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A Facile and Rapid Synthetic Method for Indole-Chalcone Hybrids

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A Facile and Rapid Synthetic Method for Indole-Chalcone Hybrids

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Abstract: Indole-chalcone hybrids are a large group of compounds known for their excellent biological properties against diverse pathogens. The current research describes a rapid synthetic pathway for the synthesis of ten (10) indole-chalcone hybrids **3**(**a-j**), from 1-Boc-3-formylindole **(1)** and acetophenone derivatives **(2**), in a one-pot approach. The synthesis involves first the condensation reaction and the subsequent deprotection of the Boc group. ^{1}H-NMR, ^{13}C-NMR, and MS were used to elucidate the structure 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

1. Introduction

Chalcones, also referred to as 1,3-diaryl-2-propen-1-ones, are widely distributed in naturally occurring compounds produced by bacteria, fungi, and numerous plant species [1, 2]. The term "chalcone" was coined by Kostanecki and Tambor for compounds with two aryl moieties (rings A and B) linked by a highly electrophilic α,β-unsaturated carbonyl system, given the trans (*E*) and cis (*Z*) forms [1, 3, 4] **(Figure 1**). Chalcones and their derivatives are known for their diversity in 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]. There are several chalcones reported to have been isolated from natural sources such as 3- deoxysapanchalcone, echinatin, licochalcone B, licochalcone E [12]. It has been previously reported that the fusion of a phenyl ring in the chalcone structure with another chemical structure will lead to more biologically active compounds, e.g. indoles, oxathiole, etc. [13].

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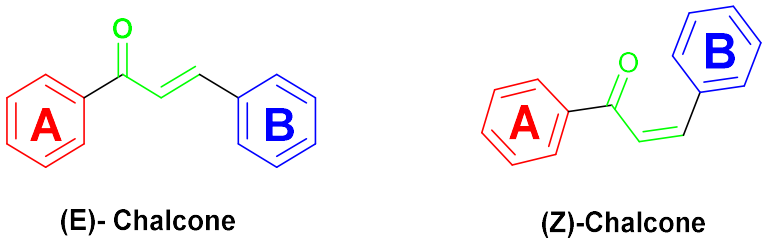


Figure 1. General structure of chalcones.

Indoles are aromatic heterocyclic compounds widely distributed in nature, notably the amino acid tryptophan, 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, hypoglycemic, etc. [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.

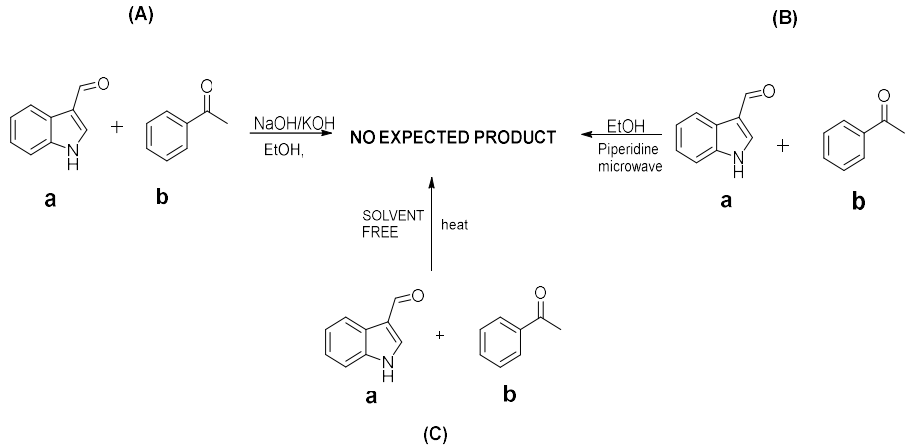
Several indole hybrids have been reported in literature with different synthetic approaches [21]. In most of these methods, long reaction times (often > 24 hours), exorbitant use of solvents, and, in some cases, multiple reaction steps that necessitate purification were used [22-24]. This work has focused on developing a more facile synthetic approach to combining these privileged scaffolds. Here, we report a novel, facile, and more efficient microwave-assisted synthesis of ten indole-chalcones starting from 1-Boc-3-formylindole.

