Research Article

Synthesis, Characterization and Antimicrobial Activity of 1,3,4-Oxadiazoles Derivatives of Benzimidazoles

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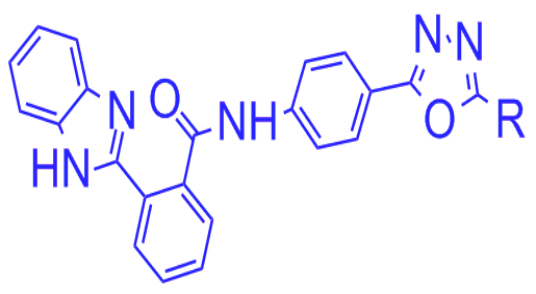
Abstract

Some new 1,3,4-oxadiazole derivatives possessing benzimidazole nucleus were synthesized by the reaction of 2-(1H-benzo[d]imidazol-2-yl)-N-(4-(hydrazinecarbonyl) phenyl)benzamide and various aryl acids in $POCl_3$ at reflux temperature and characterized by IR, NMR and mass spectral analysis. All synthesized compounds were screened for antimicrobial activity using cup plate method. All the compounds showed moderate to good antimicrobial activity and antifungal activity.

Keywords: 1,3,4-oxadiazoles, benzimidazole, antimicrobial activity



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Introduction

The heterocyclic benzimidazole structure is evolved as a prominent scaffold for pharmaceutical or biological interest. Benzimidazole is a very well-known pharmacophore in medicinal chemistry due to the fact that it shows wide spectrum of pharmacological activities such as anthelmintics, antiulcer, antihypertensive, antihistaminic, anticancer, antiphychotics etc. [1-4]. The current drugs in market such as albendazole, omeprazole, domperidone etc. are possessing benzimidazole as a core structure [**Figure 1**]

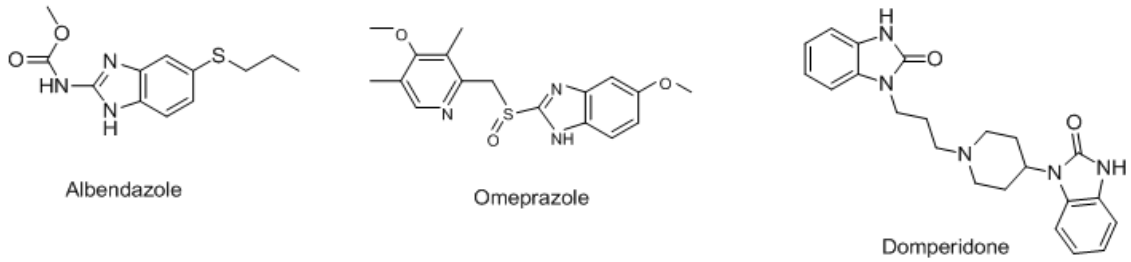


Figure 1 Current drugs in market possessing benzimidazole as a core structure

Looking in the past, we can say that synthetic organic chemistry is giving momentum to the improvement of new drug skeleton through interactive ancillary of functional group around the basic motif. 1,3,4-oxadiazoles is a class of heterocycles which have attracted significant interest in medicinal chemistry due to their wide range of biological activities [5-7]. Among the all classes of azoles 13,4-oxadiazoles have received attention owing to their broad area of activities such as antiinflammatory, antiedema [8], anticancer [9], analgesic, antibacterial[10], antifungal, anticonvulsant[11,12]etc.

