



**SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF SOME
NOVEL BENZIMIDAZOLE LINKED 1,3,4-OXADIAZOLES**

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ABSTRACT: Novel benzimidazole derivatives in combination with 1,3,4-oxadiazoles (**4a-o**) were synthesized from ethyl 3-((5-chloro-2-nitro phenyl)(phenyl)amino)-3 oxo propanoate (**1**) via three step synthetic strategy and tested for their antimicrobial activity. The newly synthesized compounds (**4a-o**) were characterized by ¹HNMR, IR and Mass spectral data. Compounds **4l** and **4m** showed significant antibacterial activity with tested bacterial pathogens (*E.Coli*, *B.subtilis*).

KEYWORDS: 1,3,4-Oxadiazoles, Benzimidazole, Antibacterial activity.

INTRODUCTION

Chemistry of the heterocyclic ring systems has occupied a prominent place among various classes of organic compounds and their derivatives due to diverse biological activity and clinical applications. Amongst several benzimidazole derivatives are the structural isosters of naturally occurring nucleotides which allow them to interact easily with biopolymers of living systems and different kinds of their biological activity have been reported. Compounds carrying benzimidazole nucleus are reported to elicit certain biological activities such as anti-allergicⁱ, antiviralⁱⁱ, antiprotozoalⁱⁱⁱ, analgesic and anti-inflammatory^{iv}, anticancer^{v,vi}, antioxidant^{vii}, antimicrobial^{viii} etc. In addition, 1,3,4-oxadiazoles showed good antibacterial, antifungal and HIV activities.

1,3,4-oxadiazole is an important core unit in medicinal chemistry, which is considered as bioisostere of carboxylic acid, ester and carboxamide. Due to having of toxophoric -N=C-O-linkage, it exhibiting potent pharmacological activities. Further, widespread use of 1,3,4-oxadiazole as a privileged scaffold in pharmaceutical field corroborate its importance among a variety of heterocycles and 1,3,4-oxadiazole derivatives have exhibited a wide range of biological activities such as antimicrobial^{ix,x}, antitumor^{xi}, anticancer^{xii}, anti-inflammatory^{xiii,xiv}, anticonvulsant^{xv}, antiviral^{xvi}, anti-tubercular^{xvii,xviii} etc.

There are several reports available in the literature on 1,3,4-oxadiazole synthesis, but frequently used synthetic route was the reaction of aromatic acidhydrazides with CS₂ in

ethanolic KOH or with aromatic acids in POCl_3 ^{xix-xxiv}. Some of the available drugs containing benzimidazole and 1,3,4-oxadiazole moieties were depicted in Figure 1^{xxv-xxvii}.

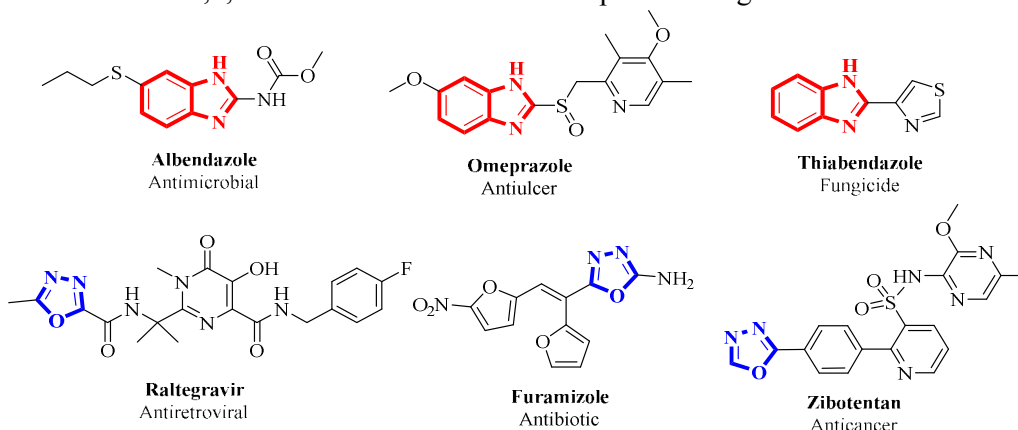


Figure 1: Available drugs in the market having benzimidazole and 1,3,4-oxadiazole scaffold.

