



# Antioxidant activities of imino chromene derivatives with add alkyl tail: synthesis and characterisation

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## Abstract

The reaction between substituted 4-hydroxy benzaldehyde, active methylene compounds imino chromene derivatives. Structures of these were established upon the basis of IR, <sup>1</sup>HNMR, <sup>13</sup>CNMR, and MASS data. In vitro, antioxidants activities of these compounds against super oxide anion radical, nitric oxide radical, DPPH radical and hydrogen peroxide were evaluated and compared with standard natural antioxidants ascorbic acid.

## Keywords

chromenes, imines, amines, antioxidants

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## 1. Introduction

Multicomponent reactions (MCRs) are reactions where numerous reactants involved in single synthetic operation and give new compounds. [1] This type of reactions avoids purification process and often wide variety of complex molecule in a single step, inturn it is very useful for saving solvent and reagents. Among many heterocyclic compounds, chromenes are very important due to its biological activity such as antioxidants, [2] anticancer, anti-microbial, [3] anti-inflammatory, [4] anti-HIV, [5] and anti-tumor, [6] alzimer disease [7] antihypertensive [8] and antileishmanial. [9] There are many reports shown that synthesis of different chromene derivatives and its applications (Figure 1). [1, 10, 11] A Knoevenagel condensation is the reaction between salicylaldehyde with active methylene compounds followed by intramolecular cyclisation to give imino derivatives [11]. As per reports, different products are obtained by control of a solvent, ratio of reagents and

temperature [3] *etc.*, Due to importance of these chromene derivatives, numerous green approaches have been developed under distinct conditions like thermal heating, microwave, ultrasonic, electrochemical, infrared, and solvent free conditions. We could not find many reports on variation of an alkyl side chain to see the effect on antioxidant properties of chromene derivatives. So we are motivated to synthesis imino and amino chromenes by taking alkylated aldehyde and malonitrile. Currently, many investigations are going on effect of free radicals in biological systems such as lipids, DNA and protein, also create many diseases like atherosclerosis, neurodegenerative disease, rheumatoid arthritis, age related disease, cancer initiation and tumor. [12, 13, 14] It is necessary to keep a proper level of natural antioxidant such as vitamin E, C and glutathione in a biological system in order to avoid serious health problems. [15, 16, 17] All these health problems are caused by action of free radical oxygen (ROS) and reactive nitrogen (RNS) species, commonly known as (RSs) [18, 19].

## 2. Results and Discussion

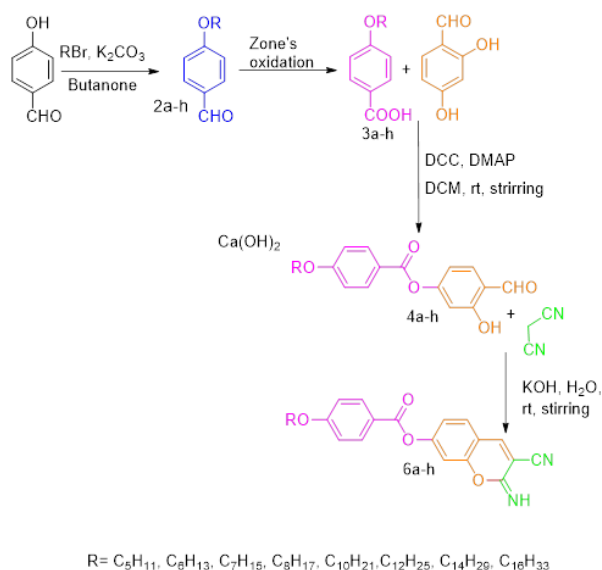
### Antioxidant activities

In the present study, antioxidant potential of synthesized 3-cyano-2-imino-2H-chromen-7-yl 4-(alkyloxy)benzoate (6a-h) were studied using DPPH, NO, O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub> radical scavenging technique by spectrophotometrically. Radical scavenging activities of all derivatives were determined from the interacting ability of derivatives with DPPH, NO, O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub> radicals. The antioxidant activities were expressed as 50% inhibitory concentration values in Table 2,

