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Access to Functionalized 2-Phenyl-4-(Indol-3-yl)-4*H*-Chromenes *via* Coupling of 2-Hydroxychalcones and Indole in PEG-400/H_2O under Catalyst-free Conditions

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Abstract

4*H*-Chromenes, particularly those appended with functionalized benzene rings at C-4′ and annulated with heterocycles exhibit a wide array of bioactivities. An innovative molecular scaffold featuring a 4*H*-chromene motif with a 3-indolyl substituent—an esteemed structural framework—anchored at C-4 was envisaged to expand the bioactivity spectrum of the resultant scaffold. This synthesis employs a straightforward domino approach towards the one-pot synthesis of 2-phenyl-4-(indol-3-yl)-4*H*-chromenes, utilizing 2-hydroxy chalcones and indoles as readily available starting materials in a PEG-400/H_2O (1:1) mixture under catalyst-free conditions. The protocol's green attributes include its atom- and step-economical nature, general applicability, procedural simplicity, hassle-free product isolation, and the use of a nontoxic, environmentally friendly reaction medium.

Keywords: Catalyst-free; 2-hydroxychalcones; Michael addition; PEG-400; 2-phenyl-4-(indol-3-yl)-4*H*-chromene.

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1. Introduction

Replacement of polluting volatile organic solvents (VOCs) by nontoxic, nonhazardous, and nonhalogenated alternative green reaction media is one of the cherished goals of green chemistry initiatives [1,2]. PEG-400, a low molecular weight liquid polymer, is a sought-after alternative in this context. It boasts qualities like thermal stability, nonvolatility, and recyclability, making it ideal for various organic reactions [3]. Its compatibility with water, stability to acid and base, as well as its biocompatibility and biodegradability, further enhance its appeal. PEG-400 has been successfully utilized in a range of organic transformations, including Heck reactions [4], click reactions [5], oxidation [6], hydrophenylation [7], three-component imino Diels-Alder reactions [8], $InBr_3$-catalyzed deprotection [9], domino reactions of 1,3-thiazolidinedione [10] and catalyst-free synthesis of 3,4-dihydropyridinones [11].

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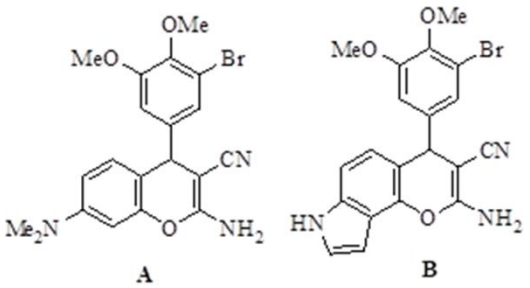
The chromene (benzopyran) [12] structure is prevalent in various naturally occurring compounds found in fruits, vegetables, and biologically active substances [13], like alkaloids, flavonoids, and anthocyanins [14-17]. These compounds demonstrate a wide array of biological activities [18], including anticancer, anti-coagulant, spasmolytic, and anti-anaphylactic [19,20] properties. They also play a significant role in combating neurodegenerative diseases and act as cognitive enhancers [21]. 4*H*-Chromenes have garnered attention in synthetic chemistry due to their presence in many biologically relevant organic compounds [22-25]. Specifically, 4-arylated-4*H*-chromenes fused with *N*-methylated pyrrole exhibit potent anticancer effects by inducing apoptosis and inhibiting tubulin, making them promising candidates against multidrug-resistant tumor cells [26] (Scheme 1).



Scheme 1

The 3-substituted indole is a versatile heterocyclic structure found in various alkaloids with pharmacological significance, including antimicrobial, antitumor, and neurotransmitter agents [27,28]. Integrating this moiety at the 4-position of the 4*H*-chromene motif was hypothesized to link their biological properties, potentially enhancing their bioactivity profile. Notably, the synthesis of indolyl chromenes is sparsely investigated. Three-component coupling of substituted indoles, salicylaldehydes, and malononitrile under indium chloride-catalysis in aqueous medium led to the above target [29]. Synthesis of enantio-enriched 2-amino-4-(indol-3-yl)-4*H*-chromenes using *N*, *N*′-dioxide-Zn(II) complex in dichloromethane was also previously reported [30]. Another direct approach to this target utilized the coupling of 2-hydroxy chalcones and indoles under the catalytic presence of iodine in refluxing toluene [31]. The existing methods suffer from one or the other limitations, *e.g*., use of metal salts [29]/ligands [30], halogenated solvents [30], prolonged reaction time [20,21], and non-compatibility of *N*-methylindole as the nucleophilic partner [30,31]. Therefore, I became interested in the rapid synthesis of 2-phenyl-4-(3-indol-3-yl)-4*H*-chromenes, avoiding metal catalysts and halogenated solvents. Inasmuch as coordination with Lewis acid catalyst often leads to blocking of lone pair of nitrogen, thereby reducing nucleophilicity of indole, a catalyst-free procedure is also highly desirable. 2-Hydroxychalcone containing electrophilic α,β-unsaturated enone moiety, and nucleophilic hydroxyl group has emerged as a modular building block capable of coupling with carbon nucleophiles to deliver structurally and functionally diversified molecular

architectures through domino reactions [32,33]. To realize our goal, coupling 2-hydroxy chalcones with indole is considered a straightforward, attractive approach. It relies on the high nucleophilic potential of C-3 of indole, and it was anticipated that indole would be a competent coupling partner of **1a** notwithstanding the unreactive nature of α,β-unsaturated enone moiety of **1a,** and unfavorable steric factor towards nucleophilic attack at its β-carbon. Herein, I reveal a catalyst-free protocol for the synthesis of 2-phenyl-4-(indol-3-yl)-4H-chromenes using PEG-400/H_2O (1:1, *v*/*v*) as the reaction medium.

