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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Comparison between antioxidant activity of 2,5-disubstituted 1,3,4-oxadiazoles containing heteroaromatic ring and aromatic ring at 2nd position

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Abstract A series of 4-[5-(substitutedphenyl)-1,3,4-oxadiazol-2-yl]-pyridine) and 2-[5-substitutedphenyl)-1,3,4-oxadiazol-2-yl]-benzenamine derivatives were synthesized from substituted esters and hydrazine hydrate in the presence of ethanol to give isonicotinic acid hydrazide and 2-aminobenzohydrazide followed by reaction with phosphorus oxychloride and various aromatic acids. All the compounds were tested for their in vitro antioxidant activity by 1,1-diphenyl-2-picryl hydrazyl (DPPH) method. Compounds containing aromatic group at 2nd position showed significant activity as compared to standard (ascorbic acid) which concludes that the presence of aromatic group increases the free radical scavenging activity.

Keywords 1,3,4-Oxadiazoles · Heteroaromatic ring · Antioxidant activity

Introduction

A diversity of useful biological effects is possessed by heterocyclic compounds containing oxadiazole nucleus (Franski, 2005). In particular, compounds bearing 1,3,4-oxadiazole nucleus are known to exhibit unique antiedema and anti-inflammatory activity (Omar *et al*., 1996; Narayana *et al*., 2005; Kamble and Sudha, 2006; Hussain and Ahuja, 2009). Differently substituted oxadiazole moiety has been found to have other interesting activities such as analgesic, antimicrobial (Ingole *et al*., 2007; Karthikeyan *et al*., 2008), antitubercular (Somani and Shirodkar, 2008), anticonvulsant (Zarghi *et al*., 2005), and antitumour activity (Holla *et al*., 2005). Not only this, 1,3,4-oxadiazole nucleus is also emerging as antioxidant moiety (Padmavathi *et al*., 2009, 2010; Rajasekaran *et al*., 2010). It is a well established that free radicals are responsible for inflammation process. Prostaglandins are important mediators of inflammation and free radicals are involved in the biosynthesis of prostaglandins. Compounds with antioxidant activity are supposed to have good anti-inflammatory activity. In view of above mentioned findings, the purpose of present study was to synthesize some novel analogues of 2,5-disubstituted 1,3,4-oxadiazole expecting their enhanced antioxidant activity.

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Experimental

Synthetic method

Synthesis of isonicotinic acid hydrazide

Isonicotinic acid ester (0.01 mol) and hydrazine hydrate (0.02 mol) were mixed gently and refluxed for 5 h with 30 ml of ethanol. Excess of solvent was distilled off. The reaction mixture was cooled to 4–5°C and separated solid crystals were filtered, washed with cold water, dried and recrystallized from ethanol (Furniss *et al*., 1989). Yield 76.6%, melting range 175–178°C.

Synthesis of 2-aminobenzhydrazide

A mixture of 2-aminomethyl benzoate (0.01 mol), excess of hydrazine hydrate (20 ml, 0.04 mol) and absolute alcohol (50 ml) was refluxed for 5 h. Excess of solvent was

distilled off. The reaction mixture was cooled to 4–5°C and separated solid crystals were filtered, washed with cold water, dried and recrystallized from ethanol. Yield 80.45%, Melting range 122–124°C.

*Syntheses of 4-[5-(4-aryl)-[1,3,4-oxadiazol-2-yl]-pyridine (**1–4**)*

1,3,4-Oxadiazoles can be synthesized by reacting hydrazides with various carboxylic acids (Reddy and Reddy, 1988; Pachhamia and Parikh, 1989). A mixture of 4-isonicotinic acid hydrazide (0.01 mol) and appropriate aromatic acid (0.01 mol) were dissolved in phosphorus oxychloride (15 ml) and refluxed over a water bath for 5 h. The progress of reaction was monitored by TLC using ethylacetate: acetone (9:1) as eluent. The reaction mixture was cooled and poured on to a crushed ice dropwise with continuous stirring. The separated solid mass was neutralized with ammonia solution. The mixture was left overnight in refrigerator. The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from absolute ethanol (Nagalakshmi, 2008).

