

Communication

Synthesis, Spectroscopic, and Thermal Analyses of 2-Oxo-1,2-dihydroquinolin-8-yl 4-chlorobenzoate

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Abstract: The 2-oxo-1,2-dihydroquinolin-8-yl 4-chlorobenzoate was synthesized in good yield using a triethylamine-mediated *O*-acylation reaction between 8-hydroxyquinolin-2(1*H*)-one and 4-chlorobenzoyl chloride in acetonitrile at room temperature. This methodology is notable for its clean reaction profile and straightforward procedure. The 2-oxoquinoline derivative was characterized using spectroscopic, spectrometric, and thermal analyses, enabling a comprehensive understanding of its molecular structure and thermal properties.

Keywords: 8-hydroxyquinolin-2(1*H*)-one; *O*-acylation reaction; 2-oxoquinoline derivatives

1. Introduction

Quinolin-2(1*H*)-one is an aza-heterocyclic compound that consists of a fused benzene ring and a 2(1*H*)-pyridone moiety. The tautomerism between 2-quinolone and hydroxyquinoline has been studied using spectroscopic and computational methods [1–4], finding that 2-quinolone is the predominant tautomer in both a nonaqueous phase liquid and a solid state due to its high hydrogen-bonded dimeric stabilization [5] (Scheme 1). According to previous studies, the tautomeric equilibrium is affected by several factors, including the electronic nature and steric hindrance of substituents [6] and solvent polarity [7].



Scheme 1. 2-Quinolone-hydroxyquinoline tautomerism.

Quinolin-2(1*H*)-ones stand out as remarkably privileged scaffolds due to their presence in natural compounds and their broad applications in medicinal chemistry and drug discovery [8–11]. In particular, compounds 1–4 represent some examples of these quinolin-2(1*H*)-one-based anticancer agents that have recently emerged as promising and effective leader structures for inhibition of key receptor tyrosine kinases (RTKs) involved in the formation and maintenance of the tumor vasculature, such as vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) kinases [8,9], as shown in Figure 1. Despite extensive research on the synthesis of functionalized quinolin-2(1*H*)-ones [12–17], limited exploration has been conducted on the synthesis of 8-hydroxyquinolin-2(1*H*)-ones [18–21]. In this category, two commercially available compounds, Indacaterol 5 and Procaterol 6, have been developed for the treatment of respiratory diseases [22,23]. Interestingly, there is a notable absence of literature regarding the functionalization of the OH group at C-8 of the quinolin-2(1*H*)-one ring. Thus, we report the triethylamine-mediated *O*-acylation reaction between 8-hydroxyquinolin-2(1*H*)-one and 4-chlorobenzoyl chloride in acetonitrile at room temperature to obtain 2-oxo-1,2-dihydroquinolin-8-yl 4-chlorobenzoate



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in good yield (Scheme 2). Additionally, our study provides valuable insights through the analysis of spectroscopic and thermal data.

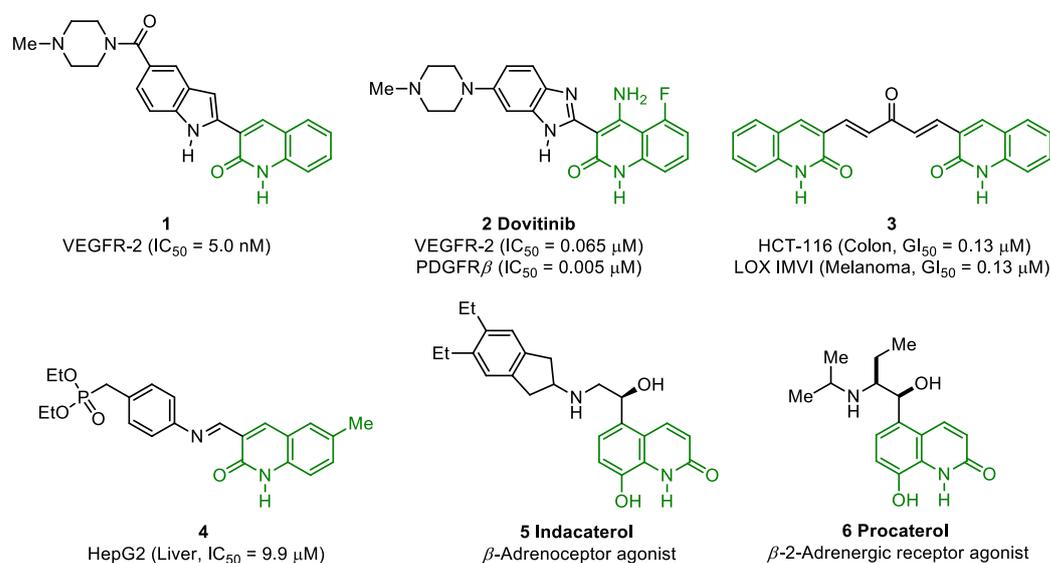
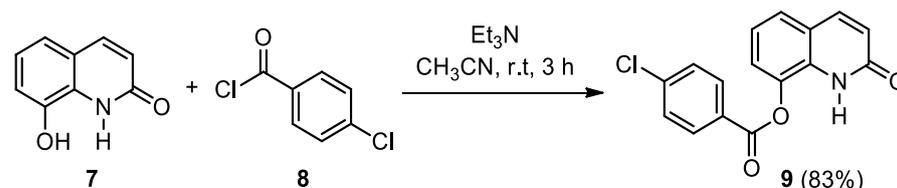


