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FULL PAPER

Synthesis and Antimicrobial Activity of 4-S-Methyl-1,3,4-Oxadiazole Derivatives of Some Natural Amino Acids Bearing Secondary Quaternary Ammonium Salt Moieties

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Abstract:

Secondary quaternary ammonium salts (QAS) derived from three natural amino acids (L-Leucine, L-Phenylalanine and L-Methionine) bearing 1,3,4-oxadiazole and acetic acid moieties have been synthesized and characterized by IR, ^{1}H and ^{13}C NMR. All the synthesized compounds were evaluated for their preliminary *in vitro* antibacterial and antifungal activity against different bacterial and fungal strains. All the synthesized compounds showed varying degrees of inhibition against the tested microorganisms.

Keywords: amino acid; quaternary ammonium salts; 1,3,4-oxadiazole; antimicrobial activity

1. Introduction

Quaternary ammoniums salts (QAS), are known for their interesting antifungal activity and have attracted considerable attention because of their diverse biological properties [1, 2]. Literature revealed that QAS, mainly those with amphiphilic properties, exhibit biological activity [3, 4]. Quaternary ammonium halides containing COOH group [5] are widely used as cationic surfactants [6], drugs [7], and herbicides [8], bactericides [9] and as therapeutic agents [10]. QAS of amino acid derivatives exhibited antifungal activity [11]. The correlation of QAS with antifungal activity is related to fungal phospholipase inhibition [12].

Amino acids play a crucial role in diverse biological functions [13], they are the building blocks for proteins in *all* living organisms [14]. Some Amino acids and their derivatives are used therapeutically [15] and those bearing 1,3,4-oxadiazole ring display a broad spectrum of biological activities for new drug development [16]. Such as antibacterial [17], antimycobacterial [18], antifungal [19], antiviral [20], anticancer [21], anti-inflammatory [22], antituberculosis [23] and diverse pharmacological activities [24].

This paper is focused on the synthesis and evaluating antimicrobial activities of secondary quaternary ammonium salts (QAS) derived from three natural amino acids (L-leucine, L-phenylalanine and L-methionine) bearing 1,3,4-oxadiazole and acetic acid moieties. This work is a part of big project to cover all natural and un-natural effective amino acids.

2. Results and Discussion

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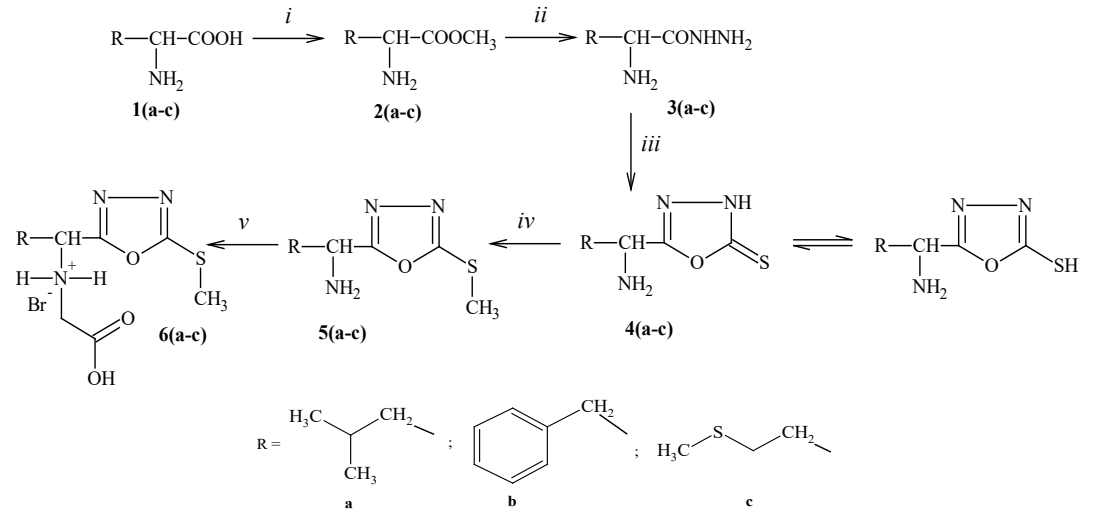
The target compounds **6(a-c)** were synthesized by a multiple-step procedure as shown in Scheme 1.



Scheme 1. *Reagents: i)* CH_3OH and concentrated H_2SO_4, *ii*) $NH_2NH_2.H_2O$ and C_2H_5OH, *iii*) CS_2 and alc. KOH, HCl *iv*) CH_3I, NaOH and C_2H_5OH, *v*) $BrCH_2COOH$ and acetone.