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-chalcones (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-

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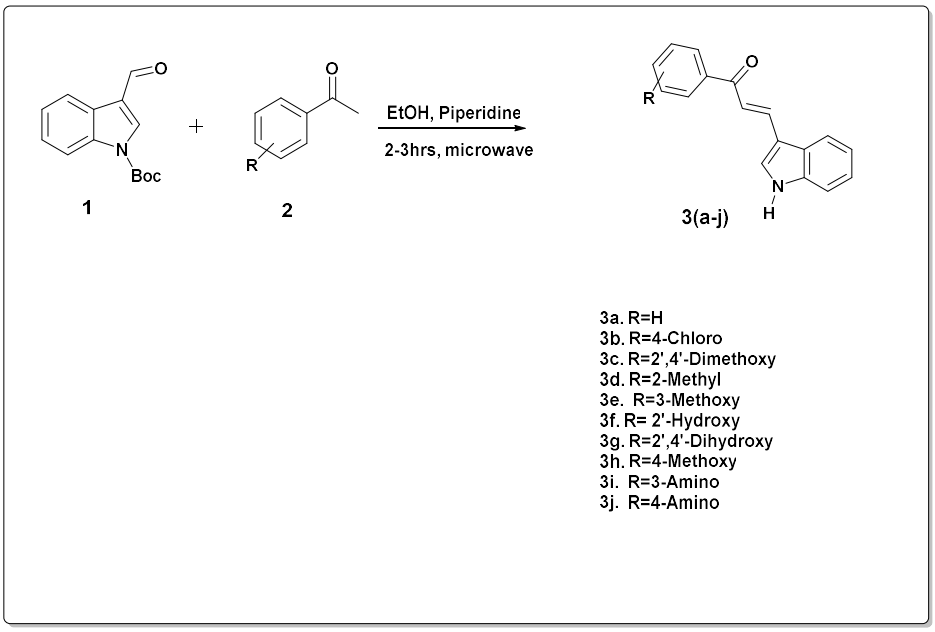
carboxaldehyde and acetophenone. **(C)** Solvent-free synthesis of 1*H*-indole-3-carboxaldehyde and acetophenone.

2.1.2. The Successful Synthetic Approach

The proposed synthetic strategy was used to obtain the desired compounds as shown in **Scheme 2**. The approach involves using a Boc-protected indole, 1-Boc-3-formylindole 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 hours) using ethanol as the solvent with a few drops of piperidine. Boc was automatically deprotected during the reaction releasing the free indole-chalcones.



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

3. Material and Methods

3.1. General Experimental Information

All the chemical reagents and solvents were purchased from commercial sources and were 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 (0.036e0.200 mm) was used. Melting points were determined without correction on a Büchi capillary melting point apparatus (Büchi Labortechnik AG, University of Buea). Purity was measured by 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, a SPD-M10A VP PDA detector, and a SIL-HT autosampler, all from the manufacturer Shimadzu (Kyoto, Japan). Mass spectrometry was measured on an Advion expression CMS (Advion Interchim Scientific, Ithaca, NY, USA). The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz, on a Varian Inova 400 Spectrometer (Bruker, 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).

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3.2. Experimental Procedures and Characterization of Compounds

General Synthetic Method

1-Boc-3-formylindole (1 equiv.) and the appropriate acetophenone derivative (1.2 equiv.) were dissolved in 5 mL ethanol and a catalytic amount of piperidine was added. The mixture was heated in a microwave reactor, Monowave 450 (Anton Paar) at 180 °C for 3 hours with constant stirring. After the completion of the reaction, the mixture was cooled to room temperature. The product was purified by chromatography on silica gel (heptane/ethyl acetate).

3.2.1. Synthesis of (E)-3-(1H-indol-3-yl)-1-phenylprop-2-en-1-one (S1-01)

Orange solid; yield 33.7%; mp: >339 °C; ^{1}H NMR (400 MHz, DMSO-d^{6}) δ ppm 11.87 (s, 1H), 8.11 – 7.98 (m, 5H), 7.67 – 7.57 (m, 2H), 7.56 – 7.50 (m, 2H), 7.48 – 7.43 (m, 1H), 7.25 – 7.16 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ ppm 189.27, 139.48, 138.95, 137.95, 133.71, 132.79, 129.11, 128.54, 125.57, 123.14, 121.60, 120.81, 115.82, 113.21, 112.88.MS(APCI): cald for $C_{17}H_{13}NO$ [M-H]$^{+}$ 248.10, found 248.1; HPLC(): t_R 14.423 mins, purity 98%.

