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RESEARCH ARTICLE

Synthesis, Characterization and Antimicrobial Evaluation of Some New 1, 3, 4-oxadiazoline Compounds

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Abstract

This study involve synthesis of some new 1,3,4-oxadiazoline compounds and screening the antibacterial activity against *Staphylococcus aureus , Escherichia coli* and *pseudomonas aeruginosa* bacteria and the antifungal activity against *Aspergillus flavus* and *Candida albicans.* The structures of newly prepared compounds (5a-5f) were confirmed by spectroscopic methods like elemental analysis (CHN), FT-IR and ^{1}H-NMR spectroscopy. All the compounds showed good antibacterial activity as compared with the standard drugs (cefepime and amoxicillin) against *Staphylococcus aureus , Escherichia coli* and *pseudomonas aeruginosa* while the compounds (5a, 5b, 5c and 5d) displayed a good inhibition zone of growth against *Aspergillus flavus* and *Candida albicans.*

Keywords: *1, 3, 4-oxadiazoline, Antimicrobial, Heterocyclic compounds, Hydrazone derivatives.*

Introduction

1, 3, 4-oxadiazolines are heterocyclic compounds with an oxygen atom and two nitrogen atoms in a five-membered ring. It is obtained from furan by substituting two groups of methine (= CH) with two types of pyridine nitrogens (-N=). There are three known isomers of oxadiazolines, depending on the location of the nitrogen atoms in the ring).These isomers include 1,3,4-oxadiazoline,1,2,5-oxadiazoline and 1,2,4-oxadiazoline [1, 2].

1,3,4-oxadiazoline and 1,2,4-oxadiazoline are best identified and studied by scientists because of their many important chemical and biological features [3, 4]. 1, 3, 4-oxadiazoline derivatives are a significant category of heterocyclic compounds with numerous biological activities. These compounds have been exhibited antibacterial [5], antifungal [6], antiviral [7], antioxidant [8], anti-inflammatory [9], anticancer [10] and anticonvulsant activity [11]. These derivatives are also extensively used for the management of rheumatic fever, arthritis (rheumatoid, osteoarthritis) and primary dysmenorrheal [12].

1,3,4-oxadiazolines are prepared through cyclization of the corresponding hydrazone derivatives in acetic anhydride which act as an oxidizing agent [13]. The aim of work to synthesize new substituted 1, 3, 4-oxadiazoline derivatives and evaluate the antimicrobial activity against G+ve bacteria (*Staphylococcus aureus)*, G-ve bacteria (*Escherichia coli* and *Pseudomonas aeruginosa)* and fungi (*Aspergillus flavus* and *Candida albicans*).

Materials and Methods

Chemicals and Instruments

Terephthalic acid, sodium bicarbonate, 2-nitrobenzaldehyde, 3-nitrobenzaldehyde, 4-nitrobenzaldehyde, 2-methoxybenzaldehyde, 4-methoxybenzaldehyde, benzaldehyde were manufactured by Sigma-Aldrich company. Hydrazine hydrate 99% and thionyl chloride were manufactured by Alpha Chemika Company. All the solvents were manufactured by Sigma-Aldrich Company. The melting point of the synthesized oxadiazoline compounds was estimated in

open capillary tubes by using the electrothermal Stuart melting point apparatus. Infrared spectra were detected with KBr disks by using Shimadzu FTIR-84005 spectrophotometer in a university of Basra/college of education for pure sciences/ chemistry department/ Iraq. ^{1}H-NMR spectra were obtained on Inova 500 MHz NMR spectrometer (Tehran University-Iran) by using tetramethylsilane (TMS) as an internal standard and deuterated dimethyl sulphoxide (DMSO) as a solvent. The mass spectra were done on 5975C VL MSD with tripe-axis detector mass spectrometer at Tehran University-Iran. The elemental analysis was carried out on Eager 300 for EA1112 CHN analyzer at Tehran University-Iran.

Methods

Synthesis of Dimethyl Terephthalate (2)

A mixture of terephthalic acid **(1)** (1.0 g, 6 mmol) and methanol (50 mL) were refluxed for 30 minutes. Thionyl chloride (18 mL, 20 eq) was added dropwise, then the mixture was kept under reflux for 4 hours. After cooling to room temperature, the solvent was removed at reduced pressure. The mixture was extracted with diethyl ether (50 mL) twice and washed with potassium hydroxide solution. Anhydrous $MgSO_4$ was used for drying the combined organic layers. Removal of the solvent allowed to yield the diester as a pure product [14]. M.p =140-141°C, yield = 85%

Synthesis of terephthalic dihydrazide (3)

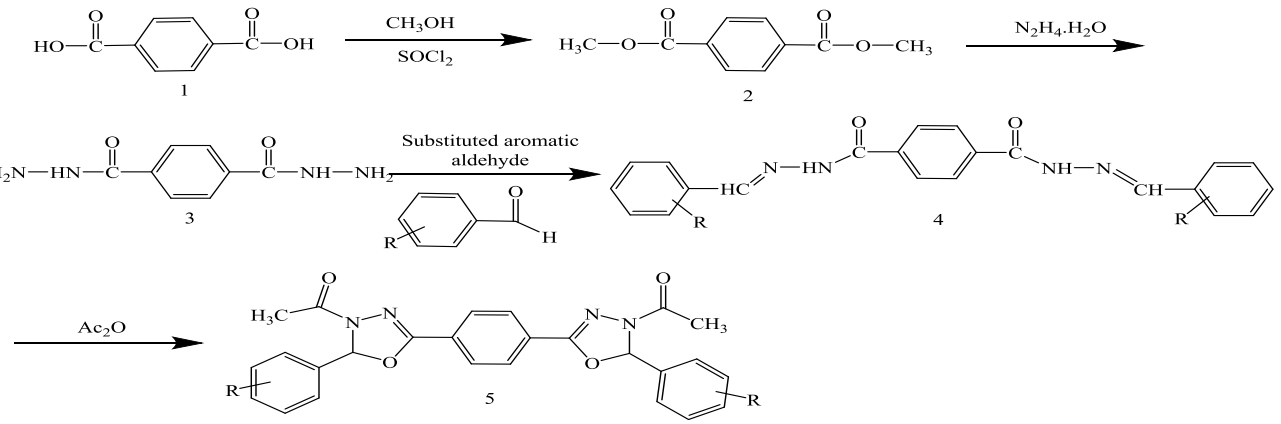
A mixture of dimethyl terephthalate **2** (2, 22 g), hydrazine hydrate (99 %, 2 ml) and methanol (30 ml) was refluxed for 5 hours and then cooled to room temperature. The solution was poured into ice water which leads to precipitate the solid product which was separated by filtration and recrystallized from ethanol [15]. M.p = >300°C, yield = 80%

