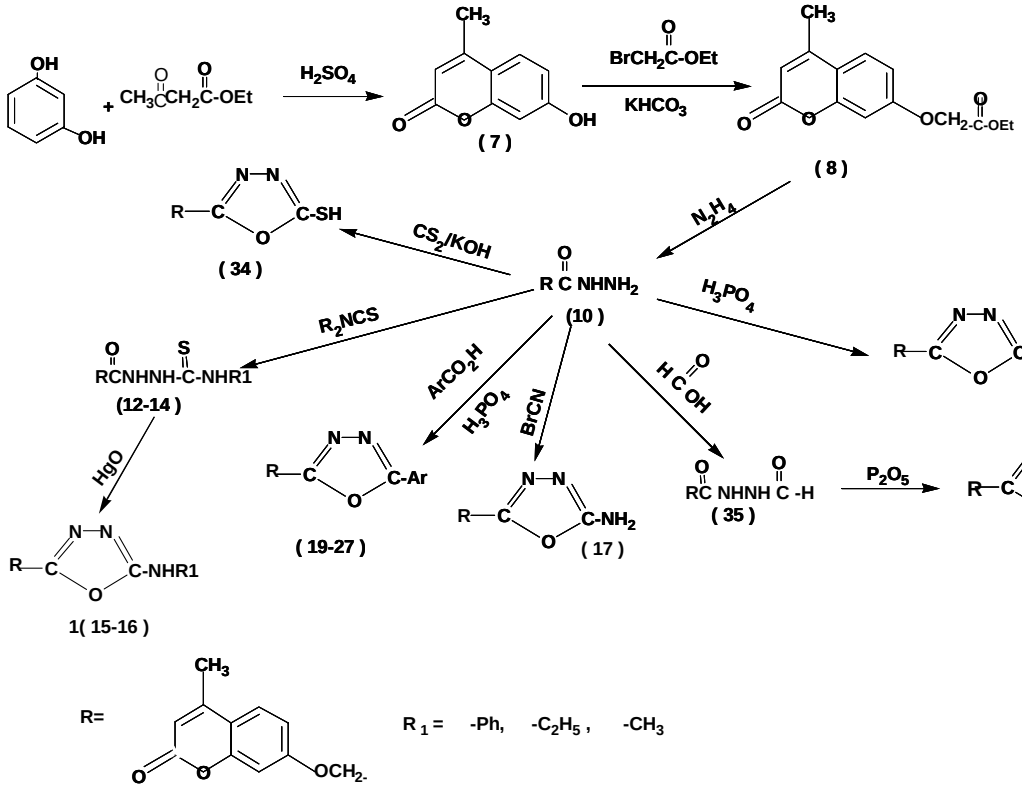
Compd. NO.	R1	R2	M.P °C	Yield %	color	Analysis Calc/Found C. H. N.
37			176-8	91	White	64.57 4.03 6.27 64.23 3.95 6.08
38			163-5	86	Yellow	67.03 2.79 7.82 66.89 2.60 7.63
39			140-2	83	white	65.67 3.48 6.96 65.34 3.37 6.80

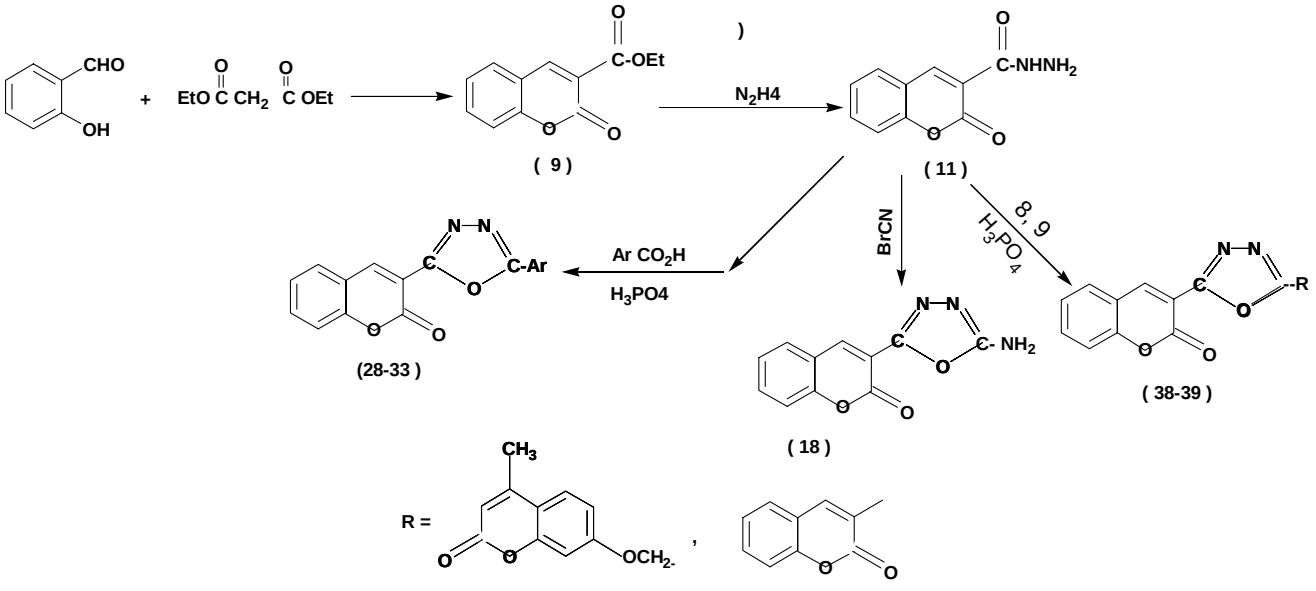
Table (12) :Spectral data for 2,5-bis(substituted)-1,3,4-oxadiazole