Hence, it is considered worthwhile to prepare a new class of bis heterocycles in combination of benzimidazole with 1,3,4-oxadiazoles by functionalization of β keto ester from synthetically vulnerable intermediate ethyl 3-(5-chloro-2-nitrophenyl)phenyl amino-3-oxo propanoate (**1**).

However, the reports about bis heterocycles like benzimidazoles in combination with 1,3,4-oxadiazoles are relatively less, hence as part of our synthesis and pharmacological evaluation of heterocycles, benzimidazole synthesis in combination with 1,3,4-oxadiazoles has been taken up. The present communication deals with the synthesis of benzimidazole-1,3,4-oxadiazole derivatives and their antibacterial activities, from the vulnerable beta keto ester intermediate which was chosen as synthon for the preparation of title compounds.

MATERIALS AND METHODS

All the chemicals used were of synthetic grade obtained from Aldrich chemicals. Completion of the reactions were monitored from time to time by analytical thin layer chromatography (TLC) using E-merck 0.25 mm silica gel plates. Visualization was accomplished with UV light (256 nm) and sodium chamber. Synthesized compounds were purified by column chromatography using hexane and ethyl acetate as eluents. All the solvents were dried by appropriate drying agents before use. The reagents were purified employing standard laboratory techniques. ACME grade silica gel (60-120 mesh) was used for column chromatography unless otherwise mentioned. All the $^1\text{H-NMR}$ spectra have been recorded with Bruker 300 MHz instrument in CDCl_3 , $\text{DMSO-}d_6$ solvents and chemical shifts were reported in δ ppm relative to TMS. The electron ionization mass spectra were recorded on Agilent 1100 series mass spectrometer. Melting points were determined in one ended capillaries on a Mel-temp apparatus and were uncorrected. IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR in KBr pellets. The starting material Ethyl 3-(5-chloro-2-nitrophenyl)phenyl amino-3-oxo propanoate was prepared by standard experimental procedure.

SYNTHESIS

Preparation of Ethyl 2-(6-chloro-1-phenyl-1H-benzimidazol-2-yl)acetate (**2**):

A mixture of **1** (10 g, 0.0275 mol) and Fe powder (3.08 g, 0.055 mol) in methanol (10 mL) was stirred for 3 h at $0-5^\circ\text{C}$. Then acetic acid 10 mL was added and stirred for 10 h at room temperature. After the product formation the solvent was distilled completely and diluted with water 50 mL, then extracted with ethyl acetate (2×30 mL) and washed with water (20 mL)

finally with brine. Evaporated the solvent under vacuum at 40 °C and the obtained crude compound was recrystallized in Hexane & Ethyl acetate (80:20) to get Off-white solid (6.04 g, 70%); m.p. 85-86 °C; (KBr v (cm⁻¹): 900, 929, 951, 1225 (C-O Str), 1599 (C=N Str), 1699 (C=O), 2965; ¹H-NMR (DMSO-*d*₆) δ (ppm): 1.03 (t, 3H, -OCH₂CH₃), 3.9 (q, 2H, -OCH₂CH₃), 4.0 (s, 2H, -CH₂-), 7.14-7.73 (m, 8H, Ar-H); MS (m/z): 315.04 (M+1) Anal. calcd.

