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Synthesis of pyrazole tethered oxadiazole and their analogs as potent antioxidant agents

Guda Mallikarjuna Reddy[1] | **Grigory V. Zyryanov**[1,2] | **Nabhubygari Mahaboob Basha**[3] | **Venkata Subbaiah Munagapati**[4] | **Jet-Chau Wen**[4,5] | **Anjani R. K. Gollakota**[5] | **Chin-Min Shu**[5] | **Bhumireddy Chinnachennaiahgari Venkatesh**[6]

[1]Ural Federal University, Chemical Engineering Institute, Yekaterinburg, Russian Federation

[2]Ural Division of the Russian Academy of Sciences, I. Ya. Postovskiy Institute of Organic Synthesis, Yekaterinburg, Russian Federation

[3]Department of Basic science and Humanities, School of Engineering and Technology, Sri Padmavathi Mahila Viswavidhyalayam, Tirupati, India

[4]Research Centre for Soil & Water Resources and Natural Disaster Prevention (SWAN), National Yunlin University of Science and Technology, Douliou, Taiwan

[5]Department of Safety, Health, and Environmental Engineering, National Yunlin University of Science and Technology, Douliou, Taiwan

[6]Department of Chemistry, Medha Degree College, Mydukur, India

Correspondence
Guda Mallikarjuna Reddy, Ural Federal University, Chemical Engineering Institute, Yekaterinburg, 620002, Russian Federation.
Email: reddy.organic@gmail.com

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Abstract

Preparation of organic compounds in environmental favor media always a fresh tool in the synthetic research. If those prepared compounds may possess therapeutically potentiality, then it called as efficient research. Herein, we report the 12 new oxadiazole linked carboxamide pyrazole substances have been synthesized and screened for their free radical scavenging activity by using hydrogen peroxide (H_2O_2), nitric oxide (N_2O), and diphenyl picryl hydrazide (DPPH) methods. All the compounds displayed reliable biological properties. Among them, compound **8f** hold high antioxidant activity may be due to the presence of methoxy group at para position of benzene ring. From the synthetic point of view, this is the novel environment favor method for the synthesis of pyrazole linked oxadiazoles, and the biological results of these compounds may stand as a referee for further development of biologically active pyrazole tethered oxadiazoles.

1 | INTRODUCTION

In oxidative stress, human body effected and damaged like membrane damage, breakage of DNA strand, peroxidation of DNA, and protein alterations through the biochemical chain reactions which produce dangerous health problems such as cardiovascular, inflammation, neurodegenerative orders, and cancer diseases.[1, 2] Thus, strong antioxidants are required as they inhibit the survival and proliferation of cancer cells by removing the oxidative stress.[3] Penta heterocycle motifs particularly oxadiazole having two nitrogen at 3rd and 4th position and one oxygen atom at first position possesses several biological properties such as antidiabetic,[4] antibacterial,[5] anti-inflammatory,[6] antifungal,[7] antitubercular,[8] analgesics,[9] anticancer,[10] antioxidant,[11] antidepressant,[12] antithrombotic,[13] and antiviral[14] bioactivities. On the other hand, many synthetic

methods existed for the preparation of 1,3,4-oxadiazoles and their derivatives. Recently, Khanam et al. developed 1,3,4-oxadizoles and their derivatives, which displayed excellent biological properties like antioxidant agent and anticancer agents.[15] A variety of oxadiazoles were reported by Sauer et al., which showed antioxidant properties.[16] In addition, Li et al. reported oxadiazole derivatives that reprogressively maintain their in vivo control abilities against plant bacteria.[17, 18] Further, thioether linked oxadiazoles were reported by Song et al., these compounds involved effectively prevent normal biological functions of phytopathogenic germs by mostly affecting their purine metabolism pathways.[19] Apart from, many other researchers reported different type of oxadiazole compounds that are possess different type of biological properties.[7, 20–22] Interestingly, the synthetic method of all the above mentioned oxadiazoles is complicated. Even though few preparation methods hold their importance, but still some defects are accompanying due to the involvement of toxic reagents, heavy spurs, metal bases, and other downsides.

In the predominant scenario, preparation of innovative potential therapeutics by using environmental favor conditions is a vital venture. The above information kept in mind and our experience in the field of organic research, which includes the biological evaluation of synthetic compounds,[23–25] the present research synthesis of pyrazole linked oxadiazole derivatives under ultrasonication method has been taken up. All the resulted compounds were identified by using their proton NMR, carbon NMR, and HRMS spectral data. In addition, total compounds tested for their free radical scavenging activity and a detailed structure activity relationship was deliberated.

2 | EXPERIMENTAL

2.1 | General

Preliminary compounds and reagents were pure and readily obtainable. Melting point numbers were noted with micro melting point operative and were uncorrected. HRMS information was recorded with the electro spray ionization (ESI). Ultrasonication experiments were performed by using Bandelin Sonorex RK 102H bath functioned at 35 KHz frequency. For ^{1}H NMR, 300 MH_Z and for ^{13}C NMR 75 MHz were used. TMS as a reference sample. The compounds infrared spectra were performed on thermo Nicolet IR 200 and wave numbers were given in centimeters.

