IJPP

International Journal of Food Safety and Public Health
Vol. 13 (1), pp. 79-84, March, 2026
ISSN: 2756-3693

Full Length Article

Formulation Of Novel 1,3,4-Oxadiazole Entities And Examination Of Their Antioxidant Efficiency

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Accepted 15th March 2026

Abstract

The 1,3,4-oxadiazole nucleus is a privileged five-membered heterocyclic scaffold with sustained relevance in medicinal chemistry because of its bioisosteric character and capacity to stabilise radical intermediates. The present work was framed to formulate a novel series of 2,5-disubstituted 1,3,4-oxadiazole entities (OX-1 to OX-8) bearing electron-donating and electron-withdrawing substituents, and to assess their antioxidant competence. Aromatic acid hydrazides were synthesised through Fischer esterification, hydrazinolysis, and subsequent cyclodehydration with phosphorus oxychloride ($POCl_3$) at reflux. Structures were verified through FT-IR, ^1H NMR, ^{13}C NMR, and LC-MS. Antioxidant potential was examined through DPPH, ABTS, hydrogen peroxide (H_2O_2), nitric oxide (NO), and ferric reducing antioxidant power (FRAP) assays, with ascorbic acid as reference. Results indicated that OX-6, carrying a 4-hydroxy-3-methoxyphenyl group, exhibited the strongest efficiency (DPPH IC_{50} = 14.82 µg/mL; ABTS IC_{50} = 11.46 µg/mL; FRAP = 1187 µM Fe^{2+}/g). Hypothesis-testing by one-way ANOVA confirmed substituent-dependent differences ($p < 0.05$). Electron-donating hydroxyl and methoxy groups markedly enhanced radical scavenging, while nitro and halogen groups reduced activity. The study concludes that properly substituted 1,3,4-oxadiazoles are valuable candidates for antioxidant drug development.

Keywords: *1,3,4-Oxadiazole; Cyclodehydration; DPPH scavenging; ABTS assay; Structure–activity relationship*

1. Introduction

Oxidative stress arises when the cellular generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) exceeds the quenching capacity of endogenous antioxidant defences, producing molecular damage to lipids, proteins, and DNA. This imbalance is mechanistically implicated in a spectrum of chronic pathologies including diabetes mellitus, cancer, hypertension, rheumatoid arthritis, asthma, and neurodegenerative disorders (Martemucci et al., 2022). Excess ROS, including superoxide anion, hydroxyl radical and hydrogen peroxide, trigger lipid peroxidation, protein carbonylation, telomere shortening, and mitochondrial dysfunction, each of which accelerates cellular senescence and age-related disease onset (Liu et al., 2024). Consequently, the design of small synthetic molecules capable of intercepting radicals in a catalytic and renewable manner remains a persistent target of medicinal chemistry (Forman & Zhang, 2021). Among the nitrogen- and oxygen-containing heterocyclic scaffolds, the 1,3,4-oxadiazole ring has emerged as a privileged pharmacophore. Structurally, replacement of two –CH= groups of furan by two –N= atoms delivers a planar, aromatic, electron-deficient ring that is metabolically stable, hydrolytically resistant, and a recognised bioisostere for ester, amide, and carbamate linkages (Głowacka et al., 2022). This scaffold underlies several clinical agents such as Raltegravir, Zibotentan, and Nesapidil, and has been documented to display antibacterial, antiviral, anticancer, anti-inflammatory, analgesic, antihypertensive and antioxidant profiles (Desai et al., 2014). The radical-scavenging competence of oxadiazole derivatives is attributed to extensive π-electron delocalisation, which resonance-stabilises the phenoxyl, aminyl or thiyl radicals generated after hydrogen-atom transfer to the ROS (Chidan Kumar et al., 2017).

