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Synthesis , Identification and Antibactrial Activity of Some New Heterocyclic Compounds Contaning 1,3,4-Thiadiazole and 1,3,4-Oxadiazole Bearing Schiff Base

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Abstract

1,3,4 -thiadiazole and 1,3,4 –Oxadiazole bearing Schiff bases derivatives were prepared in our study by reacting the 1,3,4 – thiadiazole part with 1,3,4-oxadiazole part in ethanol to produce 1,3,4-oxadiazole hydrazinyl-1,3,4-thiadiazole [C]. which were treated with aromatic aldehyde to produce of 1,3,4- thiadiazole hydrazinyl 1,3,4- oxadiazole bearing Schiff base D1 and D2 ,The structures of synthesized compound D1 and D2 have been identified on the principles of their mass, 1H-NMR,Ft-IR, Mass spectrum and C, H, N elemental analysis .The synthesized compounds C and D1 Which founded have a strong antimicrobial activity, were assessed to their antibacterial activity by inhibition the growth of 3 strains of Gram negative bacteria *Pseudomonas auerogenosia* , *Escherichia coli* and one strain which produce enzyme called extended spectrum Beta lactemse (ESBLs) and 2 strains of Gram positive bacteria such as *Bacillus cereus* and *Staphylococcus aureus*. Therefore the chemical compound [C] and [D1] it's an important source of new antimicrobial compounds to treat bacterial

1. Introduction :

Thiadiazoles thiophene derivative are important compound by substituting two -CH= groups (methine) by nitrogens (-N=) pyridine-type .Containing 4 four isomer structure depend it on the locate of the nitrogen (N) atoms . 1 ,3,4-Thiadiazole is a sulfur(S)-including aromatic heterocycle with nitrogen atoms at the positions 3 and 4 *(1)*..As shown in the figure (1) .

Oxadiazoles are furan derived substituting of two (-CH=) methine molecules by two nitrogens (-N=) of pyridine-type . There are also like the thoiadiazole 4 four isomer structure types of oxadiazoles ring depend it on the relative positions of the nitrogen atoms in the oxadiazole ring and are numbered as isomeric oxadiazoles , 1 ,3,4-Oxadiazole is a oxygen-including aromatic heterocycle with nitrogen atoms at the 3-and 4-positions (2).As shown in the figure (2) .

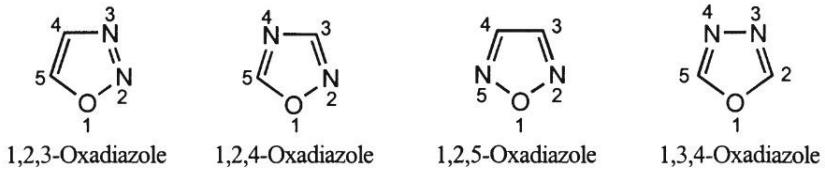


Figure (1)

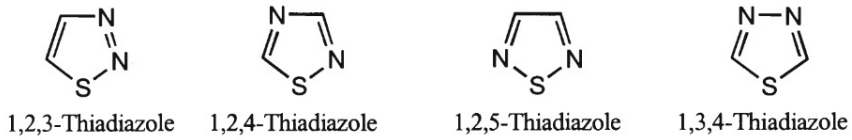


Figure (2)

1,3,4-Thiadiazole and 1,3,4-oxadiazole has shown a broad and vital role of activity against several type of pathogens . There are extensive research has been performed on the synthesis of new potent antifungal ,antibacterial agent and anticancer activity(3).Antihistaminic gents andvanti -Inflammatory(4),Anti-Osteoporotic activity(5) ,Antidiabetic and anticonvulsant activity was detected for in vivo by (MES) Maximal Electroshock model and antidiabetic activity using (OGTT) oral glucose tolerance examination by Shingalapur RV, Hosamani KM, Keri RS and Hugar MH which their synthesized 1,3,4-oxadiazoles containing 2-thio benzimidazole (6-7), As shown in the figure (2).

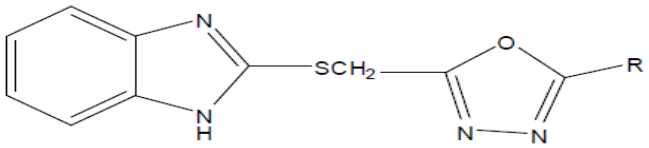


Figure (3)

2.Material , Methods :

2.1 Chemical Materials :

Methyl isonicotinate , Thiosemicarbazide , Anhydrous sodium carbonate , 4-hydrxy benzyldehyde , 4- chloro benzyldehyde , Lead acetate , Chloroform, hydrochloric acid , Ethanol , Hexane , Carbone disulfide , Hydrazine , Methanol , Ethyl acetate , Glacial acetic acid , Chloroform, hydrochloric acid HCl , Iodine , KOH , Dimethyl Sulfoxide (DMSO)

2-2 Methods :

2-2-1 Synthesis of 5-amino -1, 3, 4-thiadiazole-2-thiol [A]

Thiosemicarbazide (9.1g , 0.1 mole) was suspended in absolute ethanol (100ml) in round bottom flask (250ml), anhydrous sodium carbonate (4.46g, 0.021mole) and CS2 (19g,0.25mole) were then added respectively with continues stirring. The reactant mixture was refluxed for 5 hours; the product mixture was allowed to reduced it temperature by cool to room temperature and filtered. The filtrate was evaporated under vacuum then cold distilled water (90ml) was added, acidification with 10 % HCl drop by drop was carried out, yellow precipitate was formed of **5-amino -1,3, 4-thiadiazole-2-thiol** , The residue was collected by filtration technique, and washed with dis. Water and re-crystallized by using hot dis.water. The compound purity was checked by TLC technique , R_f value 0.83 of the eluent ratio **1:2:2 (Methanol : Chloroform : ethyl acetate)**. The spot pigment were detected visually in an Iodine chamber .The percentage of yield (81 %), melting point M.P 235 – 237 °C[8].