General procedure for synthesis of (6-chloro-1-phenyl-1H-benzimidazol-2-yl)acetic acid hydrazide (3):

A mixture of **2** (5 g, 0.015 mol) and hydrazine hydrate (3.11 mL, 0.0634 mol) in toluene (15 mL) was refluxed for 2 h and cooled at 5 °C for overnight and the resultant solid was filtered dried to yield **3** as white crystals (4.0 g, 84%); m.p. 112-114 °C; (KBr v (cm⁻¹): 1138, 1225, 1307, 1343, 1395, 1449, 1599, 2965, 3206; ¹H NMR (DMSO-*d*₆) δ (ppm): 3.61 (s, 2H, -NH₂), 4.24 (s, 2H, -CH₂-), 7.11-7.69 (m, 8H, Ar-H), 9.25 (s, 1H, -NH); MS (m/z): 301.03 ((M+1) Anal. calcd.

General procedure for the synthesis of 2-((6-chloro-1-phenyl-1H-benzo[d]imidazol-2-yl)methyl)-5-phenyl-1,3,4-oxadiazoles (4a-p):

To the mixture of acid hydrazide **3** (500 mg, 1.66 mmol) and the corresponding substituted benzoic acids (1.66 mmol) POCl₃ (3 mL) was added and the resultant total reaction mixture was refluxed at 100 °C for 2 h. Then the mixture was cooled to rt and poured into ice cold water under stirring. The solution pH was adjusted to 9 with ammonia solution. Finally obtained solid was filtered and recrystallized from methanol:water (70:30) to get a solid.

6-Chloro-2-((5-(3,5-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)methyl)-1-phenyl-1H-benzo[d]imidazole (4a):

Yellow colour solid (630 mg, 85 %); m.p. 98-100 °C; (KBr v (cm⁻¹): 1043, 1110, 1540 (C=N), 2825 (C-H str), 3054 (=CH); ¹H NMR (DMSO-*d*₆) δ (ppm): 3.81 (s, 3H, -OCH₃), 3.74 (s, 3H, -OCH₃), 4.65 (s, 2H, -CH₂-), 6.74 (1H, Ar-H), 7.00 (2H, Ar-H), 7.16 (1H, Ar-H), 7.73 (1H, Ar-H), 7.70 (m, 6H, Ar-H); ¹³C-NMR (DMSO-*d*₆) δ (ppm); 25.60 (-CH₂-), 56.08 (-OCH₃), 120.40, 122.80, 124.73, 127.02, 127.70, 129.41, 130.01, 134.13, 136.73, 140.69, 160.93, 162.34, 164.12 (aromatic & quaternary carbons); MS (m/z): 447.42 (M+1).

2-((5-(5-Bromo-2-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)-6-chloro-1-phenyl-1H-benzo[d]imidazole(4b):

Yellow colour solid (694 mg, 87 %); m.p. 110-112 °C; IR (KBr v (cm⁻¹): 1045, 1114, 1543 (C=N), 2828 (C-H str), 3050 (=CH); ¹H NMR (DMSO-*d*₆) δ (ppm): 4.69 (s, 2H, CH₂), 7.99 (d, 1H, Ar-H), 7.85 (dd, 1H, Ar-H), 7.72 (dd, 1H, Ar-H) 7.32 (dd, 1H, Ar-H), 7.17 (d, 1H, Ar-H), 7.10-7.57 (m, 5H, Ar-H); ¹³C-NMR (DMSO-*d*₆) δ (ppm); 25.6 (-CH₂-), 110.09, 120.31, 120.56, 122.91, 124.11, 127.12, 127.80, 129.50, 130.19, 131.11, 134.17, 135.15, 135.81, 140.74, 149.12, 161.25, 162.94, 164.12 (aromatic & quaternary carbons); MS (m/z): 499.42 (M+2).

2-((6-Chloro-1-phenyl-1H-benzo[d]imidazol-2-yl)methyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (4c):

Yellow colour solid (503 mg, 75 %); m.p. 94-96 °C; IR (KBr v (cm⁻¹): 1043, 1113, 1546 (C=N), 2825 (C-H str), 3051 (=CH); ¹H-NMR (DMSO-*d*₆) δ (ppm): 3.50 (s, 2H, CH₂), 6.89-7.87 (m, 12 H); ¹³C-NMR (DMSO-*d*₆) δ (ppm); 25.6 (-CH₂-), 117.1, 119.2, 126.9, 127.21, 129.58, 130.13, 130.22, 130.27, 135.68, 140.7, 161.25, 162.94, 164.12 (aromatic & quaternary carbons); MS (m/z): 402.91 (M-1).

