Full Paper

Design and One-Pot and Microwave-Assisted Synthesis of 2-Amino/5-Aryl-1,3,4-oxadiazoles Bearing a Benzimidazole Moiety as Antioxidants

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In this study, two new series of 2-amino-1,3,4-oxadiazoles and 5-aryl-1,3,4-oxadiazoles carrying a benzimidazole moiety were synthesized. The antioxidant properties of these compounds were investigated *in vitro* by the determination of the microsomal NADPH-dependent inhibition of lipid peroxidation levels (LP), the microsomal ethoxyresorufin *O*-deethylase activity (EROD), and DPPH radical scavenger effects. Among the tested compounds, 2-[(2-(4-chlorophenyl)-*1H*-benzo[d]imidazole-1-yl)methyl]-5-(4-fluorophenyl)-1,3,4-oxadiazole (**9**) was found to be the most active compound in all three *in vitro* systems.

Keywords: Antioxidant activity / Benzimidazoles / Oxadiazoles / X-ray

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Introduction

Free radicals and other oxygen-derived species are generated in aerobic organisms as part of the normal physiological and metabolic processes or from exogenous factors and agents. Overproduction of the free radicals can be responsible for damage to biological molecules, especially to DNA, lipids, and proteins that cause many health problems which include cancer, Alzheimer's and other neurodegenerative diseases, and atherosclerosis [1–3]. Free radicals are involved in normal physiological functions and antioxidant defence systems scavenge and minimize the formation of oxygen-derived species. But excess formation of free radicals or decrease in antioxidant level leads to oxidative stress. Hence, antioxidants are considered as potential drugs that may be particularly important in diminishing cumulative oxidative damage and helping to stay healthier [2–4]. 1,3,4-Oxadiazole is an important heterocyclic compound because of its different biological activities such as anticancer [5], antibacterial [6, 7], antifungal [7], anticonvulsant [8], antimycobacterial [9], analgesic-antiinflammatory [10–12], antiviral [13], and glycogen synthase kinase-3β inhibitory effects [14]. Several synthetic methods have been reported for the preparation of 1,3,4-oxadiazoles [10, 15–22]. 2-Amino-1,3,4-oxadiazoles were synthesized by the reaction of hydrazides with cyanogen bromide [10, 21]. One of the popular methods involves the microwave assisted one-step synthesis of some 5-aryl-1,3,4-oxadiazoles by reaction of hydrazides and aryl carboxylic acids in the presence of thionyl chloride or phosphorus oxychloride [22, 23]. As a part of our ongoing investigation on developing potent antioxidant compounds [24–30], we report here the synthesis of a new class of 2-amino- or 5-aryl-1,3,4-oxadiazole bearing benzimidazole derivatives and the biological evaluation of their antioxidant properties.

Results and discussion

The target 2-amino (**1**–**4**) and 5-aryl (**5**–**24**) oxadiazoles were derived from 2-phenyl/substituted phenyl-*1H*-benzimidazole acetic acid hydrazides (**1a**–**4a**). Compounds **1a**–**4a** were synthesized

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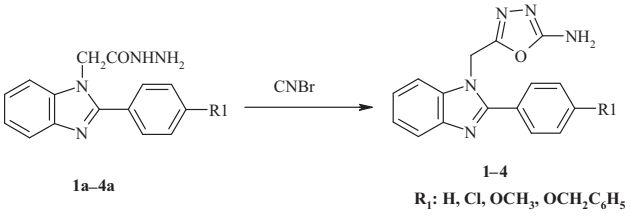
starting from *o*-phenylenediamine and benzaldehyde or *p*-substituted benzaldehydes via oxidative condensation. Treatment of 1*H*-benzimidazole derivatives with ethylchloroacetate in KOH/DMSO yielded ester compounds and then reaction with hydrazine hydrate of these compounds resulted in the desired hydrazide compounds (**1a–4a**) (Scheme 1). The hydrazides (**1a–4a**) were converted to 2-amino-5-[(2-phenyl/*p*-substituted phenyl)-1*H*-benzimidazole-1-yl-methyl]oxadiazoles (**1–4**) using cyanogen bromide (Scheme 2) [10, 21]. Reaction of 2-*p*-chlorophenyl 1*H*-benzimidazol-1-yl)-acetic acid hydrazide (**2a**) with different aromatic acids in the presence of phosphorus oxychloride (Scheme 3) gave 5-aryl-1,3,4-oxadiaxoles (**5–24**). The mass spectra of all of the synthesized compounds showed a M+H ion peak which is conforming with the molecular formula of the compounds and M+2 and M+4 isotope peaks belonging chloro and bromo atoms.

The synthesized compounds were tested for their antioxidant properties by using various *in vitro* systems. Compounds **1**, **6**, **9**, and **15** were found to be slightly scavengers of the DPPH radical (32, 47, 40, and 40%, respectively), when compared with BHT (88%). The DPPH radical scavenger capacities of compounds **2** (19%), **4** (26%), **11** (10%), **12** (15%), **16** (10%), and **19** (17%) were rather limited.

The *in vitro* effects of compounds and caffeine on ethoxyresorufin *O*-deethylase activity (EROD) are shown in Table 1. As can be seen from Table 1, the strong inhibitory activities were observed by compounds **9** (70%), **10** (68%), **11** (71%), and **16** (71%) which were close to the specific inhibitor caffeine (85%) at 10^{-3} M concentration. Significant inhibitory activities were also observed by other compound in the range of 47–66%. Compounds containing fluoro, bromo, or methoxy substituent at the 4th position of the phenyl ring have better activity than the other compounds except compound **16**. In addition, 2-amino-1,3,4-oxadiazoles or disubstituted aryl-1,3,4-oxadiazoles exhibited weaker EROD activity than the monosubstituted aryl compounds.

