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Short Note

(*E*)-3-[3-(2-Butoxyquinolin-3-yl)acryloyl]-2-hydroxy-4*H*-chromen-4-one

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Abstract: The coumarinyl-quinolinylchalcone hybrid (*E*)-3-[3-(2-butoxyquinolin-3-yl)acryloyl]-2-hydroxy-4*H*-chromen-4-one **3b** was prepared in good yield from a Claisen-Schmidt condensation reaction between 3-acetyl-4-hydroxy-2*H*-chromen-2-one **1** and 2-butoxyquinoline-3-carbaldehyde **2** in methanol at reflux and catalyzed by KOH pellets. The structure of the synthesized compound **3b** was fully confirmed by FTIR-ATR, (1D and 2D) NMR experiments, EIMS and elemental analysis.

Keywords: coumarinyl-quinolinylchalcone hybrid; Claisen-Schmidt condensation

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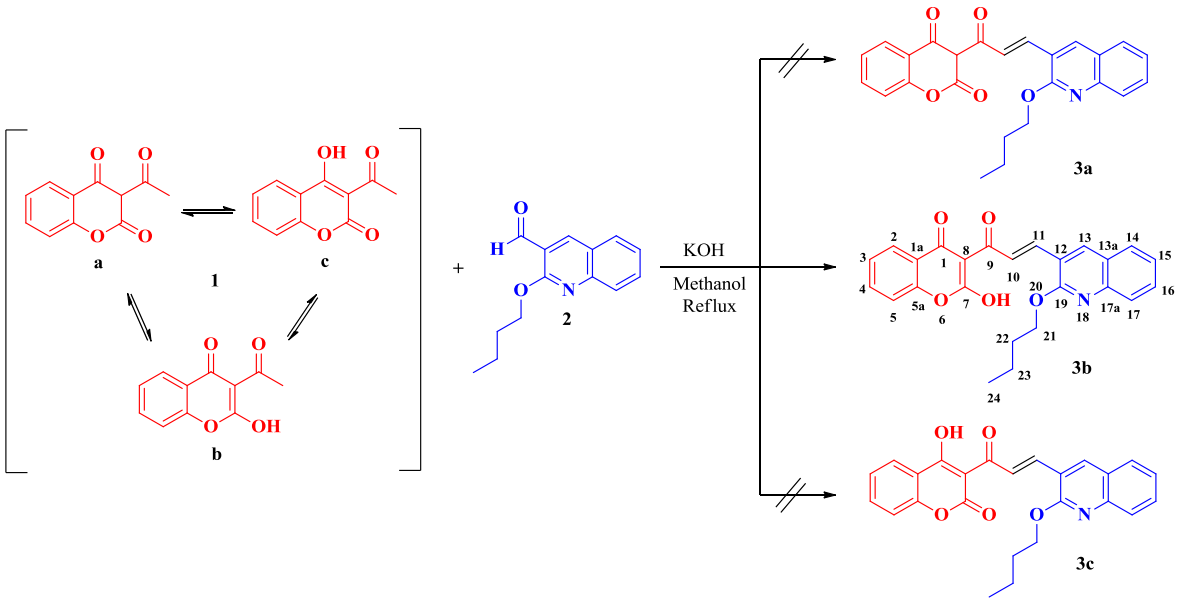
1. Introduction

Chalcones are synthetic and naturally occurring α,β-unsaturated diaryl ketones that have shown a wide spectrum of biological activities, and can act as anti-tubercular [1], anti-inflammatory [2], antimalarial [3], antibacterial [4], antifungal [5], and mainly as antitumor agents [6]. Another important class of heterocyclic system is the coumarin, which consists of a benzene ring fused to a 2-pyrone skeleton, which is present in various natural and synthetic compounds [7]. Molecules based on the coumarin moiety have been extensively studied as pharmacophore agents because of their interesting medical properties, such as their antioxidant [8], antitumor [9], or antimalarial effects [10], among others. On the other hand, quinolines have attracted considerable interest for many years due to their presence in the skeletons of a large number of pharmacologically active substances and natural products (mainly alkaloids) [11]. Quinoline-based chalcones have been found to display antitumor [12], antibacterial [13], and antiulcer activity [14]. Due to the diverse range of biological activities that these three pharmacophores possess, we hypothesized a novel molecular hybrid incorporating chalcone, coumarinyl, and quinolinyl moieties in the structure of product **3b**, as a starting point for a future project in the searching for new molecules of therapeutic potential.

