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Synthesis of New Bioactive Compounds of Pyrazino [2,3-*e*][1,3] Oxazepines and Pyrazino [2,3-*e*] [1,3] Diazepines Bearing 1,3,4-Oxadiazole Moieties

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Abstract

A series of new derivatives of 7,7'-(1,4-phenylene)bis[(5-substitutedphenyl-1,3,4-oxadiazol-2-yl)-amino(7,8-dihydropyrazino[2,3-e][1,3]oxazepine-5,9-dione)] 3a-d and 7,7'-(1,4-phenylene)bis[(5-substitutedphenyl-1,3,4-oxadiazol-2-yl)-amino(7,8-dihydro-5*H*-pyrazino[2,3-*e*][1,3]diazepine-5,9(6*H*)-dione)] 4a-d have been prepared by the cycloaddition reaction of 2,3-pyrazinedicarboxylic anhydride (and/or 2,3-pyrazinedicarboximide) with new derivatives of 1,3,4-oxadiazole bearing azomethine group which were prepared via cyclization reaction of some carbohydrazides with various benzoic acids in $POCl_3$. The structures of the desired compounds were in a coincidence as deduced from their FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectra. Antimicrobial activities of titled compounds have been recorded with good to excellent results.

Keywords: Diazpines; Oxazepines; 1,3,4-Oxadiazole; Carbohydrazide; Pyrazinedicarboxylic.

Introduction

Five and seven membered heteroaromatic systems with two or more heteroatoms are an important class of heterocyclic and bioactive compounds. Diazepine and oxazepine compounds bearing oxadiazole rings represent a good example and classified as antidepressant, antibacterial and antifungal drugs [1-5]. So, synthesis and development of new diazepines and oxazepines has attracted remarkable frameworks. However, according to the literature review and in the last five years, a large number of oxadiazole, diazepine and oxazepine derivatives have been prepared by various synthetic procedures. For example, some derivatives of 1,3,4-oxadiazole were prepared *via* reaction of benzohydrazides with substituted benzoic acid in the presence of $POCl_3$ [6]. Fused 1,3,4-oxadiazole derivatives were achieved by the dehydration of dioximes with acetic anhydride [7]. In contrast, new derivatives of benzodiazepine-4,7-dione were synthesized by cycloaddition reaction of heteroaromatic Schiff bases and phthalimide under refluxing in dry THF as a solvent [8]. Whereas, the cyclocondensation of 1,3-diketone compounds with 2-aminoethanethiols in pyridine gave 1,4-thiazepine and 1,5-thiazepine derivatives [9]. Further, 1,3-oxazepin-5(1H)-one derivatives have been obtained from the reaction of imines and isobenzofuranone [10]. Also, another oxazepineones derivatives were prepared by the treatment of aminomethylisoxazole with salicylaldehydes followed by reduction with $NaBH_4$ [11].

So, and as our interesting, it was necessary to contemplate about designing and synthesis a new derivatives of bis-pyrazino[2,3-e][1,3]oxazepines and pyrazino[2,3-e][1,3] diazepines as a novel heteroaromatic compounds bearing 1,3,4-oxadiazole ring and investigation of their antifungal activity.

Experimental

All chemicals were used as received from their suppliers companies without more purification. For monitoring reactions, TLC technique was applied with pre-coated aluminum plates. Determination of melting points were recorded with open capillary tubes and are uncorrected. Infra-red spectra (FTIR) were outlined on 8400s FTIR-Shimadzu spectrophotometer using KBr disc and expressed as a wave number (cm^{-1}). The ^{1}H and ^{13}C NMR spectra were done on Bruker spectrometer 400 and 100 MHz, respectively, in DMSO-d_6 solvent and (TMS) as internal standard reference. Microanalysis of

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elements (C, H, and N) data were founded by the Elemental Analyzer Model Fison (EA1108). GCMS QP-1000 EX MS technique was utilized for mass spectra. All the chemical structures were predicted with the ChemDraw Ultra (6.0) software application.

Synthesis of N',N''-[1,4-phenylenedimethanylylidene]bis(2 -aminoaceto hydrazide), compound 1:

1,4-phenyldialdehyde (terephthaldehyde) (0.01 mol), carbohydrazide (0.02 mol), and glacial acetic acid (3 drops) were dissolved in absolute ethanol (30 mL) and heated to reflux for 2hours. The solid precipitated was recrystallized from ethanol [12].

Synthesis of 2,2'-{1,4-phenylenebis[methanylylidene hydrazin-1-yl-2-ylidene]}bis[5-(4-substitutedphenyl)-1,3,4-oxadiazole], compounds 2a-d:

Compound 1 (2.78g, 0.01 mol), 4-substituted benzoic acid (0.02 mol),

and phosphorous oxychloride (10 ml) were refluxed for 24 hours. After completion of the reaction,(monitored by TLC), the reaction flask contents were kept to cool at 25 ^{0}C, then carefully poured into a crushed-ice bath and washed with sodium bicarbonate solution (10%). The solid was separated off and recrystallized from dimethylsulfoxide [13].

Synthesis of 7,7'-(1,4-phenylene) bis [(5-substitutedphenyl-1,3,4-oxadiazol-2-yl)-amino (7,8-dihydropyrazino[2,3-e][1,3]oxazepine-5,9-dione)], compounds 3a-d:

Compound **2** (0.001 mol) and furo[3,4-b]pyrazine-5,7-dione (0.002 mol) were dissolved in THF (10 mL) and refluxed for 5 hours. A crystalline solid is filtered out, dried and recrystallized from ethanol after cooling in ice water bath [8].