Substituent engineering at the 2- and 5-positions modulates electron density across the ring and therefore tunes antioxidant output. Prior studies have demonstrated that electron-donating groups (–OH, –OCH_3, –NH_2) substantially enhance DPPH and ABTS quenching, whereas electron-withdrawing substituents such as –NO_2 and –Cl diminish activity (Hkiri et al., 2025; Desai et al., 2014). The 4-chlorophenyl group, however, has shown selective enhancement when combined with flurbiprofen-derived scaffolds, reflecting the complexity of structure–activity relationships (SAR) (Hkiri et al., 2023). Building on these insights, and considering the need for scaffolds with multi-assay consistency, the present investigation was designed to formulate eight novel 2,5-disubstituted 1,3,4-oxadiazole entities and to quantify their antioxidant efficiency across DPPH, ABTS, H_2O_2, NO, and FRAP assays. The work thereby adds empirical evidence to the ongoing SAR discourse on oxadiazole-based antioxidants and supports their

further exploration as lead molecules for oxidative-stress-linked disease management.

2. Literature Review

The antioxidant chemistry of 1,3,4-oxadiazoles has received continuous attention over the past decade, with several well-documented reports. Ahsan et al. (2012) prepared N-substituted phenyl-5-methyl-6-(5-(4-substituted phenyl)-1,3,4-oxadiazol-2-yl)thieno[2,3-d]pyrimidin-4-amine derivatives and showed that compounds bearing electron-donating groups on either aryl ring exhibited pronounced DPPH, H_2O_2 and NO scavenging potential, whereas nitro substitution reduced the activity. Khan et al. (2012) synthesised eighteen 1,3,4-oxadiazole-2-thiol derivatives through hydrazide–CS_2 cyclisation in ethanolic KOH and reported that derivatives bearing 2-F/4-Cl and 2-OCH_3 groups displayed four-fold stronger DPPH scavenging than propyl gallate, validating halogen- and methoxy-driven activity.

Desai et al. (2014) showed that cyclodehydration of diacylhydrazides with $POCl_3$ affords 2,5-disubstituted oxadiazoles in 55–75% yield; their QSAR-coupled antibacterial screening also emphasised that electronic parameters govern biological response. Bajić et al. (2017) examined eight phenolic-acid-derived 1,3,4-oxadiazoles (7a–h) alongside their diacylhydrazine precursors and demonstrated that the oxadiazole ring participates in resonance stabilisation of phenoxyl radicals, giving higher DPPH and ABTS scavenging than the parent hydrazides. Chidan Kumar et al. (2017) synthesised thirteen 5-substituted-2-(3,4,5-trihydroxyphenyl)-1,3,4-oxadiazoles and found IC_{50} values as low as 16 µM in DPPH and ABTS assays, linking activity to the availability of phenolic –OH groups and ring conjugation. Alam et al. (2022) systematically linked 2,4-di-tert-butylphenol to the oxadiazole scaffold and obtained a FRAP value of 4612.78 µM for the lead compound, significantly surpassing ascorbic acid (848.9 µM) and BHT (488.3 µM); their DFT analysis localised HOMO electron density on the oxadiazole ring, confirming it as the radical-reactive site.

Głowacka et al. (2022) comprehensively reviewed synthetic approaches to 1,3,4-oxadiazoles, emphasising that $POCl_3$-mediated cyclodehydration remains the most reliable one-pot route because of its broad substrate compatibility and reproducible yields. Jamil et al. (2023) prepared 2,5-disubstituted flurbiprofen-oxadiazole hybrids (Ox-6a–f) and reported that the 4-chlorophenyl-substituted lead (Ox-6f) produced 80.23% DPPH inhibition at 100 µg/mL with IC_{50} = 25.35 µg/mL, accompanied by 83.88% NO scavenging and strong iron-chelation. Hkiri et al. (2025) very recently generated 1,3,4-oxadiazolyl sulfide derivatives and showed that the pyrazolone-linked analogue (4h) gave SC_{50} = 12.34 µM (DPPH) and 9.88 µM (ABTS), surpassing ascorbic acid (SC_{50} = 23.92 µM). Ibrahim et al. (2023) further reported azetidin-2-one-fused 1,3,4-oxadiazoles with notable DPPH scavenging (IC_{50} in the 30–60 µg/mL range), emphasising hybrid scaffolds as a growing direction. Shen et al. (2023) designed flavone–oxadiazole conjugates that suppressed both ROS and NO in LPS-stimulated BV2 microglia, extending the antioxidant relevance of oxadiazoles to neurodegenerative disease models. Taken together, these works confirm that electronic substituent tuning, phenolic –OH/–OCH_3 presence, and resonance-stabilised radicals are the three principal levers controlling oxadiazole antioxidant efficiency.

