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Synthesis, characterization, and antimicrobial activity of benzimidazole-derived chalcones containing 1,3,4-oxadiazole moiety

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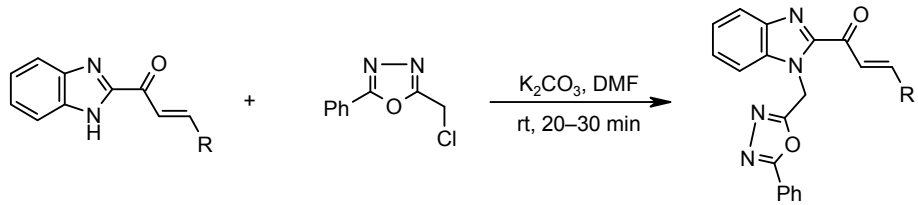


A series of novel benzimidazole-derived chalcones containing the 1,3,4-oxadiazole moiety were synthesized and characterized by IR, ^{1}H, ^{13}C NMR, and mass spectra and elemental analysis. The synthesized compounds were evaluated for their efficiency as antibacterial agents against two Gram-positive and Gram-negative strains of bacteria along with antifungal activity against three fungal species. Antibacterial activity revealed that tested compounds exhibited potent activity whereas some compounds exhibited moderate antifungal activity as compared to the standards.

Keywords: benzimidazole, chalcone, 1,3,4-oxadiazole, antibacterial activity, antifungal activity.

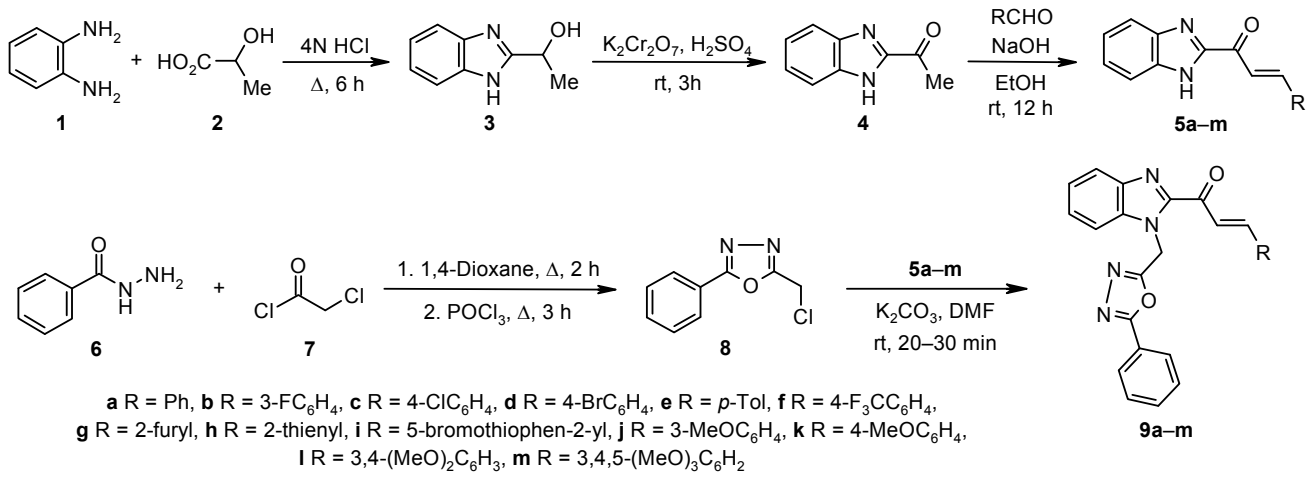
Heterocyclic compounds play an important role in designing new structural entities of medicinal importance. In particular, benzimidazole scaffold is an important pharmacophore in medicinal chemistry and modern drug discovery. Specifically, the 2-substituted benzimidazoles are known to be potent biologically active compounds.[1,2] The biological activity exhibited by compounds containing the benzimidazole moiety has prompted chemists to synthesize an increasing number of benzimidazole derivative libraries and screen them for potential activities.[3,4] 1,3,4-Oxadiazole ring system is an important heterocyclic group for medicinal chemistry. 1,3,4-Oxadiazoles have been extensively reported in literature as antimicrobial,[5] antitubercular,[5] anti-inflammatory,[6,7] analgesic,[7] antitumor,[8] and anticonvulsant agents.[9] This gives a great impetus to the search for potential pharmacologically active drugs carrying 1,3,4-oxadiazole substituent. Chalcones are biosynthetic products of the shikimate pathway, considered as the precursors of flavonoids and isoflavonoids. Chalcones possess a diverse array of pharmacological activities as well.[10,11] Natural and synthetic chalcone derivatives have been object of intense study owing to their broad spectrum of biological activities such as anti-inflammatory,[12] antituberculosis,[13] antimalarial,[14] antioxidant,[15] and anti-HIV.[16]

In present study, we have designed new hybrid molecules through the combination of three active structure units, namely, benzimidazole, chalcone, and 1,3,4-oxadiazole, in order to synthesize a novel series of benzimidazole-derived chalcones that would incorporate 1,3,4-oxadiazole and to test their antimicrobial activity.

The synthetic sequence towards the target compounds involved a convergent protocol of coupling benzimidazole and 1,3,4-oxadiazole heterocycles constructed from acyclic reactants in parallel (Scheme 1). Using readily available starting materials, *o*-phenylene diamine (**1**) and lactic acid (**2**), intermediates **3** and **4** were prepared following a previously described procedure.[17] The corresponding benzimidazole-derived chalcone derivatives **5a**–**m** were obtained by direct Claisen–Schimdt condensation between substituted aromatic aldehydes and 2-acetylbenzimidazole at room temperature in absolute ethanol, using 10% ethanolic NaOH as base. The 1,3,4-oxadiazole ring was constructed by refluxing benzohydrazide (**6**) and chloroacetyl chloride (**7**) on water bath for 2 h, then $POCl_3$ was added dropwise, and refluxing continued for 3 h. Interaction of benzimidazoles **5a**–**m** and 1,3,4-oxadiazole intermediate **8** in the presence of K_2CO_3 for 30 min led to the title compounds **9a**–**m**. All the synthetic compounds gave satisfactory analytical and spectroscopic data that were in full agreement with their proposed structures.