Synthesis of 7,7'-(1,4-phenylene) bis [(5-substitutedphenyl-1,3,4-oxadiazol-2-yl)-amino (7,8-dihydro-5*H*-pyrazino[2,3-e][1,3]diazepine-5,9(6*H*)-dione)], compounds 4a-d:

The same procedure that employed to prepare **3a-d** derivatives, was applied to synthesize compounds **4a-d** via using 5*H* pyrrolo[3,4-*b*]pyrazine-5,7(6*H*)-dione place of furo[3,4-b]pyrazine-5,7-dione.

Table 1. Physiochemical and microanalysis data of the synthesized compounds

Comp. No.	R	Empirical Formula	Mol.wt. (g/mol)	Yield (%)	mp (^{0}C)	Elemental microanalysis Found (Calculated) % C % H % N Molecular ion *m/z* (*rel. %*)
1		$C_{10}H_{14}N_8O_2$	278.27	88	138-139	C, 43.19 (43.16); H, 5.12 (5,07); N, 40.31 (40.27)
2a	CH_3	$C_{26}H_{22}N_8O_2$	478.51	69	165-166	C, 65.21 (65.26); H, 4.61 (4.63); N, 23.40 (23.42) 479(15)
2b	OCH_3	$C_{26}H_{22}N_8O_4$	510.50	77	178-179	C, 61.11 (61.17); H, 4.33 (4.34); N, 21.89 (21.95)
2c	NO_2	$C_{24}H_{16}N_{10}O_6$	540.45	81	191-193	C, 53.30 (53.34); H, 2.95 (2.98); N, 25.96 (25.92) 541(10)
2d	Br	$C_{24}H_{16}Br_2N_8O_2$	608.24	76	171-173	C, 47.35 (47.39); H, 2.64 (2.65); N, 18.39 (18.42)
3a	CH_3	$C_{38}H_{26}N_{12}O_8$	778.69	72	200-202	C, 58.66 (58.61); H, 3.39 (3.37); N, 21.62 (21.59) 780(07)
3b	OCH_3	$C_{38}H_{26}N_{12}O_{10}$	810.69	76	224-227	C, 56.28 (56.30); H, 3.21 (3.23); N, 20.71 (20.73)
3c	NO_2	$C_{36}H_{20}N_{14}O_{12}$	840.63	68	238-239	C, 51.49 (51.44); H, 2.42 (2.40); N, 23.37 (23.33) 841(20)
3d	Br	$C_{36}H_{20}Br_2N_{12}O_8$	908.43	71	221-224	C, 47.57 (47.60); H, 2.21 (2.22); N, 18.47 (18.50)
4a	CH_3	$C_{38}H_{28}N_{14}O_6$	776.72	81	202-204	C, 58.81 (58.76); H, 3.65 (3.63); N, 25.29 (25.25)
4b	OCH_3	$C_{38}H_{28}N_{14}O_8$	808.72	87	218-221	C, 56.49 (56.44); H, 3.52 (3.49); N, 25.01 (24.25) 809(10)
4c	NO_2	$C_{36}H_{22}N_{16}O_{10}$	838.66	73	234-235	C, 51.51 (51.56); H, 2.62 (2.64); N, 26.69 (26.72)
4d	Br	$C_{36}H_{22}Br_2N_{14}O_6$	906.46	69	226-229	C, 47.74 (47.70); H, 2.46 (2.45); N, 21.68 (21.63) 904(08)

Results and Discussion

Chemistry

In general, the synthetic strategy for the our compounds entitled 7,7'-(1,4-phenylene) bis[(5-substitutedphenyl-1,3,4-oxadiazol-2-yl)-amino(7,8-dihydropyrazino[2,3-e][1,3]oxazepine-5,9-dione)] **3a-d** and 7,7'-(1,4-phenylene)bis[(5-substitutedphenyl-1,3,4-oxadiazol-2-yl)-amino(7,8-dihydro-5H-pyrazino[2,3-e][1,3]diazepine-5,9(6H)-dione)] **4a-d** is outlined in Scheme 1. At the beginning, the condensation reaction of starting materials 1,4-phenyldialdehyde (terephthaldehyde) and carbohydrazide was achieved in absolute ethanol and glacial acetic acid as solvent and catalyst, respectively. After completed the reaction, compound **1** was obtained and further cyclized with different substituents of 4-substituted benzoic acid in the presence of phosphorous oxychloride to give some new derivatives of bis 1,3,4-oxadiazole, 2a-d. The cyclization mechanism steps of 1,3,4-oxadiazoles **2a-d** synthesis are illustrated in Scheme 2 [14]. Whereas the cycloaddition reaction of **2a-d** in (THF) in dry conditions afforded new derivatives of pyrazino[2,3-e][1,3]oxazepine-5,9-dione **3a-d** and pyrazino[2,3-e][1,3]diazepine-5,9(6*H*)-dione **4a-d**, respectively. The reaction initially by attack of lone-pair of the imino group to the more electrophilic anhydride or imide carbonyl carbon, an active intermediate was produced which is easily closed by dipolar cycloaddition to form a seven-membered ring as a final product. The general reaction and mechanism steps are depicted in Scheme 3.