4-(5-((6-Chloro-1-phenyl-1H-benzo[d]imidazol-2-yl)methyl)-1,3,4-oxadiazol-2-yl)benzenamine (4d):

Reddish colour solid (566 mg, 86 %); m.p. 153-155 °C; IR (KBr v (cm⁻¹): 1041, 1110, 1542 (C=N), 2825 (C-H str), 3227 (NH₂); ¹H-NMR δ (CDCl₃) (ppm): 4.22 (s, 2H, CH₂), 4.46 (s,

2H, NH₂), 6.67-7.76 (m, 12H, Aromatic); ¹³C-NMR (DMSO-*d*₆) δ (ppm); 25.09 (-CH₂-), 109.92, 110.0, 113.28, 120.56, 122.8, 124.73, 127.11, 127.70, 129.40, 130.11, 134.65, 136.73, 140.78, 150.13, 166.40; MS (m/z): 402.16 (M+1).

2-((6-Chloro-1-phenyl-1H-benzo[d]imidazol-2-yl)methyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole(4e):

Yellow colour solid (274 mg, 85%); m.p.134-136 °C; IR (KBr v (cm⁻¹): 1041, 1105, 1533 (C=N), 2832 (C-H str); ¹H-NMR (CDCl₃) δ (ppm): 4.52 (s, 2H, CH₂), 7.21-7.80 (m, 12H, Aromatic); MS (m/z): 388.02 (M+1).

6-Chloro-2-((5-(2-chloro-4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1-phenyl-1H-benzo[d]imidazole(4f):

Red colour solid (671 mg, 87 %); m.p. 170-174 °C; IR (KBr v (cm⁻¹): 1048, 1115, 1545 (C=N), 2835 (C-H str); ¹H NMR (CDCl₃) δ (ppm): 4.53 (s, 2H, CH₂), 7.15-8.45 (m, 11H, Aromatic); MS (m/z): 488.14 (M+Na).

2-((6-Chloro-1-phenyl-1H-benzo[d]imidazol-2-yl)methyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole(4g):

Red colour solid (608 mg, 85 %); m.p.190-192 °C; IR (KBr v (cm⁻¹): 1043, 1110, 1540 (C=N), 2825 (C-H str); ¹H-NMR (CDCl₃) δ (ppm): 4.72 (s, 2H, CH₂), 7.18-8.43 (m, 12H, Aromatic); MS (m/z): 432.01 (M+1).

6-Chloro-2-((5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1-phenyl-1H-benzo[d]imidazole(4h):

Red colour solid (615 mg, 88%) m.p.108-110 °C; IR (KBr v (cm⁻¹): 1041, 1109, 1546 (C=N), 2829 (C-H str); ¹H-NMR (CDCl₃) δ (ppm): 4.58 (s, 2H, CH₂), 7.18-9.2 (m, 11H, Aromatic); MS(m/z): 475.13 (M-1).

6-Chloro-2-((5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methyl)-1-phenyl-1H-benzo[d]imidazole(4i):

Yellow colour solid (593 mg, 86 %); m.p.142-144 °C; IR (KBr v (cm⁻¹): 1039, 1120, 1541 (C=N), 2835 (C-H str); ¹H-NMR (CDCl₃) δ (ppm): 3.78 (s, 3H, OCH₃), 4.58 (s, 2H, CH₂), 7.21-7.84 (m, 12H, Aromatic); MS (m/z): 417.10 (M+1).