**Table 1.** Antioxidant activity of chromene derivatives (6a-h)

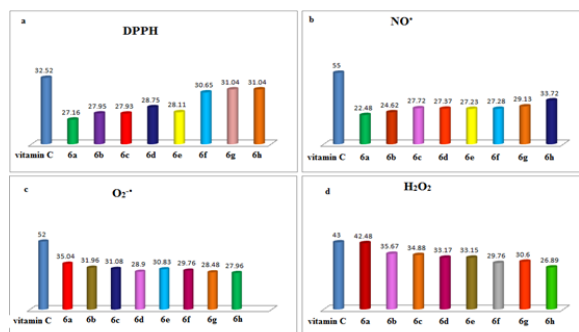
SNo	Entry	IC <sub>50</sub> ( $\mu$ M)			
		DPPH	NO $\cdot$	O <sub>2</sub> $\cdot^-$	H <sub>2</sub> O <sub>2</sub>
1	Vitamin C	32.52 $\pm$ 0.11	55.00 $\pm$ 0.12	52.00 $\pm$ 0.56	43.00 $\pm$ 0.65
2	6a	27.16 $\pm$ 0.41	22.48 $\pm$ 0.41	35.04 $\pm$ 0.49	42.48 $\pm$ 0.82
3	6b	27.95 $\pm$ 0.32	24.62 $\pm$ 0.03	31.96 $\pm$ 0.38	35.67 $\pm$ 0.15
4	6c	27.93 $\pm$ 0.36	27.72 $\pm$ 0.36	31.08 $\pm$ 0.40	34.88 $\pm$ 0.38
5	6d	28.75 $\pm$ 0.18	27.37 $\pm$ 0.92	28.90 $\pm$ 0.11	33.17 $\pm$ 0.54
6	6e	28.11 $\pm$ 0.22	27.23 $\pm$ 0.23	30.83 $\pm$ 0.92	33.15 $\pm$ 0.45
7	6f	30.65 $\pm$ 0.38	27.28 $\pm$ 0.53	29.76 $\pm$ 0.36	29.76 $\pm$ 0.43
8	6g	31.04 $\pm$ 0.58	29.13 $\pm$ 0.35	28.48 $\pm$ 0.53	30.60 $\pm$ 0.82
9	6h	31.04 $\pm$ 0.45	33.72 $\pm$ 0.18	27.96 $\pm$ 0.13	26.89 $\pm$ 0.22

Figure 2, and compared with that of standard ascorbic acid. The hydrogen donating ability of amines and imine groups present as part of all synthesized derivatives in the series 5a-h and 6a-h might be responsible for their antioxidant properties. Lower IC<sub>50</sub> value gives better radical-scavenging activity. From the table, it was clear that almost all the compounds were shown radical scavenging activities in DPPH assay. It was important to note that **6a**, **6b** and **6c**

**Figure 1.** Synthetic procedures for series 5 and 6

shown better DPPH scavenging activity than vitamin C with IC<sub>50</sub> values 27.16, 27.95 and 27.93  $\mu$ M respectively. The DPPH activities of tested were found to be in the decreasing order of **6a**, **6c**, **6b**, **6e**, **6d**, **6f**, **6g** and **6h**. We can find in case of NO radical scavenging activities, compound 6a and 6b have very low IC<sub>50</sub> values are 22.48 and 24.52  $\mu$ M respectively. The decreasing orders of antioxidant activity of these compounds were 6a, 6b, 6e, 6d, 6c, 6f, 6g and 6h. The results of the NO assay were expressed as IC<sub>50</sub> values in Table 2 revealed that **6h**, **6g** showed better super oxide radical scavenging activity than natural antioxidant vitamin C with IC<sub>50</sub> of 27.96, and 28.48  $\mu$ M respectively. Surprisingly, IC<sub>50</sub> values of all synthesized derivatives were lower than IC<sub>50</sub> Vitamin C. The super oxide anion radical scavenging activities of tested

was found to be in the decreasing order of **6h**, **6g**, **6d**, **6f**, **6e**, **6c**, **6b**, **6a** and Vitamin C. The hydrogen peroxide radical scavenging activities of tested was found to be in the decreasing order of **6h**, **6f**, **6g**, **6e**, **6d**, **6c**, **6b**, **6a** and Vitamin C.