Spectroscopic Analysis

The structural assignments of the designed compounds have been deduced initially from their physical properties identification as well as the spectroscopic analysis. The most characteristic FT-IR absorption frequencies, ^{1}H NMR and ^{13}C NMR chemical shifts of the designed compounds are given in Table 2 with a good correspondence of the proposed structures. For example, FT-IR spectrum of compound **1** displayed medium bands at 3452-3217 cm^{-1} due to the stretching vibration of both NH_2 and NH groups beside the significant peak of the imin group C=N stretching in the region 1624 cm^{-1}, Figure 1. On the other hand, FT-IR spectra of **2a-d** revealed the disappearance stretching vibrational frequencies of the primary amino group. While the new bands of C-O-C of oxadiazole ring group were recorded at 1080-1245 cm^{-1} to an evidence of the reaction succeeding. Moreover, ^{1}H NMR spectrum of **1** Fig. 2, showed the most characteristic peak as a singlet at 6.23 ppm caused by benzyliden imine proton (Ar-CH=N) beside the other singlet peaks at 5.85 and 3.21 ppm due to the primary amine protons (NH_2) and amidic proton (CO-NH), respectively [15]. In contrast, the primary amine protons peak was disappeared in the ^{1}H NMR spectrum of compounds **2a-d** as shown in Fig 3.

As for compounds **3a-d** and **4a-d**, the FT-IR spectra indicated that the more distinguished strong and sharp bands in the region 1695-1631 cm^{-1} corresponded to the lactone and lactam C=O groups stretching vibration, (see figure 4), beside the ^{1}H NMR spectra analysis Figs. 5 and 6. Furthermore, ^{13}C NMR spectra displayed other more significant signals at 163.6 and 164.3 ppm belonging to the N-C=O and O-C=O, respectively in the 7-membered heteroaromatic systems, Fig. 7 [15]. In addition, the mass spectrum of compound **4b** showed several peaks of main fragments with an agreement of the proposed structure and molecular formula, Fig 8. All elemental microanalyses and the spectroscopic data are given in Tables 1 and 2.

Bioactivity Investigation

Antimicrobial activities of the titled compounds 3a-d and 4a-d were evaluated against various bacterial strains such as *Staphylococcus Sciuri and Bacillus sphaericus* (as gram positive), *Eschrichia coli and Pseudomonas aeruginosa* (as gram negative) beside the two fungal strains, *Aspergillus flavus* and *Candida albicans* by diffusion method [16]. DMSO was used to prepare 100 µg/mL concentrations of the examined compounds. For bacterial culture, plates have been incubated for 24hours / 37 °C, whereas the fungal culture plates were kept at 25 °C and examined after 72 hours. Ciprofloxacin and fluconazole were used as reference standard drugs. The ability of growth inhibition for the tested compounds was determined as inhibition zone diameter and expressed in milliliters. The results indicated the good to excellent activities of designed compounds in comparison with standard references Table 3.

Conclusion

In summary, a series of new heterocyclic compounds of 7,7'-(1,4-phenylene) bis [(5-substitutedphenyl-1,3,4-oxadiazol-2-yl)-amino (7,8-dihydropyrazino[2,3-e][1,3] oxazepine-5,9-dione)] and 7,7'-(1,4-phenylene)bis [(5-substitutedphenyl-1,3,4-oxadiazol-2-yl)-amino (7,8-dihydro-5*H*-pyrazino[2,3-*e*][1,3]diazepine-5,9(6*H*)-dione)] have been synthesized in good yields and cost effective procedures. A coincidence for the desired structures was achieved as deduced from their microanalysis and spectroscopy data. The target compounds have been investigated for their antimicrobial properties. Most of these new heterocycles exhibited good antibacterial and antifungal activities.

