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Synthesis and antioxidant activity of some new *N*-alkylated pyrazole-containing benzimidazoles

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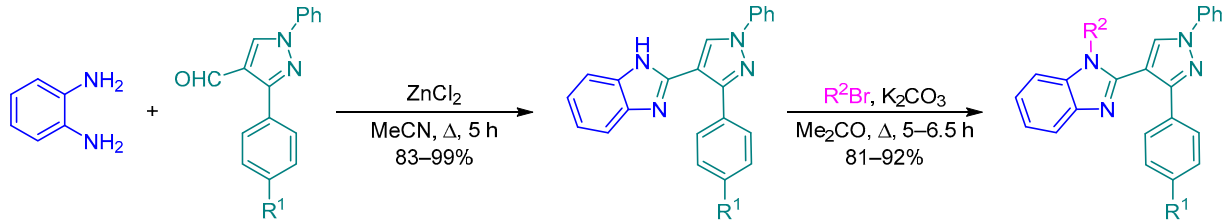


A series of new *N*-substituted pyrazole-containing benzimidazoles was synthesized starting from 1,2-diaminobenzene and pyrazole-4-carbaldehyde in good yield. Antioxidant activity of all title compounds was assessed using 2,2-diphenyl-1-picrylhydrazyl and hydrogen peroxide assays. Some of the synthesized compounds having benzyl substituent at the imidazole nitrogen exhibited good activity in both assays.

Keywords: benzimidazole, 2,2-diphenyl-1-picrylhydrazyl, hydrogen peroxide, pyrazole, zinc chloride, antioxidant activity.

The basic heterocyclic moieties play a pivotal role in regulation of macromolecular targets in the living systems. Molecular structure is the most influential factor in understanding of several biological pathways and in the design and synthesis of therapeutical and pharmacological agents for the cure of various diseases. Among the heterocyclic structures, imidazole[1–3] and pyrazole[4–6] moieties are of interest because of their wide range of clinical applications.

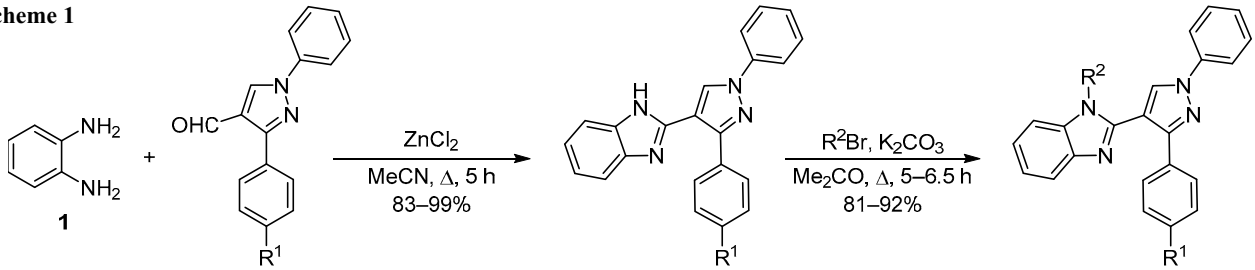
The biological importance of the benzimidazole moiety is illustrated by its presence in the structure of amino acid histidine, vitamin B12 and DNA base structure. This heterocycle is also found in a variety of drugs such as thiabendazole and flubendazole, omeprazole, lansoprazole, candesartan, telmisartan, pantoprazole, and mebendazole.[7] Benzimidazole derivatives are also known to be antimicrobial,[8] anti-inflammatory,[9] antiulcer,[10] antitubercular,[11] antiretroviral,[12] antioxidant,[13] antihypertensive,[14] and antiparasitic agents.[15] It is reported that benzimidazol-1-ylmethyl derivatives of thiadiazole, thiosemicarbazide, and triazole are good inhibitors of NADPH-dependent lipid peroxidation.[16]

Traditionally, benzimidazoles can be prepared from the reaction of 1,2-diaminobenzene and carboxylic acids under harsh dehydration conditions by using strong acids, such as polyphosphoric, hydrochloric, boric, or *p*-toluenesulfonic acids.[17] It was found that the use of milder acidic reagents, particularly Lewis acids[18] or inorganic clays[19] improves both yield and purity of the synthesized benzimidazoles. A variety of methods have been developed for the synthesis of specifically substituted imidazoles,[20] including the use of a solid-phase combinatorial approach.[21,22]

Synthesis of 2-(pyrazol-4-yl)benzimidazoles *via* condensation of 1,2-diaminobenzene with pyrazole-4-carbaldehydes requires an oxidative reagent such as H_2O_2 to generate benzimidazole nucleus.[23] These aspects have motivated us to design and synthesize various *N*-substituted benzimidazoles bearing pyrazole ring at position 2 of the benzimidazole ring and screen them for the exhibition of antioxidant activity. Hence, a rapid, simple, and inexpensive method for the synthesis of *N*-substituted pyrazole-containing benzimidazole dertivatives *via* Vilsmeier–Haack reaction has been developed. This protocol involves two steps as shown in Scheme 1. In the first step, 1,2-diaminobenzene (**1**) was reacted with 1,3-disubstituted pyrazole-5-carbaldehydes **2a**–**h** to generate 2-(pyrazol-4-yl)benzimidazoles **3a**–**h**.

