

## Design, synthesis and characterization of azo group-containing flavonoid derivatives

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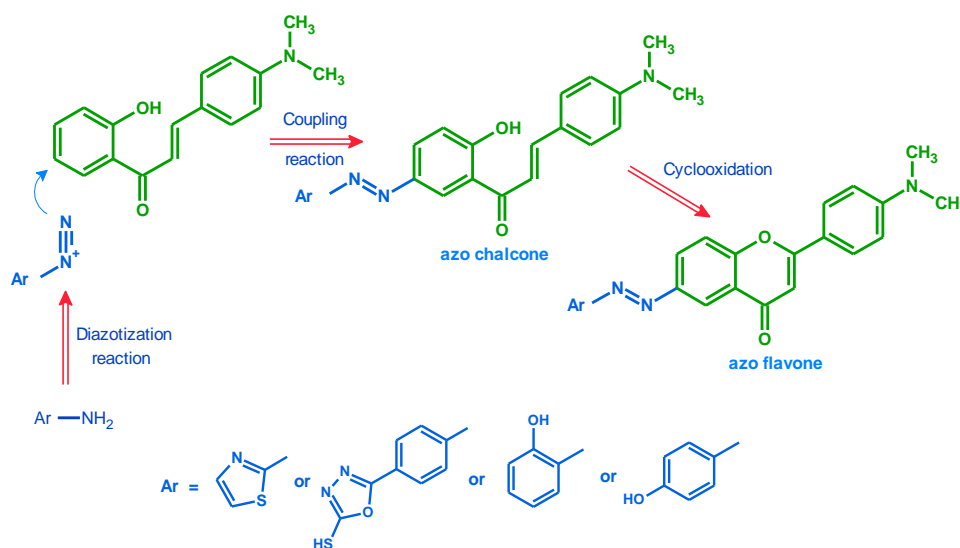
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### Abstract

A new series of azochalcone derivatives and azoflavones based on diazotization reactions of various aromatic amines (2-aminothiazol, aminophenylloxadiazol thiol, 2-aminophenol, 4-aminophenol) with chalcone A<sub>1</sub> was synthesized. Subsequently, the azo chalcone compounds were cyclized with iodine and DMSO. The physical properties and spectral analysis of the new compounds were studied (FT-IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR).



**Keywords:** Azochalcone, Azoflavone, Diazotization-Coupling Reactions.

## Introduction

Azo dyes are industrially important organic compounds used as chemical markers, sensitizers in solar cells,<sup>1</sup> and laser materials.<sup>2</sup> Azo dyes contain a functional group -N=N-, which can be attached to an aromatic or aromatic heterocycle.<sup>3</sup> This makes them suitable candidates for broad application as food additives and cosmetics.<sup>4,5</sup> In addition to biological processes as antifungal, antibacterial, antiviral and a range of diseases such as infections, tuberculosis and cancer,<sup>6,7</sup> Azoaromatic compounds are used as acid and base indicators.<sup>8</sup>

Flavonoids are low molecular weight polyphenolic compounds, and they are found in the plant kingdom.<sup>9,10</sup> They have biological activity and play an important role in biosynthetic cells. Scientific name: 2-phenyl-4*H*-1-benzopyran-4-one (or 2-phenyl-4*H*-chromen-4-one) (C<sub>15</sub>H<sub>10</sub>O<sub>2</sub>).<sup>11,12</sup> Flavonoids have pronounced biological activity as antioxidant,<sup>13</sup> antimalarial,<sup>14</sup> anti-inflammatory,<sup>15,16</sup> antibacterial,<sup>17</sup> antidiabetic,<sup>16</sup> and anticancer.<sup>18,19</sup>

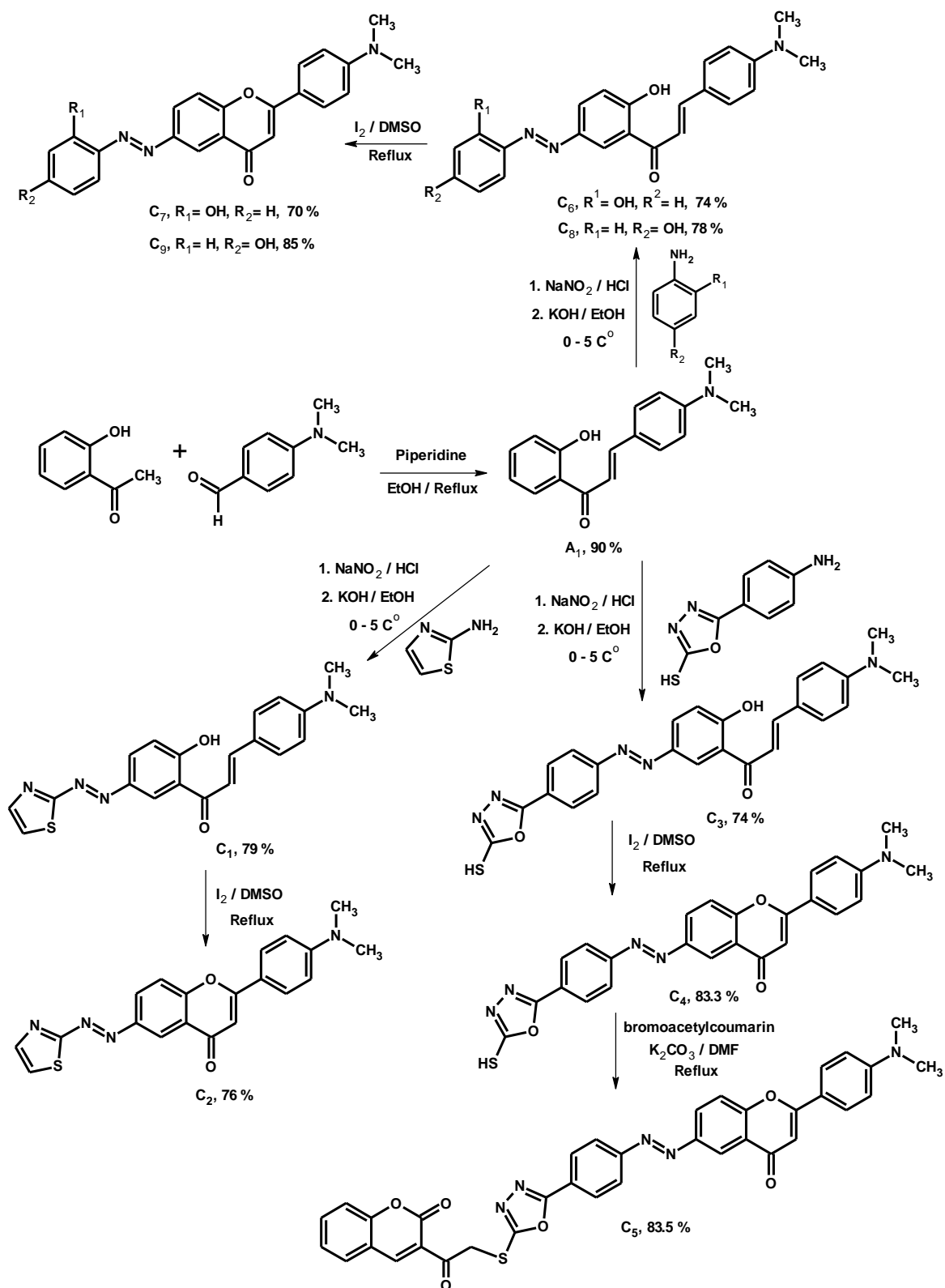
The two Iraqi researchers Ayoob and Hawaiz from Salah al-Din University were able to produce a series of flavone derivatives containing azo groups through a condensation reaction of 4-(5-chlorophenylazo)-2-hydroxyacetophenone with 2-benzyloxy-4-phenylazobenzaldehyde.<sup>20</sup>