Acknowledgement

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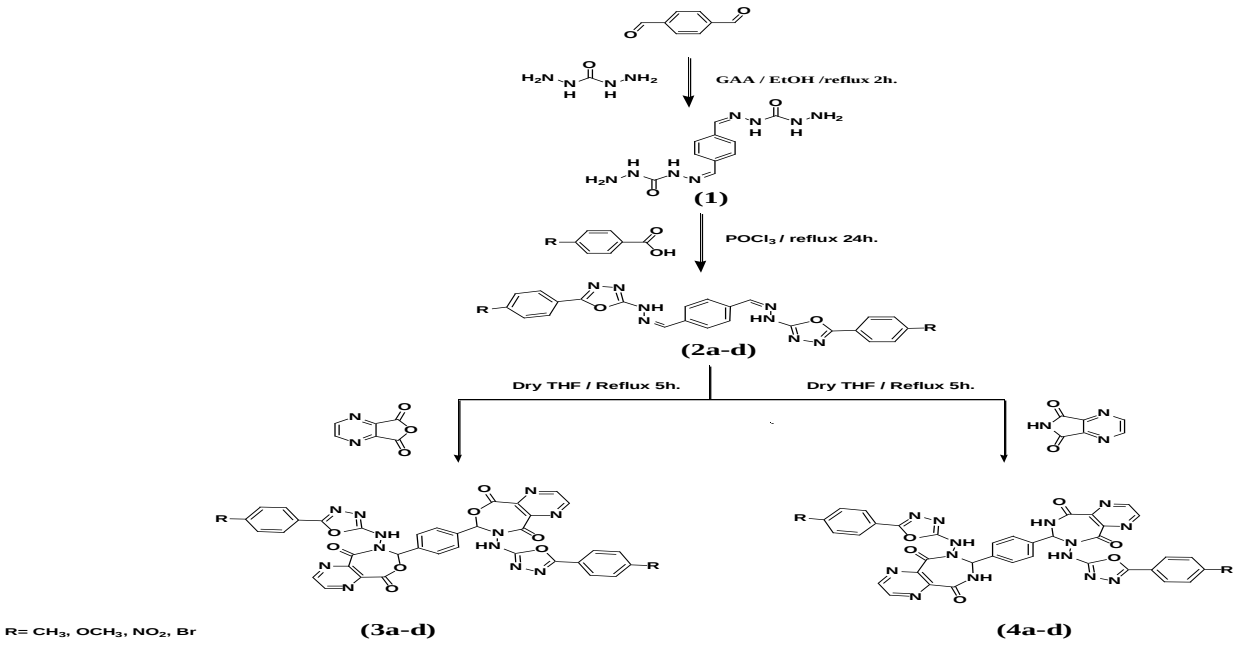
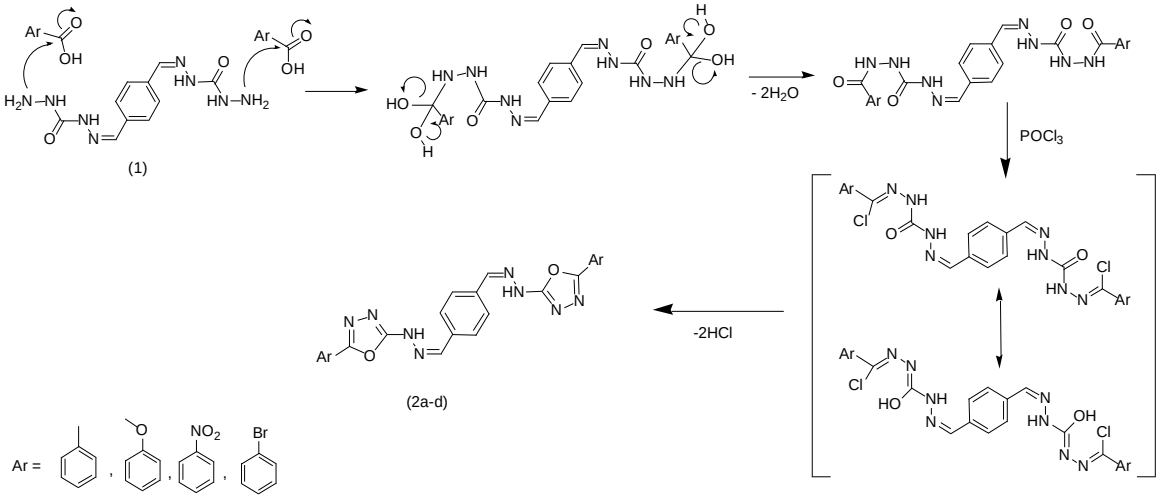
Table 2. Characteristic IR absorption frequencies, NMR chemical shifts of the designed compounds

