ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.pharmascope.org/ijrps

Synthesis, characterization and antibacterial evaluation of 1,3,4-oxadiazole derivatives

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Article History:

Received on: 04.04.2019
Revised on: 12.07.2019
Accepted on: 17.07.2019

Keywords:

heterocyclic compound, antibacterial, Oxadiazole -3- thiol deravitive

ABSTRACT

The present work includes synthesis and characterization of some novel 1,3,4-oxadiazole derivatives and the evaluation of the antibacterial activity of the synthesized compound against pathogenic isolated gram-negative and gram-positive bacteria. The activity result showed that some compound exhibited efficient effect against these bacteria. Some compounds had significant inhibition zone against Escherichia coli, pseudomonas aeruginosa and Staphylococcus aureus. The compound OXD3 and OXD4 gave inhibition zone against resistant pseudomonas aeruginosa while stander drug cefepime doesn't give an activity.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v10i3.1477

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INTRODUCTION

The compound 1,3,4-Oxadiazole is a heterocyclic compound comprising two nitrogen atoms and an oxygen atom in a pentagonal ring. Two pyridine type nitrogen replaces two methylene groups in furan to result in the oxadiazole. Three isomers are available for oxadiazole. These are 1,3,4-oxadiazole, 1,2,3-oxadiazole, and 1,2,4-oxadiazole. Two of these are more interesting to the researchers due to their known attention-grabbing biological and chemical properties. These two are 1,3,4-oxadiazole and 1,2,4-oxadiazole (Amir *et al.*, 2009; Etebu and Arikekpar, 2016; Kahne *et al.*, 2005; Kang and Park, 2015). 1,3,4-oxadiazole is a pentagonal hetrocyclic ring which is thermally stable having a boiling point at 150 °C and is liquid at room temperature.

1,3,4-Oxadiazole is a useful main molecule for designing possible bioactive agents. The derivatives of this compound can exhibit different biological properties like antimicrobial, antimalarial, anti-HIV, antitubercular, anti-inflammatory, analgesic, anticonvulsant, hypoglycemic and additional biological activities such as lipid peroxidation inhibitor (Adzitey, 2015; Bonner and Sykes, 1984).

Some compounds have been studied for their biological activity against *C.albicans* and *S.aureus* and for other two fungi. These compounds are 3 -Aetyl-5-(4-flourophenyl)-2-substituted-2,3-dihydro-1,3,4-oxadiazoles and 5-(naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-one. The screened compounds exhibited moderate activity (Papp-Wallace *et al.*, 2011; Neuman, 1984; Sanchez *et al.*, 2004).

Many methods can be used to prepare 2,5-Disubstituted 1,3,4-oxadiazoles, hydrazine and carboxylic acids can be used as the starting compounds; they are altered into diacylhydrazides via many precursors to result in 1,3,4-oxadiazole.; these compounds could also be synthesized by cyclodehydration of diacylhydrazines and diaroylhydrazines under the effect of different dehydrating agents (PCl_5, organic acid anhydrides, and H_2SO_4).

The aim of the study includes the synthesis of six 1,3,4-oxadiazole compounds starting from valeric acid (Tillotson, 1996; Eyssen *et al.*, 1971). The synthesized compounds were characterized using different spectroscopic analysis. The antibacterial activity was evaluated for these compounds against some microorganism strains. The results showed that some compounds gave significant activity (Shinabarger *et al.*, 1997).

Aim of the study

Synthesis of new compounds with antibacterial activity and to promote the elimination of antibiotic-resistant bacteria.

MATERIALS AND METHODS

Experimental

All solvents and reagents were of analytical grade unless indicated otherwise, and all experiments were performed with deionized water (Ω-cm 18.2) resistivity at 25 °C (Bugg and Walsh, 1992).

