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PAPER

Synthesis of functionalized 2-aryl-4-(indol-3-yl)-4*H*-chromenes *via* iodine-catalyzed domino Michael addition–intramolecular cyclization reaction†

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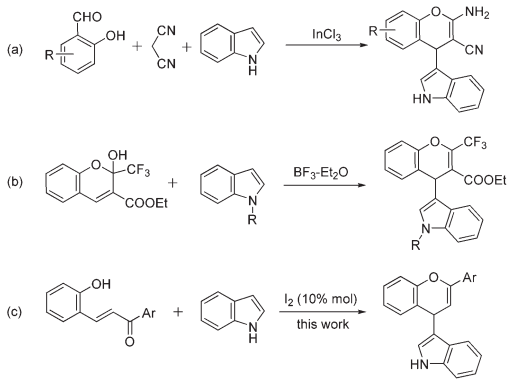
An efficient synthesis of novel functionalized 2-aryl-4-(indol-3-yl)-4*H*-chromenes has been developed, in the presence of a catalytic amount of iodine, from easily available starting materials, 2-hydroxychalcone derivatives. Indole, substituted indoles and 7-azaindole are suitable for this transformation. The possible domino Michael addition–intramolecular cyclization reaction mechanism is proposed.

Introduction

The chromene (or benzopyran) moiety often appears as an important structural component in both biologically active and natural compounds. It is widely present in natural alkaloids, flavonoids, tocopherols, and anthocyanins.[1,2] Many chromenes also exhibit photochromism in the crystalline state.[3] The wide application of these heteroaromatic compounds has made them popular synthetic targets.[4–8] In addition, indole derivatives, such as indomethacin, tryptophan and melatonin,[9] exist in a variety of natural products and medicinal agents. Generally, the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably. For example, it has been reported that 4-aryl-pyrrolo-4*H*-chromenes (7,8-fused chromenes bearing an indole moiety) are potent in cell growth inhibition assays and as inhibitors of tubulin polymerization.[10] This encouraged us to synthesize new heterocyclic systems containing both chromene and indole moieties. A literature survey revealed that only a few examples of indolyl chromenes have been reported. In 2007, Perumal[11] reported the first example of the synthesis of 2-amino-4-(indol-3-yl)-4*H*-chromene *via* a multi-component condensation reaction of 2-hydroxy-1-naphthaldehyde, malononitrile, and indole (Scheme 1a).[12] Some functionalized 4-(indol-3-yl)-4*H*-chromenes could be prepared through the reaction of 2-hydroxy-2-(trifluoromethyl)-2*H*-chromenes with indoles (Scheme 1b).[13] As such, the development of new and more general methods towards 4-(indol-3-yl)-4*H*-chromenes is of significant interest.



Scheme 1 Strategy for the synthesis of 4-(indol-3-yl)-4*H*-chromenes.

Recently, Mayr[14] and Sashidhara[15] described an efficient approach to the synthesis of 4-phenacylideneflavenes involved in the cyclization reaction of 2-hydroxychalcone intermediates. Moreover, it is well known that iodine has received considerable attention as a mild, non-toxic and selective reagent in organic synthesis due to its unique catalytic properties.[16] As a continuous study on the application of iodine in organic synthesis,[17] we herein describe an efficient iodine-catalyzed domino reaction of 2-hydroxychalcone derivatives with indole, substituted indoles, or 7-azaindole for the synthesis of novel 2-aryl-4-(indol-3-yl)-4*H*-chromenes (Scheme 1c).

Results and discussion

Initially, *trans*-2-hydroxychalcone derivatives (**3a–g**) were synthesized in 81–90% yields by the Claisen–Schmidt condensation of salicylaldehyde (**1**) with different methyl ketones (**2**) in the

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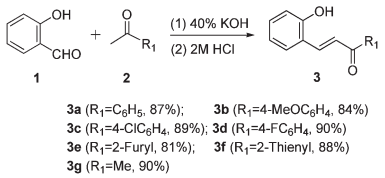
†Electronic supplementary information (ESI) available: Copies of ^{1}H, ^{13}C NMR, HSQC and HRMS spectra for the products. See DOI: 10.1039/c2ob26642c



Scheme 2 Synthesis of *trans*-2-hydroxychalcone derivatives **3a–g**.

presence of 40% potassium hydroxide solution, followed by treatment with 2 M HCl according to known methods (Scheme 2).[18]