3. Objectives

1. To formulate a novel series of eight 2,5-disubstituted 1,3,4-oxadiazole entities (OX-1 to OX-8) through a four-step synthesis and to confirm structural identity spectroscopically.
2. To evaluate the antioxidant efficiency of the synthesised entities through DPPH, ABTS, H_2O_2, NO, and FRAP assays, and to establish the substituent–activity relationship.

4. Methodology

The study followed an experimental in-vitro design. Research-grade reagents, including substituted benzoic acids, hydrazine hydrate (99%), phosphorus oxychloride ($POCl_3$), potassium hydroxide, DPPH, ABTS diammonium salt, potassium persulfate, sodium nitroprusside, Griess reagent, TPTZ and ferric chloride, were procured from Sigma-Aldrich and Merck (India). Solvents were of analytical grade and distilled before use. Thin-layer chromatography (TLC) on silica gel 60 F_{254} plates monitored reaction progress. The sample consisted of eight newly prepared compounds, designated OX-1 to OX-8, bearing para-substituents –H, –CH_3, –OCH_3, –OH, –Cl, –Br, 4-OH-3-OCH_3, and –NO_2, respectively. Synthesis involved four steps. First, substituted benzoic acids were esterified with methanol in concentrated H_2SO_4 under reflux (Fischer esterification). Second, the esters were converted to their hydrazides by refluxing with hydrazine hydrate (80%) in ethanol for 6 h. Third, equimolar amounts of two different acid hydrazides were condensed in $POCl_3$ (5 mL per mmol) under reflux for 6–7 h; on cooling, the mixture was poured onto crushed ice, neutralised with 20% $NaHCO_3$, filtered, and recrystallised from methanol to yield compounds OX-1 to OX-8 (54–74%). Structural confirmation employed FT-IR (PerkinElmer Spectrum-2), ^1H and ^{13}C NMR (Bruker 400 MHz in DMSO-d_6 with TMS), and LC-MS (Shimadzu LCMS-2020).

Antioxidant screening used five complementary assays at concentrations of 6.25, 12.5, 25, 50, and 100 µg/mL, each in triplicate. DPPH scavenging was

International Journal of Food Safety and Public Health
Vol. 13 (1), pp. 79-84, March, 2026
ISSN: 2756-3693

measured at 517 nm after 30 min of dark incubation; ABTS•+ was generated with 2.45 mM potassium persulfate and measured at 734 nm; H_2O_2 scavenging was quantified at 230 nm; NO scavenging used sodium nitroprusside/Griess reagent at 546 nm; FRAP was recorded at 593 nm after reduction of Fe^{3+}–TPTZ to Fe^{2+}–TPTZ. Ascorbic acid served as reference in all assays. IC_{50} values were computed through linear regression. Data were expressed as mean ± SD, and statistical difference was evaluated through one-way ANOVA with Tukey's post-hoc test at $p < 0.05$ using SPSS v26.

5. Results

Table 1. Physicochemical data of synthesised 1,3,4-oxadiazole entities (OX-1 to OX-8)

Compound	R substituent	M.F.	M.W. (g/mol)	Yield (%)	M.P. (°C)	Rf
OX-1	–H	$C_{14}H_{10}N_2O$	222.24	62	138–140	0.62
OX-2	–CH_3	$C_{15}H_{12}N_2O$	236.27	68	144–146	0.58
OX-3	–OCH_3	$C_{15}H_{12}N_2O_2$	252.27	71	152–154	0.54
OX-4	–OH	$C_{14}H_{10}N_2O_2$	238.24	65	176–178	0.48
OX-5	–Cl	$C_{14}H_9ClN_2O$	256.69	69	168–170	0.60
OX-6	4-OH-3-OCH_3	$C_{15}H_{12}N_2O_3$	268.27	74	184–186	0.44
OX-7	–Br	$C_{14}H_9BrN_2O$	301.14	58	172–174	0.59
OX-8	–NO_2	$C_{14}H_9N_3O_3$	267.24	54	196–198	0.51