General Procedure for the Synthesis of N, N-bis-[substituted methylidene] benzene-1, 4-dicarbohydrazone (4a-4f)

A mixture of terephthalic dihydrazide (1 mmol), substituted aromatic aldehydes (2 mmol) and dimethylformamide (DMF) (30 mL) was refluxed in the presence of the catalytic amount of glacial acetic acid (4ml) for 6 hours. On cooling, the solid was separated and collected by filtration and recrystallized from a mixture of DMF-ethanol [16]. The physical features of the hydrazone derivatives are illustrated in Table 1.

General Procedure for the Synthesis of 1, 3, 4-oxadiazoline Compounds (5a-5f)

A mixture of N, N-bis-[substituted methylidene] benzene-1, 4-dicarbohydrazone (2 mmole) and acetic anhydride (60 ml) was refluxed for 6 hours. After cooling, the solution was poured with vigorous stirring into crushed ice water (200ml). The solid produced (Scheme 1) was filtered and washed with sodium bicarbonate and water and then recrystallized from ethanol [17]. The physical features of the final products are summarized in Table 2.



Comp.	R
4a, 5a	2-NO_2
4b, 5b	3-NO_2
4c, 5c	4-NO_2
4d, 5d	2-OCH_3
4e, 5e	4-OCH_3
4f, 5f	H

Scheme 1: Synthetic pathway for 1, 3, 4-oxadiazoline compounds.

Table 1: The physical features of the hydrazone derivatives

Comp.	Chemical name	Molecular formula	M.p (°C)	Yield (%)	R_f	Eluent
4a	N'1, N'4-bis(2-nitrobenzylidene) terephthalohydrazide	$C_{22}H_{16}N_6O_6$	334-336	91.4	0.63	Hexan: EtOAc 3:2
4b	N'1, N'4-bis(3-nitrobenzylidene) terephthalohydrazide	$C_{22}H_{16}N_6O_6$	338-340	94.7	0.7	Hexan: EtOAc 3:2
4c	N'1, N'4-bis(4-nitrobenzylidene) terephthalohydrazide	$C_{22}H_{16}N_6O_6$	310-312	96.5	0.66	Hexan: EtOAc 3:2
4d	N'1, N'4-bis(2-methoxy benzylidene)terephthalohydrazide	$C_{24}H_{22}N_4O_4$	338-339	95.6	0.57	Hexan: EtOAc 3:2
4e	N'1, N'4-bis(4-methoxy benzylidene)terephthalohydrazide	$C_{24}H_{22}N_4O_4$	326-328	90.5	0.62	Hexan: EtOAc 3:2
4f	N'1, N'4-dibenzylidene terephthalohydrazide	$C_{22}H_{18}N_4O_2$	346-348	92	0.6	Hexan: EtOAc 3:2

Table 2: Physical features of 1, 3, 4-oxadiazoline compounds

Comp.	R	Chemical name	Molecular formula	M.p (°C)	Yield (%)	R_f	Eluent
5a	2-NO_2	1,1'-(1,4-phenylenebis(2-(2-nitrophenyl)-1,3,4-oxadiazole-5,3(2H)-diyl))bis(ethan-1-one)	$C_{26}H_{20}N_6O_8$	267-270	77.6	0.5	Hexan:EtOAc 1:1
5b	3-NO_2	1,1'-(1,4-phenylenebis(2-(3-nitrophenyl)-1,3,4-oxadiazole-5,3(2H)-diyl))bis(ethan-1-one)	$C_{26}H_{20}N_6O_8$	263-265	75.5	0.56	Hexan:EtOAc 1:1
5c	4-NO_2	1,1'-(1,4-phenylenebis(2-(4-nitrophenyl)-1,3,4-oxadiazole-5,3(2H)-diyl))bis(ethan-1-one)	$C_{26}H_{20}N_6O_8$	283-285	73.7	0.62	Hexan:EtOAc 1:1
5d	2-OCH_3	1,1'-(1,4-phenylenebis(2-(2-methoxyphenyl)-1,3,4-oxadiazole-5,3(2H)-diyl))bis(ethan-1-one)	$C_{28}H_{26}N_4O_6$	208-210	72.5	0.68	Hexan:EtOAc 1:1
5e	4-OCH_3	1,1'-(1,4-phenylenebis(2-(4-methoxyphenyl)-1,3,4-oxadiazole-5,3(2H)-diyl))bis(ethan-1-one)	$C_{28}H_{26}N_4O_6$	205-208	75.3	0.58	Hexan:EtOAc 1:1
5f	H	1,1'-(1,4-phenylenebis(2-phenyl-1,3,4-oxadiazole-5,3(2H)-diyl))bis(ethan-1-one)	$C_{26}H_{22}N_4O_4$	223-225	70	0.65	Hexan:EtOAc 1:1

Antimicrobial Assessment of 1, 3, 4-oxadiazoline Compounds

Antibacterial Assessment

The oxadiazoline compounds were tested for their antibacterial activity against G+ve bacteria (*Staphylococcus aureus*) and G-ve bacteria (*Escherichia coli* and *pseudomonas aeruginosa*). The procedure of filter paper disc diffusion was used to test the antibacterial activity of the synthesized oxadiazoline compounds.

Dimethyl sulphoxide (DMSO) was used as a solvent to prepare stock solutions (1000µg / ml) for each compound. Inhibition zone diameter around the disc was measured (in mm) and compared with that of standard drugs cefepime and amoxicillin. Species of bacteria are pathogenic strains [18].