Amino acid methyl ester **2(a-c)** were synthesized using starting amino acid in methanol and concentrated sulfuric *acid* in good yields (67-87%), see schema1. Esters then converted to acid hydrazides using hydrazine in ethanol. The hydrazides were converted to substituted 1,3,4-oxadiazole-2-thione **4(a-c)** using carbon disulfide and ethanolic potassium hydroxide, the compounds were alkylated with methyl iodide in ethanolic sodium hydroxide to give the S-methyl derivative **5(a-c)**. Compound **5(a-c)** were quaternized with bromoacetic acid to form the final products **6(a-c)**.

2.1. In vitro antimicrobial activities

In vitro antimicrobials activities of the tested compounds 6(a-c) were screened for antibacterial activity against both reference strains and clinical isolates. Were taken from collection of pure cultures of Laboratory of Biotoxicology, Pharmacognosy and Biological recovery of plants, University of Dr Moulay Taher, Saida.

2.2. Antibacterial screening

The Antimicrobial activities of the tested compounds **6(a-c)** were screened for in *vitro* antimicrobial activity by measuring the Minimum Inhibitory concentrations (MIC) and the minimum bactericidal concentration (*MBC)* which gives the lowest concentrations of compound inhibiting visible growth, according to the broth macrodilution method of the National Committee for Clinical Laboratory Standards (NCCLS) recommendations [26]. Three Gram-positive bacteria and three Gram-negative bacteria, stock solutions of different test compounds (100 µg per mL) were made in DMSO. A series of dilutions of each tested compound in the range concentration of 10, 5, 2.5, 1.5, 0.625, 0.3125, 0.156, 0.078, and 0.039 mg/mL were prepared. Fresh cultures of bacteria obtained by inoculating bacteria in Muller-Hinton broth. The Petri-dishes containing bacterial species were incubated at 37 °C for 24 h, and observed for antibacterial activity. Test was repeated twice and the average values of MIC and MBC results are presented in Table 1.

As indicated in Table1 all synthesized compounds are more active against Gram-positive microorganism as compared to gram negative. The results of antimicrobial evaluation suggest that the compounds **6a** have very good potential to act as antibacterial agents against Gram-positive bacteria. Compounds **6c** exhibited good inhibitory effects against *Bacillus subtilis* and *Campylobactr fetus.* Compound **6b** showed growth inhibition against *Bacillus subtilis* and

Enterobacter cloacae.

Table 1. Anti-bacterial MIC and MBC of the tested compounds **6(a-c).**

Compounds	values of MIC/MBC (mg/mL)											
	Gram positive bacteria						Gram negative bacteria					
	E. faecalis ATCC 49452		*B. subtilis* ATCC 6633		*B. cereus* ATCC 11778		*E. coli* ATCC 25933		*C. fetus* ATCC 27374		*E. cloacae* ATCC 13047	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
6a	0.156	1.5	0.312	0.625	1.5	1.5	2.5	10	5	nd	10	nd
6b	Nd	nd	5	10	10	nd	nd	nd	10	nd	5	10
6c	Nd	0.625	1.5	5	nd	nd	0.156	0.625	1.5	2.5	nd	nd

Samples with CMI>10 mg /mL were considered not determined nd

2.3. Anti-yeast activities

Compounds **6(a-c)** assayed for anti-yeast activities against two *registered* yeast species, *Candida albicans* ATCC 10231 and *Candida albicans* IPP444. They are maintained by subculturing on Sabouraud agar and stored at 4 °C, and the plates were incubated at 25 °C for 2-5 days. A Reference method for broth dilution antifungal susceptibility testing of yeasts was used to determine minimal inhibitory concentration (MIC) and minimum fungicidal concentration (MFC). Test was performed twice and average values of MIC and MFC are shown in Table 2.

Table 2. Anti yeast MIC and MFC of the tested compounds **6(a-c)**.

Compounds	Species of yeast MIC /MFC µg mL^{-1}			
	C. albicans ATCC 10231		*C. albicans* IP 444	
	MIC	MFC	MIC	MFC
6c	5	10	2.5	5
6b	1.5	1.5	10	10
6a	10	10	5	10

Regarding the Anti-yeast activity the tested compounds exhibited significant Anti-yeast activities, compounds **6b** has maximum activity against *Candida albicans* ATCC 10231 and compound **6a** displayed good activity against *Candida albicans* IP 444.