Figure 1. Quinolin-2(1H)-one derivatives 1–6 with remarkable biological activities.



Scheme 2. Synthesis of the novel 2-oxo-1,2-dihydroquinolin-8-yl 4-chlorobenzoate **9**.

2. Results and Discussion

Further delving into our previous studies on the esterification reaction of hydroxylated heterocyclic compounds [24–26], we have synthesized 8-hydroxyquinolin-2(1H)-one using a literature-reported method [27]. We then developed a practical and efficient approach for synthesizing a new 2-oxo-1,2-dihydroquinolin-8-yl 4-chlorobenzoate **9** in good yield using an *O*-acylation reaction of 8-hydroxyquinolin-2(1H)-one **7** and acyl chloride **8** in the presence of triethylamine in acetonitrile with stirring at room temperature for 3 h, as shown in Scheme 2. After evaporating the acetonitrile under vacuum conditions, we purified the material through flash column chromatography on silica gel using a dichloromethane/methanol mixture (50:1, *v/v*) as the eluent to furnish **9** in 83% yield. Notably, compound **9** does not appear in the Reaxys database, indicating that its synthesis and structural characterization are unreported. Thus, we performed a complete structural characterization of **9**, which is detailed in the Materials and Methods section. Our findings from the IR, 1D and 2D NMR, and mass spectra analyses confirm that the structure of the purified solid is identical to our compound **9**.

Figure S4 illustrates the IR spectrum of **9**, displaying the presence of a broad N–H stretching vibration ranging from 3000 to 3200 cm^{-1} . The C=O stretching vibration of the ester and six-membered lactam were identified at 1732 and 1659 cm^{-1} , respectively. In addition, the C–O stretching vibrations were assigned at 1236 and 1085 cm^{-1} , respectively, while the stretching mode of C–Cl was observed at 740 cm^{-1} .

In the proton NMR analysis, the H-3 and H-4 protons of the 2(1H)-pyridone ring were identified as two doublets at 6.55 and 7.98 ppm, respectively (Table 1 and Figure S8). In addition, the benzene fused to the 2(1H)-pyridone ring exhibited three doublets of doublets at 7.23, 7.44, and 7.63 ppm, corresponding to the H-6, H-7, and H-5 protons, respectively. The presence of ester and chloro groups resulted in greater shielding of the Hm protons

(7.68 ppm) compared to the Ho protons (8.16 ppm). Confirmation of the successful *O*-acylation process was established by the presence of a broad singlet at 11.87 ppm attributed to the NH group and the absence of a proton signal corresponding to the OH group attached at C-8 of the quinolin-2(1*H*)-one ring. Confirmation of the assignment of all proton signals was obtained through COSY and NOESY experiments, as presented in Figures S12 and S13, respectively. The examination of compound **9** through ^{13}C -NMR and DEPT-135 spectra unveiled the presence of two carbonyl carbons, five quaternary aromatic carbons, and seven aromatic methines, as summarized in Table 1. By examining the HSQC spectrum displayed in Figure S10, it was possible to assign seven methine carbons: C-6, C-3, C-7, C-5, Cm, Co, and C-4, which were observed at 121.6, 122.7, 124.0, 126.0, 128.6, 132.2, and 140.2 ppm, respectively. The analysis of the HMBC spectrum depicted in Figure S11 facilitated the assignment of five quaternary aromatic carbons: C-4a, Ci, C-8a, C-8, and Cp, exhibiting chemical shifts of 120.8, 128.6, 132.0, 136.6, and 138.5 ppm, respectively. Furthermore, the carbon C-2 (162.0 ppm) exhibited $^2\text{J}(\text{C,H})$ and $^3\text{J}(\text{C,H})$ spin couplings with H-3 and H-4 protons, respectively. Likewise, the C=O (164.1 ppm) of the ester group showed $^3\text{J}(\text{C,H})$ and $^4\text{J}(\text{C,H})$ spin couplings with the Ho and Hm protons, respectively. These findings are summarized in Table 1 and Figure 2B.

