Synthesis and antibacterial activity of bis-oxadiazole derivatives

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Abstract

New compounds containing two heterocyclic rings (1,2,4 and 1,3,4-oxadiazole)in the same molecules have been synthesized through many reactions . Prepared of 1,2,4-oxadiazole derivatives (3) by refluxing the oxime compound (2) and ethyl *p*-methyl benzoate with sodium ethoxide for 48 hrs. Synthesized the 1,3,4-oxadiazole derivatives (7_{a-l}) by reaction prepared hydrazide and many acids with phosphorus oxychloride ($POCl_3$). All the Synthesized compounds were characterized by melting points, FTIR and ^{1}H-NMR data. All the final compounds have been screened *in vitro* for their antibacterial activities against five types of bacteria [Gram-positive(*S. aureus, S. cerevisiae* and *C. diphtheria*) and the Gram-negative(*E. coli* and *P. aeruginosa*)] in two concentration (100 and 200)µg/mL. The result showed considerable antibacterial activities against Gram-positive (G+) , but did not show any antibacterial activities against Gram-negative (G-) .

الخلاصة

حضرت مركبات تحتوي على حلقتين غير متجانسة (4,2,1 و 4,3,1–اوكسادايازول) في نفس الجزيئة من خلال عدة تفاعلات , حضر مشتق للمركب 4,2,1–اوكسادايازول(3) بواسطة التصعيد العكسي لمركب الاوكسيم (2) ومركب اثيل4–مثيل بنزويت وبوجود ايثوكسيد الصوديوم ولمدة 48 ساعة . حضرت مشتقات للمركب 4,3,1–اوكسادايازول (7_{a-l}) بواسطة تفاعل الهايدرازايد المحضر مسبقا مع عدة حوامض وبوجود ثلاثي كلوريد الفسفوريل . جميع المركبات المحضرة شخصت بواسطة درجات انصهارها وبواسطة طيف الاشعة تحت الحمراء FTIR وطيف الرنين النووي المغناطيسي ^{1}H-NMR . درست الفعالية البايولوجية لجميع المركبات النهائية المحضرة (7_{a-l}) خارج الجسم تجاه خمسة انواع من البكتريا [Gram-positive(*S.aureus,* *S.cerevisiae* and *C.diphtheria*)and Gram-negative(*E.coli* and *P.aeruginosa*)] في تركيزين 100و200 µg/mL . أظهرت النتائج فعالية بايولوجية جيدة ضد البكتريل من النوع(G+) Gram-positive لكن لم تظهر اي فعالية تجاه النوع الآخر (G-) Gram-negative .

Introduction

Since their introduction, antimicrobials are one of most significant weapons in fighting bacterial infections. They have extremely benefited the health-related quality of human life. Over the past few decades, these health benefits are under threat as many commonly used antibiotics have become less effective against certain illnesses because of their toxic reactions and due to emergence of microbial resistance. Therefore, it is essential to investigate newer drugs with lower resistance.

There are four possible isomers of oxadiazole depending on the position of nitrogen atom in the ring out of these 1,3,4-oxadiazoles are found to be most potent biologically.

The development of new antimicrobial agents will remain an important challenging task for medicinal chemists. There are two basic approaches to develop a new drug: (a) synthesis of analogues, modifications or derivatives of existing compounds for shortening and improving treatment and (b) searching for novel structures, that the bacteria has never been presented before. To pursue this goal, our research efforts are directed to synthesize new pharmacophores. Substituted oxadiazoles are of considerable pharmaceutical importance, which is documented by several numbers of publications and patents. A large number of drugs used clinically have oxadiazole ring as a structural building block.

Literature survey reveals that particularly 1, 3, 4-oxadiazole derivatives exhibit wide range of biological activities including anticancer [1], anti-inflammatory [2], fungicidal[3], herbicidal[4], pesticidal, analgesic [5], anticonvulsant [6], anti-HIV [7], antibacterial and plant growth regulator activities [8].

According to these observations, in the design of new bioactive compounds, the development of hybrid molecules through the combination of different pharmacophores in one frame may lead to compounds with interesting biological profiles. In the present study, prompted by these observations, the synthesis and antimicrobial screening of new 1,2,4- and 1,3,4-oxadiazole derivatives in the same molecules incorporating different pharmacophores as hybrid molecules possessing antimicrobial activity were aimed.