*Syntheses of 2-aryl-5-(2-aminophenyl)-1,3,4-oxadiazole (**5–9**)*

A mixture of 2-aminobenzhydrazide (0.01 mol) and appropriate aromatic acid was dissolved in phosphorus oxychloride (15 ml) refluxed over a water bath for 3–5 h. The progress of reaction was monitored by TLC using ethylacetate: acetone (9:1) as eluent. The reaction mixture was cooled and poured on to a crushed ice drop wise with continuous stirring. The separated solid mass was neutralized with ammonia solution. The mixture was left overnight in refrigerator. The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from absolute ethanol. The physicochemical parameters of the synthesized compounds are given in Table 1 (Scheme 1).

Melting points of the synthesized compounds were taken in open-end capillary tubes and are uncorrected. Purity of compounds was checked by TLC on silica gel plates and spots were visualized by exposure to iodine vapours. IR spectra were recorded on Perkin Elmer Spectrum RX1 FTIR spectrophotometers. NMR spectra were recorded on Bruker DRX 300 spectrophotometer. Mass spectra were recorded on JEOL-Accu TOF JMS-T100LC spectrometer at Central Drug Research Institute, Lucknow. The spectral data of the synthesized compounds are summarized below.

*4-[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-pyridine (**1**)*

$C_{13}H_8N_3OCl$, yield: 85.6%, Mp: 110–117°C. TLC ethylacetate: acetone (9:1) R_f: 0.71. IR cm^{-1} (KBr): υ 3095 (aromatic C–H), 1598, 1481(aromatic C=C), 1722.7 (C=N), 1227 (asymmetric C–O–C), 1087 (symmetric C–O–C), 1050 (Ar-Cl), 738.4 (C–H Para subst); ^{1}HNMR (DMSO-d_6, δ ppm): 7.38–8.59 (m, 4H, C–H Pyr), 7.30–7.32 (m, 4H); MS (FAB) m/z: 257 (M^+), 258 ($M^+ + 1$, 100%).

*4-[5-(4-Aminophenyl)-1,3,4-oxadiazol-2-yl]-pyridine (**2**)*

$C_{13}H_{10}N_4O$, yield: 82.5%, Mp: 100–105°C. TLC ethylacetate: acetone (9:1) R_f: 0.72. IR cm^{-1} (KBr): υ 3443 (stretch NH_2), 1600 (bend NH_2), 3100 (aromatic C–H), 1654, 1405 (aromatic C=C), 1654 (C=N), 1256 (asymmetric C–O–C), 1182 (symmetric C–O–C), 846 (C–H Para subst); ^{1}HNMR (DMSO-d_6, δ ppm): 7.41–8.59 (m, 4H, C–H Pyr), 7.30–7.35 (m, 4H Arom.), 4.13 (s, NH_2); MS (FAB) m/z: 238 (M^+), 239 ($M^+ + 1$, 100%).

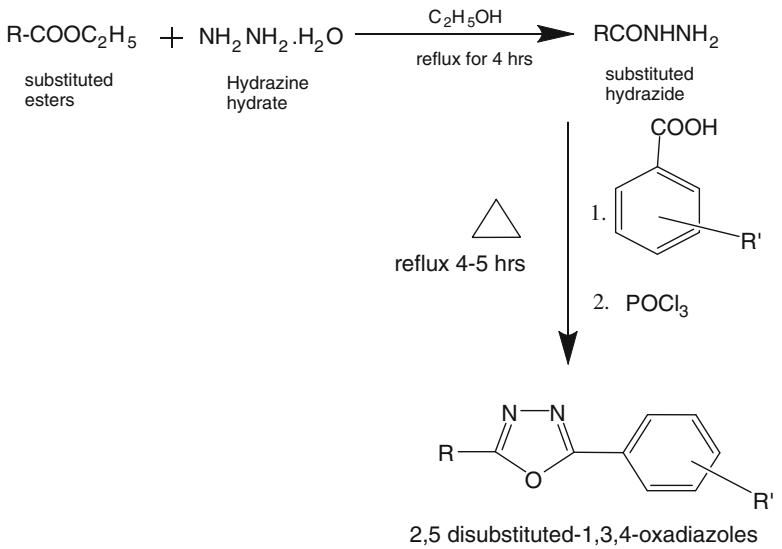
*4-[5-(4-Nitrophenyl)-1,3,4-oxadiazole-2-yl]-pyridine (**3**)*