2.1.1 | Synthetic method for the compound 3

Acetic anhydride **2** (5 mmol) was dissolved in ethanol solvent (7 ml), to this 2-thiol-5-amino-1,3,4-oxadiazole **1** (1 mmol) was added. The total reaction mixture contained flask was kept under sonication by using ultrasonic bath about 1–5 h. After the product formation, product crude was poured into cool water the resultant solid was filtered through a Buckner funnel. The solid was compound **3**.

N-(5-mercapto-1,3,4-oxadiazol-2-yl)acetamide (3): Pale yellow solid; Yield 75%; Melting point 129–131°C; ^{1}H NMR (300 $MH_{Z,}$ $CDCl_3$): δ 2.10 (s, 3H, Me), 12.1 (1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 23.2 (Me), 152.5 (C2), 166.5 (CO), 174.3 (C5).

2.1.2 | Intermediate compound 4 experimental method

To a mixture of compound 3 (1 mmol) and benzaldehyde (1 mmol) in a small bottom flask, 5 ml methanol and LiOH (10 mmol) were added. The total reaction setup was kept for 1–5 h in sonication under ultrasonic bath, product formation was monitored by TLC. After the product formation, crude was poured onto crushed ice followed by acidified with dil HCl, resultant solid was separated by filtration, and the filtered solid was purified by using dilute ethanol formed the pure compound **4**.

*N-(5-mercapto-1,3,4-oxadiazol-2-yl)cinnamamide (**4**)*: Pale yellow solid; Yield 79%; Melting point 111–113°C; ^{1}H NMR (300 $MH_{Z,}$ $CDCl_3$): δ 6.85 (d, 1H, CO attached CH), 7.33 (d, 1H, phenyl attached CH), 7.49–7.62 (m, 5H, Ar), 11.92 (1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 152.7 (NH attached carbon of oxadiazole), 165.9 (CO), 174.8 (SH attached carbon), 109.2, 124.5, 126.4, 129.4, 133.5, 141.2 (aromatic and alkene carbons).

2.1.3 | Preparation of compound 5

The oxadiazole contained unsaturated N-carbonyl compound 4 (1 mmol) was taken in a little beaker which already contained ethanol and KOH. To this, semicarbazide (2 mmol) was added and the reaction mixture contained in beaker was kept in an ultrasonicated bath for 40–60 min. The reaction was monitored by using TLC weather product formation or not. After successful product formation, the crude of the product was poured onto ice flask and extracted by using dichloromethane followed by rota evaporation of the solvent. Resultant solid (**5**) was purified by using isopropyl alcohol.

3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (5): Yellow solid; Yield 74%; Melting point 115–117°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 5.28 (dd, H_A, 1H, $J_{AX} = 6.8$ H_Z, $J_{AM} = 14.7$ H_Z), 3.84 (dd, H_M, 1H, $J_{MX} = 11.0$ H_Z, $J_{AM} = 14.7$ Hz), 3.17 (dd, H_X, 1H, $J_{MX} = 11.0$ H_Z, $J_{AX} = 6.8$ H_Z), 6.61 (br, NH_2), 7.19–7.52 (m, 5H, aromatic); 11.9 (1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 61.5 (Pyrazolyl, CH_2), 83.3 (Pyrazolyl, CH), 138.4 (pyrazolyl, N=C(CH_2NH)), 150.3 (C2), 166.3 (CO), 172.5 (C5), 127.3, 129.4, 132.3, 135.8; HRMS: *m/z* calcd for $C_{12}H_{13}N_6O_2S$ $(M+H)^+$ 305.0821; Found 305.0817.

2.1.4 | Experimental method for the compound 6

Chloranil (2 mmol) was added to the flask, which contained xylene solvent (5 ml). The compound **5** was added to solvent solution and were refluxed at 130°C for 20–24 h. After the completion of the reaction, the product mixture cooled and washed with sodium hydroxide solution. The washed crude was extracted by using dichloromethane and the organic layer dried resulted the compound **6**. The obtained solid was purified by using 2-propanol solvent.

3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-5-phenyl-1H-pyrazole-1-carboxamide (**6**):Yellow solid; Yield 71%; Melting point 122–124°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 6.94–7.59 (m, 6H, aromatic); 7.79 (br, NH_2), 11.52 (1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 136.3 (pyrazolyl, N=C—NH), 151.5 (C2), 165.1 (CO), 170.3 (C5), 120.6, 126.5, 128.2, 131.4, 136.5, 139.7; HRMS: *m/z* calcd for $C_{12}H_{11}N_6O_2S$ $(M+H)^+$ 303.0664; Found 303.0662.