The structures of intermediates **5a**–**m** and **8** and those of products **9a**–**m** were determined by IR, ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, and mass spectrometry. In the IR spectra, all compounds **5a**–**m** showed an

Scheme 1



a R = Ph, **b** R = 3-FC_6H_4, **c** R = 4-ClC_6H_4, **d** R = 4-BrC_6H_4, **e** R = *p*-Tol, **f** R = 4-$F_3CC_6H_4$, **g** R = 2-furyl, **h** R = 2-thienyl, **i** R = 5-bromothiophen-2-yl, **j** R = 3-$MeOC_6H_4$, **k** R = 4-$MeOC_6H_4$, **l** R = 3,4-$(MeO)_2C_6H_3$, **m** R = 3,4,5-$(MeO)_3C_6H_2$

absorption band at 3235–3267 cm^{-1} assigned to N–H bond, which was absent in the spectra of compounds **9a**–**m** due to the alkylation of benzimidazole nitrogen atom. The IR spectra of compounds **9a**–**m** also displayed absorption bands of α,β-unsaturated carbonyl system at 1645–1669 cm^{-1}, C–O–C stretching of the oxadiazole ring around 1054–1069 cm^{-1}, and C=N bonds at 1574–1611 cm^{-1}. In the ^1H NMR spectra of compounds **5a**–**m** the signal of NH proton was observed at 13.56–14.42 ppm. In the spectra of compounds **9a**–**m** such signal was not observed. The CH_2 protons of compounds **9a**–**m** were represented as a singlet at 6.32–6.36 ppm. The two doublets at 7.76–8.05 and 8.13–8.39 ppm were attributed to the protons of α,β-unsaturated system with coupling constant of 15–16 Hz characteristic of the *trans* isomer, although in some cases it was difficult to measure the coupling constant because the signals overlapped with those of the aromatic ring protons. Other protons appeared in the expected region. The ^{13}C NMR spectrum of compounds **9a**–**m** featured signals of carbonyl carbon atoms of the chalcone fragment at ~182–183 ppm while the signal at ~40 ppm was assigned to CH_2 group in the products **9a**–**m**. Additionally, the presence of CH_2 protons was also confirmed by DEPT-135 method. The mass spectra of compounds were also found to be in full agreement with the proposed molecular formula.

Antimicrobial activity of the synthesized compounds **5a**–**m** and **9a**–**m** were determined by broth microdilution method.[18] The results are summarized in Table 1. Compounds **5a**–**m** were found to be less active against Gram-negative strains while compounds **5a**–**d**,**g**,**l**,**m** were more active against Gram-positive strains, especially *S. aureus*, in comparison with standard drug ampicillin. The antibacterial study of compounds **9a**–**m** revealed that compounds **9c**,**f**,**h**,**k**,**m** showed similar level of activity while compound **9e** showed higher activity than the standard drug ampicillin against *Escherichia coli*. Compounds **9a**–**d**,**f**–**j**,**l**,**m** showed higher activity than ampicillin against *Staphylococcus aureus*. Compounds **9i**,**j** displayed equal inhibitory activity, whereas compounds **9b**,**c**,**m** exhibited higher activity than ampicillin against *Streptococcus pyogenes*. All the compounds were found to be more active towards Gram-positive strains, especially *S. aureus*, than against Gram-negative strains. 3,4,5-Trimethoxy-substituted compound **9m** was found to be more active than mono- and disubstituted compounds **9j**,**k** against the Gram-negative bacterial strains. In contrast, monomethoxy derivatives **9j**,**k** were equipotent or more potent than its di- or trisubstituted analogs **9l**,**m** against Gram-negative bacteria. It was noteworthy that *p*-tolyl (**9e**), furyl (**9g**), 4-bromophenyl (**9d**), and 4-chlorophenyl (**9c**) derivatives exhibited potent inhibitory activity (MIC= 150, 150, 100, and 125 μM, respectively) against *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. pyogenes*, respectively, compared to both standard drugs chloramphenicol and ampicillin (MIC 150 and 250 μM, respectively). Compounds **9c**,**d**,**g**,**e** showed promising activity compared to chloramphenicol which may be explained by the presence of halogen, furan ring, and methyl group in the structure, respectively. Presence of an electron-donating group like methyl, chloro, bromo at position 4 of aromatic ring and furan ring seem to be important for antibacterial activity due to resonance effect.

The antifungal activity test indicated that compounds **5a**–**m** are less active against all fungal strains in comparison with standard drugs. Compounds **9b**,**d**,**g**,**l**,**m** showed higher activity than the standard drug griseofulvin against *Candida albicans*. 3,4-Dimethoxy- (**9l**) and 3,4,5-trimethoxy-substituted (**9m**) compounds were more active than all other tested compounds against *Candida albicans*. Compound **9m** possessing three methoxy groups exhibited moderate antifungal activity (MIC = 400 μM) in comparison to nystatin and griseofulvin (MIC 125 and 1500 μM) against *Candida albicans*. However, the rest of the tested compounds showed poor to moderate antifungal activity against all fungal strains.

In conclusion, 13 new compounds based on the molecular hybridisation of benzimidazole derived chalcone with 1,3,4-oxadiazole were synthesized and evaluated for their antimicrobial activity. From the antimicrobial screening results, it can be concluded that addition of 1,3,4-oxadiazole ring to benzimidazole derivatives containing chalcone fragment has enhanced their antimicrobial activity as compared to the parent compounds. All the tested compounds were significantly more active towards bacteria than against fungi.