Antifungal Assessment

The oxadiazoline compounds were tested for their antifungal activity against *Aspergillus flavus* and *Candida albicans* by the agar diffusion method. Stock solutions for each compound (1000µg/ml) were prepared by using dimethyl sulphoxide (DMSO) as a solvent. Zone of fungal growth inhibition diameter was calculated (in mm) and compared with that of the standard drugs fluconazole and clotrimazole. Pathogenic isolated fungal was used [19].

Result and Discussion

Elemental analysis (CHN) results of all compounds are summarized in Table 4 and it has been found that the analysis findings are closely related to the calculated values, ensuring that the results are true [20].

Table 3: Elemental analysis of the synthesized oxadiazoline compounds

Comp.	Molecular formula	Molecular weight	Calculated			Found		
			C%	H%	N%	C%	H%	N%
5a	$C_{26}H_{20}N_6O_8$	544.48	57.35	3.70	15.44	57.85	3.79	15.27
5b	$C_{26}H_{20}N_6O_8$	544.48	57.35	3.70	15.44	57.97	3.78	15.26
5c	$C_{26}H_{20}N_6O_8$	544.48	57.35	3.70	15.44	57.71	4.2	15.01
5d	$C_{28}H_{26}N_4O_6$	514.54	65.36	5.09	10.89	65.17	5.37	11.11
5e	$C_{28}H_{26}N_4O_6$	514.54	65.36	5.09	10.89	64.38	5.28	11.17
5f	$C_{26}H_{22}N_4O_4$	454.49	68.71	4.88	12.33	69.23	4.66	12.60

FT-IR Spectra

The IR spectra of all compounds (Figures 1 to 6) displayed two absorption bands at (3009-3111 cm-1) and at (686-851 cm-1) that are assigned to the stretching vibrations and out-of-plane (O.O.P.) bending vibrations of the aromatic C-H bond respectively [21]. Distinctive absorption bands at approximately (1663-1668 cm^{-1}) are attributed to the carbonyl C=O stretching vibrations of the acetyl group for all oxadiazoline compounds [22]. Besides, all the IR spectra revealed absorption bands at (1605-1626 cm^{-1}) that are related to the stretching vibrations of the C=N bond of the oxadiazoline ring [23]. There are two absorption bands in the IR spectra for the aromatic C=C bond at (1477-1497 cm^{-1}) and (1516-1600 cm^{-1}) [24]. An absorption band at (1051-1074 cm-1) and (1215-1292 cm-1) were identified in the IR spectra of all compounds are due to the C-O-C stretching vibrations of the oxadiazoline ring [25]. The oxadiazoline compounds (5a-5c) were shown to have two bands of absorption at (1350-1356 cm^{-1}) and (1526-1530 cm^{-1}) corresponding to the symmetric and asymmetric stretching vibrations of the nitro NO_2 group respectively [26]. The results of the analysis are summarized in Table 4.

Table 4: IR absorption bands of the synthesized oxadiazoline compounds

Comp.	C-H Arom.		C-H Aliph. (Str.)	C=O	C=N (Str.)	C=C Arom.	NO_2 (Str.)		C-N	C-O-C (Str.)
	(Str.)	(O.O.P.) Bend.					Sym.	Asym.		
5a	3010 w	743 m	2880 w	1668 s	1626 w	1584 w	1356 m	1530 s	1325 m	1277 w 1074 w
5b	3094 w	738m 686 m	2890 w	1667 s	1624 m	1589 w 1477 m	1352 s	1531 s	1321 m	1215 m 1070 m
5c	3111 w	851 s	2824 w	1667 s	1611 m	1600 w 1493 w	1350 m	1526 s	1323 m	1292 w 1072 m
5d	3009 w	754 s	2941 w	1668 s	1605 m	1591 m 1497 s	-	-	1327 m	1292 m 1051 m
5e	3073 w	849 s	2936 w	1663 s	1611 s	1516 s 1497 s	-	-	1323 m	1252 s 1070 m
5f	3065 w	758 m 692 m	2820 w	1665 s	1620 m	1516 w 1477 m	-	-	1323 m	1290 m 1069 m

