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A Facile and Rapid Method for Synthesizing Indole–Chalcone Hybrids

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Abstract: Indole–chalcone hybrids are a large group of compounds known for their excellent biological properties the help combat diverse pathogens. This study describes a rapid synthetic pathway for the synthesis of ten indole–chalcone hybrids, namely, **3**(**a**–**j**), from 1-Boc-3-formylindole (**1**) and acetophenone derivatives (**2**), in a one-pot approach. This synthesis involved an initial condensation reaction and subsequent deprotection of the Boc group. ^{1}H-NMR, ^{13}C-NMR, and MS were used to elucidate the structures of the final compounds. Contrary to previous methods for the synthesis of indole–chalcone hybrids, this novel synthetic method, which involves using a Boc-protected indole via microwave-assisted synthesis, is advantageous because it is a one-pot approach, making it facile and rapid.

Keywords: chalcones; indole–chalcone hybrids; synthesis; aldehyde; acetophenone; microwave

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1. Introduction

Chalcones, also referred to as 1,3-diaryl-2-propen-1-ones, are widely difstributed in naturally occurring compounds produced by bacteria, fungi, and numerous plant species [1,2]. The term "chalcone" was coined by Kostanecki and Tambor; it refers compounds with two aryl moieties (rings A and B) linked by a highly electrophilic α,β-unsaturated carbonyl system, appearing in trans (*E*) and cis (*Z*) forms [1,3,4] (Figure 1). Chalcones and their derivatives are known for their diversity in terms of biological and pharmacological properties, including antibacterial, antimalarial, anti-inflammatory, antihistamine, anticancer, antileishmanial, antiulcer, antimicrobial, antiviral, antioxidant, and antidiabetic activities [5–10]. They are a sub-class of flavonoids known to be predecessors of other flavonoid sub-classes and other important natural products [11]. Several chalcones are reported to have been isolated from natural sources, such as 3-deoxysapanchalcone, echinatin, licochalcone B, and licochalcone E [12]. It has been previously reported that the fusion of a phenyl ring in the structure of chalcone with another chemical structure will lead to more biologically active compounds, e.g., indoles, oxathiole, etc. [13].

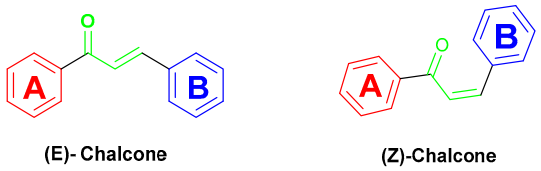


Figure 1. General structures of chalcones.

Indoles are aromatic heterocyclic compounds widely distributed in nature. Notable examples are the amino acid tryptophan and the neurotransmitter serotonin. In the literature, the indole fragment is often seen as a building block for various compounds with potent pharmacological activities [14–16].

When chalcones and indoles form hybrids, the indole–chalcone derivatives display a broad spectrum of biological activities, such as antimicrobial, anti-HIV, analgesic, antitumor, and hypoglycemic properties [17]. Over the years, natural and synthetic indole–chalcone hybrids isolated and designed around the indole fragment have shown notable biological activities against several diseases [18–20]. Therefore, molecular hybridization of this privileged scaffold could be a potential breakthrough point for searching for novel pharmaceuticals relative to an improved or novel biological property.