2. Results and Discussion

Continuing with our studies on the synthetic utility of chalcones, as key precursors for the synthesis of diverse derivatives with interesting biological properties [15–17], herein, we report an efficient synthesis of a novel coumarinyl-quinolinylchalcone hybrid **3** in good yield. Product **3** was obtained from a mixture of 3-acetyl-4-hydroxy-2*H*-chromen-2-one **1** and 2-butoxyquinoline-3-carbaldehyde **2** via a Claisen-Schmidt condensation reaction as shown in Scheme 1. The reaction proceeded in methanol at reflux and was catalyzed by a KOH pellet. Upon consumption of the starting materials **1** and **2**, after 4 h of heating (monitored by TLC), the obtained solution was neutralized with acetic acid and isolated by filtration, affording a yellow solid as the new product.



Scheme 1. Synthesis of the coumarinyl-quinolinylchalcone hybrid **3b**.

It is well known that the 2,4-dioxocoumarin exist as an equilibrium mixture of their 2,4-dioxo- (**a**), 2-hydroxy-4-oxo- (**b**) and 4-hydroxy-2-oxo- (**c**) forms, being this latter the main component of the mixture [18]. In consequence, it is expected that its 3-acetyl derivative **1** should exist as the same type of mixtures with the tautomer **1c** as the main component [19]. In principle, the IR, 1D NMR, mass spectrum and microanalyses data suggested that effectively the structure of the isolated yellow solid corresponded to the chalcone isomer **3c**, taking into account that it proceeded from the majority isomer **1c**. Nevertheless, as a challenge, we attempted to assign all protons and carbon atoms from the NMR spectra and mainly by using the 2D HSQC and HMBC experiments, but some drawbacks with structure **3c** were found.

Thus, the most relevant spectroscopic features for the isolated product corresponded to a molecular ion with *m/z* 415 and a base peak with *m/z* 170, in the mass spectrum, which agree with all three expected isomers **3a–c**. The presence of broad absorption bands at 3401 cm^{-1} and 1735, 1711 cm^{-1} assigned to the OH and two C=O functionalities, respectively, are the most relevant features of the IR spectrum. (Isomers **3b** and **3c** matches with this spectral finding). The presence of a very low field OH signal at 18.9 ppm, as well as, two doublets at 8.37 (J = 15.9 Hz, 1H) and 8.74 (J = 15.9 Hz, 1H) ppm associated with the α,β-vinylic protons 10 and 11 in *E* configuration of the new C=C bond formed, and the absence of a 8-H aliphatic proton, are the most relevant features of the ^{1}H-NMR spectrum (just isomers **3b**, and **c** match with this finding). The presence of ten quaternary Cq carbon atoms involving two C=O functionalities at 181.6 and 192.6 ppm are the most relevant features of the ^{13}C-NMR spectrum. A signal at 192.6 ppm was assigned without doubt to the C=C-C=O carbonyl moiety. In Addition, only isomers **3b**,**c** matched with this finding.

Finally, the proposal of the tautomer **3b** as the true obtained product helped us to solve the above drawbacks. A three bonding correlation of H-2 with the C=O functionality at 181.6 ppm and a complete agreement of the remaining 2D NMR correlations in the HMBC experiment confirmed the above. Hence, the signal at 181.6 ppm is associated with the ketonic C-1 carbon atom, indicating that the OH group is effectively located on C-7 (see **3b**), and not on C-1 as it would have happened if isomer **3c** would have been obtained. Thus, after a complete study by analytical and spectroscopic techniques, the formation of chalcone **3b** in 75% yield (but not their isomers **3a**, **3c**), was determined. Moreover, 1D and 2D NMR experiments permitted us the assignment of all proton and carbon atoms (see experimental), confirming the proposed structure for **3b** without ambiguity. A comparison of our

carbon atom assignment with the Automatic Evaluation Report from CSEARCH [20] also matched quite well (see Supplementary Materials).

3. Materials and Methods

3.1. General Information

Melting point was determined on a Büchi melting point B-450 apparatus (Instrumart, South Burlington, VT, USA) and is uncorrected. The IR spectrum was recorded on a Shimadzu FTIR 8400 spectrophotometer by ATR technique (Scientific Instruments Inc., Seattle, WA, USA). ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Avance 400 spectrophotometer (Bruker BioSpin GmbH, Rheinstetten, Germany), operating at 400 MHz and 100 MHz, respectively, while using $CDCl_3$ as solvent and tetramethylsilane as the internal standard. Mass spectrum was run on a SHIMADZU-GCMS 2010-DI-2010 spectrometer (Scientific Instruments Inc., Columbia, WA, USA) (equipped with a direct inlet probe) operating at 70 eV. Microanalyses was performed on an Agilent CHNS elemental analyzer (Thermo Fischer Scientific Inc., Madison, WI, USA) and the values are within $\pm$0.4% of the theoretical values.

