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Original Article

Synthesis and Identification of New 2-Substituted-1,3,4-Oxadiazole Compounds from Creatinine and Study Their Antioxidant Activities

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ABSTRACT

The synthesis of many new 2-substituted 1,3,4-oxadiazoles from creatinine is studied in this research. The ester of creatinine **1a** was formed by the reaction of creatinine with ethylchloroacetate, and then with two of alkyl halides to produce compounds **2a-2b**. Following that, hydrazide derivatives **3a-3b** were produced by compounds **2a-2b** with semicarbazide hydrochloride. These hydrazides were cyclized with 5 percent sodium hydroxide to produce 1,3,4-oxadiazole derivatives **4a-4b**. The reaction of these compounds with aromatic aldehydes produced Schiff bases **5a-5d**. Finally, diazetidine **6a-6h** and β-lactam **7a-7d** derivatives on position (2) from 1,3,4-oxadiazole were formed by reacting Schiff bases with various reagents. FT-IR spectroscopy and ^{1}H-NMR for some synthesized compounds were used to identify the newly synthesized compounds. *In vitro*, antioxidant activities of some synthesized compounds were also investigated with promising results.

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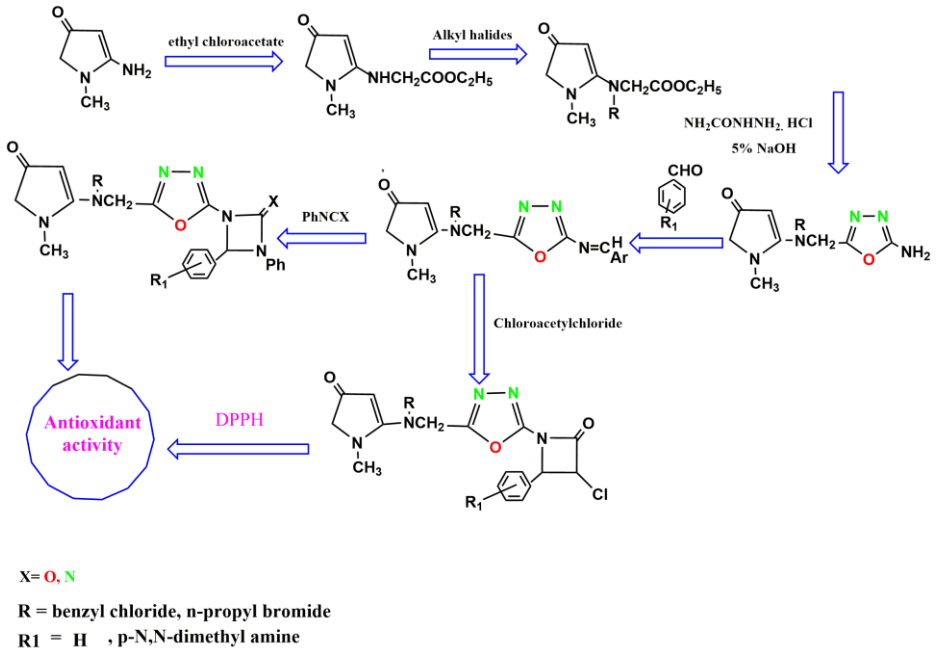
GRAPHICAL ABSTRACT



Introduction

Creatinine is generated when creatine is broken down in the body, and then passed through the kidneys [1]. A creatinine serum test can be used to determine the amount of creatinine in the blood. Men have a normal percentage of 1.14 mg/dL and women have a normal percentage of 0.93 mg/dL [2]. 1,3,4-Oxadiazole derivatives are important compounds in many fields, including medicine. Anticancer, antimicrobial, and anti-inflammatory activities have been described for these compounds [3]. 1,3,4-oxadiazoles were important for the development of heterocyclic chemistry theory and are widely used in organic synthesis [4]. Schiff bases prepared from the reaction of carbonyl group with primary amine in the carbonyl group reacts with a primary amine in the acids presence to create Schiff bases. Schiff bases, especially those with a heterocyclic moiety, such as 1,3,4-oxadiazole, have cytotoxic, antibacterial, and antifungal properties [5, 6]. Diazetidine is one of the most important nitrogen-containing compounds, and it has become extremely important in medical and pharmaceutical applications such as antibacterial activity [7-9].

Materials and Methods

Sigma-Aldrich and Fluka supplied all of the starting materials and solvents that were used without further purification. Uncorrected melting points were recorded with a Gallen Kamp capillary melting point apparatus, and FT-IR measurements taken with a SHIMADZU model FTIR-8400S. ^{1}H-NMR spectra were recorded in DMSO solution with TMS as an internal standard using a Bruker spectrophotometer model ultra-shield at 400 MHz.