**Figure 2.** Antioxidant activity of 6a-h in IC<sub>50</sub> values

### 3. Experimental

<sup>1</sup>H NMR spectra were recorded using Bruker (300MHz) spectrometer. For the <sup>1</sup>H NMR spectra, the chemical shifts are reported in ppm relative to SiMe<sub>4</sub>(TMS) as an internal standard and coupling constants are presented in Hz. Infrared spectra were recorded on JASCO- FTIR spectrometer(4000-400cm<sup>-1</sup>); the spectral positions are given in wave numbers (cm<sup>-1</sup>). Electrospray ionization mass spectrometry (ESI-MS) analysis was performed in the negative ion mode on a liquid chromatography-ion trap mass spectrometer (LCQ Fleet, Thermo Fisher Instruments Limited, US). Spectra of these compounds were given in supplementary information. The DPPH radical scavenging activity of the compounds was measured according to the method of Blios.<sup>20</sup> The assay of nitric oxide (NO $\cdot$ ) scavenging activity is measured based on method reported. [21] The ability of the compounds to scavenge hydrogen peroxide was determined using the method available in literature. [22] The superoxide anion radical (O<sub>2</sub> $\cdot^-$ ) scavenging assay was based on the capacity of the complexes to inhibit formazan formation by scavenging the superoxide radicals generated in the riboflavin-light-NBT system [23].

#### 3.1 General procedure for the preparation of 3-cyano-2-imino-2H-chromen-7-yl-4(pentyloxy) benzoate: 6a-h

To a stirred solution of 4-formyl-3-hydroxy phenyl 4- (pentyloxy) benzoate (0.08 Mol, 1eq) and malononitrile (0.081 Mol, 1eq) in water (50 mL) was added excess amount of KOH. The resulting mixture was stirred for 5 min at room temperature. The formed precipitate was isolated by filtration and washed with ethanol to get pure product as yellow solid and was recrystallized from ethanol to obtain a white solid.

#### 3.5a 3-cyano-2-imino-2H-chromen-7-yl 4-(methyloxy) benzoate (6a)

**Mp:** 170°C; **Y=**70%; white solid; **IR,  $\nu$  max(KBr, cm<sup>-1</sup>):** 3433.85 (NH), 2227.98 (C=N), 1602.66 (-C=C-), 1724 (C=O),



3058 Ar(C-H), 2883.69 Aliphatic (C-H);  $^1\text{H NMR}$  (300 MHz, DMSO- $d_6$ ):  $\delta$  = 8.58 (1H, s, -C=NH), 8.04 (d,  $J$ =9.0Hz, 2H, ArH), 7.76 (d,  $J$ =9.0Hz, 1H, ArH), 7.61 (s, 1H, C=CH), 7.27-7.25 (m, 2H, ArH), 6.93 (d,  $J$ =9.0Hz, 2H, ArH), 3.98 (t,  $J$ =6.0Hz, 2H, O-CH<sub>2</sub>), 1.78-1.69 (m, 2H, CH<sub>2</sub>), 1.38-1.32 (m, 4H, CH<sub>2</sub>) 0.85 (t,  $J$ =9.0Hz, 3H, -CH<sub>3</sub>);  $^{13}\text{C-NMR}$  (75 MHz, DMSO- $d_6$ ): 164.08, 156.53, 155.29, 152.43, 132.51, 130.86, 119.97, 115.01, 114.59, 110.72, 101.69, 68.37, 28.63, 28.00, 22.30, 14.02; MS (EI):  $m/z$ =377.17( $M^+$ ).