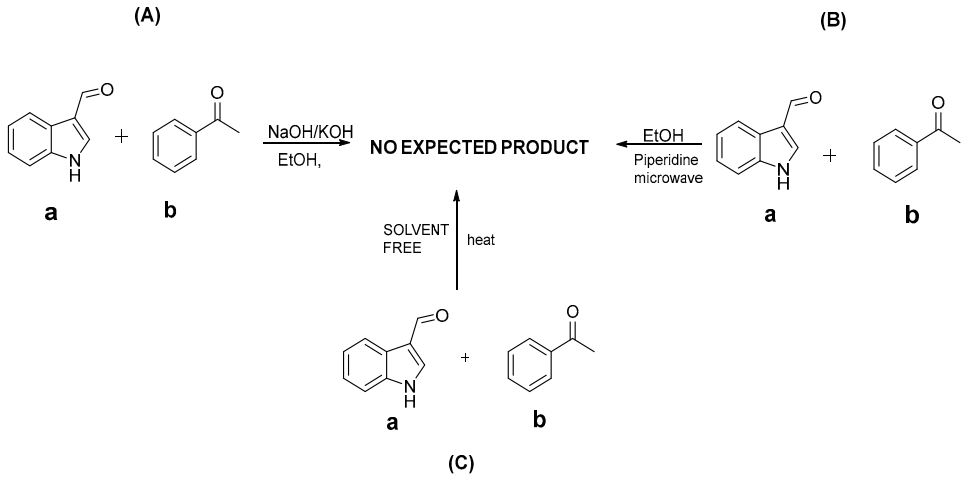
Several indole hybrids synthesized through different approaches have been reported in the literature [21]. Most of these methods entailed long reaction times (often > 24 h), exorbitant use of solvents, and, in some cases, multiple reaction steps that necessitate purification [22–24]. In this work, we focused on developing a more facile synthesis approach to combining these privileged scaffolds. Here, we report a novel, facile, and more efficient microwave-assisted synthesis of ten indole–chalcones, using 1-Boc-3-formylindole as a starting point.

2. Results and Discussion

2.1. Chemistry

2.1.1. Unsuccessful Synthetic Approaches

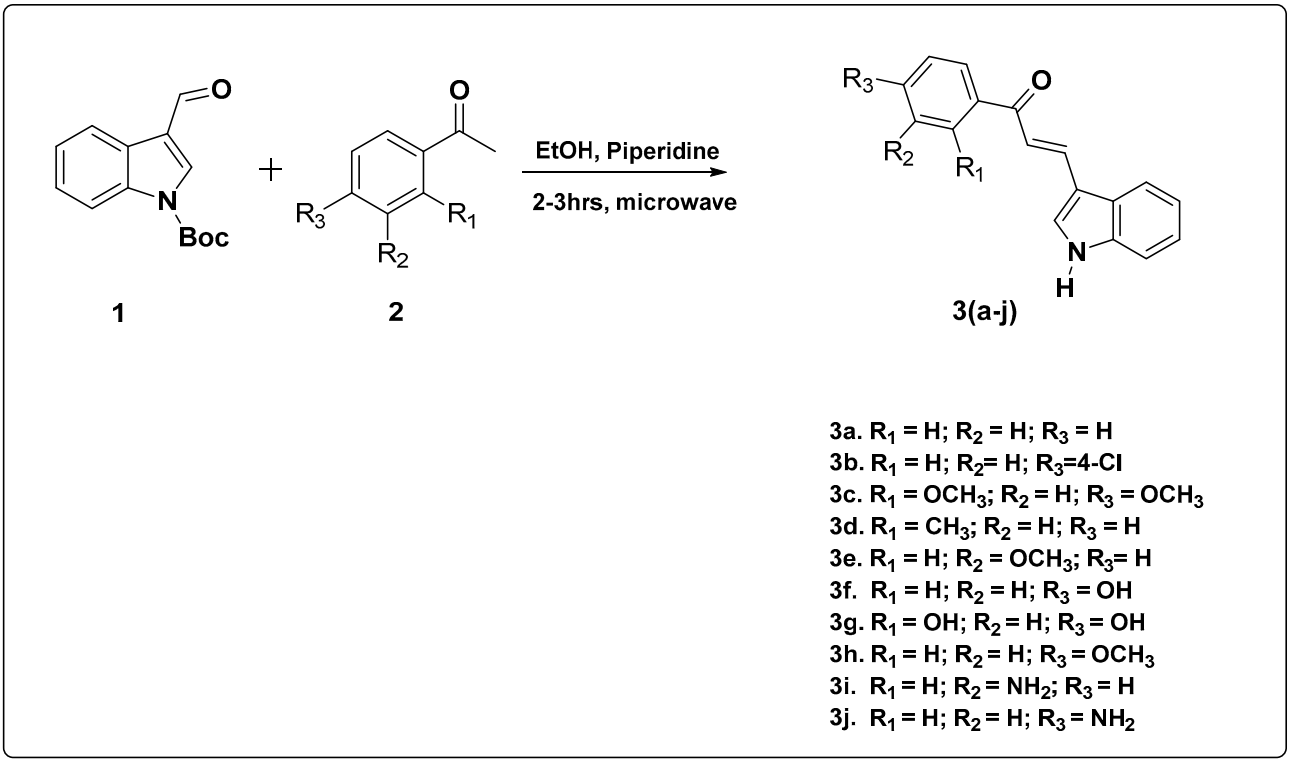
Several synthetic methods were attempted, aiming to obtain the target compounds. 1*H*-indole-3-carboxaldehyde (**a**, 200 mg, 0.82 mmol) and acetophenone (**b**, 120 mg, 0.97 mmol) were reacted as described in Scheme 1.