Experimental

Materials and physical measurements

All starting materials and solvents were purchased from Aldrich and Fluka and used without further purification. Melting points were determined on Electrothermal capillary apparatus and are uncorrected, FT-IR measurements were recorded on Shimadzu model FT-IR-8400S in university of Al-Mustanseriya , department of chemistry, college of science, Baghdad, Iraq. ^{1}H-N**M**R spectra were obtained with Bruker spectrophotometer model ultra shield at 300 MHz. in university of Ahl-albait, Amman, Jordan. The compounds dissolved in DMSO-d_6 solution with TMS as internal standard. Note: in some ^{1}H-NMR spectra, the peaks at δ 2.5 and 3.35 are for the solvent (DMSO-d_6) and dissolved water in (DMSO-d_6) respectively.

Preparation methods and physical data of the synthesized compounds 1-7$_{(a-l)}$

All compounds (**1 , 2 , 3 , 4 , 5 , 6** , and **7$_{a-l}$**) were synthesized according to the procedures previously described by I. H. R. tomi [9] .

4-Butoxybenzonitrile (1)

A mixture of (10.36 g, 87 mmol) of 4-cyanophenol, (4.88 g, 87 mmol) potassium hydroxide and (50 ml) of absolute ethanol was heated at reflux for several minutes. Then (13.95 ml, 130 mmol) n-butyl bromide was added dropwise and the reaction mixture was refluxed for 72 hr. After cooling, the potassium bromide was precipitate then (50 ml) of water, (50 ml) of diethyl ether were added. The mixture was extracted and the organic layer washed with (25 ml) of water and (25 ml) of 10% sodium hydroxide solution then (25 ml) of water, dried the organic layer over anhydrous magnesium sulfate overnight. After filtration and evaporation the solvent, the oil residue was contained yield (95%); FT-IR (film, cm^{-1}) 2960, 2874 (C_{sp3}-H), 2224 (C≡N), 1606, 1508 (C_{sp2}-H), 1259, 1172 (C-O-C).

4-Butoxybenzamidoxime (**2**)

A mixture of (23.5 g, 134 mmol) of nitrile (**1**), (10.0 g, 144 mmol) of hydroxyl amine hydrochloride, (6g) sodium hydroxide in (200 ml) ethanol with (50 ml) water was stirred for 24 hrs at refluxed, then concentrated the mixture in vacuum. The residue was placed in (500 ml) of cold water, filtered, washed with water and dried. The product was purified by washing it with n-hexane. Yield (85%); mp 100-102°C; FT-IR (KBr disk, cm^{-1}) 3441, 3350 (N-H), 3174 (O-H), 1647 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ) 0.92 (t, 3H, lateral CH_3), 1.44 (m, 2H, CH_3-$\underline{C}H_2$-CH_2-), 1.69 (m, 2H, -CH_2-$\underline{C}H_2$-CH_2O-), 3.95 (t, 2H, -CH_2O-), 5.70 (s, 2H, NH_2), 6.90 (d, 2H, 2 arom. H), 7.58 (d, 2H, 2 arom. H), 9.43 (s, 1H, OH of the amidoxime group).

3-(4-Butoxyphenyl)-5-(4-methylphenyl)-1,2,4-oxadiazole (**3**)

This compound was synthesized according to the procedure previously described by M. Parra, [12]. A mixture of (2.7 g, 13 mmol) amidoxime (**2**) and (4.1 g, 25 mmol) of ethyl 4-methylbenzoate dissolved in sodium ethoxide solution (prepared from dissolving 0.32 g, 14 mmol of sodium metal in (27 ml) of absolute ethanol), then the reaction mixture was heated under reflux for 48 hrs. After the mixture was cooled, off white crystals were collected by filtration and dried. The crystals were recrystallized from ethanol. Yield (68%); mp 112°C; FT-IR (KBr disk, cm^{-1}) 2943, 2852 (C_{sp3}-H), 1610 (C=N), 1591 (C=C), 1248, 1178 (C-O-C), 924 (N-O); ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 0.95 (t, 3H, lateral CH_3), 1.46 (m, 2H, CH_3-$\underline{C}H_2$-CH_2-), 1.73 (m, 2H, -CH_2-$\underline{C}H_2$-CH_2O-), 2.42 (s, 3H, -C_6H_4-CH_3), 4.07 (t, 2H, -CH_2O-), 7.15 (d, 2H, 2 arom. H of –C_6H_4- linked to methyl group), 7.46 (d, 2H, 2 arom. H of –C_6H_4- linked to methyl group), 7.98 (d, 2H, 2 arom. H of –C_6H_4- linked to butoxy group), 8.09 (d, 2H, 2 arom. H of –C_6H_4- linked to butoxy group).