s= strong, m= medium, w= weak

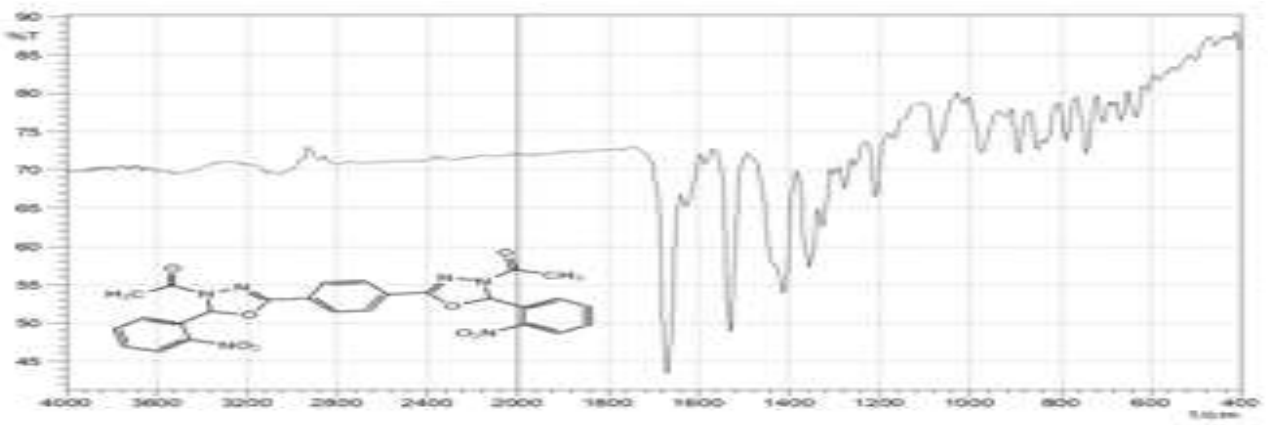


Figure 1: FT-IR spectrum of 5a

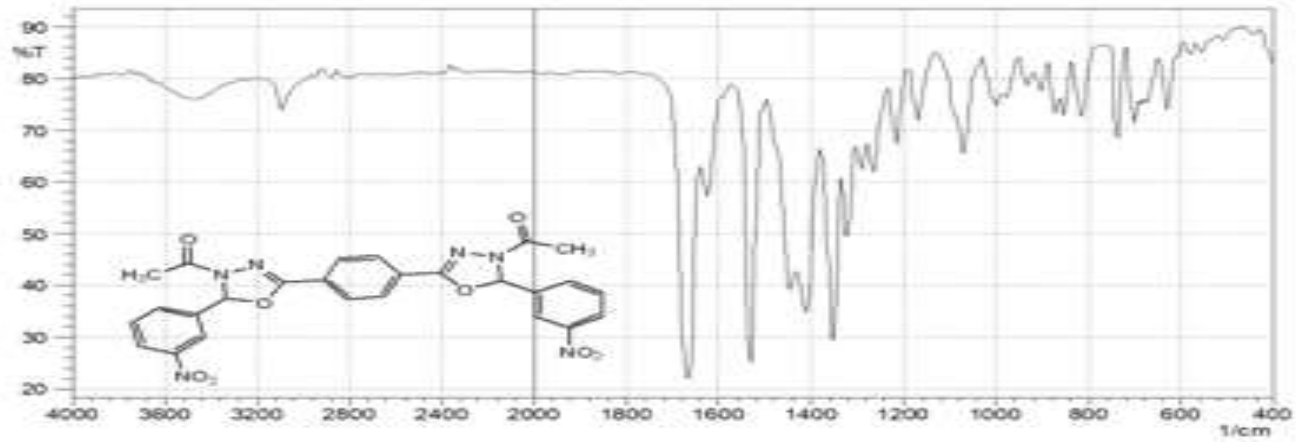


Figure 2: FT-IR spectrum of 5b

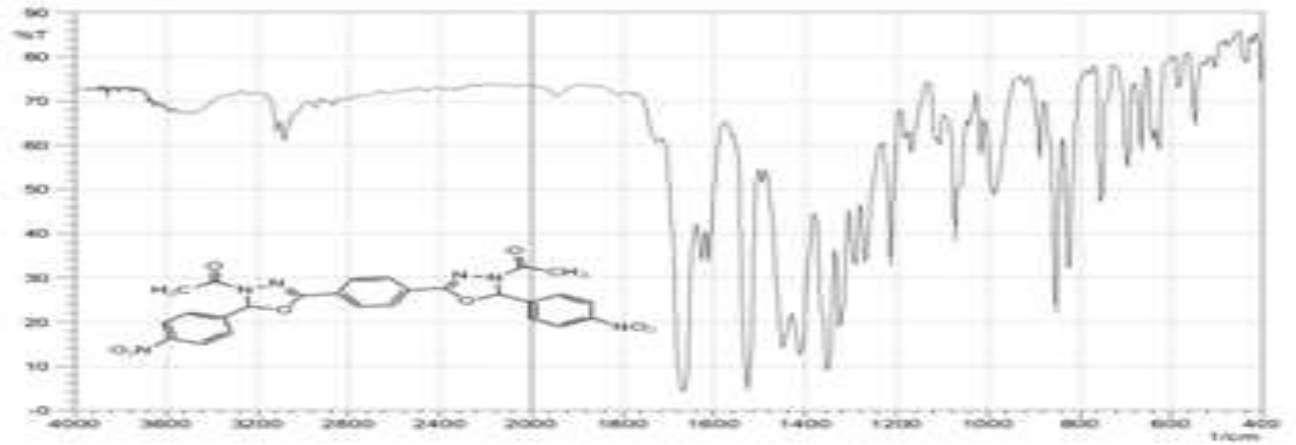


Figure 3: FT-IR spectrum of 5c

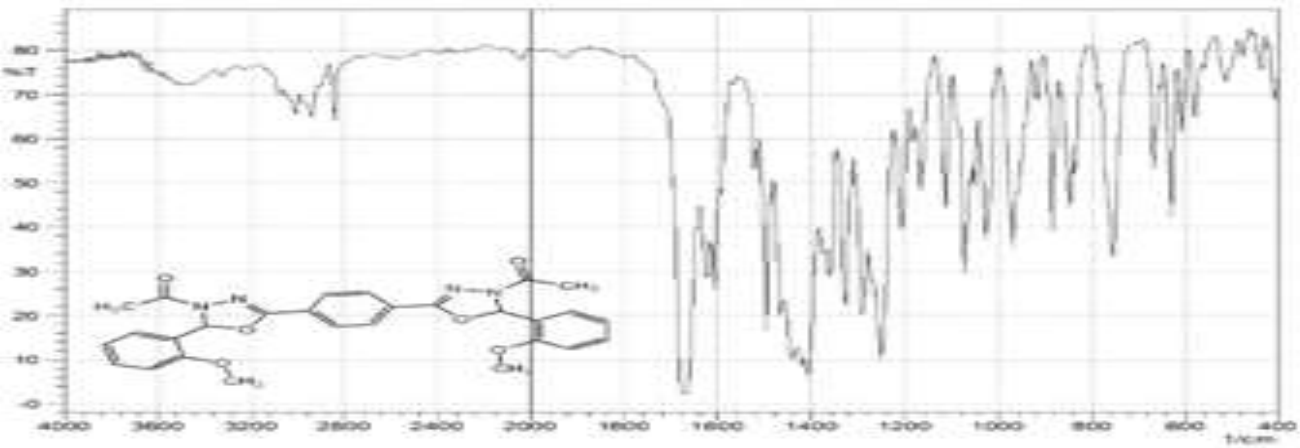


Figure 4: FT-IR spectrum of 5d

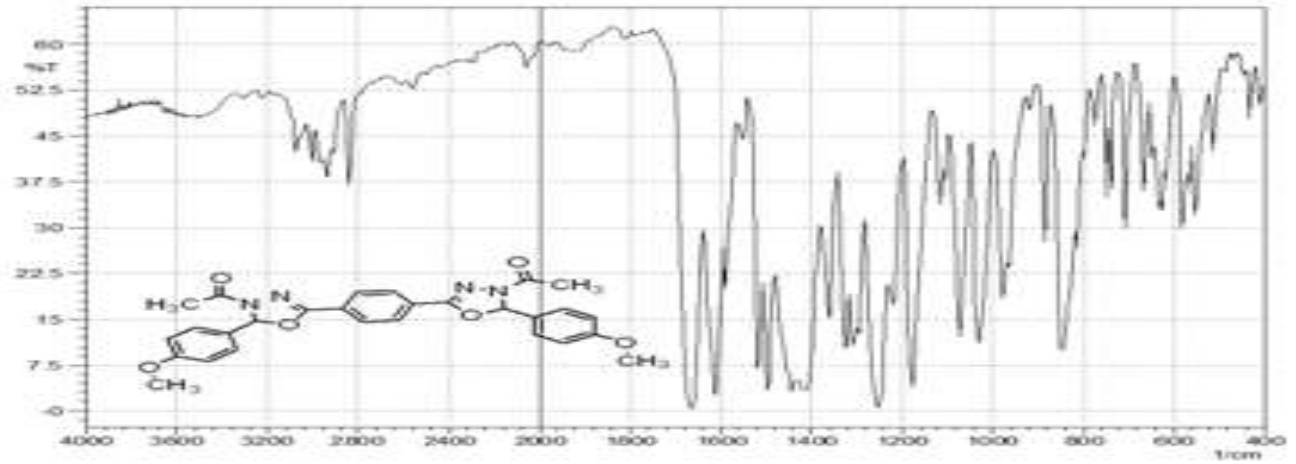


Figure 5: FT-IR spectrum of 5e

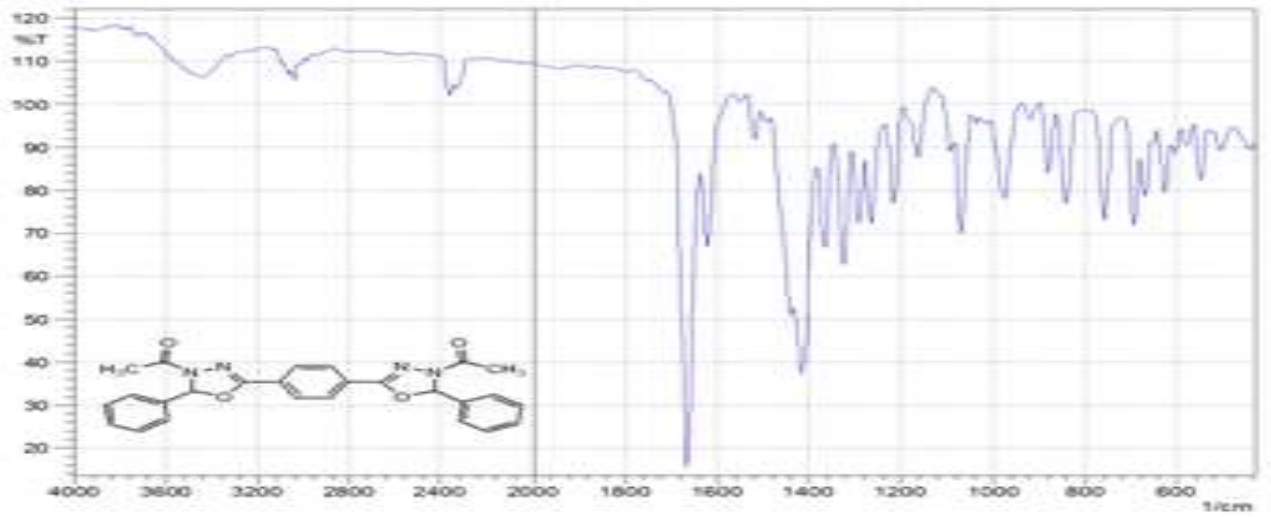


Figure 6: FT-IR spectrum of 5f

^{1}H-NMR Spectra

The ^{1}H-NMR spectra as shown in Figures 8 to 12 showed singlet signals at (2.27-2.3 ppm) attributed to the protons (H-13, H-13a) of acetylated methyl (-COCH3) group [27]. The all spectra displayed singlet signals at (7.299-7.602 ppm) that are assigned to the protons (H-2, H-2a) of the oxadiazoline ring [28]. Also, there are singlet signals at (7.896-7.990 ppm) that are related to the protons (H-15, H-16, H-18, H-19) of the phenyl ring in the spectra of all compounds as shown in Scheme 2 [29]. The spectrum of the compound (5d) gave a singlet signal at (3.797 ppm) referring to the protons of the methoxy groups. Table 5 lists the other ^{1}H-NMR distinct signals attributed to the aromatic H (Ar-H) [30].