2. Materials and Methods

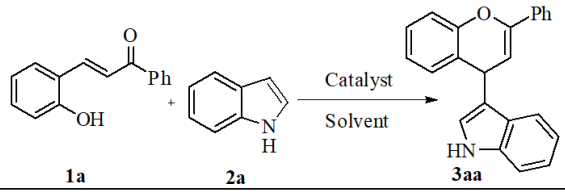
Salicylaldehyde, acetophenone, and indoles were procured from E. Merck, India/ SRL, India, and were used as such. NMR spectra were measured on Bruker DPX-400(400MHz), and IR spectra were recorded as KBr pellets on a Perkin Elmer FTIR (L120-000A). Silica gel (60-120 mesh) used for chromatographic separations and purifications was supplied by Spectrochem, India. Solvents such as light petrol (b.p. 60-80 ^oC) and ethyl acetate were purchased from E. Merck, India, and used without further purification. Anhydrous sodium sulfate was used to dry organic extracts. Silica gel G and silica gel GF (3:1) were used for TLC experiments.

3. Results and Discussion

To find suitable reaction conditions for the realization of the target compounds, a set of optimization experiments were performed under various conditions using an assembly of 2-hydroxychalcone **1a** and indole **2a** in a 1:1 millimolar ratio. The results of these initial exploratory experiments are shown in Table 1. First, an agitated neat mixture of **1a** and **2a** was heated at 90-100 °C for 4 h. The reaction did not proceed to any significant extent, and TLC monitoring indicated only trace formation of a product, with the rest of the starting materials remaining unchanged (entry 1, Table 1). Heating the reaction mixture in toluene at reflux temperature for 8 h resulted in the isolation of the anticipated product **3aa** in a modest 40 % yield (entry 2). I explored PEG-400 as an additive to toluene (0.1 g/mL) in view of its reported efficiency as a phase transfer catalyst [3]. The yield improved substantially to 65 % under the same conditions (entry 3). This observation suggests a facilitatory role of the liquid polymer in the coupling process. I also screened a few protic and aprotic polar solvents (EtOH, H_2O, CH_3CN), but they were found to be ineffective (entries 4-6). The reaction was also performed under aqueous micellar conditions in the presence of sodium dodecyl sulfate (SDS) above its critical micellar concentration in order to solubilize the nonpolar reactants, but it did not work satisfactorily (30 %, 8 h, entry 7). Next, I switched over to PEG-400 as the reaction medium in view of its supportive role as an additive to toluene. The reaction rate was substantially accelerated, and the reaction delivered 42 % yield upon exposure for 4 h at 70-80 °C (entry 8). The reaction under L-proline and $CeCl_3.7H_2O$ (each 10 mol%) catalysis in PEG-400 was also not very promising (entries 9, 10). At this stage, I screened aqueous solutions of PEG, and to our gratification, an aqueous PEG solution (PEG-400/H_2O: 1:1 *v*/*v*) outperformed all solvents examined so

far. **1a** and **2a** underwent smooth coupling upon heating in it for 4 hours to provide **3aa** selectively and cleanly in 95 % yield (entry 11). Different mixtures of PEG-400 and H_2O were also assessed, but none of them could surpass it (entries 12-13). Another significant observation was the sharp drop in yield upon lowering of temperature from 70-80 °C to 40 °C, suggesting the marked dependence of yield upon temperature (entry 14).

Table 1. Optimization experiments for the synthesis of **3aa**.



1a **2a** **3aa**

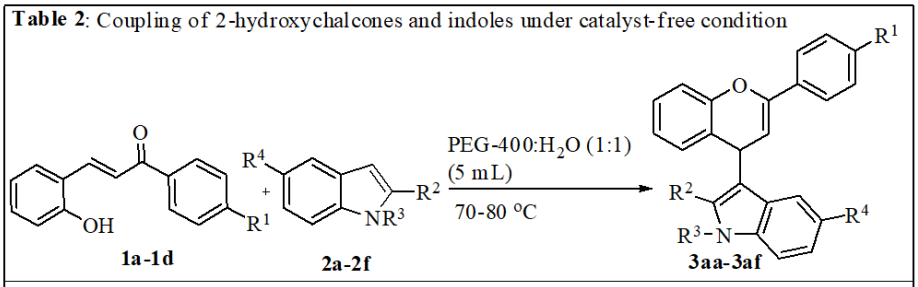
Entry	Solvent (5 mL)	Additive	Catalyst (mol%)	Temperature (°C)	Time[a] (h)	Isolated Yield (%)
1	-	-	-	90-100	4	Trace
2	Toluene	-	-	Reflux	8	40
3	Toluene	PEG-400 (0.5g)	-	110	8	65
4	EtOH	-	-	Reflux	8	Trace
5	MeCN	-	-	Reflux	8	NR
6	H_2O	-	-	Reflux	8	12
7	H_2O	SDS (0.058g)	-	70-80	8	30
8	PEG-400	-	-	70-80	4	42
9	PEG-400	-	L-Proline (10)	70-80	4	60
10	PEG-400	-	$CeCl_3.7H_2O$ (10)	70-80	4	49
11	**PEG-400:H_2O (1:1)**	-	-	**70-80**	**4**	**95**
12	PEG-400:H_2O (2:1)	-	-	70-80	4	80
13	PEG-400:H_2O (1:2)	-	-	70-80	4	90
14	PEG-400:H_2O (1:1)	-	-	40	6	48

[a]Reactions were performed on 1 mmol scale.
NR stands for reaction.

