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Construction of the 1,3,4-Oxadiazole Rings at C-5 of Benzotriazole and Investigation of Its Biological Activities

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Abstract

This study reports the synthesis of novel benzotriazole-substituted 1,3,4-oxadiazole rings **4**-**17** through a four-step reaction sequence. Initially, benzotriazole-5-carboxylic acid (**1**) was converted to its acid chloride derivative **2** *via* treatment with thionyl chloride. Subsequently, nucleophilic addition of hydrazine hydrate yielded 89% of hydrazide **3**. The desired compounds **4**-**17** were then obtained *via* condensation of compound **3** with different aromatic aldehydes, followed by an oxidative cyclization reaction using I_2/K_2CO_3. The target compounds **4**-**17** were obtained in yields ranging from 65 to 90%. The structures were confirmed using FT-IR and ^{1}H NMR spectroscopy. Additionally, the antioxidant and antibacterial properties of a few of these products were investigated.

Keywords: Antioxidant activity, Benzotriazole, 1,3,4-Oxadiazole, Oxidative cyclization.

بناء حلقات 1،3،4-أوكسادايازول في C-5 من البنزوتريازول و دراسة أنشطتها البيولوجية

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الخلاصة

تقدم هذه الدراسة تخليق مركبات جديدة للبنزوتريازول المعوض بحلقات 1،3،4-أوكساديازول **4**-**17** من خلال تفاعل متسلسل من أربع خطوات. في البداية، تم تحويل بنزوتريازول-5-كاربوكسيليك أسيد (**1**) إلى مشتق كلوريد الحامض **2** عن طريق المعالجة بكلوريد الثايونيل. بعد ذلك، إضافة نيوكليوفيلية للهايدرازين المائي، أنتج 89% من الهيدرازيد **3**. تم بعد ذلك الحصول على المنتجات المرغوبة **4**-**17** عن طريق تكاثف المركب **3** مع الديهايدات عطرية مختلفة، و التي أعقبها مباشرة تفاعل الاكسدة الحلقية بأستخدام I_2/K_2CO_3. تم الحصول على المركبات المستهدفة **4**-**17** بإنتاجية تتراوح من 65 إلى 90%. تم تأكيد تراكيب المركبات باستعمال مطيافية الاشعة تحت الحمراء و الرنين النووي المغناطيسي. بالإضافة إلى ذلك، تمت دراسة الخصائص المضادة للأكسدة و البكتيريا لعدد من هذه المنتجات.

1. Introduction

Benzotriazole (1*H*-benzo[*d*][1,2,3]triazole, or simply BT_Z) is a heterocyclic compound with the molecular formula $C_6H_5N_3$. It features a fused ring structure composed of a six-

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membered aromatic ring and a five-membered ring with three adjacent nitrogen atoms. This unique structure exhibits a wide range of biological effects [1], such as antimicrobial [2], antifungal [3], anti-mycobacterial [4], antitumor [5], antiviral [6], anti-tubercular [7], anti-proliferative [8], anesthetic [9], and anti-inflammatory [10]. In the industrial field, benzotriazole and its derivatives have been employed as anti-icing fluids for aircraft, dishwashing detergents for silver protection, and corrosion inhibitors [11]. On the other hand, a 1,3,4-oxadiazole ring is a five-membered heterocyclic molecule with one oxygen and two nitrogen atoms. The compounds containing this ring in their structures have demonstrated a diverse array of biological activities, including anti-inflammatory [12], anticonvulsant [13], anticancer [14], antioxidant [15], anti-tubercular [16], antihypertensive [17], antimicrobial [18], antiviral [19], analgesic [20], antifungal [21], and anti-proliferative [22]. Because of their significant applications, benzotriazole and 1,3,4-oxadiazole hold a prominent position as essential compounds in organic chemistry. Our research aims to synthesise novel 2,5-disubstituted 1,3,4-oxadiazoles derived from benzotriazole through a four-step process. This involves functionalization of the carboxyl group at C-5 of benzotriazole. Initially, benzotriazole will be treated with thionyl chloride to produce the corresponding acid chloride form. In the second step, this product will react with hydrazine hydrate (99%) to produce the hydrazide derivative. The third step entails condensation between the hydrazide derivative and various aldehydes will be conducted to obtain the corresponding imines. Finally, a transition metal-free oxidative cyclization (using I_2/K_2CO_3) will be performed on the synthesized imines to yield the desired benzotriazole-bearing substituted 1,3,4-oxadiazole rings.