Table 1. Antimicrobial activity of compounds **5a**–**m** and **9a**–**m** (MIC, μM)

Compound	Gram-negative bacteria		Gram-positive bacteria		Fungi		
	Escherichia coli	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Streptococcus pyogenes*	*Candida albicans*	*Aspergillus niger*	*Aspergillus clavatus*
5a	1000	500	500	500	>2000	>2000	>2000
5b	1000	500	500	300	1500	>2000	>2000
5c	500	500	500	300	>2000	1000	1000
5d	2000	>2000	300	500	1500	2000	2000
5e	500	500	>2000	1000	>2000	1500	1500
5f	250	500	1000	1000	>2000	1000	1000
5g	1000	300	500	1000	1500	1500	1500
5h	5000	1000	1000	>2000	>2000	1000	>2000
5i	1000	1000	1000	1000	>2000	1500	1500
5j	500	500	1000	1000	>2000	500	1500
5k	500	500	1000	500	>2000	2000	>2000
5l	1000	1000	500	1000	1000	1000	1500
5m	500	1000	500	500	1000	>2000	>2000
9a	500	500	250	300	2000	2000	2000
9b	500	500	250	200	1000	2000	2000
9c	250	500	250	125	2000	500	1000
9d	1000	1000	100	350	1000	2000	2000
9e	150	300	1000	500	2000	1000	1000
9f	250	200	500	500	2000	500	500
9g	500	150	250	500	1000	1000	1000
9h	250	500	300	1000	2000	1000	2000
9i	500	500	500	500	2000	1000	1000
9j	300	250	500	500	2000	500	1000
9k	250	250	1000	250	2000	2000	2000
9l	500	550	250	500	500	1000	1000
9m	250	500	200	250	400	2000	2000
Ampicilin	250	-	750	250	–	–	–
Chloramphenicol	150	150	150	150	–	–	–
Griseovulfin	–	–	–	–	1500	300	300
Nystatin	–	–	–	–	125	125	125

Hence, they are promising scaffolds for further modifications to obtain more efficacious antibacterial compounds.

Experimental

The IR spectra of compounds **5a**–**m** and **8** were obtained on a Perkin–Elmer FT-IR Spectrum 2000 spectrophoto-meter using KBr pellets while the IR spectra of compounds **9a**–**m** were obtained on a Perkin–Elmer Frontier 91579 FT-IR spectrophotometer using an ATR attachment. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (300 and 75 MHz, respectively) with 1% TMS as internal standard. Mass spectra were obtained on a Thermo Finnigan Discovery GC-MS instrument. Elemental analysis was performed on a EURO EA 3000 elemental analyzer. Melting points were determined in an open capillary tube using Buchi M-560 melting point instrument. Completion of the reactions was monitored by TLC using glass plates coated with silica gel. All the reagents and solvents of analytical grade (AR) and used without further purification.

Synthesis of 3-aryl(heteroaryl)-1-(1*H*-benzimidazol-2-yl)-2-propen-1-ones 5a–m (General Method). A 10% solution of NaOH (5 ml) in EtOH was added to a solution of 2-acetylbenzimidazole (**4**) (1.6 g, 0.01 mol) in absolute EtOH (20 ml) at 0°C with stirring. Then the solution of an aromatic aldehyde (0.01 mol) in absolute EtOH (10 ml) was added dropwise. The reaction mixture was stirred for 12 h at room temperature. After completion of reaction (monitored by TLC), the reaction mixture was poured onto crushed ice. The separated solid was filtered off, washed with water, and dried. The residue was purified by column chromatography (silica gel, eluent 10% ethyl acetate in petroleum ether) to afford pure benzimidazole-derived chalcone **5a**–**m**.

1-(1*H*-Benzimidazol-2-yl)-3-phenyl-2-propen-1-one (5a). Yield 1.92 g (77%). Pale-yellow crystals. Mp 195–196°C (mp 194–196°C[19]). IR spectrum, ν, cm^{-1}: 3242 (N–H), 3062 (C–H Ar), 2974 (C–H Alk), 1659 (C=O), 1593 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz):

13.51 (1H, s, NH); 8.13 (1H, d, *J* = 15.6, CH=); 7.98 (1H, d, *J* = 15.9, CH=); 7.87–7.58 (4H, m, H Ar); 7.49–7.30 (5H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 248 $[M]^+$ (22), 219 (100), 165 (4), 118 (8), 91 (5).

1-(1*H*-Benzimidazol-2-yl)-3-(3-fluorophenyl)-2-propen-1-one (5b). Yield 2.01 g (76%). Yellow crystals. Mp 190–191°C. IR spectrum, ν, cm^{-1}: 3248 (N–H), 3060 (C–H Ar), 2971 (C–H Alk), 1659 (C=O), 1579 (C=N), 1086 (C–F). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.53 (1H, s, NH); 8.17 (1H, d, *J* = 16.2, CH=); 7.98 (1H, d, *J* = 15.9, CH=); 7.84–7.71 (3H, m, H Ar); 7.61–7.48 (2H, m, H Ar); 7.41–7.29 (3H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 266 $[M]^+$ (46), 237 (100), 144 (4), 101 (12), 74 (12). Found, %: C 72.35; H 4.31; N 10.74. $C_{16}H_{11}FN_2O$. Calculated, %: C 72.17; H 4.16; N 10.52.

1-(1*H*-Benzimidazol-2-yl)-3-(4-chlorophenyl)-2-propen-1-one (5c) Yield 2.28 g (80%). Yellow crystals. Mp 200–201°C (mp 202–204°C[19]). IR spectrum, ν, cm^{-1}: 3267 (N–H), 3065 (C–H Ar), 2975 (C–H Alk), 1662 (C=O), 1591 (C=N), 819 (C–Cl). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.49 (1H, s, NH); 8.10 (1H, d, *J* = 16.2, CH=); 7.92 (1H, d, *J* = 16.2, CH=); 7.86–7.83 (3H, m, H Ar); 7.61–7.36 (5H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 282 $[M]^+$ (44), 253 (100), 218 (16), 144 (14), 118 (32).