Experimental

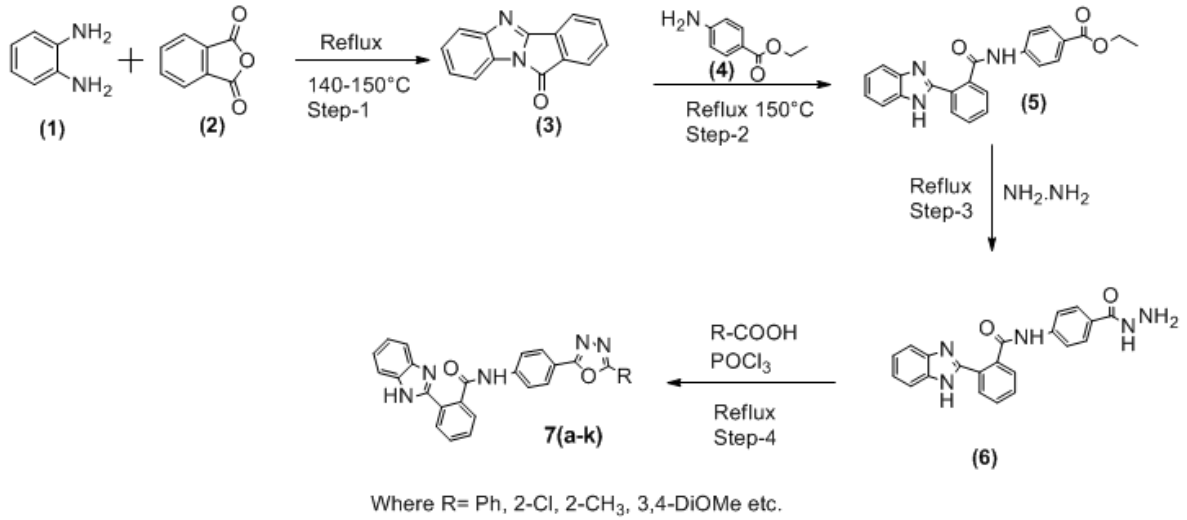
All chemicals and solvents were purchased from Spectrochem Pvt Ltd., Mumbai of LR grade and were used without further purification. Melting points were taken in open capillary method and are uncorrected. IR spectra were recorded on FTIR-8400 spectrophotometer (Shimadzu, Kyoto, Japan), using DRS probe KBr pallet. ^{1}HNMR spectra of the synthesized compounds were recorded on a Bruker-Avance-II (400MHz) in DMSO-d_6 solvent. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu, Kyoto, Japan).

Synthetic procedure of 11H-benzo[4,5]imidazo[2,1-a]isoindol-11-one (3)
An equimolar amount of pthalic anhydride and o-phenylenediamine were taken in RBF. Reaction mass was heated at 140-150^{0}C to obtained o-Benzoylene 2-1-benzimidazole. Reaction mass was Poured in chilled water and precipitates were collected. Yield 79%

Synthetic procedure of ethyl 4-(2-(1H-benzo[d]imidazol-2-yl)benzamido)benzoate (5)
A mixture of o-benzoylene 2-1-benzimidazole (1 mmol) and benzocaine (1mmol) were refluxed for 4-5 hours in DMF at 150^{0}C. Completion of reaction was monitored by TLC. Reaction mass was Poured in chilled water and precipitates were collected as crude product. Dry in vacuo. Crystalline from DMSO to obtained analytical grade pure 2-o-(4'-carbethoxyphenyl amino carbonyl phenyl) benzimidazole. Yield 85%

Synthetic procedure of 2-(1H-benzo[d]imidazol-2-yl)-N-(4-(hydrazinecarbonyl)phenyl) benzamide (6)
In ethanolic solution of 2-o(4'-carbethoxyphenyl amino carbonyl phenyl)-benzimidazole (1mmol), hydrazine hydrate(10mmol) was added and reflux overnight. Reaction mass was cooled to RT, the precipitates were filtered and washed with chilled ethanol to collect the analytical pure 2-(1H-Benzimidazol-2-yl)-N-(4-hydrazinocarbonyl-phenyl) benzamide**.** Yield 80%

General procedure for the synthesis of 2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-substitutedphenyl 1,3,4-oxadiazol-2-yl)phenyl)benzamide derivatives 7(a-k).
A mixture of 2-(1H-benzo[d]imidazol-2-yl)-N-(4-(hydrazinecarbonyl)phenyl)benzamide **(6)** (1mmol) , various aryl acids (1mmol) and $POCl_3$ as a solvent were taken in RBF and refluxed with stirring until the reaction got complete .completion of reaction was monitored by TLC. The mixture was then cooled down, poured on to crushed ice and neutralize with sodium bicarbonate. The solid product was filtered, dried and purified by crystallization.