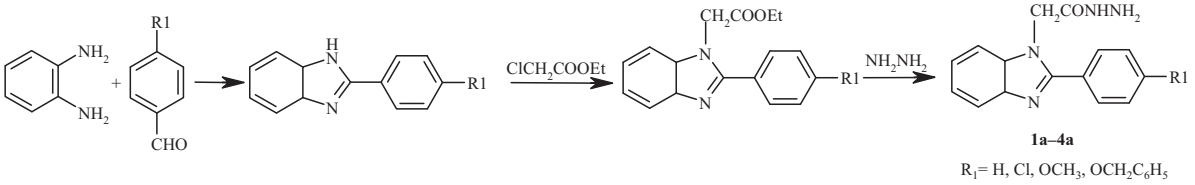
The NADPH-dependent lipid peroxidation (LP) inhibition produced by the new compounds in rat liver microsomes was examined by measuring the formation of 2-thiobarbituric acid reactive substance (TBARS) for their antioxidant capacity. It appears that compound **9** was found to be a good inhibitor (54%) of liver LP levels when compared to BHT (65%) at 10^{-3} M concentration. Compounds **6** and **10** also decreased the LP levels by about 31 and 26%, respectively. Rest of the compounds showed pro-oxidant properties at the same concentration.



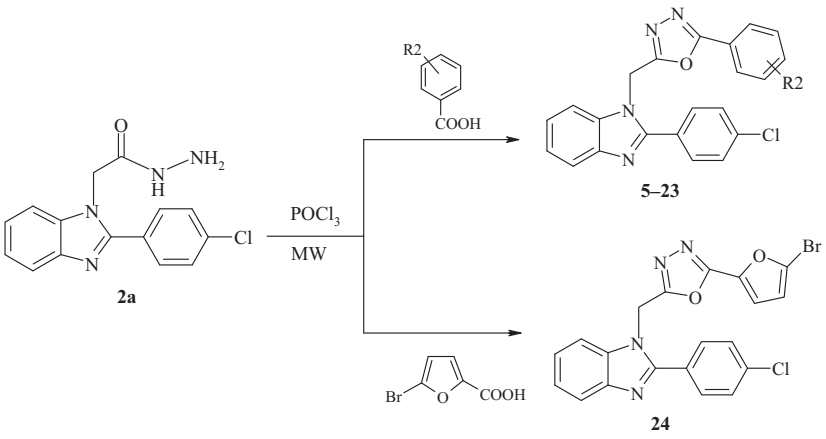
Scheme 2. Synthesis of 2-amino-1,3,4-oxadiazole (**1–4**) derivatives.

It was observed that the effects of the compounds on the DPPH radical, LP, and EROD activity levels were variable. The observation of distinct effects of the synthesized compounds on the DPPH radical, LP levels, and EROD is not surprising since the mechanisms of production of oxidative stress using these methods are different.

The ORTEP drawing [31] of the structure **20** shown in Fig. 1 clearly establishes the structural formula and also shows the conformation of the molecule. The benzimidazole ring system is almost planar; the displacements of all nine atoms contained in the ring are less than 0.031 (5) Å (for C4) from the least-squares plane. The orientation of the oxadiazoylmethyl substituent at N1 is defined by the torsion angles of C1–N1–C14–C15 105.5(3)° and N1–C14–C15–N4 −107.1(4)°. The oxadiazole ring is also planar [maximum deviation 0.005(3) Å for C16] and forms a dihedral angle of 63.75(8)° with the best plane of the benzimidazole ring system. The 3,5-dinitrophenyl ring attached to the oxadiazole ring is nearly coplanar with this ring and makes a dihedral angle of 3.59(8)° with the oxadiazole ring plane. The planar *p*-chlorophenyl moiety at C2 makes a dihedral angle of 42.58(8)° with the benzimidazole ring; the orientation of the phenyl moiety is also defined by the torsion angle N1–C1–C8–C9 135.0(3)°. The packing diagram (Fig. 2) shows that the molecules are arranged into infinite one-dimensional chains along the *c*-axis. C–H Cl interactions between molecules related by the screw symmetry running down the *c*-axis, [H4

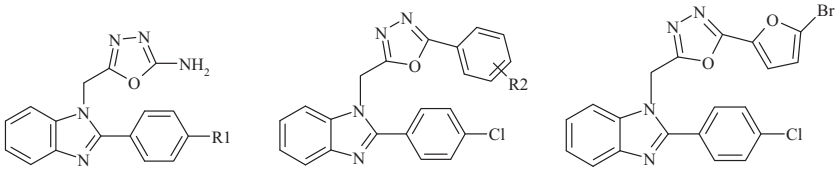


Scheme 1. Synthesis of compounds **1a–4a**.



Scheme 3. Synthesis of 5-aryl-1,3,4-oxadiazoles (**5–24**).