Chemicals

Valeric acid, BDH, UK, Ethylbromide, standard Sigma-Aldrich German,

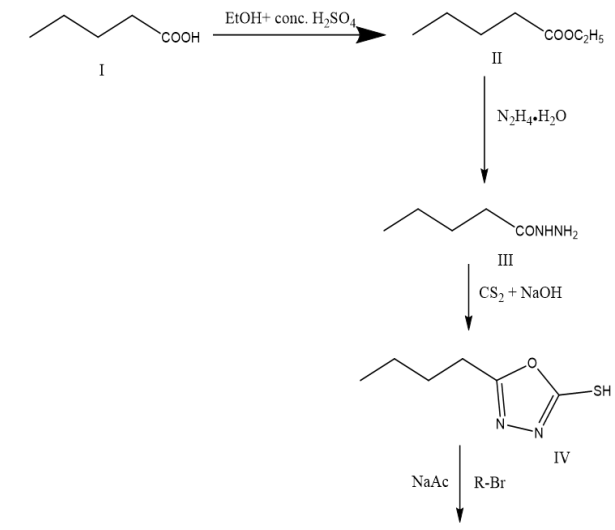
1. Butyl bromide, sigma –aldrich German.
2. Pentyle bromide, sigma –aldrich
3. Benzyl bromide, BDH M/231/202LTD 12526 Cas98-142-2.
4. Sulphoric acid 99%, Aldrich 49/1586-LTD.
5. Hydrochloric acid 36%, BDH Chem. LTD.
6. n-Hexane, BDH M/405/9 LTD.
7. Bromo ethyl acetate, sigma –aldrich,
8. Absolute ethanol and methanol, sigma –aldrich pvt., Ltd., Bengaluru, India.
9. Sodium hydroxide and ethyle acetate, Merck, Germany.
10. Hydrazine hydrate 99.5%, ALPHA company, India.
11. Sodium acetate, Fluka switizland.
12. Nutrient agar
13. Nutrient broth, OXOID, England.
14. Mueller-Hinton agar, CDH, India

Synthesis of the compound

The starting materials ethyl valerate and valeric acid hydrazide were prepared according to the literatures. (Du *et al.*, 2006; Kidwai and Bhushan, 1999)

Synthesis of 1,3,4-oxadiazole (Katritzky and Rees, 1984)

To a solution containing 95% ethanol and 4 g (0.1 mole) of sodium hydroxide (dissolved in the least amount of water), 11.6 g (0.1 mole) of valeric hydrazide was added, followed by 9.4 ml (0.15 mole) of carbon disulfide. The reaction mixture was heated under reflux for 3hr till all the evolution of hydrogen sulfide ceased. The resulting mixture was diluted with water and acidified with diluted hydrochloric acid containing ice. The reaction mixture was allowed to stand at the ice bath for 30 minutes. The mixture was poured to a separation funnel, where chloroform used to extract the product. The organic layer separated and evaporated to obtain the product. The characterizations of the product are listed in Table 2.



Comp.	R
OXD1	C_2H_5
OXD2	C_4H_{10}
OXD3	C_5H_{12}
OXD4	$CH_2C_6H_5$
OXD5	CH_2COOH
OXD6	$CH_2COOC_2H_5$

Scheme 1: Synthesispathway for series compounds; OXD1 to OXD6

Synthesis of Mercaptoalkyl 1,3,4-Oxidiazole and Mercaptocarboxylic acid (Potts, 1961)

All compounds; 2 -butyl-5-(ethylthio)-1,3,4-oxadiazole (OXD1), 2 -butyl-5-(butylthio)-1,3,4-oxadiazole (OXD2), 2 -butyl-5-(pentylthio)-1,3,4-oxadiazole (OXD3), and 2 - ((5-butyl-1,3,4-oxadiazol-2-yl)thio)acetic acid (OXD5), were

Table 1: synthesized Oxadiazole compounds

Name of compounds	R	Symbol	No.
5 -butyl-1,3,4-oxadiazole-2-thiol	-H	OXD	1
2 -butyl-5-(ethylthio)-1,3,4-oxadiazole	-CH2CH3	OXD1	2
2 -butyl-5-(butylthio)-1,3,4-oxadiazole	-(CH2)3CH3	OXD2	3
2 -butyl-5-(pentylthio)-1,3,4-oxadiazole	-(CH2)4CH3	OXD3	4
2 -benzyl-5-butyl-1,3,4-oxadiazole	-(CH2)C6H5	OXD4	5
2 - ((5-butyl-1,3,4-oxadiazol-2-yl)thio)acetic acid	-CH2COOH	OXD5	6
ethyl 2-(5-butyl-1,3,4-oxadiazol-2-yl)acetat	-CH2COOCH2CH3	OXD6	7