2.4. Antifungal Activities

In order to investigate the antifungal activity of the final compounds **6(a-c)**, four fresh cultures of fungal strains were used such as *Aspergillus niger, Alternaria alternata, Rhizopus stolinifer* and *Aspergillus flavus.* Dimethylsulphoxide (DMSO) was used as a solvent for all the compounds and as negative control. Compounds were tested with the following concentrations: 2.5; 1.25; 0.5 and 0.25 µL/mL in 20 mL of tepid PDA medium in the test tube. The test plates were incubated at 27 ˚C. When the mycelium of fungi reached the edge of the control plate, the antifungal index was calculated as follows:

$$\text{Antifungal index (\%)} = (1 - Da/Db) \times 100$$

Where Da is the diameter of the growth zone in the experimental dish (cm) and Db is the diameter of the growth zone in the control dish (cm). The average results of the antifungal activities of the tested compounds **6(a-c)** for two times are presented in Table 3.

Table 3. Antifungal indices (%) of tested compounds **6(a-c).**

	Antifungal index (%)of the tested compounds															
	Aspergillus niger				*Alternaria alternata*				*Rhizopus stolinifer*				*Aspergillus flavus*			
Conc. (µL/mL)	2.5	1.25	0.5	0.25	2.5	1.25	0.5	0.25	2.5	1.25	0.5	0.25	2.5	1.25	0.5	0.25
6a	85	75	63.3	60	70.9	65	63.6	52,7	42.1	36.4	17.3	8.8	80.4	73.1	61.2	44
6b	81.6	78	70	60	60	49	23.6	9	43.2	32.2	22.3	10	62	53.2	43.1	32.2
6c	85	81.6	68.3	66.6	76.3	63,6	58.1	45.4	46	39	25	13	79	69	57	35

The results listed in Table 3 indicated that the compounds **6a**, **6b** and **6c** exhibited more than 80% inhibitory activity against *A. niger,* compounds **6b** showed prominent activity showed prominent activity against *A. flavus*, the tested compounds exhibited slightly lower activity against *R. stolinifer*

3. Material and Methods

3.1. General

All solvents and reagents used in this study were obtained from Sigma Aldrich and BIOCHEM. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using silica gel F254 supplied by MERCK, while spots were observed by using iodine as visualizing agent. All Melting points were determined in open capillary tubes on a BÜCHI 540 melting point apparatus and are uncorrected. The Infrared spectra as potassium bromide discs recorded on a Shimadzu FTIR-8300 Fourier Transform infrared spectrophotometer and expressed in cm^{-1}. The ^{1}H-and^{13}C-NMR Spectra were measured in protic deuterated solvents such as methanol and water on Bruker AM 300 MHZ Spectrometer (University of Oran, Essenia), relative to the internal standard tetramethylsilane (TMS), and chemical shift values are expressed in parts per million (δ, ppm).

3.2. General procedure for the preparation of amino acid methyl esters 2(a-c):

Amino acid methyl esters was prepared according to literature [25], into a solution of the corresponding amino acid 1(a-c) (0.018 mole) in absolute methanol and concentrated sulfuric acid (2 ml) was heated at 80°C in an oil bath. Reaction followed with TLC to obtain the desired compound. The excess of acid neutralized with sodium bicarbonate, washed with methylene chloride. Solvent evaporated and the product collected.

Leucine methyl ester ***(2a)***: R*f*=0.23($CHCl_3$); yield 72%; mp 129-130˚C; IR (KBr ν max cm^{-1}): 3421 (N-H), 1747 (C=O), 1006 (C-O-C).

Phenylalanine methyl ester ***(2b)***: R*f*=0.8($CHCl_3$); yield 84%; mp 164-165˚C; IR (KBr ν max cm^{-1}): 3485 (N-H), 3030 (=C-H), 2954 (C-H), 1747 (C=O), 1562 (C=C), 1008 (C-O-C).

Methionine methyl ester ***(2c)***: R*f*=0.66($CHCl_3$/MeOH 4/1); yield 67%; mp 234 - 235˚C; IR (KBr ν max cm^{-1}): 3414(N-H), 2923 (C-H), 1743 (C=O), 1016 (C-O-C), 802 (C-S-C).

3.3. General procedure for the preparation of amino acidhydrazide 3(a-c):

Amino acid methyl esters **2(a-c)** (0.011 mole) were refluxed with hydrazine hydrate (0.1 mole, 3 ml) in absolute ethanol for 4-5 hours. Reactions were monitored by TLC. Mixtures were cooled down, solvent evaporated and the products collected.