Scheme 1

Results and discussion

All the glass apparatus used were sterilized before use. The Cup plate method was used to determine the minimum inhibitory concentration (MIC) of the synthesized compounds. [17] Zone of inhibition was measured in millimetre. Bacterial strain of *Bacillus megaterium, Staphylococcus citrus, Escherichia coli, Salmonella typhosa* and fungal strain of *Aspergillus niger* were used in the present study. DMSO was used as the control solvent for the compounds. A blank test was carried out to check the antimicrobial activity of DMSO. Ampicillin, norfloxacin and Chloramphenicol were used as the standard drugs for antibacterial activity. Greseofulvin was used as the standard drug for antifungal activity.

The synthesized 1,3,4-oxadiazoles were screened for their antimicrobial activity by the cup plate method to evaluate the minimum inhibitory concentration Table1b. All of the precursors 7(a–k) of the title compounds showed antibacterial activity in the range of 12-24 mm for *Bacillus megaterium*, 10-17 mm for *Staphylococcus citrus,* 10-18 mm for *Escherichia coli,* and 10-121 mm for *Salmonella typhosa*. It was observed that compound **7k** is more active against B. Megaterian as compared to ampicillin and chloramphenicol but poorly active against S. citrus, E. coli and S. thphosa. Remaining all compound shows moderate to poor activity against gram positive as well as gram negative bacteria.

Against fungal pathogen all compound have shown moderate activity as compared to griseofulvin.

Table 1a Physical Constant table of 2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-substitutedphenyl-1,3,4-oxadiazol-2-yl)phenyl)benzamide derivatives (7a-7k)

Sr. No	Compound	Substitution R	M. F.	M. W.	Yield (%)
1	7a	Phenyl	$C_{28}H_{19}N_5O_2$	457	59
2	7b	2-Acteylphenyl	$C_{30}H_{21}N_5O_3$	499	47
3	7c	Benzyl	$C_{29}H_{21}N_5O_2$	471	51
4	7d	2-Chlorophenyl	$C_{28}H_{18}ClN_5O_2$	491	55
5	7e	4-Chlorophenyl	$C_{28}H_{18}ClN_5O_2$	491	59
6	7f	3,4-Dimethoxyphenyl	$C_{30}H_{23}N_5O_4$	640	61
7	7g	2-Methyl phenyl	$C_{29}H_{21}N_5O_2$	471	64
8	7h	3-Methylphenyl	$C_{29}H_{21}N_5O_2$	471	49
9	7i	4-methylphenyl	$C_{29}H_{21}N_5O_2$	471	43
10	7j	4-Mehoxyphenyl	$C_{29}H_{21}N_5O_3$	487	53
11	7k	4-Nitrophenyl	$C_{28}H_{18}N_6O_4$	502	65

Table 1b Anti microbial activity of 2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-substitutedphenyl-1,3,4-oxadiazol-2-yl)phenyl)benzamide derivatives (7a-7k)

Sr. No.	Antibacterial Activity (Zone of inhibition in m.m.)				Antifungal activity (Zone of inhibition in m.m.)
	Gram +*ve* Bacteria		Gram –*ve* Bacteria		
	B.megateriun	S.citrus	E.coli	S.thyphosa	A. niger
7a	12	12	18	12	11
7b	14	14	13	14	10
7c	17	10	10	18	13
7d	18	11	10	20	16
7e	18	10	11	10	17
7f	16	10	11	17	14
7g	13	13	15	21	18
7h	21	16	13	12	12
7i	22	17	10	11	16
7j	18	12	10	11	13
7k	24	14	14	10	11

