




# Synthesis, characterization and antioxidant activity studies of new coumarin tethered 1,3,4-oxadiazole analogues

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**Abstract.** The present work describes the synthesis of a series of substituted 3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-ones **7(a–j)** using substituted aldehydes with analogues of hydrazine hydrates by grinding technique in the presence of Iodine which helps in the cyclization process. The structures of the synthesized compounds were elucidated by spectroscopic techniques such as IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and LCMS. The comparative antioxidant property (using DPPH and hydroxyl radical scavenging) has been studied with the synthesized compounds **7(a–j)** and the standards. Compounds **7d** and **7i** show the prominent radical scavenging activity.

**Keywords.** Coumarin tethered 1,3,4-oxadiazoles; Aryl hydrazide; Fused heterocycle; Iodine; Grinding technique; Cyclization.

## 1. Introduction

Heterocyclic chemistry is a predominant branch of the synthetic organic chemistry field with years of history and prospects. The heterocycles play a vital and primordial role in the synthesis of drugs for the future generation.<sup>1</sup> In the last few decades, the synthesis of five-membered heterocyclic compounds due to their extensive array of biological activities have acknowledged extensive interest. Among the heterocycles, coumarin and 1,3,4-oxadiazoles attained more consideration in recent years because of their natural occurrence and immense biological activities. The 1,3,4-oxadiazoles are five-member heterocycles, generally prepared by oxidative cyclization of *N*-acyl hydrazones, and by the reaction of aromatic hydrazides with aromatic aldehydes through the dehydrative cyclization of 1,2-diacylhydrazines.<sup>1</sup> The 1,3,4-oxadiazoles were efficiently prepared by the reaction of carboxylic acids with benzoic acid hydrazides using melamine-formaldehyde resin supported sulfuric acid as dehydration reagent under microwave-accelerated solvent-free conditions.<sup>2</sup> The oxidative cyclization can be achieved with the utility of different oxidizing

agents, which includes lead tetraacetate,<sup>3</sup> lead dioxide,<sup>4</sup> potassium permanganate,<sup>5</sup> chloramine-T,<sup>6</sup> HgO-I<sub>2</sub>,<sup>7</sup> ferric chloride,<sup>8</sup> and iodobenzenediacetate.<sup>9</sup>

Amongst the heterocycles, 1,3,4-oxadiazoles are an interesting class of compounds with  $\pi$ -conjugated electrons, and also due to their structural skeleton, which have been widely used in materials science, particularly organic light-emitting diodes (OLEDs), as electron conducting and hole blocking materials. Due to their electron-deficient and electron transporting abilities, they are utilized in energy-efficient, full color, flat-panel displays.<sup>10–16</sup> The oxadiazoles are often occurring as motifs in drug-like molecules.<sup>17,18</sup> The oxadiazoles have been extensively used as scaffolds in drug synthesis, particularly in the production of fasilplon, raltegravir, oxolamine, butalamine, and pleconaril. These have vital applications in medicinal chemistry due to their various biological activities including antibacterial,<sup>19–21</sup> antifungal,<sup>22</sup> analgesic and anti-inflammatory,<sup>23</sup> anticonvulsant,<sup>24</sup> hypoglycemic<sup>25</sup> and anticancer, etc.<sup>26</sup>

The coumarin derivatives have been synthesized for decades with variant protocols, significantly through synthetic routes like Knoevenagel, Pechmann, Perkin,

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and Wittig reaction, etc. The coumarins endowed with various pharmacological properties such as antioxidant,<sup>27</sup> antitubercular,<sup>28</sup> antimalarial,<sup>29</sup> antibacterial,<sup>30,31</sup> antitumor,<sup>32</sup> anti-inflammatory,<sup>33</sup> antiviral,<sup>34</sup> anti-Alzheimer,<sup>35,36</sup> and antifungal,<sup>37,38</sup> etc. Indeed, the coumarin-heterocycle hybrids possess enhanced biological potencies comparable with their parent moieties. In this context, the coumarin-1,3,4-oxadiazole hybrids were efficiently synthesized by the condensation reaction of coumarin-3-carboxylic acid with benzoic acid hydrazides using poly(ethylene glycol) supported dichlorophosphate as a dehydrating agent under the microwave-accelerated solvent-free procedure.<sup>39</sup> A series of *N*-[5-(2-oxo-2*H*-chromen-3-yl)-[1,3,4]oxadiazol-2-yl]-benzamide derivatives displayed inhibition against COX-1, COX-2, LOX-5, LOX-12, and LOX-15, and thereby showed enhanced anti-inflammatory, and analgesic activities.<sup>40</sup>