*Synthesis of ester **1a** [10]*

In round-bottomed flask creatinine (0.01 mol, 1.13 g), (0.01 mol, 1 mL) ethyl chloroacetate, and potassium carbonate (0.015 mol, 2.07 g) in 1,4-dioxane (20 mL) were refluxed at 70 °C for 24 hours. The reaction mixture was cooled, filtered, and recrystallized from ethanol.

*Synthesis of compound **2a-2b** [11]*

Compound 1a (0.01 mol, 1.99 g), (0.01 mol) of benzyl chloride/ n-propyl bromide and potassium carbonate (0.015 mol, 2.07 g) in 20 mL 1,4-dioxane were refluxed at 70 °C for 24 hours. The reaction mixture was cooled and filtered and the product was recrystallized from ethanol.

Compound **1a** (0.01 mol, 1.99 g), (0.01 mol) of benzyl chloride/ n-propyl bromide and potassium carbonate (0.015 mol, 2.07 g) in 20 mL 1,4-dioxane were refluxed at 70 °C for 24 hours. The reaction mixture was cooled and filtered and the product was recrystallized from ethanol.

*Synthesis of derivatives **3a-3b** [12]*

These compounds were produced using the procedure described in the literature with some modifications. Compounds **2a-2b** (0.01 mol) were dissolved in 20 mL ethanol, followed by the addition of semicarbazide hydrochloride (0.06 mol) and sodium acetate (0.036 mol). After 3 hours of refluxing the reaction mixture, the precipitate was filtered and recrystallized from ethanol. *Synthesis of 1,3,4-oxadiazole derivatives **4a-4b** [13]*

In a round-bottomed flask, (0.003 mol) of compounds **3a-3b**, 40 mL of 5 percent of sodium hydroxide was placed. The mixture was refluxed for 5 hours. The solution was cooled and naturalized with dil. HCl. The separated precipitate was filtered and recrystallized from ethanol.

*Synthesis of Schiff bases **5a-5d** [14]*

To prepare the solution of aromatic aldehyde (0.01 mol) (dimethylaminobenzaldehyde/benzaldehyde), glacial acetic acid as a catalyst, (0.01 mol) of compounds **4a-4b** was added to 15 ml of ethanol absolute. This mixture was refluxed for 12 hours. Then, the excess solvent was evaporated and the products were recrystallized from ethanol.

*Synthesis of diazetidine derivatives **6a-6h** [15]*

These compounds were prepared according to the literature procedure with some modifications. Phenyl isocyanate/phenyl isothiocyanate (0.04 mol) was added to a solution of Schiff bases (0.01 mol) **5a-5d** in 50 mL dimethyl formamide, and the mixed reaction was heated for 10 hours at 60-65 °C. After cooling the reaction mixture, the precipitate was formed, and then recrystallized from ethanol.

*Synthesis of β-lactam derivatives **7a-7d** [16]*

To a solution of Schiff bases compounds **5a-5d** (0.002 mol) in 20 ml 1,4-dioxane chloroacetylchloride (0.002 mol, 0.15 mL) was added dropwise to the mixture at 0-5 °C in triethylamine, and then stirred at room temperature for 8 hours. After that, the precipitate was filtered, dried, and recrystallized from diethyl ether. All physical properties of the synthesized compounds are presented in Table 1.

Antioxidant activity [17, 18]

The DPPH radical scavenging activity of the samples was tested using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. At a concentration of 20 mg/L, the DPPH solution in ethanol was made on a regular basis. 0.75 mL sample or standard solution (250-1000 g/mL) was put on top of 1.5 mL DPPH solution. After 30 minutes in the dark, the absorbance readings were measured at 517 nm against a blank, and calculations were made using the following formula.

DPPH Radical Scavenging Activity (percent) = $[(A_0-A_1) / (A_0)] \times 100$

A_0 is the absorbance control value, while A_1 is the absorbance sample or the standard value.