2. Experimental part

2.1. Materials and instruments

All compounds were purchased from commercial suppliers and utilized without additional purification, unless otherwise specified. Merck silica gel 60 F_{254} was employed for TLC, while UV light and aqueous alkaline potassium permanganate were used for visualization. The uncorrected melting points were recorded in open capillary tubes using a Stuart Scientific SMP3. A Shimadzu 8400 FTIR spectrometer was used to record infrared spectral data. The ^{1}H NMR spectra were recorded by a Bruker AV400 spectrometer. Using tetramethylsilane (TMS) as an internal benchmark or DMSO (deuterated) as a reference (δ_H 2.50 ppm) in a ^{1}H NMR experiment, the chemical shifts are shown in parts per million (ppm) concerning the mentioned substance. The data on antioxidant activities were obtained utilizing a Shimadzu UV-1800 Spectrophotometer.

2.2. Chemistry

*2.2.1. Preparation of 1H-benzo[d][1,2,3]triazole-5-carbohydrazide (**3**)[23]*

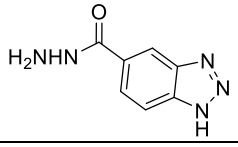
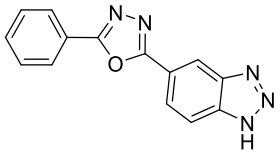
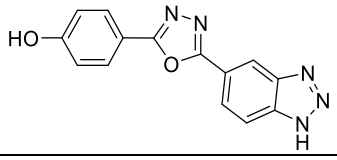
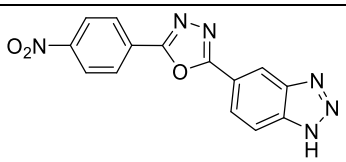
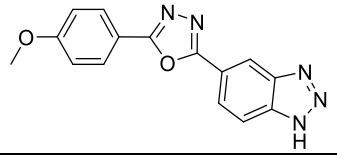
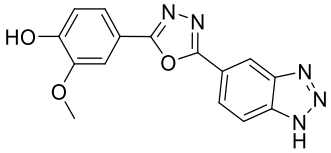
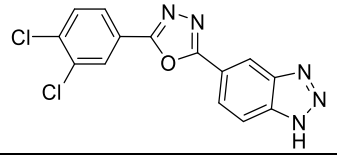
To a solution of 1*H*-benzotriazole-5-carboxylic acid (**1**) (2 g, 12.26 mmol, 1.0 eq.) in THF (25 mL), thionyl chloride (excess, *circa*. 3 mL) was added before reflux for 2 hours. The progress of the reaction was monitored by TLC using an eluent of *n*-hexane/ethyl acetate in a 1:1 ratio until compound **1** was consumed entirely. Following the evaporation of excess thionyl chloride, the resulting crude intermediate **2** was obtained. The quantitative transformation of acid precursor to acid chloride was confirmed using 10% sodium bicarbonate. The crude material **2** (1.7 g, 9.36 mmol, 1.0 eq.) was then dissolved in THF (25 mL) before adding hydrazine hydrate (99%, M = 31, 906 µL, 28.08 mmol, 3.0 eq.) slowly. The reaction mixture was then refluxed for 3 hours, as determined by TLC (usin an eluent of *n*-hexane/ethyl acetate in a 1:1 ratio). The mixture was subsequently allowed to cool to ambient temperature before the addition of brine (25 mL). The solid crude material was then filtered, washed with water, and recrystallized from ethanol to provide the desired hydrazide **3**