Table 1. The 1D and 2D NMR assignments and correlations of **9**.

Number	δ_{H} (Mult, <i>J</i> in Hz)	δ_{C} (ppm)	COSY	NOESY	HMBC
2	--	162.0	--	--	H-3 (^2J) H-4 (^3J)
3	6.55 (d, <i>J</i> = 9.6)	122.7	H-4 (^3J)	H-4	--
4	7.98 (d, <i>J</i> = 9.6)	140.2	H-3 (^3J)	H-3 H-5	H-5 (^3J)
4a	--	120.8	--	--	H-3 (^3J) H-4 (^2J) H-5 (^2J) H-6 (^3J)
5	7.63 (dd, <i>J</i> = 7.8, 1.2)	126.0	H-6 (^3J)	H-4 H-6	H-4 (^3J) H-7 (^3J)
6	7.23 (dd, <i>J</i> = 7.8, 7.8)	121.6	H-5 (^2J) H-7 (^3J)	H-5 H-7	--
7	7.44 (dd, <i>J</i> = 8.0, 1.2)	124.0	H-6 (^3J)	H-6	H-5 (^3J) H-6 (^2J)
8	--	136.6	--	--	H-4 (^4J) H-6 (^3J) H-7 (^2J)
8a	--	132.0	--	--	H-4 (^3J) H-5 (^3J) H-7 (^3J)
i	--	128.6	--	--	Hm (^3J)
o	8.16 (d, <i>J</i> = 8.6)	132.2	Hm (^3J)	Hm	--
m	7.68 (d, <i>J</i> = 8.6)	128.6	Ho (^3J)	Ho	Ho (^2J)
p	--	138.5	--	--	Ho (^3J) Hm (^2J)
NH	11.87 (br s)	--	--	--	--
CO ₂ Ar	--	164.1	--	--	Ho (^3J) Hm (^4J)

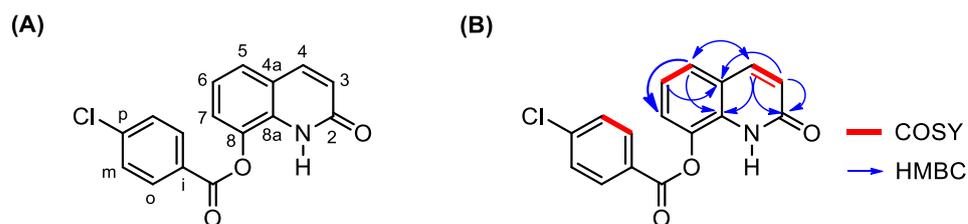


Figure 2. (A) Structure of **9**; (B) Correlations in **9** via COSY and HMBC analysis.

The mass spectrum exhibits a base peak at m/z 141/139, which corresponds to the (4-chlorobenzylidene)oxonium ion, and a peak at m/z 113/111, which correlates to the 4-chlorobenzene-1-ylum ion, as depicted in Figure S2. These findings are consistent with the proposed structure of **9**.

Compound **9** was subjected to separate TGA and DSC analyses, as depicted in Figure 3. The thermal analysis of **9** was conducted under a nitrogen atmosphere, at a gas flow of 25 mL min^{-1} and a heating rate of $10 \text{ }^\circ\text{C min}^{-1}$, covering a temperature range of 25 to $400 \text{ }^\circ\text{C}$. Based on the TGA analysis, it can be concluded that compound **9** has relatively good thermal stability up to $252 \text{ }^\circ\text{C}$, beyond which it undergoes a melting process. The endothermic peak observed in the DSC thermogram at approximately $254 \text{ }^\circ\text{C}$ suggests that the melting process is accompanied by significant heat absorption ($\Delta H = 125.3 \text{ J g}^{-1}$).