3-(4-Butoxyphenyl)-5-(4-carboxyphenyl)-1,2,4-oxadiazole (**4**)

To a stirred solution of (0.77 g, 2.5 mmol) of compound (**3**) in (16 ml) pyridine and (11 ml) water at 70°C, (3.33 g, 21 mmol)of potassium permanganate was added portionwise. Then the mixture was heated under reflux for 6 hrs. The solvents were evaporated in vacuum, then (35 ml) of water was added to the mixture and filtered. The acid (4) was precipitated by acidification the aqueous solution (2M HCl). It was filtered under vacuum, washed with water and dried at 100°C. Yield (82%); mp > 300°C; FT-IR (KBr disk, cm^{-1}) 3100 – 2544 (carboxylic O-H), 2960, 2874 (C_{sp3}-H), 1697 (C=O), 1608 (C=N), 1589 (C=C), 1249, 1176 (C-O-C), 931 (N-O); ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 0.96 (t, 3H, lateral CH_3), 1.49 (m, 2H, CH_3-$\underline{C}H_2$-CH_2-), 1.77 (m, 2H, -CH_2-$\underline{C}H_2$-CH_2O-), 4.09 (t, 2H, -CH_2O-), 7.17 (d, 2H, 2 arom. H of –C_6H_4- linked to carboxy group), 8.05 (d, 2H, 2 arom. H

of $-C_6H_4-$ linked to carboxy group), 8.18 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to butoxy group), 8.28 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to butoxy group), 13.4 (s, 1H, very week and broad COOH).

3-(4-Butoxyphenyl)-5-(4-Ethoxycarbonylphenyl)-1,2,4-oxadiazole (5)

As a general method, a solution of (3.2 g, 9.47 mmol) of compound (**4**) and (0.11 ml) of H_2SO_4 in (50 ml) absolute ethanol were heating under reflux for 72 hrs. After hot solution was filtered and evaporated the solvent, the crude ester was precipitated. The white crystal of ester was washed with 10% of $NaHCO_3$ solution then with water. After dried, we purified it by recrystalization from ethyl acetate. Yield (80%); mp 242°C; FT-IR (KBr disk, cm^{-1}) 2962, 2872 (C_{sp3}-H), 1726 (C=O), 1610 (C=N), 1591 (C=C), 1249, 1172 (C-O-C), 904 (N-O); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ) 0.94 (t, 3H, lateral CH_3), 1.35 (t, 3H, O-CO-CH_2-CH_3), 1.45 (m, 2H, CH_3-CH_2-CH_2-), 1.72 (m, 2H, -CH_2-CH_2-CH_2O-), 4.06 (t, 2H, -CH_2O-), 4.37 (q, 2H, -O-CO-CH_2CH_3), 7.14 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to ester group), 8.02 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to ester group), 8.19 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to butoxy group), 8.30 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to butoxy group).

3-(4-Butoxyphenyl)-5-(4-benzoylhydrazine)-1,2,4-oxadiazole (6)

Hydrazine hydrate (2.5 g, 50 mmol) was added to a solution of compound (**5**), (3.66 g, 10 mmol) in ethanol (25 ml). The reaction mixture was heated under reflux for 48 hrs, concentrated in vacuum, the precipitate obtained was filtered, washed with cold water, dried and recrystalized from ethanol. Yield (79%); mp 220°C (decom.); FT-IR (KBr disk, cm^{-1}) 3282 (N-H), 3205, 3160 (NH_2), 2955, 2872 (C_{sp3}-H), 1635 (C=O), 1612 (C=N), 1585 (C=C), 1247, 1172 (C-O-C), 902 (N-O); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ) 0.91 (t, 3H, lateral CH_3); 1.43 (m, 2H, CH_3-CH_2-CH_2-); 1.74 (m, 2H, -CH_2-CH_2-CH_2O-); 4.05 (t, 2H, -CH_2O-); 4.62 (s, 2H, NH_2); 7.13 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to hydrazide group); 8.01 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to hydrazide group); 8.08 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to butoxy group); 8.25 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to butoxy group); 10.07 (s, 1H, N-H).