Leucine acid hydrazide ***(3a)*** R*f*=0.71($CHCl_3$); yield 84%; thick syrup; IR (KBr υ max cm^{-1}): 3419 (N-H), 1625 (C=O).

Phenylalanine acid hydrazide ***(3b)***: R*f*=0.69 ($CHCl_3$/MeOH 4/1); yield 92%; thick syrup; IR (KBr ν maxcm^{-1}): 3303 (N-H), 3055 (=C-H), 2927(C-H), 1618 (C=O), 1510 (C=C), 1093 (C-N).

Methionine acid hydrazide ***(3c)***: R*f*=0.38($CHCl_3$); yield 87%; mp104-105˚C; IR (KBr ν maxcm^{-1}): 3419 (N-H), 2923 (C-H), 1685 (C=O), 1112 (C-N), 619 (C-S-C).

3.4. General procedure for synthesis of 5-Subtituted-1, 3, 4-oxadiazoles-2-thione 4(a-c):

Aminoacid hydrazides **3(a-c)** (0.0083 mole) were reacted with carbon disulfide (0.02 mole, 1.2 mL) and potassium hydroxide (0.33g, 0.0083 mole) in absolute ethanol, to solubility, refluxed for 5h.Reactions were monitored by TLC. The resulting solution was cooled to room temperature; bulk of EtOH was evaporated, acidified with hydrocholoric acid to pH 5-6. The forming precipitates were isolated.

*5-(1-amino-3-methylbutyl)-1,3,4-oxadiazole-2(3H)-thione****(4a)***:R*f* = 0.58 ($CHCl_3$/MeOH 4/1); yield 83%; mp96-97˚C; IR (KBr ν max cm^{-1}): 3423 (N-H), 2923 (C-H), 1645 (C=N), 1265 (C=S), 1051 (C-O-C). ^{1}H-NMR (300MHz, CD_3OD), δ (ppm): 4.92 (3H, N**H**-C=S, N**H**$_2$); 2.65 (1H, C**H**-NH_2); 1.79 (1H, C**H**-CH_3); 1.29 (2H, CH-C**H**$_2$); 0.97 (6H, CH-(C**H**$_3$)$_2$). ^{13}C-NMR (300MHz,

CD_3OD), δ (ppm): 188.9 (**C**=S), 159.8 (CH-**C**=N), 36.5 (**C**H-NH_2), 29.9 (CH-**C**H_2); 21.1 (CH-(**C**H_3)$_2$).

5-(1-amino-2-phenylethyl)-1,3,4-oxadiazole-2(3H)-thione ***(4b)***:R*f*=0.76($CHCl_3$/MeOH 4/1); yield 89%; thick syrup**;** IR (KBr ν max cm^{-1}): 3435 (N-H), 2925 (C-H), 1635 (C=N), 1562 (C=C), 1388 (C=S),1002 (C-O-C). ^{1}H-NMR (300MHz, CD_3OD), δ (ppm): 8.38-7.05(1H, C**H**-arm); 6.34 (3H, N-N**H**C=S-, CH-N**H**$_2$); 3.64 (1H, C**H**-NH_2); 2.56 (2H, ar-C**H**$_2$-CH). ^{13}C-NMR (300MHz, CD_3OD), δ (ppm): 172.5(**C**=S); 155.7(**C**=N); 138.3-126.2 (**C**arm); 54.0 (CH_2-**C**H); 25.8 (Arm-**C**H_2-CH).

5-[1-amino-3-(methylthio)propyl]-1,3,4-oxadiazole-2(3H)-thione ***(4c)***: R*f*=0.53 ($CHCl_3$/MeOH 2/1); yield 90%; thick syrup; IR (KBr ν max cm^{-1}): 3429 (N-H), 2925 (C-H), 1643 (C=N), 1434 (C=S), 1004 (C-O-C), 840 (C-S-C). ^{1}H-NMR (300MHz, D_2O), δ (ppm): 4.80(3H, N**H**-C=S, CH-N**H**$_2$); 2.48(1H, C**H**-NH_2); 2.03(2H, SC**H**$_2$); 1.23(3H, SC**H**$_3$); 1.19(2H, SCH_2-C**H**$_2$). ^{13}C-NMR (300MHz, D_2O), δ (ppm): 181.2 (**C**=S); 157.8(**C**=N); 67.5 (**C**H-NH_2); 43.7 (SCH_2-**C**H_2); 30.5 (S**C**H_2); 14.2 (S**C**H_3).