To optimize the experimental conditions for the synthesis of 2-substituted benzimidazoles **3a**–**h**, the reaction of

Scheme 1



2a, **3a**, **4a–c** R^1 = H; **2b**, **3b**, **4d–f** R^1 = NO_2; **2c**, **3c**, **4g–i** R^1 = OMe; **2d**, **3d**, **4j–l** R^1 = Cl;
2, **3 e** R^1 = OH, **f** R^1 = NH_2, **g** R^1 = Me, **h** R^1 = Br;
4a,**d**,**g**,**j** R^2 = *n*-C_5H_{11}; **4b**,**e**,**h**,**k** R^2 = $CH_2C{\equiv}CH$; **4c**,**f**,**i**,**l** R^2 = Bn

1,2-diaminobenzene (**1**) and 1,4-diphenylpyrazole-4-carbaldehyde (**2a**) was studied as a model reaction under various reaction conditions (Table 1). Initially, the catalyst-free reaction resulted in poor yield of product **3a** (Table 1, entry 1). The model reaction carried out with catalysts like iodine, neutral alumina, Silicagel 60, and Amberlyst 15® in ethanol produced low to moderate yields of product (42–51%, Table 1, entries 2–5). The use of Lewis acid catalysts $FeCl_3$, $AlCl_3$, $InCl_3$ in ethanol resulted in higher yields (69–72%, Table 1, entries 6–8). Another catalyst $ZnCl_2$ showed still higher catalytic activity, allowing to increase the yield to 88% with 10 mol % catalyst load (Table 1, entry 9). Optimizing the minimum effective concentration of the $ZnCl_2$, the same reaction was carried out with 3 and 5 mol % of catalyst. In the case of the reaction with 3 mol % of the catalyst, the yield was significantly lower (Table 1, entry 11), while the use of 5 mol % concentration of the $ZnCl_2$ catalyst was found as the effective and sufficient concentration for the completion of the reaction and yielded 82% of the product (Table 1, entry 10). Finally, different solvents were screened in the model reaction (Table 1, entries 12–15), and acetonitrile was identified as the most effective (Table 1, entry 14).

The use of 5 mol % of $ZnCl_2$ in refluxing acetonitrile was identified as the optimal experimental conditions, and such amount was applied for the synthesis of 2-pyrazolyl-substituted benzimidazoles **3a**–**h** in excellent yields (Scheme 1). Since both electron-withdrawing and electron-donating substituents on 4-phenyl group at the pyrazole cycle are far away from the reacting center, the effect of substituent does not significantly affect the product formation. In the next step, pyrazole-substituted benzimidazoles were alkylated by various alkyl bromides in the presence of K_2CO_3 in acetone to produce a series of *N*-substituted pyrazolylbenzimidazoles **4a**–**l** (Scheme 1).

We have studied the antioxidant properties of the synthesized compounds **4a**–**l** by evaluating their radical scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) and H_2O_2. The obtained results reveal that all of the tested compounds have an activity comparable to the ascorbic acid standard (Table 2). Particularly, compounds **4c**,**f**,**l** containing benzyl group as substituent on imidazole nitrogen exhibit a good activity (especially compound **4f**) which may be attributed to the extended resonance by the

Table 1. Synthetic condition optimization for the synthesis of compound **3a***

Entry	Catalyst (mol %)	Solvent	Yield, %
1	–	EtOH	21
2	I_2 (10)	EtOH	42
3	Neutral alumina (10)	EtOH	51
4	Silicagel 60 (10)	EtOH	47
5	Amberlyst 15® (10)	EtOH	51
6	$FeCl_3$ (10)	EtOH	72
7	$AlCl_3$ (10)	EtOH	69
8	$InCl_3$ (10)	EtOH	71
9	$ZnCl_2$ (10)	EtOH	88
10	$ZnCl_2$ (5)	EtOH	82
11	$ZnCl_2$ (3)	EtOH	76
12	$ZnCl_2$ (5)	$CHCl_3$	77
13	$ZnCl_2$ (5)	PhMe	69
14	$ZnCl_2$ (5)	MeCN	91
15	$ZnCl_2$ (5)	DMF	75

* Experimental conditions: 1,2-diaminobenzene (**1**) and 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**2a**) at equimolar ratio (1.00 mmol) in 15 ml of solvent under reflux, reaction time 5 h.

Table 2. Antioxidant activity of compounds **4a**–**l** determined by DPPH and H_2O_2 radical scavenging assays

Compounds	IC_{50}, mg · ml^{-1}	
	DPPH	H_2O_2
4a	144.00 ± 0.27	163.98 ± 0.92
4b	118.60 ±0.59	134.93 ± 0.48
4c	82.79 ± 0.77	99.02 ± 0.81
4d	132.46 ± 0.56	143.96 ± 0.86
4e	100.46 ± 0.68	105.98 ± 0.74
4f	49.48 ± 0.87	79.95 ± 0.59
4g	169.98 ± 1.22	179.65 ± 1.70
4h	119.07 ± 0.39	133.70 ± 0.35
4i	111.00 ± 0.16	115.22 ± 0.61
4j	134.83 ± 0.96	147.15 ± 0.96
4k	112.61 ±0.83	118.50 ± 0.98
4l	80.00 ± 0.78	98.44 ± 0.77
Ascorbic acid	31.42 ± 0.41	55.59 ± 0.56

radical that is formed from the benzyl group upon reaction. Propargyl derivatives **4b**,**e**,**h**,**k** have lower activity than compounds **4c**,**f**,**l**, but higher than pentyl derivatives **4a**,**d**,**g**,**j**.

In conclusion, new *N*-substituted pyrazolylbenzimidazoles were successfully synthesized in a two-step process. Since some of the synthesized compounds possess potent antioxidant activity comparable to that of ascorbic acid, we hope these compounds will find application in the field of medicinal chemistry.