2-2-2 Synthesis of pyridine-4-carbohydrazide [B1] :-

A mixture of 0.2 mole (27.4 gm) of methyl isonicotinate and 0.4 mole (20ml) Hydrazine hydrate were refluxed in 100 ml of absolute ethanol for 6hr.The resultant mixture [A] was concentrated, cooled, to give white Crystal precipitate of **pyridine-4-carbohydrazide [B1] .** The compound purity was checked by TLC technique, The yield : 72.3 % and melting point M.P. 144-146C °[9].

2-2-3 Synthesis of 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol [B2]:-

A mixture of [B1] (13.7 gm, 0.1 mole), KOH (5.6 gm, 0.1mole) and CS2 (12 ml, 0.2 mole) was heated by refluxed in 100 ml of absolute ethanol for 25 hours until development of all hydrogen di sulfide discontinue . The extra of solvent extracted by vacuum and the precipitate was mixed with ice and poured onto ice water containing hydrochloric acid HCl.The white precipitate which separated was filtered and recrystallized from ethanol to give white precipitate of **5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol [B2]** , The purity of the compound was checked by TLC technique ,RF Value 0.61 of Eluent Ratio 7:3(ethanol: hexane) . and The spot pigment were detected visually in an Iodine chamber , Yield (٦٥.2 %) and melting point M.P. 217-219 C°(10).

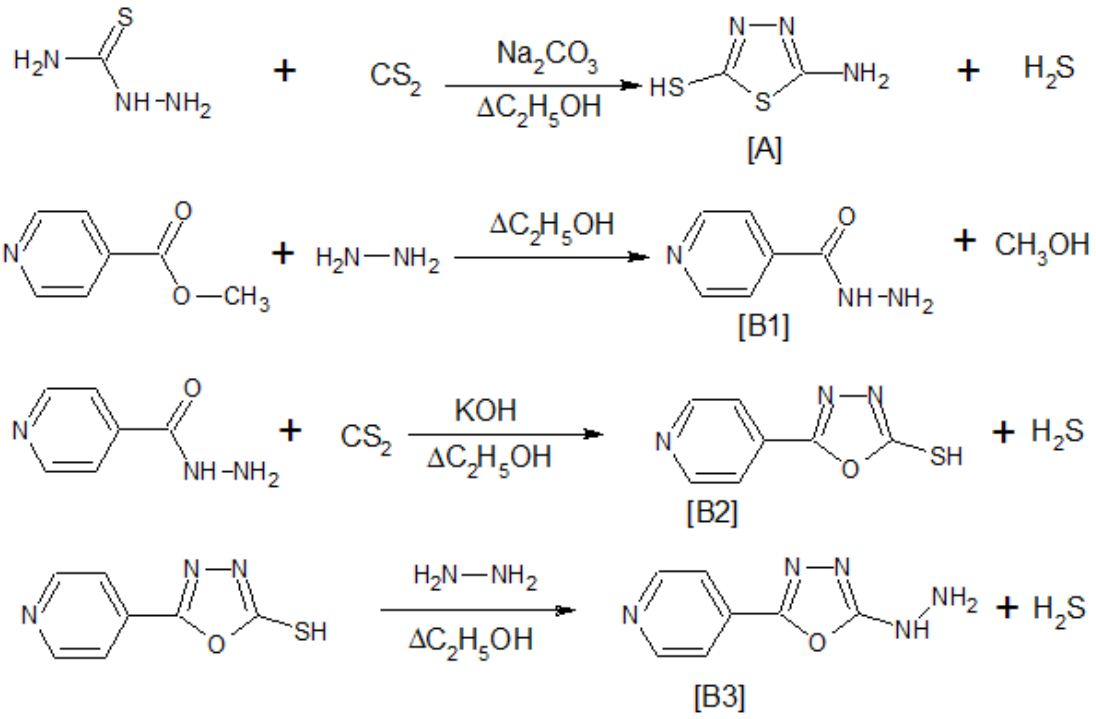
2-2-4 Synthesis of 4-(5-hydrazinyl-1,3,4-oxadiazol-2-yl)pyridine [B3]

A mixture of [B2] (3.58 gm , 0.02 mol) and hydrazine hydrate (10 mL , 0.2 mol) was heate by refluxed technique in 100% absolute ethanol (60 mL) for 6 hours until evolution of H_2S ceased ,then allow to cool, The Pale pink precipitate was filtered ,dried and recrystallized from ethanol to give light pink precipitate of 4-(5-hydrazinyl-1,3,4-oxadiazol-2-yl)pyridine [B3] . The compound purity of the synthesized derivative was followed by TLC . The pigment were detected visually in an Iodine chamber, Yield (85. ٨%) and melting M.P. 185-187 C °