The present study describes the synthesis of four chalcone derivatives and five flavonoid derivatives that include an azo group in its structure, through diazotization-coupling and cyclization reactions using iodine in dimethyl sulfoxide. The new compounds were characterized using spectroscopic methods (FT-IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR).

## Results and Discussion

For the first time, diazotization-coupling reactions of two different aromatic amines with hydroxychalcone A<sub>1</sub> were carried out and we obtained azo chalcone derivatives (C<sub>1</sub> and C<sub>3</sub>) with yields of 79% and 74%, respectively. The C<sub>1</sub> derivative contains a thiazole ring in its structure in the form of a reddish-brown precipitate, while the C<sub>3</sub> derivative contains an oxadiazole ring in the form of an orange precipitate. The melting points of the two derivatives differ significantly: the melting point of the chalcone derivative (C<sub>1</sub>) is 173 - 175 °C and that of the chalcone derivative (C<sub>3</sub>) is 146 - 148 °C, which contains the -SH group. The cyclization reaction of the two derivatives (C<sub>1</sub>, C<sub>3</sub>) was carried out with iodine in dimethyl sulfoxide, and we obtained the flavonoid derivatives (C<sub>2</sub>, C<sub>4</sub>), noting the obvious difference in colors and melting points due to the different structure of the two base derivatives (C<sub>1</sub> and C<sub>3</sub>).

Alkylation of the thiol group (-SH) of flavonoid derivative C<sub>4</sub> with bromoacetyl coumarin resulted in flavonoid derivative C<sub>5</sub>, which has a dark brown color and a very high melting point (> 300 °C) due to its high molecular weight and the presence of several functional groups. Scheme 1 shows a reaction scheme for the synthesis of azochalcone (C<sub>1</sub>, C<sub>3</sub>, C<sub>6</sub>, C<sub>8</sub>) and azoflavone derivatives (C<sub>2</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>7</sub>, C<sub>9</sub>). Table 1 contains the physical properties (melting point, sample color, yield, molecular formula, molecular weight, R<sub>f</sub>) of the new flavonoids. New flavonoid derivatives (C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>) have been prepared that include an azo group in its structure, based on the diazotization - coupling reactions of different aromatic amines (o-aminophenol, p-aminophenol) with the chalcone compound, with a yield of 70-85%.



**Scheme 1.** Reaction scheme of the synthesis of azo chalcone ( $C_1$ ,  $C_3$ ,  $C_6$ ,  $C_8$ ) and azo flavone derivatives ( $C_2$ ,  $C_4$ ,  $C_5$ ,  $C_7$ ,  $C_9$ ).

Spectroscopic analysis of the chalcone compound (C<sub>1</sub>) showed an absorption band at frequency 3415 cm<sup>-1</sup> belonging to the group -OH, an absorption band at frequency 1577 cm<sup>-1</sup> belonging to the C=N group in the thiazole ring, and an absorption band at 1381 cm<sup>-1</sup> belonging to the azo group (-N=N-), indicating the occurrence of a diazotization - coupling interaction and the formation of the new derivative. Moreover, spectroscopy of the flavonoid compound (C<sub>2</sub>) showed the disappearance of the absorption band characteristic of the -OH group, indicating the occurrence of a cyclic reaction using iodine and the formation of the new derivative.

Spectroscopic analysis of the chalcone compound (C<sub>3</sub>) showed an absorption band at 3414 cm<sup>-1</sup> belonging to the -OH group, and a new absorption band at a frequency of 2396 cm<sup>-1</sup> belonging to the -SH group, as well as an absorption band at 1383 cm<sup>-1</sup> belonging to the azo group (-N=N-), indicating a diazotization and coupling reaction, while the spectroscopic analysis of the flavonoid compound (C<sub>4</sub>) showed the disappearance of the absorption band of the phenol group -OH, indicating a cyclic reaction and the formation of the new derivative. Spectroscopic analysis of compound (C<sub>5</sub>) showed the disappearance of the absorption band belonging to the thiol group (-SH) and the appearance of a new absorption band belonging to the carbonyllactone group in the coumarin structure, indicating the occurrence of an alkylation reaction at the -SH group in compound (C<sub>4</sub>) with bromoacetylcoumarin and the formation of the new derivative (C<sub>5</sub>). The infrared spectra of the prepared chalcone compounds (C<sub>6</sub>, C<sub>8</sub>) showed the presence of absorption bands at the frequency 3415 cm<sup>-1</sup> due to the -OH bond, and an absorption band at the frequency 1621, 1620 cm<sup>-1</sup> belongs to the stretchy carbonyl group C=O, and an absorption band at frequency 1382 cm<sup>-1</sup> belongs to the azo group (-N=N-). The infrared spectra of compounds (C<sub>7</sub>, C<sub>9</sub>) showed the presence of absorption bands at the frequency 3425, 3420 cm<sup>-1</sup> due to the stretching of the -OH bond, and an absorption band at the frequency 1636 - 1599 cm<sup>-1</sup> due to the stretching of the carbonyl group (C = O) in the pyran ring.