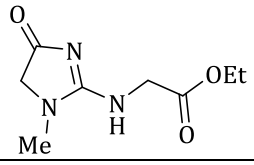
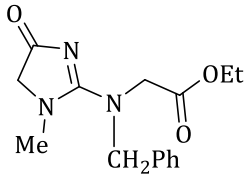
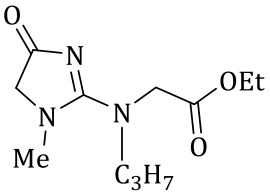
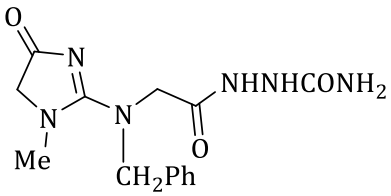
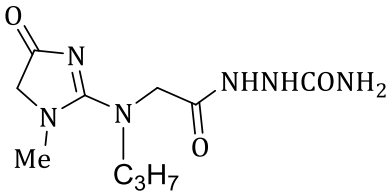
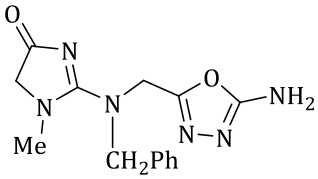
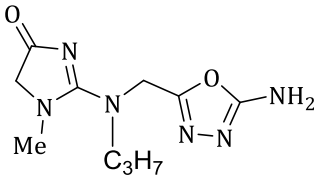
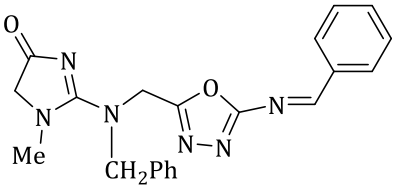
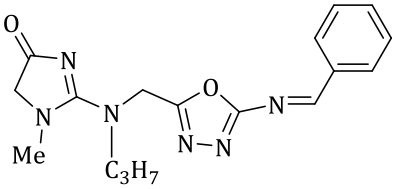
Results and Discussion

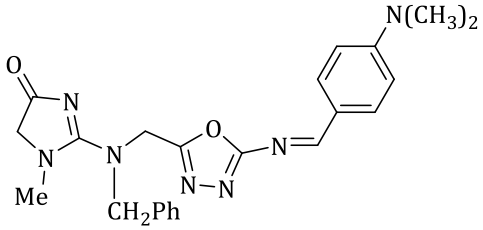
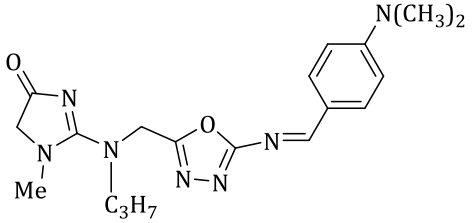
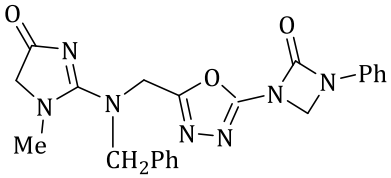
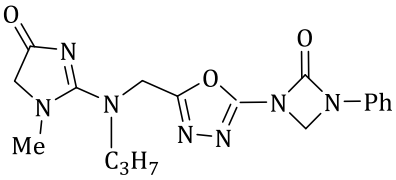
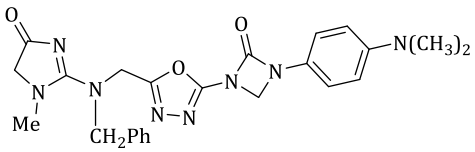
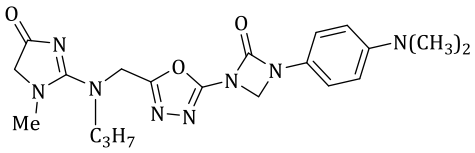
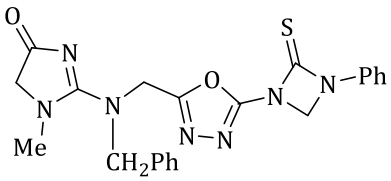
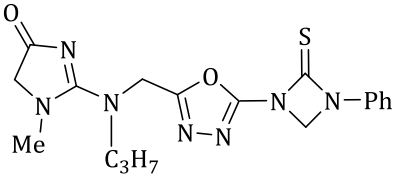
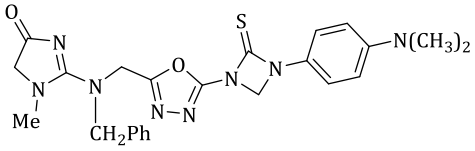
In this study, several novel heterocyclic compounds obtained from creatinine were synthesized, as displayed in Scheme 1.