### 3.5b 3-cyano-2-imino-2H-chromen-7-yl 4-(penyloxy) benzoate (6b)

**Mp:** 132°C; **Y**=75%; white solid; **IR**,  $\nu_{\max}$ (KBr,  $\text{cm}^{-1}$ ): 3446.64 (NH), 2227.98 (C=N), 1609.06 (-C=C-), 1733.80 (C=O), 3058 Ar(C-H), 2874.50 Aliphatic (C-H);  $^1\text{H NMR}$  (300 MHz, DMSO- $d_6$ ):  $\delta$ =8.59 (1H, s, C=NH) 8.12 (d,  $J$ =9.0 Hz, 2H, ArH), 7.8 (d,  $J$ =6.0Hz, 1H, ArH), 7.58 (s, 1H, C=CH), 7.36 (m, 2H, ArH), 7.02 (d,  $J$ =6.0Hz, 2H, ArH), 4.09 (t,  $J$ =6.0Hz, 2H, O-CH<sub>2</sub>), 1.83 (m, 2H, CH<sub>2</sub>), 1.50 (m, 6H), 0.93 (t,  $J$ =6.0Hz, 3H, -CH<sub>3</sub>);  $^{13}\text{C NMR}$  (75 MHz, DMSO- $d_6$ ): 161.26, 157.01, 140.04, 137.21, 124.68, 119.28, 115.44, 73.09, 58.44, 36.10, 33.60, 31.22, 30.21, 27.16, 18.71; MS (EI):  $m/z$ =391.50( $M^+$ ).

### 3.5c 3-cyano-2-imino-2H-chromen-7-yl 4-(pentyloxy) benzoate (6c);

**Mp:** 140°C; **Y**=85%; white solid; **IR**,  $\nu_{\max}$ (KBr,  $\text{cm}^{-1}$ ): 3456.24 (NH), 2227.98 (C=N), 1613.86 (-C=C-), 1738.60 (C=O), 3058 Ar(C-H), 2883.69 Aliphatic (C-H);  $^1\text{H NMR}$  (300 MHz, DMSO- $d_6$ ):  $\delta$ =8.69 (1H, s, C=NH), 8.15 (d,  $J$ =9.0Hz, 2H, ArH), 7.87 (d,  $J$ =6.0Hz, 1H, ArH), 7.70 (s, 1H, C=CH), 7.39 (m, 2H, ArH), 7.06 (d,  $J$ =9.0Hz, 2H, ArH), 4.10 (t,  $J$ =6.0Hz, 2H, OCH<sub>2</sub>), 1.86 (m, 2H, CH<sub>2</sub>) 1.51 (m, 9H), 0.93 (t,  $J$ =6.0Hz, 3H, CH<sub>3</sub>);  $^{13}\text{C NMR}$  (75 MHz, DMSO- $d_6$ ): 164.27, 163.66, 156.80, 156.10, 155.55, 132.58, 130.06, 125.06, 120.17, 120.01, 114.70, 114.64, 111.05, 102.39, 68.52, 31.71, 29.05, 28.96, 25.91, 22.54, 13.98; MS (EI):  $m/z$ =405.17( $M^+$ ).

### 3.5d 3-cyano-2-imino-2H-chromen-7-yl 4-(heptyloxy) benzoate (6d)

**Mp:** 120°C; **Y**=80%; white solid; **IR**,  $\nu_{\max}$ (KBr,  $\text{cm}^{-1}$ ): 3437.05 (NH), 2227.81 (C=N), 1725.81 (-C=C-), 1610.60 (C=O). 3078.80 Ar(C-H), 2874.10 Aliphatic (C-H);  $^1\text{H-NMR}$  (300 MHz, DMSO- $d_6$ ):  $\delta$  = 8.69 (1H, s, C=NH) 8.13 (d,  $J$ =9.0 Hz, 2H, ArH), 7.86 (d,  $J$ =9.0Hz, 1H, ArH), 7.72 (s, 1H, -C=CH), 7.37-7.35 (m, 2H, ArH), 7.03 (d,  $J$ =9.0Hz, 2H, ArH), 4.08 (t,  $J$ =6.0Hz, 2H, OCH<sub>2</sub>), 1.85-1.80 (m, 2H, CH<sub>2</sub>) 1.49-1.30 (m, 10H), 0.89 (t,  $J$ =6.0Hz, 3H, CH<sub>3</sub>);  $^{13}\text{C NMR}$  (75 MHz, DMSO- $d_6$ ): 164.30, 163.68, 156.82, 156.10, 155.58, 151.04, 132.60, 130.04, 120.19, 120.02, 115.47, 114.66, 113.47, 111.08, 102.45, 68.54, 31.77, 29.28, 25.96, 22.61, 14.02; MS (EI):  $m/z$ = 442.25( $M^+$ ).

