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Functionalization of N-H Linkage at Benzimidazole for the Construction of 1,3,4-Oxadiazole Derivatives

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Abstract

Benzimidazole is a bicyclic heterocyclic aromatic compound that contains a combination of a six-membered ring and a five-membered ring with two nitrogen atoms. The current study aims to combine these two moieties to identify new benzimidazole-based 1,3,4-oxadiazole derivatives. In this work, the preparation of new benzimidazole-containing substituted 1,3,4-oxadiazoles 3-16 has been described using a five-step process. The S_N2 displacement reaction between benzimidazole and bromoacetic acid afforded the corresponding acid 1 in an 87% yield. Product 1 was treated with thionyl chloride to furnish the desired acid chloride form of 1. The next step involved the nucleophilic addition of hydrazine hydrate (99%) to the acid chloride derivative, yielding 91% of hydrazide 2. The aldimines derived from hydrazide 2 were obtained by treating compound 2 with different aromatic aldehydes, which were then used to access the desired products (3-16) *via* an oxidative cyclization reaction. This was achieved through treatment with I_2/K_2CO_3 in dimethyl sulfoxide. The target compounds (3-16) were synthesized in yields ranging from 50% to 88%. The structures of the synthesized products were characterized using FT-IR and ^{1}H NMR spectroscopy for some of them.

Keywords: Benzimidazole, 1,3,4-Oxadiazole, Oxidative cyclization, S_N2 displacement reaction.

1. Introduction

Benzimidazole (1*H*-1,3-benzimidazole, also called 1*H*-benzo[d]imidazole) is a bicyclic heterocyclic aromatic compound that contains a combination of a six-membered ring and a five-membered ring with two nitrogen atoms (imidazole ring). Hobrecker introduced the first benzimidazole moiety in 1872, reporting the synthesis of 2,5- and 2,6-dimethyl benzimidazole1[1]. In 1949, Brink and Folkers[2] extracted 5,6-dimethyl-l-(α-D-ribofuranosyl)benzimidazole from vitamin B_{12} during their work on the acidic degradation of this vitamin. Floyd, Holiday, and Petrow then identified the structure of the extracted compound in the same year[3]. Following this, researchers isolated numerous benzimidazole derivatives from natural products and synthesized other derivatives. Natural products bearing benzimidazoles in their structure are found to be associated with several biological and pharmacological activities. For example, the marine natural products kealiinines A-C were isolated in 2004 from *Leucetta* (a genus of sponges in the family Leucettidae) and *Clathrina* (a genus of calcareous sponges in the family Clathrinidae) by Proksch and co-workers[4]. These three natural products are effectively used as anti-cancer agents for breast cancer[5]. A variety of essential bioactivities are also shown by several synthetic benzimidazoles, which have gained popularity as scaffolds in contemporary drug development. For example, the product Lariozole was used as an anticancer medication[6]. The compound lerisetron exhibited potent antimalarial activity[7]. Additionally, mibefradil demonstrated significant antihypertensive effects[8]. The medicines maribavir, benoxaprofen, and ilaprazole

were employed as antiviral[9], anti-inflammatory[10], and antiulcer[11] agents. On the other hand, it has been demonstrated that 1,3,4-oxadiazole rings exhibit a wide range of biological functions, 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 activities[22]. The current study aims to combine these two moieties to identify new benzimidazole-based 1,3,4-oxadiazole derivatives for further biological activity testing, including antioxidant evaluation, molecular docking, and DFT studies.

2. Materials and Methods

2.1. Materials and instruments

Unless otherwise noted, all chemicals in this work were supplied by commercial vendors and employed without further purification. Merck silica gel 60 F254 was employed for TLC, while UV light and aqueous alkaline potassium permanganate were used for visualization. A Shimadzu 8400 FTIR spectrometer was used to acquire infrared spectra. A Bruker AV400 spectrometer was used to measure the ^{1}H NMR spectra. Using tetramethylsilane (TMS) as an internal benchmark and dimethyl sulfoxide (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) about the mentioned substance.