6-Chloro-1-phenyl-2-((5-*p*-tolyl-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d]imidazole(4j):

Yellow colour solid (557 mg, 84 %); m.p. 160-162 °C; IR (KBr v (cm⁻¹): 1047, 1118, 1548 (C=N), 2838 (C-H str); ¹H-NMR (CDCl₃) δ (ppm): 2.48 (s, 3H, CH₃), 4.58 (s, 2H, CH₂), 7.21-8.00 (m, 12H, Aromatic); MS (m/z): 401.06 (M+1).

6-Chloro-2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1-phenyl-1H-benzo[d]imidazole (4k):

Yellow colour solid (585 mg, 84 %); m.p.156-158 °C; IR (KBr v (cm⁻¹): 1043, 1117, 1544 (C=N), 2830 (C-H str); ¹H NMR (CDCl₃) δ (ppm): 4.50 (s, 2H, CH₂), 7.14-7.94 (m, 12H, Aromatic); MS (m/z): 421.01 (M+1).

6-Chloro-1-phenyl-2-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d]imidazole (4l):

Yellow colour solid (544 mg, 85 %); m.p. 80-82 °C; IR (KBr v (cm⁻¹): 1041, 1119, 1548 (C=N), 2835 (C-H str);¹H-NMR (CDCl₃) δ (ppm): 4.58 (s, 2H, CH₂), 7.20-8.21 (m, 13 H, Aromatic); MS (m/z): 387.10 (M+1).

6-Chloro-2-((5-(2,3,4,5-tetrafluorophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1-phenyl-1H-benzo[d]imidazole(4m):

Off white colour solid (623 mg, 82 %); m.p. 92-94 °C; IR (KBr v (cm⁻¹): 1055, 1124, 1550 (C=N), 2838(C-H str);¹H NMR (CDCl₃) δ (ppm): 4.56 (s, 2H, CH₂), 7.15-7.15 (m, 9H, Aromatic); MS (m/z): 459.08 (M+1).

2-((5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)methyl)-6-chloro-1-phenyl-1H-benzo[d]imidazole (4n): Brownish colour solid (640 mg, 83 %); m.p. 94-96 °C; IR (KBr v (cm⁻¹):

1044, 1116, 1547 (C=N), 2832 (C-H str); ¹H-NMR(CDCl₃) δ (ppm): 4.58 (s, 2H, CH₂), 7.20-8.21 (m, 12H, Aromatic); MS (m/z): 465.10 (M+H).

6-Chloro-2-((5-(4-iodophenyl)-1,3,4-oxadiazol-2-yl)methyl)-1-phenyl-1H-benzo[d]imidazole(4o):

Off colour solid (640 mg, 83 %); m.p. 87-89 °C; IR (KBr v (cm⁻¹): 1045, 1117, 1544 (C=N), 2829 (C-H str); ¹H-NMR (CDCl₃) δ (ppm): 4.51 (s, 2H, CH₂), 7.11-7.85 (m, 12H, Aromatic); MS (m/z): 513.06 (M+1).

Biological activity

Antibacterial studies

A series of novel 2-((6-chloro-1-phenyl-1H-benzo[d]imidazol-2-yl)methyl)-5-phenyl-1,3,4-oxadiazoles (**4a-o**) were screened for their antimicrobial activity against two bacterial strains such as *Escherichia coli* and *Bacillus subtilis* using plate method^{xxviii}. Values were taken as inhibition zone in cm at 25, 50, 100, 250, 500 µg/mL and compared with standard Ampicillin (ZOI: 1.6 cm at 10 µg/mL). A standard inoculum of the culture prepared for the assay was added to each petri plate, then test compounds loaded discs at various concentrations were placed on the agar surface and incubated for 16-18 hours at 37 °C. After that the ZOI formed around each disk was measured in cm.