1-(1*H*-Benzimidazol-2-yl)-3-(4-bromophenyl)-2-propen-1-one (5d). Yield 2.48 g (76%). Yellow crystals. Mp 220–221°C (mp 224–226°C[19]). IR spectrum, ν, cm^{-1}: 3251 (N–H), 3062 (C–H Ar), 2978 (C–H Alk), 1659 (C=O), 1598 (C=N), 549 (C–Br). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.51 (1H, s, NH); 8.16 (1H, d, *J* = 16.2, CH=); 7.95 (1H, d, *J* = 16.2, CH=); 7.88–7.80 (3H, m, H Ar); 7.66–7.58 (3H, m, H Ar); 7.43–7.33 (2H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 328 $[M(^{81}Br)]^+$ (30), 326 $[M(^{79}Br)]^+$ (29), 299 (72), 218 (30), 144 (20), 102 (100).

1-(1*H*-Benzimidazol-2-yl)-3-(*p*-tolyl)-2-propen-1-one (5e). Yield 2.05 g (78%). Pale-yellow crystals. Mp 209–210°C (mp 210–212°C[20]). IR spectrum, ν, cm^{-1}: 3243 (N–H), 3067 (C–H Ar), 2980 (C–H Alk), 1658 (C=O), 1590 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.49 (1H, s, NH); 8.09 (1H, d, *J* = 16.2, CH=); 7.95 (1H, d, *J* = 16.2, CH=); 7.76–7.74 (3H, m, H Ar); 7.35–7.28 (5H, m, H Ar); 2.35 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 262 $[M]^+$ (34), 233 (100), 118 (52), 115 (64), 91 (34).

1-(1*H*-Benzimidazol-2-yl)-3-(4-trifluoromethylphenyl)-2-propen-1-one (5f). Yield 2.27 g (72%). Yellow crystals. Mp 203–204°C. IR spectrum, ν, cm^{-1}: 3262 (N–H), 3065 (C–H Ar), 2976 (C–H Alk), 1664 (C=O), 1606 (C=N), 1085 (C–F); ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.55 (1H, s, NH); 8.25 (1H, d, *J* = 16.2, CH=); 8.10 (1H, d, *J* = 8.4, H Ar); 8.04 (1H, d, *J* = 16.2, CH=); 7.99–7.80 (4H, m, H Ar); 7.61 (1H, d, *J*= 7.8, H Ar); 7.42–7.34 (2H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 316 $[M]^+$ (52), 287 (100), 218 (6), 151 (24), 118 (14). Found, %: C 64.77; H 3.69; N 9.08. $C_{17}H_{11}F_3N_2O$. Calculated, %: C 64.56; H 3.51; N 8.86.

1-(1*H*-Benzimidazol-2-yl)-3-(2-furyl)-2-propen-1-one (5g). Yield 1.87 g (79%). Yellow crystals. Mp 214–215°C (mp 215–216°C[21]). IR spectrum, ν, cm^{-1}: 3248 (N–H), 3062 (C–H Ar), 2979 (C–H Alk), 1649 (C=O), 1575 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.45 (1H, s, NH); 7.95–7.79 (4H, m, H Ar); 7.58 (1H, d, *J* = 8.1, H Ar); 7.38–7.30 (2H, m, H Ar); 7.16 (1H, d, *J* = 3.6, H Fur); 6.71 (1H, dd, *J* = 3.3, *J* = 1.8, H Fur). Mass spectrum, *m/z* (I_{rel}, %): 238 $[M]^+$ (82), 208 (46), 183 (94), 155 (100), 118 (22).

1-(1*H*-Benzimidazol-2-yl)-3-(2-thienyl)-2-propen-1-one (5h). Yield 1.91 g (75%). Yellow crystals. Mp 201–202°C (mp 201°C[21]). IR spectrum, ν, cm^{-1}: 3253 (N–H), 3063 (C–H Ar), 2970 (C–H Alk), 1649 (C=O), 1574 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.47 (1H, s, NH); 8.16 (1H, d, *J* = 15.9, CH=); 7.85 (1H, d, *J* = 4.8, H thiophene); 7.81 (1H, d, *J* = 15.9, CH=); 7.72 (1H, d, *J* = 3.0, H thiophene); 7.36–7.34 (4H, m, H Ar); 7.32 (1H, dd, *J* = 3.6, *J* = 1.2, H thiophene). Mass spectrum, *m/z* (I_{rel}, %): 254 $[M]^+$ (46), 225 (100), 193 (10), 118 (30), 65 (28).

1-(1*H*-Benzimidazol-2-yl)-3-(5-bromothiophen-2-yl)-2-propen-1-one (5i). Yield 2.50 g (75%). Yellow crystals. Mp 237–238°C. IR spectrum, ν, cm^{-1}: 3241 (N–H), 3063 (C–H Ar), 2970 (C–H Alk), 1654 (C=O), 1576 (C=N), 546 (C–Br). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.47 (1H, s, NH); 8.09 (1H, d, *J* = 15.9, CH=); 7.74–7.69 (3H, m, H Ar); 7.57 (1H, d, *J* = 4.2, H thiophene); 7.74–7.34 (3H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 334 $[M(^{81}Br)]^+$ (12), 332 $[M(^{81}Br)]^+$ (11), 253 (100), 221 (22), 193 (12), 107 (8). Found, %: C 50.68; H 2.93; N 8.59; S 9.85. $C_{14}H_9BrN_2OS$. Calculated, %: C 50.46; H 2.72; N 8.41; S 9.62.