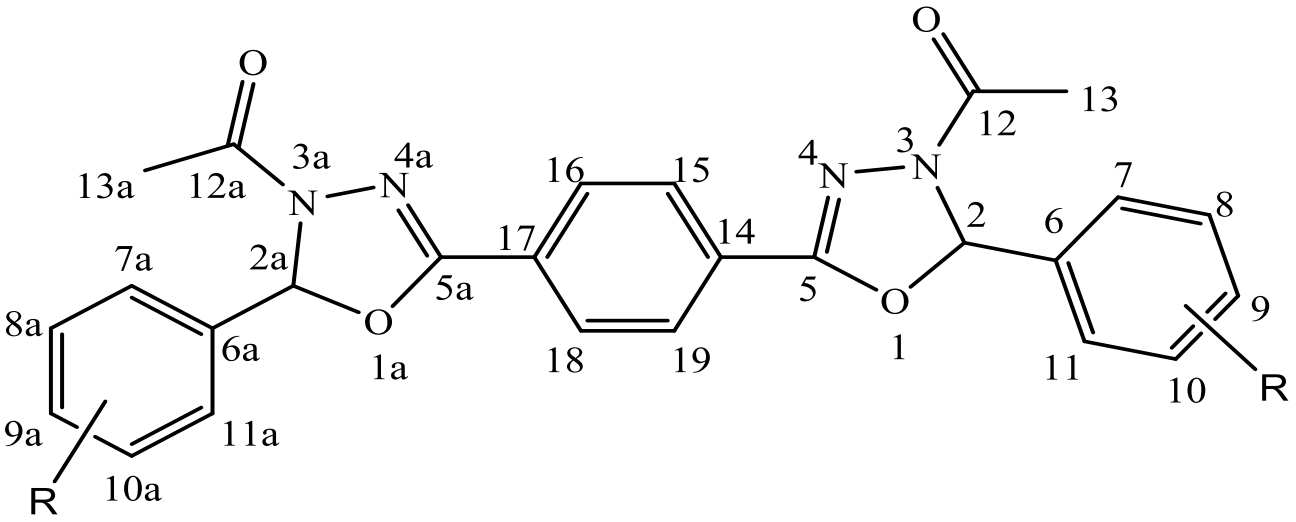


Figure 7: Structure of the oxadiazoline compounds for clarification ^{1}H-NMR

Table 5: Data for ^{1}H.NMR spectra [δ (ppm), J (Hz)] of oxadiazoline compounds

Compd.	-$COCH_3$ (s)	2H H-2, H-2a (d)	4H 15, 16, 18, 19	-OCH_3 (s)	Aromatic C-H
5a	2.284	7.602	7.933	-----	7.663 (d, 2H, H-7, H-7a, J = 7.5) 7.737 (t, 2H, H-8 H-8a, J = 7.5) 7.815 (t, 2H, H-9, H-9a, J = 8) 8.103 (d, 2H, H-10, H-10a, J = 7.5)
5b	2.301	7.409	7.990	-----	7.990-7.966 (d, 2H, H-7, H-7a) 7.763 (t, 2H, H-8 H-8a, J = 8) 8.307 (d, 2H, H-9, H-9a, J = 8) 8.357 (s, 2H, H-11, H-11a)
5c	2.294	7.376	7.988	-----	8.296 (d, 4H, H-8, H-8a, H-10, H-10a, J = 8.5) 7.806 (d, 4H, H-7 H-7a, H-11, H-11a, J = 8)
5d	2.270	7.299	7.896	3.797	7.111 (d, 2H, H-7, H-7a, J = 8.5) 6.978 (t, 2H, H-8 H-8a, J = 7.5) 7.423 (t, 2H, H-9, H-9a, J = 8) 7.277-7.299 (d, 2H, H-10, H-10a, J = 10)
5f	2.280	7.208	7.954	-----	7.442-7.475 (m, 10H, H-7, H-7a, H-8, H-8a, H-9, H-9a, H-10, H-10a, H-11, H-11a)