Next, *trans*-2-hydroxychalcone (**3a**, 1.0 mmol) was used as the model substrate to react with indole (**4a**, 1.0 mmol) for the synthesis of desired product 3-(2-phenyl-4*H*-chromen-4-yl)-1*H*-indole (**5a**). As shown in Table 1, **5a** was obtained in 68% yield in refluxing toluene for 3 h in the presence of a catalytic amount (0.1 mmol) of iodine (Table 1, entry 1). Prolonging the reaction time to 10 h and increasing the ratio of indole to **3a** to 2 : 1 did not efficiently improve the yield (Table 1, entry 2). Decreasing the reaction temperature resulted in a lower yield of **5a** (Table 1, entries 3, 4). There was no obvious effect on the yield when 0.2 or 0.05 molar equivalent iodine was employed (Table 1, entries 5, 6). It should be noted that even in the absence of iodine, the reaction could also deliver **5a** in 38% yield (Table 1, entry 7). Also, the reaction occurred in other solvents (THF, MeCN, EtOH and *t*-BuOH) and **5a** was isolated in 32–50% yield (Table 1, entries 8–11). It was found that the reactions also gave **5a** in moderate yield (45–66%) using a Brønsted acid (AcOH) or other Lewis acids ($ZnBr_2$, $ZnCl_2$, $InCl_3$, $InBr_3$, AgOTf and $BF_3{\cdot}Et_2O$) as the catalyst (Table 1, entries 12–18). Accordingly, the optimal reaction conditions were identified as the reaction of **3a** with 1.0 equiv. of indole in the presence of 0.1 equiv. iodine.

The structure of compound **5a** was confirmed by means of ^{1}H NMR, ^{13}C NMR, HRMS, and IR. The ^{1}H NMR spectrum exhibited the characteristic two sets of doublets at 5.67 and 5.16 ppm with the coupling constant of 4.0 Hz, which were assigned to the 3- and 4-position protons of the chromene ring, respectively. The NH signal as a broad peak at 7.99 ppm indicated the existence of the indole ring of **5a**. In addition, in the ^{13}C NMR spectrum, no carbonyl signal (C=O) was observed and the distinguishing resonances at 101.0 ppm for C-3 and 32.1 ppm for C-4 proved the formation of the chromene ring.

With the optimal reaction conditions in hand, we then examined the reactions of *trans*-2-hydroxychalcone derivatives (**3**) with a variety of substituted indoles (**4**) to establish the generality of the present transformation. The results are listed in Table 2. It was observed that substituents on the indole ring had an obvious effect on the reaction yields. The treatment of **3a** with 4-chloro-, 5-bromo-, 5-fluoro-substituted indoles gave the desired products **5b–d** in 63–70% yields. 2-Methyl indole also delivered **5e** in good yield (71%). However, when *N*-methyl indole was employed, the reaction gave a complex mixture and only a trace of **5f** was detected by the mass spectrum.

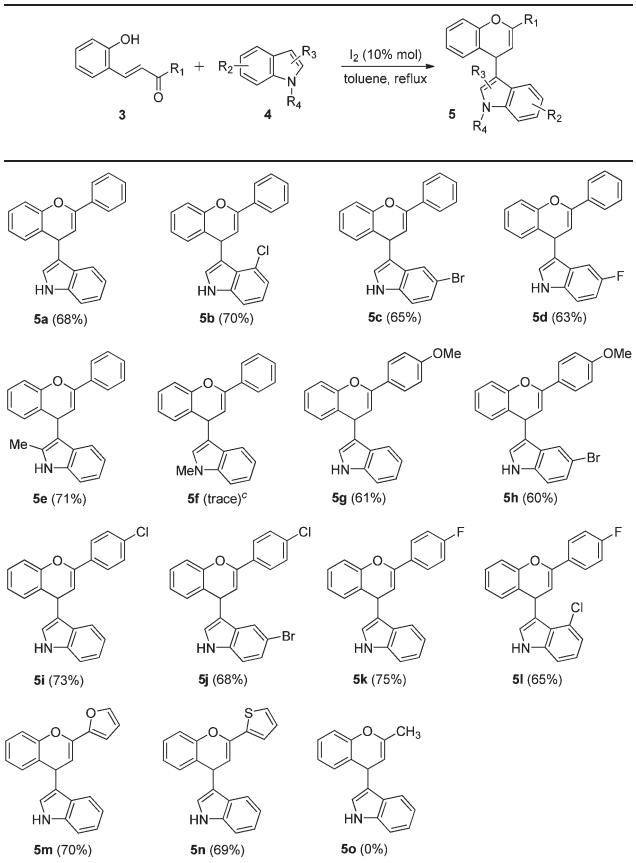
On the other hand, the transformation was extended to other α,β-unsaturated ketones. In the case of substrates bearing an electron-donating group (–OMe) on the phenyl ring, **5g** and **5h** were obtained in slightly lower yields. The substrates bearing

Table 1 Optimization of reaction conditions for the synthesis of **5a**[a]

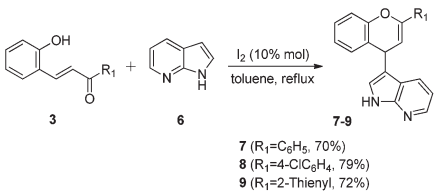
Entries	Solvent	Catalyst (mmol)	Temp. (°C)	Yield[b] (%)
1	Toluene	I_2 (0.1)	Reflux	68
2	Toluene	I_2 (0.1)	Reflux	69[c]
3	Toluene	I_2 (0.1)	70	53
4	Toluene	I_2 (0.1)	25	5
5	Toluene	I_2 (0.2)	Reflux	68
6	Toluene	I_2 (0.05)	Reflux	65
7	Toluene	I_2 (0)	Reflux	38[d]
8	THF	I_2 (0.1)	Reflux	45
9	MeCN	I_2 (0.1)	Reflux	32
10	EtOH	I_2 (0.1)	Reflux	48
11	*t*-BuOH	I_2 (0.1)	Reflux	50
12	Toluene	AcOH (0.1)	Reflux	66
13	Toluene	$ZnBr_2$ (0.1)	Reflux	62
14	Toluene	$ZnCl_2$ (0.1)	Reflux	60
15	Toluene	$InCl_3$ (0.1)	Reflux	60
16	Toluene	$InBr_3$ (0.1)	Reflux	48
17	Toluene	AgOTf (0.1)	Reflux	45
18	Toluene	$BF_3{\cdot}Et_2O$ (0.1)	Reflux	40