**Table 1.** Physical properties of the new flavonoids

Compound	Yield %	M.w (g/mol)	Molecular formula	Color	m.p °C	R <sub>f</sub>
A <sub>1</sub>	90	267.3	C <sub>17</sub> H <sub>17</sub> O <sub>2</sub> N	Bright pink	178 - 179	0.45 <sup>a</sup>
C <sub>1</sub>	79	378.44	C <sub>20</sub> H <sub>18</sub> O <sub>2</sub> N <sub>4</sub> S	Reddish brown	173 - 175	0.41 <sup>a</sup>
C <sub>2</sub>	76	376.43	C <sub>20</sub> H <sub>16</sub> O <sub>2</sub> N <sub>4</sub> S	Yellow	157 - 159	0.32 <sup>a</sup>
C <sub>3</sub>	74	471.53	C <sub>25</sub> H <sub>21</sub> O <sub>3</sub> N <sub>5</sub> S	Orange	146 - 148	0.37 <sup>b</sup>
C <sub>4</sub>	83.3	469.51	C <sub>25</sub> H <sub>19</sub> O <sub>3</sub> N <sub>5</sub> S	Brown	195 - 197	0.29 <sup>b</sup>
C <sub>5</sub>	83.5	655.67	C <sub>36</sub> H <sub>25</sub> O <sub>6</sub> N <sub>5</sub> S	Brown	320 ° C	0.18 <sup>b</sup>
C <sub>6</sub>	74	387.44	C <sub>23</sub> H <sub>21</sub> O <sub>3</sub> N <sub>3</sub>	Reddish brown	162-164	0.47 <sup>a</sup>
C <sub>7</sub>	70	385.42	C <sub>23</sub> H <sub>19</sub> O <sub>3</sub> N <sub>3</sub>	Yellow	153-155	0.25 <sup>a</sup>
C <sub>8</sub>	78	387.44	C <sub>23</sub> H <sub>21</sub> O <sub>3</sub> N <sub>3</sub>	Reddish brown	169-170	0.4 <sup>a</sup>
C <sub>9</sub>	85	385.42	C <sub>23</sub> H <sub>19</sub> O <sub>3</sub> N <sub>3</sub>	Yellow	185-187	0.24 <sup>a</sup>

a. Acetone: hexane 1:3

b. Acetone: hexane 2:3

Spectroscopic analysis by  $^1\text{H-NMR}$  spectroscopy revealed several chemical shifts of various protons for all the compounds prepared, the most characteristic of which are the chemical shifts of the protons of the -OH group and -SH and the -CH=CH- group in the thiazole ring, as well as the shifts of the chemical protons of the -CH=CH- group, confirming the chemical structure of the flavonoids prepared. The carbon nuclear magnetic resonance spectra  $^{13}\text{C-NMR}$  of the prepared compounds showed several peaks, the most distinct of which were the peaks belonging to the C=C carbon atoms in the thiazole ring and the C=C ethene carbon atoms, as well as the carbon atom of the unsaturated alpha-beta carbonyl group and the carbonyl group in each of the pyran and lactone rings, in addition to other peaks common to all the prepared compounds.

## Conclusions

New flavonoid derivatives containing azo groups and heterocyclic rings were obtained through dialysis and coupling reactions of different aromatic amines with hydroxy chalcone A<sub>1</sub>, followed by cyclic oxidation of azo chalcone derivatives, and the yield was good.

## Experimental Section

**General.** All compounds were purified by recrystallization and chromatographically separated using Prep-TLC. The course of the reactions were monitored by thin-layer chromatography (TLC) on aluminium plates coated with silica gel with a fluorescent indicator (DC-Fertigfolien ALUGRAM) and using a DESAGA-UVIS/254/366 nm UV lamp. Melting points were measured using the Stuart Electrothermal Engineering LTD 9100 (measuring melting points up to 400 °C). The Jasco-460-Plus spectrophotometer was used to record IR spectra by KBr disks method. Elemental analyses were recorded on an Elementar Vario EL III analyser. A Bruker Avance II 400 (model 400 MHz AVANCE SPECTROMETER) at 100 and 400 MHz was used to record the  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectra and the samples were prepared with DMSO-*d*<sub>6</sub> as the solvent.

**Chemical and Starting Materials:** absolute ethanol, dry methanol, Dry acetone, *N,N*-dimethylformamide (DMF), Hexane, Chloroform, dimethylsulfoxide (DMSO) (Sigma Aldrich, Merck, Fluka, HIMEDIA). the materials used are: *o*-hydroxyacetophenone, 4-(dimethylamino)benzaldehyde, 2-aminophenol, 4-aminophenol, 2-aminothiazol, potassium hydroxide, iodine, sodium nitrite, potassium carbonate, Sodium thiosulfate, concentrated hydrochloric acid from different companies (Merck, Fluka, BDH, Sigma Aldrich).

**Preparation of 3-(bromoacetyl) coumarin** was prepared according to the method used in reference.<sup>21</sup> Yield (85%). M.p. 165 – 167 °C.

**Preparation of 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol** was prepared according to the method used in reference.<sup>22,23</sup> Yield (64%). Melting point 243 - 245 °C.

**Chalcone (*E*)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (A<sub>1</sub>)**

was prepared according to the method used in the reference.<sup>24</sup> Yield (90%). M.p. 178 - 179 °C.

**Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxy-5-((*E*)-thiazol-2-ylidiazonyl)phenyl) prop-2-en-1-one (C<sub>1</sub>)**

Step [1]: 2-aminothiazole (3.7 mmol, 0.38 g) was dissolved in a solution of water (20 ml) + hydrochloric acid 37% (6 ml) and cooled to (0 – 5 °C). Then of sodium nitrite (4 mmol, 0.28 g) dissolved in water (10 ml) was added with good stirring for 20 minutes to form the corresponding diazonium salt. Step [2]: chalcone (A<sub>1</sub>) (3.7

mmol, 1 g) is dissolved in of ethanolic solution (50 ml) containing potassium hydroxide (22 mmol, 1.25 g) and cooled to (0 – 5 °C). The diazonium solution prepared in the first step was slowly added to the chalcone solution, stirring for 4 hours. After the reaction was complete, the medium was neutralized by adding a dilute hydrochloric acid solution until the litmus paper turned from blue to red. The precipitate was filtered, washed with water and ethanol and finally recrystallized with ethanol to give compound (C<sub>1</sub>). NMR and elemental analysis are used to confirm purity.