In recent years many protocols have been followed for the cyclization using iodine in the synthesis of oxadiazole.<sup>41,42</sup> In the present work, we have adopted the I<sub>2</sub> catalyzed oxidative cyclization for the synthesis of 1,3,4-oxadiazoles from substituted coumarin hydrazides and aromatic aldehydes through a grinding technique<sup>43</sup> to obtain the desired products in moderate to good yields. The synthesized new coumarin-oxadiazole hybrids were evaluated *in vitro* for the free radical scavenging susceptibilities.

## 2. Experimental

### 2.1 Materials and methods

All the reagents and chemicals were purchased from Sigma Aldrich, SD Fine, SRL and used without further purification. Thin-layer chromatography (TLC) was accomplished by pre-coated aluminum plates purchased from Merck (silica gel, 60 F-254). TLC plates were visualized under UV light and iodine chamber. <sup>1</sup>H NMR spectra were recorded by 400 MHz and <sup>13</sup>C NMR spectra by 100 MHz Agilent NMR spectrometer using with DMSO, and CD<sub>6</sub> as solvents, TMS used as an internal standard. Mass spectra were recorded under Lynx SCN781 spectrometer TOF mode.

### 2.2 Synthesis

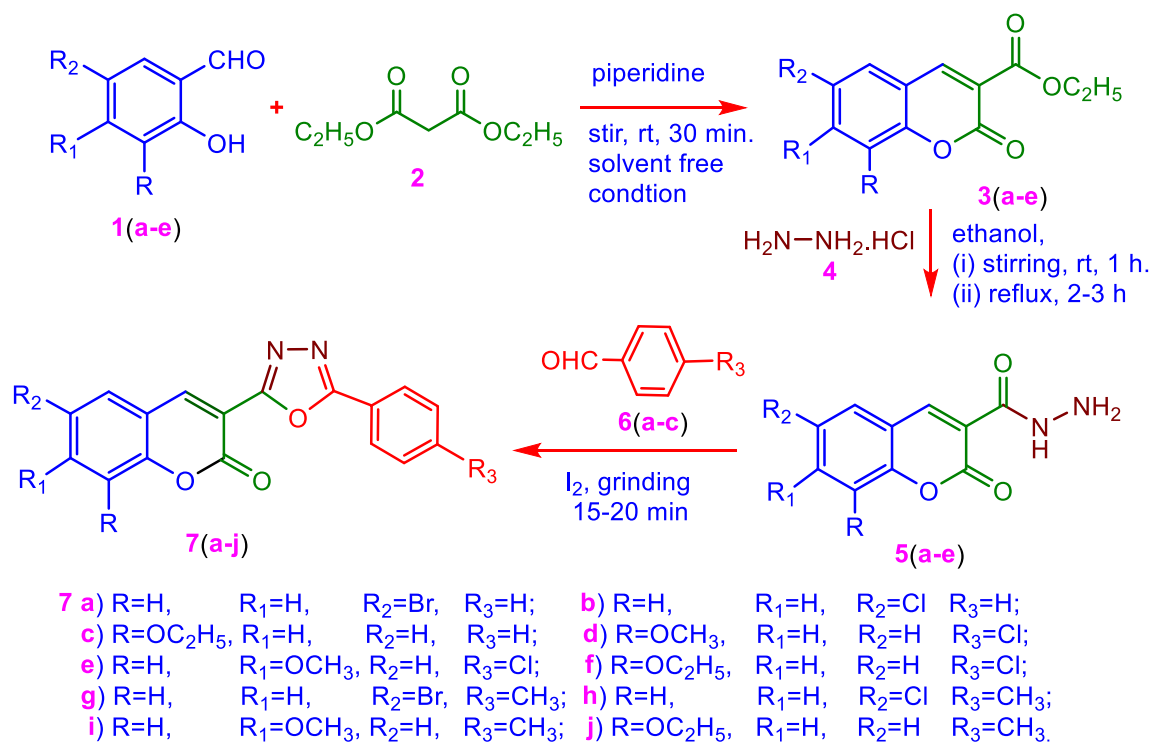
A series of ethyl-2-oxo-2*H*-chromene-3-carboxylates **3(a-e)** were synthesized from various substituted salicylaldehyde **1(a-e)**, and diethylmalonate **2**, in the presence of 2-3 drops of piperidine. A solution mixture