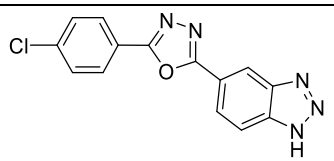
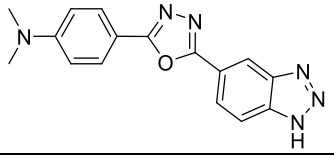
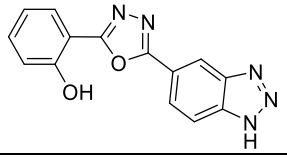
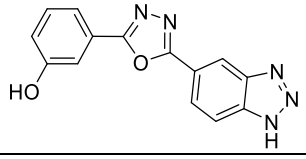
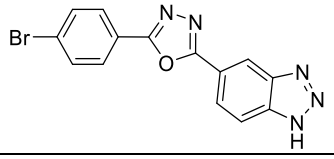
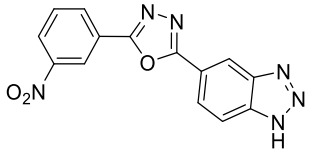
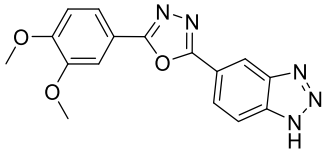
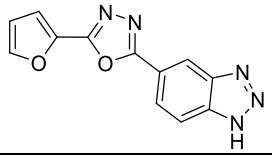
(1.48 g, 8.33 mmol, 89%). Tables 1 and 3 display the physical properties and FT-IR analysis data of product **3**, respectively.

*2.2.2. General procedure for the preparation of 1,3,4-oxadiazoles derived from benzotriazole **4-17** [24,25]*

In a round-bottom flask, a solution of hydrazide derivative **3** (250 mg, 1.41 mmol, 1.0 eq.) in EtOH (15 mL) was stirred for 10 minutes. Subsequently, an appropriate aldehyde (1.41 mmol, 1.0 eq.) in EtOH (10 mL) was slowly added, followed by reflux for 5-15 hours. The completeness of the reaction was examined by TLC using an eluent composed of *n*-hexane and ethyl acetate. The solvent was then evaporated, and the residue was dissolved in DMSO (10 mL) before adding K_2CO_3 (585 mg, 4.23 mmol, 3.0 eq.) and I_2 (215 mg, 1.69 mmol, 1.2 eq.). The reaction mixture was heated at 90 °C for 10-18 hours, as determined by TLC (eluent with *n*-hexane/ethyl acetate). A solution of $Na_2S_2O_3$ (5%, 15 mL) was added before extraction of the organic layer with ethyl acetate (2 × 15 mL), washing with brine (15 mL), drying using magnesium sulfate (anhydrous), and re-crystallization in a suitable solvent to afford the title products **4-17**. Tables 1 and 3 present the physical properties and FT-IR analysis data of the products **4-17**, respectively.

Table 1: Physical properties of compounds **3-17**

No.	Compound Structure	Compound formula	M.wt (g/mol)	m.p. (°C)	Color	Recryst. Solvent	Yield (%)
3		$C_7H_7N_5O$	177.17	288-290	White	Ethanol	89
4		$C_{14}H_9ON_5$	263.26	203-205	Brown	Ethanol	73
5		$C_{14}H_9O_2N_5$	279.26	213-215	Orange	Ethanol	65
6		$C_{14}H_8O_3N_6$	308.26	208-210	Yellow	Toluene	90
7		$C_{15}H_{11}O_2N_5$	293.29	197-199	Yellow	Acetone	69
8		$C_{15}H_{11}O_3N_5$	309.03	201-203	White	Toluene	71
9		$C_{14}H_7ON_5Cl_2$	332.14	191-193	Orange	Benzene	70

10		$C_{14}H_8ON_5Cl$	297.70	187-189	Orange	Benzene	72
11		$C_{16}H_{14}ON_6$	306.3	215-217	Yellow	Toluene	69
12		$C_{14}H_9O_2N_5$	279.26	214-216	Brown	Toluene	68
13		$C_{14}H_9O_2N_5$	279.26	210-212	Brown	Toluene	67
14		$C_{15}H_8ON_5Br$	342.16	190-192	Orange	Ethanol	72
15		$C_{14}H_8O_3N_6$	308.26	217-219	Yellow	Ethanol	88
16		$C_{16}H_{13}O_3N_5$	323.31	206-208	White	Ethanol	66
17		$C_{12}H_7O_2N_5$	253.22	209-211	Yellow	Toluene	70