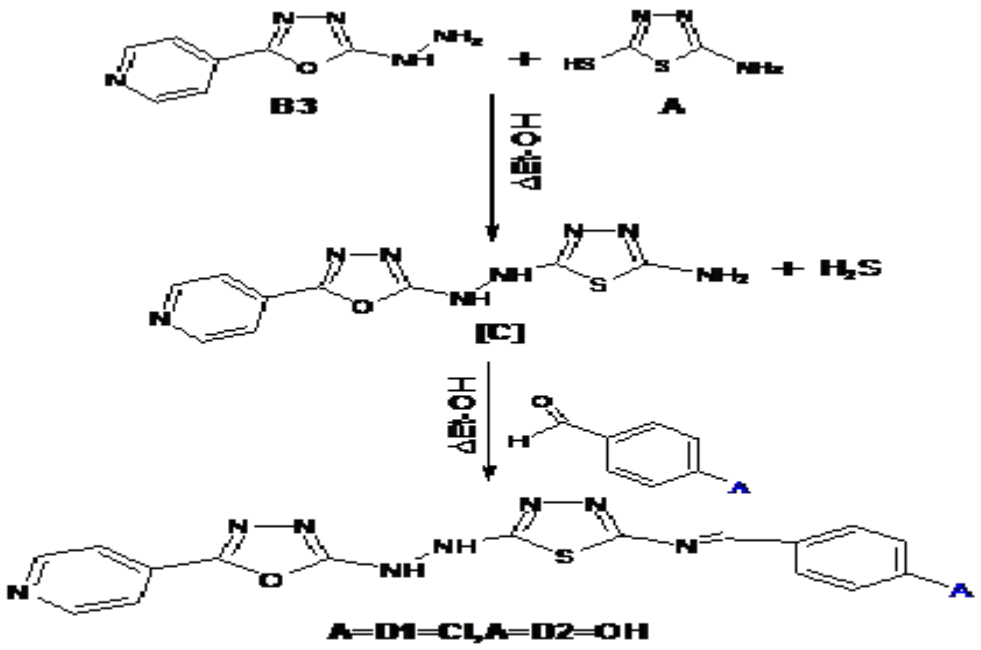
2-2-5 5-{2-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]hydrazinyl}-1,3,4-thiadiazol-2-amine [C] : A mixture of [A] (1.33 gm , 0.011 mol) and [B2] (2.76 gm of , 0.01 mol) refluxed in 100% absolute ethanol (70 mL) for 9 hours until evolution of H_2S ceased ,then cooled , The brownish yellow precipitate was filtered ,dried and recrystallized from ethanol to give The brownish yellow precipitate 5-{2-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]hydrazinyl}-1,3,4-thiadiazol-2-amine[C].The compound purity was checked by TLC technique . The pigment were visually checked in an Iodine chamber .Yield (68 %), M.P. 190-192 C °(11).

2-2-6 1-(4-chlorophenyl)-*N*-(5-{2-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]hydrazinyl}-1,3,4-thiadiazol-2-yl)methanimine [D1] A mixture (1.1 gm , 0.004 mol) of [C] and (0.85 gm of , 0.008 mol) of 4-chloro benzaldehyde then acidify by 3 drops of acetic acid ,The mixture refluxed in 50 mL of absolute ethanol for 7 hour The precipitate of 1-(4-chlorophenyl)-*N*-(5-{2-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]hydrazinyl}-1,3,4-thiadiazol-2-yl)methanimine **[D1]** was filtered then was dry the synthesized compound and recrystallized from ethanol .The compound purity was checked by TLC technique, chloroform-methanol (7:3) as eluent . the pigment were detected visually in an Iodine chamber .yield, M.P, Rf value are tabulated in a table No 2

2-2-7 4-[(5-{2-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]hydrazinyl}-1,3,4-thiadiazol-2-yl) imino]methyl}phenol[D2] A mixture (1.1 gm , 0.004 mol) of [C] and (1.0 gm of , 0.008 mol) of 4-Hydroxo benzaldehyde then acidify by 3 drops of acetic acid , The mixture was refluxed in 50 mL absolute ethanol for 7 hours The precipitate **of** 4-[(5-{2-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]hydrazinyl}-1,3,4-thiadiazol-2-yl)imino]methyl} phenol **[D2]** was filtered the left mit for time to dry and recrystallized from ethanol (12) . The purity of the compound was checked by TLC technique, chloroform-methanol (7:3) as eluent. the spot were checked visually in an Iodine chamber .Yield , M.P, Rf value are tabulated in a table No2.



Scheme 1. preparation of A and B3 Compound



Scheme 2. Preparation of D1 and D2 compound

3. Results and Discussions :

The physical properties of the prepared derivatives 1,3,4- oxadiazole hydrazinyl 1,3,4-thiadiazole bearing Schiff base which included molecular formula and melting points and elemental analyses (C, H, N) as shown in Tables (2 - 3). The structures formula of the newly synthesized compound are assigned by the mass spectra , 1H-NMR , FT- IR and C, H, N elemental analyses. The results obtained are in good agreement with those calculated for the suggested formula .