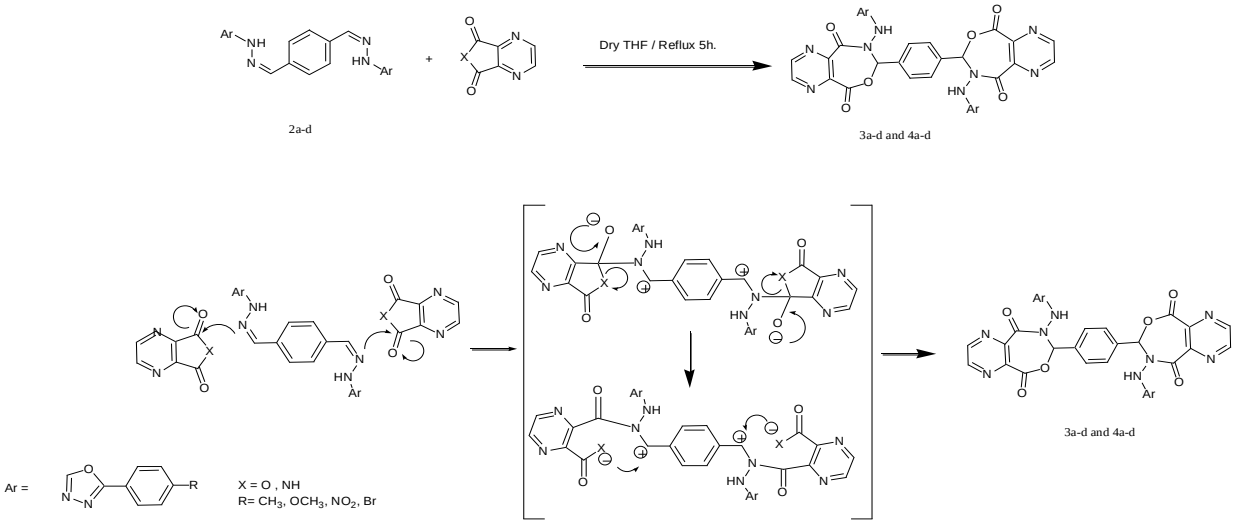
No.	Spectral data IR (KBr) (*v*, cm-1) / 1H NMR (400 MHz, DMSO-d6) (δ, ppm) / 13C NMR (100 MHz, DMSO-d6) (δ, ppm)
1	IR : 3452-3217 (NH_2, NH), 3080 ($CH_{aro.}$), 2982,2935 ($CH_{ali.}$), 1653 (Amide C=O), 1624 (C=N). ^{1}H NMR : 7.61-7.28 (m, 4H, ArH), 6.23 (s, 2H, Ar-C<u>H</u>=N), 5.85 (s, 4H, CO-NH-N), 3.21 (s, 4H, NH_2).
2a	IR : 3410-3167 (NH), 3080 ($CH_{aro.}$), 2972, 2899 ($CH_{ali.}$), 1660 (C=N).1261, 1080 (C-O-C). ^{1}H NMR: 8.71 (s, 2H, Ar-CH=N), 8.30-7.59 (m, 12H, ArH), 5.78 (s, 2H, Ar-C-NH-N), 1.98 (s, 6H, Ar-CH_3).
2b	IR : 3321-3167 (NH), 3076 ($CH_{aro.}$), 2992, 2895 ($CH_{ali.}$), 1645 (C=N).1242, 1080 (C-O-C). ^{1}H NMR : 8.33 (s, 2H, Ar-CH=N), 8.00-7.13 (m, 12H, ArH), 6.55 (s, 2H, Ar-C-NH-N), 2.50 (s, 6H, Ar-OCH_3).
2c	IR: 3335-3193 (NH), 3071 ($CH_{aro.}$), 1649 (C=N).1240, 1076 (C-O-C). ^{1}H NMR: 8.70 (s, 2H, Ar-CH=N), 6.98-7.59 (m, 12H, ArH), 4.78 (s, 2H, Ar-C-NH-N).
2d	IR: 3410-3170 (NH), 3070 ($CH_{aro.}$), 1665 (C=N).1258, 1080 (C-O-C). ^{1}H NMR: 8.70 (s, 2H, Ar-CH=N), 6.98-7.59 (m, 12H, ArH), 4.78 (s, 2H, Ar-C-NH-N).
3a	IR: 3219-3149 (NH), 3074($CH_{aro.}$), 2958,2856 ($CH_{ali.}$), 1695 (Lactone C=O), 1631 (Lactam C=O), 1614 (C=N), 1244, 1082 (C-O-C). ^{1}H NMR: 8.56 (s, 4H, Pyrazine CH=N), 8.33 (s, 2H, *sec*. amide C–CO-N<u>H</u>-C), 7.87-7.02 (m, 12H, ArH), 6.62 (s, 2H, Methine -C_3H), 5.51 (s, 2H, Ar 164.3,163.5 (O-C=O, N-C=O); 147.9 (N-C=N); 141.43 -118.48 (Ar-Carbons); 54.55 (N-C-N); 43.38 (CH-<u>C</u>H_2-C=N), 24.38 (Ar-<u>C</u>H3).
3b	IR: 3248-3128 (NH), 3081($CH_{aro.}$), 2951, 2866 ($CH_{ali.}$), 1677 (Lactone C=O), 1634 (Lactam C=O), 1627 (C=N), 1240, 1080 (C-O-C). ^{1}H NMR: 9.02 (s, 4H, Pyrazine CH=N), 8.41 (s, 2H, *sec*. amide C–CO-N<u>H</u>-C), 7.88-7.37 (m, 12H, ArH), 6.82 (s, 2H, Methine -C_3H) 5.02 (s, 2H, Ar-C-NH-N), 3.02 (s, 6H, Ar-OCH_3).