**C<sub>1</sub>.** Reddish brown solid; Yield: (1.13 g, 79%); mp 173-175 °C; R<sub>f</sub> = 0.41 (acetone : hexane 1:3); IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$ : 3415 (OH), 2845-2910 (C-H<sub>aliphatic</sub>), 1621-1599 (C=O), 1487-1577 (C=C), 1381 (N=N), 1061-1204 (C-O). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 3.02 (s, 6H, 2 CH<sub>3</sub>), 6.71 (d, 2H, *J* = 8.8 Hz, H<sub>3',5'</sub>), 7.09 (d, 1H, *J* = 7.8 Hz, H<sub>3</sub>), 7.32 (d, 1H, *J* = 1.8 Hz, H<sub>6</sub>), 7.35 (dd, 1H, *J* = 7.8 Hz, *J* = 1.8 Hz, H<sub>4</sub>), 7.48 (d, 1H, *J* = 4 Hz, H<sub>5'',thiazol</sub>), 7.56 (d, 2H, *J* = 8.8 Hz, H<sub>2',6'</sub>), 7.60 (d, 1H, *J* = 14.4 Hz, H <sub>$\alpha$</sub> ), 7.82 (d, 1H, *J* = 4 Hz, H<sub>4'',thiazol</sub>), 7.99 (d, 1H, *J* = 14.4 Hz, H <sub>$\beta$</sub> ), 11.38 (s, 1H, OH). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 40.41 (CH<sub>3</sub>, 2 CH<sub>3</sub>), 111.72 (C<sub>3',5'</sub>), 115.77 (CH <sub>$\alpha$</sub> ), 116.38 (C<sub>3</sub>), 117.71 (C<sub>5''</sub>), 122.75 (C<sub>1</sub>), 123.76 (C<sub>1'</sub>), 124.13 (C<sub>6</sub>), 130.41 (C<sub>4</sub>), 129.27 (C<sub>2',6'</sub>), 140.76 (C<sub>4''</sub>), 145.51 (C<sub>5</sub>), 145.76 (CH <sub>$\beta$</sub> ), 151.45 (C<sub>4'</sub>), 160.97 (C<sub>2''</sub>), 165.45 (C<sub>2</sub>), 192.12 (C=O). Anal Calcd for C<sub>20</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S, C, 63.46; H, 4.80; N, 14.81; S, 8.46 found C, 63.39; H, 4.84; N, 14.86; S, 8.41.

#### Synthesis of (E)-2-(4-(dimethylamino)phenyl)-6-(thiazol-2-yl)diazenyl)-4H-chromen-4-one (C<sub>2</sub>)

azochalcone (C<sub>1</sub>) (1.58 mmol, 0.6 g) was dissolved in DMSO (30 ml), and iodine (0.8 mmol, 0.2 g) was added to the previous solution. The reaction mixture was refluxed for 5 h. After completion of the reaction, the mixture is added to another mixture consisting of crushed ice and a saturated solution of sodium thiosulfate and stirred for 30 minutes. The precipitate was filtered, washed with water and ethanol, and dried. The flavonoid (C<sub>2</sub>) was purified by preparative thin-layer chromatography (P-TLC) using a mobile phase (acetone : hexane 1:3). NMR and elemental analysis are used to confirm purity.

**C<sub>2</sub>.** Yellow solid; Yield: (0.45 g, 76%); mp 157-159 °C; R<sub>f</sub> = 0.32 (acetone : hexane 1:3); IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$ : 2845-2910 (C-H<sub>aliphatic</sub>), 1633-1597 (C=O), 1464-1563 (C=C), 1367 (N=N), 1064-1171 (C-O). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 3.02 (s, 6H, 2 CH<sub>3</sub>), 6.70 (s, 1H, =CH), 6.82 (d, 2H, *J* = 8.6 Hz, H<sub>3',5'</sub>), 7.05 (d, 1H, *J* = 8.6 Hz, H<sub>8</sub>), 7.31 (d, 1H, *J* = 1.9 Hz, H<sub>5</sub>), 7.35 (dd, 1H, *J* = 8.6 Hz, *J* = 1.9 Hz, H<sub>7</sub>), 7.46 (d, 1H, *J* = 4 Hz, H<sub>5'',thiazol</sub>), 7.82 (d, 1H, *J* = 4 Hz, H<sub>4'',thiazol</sub>), 8.05 (d, 2H, *J* = 8.6 Hz, H<sub>2',6'</sub>). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 40.38 (CH<sub>3</sub>, 2 CH<sub>3</sub>), 105.25 (C<sub>3</sub>), 111.74 (C<sub>3',5'</sub>), 115.67 (C<sub>8</sub>), 117.67 (C<sub>5''</sub>), 123.68 (C<sub>1'</sub>), 123.87 (C<sub>5</sub>), 123.97 (C<sub>10</sub>), 129.27 (C<sub>2',6'</sub>), 129.70 (C<sub>7</sub>), 140.48 (C<sub>4''</sub>), 146.32 (C<sub>6</sub>), 152.47 (C<sub>4'</sub>), 157.47 (C<sub>9</sub>), 160.96 (C<sub>2''</sub>), 164.34 (C<sub>2</sub>), 178.90 (C=O pyron). Anal Calcd for C<sub>20</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>S, C, 63.80; H, 4.29; N, 14.84; S, 8.51 found C, 63.76; H, 4.35; N, 14.79; S, 8.54.

#### Synthesis of (E)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxy-5-((E)-4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)phenylprop-2-en-1-one (C<sub>3</sub>)

Step [1]: The aromatic amine 5-(4-aminophenyl)-1,3,4-oxadiazol-2-thiol (5 mmol, 0.96 g) was dissolved in ethanolic solution (50 ml) containing an equivalent amount of potassium hydroxide, the mixture was cooled to (0 – 5 °C) and of concentrated hydrochloric acid (4 ml) was slowly added, then sodium nitrite (5.5 mmol, 0.38 g) dissolved in water (10 ml) was added with good stirring for 20 minutes to form the corresponding diazonium salt. Step [2]: chalcone (5 mmol, 1.335 g) was dissolved in ethanolic solution (50 ml) containing potassium hydroxide (30 mmol, 1.68 g) and cooled to (0 – 5 °C). The diazonium solution prepared in the first step was slowly added to the chalcone solution and stirred for 4 h. After the reaction was complete, the medium was neutralized by adding a dilute hydrochloric acid solution until the litmus paper turned from blue to red. The precipitate was filtered, washed with water and ethanol and finally recrystallized with ethanol to give compound (C<sub>3</sub>). NMR and elemental analysis are used to confirm purity.