With the optimized reaction condition in hand, I investigated its substrate scope for various 4′-substituted 2-hydroxy chalcones and indoles substituted in both rings. The results of these experiments are exhibited in Table 2. The protocol proved successful in all cases (11 examples) studied. It was demonstrated that the presence of electron-releasing 4′-OMe in 2-hydroxychalcone **1c** lowered the yield of the product **3ca** (80 %) with unsubstituted indole as its reaction partner, and it also required extended time (5 h) (entry 3). Presumably, decreased electrophilicity of the enone moiety accounts for the result. Similar lower yields were also scored in the case of coupling of **1a** with 2-methylindole (**2b**) and *N*-methylindole (**2d**). Notably, a previous report of I_2-catalyzed reaction of *N*-methylindole [13] was unsuccessful and yielded a trace of product and a complex mixture. However, the electronic nature of 5-substituents of the indole (5-OMe, 5-CN) had no perceptible influence as both **2e** and **2f** rapidly and efficiently afforded excellent yields of the corresponding coupling products **3ae** and **3af** (entries 10, 11).

Table 2. Coupling of 2-hydroxychalcone and indoles under catalyst-free conditions.

Table 2: Coupling of 2-hydroxychalcones and indoles under catalyst-free condition

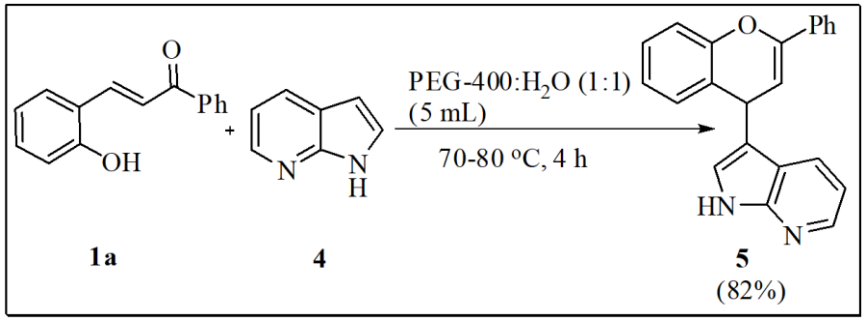


1a-1d **2a-2f** **3aa-3af**

Entry	2-Hydroxychalcones (**1a-1d**) R^1	Indoles (**2a-2f**) R^2	R^3	R^4	Product	Time[a] (h)	Isolated Yield(%)
1	**1a**, H	**2a**, H	H	H	**3aa**	4	95
2	**1b,** Cl	**2a**, H	H	H	**3ba**	4	92
3	**1c**, OMe	**2a**, H	H	H	**3ca**	5	85
4	**1d**, Allyloxy	**2a**, H	H	H	**3da**	4	88
5	**1a**, H	**2b**, Me	H	H	**3ab**	3	90
6	**1c**, OMe	**2b**, Me	H	H	**3cb**	3	80
7	**1d**, Allyloxy	**2b**, Me	H	H	**3db**	3	91
8	**1a**, H	**2c**, Ph	H	H	**3ac**	3	94
9	**1a**, H	**2d**, H	Me	H	**3ad**	4	82
10	**1a**, H	**2e**, H	H	OMe	**3ae**	3	97
11	**1a**, H	**2f**, H	H	CN	**3af**	3	92

[a]Reaction were performed on 1 mmol scale.

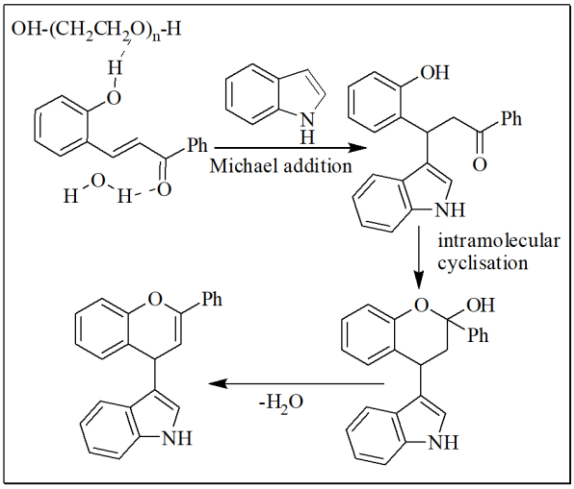
The method also worked for 7-azaindole **4,** and the replacement of the benzene ring with an electron-withdrawing pyridine ring had little effect on yield and facility (82 %, 4 h) (Scheme 2).



Scheme 2

The coupling products were characterized by the spectral features (FTIR, ^{1}H-, ^{13}C-NMR, elemental analysis data). The melting points of known compounds **3aa**, **3ba, 3ca,** and **5** were in good agreement with their literature value [31].

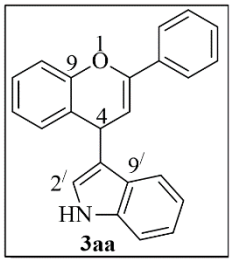
The success of the domino reaction-based current protocol primarily hinges upon the efficient formation of the key Michael adduct intermediate, which was favored in nonpolar toluene rather than polar protic or aprotic media (EtOH, H_2O, CH_3CN). The electrophilic activation of carbonyl by hydrogen bond donor activity of water is a necessary but not sufficient facilitator of the key C-C bond construction. The co-solvent, PEG, decreases the polarity of its aqueous solution, consequently increasing the solubility of the chalcone and indole. This is further coupled with the facilitatory role of ether groups interspersed between methylene units as hydrogen bond bases. It boosts the nucleophilicity of the 2-hydroxy group of chalcone, helping the subsequent C-O bond formation that leads to the chromene ring. Therefore, water and PEG-400 offer complementary roles through their hydrogen-bonded structures, facilitating synergistic electrophilic and nucleophilic activation. Finally, dehydration is mainly driven by the extension of conjugation with the 2-phenyl group. This step is presumably very temperature-dependent. The tentative mechanistic scenario of the domino C-C and C-O bond formations is depicted in Scheme 3.