[a] Unless otherwise noted, reactions were performed with **3a** (1.0 mmol) and **4a** (1.0 mmol) in solvent (6 mL) for 3 h. [b] Isolated yield. [c] The reaction time was 10 h, with **3a**/**4a** = 1 : 2. [d] The yield was 40% while prolonging the reaction time to 10 h, with **3a**/**4a** = 1 : 2.

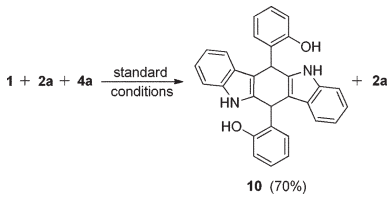
Table 2 Synthesis of 2-aryl-4-(indol-3-yl)-4*H*-chromenes[a,b]



[a] Reaction conditions: **3** (1.0 mmol), **4** (1.0 mmol) and iodine (0.1 mmol) in toluene (6 mL) for 3 h. [b] Isolated yields. [c] Complex mixtures.



Scheme 3 Synthesis of 4-(3-(7-azaindolyl))-4*H*-chromenes.



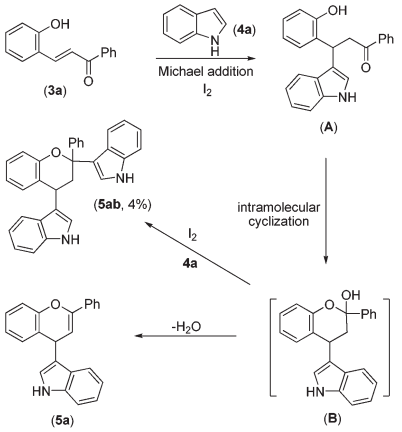
Scheme 4 One-pot reaction.

electron-withdrawing groups (–Cl and –F) led to the corresponding **5i–l** in 65–75% yields. To our delight, heterocyclic (furan and thiophene) substrates were also suitable for the reactions resulting in **5m** and **5n** in 70% and 69% yields, respectively. However, when R_1 was an alkyl group (CH_3), **5o** was not observed even after 8 h.

Furthermore, the reaction of 7-azaindole (**6**) with **3a**, **3c** and **3f** under the above-mentioned standard conditions furnished the corresponding 2-aryl-4-(3-(7-azaindolyl))-4*H*-chromenes (**7–9**) in 70–79% yields (Scheme 3). No expected products were obtained using furan, benzofuran and benzothiophene as substrates probably owing to their weak nucleophilicity.

In recent years, much attention has been paid to one-pot syntheses.[19] It has been reported that chalcone derivatives can be synthesized *in situ* by condensation of aromatic aldehyde with acetophenone in the presence of iodine[20] or without any catalyst.[21] Therefore, we attempted to synthesize **5a** from salicylaldehyde (**1**), acetophenone (**2a**) and indole (**4a**) in a one-pot procedure under the standard conditions. However, **5a** was not formed and the reaction only occurred between **1** and **4a** to give the unexpected product 6,12-bis(2-hydroxylphenyl)-6,12-dihydroindolo-[3,2-*b*]carbazole (**10**)[22] in 70% yield with recovery of unreacted starting material **2a** (Scheme 4).

Next, the plausible mechanism was further investigated using α,β-unsaturated ketone (**3a**) as an example (Scheme 5). First, indole reacts with **3a** *via* a Michael-type addition reaction to deliver intermediate **A** and this process could take place without any catalyst (Table 1, entry 7).[23] In the presence of a catalytic amount of iodine, the reaction efficiency could be improved.[24] Subsequently, **A** could easily undergo an intramolecular cyclization to give intermediate **B**, which is converted to the expected product **5a** after loss of water. Attempts to isolate the intermediate **A** (observed in the reaction mixture after 10 min using ESI-mass spectrometry, see ESI†), were unsuccessful, probably due to the fast transformation to **B**.[25] In addition, the unexpected 3,3′-(2-phenylchroman-2,4-diyl)bis(1*H*-indole) (**5ab**) was obtained in 4% yield when increasing the amounts of substrates. These results indicate that intermediate **B** is formed during the reaction, which can be converted to **5ab** after substitution of the



Scheme 5 Proposed mechanism for the domino reaction.

hydroxyl group (–OH) with indole in the presence of the Lewis acid (iodine)[26,13a] or to **5a** after loss of water. Obviously, formation of **5a** was a more favorable process.