of compounds **3(a-e)** (10 mmol), hydrazine hydrochloride, **4** in (15 mL) was initially stirred at room temperature for an hour, then was refluxed for about 2-3 h to get the corresponding hydrazides **5(a-e)**.<sup>44</sup> The mixture of resulting hydrazides, substituted benzaldehydes **6(a-c)** in the presence of I<sub>2</sub> was finely ground in a mortar for 10-15 min, the process leads to giving the target compounds 3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-ones, **7(a-j)** in moderate yields (Figure 1).

**2.2a General procedure for the synthesis of compounds 7(a-j):** A mixture of coumarin hydrazide **5(a-e)** (10 mmol) and substituted benzaldehydes, **6(a-c)** (10 mmol), and iodine (20 mmol) were ground with a pestle for 15-20 min in a clean and dry mortar till a paste/semi-solid mass is obtained. The reaction progress was monitored by TLC at regular intervals of time. After confirming that the reaction has been completed, the mixture is washed successively with an ice-cold solution of sodium thiosulfate (20%) (3×10 mL) to remove residual iodine. The solid separated out was filtered, washed with cold water, and obtained mass was recrystallized using ethanol to get 3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-ones **7(a-j)**.

### 2.3 Biological activity

**2.3a DPPH radical scavenging activity:** The antioxidant property of the synthesized oxadiazole compounds was evaluated through free radical scavenging assay by observing the changes in optical density of 1,1-diphenyl-2-picryl hydrazyl (DPPH) radical solution.<sup>45,46</sup> The standard solution and solutions of different concentration of synthesized oxadiazole compound **7(a-j)** were used for DPPH radical scavenging analysis. The DPPH produces violet color in ethanol solution and fades to shades of yellow/pale yellow color in the presence of antioxidant. The DPPH radical scavenging activity was performed as follows: A known volume of DPPH radical solution in ethanol solvent (0.4 mM) was mixed with test samples of different concentrations (0.15 mM, 0.30 mM, and 0.45 mM) in 25 mL standard flask, and kept at 37 °C for 30 min. The violet color of DPPH solution is decreasing depending on the efficiency of the sample. The experiment is carried out with ascorbic acid as the standard under similar conditions. The absorbance of standard and tested oxadiazoles were measured using Elico SL 159



**Figure 1.** Schematic diagram for the synthesis of coumarin tethered oxadiazoles, **7(a-j)**.

UV-Vis spectrophotometer at 517 nm. The experiments were done in triplicate.

The percentage DPPH radical scavenging activity was calculated using the equation:

$$\% \text{ DPPH radical scavenging activity} = [(A_0 - A_1)/A_0] \times 100$$

where  $A_0$  is the absorbance of the standard, and  $A_1$  is the absorbance of the test samples at different concentrations. The % inhibition was plotted against concentration, and from the graph,  $IC_{50}$  was calculated.

**2.3b Hydroxyl radical scavenging activity:** The hydroxyl radical scavenging assay was performed using butylated hydroxyanisole (BHA) following a known protocol.<sup>47</sup> A mixture of 0.1 mL of phosphate buffer, 0.2 mL of 2-deoxyribose with different concentration of synthesized compounds, **7(a-j)** (0.2, 0.4, 0.6 and 0.8 mM in methanol), 0.01 mL of FeCl<sub>3</sub> (100 mM), 0.1 mL of H<sub>2</sub>O<sub>2</sub> (10 mM), 0.1 mL of ascorbic acid (1 mM), and 0.1 mL of EDTA was incubated at 37 °C for 60 min. Thereafter, the reaction was terminated by adding 1 mL of cold 2.8% trichloroacetic acid and the reaction product was measured by adding 1 mL of 1% thiobarbituric acid (1g in 100 mL of 0.05 N NaOH) in boiling water for