Antibacterial Activity (Zone of inhibition in m.m.)				
Standard Drugs	**B.megateriun**	**S.citrus**	**E.coli**	**S.thyphosa**
Ampicillin	23	23	23	24
Chloramphenicol	24	-	23	-
Norfloxacin	-	24	26	24

Antifungal activity (Zone of inhibition in m.m.)	
Standard Drug	**A. niger**
Greseofulvin	24

Analytical Data

2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl)benzamide(7a)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.), 700 (mono substituted phenyl). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 7.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.83 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.66 – 7.44 (m, 10H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.35 – 7.30 (m, 2H), 7.27 – 7.19 (m, 2H). EI^+ m/z: 457 Anal. Calcd for $C_{28}H_{19}N_5O_2$: C, 73.51%; H, 4.19%; N, 15.31%; O, 6.99%.

N-(4-(5-(2-acetylphenyl)-1,3,4-oxadiazol-2-yl)phenyl)-2-(1H-benzo[d]imidazol-2-yl)benzamide(7b)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 1750(Acetyl –C=O str.), 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.), 740 (1,2-disubstituted). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.69 (s, 1H), 7.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.89 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.81 (dt, *J* = 25.2,

12.5 Hz, 1H), 7.72 – 7.61 (m, 4H), 7.61 – 7.53 (m, 3H), 7.53 – 7.41 (m, 4H), 7.32 (s, 1H), 7.27 – 7.18 (m, 2H), 2.54 (s, 3H). EI$^+$ m/z: 499 Anal. Calcd for $C_{30}H_{21}N_5O_3$: C, 72.13%; H, 4. 0 %; N, 14.02%; O, 9.6%.

2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-benzyl-1,3,4-oxadiazol-2-yl)phenyl)benzamide(7c)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 2970(Alkane symm. Str.),2873(Alkane asymm. str.) 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.), 709 (mono substituted).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.81 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.70 – 7.52 (m, 5H), 7.52 – 7.39 (m, 4H), 7.28 – 7.09 (m, 7H), 3.88 (s, 2H). EI$^+$ m/z: 471 Anal. Calcd for $C_{30}H_{21}N_5O_3$: C, 73.87%; H, 4. 49 %; N, 14.85%; O, 6.79%.

2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)phenyl) benzamide(7d)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.), 850(C-Cl str.), 738 (1,2- disubstituted).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.91 – 7.73 (m, 2H), 7.65 (td, *J* = 7.5, 1.5 Hz, 1H), 7.62 – 7.42 (m, 9H), 7.32 – 7.17 (m, 4H). EI$^+$ m/z: 491 Anal. Calcd for $C_{28}H_{18}ClN_5O_2$: C, 68.36%; H, 3.69 %; Cl,7.21%; N, 14.24%; O, 6.50%.

2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)phenyl) benzamide(7e)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.), 850(C-Cl str.), 800 (1,4- disubstituted).^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 7.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.82 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.65 – 7.52 (m, 5H), 7.52 – 7.33 (m, 7H), 7.31 (s, 1H), 7.27 – 7.18 (m, 2H). EI$^+$ m/z: 491 Anal. Calcd for $C_{28}H_{18}ClN_5O_2$: C, 68.36%; H, 3.69 %; Cl,7.21%; N, 14.24%; O, 6.50%.

2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl) benzamide (7f)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 2970(Alkane symm. Str.), 2873(Alkane asymm. str.) 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.).^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84 (s, 1H), 7.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.82 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.71 – 7.54 (m, 7H), 7.51 (td, *J* = 7.5, 1.5 Hz, 1H), 7.39 (s, 1H), 7.27 – 7.15 (m, 4H), 6.99 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 6H). EI$^+$ m/z: 517 Anal. Calcd for $C_{30}H_{23}N_5O_4$: C, 69.62%; H, 4.48 %; N, 13.53%; O, 12.37%.