**C<sub>3</sub>.** Orange solid; Yield: (1.73 g, 74%); mp 146-148 °C; R<sub>f</sub> = 0.37 (acetone : hexane 2:3); IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$ : 3414 (OH), 2852-2920 (C-H<sub>aliphatic</sub>), 2396 (SH), 1618 (C=O), 1487-1599 (C=C), 1383 (N=N), 1071-1177 (C-O). <sup>1</sup>H-NMR

(400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 3.02 (s, 6H, 2 CH<sub>3</sub>), 6.72 (d, 1H, *J* = 8.8 Hz, H<sub>3',5'</sub>), 7.22 (d, 1H, *J* = 7.8 Hz, H<sub>3</sub>), 7.52 (d, 1H, *J* = 14.3 Hz, H <sub>$\alpha$</sub> ), 7.54 (d, 2H, *J* = 8.8 Hz, H<sub>2',6'</sub>), 7.94 (d, 1H, *J* = 1.9 Hz, H<sub>6</sub>), 7.97 (dd, 1H, *J* = 7.8 Hz, *J* = 1.9 Hz, H<sub>4</sub>), 7.99 (d, 1H, *J* = 14.3 Hz, H <sub>$\beta$</sub> ), 8.06 (d, 2H, *J* = 8 Hz, H<sub>2'',6''</sub>), 8.15 (d, 2H, *J* = 8 Hz, H<sub>3'',5''</sub>), 11.36 (s, 1H, OH), 13.25 (s, 1H, SH). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 40.14 (CH<sub>3</sub>, 2 CH<sub>3</sub>), 112.10 (C<sub>3',5'</sub>), 116.34 (CH <sub>$\alpha$</sub> ), 117.15 (C<sub>3</sub>), 122.55 (C<sub>1</sub>), 123.66 (C<sub>1'</sub>), 124.01 (C<sub>6</sub>), 124.69 (C<sub>2'',6''</sub>), 129.35 (C<sub>4''</sub>), 130.11 (C<sub>4</sub>), 130.46 (C<sub>3'',5''</sub>), 131.39 (C<sub>2',6'</sub>), 145.33 (C<sub>5</sub>), 146.33 (CH <sub>$\beta$</sub> ), 151.19 (C<sub>1''</sub>), 152.45 (C<sub>4'</sub>), 163.69 (C<sub>2'''</sub>), 164.77 (C<sub>2</sub>), 177.66 (C<sub>5'''</sub>), 193.25 (C=O). Anal Calcd for C<sub>25</sub>H<sub>21</sub>N<sub>5</sub>O<sub>3</sub>S, C, 63.68; H, 4.51; N, 14.84; S, 6.79 found C, 63.62; H, 4.57; N, 14.81; S, 6.81.

#### Synthesis of (*E*)-2-(4-(dimethylamino)phenyl)-6-((4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl)diazenyl)-4*H*-chromen-4-one (C<sub>4</sub>)

azochalcone (C<sub>3</sub>) (2.8 mmol, 1.33 g) was dissolved in dimethyl sulfoxide (50 ml), and iodine (1.6 mmol, 0.4 g) was added to the previous solution. The reaction mixture was refluxed for 5 h. After completion of the reaction, the mixture is added to another mixture consisting of crushed ice and a saturated solution of sodium thiosulfate and stirred for 30 minutes. The precipitate was filtered, and washed with water and ethanol. The precipitate was recrystallized with ethanol to give compound (C<sub>4</sub>). NMR and elemental analysis are used to confirm purity.

**C<sub>4</sub>.** Brown solid; Yield: (1.1 g, 84%); mp 195-197 °C; R<sub>f</sub> = 0.29 (acetone : hexane 2:3); IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$ : 2856-2921 (C-H aliphatic), 2359 (SH), 1600 (C=O), 1473-1562 (C=C), 1382 (N=N), 1069-1197 (C-O). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 3.02 (s, 6H, 2 CH<sub>3</sub>), 6.73 (s, 1H, =CH), 6.78 (d, 2H, *J* = 8.8 Hz, H<sub>3',5'</sub>), 7.22 (d, 1H, *J* = 7.8 Hz, H<sub>8</sub>), 7.98 (d, 1H, *J* = 2 Hz, H<sub>5</sub>), 8.01 (dd, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>7</sub>), 8.05 (d, 2H, *J* = 8.8 Hz, H<sub>2',6'</sub>), 8.12 (d, 2H, *J* = 8.2 Hz, H<sub>2'',6''</sub>), 8.17 (d, 2H, *J* = 8.2 Hz, H<sub>3'',5''</sub>), 13.26 (s, 1H, SH). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 40.27 (CH<sub>3</sub>, 2 CH<sub>3</sub>), 105.22 (C<sub>3</sub>), 111.56 (C<sub>3',5'</sub>), 115.36 (C<sub>8</sub>), 122.24 (C<sub>1'</sub>), 123.76 (C<sub>5</sub>), 124.10 (C<sub>10</sub>), 124.52 (C<sub>2'',6''</sub>), 128.71 (C<sub>4''</sub>), 129.11 (C<sub>2',6'</sub>), 129.57 (C<sub>7</sub>), 130.33 (C<sub>3'',5''</sub>), 146.56 (C<sub>6</sub>), 151.96 (C<sub>1''</sub>), 152.44 (C<sub>4'</sub>), 157.80 (C<sub>9</sub>), 163.05 (C<sub>2</sub>), 163.83 (C<sub>2'''</sub>), 177.46 (C<sub>5'''</sub>), 178.69 (C=O pyron). Anal Calcd for C<sub>25</sub>H<sub>19</sub>N<sub>5</sub>O<sub>3</sub>S, C, 63.94; H, 4.09; N, 14.92; S, 6.82 found C, 63.88; H, 4.13; N, 14.87; S, 6.76.

#### Synthesis of (*E*)-3-(2-((5-(4-((2-(4-(dimethylamino) phenyl)-4-oxo-4*H*-chromen-6-yl)diazenyl)phenyl)-1,3,4-oxadiazol-2-yl)thio)acetyl)-2*H*-chromen-2-one (C<sub>5</sub>)

flavonoid compound (C<sub>4</sub>) (0.64 mmol, 0.3 g) was dissolved in of *N,N*-dimethylformamide (DMF) (20 ml), then an excess of potassium carbonate (K<sub>2</sub>CO<sub>3</sub>) was added and stirred for 10 min. To the previous mixture was added bromoacetyl coumarin (0.64 mmol, 0.18 g) dissolved in DMF (5 ml). The reaction mixture was heated for 72 h at 140 °C. After completion of the reaction, the mixture was poured into a beaker containing crushed ice and the medium was neutralized with dilute hydrochloric acid. The precipitate was filtered, washed with water and then recrystallized with absolute ethanol to give compound (C<sub>5</sub>). NMR and elemental analysis are used to confirm purity.