3.5. General procedure for synthesis of 5-Subtituted -1,3,4-oxadiazoles-2-methylthio 5(a-c):

Equimolar mixtures of thiones **4(a-c)** (0.0045mole), sodium hydroxide (0.18 g, 0.0045 mole), and methyliodide (0.64 g,0.0045mole), dissolved in ethanol (50 mL) was heated under reflux for 8h on a water-bath. Reactions were monitored by TLC. Reaction mixtures were cooled. The solvent was removed under reduced pressure and the precipitates, formed were filtered.

3-methyl-1-[5-(methylthio)-1,3,4-oxadiazol-2-yl]butan-1-amine ***(5a)***: R*f* =0.33 ($CHCl_3$/MeOH 3/1); yield 75%; thick syrup; IR (KBr ν max cm^{-1}): 3433 (N-H), 2927 (C-H), 1643 (C=N), 1110 (C-O-C), 842 (C-S-C). ^{1}H-NMR (300MHz, CD_3OD), δ (ppm): 4.99 (1H, C**H**-NH_2); 3.09 (2H, N**H**$_2$); 2.96 (3H, S-C**H**$_3$); 1.09 (1H, C**H**-CH_3); 0.83 (6H, CH-(C**H**$_3$)$_2$). ^{13}C-NMR (300MHz, CD_3OD), δ (ppm): 162.5 (S-**C**=N), 158.8 (CH-**C**=N), 68.1 (**C**H-NH_2), 55.7 (CH-**C**H_2), 39.1(CH-(**C**H_3)$_2$), 30.1 (**C**H-(CH_3)$_2$), 21.7 (S-**C**H_3).

{1-[5-(methylthio)-1,3,4-oxadiazol-2-yl]-2-phenylethyl}amine ***(5b)***: R*f*=0.8 ($CHCl_3$/MeOH 2/1); yield 86%; thick syrup; IR (KBr ν max cm^{-1}): 3355 (N-H), 2931 (C-H), 1633 (C=N), 1442 (C=C), 1076 (C-O-C), 875 (C-S-C). ^{1}H-NMR (300MHz, D_2O), δ (ppm): 7.71-7.64 (1H, Arm); 4.71(1H, C**H**-NH_2); 3.66 (2H, Ar- C**H**$_2$-CH); 2.58 (2H, CH-N**H**$_2$); 2.56 (3H, S- C**H**$_3$). ^{13}C-NMR (300MHz, D_2O), δ (ppm): 158.9 (S-**C**=N); 156.6 (C-**C**=N); 158.9-128.9 (**C**arom); 49.2 (**C**H_2-CH-); 22.4 (CH_2-**C**H-); 15.4 (S- **C**H_3).

3-(methylthio)-1-[5-(methylthio)-1,3,4-oxadiazol-2-yl]propyl}amine ***(5c)***: R*f* =0.33 ($CHCl_3$/MeOH 8/2); yield 80%; thick syrup; IR (KBr ν max cm^{-1}): 3446 (N-H), 2925 (C-H), 1637 (C=N), 1120 (C-O-C), 871 (C-S-C). ^{1}H-NMR (300MHz, CD_3OD), δ (ppm): 3.33 (1H, C**H**-NH_2); 2.07 (3H, S-C**H**$_3$); 2.03 (2H, SC**H**$_2$); 1.81 (2H, SCH_2-C**H**$_2$), 1.73 (3H, S-C**H**$_3$), 1.56 (2H, N**H**$_2$). ^{13}C-NMR (300MHz, CD_3OD), δ (ppm): 174.8 (**C**=S); 171.8 (**C**=N); 52.1 (**C**H-NH_2); 33.8 (SCH_2-**C**H_2); 32.7 (S**C**H_2); 16.8 (S**C**H_3); 15.7 (N=C-S**C**H_3).

3.6. General procedure for synthesis of 5-Subtituted -1, 3, 4-oxadiazoles-2-methylthio N-carboxymethyl ammonium bromides 6(a-c):

Secondary quaternary ammonium salts were prepared by direct quaternisation of primary amine with molar equivalent quantity of compound **5(a-c)** (0.0042 mole) and bromoacetic acid (0.58g, 0.0042 mole) dissolved in dry acetone (50 mL), these mixture were gently refluxed for 8 hours. After that, solvent was evaporated the residue were washed several times with cold diethyl ether and allowed to dry.