3c	IR: 3189-3140 (NH), 3088 ($CH_{aro.}$), 2929,2853 ($CH_{ali.}$), 1669 (Lactone C=O), 1635 (Lactam C=O), 1610 (C=N), 1249, 1078 (C-O-C). ^{1}H NMR: 9.28 (s, 4H, Pyrazine CH=N), 8.13 (s, 2H, *sec*. amide C–CO-N<u>H</u>-C), 7.94-7.37 (m, 12H, ArH), 6.44 (s, 2H, Methine -C_3H) 5.21 (s, 2H, Ar-C-NH-N).
3d	IR: 3245-3146 (NH), 3068 ($CH_{aro.}$), 2955,2839 ($CH_{ali.}$), 1692 (Lactone C=O), 1640 (Lactam C=O), 1624 (C=N), 1244, 1080 (C-O-C). ^{1}H NMR: 9.17 (s, 4H, Pyrazine CH=N), 8.23 (s, 2H, *sec*. amide C–CO-N<u>H</u>-C), 7.68-7.08 (m, 12H, ArH), 6.22 (s, 2H, Methine -C_3H) 4.81 (s, 2H, Ar-C-NH-N).
4a	IR: 3241-3188 (NH), 3061($CH_{aro.}$), 2960,2889 ($CH_{ali.}$), 1648 (Lactam C=O), 1624 (C=N).1243, 1082 (C-O-C). ^{1}H NMR: 9.17 (s, 4H, Pyrazine CH=N), 8.23 (s, 2H, *sec*. amide C–CO-N<u>H</u>-C), 7.58-7.02 (m, 12H, ArH), 6.74 (s, 2H, Methine -C_3H) 4.81 (s, 2H, Ar-C-NH-N), 1.72 (s, 6H, Ar-CH_3). ^{13}C NMR;162.11 (N-C=O); 148.86 (N-C=N); 143.87 -120.48 (Ar-Carbons); 59.52 (N-C-N); 47.11 (CH-<u>C</u>H_2-C=N), 22.02 (Ar-<u>C</u>H3).
4b	IR: 3189-3160 (NH), 3085 ($CH_{aro.}$), 2955,2855 ($CH_{ali.}$), 1660 (Lactam C=O), 1618 (C=N).1252, 1081 (C-O-C). ^{1}H NMR: 8.55 (s, 4H, Pyrazine CH=N), 8.22 (s, 2H, *sec*. amide C–CO-N<u>H</u>-C), 7.83-7.12 (m, 12H, ArH), 6.72 (s, 2H, Methine -C_3H) 3.41 (s, 2H, Ar-C-NH-N), 2.72 (s, 6H, Ar-OCH_3).
4c	IR: 3245-3180 (NH), 3088 ($CH_{aro.}$), 2958,2889 ($CH_{ali.}$), 1645 (Lactam C=O), 1610 (C=N).1243, 1089 (C-O-C). ^{1}H NMR: 8.57 (s, 4H, Pyrazine CH=N), 8.05 (s, 2H, *sec*. amide C–CO-N<u>H</u>-C), 7.88-7.31 (m, 12H, ArH), 6.64 (s, 2H, Methine -C_3H) 4.81 (s, 2H, Ar-C-NH-N).
4d	IR: 3269-3193 (NH), 3080 ($CH_{aro.}$), 2972,2879 ($CH_{ali.}$), 1665 (Lactam C=O), 1637 (C=N).1250, 1088 (C-O-C). ^{1}H NMR: 9.38 (s, 4H, Pyrazine CH=N), 8.77 (s, 2H, *sec*. amide C–CO-N<u>H</u>-C), 7.98-7.42 (m, 12H, ArH), 6.92 (s, 2H, Methine -C_3H) 5.81 (s, 2H, Ar-C-NH-N).