**C<sub>5</sub>.** Brown solid; Yield: (0.35 g, 83.5%); m.p. 320 °C; R<sub>f</sub> = 0.18 (acetone : hexane 2:3); IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$ : 2805-2952 (C-H aliphatic), 1615 (C=O pyrone), 1636 (C=O acetyl), 1736 (C=O lactone), 1410-1522 (C=C), 1384 (N=N), 1079-1197 (C-O). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 3.02 (s, 6H, 2 CH<sub>3</sub>), 4.56 (s, 2H, CH<sub>2</sub>), 6.73 (s, 1H, =CH), 6.78 (d, 2H, *J* = 8.6 Hz, H<sub>3',5'</sub>), 7.22 (d, 2H, *J* = 7.8 Hz, H<sub>8</sub>), 7.36 (td, 1H, *J* = 7.6 Hz, *J* = 1.6 Hz, H<sub>6'''</sub>), 7.44 (dd, 1H, *J* = 7.6 Hz, *J* = 1.6 Hz, H<sub>8'''</sub>), 7.61 (td, 1H, *J* = 7.6 Hz, *J* = 1.6 Hz, H<sub>7'''</sub>), 7.84 (dd, 1H, *J* = 7.6 Hz, *J* = 1.6 Hz, H<sub>5'''</sub>), 7.98 (d, 1H, *J* = 2 Hz, H<sub>5</sub>), 8.01 (dd, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>7</sub>), 8.08 (d, 2H, *J* = 8.6 Hz, H<sub>2',6'</sub>), 8.13 (d, 2H, *J* = 8.2 Hz, H<sub>2'',6''</sub>), 8.19 (d, 2H, *J* = 8.2 Hz, H<sub>3'',5''</sub>), 8.55 (s, 1H, =CH<sub>4'''</sub>). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 40.28 (CH<sub>3</sub>, 2 CH<sub>3</sub>), 43.14 (CH<sub>2</sub>), 105.18 (C<sub>3</sub>), 111.50 (C<sub>3',5'</sub>), 115.39 (C<sub>8</sub>), 115.65 (C<sub>8'''</sub>), 118.43 (C<sub>10'''</sub>), 122.25 (C<sub>1'</sub>), 123.73 (C<sub>5</sub>), 124.15 (C<sub>10</sub>), 124.51 (C<sub>2'',6''</sub>), 125.32 (C<sub>6'''</sub>), 127.84 (C<sub>5'''</sub>), 128.70 (C<sub>4''</sub>), 129.14 (C<sub>2',6'</sub>), 129.29 (C<sub>7'''</sub>), 129.61 (C<sub>7</sub>), 130.31 (C<sub>3'',5''</sub>), 130.77 (C<sub>3'''</sub>), 136.72 (C<sub>4'''</sub>), 146.36 (C<sub>6</sub>), 151.95 (C<sub>1''</sub>), 152.42 (C<sub>4'</sub>), 152.89 (C<sub>9'''</sub>), 157.82 (C<sub>9</sub>),

160.11 (C=O lactone), 163.07 (C<sub>2</sub>), 163.88 (C<sub>2''</sub>), 168.40 (C<sub>5''</sub>), 178.76 (C=O pyron), 192.39 (C=O ketone). Anal Calcd for C<sub>36</sub>H<sub>25</sub>N<sub>5</sub>O<sub>6</sub>S, C, 65.94; H, 3.84; N, 10.69; S, 4.88 found C, 63.87; H, 3.82; N, 10.72; S, 4.90.

### Synthesis of (E)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxy-5-((E)-(2-hydroxyphenyl)diazenyl)phenyl)prop-2-en-1-one (C<sub>6</sub>)

Step [1]: 2-Aminophenol (5 mmol, 0.56 g) was dissolved in ethanolic solution (30 ml) containing an equivalent amount of potassium hydroxide and cooled to (0 – 5 °C), and of concentrated hydrochloric acid (4 ml) was slowly added, then sodium nitrite (5.5 mmol, 0.38 g) dissolved in water (10 ml) was added with good stirring for 20 minutes to form the corresponding diazonium salt. Step [2]: chalcone (A<sub>1</sub>) (5 mmol, 1.335 g) is dissolved in ethanolic solution (50 ml) containing potassium hydroxide (30 mmol, 1.7 g) and cooled to (0 – 5 °C). The diazonium solution prepared in the first step was slowly added to the chalcone solution, stirring for 4 hours. After the reaction was complete, the medium was neutralized by adding a dilute hydrochloric acid solution until the litmus paper turned from blue to red. The precipitate was filtered, washed with water and ethanol and finally recrystallized with ethanol to give compound (C<sub>6</sub>). NMR and elemental analysis are used to confirm purity.

C<sub>6</sub>. Reddish brown solid; Yield: (1.41 g, 74%); m.p. 162-164 °C; R<sub>f</sub> = 0.47 (acetone : hexane 1:3); IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$ : 3415 (OH), 2852-2919 (C-H<sub>aliphatic</sub>), 1621 (C=O), 1487-1599 (C=C), 1382 (N=N), 1124-1277 (C-O). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 3.02 (s, 6H, 2 CH<sub>3</sub>), 6.72 (d, 2H, *J* = 8.6 Hz, H<sub>3',5'</sub>), 7.03 (dd, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>3''</sub>), 7.14 (td, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>5''</sub>), 7.22 (d, 1H, *J* = 7.8 Hz, H<sub>3</sub>), 7.41 (td, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>4''</sub>), 7.50 (d, 2H, *J* = 8.6 Hz, H<sub>2',6'</sub>), 7.55 (d, 1H, *J* = 14.4 Hz, CH <sub>$\alpha$</sub> ), 7.71 (dd, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>6''</sub>), 7.91 (d, 1H, *J* = 2 Hz, H<sub>6</sub>), 7.92 (dd, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>4</sub>), 8.02 (d, 1H, *J* = 14.4 Hz, H <sub>$\beta$</sub> ), 10.12 (s, 1H, OH), 11.41 (s, 1H, OH). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 40.22 (CH<sub>3</sub>, 2 CH<sub>3</sub>), 111.94 (C<sub>3',5'</sub>), 116.63 (CH <sub>$\alpha$</sub> ), 117.06 (C<sub>3</sub>), 118.52 (C<sub>3''</sub>), 121.21 (C<sub>5''</sub>), 122.84 (C<sub>1</sub>), 123.61 (C<sub>1'</sub>), 123.77 (C<sub>6</sub>), 124.75 (C<sub>6''</sub>), 126.17 (C<sub>1''</sub>), 130.43 (C<sub>4</sub>), 130.91 (C<sub>2',6'</sub>), 132.14 (C<sub>4''</sub>), 145.35 (C<sub>5</sub>), 146.34 (CH <sub>$\beta$</sub> ), 152.25 (C<sub>4'</sub>), 155.23 (C<sub>2''</sub>), 164.83 (C<sub>2</sub>), 191.94 (C=O). Anal Calcd for C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>, C, 71.29; H, 5.46; N, 10.84; found C, 71.24; H, 5.42; N, 10.87.

### Synthesis of (E)-2-(4-(dimethylamino)phenyl)-6-((2-hydroxyphenyl)diazenyl)-4H-chromen-4-one (C<sub>7</sub>)

azochalcone (C<sub>6</sub>) (1.25 mmol, 0.5 g) was dissolved in DMSO (30 ml), and iodine (0.4 mmol, 0.1 g) was added to the previous solution. The reaction mixture was refluxed for 6 h. After completion of the reaction, the mixture is added to another mixture consisting of crushed ice and a saturated solution of sodium thiosulfate and stirred for 30 minutes. The precipitate was filtered, washed with water and ethanol, and dried. The flavonoid (C<sub>7</sub>) was purified by preparative thin-layer chromatography (P-TLC) using a mobile phase (acetone : hexane 1:3). NMR and elemental analysis are used to confirm purity.