According to the activity data, **table 1**, compounds **4a-o** showed good antibacterial activity against *Bacillus subtilis* at 250, 500 µg/mL when compared with *Escherichia coli* at same concentrations. Among the screened samples compounds **4l** (At 500 µg/mL, ZOI: 1.2 cm) and **4m** (At 250-500 µg/mL, ZOI: range 1.1-1.2 cm) showed excellent antimicrobial activity against two tested microorganisms (Figure 2) as compared with Ampicillin standard (ZOI: 1.6 cm). This result may be due to the presence of unsubstituted or tetra fluoro substituted phenyl rings on the 1,3,4-oxadiazole moiety. Furthermore, compounds **4b**, **4c**, **4d**, **4f** and **4n** exhibited good activity at 500 µg/mL and **4i**, **4j**, **4k** showed at 250, 500 µg/mL towards *Bacillus subtilis*.

Based on activity data we conclude that either unsubstituted or tetrafluoro substituted phenyl ring on 1,3,4-oxadiazole was suitable for potent activity.

Table 1. Antibacterial activity of synthesized compounds (**4a-o**)

Compound Codes	<i>E.coli</i>				<i>B.subtilis</i>			
	500 µg/ml	250 µg/ml	100 µg/ml	50 µg/ml	500 µg/ml	250 µg/ml	100 µg/ml	50 µg/ml
4a	---	---	---	---	0.9	0.7	0.6	0.6
4b	0.8	0.7	---	---	1.3	0.9	0.7	0.7
4c	0.8	---	---	0.6	1.1	1.0	0.9	0.7
4d	0.8	0.9	0.8	0.7	1.2	1.0	0.8	0.7
4e	1.1	0.9	0.7	0.7	0.6	0.9	0.8	0.6
4f	0.9	0.8	0.7	0.7	1.3	0.9	0.9	0.7
4g	0.8	---	---	---	1.0	0.8	0.7	0.6
4h	1.0	0.8	0.6	0.6	1.0	0.9	0.9	0.6
4i	0.7	0.6	---	---	1.2	1.1	0.9	0.7
4j	0.7	0.6	---	---	1.1	1.1	0.9	0.8
4k	0.9	0.9	0.8	0.6	1.3	1.2	0.8	0.7
4l	1.2	1.0	0.7	0.7	1.2	1.1	0.8	0.6
4m	1.1	0.8	0.7	0.7	1.2	1.1	1.0	0.8
4n	1.0	---	---	---	1.2	0.8	0.8	0.7
4o	0.8	---	---	---	1.0	0.9	0.8	0.6
Ampicillin	1.6				1.6			

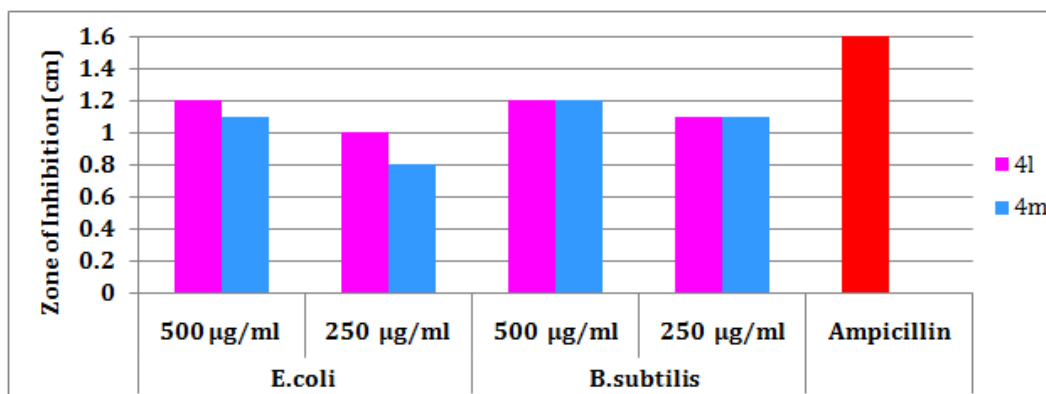


Figure 2. Antibacterial activity of most active compounds **4l** and **4m**.