Experimental

IR spectra were recorded as neat samples on a Bruker Alpha FTIR spectrometer with an Eco ATR single-reflection sampling module equipped with ZnSe crystal. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 with TMS as internal standard. Partial assignment of ^{13}C NMR signals was made using APT experiment. ESI mass spectra were recorded on a Q-TOF Micromass spectrometer. Melting points were determined using a Guna Digital Melting Point apparatus and elemental analysis was performed on a Thermo Finnigan Instrument. All the chemicals were procured from Sigma-Aldrich and used as such without further purification. All solvents used for the spectroscopic and other physical studies were reagent grade and were further purified by standard methods.

Synthesis of 2-(1,3-diaryl-1*H*-pyrazol-4-yl)-1*H*-benzimidazoles 3a–h (General method). 1,2-Diaminobenzene (**1**) (0.108 g, 1.00 mmol), an appropriate pyrazole aldehyde **2a**–**h** (1.00 mmol), and $ZnCl_2$ (6.82 mg, 5 mol %) were placed into a 50-ml round-bottomed flask, and acetonitrile (15 ml) was added. The contents were refluxed for about 5 h. The reaction progress was monitored by TLC on silica gel (hexane–AcOEt, 2:1). After completion of the reaction, as indicated by TLC, the reaction mixture was poured into ice water, the precipitate was filtered off and dried under vacuum.

2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-1*H*-benzimidazole (3a). Yield 91%, mp 200–202°C (mp 200°C).[23] IR spectrum, ν, cm^{-1}: 3356 (N–H), 2910 (C–H). ^{1}H NMR spectrum, δ, ppm: 5.23 (1H, br. s, NH); 7.15–7.18 (2H, m, H Ar); 7.32–7.50 (10H, m, H Ar); 7.64–7.67 (2H, m, H Ar); 9.08 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 148.8 (C Ar); 146.0 (C Ar); 143.2 (C Ar); 135.3 (C Ar); 134.2 (C Ar); 132.5 (CH Ar); 129.9 (2CH Ar); 129.8 (2CH Ar); 128.1 (CH Ar); 127.6 (2CH Ar); 127.0 (CH Ar); 122.9 (2CH Ar); 119.7 (2CH Ar); 115.0 (2CH Ar); 109.1 (C-4 pyrazole). Mass spectrum, *m*/*z*: 337 [M+H]$^+$. Found, %: C 78.35; H 4.61; N 16.45. $C_{22}H_{16}N_4$. Calculated, %: C 78.55; H 4.79; N 16.66.

2-[3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-benzimidazole (3b). Yield 92%, mp 230–232°C (mp 230°C[23]). IR spectrum, ν, cm^{-1}: 3343 (N–H), 2912 (C–H), 1346 (NO_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.24 (1H, br. s, NH); 7.37–7.40 (2H, m, H Ar); 7.46–7.50 (2H, m, H Ar); 7.56–7.74 (5H, m, H Ar); 8.80 (2H, d, *J* = 7.7, H Ar); 8.92 (2H, d, *J* = 5.7, H Ar); 9.25 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 148.0 (C Ar); 147.7 (C Ar); 146.1 (C Ar); 143.8 (C Ar); 140.3 (2C Ar); 139.2 (C Ar); 132.5 (CH Ar); 129.6 (4CH Ar); 127.0 (CH Ar); 124.7 (2CH Ar); 123.3 (2CH Ar); 120.2 (2CH Ar); 115.1 (2CH Ar); 109.5 (C-4 pyrazole). Mass spectrum, *m*/*z*: 382 [M+H]$^+$. Found, %: C 69.17; H 3.90; N 18.21. $C_{22}H_{15}N_5O_2$. Calculated, %: C 69.28; H 3.96; N 18.36.

2-[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-benzimidazole (3c). Yield 89%, mp 151–153°C (mp 150°C[23]). IR spectrum, ν, cm^{-1}: 3349 (N–H), 2918 (C–H), 1105 (C–O–C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.86 (3H, s, OCH_3); 5.19 (1H, br. s, NH); 7.33–7.36 (2H, m, H Ar); 7.41–7.45 (2H, m, H Ar); 7.54–7.72 (5H, m, H Ar); 8.62 (2H, d, *J* = 5.5, H Ar); 8.83 (2H, d, *J* = 5.4, H Ar); 9.24 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 199.6 (C Ar); 153.0 (C Ar); 146.1 (C Ar); 143.2 (C Ar); 141.3 (2C Ar); 132.7 (CH Ar); 129.7 (2CH Ar); 128.7 (2CH Ar); 126.8 (CH Ar); 124.3 (C Ar); 122.9 (2CH Ar); 119.6 (2CH Ar); 116.3 (2CH Ar); 115.1 (2CH Ar); 109.1 (C-4 pyrazole) 55.8 (OCH_3). Mass spectrum, *m*/*z*: 367 [M+H]$^+$. Found, %: C 75.32; H 4.48; N 15.21. $C_{23}H_{18}N_4O$. Calculated, %: C 75.39; H 4.95; N 15.29.