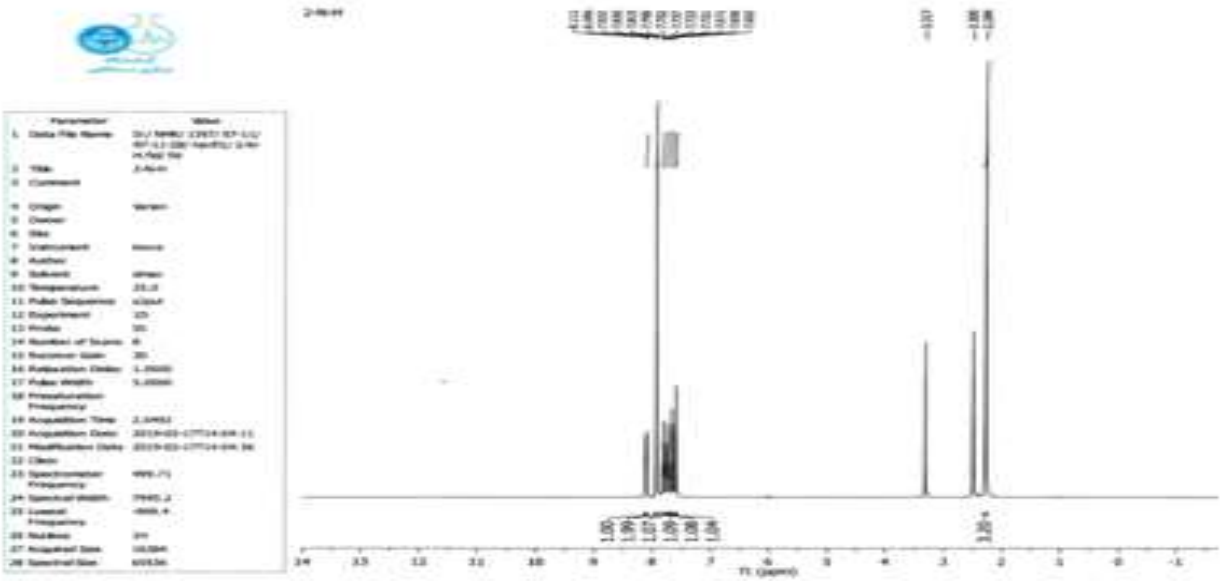


Figure 8: ^{1}H-NMR spectrum of 5a

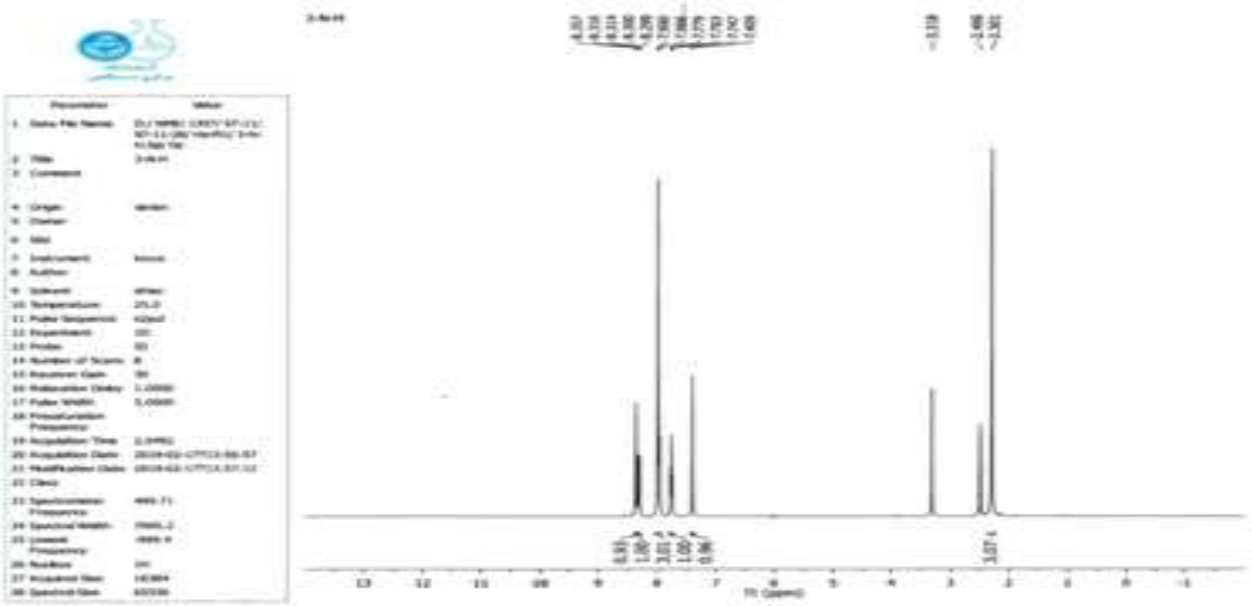


Figure 9: ^{1}H-NMR spectrum of 5b

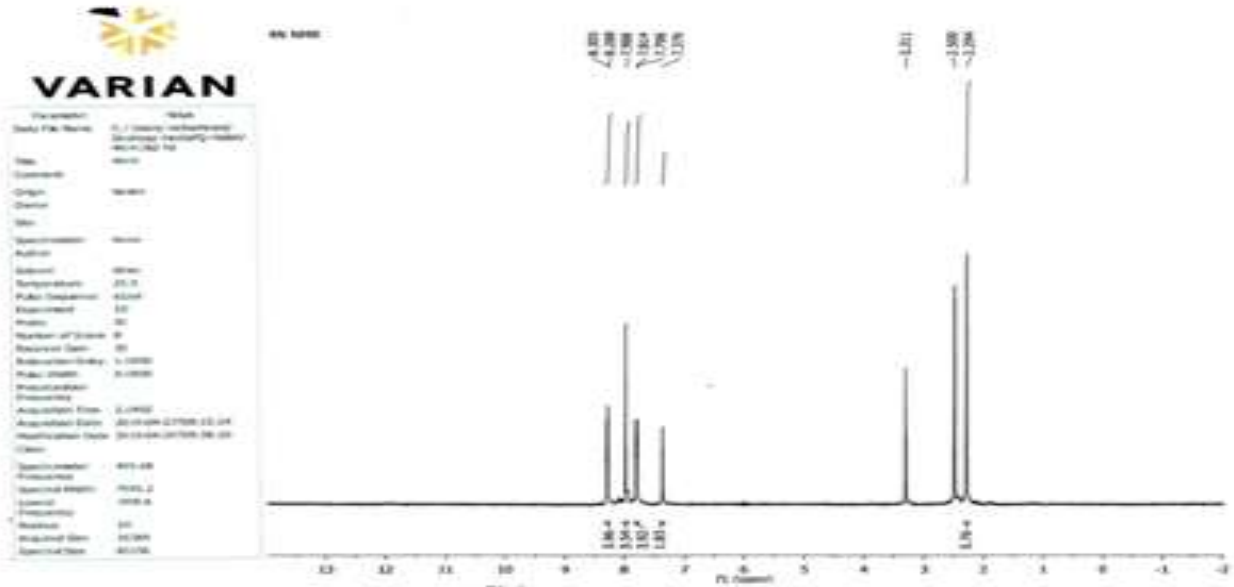


Figure 10: ^{1}H-NMR spectrum of 5c

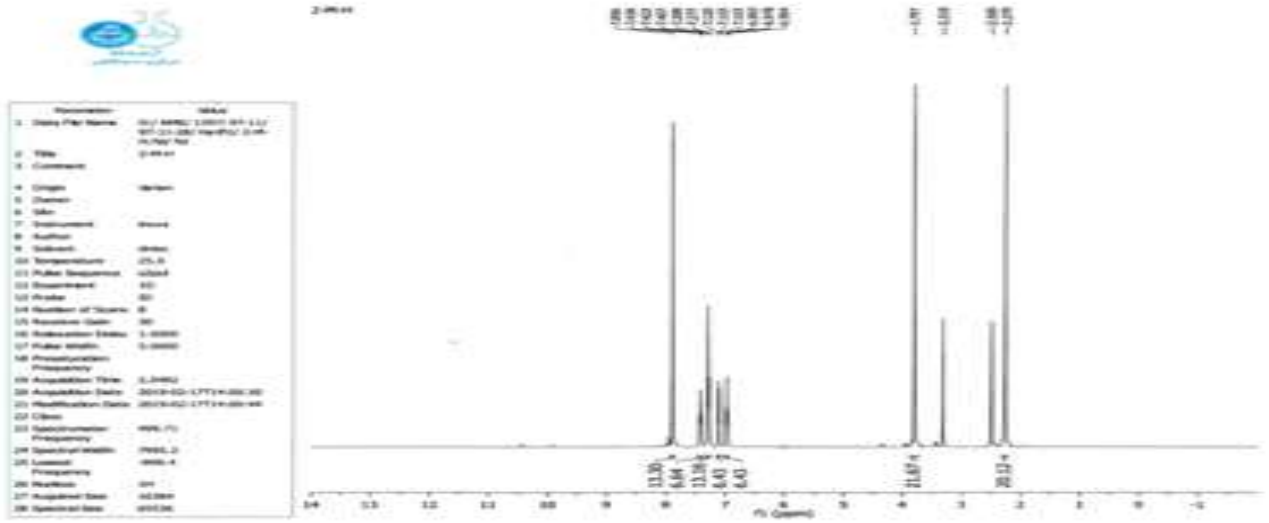


Figure 11: ^{1}H-NMR spectrum of 5d

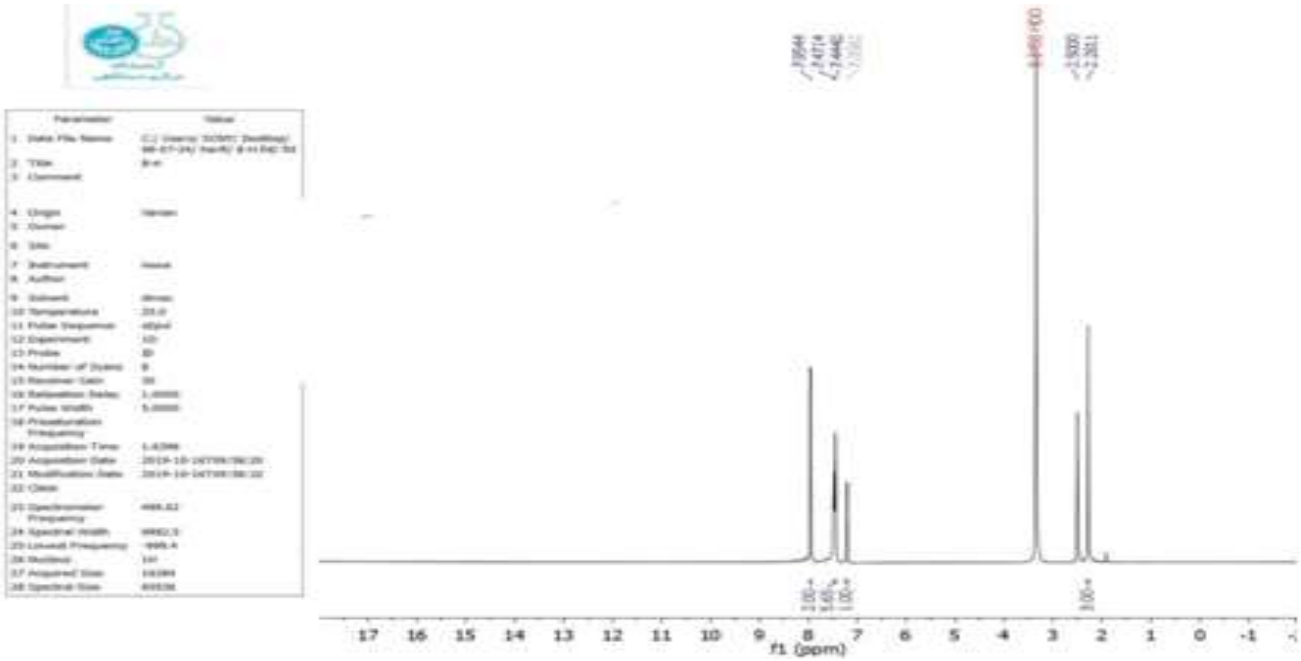


Figure 12: ^{1}H-NMR spectrum of 5f

Antimicrobial Activity

The examination of antibacterial evaluation data demonstrated that all the tested compounds (5a-5e) displayed excellent antibacterial activity against G+ve bacteria (*Staphylococcus aureus*) and G-ve bacteria (*Escherichia coli* and *pseudomonas aeruginosa*) as compared to standard drugs cefepime and amoxicillin as shown in Table 6. The examination of antifungal testing data revealed that all the prepared compounds showed good antifungal activity against *Aspergillus flavus* compared to the standard drug fluconazole but these compounds showed moderate activity against Aspergillus flavus compared to the standard drug clotrimazole. In the investigation of antifungal activity against *Candida albicans*, all the compounds were shown a moderate antifungal action compared to fluconazole and clotrimazole standard drugs. Among all the prepared derivatives the compounds (5a, 5b, 5c and 5d) showed significant antifungal activity while the compound (5f) was found to be least active against the fungal strain as shown in Table 7.

Table 6: *In vitro* antibacterial activity of the tested compounds and standard antibacterial drugs

Comp.	Conc.(µg/ml)	Inhibition zone (mm) of oxadiazolines		
		Staphylococcus aureus	***Escherichia coli***	***Pseudomonas aeruginosa***
5a	500	41	28	15
	1000	42	32	18
5b	500	40	30	20
	1000	42	33	23
5c	500	40	29	18

	1000	43	33	20
5d	500	39	28	17
	1000	42	32	19
5e	500	41	27	18
	1000	44	31	20