2.2. Chemistry

2.2.1. Preparation of 2-(1*H*-benzo[*d*]imidazol-1-yl)acetic acid (1)

This product (1) was synthesized according to the modified procedure in the literature[23]. A mixture of benzimidazole (2.0 g, 16.93 mmol, 1.0 equiv.) and NaOH (0.677 g, 16.93 mmol, 1.0 equiv.) in distilled water (25 mL) was stirred at ambient temperature for 10 minutes. Thereafter, bromoacetic acid (1.22 mL, 16.93 mmol, 1.0 equiv.) was slowly added to the reaction mixture, followed by heating at 70 °C for 8 hours. TLC monitored the reaction's progress (eluent: n-hexane/ethyl acetate, 3:1) until the benzimidazole was consumed entirely. The reaction mixture was allowed to reach room temperature before adding HCl solution (10%) to neutralize the reaction mixture, then a solution of brine (25 mL). The organic layer was separated with diethyl ether (3×15 mL), dried, and recrystallized from dioxane to provide the title compound 1. **Tables 1** and **2** show the physical characteristics and FT-IR analysis data of product 1, respectively.

2.2.2. Preparation of 2-(1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide (2)[24]

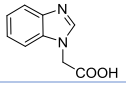
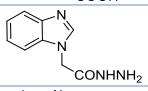
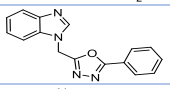
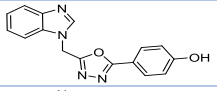
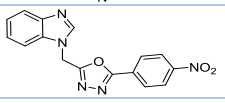
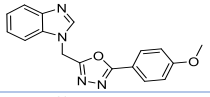
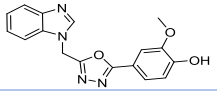
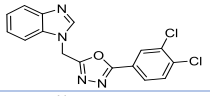
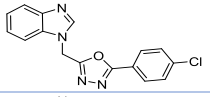
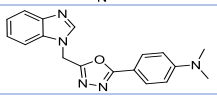
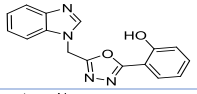
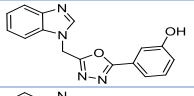
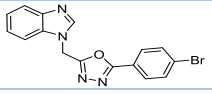
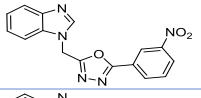
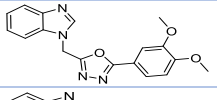
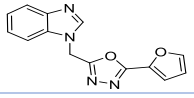
To a solution of 2-(1*H*-benzo[d]imidazol-1-yl)acetic acid (1) (1.5 g, 8.51 mmol, 1.0 equiv.) in THF (25 mL), thionyl chloride (excess, circa. 1 mL) was added before reflux for 7 hours. The progress of the reaction was monitored using TLC (eluent: *n*-hexane/ethyl acetate, 3:1) until no starting material (1) remained. The excess thionyl chloride was removed, yielding a crude solid of the acid chloride intermediate, which was tested with sodium bicarbonate (10%) to confirm the conversion of all acid-starting material to the acid chloride. The crude material of the intermediate (1.0 g, 5.14 mmol, 1.0 equiv.) was then dissolved in THF (20 mL), and hydrazine hydrate (99%, M= 31, 497 µL, 15.42 mmol, 3.0 equiv.) was added slowly. The reaction mixture was then refluxed for 11 hours, as determined by TLC using *n*-hexane and ethyl acetate (3:1) as the eluent. The mixture was subsequently cooled to ambient temperature before being treated with brine (20 mL). The solid crude material was then filtered, rinsed with water, and recrystallized from ethanol to provide the desired hydrazide 2. **Tables 1** and **2** display the physical characteristics and FT-IR analysis data of product 2, respectively.

2.2.3. General procedure for the preparation of the 1,3,4-oxadiazoles derived from benzimidazole 3-16[25,26]

In a round-bottom flask, a solution of hydrazide derivative 2 (0.25 g, 1.31 mmol, 1.0 equiv.) in EtOH (25 mL) was stirred for 10 minutes. Thereafter, a solution of an appropriate aldehyde (1.31 mmol, 1.0 equiv.) in EtOH (15 mL) was added to the reaction mixture, which was then refluxed for 5-8 hours. The reaction's completeness was evaluated using TLC (eluent: *n*-hexane/ethyl acetate). The solvent was then evaporated, and the residue was dissolved in DMSO (15 mL)