2-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-benzimidazole (3d). Yield 85%, mp 189–191°C. IR spectrum, ν, cm^{-1}: 3343 (N–H), 2912 (C–H). ^{1}H NMR spectrum, δ, ppm: 5.00 (1H, br. s, NH); 7.42–7.61 (11H, m, H Ar); 8.79–8.82 (2H, m, H Ar); 9.25 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 149.0 (C Ar); 146.1 (C Ar); 143.6 (C Ar); 140.3 (2C Ar); 133.0 (C Ar); 131.6 (CH Ar); 131.1 (C Ar); 129.4 (2CH Ar); 129.3 (2CH Ar); 128.5 (2CH Ar); 127.0 (CH Ar); 122.9 (2CH Ar); 120.3 (2CH Ar); 115.6 (2CH Ar); 109.2 (C-4 pyrazole). Mass spectrum, *m*/*z*: 371 [M+H]$^+$. Found, %: C 71.24; H 4.34; N 15.54. $C_{22}H_{15}ClN_4$. Calculated, %: C 71.25; H 4.08; N 15.11;

4-[4-(1*H*-Benzimidazol-2-yl)-1-phenyl-1*H*-pyrazol-3-yl]-phenol (3e). Yield 90%, mp 200–202°C. IR spectrum, ν, cm^{-1}: 3496 (O–H), 3343 (N–H), 2912 (C–H). ^{1}H NMR spectrum, δ, ppm: 5.00 (1H, br. s, NH); 5.86 (1H, br. s, OH); 6.45–6.48 (2H, m, H Ar); 7.42–7.60 (11H, m, H Ar); 9.03 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 148.3 (C Ar); 153.4 (C Ar); 146.0 (C Ar); 143.0 (C Ar); 140.9 (2C Ar); 131.4 (CH Ar); 129.7 (2CH Ar); 128.6 (2CH Ar); 126.2 (CH Ar); 126.1 (C Ar); 123.0 (2CH Ar); 119.9 (2CH Ar); 118.4 (2CH Ar); 115.7 (2CH Ar); 110.0 (C-4 pyrazole). Mass spectrum, *m*/*z*: 353 [M+H]$^+$. Found, %: C 74.74; H 4.44; N 15.86. $C_{22}H_{16}N_4O$. Calculated, %: C 74.98; H 4.58; N 15.90.

4-[4-(1*H*-Benzimidazol-2-yl)-1-phenyl-1*H*-pyrazol-3-yl]-aniline (3f). Yield 92%, mp 211–213°C. IR spectrum, ν, cm^{-1}: 3388 (N–H), 3343 (N–H), 2912 (C–H). ^{1}H NMR spectrum, δ, ppm: 5.00 (1H, br. s, NH); 5.99 (2H, br. s, NH_2); 6.66–6.69 (2H, m, H Ar); 7.41–7.59 (11H, m, H Ar); 8.79 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 149.6 (C Ar); 146.3 (C Ar); 145.9 (C Ar); 143.8 (C Ar); 142.0 (2C Ar); 131.5 (CH Ar); 129.7 (2CH Ar); 128.4 (2CH Ar); 126.5 (CH Ar); 123.0 (2CH Ar); 124.3 (C Ar); 119.9 (2CH Ar); 116.7 (2CH Ar); 115.2 (2CH Ar); 109.1 (C-4 pyrazole). Mass spectrum, *m*/*z*: 352 [M+H]$^+$. Found, %: C 75.14; H 4.65; N 19.68. $C_{22}H_{17}N_5$. Calculated, %: C 75.19; H 4.88; N 19.93;

2-[3-(4-Methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-benzimidazole (3g). Yield 87%, mp 205–207°C. IR spectrum, ν, cm^{-1}: 3349 (N–H), 2918 (C–H). ^1H NMR spectrum, δ, ppm: 2.36 (3H, s, CH_3); 5.01 (1H, br. s, NH); 7.18–7.22 (6H, m, H Ar); 7.91–8.01 (7H, m, H Ar); 8.95 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 148.9 (C Ar); 145.9 (C Ar); 143.2 (C Ar); 141.4 (2C Ar); 131.4 (CH Ar); 130.9 (C Ar); 130.1 (C Ar); 129.6 (2CH Ar); 128.7 (2CH Ar); 126.3 (CH Ar); 125.2 (2CH Ar); 123.3 (2CH Ar); 119.5 (2CH Ar); 115.4 (2CH Ar); 109.7 (C-4 pyrazole); 21.7 (CH_3). Mass spectrum, *m*/*z*: 351 $[M+H]^+$. Found, %: C 78.81; H 5.11; N 15.88. $C_{23}H_{18}N_4$. Calculated, %: C 78.83; H 5.18; N 15.99.

2-[3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-benzimidazole (3h). Yield 85%, mp 215–217°C. IR spectrum, ν, cm^{-1}: 3343 (N–H), 2912 (C–H). ^1H NMR spectrum, δ, ppm: 5.03 (1H, br. s, NH); 7.48–7.63 (11H, m, H Ar); 8.83–8.87 (2H, m, H Ar); 9.23 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 149.1 (C Ar); 146.1 (C Ar); 143.4 (C Ar); 140.4 (2C Ar); 131.9 (CH Ar); 131.2 (C Ar); 129.4 (4CH Ar); 128.5 (2CH Ar); 126.7 (CH Ar); 126.0 (C Ar); 123.0 (2CH Ar); 120.3 (2CH Ar); 115.7 (2CH Ar); 109.2 (C-4 pyrazole). Mass spectrum, *m*/*z*: 416 $[M+H]^+$. Found, %: C 63.49; H 3.38; N 13.28. $C_{22}H_{15}BrN_4$. Calculated, %: C 63.63; H 3.64; N 13.49.