Table 1 shows that the yields of OX-1 to OX-8 ranged from 54% to 74%, with OX-6 (4-hydroxy-3-methoxyphenyl) displaying the highest yield (74%) and OX-8 (nitro-substituted) the lowest (54%). Melting points rose from 138–140 °C (OX-1) to 196–198 °C (OX-8), reflecting the influence of substituent polarity and intermolecular hydrogen bonding. Rf values (0.44–0.62) confirmed purity and distinct chromatographic behaviour. The data corroborate that cyclodehydration with $POCl_3$ is operationally efficient across both electron-donating and electron-withdrawing substrate

Table 2. DPPH radical scavenging activity (% inhibition) at different concentrations

Compound	25 µg/mL	50 µg/mL	100 µg/mL	IC_{50} (µg/mL)
OX-1	28.41 ± 0.6	46.20 ± 0.9	64.32 ± 1.1	56.18
OX-2	34.62 ± 0.7	52.40 ± 0.8	71.22 ± 0.9	46.77
OX-3	41.25 ± 0.5	60.82 ± 0.7	78.50 ± 0.6	35.94
OX-4	44.91 ± 0.8	65.31 ± 1.0	81.67 ± 0.8	30.62
OX-5	30.18 ± 0.6	48.72 ± 0.9	66.04 ± 0.9	52.41
OX-6	58.74 ± 0.7	75.41 ± 0.6	88.13 ± 0.5	14.82
OX-7	29.02 ± 0.8	47.18 ± 1.0	65.92 ± 0.7	54.26
OX-8	22.18 ± 0.5	39.76 ± 0.8	58.24 ± 1.0	71.05
Ascorbic acid	63.25 ± 0.4	80.74 ± 0.5	92.18 ± 0.3	10.14

As shown in Table 2, DPPH scavenging increased dose-dependently for all entities. OX-6 delivered 88.13% inhibition at 100 µg/mL and the lowest IC_{50} of 14.82 µg/mL, approaching ascorbic acid (IC_{50} = 10.14 µg/mL). OX-4 (–OH) and OX-3 (–OCH_3) also gave IC_{50} values below 40 µg/mL, whereas OX-8 (–NO_2) showed the weakest activity (IC_{50} = 71.05 µg/mL). One-way ANOVA confirmed significant differences between groups ($F = 128.6$; $p < 0.001$).

Table 3. ABTS, H_2O_2 and NO scavenging activity (IC_{50}, µg/mL)

Compound	ABTS IC_{50}	H_2O_2 IC_{50}	NO IC_{50}
OX-1	48.72	74.15	68.42
OX-2	39.61	62.38	57.16
OX-3	28.94	48.72	42.37
OX-4	24.55	43.61	38.92
OX-5	44.28	69.54	61.05
OX-6	11.46	26.18	22.91
OX-7	46.82	71.72	64.73
OX-8	62.47	89.26	82.51
Ascorbic acid	8.92	21.48	19.67

International Journal of Food Safety and Public Health
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ISSN: 2756-3693

Table 3 confirms a parallel ranking trend across three complementary assays. OX-6 again outperformed the rest with IC_{50} values of 11.46 µg/mL (ABTS), 26.18 µg/mL (H_2O_2) and 22.91 µg/mL (NO), closely matching ascorbic acid. Compounds OX-4 and OX-3 followed. The nitro-substituted OX-8 showed the highest IC_{50} across all three assays, supporting the inhibitory influence of $–NO_2$ groups. ANOVA indicated significant inter-compound variation ($F = 96.2$; $p < 0.001$).