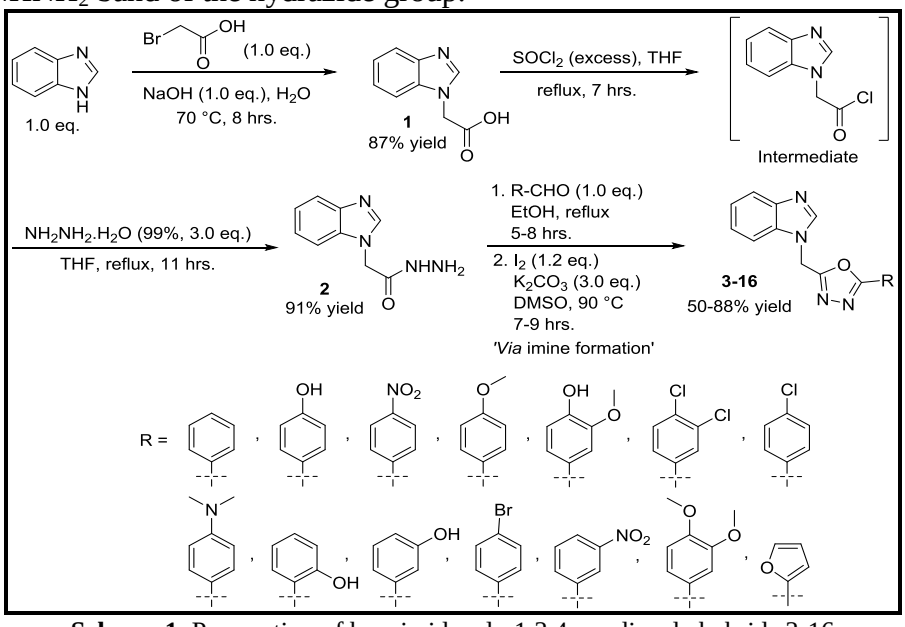
before adding K_2CO_3 (0.543 g, 3.93 mmol, 3.0 equiv.) and I_2 (0.199 g, 1.57 mmol, 1.2 equiv.). The reaction mixture was heated at 90 °C for 7-9 hours, as determined by TLC (using n-hexane/ ethyl acetate as the eluent). A solution of $Na_2S_2O_3$ (20 mL, 5%) was added before the extraction of the organic layer with ethyl acetate (2×20 mL), washing with a solution of brine (20 mL), drying with magnesium sulfate (anhydrous), and recrystallization in a suitable solvent to afford the title products 3-16. **Tables 1** and **2** list the physical characteristics and FT-IR analysis data of products 3-16, respectively.

Table 1. Physical characteristics of the synthesized compounds 1-16

No.	Compound structure	Reaction time (hours)	Eluent ratio (Hexane/ EtOAc)	Rf value	M.wt (g/mol)	m.p. (°C)	Color	Yield (%)
1		8	3:1	0.25	176.175	193-195	Brown	87
2		R^1 = 7 R^2 = 11	3:1	0.27	190.206	209-211	Brown	91
3		R^1 = 7 R^2 = 9	3:1	0.29	276.299	201-203	White	71
4		R^1 = 6 R^2 = 8	2:1	0.3	292.298	198-200	Yellow	62
5		R^1 = 7 R^2 = 9	2:1	0.25	321.296	192-194	White	88
6		R^1 = 7 R^2 = 8	1:1	0.26	306.325	184-186	White	64
7		R^1 = 5 R^2 = 8	1:1	0.25	322.324	202-204	Yellow	53
8		R^1 = 5 R^2 = 8	2:1	0.28	345.183	216-218	Yellow	62
9		R^1 = 8 R^2 = 9	2:1	0.27	310.741	208-210	Brown	65
10		R^1 = 7 R^2 = 9	1:1	0.26	319.368	188-190	White	66
11		R^1 = 8 R^2 = 9	2:1	0.29	292.298	208-210	Yellow	60
12		R^1 = 5 R^2 = 8	2:1	0.29	292.298	188-190	White	61
13		R^1 = 7 R^2 = 8	3:1	0.26	355.195	195-197	Yellow	64
14		R^1 = 7 R^2 = 9	2:1	0.25	321.296	209-211	Yellow	83
15		R^1 = 7 R^2 = 7	1:1	0.27	336.351	199-201	White	50
16		R^1 = 7 R^2 = 9	3:1	0.28	266.260	204-206	Brown	63