Conclusions

In summary, this paper describes a novel and efficient method for the synthesis of functionalized 2-aryl-4-(indol-3-yl)-4*H*-chromenes from easily available starting materials, 2-hydroxychalcone and indole derivatives. In this transformation, a broad substrate scope has been demonstrated and iodine (10 mmol%) is proven to be an efficient catalyst. The possible domino Michael addition–intramolecular cyclization reaction mechanism is also proposed.

Experimental

General remarks

All chemicals were commercial and used without further purification. All organic solvents were dried and freshly distilled before use. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 300 MHz spectrometers using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts are reported relative to TMS (internal standard). HSQC NMR spectrum was recorded on Varian 600 MHz spectrometers ($CDCl_3$). Mass spectra were measured on a LCQ Advantage MAX (ESI). HRMS were obtained on a Bruker 7-T FT-ICR MS and apex-Ultra MS equipped with an ACPI source. IR spectra were obtained as KBr pellet samples on a Nicolet 5700 FTIR spectrometer. Flash column chromatography was performed on silica gel (200–300 mesh).

General experimental procedure for the synthesis of 3[18]

To a solution of aromatic methyl ketones (40 mmol) and salicylaldehyde (6.10 g, 50 mmol) in EtOH (50 mL) was added 40% KOH (10 mL) aqueous solution dropwise and the reaction was carried out at 60 °C (or room temperature) for 2–4 h until the disappearance of starting material (monitored by thin layer chromatography). The solution/suspension was poured into cold H_2O and the mixture neutralized with 2 M HCl to a pH in the

range of 2–3. The resulting precipitate was collected, washed with H_2O and recrystallized from EtOH to give **3a–f**. Compound **3g** was synthesized according to the analogous method using acetone as the solvent.

(*E*)-3-(2-Hydroxyphenyl)-1-phenyl-2-propen-1-one (3a).[27] Yellow solid, 7.80 g, yield 87%; mp 154–155 °C. IR (KBr) *v* 3209, 1639, 1592, 1567, 1451, 1345, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 15.9 Hz, 1H), 8.03 (d, J = 7.1 Hz, 2H), 7.72 (d, J = 15.9 Hz, 1H), 7.62–7.48 (m, 4H), 7.30–7.25 (m, 1H), 7.00–6.91 (m, 2H), 6.52 (br, 1H, OH); ESI-MS: *m/z* 224.76 $[M + H]^+$.

(*E*)-3-(2-Hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (3b).[28] Yellow solid, 8.57 g, yield 84%; mp 148–149 °C. IR (KBr) *v* 3433, 3235, 1642, 1595, 1254, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 15.8 Hz, 1H), 8.06 (d, J = 6.9 Hz), 7.69 (d, J = 15.8 Hz, 1H), 7.60 (dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1H), 7.29–7.25 (m, 1H), 7.00–6.92 (m, 4H), 6.82 (br, 1H, OH), 3.89 (s, 3H, OCH_3); ESI-MS: *m/z* 254.82 $[M + H]^+$.

(*E*)-1-(4-Chlorophenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one (3c).[29] Yellow solid, 9.21 g, yield 89%; mp 151–152 °C. IR (KBr) *v* 3438, 1643, 1592, 1392, 1342, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 15.8 Hz, 1H), 8.06 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 15.8 Hz, 1H), 7.60 (dd, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.31–7.25 (m, 1H), 6.99–6.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 155.8, 141.4, 139.1, 136.6, 131.9, 130.0, 129.6, 128.8, 122.2, 122.0, 120.9, 116.5; ESI-MS: *m/z* 258.70 $[M + H]^+$.

(*E*)-1-(4-Fluorophenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one (3d).[29] Yellow solid, 8.74 g, yield 90%; mp 164–165 °C. IR (KBr) *v* 3307, 1646, 1600, 1568, 1334, 1229, 1150 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, 1H, OH), 8.26–8.21 (m, 2H), 8.15 (d, J = 15.8 Hz, 1H), 7.93–7.88 (m, 2H), 7.43–7.30 (m, 3H), 7.01–6.90 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 188.0, 164.9 (d, $^1J_{C-F}$ = 250.3 Hz), 157.4, 139.7, 134.6 (d, $^4J_{C-F}$ = 2.8 Hz), 132.1, 131.2 (d, $^3J_{C-F}$ = 9.3 Hz), 128.7, 121.4, 120.6, 119.4, 116.3, 115.7 (d, $^2J_{C-F}$ = 21.6 Hz); ESI-MS: *m/z* 242.77 $[M + H]^+$.

(*E*)-1-(Furan-2-yl)-3-(2-hydroxyphenyl)prop-2-en-1-one (3e).[30] Yellow solid, 6.97 g, yield 81%; mp 149–150 °C. IR (KBr) *v* 3440, 1640, 1580, 1456, 1390, 1249, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 16.0 Hz, 1H), 7.66–7.55 (m, 3H), 7.35 (dd, J_1 = 3.6 Hz, J_2 = 0.7 Hz, 1H), 7.30–7.24 (m, 1H), 6.98–6.91 (m, 2H), 6.59 (dd, J_1 = 3.6 Hz, J_2 = 1.7 Hz, 1H), 6.50 (br, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0 (C═O), 155.9, 153.8, 146.6, 139.9, 131.9, 129.3, 122.0, 121.6, 120.8, 117.8, 116.7, 112.5; ESI-MS: *m/z* 215.16 $[M + H]^+$.