C<sub>7</sub>. Yellow solid; Yield: (0.7 g, 70%); m.p. 153-155 °C; R<sub>f</sub> = 0.25 (acetone : hexane 1:3); IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$ : 3425 (OH), 2857-2924 (C-H<sub>aliphatic</sub>), 1630 (C=O), 1524-1584 (C=C), 1383 (N=N), 1062-1203 (C-O). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 3.02 (s, 6H, 2 CH<sub>3</sub>), 6.70 (s, 1H, CH), 6.81 (d, 2H, *J* = 8.2 Hz, H<sub>3',5'</sub>), 7.03 (dd, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>3''</sub>), 7.16 (td, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>5''</sub>), 7.24 (d, 1H, *J* = 7.9 Hz, H<sub>8</sub>), 7.43 (td, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>4''</sub>), 7.71 (dd, 1H, *J* = 7.8 Hz, *J* = 2 Hz, H<sub>6''</sub>), 8.02 (d, 1H, *J* = 2.1 Hz, H<sub>5</sub>), 8.04 (dd, 1H, *J* = 7.9 Hz, *J* = 2.1 Hz, H<sub>7</sub>), 8.12 (d, 2H, *J* = 8.2 Hz, H<sub>2',6'</sub>), 9.97 (s, 1H, OH). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 40.38 (CH<sub>3</sub>, 2 CH<sub>3</sub>), 105.06 (C<sub>3</sub>), 111.74 (C<sub>3',5'</sub>), 115.35 (C<sub>8</sub>), 118.42 (C<sub>3''</sub>), 121.15 (C<sub>5''</sub>), 122.47 (C<sub>1'</sub>), 123.64 (C<sub>5</sub>), 124.13 (C<sub>10</sub>), 124.37 (C<sub>6''</sub>), 127.10 (C<sub>1''</sub>), 129.15 (C<sub>2',6'</sub>), 129.78 (C<sub>7</sub>), 131.83 (C<sub>4''</sub>), 146.14 (C<sub>6</sub>), 152.38 (C<sub>4'</sub>), 156.23 (C<sub>2''</sub>), 157.26 (C<sub>9</sub>), 163.64 (C<sub>2</sub>), 179.17 (C=O pyron). Anal Calcd for C<sub>23</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>, C, 71.66; H, 4.97; N, 10.89; found C, 71.61; H, 5.02; N, 10.85.

### Synthesis of (E)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxy-5-((E)-(4-hydroxyphenyl)diazenyl)phenyl)prop-2-en-1-one (C<sub>8</sub>)

Step [1]: 2-Aminophenol (5 mmol, 0.56 g) was dissolved in ethanolic solution (30 ml) containing an equivalent amount of potassium hydroxide and cooled to (0 – 5 °C), and concentrated hydrochloric acid (4 ml) was slowly

added, then sodium nitrite (5.5 mmol, 0.38 g) dissolved in water (10 ml) was added with good stirring for 20 minutes to form the corresponding diazonium salt. Step [2]: chalcone (A<sub>1</sub>) (5 mmol, 1.335 g) is dissolved in ethanolic solution (50 ml) containing potassium hydroxide (30 mmol, 1.7 g) and cooled to (0 – 5 °C).

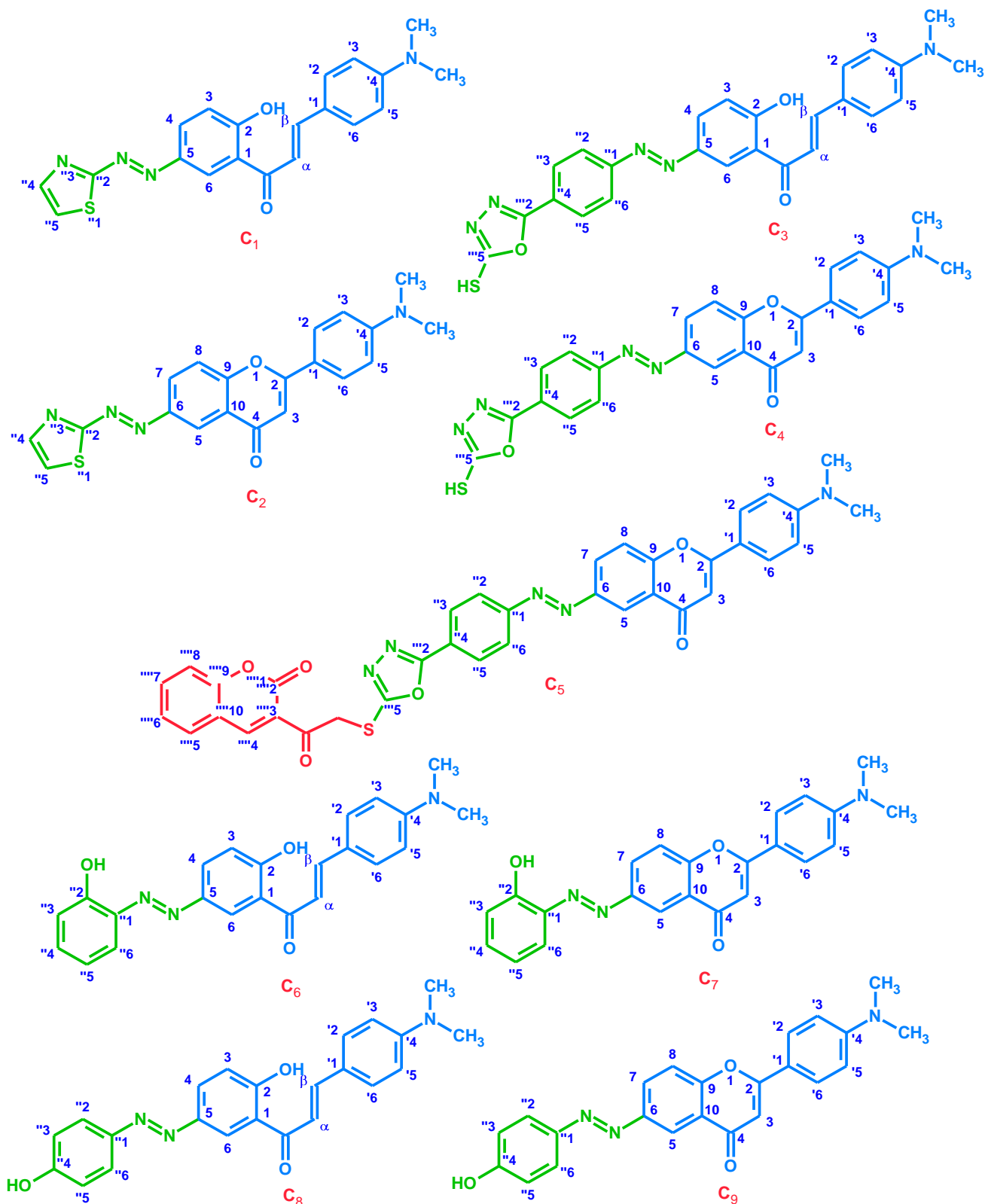


Figure 2. numbering of carbon atoms in flavonoid structures.