$C_{13}H_8N_4O_3$, yield: 60.2%, Mp: 160–166°C. TLC ethylacetate: acetone (9:1) R_f: 0.48. IR cm^{-1} (KBr): υ 3091 (aromatic C–H), 1606, 1485 (aromatic C=C), 1664 (C=N), 1220 (asymmetric C–O–C), 1066 (symmetric C–O–C), 858

Table 1 Physical characterization of synthesized compounds (**1–9**)

S. no.	Compound code	R′	Molecular formula	Molecular weight	Reaction time (h)	% Yield	Melting range (°C)	R_f value
1	**1**	4-Cl	$C_{13}H_8N_3OCl$	257	4	85.6	110–115	0.71
2	**2**	4-NH_2	$C_{13}H_{10}N_4O$	238	4	82	100–105	0.72
3	**3**	4-NO_2	$C_{13}H_8N_4O_3$	268	5	60	160–165	0.48
4	**4**	3-NO_2	$C_{13}H_8N_4O_3$	268	4	79	126–130	0.63
5	**5**	4-Cl	$C_{14}H_{10}N_3OCl$	271	3	80	152–157	0.60
6	**6**	3-NO_2	$C_{14}H_{10}N_4O_3$	282	4	80	170–175	0.48
7	**7**	2-OH-4-NH_2	$C_{14}H_{12}N_4O_2$	268	5	75	166–169	0.71
8	**8**	2-NH_2	$C_{12}H_{12}N_4O$	258	2	88	155–160	0.66
9.	**9**	2-OH-3-CH_3	$C_{15}H_{13}N_3O_2$	267	4	84	141–145	0.56

Scheme 1 Synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives



R=C_6H_5, C_6H_4N; R'= 4-ClC_6H_4, 4-$NH_2C_6H_4$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-OH-3-$CH_3C_6H_3$, 4-NH_2-2-OHC_6H_3

(C–H Para subst); 1549 (asymm. Ar-NO_2), 1341(symm. Ar-NO_2); ^{1}HNMR (DMSO-d_6, δ ppm): 7.40–8.62 (m, 4H, C–H Pyr), 7.28–7.35 (m, 4H Arom.); MS (FAB) m/z: 268 (M^+), 269 ($M^+ + 1$, 100%).

*4-[5-(3-Nitrophenyl)-1,3,4-oxadiazol-2-yl]-pyridine (**4**)*

$C_{13}H_8N_4O_3$, yield: 79.8%, Mp: 125–130°C. TLC ethyl-acetate: acetone (9:1) R_f: 0.63. IR cm^{-1} (KBr): υ 3074 (aromatic C–H), 1596, 1475 (aromatic C=C), 1716 (C=N), 1225 (asymmetric C–O–C), 1062 (symmetric C–O–C), 725, 827 (C–H meta subst); 1528 (asymm. Ar-NO_2), 1344 (symm. Ar-NO_2); ^{1}HNMR (DMSO-d_6, δ ppm): 7.40–8.62 (m, 4H, C–H Pyr), 7.35–8.19 (m, 4H Arom.); MS (FAB) m/z: 268 (M^+), 269 ($M^+ + 1$, 100%).

*2-[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-benzenamine (**5**)*

$C_{14}H_{10}N_3OCl$, yield: 80.3%, Mp: 152–157°C. TLC ethyl-acetate: acetone (9:1) R_f: 0.60. IR cm^{-1} (KBr): υ 3413 (stretch NH_2), 1560 (bend NH_2), 3074 (aromatic C–H), 1596, 1475 (aromatic C=C), 1614 (C=N), 1217 (asymmetric C–O–C), 1087 (symmetric C–O–C), 1050 (Ar-Cl), 769, 827 (C–H ortho and para subst); ^{1}HNMR (DMSO-d_6, δ ppm): 6.52–7.01 (m, 4H, C–H Arom.), 7.22–7.34 (m, 4H Arom.), 4.21 (s, NH_2); MS (FAB) m/z: 281 (M^+), 282 ($M^+ + 1$, 100%).