Scheme 3

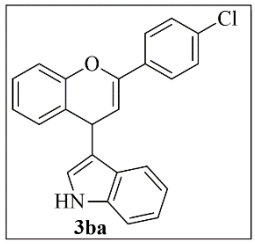
4. Experimental

Typical procedure for the synthesis of 3-(2-Phenyl-4*H*-chromen-4-yl)-1*H*-indole (3aa): To a mixture of 2-hydroxychalcone (**1a)** (220 mg, 0.98 mmol) and indole (**2a**) (120 mg, 1.02 mmol) was added PEG-400/H_2O (5 mL, 1:1 *v*/*v*) and the resulting solution was heated with stirring at 70-80 °C for 4 h (TLC monitoring). TLC was carried out with ethyl acetate: *n*-hexane 60:40 as a mobile phase and iodine vapors as a visualizing agent. To the cooled reaction mixture, brine water (5 mL) was added, and the product was cleanly separated out as a red semisolid mass. It was dissolved in ethyl acetate (5 mL), dried, and recrystallized from ethyl acetate-*n*-hexane to yield 3-(2-phenyl-4*H*-chromen-4-yl)-1*H*-indole **3aa** (300 mg, ~ 95 %), **Rf**: 0.38 **mp**. 106-108 °C (lit [22]. 100-102 °C).



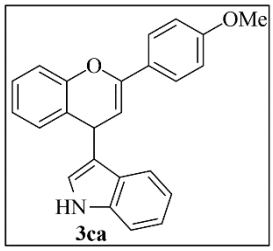
3aa

IR (KBr) ν_{max}: 3426 (NH), 2920 (NH), 2856, 1634, 1454, 1228, 745 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, s, NH), 7.74-7.71 (2H, m, ArH), 7.62 (1H, d, J=8 Hz, ArH), 7.39-7.30 (4H, m, ArH), 7.19-7.11 (4H, m, ArH), 7.07-7.03 (2H, m, ArH), 6.94-6.90 (1H, m, ArH, H-2/), 5.68 (1H, d, *J* = 4Hz, H-3), 5.17 (1H , d, *J* = 4 Hz, H-4) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3 (C-9), 147.9 (C-2), 136.8, 134.5, 129.1, 128.4, 128.2, 127.7, 126.6, 124.8, 123.5, 121.9 (2C), 121.7, 119.7, 119.6, 116.4, 111.0, 101.1 (C-3), 32.1 (C-4) ppm.
Anal. Calcd. For $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33 %. Found: C, 85.37; H, 5.41; N, 4.28 %.



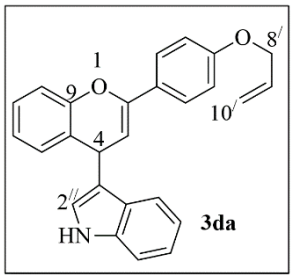
3ba

3ba: 3-(2-(4-Chlorophenyl)-4*H*-chromen-4-yl)-1*H*-indole, **Rf**: 0.47, pale red solid, **mp** 82-84 ºC [lit [22]. 83–85 °C].
IR (KBr) ν_{max}: 3417 (NH), 2920 (NH), 2355, 1723, 1668, 1584, 1481, 1330, 1235, 1181 cm^{-1}.



3ca

3ca: 3-(2-(4-Methoxyphenyl)-4*H*-chromen-4-yl)-1*H*-indole, **Rf**: 0.28, pale red solid, **mp** 96–98 °C [lit [31]. 96–97 °C].
IR (KBr) ν_{max}: 3425 (NH), 2926 (NH), 1648, 1507, 1235, 1171 cm^{-1}.



3da

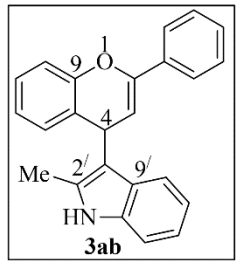
3da: 3-(2-(4-(Allyloxy)phenyl)-4*H*-chromen-4-yl)-1*H*-indole, **Rf**: 0.49, pale red solid, **mp** 76–78 °C.

IR (KBr) ν_{max}: 3409 (NH), 2918 (NH), 1719, 1603, 1228, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (1H, s, NH), 7.63 (2H, t, *J* = 8.8 Hz, ArH), 7.36 (2H, d, *J* = 8 Hz, ArH), 7.19-7.09 (4H, m, ArH), 7.06-7.03 (2H, m, ArH), 6.91 (3H, dd, *J*= 6.8 Hz, ArH), 6.11-6.01 (1H, m, H-9′), 5.56 (1H, d, *J* = 4 Hz, H-3), 5.41 (1H, dd, *J* = 17.2, 1.2 Hz, H-10′), 5.33-5.28 (1H, m, H-10′), 5.15 (1H, d, *J* = 4 Hz, H-4), 4.56 (2H, dd, *J* = 5.2, 1.2 Hz, H-8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8 (C-4′), 151.2 (C-9), 147.6 (C-2), 136.7, 133.2 (C-9′), 129.6, 127.5, 127.3, 126.4, 126.1, 123.6, 123.4, 122.2, 121.6, 120.8, 119.6, 117.9 (C-10′), 116.5, 114.6, 111.3, 99.5 (C-3), 68.9 (C-8′), 32.1 (C-4) ppm.

Anal. Calcd. For $C_{26}H_{21}NO_2$: C, 82.30; H, 5.58; N, 3.69 %. Found: C, 82.23; H, 5.61; N, 3.62 %.



3ab

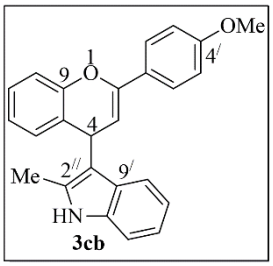
3ab: 2-Methyl-3-(2-phenyl-4*H*-chromen-4-yl)-1*H*-indole, **Rf**: 0.35, pale red solid, **mp** 142–144 °C.