N-(carboxymethyl)-3-methyl-1-[5-(methylthio)-1,3,4-oxadiazol-2-yl]butan-1-ammonium bromide ***(6a)***: R*f*=0.3($CHCl_3$/MeOH 4/1); yield 44%; thick syrup; IR (KBr ν max cm^{-1}): 3419 (O-H), 2927 (C-H), 1720 (C=O), 1647 (C=N), 1091 (C-O-C), 887 (C-S-C). ^{1}H-NMR (300MHz, D_2O), δ (ppm): 8.36 (3H, O**H**, N**H**$_2^+$); 4.06 (1H, C**H**-NH_2^+); 4.01 (2H, C**H**$_2$-COOH); 3.46 (3H, S-C**H**$_3$); 1.52 (2H, CH-C**H**$_2$); 0.83 (6H, CH-(C**H**$_3$)$_2$). ^{13}C-NMR (300MHz, D_2O), δ (ppm): 176.1 (S-**C**=N), 171.9 (**C**=O), 163.4 (CH-**C**=N), 55.8 (C**H**-NH_2^+); 41.8 (**C**H_2-COOH), 21.2 (CH-(**C**H_3)$_2$), 14.2 (S-**C**H_3).

N-(carboxymethyl)-1-[5-(methylthio)-1,3,4-oxadiazol-2-yl]-2-phenylethan ammonium

bromide ***(6b)***: R*f*=0.5 ($CHCl_3$/MeOH 9/1); yield 58%;thick syrup; R (KBr ν max cm^{-1}): 3419 (O-H), 2927 (C-H), 1706 (C=O), 1595 (C=N), 1423 (C=C), 1099 (C-O-C), 833 (C-S-C). ^{1}H-NMR (300MHz, CD_3OD), δ (ppm)**:** 8.38 (3H, O**H**, **H**$_2N^+$); 7.29-7.24 (1H, Ar); 4.0 (1H, C**H**-NH_2); 3.79 (2H, C**H**$_2$-COOH), 3.50 (2H, C**H**$_2$-CH), 2.74 (3H, S- C**H**$_3$). ^{13}C-NMR (300MHz, CD_3OD), δ (ppm): 178.6 (S-**C**=N); 157.5 (**C**=O);152.8 (C-**C**=N);128.9-126.1(**C**arom); 62.8 (CH_2-**C**H-);50.1 (H_2N^+**C**H_2-COOH);34.6 (**C**H_2-CH-);15.4 (S- **C**H_3).

N-(carboxymethyl)-3-(methylthio)-1-[5-(methylthio)-1,3,4-oxadiazol-2-yl]propan-1-ammonium bromide ***(6c)***: R*f*=0.54 ($CHCl_3$/MeOH 8/2); yield 47%; thick syrup; IR (KBr υ max cm^{-1}): 3433 (O-H), 2927 (C-H), 1701 (C=O), 1647 (C=N), 1110 (C-N),1024 (C-O-C), 871 (C-S-C). ^{1}H-NMR (300MHz, CD_3OD), δ (ppm): 8.37 (3H, N**H**$_2^+$, O**H**); 4.69 (1H, C**H**-NH_2^+); 4.45 (2H, C**H**$_2$-COOH); 3.85 (2H, SC**H**$_2$), 2.85 (3H, S**C**H_3); 2.66 (2H, SCH_2-C**H**$_2$); 2.14 (3H, CH_2- S-C**H**$_3$). ^{13}C-NMR (300MHz, CD_3OD), δ (ppm): 180.9 (S-**C**=N); 171.1 (**C**=O); 168.8 (CH-**C**=N); 63.3 (CH_2-**C**H-); 61.3 (**C**H_2-COOH); 59.5 (SCH_2-**C**H_2); 40.2 (S**C**H_2); 23.4 (CH_2- S-**C**H_3); 17.3 (N=C-S-**C**H_3).

4. Conclusions

In this paper, new QAS compounds containing active moiety 1,3,4-oxadiazole L-amino acids, L-Leucine, L-Phenylalanine and L-Methionine attached to secondary ammonium bromide group were successfully synthesized and characterized. Physical and antimicrobial (antibacterial, antiyeast and antifungal) properties were studied. The synthesized compounds showed promising antimicrobial potential against some of the *tested microorganisms.* The newly synthesized compounds were prepared with an objective of developing better antimicrobial activity and for future investigations.

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