Table 2: Physical properties of products

Compound	M. Wt. (gm/mol	p.b (oC)	Appearance	Yield (%)	Rf	Eluent
OXD	158.05	155-157	Yellowish oily liquid	72.8	0.78	Ethyl acetate:
OXD1	186.27	174-176	Pale yellowish oily liquid	69.28	0.70	ethanol (7:3)
OXD2	182.14	184-187	Yellowish oily liquid	86.11	0.82	Ethyl acetate:
OXD3	192.16	192-194	Pale yellowish oily liquid	85.93	0.72	ethanol (9:1)
OXD4	213.16	230-232	Dark yellowish liquid	74.3	0.86	Ethyl acetate: ethanol (9:1)
OXD5	216.06	217-219	Yellowish oily liquid	65.7	0.74	Ethyl acetate:
OXD6	244.09	220-222	Yellowish oily liquid	68.8	0.84	ethanol (7:3)

prepared by the same method and listed in the Table 1.

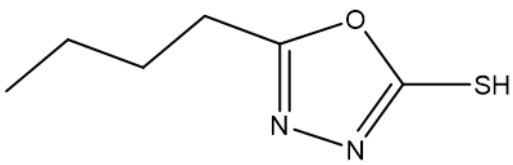
A mixture of 0.015 mole of OXD 0.018 mole of alkyl bromides (ethyl bromide, bentyl bromide, or monobromoacetic acid) and 0.02 mole of sodium acetate in 50 ml of ethanol was heated under reflux for 3 hr., then allowed to cool, and poured into 100 ml of cold water containing ice. The mixture was poured to a separation funnel, where chloroform used to extract the product. Then the organic layer separated and evaporated to obtain the product. The characterizations of the products are listed in Table 2.

Synthesis of 2 -Benzyl-5-Butyl-1,3,4-Oxadiazole (Eicher *et al.*, 2003)

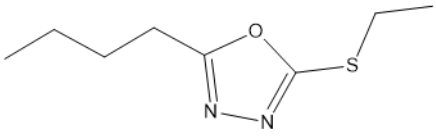
To a solution of 1.58g (0.01 mole) of OXD and 4.1g (0.05 mole) of sodium acetate in 30 ml of absolute ethanol,1.9 ml (0.01 mole) of benzyl bromide was added. The reaction mixture was refluxed for 4 hrs. The content was then poured into crushed ice, and the mixture was transferred to a separation funnel, where chloroform used to extract the product. Then the organic layer separated and evaporated to obtain the product. The characterizations of the product are listed in Table 2 -Table 3.

Synthesis of Ethyle 2-(5-Butyl-1,3,4-Oxadiazol-2-yl)] Acetat (Alkan *et al.*, 2007)

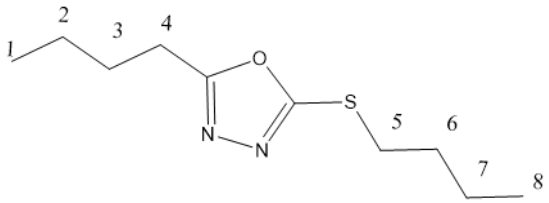
A solution of 3.5 g (0.01 mole) of OXD and 1.2 g (0.01 mole) of sodium hydroxide in 30 ml of absolute ethanol was heated under reflux for 30 minutes. A 0.01 mole ethyl bromoacetate was added, and the resulting mixture was refluxed for 4 hrs. After cooling, the solution was poured on ice, and the mixture was transferred to a separation funnel, where chloroform used to extract the product. Then the organic layer separated and evaporated to obtain the product. The characterizations of the product are listed in Table 2.