Table 2. Molecular formula, physical properties and Molecular weight data of the compound. [D1],[D2]

NO	Formula	M.Wt	Color	M.P C°	%Yield	Rf
1 D1	$C_{16}H_{11}ClN_8OS$	398	Yellow	257	% 77	0.81
2 D1	$C_{16}H_{12}N_8O_2S$	380	Dark yellow	265	% 73	0.76

Table (3) Elemental analysis of the synthesizes compound [D1],[D2]

NO	Formula	C	H	N
1 D1	**$C_{16}H_{11}ClN_8OS$**	**%Theoretical data**		
		(48.18%)	**(2.78%)**	**(28.10%)**
		% Practical data		
		(48.29%)	**(2.63%)**	**(28.02%)**
		% Theoretical data		
2 D2	**$C_{16}H_{12}N_8O_2S$**	**(50.52%)**	**(3.18%)**	**(29.46%)**
		% Practical data		
		(50.68%)	**(3.27%)**	**(29.38%)**

3.1 Infra-Red Spectroscopy:

The FTIR spectrum for synthesis compound D1 shows a characteristic stretching absorption bands. 34091cm-1, 3062cm-1 ,2940cm-1,1636 cm-1 ,1575 ,1489 cm-1 1373cm-1,1450cm-1, 1327cm-1,1076cm-1 assigned to , υN-H, υ C-H Aromatic , υC-H Aliphatic , C=N of azomethen group C=N of the hetero cyclic ring, Asymmetric C-O-C Symmetric C-O-C stretching, asymmetric C-S-C, symmetric C-S-C stretching and Strcural motion respectively. Also the FT-IR spectrum for synthesis compound D2 showed a characteristic stretching absorption bands in

3494cm-1, 34031cm-1, 3077cm-1 ,2915cm-1,1600 cm-1 ,1580 ,1397 cm-1 1290cm-1,1380cm-1, 1365 cm-1,1060cm-1 assigned to υO-H , υN-H, υ C-H aromatic,υC-H aliphatic ,C=N of azomethen group C=N of the hetero cyclic ring,asymmetrical C-O-C , symmetrical C-O-C stretching, asymmetric C-S-C , symmetric C-S-C stretching and strcural motion respectively. The IR data of the synthesized compound D1 and D2 are shown in Table (4) and figure(1,2).[13]

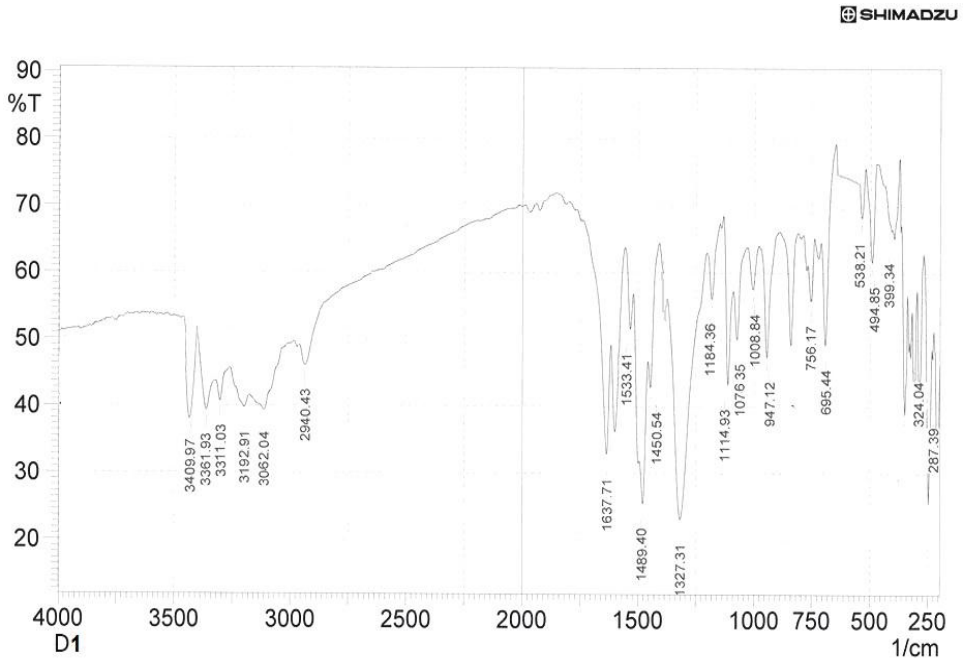


Figure (4) : Ft-IR spectrum of D1 compound

Table (4) : FT-Ir spectra data of compounds [D1 – D2]								
Comp. Sym.	uO-H	uN-H	uC-H Aromatic cm-1	uC-H aliphatic cm-1	uC=N of ring uC=N out ring	uC-O-C sym asym	uC-S-C sym asym	Structural Motion
D1	---	3409	3062	2940	1575 1636	1394 1489	1373 1450	1076
D2	3493	3403	3077	2915	1580 1600	1290 1397	1265 1380	1060