Scheme 1. General synthetic route for the designed compounds



Scheme 2. General mechanism of the reaction synthesis of 2a-d compounds



Scheme 3. General synthetic reaction and suggested mechanism of the target compounds 3a-d and 4a-d

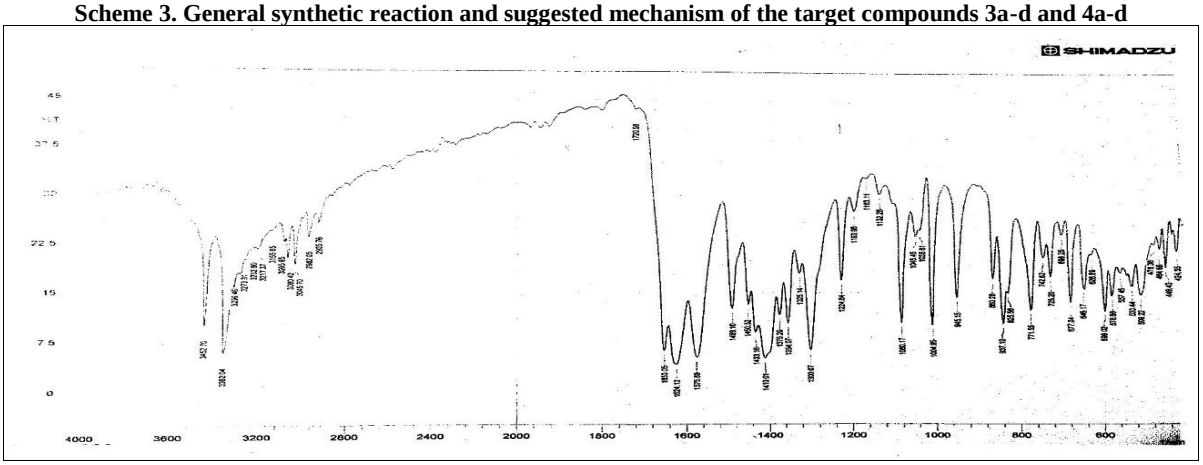


Fig 1. FT-IR spectrum of compound 1

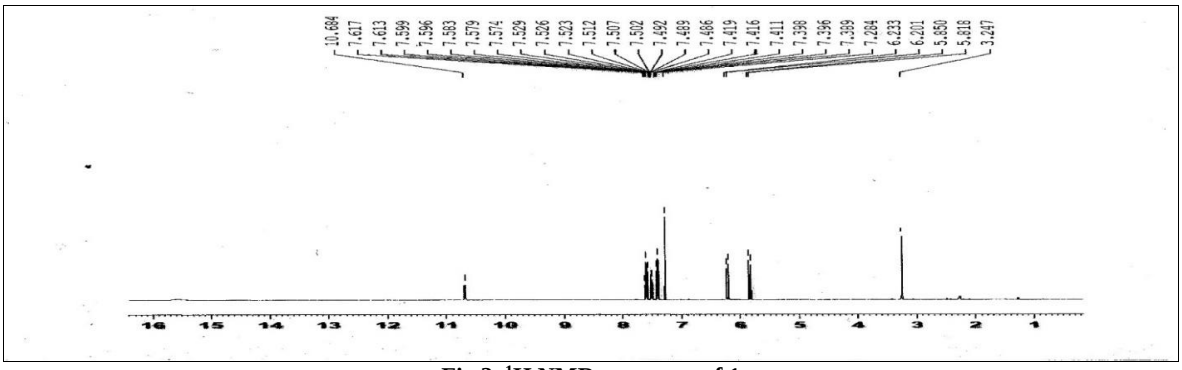


Fig 2. ^{1}H NMR spectrum of 1

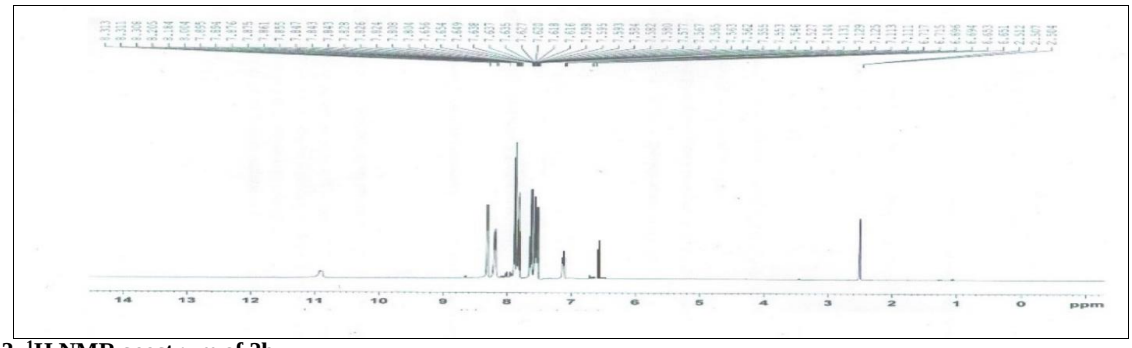


Fig 3. ^{1}H NMR spectrum of 2b

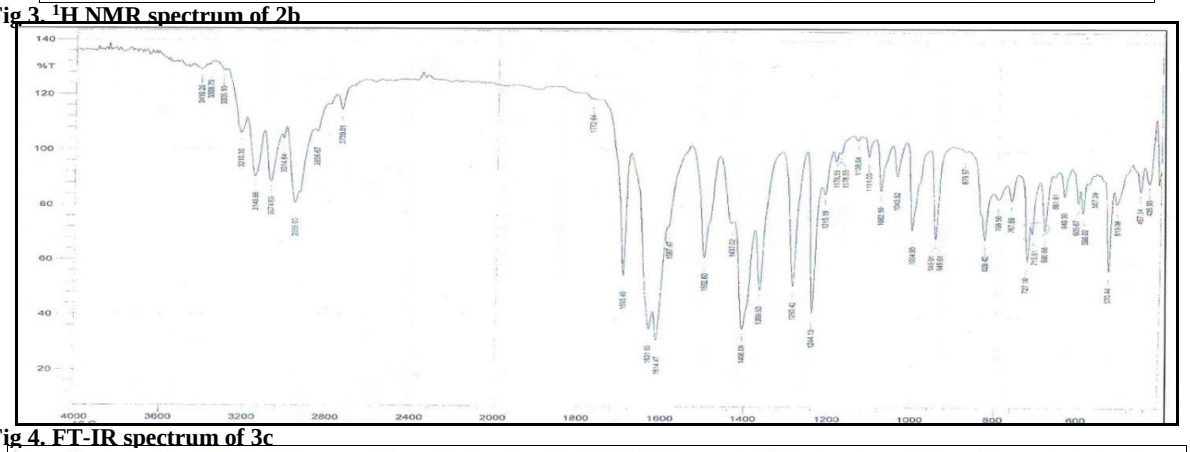


Fig 4. FT-IR spectrum of 3c

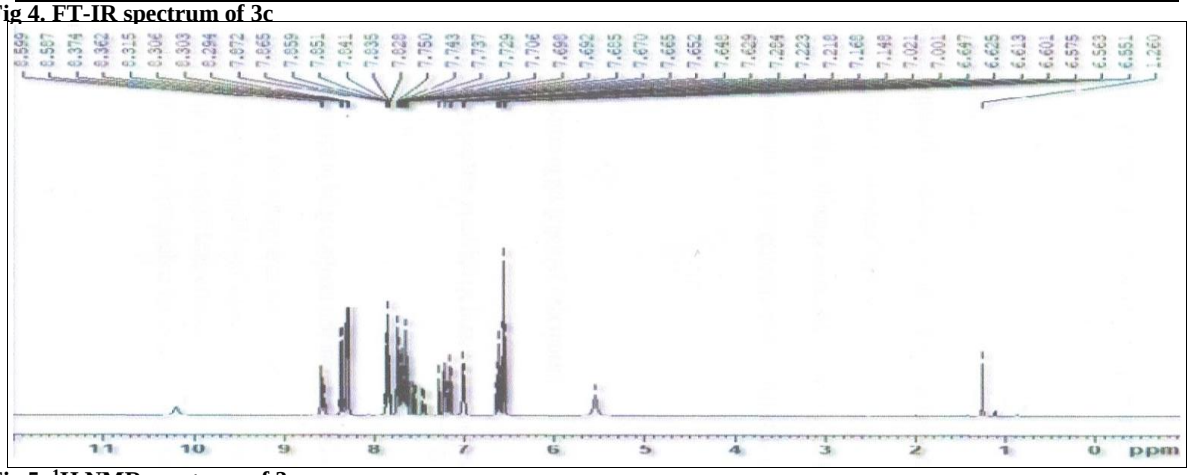


Fig 5. ^{1}H NMR spectrum of 3a

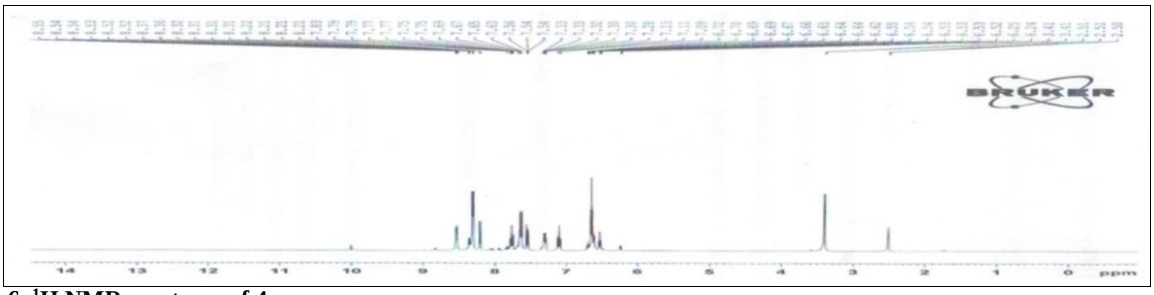


Fig 6. ^{1}H NMR spectrum of 4a

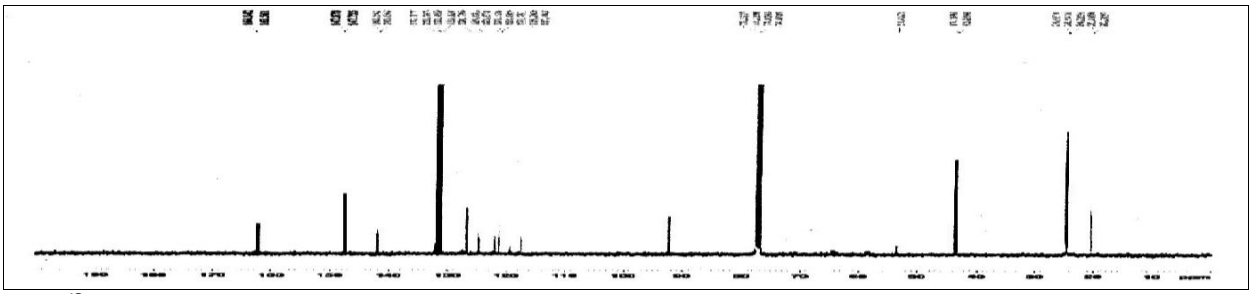


Fig 7. ^{13}C NMR spectrum of 3a

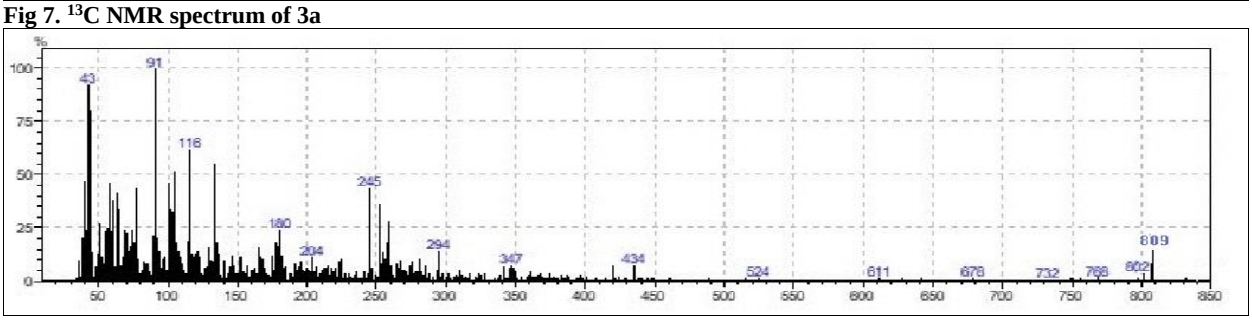


Fig 8. GC-MS spectrum of 4b

Table 3. Antimicrobial activities of newly synthesized compounds

Zone of Inhibition (mm)						
	Bacterial Strains				Fungal Strains	
	gram positive		gram negative			
Compd. No.	*Staphylococcus Sciuri*	*Bacillus Sphaericus*	*Eschrichia Coli*	*Pseudomonas Aeruginosa*	*Aspergillus flavus*	*Candida albicans*