3. Results

The chemical reactions for the synthesis of products 1-16 are illustrated in **Scheme 1**. There are five steps in the synthesis of these products (1-16), starting with benzimidazole. Derivative 3 was used as a key intermediate to access the desired compounds 3-16, which were obtained in three steps. The first step involved a nucleophilic substitution of the benzimidazole with bromoacetic acid, providing benzimidazole-1-acetic acid (1) in 87% yield. The FT-IR analysis data of compound 1 includes information about the disappearance of the absorption bands of the N-H bond for benzimidazole starting material and the appearance of new absorption bands at 1736 and 3425 cm^{-1} for the C=O and O-H of the carboxyl group, as well as the stretching vibrations of C-H aliphatic at 2926 and 2856 cm^{-1} [27-29]. The second step involved converting product 1 to the corresponding acid chloride through a reaction with thionyl chloride. The resulting acid chloride intermediate 1 was then employed in the third step to react with hydrazine hydrate (99%) to provide the hydrazide derivative 2 in an excellent yield (91%)[27]. The FT-IR spectral data of compound 2 should reveal three new absorptions due to the two stretching vibrations (symmetric and asymmetric) of the hydrazide group ($NH-NH_2$). Unfortunately, our FT-IR spectrum showed a single absorption at 3317 cm^{-1} rather than the expected three. The carbonyl absorption of the carboxyl group at benzimidazole was observed at 1736 cm^{-1}, as mentioned above, which shifted to 1657 cm^{-1} upon the conversion to the hydrazide derivative 2. This hydrazide was then used to access the target products 3-16. This reaction proceeded smoothly via the condensation of compound 2 with 14 different aromatic aldehydes, affording the corresponding imines. These imines were then subjected to oxidative cyclization using iodine as the oxidant and potassium carbonate as the base, furnishing the desired benzimidazole-substituted 1,3,4-oxadiazole hybrid molecules in yields ranging from 50% to 88%. The conversion to the desired products 3-16 was monitored by TLC over two stages: consuming product 2 to form imine intermediates (the first stage) and consuming imines to afford compounds 3-16 (the second stage). The derivatives 5 and 14 were obtained with higher yields (88% for 5 and 83% for 14) than the other 12 derivatives. The FT-IR spectral data of compounds 3-16 showed new stretching vibrations ranging from 1620 to 1639 cm^{-1} ascribed to the C=N bond of the oxadiazole rings[27-33]. Furthermore, the disappearance of the absorption band at 3317 cm^{-1} for the $NHNH_2$ band of the hydrazide group.

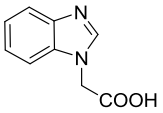
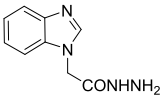
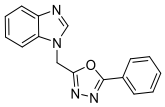
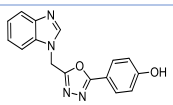
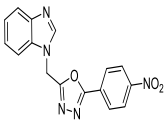
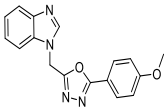
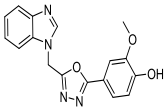
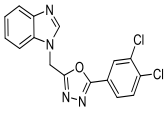
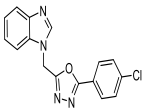
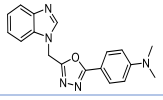


Scheme 1. Preparation of benzimidazole-1,3,4-oxadiazole hybrids 3-16

Table 2 provides a detailed overview of the FT-IR analysis data for products 1-16. The ^1H NMR spectra of products 3, 5, 6, and 7 showed signals at 9.25, 9.27, 9.22, and 9.27 ppm, respectively,

assigned to the proton on the benzimidazole moiety. The chemical shifts ranging from 7.77 to 6.82, 7.79 to 6.86, 7.75 to 6.84, and 7.79 to 6.82 ppm are for the aromatic protons of compounds 3, 5, 6, and 7, respectively[27-33]. The three protons of the OCH_3 group at derivatives 7 and 8 appeared at 3.79 and 3.78 ppm, respectively. **Table 3** and **Figures 1-3** present all the information regarding the ^1H NMR spectral data for compounds 3, 5-7.