2.3. Biological activity

2.3.1. Antibacterial activity test

The *in vitro* antibacterial activity of various samples (**4**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **14**, **15**, **16**, and **17**) was evaluated using two bacterial strains: *Staphylococcus aureus* and *Escherichia coli* [26]. Amikacin was used as the reference antibiotic. To achieve a concentration of 1 mg/mL, Amikacin was dissolved in dimethyl sulfoxide (DMSO) to produce both test samples and standard references. Following the liquefaction of sterilised agar and its inoculation with a microbial suspension (1 mL per 100 mL of medium), the resultant liquid was transferred to Petri plates with a depth of around 3 mm. After the wells were formed in the agar that had hardened, the test samples and references were placed in them. There was a 21-hour incubation period at 37 °C for the plates after an hour of cooling to 5 °C.

2.3.2. Antioxidant activity test

The radical scavenging activity of the synthesized derivatives was assessed by employing the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay [27]. DPPH (4 mg) was dissolved in methanol (100 mL) in test tubes before being shielded with aluminium foil and then kept

shielded from light. Five concentrations (6.25, 12.5, 25, 50, and 100 ppm) were prepared from compounds **4**, **6**, **7**, **9**, **11**, and **14** by dissolving 1 mg of each compound in methanol (10 mL) to prepare 100 ppm. This concentration was then diluted to prepare the abovementioned concentrations. The absorbance of each sample at 517 nm was measured using a spectrophotometer after incubating for one hour at 37 °C. The following equation was used to determine the ability to scavenge DPPH (triplicate measurements were done). Ascorbic acid (vitamin C) served as a reference and was prepared in similar concentrations (6.25, 12.5, 25, 50, and 100 ppm) of the prepared compounds. The radical scavenging activity of the synthesized compounds was assessed utilizing the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay [28].

$$I\% = (Abs\ blank - Abs\ sample) / Abs\ blank \times 100 \text{ [28]}$$

The antioxidant activity classification is based on IC_{50} range values, as reported by Phongpaichit (Table 2).

Table 2: Antioxidant activity according to Phongpaichit, 2007 [29]

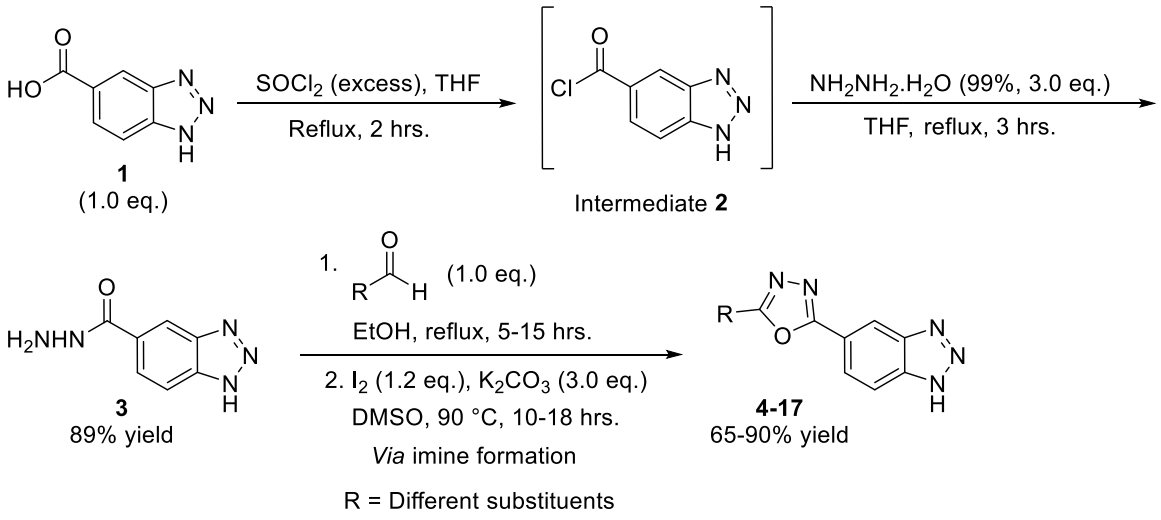
IC_{50} (µg/mL)	Mark
10-50 µg/mL	Strong antioxidant activity
50-100 µg/mL	Intermediate antioxidant activity
>100 µg/mL	Weak antioxidant activity