### 3.5e 3-cyano-2-imino-2H-chromen-7-yl 4-(nonanyloxy) benzoate (6e)

**Mp:** 116°C; **Y**=80%; white solid; **IR**,  $\nu_{\max}$ (KBr,  $\text{cm}^{-1}$ ): 3437.05 (NH), 2226.38 (C=N), 1612.26 (-C=C-), 1737(C=O), 3078.80 Ar(C-H), 2862.90 Aliphatic (C-H).  $^1\text{H NMR}$  (300 MHz, DMSO- $d_6$ ):  $\delta$ = 8.61 (1H, s, C=NH), 8.13 (d,  $J$ =9.0 Hz, 2H, ArH), 7.82 (d,  $J$ =6.0Hz, 1H, ArH), 7.60 (s, 1H, -C=CH), 7.36-7.35 (m, 2H, ArH), 7.02(d,  $J$ =9.0 Hz, 2H, ArH), 4.07 (t,  $J$ =6.0Hz, 2H, O-CH<sub>2</sub>), 1.85-1.78 (m, 2H, CH<sub>2</sub>) 1.48-1.28 (m, 14H, CH<sub>2</sub>), 0.88 (t,  $J$ =6.9Hz, 3H, CH<sub>3</sub>);  $^{13}\text{CNMR}$  (75 MHz, DMSO- $d_6$ ): 164.44, 164.03, 163.95, 159.66, 155.67, 133.05, 132.92, 120.36, 115.07, 111.09, 102.01, 68.80, 32.18, 29.83, 29.59, 29.37, 26.28, 22.98, 14.63; MS (EI):  $m/z$ = 447.33( $M^+$ ).

### 3.5f 3-cyano-2-imino-2H-chromen-7-yl 4-(undecyloxy) benzoate (6f)

**Mp:** 124°C; **Y**=75%; white solid; **IR**,  $\nu_{\max}$ (KBr,  $\text{cm}^{-1}$ ): 3427.45 (NH), 2227.98 (C=N), 1613.86 (-C=C-), 1738.60 (C=O). 3048.42 Ar(C-H), 2842.11 Aliphatic (C-H);  $^1\text{H NMR}$  (300 MHz, DMSO- $d_6$ )  $\delta$ =8.66 (1H, s, C=NH), 8.13 (d,  $J$ =9.0 Hz, 2H, ArH), 7.84 (d,  $J$ =6.0Hz, 1H, ArH), 7.68 (s, 1H, -C=CH), 7.37-7.36 (m, 2H, ArH), 7.03 (d,  $J$ =9.0Hz, 2H, Ar), 4.07 (t,  $J$ =6.0Hz, 2H, O-CH<sub>2</sub>), 1.85-1.80 (m, 2H, CH<sub>2</sub>) 1.48-1.27 (m, 18H), 0.88 (t,  $J$ =6.0Hz, 3H, -CH<sub>3</sub>);  $^{13}\text{C NMR}$  (75 MHz, DMSO- $d_6$ ): 164.44, 164.03, 163.95, 159.66, 155.67, 133.05, 132.92, 120.36, 115.07, 111.09, 102.01, 68.80, 32.18, 29.83, 29.59, 29.37, 26.28, 22.98, 14.63; MS (EI):  $m/z$ = 475.33( $M^+$ ).