3a	14	15	16	18	19	24
3b	14	16	16	15	17	18
3c	19	14	19	15	14	21
3d	20	13	17	20	20	22
4a	15	11	15	14	18	19
4b	12	14	18	12	18	21
4c	17	16	20	18	17	20
4d	15	14	18	16	16	26
Ciprofloxacin	16	16	22	22	18	19
Fluconazole					20	24

***concentration (100 µg/mL), diameter (mm); milliliter**

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تحضير مركبات جديدة فعالة بيولوجيا من مشتقات بايرازينو (e- 2،3) (13،) اوكسازيبين و بايرازينو (e- 2،3) (13،) دايازيبين تحمل حلقات (1،4،3 اوكساديازول)

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الخلاصة

تم تحضير مجموعة جديدة من مشتقات البايرازينواوكسازبين دايكاربوكسيليك انهيدريد او البايرازين دايكاربوكسي ايميد مع مشتقات جديدة من مركبات 1،3،4-اوكسادايازول تحمل مجموعة الازوميثين والتي تم تحضيرها من خلال تفاعل التحلق بين بعض الكاربوهيدرازيادات وحوامض كربوكسيلية مختلفة بوجود $POCl_3$. تراكيب المركبات المحضرة كانت متوافقة مع أطياف الأشعة تحت الحمراء، الرنين النووي المغناطيسي البروتوني والكربوني بالإضافة الى اطياف الكتلة. تم تسجيل وتحديد الفعالية الميكروبية للمركبات المحضرة وكانت النتائج جيدة إلى ممتازة.