3. Results and discussion

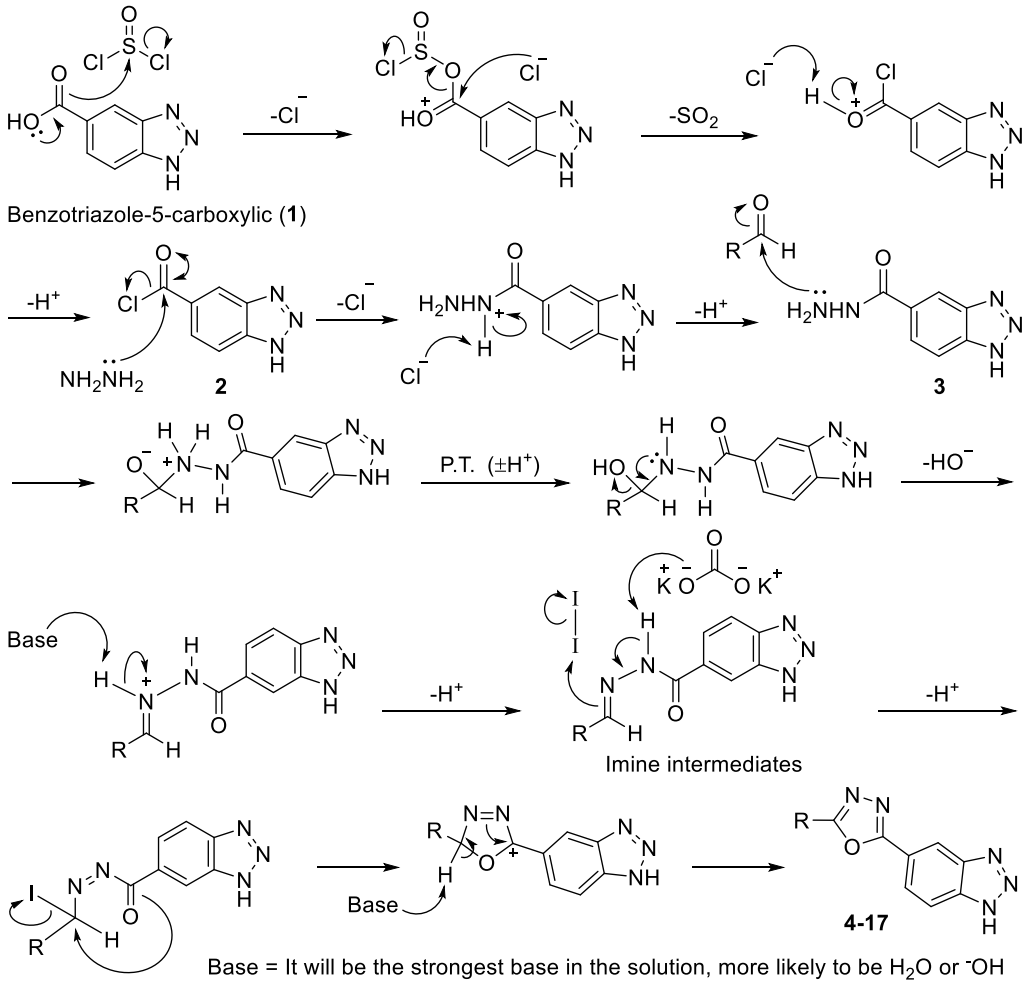
3.1. Chemistry

The synthesis of benzotriazole-containing substituted 1,3,4-oxadiazoles **4**-**17** outlined in Scheme 1, involves four steps. Compound **3** serves as a crucial intermediate for obtaining the desired products **4**-**17** and is prepared through two steps. By reacting benzotriazole-5-carboxylic acid (**1**) with thionyl chloride, the first step turned it into the corresponding acid chloride **2**. The chloride atom has a lower Pk_a value than the hydroxyl group (-9 *vs*. 15.7), making it a better leaving group. This process makes the acid chloride derivative of **1** more reactive with nucleophiles than the acid form. The resulting product **2** was then used in the second step without further purification due to its high sensitivity to moisture, which could lead to hydrolysis to give benzotriazole-5-carboxylic acid (**1**), which was employed in the first step. Hence, the reaction of product **2** with hydrazine hydrate (99%) afforded the hydrazide derivative **3** in a very good yield (89%) [30]. The FT-IR spectrum of compound **3** should show three new absorptions that are caused by the hydrazide group's N-H bonds ($NH\text{-}NH_2$) stretching vibrations that are both asymmetric and symmetric. Unfortunately, it was observed that a single absorption peak was present at 3163 cm^{-1} in our FT-IR spectrum, which is attributed to the overlap of absorptions in this range [31,32]. The carbonyl absorption of the carboxyl group in benzotriazole was observed at 1705 cm^{-1}, shifting to 1657 cm^{-1} upon conversion to the hydrazide derivative **3** [31]. This hydrazide was employed to synthesize the target products **4**-**17** by a two-step process. First, compound **3** was smoothly condensed with various aromatic aldehydes to form the corresponding imines. These imines were then subjected to oxidative cyclization using iodine as the oxidant and potassium carbonate as the base to provide the desired benzotriazole-substituted 1,3,4-oxadiazole hybrid molecules in yields ranging from 65 to 90%. The conversion to the desired products **4**-**17** was monitored by TLC over two stages: consuming compound **3** to form imine intermediates (the first stage) and consuming imines to yield compounds **4**-**17** (the second stage). The FT-IR analysis data of compounds **4**-**17** showed new stretching vibrations ranging from 1616 to 1666 cm^{-1} attributed to the C=N bond of the oxadiazole rings [31,32]. Furthermore, the absorption band at 3163 cm^{-1} corresponding to the N-H band of the hydrazide group disappeared during the