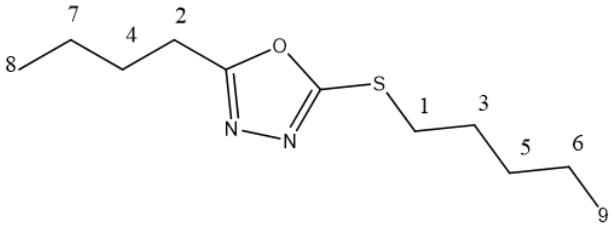
Scheme 2: The structure of OXD



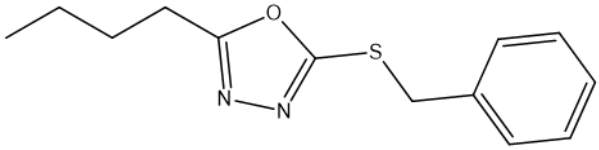
Scheme 3: The structure of OXD1



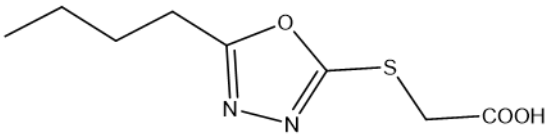
Scheme 4: The structure of OXD2



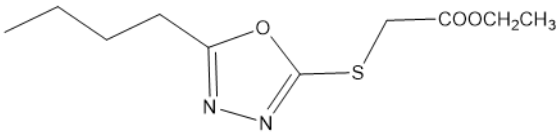
Scheme 5: The structure of OXD3



Scheme 6: The structure of OXD4



Scheme 7: The structure of OXD5



Scheme 8: The structure of OXD6

RESULTS AND DISCUSSION

The study involves synthesis of new 1,3,4 oxidiazole from valeric acid, which followed by synthesis s-substitution oxidiazole derivative as shown in scheme (1). Sulfur act as nucleic substituted for different alkyl carbon of R-X in preparation of mercapto substituted 1,3,4 Oxidiazole (Dabiri *et al.*, 2006).

The hydrazides undergo cyclization reaction by CS_2 in alcoholic sodium hydroxide and the release of hydrogen disulfide gas to give 1,3,4-oxadiazzole-2-thiol IV. The compound IV reacted with diverse compounds to give mercaptosubstituted-OXD . These reactions involved sulfur nucleophilic substitution (an attack by SH) at the alkyl carbon of different R-X, as shown in scheme 1.

The cyclization of compound III, to form compound IV, involved the nucleophilic attack of the enol form of hydrazide at carbon disulfide to form xanthate salt, the intranucleophilic addition of amino group and losing the hydrogen disulfide to form sodium-OXD ion which was converted to OXD-thiol in acidic medium.

FT-IR spectrum of OXD (Mashraqui *et al.*, 2003; El-Sayed *et al.*, 2012; Arora *et al.*, 2013; Oliveira *et al.*, 2012; Fuloria *et al.*, 2009; Kashaw *et al.*, 2010; Zarghi *et al.*, 2005)

The IR spectra for all OXD performed by the KBr disc method. FT-IR spectra for all studied compounds were measured as KBr disks using FT-IR 8400S SHIMADZU (Japan), in the technique Laboratory of Pharmaceutical Chemistry Department / College of Pharmacy / Basra University.

FT-IR spectrum of OXD

The compound non substituted (OXD) showed absorption band at 2777 cm^{-1} which characteristic of S-H stretching. While this band disappear in substituted derivative S-R, strong-medium band absorption 2870-2958 cm^{-1} attributed to C-H stretching of aliphatic. Also a strong band absorption at 1620 which characteristic of C=N stretching. Medium absorption band at 1165 cm^{-1} which attributed to C-O stretching and strong absorption band at 1481 cm^{-1} which attributed to C-H bending.

FT-IR spectrum of OXD1

The compound (OXD1) show strong absorption band at 1620cm^{-1} refer to C=N stretching, the medium-strong band 2870-2958 cm^{-1} attributed C-H stretching of aliphatic alkyl, strong band at 1489 cm^{-1} refer to C-H bending, medium band 1161 cm^{-1} attributed to C-O stretching.

FT-IR spectrum of OXD2

The compound(OXD2) show strong absorption band at 1613cm^{-1} refer to C=N stretching, the medium-strong band 2870-2960 cm^{-1} attributed C-H stretching of aliphatic alkyl, strong band at 1483 cm^{-1} refer to C-H bending, medium band 1155 cm^{-1} attributed to C-O stretching.