Compd.No.	R1	R2	U.V λmax nm EtoH	I.R V CM^{-1} C=N C-OC
37			330	1650 1050
38			307	1640 1130
39			304	1640 1120



Schem (1) ;Synthesis of oxadiazol derivatives drive from 4-methyl 7-hydroxy coumarine



Schem (2); Synthesis oxadiazol derivatives derive from Coumarin-2-Carboxylate

The biological Methods:

1-Bacteria;

The bacteria species used were Gram positive and Gram negative bacteria as listed in Table (13). All strains were obtained from the Department of Biology, College of Science , Mosul University. They were grown up to the stationary phase in a nutrient bath at 37ċ and a sample of 0.5 ml of each bacteria was spread over a surface of a nutrient agar plate[22].

Sensitivity Test; (Disc Diffusion Method):

Discs of filter paper (6mm diameter)were sterilized at 140ċ for 1 hour, impregnated with one of different prepared solution compounds, and then dried-DMSO(dimethylsulfoxide) was used as a solvent for compounds (22, 23, 26, 35). The same solvent was used for antibiotics cephalexine (keflex) for treating pseudomonas aeruginosa salmonella typhimurium. Cefotaxime (claforan) for Escherichia Coli, staphylococcus aureus and chloramphenicol for Bacillus subtilis were used for comparison .

We also used paper disk of DMSO as control[23].The inculcated plates were incubated at 37˚ for 14-16 hours, and the inhibition zones (mm) were measured prescott[24]. In all experiment ,the mean of each triplicate was measured[25].

Results and Discussion

The antibacterial activities of compounds (22, 23, 31, 34) were evaluated using various species of bacteria:

Staphylococcus aureus, Bacillus subtilis ,Pseudomonas aeruginosa, salmonella typhimurium and Escherichia coli. The results showed that these compounds were active in inhibiting the growth of nearly all micro-organisms and showed that the antibacterial effect on staphylococcus aureus, Bacillus subtiles, Pseudomonas aeruginosa and salmonella typhimurium was higher than that on Escherichia coli as indicated from the diameter of inhibition zone. Table(13).

Blank discs DMSO did not show any activity .The activities of the tested compounds against the studied bacteria were compared with the standard antibiotics. The results showed that some of the compounds had an inhibition zone more than the studied antibiotics, whereas the others showed less effect. It was observed that the compounds (22, 23, 34)had more inhibition zones for Staphylococcus aureus, Bacillus subtilis and Salmonella typhimurium than the antibiotics cefotaxim, Chloroamph enicol and Cephalexine respectively, while compound (31)showed less antimicrobial effect against these microorganism bacteria Table (13).

According to the data (Table 31, 32, 33, 36) it was evident that the activity of tested compounds decreased considerably at lower concentration (0.62 mg /disk). On increasing the Concentration up to (10 mg /disk) a large inhibition zone was observed for these compounds against Pseudomonas aeruginosa.

Table (13): The activities of compounds against bacteria.

Compound		Test Organisms				
		Staph.aures	Bacillis sub	Psedo.ueru	Sal.typh	E.coli
22	control	S	S+2	MS	S	MS
23		S	S	MS	S	MS
31		MS	S+1	MS	MS	MS
34		S	S	MS	S	MS
Cefotaxime		9				17
Cephalexine				16	10	
Chloramphenicol			8			

Activity of compound (22, 23, 31, 34) against bacteria.

Test Bacteria	Conc. Of 22 mg / disk					Conc. Of 23 mg / disk					Conc. Of 31 mg /disk					Conc. Of 34 mg/disk				
	0.62	1.25	2.5	5.0	10.0	0.62	1.25	2.5	5.0	10.0	0.62	1.25	2.5	5.0	10.0	0.62	1.25	2.5	5.0	10.0
Staph.arues	MS	MS	MS	S	S	MS	MS	S	S	MS	MS	MS	MS	MS	MS	MS	MS	MS	S	S
	S	S	MS	S	S+2	R	MS	S	S	S	MS	MS	MS	S	S+1	S	MS	MS	MS	S
BacillsSub.	R	R	MS	MS	MS	R	MS	MS	MS	MS	R	MS	MS	MS	MS	R	MS	MS	MS	MS
Psed.aeru.	MS	MS	MS	S	S	MS	MS	MS	S	S	MS	MS	MS	MS	MS	MS	MS	MS	S	S
Sal.typh.	MS	R	MS	MS	MS	R	R	MS	MS	MS	R	R	MS	MS	MS	R	R	MS	MS	MS
E.coil	R		MS	MS																

S: Sensitive (Diameter of inhibition zone 6mm less than control sample)

MS: Middle sensitive (Diameter of inhibition zone between 6-12 mm less than control sample)

R: Resistance (Diameter of inhibition zone 12mm larger than control sample)

*: Micro organism under test.

The number of microbial cell in 1mm= 1.0×10^{8} /ml.

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