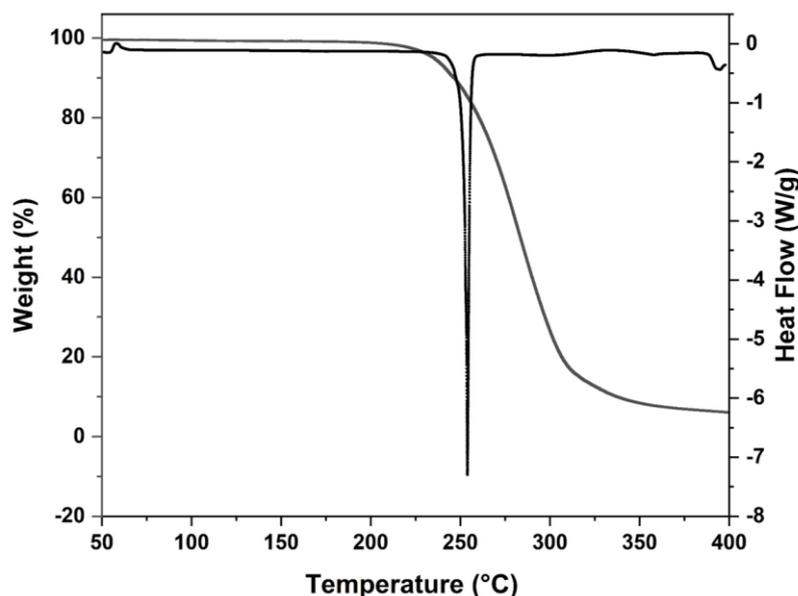


Figure 3. TGA and DSC curves of compound **9**.

To summarize, we have demonstrated a successful triethylamine-mediated synthesis of 2-oxo-1,2-dihydroquinolin-8-yl 4-chlorobenzoate **9** in good yield under mild reaction conditions. The straightforward operation and clean reaction profile of this method are particularly notable. Furthermore, the IR, NMR, and MS spectra of compound **9**, in conjunction with its thermal behavior, offer new insights that were previously unreported. The potential for further functionalization reactions of the quinolin-2(1*H*)-one scaffold is remarkable, including electrophilic aromatic substitution, carbonyl group reduction, and alkylation. By exploiting this reactivity, it may be possible to synthesize novel 2-oxoquinoline derivatives with potential applications in drug discovery and medicinal chemistry.

3. Materials and Methods

3.1. General Information

The progress of the reactions was monitored through thin-layer chromatography and evaluated using a UV lamp with options of either 254 or 365 nm. Flash-column chromatography was performed using silica gel 60 (230–400 mesh) (Alfa Aesar, Tewksbury, MA, USA). A Spectrum Two FT-IR Spectrometer (PerkinElmer, Waltham, MA, USA) with an ATR accessory was utilized to acquire IR spectra at ambient temperature. The Bruker Avance 400 spectrophotometer (Bruker BioSpin GmbH, Rheinstetten, Germany) was employed to acquire NMR spectra in DMSO- d_6 . Chemical shifts are reported in ppm (δ) and coupling constants are quoted in Hz (J). The ^1H and ^{13}C NMR spectra were calibrated using the residual nondeuterated signal ($\delta = 2.50$ ppm) and the deuterated solvent signal ($\delta = 39.52$ ppm), respectively. The high-resolution mass spectrum (HRMS) was recorded using a Q-TOF spectrometer (Agilent Technologies Inc., Santa Clara, CA, USA) via an electrospray ionization (ESI, 4000 V). The SHIMADZU-GCMS 2010-DI-2010 spectrometer (Scientific Instruments Inc., Columbia, WA, USA) equipped with a direct inlet probe operating at 70 eV was used for acquiring mass spectra. The thermogravimetry/differential thermal analyzer STA7200 (Hitachi America Ltd., Santa Clara, CA, USA) was utilized to perform separate differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) measurements.

3.2. Synthesis of 8-Hydroxyquinolin-2(1H)-one (7)

In accordance with the methodology established by Jhong and colleagues [27], a mixture of 8-hydroxyquinoline 1-oxide (1.0 g, 6.21 mmol) in acetic anhydride (4 mL, 42.3 mmol) was refluxed for 3 h. After cooling the resulting reaction mixture to room temperature, an aqueous sodium hydroxide solution (5.0 M) was added until the pH reached 8. The 2-oxo-1,2-dihydroquinolin-8-yl acetate was obtained by filtration. Subsequently, without undergoing further purification, a solution of this acetate (1.02 g, 5.0 mmol) in methanol (10 mL) was treated with K_2CO_3 (831 mg, 6.0 mmol) and stirred at room temperature for 1 h. The methanol was then evaporated under reduced pressure, and the resulting residue was dissolved in water (10 mL), and an aqueous HCl solution (10%) was added until the pH reached 5. The resulting precipitate was filtered, washed with cold water, and dried to yield **7** as a brown solid (804 mg, 80%). Rf ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$) = 0.34. M.p. 287–288 °C. FTIR-ATR: $\nu = 3144$ (ν N-H and ν O-H), 3068, 3013, 1632 (ν C=O), 1597 (ν C=C), 1554, 1471, 1410, 1327, 1286, 1155, 1086, 1051, 873, 832, 790, 742, 570 cm^{-1} . ^1H NMR (400 MHz, DMSO- d_6): $\delta = 6.48$ (d, $J = 9.2$ Hz, 1H), 6.95 (dd, $J = 7.6, 1.2$ Hz, 1H), 6.99 (dd, $J = 7.8, 7.8$ Hz, 1H), 7.10 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.84 (d, $J = 9.2$ Hz, 1H), 10.45 (br s, 2H, NH and OH) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6): $\delta = 114.6$ (CH), 118.2 (CH), 120.0 (Cq), 121.9 (CH), 122.2 (CH), 128.1 (Cq), 140.5 (CH), 143.7 (Cq), 161.4 (Cq, C=O) ppm. MS (EI, 70 eV) m/z (%): 161 (100) [M^+], 160 (29), 133 (39), 115 (20), 104 (37), 77 (16), 51 (12).