FT-IR spectrum of OXD3

The compound(OXD3) show strong absorption

Table 3: C.H.N. data of valeric-ester and hydrazide

Compd	Molecular formula	Molecular weight	Observed and Calculated	C	H	N
VE	C7H14O2	130.19	Observed	64.31	10.73	
			Calculated	64.58	10.84	
HZ	C5H12N2O	116.16	Observed	51.58	10.32	23.89
			Calculated	51.7	10.41	24.12

Table 4: C.H.N.S data of valeric-OXD derivatives

Compd	Molecular formula	Molecular weight	Observed and Calculated	C%	H%	N%	S%
OXD	C6H16N2O3S	158.05	Observed	45.18	6.11	17.37	19.92
			Calculated	45.55	6.37	17.71	20.26
OXD1	C8H14N2OS	186.27	Observed	51.91	7.44	15.49	17.67
			Calculated	51.58	7.58	15.04	17.21
OXD2	C10H18N2OS	182.14	Observed	55.73	4.67	13.44	15.33
			Calculated	56.04	8.47	13.07	14.96
OXD3	C12H22N2OS	192.16	Observed	59.91	8.96	11.87	12.84
			Calculated	59.47	9.15	11.56	13.23
OXD4	C13H16N2OS	213.16	Observed	63.12	6.77	10.88	13.38
			Calculated	62.87	6.49	11.28	12.91
OXD5	C8H12N2OS	216.06	Observed	44.92	5.33	13.25	14.45
			Calculated	44.43	5.59	12.95	14.83
OXD6	C10H16N2O3S	244.09	Observed	48.88	6.45	11.91	13.56
			Calculated	49.16	6.6	11.47	13.12

band at 1618 cm^{-1} refer to C =N stretching, the medium-strong band 2868-2958 cm^{-1} attributed C-H stretching of aliphatic alkyl, strong band at 1483 cm^{-1} refer to C-H bending, medium band 1155 cm^{-1-}which characteristic to C-O stretching.

FT-IR spectrum of OXD4

The compound (OXD4) show strong absorption band at 1620cm^{-1} refer to C=N stretching, medium band at 3065 cm^{-1-}which characteristics of C-H aromatic, medium-strong band 2873-2958 cm^{-1} attributed C-H stretching of aliphatic alkyl, strong band at 1458 cm^{-1} refer to C-H bending, medium band 1130 cm^{-1-}which characteristic to C-O stretching.

FT-IR spectrum of OXD5

The compound (OXD5) was characterized by a strong absorption band at 1720 cm^{-1} which attributed C=O stretching of the carboxylic acid in this compound and also showed a broadband in the range 3153 cm^{-1} which is characteristic of O-H stretching that appeared at lower frequency due to strong intermolecular hydrogen bonding, strong absorption band at 1620 cm^{-1} refer to C=N stretching, medium-strong band 2872-2935 cm^{-1} attributed C-H stretching of aliphatic alkyl, strong band at 1379 cm^{-1} refer to C-H bending, medium band 1163 cm^{-1} which characteristic to C-O stretching.

FT-IR spectrum of OXD6

The compound (OXD6) was characterized by a strong absorption band at 1741cm^{-1} which attributed C =O stretching and this absorption band of carbonyl group gave good indication about formation of the of ester, strong absorption band at 1620 cm^{-1} refer to C=N stretching, medium-strong band 2872-2960 cm^{-1} attributed C-H stretching of aliphatic alkyl, strong band at 1489 cm^{-1} refer to C-H bending, medium band 1155cm^{-1} which characteristic to C-O stretching.

^{1} H-NMR Spectrum (Manjunatha *et al.*, 2010; Amir and Kumar, 2007; Gilani *et al.*, 2010; Husain *et al.*, 2009)

The studied compounds were performed at the analytical Laboratory of Tehran University/College of sciences/ Chemistry department, use 500MHz NMR (INOVA Switzerland). DMSO-d_6 was used as a solvent and TMS as an internal standard.