Table 4. Ferric Reducing Antioxidant Power (FRAP, µM Fe^{2+}/g at 100 µg/mL)

Compound	FRAP value	Compound	FRAP value
OX-1	412 ± 8	OX-5	467 ± 7
OX-2	584 ± 9	OX-6	1187 ± 11
OX-3	746 ± 10	OX-7	438 ± 6
OX-4	892 ± 12	OX-8	318 ± 9
Ascorbic acid	1284 ± 10		

Table 4 shows the reducing competence of each entity. OX-6 recorded 1187 µM Fe^{2+}/g, approaching ascorbic acid (1284 µM Fe^{2+}/g) and clearly outperforming OX-1 (412 µM) and OX-8 (318 µM). The 4-OH-3-OCH_3 substitution in OX-6 evidently enables multi-electron transfer through resonance-stabilised phenoxyl-oxadiazolyl radicals. Statistical analysis (ANOVA, $F = 154.8$; $p < 0.001$) confirmed that FRAP values among the eight entities differed significantly, validating substituent-dependent reducing power.

Table 5. Structure–activity summary of the eight 1,3,4-oxadiazole entities

Substituent type	Example	Electronic nature	Observed trend
Unsubstituted	OX-1	Neutral	Moderate activity
Alkyl (–CH_3)	OX-2	Weak donor (+I)	Minor enhancement
Alkoxy (–OCH_3)	OX-3	Strong donor (+M)	High activity
Hydroxy (–OH)	OX-4	Strong donor (+M, H-donor)	Very high activity
Halogen (–Cl, –Br)	OX-5, OX-7	Weak withdrawing (–I)	Reduced activity
Ortho-OCH_3 + para-OH	OX-6	Dual donor (synergistic)	Highest activity
Nitro (–NO_2)	OX-8	Strong withdrawing (–M, –I)	Lowest activity

Table 5 consolidates the SAR. Electron-donating –OH and –OCH_3 groups progressively enhanced scavenging efficiency, whereas halogens and the –NO_2 group suppressed it. The dual-donor OX-6 exerted a synergistic effect through extended resonance stabilisation of the phenoxyl radical after H-atom transfer. The trend aligns with expected electronic theory: ring electron density enriches HOMO orbital availability, lowering the bond-dissociation energy of the O–H bond.

Table 6. Correlation of antioxidant parameters (Pearson r)

Assay pair	Correlation coefficient (r)	p-value
DPPH vs ABTS	0.987	< 0.001
DPPH vs FRAP	0.961	< 0.001
ABTS vs H_2O_2	0.943	< 0.001
FRAP vs NO	0.918	< 0.001
H_2O_2 vs NO	0.954	< 0.001

Table 6 demonstrates strong positive correlations ($r > 0.91$) among all five antioxidant endpoints, showing that the synthesised entities act through coherent electron-transfer/H-atom-transfer mechanisms. The DPPH–ABTS correlation ($r = 0.987$) is particularly strong, indicating parallel radical-quenching behaviour. These findings reinforce the reliability of multi-assay evaluation and demonstrate internal consistency across mechanistically distinct probes.

6. Discussion

The formulation of eight novel 1,3,4-oxadiazole entities and their systematic antioxidant profiling yielded three clear findings that match the stated objectives: (i) the $POCl_3$-mediated cyclodehydration protocol delivered all target compounds in satisfactory yields and purity, (ii) the compounds exhibited differential antioxidant efficiency, and (iii) substituent electronics decisively controlled the observed activity. The synthetic route chosen in this study employed acid-hydrazide cyclodehydration with $POCl_3$, a method historically regarded as the most reliable for 2,5-disubstituted 1,3,4-oxadiazoles due to its operational simplicity and broad functional-group tolerance (Głowacka et al., 2022; Desai et al., 2014). Yields of 54–74% closely match the range (55–75%) reported by Desai et al. (2014) for structurally related derivatives, supporting the reproducibility of the protocol. Structural elucidation through FT-IR, NMR

and LC-MS confirmed the absence of residual hydrazide and the formation of the oxadiazole ring, as evidenced by the disappearance of N–H bands near 3300 cm^{-1} and the emergence of the C=N stretch around 1610 cm^{-1}.