*3.2. Synthesis of ((E)-3-(3-(2-Butoxyquinolin-3-yl)acryloyl)-2-hydroxy-4H-chromen-4-one (***3b***)*

A mixture of acetyl-4-hydroxy-2*H*-chromen-2-one **1** (0.1 g, 1.0 mmol), 2-butoxyquinoline-3-carbaldehyde **2** (1.1 mmol) and a KOH pellet in methanol (5 mL) was heated to reflux for 4 h. After disappearance of the starting materials, as monitored by TLC, acetic acid was added portion-wise with stirring, to the reaction mixture until formation of a precipitate. The solid was collected by filtration and washed with cold methanol (2 $\times$ 0.5 mL) to afford **3b** (75% yield, yellow solid, m.p. 180–182 °C). FTIR-ATR: ν = 3401 br (OH), 2961, 1735 (C=O), 1711 (C=O), 1603 (C=N), 1565 (C=C), 1489, 1424, (1305, 1257, 1220, 1176, 1098) (C-O), 989 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.4 Hz, 3H, H-24), 1.59–1.66 (m, 2H, H-23), 1.95–2.03 (m, 2H, H-22), 4.63 (t, *J* = 6.7 Hz, 2H, H-21), 7.30–7.40 (m, 3H, H-15, H-3, H-5), 7.62–7.70 (m, 2H, H-4, H-16), 7.77–7.81 (m, 2H, H-14, H-17), 8.10 (dd, *J* = 7.9, 1.7 Hz, 1H, H-2), 8.33 (d, *J* = 15.9 Hz, 1H, H-11), 8.38 (s, 1H, H-13), 8.70 (d, *J* = 15.9 Hz, 1H, H-10), 18.90 (s, 1H, OH) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.9 (C-24), 19.5 (C-23), 30.9 (C-22), 66.6 (C-21), 100.9 (C-8), 116.3 (C-1a), 117.0 (C-5), 120.0 (C-12), 124.4 (C-3), 124.6 (C-15), 124.9 (C-13a), 125.1 (C-10), 125.8 (C-2), 127.0 (C-17), 128.4 (C-14), 131.2 (C-16), 136.0 (C-4), 139.5 (C-13), 141.6 (C-11), 147.6 (C-17a), 154.8 (C-5a), 160.1 (C-19, C-7), 181.6 (C-1), 192.6 (C-9) ppm. Anal. calcd. for $C_{25}H_{21}NO_5$ (415.44): C, 72.28; H, 5.10; N, 3.37. Found: C, 72.05; H, 4.98; N, 3.51. MS (EI, 70 eV) *m*/*z* (%): 415 (26) [M+], 397 (17), 386 (9), 359 (29), 226 (19), 170 (100), 121 (14), 41 (26).

Supplementary Materials: The following are available online. Figure S1: ^{1}H-NMR spectrum of compound **3b** in $CDCl_3$, Figure S2: ^{13}C-NMR spectrum of compound **3b** in $CDCl_3$, Figure S3: DEPT-135 experiment of compound **3b**, Figure S4: HMBC experiment of compound **3b** in $CDCl_3$, Figure S5: Expansion 1 of HMBC experiment of compound **3b** in $CDCl_3$, Figure S6: Expansion 2 of HMBC experiment of compound **3b** in $CDCl_3$, Figure S7: Expansion 3 of HMBC experiment of compound **3b** in $CDCl_3$, Figure S8: HSQC experiment of compound **3b** in $CDCl_3$, Figure S9: Expansion of HSQC experiment of compound **3b** in $CDCl_3$, Figure S10: COSY experiment of compound **3b** in $CDCl_3$, Figure S11: Expansion of COSY experiment of compound **3b** in $CDCl_3$, Figure S12: Mass spectrum of compound **3b** (EI technique), Figure S13: IR spectrum of compound **3b** (ATR technique).

Author Contributions: R.A. designed the experiments; L.G. performed the experiments; R.A., L.G., J.Q. and B.I. analyzed the IR, MS and NMR spectral data and wrote the manuscript. All authors read and approved the final manuscript.

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