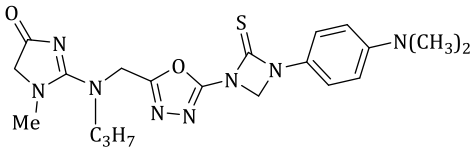
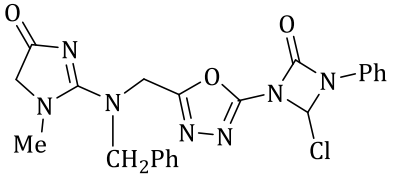
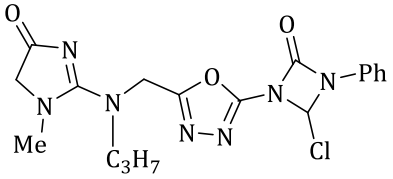
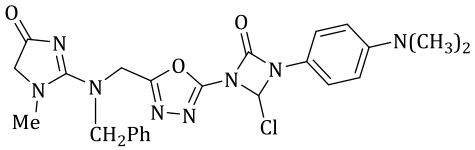
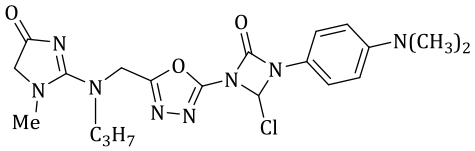
The FT-IR spectrum of compound **1a** shows the appearance of a new band at 1745 cm^{-1} that corresponds to the (C=O) ester group, 3278 cm^{-1} that corresponds to NH, and the disappearance of the NH_2 band, as listed in Table 2. The appearance of the ester group and N-H band, as well as the disappearance of the NH_2 band indicates that a reaction has occurred. The FT-IR spectra of compounds **2a-2b** indicated that it disappeared from NH, as provided in Table 2.

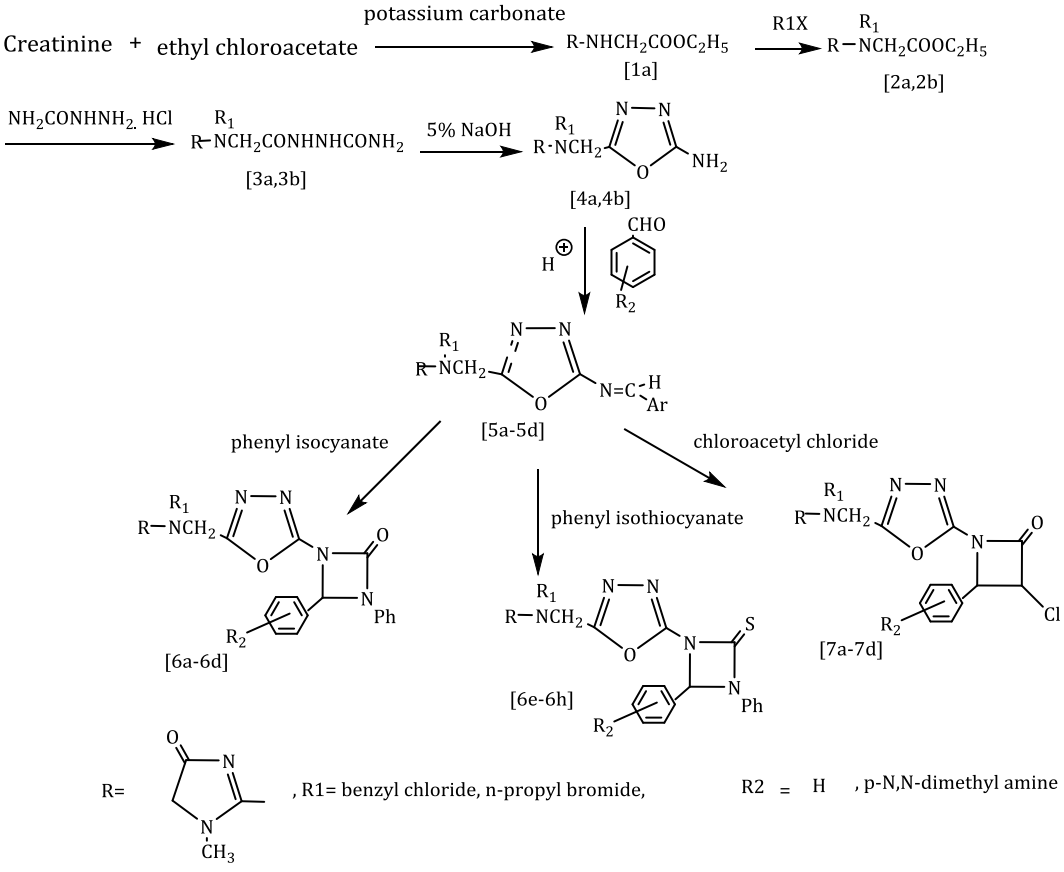
The FT-IR of compounds **3a-3b** demonstrated the disappearance of ester bands and the appearance of NH band and NH_2 band.