2.1.5 | Experimental method for the synthesis of compounds 8(a-l)

The equimolar quantity of compound **6** and aldehyde **7a** were taken in a small beaker and the setup was sonicated by ultrasonic bath for 40 min. The condensation product formation was confirmed by using TLC. The reaction crude was cooled in a refrigerator. The bottom solid in the beaker was separated by means of filtration, followed by washed with dil hydrochloric acid. Resulted pure compound **8a.** The other compounds **(8(b-l))** were prepared using this method.

(Z)-N-Benzylidene-3-((5-mercapto-1,3,4-oxadiazol-2-yl)amino)-5-phenyl-1H-pyrazole-1-carboxamide (**8a**): Pale yellow solid; Yield 79%; Melting point 176–178°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 6.41 (s, 1H, Pyrazole CH), 7.18–7.89 (m, 10H, aromatic), 9.21 (s, 1H, PhHC=NCO), 11.42 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 108.4 (Pyrazole, CH), 140.9 (C3′), 152.1 (C2), 161.4 (PhHC=NCO), 179.2 (C5), 189.2 (CO); 121.6, 124.5, 126.3, 129.3, 130.2, 131.1, 138.9, 142.8, 146.3; HRMS: *m/z* calcd for $C_{19}H_{15}N_6O_2S$ $(M+H)^+$ 391.0977; Found 391.0974; IR (KBr) υ_{max} (cm^{-1}): 1541 (C=N), 1610 (C=C), 1660 (CO), 3220 (NH); MS(m/z): 390.4185 [$M^{+\cdot}$]: C = 58.30; H = 3.86; N = 21.47. Found: C = 58.36; H = 3.90; N = 21.42.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-N-(4-hydroxybenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8b**): Pale yellow solid; Yield 82%; Melting point 139–141°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 6.42 (s, 1H, Pyrazole CH), 7.21–7.92 (m, 9H, aromatic), 9.20 (s, 1H, PhHC=NCO), 11.41 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 109.5 (Pyrazole, CH), 141.0 (C3′), 152.4 (C2), 160.9 (PhHC=NCO), 178.8 (C5), 189.4 (CO); 121.3, 124.2, 126.6, 128.9, 130.3, 132.0, 138.6, 142.3, 147.1; HRMS: *m/z* calcd for $C_{19}H_{15}N_6O_3S$ $(M+H)^+$ 407.0926; Found 407.0921; IR (KBr) υ_{max} (cm^{-1}): 1548 (C=N), 1620 (C=C), 1675 (CO), 3228 (NH); MS(m/z): 406.4179 [$M^{+\cdot}$]: C = 56.15; H = 3.47; N = 20.68. Found: C = 58.10; H = 3.51; N = 20.59.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-N-(2-hydroxybenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8c**): Pale yellow solid; Yield 80%; Melting point 129–131°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 6.40 (s, 1H, Pyrazole CH), 7.20–7.89 (m, 9H, aromatic), 9.19 (s, 1H, PhHC=NCO), 11.40 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 109.1 (Pyrazole, CH), 141.5 (C3′), 153.2 (C2), 160.8 (PhHC=NCO), 179.2 (C5), 189.3 (CO); 122.1, 124.3, 126.5, 128.1, 129.3, 131.1, 132.4, 133.4, 136.5, 139.2, 147.5; HRMS: *m/z* calcd for $C_{19}H_{15}N_6O_3S$ $(M+H)^+$ 407.0926; Found 407.0923; IR (KBr) υ_{max} (cm^{-1}): 1549 (C=N), 1621 (C=C), 1672 (CO), 3230 (NH); MS(m/z): 406.4179 [$M^{+\cdot}$]: C = 56.15; H = 3.47; N = 20.68. Found: C = 58.19; H = 3.50; N = 20.69.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-N-(4-methylbenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8d**): Pale yellow solid; Yield 76%; Melting point 131–133°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 2.20 (s, 3H, Me), 6.41 (s, 1H, Pyrazole CH), 7.16–7.90 (m, 9H, aromatic), 9.21 (s, 1H, PhHC=NCO), 11.43 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 19.3 (Me), 108.2 (Pyrazole, CH), 141.2 (C3′), 153.5 (C2), 161.2 (PhHC=NCO), 179.2 (C5), 189.2 (CO); 120.2, 122.4, 126.7, 129.2, 131.6, 135.3, 137.1, 142.2, 147.0; HRMS: *m/z* calcd for $C_{20}H_{17}N_6O_2S$ $(M+H)^+$ 405.1134; Found 405.1130; IR (KBr) υ_{max} (cm^{-1}): 1540 (C=N), 1617 (C=C), 1664 (CO), 3222 (NH); MS(m/z): 404.4450 [$M^{+\cdot}$]: C = 59.39; H = 3.99; N = 20.78. Found: C = 59.46; H = 3.87; N = 20.82.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)]amino)-N-(2-methylbenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8e**): Pale yellow solid; Yield 79%; Melting point 152–154°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 2.21 (s, 3H, Me),