The diazonium solution prepared in the first step was slowly added to the chalcone solution, stirring for 4 hours. After the reaction was complete, the medium was neutralized by adding a dilute hydrochloric acid solution until the litmus paper turned from blue to red. The precipitate was filtered, washed with water and ethanol and finally recrystallized with ethanol to give compound (C<sub>8</sub>). NMR and elemental analysis are used to confirm purity.

**C<sub>8</sub>**. Reddish brown solid; Yield: (1.49 g, 78%); m.p. 169-170 °C; R<sub>f</sub> = 0.4 (acetone : hexane 1:3); IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$ : 3415 (OH), 2852-2919 (C-H<sub>aliphatic</sub>), 1620 (C=O), 1487-1599 (C=C), 1382 (N=N), 1125-1177 (C-O). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 3.01 (s, 6H, 2 CH<sub>3</sub>), 6.73 (d, 2H, *J* = 8.4 Hz, H<sub>3',5'</sub>), 6.90 (d, 2H, *J* = 8.2 Hz, H<sub>3'',5''</sub>), 7.21 (d, 1H, *J* = 8 Hz, H<sub>3</sub>), 7.51 (d, 2H, *J* = 8.4 Hz, H<sub>2',6'</sub>), 7.55 (d, 1H, *J* = 14.3 Hz, CH <sub>$\alpha$</sub> ), 7.73 (d, 2H, *J* = 8.2 Hz, H<sub>2'',6''</sub>), 7.93 (d, 1H, *J* = 2 Hz, H<sub>6</sub>), 7.96 (dd, 1H, *J* = 8 Hz, *J* = 2 Hz, H<sub>4</sub>), 8.02 (d, 1H, *J* = 14.3 Hz, CH <sub>$\beta$</sub> ), 9.67 (s, 1H, OH), 11.32 (s, 1H, OH). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 40.13 (CH<sub>3</sub>, 2 CH<sub>3</sub>), 112.13 (C<sub>3',5'</sub>), 115.73 (CH <sub>$\alpha$</sub> ), 117.23 (C<sub>3</sub>), 116.34 (C<sub>3'',5''</sub>), 122.72 (C<sub>1</sub>), 123.72 (C<sub>1'</sub>), 124.11 (C<sub>6</sub>), 122.95 (C<sub>2'',6''</sub>), 144.92 (C<sub>1''</sub>), 130.33 (C<sub>4</sub>), 131.38 (C<sub>2',6'</sub>), 162.41 (C<sub>4''</sub>), 145.42 (C<sub>5</sub>), 146.58 (CH <sub>$\beta$</sub> ), 152.30 (C<sub>4'</sub>), 164.52 (C<sub>2</sub>), 193.03 (C=O). Anal Calcd for C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>, C, 71.30; H, 5.45; N, 10.85; found C, 71.26; H, 5.40; N, 10.88.

#### Synthesis of (*E*)-2-(4-(dimethylamino)phenyl)-6-((4-hydroxyphenyl)diazenyl)-4*H*-chromen-4-one (C<sub>9</sub>)

azochalcone (C<sub>8</sub>) (1.25 mmol, 0.5 g) was dissolved in DMSO (30 ml), and iodine (0.4 mmol, 0.1 g) was added to the previous solution. The reaction mixture was refluxed for 6 h. After completion of the reaction, the mixture is added to another mixture consisting of crushed ice and a saturated solution of sodium thiosulfate and stirred for 30 minutes. The precipitate was filtered, washed with water and ethanol, and dried. The flavonoid (C<sub>9</sub>) was purified by preparative thin-layer chromatography (P-TLC) using a mobile phase (acetone : hexane 1:3).

**C<sub>9</sub>**. Yellow solid; Yield: (0.84 g, 85%); m.p. 185-187 °C; R<sub>f</sub> = 0.24 (acetone : hexane 1:3); IR (KBr, cm<sup>-1</sup>)  $\nu_{\max}$ : 3420 (OH), 2854-2922 (C-H<sub>aliphatic</sub>), 1599-1632 (C=O), 1474-1564 (C=C), 1368 (N=N), 1042-1259 (C-O). <sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 3.02 (s, 6H, 2 CH<sub>3</sub>), 6.71 (s, 1H, CH), 6.81 (d, 2H, *J* = 8.6 Hz, H<sub>3',5'</sub>), 6.89 (d, 2H, *J* = 7.8 Hz, H<sub>3'',5''</sub>), 7.23 (d, 1H, *J* = 8.3 Hz, H<sub>8</sub>), 7.70 (d, 2H, *J* = 7.8 Hz, H<sub>2'',6''</sub>), 8.02 (d, 1H, *J* = 1.8 Hz, H<sub>5</sub>), 8.05 (dd, 2H, *J* = 8.3 Hz, *J* = 1.8 Hz, H<sub>7</sub>), 8.09 (d, 2H, *J* = 8.6 Hz, H<sub>2',6'</sub>), 9.59 (s, 1H, OH). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>,  $\delta$  ppm): 40.20 (CH<sub>3</sub>, 2 CH<sub>3</sub>), 105.15 (C<sub>3</sub>), 111.85 (C<sub>3',5'</sub>), 115.46 (C<sub>8</sub>), 116.27 (C<sub>3'',5''</sub>), 122.36 (C<sub>1'</sub>), 123.72 (C<sub>5</sub>), 124.05 (C<sub>10</sub>), 124.35 (C<sub>2'',6''</sub>), 129.26 (C<sub>2',6'</sub>), 129.87 (C<sub>7</sub>), 145.12 (C<sub>1''</sub>), 146.35 (C<sub>6</sub>), 152.46 (C<sub>4'</sub>), 157.54 (C<sub>9</sub>), 162.08 (C<sub>4''</sub>), 163.83 (C<sub>2</sub>), 178.54 (C=O pyron). Anal Calcd for C<sub>23</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>, C, 71.68; H, 4.97; N, 10.90; found C, 71.65; H, 5.01; N, 10.86.

## Supplementary Material

Supplementary content are attached to the manuscript

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