(*E*)-3-(2-Hydroxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one (3f).[30] Yellow solid, 8.12 g, yield 88%; mp 158–159 °C. IR (KBr) *v* 3439, 1636, 1567, 1403, 1230 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.31 (s, 1H, OH), 8.24 (dd, J_1 = 3.8 Hz, J_2 = 1.0 Hz, 1H), 8.10–8.03 (m, 2H), 7.90 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.80 (d, J = 16.0 Hz, 1H), 7.33–7.26 (m, 2H), 6.98–6.87 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 181.8, 157.3, 145.7, 138.6, 135.1, 133.1, 132.2, 128.9, 128.6, 121.2, 120.7, 119.4, 116.3; ESI-MS: *m/z* 230.82 $[M + H]^+$.

(*E*)-4-(2-Hydroxyphenyl)but-3-en-2-one (3g).[31] Yellow solid, 5.83 g, yield 90%; mp 138–139 °C. IR (KBr) *v* 3356, 2358, 1635, 1611, 1461, 1357, 1255, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 16.4 Hz, 1H), 7.63 (s, 1H, OH), 7.47 (dd, J_1 = 7.8, J_2 = 1.5 Hz, 1H), 7.29–7.23 (m, 1H), 7.05 (d, J = 16.4 Hz, 1H), 6.95–6.89 (m, 2H), 2.44 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 156.1, 141.0, 131.9, 129.7, 127.7, 121.5, 120.6, 116.6, 26.8; ESI-MS: *m/z* 162.88 $[M + H]^+$.

General experimental procedure for the synthesis of compounds 5 and 7–9

A mixture of **3** (1.0 mmol), indole (substituted indoles or 7-azaindole) (1.0 mmol) and iodine (25 mg, 0.1 mmol) was heated at 110 °C in anhydrous toluene (6 mL). After the reactant disappeared (2–4 h, monitored by thin layer chromatography), the mixture was cooled to room temperature. The reaction mixture was directly added to the column chromatography using petroleum ether as the eluent to remove toluene, then eluted with petroleum ether/EtOAc to give the expected compounds **5** and **7–9**.

3-(2-Phenyl-4*H*-chromen-4-yl)-1*H*-indole (5a). Pale red solid, 220 mg, yield 68%; mp 100–102 °C. IR (KBr) *v* 3424, 2922, 2855, 1632, 1454, 1227, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H, NH), 7.74–7.70 (m, 2H), 8.62 (d, J = 7.8 Hz, 1H), 7.38–7.31 (m, 4H), 7.19–7.02 (m, 6H), 6.94–6.89 (m, 1H), 5.67 (d, J = 4.0 Hz, 1H, chromene H-3), 5.16 (d, J = 4.0 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 147.7 (chromene C-2), 136.6, 134.4, 129.5, 128.3, 128.2, 127.5, 126.3, 124.7, 123.3, 122.1, 122.0, 121.5, 119.6, 119.4, 116.5, 111.2, 101.0 (chromene C-3), 32.1 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}NO$: 324.1383, found: 324.1387.

4-Chloro-3-(2-phenyl-4*H*-chromen-4-yl)-1*H*-indole (5b). Pale red solid, 250 mg, yield 70%; mp 83–85 °C. IR (KBr) *v* 3419, 2921, 2357, 1721, 1666, 1587, 1486, 1333, 1231, 1183 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H, NH), 7.68 (d, J = 8.0 Hz, 2H), 7.36–6.93 (m, 10H), 6.64 (d, J = 2.4 Hz, 1H), 5.86 (d, J = 4.2 Hz, 1H, chromene H-3), 5.78 (d, J = 4.2 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 146.9 (chromene C-2), 137.5, 134.4, 130.0, 128.2, 127.4, 125.9, 124.6, 124.0, 123.3, 123.1, 123.0, 122.5, 120.9, 116.4, 110.0, 102.1 (chromene C-3), 31.2 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}ClNO$: 358.0993, found: 358.1000.

5-Bromo-3-(2-phenyl-4*H*-chromen-4-yl)-1*H*-indole (5c). Pale red solid, 260 mg, yield 65%; mp 100–101 °C. IR (KBr) *v* 3423, 1663, 1451, 1227, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H, NH), 7.75–7.70 (m, 3H), 7.42–7.06 (m, 8H), 7.01–6.94 (m, 2H), 5.63 (d, J = 4.0 Hz, 1H, chromene H-3), 5.11 (d, J = 4.0 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 148.0 (chromene C-2), 135.2, 134.3, 129.3, 128.5, 128.3, 128.0, 127.7, 125.1, 124.7, 123.5, 123.4, 123.0, 121.8, 121.4, 116.7, 113.0, 112.7, 100.5 (chromene C-3), 31.8 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}BrNO$: 402.0488, found: 402.0487.