*2-[5-(3-Nitrophenyl)-1,3,4-oxadiazol-2-yl]-benzenamine (**6**)*

$C_{14}H_{10}N_4O_3$, yield: 80.6%, Mp: 170–175°C. TLC ethyl-acetate: acetone (9:1) R_f: 0.48. IR cm^{-1} (KBr): υ3440 (stretch NH_2), 1551 (bend NH_2), 3167 (aromatic C–H), 1619, 1402 (aromatic C=C), 1681 (C=N), 1258 (asymmetric C–O–C), 1086 (symmetric C–O–C), 746, 815 (C–H ortho and meta subst); 1531 (asymm. Ar-NO_2), 1350 (symm. Ar-NO_2); ^{1}HNMR (DMSO-d_6, δ ppm): 6.52–7.01 (m, 4H, C–H Arom.), 7.52–8.19 (m, 4H Arom.), 4.20 (s, NH_2); MS (FAB) m/z: 282 (M^+), 283 ($M^+ + 1$, 100%).

*2-[5-(4-Amino-2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]-benzenamine (**7**)*

$C_{14}H_{12}N_4O_2$, yield: 75.1%, Mp: 163–169°C. TLC ethyl-acetate: acetone (9:1) R_f: 0.71. IR cm^{-1} (KBr): υ 3695 (Aromatic OH), 3190 (stretch NH_2), 1565 (bend NH_2), 3167 (aromatic C–H), 1596, 1477 (aromatic C=C), 1670 (C=N), 1256 (asymmetric C–O–C), 1093 (symmetric C–O–C), 768, 831 (C–H ortho and para subst); ^{1}HNMR (DMSO-d_6, δ ppm): 4.22 (s, NH_2), 6.51–7.01 (m, 4H, C–H Arom.), 6.75–7.10 (m, 4H Arom.), 5.92 (d, OH), 4.03 (d, NH_2); MS (FAB) m/z: 268 (M^+), 269 ($M^+ + 1$, 100%).

*2-[5-(2-Aminophenyl-(1,3,4-oxadiazol-2-yl]-benzenamine (**8**)*

$C_{12}H_{12}N_4O$, yield: 88.3%, Mp: 155–160°C. TLC ethyl-acetate: acetone (9:1) R_f: 0.66. IR cm^{-1} (KBr): υ 3213 (stretch NH_2), 1562 (bend NH_2), 3020 (aromatic C–H), 1597, 1490 (aromatic C=C), 1674 (C=N), 1216 (asymmetric C–O–C), 1094 (symmetric C–O–C), 1050 (Ar-Cl), 827 (C–H ortho subst); ^{1}HNMR (DMSO-d_6, δ ppm): 6.49–7.01 (m, 4H, C–H Arom.), 6.51–7.01 (m, 4H Arom.), 4.28 (d, NH_2); MS (FAB) m/z: 258 (M^+), 260 ($M^+ + 2$, 100%).

*2-(5-(2-Hydroxy-3-methylphenyl)-1,3,4-oxadiazol-2-yl]-benzenamine (**9**)*

$C_{15}H_{13}N_3O_2$, yield: 84.4%, Mp: 141–145°C. TLC ethyl-acetate: acetone (9:1) R_f: 0.56. IR cm^{-1} (KBr): υ 3506 (Aromatic OH), 3418 (stretch NH_2), 1601 (bend NH_2), 3157 (aromatic C–H), 1597, 1490 (aromatic C=C), 1674 (C=N), 1254 (asymmetric C–O–C), 1087 (symmetric C–O–C), 690, 770, 837 (C–H ortho and meta subst); ^{1}HNMR (DMSO-d_6, δ ppm): 6.49–7.01 (m, 4H, C–H Arom.), 6.79–7.01 (m, 4H Arom.), 4.01 (s, NH_2), 1.30 (d, CH_3), 5.82 (s, OH Phenolic); MS (FAB) m/z: 267 (M^+), 268 ($M^+ + 1$, 100%).

Antioxidant activity

Synthesized compounds were subjected to free radical scavenging activity by DPPH assay method. This assay has often been used to estimate the antiradical activity of antioxidants. The free radical scavenging capabilities of the compounds were measured in terms of hydrogen donating or free radical scavenging ability after adding methanolic solution of DPPH (2,2-Diphenyl-1-Picrylhydrazyl) to the sample solution of different concentrations. The test compounds react with DPPH and convert it to 1,1-diphenyl-2-picrylhydrazine. The degree of decolorizing indicates the potentialities of the antioxidant drug. Ascorbic acid was used as standard.