Table 2. The FT-IR analysis data (υ, cm^{-1}) of the products 1-16

No.	Compound structure	C-H Olefinic	C-H Aromatic	C-H Aliphatic	C=N Benzimidazole and oxadiazole	C=C Aromatic	C-O-C Oxadiazole	Other bands
1		3134	3094 3053	2926 2856	1626 -	1551	-	OH 3425 C=O 1736 C-N 1084
2		3163	3072 3045	2976 2889	1609 -	1568	-	$NHNH_2$ 3317 (overlap) C=O 1657 C-N 1088
3		3144	3053 3026	2924 2853	1624 (one band)	1576	1288 1115	C-N 1018
4		3148	3075 3033	2924 2854	1636 (one band)	1578	1267 1148	O-H 3412 C-N 1013
5		3115	3096 3047	2922 2851	1628 (one band)	1524	1213 1107	NO_2 1597 (asym.) 1346 (sym.) C-N 1011
6		3195	3074 3032	2924 2853	1624 (one band)	1508	1252 1109	C-N 1024
7		3142	3072 3032	2924 2854	1628 (one band)	1514	1261 1120	O-H 3427 C-N 1005
8		3107	3076 3022	2924 2854	1628 (one band)	1551	1259 1128	C-N 1030 C-Cl 955
9		3184	3053 3032	2924 2853	1622 (one band)	1543	1279 1092	C-N 1014 C-Cl 960
10		3185	3086 3046	2924 2854	1634 (one band)	1578	1158 1126	C-N 1005

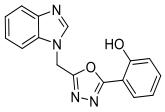
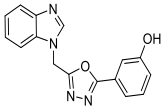
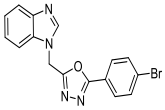
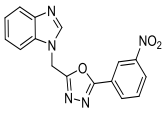
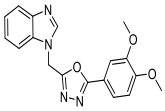
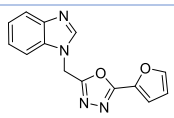
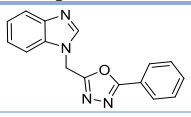
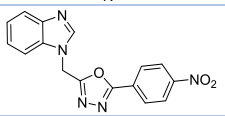
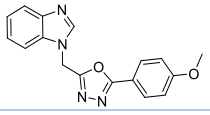
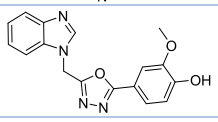
No.	Compound structure	C-H Olefinic	C-H Aromatic	C-H Aliphatic	C=N Benzimidazole and oxadiazole	C=C Aromatic	C-O-C Oxadiazole	Other bands
11		3163	3079 3045	2922 2854	1622 (one band)	1574	1271 1117	O-H 3473 C-N 1034
12		3107	3082 3049	2926 2854	1620 (one band)	1578	1259 1109	O-H 3429 C-N 1045
13		3124	3084 3047	2924 2853	1624 (one band)	1585	1277 1121	C-N 1007 C-Br 961
14		3209	3096 3076	2924 2853	1626 (one band)	1524	1263 1109	NO_2 1524 (asym.) 1350 (sym.) C-N 1067
15		3144	3076 3001	2926 2853	1624 (one band)	1580	1263 1140	C-N 1016
16		3186	3072 3047	2928 2866	1639 (one band)	1582	1236 1157	C-N 1014

Table 3. The ^{1}H NMR analysis data (δ, ppm) of derivatives 3, 5, 6, and 7

No.	Compound structure	^{1}H NMR analysis data (δ, ppm)
3		9.25 (s, 1H, benzimidazole-H), 7.77-7.65 (m, 2H, Ar-H), 7.39-7.24 (m, 3H, Ar-H), 7.10-6.82 (m, 4H, Ar-H), 4.95 (s, 2H, CH_2)
5		9.27 (s, 1H, benzimidazole-H), 7.79-7.63 (m, 2H, Ar-H), 7.40-7.21 (m, 3H, Ar-H), 7.08-6.86 (m, 3H, Ar-H), 4.96 (s, 2H, CH_2)
6		9.22 (s, 1H, benzimidazole-H), 7.75-7.69 (m, 2H, Ar-H), 7.38-7.25 (m, 3H, Ar-H), 7.11-6.84 (m, 3H, Ar-H), 4.95 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3)
7		9.40 (s, 1H, OH), 9.27 (s, 1H, benzimidazole-H), 7.79-7.67 (m, 2H, Ar-H), 7.37-7.24 (m, 3H, Ar-H), 7.12-6.82 (m, 2H, Ar-H), 4.97 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3)