15 min. The BHA was used as a standard. The absorbance was measured at 535 nm with Elico SL 159 UV-Vis spectrophotometer. The hydroxyl radical scavenging capacity was evaluated with the inhibition of the percentage of 2-deoxyribose oxidation on hydroxyl radicals. The percentage of hydroxyl radical scavenging activity was calculated using the relation:

$$\% \text{ hydroxyl radical scavenging activity} = [(A_0 - (A_1 - A_2)/A_0] \times 100$$

where  $A_0$  is the absorbance of the control without any sample.  $A_1$  is the absorbance after adding a sample and 2-deoxyribose.  $A_2$  is the absorbance of the sample without 2-deoxyribose. The % inhibition was plotted against concentration, and from the graph  $IC_{50}$  was calculated. The experiment was repeated three times at each concentration.

### 3. Results and Discussions

#### 3.1 Spectral characterization

The IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, Mass spectral studies provide the structural proof for compounds **7(a-j)**. In IR spectra, compounds **7(a-j)** (Figure S1-S4, Supplementary Information) showed the absorption bands for

C=N, C=C, lactone-COO and C-H groups in the region: 1561-1579  $\text{cm}^{-1}$ , 1642-1669  $\text{cm}^{-1}$ , 1750-1759  $\text{cm}^{-1}$ , 1804-1822  $\text{cm}^{-1}$  for aromatic (C-H) and 2731-2758  $\text{cm}^{-1}$  for alkane (C-H), respectively. Other than these absorption bands, compound **7a** (Figure S1, Supplementary Information) show a band at 625  $\text{cm}^{-1}$  due to C-Br stretching.

The  $^1\text{H}$  NMR spectra of compounds **7(a-j)** were discussed by taking a representative compound **7f**. The compound 3-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-8-ethoxy-2H-chromen-2-one, **7f** (Figure S8, SI) shows a triplet at 1.136-1.172 ( $J=14.4\text{Hz}$ ) ppm for methyl protons of  $-\text{OCH}_2\text{CH}_3$  substituent, a quadrate at 4.134-4.187 ( $J=21.2\text{Hz}$ ) ppm for methylene protons of  $-\text{OCH}_2\text{CH}_3$  substituent, a singlet at  $\delta$  8.486 ppm for  $\text{C}_4\text{-H}$ , and an array of signals as multiplet within the region  $\delta$  7.202-7.270 ppm and  $\delta$  7.492-7.582 ppm for aromatic protons. For compounds; **7d**, (Figure S7, SI) a singlet at  $\delta$  3.810 ppm for a methoxy proton, **7g**, (Figure S9, SI) and **7j**, (Figure S10, SI) singlets at  $\delta$  2.356 ppm and  $\delta$  2.249 ppm for a methyl proton respectively, In the series of compounds **7(a-j)**, a singlet for  $\text{C}_4\text{-H}$  varies from  $\delta$  8.034-8.456 ppm. All the designed series of compounds **7(a-j)** (Figure S5-S10, SI) showed similar and consistent pattern signal for the aromatic protons in their respective spectra between the range  $\delta$  6.973-7.946 ppm and good agreement with the reported analogues<sup>39,48,49</sup> of the coumarin tethered oxadiazole moieties.

In the  $^{13}\text{C}$  NMR spectrum, compound **7c**, (Figure S12, SI) shows the absorption signals at  $\delta$  13.85 ppm for  $-\text{CH}_3$ , and  $\delta$  60.50 ppm for  $-\text{CH}_2$  carbons of  $-\text{OCH}_2\text{CH}_3$  substituent. The signals at  $\delta$  169.26 ppm, and  $\delta$  163.66 ppm appeared for carbons of the oxadiazole ring; while the signal for lactone C=O carbon appeared at  $\delta$  178.89 ppm. In the series of compounds **7(a-j)**, (Figure S11-S15, SI) the signal for lactone C=O carbon appeared in the region  $\delta$  177.93-179.89 ppm, and signals for oxadiazole ring carbons within the region  $\delta$  163.05-169.26 ppm; for a compound **7e**, (Figure S13, SI) and **7i**, (Figure S15, SI) a signal at  $\delta$  55.429 ppm and  $\delta$  55.438 ppm for a methoxy carbon atom; For a compound **7h**, (Figure S14, SI) and **7i**, (Figure S15, SI) signals appeared at  $\delta$  21.758 ppm and  $\delta$  21.652 ppm for methyl carbons, respectively. Further, all showed an array of signals within the aromatic carbon absorption region for aromatic carbons.