6.41 (s, 1H, Pyrazole CH), 7.14–7.88 (m, 9H, aromatic), 9.20 (s, 1H, PhHC=NCO), 11.45 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 19.4 (Me), 108.6 (Pyrazole, CH), 141.3 (C3′), 152.9 (C2), 161.0 (PhHC=NCO), 178.5 (C5), 189.4 (CO); 121.3, 123.5, 125.2, 127.4, 129.3, 131.2, 133.5, 135.8, 137.9, 143.4, 147.8; HRMS: *m/z* calcd for $C_{20}H_{17}N_6O_2S$ $(M+H)^+$ 405.1134; Found 405.1129. IR (KBr) υ_{max} (cm^{-1}): 1542 (C=N), 1613 (C=C), 1662 (CO), 3220 (NH); MS(m/z): 404.4450 [$M^{+\cdot}$]: C = 59.39; H = 3.99; N = 20.78. Found: C = 59.47; H = 3.94; N = 20.71.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-N-(4-methoxybenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8f**): Pale yellow solid; Yield 83%; Melting point 142–144°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 3.61 (s, 3H, OMe), 6.42 (s, 1H, Pyrazole CH), 7.17–7.89 (m, 9H, aromatic), 9.20 (s, 1H, PhHC=NCO), 11.42 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 59.4 (OMe), 109.1 (Pyrazole, CH), 141.0 (C3′), 152.9 (C2), 160.9 (PhHC=NCO), 179.4 (C5), 189.5 (CO); 122.3, 125.4, 128.1, 129.2, 132.4, 136.4, 138.2, 142.3, 148.1; HRMS: *m/z* calcd for $C_{20}H_{17}N_6O_3S$ $(M+H)^+$ 421.1083; Found 421.1079; IR (KBr) υ_{max} (cm^{-1}): 1559 (C=N), 1622 (C=C), 1676 (CO), 3231 (NH); MS(m/z): 420.4444 [$M^{+\cdot}$]: C = 57.13; H = 3.84; N = 19.99. Found: C = 57.06; H = 3.87; N = 20.06.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-N-(2-methoxybenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8g**): Pale yellow solid; Yield 77%; Melting point 168–170°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 3.60 (s, 3H, OMe), 6.41 (s, 1H, Pyrazole CH), 7.21–7.86 (m, 9H, aromatic), 9.23 (s, 1H, PhHC=NCO), 11.40 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 59.8 (OMe), 108.3 (Pyrazole, CH), 141.0 (C3′), 152.3 (C2), 161.1 (PhHC=NCO), 178.8 (C5), 189.3 (CO); 120.1, 123.5, 125.9, 127.8, 130.1, 132.5, 134.6, 136.4, 138.6, 142.7, 147.2; HRMS: *m/z* calcd for $C_{20}H_{17}N_6O_3S$ $(M+H)^+$ 421.1083; Found 421.1081; IR (KBr) υ_{max} (cm^{-1}): 1551 (C=N), 1624 (C=C), 1679 (CO), 3230 (NH); MS(m/z): 420.4444 [$M^{+\cdot}$]: C = 57.13; H = 3.84; N = 19.99. Found: C = 57.21; H = 3.80; N = 19.86.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-N-(4-bromobenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8h**): Pale yellow solid; Yield 80%; Melting point 193–195°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 6.41 (s, 1H, Pyrazole CH), 7.19–7.92 (m, 9H, aromatic), 9.20 (s, 1H, PhHC=NCO), 11.40 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 109.4 (Pyrazole, CH), 142.1 (C3′), 153.0 (C2), 161.2 (PhHC=NCO), 179.2 (C5), 188.9 (CO); 121.2, 123.5, 127.1, 130.2, 133.1, 136.2, 139.2, 143.3, 148.5; HRMS: *m/z* calcd for $C_{19}H_{14}BrN_6O_2S$ $(M+H)^+$ 469.0082; Found 469.0080; Second peak at 471 in the spectra; IR (KBr) υ_{max} (cm^{-1}): 1541 (C=N), 1614 (C=C), 1668 (CO), 3228 (NH); MS(m/z): 469.3145 [$M^{+\cdot}$]: C = 48.62; H = 2.79; N = 17.91. Found: C = 48.51; H = 2.81; N = 17.93.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-N-(2-bromobenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8i**): Pale yellow solid; Yield 79%; Melting point 122–124°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 6.43 (s, 1H, Pyrazole CH), 7.18–7.84 (m, 9H, aromatic), 9.21 (s, 1H, PhHC=NCO), 11.42 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 108.2 (Pyrazole, CH), 142.2 (C3′), 153.3 (C2), 160.4 (PhHC=NCO), 179.6 (C5), 188.3 (CO); 123.2, 125.1, 127.2, 129.0, 131.3, 132.5, 134.3, 137.2, 139.0, 140.1, 147.5; HRMS: *m/z* calcd for $C_{19}H_{14}BrN_6O_2S$ $(M+H)^+$ 469.0082; Found 469.0079; Second peak at 471 in the spectra; IR (KBr) υ_{max} (cm^{-1}): 1543 (C=N), 1611 (C=C), 1667 (CO), 3226 (NH); MS(m/z): 469.3145 [$M^{+\cdot}$]: C = 48.62; H = 2.79; N = 17.91. Found: C = 48.69; H = 2.83; N = 17.88.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-N-(2-chlorobenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8j**): Pale yellow solid; Yield 81%; Melting point 146–148°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 6.40 (s, 1H, Pyrazole CH), 7.21–7.79 (m, 9H, aromatic), 9.20 (s, 1H, PhHC=NCO), 11.42 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 108.4 (Pyrazole, CH), 141.2 (C3′), 153.5 (C2), 163.2 (PhHC=NCO), 179.1 (C5), 189.2 (CO); 121.4, 122.0, 124.6, 127.1, 130.5, 132.3, 134.4, 137.2, 139.1, 142.8, 147.7; HRMS: *m/z* calcd for $C_{19}H_{14}ClN_6O_2S$ $(M+H)^+$ 425.0587; Found 425.0586; Second peak at 427 in the spectra; IR (KBr) υ_{max} (cm^{-1}): 1560 (C=N), 1628 (C=C), 1688 (CO), 3240 (NH); MS(m/z): 424.8635 [$M^{+\cdot}$]: C = 53.71; H = 3.08; N = 19.78. Found: C = 53.69; H = 2.99; N = 19.84.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-N-(4-chlorobenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8k**): Pale yellow solid; Yield 80%; Melting point 159–161°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 6.42 (s, 1H, Pyrazole CH), 7.22–7.90 (m, 9H, aromatic), 9.21 (s, 1H, PhHC=NCO), 11.41 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 108.9 (Pyrazole, CH), 141.1 (C3′), 152.7 (C2), 162.5 (PhHC=NCO), 178.2 (C5), 188.8 (CO); 120.3, 124.2, 128.6, 132.2, 134.5, 138.1, 139.9, 142.5, 147.1; HRMS: *m/z* calcd for $C_{19}H_{14}ClN_6O_2S$ $(M+H)^+$ 425.0587; Found 425.0584; Second peak at 427 in the spectra; IR (KBr) υ_{max} (cm^{-1}): 1562 (C=N), 1626 (C=C), 1681 (CO), 3244 (NH); MS(m/z): 424.8635 [$M^{+\cdot}$]: C = 53.71; H = 3.08; N = 19.78. Found: C = 53.77; H = 3.11; N = 19.82.