Table 1. The *in vitro* effects of some compounds on liver LP levels, on EROD, and DPPH free radical scavenging activities[a)]



Compd.	R_1	R_2	EROD (pmol/mg/min)	% of contr.	LP (nmol/mg/min)	% of contr.	DPPH (% of control) (1 mM)
1	H		22.18 ± 2.33	53	23.87 ± 0.30	147	68 ± 3.0
2	Cl		14.38 ± 0.01	35	35.54 ± 3.54	218	81 ± 2.5
3	OCH_3		16.72 ± 0.31	40	22.09 ± 0.41	136	ne
4	$OCH_2C_6H_5$		19.60 ± 0.01	47	32.43 ± 4.35	199	74 ± 3.0
5		4-C_2H_5	21.25 ± 0.13	50	23.28 ± 2.53	143	ne
6		4-CH_3	15.05 ± 0.71	35	11.27 ± 1.02	69	53 ± 3.2
7		3-CH_3	15.32 ± 0.22	36	24.82 ± 3.81	152	ne
8		2-CH_3	14.55 ± 1,65	34	23.66 ± 2.74	146	ne
9		4-F	12.68 ± 0.08	30	7.45 ± 1.55	46	60 ± 3
10		4-OCH_3	13.75 ± 1.41	32	12.02 ± 2.02	74	ne
11		4-Br	12.49 ± 0.30	29	27.00 ± 2.42	166	90 ± 1.4
12		4-CF_3	20.17 ± 0.52	47	31.31 ± 3.32	193	85 ± 2.4
13		3-CN	nt		nt		nt
14		4-Cl	22.34 ± 3.20	53	21.30 ± 1.26	131	ne
15		3-Cl	19.04 ± 0.07	45	24.58 ± 1.12	151	60 ± 2.0
16		2-Cl	12.39 ± 0.05	29	18.84 ± 0.48	115	90 ± 2.0
17		2,4-*di*Cl	16.03 ± 0.70	38	32.29 ± 2.98	198	ne
18		4-NO_2	22.43 ± 0.33	53	18.30 ± 0.52	113	ne
19		3-NO_2	16.59 ± 0.21	39	16.70 ± 1.30	103	83 ± 2.0
20		3,5-*di*NO_2	nt		nt		nt
21		3-NO_2 4-OCH_3	20.65 ± 0.38	49	21.07 ± 3.37	130	ne
22		3-NO_2 4-Cl	17.34 ± 0.36	41	33.39 ± 0.35	205	ne
23		2-F 5-NO_2	18.05 ± 0.89	43	30.66 ± 3.47	188	ne
24			15.54 ± 0.49	37	40.08 ± 4.39	246	ne
BHT			–	–	5.68 ± 0.22	35	12 ± 3.0
Caffeine			6.41 ± 036	15	–	–	–
Control[b)]			41.53 ± 0.99	100	16.25 ± 1.45	100	100

[a)] Each value represents the mean ± SD of 2–4 independent experiments.
[b)] Dimethylsulfoxide only, control for compounds, BHT and caffeine ne.
no effect; nt: not tested.

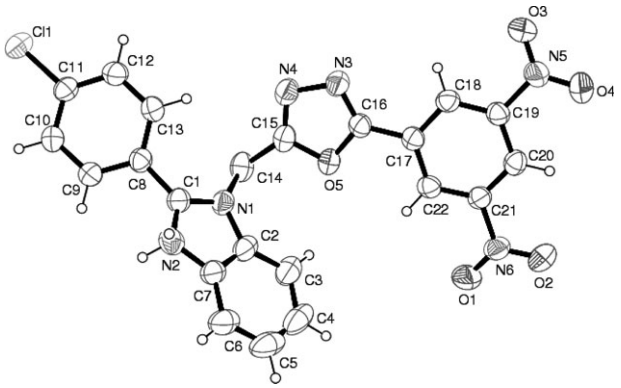


Figure 1. ORTEP drawing of compound **20** with the displacement ellipsoids drawn at the 35% probability level.

$Cl1^{i} = 2.818(1)$ Å; C18 Cl1 = 3.727(3) Å, C18- H4 Cl1 = 165.78(0.17); symmetry code (i) = $-x,-y+1,-z+2$]; this is a presumably weak.

Experimental

Chemistry

Melting points were measured in open capillary tubes on a Thermo Scientific Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C spectra were measured with a Varian Mercury 400 MHz instrument using TMS as an internal standard; $CDCl_3$ and DMSO-d_6, coupling constants (J) are reported in Hertz. Chemical shifts were reported in ppm units with use of δ scale. ES-MS were obtained with a Waters ZQ Micromass LC-MS spectrometer with positive electrospray ionization method. The reactions were carried out in an unmodified domestic microwave oven (White Westinghouse SG Typ KM97UL, 1400 Watt, US). All instrumental analyses were performed at the Central Laboratory, Faculty of Pharmacy, Ankara University. The chemical reagents used in synthesis were purchased from E. Merck and Aldrich. Butylated hydroxy toluene (BHT) and caffeine were obtained from Sigma. Analytical thin-layer chromatography was performed with Merck precoated TLC plates and spots were visualized with ultraviolet light.

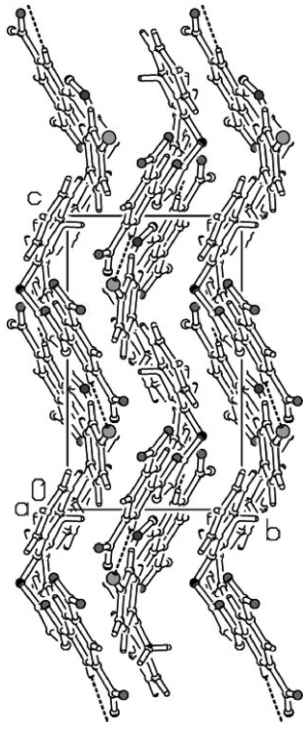


Figure 2. The crystal packing in **20**, showing the stacks of molecules running down the *b*-axis.

*2-Phenyl/(p-chlorophenyl)/(p-methoxyphenyl)/(p-benzyloxyphenyl)-1H-benzimidazol-1-yl)-acetic acid hydrazides (**1a**–**4a**)*

2-Phenyl/(*p*-chlorophenyl)/(*p*-methoxyphenyl)/(*p*-benzyloxyphenyl)-1*H*-benzimidazole-1-yl)-acetic acid hydrazides were synthesized starting from *o*-phenylenediamine and corresponding benzaldehydes according to the literature methods (Scheme 1) [27, 29].