In mass spectrum, compound **7b**, (Figure S17, SI) showed a base peak at  $m/z$  324.1 (90%) corresponds to  $^{35}\text{Cl}$  isotope and its molecular mass ( $\text{C}_{17}\text{H}_9\text{N}_2\text{O}_3\text{Cl}$ ; MW=324.04), and peak at  $m/z$  326.1 (26%) comparable to  $^{37}\text{Cl}$  isotope (M+2) ion. Other compounds of the series **7(a-j)**, (Figure S16-S20, SI) showed the

peaks corresponding to their M+ and (M+1) peaks. The chloro and bromo substituted compounds showed M+ and M+2 peaks according to their molecular masses in the ratio 3:1 and 1:1, respectively. All the designed series of compounds **7(a-j)**, (Figure S1-S20, SI) showed similar and consistent pattern signal in their respective spectra and have their comparable elemental analysis.

### 3.2 DPPH and hydroxyl radical scavenging activity

The results of the DPPH and hydroxyl radical scavenging abilities of synthesized compounds **7(a-j)** are tabulated in Table 1.

From the results of the antioxidant activity screening of the tested compounds **7(a-j)**, it was observed that all newly synthesized compounds show good to moderate antioxidant activity as compared to the standard drugs employed. From the DPPH assay analyzed in triplicate, some compounds of the series displayed the promising radical scavenging activities with  $\text{IC}_{50}$  values of **7d** (19.47  $\mu\text{M}$ ), **7e** (18.62  $\mu\text{M}$ ), **7g** (23.28  $\mu\text{M}$ ), **7h** (22.78  $\mu\text{M}$ ) and **7i** (17.19  $\mu\text{M}$ ), and these results were comparable with antioxidant ascorbic acid ( $\text{IC}_{50} = 23.80 \mu\text{M}$ ), and therefore these compounds might act as lead molecules for DPPH radical scavenging activity. The compound **7c** (29.33  $\mu\text{M}$ ) showed the lowest activity amongst the series, while the remaining compounds of the series show moderate activity.

From the hydroxyl radical scavenging assay results analyzed in triplicate, the compounds **7d** ( $\text{IC}_{50} = 32.62 \mu\text{M}$ ) and **7i** ( $\text{IC}_{50} = 28.51 \mu\text{M}$ ) exhibited promising radical scavenging activities, and these values were comparable with antioxidant BHA ( $\text{IC}_{50} = 36.05 \mu\text{M}$ ). The rest of the synthesized compounds show moderate to poor antioxidant activity ( $\text{IC}_{50} = 36.88\text{-}47.81 \mu\text{M}$ ) comparable to the reference standard. The better DPPH and hydroxyl radical scavenging activity showed by the compounds **7d** and **7i** are comparable with respective standards and also with the reported structurally related compounds.

### 3.3 Analytical data

3.3a 6-Bromo-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one, **7a**: Obtained from reaction between **5a** (10 mmol) and **6a** (10 mmol) in the presence of  $\text{I}_2$  (15 mmol) in 68% yield (yellowish powder), M.p. 243-245  $^\circ\text{C}$ . IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 625 (C-Br), 1570 (C=N),