1-[3-(4-Butoxyphenyl)-1,2,4-oxadiazole-5-yl]-4-[5-(n-substitutedphenyl)-1,3,4-oxadiazole-2-yl]-benzene 7$_{(a-l)}$

A mixture (0.7 g, 2 mmol) of compound (**6**) and (2 mmol) of appropriate n-substituted benzoic acid in (5 ml) of phosphorous oxychloride was heated gently under reflux for 24 hrs. The paste white residue was poured into ice water and made the mixture basic by adding (10 g) sodium bicarbonate in (50 ml) water. The resulting off white powder was filtered, dried and recrystalized from chloroform to give the desired product. Yield (60-65%).

Data for 1-[3-(4-Butoxyphenyl)-1,2,4-oxadiazole-5-yl]-4-[5-(4-nitrophenyl)-1,3,4-oxadiazole-2-yl]-benzene (**7**)$_c$. FT-IR (KBr disk, cm^{-1}) 2972, 2866 (C_{sp3}-H), 1618 (C=N of 1,2,4-oxadiazole ring), 1602 (C=N of 1,3,4-oxadiazole ring), 1581 (C=C), 1246, 1168 (C-O-C), 901 (N-O of 1,2,4-oxadiazole ring); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ) 1.05 (t, 3H, lateral CH_3); 1.43 (m, 2H, CH_3-CH_2-CH_2-); 1.70 (m, 2H, -CH_2-CH_2-CH_2O-); 3.85 (s, 3H, lateral CH_3O); 4.05 (t, 2H, -CH_2O-); 7.11 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to methoxy group); 7.19 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to methoxy group); 8.04 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to butoxy group); 8.15 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to

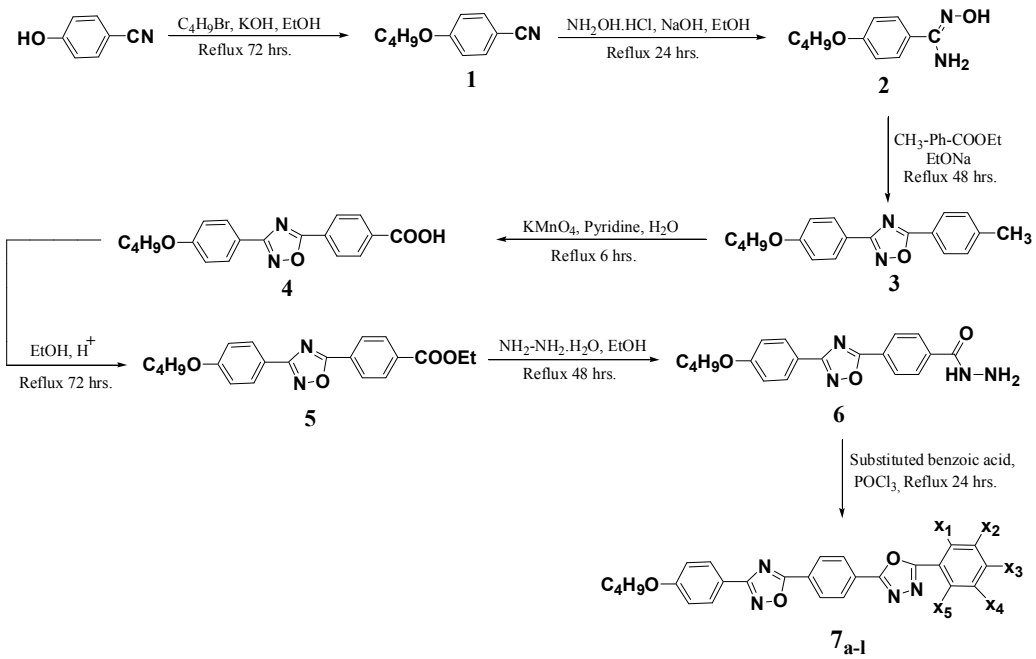
butoxy group); 8.39 (s, 4H, 4 arom H of $-C_6H_4-$ between 1,2,4- and 1,3,4-oxadiazole rings).