*General synthesis of 2-amino-1,3,4-oxadiazole (**1**–**4**)*

Compounds **1a**–**4a** (0.33 mmol) and cyanogen bromide (0.33 mmol) were dissolved in absolute ethanol (2 mL) and warmed at 60–70°C for 6 h. The resulting solution was cooled and neutralized with sodium bicarbonate solution. Solid product was collected by filtration, washed with water, and crystallized from ethanol.

*5-[(2-Phenyl)-1H-benzo[d]imidazo-1-yl)methyl]-1,3,4-oxadiazole-2-amine (**1**)*

Yield 60%, m.p.: 265°C, ^{1}H NMR δ ppm (DMSO-d_6, 400 MHz): 5.60 (s, 2H, $-CH_2$), 7.11 (s, 2H, NH_2), 7.27–7.33 (m, 2H, Ar–H), 7.58–7.64 (m, 4H, Ar–H), 7.71 (dd, 1H, Jo = 7.03 Hz, Jm = 1.57 Hz, Ar–H), 7.83–7.85 (m, 2H, Ar–H), ^{13}C NMR δ ppm (DMSO-d_6, 100 MHz): 110.8, 119.2, 122.5, 123.0, 128.3, 128.8, 130.9, 134.8, 135.6, 142.2, 151.7, 154.5, 164.0, LC-MS m/z (ESI+): 292.0 (M+H).

*5-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazo-1-yl)methyl]-1,3,4-oxadiazole-2-amine (**2**)*

Yield 37%, m.p.: 256°C, ^{1}H NMR δ ppm (DMSO-d_6, 400 MHz): 5.62 (s, 2H, $-CH_2$), 7.11 (s,2H, NH_2), 7.27–7.34 (m, 2H, Ar–H), 7.63–7.73 (m, 4H, Ar–H), 7.86 (d, 1H, Jo = 8.60 Hz, Ar–H), LC-MS m/z (ESI+): 326.1 (M+H) (76%), 328.1 (M+2) (24%).

*5-[(2-(4-Methoxyphenyl)-1H-benzo[d]imidazo-1-yl)-methyl]-1,3,4-oxadiazole-2-amine (**3**)*

Yield 33%, m.p.: 265°C, ^{1}H NMR δ ppm (DMSO-d_6, 400 MHz): 3.85 (s, 3H, OCH_3), 5.58 (s, 2H, $-CH_2$), 7.11–7.30 (m, 6H, NH_2, Ar–H), 7.59–7.69 (m, 2H, Ar–H), 7.79 (d, 1H, Jo = 8.60 Hz, Ar–H), LC-MS m/z (ESI+): 322.1 (M+H).

*5-[(2-(4-Benzyloxyphenyl)-1H-benzo[d]imidazo-1-yl)-methyl]-1,3,4-oxadiazole-2-amine (**4**)*

Yield 38%, m.p.: 255°C, ^{1}H NMR δ ppm (DMSO-d_6, 400 MHz): 5.21 (s, 2H, OCH_2), 5.58 (s, 2H, $-CH_2$), 7.11 (s, 2H, NH_2), 7.21 (d, 2H,

Jo = 8.60 Hz, Ar–H), 7.26–7.44 (m, 5H, Ar–H), 7.50 (d, 2H, Jo = 7.03 Hz, Ar–H), 7.59–7.69 (m, 2H, Ar–H), 7.79 (d, 2H, Jo = 8.60 Hz, Ar–H), ^{13}C NMR δ ppm (DMSO-d_6, 100 MHz): 69.3, 110.6, 114.9, 118.9, 121.8, 122.2, 122.5, 127.7, 127.8, 128.4, 130.7, 135.6, 136.6, 142.4, 152.8, 154.6, 159.5, 164.0, LC-MS *m/z* (ESI+)**: 398.2 (M+H).

*General synthesis of 5-aryl-1,3,4-oxadiazoles (**5**–**24**)*

2-(*p*-Chlorophenyl)-1*H*-benzimidazol-1-yl-acetic acid hydrazide (0.166 mmol) (**2a**) and appropriate aromatic acid (0.166 mmol) in 1 mL phosphorus oxychloride were ground with a mortar in a beaker and then heated in a domestic microwave irradiation for 30 min. After the cooling to room temperature crushed ice-water was added with continuous stirring, solid mass was filtered, and neutralized with sodium bicarbonate solution (10% w/v). The resulting solid was filtered, washed with water, and was purified with column chromatograpy using hexane–ethyl acetate (2:1) as eluent.

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(4-ethylphenyl)-1,3,4-oxadiazole (**5**)*

Yield 22%, m.p.: 178°C, ^{1}H NMR δ ppm (DMSO-d_6, 400 MHz): 1.16 (t, 3H, CH_2-CH_3), 2.64 (q, 2H, CH_2-CH_3), 5.88 (s, 2H, $-CH_2$), 7.22–7.24 (m, 2H, Ar–H), 7.39 (d, 2H, Jo = 8.21 Hz, Ar–H), 7.64 (d, 2H, Jo = 8.59 Hz, Jm = 1.96 Hz, Ar–H), 7.71 (dd, 2H, Jo = 7.43 Hz, Jm = 1.17 Hz, Ar–H), 7.77 (d, 2H, Jo = 8.20 Hz, Ar–H), 7.86 (dd, 2H, Jo = 8.60 Hz, Ar–H), LC-MS *m/z* (ESI+): 415.8 (M+H) (74%), 417 (M+2) (26%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-p-tolyl-1,3,4-oxadiazole (**6**)*