Synthesis of 2-(1,3-diaryl-1*H*-pyrazol-4-yl)-1-pentyl-1*H*-benzimidazoles 4a–l (General method). 2-(1,3-Diaryl-1*H*-pyrazol-4-yl)-1*H*-benzimidazole **3a**–**d** (1.00 mmol), alkyl bromide (3.00 mmol), and K_2CO_3 (5.0 mol %, 6.90 mg) were placed into a 50-ml round-bottomed flask, and acetone (15 ml) was added. The reaction mixture was refluxed for 5–6.5 h. The reaction progress was monitored by TLC (hexane–AcOEt, 2:1). After completion of the reaction, as indicated by TLC, K_2CO_3 was separated by filtration, the filtrate was evaporated, and the crude product was purified by column chromatography by using 100–200 mesh silica gel as adsorbent and hexane–AcOEt, 2:3.

2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-1-pentyl-1*H*-benzimidazole (4a). Yield 89%, mp 205–207°C. IR spectrum, ν, cm^{-1}: 2910 (C–H), 1680 (–C=N–). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.62 (3H, t, *J* = 5.5, CH_3); 0.90–0.93 (2H, m, CH_2); 0.94–0.97 (2H, m, CH_2); 1.52–1.55 (2H, m, CH_2); 4.10 (2H, t, *J* = 5.9, CH_2); 6.86 –7.00 (2H, m, H Ar); 7.01–7.36 (10H, m, H Ar); 7.82 (2H, d, *J* = 8.2, H Ar); 8.49 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 147.2 (C Ar); 146.27 (C Ar); 145.9 (C Ar); 143.6 (C Ar); 135.6 (8-C); 134.0 (C Ar); 133.5 (CH Ar); 129.8 (4CH Ar); 128.0 (CH Ar); 127.9 (2CH Ar); 126.0 (CH Ar); 121.9 (2CH Ar); 119.2 (2CH Ar); 118.7 (CH Ar); 111.0 (CH Ar); 109.9 (C-4 pyrazole); 43.6 (NCH_2); 28.6 (CH_2); 27.9 (CH_2); 21.4 (CH_2); 13.4 (CH_3). Mass spectrum, *m*/*z*: 407 $[M+H]^+$. Found, %: C 79.64; H 6.35; N 13.66. $C_{27}H_{26}N_4$. Calculated, %: C 79.77; H 6.45; N 13.78.

2-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-1-(prop-2-yn-1-yl)-1*H*-benzimidazole (4b). Yield 94%, mp 161–163°C. IR spectrum, ν, cm^{-1}: 2916 (C–H), 2099 (C≡C), 1688 (–C=N–). ^1H NMR spectrum, δ, ppm: 3.66 (1H, s, ≡CH); 5.14 (2H, s, CH_2); 6.89–7.01 (4H, m, H Ar); 7.65–7.70 (2H, m, H Ar); 7.79–7.97 (4H, m, H Ar); 8.05–8.11 (2H, m, H Ar); 8.54–8.58 (2H, m, H Ar); 8.88 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 148.0 (C Ar); 145.7 (2C Ar); 145.0 (C Ar); 136.3 (8-C); 133.0 (C Ar); 131.4 (CH Ar); 131.0 (2CH Ar); 130.4 (2CH Ar); 129.6 (CH Ar); 127.7 (2CH Ar); 126.2 (CH Ar); 122.4 (2CH Ar); 120.1 (2CH Ar); 119.3 (CH Ar); 109.9 (CH Ar); 109.6 (C-4 pyrazole); 78.0 (C≡C); 75.3 (C≡C); 32.8 (CH_2). Mass spectrum, *m*/*z*: 375 $[M+H]^+$. Found, %: C 80.11; H 4.80; N 14.35. $C_{25}H_{18}N_4$. Calculated, %: C 80.19; H 4.85; N 14.96.

1-Benzyl-2-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1*H*-benzimidazole (4c). Yield 98%, mp 164–166°C. IR spectrum, ν, cm^{-1}: 2918 (C–H), 1679 (–C=N–). ^1H NMR spectrum, δ, ppm: 5.25 (2H, s, CH_2); 7.22–7.27 (2H, m, H Ar); 7.30–7.38 (4H, m, H Ar); 7.47–7.55 (6H, m, H Ar); 7.60–7.67 (5H, m, H Ar); 7.92–7.97 (2H, m, H Ar); 8.41 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 149.4 (C Ar); 145.5 (C Ar); 143.0 (C Ar); 142.9 (C Ar); 136.3 (C Ar); 136.0 (C Ar) 133.7 (C Ar); 131.7 (CH Ar); 130.5 (2CH Ar); 129.7 (2CH Ar); 128.6 (2CH Ar); 128.0 (CH Ar); 127.6 (2CH Ar); 127.4 (2CH Ar); 125.7 (CH Ar); 124.9 (CH Ar); 122.8 (2CH Ar); 120.3 (2CH Ar); 120.0 (CH Ar); 119.6 (CH Ar); 110.1 (C-4 pyrazole); 51.2 (CH_2). Mass spectrum, *m*/*z*: 427 $[M+H]^+$. Found, %: C 81.35; H 5.34; N 13.00. $C_{29}H_{22}N_4$. Calculated, %: C 81.66; H 5.20; N 13.14.