conversion to the products [33-38]. Two strong absorption bands at 1346 and 1568 cm^{-1} were indetified in compound **6**, corresponding to the symmetric and asymmetric stretching vibrations of the NO_2 group, respectively [31]. All details of the FT-IR analysis data for the prepared products **3**-**17** are listed in Table 3. The ^1H NMR spectra of products **5** and **8** revealed singlet signals at 9.38 and 9.32 ppm attributed to the O-H proton in the aromatic ring [39]. The chemical shifts ranging from 8.49 to 6.59 ppm and 8.59 to 7.01 ppm correspond to the aromatic protons of compounds **5** and **8**, respectively [31]. The N-H proton of the benzotriazole moiety appeared as a singlet at 6.35 ppm in compound **5** and 6.32 ppm in derivative **8**. The three protons of the OCH_3 group at derivative **8** appeared at 3.80 ppm. The ^1H NMR spectral data of compound **17** showed signals from 9.16 to 7.48 ppm belonging to the furan and aromatic ring protons. The N-H proton of the benzotriazole scaffold is responsible for the singlet signal at 6.31 ppm. Table 4 displays all the ^1H NMR data for compounds **5**, **8**, and **17**. Scheme 2 displays the mechanism for the formation of benzotriazole-containing substituted 1,3,4-oxadiazoles **4**-**17**, starting from benzotriazole-5-carboxylic acid **(1)**.

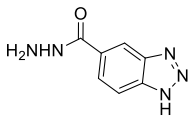
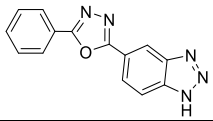
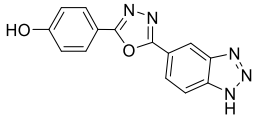
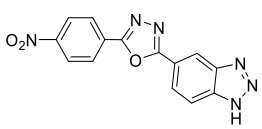


Scheme 1: Synthesis of benzotriazole-bearing substituted 1,3,4-oxadiazoles **4**-**17**



Scheme 2: The mechanism for the generation of benzotriazole-containing substituted 1,3,4-oxadiazoles **4-17** starting from benzotriazole-5-carboxylic

Table 3: FT-IR analysis data (υ, cm^{-1}) of the products **3-17**

No	Compound Structure	N-H Triazole	C-H Aromatic	C=N Oxadiazole	C=C Aromatic	N=N Triazole	C-O-C Oxadiazole	Other bands
3		3317	3072	-	1568	1524	-	C-N 1087 C=O 1657 $NHNH_2$ 3163 (overlap)
4		3427	3091	1622	1551	1442	1213 1072	C-N 1142
5		3431	3086	1628	1512	1462	1279 1034	C-N 1163 C-O 1209 O-H 3271
6		3433	3090	1634	1524	1462	1292 1057	C-N 1107 NO_2 1346 (sym.) 1568 (asym.)