Scheme 1. Failed synthesis of indole–chalcone hybrids (trial reactions). (**A**) Base-catalyzed aldol condensation of 1*H*-indole-3-carboxaldehyde (**a**) and acetophenone (**b**). (**B**) Microwave-assisted synthesis of 1*H*-indole-3-carboxaldehyde and acetophenone. (**C**) Solvent-free synthesis of 1*H*-indole-3-carboxaldehyde and acetophenone.

2.1.2. The Successful Synthesis Approach

The proposed synthesis strategy was used to obtain the desired compounds, as shown in Scheme 2. This approach involves using a Boc-protected indole, namely, 1-Boc-3-formylindole, along with different acetophenones. Interestingly, the expected compound was obtained in a one-step reaction. The reaction mixture was placed in a microwave at 180 °C for three hours (3 h), using ethanol as the solvent with a few drops of piperidine. The Boc was deprotected during the reaction due to thermolysis [25,26], releasing the free indole–chalcone hybrids. Generally, the reactions resulted in low yields of the target compound as a result of the several bi-products indicated by the prep HPLC in Figures S36 and S37 (Supplementary data).



Scheme 2. The successful synthetic pathway towards the eleven indole–chalcone hybrids. **1** = 1-Boc-3-formylindole. **2** = acetophenones. **3**(**a**–**j**) = indole–chalcone hybrids.

3. Material and Methods

3.1. General Experimental Information

All the chemical reagents and solvents were purchased from commercial sources and used without further purification [Sigma-Aldrich Co., Ltd. (Darmstadt, Germany) and abcr GmbH (Karlsruhe, Germany)]. Thin-layer chromatography was carried out on aluminum sheets coated with silica gel 60 F254 (Merck, Darmstadt, Germany). For medium-pressure liquid chromatography (MPLC), silica gel 60 (0.063–0.200 mm) was used. Melting points were determined without correction using a Büchi capillary melting point apparatus (Büchi Labortechnik AG, Flawil, Switzerland). Purity was measured via UV absorbance at 254 nm. The HPLC consisted of a LiChrosorb® RP-18 (5 m) 100–4.6 Merck column (Merck, Darmstadt, Germany), two LC-10AD pumps, an SPD-M10A VP PDA detector, and an SIL-HT autosampler, all from the manufacturer Shimadzu (Kyoto, Japan). Mass spectrometry was measured using an Advion expression CMS (Advion Interchim Scientific, Ithaca, NY, USA). The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively, using a Varian Inova 400 Spectrometer (Bruker, Bremen, Germany) in deuterated dimethyl sulfoxide (DMSO-d_6). Peak multiplicities were expressed as follows:

singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad singlet (br s), doublet of doublets (dd), doublet of triplets (dt), and quartet of doublets (qd).

3.2. Experimental Procedures and Characterization of Compounds

General Synthetic Method

1-Boc-3-formylindole (500 mg, 2.04 mmol) and the appropriate acetophenone derivative (333.05 mg, 2.45 mmol) were dissolved in 5 mL of ethanol, and a catalytic amount of approximately 1 mL of piperidine was added. The mixture was heated in a microwave reactor, Monowave 450 (Anton Paar, Graz, Austria), at 180 °C for 3 h and constantly stirred. After the completion of the reaction, the mixture was cooled to room temperature. The product was purified via chromatography on silica gel (ethyl acetate/heptane = 20:80, *v*/*v*) using standard procedures, as reported by Liang et al. (2015) [25].