Procedure

Free radical scavenging activity of the test compounds was studied by the diphenyl picryl hydrazyl (DPPH) assay method. Drug stock solution (1 mg/ml) was diluted to final concentrations of 2, 4, 6, 8 and 10 µg/ml in methanol. Minimum amount of dimethyl sulphoxide was used to solubilize the samples (George *et al*., 2008). Methanolic DPPH solution (1 ml, 0.3 mmol) was added to 3.0 ml of drug solutions of different concentrations and allowed to react at room temperature. After 30 min the absorbance values were measured at 517 nm in Schimadzu 1700 UV–Visible Spectrophotometer and converted into the percentage antioxidant activity. Each experiment was performed in triplicate. Scavenging activity was calculated by following formula (Chandrashekar and Karvekar, 2008).

$$\% \text{ Reduction} = \frac{\text{Control absorbance} - \text{Test absorbance}}{\text{Control absorbance}} \times 100$$

Ascorbic acid was used as standard. Methanolic DPPH solution (1 ml, 0.3 mM) was used as control. The inhibitory concentration (IC_{50}) value, representing the concentration required to exhibit 50% antioxidant activity

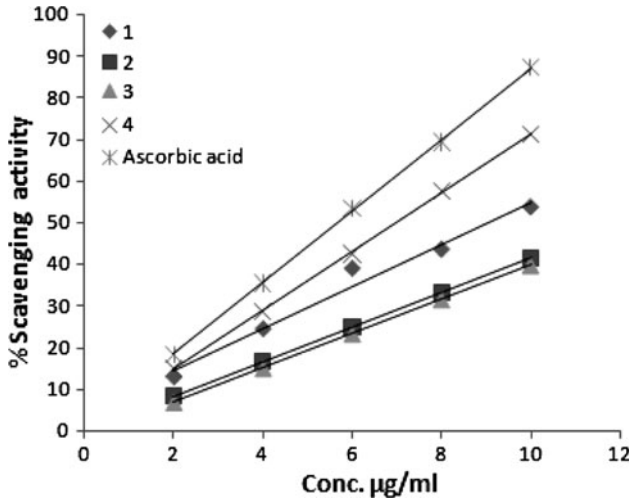


Fig. 1 Antioxidant activity compounds **1–4**

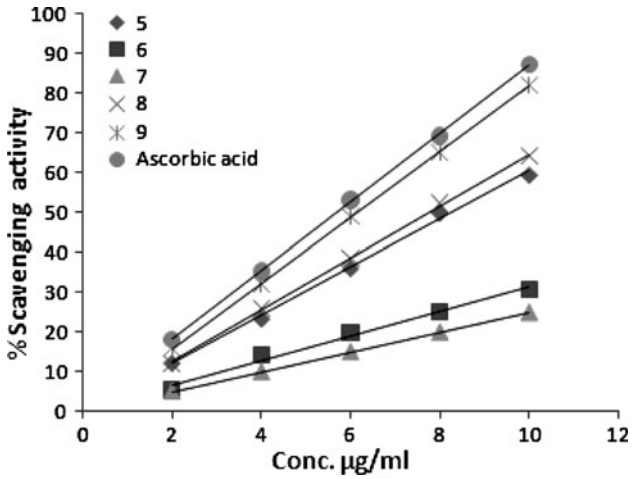


Fig. 2 Antioxidant activity of compounds **5–9**

(Figs. 1, 2). The IC_{50} values were calculated by linear regression of plots where the abscissa represented the concentration of the compounds (µg/ml) and the ordinate, the average percentage of antioxidant activity. Results in the form of percent inhibition are summarized in Table 2.

Results and discussion

The free radical scavenging activity was carried out for the synthesized compounds 4-[5-(substitutedphenyl)-1,3,4-oxadiazol-2-yl]-pyridine) (**1–4**) and 2-[5-substitutedphenyl)-1,3,4-oxadiazol-2-yl]-benzenamine (**5–9**).