IR (KBr) ν_{max}: 3401 (NH), 2922 (NH), 1715, 1618, 1457, 1230, 1060, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (1H, s, NH), 7.63-7.71 (2H, m, ArH), 7.45 (1H, d, *J* = 7.6 Hz, ArH), 7.41-7.27 (4H, m, ArH), 7.14 (1H, dd, *J* = 6.8, 1.6 Hz, ArH), 7.12 (1H, dd, *J* = 8, 1.6 Hz, ArH), 7.08 (1H, dd, *J* = 8, 0.8 Hz, ArH), 6.96 (2H, t, *J* = 7.2 Hz, ArH), 6.90 (1H, d, *J* = 6.4, 1.6 Hz, ArH), 5.65 (1H, d, *J* = 4 Hz, H-3), 5.19 (1H, d, *J* = 3.6 Hz, H-4), 2.40 (3H, s, 2′ -C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2 (C-9), 147.7 (C-2), 135.1, 134.4, 131.4, 129.4, 128.3, 127.8, 127.4, 124.6, 123.4, 123.3, 121.1, 119.5, 118.6, 116.3, 116.0, 110.2, 100.9 (C-3), 40.0 (C-4), 11.9 (2′-**C**H_3) ppm.

Anal. Calcd. For $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15 %. Found: C, 85.37; H, 5.61; N, 4.08%.



3cb

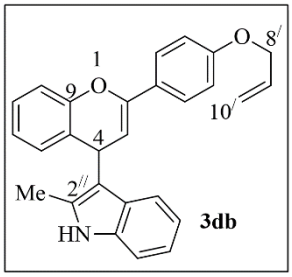
3cb: 3-(2-(4-Methoxyphenyl)-4*H*-chromen-4-yl)-2-methyl-1*H*-indole, **Rf**: 0.37, pale red solid, **mp** 130–122 °C.

IR (KBr) ν_{max}: 3387 (NH), 2932 (NH), 1717, 1604, 1458, 1255, 1166, 751 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (1H, s, NH), 7.65 (2H, d, *J* = 8.8Hz, ArH), 7.44 (1H, d, *J* = 8 Hz, ArH), 7.25 (1H, d, *J* = 8 Hz, ArH), 7.12-7.05 (3H, m, ArH), 6.97-6.88 (5H, m, ArH), 5.43 (1H, d, *J* = 3.6 Hz, H-3), 5.17 (1H, d, *J* = 3.6 Hz, H-4), 3.82 (3H, s, 4′-OC**H$_3$**), 2.39 (3H, s, 2″ -C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (C-4′), 151.3 (C-9), 147.4 (C-2), 135.2, 132.3, 131.4, 129.4, 127.8, 127.4, 127.1, 126.0, 123.4, 123.3, 121.0, 119.3, 118.6, 116.3, 116.1, 114.0, 113.8, 113.7, 110.2, 99.2 (C-3), 55.5 (4′-O**C**H$_3$), 30.9 (C-4), 11.9 (C-2′) ppm.

Anal. Calcd. For $C_{25}H_{21}NO_2$: C, 81.72; H, 5.76; N, 3.81%. Found: C, 81.83; H, 5.85; N, 3.73 %.



3db

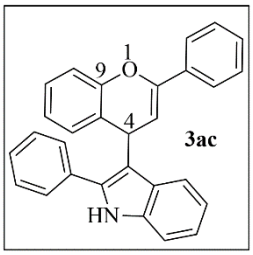
3db: 3-(2-(4-(Allyloxy)phenyl)-4*H*-chromen-4-yl)-2-methyl-1*H*-indole, **Rf**: 0.5, pale red solid, **mp** 106-108 °C.

IR (KBr) ν_{max}: 3416 (NH), 2859 (NH), 1672, 1509, 1236, 1181, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (1H, s, NH), 7.64 (2H, d, *J* = 8.8 Hz, ArH), 7.44 (1H, d, *J* = 8 Hz, ArH), 7.27-7.25 (1H, m, ArH), 7.16-7.03 (3H, m, ArH), 7.00-6.89 (5H, m, ArH), 6.09-6.02 (1H, m, H-9′), 5.44 (1H, d, *J* = 4 Hz, H-3), 5.40-5.28 (2H, m, H-10′), 5.17 (1H, d, *J* = 3.6 Hz, H-4), 4.56 (2H, d, *J* = 5.2 Hz, H-8′), 2.39 (3H, s, 2′ -C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8 (C-4′), 151.3 (C-9), 147.5 (C-2), 135.2, 133.2 (C-9′), 131.4, 129.5, 127.9, 127.4, 127.3, 126.0, 123.5, 123.4, 121.1, 119.4, 118.7, 117.8 (C-10′), 116.2, 114.5, 110.2, 99.3 (C-3), 68.9 (C-8′), 31.0 (C-4), 11.9 (2″-**C**H$_3$) ppm.

Anal. Calcd. For $C_{27}H_{23}NO_2$: C, 82.42; H, 5.89; N, 3.56 %. Found: C, 82.33; H, 5.97; N, 3.49 %.



3ac

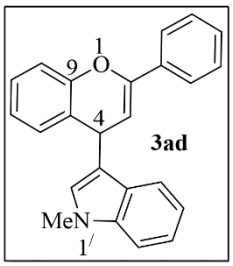
3ac: 2-Phenyl-3-(2-phenyl-4*H*-chromen-4-yl)-1*H*-indole, **Rf**: 0.29, reddish black solid, **mp** 162-164 °C.