3.2.1. Synthesis of (*E*)-3-(1*H*-Indol-3-yl)-1-phenylprop-2-en-1-one (**3a**)

Orange solid; yield 34% (68 mg); mp: >339 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.87 (s, 1H, N-H), 8.11–7.98 (m, 5H, H-1, H-2, H-3, H-4, H-6), 7.67–7.57 (m, 2H, H-8, H-10), 7.56–7.50 (m, 2H, H-12, H-19), 7.48–7.43 (m, 1H, H-16), 7.25–7.16 (m, 2H, H-17, H-18). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 189.3(C-7), 139.5(C-10) 138.9,-(C-8) 137.9(C-5)133.7,-(C-14) 132.7 (C-2), 129.1,-(C-1, C-3) 128.5(C-4, C-6) 125.5-(C-12) 123.1,(C-15) 121.6,(C-17) 120.8(C-18) 115.8,(C-19), 113.2,-(C-11), 112.8,(C-16). MS(APCI): calculated for $C_{17}H_{13}NO$ [M-H]$^{+}$ 248.10, found 248.1; HPLC: t_R, 14.423 min; purity, 98%.

3.2.2. Synthesis of (*E*)-1-(4-Chlorophenyl)-3-(1*H*-indol-3-yl)prop-2-en-1-one (**3b**)

Gold solid; yield 48% (257 mg); mp: 195.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.90 (s, 1H, N-H), 8.14–8.07 (m, 3H, H-10, H-8, H-13), 8.10–7.99 (m, 2H, H-20, H-19), 7.63–7.52 (m, 3H,H-1, H-3, H-4), 7.50–7.42 (m, 1H, H-6), 7.30–7.15 (m, 2H, H-17, H-18). ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm 188.0(C-7), 140.0(C-10), 137.9(C-2), 137.6(C-15), 137.5(C-6, C-4), 134.0(C-1, C-3), 130.4(C-3), 129.1(C-16), 125.5(C-8), 123.2(C-18), 121.6(C-19), 120.8(C-20), 115.3(C-11), 113.2(,C-17) 112.9(C-16). MS(APCI): calculated for $C_{17}H_{12}ClNO$ [M-H]$^{+}$ 282.2, found 281.2; HPLC: t_R, 15.469 min; purity, 92%.

3.2.3. Synthesis of (*E*)-1-(2,4-Dimethoxyphenyl)-3-(1*H*-indol-3-yl)prop-2-en-1-one (**3c**)

Bronze solid; yield 26% (162 mg); mp: 184.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.75 (s, 1H, N-H), 7.92 (d, *J* =2.9 Hz, 1H, H-6), 7.88–7.83 (m, 1H, H-12), 7.79 (d, *J* = 15.8 Hz, 1H, H-10), 7.59 (d, *J* = 8.5 Hz, 1H, H-8), 7.50–7.42 (m, 2H,H-1, H-3), 7.23–7.14 (m, 2H, H-18, H-19), 6.66 (d, *J* = 2.3 Hz, 1H), 6.61 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.90 (s, 3H, H-23), 3.82 (s, 3H, H-21). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 189.5(C-7), 163.7(C-2), 160.2(C-4), 138.0(C-10), 137.2(C-14), 133.0(C-6), 132.2(C-12), 125.4(C-15), 122.9(C-8), 122.5(C-5), 121.8(C-17), 121.4(C-18), 120.3(C-19), 113.1(C-11), 112.9(C-1), 106.2(C-16), 99.1(C-3), 56.3(C-23), 55.9(C-21). MS(APCI): calculated for $C_{19}H_{17}NO_3$ [M-H]$^{+}$ 307.35, found 307.30; HPLC: t_R, 14.167 min; purity, 94%.

3.2.4. Synthesis of (*E*)-3-(1*H*-Indol-3-yl)-1-(o-tolyl)prop-2-en-1-one (**3d**)

Lemon solid; yield 32% (71 mg); mp: 338.4 °C; 1H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H, N-H), 7.98 (s, 1H, H-19), 7.90–7.83 (m, 1H, H-12), 7.65 (d, *J* = 15.9 Hz, 1H, H-10), 7.51–7.10 (m, 7H,H-1, H-2, H-3, H-4, H-16, H-17, H-18), 7.06 (d, *J* = 15.9 Hz, 1H, H-8), 2.32 (s, 3H, H-21). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 195.8(C-7), 140.7(C-10), 140.4(C-4), 137.9(C-14), 136.0(C-2), 133.6(C-5), 131.3(C-3), 130.2(C-12), 128.0(C-6), 126.0(C-8), 125.3(C-15), 123.1(C-1), 121.6(C-17), 120.9(C-18), 120.5(C-19), 112.9(C-11), 112.6(C-16),

20.1(C-20). MS(APCI): calculated for $C_{18}H_{16}NO$ $[M-H]^+$ 262.0, found 261.0; HPLC: t_R, 14.340 min; purity, 98%.