Yield 38%, m.p.: 132°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 2.62 (s, 3H,CH_3), 5.65 (s, 2H, CH_2), 7.28–7.44 (m, 5H, Ar–H), 7.57 (d, 2H, Jo = 8.20 Hz, Ar–H), 7.62–7.65 (m, 1H, Ar–H), 7.80 (d, 1H, Jo = 7.82 Hz, Ar–H), 7.84–7.86 (m, 1H, Ar–H), 7.89 (d, 2H, Jo = 8.21 Hz, Ar–H), ^{13}C NMR δ ppm ($CDCl_3$, 100 MHz): 22.3, 39.9, 110.3, 120.5, 123.7, 124.1, 126.5, 129.2, 129.6, 131.2, 132.0, 132.1, 135.7, 137.0, 138.8, 143.1, 152.8, 160.9, 166.5, LC-MS *m/z* (ESI+): 401.1 (M+H) (74%), 403.4 (M+2) (26%).

2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-m-tolyl-1,3,4-oxadiazole (7)

Yield 21%, m.p.: 147°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 2.39 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 7.32–7.38 (m, 4H, Ar–H), 7.55–7.60 (m, 3H, Ar–H), 7.70–7.87 (m, 5H, Ar–H), ^{13}C NMR δ ppm ($CDCl_3$, 100 MHz): 21.5, 39.9, 110.3, 120.5, 123.1, 123.7, 124.2, 124.3, 127.7, 127.9, 129.3, 129.7, 131.1, 133.4, 135.7, 137.0, 139.3, 143.0, 152.7, 161.2, 166.3, LC-MS *m/z* (ESI+): 401.3 (M+H) (76%), 403.3 (M+2) (24%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-o-tolyl-1,3,4-oxadiazole (**8**)*

Yield 23%, m.p.: 146°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 2.59 (s, 3H, CH_3), 5.62 (s, 2H, CH_2), 7.25–7.41 (m, 5H, Ar–H), 7.53–7.56 (m, 3H, Ar–H), 7.76–7.87 (m, 4H, Ar–H), ^{13}C NMR δ ppm ($CDCl_3$, 100 MHz): 22.3, 40.0, 110.4, 120.3, 122.2, 124.1, 124.5, 126.5, 129.2, 129.7, 131.3, 131.4, 132.1, 132.2, 135.4, 137.4, 138.9, 151.2, 152.5, 160.7, 166.4, LC-MS *m/z* (ESI+): 401.8 (M+H) (73%), 403.8 (M+2) (27%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(4-fluorophenyl)-1,3,4-oxadiazole (**9**)*

Yield 31%, m.p.: 199°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.62 (s, 2H, CH_2), 7.16–7.20 (td, 2H, Ar–H), 7.35–7.38 (m, 2H, Ar–H), 7.56–7.61 (m, 3H, Ar–H), 7.83–7.86 (m, 3H, Ar–H), 7.93–7.97 (m, 2H, Ar–H).

^{13}C NMR δ ppm ($CDCl_3$, 100 MHz): 39.9, 110.2, 116.8 (d, J = 22.2 Hz), 119.5 (d, J = 3.8 Hz), 120.6, 124.0 (d, J = 32.4 Hz), 127.9, 129.5, 129.6, 129.7, 131.1, 135.7, 137.0, 143.1, 152.8, 161.4, 165.3, 165.4 (d, J = 254.57 Hz), LC-MS *m/z* (ESI+): 405.8 (M+H) (74%), 407.8 (M+2) (26%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(4-methoxyphenyl)-1,3,4-oxadiazole (**10**)*

Yield 19%, m.p.: 167.5°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 3.86 (s, 3H,$-OCH_3$), 5.60 (s, 2H, $-CH_2$), 6.98 (d, 2H, Jo = 8.8 Hz, Ar–H), 7.34–7.39 (m, 2H, Ar–H), 7.56–7.63 (m, 3H, Ar–H), 7.82–7.89 (m, 5H, Ar–H), LC-MS *m/z* (ESI+): 417.8 (M+H) (74%), 419.8 (M+2) (26%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(4-bromophenyl)-1,3,4-oxadiazole (**11**)*

Yield 21%, m.p.: 201°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.62 (S, 2H, $-CH_2$), 7.36–7.38 (m, 2H, Ar–H), 7.56–7.65 (m, 10H, Ar–H), ^{13}C NMR δ ppm ($CDCl_3$,100 MHz): 39.9, 110.2, 120.6, 122.1, 123.8, 124.2, 127.4, 127.9, 128.6, 129.7, 131.1, 132.8, 135.7, 137.1, 143.1, 152.7, 161.5, 165.4, LC-MS *m/z* (ESI+): 465.7 (M+H) (36%), 467.7 (M+2) (51%), 469.7 (M+4) (13%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(4-trifluoromethylphenyl)-1,3,4-oxadiazole (**12**)*

Yield 15%, m.p.: 178°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.65 (s, 2H, CH_2), 7.35–7.38 (m, 2H, Ar–H), 7.56–7.60 (m, 3H, Ar–H), 7.76 (d, 2H, Jo = 8.00 Hz, Ar–H), 7.83–7.86 (m, 3H, Ar–H), 8.07 (d, 2H, Jo = 8.40 Hz, Ar–H), ^{13}C NMR δ ppm ($CDCl_3$, 100 MHz): 39.9, 110.1,120.6, 122.2, 123.8, 124.9, 126.4 (q), 127.6, 127.8, 131.1, 134.0, 134.3, 135.6, 137.1, 143.1, 152.7, 162.0, 164.9, LC-MS *m/z* (ESI+): 455.8 (M+H) (73%), 457.8 (M+2) (27%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(3-cyanophenyl)-1,3,4-oxadiazole (**13**)*