Table 1: Physical properties for the synthesized compounds

Compound No.	Structure	Molecular formula	M.wt g/mol	Yield (%)	mp (°C)	Color
1a		$C_8H_{13}N_3O_3$	199.20	91	209-210	Yellow
2a		$C_{15}H_{19}N_3O_3$	289.32	96	199-200	Pale Yellow
2b		$C_{11}H_{19}N_3O_3$	241.28	88	223-224	Yellow
3a		$C_{14}H_{18}O_3N_6$	318.33	90	254-256	Yellow
3b		$C_{10}H_{18}O_3N_6$	270.28	89	270-272	Yellow
4a		$C_{14}H_{16}O_2N_6$	300.32	74	235-237	Yellow
4b		$C_{10}H_{16}O_2N_6$	252.27	85	225-227	Pale Yellow
5a		$C_{21}H_{20}O_2N_6$	388.42	65	218-220	Deep Yellow
5b		$C_{17}H_{20}O_2N_6$	340.38	70	248-250	Yellow

5c		$C_{23}H_{25}O_2N_7$	431.49	80	195-197	Red
5d		$C_{19}H_{25}O_2N_7$	383.45	83	168-170	Yellow
6a		$C_{28}H_{25}O_3N_7$	507.54	94	132-134	Yellow
6b		$C_{24}H_{25}O_3N_7$	459.50	85	183-185	White
6c		$C_{30}H_{30}O_3N_8$	550.61	65	198-200	Orange
6d		$C_{26}H_{30}O_3N_8$	502.57	70	148-150	Yellow
6e		$C_{28}H_{25}O_2N_7S$	523.61	60	270-272	Yellow
6f		$C_{24}H_{25}O_2N_7S$	475.57	65	250-252	Yellow
6g		$C_{30}H_{30}O_2N_8S$	566.68	60	210-212	Orange

6h		$C_{26}H_{30}O_2N_8S$	518.63	70	248-250	Yellow
7a		$C_{23}H_{21}ClN_6O_3$	464.90	60	178-180	Off White
7b		$C_{19}H_{21}ClN_6O_3$	416.86	70	158-160	Off White
7c		$C_{25}H_{26}ClN_7O_3$	507.97	66	150-152	Red
7d		$C_{21}H_{26}ClN_7O_3$	459.93	71	168-170	Orange



Scheme 1: Synthetic rote of synthesized compounds

Table 2: FT-IR spectral data of synthesized compounds in cm^{-1}

Compound No.	υ C=N υ C-N	υ C-H aliphatic	υ C-H aromatic	υ C=C aromatic	υ C=O cyclic amide	υ NH	υ C=O Ester υ c-o-c Ester	υNH_2	υ N-N	υ C-O-C
1a	1639 1338	Asy 2981 Sy 2875	-	-	1668	3278	1745 1118	-	-	-
2a	1650 1371	Asy2950 Sy 2879	3001	1625 1575	1666	-	1740 1118	-	-	-
2b	1639 1332	Asy2937 Sy 2870	-	-	1670	-	1740 1116	-	-	-
3a	1639 1340	Asy2906 Sy 2831	3120	1558 1520	1712	3220	-	Asy3429 Sy 3348	-	-
3b	1641 1340	Asy 2889 Sy 2819	-	-	1712	3220	-	Asy3460 Sy 3340	-	-
4a	1637 1346	Asy 2906 Sy 2825	3072	1583 1562	1670	-	-	Asy 3434 Sy 3311	1413	1238
4b	1639 1340	Asy2983 Sy 2879	-	-	1679	-	-	Asy 3461 Sy 3311	1415	1232

Compounds **4a-4b** showed special bands due to (N-N) band and C-O-C band, as depicted in Table 2 [19]. These bands and others are illustrated in Table 2.

Schiff bases **5a-5d** showed the appearance of special bands due to (C=N), as shown in Table 3.

Compounds **6a-6d** showed the disappearance of imine bands and appearance of special bands at 1703-1708 cm^{-1} due to C=O 1,3-diazetidine, while compounds **6e-6h** showed the disappearance of imine bands and appearance of special band at 1230 cm^{-1} due to C=S and compounds **7a-7d** indicated disappearance of imine bands and appearance of special bands at 1701-1708 cm^{-1} due to C=O β-lactam, these bands and others are displayed in Table 4.