(Z)-3-((5-Mercapto-1,3,4-oxadiazol-2-yl)amino)-N-(3-methylbenzylidene)-5-phenyl-1H-pyrazole-1-carboxamide (**8l**): Pale yellow solid; Yield 81%; Melting point 185–187°C; ^{1}H NMR (300 MH_Z, $CDCl_3$): δ 2.20 (s, 3H, Me), 6.42 (s, 1H, Pyrazole CH), 7.17–7.98 (m, 9H, aromatic), 9.22 (s, 1H, PhHC=NCO), 11.42 (s, 1H, SH) ppm; ^{13}C NMR (75 MH_Z, $CDCl_3$): δ 19.6 (Me), 108.4 (Pyrazole, CH), 141.2 (C3′), 153.1 (C2), 161.1 (PhHC=NCO), 178.6 (C5), 188.3 (CO); 120.2, 122.9, 124.5, 126.2, 128.3, 130.3, 131.2, 132.8, 133.6, 136.9, 138.1, 143.0, 147.9; HRMS: *m/z* calcd for $C_{20}H_{17}N_6O_2S$ $(M+H)^+$ 405.1134; Found 405.1131; IR

(KBr) υ_{max} (cm^{-1}): 1540 (C═N), 1618 (C═C), 1665 (CO), 3221 (NH); MS(m/z): 404.4450 [$M^{+\cdot}$]: C = 59.39; H = 3.99; N = 20.78. Found: C = 59.32; H = 3.88; N = 20.84.