Yield 9%, m.p.: 147.5°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.66 (s, 2H, $-CH_2$), 7.36–7.41 (m, 2H, Ar–H), 7.58 (dd, 2H, Jo = 8.00 Hz, Jm = 2.00 Hz, Ar–H) 7.65 (td, 2H, Jo = 8.00 Hz, 7.60 Hz, Ar–H), 7.85 (qd, 2H, Jo = 7.2 0Hz, 6.80 Hz, Ar–H), 8.18 (d, 1H, Jo = 7.60 Hz, Ar–H), 8.22 (s, 1H, Ar–H), LC-MS *m/z* (ESI+): 412.8 (M+H) (70%), 414.8 (M+2) (30%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(4-chlorophenyl)-1,3,4-oxadiazole (**14**)*

Yield 10%, m.p.: 199°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.62 (s, 2H, CH2), 7.34–7.39 (m, 2H, Ar–H), 7.47 (d, 2H, Jo = 8.40 Hz, Ar–H), 7.56–7.60 (m, 3H, Ar–H), 7.83–7.89 (m, 5H, Ar–H), LC-MS *m/z* (ESI+): 421.7 (M+H) (47%), 423.7 (M+2) (44%), 425.7 (M+4) (9%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(3-chlorophenyl)-1,3,4-oxadiazole (**15**)*

Yield 11%, m.p.: 190°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.62 (s, 2H, $-CH_2$), 7.35–7.59 (m, 7H, Ar–H), 7.81–7.85 (m, 4H, Ar–H),

7.92–7.93 (m, 1H, Ar–H), LC-MS *m/z* (ESI+): 421.7 (M+H) (46%), 423.7 (M+2) (44%), 425.7 (M+4) (10%), ^{13}C NMR δ ppm ($CDCl_3$, 100 MHz): 39.9, 110.2, 120.6, 123.8, 124.2, 124.8, 125.3, 127.2, 127.9, 129.7, 130.8, 131.1, 132.6, 135.6, 135.7, 137.1, 143.1, 152.7, 161.7, 164.9.

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(2-chlorophenyl)-1,3,4-oxadiazole (**16**)*

Yield 13%, m.p.: 193°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.65 (s, 2H, $-CH_2$), 7.35–7.41 (m, 3H, Ar–H), 7.46–7.58 (m, 4H, Ar–H), 7.64–7.67 (m, 1H, Ar–H), 7.82–7.85 (m, 1H, Ar–H), 7.91 (dd, 2H, Jo = 8.60 Hz, Jm = 1.96 Hz, Ar–H), 7.96 (dd, 1H, Jo = 7.81 Hz, Jm = 1.56 Hz, Ar–H), LC-MS *m/z* (ESI+): 421.7 (M+H) (55%), 423.7 (M+2) (38%), 425.8 (M+4) (7%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole (**17**)*

Yield 29%, m.p.: 199°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.65 (s, 2H, $-CH_2$), 7.34–7.42 (m, 3H, Ar–H), 7.54–7.64 (m, 4H, Ar–H), 7.82–7.92 (m, 4H, Ar–H), ^{13}C NMR δ ppm ($CDCl_3$, 100 MHz): 39.7, 110.2, 120.1, 120.8, 123.8, 124.1, 127.7, 127.8, 129.5, 130.7, 131.0, 131.3, 132.0, 133.8, 135.3, 137.0, 138.9, 152.4, 161.6, 163.7, LC-MS *m/z* (ESI+): 455.9 (M+H) (45%), 457.9 (M+2) (39%), 459.8 (M+4) (16%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(4-nitrophenyl)-1,3,4-oxadiazole (**18**)*

Yield 17%, m.p.: 237°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.67 (s, 2H, $-CH_2$), 7.36–7.38 (m, 2H, Ar–H), 7.57 (d, 2H, Jo = 8.21 Hz, Ar–H) 7.82 (d, 2H, Jo = 8.20 Hz, Ar–H), 8.13 (d, 2H, Jo = 8.59 Hz, Ar–H), 8.35 (d, 2H, Jo = 8.99 Hz, Ar–Ar–H), ^{13}C NMR *ii* ppm ($CDCl_3$, 100 MHz): 39.9, 110.0, 120.7, 123.9, 124.3, 124.7, 124.8, 128.2, 128.6, 129.7, 131.1, 135.6, 137.2, 143.1, 150.1, 152.7, 162.4, 164.3, LC-MS *m/z* (ESI+): 432.8 (M+H) (73%), 434.9 (M+2) (27%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(3-nitrophenyl)-1,3,4-oxadiazole (**19**)*

Yield 18%, m.p.: 219°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.67 (s, 2H, $-CH_2$), 7.38–7.85 (m, 9H, Ar–H), 8.29–8.41 (m, 2H, Ar–H), 8.77 (s, 1H, Ar–H), ^{13}C NMR δ ppm ($CDCl_3$, 100 MHz): 39.8, 110.2, 120.7, 122.2, 123.9, 124.3, 124.8, 126.9, 127.9, 129.7, 130.8, 131.1, 132.6, 135.6, 137.2, 143.1, 148.8, 152.8, 162.1, 164.2, LC-MS *m/z* (ESI+): 432.8 (M+H) (73%), 434.8 (M+2) (27%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(3,5-dinitrophenyl)-1,3,4-oxadiazole (**20**)*