2-[3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-pentyl-1*H*-benzimidazole (4d). Yield 83%, mp 223–225°C. IR spectrum, *ν*, cm^{-1}: 2951 (C–H), 1682 (–C=N–), 1345 (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.61 (3H, t, *J* = 5.2, CH_3); 0.93–0.98 (4H, m, CH_2); 1.53–1.56 (2H, m, CH_2); 4.13 (2H, t, *J* = 5.4, CH_2); 7.30–7.34 (2H, m, H Ar); 7.44 (1H, t, *J* = 7.0 H Ar); 7.52–7.80 (4H, m, H Ar); 7.88 (2H, d, *J* = 8.3, H Ar); 8.05 (2H, d, *J* = 7.7, H Ar); 8.12–8.36 (2H, m, H Ar); 9.15 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 148.2 (C Ar); 146.2 (C Ar); 145.9 (C Ar); 143.6 (C Ar); 139.1 (C Ar); 138.0 (C Ar); 135.6 (C Ar); 133.5 (CH Ar); 129.8 (2CH Ar); 128.9 (2CH Ar); 126.0 (CH Ar); 125.0 (2CH Ar); 121.9 (2CH Ar); 119.2 (2CH Ar); 118.7 (CH Ar); 111.0 (CH Ar); 109.9 (C-4 pyrazole); 43.6 (NCH_2); 28.8 (CH_2); 28.0 (CH_2); 21.4 (CH_2); 13.9 (CH_3). Mass spectrum, *m*/*z*: 452 $[M+H]^+$. Found, %: C 71.57; H 5.21; N 15.32. $C_{27}H_{25}N_5O_2$. Calculated, %: C 71.82; H 5.58; N 15.51.

2-[3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-(prop-2-yn-1-yl)-1*H*-benzimidazole (4e). Yield 96%, mp 170–171°C. IR spectrum, ν, cm^{-1}: 3240 (≡C–H), 2191 (C≡C), 1671 (–C=N–); 1330 (NO_2). ^1H NMR spectrum, δ ppm (*J*, Hz): 3.32 (1H, s, ≡CH); 5.14 (2H, s, CH_2); 7.20–7.51 (3H, m, H Ar); 7.62 (2H, t, *J* = 7.1, H Ar); 7.74 (2H, t, *J* = 6.9, H Ar); 7.88 (2H, d, *J* = 7.3, H Ar); 8.05 (2H, d, *J* = 7.7, H Ar); 8.26 (2H, d, *J* = 7.9, H Ar); 9.19 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 148.9 (C Ar); 147.1 (C Ar); 145.5 (C Ar); 142.6 (C Ar); 138.9 (C Ar); 138.4 (C Ar); 134.6 (C Ar); 131.5 (CH Ar); 129.7 (2CH Ar); 128.3 (2CH Ar); 127.5 (CH Ar); 123.8 (2CH Ar); 123.0 (2CH Ar); 122.4 (2CH Ar); 119.3 (CH Ar); 119.1 (CH Ar); 111.0 (C-4 pyrazole); 78.0 (C≡C); 75.8 (C≡C); 47.0 (CH_2). Mass spectrum, *m*/*z*: 420 $[M+H]^+$. Found, %: C 71.33; H 4.01; N 16.51. $C_{25}H_{17}N_5O_2$. Calculated, %: C 71.59; H 4.09; N 16.70.

1-Benzyl-2-[3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-benzimidazole (4f). Yield 99%, mp 205–207°C. IR spectrum, ν, cm^{-1}: 2951 (C–H), 1691 (–C=N–), 1351 (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.37 (2H, s, CH_2); 6.78–6.84 (2H, m, H Ar); 7.00–7.08 (3H, m, H Ar); 7.18–7.24 (2H, m, H Ar); 7.35 (1H, t, *J*= 7.3, H Ar); 7.51 (3H, t, *J* = 7.7, H Ar); 7.60–7.72 (3H, m, H Ar); 7.91 (2H, d, *J* = 8.1, H Ar); 8.09 (2H, d, *J* = 8.5, H Ar); 8.98 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 148.7 (C Ar); 146.9 (C Ar); 146.0 (C Ar); 142.7 (C Ar); 138.9 (C Ar); 138.4 (C Ar); 136.6 (C Ar); 136.2 (C Ar); 135.3 (CH Ar); 131.5 (2CH Ar); 129.7 (2CH Ar); 128.5 (2CH Ar); 128.0 (2CH Ar); 127.4 (CH Ar); 126.6 (CH Ar); 123.7 (2CH Ar); 122.9 (CH Ar); 122.2 (CH Ar); 119.3 (2CH Ar); 119.0 (CH Ar); 111.6 (CH Ar); 111.1 (C-4 pyrazole); 47.07 (CH_2). Mass spectrum, *m*/*z*: 472 $[M+H]^+$. Found, %: C 73.71; H 4.44; N 14.80. $C_{29}H_{21}N_5O_2$. Calculated, %: C 73.87; H 4.49; N 14.85.

2-[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-pentyl-1*H*-benzimidazole (4g). Yield 81%, mp 159–161°C. IR spectrum, ν, cm^{-1}: 2918 (C–H), 1650 (–C=N–), 1105 (C–O–C). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.62 (3H, t, *J* = 5.5, CH_3); 0.94–0.97 (2H, m, CH_2); 1.12–1.16 (2H, m, CH_2); 1.52–1.55 (2H, m, CH_2); 3.81 (3H, s, OCH_3); 4.13 (2H, t, *J* = 5.2, CH_2); 7.31–7.33 (2H, m, H Ar); 7.45 (1H, t, *J* = 7.1, H Ar); 7.50–7.81 (4H, m, H Ar); 7.88 (2H, d, *J* = 8.2, H Ar); 8.06 (2H, d, *J* = 7.6, H Ar); 8.12–8.36 (2H, m, H Ar); 9.16 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 160.0 (C Ar); 148.1 (C Ar); 146.1 (C Ar); 144.0 (C Ar); 143.0 (C Ar); 134.0 (C Ar); 132.1 (CH Ar); 129.7 (2CH Ar); 128.1 (2CH Ar); 126.0 (CH Ar); 124.0 (C Ar); 123.8 (2CH Ar); 119.9 (2CH Ar); 119.2 (CH Ar); 116.3 (2CH Ar); 110.0 (CH Ar); 109.0 (C-4 pyrazole); 59.3 (OCH_3); 48.5 (NCH_2); 30.0 (CH_2); 28.8 (CH_2); 21.9 (CH_2); 13.9 (CH_3). Mass spectrum, *m*/*z*: 437 $[M+H]^+$. Found, %: C 77.01; H 6.33; N 12.69. $C_{28}H_{28}N_4O$. Calculated, %: C 77.04; H 6.46; N 12.83.