1-(1*H*-Benzimidazol-2-yl)-3-(3-methoxyphenyl)-2-propen-1-one (5j). Yield 2.19 g (79%). Yellow crystals. Mp 175–176°C. IR spectrum, ν, cm^{-1}: 3259 (N–H), 3062 (C–H Ar), 2932 (C–H Alk), 1658 (C=O), 1593 (C=N), 1252 and 1157 (C–O–C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.42 (1H, s, NH); 8.15 (1H, d, *J* = 15.9, CH=); 7.97 (1H, d, *J* = 15.9, CH=); 7.75–7.72 (2H, m, H Ar); 7.44–7.35 (5H, m, H Ar); 7.08–7.05 (1H, m, H Ar); 3.84 (3H, s, OCH_3). Mass spectrum, *m/z* (%): 278 $[M]^+$ (52), 249 (100), 234 (18), 118 (8), 62 (12). Found, %: C 73.50; H 5.07; N 10.33. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.37; H 5.29; N 10.07.

1-(1*H*-Benzimidazol-2-yl)-3-(4-methoxyphenyl)-2-propen-1-one (5k). Yield 2.30 g (83%). Yellow crystals. Mp 185–187°C (mp 184–188°C[19]). IR spectrum, ν, cm^{-1}: 3257 (N–H), 3064 (C–H Ar), 2979 (C–H Alk), 1651 (C=O), 1573 (C=N), 1266 and 1165 (C–O–C); ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.48 (1H, s, NH); 8.03 (1H, d, *J* = 15.9, CH=); 7.96 (1H, d, *J* = 15.9, CH=); 7.85–7.67 (4H, m, H Ar); 7.37–7.36 (2H, m, H Ar); 7.06–7.03 (2H, m, H Ar); 3.83 (3H, s, OCH_3). Mass spectrum, *m/z* (I_{rel}, %): 278 $[M]^+$ (42), 249 (100), 206 (30), 118 (38), 89 (30).

1-(1*H*-Benzimidazol-2-yl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one (5l). Yield 2.33 g (76%). Yellow crystals. Mp 195–196°C (mp 196–198°C[19]). IR spectrum, ν, cm^{-1}: 3235 (N–H), 3059 (C–H Ar), 2968 (C–H Alk), 1651 (C=O), 1572 (C=N), 1265 and 1163 (C–O–C); ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.44 (1H, s, NH); 8.02 (1H, d, *J* = 15.9, CH=); 7.94 (1H, d, *J* = 16.2, CH=); 7.84–7.56 (2H, m, H Ar); 7.46–7.31 (4H, m, H Ar); 7.06 (1H, d, *J* = 8.4, H Ar); 3.86 (3H, s, OCH_3), 3.81 (3H, s,

OCH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 308 $[M]^+$ (62), 279 (100), 263 (20), 207 (14), 118 (8).

1-(1*H*-Benzimidazol-2-yl)-3-(3,4,5-trimethoxyphenyl)-2-propen-1-one (5m). Yield 2.37 g (70%). Yellow crystals. Mp 215–216°C (mp 217°C[22]). IR spectrum, ν, cm^{-1}: 3250 (N–H), 3065 (C–H Ar), 2980 (C–H Alk), 1658 (C=O), 1596 (C=N), 1271 and 1127 (C–O–C); ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.47 (1H, s, NH); 8.09 (1H, d, *J* = 16.2, CH=); 7.97 (1H, d, *J* = 16.2, CH=); 7.74 (2H, m, H Ar); 7.38–7.36 (2H, m, H Ar); 7.21–7.15 (2H, m, H Ar); 3.88 (6H, s, $2OCH_3$); 3.73 (3H, s, OCH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 338 $[M]^+$ (97), 309 (100), 295 (22), 263 (20), 179 (14).

2-Chloromethyl-5-phenyl-1,3,4-oxadiazole (8). Benzohydrazide (**6**) (1.36 g, 0.01 mol) was dissolved in dry 1,4-dioxane (20 ml), and chloroacetyl chloride (**7**) (0.8 ml, 0.01 mol) was added dropwise. The reaction mixture was refluxed on water bath for about 2 h, until evolution of HCl gas ceased. $POCl_3$ (5 ml) was added to the reaction mixture, and the reaction was continued on water bath for 3 h till evolution of HCl gas ceased. The reaction mixture was brought to room temperature, poured carefully into ice-cold water (100 ml), and neutralized with Na_2CO_3 to obtain a precipitate. The solid was filtered off, washed with water, and dried. The crude product was recrystallized from MeOH. Yield 1.37 g (70%). Off-white crystals. Mp 117–118°C (mp 118°C[23]). IR spectrum, ν, cm^{-1}: 3027 (C–H Ar), 2970 (C–H Alk), 1604 (C=N), 1057 (C–O–C oxadiazole), 742 (C–Cl). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.09–8.05 (2H, m, H Ar); 7.59–7.48; (3H, m, H Ar); 4.78 (2H, s, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 161.7 (C-2 oxadiazole); 165.5 (C-5 oxadiazole); 131.8; 128.9; 127.0; 123.4; 32.8 (CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 195 $[M]^+$ (35), 160 (28), 146 (17), 104 (100), 77 (48). Found, %: C 55.70; H 3.74; N 14.45. $C_9H_7ClN_2O$. Calculated, %: C 55.54; H 3.63; N 14.39.

Synthesis of 3-aryl(heteroaryl)-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one 9a–m (General Method). K_2CO_3 (0.29 g, 2 mmol) was added to a mixture of the appropriate benzimidazole-derived chalcone **5a–m** (2 mmol) and 2-chloromethyl-5-phenyl-1,3,4-oxadiazole (**8**) (0.39 g, 2 mmol) in DMF (5 ml). The reaction mixture was stirred at room temperature for 20–30 min. After completion of reaction, the reaction mixture was poured onto crushed ice. The solid that separated was filtered off, washed with water, and dried. The residue was purified by column chromatography (silica gel, eluent 10% ethyl acetate in petroleum ether).