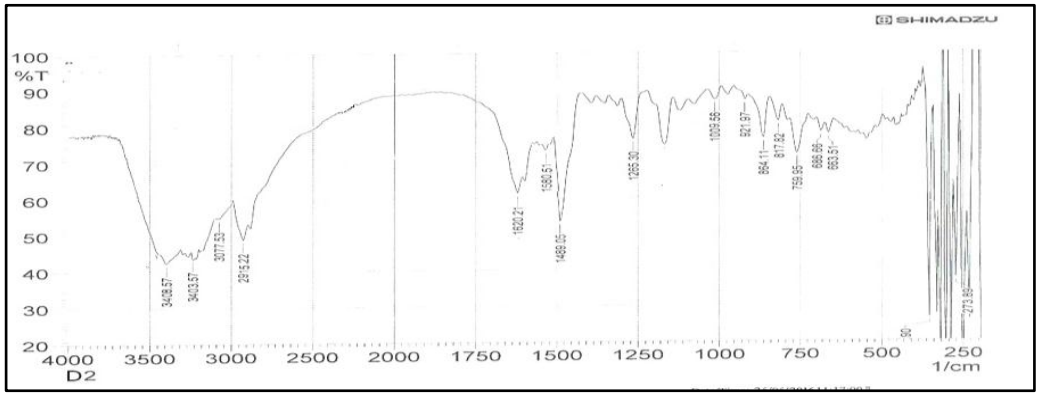


Figure (5) : Ft-IR spectrum of D2 compound

3.2 ^{1}H–NMR Spectra of 1,3,4-oxadiazole hydrazinyl 1,3,4-thiadiazole containing schiff base : The 1H – NMR spectral data of prepared **1,3,4-oxadiazole hydrazinyl 1,3,4-thiadiazole containing schiff base :**are summarized in **Table (5)** and some of their representative spectra are shown in **Figures (6 – 7).** Concerning the aromatic region of the spectra of **[D1] , [D2] ,** are appeared as multiplet signal within the rang (6.61 – 8.01) ppm attributed to Pyridyl and phenyl group in the **[D1]** and **[D2]** compounds . Whereas the second singlet signal is returned to the chemical shift value of Azomethene group CH=N– which appeared within the range (8.99 – 9.21) ppm . Also we noticed that the spectrum of **[D1] ,[D2]** showed two singlet signals at (9.82-9.97) ppm attributed to – NH– NH– respectively . **, [D2]** spectrum showed at 10.85 ppm is attributed to the phenolic –OH . All spectra showed a signal at δ 2.5 ppm for the **DMSO-*d6*** solvent as shown in Table (5) and figure(6,7). (14).

Table (5) : 1H – NMR spectra data of compounds [D1 – D2]

Comp . Symbol	**Aromatic protons**	CH=N–	**-NH**	**-OH**
D1	**6.6-7.9**	**8.9**	**9.8-9.9**	**-**
D2	**6.7-8.0**	**9.2**	**9.8-9.9**	**10.85**