5f	500	38	28	17
	1000	41	30	19
Cefepime	500	25	18	0
	1000	25	20	0
Amoxicillin	500	0	0	0
	1000	0	0	0

Table 7: *In vitro* antifungal activity of the tested compounds and standard antifungal drugs

Comp.	Conc.(µg/ml)	Inhibition zone (mm) of oxadiazolines	
		Aspergillus flavus	***Candida albicans***
5a	500	15	30
	1000	18	35
5b	500	13	15
	1000	15	27
5c	500	16	17
	1000	17	23
5d	500	14	11
	1000	16	24
5e	500	12	NI
	1000	16	21
5f	500	10	NI
	1000	13	10
Fluconazole	500	10	25
	1000	15	30
Clotrimazole	500	22	35
	1000	25	40

NI= No inhibition

The testing results demonstrated that all the oxadiazoline compounds have shown excellent growth-inhibiting activity against G+ve bacteria *Staphylococcus aureus* and G-ve bacteria *Escherichia coli* while these compounds showed moderate growth-inhibiting activity against G-ve bacteria *pseudomonas aeruginosa* indicating that all the synthesized compounds have broad-spectrum antibacterial activity. While, the compounds (5a, 5b, 5c and 5d) exhibited a good antifungal efficacy against *Aspergillus flavus* and *Candida albicans*.Structurally, the most promising antifungal effectiveness was associated with the presence of a nitro group in the phenyl moiety of the oxadiazoline ring

Conclusion

This study involves the synthesis of new 1, 3, 4-oxadiazoline derivatives by the cyclization reaction of hydrazones (4a-4f) with acetic anhydride. The testing results revealed that all the 1,3,4-oxadiazoline derivatives displayed a considerable antibacterial activity against G+ve and G-ve bacteria while the compounds (5a, 5b, 5c and 5d) showed good antifungal activity against the testing fungal strain. So, these new compounds could be regarded as an important molecule for the development of drugs that can be used as antimicrobials.

Acknowledgments

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