2-[3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-(prop-2-yn-1-yl)-1*H*-benzimidazole (4h). Yield 85%, mp 131–133°C. IR spectrum, ν, cm^{-1}: 3265 (≡C–H), 2918 (N–H), 2121 (C≡C), 1690 (–C=N–), 1105 (C–O–C). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.62 (1H, s, ≡CH); 3.64 (3H, s, OCH_3); 5.14 (2H, s, CH_2); 7.43–7.50 (3H, m, H Ar); 7.61 (2H, t, *J* = 7.1, H Ar); 7.80 (2H, t, *J* = 7.1, H Ar); 7.89 (2H, d, *J* = 7.1, H Ar); 8.11 (2H, d, *J* = 7.9, H Ar); 8.19 (2H, d, *J* = 8.1, H Ar); 9.22 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 153.9 (C Ar); 149.8 (C Ar); 145.1 (C Ar); 143.7 (C Ar); 142.2 (C Ar); 134.3 (C Ar); 131.6 (CH Ar); 130.1 (2CH Ar); 128.0 (2CH Ar); 126.2 (CH Ar); 126.0 (C Ar); 122.6 (2CH Ar); 119.6 (CH Ar); 119.1 (2CH Ar); 114.3 (2CH Ar); 110.4 (CH Ar); 109.3 (C-4 pyrazole); 78.3 (C≡C); 76.3 (C≡C); 59.3 (OCH_3); 34.0 (CH_2). Mass spectrum, *m*/*z*: 405 $[M+H]^+$. Found, %: C 77.54; H 4.84; N 13.55. $C_{26}H_{20}N_4O$. Calculated, %: C 77.21; H 4.98; N 13.85.

1-Benzyl-2-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-benzimidazole (4i). Yield 90%, mp 136–138°C. IR spectrum, ν, cm^{-1}: 2918 (C–H), 1690 (–C=N–), 1105 (C–O–C). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.76 (3H, s, OCH_3); 5.36 (2H, s, CH_2); 6.82 (2H, t, *J* = 7.8); 7.04 (3H, d, *J* = 7.1); 7.18–7.24 (2H, m, H Ar); 7.36 (1H, t, *J* = 7.3, H Ar); 7.50 (3H, t, *J* = 7.7, H Ar); 7.69-7.74 (3H, m, H Ar); 7.89 (2H, d, *J* = 8.1, H Ar); 8.19 (2H, d, *J* = 8.5, H Ar); 8.68 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 150.6 (C Ar); 149.1 (C Ar); 144.8 (C Ar); 143.3 (C Ar); 142.6 (C Ar); 137.0 (C Ar); 136.2 (C Ar); 131.8 (CH Ar); 130.0 (2CH Ar); 128.1 (2CH Ar); 127.9 (2CH Ar); 127.0 (2CH Ar); 126.3 (CH Ar); 125.1 (CH Ar); 123.7 (C Ar); 123.0 (2CH Ar); 119.8 (2CH Ar); 119.0 (CH Ar); 118.7 (CH Ar); 115.7 (2CH Ar); 109.2 (C-4 pyrazole); 54.3 (OCH_3); 51.8 (CH_2). Mass spectrum, *m*/*z*: 457 $[M+H]^+$. Found, %: C 78.84; H 5.12; N 12.21. $C_{30}H_{24}N_4$. Calculated, %: C 78.92; H 5.30; N 12.27.

2-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-pentyl-1*H*-benzimidazole (4j). Yield 81%, mp 195–197°C. IR spectrum, ν, cm^{-1}: 2900 (C–H), 1681 (–C=N–). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.60–0.63 (3H, m, CH_3); 0.91–0.95 (2H, m, CH_2); 1.12–1.16 (2H, m, CH_2); 1.53 (2H, m, CH_2); 4.12 (2H, t, *J* = 5.4, CH_2); 7.29–7.34 (2H, m, H Ar); 7.43 (1H, t, *J* = 7.0, H Ar); 7.08 (2H, d, *J* = 7.7, H Ar); 7.26 (2H, d, *J*= 7.8, H Ar); 7.52–7.80 (4H, m, H Ar); 8.12–8.34 (2H, m, H Ar); 9.11 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 149.3 (C Ar); 147.4 (C Ar); 144.0 (C Ar); 143.0 (C Ar); 135.3 (C Ar); 135.2 (C Ar); 132.2 (C Ar); 131.3 (CH Ar); 129.5 (2CH Ar); 129.4 (2CH Ar); 128.0 (2CH Ar); 125.9 (CH Ar); 122.3 (2CH Ar); 119.4 (2CH Ar); 118.8 (CH Ar); 110.0 (CH Ar); 109.3 (C-4 pyrazole); 46.8 (NCH_2); 29.0 (CH_2); 28.5 (CH_2); 21.9 (CH_2); 14.0 (CH_3). Mass spectrum, *m*/*z*: 441 $[M+H]^+$. Found, %: C 73.35; H 5.62; N 12.57. $C_{27}H_{25}ClN_5$. Calculated, %: C 73.54; H 5.71; N 12.71.