Table 3: FT-IR Spectral data of synthesized compounds **5a-5d** in cm^{-1}

Compound No.	υ C=N	υ N-N	υC-O-C	υ C-H aliphatic	υ C=O cyclic amide	υC=N Creatinine ring υ C-N	υ C-H aromatic	υ C=C aromatic
5a	1649	1425	1230	Asy 2939 sy 2829	1712	1689 1355	3070	1598 1575
5b	1649	1429	1211	Asy 2937 Sy 2864	1712	1687 1352	3064	1598 1575
5c	1662	1415	1232	Asy 2908 Sy 2821	1712	1683 1371	3060	1600 1554
5d	1658	1443	1232	Asy 2912 Sy 2813	1710	1681 1369	3060	1598 1552

Table 4: FT-IR spectral data of diazetidine and β-lactam compounds

Compound No.	υ C=O diazetidine	υ C-H aromatic	υ C-H aliphatic	υ C=C aromatic	υC=O Cyclic amide	υ C=N Creatinine ring υ C-N	υ C=S υC-S	υ C=O β-Lactam
6a	1708	3035	Asy 2939 Sy 2835	1593 1556	1676	1641 1315	-	-
6b	1703	3180	Asy 2937 Sy 2820	1560 1520	1687	1641 1338	-	-
6c	1703	3035	Asy 2937 Sy2802	1595 1558	1681	1645 1315	-	-
6d	1708	3056	Asy 2904 Sy 2830	1591 1554	1676	1643 1311	-	-
6e	-	3066	Asy 2991 Sy 2937	1595 1573	1685	1649 1353	1230 649	-
6f	-	3064	Asy 2937 Sy 2871	1598 1564	1683	1649 1357	1230 621	-
6g	-	3060	Asy 2935 Sy 2827	1596 1573	1685	1643 1359	1230 649	-
6h	-	3035	Asy 2910 Sy 2808	1602 1558	1685	1643 1346	1230 648	-
7a	-	3064	Asy 2974 Sy 2937	1600 1564	1685	1647 1355	-	1701
7b	-	3064	Asy 2939 Sy 2881	1600 1556	1687	1649 1315	-	1703
7c	-	3114	Asy 2939 Sy 2881	1600 1575	1685	1649 1338	-	1701
7d	-	3029	Asy 2981 Sy 2885	1600 1560	1689	1641 1336	-	1708

The ^{1}H-NMR spectrum of compounds **1a,2b** showed signals δ at 1.6-1.7 ppm due to (s, 3H-CH_3), δ at 3.6 ppm due to (s, 2H, CH_3-N-CH_2), and δ at 3.3 ppm belong to (d, 2H, NH-CH_2).

Compounds **5a** and **5d** showed at δ 1.2-1.7 ppm due to (s, 3H-CH_3), δ at 3.3-3.4 ppm due to (s, 2H, CH_3-N-CH_2), δ at 4.3 ppm due to (s, 2H, benzyl), and δ at 6.3-6.5 ppm due to (s, 1H, N=CH).

Compounds **6c** and **6d** showed δ at 1.6-1.7 ppm due to (s, 3H-CH_3), δ at 3.3 ppm due to (s, 2H, CH_3-N-CH_2), δ at 6.4-6.5 ppm belong to (s, 1H, Ph-CH), and δ at 2.9 ppm due to (s, 6H, N-(CH_3)$_2$.

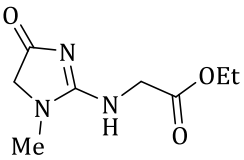
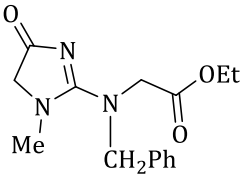
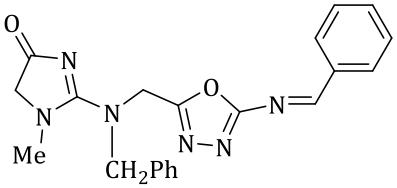
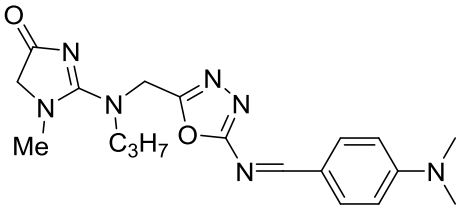
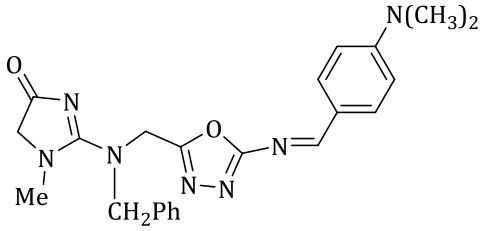
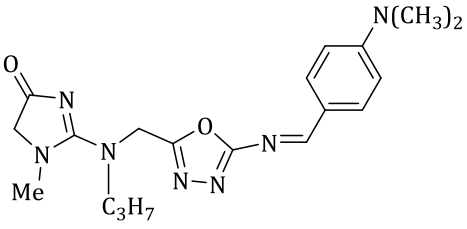
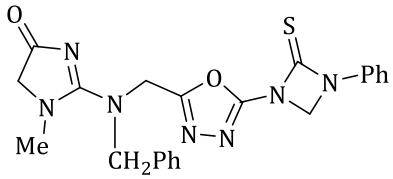
Compound **6e** and **6h** observed δ at 1.2-1.7 ppm due to (s, 3H-CH_3), δ at 3.4 ppm due to (s, 2H, CH_3-N-CH_2), and δ at 6.3-6.5 ppm due to (s, 1H, CH-Ph).