3.2.5. Synthesis of (*E*)-3-(1*H*-Indol-3-yl)-1-(3′-Methoxyphenyl)prop-2-en-1-one (**3e**)

Lemon solid; yield 5% (29 mg); mp: 167.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.87 (s, 1H, N-H), 8.09 (s, 1H, H-6), 8.05–7.97 (m, 2H, H-10, H-12), 7.68 (d, *J* = 7.6 Hz, 1H, H-8), 7.60–7.49 (m, 2H, H-19, H-18), 7.48–7.42 (m, 2H, H-16, H-17), 7.25–7.12 (m, 3H, H-1, H-2, H-4), 3.81 (s, 3H, H-21). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 189.0(C-7), 159.9(C-3), 140.4(C-10), 139.5(C-14), 137.9(C-6), 133.6(C-5), 130.2(C-12), 125.6(C-15), 123.1(C-8), 121.6(C-17), 121.0(C-2), 120.7(C-18), 118.7(C-19), 115.9(C-1), 113.1(C-4), 113.1(C-11), 112.8(C-16), 55.7(C-21). MS(APCI): calculated for $C_{17}H_{15}NO_2$ $[M-H]^+$ 262.0, found 261.0; HPLC: t_R, 14.736 min; purity, 97%.

3.2.6. Synthesis of (*E*)-1-(4-Hydroxyphenyl)-3-(1*H*-indol-3-yl)prop-2-en-1-one (**3f**)

Yellow solid; yield 15% (84 mg); mp: 196.7 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ ppm 11.79 (s, 1H, N-H), 10.22 (s, 1H, C_2-0H), 8.92–7.99 (m, 3H, H-8, H-4, H-3), 7.95 (d, *J* = 15.5 Hz, 1H, H-10), 7.60 (d, *J* = 15.5 Hz, 1H, H-6), 7.49–7.34 (m, 1H, H-12), 7.19 (m, 2H, H-19, H-18), 6.87 (d, *J* = 2.0 Hz, 1H, H-1), 6.86 (m, 1H, H-17). ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm 207.2 (C-7), 187.4(C-2), 162.0(C-10), 138.0(C-14), 137.8(C-6), 132.9(C-5), 131.0(C-15), 130.2(C-8), 125.5(C-12), 122.9(C-17), 121.4(C-18), 120.7(C-19), 115.8(C-1), 115.7(C-3), 113.2(C-11), 112.7(C-16). MS(APCI): calculated for $C_{17}H_{13}NO_2$ $[M-H]^+$ 262.0, found 261.0; HPLC: t_R, 14.340 min; purity, 95%.

3.2.7. Synthesis of (*E*)-1-(2,4-Dihydroxyphenyl)-3-(1*H*-indol-3-yl)prop-2-en-1-one (**3g**)

Orange solid; yield 5% (29 mg); mp: >339 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 11.86 (s, 1H, N-H), 7.98 (s, 1H, C_4-0H), 7.90–7.83 (m, 1H,C_6-0H), 7.65 (d, *J* = 15.9 Hz, 1H, H-10), 7.51–7.10 (m, 8H, H-1, H-3, H-6, H-12, H-16, H-17, H-18, H-19), 7.06 (d, *J* = 15.9 Hz, 1H, H-8). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 195.8(C-7), 140.7(C-2), 140.4(C-4), 137.9(C-10), 136.0(C-6), 133.6(C-12), 131.3(C-14), 130.2(C-8), 128.0(C-15), 126.0(C-17), 125.3(C-18), 123.1(C-19), 121.6(C-5), 120.9(C-1), 120.5(C-11), 112.9(C-16), 112.6(C-3). MS(APCI): calculated for $C_{18}H_{16}NO$ $[M-H]^+$ 280.0, found 279.0; HPLC: t_R, 13.748 min; purity, 91%.