Results and Discussion:

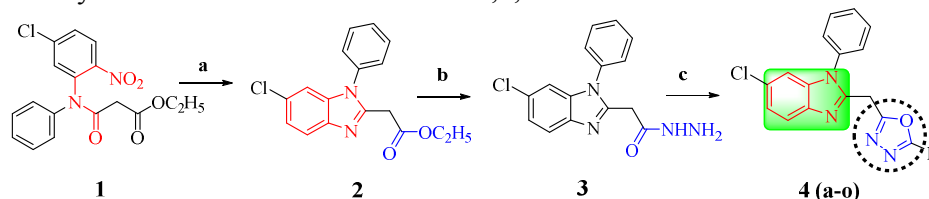
Chemistry and analytical aspect

Ethyl 3-([5-chloro-2-nitrophenyl]phenylamino)-3-oxopropanoate (**1**) was served as a synthetic intermediate having multi functionalities such as keto and ester groups, which were further exploited to corresponding benzimidazoles as well as 1,3,4-oxadiazole derivatives. The compound (**1**) in turn was prepared by the condensation of mono ethyl malonic acid with 5-chloro-2-nitro diphenyl amine.

Next in order to construct the benzimidazole ring, the pathway involving the reduction of nitro to amino group followed by intra molecular cyclocondensation of amine with keto functionality was selected to achieve the target compound (**2**). The ester (**1**) was first subjected to single pot two reaction sequence to obtain the benzimidazole ester (**2**) in the presence of Fe powder in acetic acid. The signals appeared at δ 1.03, 3.90 ppm in the ^1H NMR spectrum of compound **2** confirms the ester functionality. A sharp singlet at δ 4.0 ppm corresponding to the methylene group existed between keto and ester functionality, the structure of compound **2** was further confirmed by ^{13}C NMR and Mass spectra.

The ester functionality in **2** was then treated with hydrazine hydrate in the presence of toluene to give corresponding acid hydrazide (**3**), which served as key intermediate for construction of 1,3,4-oxadiazoles. Compound **3** was confirmed by appearance of two singlets at δ 3.61, 9.25 ppm pertaining to $-\text{CONHNH}_2$ group in the ^1H NMR spectrum. The formed hydrazide (**3**) was further treated with various substituted benzoic acids in presence of POCl_3 to yield requisite benzimidazole-1,3,4-oxadiazole derivatives (**4a-o**). The synthetic route used for the formation of **4a-o** was demonstrated in Scheme 1. The synthesized compounds have been well characterized by advanced analytical techniques like NMR, IR and Mass spectra.

Scheme 1. Synthesis of novel benzimidazole-1,3,4-oxadiazole derivatives



Reagents and Conditions: (a) Fe Powder, Methanol, Acetic acid, rt, 6 h; (b) Hydrazine hydrate, Toluene, 1 h, reflux; (c) R-COOH, POCl_3 , 110 $^\circ\text{C}$, 2 h.

Table 2. Various substituents of benzimidazole-oxadiazole derivatives

S. No	Compounds	R	S. No	Compounds	R
1.	4a		9.	4i	
2.	4b		10.	4j	
3.	4c		11.	4k	
4.	4d		12.	4l	
5.	4e		13.	4m	
6.	4f		14.	4n	
7.	4g		15.	4o	
8.	4h		Here "R" demonstrates various substituted phenyl rings of 1,3,4-oxadiazole.		

CONCLUSION:

Novel benzimidazole derivatives in combination with 1,3,4-oxadiazoles were prepared from ethyl 3-((5-chloro-2-nitro phenyl) (phenyl)amino)-3 oxo propanoate (**1**) by using reduction followed by manipulation of ester group in the benzimidazole through hydrazide. The newly synthesized compounds (**4a-o**) have been characterized by ¹H NMR, IR and Mass spectral data. Further they were screened for their antibacterial studies which revealed that compounds **4l** and **4m** have significant antibacterial activity against two tested strains.

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