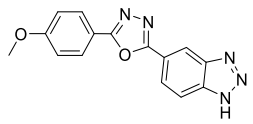
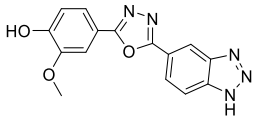
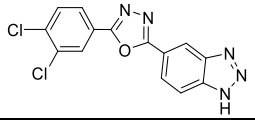
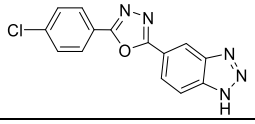
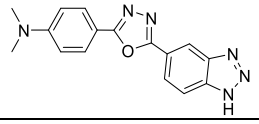
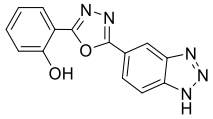
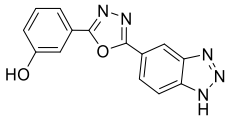
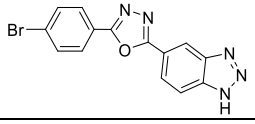
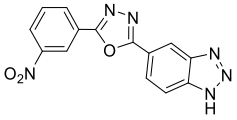
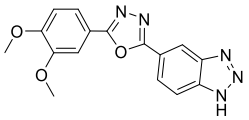
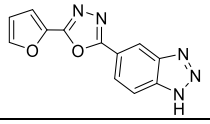
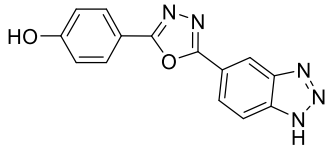
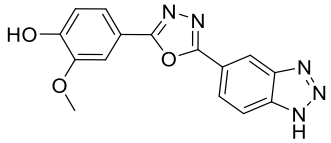
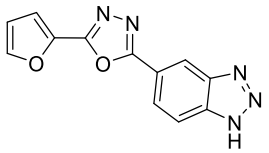
7		3431	3092	1632	1559	1445	1252 999	C-N 1121 C-O 1142 C-$H_{aliphatic}$ 2926
8		3427	3091	1666	1591	1427	1261 1026	C-N 1124 C-O 1155 1234 C-$H_{aliphatic}$ 2961
9		3421	3090	1628	1549	1406	1213 1065	C-Cl 1009 C-N 1121
10		3427	3088	1624	1549	1404	1279 1055	C-Cl 1011 C-N 1126
11		3441	3080	1661	1551	1433	1231 1065	C-N 1173 C-$H_{aliphatic}$ 2916
12		3429	3092	1636	1570	1406	1273 1049	C-N 1142 C-O 1207 O-H 3680
13		3437	3099	1645	1543	1456	1282 1055	C-N 1170 C-O 1232 O-H 3406
14		3433	3049	1626	1585	1481	1292 1065	C-Br 1007 C-N 1173
15		3433	3084	1628	1528	1438	1267 1078	C-N 1150 N-O 1354 (sym.) 1572 (asym.)
16		3433	3084	1616	1577	1445	1263 1061	C-O-C 1014 1232 C-N 1237 C-$H_{aliphatic}$ 2922
17		3431	3070	1626	1564	1416	1296 1051	C-O 1136 C-N 1261

Table 4: ^{1}H NMR analysis data (δ, ppm) of derivatives **5**, **8**, and **17**