Table 5: Inhibition zone of tested compounds and standard drugs

s.aureus	P.aeruginosa	E.coli	Conc. (μg/ml)	Compounds
0	0	0	50	OXD
0	0	0	125	
0	0	0	250	
0	0	0	500	
0	0	0	1000	
6	0	0	50	OXD1
6	0	0	125	
8	0	0	250	
8	0	0	500	
10	0	0	1000	
6	0	0	50	OXD2
6	0	0	125	
7	0	0	250	
11	0	0	500	
12	0	0	1000	
0	0	0	50	OXD3
0	0	0	125	
10	10	0	250	
12	12	0	500	
15	15	0	1000	
6	5	0	50	OXD4
6	7	0	125	
9	8	0	250	
11	11	0	500	
12	14	0	1000	
6	0	0	50	OXD5
7	0	0	125	
5	0	6	250	
8	0	10	500	
19	0	12	1000	
0	0	0	50	OXD6
0	0	0	125	
8	0	10	250	
13	0	13	500	
18	0	17	1000	
0	0	0	50	Amoxicillin
0	0	0	125	
0	0	0	250	
6	0	0	500	
8	0	15	1000	
0	0	8	50	Cefepime
0	0	12	125	
0	0	15	250	
0	0	18	500	
0	0	20	1000	

^{1}H-NMR Spectrum of prepared OXD compounds

^{1}H-NMR spectrum of prepared OXD derivatives were performed in deuterated dimethyl sulfoxide solutions with tetramethylsaline as an internal standard. The represent the ^{1}H-NMR spectra of the OXD derivatives. All these spectra showed a peak at 2.5 ppm, which was due to DMSO solvent, and some spectra showed a sharp peak at 3.33 ppm due to dissolved water in DMSO.

^{1} H-NMR Spectrum of OXD

The ^{1}HNMR spectrum of compound OXD displayed characteristic aliphatic signals of alkyl chain protons represented by the following, triplet signal at 0.801 ppm related to protons of -CH_3 group, 1.267 ppm as sixtet related to -CH_2- beside -CH_3, another signal at 1.532 ppm related to -CH_2- (-$CH_2CH_2CH_3$), last signal at 2.469 ppm related to –CH_2- beside oxadiazole ring, as shown in Scheme 2.

^{1} H-NMR Spectrum of OXD1

The ^{1}HNMR spectrum of compound OXD1 (Scheme 3) showed aliphatic signals at 0.851 ppm as *triplet* related to three protons of -CH_3 ($CH_3CH_2CH_2CH_2$-), *sixtet* signal at 1.337 ppm related to (CH_2) adjacent to CH_3 and CH2, another signal *pentet* at 1.656 ppm characteristic to protons (-CH_2) which between CH_2 and CH_2 , also there is *triplet* signal at 1.371 attributed to CH_2 adjacent to oxidiazole ring. There is another aliphatic system referred to mercaptoethyl moiety which gave two signals, the first showed as *triplet* at 2.734 ppm and the second as *quartet* at 3.146 and related to(-CH_3) and (-CH_2-S-) respectively.

^{1}H-NMR Spectrum OXD2

The ^{1}HNMR spectrum of compound OXD 2 (Scheme 4) illustrated two triplet signals at 0.73ppm, and 0.83 ppm are mainly resulting from the presence of six protons of terminated methyl groups , two sixtet signals at 1.2 ppm and 1.295 ppm related to two groups, the first methylene group 2 and the second for methylene group 7, another two pentet signals at 1.33 ppm and 1.38 ppm refer to two -CH_2- groups which are no.3 and no.6 respectively, the last two triplet signals at 2.94 ppm and 3 ppm characteristic of two methylene groups one adjacent to oxidiazole ring moiety and other is beside sulfur atom.

^{1}H-NMR Spectrum OXD3

The ^{1}HNMR spectra of compound OXD3 (Scheme 5) showed characteristic two *triplet* signals at 0.874 ppm and 0.891 ppm related to six protons of terminated two methyl groups, *multiplet* signals in the range 1.289-1.307ppm related to six protons of three methylene groups (5,6 and 7). Another multiplet signals in the range between 1.321-1.350 ppm related to four protons of two methylene groups 3 and 4, triplet signal at 2.762 ppm related to two protons of –CH_2- beside oxadiazole moiety (2). The last signal at 1.160ppm is triplet related to protons of a methylene group(-CH_2-S-), which apparent downfield because of deshielded of a sulfur atom compared with signal methylene group (no. 2).