3.2.2. Synthesis of (E)-1-(4-chlorophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (S1-03)

Gold solid; yield 44.7%; mp: 195.1 °C; ^{1}H NMR (400 MHz, DMSO-d^{6}) δ ppm 11.90 (s, 1H), 8.14 – 8.07 (m, 3H), 8.10 – 7.99 (m, 2H), 7.63 – 7.52 (m, 3H), 7.50 – 7.42 (m, 1H), 7.30 – 7.15 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d^{6}) δ ppm 188.07, 140.02, 137.97, 137.66, 137.59, 134.06, 130.49, 129.18, 125.54, 123.21, 121.65, 120.88, 115.35, 113.25, 112.91. MS(APCI): cald for $C_{17}H_{12}ClNO$ [M-H]$^{+}$ 282.2, found 281.2; HPLC: t_R 15.469 mins, purity 92%.

3.2.3. Synthesis of (E)-1-(2,4-dimethoxyphenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (S1-04)

Bronze solid; yield 25.8%; mp: 184.7°C; ^{1}H NMR (400 MHz, DMSO-d^{6}) δ ppm 11.75 (s, 1H), 7.92 (d, *J* =2.9 Hz, 1H), 7.88 - 7.83 (m, 1H), 7.79 (d, *J* = 15.8 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.23 – 7.14 (m, 2H), 6.66 (d, *J* = 2.3 Hz, 1H), 6.61 (dd, J=8.6, 2.3Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ ppm 189.50, 163.77, 160.27, 138.00, 137.20, 133.03, 132.25, 125.43, 122.54, 121.87, 121.47, 120.31, 113.12, 112.93, 106.29, 99.17, 56.34, 55.98. MS(APCI): cald for $C_{19}H_{17}NO_3$ [M-H]$^{+}$ 307.35, found 307.30; HPLC: t_R 14.167 mins, purity 94%.

3.2.4. Synthesis of (E)-3-(1H-indol-3-yl)-1-(o-tolyl)prop-2-en-1-one (**S1-05**)

Lemon solid; yield 32%; mp:338.4 °C; 1H NMR (400 MHz, DMSO-d^{6}) δ 11.86 (s, 1H), 7.98 (s, 1H), 7.90 – 7.83 (m, 1H), 7.65 (d, *J* = 15.9 Hz, 1H), 7.51 – 7.10 (m, 8H), 7.06 (d, *J* = 15.9 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d^{6}) δ ppm 195.88, 140.76, 140.44, 137.99, 136.01, 133.67, 131.34, 130.23, 128.02, 126.08, 125.38, 123.18, 121.67, 120.96, 120.50, 112.93, 112.66, 20.14. MS(APCI): cald for $C_{18}H_{16}NO$ [M-H]$^{+}$ 262.0, found 261.0; HPLC: t_R 14.340 mins, purity 98%.

3.2.5. Synthesis of (E)-3-(1H-indol-3-yl)-1-(3'-Methoxyphenyl)prop-2-en-1-one (S1-06)

Lemon solid; yield 5%; mp: 167.5 °C; ^{1}H NMR (400 MHz, DMSO-d^{6}) δ ppm 11.87 (s, 1H), 8.09 (s, 1H), 8.05 – 7.97 (m, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.48 – 7.42 (m, 2H), 7.25 – 7.12 (m, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ ppm 189.09, 159.92, 140.45, 139.52, 137.92, 133.61, 130.28, 125.60, 123.16, 121.64, 121.04, 120.72, 118.75, 115.94, 113.18, 113.11, 112.89, 55.73. MS(APCI): cald for $C_{17}H_{15}NO_2$ [M-H]$^{+}$ 262.0, found 261.0; HPLC(): t_R 14.736 mins, purity 97%.

3.2.6. Synthesis of (E)-1-(4-hydroxyphenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (S1-07)

Yellow solid; yield 15%; mp: 196.7 °C; ^{1}H NMR (400 MHz, DMSO-d^{6}) δ ppm 11.79 (s, 1H), 10.22 (s, 1H), 8.92 – 7.99 (m, 3H), 7.95 (d, *J* = 15.5 Hz, 1H), 7.60 (d, *J*=15.5Hz, 1H), 7.49 – 7.34 (m, 1H),7.19 (m, 2H), 6.87 (d, *J* = 2.0Hz, 1H), 6.86 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d^{6}) δ ppm 207.21, 187.43, 162.01, 138.06, 137.89, 132.93, 131.05, 130.26, 125.59, 122.99, 121.40, 120.75, 115.89, 115.70, 113.21, 112.79. MS(APCI): cald for $C_{17}H_{13}NO_2$ [M-H]$^{+}$ 262.0, found 261.0; HPLC(): t_R 14.340 mins, purity 95%.