Compound **7a,7d** showed δ at 1.2-1.8 ppm due to (s, 3H-CH_3), at 6.3-6.5 ppm due to (s, 1H, CH-Ph), and δ at 4.2-4.3 ppm due to (d,1H, CH-Cl). These bands and others are listed in Table 5 [20, 21].

Antioxidant activities [22]

The DPPH method was used to evaluate some newly synthesized compounds for vitamin C as a reference. As indicated in Table 6, the newly prepared compounds **5d, 6e, 6h,** and **7d** were given a highly antioxidant assay, whereas compound **7a** had a high antioxidant capacity at a dose of 50 mg/mL, as exhibited in Table 6 and Figure 1.

Table 5: ^{1}H-NMR of some newly prepared compounds

Compound No.	Compound structure	^{1}H-NMR spectral data (δ ppm)
1a		^{1}H-NMR (400 MHz, DMSO): δ 1.7 (s, 3H-CH_3), 2.9 (t, 3H, CH_3), 3.3 (d, 2H, NH-CH_2), δ 3.4 (q, 2H, CH_2), 3.6 (s, 2H, CH_3-N-CH_2).
2b		^{1}H-NMR (400 MHz, DMSO): δ 1.2 (t, 3H, CH_3), 1.6 (s, 3H-CH_3), 2.9 (t, 3H, CH_3), 3 (m, 2H, CH_2), 3.4 (q, 2H, CH_2), 3.6 (t, 2H, N-CH_2), 3.6 (s, 2H, N-CH_2), 3.7 (s, 2H, CH_3-N-CH_2).
5a		^{1}H-NMR (400 MHz, DMSO): δ 1.2 (s, 3H-CH_3), 3.3 (s, 2H, CH_3-N-CH_2), 3.3 (S, 2H, N-CH_2), 4.3 (s, 2H, benzyl), 6.5 (s, 1H, N=CH), 7.3-7.8 (m, 10, H aromatic).
5d		^{1}H-NMR (400 MHz, DMSO): δ 1.7 (t, 3H, CH_3), 1.7 (s, 3H-CH_3), 2.9 (s, 6H, N-$(CH_3)_2$, 3 (m, 2H, CH_2), 3.4 (s, 2H, CH_3-N-CH_2), 3.4 (t, 2H, N-CH_2), 6.3 (s, 1H, N=CH), 6.5-7.7 (m, 4H aromatic).
6c		^{1}H-NMR (400 MHz, DMSO): δ 1.6 (s, 3H-CH_3), 2.9 (s, 6H, N-$(CH_3)_2$), 3.3 (s, 2H, CH_3-N-CH_2), 3.3 (S, 2H, N-CH_2), 4.2 (s, 2H, benzyl), 6.4 (s, 1H, Ph-CH), 6.7-7.4 (m, 14, H aromatic).
6d		^{1}H-NMR (400 MHz, DMSO): δ 1.3 (t, 3H, CH_3), 1.7 (s, 3H-CH_3), 2.9 (s, 6H, N-$(CH_3)_2$, 3 (m, 2H, CH_2), 3.3 (s, 2H, CH_3-N-CH_2), 3.3 (t, 2H, N-CH_2), 6.5 (s, 1H, CH-Ph), 6.9-7.5 (m, 9H aromatic).
6e		^{1}H-NMR (400 MHz, DMSO): δ 1.3 (s, 3H-CH_3), 3.3 (s, 2H, CH_3-N-CH_2), 4.1 (s, 2H, benzyl), 3.3 (S, 2H, N-CH_2), 6.5 (s, 1H, Ph-CH), 7.2-7.8 (m, 15H, aromatic).