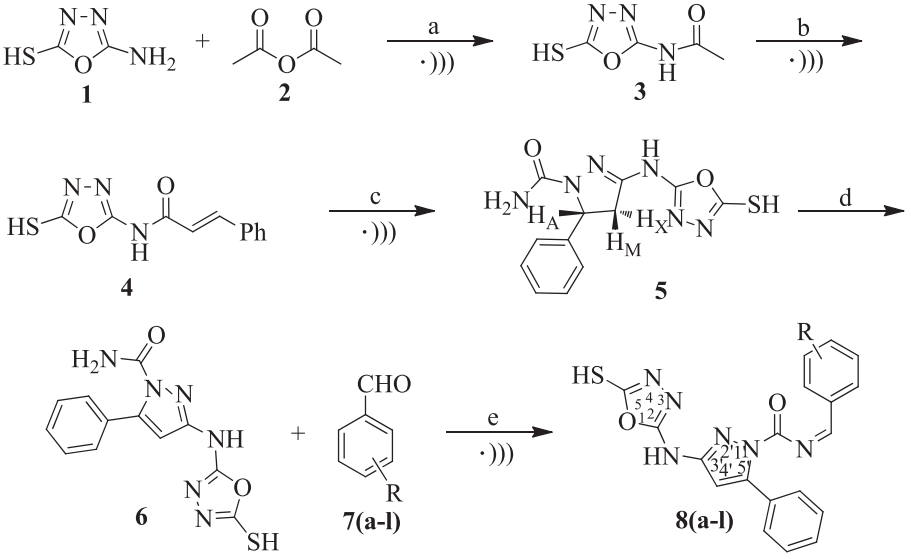
3 | RESULTS AND DISCUSSION

3.1 | Chemistry and biological activity

The synthetic strategy for the preparation of novel pyrazole included oxadiazole and their derivatives were figured out as Scheme 1. Initially, 2-thiol-5-amino-1,-3,4-oxadiazole (1) was treated with acetic anhydride (**2**) as a result formation of compound N-(5-mercapto-1,-3,4-oxadiazol-2-yl)acetamide (**3**) (Scheme 1). The proton NMR spectra of compound **3** which consisted carbonyl linked methyl proton at δ 2.10 ppm. This reaction was carried out under ultrasonication irradiation method as a result, 75% yield was observed. Solvent free, no catalyst, time save, prominent yield of the product are the advantageous tools of this step. Later, intermediate **3** was reacted with benzaldehyde in the presence of base such as lithium oxide by ultrasound irradiation formed the unsaturated compound **4**. In addition, if observed the proton spectra of the unsaturated compound (**4**), which hold the protons at δ 6.85 and 7.33 ppm. Coupling constant of these adjacent protons was J = 15 Hz indicated that those were trans protons. Further, cycloaddition of compound **4** with semicarbazide, provided the dihydropyrazolyl linked oxadiazole compound **5**, which undergoes further dehydrogenation reaction resulted the *N*-substituted pyrazolyl oxadiazole compound **(6)**. The compound **6** was confirmed by the proton NMR spectroscopic, carbon spectroscopy and HRMS spectral studies. By using compound **6**, the final compounds 8(a-l) were prepared. Treatment of compound **6** with benzaldehyde **(7a)**, provided final target compound (*Z*)-*N*-benzylidene-3-((5-mercapto-1,3,4-oxadiazol-2-yl)amino)-5-phenyl-1*H*-pyrazole-1-carboxamide (**8a**) in 76% yield. The final reaction holds a lot of advantageous tools. The main advantage is time minimized condition by using Sonochemical approach. Due to uniform irradiation around the reaction flask, bubble formation inside the flask and complete volume of starting compounds involved for the formation of product, which may result in good yield. Moreover, no side products, mild condition, simple workup process, and no catalyst are the other keynotes that were hidden in this synthetic method. In fact, the other compounds **8 (b-l)** prepared with this method and resulted promising yield of the products.

3.2 | Free radical scavenging activity

Total synthetic products were screened for their free radical scavenging properties by using three methods such as hydrogen peroxide, nitric oxide, and diphenyl picryl hydrazide. According to the methods sited there in Reference,[26] antioxidant screening was done. From the



SCHEME 1 Synthesis of 2,5-di substituted1,3,4-oxadiazoles and their derivatives

a) EtOH; b) Benzaldehyde, Methanol / LiOH; c) KOH, EtOH, $NH_2NHCONH_2$; d) Chloranil, Xylene, 130°C, Reflux; e) 40 min / ultrasound irradiation

results tabulated in Tables 1–3, it was observed that all the compounds displayed reliable free radical scavenging activity in all the three methods. Interestingly, In DPPH method, all compounds showed high free radical scavenging activity than other two methods. In three methods, ascorbic acid is used as reference compound. Besides, when compared to the reference compound **8f** displayed higher antioxidant properties than other compounds in all the three methods. Moreover, **8b**, **8g**, and **8c** were displayed prominent free radical scavenging activities, while the other compounds delivered good to moderate antioxidant properties.

When it comes to structure activity relationships, some fascinating key points were observed. Compound **8f** hold high antioxidant properties may be due to the presence of methoxy group at para position of benzene ring. This substituent donates the electron to the oxidation chain and suppress the oxidation process by means of pairing with oxidation chain (Figure 1). Moreover, methoxy group at para position may involve the resonance lead to stable the compound than methoxy group at meta or ortho position. This statement was supported by the results of compound **8b**. It has less free radical scavenging activity than **8f** even though both have the same attached substituent. But **8b** hold the attached group at ortho position. On the other hand, the same scenario was happened in the case of compounds **8c** and **8g** (Figures 2–4). Meanwhile, if we noticed the least active compounds **8h**, **8i**, **8j**, and **8k**, the reason for low antioxidant properties was due to the presence of electron withdrawing groups which may not supply free radicals easily.