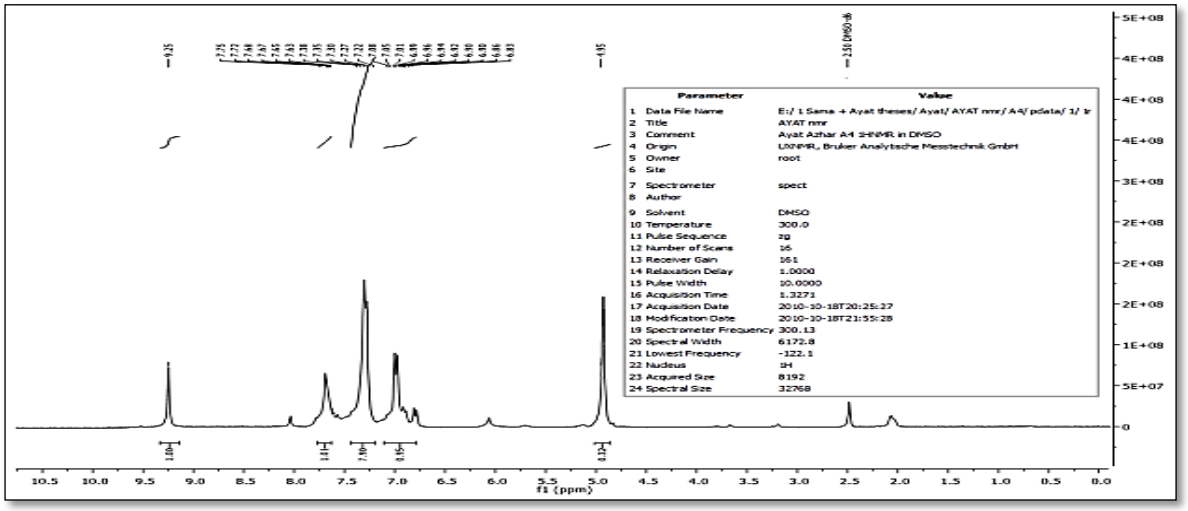


Figure 1. The ^{1}H NMR spectrum of compound 3.

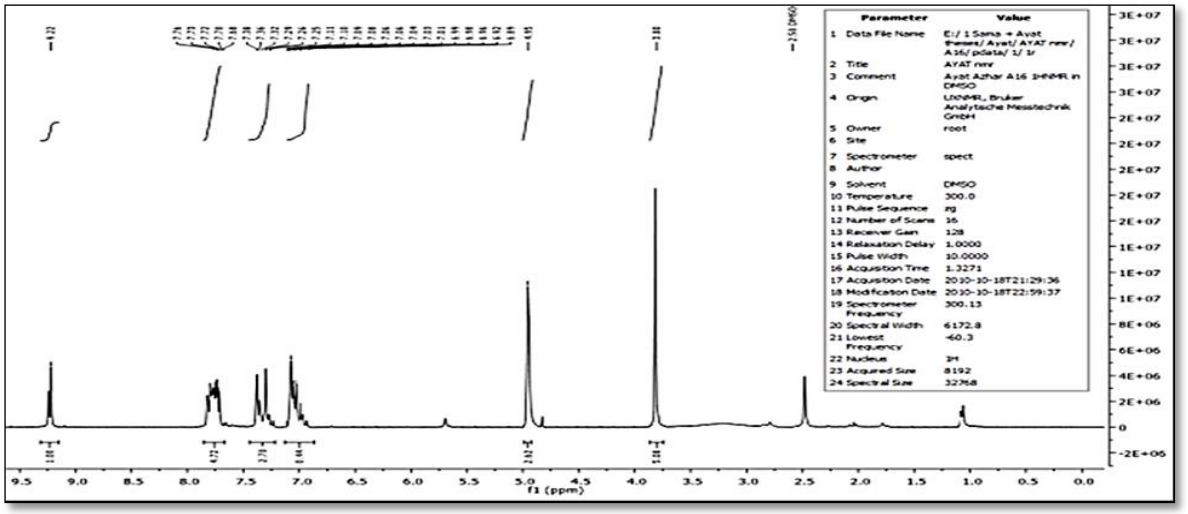


Figure 2. The ^{1}H NMR spectrum of compound 6.