3-Phenyl-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one (9a). Yield 0.71 g (82%). Pale-yellow crystals. Mp 178–179°C. IR spectrum, ν, cm^{-1}: 3027 (C–H Ar), 2963 (C–H Alk), 1657 (C=O), 1603 (C=N), 1069 (C–O–C oxadiazole). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.30 (1H, d, *J* = 16.2, CH=); 8.01–7.91 (3H, m, H Ar); 7.77–7.73 (3H, m, H Ar); 7.66–7.63 (1H, m, H Ar); 7.48–7.25 (8H, m, H Ar); 6.34 (2H, s, NCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.9 (C=O); 165.7; 161.5; 146.2; 145.4; 141.8; 136.2; 134.5; 131.9; 131.0; 129.1 (2C); 129.0 (2C); 128.9 (2C); 127.0 (2C); 124.5; 123.2; 122.6; 122.3; 120.9; 110.7; 40.0 (CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 406 $[M]^+$ (48), 405 (100), 272 (26), 247 (82). Found, %: C 74.12; H 4.73; N 13.89. $C_{25}H_{18}N_4O_2$. Calculated, %: C 73.88; H 4.46; N 13.78.

3-(3-Fluorophenyl)-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one (9b). Yield 0.66 g (78%). Pale-yellow crystals. Mp 190–191°C. IR spectrum, ν, cm^{-1}: 3063 (C–H Ar), 2970 (C–H Alk), 1666 (C=O), 1607 (C=N), 1161 (C–F), 1057 (C–O–C oxadiazole). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.31 (1H, d, *J* = 15.9, CH=); 7.98–7.88 (4H, m, H Ar); 7.66–7.64 (1H, m, H Ar); 7.53–7.37 (8H, m, H Ar); 7.17–7.11 (1H, m, H Ar); 6.32 (2H, s, NCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.5 (C=O); 165.7; 164.7; 161.4; 145.8; 143.8; 141.7; 136.8; 136.2; 132.0; 130.5; 128.9 (2C); 127.1 (2C); 126.9; 125.0; 124.6; 123.7; 123.2; 122.2; 118.0; 115.2; 110.7; 40.0 (CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 424 $[M]^+$ (28), 416 (10), 290 (22), 277 (41), 264 (98); Found, %: C 70.58; H 4.17; N 13.38. $C_{25}H_{17}FN_4O_2$. Calculated, %: C 70.75; H 4.04; N 13.20.

3-(4-Chlorophenyl)-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)-methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one (9c). Yield 0.70 g (81%). Pale-yellow crystals. Mp 203–204°C. IR spectrum, ν, cm^{-1}: 3027 (C–H Ar), 2966 (C–H Alk), 1666 (C=O), 1607 (C=N), 1054 (C–O–C oxadiazole), 822 (C–Cl); ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.30 (1H, d, *J* = 15.6, CH=); 7.97–7.88 (4H, m, H Ar); 7.70–7.63 (3H, m, H Ar); 7.52–7.39 (7H, m, H Ar); 6.33 (2H, s, NCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.7 (C=O); 165.8; 161.4; 145.9; 143.9; 141.7; 137.0; 136.2; 136.0; 132.0; 130.2 (2C); 129.3 (2C); 129.0 (2C); 127.1 (2C); 127.0; 124.6; 123.2; 122.9; 122.2; 110.7; 39.9 (CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 440 $[M]^+$ (2), 328 (5), 306 (26), 295 (38), 280 (100), 252 (64). Found, %: C 68.24; H 4.04; N 12.57. $C_{25}H_{17}ClN_4O_2$. Calculated, %: C 68.11; H 3.89; N 12.71.

3-(4-Bromophenyl)-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)-methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one (9d). Yield 0.70 g (82%). Yellow crystals. Mp 196–197°C. IR spectrum, ν, cm^{-1}: 3025 (C–H Ar), 2967 (C–H Alk), 1666 (C=O), 1605 (C=N), 1055 (C–O–C oxadiazole), 598 (C–Br). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.31 (1H, d, *J* = 15.9, CH=); 7.97–7.91 (3H, m, H Ar); 7.89 (1H, d, *J* = 15.9, CH=); 7.66–7.55 (5H, m, H Ar); 7.50–7.42 (5H, m, H Ar); 6.32 (2H, s, NCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.7 (C=O); 165.9; 161.4; 146.0; 144.0; 141.8; 136.1; 133.4; 132.2; 132.0 (2C); 130.4 (2C); 128.9 (2C); 127.1 (2C); 126.9; 125.5; 124.7; 123.2; 123.0; 122.1; 110.7; 39.9 (CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 486 $[M(^{81}Br)]^+$ (20), 484 $[M(^{79}Br)]^+$ (17), 483 (42), 351 (29), 339 (49); Found, %: C 61.99; H 3.39; N 11.61. $C_{25}H_{17}BrN_4O_2$. Calculated, %: C 61.87; H 3.53; N 11.54.

1-{1-[(5-Phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-3-(*p*-tolyl)-2-propen-1-one (9e). Yield 0.76 g (85). Pale-yellow crystals. Mp 190–191°C. IR spectrum, ν, cm^{-1}: 3021 (C–H Ar), 2968 (C–H Alk), 1656 (C=O), 1595 (C=N), 1055 (C–O–C oxadiazole). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.28 (1H, d, *J* = 15.9, CH=); 8.00–7.90 (4H, m, H Ar); 7.68–7.63 (3H, m, H Ar); 7.51–7.38 (5H, m, H Ar); 7.29 (2H, d, *J* = 6.9, H Ar); 6.34

(2H, s, NCH_2); 2.40 (3H, s, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.9 (C=O); 165.8; 161.5; 146.3; 145.6; 141.9; 141.8; 136.2; 131.9; 131.8; 129.7 (2C); 129.1 (2C); 128.9 (2C); 127.0 (2C); 126.8; 124.4; 123.3; 122.1; 121.5; 110.6; 39.9 (CH_2); 21.6 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 420 $[M]^+$ (17), 419 (36), 390 (10), 286 (18), 260 (100). Found, %: C 74.38; H 4.93; N 13.65. $C_{26}H_{20}N_4O_2$. Calculated, %: C 74.27; H 4.79; N 13.33.