Data for 1-[3-(4-Butoxyphenyl)-1,2,4-oxadiazole-5-yl]-4-[5-(4-methoxyphenyl)-1,3,4- oxadiazole-2-yl]-benzene (**7**)$_e$. FT-IR (KBr disk, cm^{-1}) 2960, 2872 (C_{sp3}-H), 1612 (C=N of 1,2,4-oxadiazole ring), 1595 (C=N of 1,3,4-oxadiazole ring), 1580 (C=C), 1251, 1174 (C-O-C), 906 (N-O); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ) 0.94 (t, 3H, lateral CH_3); 1.45 (m, 2H, CH_3-$\underline{C}H_2$-CH_2-); 1.68 (m, 2H, -CH_2-$\underline{C}H_2$-CH_2O-); 4.02(t, 2H, -CH_2O-); 7.14 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to nitro group); 7.99 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to nitro group); 8.09 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to butoxy group); 8.33 (d, 2H, 2 arom. H of $-C_6H_4-$ linked to butoxy group); 8.41 (s, 4H, 4 arom H of $-C_6H_4-$ between 1,2,4- and 1,3,4- oxadiazole rings).

Results and Discussion

Synthesis

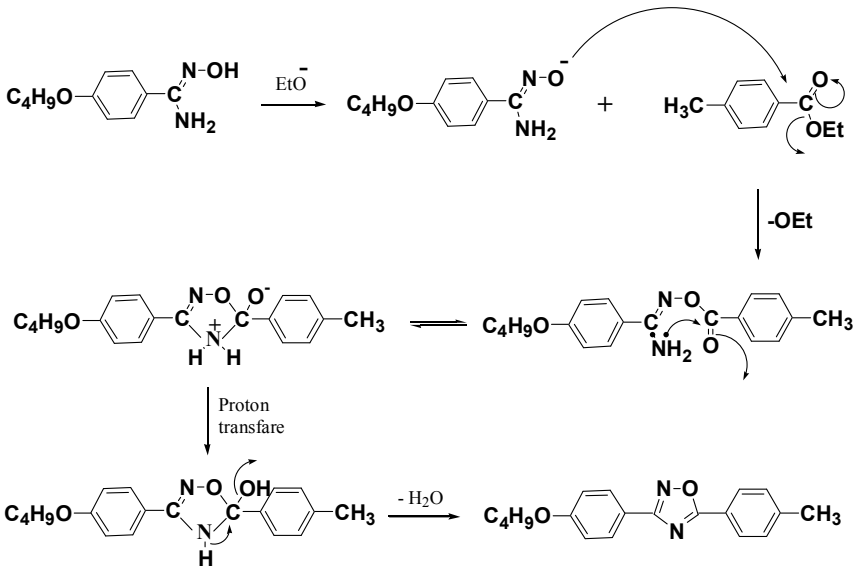
The synthesis of compounds **7**$_{(a-j)}$ is outlined in scheme 1.



Scheme 1 Synthetic route of compounds 1-7$_{(a-l)}$

All the newly synthesized compounds gave satisfactory analysis for the proposed structures, which were confirmed on the basis of their spectral (FT-IR and ^{1}H-NMR) data.

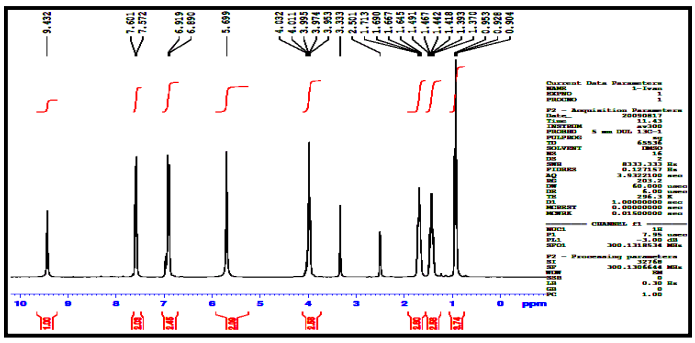
The bis-oxadiazoles compounds (**7**)$_{a-l}$ were synthesized starting with an alkylation reaction of 4-hydroxybenzonitrile with 1-bromobutane in ethanolic solution of potassium hydroxide to give the 4-butyloxybenzonitrile (**1**). The reaction of compound (**1**) with hydroxylamine hydrochloride was yielded the corresponding amidoxime (**2**). This compound (**2**) was reacted with ethyl 4-methylbenzoate in sodium ethoxide solution leading to the formation of 1,2,4-oxadiazole compound (**3**)[12]. The suggestion mechanism of this reaction may be outlined as follows in scheme 2.