IR (KBr) ν_{max}: 3439 (NH), 3025 (NH), 1663, 1454, 1227, 724 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (1H, s, NH), 7.70 (2H, dd, *J* = 8.8, 0.8 Hz, ArH), 7.62 (2H, dd, *J* = 8.8, 0.8 Hz, ArH), 7.50-7.46 (2H, m, ArH), 7.43-7.40 (2H, m, ArH), 7.38-7.28 (4H, m, ArH), 7.14-7.12 (3H, m, ArH), 6.95 (1H, d, *J* = 7.6 Hz, ArH), 6.91 (1H, d, *J* = 7.2 Hz, ArH), 6.87-6.83 (1H, m, ArH), 5.60 (1H, d, *J* = 3.2 Hz, H-3), 5.37 (1H, d, *J* = 3.2 Hz, H-4) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3 (C-9), 147.9 (C-2), 136.2, 135.0, 134.3, 132.8, 129.3, 129.0, 128.6, 128.3, 127.8, 127.6, 124.7, 123.5, 123.3, 122.3, 120.5, 119.8, 116.3, 110.8, 101.3 (C-3), 31.4 (C-4) ppm.

Anal. Calcd. For $C_{29}H_{21}NO$: C, 87.19; H, 5.30; N, 3.51 %. Found: C, 87.11; H, 5.38; N, 3.43 %.



3ad

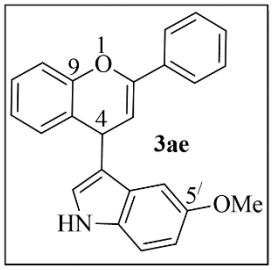
3ad: 1-Methyl-3-(2-phenyl-4*H*-chromen-4-yl)-1*H*-indole, **Rf**: 0.50, pale red solid, **mp** 126–128 °C.

IR (KBr) ν_{max}: 1731, 1613, 1484, 1449, 1231, 1060, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.71 (2H, m, ArH), 7.63 (1H, d, *J* = 8 Hz, ArH), 7.38-7.34 (2H, m, ArH), 7.32-7.31 (1H, m, ArH), 7.27 (1H, d, *J* = 8 Hz, ArH), 7.22 (1H, d, *J* = 4 Hz, ArH), 7.19-7.16 (2H, m, ArH), 7.14-7.12 (2H, m, ArH), 7.07-7.03 (1H, m, ArH), 6.93-6.91 (1H, m, ArH), 5.67 (1H, d, *J* = 4 Hz, H-3), 5.14 (1H, d, *J* = 3.6 Hz, H-4), 3.70 (3H, s, 1′ -NC**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1 (C-9), 147.6 (C-2), 137.3, 134.4, 129.5, 128.5, 128.3, 127.5, 127.0, 126.8, 124.7, 123.6, 123.4, 121.7, 120.2, 119.4, 119.1, 116.5, 109.3, 101.2 (C-3), 31.5 (C-4), 22.7 (1′-N**C**H_3) ppm.

Anal. Calcd. For $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15%. Found: C, 85.37; H, 5.71; N, 4.08 %.



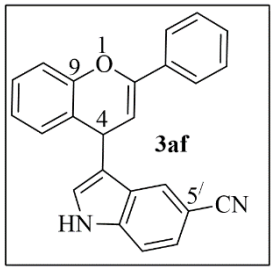
3ae: 5-Methoxy-3-(2-phenyl-4*H*-chromen-4-yl)-1*H*-indole, **Rf**: 0.35, pale red solid, **mp** 124–126 °C.

IR (KBr) ν_{max}: 3350 (NH), 2833 (NH), 1666, 1485, 1229, 801, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92(1H, s, NH), 7.76(1H, dd, *J* = 3.6, 1.6 Hz, ArH), 7.75-7.74 (1H, m, ArH), 7.43-7.35 (3H, m, ArH), 7.27 (1H, t, *J* = 4 Hz, ArH), 7.20 (1H, dd, *J* = 6.8, 1.2 Hz, ArH), 7.16 (2H, d, *J* = 8 Hz, ArH), 7.05 (2H, dd, *J* = 13.2, 2.4 Hz, ArH), 6.99-6.96 (1H, m, ArH), 6.86 (1H, d, *J* = 8.8, 2.4 Hz, ArH), 5.70 (1H, d, *J* = 4 Hz, H-3), 5.15 (1H, d, *J* = 3.6 Hz, H-4), 3.77 (3H, s, 5′-OC**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9 (C-5′), 151.2 (C-9), 147.8 (C-2), 134.4, 131.8, 129.5, 128.4, 127.5, 126.8, 124.7, 123.4, 123.3, 122.7, 121.3, 116.4, 112.3, 111.9, 101.1, 101.0 (C-3), 55.75 (5′-O**C**H_3), 32.1 (C-4) ppm.

Anal. Calcd. For $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96 %. Found: C, 81.49; H, 5.51; N, 4.05 %.



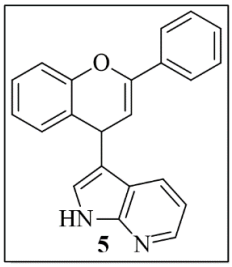
3af: 3-(2-Phenyl-4*H*-chromen-4-yl)-1*H*-indole-5-carbonitrile, **Rf**: 0.27, pale red solid, **mp** 184–186 °C.