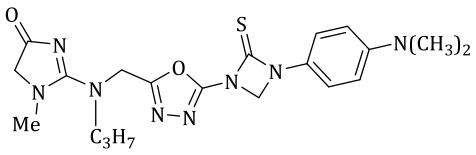
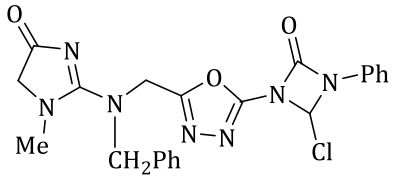
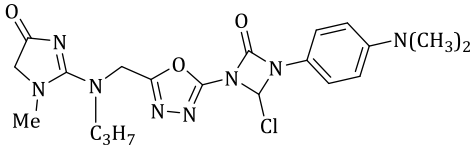
6h		^{1}H-NMR (400 MHz, DMSO): δ 1.3 (t, 3H, CH_3), 1.7 (s, 3H-CH_3), 2.9 (s, 6H, N-(CH_3)$_2$, 3 (m, 2H, CH_2), 3.4 (s, 2H, CH_3-N-CH_2), 3.4 (t, 2H, N-CH_2, 6.3 (s, 1H, CH-Ph), 6.5-7.7 (m, 9H, aromatic).
7a		^{1}H-NMR (400 MHz, DMSO): δ 1.2 (s, 3H-CH_3), 3.4 (s, 2H, CH_3-N-CH_2), 3.4 (S, 2H, N-CH_2), 4.2 (s, 2H, benzyl), 4.3 (CH-Cl), 6.5 (s, 1H, Ph-CH), δ 7.3-7.9 (m, 10 H, aromatic).
7d		^{1}H-NMR (400 MHz, DMSO): δ 1.2 (t, 3H, CH_3), 1.8 (s, 3H-CH_3), 2.9 (s, 6H, N-(CH_3)$_2$, 3 (m, 2H, CH_2), 3.4 (s, 2H, CH_3-N-CH_2), 3.4 (t, 2H, N-CH_2), 4.2 (d,1H, CH-Cl), 6.3 (d, 1H,CH-Ph), 6.6-7.7 (m, 4H aromatic).

Table 6: Scavenging for some compounds **5d, 6e, 6h, 7a, and 7d**

Compound	25 ppm	50 ppm	100 ppm
5d	51.6	56.04	58.78
6e	88.65	90.91	90.82
6h	75.26	77.31	77.94
7a	22.46	44.31	45.5
7d	11.46	37.17	70.07
Vitamin C	22.46	44.13	45.5

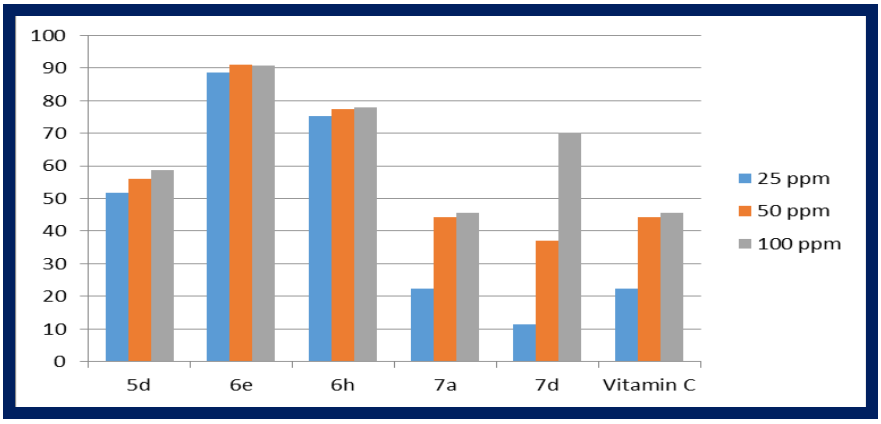


Figure 1: Antioxidant activity for some synthesized compounds **5d, 6e, 6h, 7a and 7d**

Conclusion

The new 2-substituted 1,3,4-oxadiazole compounds were synthesized in the present research. In the first step, 1,3,4-oxadiazole was produced by cyclizing hydrazide derivatives, and in the second step, Schiff bases were synthesized by reacting with various aldehydes. These Schiff bases were used to synthesize diazetidine and β-lactam, by reacting with various reagents (phenyl isocyanate/phenyl isothiocyanate and chloroacetyl chloride), respectively. Spectral data was used to establish these new substances (FT-IR and ^{1}H-NMR). In addition, *in vitro* synthetic molecules exhibit good antioxidant activity.

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Authors' contributions

All Authors contributed toward data analysis, drafting, and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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