2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-(o-tolyl)-1,3,4-oxadiazol-2-yl)phenyl)benzamide (7g)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 2970(Alkane symm. Str.), 2873(Alkane asymm. str.) 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.) 739(1,2-disubstituted).^{1}H NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), 7.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.81 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.71 – 7.46 (m, 9H), 7.39 (s, 1H), 7.33 – 7.16 (m, 5H), 2.37 (s, 3H). EI$^+$ m/z: 471 Anal. Calcd for $C_{29}H_{21}N_5O_2$: C, 73. 87%; H, 4.49 %; N, 14.85%; O, 6.79%.

2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-(m-tolyl)-1,3,4-oxadiazol-2-yl)phenyl)benzamide (7h)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 2970(Alkane symm. Str.), 2873(Alkane asymm. str.) 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.) 790(1,3-disubstituted).^{1}H NMR (400 MHz,) δ 10.60 (s, 1H), 7.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.83 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.70 – 7.39 (m, 10H), 7.33 (dd, *J* = 12.7, 5.3 Hz, 2H), 7.29 – 7.15 (m, 3H), 2.33 (s, 3H). EI$^+$ m/z: 471 Anal. Calcd for $C_{29}H_{21}N_5O_2$: C, 73. 87%; H, 4.49 %; N, 14.85%; O, 6.79%.

2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-(p-tolyl)-1,3,4-oxadiazol-2-yl)phenyl)benzamide (7i)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 2970(Alkane symm. Str.), 2873(Alkane asymm. str.) 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.) 832(1,4-disubstituted).^{1}H NMR (400 MHz, CDCl3) δ 10.80 (s, 1H), 7.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.82 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.71 – 7.45 (m, 10H), 7.39 (s, 1H), 7.32 – 7.16 (m, 4H), 2.34 (s, 3H). EI^+ m/z: 471 Anal. Calcd for $C_{29}H_{21}N_5O_2$: C, 73. 87%; H, 4.49 %; N, 14.85%; O, 6.79%.

2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl) benzamide(7j)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 2970(Alkane symm. Str.), 2873(Alkane asymm. str.) 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.) 840(1,4-disubstituted).^{1}H NMR (400 MHz, CDCl3) δ 10.61 (s, 1H), 7.95 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.83 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.69 – 7.42 (m, 10H), 7.31 (s, 1H), 7.29 – 7.16 (m, 2H), 7.01 (d, *J* = 7.4 Hz, 2H), 3.80 (s, 3H). EI^+ m/z: 471 Anal. Calcd for $C_{29}H_{21}N_5O_3$: C, 71. 45%; H, 4.34 %; N, 14.37%; O, 9.85%.

2-(1H-benzo[d]imidazol-2-yl)-N-(4-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)phenyl) benzamide (7k)
IR (ν_{max} cm^{-1}, KBr): 3340(Amide-NH str.), 3200 (Benzimidazole N-H str.), 3010 (Ar-C-H str.), 2970(Alkane symm. Str.), 2873(Alkane asymm. str.) 1640 (Amide-C=O str.), 1592(Ar-C=C str.), 1548 (Nitro N-O str.), 1525 (Benzimidazole C=C str.), 1410(C-H bend.), 1350 (Benzimidazole C-N str.), 1240(Ether linkage–C-O-C, str.), 1000.12(=C-H bend.) 840(1,4-disubstituted).^{1}H NMR (400 MHz, CDCl3) δ 10.52 (s, 1H), 8.19 (dd, *J* = 73.5, 6.8 Hz, 2H), 7.95 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.86 – 7.75 (m, 3H), 7.71 – 7.42 (m, 8H), 7.32 (s, 1H), 7.29 – 7.16 (m, 2H). EI^+ m/z: 502 Anal. Calcd for $C_{28}H_{18}N_6O_4$: C, 66. 93%; H, 3.61 %; N, 16.73%; O, 12.74%.

Conclusions

In summary, a new series of compound **7**(**a**–**k**) were synthesized. Synthesized compounds screened for their biological study. The investigation of antimicrobial (antibacterial and antifungal) activities data revealed that the compound **7k** displayed good activity, the compound **7i & 7h** showed moderate activity and rest compounds showed less activity compared with standard drugs.

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