5-Fluoro-3-(2-phenyl-4*H*-chromen-4-yl)-1*H*-indole (5d). Pale red solid, 215 mg, yield 63%; mp 98–100 °C. IR (KBr) *v* 3422, 3064, 2358, 1724, 1587, 1484, 1452, 1266, 1228, 1175, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H, NH), 7.73–7.69 (m, 2H), 7.39–7.02 (m, 9H), 6.94–6.84 (m, 2H), 5.62 (d, J = 4.2 Hz, 1H, chromene H-3), 5.08 (d, J = 4.0 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (d, $^1J_{C-F}$ = 233.1 Hz), 151.1, 147.9 (chromene C-2), 134.2, 133.1, 129.3, 128.4, 128.3, 127.6, 126.5 (d, $^3J_{C-F}$ = 9.8 Hz), 124.7, 123.8, 123.4, 123.0, 121.5 (d, $^4J_{C-F}$ = 4.8 Hz), 116.6, 111.9 (d, $^3J_{C-F}$ = 9.7 Hz), 110.5 (d, $^2J_{C-F}$ = 26.3 Hz), 104.2 (d, $^2J_{C-F}$ = 23.5 Hz), 100.1 (chromene C-3), 32.1 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}FNO$: 342.1289, found: 342.1292.

2-Methyl-3-(2-phenyl-4*H*-chromen-4-yl)-1*H*-indole (5e). Pale red solid, 240 mg, yield 71%; mp 97–98 °C. IR (KBr) *v* 3409, 3053, 2920, 1586, 1488, 1453, 1328, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.62 (s, 1H, NH), 7.43 (d, J = 7.8 Hz, 1H), 7.36–7.28 (m, 3H), 7.19–6.84 (m, 7H), 5.53 (d, J = 4.2 Hz, 1H, chromene H-3), 5.14 (d, J = 4.0 Hz, 1H, chromene H-4), 2.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 147.6 (chromene C-4), 135.1, 134.3, 131.4, 129.4, 128.3, 127.8, 127.4, 124.6, 123.4, 123.3, 121.0, 119.4, 118.5, 116.3, 115.9, 110.2, 100.9 (chromene C-3), 30.9 (chromene C-4), 11.8 (CH_3); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}NO$: 338.1539, found: 338.1542.

3-(2-(4-Methoxyphenyl)-4*H*-chromen-4-yl)-1*H*-indole (5g). Pale red solid, 216 mg, yield 61%; mp 96–97 °C. IR (KBr) *v* 3423, 2924, 1639, 1501, 1238, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H, NH), 7.63–7.58 (m, 3H), 7.24–6.98 (m, 6H), 6.89–6.86 (m, 4H), 5.50 (d, J = 4.0 Hz, 1H, chromene H-3), 5.08 (d, J = 4.0 Hz, 1H, chromene H-4), 3.75 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 151.1, 147.4 (chromene C-2), 136.5, 129.4, 127.4, 127.0, 126.2, 126.0, 123.5, 123.2, 122.0, 121.9, 121.5, 119.5, 119.3, 116.4, 113.6, 111.2, 99.3 (chromene C-3), 55.5 (OCH_3), 32.0 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}NO_2$: 354.1487, found: 354.1491.

5-Bromo-3-(2-(4-methoxyphenyl)-4*H*-chromen-4-yl)-1*H*-indole (5h). Pale red solid, 260 mg, yield 60%; mp 92–93 °C. IR (KBr) *v* 3421, 2923, 1719, 1602, 1505, 1452, 1242, 1173, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H, NH), 7.74 (s, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.25–6.88 (m, 9H), 5.50 (d, J = 4.0 Hz, 1H, chromene H-3), 5.08 (d, J = 4.0 Hz, 1H, chromene H-4), 3.82 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 151.2, 147.8 (chromene C-2), 135.2, 129.3, 128.1, 127.6, 127.0, 126.1, 125.0, 123.5, 123.4, 123.1, 121.8, 121.6, 116.6, 113.7. 112.9, 112.7, 98.9 (chromene C-3), 55.3 (OCH_3), 31.8 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}BrNO_2$: 432.0594, found: 432.0594.

3-(2-(4-Chlorophenyl)-4*H*-chromen-4-yl)-1*H*-indole (5i). Pale red solid, 261 mg, yield 73%; mp 85–86 °C. IR (KBr) *v* 3426, 1636, 1486, 1394, 1225, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H, NH), 7.61–7.55 (m, 3H), 7.31–7.27 (m, 3H), 7.14–7.00 (m, 5H), 6.93–6.86 (m, 2H), 5.62 (d, J = 4.0 Hz, 1H, chromene H-3), 5.11 (d, J = 4.0 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 146.7 (chromene C-2), 136.5, 134.0, 132.7, 129.5, 128.4, 127.6, 126.2, 125.9, 123.5, 123.1, 122.1, 122.0, 121.2, 119.6, 119.2, 116.4, 111.2, 101.4 (chromene C-3), 32.0 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}ClNO$: 358.0993, found: 358.0992.