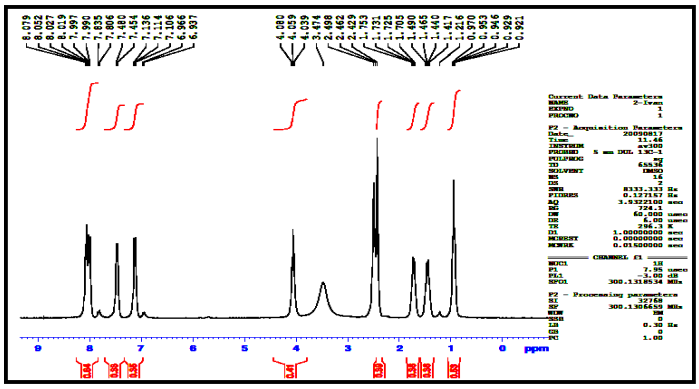
Scheme 2 The mechanism steps of formation of compound 3.

The acid compound of 1,2,4-oxadiazole(**4**) was obtained by the standard procedures of oxidation reaction of compound (**3**) by potassium permanganate in pyridine and water. Then, esterification of the acid compound (**4**) by general method yielding the ester compound of 1,2,4-oxadiazole (**5**). The reaction between the ester (**5**) and hydrazine hydrate 80% in ethanol leading to formation the hydrazide of 1,2,4-oxadiazole (**6**). The condensation reaction of hydrazide (**6**) with appropriate 4-alkoxybenzoic acid in phosphorousoxy chloride leads to the bis-(1,2,4- and 1,3,4-)oxadiazole compounds $(\mathbf{7})_{\mathbf{a\text{-}l}}$. The mechanism steps of the ring closer of 1,3,4-oxadiazole described by Tomi et al., [9].

Figure 1, 2 and 3 showed the ^{1}H-NMR spectra of compounds **2-6,** $\mathbf{7}_{\mathbf{c}}$ and $\mathbf{7}_{\mathbf{e}}$ respectively, Table 1 and Table 2 showed the physical properties and FT IR data of all compounds $(\mathbf{7})_{\mathbf{a\text{-}l}}$ respectively.

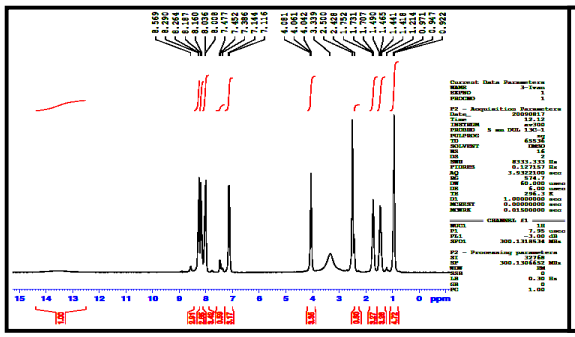


Compound **2**

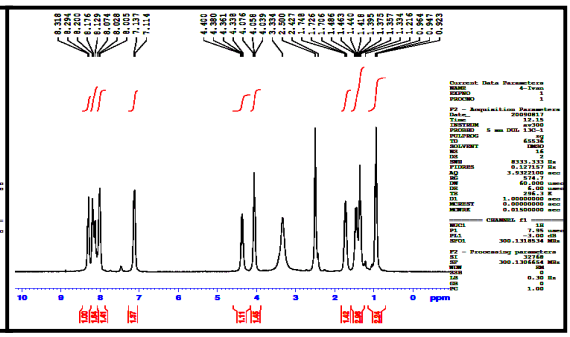


Compound **3**

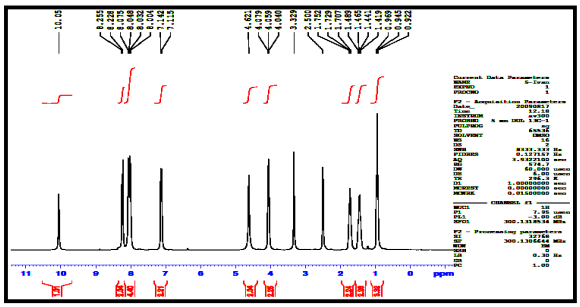
Figure 1 ^{1}H-NMR spectra of compounds 2 and 3