Yield 13%, m.p.: 231°C, ^{1}H NMR δ ppm (DMSO-d_6, 400 MHz): 5.98 (s, 2H, CH_2), 7.30–7.39 (m, 2H, Ar–H), 7.67 (dd, 2H, Jo = 8.59 Hz, Jm = 1.95 Hz, Ar–H), 7.74–7.78 (m, 2H, Ar–H), 7.90 (dd, 2H, Jo = 8.60 Hz, Jm = 1.96 Hz, Ar–H), 8.87 (d, 2H, Jm = 2.35 Hz, Ar–H), 8.99 (td, 1H, Jm = 2.34 Hz, 1.96 Hz, Ar–H), LC-MS *m/z* (ESI+): 477.8 (M+H) (72%), 479.7 (M+2) (28%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(4-methoxy-3-nitrophenyl)-1,3,4-oxadiazole (**21**)*

Yield 16%, m.p.: 195°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 4.03 (s, 3H, $-OCH_3$), 5.63 (s, 2H, $-CH_2$), 7.21 (d, 1H, Jo = 8.99 Hz, Ar–H), 7.35–7.38 (m, 2H, Ar–H), 7.56–7.59 (m, 2H, Ar–H), 7.82–7.85 (m, 3H, Ar–H), 8.13 (dd, 1H, Jo = 8.99 Hz, Jm = 2.35 Hz, Ar–H), 8.39 (d, 1H, Jm = 1.95 Hz, Ar–H), ^{13}C NMR δ ppm ($CDCl_3$, 100 MHz): 39.8, 57.2, 110.1, 114.5, 115.6, 120.6, 123.8, 124.2, 124.8, 127.8, 129.7, 131.1, 132.7, 135.6, 137.1, 139.9, 143.0, 152.7, 155.7, 161.5, 164.1, LC-MS *m/z* (ESI+): 462.8 (M+H) (72%), 464.8 (M+2) (28%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(3-nitro-4-chlorophenyl)-1,3,4-oxadiazole (**22**)*

Yield 28%, m.p.: 217°C, ^{1}H NMR δ ppm (DMSO-d_6, 400 MHz): 5.93 (s, 2H, $-CH_2$), 7.31–7.38 (m, 2H, Ar–H), 7.66 (d, 2H, Jo = 8.59 Hz, Ar–H), 7.75 (d, 2H, Jo = 7.42 Hz, Ar–H), 7.89 (d, 2H, Jo = 8.59 Hz, Ar–H), 7.99 (d, 1H, Jo = 8.59 Hz, Ar–H), 8.18 (dd, 1H, Jo = 8.60 Hz, Jm = 1.95 Hz, Ar–H), 8.52 (d, 1H, Jm = 1.95 Hz, Ar–H), ^{13}C NMR δ ppm (DMSO-d_6, 100 MHz): 111.0, 119.1, 122.8, 123.1, 123.2, 123.5, 127.9, 128.4, 128.9, 131.1, 131.2, 133.0, 135.0, 135.5, 141.8, 147.9, 151.9, 162.5, 162.8, LC-MS *m/z* (ESI+): 466.9 (M+H) (56%), 468.8 (M+2) (35%), 470.7 (M+4) (9%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(2-fluoro-5-nitrophenyl)-1,3,4-oxadiazole (**23**)*

Yield 20%, m.p.: 150°C, ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 5.65 (s, 2H, CH_2), 7.39–7.43 (m, 3H, Ar–H), 7.55–7.61 (m, 3H, Ar–H), 7.78–7.86 (m, 3H, Ar–H), 8.37–8.41 (m, 1H, Ar–H), 8.90–8.92 (m, 1H, Ar–H), ^{13}C NMR δ ppm ($CDCl_3$, 100 MHz): 39.7, 110.3, 113.1 (d, J = 13.78 Hz), 118.7 (d, J = 23.64 Hz), 120.6, 124.1 (d, J = 38.33 Hz), 126.07 (d, J = 3.02), 127.7, 129.3 (d, J = 9.96 Hz), 129.7, 131.2, 135.5, 137.2, 142.9, 146.6, 152.8, 161.1, 161.2, 162.4, 163.0 (d, J = 269.07 Hz), LC-MS *m/z* (ESI+): 450.8 (M+H) (72%), 452.8 (M+2) (28%).

*2-[(2-(4-Chlorophenyl)-1H-benzo[d]imidazole-1-yl)-methyl]-5-(5-bromo-2-furyl)-1,3,4-oxadiazole (**24**)*

Yield 50%, m.p.: 138°C, ^{1}H NMR δ ppm (DMSO-d_6, 400 MHz): 5.90 (s, 2H, $-CH_2$), 6.94 (d, 1H, Jo = 3.52 Hz, Furil-H), 7.31–7.35 (m, 2H, Ar–H), 7.38 (d, 1H, Jo = 3.52 Hz, Furil-H), 7.65–7.76 (m, 4H, Ar–H), 7.84 (dd, 2H, Jo = 8.59 Hz, Jm = 1.95 Hz, Ar–H), LC-MS *m/z* (ESI+): 455.1 (M+H) (34%), 457.6 (M+2) (55%), 459.7 (M+4) (11%).

Antioxidant activity

Lipid peroxidation level

Male albino Wistar rats (200–225 g) used in the experiments were fed with standard laboratory rat chow and tap water *ad libitum*. The animals were starved for 24 h prior to sacrifice and then killed by decapitation under anesthesia. The livers were removed immediately and washed in ice-cold distilled water and the microsomes were prepared as described previously [32]. NADPH-dependent LP was determined using the optimum conditions determined and described previously [32] and measured spectrophotometrically by estimation of TBARS. Amounts of TBARS were expressed in terms of nmol malondialdehyde (MDA)/mg protein. The assay was essentially derived from the methods of Wills [33, 34] as modified by Bishayee and Balasubramanian [35]. LP was determined spectrophotometrically at 532 nm as the thiobarbituric acid reactive material. Compounds inhibit the production of MDA and therefore the produced color after addition of thiobarbituric acid is less intensive. A typical optimized assay mixture contained 10^{-3} M test compound, 0.2 nM Fe^{++}, 90 mM KCl, 62.5 mM potassium phosphate buffer, pH 7.4, NADPH-generating system consisting of 0.25 mM $NADP^+$, 2.5 mM $MgCl_2$, 2.5 mM glucose-6-phosphate,

1.0 U glucose-6-phosphate dehydrogenase, and 14.2 mM potassium phosphate buffer pH 7.8 and 0.2 mg microsomal protein in a final volume of 1.0 mL.