3.2.8. Synthesis of (*E*)-3-(1*H*-Indol-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (**3h**)

Yellow solid; yield 21% (158 mg); mp: 185.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88–11.77 (m, 1H, N-H), 8.12–8.07 (m, 2H,H-6, H-4), 8.04 (dd, *J* = 8.5, 2.7 Hz, 2H, H-19, H-18), 7.96 (s, 1H, H-10), 7.62 (d, *J* = 15.5 Hz, 1H, H-8), 7.48–7.41 (m, 1H, H-12), 7.24–7.15 (m, 2H, H-1, H-3), 7.03–7.00 (m, 2H, H-27, H-18), 3.83 (s, 3H, H-21). ^{13}C NMR (100 MHz, DMSO-*d*) δ ppm 187.6(C-7), 163.1(C-2), 138.5(C-10), 137.9(C-14), 133.1(C-4, C-6), 131.6(C-5), 130.8(C-12), 125.6(C-8), 123.0(C-15), 121.4(C-17), 120.7(C-18), 115.8(C-19), 114.3(C-1, C-3), 113.2(C-11), 112.8(C-16), 55.9(C-21). MS(APCI): calculated for $C_{18}H_{15}NO_2$ $[M-H]^+$ 277.32, found 277.10; HPLC: t_R, 14.340 min; purity, 95%.

3.2.9. Synthesis of (*E*)-1-(3-Aminophenyl)-3-(1*H*-indol-3-yl)prop-2-en-1-one (**3i**)

Yellow solid; yield 26% (83 mg); mp: >339 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.83 (s, 1H, N-H), 8.08–7.89 (m, 3H, H-10, H-4, H-6), 7.55–7.43 (m, 2H, H-1, H-2), 7.26–7.12 (m, 5H, H-12, H-16, H-17,H-18, H-19), 6.77 (ddd, *J* = 7.8, 2.3, 1.1 Hz, 1H, H-8), 5.29 (s, 2H, H-20). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 189.7(C-7), 149.4(C-3), 139.7(C-10), 138.7(C-5), 137.9(C-14), 133.4(C-1), 129.5(C-12), 125.5(C-15), 123.0(C-8), 121.5(C-17), 120.6(C-2), 118.2(C-18), 116.2(C-19), 116.1(C-6), 113.4(C-4), 113.1(C-11), 112.9(C-16). MS(APCI): calculated for $C_{17}H_{14}N_2O$ $[M-H]^+$ 263.12, found 263.3; HPLC: t_R, 11.345 min; purity, 93%.

3.2.10. Synthesis of (*E*)-1-(4-Aminophenyl)-3-(1*H*-indol-3-yl)prop-2-en-1-one (**3j**)

Yellow solid; yield 32% (103 mg); mp: >339 °C; 1H NMR (400 MHz, DMSO-d_6) δ ppm 11.83 (s, 1H, N-H), 8.08–7.89 (m, 3H, H-10, H-6, H-4), 7.55–7.43 (m, 2H, H-1, H-3), 7.26–7.12 (m, 5H, H-12, H-16, H-17, H-18, H-19), 6.77 (ddd, *J* = 7.8, 2.3, 1.1 Hz, 1H, H-8), 5.29 (s, 2H, H-20). ^{13}C NMR 100 MHz, DMSO-d_6) δ ppm 189.7(C-7), 149.4(C-2), 139.7(C-10), 138.7(C-5), 137.9(C-14), 133.4(C-1), 129.5(C-12), 125.5(C-15), 123.0(C-8), 121.5(C-17), 120.6(C-3), 118.2(C-18), 116.2(C-19), 116.1(C-6), 113.4(C-4), 113.1(C-11), 112.9(C-16). MS(APCI): calculated for $C_{17}H_{14}N_2O$ $[M-H]^+$ 262.1, found 262.1; HPLC: t_R, 12.111 min; purity, 97%.

4. Conclusions

We report here the successful synthesis of 11 indole–chalcone hybrid compounds using a one-step method that has not been previously described. The reaction was quite rapid and easy to carry out when compared to previously described approaches for the synthesis of chalcones, and the end products were obtained in relatively high yields.

Supplementary Materials: The following supporting information is available online: the structures of the compounds and copies of ^{1}H-NMR, ^{13}C-NMR, HPLC, and MS.

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Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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

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