1-{1-[(5-Phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-3-(4-trifluoromethylphenyl)-2-propen-1-one (9f). Yield 0.78 g (81%). Pale-yellow crystals. Mp 202–203°C. IR spectrum, ν, cm^{-1}: 3032 (C–H Ar), 2981(C–H Alk), 1669 (C=O), 1611 (C=N), 1125 (C–F), 1057 (C–O–C oxadiazole). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.39 (1H, d, *J* = 16.2, CH=); 7.99–7.84 (6H, m, H Ar); 7.70–7.51 (3H, m, H Ar); 7.49–7.39 (5H, m, H Ar); 6.33 (2H, s, NCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.4 (C=O); 165.7; 161.4; 145.8; 143.2; 141.7; 137.9; 136.2; 132.5; 132.1; 132.0; 129.1 (2C); 129.0 (2C); 127.2; 127.0 (2C); 126.0; 125.9 (2C); 124.7; 123.2; 122.3; 110.7; 40.0 (CH_2). Mass spectrum, *m/z* (I_{rel}, %): 474 $[M]^+$ (15), 463 (30), 456 (25), 315 (100). Found, %: C 66.01; H 3.34; N 12.01. $C_{26}H_{17}F_3N_4O_2$. Calculated, %: C 65.82; H 3.61; N 11.81.

3-(Furan-2-yl)-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)-methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one (9g). Yield 0.70 g (89%). Yellow crystals. Mp 176–177°C. IR spectrum, ν, cm^{-1}: 3026 (C–H Ar), 2984 (C–H Alk), 1661 (C=O), 1599 (C=N), 1059 (C–O–C oxadiazole). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.14 (1H, d, *J* = 15.3, CH=); 7.96–7.90 (3H, m, H Ar); 7.76 (1H, d, *J* = 15.9, CH=); 7.64–7.49 (2H, m, H Ar); 7.47–7.38 (5H, m, H Ar); 6.84 (1H, d, *J* = 3.3, H Fur); 6.54 (1H, dd, *J* = 3.5, *J* = 1.8, H Fur); 6.32 (2H, s, NCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.5 (C=O); 165.7; 161.5; 151.7; 146.1; 145.7; 141.8; 136.1; 131.9; 131.1; 128.9 (2C); 127.0 (2C); 126.8; 124.5; 123.3; 122.2; 120.4; 117.2; 112.9; 110.6; 39.9 (CH_2). Mass spectrum, *m/z* (I_{rel}, %): 396 $[M]^+$ (27), 395 (55), 366 (41), 341 (100). Found, %: C 70.05; H 4.32; N 14.37. $C_{23}H_{16}N_4O_3$. Calculated, %: C 69.69; H 4.07; N 14.13.

1-{1-[(5-Phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-3-(thiophen-2-yl)-2-propen-1-one (9h). Yield 0.69 g (83%). Pale yellow crystals. Mp 187–188°C. IR spectrum, ν, cm^{-1}: 3054 (C–H Ar), 2981 (C–H Alk), 1651 (C=O), 1579 (C=N), 1065 (C–O–C oxadiazole), 706 (C–S). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.13 (1H, d, *J* = 15.6, CH=); 8.05 (1H, d, *J* = 15.9, CH=); 7.97–7.89 (3H, m, H Ar); 7.64–7.61 (1H, m, H Ar); 7.50–7.38 (7H, m, H Ar); 7.12 (1H, dd, *J* = 3.6, *J* = 1.2, H thiophene); 6.32 (2H, s, NCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.4 (C=O); 165.6; 161.5; 146.1; 141.8; 140.2; 137.7; 136.2; 132.8; 131.9; 130.1; 128.9 (2C); 128.4; 126.9 (2C); 126.8; 124.4; 123.2; 122.1; 121.3; 110.6; 39.9 (CH_2). Mass spectrum, *m/z* (I_{rel}, %): 412 $[M]^+$ (7), 409 (89), 330 (33), 251 (100). Found, %: C 67.16; H 4.09; N 13.74; S 7.98. $C_{23}H_{16}N_4O_2S$. Calculated, %: C 66.97; H 3.91; N 13.58; S 7.77.

3-(5-Bromothiophen-2-yl)-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one (9i). Yield 0.84 g (85%). Yellow crystals. Mp 199–200°C. IR spectrum, ν, cm^{-1}: 3053 (C–H Ar), 2945 (C–H Alk), 1645 (C=O), 1574 (C=N), 1069 (C–O–C oxadiazole), 707 (C–S), 556 (C–Br). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.96–7.90 (5H, m, H Ar, CH=); 7.65 (1H, d, *J* = 8.1, H Ar); 7.52–7.40 (5H, m, H Ar); 7.21 (1H, d, *J* = 3.9, H thiophene); 7.09 (1H, d, *J* = 3.9, H thiophene); 6.32 (2H, s, NCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.2 (C=O); 165.8; 161.6; 146.0; 141.8; 140.1; 136.6; 136.4; 133.0; 131.9; 131.4; 128.9 (2C); 127.0 (2C); 126.0; 124.5; 123.3; 122.2; 121.7; 117.9; 110.6; 39.9 (CH_2). Mass spectrum, *m/z* (I_{rel}, %): 492 $[M(^{81}Br)]^+$ (5), 490 $[M(^{79}Br)]^+$ (3), 411 (100), 331 (22), 252 (50). Found, %: C 56.51; H 2.81; N 11.19; S 6.74. $C_{23}H_{15}BrN_4O_2S$. Calculated, %: C 56.22; H 3.08; N 11.40; S 6.53.