TABLE 1 The in vitro antioxidant activity of compounds **8(a-l)** in H_2O_2 method

	Concentration (μg/ml)	
Sample	**50**	**100**
8a	45 ± 0.05	52 ± 0.93
8b	64 ± 0.54	72 ± 0.34
8c	56 ± 0.56	67 ± 0.46
8d	49 ± 0.51	56 ± 0.23
8e	53 ± 0.28	62 ± 0.56
8f	69 ± 0.11	74 ± 0.15
8g	59 ± 0.43	70 ± 0.23
8h	25 ± 0.17	30 ± 0.52
8i	34 ± 0.21	41 ± 0.16
8j	36 ± 0.45	45 ± 0.38
8k	39 ± 0.13	47 ± 0.63
8l	42 ± 0.21	51 ± 0.29
Ascorbic acid	75 ± 0.52	81 ± 0.13
Blank	—	—

Note: (—) Showed no scavenging activity. Values were the means of three replicates ± S.D.

TABLE 2 The in vitro antioxidant activity of compounds **8(a-l)** in NO method

	Concentration (μg/ml)	
Sample	**50**	**100**
8a	53 ± 0.12	57 ± 0.06
8b	70 ± 0.46	73 ± 0.34
8c	64 ± 0.25	68 ± 0.65
8d	55 ± 0.64	61 ± 0.50
8e	58 ± 0.31	66 ± 0.42
8f	74 ± 0.18	77 ± 0.94
8g	68 ± 0.53	72 ± 0.11
8h	31 ± 0.37	36 ± 0.19
8i	37 ± 0.28	46 ± 0.11
8j	41 ± 0.82	49 ± 0.12
8k	45 ± 0.41	50 ± 0.72
8l	49 ± 0.24	53 ± 0.64
Ascorbic acid	81 ± 0.49	84 ± 0.12
Blank	—	—

Note: (—) Showed no scavenging activity. Values were the means of three replicates ± S.D.

TABLE 3 The in vitro antioxidant activity of compounds **8(a-l)** in DPPH method

	Concentration (μg/ml)	
Sample	**50**	**100**
8a	59 ± 0.23	66 ± 0.09
8b	75 ± 0.65	78 ± 0.75
8c	69 ± 0.66	73 ± 0.38
8d	64 ± 0.05	69 ± 0.29
8e	67 ± 0.12	70 ± 0.63
8f	79 ± 0.51	81 ± 0.63
8g	71 ± 0.12	76 ± 0.12
8h	37 ± 0.14	45 ± 0.25
8i	41 ± 0.35	49 ± 0.47
8j	45 ± 0.46	52 ± 0.32
8k	49 ± 0.05	56 ± 0.22
8l	54 ± 0.78	60 ± 0.36
Ascorbic acid	85 ± 0.69	88 ± 0.72

Note: (—) Showed no scavenging activity. Values were the means of three replicates ± S.D.

