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# The synthesis and optical characterization of novel iminocoumarin derivatives

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ABSTRACT

A series of novel long-wavelength, fluorescent, novel iminocoumarin derived dyes were synthesized by extending the π-conjugation and spatial location of the benzimidazolic and iminochromene rings in a planar structure. Several dyes display a fluorescent maxima ≥600 nm whilst others showed fluorescent maxima in the NIR region.



## 1. Introduction

Fluorescence has long been viewed as a powerful tool for basic research in the biological sciences, for instance in the development of new drugs, the assurance of food safety and environmental quality as well as the clinical diagnosis of diseases, owing to its high resolution and sensitivity [1]. Recent breakthroughs in fluorescence microscopy are producing notable improvements in imaging resolution [2,3]. Such technical advances should have a major positive impact on the emerging field of cell imaging using single-molecule methods and help merge the subdisciplines of cell and molecular biology [4,5]. Bright, long-wavelength ($\lambda_{em} > 600$ nm) fluorescent dyes, which emit light in the red or near-infrared (NIR) region, have recently enjoyed interest as luminescent dyes and as fluorescent probes for biomolecules. The demand for fluorescent dyes with a spectral range between 600 and 900 nm has grown [2–5]. Employing long-wavelength dyes in biological imaging significantly reduces the background signal due to the lowest autoabsorption and autofluorescence of biomolecules in the long-wavelength region of the spectrum. In addition, the low light scattering and deep penetration of long-wavelength light required to excite the long-wavelength dyes allows the possibility of using a low-cost excitation light source [6]. However, the full potential of many of these new imaging methods will only be achieved depending upon the availability of suitable dyes.

Fluorescent coumarin derivatives have been widely used in many applications from cell biology, medical analysis, lasers, sensors, to the advanced photophysical systems [7,8]. In contrast, very few reports have been carried out on the neighboring series of iminocoumarin dyes. Of the reported iminocoumarin derivatives, the iminocoumarin moiety has been incorporated as a fluorescence signaling unit in $Ca^{2+}$, $Zn^{2+}$, or $H^{+}$ indicators [9–11]. In these reports, the molecular structure of these iminocoumarin moieties incorporate a push-pull functionality, the *N*,*N*-dialkylamino group at the 7-pointion is an electron donor, while an electron withdrawing group, such as the benzimidazole fragment at the 3-position, enhances the fluorescence efficiency [12]. Despite the spectacular successes that have been achieved using coumarin or iminocoumarin derived fluorophores in contemporary pure and applied science; most of these fluorophores illuminate in the blue green region which might limit these dyes for use in biological applications. Many biological samples fluoresce on their own, typically in the blue green region of the spectrum; thus this would interfere with the fluorescence signals generated from the coumarin or iminocoumarin derived fluorophores.

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The iminocoumarin derived fluorophores are known for their high fluorescence ability and efficient quantum yield [12]. The 3-benzimidazol-2-yl-2-iminocoumarin structure **1** is an extensively employed synthon for the preparation of new fluorophores (Fig. 1). Recently, several groups reported the condensation reaction between the aromatic aldehydes with 3-benzimidazol-2-yl-2-iminocoumarin to produce a rigid molecular structure **2** [13,14], or condensed the same synthon with malononitrile to produce a rigid benzopyran **3** [15] (Fig. 1). However, the fluorescence peaks of both the **2** and **3** structural derivatives still fall short of the long-wavelength region of the spectrum which thus limited their biomedical applications. Our group recently reported the synthesis and evaluation of several 3-benzimidazol-2-yl-2-iminocoumarin derivatives for the dye-sensitized solar cell applications [16]. We were interested in further exploring the chemistry of 3-benzimidazol-2-yl-2-iminocoumarin and have synthesized a series of conformational restricted derivatives i.e. dyes **4**, **5**, **6** and **7** (Fig. 2). We envisioned that the spatial fixation of the benzimidazolic and chromene rings into a planar structure would enhance electron flow within the conjugated ring system. Furthermore, we also introduced various electron withdrawing groups to the C=N group of **3**, **4**, and **5** to enhance the push-pull effect on the molecules. We believed that introducing these structural modifications onto the 3-benzimidazol-2-yl-2-iminocoumarin could create new fluorophores that would emit in the long-wavelength region of the spectrum. In this paper, we report the synthesis of **4**, **5**, **6** and **7** and also the evaluation of their optical properties.