EROD enzyme activity

EROD activity was measured by the spectrofluorometric method of Burke et al. [36]. A typical optimized assay mixture contained 1.0 mM ethoxyresorufin, 10^{-3} M test compound, 100 mM Tris–HCl buffer pH 7.8, NADPH generating system consisting of 0.25 mM $NADP^+$, 2.5 mM $MgCl_2$, 2.5 mM glucose-6-phosphate, 1.0 U glucose-6-phosphate dehydrogenase, and 14.2 mM potassium phosphate buffer pH 7.8 and 0.2 mg liver microsomal protein in a final volume of 1.0 mL.

DPPH free radical scavenging activity

The radical scavenging assay was determined by the modified method described by Blois [37]. BHT and stock solutions of the compounds were prepared at 10^{-2} M in DMSO. A series of solutions in DMSO were diluted to varying concentrations in 96-well microplates. Then, methanolic DPPH solution (100 μM) was added to each well. The plate was shaken and placed in the dark. After 30 min, the optical density (OD) of the solution was read at 517 nm. The methanolic solution of DPPH served as a control. Percentage inhibition was calculated using the following formula: % Inhibition = $(OD_{control} - OD_{sample})/OD_{control} \times 100$, where $OD_{control}$ is the absorbance of the control with DMSO and OD_{sample} is the absorbance of the sample in the presence of the compounds. A dose–response curve was plotted to determine the IC_{50} values. IC_{50} is defined as the concentration sufficient to obtain 50% of a maximum scavenging capacity. All tests and analyses were run in triplicate and averaged. The standard used in this assay was BHT.

Table 2. Crystal data and details of the structure determination of (**20**)

Formula	$C_{22}H_{13}ClN_6O_5$
Formula weight	476.83
Crystal system	Monoclinic
Space group	$P2_1/c$
Cell constants	
a (Å)	20.0095(6)
b (Å)	7.8099(3)
c (Å)	13.6096(9)
α (°)	90
β (°)	103.565(4)
γ (°)	90
V (Å^3)	2067.49(15)
Z; D_{calc},(g/cm^3)	4; 1.532
μ (MoKα) (mm^{-1})	0.236
Crystal size (mm)	0.32 × 0.29 × 0.24
Radiation	MoKα (λ = 0.71073 Å)
Temp (K)	293(2)
θ Limits (°)	2.1–26.0
Index ranges	$-24 \leq h \geq 24$; $-9 \leq k \geq 9$; $-16 \leq l \geq 16$
Reflections collected	28 846
Reflns. used in refinement	4068 [$I > 2\sigma(I)$]
No. of refined parameters	307
R/R_w values	0.0549/0.1568
GOF	0.92
Final shift	0.001
$(\Delta\rho)_{min}$, $(\Delta\rho)_{max}$ (e Å^{-3})	−0.368, 0.412

Table 3. Selected bond distances (A), bond angles (°), and torsion angles (°) of compound (**20**)

C11–C11	1.743(3)	N3–C16	1.285(4)
O1–N6	1.214(4)	N4–C15	1.295(5)
O2–N6	1.231(4)	N6–C21	1.470(4)
O3–N5	1.207(4)	N2–C7	1.371(4)
O4–N5	1.222(4)	N3–N4	1.410(4)
O5–C15	1.359(4)	N2–C7	1.371(4)
O5–C16	1.353(3)	C14–C15	1.485(5)
N1–C1	1.384(4)	C16–C17	1.461(4)
N1–C2	1.387(4)	C21–C22	1.373(4)
N1–C14	1.456(4)	N5–C19	1.477(4)
N2–C1	1.3048(4)	C1–C8	1.471(4)
O1–N6–O2	124.4(3)	O3–N5–O4	124.5(3)
O1–N6–C21	118.1(3)	O3–N5–C19	117.9(3)
C1–N1–C14	128.4(3)	N4–C15–C14	130.0(3)
N2–C1–N1	111.8(3)	N1–C14–C15	111.0(2)
N2–C1–C8	123.1(3)	O5–C16–C17	117.4(2)
C1–N1–C14–C15	105.5(3)	N1–C1–C8–C9	135.0(3)
N4–C15–C14–N1	−107.1(4)	O1–N6–C21–C20	−173.9(3)
C22–C17–C16–N3	178.0(3)	C18–C19–N5–O4	172.9(3)

*X-ray analysis of compound **20***

The intensity reflections were measured by using a STOE IPDS 2 diffractometer using graphite monochromatized MoKα radiation [λ = 0.71073 Å] and $\omega/2\theta$ scan mode to $2\theta = 52°$. 4068 reflections were used for refinement on F^2. An integration absorption correction was applied to the data. The structure was solved by direct methods [38] and subjected to full-matrix refinement [39]. The refinement was made with anisotropic displacement factors for all non-hydrogen atoms. All hydrogen atoms were calculated to their idealized positions and refined as riding atoms. Crystal data and a summary of intensity data collection and structure refinement are presented in Table 2; the selected bond lengths, bond angles, and torsion angles are given in Table 3.

The authors have declared no conflict of interest.

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