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3.2.7. Synthesis of (E)-1-(2,4-dihydroxyphenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (S1-08)

Orange solid; yield 5%; mp: >339 °C; ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ 11.86 (s, 1H), 7.98 (s, 1H), 7.90 – 7.83 (m, 1H), 7.65 (d, *J* = 15.9 Hz, 1H), 7.51 – 7.10 (m, 8H), 7.06 (d, *J* = 15.9 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d^{6}) δ ppm 195.88, 140.76, 140.44, 137.99, 136.01, 133.67, 131.34, 130.23, 128.02, 126.08, 125.38, 123.18, 121.67, 120.96, 120.50, 112.93, 112.66, 20.14. MS(APCI): cald for $C_{18}H_{16}NO$ [M-H]$^{+}$ 280.0, found 279.0; HPLC(): t_R 13.748 mins, purity 91 %.

3.2.8. Synthesis of (E)-3-(1H-indol-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (S1-09)

Yellow solid; yield 21%; mp: 185.8 °C; ^{1}H NMR (400 MHz, DMSO-d^{6}) δ 11.88 – 11.77 (m, 1H), 8.12 – 8.07 (m, 2H), 8.04 (dd, *J* = 8.5, 2.7 Hz, 2H), 7.96 (s, 1H), 7.62 (d, *J* = 15.5 Hz, 1H), 7.48 – 7.41 (m, 1H), 7.24 – 7.15 (m, 2H), 7.03 – 7.00 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ ppm 187.64, 163.10, 138.52, 137.91, 133.17, 131.69, 130.82, 125.60, 123.05, 121.47, 120.76, 115.81, 114.33, 113.21, 112.83, 55.91. MS(APCI): cald for $C_{18}H_{15}NO_2$ [M-H]$^{+}$ 277.32, found 277.10; HPLC(): t_R 14.340 mins, purity 95%.

3.2.9. Synthesis of (E)-1-(3-aminophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (S1-10)

Yellow solid; yield 25.8%; mp: >339 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.83 (s, 1H), 8.08 – 7.89 (m, 3H), 7.55 – 7.43 (m, 2H), 7.26 – 7.12 (m, 5H), 6.77 (ddd, *J* = 7.8, 2.3, 1.1 Hz, 1H), 5.29 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d^{6}) δ ppm 189.74, 149.45, 139.79, 138.79, 137.96, 133.41, 129.50, 125.52, 123.09, 121.53, 120.65, 118.24, 116.29, 116.19, 113.40, 113.16, 112.90.MS(APCI): cald for $C_{17}H_{14}N_2O$ [M-H]$^{+}$ 263.12, found 263.3; HPLC(): t_R 11.345 mins, purity 93%.

3.2.10. Synthesis of (E)-1-(4-aminophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (S1-11)

Yellow solid; yield 32%; mp: >339 °C; 1H NMR (400 MHz, DMSO-d6) δ ppm 11.83 (s, 1H), 8.08 – 7.89 (m, 3H), 7.55 – 7.43 (m, 2H), 7.26 – 7.12 (m, 5H), 6.77 (ddd, *J* = 7.8, 2.3, 1.1 Hz, 1H), 5.29 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d^{6}) δ ppm 189.74, 149.45, 139.79, 138.79, 137.96, 133.41, 129.50, 125.52, 123.09, 121.53, 120.65, 118.24, 116.29, 116.19, 113.40, 113.16, 112.90.MS(APCI): cald for $C_{17}H_{14}N_2O$ [M-H]$^{+}$ 262.1, found 262.1; HPLC(): t_R 12.111 mins, purity 97%.

Conclusion

The successful synthesis of 11 indole-chalcone hybrid compounds has been described using a one-step method not 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 in relatively high yields.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Structures of the compounds, copies of ^{1}H-NMR, ^{13}C-NMR, HPLC, and MS.

Author Contributions: Conceptualization, W.S. and F.N.K.; validation, W.S., M.S. and F.N.K.; investigation, S.A.T., E.G., D.B.E., and M.A.; writing—original draft preparation, S.A.T., E.G., F.N.K., and D.B.E.; writing—review and editing, S.A.T., E.G., D.B.E., W.S., M.S. and F.N.K.; funding acquisition, W.S., M.S. and F.N.K. supervision, W.S., M.S. and F.N.K. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest

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