## 2. Experimental

### 2.1. Apparatus and chemicals

$^1$H and $^{13}$C NMR were obtained on a Bruker AMX-500 spectrometer; chemical shifts are reported in ppm relative to tetramethylsilane ($\delta$ units). Electrospray ionization (ESI) was preformed at the Analytical Facility of The National Taiwan University. All chemicals were purchased from Acros, Aldrich or TCI and used without future purification. The iminocoumarin **1a**–**b**, dyes **3a**–**b** and **5a** were prepared according to the published procedures [15–19]. Various phenyl isocyanide dichlorides derivatives were prepared in two steps according to known procedures [20].

### 2.2. General procedures for preparing dyes ***4a–j***

In a flask fitted with a magnetic stirrer was placed iminocoumarin **1a** (3 mmol), phenyl-isocyanide dichlorides (caution: incompatible with strong oxidizing agents; corrosive) (6 mmol), and isopropanol (5 ml) and then a catalytic amount of piperidine. The resulting reaction mixture was stirred at reflux temperature for 16 h. The precipitate was filtered and purified by recrystallisation with DMF to give **4**.

#### 2.2.1. N,N-Diethyl-7-[(4-nitropheyl)imino]-7H-chromeno [2′, 3′: 4, 5] pyrimido [1, 6-a] benzimidazol-3-amine (***4a***)

Red solid (54% yield) m.p. > 300 °C. FT-IR v/cm$^{-1}$ = 2975, 2929, 2871, 1643, 1596, 1553, 1527, 1505, 1427, 1333, 1266, 1234, 1204, 1181, 1135, 1113, 1080, 1005 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.71 (d, $J$ = 7.9 Hz, 1H), 8.67 (s, 1H), 8.28 (d, $J$ = 8.9 Hz, 2H), 7.85 (d, $J$ = 7.9 Hz, 1H), 7.51–7.42 (m, 3H), 7.38 (d, $J$ = 8.9 Hz, 2H), 6.76 (dd, $J$ = 9.0, 2.3 Hz, 1H), 6.68 (d, $J$ = 2.3 Hz, 1H), 3.49 (q, $J$ = 7.1 Hz, 4H), 1.27 (t, $J$ = 7.1 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 162.1, 156.3, 155.0, 153.3, 145.7, 145.0, 144.6, 143.4, 136.9, 131.2, 131.1, 125.1, 124.7, 124.0, 123.8, 118.9, 116.6, 111.4, 110.3, 104.3, 97.5, 45.4, 12.4. HRMS-ESI (m/z): [M + 1] For $C_{27}H_{22}N_6O_3$, 478.1753 calcd; 479.1855 found.

#### 2.2.2. N,N-Dibutyl-7-[(4-nitropheyl) imino]-7H-chromeno [2′, 3′: 4, 5] pyrimido [1, 6-a] benzimidazol-3-amine (***4b***)

Red solid (61% yield) m.p. 244–246 °C. FT-IR v/cm$^{-1}$ = 2957, 2929, 2871, 1639, 1595, 1553, 1525, 1505, 1484, 1421, 1332, 1276, 1218, 1136, 1111, 1097 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.70 (d, $J$ = 8.0 Hz, 1H), 8.66 (s, 1H), 8.28 (d, $J$ = 8.9 Hz, 2H), 7.84 (d, $J$ = 8.0 Hz, 1H), 7.49–7.41 (m, 3H), 7.38 (d, $J$ = 8.9 Hz, 2H), 6.72 (dd, $J$ = 9.0, 2.2 Hz, 1H), 6.63 (d, $J$ = 2.2 Hz, 1H), 3.39 (t, $J$ = 7.8 Hz, 4H), 1.66–1.60 (t, $J$ = 7.2, 4H), 1.43–1.36 (m, 4H), 0.99 (t, $J$ = 7.3 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 162.1, 156.2, 155.0, 153.7, 145.7, 144.9, 143.4, 136.9, 131.2, 130.9, 125.1, 124.7, 124.0, 123.7, 118.9, 116.6, 111.5, 110.3, 104.1, 97.6, 51.5, 29.3, 20.2, 13.9. HRMS-ESI (m/z): [M + 1] For $C_{31}H_{30}N_6O_3$, 534.2379 calcd; 535.2457 found.