**Table 1.** The DPPH and hydroxyl radical scavenging activity of compounds **7(a-j)**.

Compound	DPPH radical scavenging IC <sub>50</sub> (μM)	Hydroxyl radical scavenging IC <sub>50</sub> (μM)
<b>7a</b>	25.08 ± 0.87	40.13 ± 1.21
<b>7b</b>	26.14 ± 0.93	42.02 ± 1.72
<b>7c</b>	29.33 ± 1.02	47.81 ± 1.10
<b>7d</b>	<b>19.47 ± 1.28</b>	<b>32.62 ± 0.98</b>
<b>7e</b>	<b>18.62 ± 1.46</b>	36.21 ± 2.12
<b>7f</b>	27.51 ± 1.07	46.92 ± 1.54
<b>7g</b>	<b>23.28 ± 0.88</b>	39.71 ± 1.83
<b>7h</b>	<b>22.78 ± 0.98</b>	36.88 ± 1.31
<b>7i</b>	<b>17.19 ± 0.81</b>	<b>28.51 ± 1.41</b>
<b>7j</b>	25.81 ± 1.41	44.32 ± 1.29
<b>AA</b> <sup>a</sup>	23.80 ± 1.21	–
<b>BHA</b> <sup>b</sup>	–	36.05 ± 1.68

Values are mean ± SD of three replicates (n=3);

<sup>a</sup>Ascorbic acid and <sup>b</sup>Butylated hydroxy anisole—positive controls.

1642 (C=C), 1750 (lactone-COO), 1804, 2749 (C-H); <sup>1</sup>H NMR (DMSO, δ ppm): 7.102-7.160 (m, 4H, Ar-H), 7.249-7.279 (m, 1H, Ar-H), 7.422-7.448 (m, 3H, Ar-H), 8.118 (s, 1H, Ar-H); <sup>13</sup>C NMR (DMSO, δ ppm): 107.06 (1C), 111.54 (1C), 113.09 (1C), 113.66 (2C), 115.72 (1C), 120.14 (1C), 130.42 (1C), 130.64 (1C), 131.64 (1C), 139.26 (1C), 143.26 (1C), 152.29 (1C), 154.51 (1C), 163.05 (1C), 167.05 (1C), 179.297 (1C, C=O); MS (m/z): 367.9 (M+, 96), 369.1 (M+2, 88). Anal. Calcd. for C<sub>17</sub>H<sub>9</sub>BrN<sub>2</sub>O<sub>3</sub> (%): C, 55.31; H, 2.46; N, 7.59; Found: C, 55.20; H, 2.36; N, 7.51.

**3.3b** *6-Chloro-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one*, **7b**: Obtained from reaction between **5b** (10 mmol) and **6a** (10 mmol) in the presence of I<sub>2</sub> (15 mmol) in 48% yield (yellowish gummy mass). IR ν<sub>max</sub> (cm<sup>-1</sup>): 832 (C-Cl), 1579 (C=N), 1651 (C=C), 1759 (lactone-COO), 1822, 2731 (C-H); <sup>1</sup>H NMR (DMSO, δ ppm): 7.340-7.486 (m, 3H, Ar-H), 7.653-7.798 (m, 3H, Ar-H), 7.911-7.930 (d, 1H, Ar-H), 8.046 (d, 1H, Ar-H); MS (m/z): 324.1 (M+, 90), 326.10 (M+2, 26). Anal. Calcd. for C<sub>17</sub>H<sub>9</sub>ClN<sub>2</sub>O<sub>3</sub> (%): C, 62.88; H, 2.79; N, 8.63; Found: C, 62.70; H, 2.70; N, 8.59.

**3.3c** *8-Ethoxy-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one*, **7c**: Obtained from reaction between **5e** (10 mmol) and **6a** (10 mmol) in the presence of I<sub>2</sub> (15 mmol) in 61% yield (yellowish solid), M.p. 268-270°C. IR ν<sub>max</sub> (cm<sup>-1</sup>): 1570 (C=N), 1660 (C=C), 1750 (lactone-COO), 1813, 2749 (C-H); <sup>13</sup>C NMR (DMSO, δ ppm): 13.85 (1C, CH<sub>3</sub>), 60.50 (1C, OCH<sub>2</sub>), 110.72 (1C), 113.29 (1C), 119.05 (1C), 125.74

(1C), 125.90 (1C), 127.37 (1C), 128.00 (1C), 129.27 (1C), 129.91 (1C), 132.42 (1C), 134.07 (1C), 137.33 (1C), 139.42 (1C), 145.24 (1C), 156.02 (1C), 163.66 (1C), 169.26 (1C), 178.03 (1C, C=O); MS (m/z): 335.1 (M+1, 88), 336.1 (M+2, 11). Anal. Calcd. for C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub> (%): C, 68.26; H, 4.22; N, 8.38; Found: C, 68.10; H, 4.10; N, 8.33.