2-[3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-(prop-2-yn-1-yl)-1*H*-benzimidazole (4k). Yield 87%, mp 173–175°C. IR spectrum, ν, cm^{-1}: 3240 (≡C–H), 2903 (N–H), 2151 (C≡C), 1690 (–C=N–). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.61 (1H, s, ≡CH); 5.13 (2H, s, CH_2); 7.43–7.49 (3H, m, H Ar); 7.62 (2H, t, *J* = 7.0, H Ar); 7.80 (2H, t, *J* = 7.1, H Ar); 7.90 (2H, d, *J* = 7.4, H Ar); 8.11 (2H, d, *J* = 7.5, H Ar); 8.18 (2H, d, *J* = 7.8, H Ar); 8.56 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 147.4 (C Ar); 145.9 (C Ar); 144.4 (C Ar); 143.3 (C Ar); 135.2 (C Ar); 134.7 (C Ar); 131.6 (C Ar); 131.5 (CH Ar); 130.9 (2CH Ar); 130.2 (2CH Ar); 128.1 (2CH Ar); 126.2 (CH Ar); 122.7 (2CH Ar); 120.0 (2CH Ar); 119.4 (CH Ar); 110.1 (CH Ar); 109.6 (C-4 pyrazole); 79.1 (C≡C); 73.9 (C≡C); 33.7 (CH_2). Mass spectrum, *m*/*z*: 409 $[M+H]^+$. Found, %: C 73.39; H 4.24; N 13.35. $C_{25}H_{17}ClN_4$. Calculated, %: C 73.44; H 4.19; N 13.70.

1-Benzyl-2-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1*H*-benzimidazole (4l). Yield 92%, mp 154–156°C. IR spectrum, ν, cm^{-1}: 2918 (C–H), 1691 (–C=N–). ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.36 (2H, s, CH_2); 6.83 (2H, t, *J* = 7.8); 7.04 (3H, d, *J* = 5.2, H Ar); 7.17–7.22 (2H, m, H Ar); 7.34 (1H, t, *J* = 7.3, H Ar); 7.49 (3H, t, *J* = 7.7, H Ar); 7.63–7.68 (3H, m, H Ar); 7.81 (2H, d, *J* = 8.1, H Ar); 7.89 (2H, d, *J* = 8.6, H Ar); 8.97 (1H, s, H-5 pyrazole). ^{13}C NMR spectrum, δ, ppm: 148.9 (C Ar); 146.0 (C Ar); 143.7 (C Ar); 142.9 (C Ar); 137.4 (C Ar); 136.8

(C Ar); 134.0 (C Ar); 132.6 (C Ar); 131.7 (CH Ar); 129.7 (2CH Ar); 129.5 (2CH Ar); 128.4 (2CH Ar); 128.0 (2CH Ar); 126.7 (2CH Ar); 125.8 (CH Ar); 125.1 (CH Ar); 122.8 (2CH Ar); 120.0 (2CH Ar); 119.6 (CH Ar); 118.9 (CH Ar); 109.9 (C-4 pyrazole); 51.24 (CH_2). Mass spectrum, *m*/*z*: 461 $[M+H]^+$. Found, %: C 75.41; H 4.69; N 12.13. $C_{29}H_{21}ClN_4$. Calculated, %: C 75.56; H 4.59; N 12.15.

The antioxidant activity by DPPH and H_2O_2 radical scavenging tests has been evaluated following the literature protocols.[24–26] Mean and standard deviation of radical scavenging activity (RSA) values in % were obtained for all the compounds along with ascorbic acid standard. Absorbance for all the samples was recorded on a Varian, CARY-300 Bio UV-visible spectrophotometer. The linear regression analysis has been carried out for mean and standard deviation values separately to obtain IC_{50} values in mean ± SD mode, IC_{50} being the concentration at RSA 50%. Experiment was conducted in triplicate, and radical scavenging activity values are calculated from the absorbance values using the following formula:

$$\text{RSA} = [(A_{\text{control}} - A_{\text{sample}}) / A_{\text{control}}] \times 100,$$

where A_{control} is absorbance of the control, A_{sample} is absorbance of the sample.

DPPH method. DPPH (10 mg) was dissolved in methanol (10 ml) to obtain stock solution. Solutions of the test compounds in various concentrations (25, 50, 75, 100 μg/ml) as well as of ascorbic acid as reference standard were prepared in methanol. An aliquot of each of these solutions (1.0 ml) was taken in different 10-ml volumetric flasks to which the DPPH stock solution (1.0 ml) was added and volume was made to 10 ml. The absorbance was recorded for these test solutions at 517 nm after incubation of 30 min.

H_2O_2 method. A solution of hydrogen peroxide (20 mM) was prepared in phosphate buffer. To a solution containing test compound of different concentrations (25, 50, 75 and 100 μl) in methanol (2 ml), prepared hydrogen peroxide solution (2 ml) was added. Methanol was used as blank, and ascorbic acid was used as standard for comparison. After incubation for 10 min in dark, absorbance was recorded at 230 nm using UV/Vis spectrophotometer.

The Supplementary information file, containing detailed description on antioxidant activity tests, as well as and NMR and mass spectra of selected compounds, is available from the journal website at http://link.springer.com/journal/10593.

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