#### 2.2.3. 4-{[3-Diethylamino]-7H-chromeno [2′, 3′: 4, 5] pyrimidol [1, 6-a] benzimidazol-7-ylidene] amino} benzonitrile (***4c***)

Red solid (65% yield) m.p. > 300 °C. FT-IR v/cm$^{-1}$ = 2974, 2932, 2870, 2214, 1631, 1603, 1555, 1524, 1508, 1492, 1424, 1338, 1276, 1264, 1232, 1200, 1184, 1167, 1133, 1112, 1080, 1012 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.71 (d, $J$ = 8.0 Hz, 1H), 8.66 (s, 1H), 7.85 (d, $J$ = 8.0 Hz, 1H), 7. 67(d, $J$ = 8.4 Hz, 2H), 7.51–7.41 (m, 3H), 7.35 (d, $J$ = 8.4 Hz, 2H), 6.75 (dd, $J$ = 9.1, 2.3 Hz, 1H), 6.68 (d, $J$ = 2.3 Hz, 1H), 3.49 (q, $J$ = 7.1 Hz, 4H), 1.27 (t, $J$ = 7.1 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 162.0, 156.2, 153.2, 152.7, 145.7, 144.8, 144.6, 136.7, 132.8, 131.3, 131.0, 125.0, 124.1, 124.0, 120.0, 118.9, 116.7, 111.3, 110.3, 105.9, 104.5, 97.5, 45.4, 29.7, 12.4. HRMS-ESI (m/z): [M + 1] For $C_{28}H_{22}N_6O$, 458. 1855 calcd; 459.1975 found.

#### 2.2.4. 4-{[3-Dibutylamino]-7H-chromeno [2′, 3′: 4, 5] pyrimidol [1, 6-a] benzimidazol-7-ylidene] amino} benzonitrile (***4d***)

Red solid (65% yield) m.p. 256–258 °C. FT-IR v/cm$^{-1}$ = 2957, 2931, 2870, 2218, 1636, 1601, 1554, 1527, 1507, 1443, 1421, 1338, 1291, 1273, 1256, 1218, 1168, 1135, 1112, 1096 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 8.71 (d, $J$ = 7.9 Hz, 1H), 8.65 (s, 1H), 7.84 (d, $J$ = 7.9 Hz, 1H), 7. 67 (d, $J$ = 8.4 Hz, 2H), 7.49–7.41 (m, 3H), 7.35 (d, $J$ = 8.4 Hz, 2H), 6.72 (dd, $J$ = 9.0, 2.2 Hz, 1H), 6.64 (d, $J$ = 2.2 Hz, 1H), 3.39 (t, $J$ = 7.4 Hz, 4H), 1.66–1.60 (m, 4H), 1.44–1.36 (m, 4H), 0.99 (t, $J$ = 7.3 Hz, 6H). $^{13}$C-NM (125 MHz, $CDCl_3$): $\delta$ = 162.1, 156.2, 153.6, 152.7, 145.7, 144.8, 144.6, 136.7, 132.9, 131.3, 130.9, 125.0, 124.1, 124.0, 118.9, 116.7, 111.4, 110.2, 104.3, 97.7, 51.5, 29.3, 20.2, 13.9.

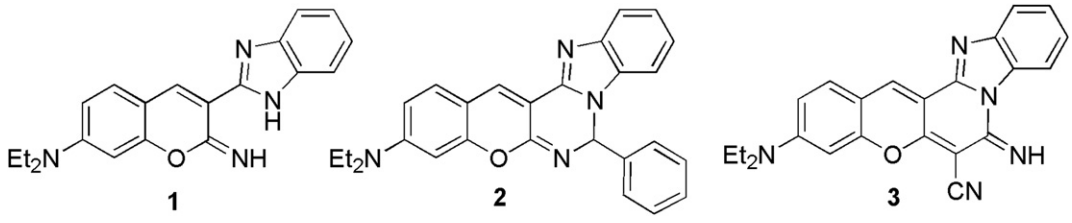


**Fig. 1.** Chemical structural of **1**, **2**, and **3**.