Compound **4**

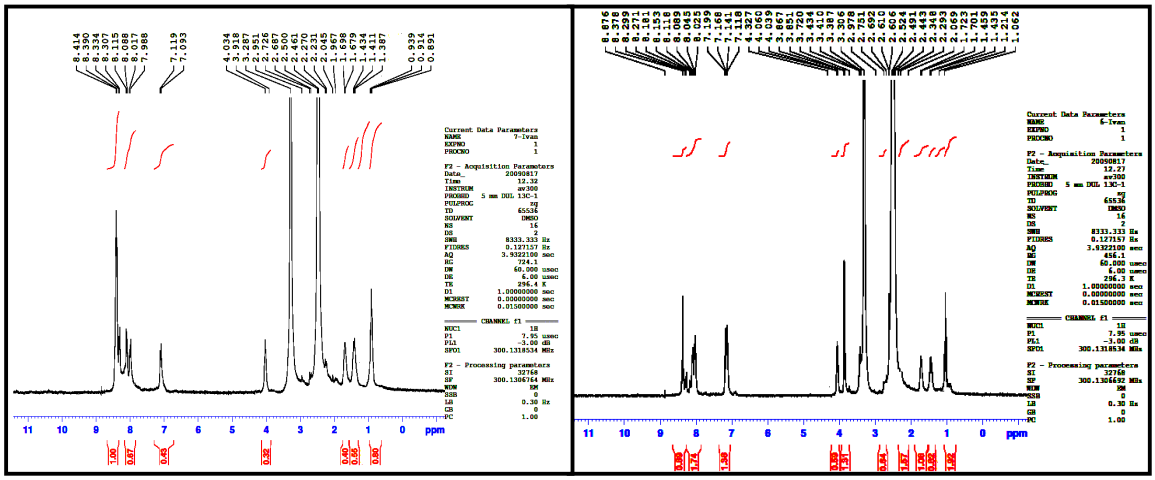


Compound **5**



Compound **6**

Figure 2 ^{1}H-NMR spectra of compounds 4 , 5 and 6



Compound 7_c Compound 7_e

Figure 3 ^{1}H-NMR spectra of compounds 7_c and 7_e

Table 1Some physical properties of compounds 7_{a-l}

Comp.	Substituents	Mol. Formula /	Yields%	Mp ºC
7a	X_1=X_2=X_3=X_4=X_5=H	$C_{26}H_{22}N_4O_3$	53	275-281
7b	X_1=X_2 =X_4=X_5=H, X_3=CH_3	$C_{27}H_{24}N_4O_3$	55	300
7c	X_1=X_2 =X_4=X_5=H, X_3=NO_2	$C_{26}H_{21}N_5O_5$	55	>300
7d	X_1=X_2 =X_4=X_5=H, X_3=Cl	$C_{26}H_{21}ClN_4O_3$	62	>300
7e	X_1=X_2 =X_4=X_5=H, X_3=OCH_3	$C_{27}H_{25}N_4O_4$	40	298-300
7f	X_1= X_3=X_4=X_5=H, X_2=NO_2	$C_{26}H_{21}N_5O_5$	65	290-297
7g	X_1= X_3=X_4=X_5=H, X_2=Cl	$C_{26}H_{21}ClN_4O_3$	65	285-290
7h	X_2=X_3=X_4=X_5=H, X_1=NO_2	$C_{26}H_{21}N_5O_5$	45	290-294
7i	X_2=X_3=X_4=X_5=H, X_1=Cl	$C_{26}H_{21}ClN_4O_3$	65	297-306
7j	X_2= X_4=X_5=H, X_1=X_3=OCH_3	$C_{28}H_{27}N_4O_5$	40	280-288
7k	X_2= X_3=X_5=H, X_1=X_4=OCH_3	$C_{28}H_{27}N_4O_5$	55	>300
7l	X_2= X_3=X_5=H, X_1=X_4=NO_2	$C_{26}H_{20}N_6O_7$	60	>300