IR (KBr) ν_{max}: 3314 (NH), 2845 (NH), 2219 (CN), 1486, 1325, 1232, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.58 (1H, s, NH), 7.94 (1H, s, ArH), 7.79 (2H, dd, *J* = 7.2 Hz, ArH), 7.53 (1H, ArH, *J* = 8.4 Hz), 7.46-7.37 (5H, m, ArH), 7.23-7.22 (2H, m, ArH), 7.11 (1H, d, *J* = 7.2 Hz, ArH), 7.02-6.99 (1H, m, ArH), 5.91 (1H, d, *J* = 4.8 Hz, H-3), 5.23 (1H, d, *J* = 4 Hz, H-4) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): δ 151.0 (C-9), 147.4 (C-2), 138.8, 133.9, 129.9, 129.1, 129.0, 128.3, 126.2, 126.1, 124.8 , 124.6 , 124.3 , 124.2 , 123.7 , 121.3 , 116.9 (5′-CN) , 113.5 , 101.4 (C-5′) , 101.1 (C-3), 31.5 (C-4) ppm.

Anal. Calcd. For $C_{24}H_{16}N_2O$: C, 82.74; H, 4.63; N, 8.04 %. Found: C, 82.69; H, 4.71; N, 8.12 %.



5

5: 3-(2-Phenyl-4*H*-chromen-4-yl)-1*H*-pyrrolo[2,3-b]pyridine, **Rf**: 0.35, white solid, **mp** 152–154 °C [22]. 155–156 ºC].
IR (KBr) ν_{max}: 3438 (NH), 3145, 2355 (NH), 1660, 1581, 1488, 1321, 1111, 1069 cm^{-1}.

5. Conclusion

Herein, a simple domino method is presented for the one-pot synthesis of 2-phenyl-4-(indol-3-yl)-4*H*-chromenes, utilizing 2-hydroxy chalcones and indoles as easily obtainable starting materials in PEG-400/H_2O (1:1) mixture under catalyst-free conditions. Under optimized conditions at 70-80 °C, the reaction efficiently proceeded with a diverse range of substrates, giving excellent yields in the range 80 to 97 %. Water and PEG play a complementary role in this process, activating the carbonyl group and enhancing solubility. The protocol's green credentials lie in its efficient use of atoms and steps, its broad applicability, straightforwardness, easy product isolation, and the utilization of a nontoxic, environmentally friendly reaction medium.

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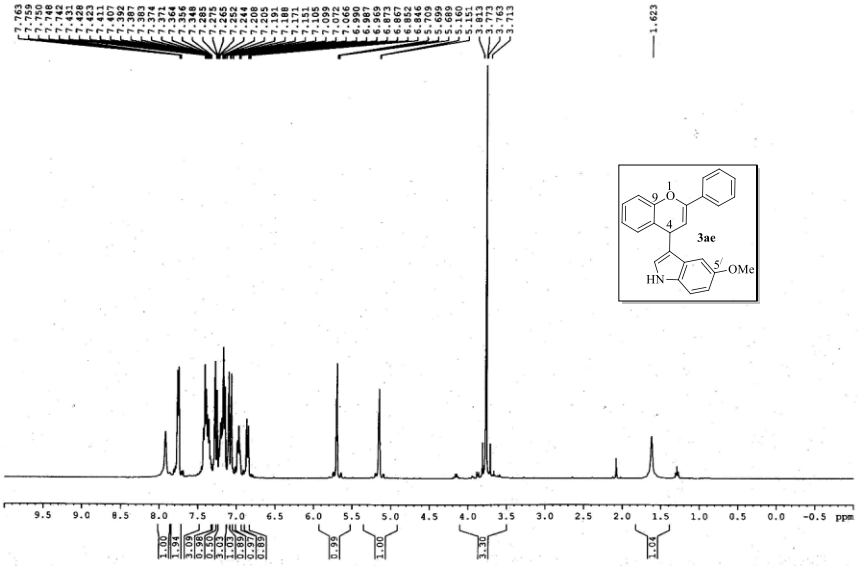
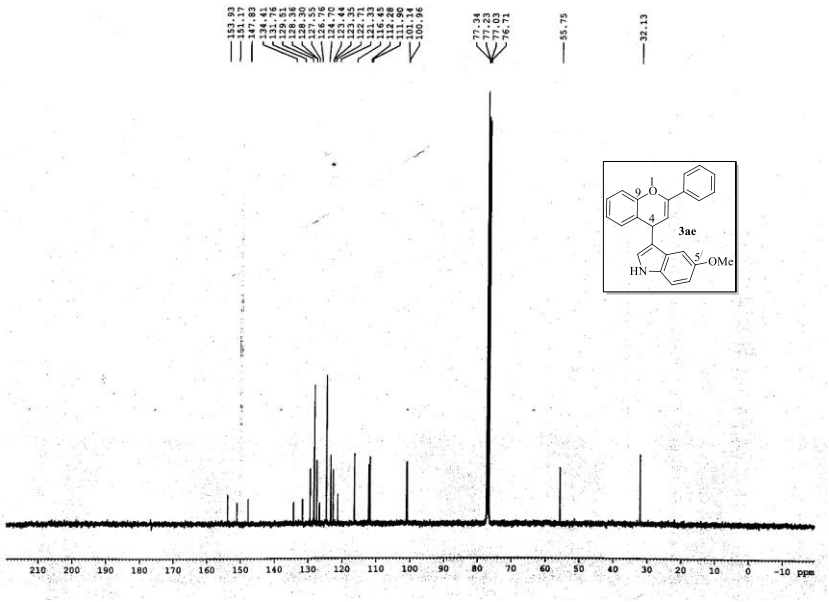
Supplementary file