**3.3d** *3-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-8-methoxy-2H-chromen-2-one*, **7d**: Obtained from reaction between **5c** (10 mmol) and **6b** (10 mmol) in the presence of I<sub>2</sub> (15 mmol) in 50% yield (yellowish gummy mass). IR ν<sub>max</sub> (cm<sup>-1</sup>): 850 (C-Cl), 1561 (C=N), 1669 (C=C), 1759 (lactone-COO), 1804, 2758 (C-H); <sup>1</sup>H NMR (DMSO, δ ppm): 3.810 (s, 3H, OCH<sub>3</sub>), 7.103 (s, 1H, Ar-H), 7.337-7.376 (m, 2H, Ar-H), 7.415-7.462 (m, 1H, Ar-H), 7.592-7.620 (m, 1H, Ar-H), 7.918-7.946 (m, 2H, Ar-H), 8.055 (s, 1H, Ar-H); MS (m/z): 354.1 (M+, 100), 356.1 (M+2, 32). Anal. Calcd. for C<sub>18</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>4</sub> (%): C, 60.94; H, 3.13; N, 7.90; Found: C, 60.81; H, 3.02; N, 7.87.

**3.3e** *3-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-7-methoxy-2H-chromen-2-one*, **7e**: Obtained from reaction between **5e** (10 mmol) and **6b** (10 mmol) in the presence of I<sub>2</sub> (15 mmol) in 66% yield (yellowish solid), M.p. 212-214 °C. <sup>13</sup>C NMR (DMSO, δ ppm): 55.42 (1C, OCH<sub>3</sub>), 107.06 (1C), 111.98 (1C), 114.94 (1C), 115.16 (1C), 123.35 (1C), 125.34 (1C), 125.34 (1C), 127.86 (1C), 128.78 (1C), 128.91 (1C), 131.15 (1C), 131.91 (1C), 132.06 (1C), 145.07 (1C), 151.85 (1C), 163.61 (1C), 168.03 (1C), 179.89 (1C, C=O); MS (m/z): 354.0 (M+, 100), 356.0 (M+2, 32). Anal.



Calcd. for  $C_{18}H_{11}ClN_2O_4$  (%): C, 60.94; H, 3.13; N, 7.90; Found: C, 60.84; H, 3.04; N, 7.85.

3.3f 3-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-8-ethoxy-2H-chromen-2-one, **7f**: Obtained from reaction between **5e** (10 mmol) and **6b** (10 mmol) in the presence of  $I_2$  (15 mmol) in 48% yield (greenish gummy mass).  $^1H$  NMR (DMSO,  $\delta$  ppm): 1.136-1.172 (t, 3H,  $CH_3$ ), 4.134-4.187 (q, 2H,  $CH_2$ ), 7.202-7.270 (m, 5H, Ar-H), 7.492-7.582 (m, 2H, Ar-H), 8.486 (s, 1H, Ar-H); MS (m/z): 368.1 (M+, 100), 370.1 (M+2, 32). Anal. Calcd. for  $C_{19}H_{13}ClN_2O_4$  (%): C, 61.88; H, 3.55; N, 7.60; Found: C, 61.77; H, 3.42; N, 7.57.

3.3g 6-Bromo-3-(5-(p-tolyl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one, **7g**: Obtained from reaction between **5a** (10 mmol) and **6c** (10 mmol) in the presence of  $I_2$  (15 mmol) in 62% yield (yellow powder), M.p. 223-225°C.  $^1H$  NMR (DMSO,  $\delta$  ppm): 2.356 (s, 3H,  $CH_3$ ), 6.869-6.876 (s, 1H, Ar-H), 7.114-7.276 (m, 3H, Ar-H), 7.418-7.463 (m, 2H, Ar-H), 7.911-7.996 (m, 1H, Ar-H), 8.034 (d, 1H, Ar-H); MS (m/z): 382.1 (M+, 94), 384.2 (M+2, 87). Anal. Calcd. for  $C_{18}H_{11}BrN_2O_3$  (%): C, 56.42; H, 2.89; N, 7.31; Found: C, 56.30; H, 2.70; N, 7.28.