DPPH is a stable free radical that can accept electron or hydrogen radical to become a diamagnetic molecule. Due to its odd electron, the methanolic solution of DPPH shows a strong absorption at 517 nm. DPPH radical reacts with suitable reducing agent, then electrons become paired off,

Table 2 Quantitative screening of antioxidant activity by DPPH assay method ($n = 3$)

S.no	Compound	Absorbance	Absorbance at 517 nm					IC_{50} μg/ml
			2 μg/ml	4 μg/ml	6 μg/ml	8 μg/ml	10 μg/ml	
1	Control	($Abs_{control}$)	0.9426 ± 0.08	0.9426 ± 0.08	0.9426 ± 0.09	0.9426 ± 0.09	0.9426 ± 0.08	
2	**1**	Abs_{sample}	0.8223 ± 0.71	0.7127	0.6127	0.5316	0.4353	9.01
		(AA%)	12.76	24.38	38.99	43.60	53.81	
3	**2**	Abs_{sample}	0.8646 ± 0.07	0.7866 ± 0.07	0.7086 ± 0.07	0.6306 ± 0.06	0.5526 ± 0.06	12.08
		(AA%)	8.27	16.54	24.82	33.09	41.37	
4	**3**	Abs_{sample}	0.8798 ± 0.09	0.8018 ± 0.08	0.7238 ± 0.08	0.6458 ± 0.07	0.5678 ± 0.07	12.47
		(AA %)	6.66	14.93	23.21	31.48	39.76	
5	**4**	Abs_{sample}	0.8012 ± 0.08	0.6719 ± 0.07	0.5423 ± 0.06	0.3991 ± 0.04	0.2718 ± 0.03	6.99
		(AA%)	15.00	28.71	42.46	57.659	71.16	
6	**5**	Abs_{sample}	0.8226 ± 0.09	0.7213 ± 0.08	0.6016 ± 0.07	0.4914 ± 0.04	0.3817 ± 0.04	8.26
		(AA %)	12.30	23.47	36.17	49.98	59.50	
7	**6**	Abs_{sample}	0.8906 ± 0.09	0.8086 ± 0.09	0.7566 ± 0.08	0.7046 ± 0.07	0.6526 ± 0.07	16.04
		(AA%)	5.51	14.21	19.73	25.24	30.76	
8	**7**	Abs_{sample}	0.8956 ± 0.09	0.8486 ± 0.09	0.8016 ± 0.09	0.7546 ± 0.08	0.7076 ± 0.07	20.05
		(AA%)	4.98	9.97	14.95	19.94	24.93	
9	**8**	Abs_{sample}	0.8228 ± 0.09	0.6991 ± 0.07	0.5791 ± 0.06	0.4593 ± 0.05	0.3397 ± 0.04	7.76
		(AA%)	12.07	25.83	38.56	52.12	63.96	
10	**9**	Abs_{sample}	0.7924 ± 0.08	0.6420 ± 0.07	0.4825 ± 0.05	0.3310 ± 0.04	0.1706 ± 0.02	6.00
		(AA%)	15.93	31.89	48.81	64.88	81.90	
11	Std.	Abs_{sample}	0.7723 ± 0.08	0.6113 ± 0.06	0.4424 ± 0.05	0.2912 ± 0.03	0.1217 ± 0.01	5.68
		(AA%)	18.24	35.32	53.24	69.28	87.26	

and the solution loses colour stoichiometrically with the number of electrons taken up. Such reactivity has been widely used to test the ability of compound to act as free radical scavengers. Reduction of the DPPH radicals can be observed by the decrease in absorbance at 517 nm. The IC_{50} are the 50% inhibition concentration and were calculated from regression lines.

In the series of synthesized compounds, Compound **9** was found to possess maximum antioxidant activity (IC_{50} 6.00) against the standard drug ascorbic acid (IC_{50} 5.68). However, 4-(5-methyl-[1,3,4] oxadiazole-2-yl)-pyridine compound with substituted benzene and 2-(4-substituted phenyl)-5-(2-aminophenyl)-1,3,4-oxadiazole (**4**), (**5**) and (**8**) showed good free radical scavenging activity (IC_{50} 6.99, 8.26, 7.76). Moderate activity was shown by (3-nitrophenyl)-5-(2-aminophenyl)1,3,4-oxadiazole (**1**), 4-[5-(4-nitrophenyl)-[1,3,4-oxadiazol-2-yl]-pyridine) (**2**) (IC_{50} 9.01 and 12.08, respectively), whereas phenyl substituted compound 2-(4-amino-2-hdroxyphenyl)-5-(2-aminophenyl)-1,3,4-oxadiazole (**7**) showed minimum antioxidant activity (IC_{50} 20.05). To conclude, aromatic ring at position 2 of oxadiazole possesses better activity as compared to heteroaromatic group. However, heteroaromatic ring gives considerable activity with meta nitro group.

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