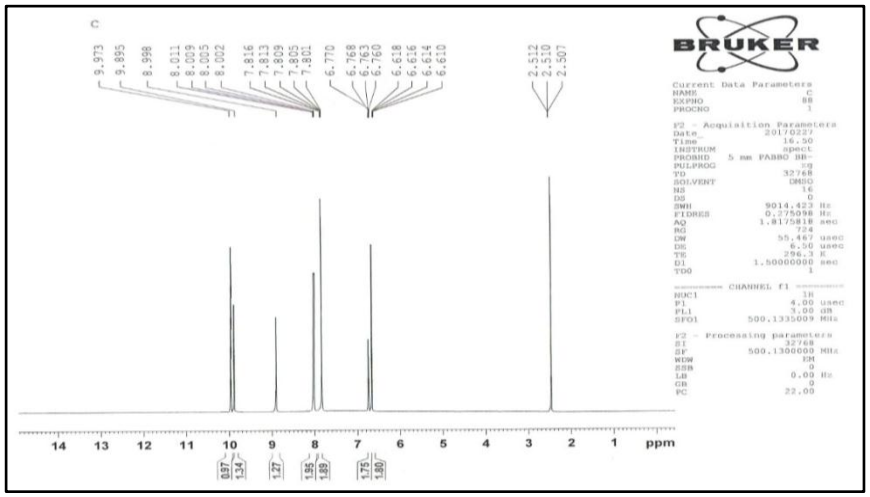


Figure (6) : 1 H–NMR spectrum of D1 compound

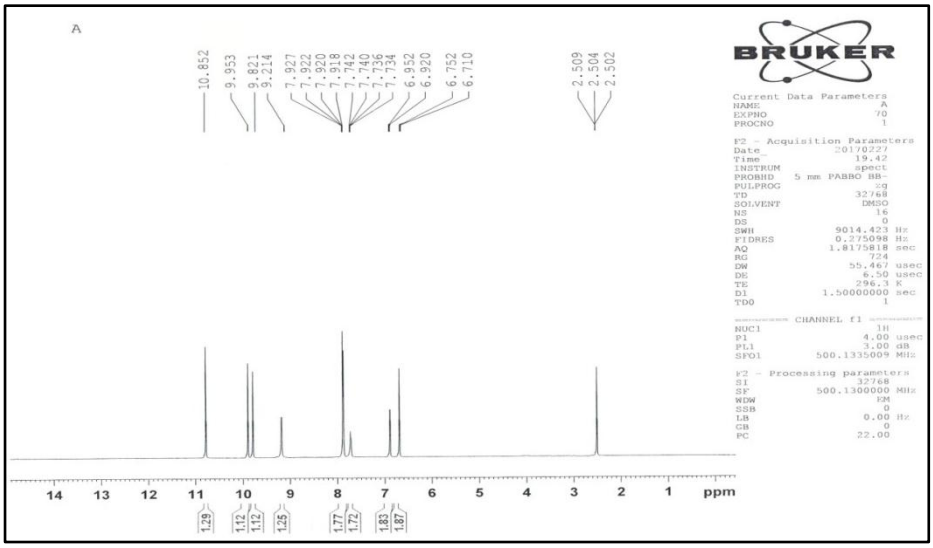


Figure (7):1H–NMR spectrum of D2 compound

3.3 Mass spectra of Schiff bases : The mass spectrum of the D1 showed a molecular ion peak [M/e] at 380 and the fragmentation of [D1] showed the peaks at (363,287,260, 146,118,114,106,104,76,64 m/z which are attributed to the fragment of [$C_{16}H_{11}N_8OS$+ , $C_{10}H_7N_8OS$+ , $C_9H_6N_7OS$+ ,$C_7H_4N_3O$+ $C_6H_4N_3$+ , $C_2H_2N_4S$+ , C_6H_4NO+ , $C_6H_4N_2$+, C_6H_4+ , C_5H_4+] respectively.

Also the mass spectrum of the D2 showed a molecular ion peak [M/e] at 398 and the fragmentation of [D2] showed the peaks at (363,287,260, 176,118,106,84,,78,76,64 m/z which are attributed to the fragment of [$C_{16}H_{11}N_8OS$+ , $C_{10}H_7N_8OS$+ , $C_9H_6N_7OS$+, $C_7H_6N_5O$ +, $C_6H_4N_3$+ , C_6H_4NO+, C_2N_2S+, C_5H_4N+, C_6H_4+, C_5H_4+] respectively are shown in **Figures (8 – 9)** (15).