5-Bromo-3-(2-(4-chlorophenyl)-4*H*-chromen-4-yl)-1*H*-indole (5j). Pale red solid, 296 mg, yield 68%; mp 75–77 °C. IR (KBr) *v* 3428, 1656, 1488, 1451, 1399, 1225, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H, NH), 7.70 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.22–7.01 (m, 5H), 6.93–6.87 (m, 2H), 5.55 (d, J = 4.0 Hz, 1H, chromene H-3), 5.02 (d, J = 4.0 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 147.0 (chromene C-2), 135.1, 134.2, 132.6, 129.3, 128.4, 127.9, 127.8, 125.9, 125.0, 123.6, 123.5, 122.7, 121.6, 121.0, 116.6, 112.9, 112.7, 101.9 (chromene C-3), 31.8 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{16}BrClNO$: 436.0098, found: 436.0097.

3-(2-(4-Fluorophenyl)-4*H*-chromen-4-yl)-1*H*-indole (5k). Pale red solid, 256 mg, yield 75%; mp 69–70 °C. IR (KBr) *v* 3414, 1611, 1500, 1326, 1225, 1100, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H, NH), 7.68–7.64 (m, 2H), 7.59 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.18–6.98 (m, 8H), 6.93–6.88 (m, 1H), 5.59 (d, J = 4.0 Hz, 1H, chromene H-3), 5.12 (d, J = 4.0 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (d, $^1J_{C-F}$ = 246.1 Hz), 151.0, 146.9 (chromene C-2), 136.6, 130.4 (d, $^4J_{C-F}$ = 3.3 Hz), 129.5, 127.5, 126.5 (d, $^3J_{C-F}$ = 8.1 Hz), 126.2, 123.5, 122.1, 122.0, 121.4, 119.6, 119.3, 116.4, 115.2 (d, $^2J_{C-F}$ = 21.5 Hz), 111.2, 101.7 (d, $^5J_{C-F}$ = 1.7 Hz, chromene C-3), 32.0 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}FNO$: 342.1289, found: 342.1292.

4-Chloro-3-(2-(4-fluorophenyl)-4*H*-chromen-4-yl)-1*H*-indole (5l). Pale red solid, 244 mg, yield 65%; mp 70–71 °C. IR (KBr) *v* 3422, 2358, 1598, 1499, 1333, 1228, 1154, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H, NH), 7.67–7.62 (m, 2H), 7.24–6.94 (m, 10H), 6.68 (d, J = 2.5 Hz, 1H), 5.80 (d, J = 4.3 Hz, 1H, chromene H-3), 5.78 (d, J = 4.3 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{C-F}$ = 246.0 Hz), 151.2, 146.1 (chromene C-2), 137.5, 130.6 (d, $^4J_{C-F}$ = 3.2 Hz), 130.0, 127.5, 126.4 (d, $^3J_{C-F}$ = 8.1 Hz), 125.9, 125.0, 123.9, 123.4, 123.0, 122.6, 121.0, 119.5, 116.4, 115.2 (d, $^2J_{C-F}$ = 21.5 Hz), 110.2, 101.8 (d, $^5J_{C-F}$ = 1.7 Hz, chromene C-3), 31.3 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{16}ClFNO$: 376.0899, found: 376.0899.

3-(2-(Furan-2-yl)-4*H*-chromen-4-yl)-1*H*-indole (5m). Pale red solid, 220 mg, yield 70%; mp 97–99 °C. IR (KBr) *v* 3415, 1627, 1453, 1228, 1056, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H, NH), 7.59 (d, J = 7.9 Hz, 1H), 7.34–7.29 (m, 2H), 7.22–7.02 (m, 5H), 6.97 (d, J = 2.4 Hz, 1H), 6.93–6.87 (m, 1H), 6.64 (d, J = 3.3 Hz, 1H), 6.42 (dd, J_1 = 3.3 Hz, J_2 = 1.8 Hz, 1H), 5.68 (d, J = 4.1 Hz, 1H, chromene H-3), 5.11 (d, J = 4.1 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 148.7 (chromene C-2), 142.2, 141.0, 136.6, 129.6, 127.5, 126.2, 123.5, 123.3, 122.12, 122.09, 121.2, 119.6, 119.3, 116.4, 111.2, 111.1, 106.4, 100.0 (chromene C-3), 31.4 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{16}NO_2$: 314.1176, found: 314.1178.

3-(2-(Thiophen-2-yl)-4*H*-chromen-4-yl)-1*H*-indole (5n). Pale red solid, 228 mg, yield 69%; mp 74–75 °C. IR (KBr) *v* 3417, 1634, 1397, 1229, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H, NH), 7.61 (d, J = 7.8 Hz, 1H), 7.37–7.34 (m, 2H), 7.25–7.00 (m, 8H), 6.95–6.91 (m, 1H), 5.59 (d, J = 4.1 Hz, 1H, chromene H-3), 5.14 (d, J = 4.1 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 143.9 (chromene C-2), 138.2, 136.6, 129.5, 127.5, 127.2, 126.3, 124.7, 123.5, 123.4, 123.2, 122.2, 122.1, 121.3, 119.6, 119.4, 116.4, 111.2, 100.4 (chromene C-3), 32.0 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{16}NOS$: 330.0947, found: 330.0951.