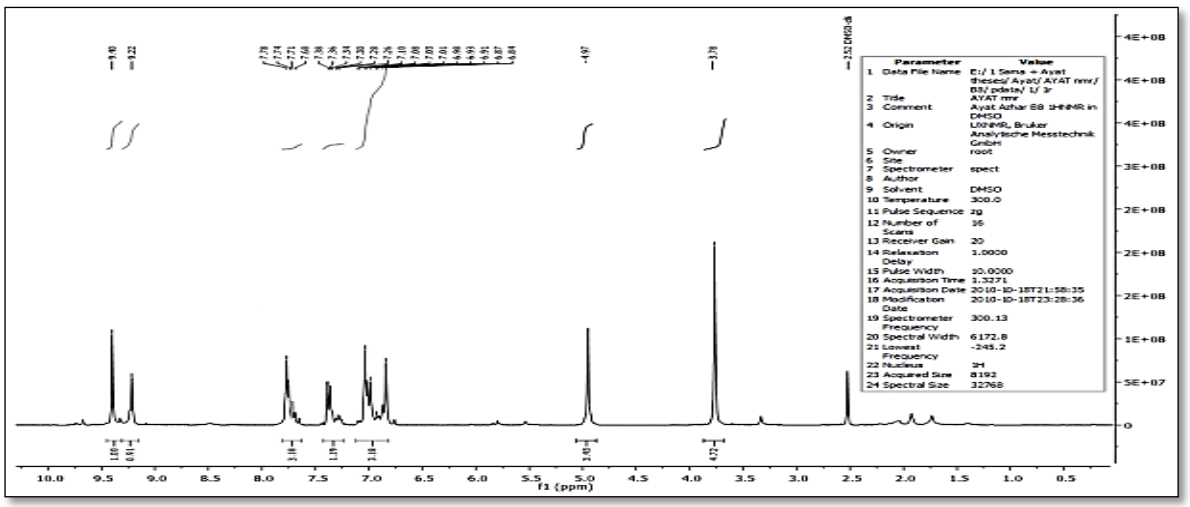


Figure 3. The ^{1}H NMR spectrum of compound 7

4. Discussion

The S_N2 displacement of the benzimidazole with bromoacetic acid in the first step of this work was activated *via* deprotonation of the N-H of the benzimidazole to afford the corresponding anion form, which could be considered more nucleophilic than the neutral form of benzimidazole and will encourage the nucleophilic substitution to give the desired acid 2. In the second step, acid 1 is converted to the acid chloride to provide effective access to the hydrazide key intermediate (2). This change is because the chloride atom has a lower pKa value than the hydroxyl group (-9 vs. 15.7), making it a better leaving group[34]. This attribute makes the acid chloride derivative more reactive with nucleophiles than the acid form. In the third step, due to the acid-chloride form's high sensitivity, it was reacted directly with hydrazine hydrate (99%) without additional purification. The single absorption at 3317 cm^{-1} in the FT-IR spectrum of hydrazide derivative 2, rather than the expected three absorptions, can be attributed to the overlap of the absorptions in this range[27]. The hybrid benzimidazole-1,3,4-oxadiazole compounds bearing electron-withdrawing groups (5 and 14) were isolated in higher yields than other derivatives, as shown in **Table 1**. This may be due to the electron-withdrawing groups at the aromatic aldehydes, which are considered more reactive to attack by the NH_2 group of the hydrazide moiety. Conversely, the derivatives bearing electron-donating groups at the aromatic aldehydes will deactivate them when struck by the NH_2 of the hydrazide moiety, as displayed in the derivatives 4, 6, 7, 10, 11, 12, and 15, as shown in **Table 1**.

5. Conclusion

In five steps, a new series of benzimidazole-substituted 1,3,4-oxadiazole hybrid compounds 3-16 was efficiently synthesized, starting from benzimidazole. These products (3-16) were obtained with yields up to 88%.

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Conflict of Interest

The authors disclose no conflicts of interest.

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