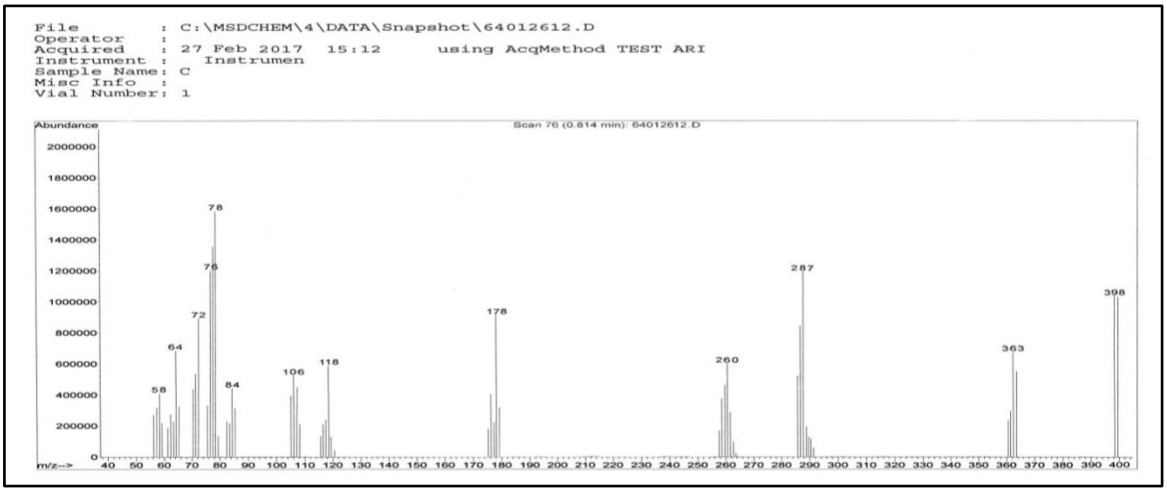


Figure (8) : Mass spectrum of D1 compound

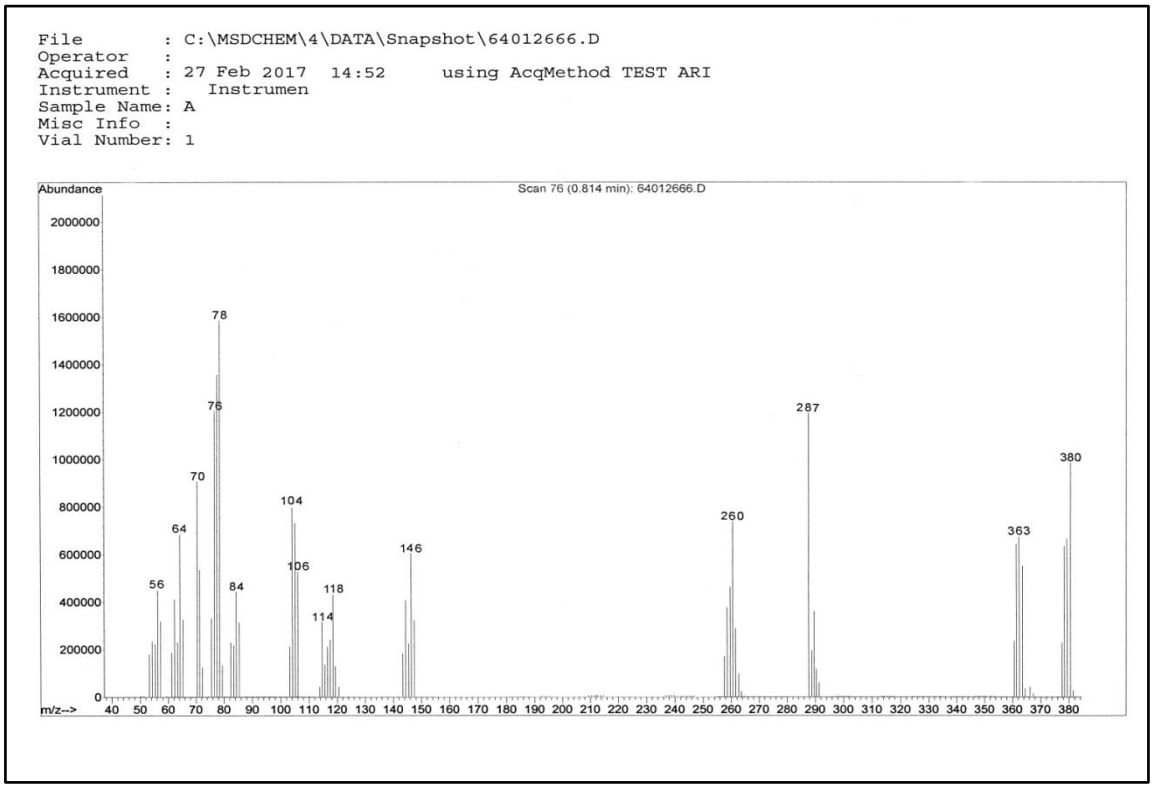


Figure (9) : Mass spectrum of D2 compound

4. antibacterial activity :

The chemical compound No.**1[A],2 [B2] ,3 [C] and 4 [D1]** were assessed to their antibacterial activity by inhibition the growth of 3 strains of Gram negative bacteria *Pseudomonas auerogenosia* , *Escherichia coli* and one strain which produce enzyme called extended spectrum Beta lactemse (ESBLs) and 2 strains of Gram positive bacteria such as *Bacillus cereus* and *Staphylococcus aureus*. These five kinds of bacteria got it from different clinical swabs were collected from children suffering from severe **diarrhea in Hospital Bint AL Huda and from Al- Hussein hospital at Thi-Qar province**. At the other hand all the eight types were showed a different degree of sensitivity toward the different of antibiotic used .

Theses bacteria are resistant to different types of antibiotics such as **Impenem , Ampicillin Sulbactum, Cephalothin , Norfloxacin, cefoxitin and Tetracyclin**.

Then by using the technic of wall diffusion method of chemical compound **No.3 [C]** exhibited high activity against all the 5 strains which mean of zone of inhibition of **(17-22 mm)** .but the chemical compound **No.4 [D1]** exhibited high activity of **(16-24 mm).**

The chemical compound **No.3[C] and 4[D1]** and have a strong antimicrobial activity. Therefore it's an important source of new antimicrobial compounds to treat bacterial infections. While the chemical compound **No.1[A] and 2 [B2]** was not found effective than against all the tested microorganisms(16-19).As shown in the figure (10-14) .

Table (6) : Mean of Diameter of the Inhibition zones Induced by deferent subtypes of different types of antibiotics

Type of antibiotic	***E.coli* without producing ESBLs**		***Bacillus cereus***		***Staphylococcus aureus***		*E.coli* producing ESBLs	
	Diameter (mm)	Result	Diameter (mm)	Result	Diameter (mm)	Result	Diameter (mm)	Result
Impenem (IMI)	21	S	٣١	S	18	R	0	R
Ampicillin-sulbactam (SAM)	0	R	0	R	0	R	0	R
Cephalothin(KF)	0	R	0	R	15	I	0	R
Gentamicin(GM)	17	S	02	S	19	S	15	S
Amikacin (AK)	19	S	20	S	17	S	16	I
Norfloxacin (NOR)	0	R	16	I	24	S	19	S
Cefoxitin (FOX)	0	R	10	R	0	R	0	R
Tetracyclin (T)	18	I	18	I	21	S	0	R

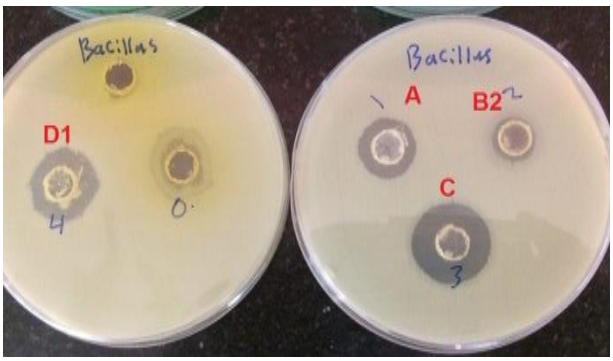


Figure 10 Showing zone of growth inhibition of multidrug-resistant bacteria *Bacillus cereus* without produce ESBLs by synthesized derivative C and D1 (MacConkey agar).