Antioxidant screening across DPPH, ABTS, H_2O_2, NO and FRAP assays revealed that OX-6 bearing a 4-hydroxy-3-methoxyphenyl group was consistently the most active (DPPH IC_{50} = 14.82 µg/mL; ABTS IC_{50} = 11.46 µg/mL; FRAP = 1187 µM Fe^{2+}/g). This is congruent with Chidan Kumar et al. (2017) who reported that 5-substituted-2-(3,4,5-trihydroxyphenyl)-1,3,4-oxadiazoles scavenged DPPH with IC_{50} values as low as 16 µM, and with Alam et al. (2022) who obtained a FRAP value of 4612.78 µM for a di-tert-butylphenol-linked oxadiazole. The strong performance of OX-6 is attributable to two synergistic factors: the phenolic –OH donates the initial hydrogen atom to a radical, while the adjacent $–OCH_3$ group stabilises the resulting phenoxyl radical through resonance and intramolecular hydrogen bonding. This mechanism is the classical "guaiacol-type" stabilisation documented for vanillin-derived antioxidants and is further supported by DFT analyses that localise HOMO electron density on the oxadiazole–phenolic conjugate system (Alam et al., 2022). The generally weak activity of OX-8 ($–NO_2$; IC_{50} = 71.05 µg/mL in DPPH) mirrors the findings of Ahsan et al. (2012), who showed that nitro-substitution decreases DPPH scavenging due to lowering of ring electron density and destabilisation of the phenoxyl radical.

The strong inter-assay correlations shown in Table 6 ($r > 0.91$) demonstrate that the synthesised entities operate through coordinated hydrogen-atom-transfer (HAT) and single-electron-transfer (SET) pathways. Bajić et al. (2017) reported analogous correlations for phenolic-acid-derived oxadiazoles, reinforcing the view that phenolic –OH availability drives multi-assay competence. Moreover, the closeness of OX-6 to ascorbic acid across five assays suggests it is a promising lead for oxidative-stress-related therapeutic investigations, particularly in pathologies such as Alzheimer's disease, cardiovascular disorders and metabolic syndromes where redox imbalance is a recognised driver (Houldsworth, 2024; Liu et al., 2024). The recent report by Hkiri et al. (2025) that oxadiazolyl sulfides can outperform ascorbic acid (SC_{50} = 9.88 µM) at the ABTS endpoint further indicates that sulfur- or amide-linker inclusion could, in future work, further enhance the OX-6 scaffold. Comparable neuroprotective performance of flavone–oxadiazole hybrids against ROS and NO in LPS-stimulated microglia (Shen et al., 2023) reinforces the translational relevance of the current series. Overall, the observed trends align well with recent literature and strengthen the proposition that 1,3,4-oxadiazole derivatives bearing phenolic donor substitution constitute a mechanistically sound, reproducible and pharmacologically relevant antioxidant class.

7. Conclusion

The present investigation successfully formulated eight novel 2,5-disubstituted 1,3,4-oxadiazole entities (OX-1 to OX-8) through a reliable $POCl_3$-mediated cyclodehydration route and examined their antioxidant efficiency across five complementary in-vitro assays. Compound OX-6, bearing a 4-hydroxy-3-methoxyphenyl group, emerged as the most efficient antioxidant (DPPH IC_{50} = 14.82 µg/mL; ABTS IC_{50} = 11.46 µg/mL; FRAP = 1187 µM Fe^{2+}/g), approaching the reference ascorbic acid. Electron-donating –OH and $–OCH_3$ substituents strongly enhanced activity, whereas the $–NO_2$ group suppressed it, confirming that substituent electronics decisively govern radical scavenging competence of the oxadiazole core. The strong inter-assay correlations validate that the entities operate through coherent HAT/SET mechanisms. OX-6 therefore constitutes a promising antioxidant lead deserving further pharmacological exploration for oxidative-stress-linked pathologies.

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