^{1}H-NMR of 3ae



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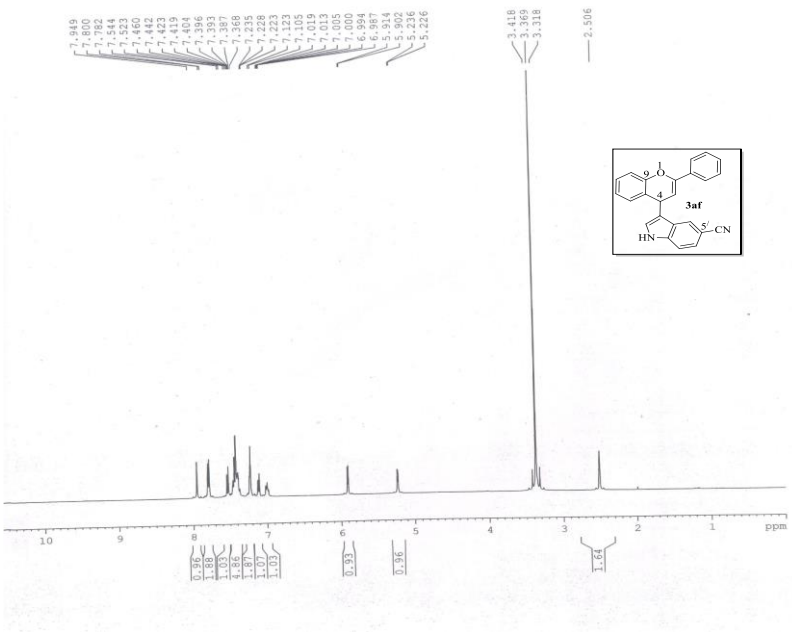
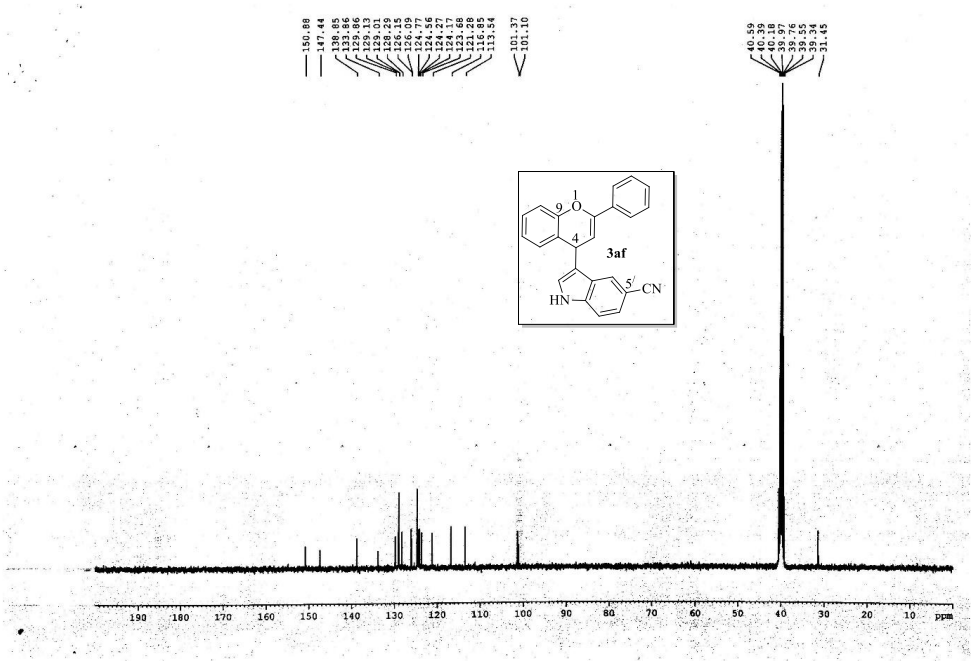
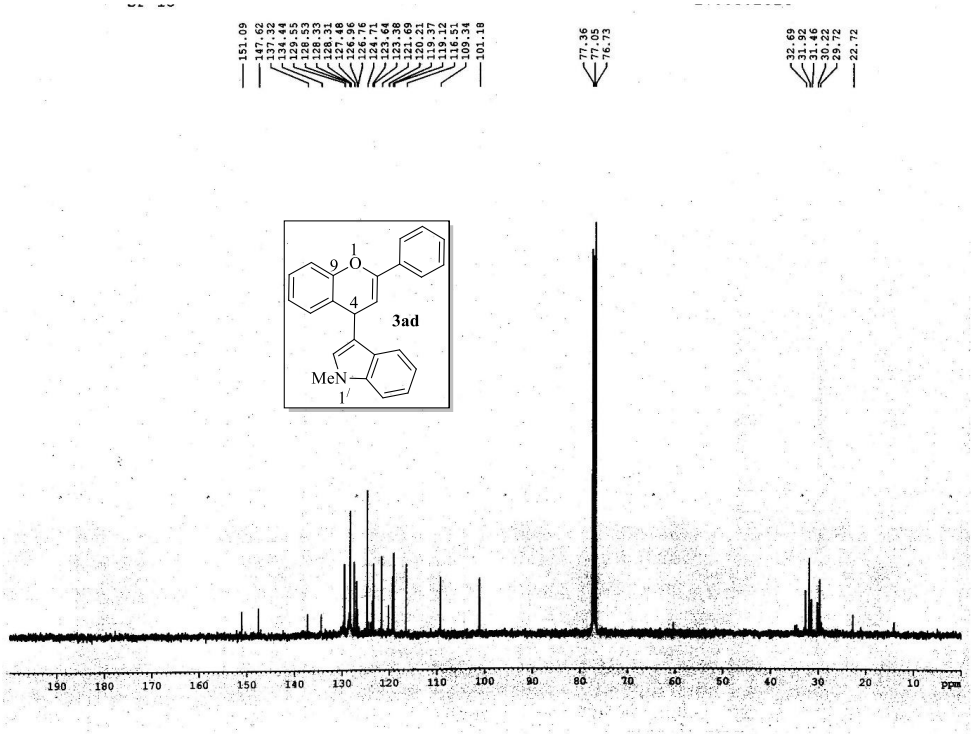


^{1}H-NMR of 3af



^{13}C-NMR of 3af



^{13}C-NMR of 3ad