3.3h 6-Chloro-3-(5-(p-tolyl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one, **7h**: Obtained from reaction between **5b** (10 mmol) and **6c** (10 mmol) in the presence of  $I_2$  (15 mmol) in 50% yield (greenish gummy mass).  $^{13}C$  NMR (DMSO,  $\delta$  ppm): 21.75 (1C,  $CH_3$ ), 119.76 (1C), 120.32 (1C), 120.75 (1C), 120.87 (1C), 121.68 (1C), 127.36 (1C), 129.22 (1C), 129.53 (1C), 130.03 (1C), 131.44 (1C), 134.53 (1C), 139.68 (1C), 142.79 (1C), 159.85 (1C), 164.05 (1C), 167.83 (1C), 179.46 (1C, C=O); MS (m/z): 338.5 (M+, 100), 340.0 (M+2, 30). Anal. Calcd. for  $C_{18}H_{11}ClN_2O_3$  (%): C, 63.82; H, 3.27; N, 8.27; Found: C, 63.70; H, 3.17; N, 8.23.

3.3i 7-Methoxy-3-(5-(p-tolyl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one, **7i**: Obtained from reaction between **5d** (10 mmol) and **6c** (10 mmol) in the presence of  $I_2$  (15 mmol) in 45% yield (buff gummy mass).  $^{13}C$  NMR (DMSO,  $\delta$  ppm): 21.65 (1C,  $CH_3$ ), 55.43 (1C,  $OCH_3$ ), 112.79 (1C), 119.42 (1C), 120.32 (1C), 120.81 (1C), 121.68 (1C), 127.36 (1C), 129.40 (1C), 130.03 (1C), 131.44 (1C), 134.53 (1C), 135.56 (1C), 139.68 (1C), 142.79 (1C), 159.85 (1C), 164.05 (1C), 177.93 (1C, C=O); MS (m/z): 334.3 (M+, 100), 335.3 (M+1, 12). Anal. Calcd. for  $C_{19}H_{14}N_2O_4$  (%):

C, 68.26; H, 4.22; N, 8.38; Found: C, 68.12; H, 4.12; N, 8.34.

3.3.3a. 8-Ethoxy-3-(5-(p-tolyl)-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one, **7j** Obtained from reaction between **5e** (10 mmol) and **6c** (10 mmol) in the presence of  $I_2$  (15 mmol) in 43% yield (greenish gummy mass).  $^1H$  NMR (DMSO,  $\delta$  ppm): 1.107-1.142 (t, 3H,  $CH_3$ ), 2.249 (s, 3H,  $OCH_3$ ), 4.124-4.178 (q, 2H,  $CH_2$ ), 6.973-6.992 (d, 2H, Ar-H), 7.171-7.248 (d, 2H, Ar-H), 7.592-7.620 (d, 2H, Ar-H), 7.918-7.946 (m, 2H, Ar-H), 8.105 (s, 1H, Ar-H); MS (m/z): 348.0 (M+, 96). Anal. Calcd. for  $C_{20}H_{16}N_2O_4$  (%): C, 68.96; H, 4.63; N, 8.04; Found: C, 68.83; H, 4.58; N, 8.00.

#### 4. Conclusions

The new series of coumarin tethered compounds have been synthesized by a green chemistry method using the molecular iodine by a simple grinding technique. The structures of the newly synthesized compounds were confirmed by their spectral data. The results of DPPH and hydroxyl radical scavenging assay, the coumarin appended oxadiazole derivatives, **7(a-j)** exhibit modest to good radical scavenging susceptibilities. The compounds, **7d** ( $IC_{50}=19.47 \mu M$ , and  $32.62 \mu M$ ) and **7i** ( $IC_{50}=17.19 \mu M$ , and  $28.51 \mu M$ ) of the synthesized series, demonstrated potent DPPH and hydroxyl radical scavenging abilities, respectively, and therefore these could act as antioxidant leads in the future.

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