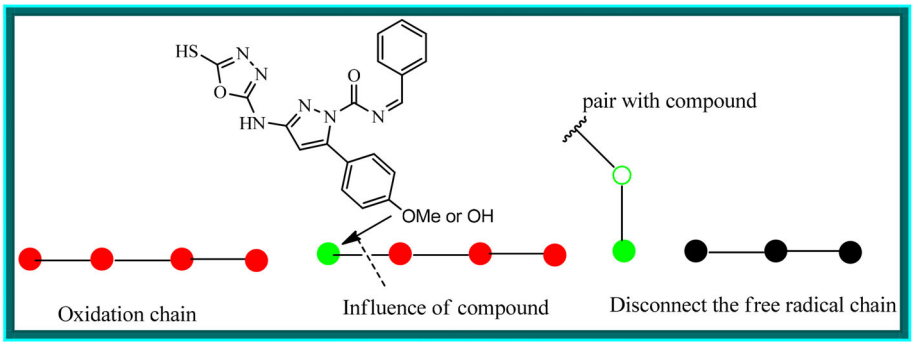


FIGURE 1 Graphical representation of compound involvement in antioxidant process

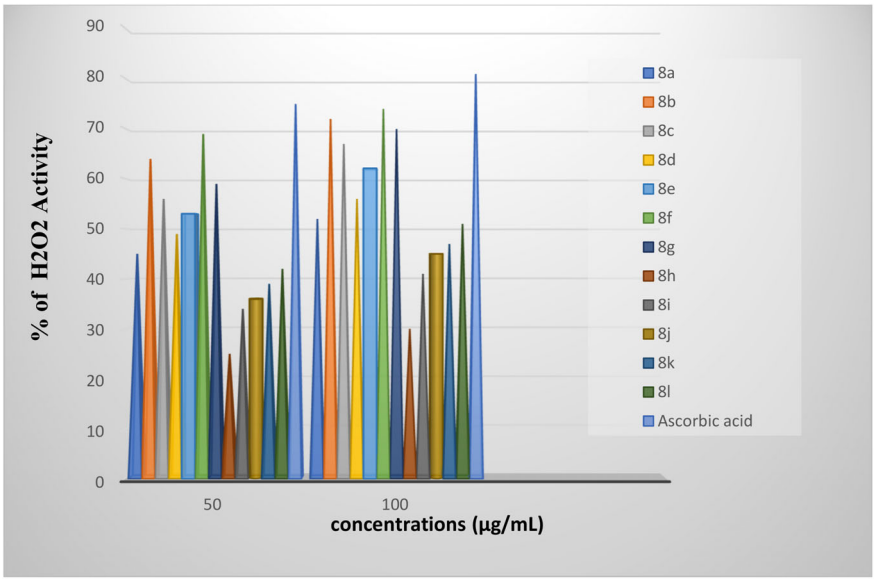


FIGURE 2 The in vitro antioxidant activity of compounds **8(a-l)** in H_2O_2 method

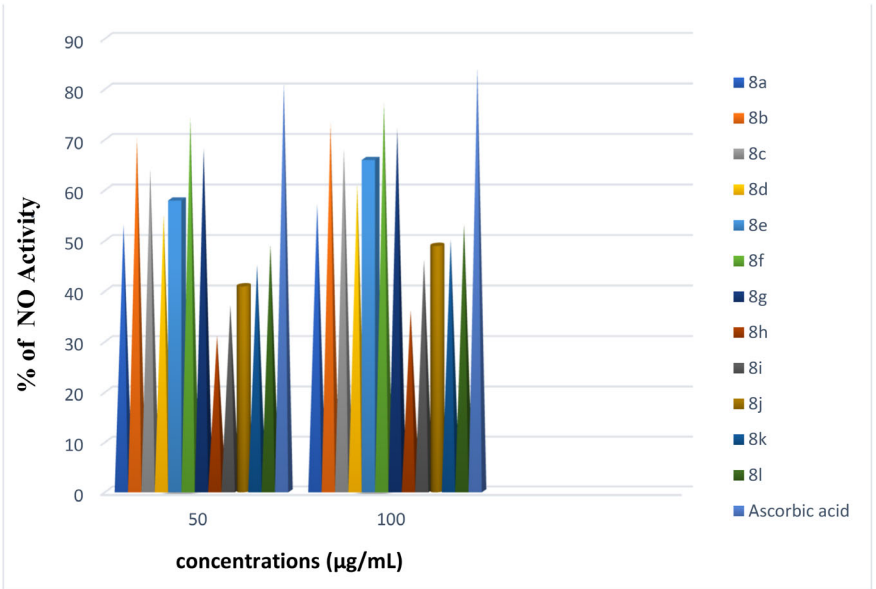


FIGURE 3 The in vitro antioxidant activity of compounds **8(a-l)** in NO method

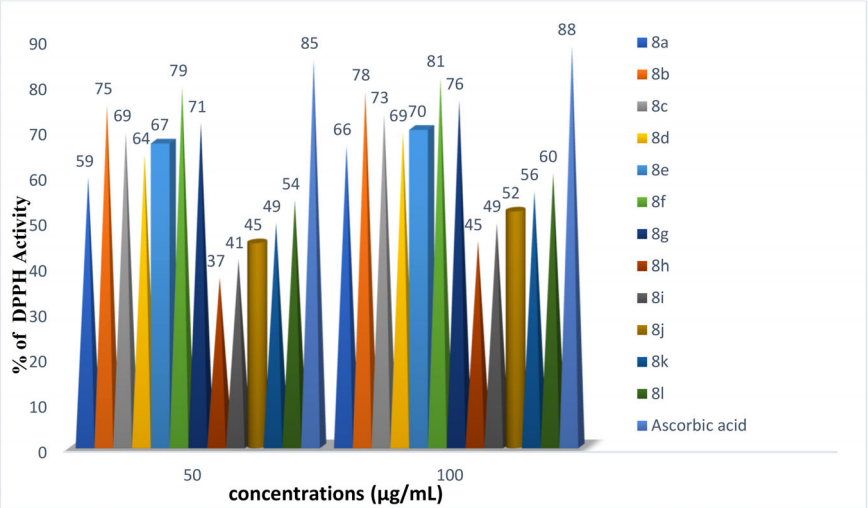


FIGURE 4 The in vitro antioxidant activity of compounds **8(a-l)** in DPPH method

4 | CONCLUSION

In this research, oxadiazol liked pyrazole derivatives were prepared by suing ultrasound irradiation method which included green synthetic and time saved condition. As a result, all the final targets formed with good yields. Besides, free radical scavenging property tests were carried out to all compounds in three methods. The biological results exposed that; total compounds displayed reliable biological properties in all the methods. In fact, compound **8f** displayed highest antioxidant assay than other may be due to the presence of methoxy group. While the motifs **8h**, **8i**, **8j**, and **8k** were showed low activity may be due to electron withdrawing group attached in their core.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Guda Mallikarjuna Reddy https://orcid.org/0000-0003-3903-1720

Venkata Subbaiah Munagapati https://orcid.org/0000-0001-6063-4097

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