No.	Compound structure	^{1}H NMR analysis data (δ, ppm)
5		9.38 (s, 1H, OH), 8.49-8.19 (m, 2H, Benzotriazole-H), 7.95-7.32 (m, 3H, Benzotriazole-H and Ar-H), 6.99-6.59 (m, 2H, Ar-H), 6.35 (s, 1H, N-H)
8		9.32 (s, 1H, OH), 8.59-8.32 (m, 2H, Benzotriazole-H), 7.75-7.52 (m, 2H, Benzotriazole-H and Ar-H), 7.38-7.01 (m, 2H, Ar-H), 6.32 (s, 1H, N-H), 3.80 (s, 3H, OCH_3)
17		9.16 (d, 1H, *J* = 6.6 Hz, furan-H), 8.83-8.60 (m, 1H, furan-H or Benzotriazole-H), 8.45-8.24 (m, 1H, furan-H or Benzotriazole-H), 8.09-7.94 (m, 1H, furan-H or Benzotriazole-H), 7.90-7.73 (m, 1H, Benzotriazole-H), 7.71-7.48 (m, 1H, Benzotriazole-H), 6.31 (s, 1H, N-H)

3.2. Antibacterial activity

Amikacin served as the control antibiotic for this experiment, with DMSO used as the solvent. The antibacterial activities of the prepared products **4**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **14**, **15**, **16**, and **17** were evaluated against two types of bacteria: gram-negative bacteria (*Escherichia coli*) and gram-positive bacteria (*Staphylococcus aureus*) to assess their antibacterial properties. All the tested compounds showed low activity against the positive bacteria. While these compounds showed better activity against the negative bacteria compared with the positive bacteria, compound **16** was the most effective among them (Table 5).

Table 5: Antibacterial activity of selected tested compounds (**4**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **14**, **15**, **16**, and **17**) assessed *via* diameter of the inhibition zone (mm)

Compound number	Gram-negative bacteria (*Escherichia coli*)	Gram-positive bacteria (*Staphylococcus aureus*)
4	13	9
6	11	10
7	14	11
8	14	8
9	12	10
10	14	9
11	12	10
12	12	9
14	14	9
15	14	10
16	17	9
17	14	10
DMSO	8	8
Amikacin	32	38

3.3. Antioxidant activity

The antioxidant activity of the derivatives **4**, **6**, **7**, **9**, **10**, and **14** was evaluated using the spectrophotometric DPPH assay at five different concentrations (6.25, 12.5, 25, 50, and 100 ppm). The process included measuring the DPPH radical scavenging activity and comparing the findings to those of ascorbic acid, which served as a reference. Derivative **6** displayed the best antioxidant activity compared to the others, with an IC_{50} value of 7.89. The derivative **9** also showed excellent activity (8.56 of IC_{50}). Conversely, the compounds **4**, **7**, **10**, and **14** demonstrated the lowest antioxidant activities among the tested compounds. Table 6 presents all the data for all the tested compounds.

Table 6: The activity of the free radical-scavenging for several synthesized products **4**, **6**, **7**, **9**, **10**, and **14**

Compound number	Concentration					IC_{50}
	100 µg/mL	50 µg/mL	25 µg/mL	12.5 µg/mL	6.25 µg/mL	
4	71.36	66.50	53.40	46.60	36.41	24.49
6	92.23	80.83	66.26	51.21	39.56	7.89
7	87.62	72.09	60.68	41.02	29.13	24.56
9	91.99	77.67	58.01	51.70	45.39	8.56
10	73.30	67.48	53.40	45.63	35.92	24.83
14	84.22	78.40	53.16	43.69	33.74	22.37
Ascorbic acid	93.12	76.57	65.41	53.44	46.89	11.7

4. Conclusion

A novel series of benzotriazole-substituted 1,3,4-oxadiazole hybrid compounds **4**-**17** was successfully prepared in four steps starting from 1*H*-benzotriazole-5-carboxylic acid (**1**). The compounds were isolated in moderate to excellent yields ranging from 65 to 90%. A number of the produced compounds demonstrated diverse antioxidant and antibacterial activities. In terms of the antibacterial activity, the compounds **4**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **14**, **15**, **16**, and **17** were tested. Compound **16** displayed the best inhibition against gram-negative bacteria (*Escherichia coli*). Some of these compounds (**4**, **6**, **7**, **9**, **10**, and **14**) were evaluated for their antioxidant properties. These tested compounds exhibited antioxidant activities ranging from moderate to excellent when compared to ascorbic acid. Notably, compound **6** demonstrated the strongest scavenging effect across all concentrations, outperforming the other compounds at equivalent levels.

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