### 3.5g 3-cyano-2-imino-2H-chromen-7-yl 4-(tridecyloxy) benzoate (6g)

**Mp:** 108°C; **Y**=80%; white solid; **IR**,  $\nu_{\max}$ (KBr,  $\text{cm}^{-1}$ ): 3435.45 (NH), 2226.38 (C=N), 1602.66 (-C=C-), 1737 (C=O), 3048.42 (Ar(C-H), 2874.10 Aliphatic (C-H).  $^1\text{H NMR}$  (300 MHz, DMSO- $d_6$ ):  $\delta$  = 8.60 (1H, s, C=NH), 8.05 (d,  $J$ =9.0 Hz, 2H, ArH), 7.77 (d,  $J$ =6.0 Hz, 1H, ArH), 7.64 (s, 1H, -C=CH), 7.28-7.26 (m, 2H, ArH), 6.95 (d,  $J$ =9.0 Hz, 2H, ArH), 3.99 (t,  $J$ =6.0Hz, 2H, O-CH<sub>2</sub>), 1.77-1.72 (m, 2H, - (CH<sub>2</sub>)-) 1.40-1.18 (m, 22H), 0.80 (t,  $J$ =6.0Hz, 3H, -CH<sub>3</sub>).  $^{13}\text{C-NMR}$  (75 MHz, DMSO- $d_6$ ): 168.87, 161.31, 160.08, 157.12, 137.24, 135.60, 124.65, 119.78, 119.40, 115.43, 106.47, 73.18, 36.51, 34.26, 34.16, 33.93, 33.93, 33.69, 30.59, 27.27, 18.82; MS (EI):  $m/z$ = 503.33( $M^+$ ).

### 3.5h 3-cyano-2-imino-2H-chromen-7-yl 4-(hexadecyloxy) benzoate (6h)

**Mp:** 143°C; **Y**=70%; white solid; **IR**,  $\nu_{\max}$ (KBr,  $\text{cm}^{-1}$ ): 3437.05 (NH), 2227.98 (C=N), 1604.26 (-C=C-), 1738.60(C=O), 3058 (Ar(C-H), 2862.90 Aliphatic (C-H).  $^1\text{H NMR}$  (300 MHz, DMSO- $d_6$ ):  $\delta$  = 8.67 (1H, s, -C=NH), 8.13 (d,  $J$ =9.0Hz, 2H, ArH), 7.92 (d,  $J$ =9.0Hz, 1H, ArH), 7.69 (s, 1H, -C=CH), 7.36-7.34 (m, 2H, ArH), 6.99 (d,  $J$ =9.0 Hz, 2H, ArH), 4.07 (t,  $J$ =6.0Hz, 2H, O-CH<sub>2</sub>), 1.82-1.80 (m, 2H, (CH<sub>2</sub>)-) 1.46-1.16 (m, 26H), 0.87 (t,  $J$ =6.0Hz, 3H, (-CH<sub>3</sub>)).  $^{13}\text{C NMR}$  (75 MHz, DMSO- $d_6$ ): 168.87, 161.31, 160.08, 157.12, 137.24, 135.60, 124.65, 119.78, 119.40, 115.43, 106.47, 73.18, 36.51,



34.26, 34.16, 33.93, 33.93, 33.69, 30.59, 27.27, 18.82; MS (EI): $m/z=$  531.33( $M^+$ ).

#### 4. Conclusion

A series of 3-cyano-2-imino-2H-chromen-7-yl 4-(alkyloxy) benzoate have been synthesized. The structures were confirmed by  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , FT-IR and mass spectroscopic techniques. The compounds exhibited excellent radical scavenging activities against super oxide anion radical, nitric oxide radical, DPPH radical and hydrogen peroxide. Among all the derivatives 6a, 6c (DPPH), 6a, 6b (NO), 6g, 6h ( $\text{O}_2^-$ ), 6h, 6f ( $\text{H}_2\text{O}_2$ ) having better free radical scavenging ability. Based on the result, it is clear that these can be used as good antioxidant in the field of medicinal and food industry.

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