^{1} H-NMR Spectrum OXD4

The ^{1}HNMR spectrum of compound OXD4 (Scheme 6) gave the following signals, triplet signal at 1.388ppm related to three protons of terminated methyl group, sixtet signal at 1.380 characteristic of two protons of methylene group which between –CH_3- and –CH_2-, pentet signals at 1.711ppm related to methylene group between –CH_2- and –CH_2-, triplet signal at 2.782 ppm related methylene group adjacent to oxidiazole ring moiety, a singlet signal at 5.098 ppm which a good distinguish feature related to methylene group beside sulfur atom, the last characteristic multiplet signals in the range 7.305 – 7.322ppm related to five protons of phenol ring .

^{1}H-NMR Spectrum OXD5

The ^{1}HNMR spectra of compound OXD5 (Scheme 7) showed characteristic triplet signal at 0.93ppm related to three protons of terminated methyl group, sixtet signal at 1.36 ppm referred to the two protons of -CH_2- which between -CH_3- and -CH_2-, another signal as pentet at 1.64 ppm attributed to -CH_2- between two methylene groups, also there is triplet signal at 2.29 ppm related to -CH2- adjacent to oxidiazole ring moiety, a singlet signal at 4.35 ppm related to methylene group adjacent to carbonyl group.

^{1}H-NMR Spectrum OXD6

The ^{1}HNMR spectra of compound OXD 6 (Scheme 8) displayed characteristic aliphatic system represented by triplet signal at 1.196 ppm related to three protons of terminated methyl group which beside oxidiazole moiety , sixtet signal at 1.268 ppm which attributed to -CH_2 between CH_3 and -CH_2, two protons of methylene groups gave pentet signal at 1.376 ppm related to -CH_2- group between two methylene groups, another signal which is triplet at 2.758 ppm related to -CH_2- beside oxidiazole side, also there is singlet signal at 4.137 ppm related to methylene group between sulphur atom and carbonyl group, the last two signals at 4.160 ppm as triplet related to methyl group of ester and quartet signal at 4.175 ppm indicated methylene group which apparent at downfield because de shielded of oxygen atom.

C. H. N. Analysis (Bankar *et al.*, 2009; Somani *et al.*, 2011)

Elemental analysis of prepared compounds the mea-

sured value in a good agreement with the calculated value, shown in Table 3 andTable 4

Antibacterial activity

All synthesized OXD derivative compounds were evaluated against certain kinds of Gram-positive bacteria (S. aureus) for their antibacterial activity, and Gram-negative bacteria (*E. coli*) used the diffusion technique of the filter paper disk, measuring the diameter of the inhibition area after 24 hours. The preliminary findings showed that there were some active compounds against *E. Coli* or and S. *Aureus*, as shown in Table 5

Most compounds prepared showed bacterial activity against Gram-negative and Gram-positive bacteria. Compound OXD gave no activity while OXD1, OXD2, OXD3, OXD4, OXD5, OXD6 show good bacterial activity against (*Staphylococcus aureus*), and also OXD3 and OXD4 had good activity against resistant bacteria *Pseudomonas aerogenosa.* While both standards drugs used did not gave activity against this bacteria. The acid and ester group of OXD5 and OXD6 respectively showed good bacterial activity at high concertation against Gram-negative (*E. coli*) and Gram-positive (*S. aureus*).

CONCLUSIONS

The study included the synthesis of the new compounds 1,3,4-oxadiazole-2-thiol (OXD) series derived from valeric acid and followed by the synthesis of S-substituted-OXD. The synthesized compounds were tested as antibacterial agents against some microorganism (Gram-negative and Gram-positive strains) which gave good inhibition zone as compared with standard drugs.

ACKNOWLEDGEMENT

The authors thank the University of Basra, college of pharmacy and department of pharmaceutical chemistry for supporting this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Suhail H. Derawey conceived and designed the study**.** Mazin N. Mosa designed all the experiments and revised the manuscript. Ekhlas Qanber Jasim and Rawaa M. O.Hraishawi performed the experiments, collected, analyzed the data, and wrote the manuscript.

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