3-(3-Methoxyphenyl)-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one (9j). Yield 0.72 g (83%). Pale-yellow crystals. Mp 204–205°C. IR spectrum, ν, cm^{-1}: 3060 (C–H Ar), 2966 (C–H Alk), 1662 (C=O), 1600 (C=N), 1252 and 1161 (C–O–C), 1059 (C–O–C oxadiazole). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.30 (1H, d, *J* = 15.9, CH=); 7.99–7.91 (4H, m, H Ar); 7.67 (1H, d, *J* = 8.4, H Ar); 7.53–7.29 (8H, m, H Ar); 7.02–6.99 (1H, m, H Ar); 6.35 (2H, s, NCH_2); 3.89 (3H, s, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.8 (C=O); 165.9; 161.4; 160.0; 146.1; 145.5; 141.8; 136.2; 135.9; 131.9; 129.9; 128.9 (2C); 127.0 (2C); 126.9; 124.5; 123.2; 122.7; 122.2; 122.0; 117.3; 113.5; 110.6; 55.4 (CH_3); 39.9 (CH_2). Mass spectrum, *m/z* (I_{rel}, %): 436 $[M]^+$ (9), 435 (35), 406 (4), 302 (20), 276 (100). Found, %: C 71.69; H 4.81; N 12.95. $C_{26}H_{20}N_4O_3$. Calculated, %: C 71.55; H 4.62; N 12.84.

3-(4-Methoxyphenyl)-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one (9k). Yield 0.75 g (86%). Pale-yellow crystals. Mp 164–165°C. IR spectrum, ν, cm^{-1}: 3030 (C–H Ar), 2964 (C–H Alk), 1659 (C=O), 1695 (C=N), 1258 and 1164 (C–O–C), 1062 (C–O–C oxadiazole). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.19 (1H, d, *J* = 15.9, CH=); 7.98–7.90 (4H, m, H Ar); 7.74–7.71 (2H, m, H Ar); 7.65–7.63 (1H, m, H Ar); 7.48–7.41 (5H, m, H Ar); 6.97–6.94 (2H, m, H Ar); 6.34 (2H, s, NCH_2); 3.86 (3H, s, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.6 (C=O); 165.7; 162.2; 161.5; 146.3; 145.5; 141.6; 136.1; 135.9; 131.9; 131.0 (2C); 128.9 (2C); 127.4; 127.0 (2C); 126.7; 124.5; 123.2; 122.0; 120.1; 114.4; 110.6; 55.4 (CH_3); 39.9 (CH_2). Mass spectrum, *m/z* (I_{rel}, %): 436 $[M]^+$ (10), 435 (15), 406 (11), 302 (42), 276 (100). Found, %: C 71.75; H 4.84; N 13.01. $C_{26}H_{20}N_4O_3$. Calculated, %: C 71.55; H 4.62; N 12.84.

3-(3,4-Dimethoxyphenyl)-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one (9l). Yield 0.76 g (81%). Yellow crystals. Mp 196–197°C. IR spectrum, ν, cm^{-1}: 3061 (C–H Ar), 2960 (C–H Alk), 1658 (C=O), 1574 (C=N), 1262 and 1159 (C–O–C), 1058 (C–O–C oxadiazole). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.18 (1H, d, *J* = 15.6, CH=); 7.98–7.91 (4H, m, H Ar); 7.66 (1H, d, *J* = 7.8, H Ar); 7.51–7.30 (7H, m, H Ar); 6.93 (1H, d, *J* = 8.7, H Ar); 6.35 (2H, s, NCH_2); 3.99 (3H, s, OCH_3); 3.94 (3H, s, OCH_3). ^{13}C NMR

spectrum ($CDCl_3$), δ, ppm: 182.5 (C=O); 165.6; 161.5; 152.1; 149.3; 146.3; 145.9; 141.6; 136.1; 131.9; 128.9 (2C); 127.6; 127.0 (2C); 126.8; 124.7; 124.6; 123.2; 121.9; 120.1; 111.0; 110.7; 110.2; 56.1 (CH_3); 56.0 (CH_3); 40.0 (CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 466 $[M]^+$ (12), 417 (20) 309 (100). Found, %: C 69.70; H 4.93; N 12.29. $C_{27}H_{22}N_4O_4$. Calculated, %: C 69.52; H 4.75; N 12.01.

3-(3,4,5-Trimethoxyphenyl)-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-2-propen-1-one (9m). Yield 0.79 g (80%). Yellow crystals. Mp 200–201°C. IR spectrum, ν, cm^{-1}: 3059 (C–H Ar), 2939 (C–H Alk), 1660 (C=O), 1595 (C=N), 1277 and 1115 (C–O–C), 1060 (C–O–C oxadiazole). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 8.20 (1H, d, *J* = 15.9, CH=); 7.98–7.89 (4H, m, H Ar); 7.67–7.64 (1H, m, H Ar); 7.50–7.40 (5H, m, H Ar); 7.00–6.98 (2H, m, H Ar); 6.36 (2H, s, NCH_2); 3.94 (3H, s, OCH_3); 3.93 (3H, s, OCH_3); 3.92 (3H, s, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 182.6 (C=O); 165.7; 161.5; 153.4 (2C); 146.2; 145.8; 141.0; 136.3; 132.0; 130.1; 128.9 (2C); 127.0 (2C); 126.9; 124.5; 123.2; 122.0; 121.5; 119.9; 110.6; 106.4 (2C); 61.0 (CH_3); 56.3 (CH_3); 56.3 (CH_3); 40.0 (CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 496 $[M]^+$ (8), 453 (10), 337 (100). Found, %: C 67.94; H 5.06; N 11.51. $C_{28}H_{24}N_4O_5$. Calculated, %: C 67.73; H 4.87; N 11.28.

Supporting material to this article containing ^1H and ^{13}C NMR spectra compounds **9a**–**m** are available for the authorized users.

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