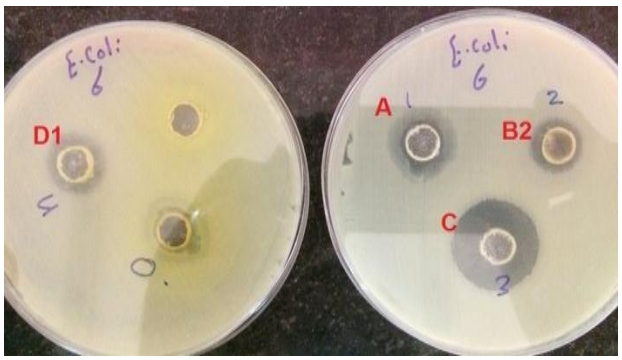


Figure 11 : Showing zone of growth inhibition of multidrug-resistant bacteria Escherichia coli with produce ESBLs by synthesized derivative C and D1 (MacConkey agar).

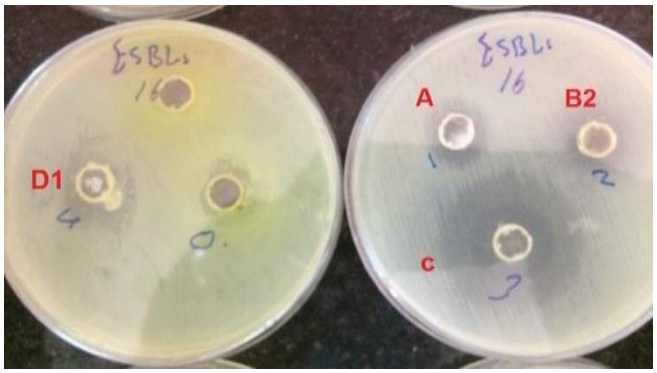


Figure 12: Showing zone of growth inhibition of multidrug-resistant bacteria Escherichia coli with produce ESBLs by synthesized derivative C and D1 (MacConkey agar).

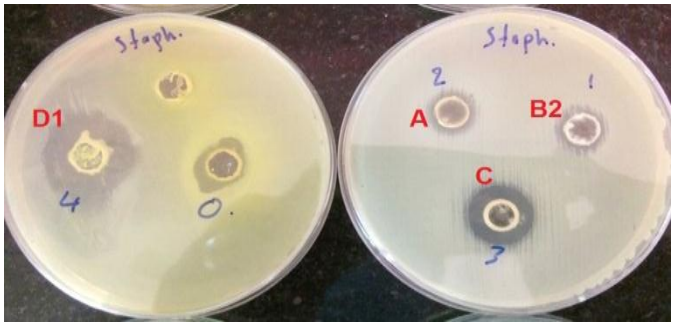


Figure 13: Showing zone of growth inhibition of multidrug-resistant bacteria *Staphylococcus aureu* without produce ESBLs by synthesized derivative D1and D2 (MacConkey agar).

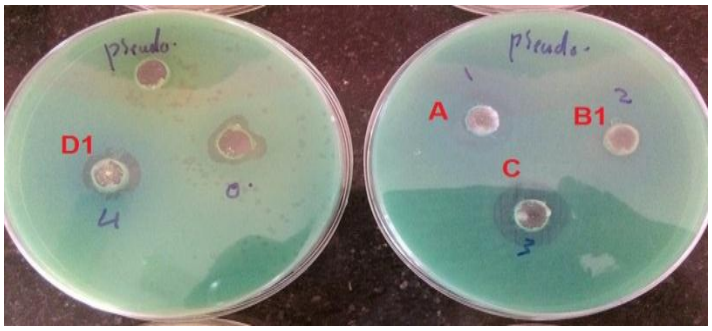


Figure 14: Showing zone of growth inhibition of multidrug-resistant bacteria *Pseudomonas auerogenosia* without produce ESBLs by synthesized derivative C and D1 (MacConkey agar).

5. CONCLUSION

In the present work,1,3,4-oxadiazole hydrazinyl 1,3,4-thiadiazole bearing Schiff base derivative,(1-(4-chlorophenyl)-*N*-(5-{2-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl] hydrazinyl}-1,3,4-thiadiazol-2-yl)methanimine[D1],4-[(5-{2-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]hydrazinyl}-1,3,4-thia diazol-2-yl)imino]methyl}phenol[D2] have been prepared and characterized on the basis of,1HNMR, Mass spectroscopic and elemental analyses .According to all and physiochemical measurements as the prepared complexes, we can suggested the chemical structure for the synthesized compounds C and D1 was successfully synthesized .

The synthesized compounds C and D1 Which founded have a strong antimicrobial activity, were assessed to their antibacterial activity by inhibition the growth of 3 strains of Gram negative bacteria *Pseudomonas auerogenosia* , *Escherichia coli* and one strain which produce enzyme called extended spectrum Beta lactemse (ESBLs) and 2 strains of Gram positive bacteria such as *Bacillus cereus* and *Staphylococcus aureus.* Therefore the chemical compound [C] and [D1] it's an important source of new antimicrobial compounds to treat bacterial

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