Table 2 FT IR data of compounds 7_{a-l}

Comp	υ C=C-H CH aromatic(sp2)	υ C-C-H CH aliphatic(sp3)	υC=N oxadiazole	υC=C	υC-O-C asym.- sym.	υNO_2 asym.- sym.
7a	3061	2954 , 2929	1602	1583	1258-1140	-
7b	3034	2924 , 2867	1608	1585	1266-1135	-
7c	3080	2972 , 2866	1618	1590	1246-1168	1525 , 1344
7d	3077	2936 , 2890	1612	1588	1250-1152	-
7e	3085	2935 , 2875	1610	1586	1251-1174	-
7f	3070	2966 , 2881	1608	1590	1265-1126	1533 , 1350
7g	3091	2926 , 2854	1600	1582	1253-1166	-
7h	3045	2958 , 2902	1605	1586	1244-1118	1520 , 1345
7i	3092	2955 , 2928	1600	1580	1246-1177	-
7j	3065	2938 , 2880	1605	1580	1250-1150	-
7k	3075	2955 , 2870	1609	1586	1268-1145	-
7l	3062	2947 , 2868	1611	1588	1250-1161	1530 , 1352

Biological properties

To determine the antibacterial activity of these compounds, the filter paper disc technique [13, 14] at two concentrations (50 and 100 ppm) was carried out using ampicillin and streptomycin as the reference antibiotics. Dimethylsulphoxide (DMSO) was used as solvent control. The prepared compounds were screened for their antibacterial activity against *Escherichia coli* (*Ec*), *Staphylococcus aureus* (*Sa*), *Klebsiella pneumoniae* (*Kp*) and *Bacillus substilis* (*Bs*), the test results presented in Table 3.

Table 3 Effect of new bis-oxadiazole on the growth of tested bacteria

Compounds No.	Concentration (µg/ml)	Zone of inhibition (in mm)*				
		Gram-positive (G+)			Gram-negative (G-)	
		S. aureus	*S.cerevisiae*	*C.diphtheria*	*E. coli*	*P.aeruginosa*
7_a	100 ---------- 200	16 ---------- 18	22 ---------- 23	20 ---------- 21	- ---------- 7	- ---------- 7
7_b	100 ---------- 200	19 ---------- 18	19 ---------- 22	20 ---------- 23	- ---------- 8	- ---------- 8
7_c	100 ---------- 200	20 ---------- 19	22 ---------- 23	20 ---------- 22	- ---------- 9	- ---------- 8
7_d	100 ---------- 200	19 ---------- 22	19 ---------- 24	21 ---------- 22	- ---------- 9	- ---------- 9
7_e	100 ---------- 200	22 ---------- 21	21 ---------- 24	21 ---------- 23	- ---------- 7	- ---------- 9
7_f	100 ---------- 200	22 ---------- 24	19 ---------- 22	24 ---------- 22	- ---------- 7	- ---------- 9
7_g	100 ---------- 200	19 ---------- 20	20 ---------- 22	21 ---------- 22	- ---------- 7	- ---------- 8
7_h	100 ---------- 200	20 ---------- 23	19 ---------- 22	22 ---------- 24	- ---------- 9	- ---------- 10
7_i	100 ---------- 200	24 ---------- 22	23 ---------- 21	24 ---------- 22	- ---------- 8	- ---------- 9
7_j	100 ---------- 200	20 ---------- 22	20 ---------- 23	24 ---------- 23	- ---------- 9	- ---------- 10
7_k	100 ---------- 200	23 ---------- 22	20 ---------- 21	18 ---------- 20	- ---------- 11	- ---------- 10
7_l	100 ---------- 200	22 ---------- 24	20 ---------- 20	16 ---------- 18	- ---------- 11	- ---------- 11
Ampicillin Trihydrate	50	26	23	38	38	21
DMSO	-	0	0	0	0	0

*Diameter of the hole was 6mm

The compounds tested displayed good activity toward the Gram-positive bacteria, but were less active against Gram-negative.

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