3.3. Synthesis of 2-Oxo-1,2-dihydroquinolin-8-yl 4-chlorobenzoate (9)

In a 10 mL tube, the starting materials **7** (162 mg, 1.0 mmol) and **8** (128 μL , 1.0 mmol) were combined with Et_3N (168 μL , 1.2 mmol) in CH_3CN (3.0 mL) along with a magnetic stir bar. The mixture was stirred at room temperature for 3 h. Subsequently, acetonitrile was removed under vacuum, and the crude product was purified by column chromatography on silica gel using a mixture of dichloromethane and methanol (50:1, v/v), leading to **9** as colorless needles (248 mg, 83% yield). Rf ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 50/1$) = 0.25. M.p. 259–260 °C. FTIR-ATR: $\nu = 3158$ (ν N-H), 3003, 2886, 2822, 1732 (ν C=O), 1659 (ν C=O), 1604 (ν C=C), 1595 (ν C=C), 1478, 1434 (ν C-C), 1398 (ν C-C), 1271 (ν C-N and ν C-C), 1236 (ν C-C(=O)-O and ν C-N), 1178, 1168, 1085 (ν O-C-C), 1067, 1012, 860, 842, 832, 740 (ν C-Cl), 678, 596 cm^{-1} . ^1H NMR (400 MHz, DMSO- d_6): $\delta = 6.55$ (d, $J = 9.6$ Hz, 1H, H-3), 7.23 (dd, $J = 7.8, 7.8$ Hz, 1H, H-6), 7.44 (dd, $J = 8.0, 1.2$ Hz, 1H, H-7), 7.63 (dd, $J = 7.8, 1.2$ Hz, 1H, H-5), 7.68 (d, $J = 8.6$ Hz, 2H, Hm), 7.98 (d, $J = 9.6$ Hz, 1H, H-4), 8.16 (d, $J = 8.6$ Hz, 2H, Ho), 11.87 (br s, 1H, NH) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6): $\delta = 120.8$ (Cq, C-4a),

121.6 (CH, C-6), 122.7 (CH, C-3), 124.0 (CH, C-7), 126.0 (CH, C-5), 128.6 (Cq, Ci), 128.6 (2CH, Cm), 132.0 (Cq, C-8a), 132.2 (2CH, Co), 136.6 (Cq, C-8), 138.5 (Cq, Cp), 140.2 (CH, C-4), 162.0 (Cq, C-2), 164.1 (Cq, C=O ester) ppm. HRMS (ESI+): calcd for $C_{16}H_{11}ClNO_3^+$, 300.0422 [M + H]⁺; found, 300.0422. MS (EI, 70 eV) *m/z* (%): 301/299 (2/6) [M⁺], 160 (4), 141/139 (33/100), 113/111 (9/27).

Supplementary Materials: The following are available online. Figure S1: MS spectrum of the compound 7 (EI technique), Figure S2: MS spectrum of the compound 9 (EI technique), Figure S3: IR spectrum of the compound 7 (ATR technique), Figure S4: IR spectrum of the compound 9 (ATR technique), Figure S5: ¹H NMR spectrum of the compound 7, Figure S6: ¹³C{¹H} NMR and DEPT-135 spectra of the compound 7, Figure S7: HSQC spectrum of the compound 7, Figure S8: ¹H NMR spectrum of the compound 9, Figure S9: ¹³C{¹H} NMR and DEPT-135 spectra of the compound 9, Figure S10: HSQC spectrum of the compound 9, Figure S11: HMBC spectrum of the compound 9, Figure S12: COSY spectrum of the compound 9, Figure S13: NOESY spectrum of the compound 9, and Figure S14: HRMS spectrum of the compound 9.

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Conflicts of Interest: The authors declare no conflict of interest.

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