3,3′-(2-Phenylchroman-2,4-diyl)bis(1*H*-indole) (5ab). Mp 230–232 °C. IR (KBr) *v* 3460, 3458, 1459, 1318, 1256, 1180, 1052, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H, NH), 7.85 (s, 1H, NH), 7.73 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.27–6.89 (m, 12H), 6.79–6.58 (m, 3H), 4.05–3.99 (m, 1H), 3.24–3.15 (m, 1H), 2.94–2.85 (m, 1H); ^1H NMR (300 MHz, DMSO-d_6) δ 11.04 (s, 1H, NH), 10.97 (s, 1H, NH), 7.70 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.39–7.04 (m, 12H), 6.96–6.83 (m, 2H), 6.72–6.63 (m, 2H), 3.97–3.91 (m, 1H), 3.17–3.14 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.7, 144.2, 136.8, 136.7, 128.9, 128.2, 127.6, 126.6, 126.0, 125.8, 125.7, 125.0, 123.7, 122.4, 121.1, 120.9, 120.6, 120.5, 119.9, 118.7, 118.6, 118.3, 116.4, 116.0, 111.7, 111.6, 80.4, 30.3; ESI-MS: *m/z* 440.03 $[M + H]^+$.

3-(2-Phenyl-4*H*-chromen-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (7). White solid, 228 mg, yield 70%; mp 155–156 °C. IR (KBr) *v* 3437, 3140, 2357, 1663, 1582, 1490, 1329, 1116, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.68 (s, 1H, NH), 8.27 (d, J = 4.2 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.2 Hz, 2H), 7.39–6.93 (m, 9H), 5.65 (d, J = 4.0 Hz, 1H, chromene H-3), 5.10 (d, J = 4.0 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 149.2 (chromene C-2), 148.0, 142.5, 134.2, 129.4, 128.5, 128.3, 128.1, 127.7, 124.7, 123.5, 122.9, 122.3, 119.6, 119.1, 116.6, 115.6, 100.6 (chromene C-3), 32.6 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O$: 325.1335, found: 325.1338.

3-(2-(4-Chlorophenyl)-4*H*-chromen-4-yl)-1*H*-pyrrolo[2,3-*b*]-pyridine (8). Pale red solid, 284 mg, yield 79%; mp 178–180 °C. IR (KBr) *v* 3440, 3412, 2891, 1491, 1328, 1229, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H, NH), 8.27 (d, J = 3.5 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.19–6.92 (m, 6H), 5.63 (d, J = 4.0 Hz, 1H, chromene H-3), 5.10 (d, J = 4.0 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 149.2 (chromene C-2), 147.1, 143.1, 134.3, 132.6, 129.5, 128.5, 127.9, 127.8, 126.0, 123.7, 122.6, 122.0, 119.6, 118.8, 116.6, 115.8, 101.0 (chromene C-3), 32.6 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}ClN_2O$: 359.0946, found: 359.0948.

3-(2-(Thiophen-2-yl)-4*H*-chromen-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (9). Pale red solid, 238 mg, yield 72%; mp 150–151 °C. IR (KBr) *v* 3432, 3138, 2925, 2395, 1656, 1578, 1412, 1234, 1115, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 1H, NH), 8.27 (d, J = 4.2 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 3.6 Hz, 1H), 7.26–6.91 (m, 8H), 5.57 (d, J = 4.1 Hz, 1H, chromene H-3), 5.08 (d, J = 4.1 Hz, 1H, chromene H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 149.2 (chromene C-2), 144.1, 142.8, 138.0, 129.4, 128.0, 127.8, 127.3, 124.9, 123.7, 123.6, 122.7, 122.2, 119.4, 119.0, 116.6, 115.7, 99.9 (chromene C-3), 32.4 (chromene C-4); HRMS (ACPI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{15}N_2OS$: 331.0900, found: 331.0903.

One-pot reaction procedure

The mixture of salicylaldehyde (**1**, 305 mg, 2.5 mmol), acetophenone (**2a**, 300 mg, 2.5 mmol) and indole (**4a**, 295 mg, 2.5 mmol) and iodine (63 mg, 0.25 mmol) was heated at 110 °C in anhydrous toluene (8 mL) for 3 h. The mixture was cooled to room temperature. The precipitate was filtered off, washed with EtOH and carefully dried to give 6,12-bis(2-hydroxylphenyl)-6,12-dihydroindolo[3,2-*b*]carbazole (**10**)[22] in 70% yield (388 mg) as a white solid. mp > 300 °C. IR (KBr) *v* 3450, 3400, 1454, 1323, 1267, 1184, 1082, 753 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.42 (s, 2H, NH), 9.87 (s, 2H, OH), 7.28–7.23 (m, 4H), 6.99–6.95 (m, 6H), 6.93–6.90 (m, 2H), 6.81–6.54 (m, 4H), 6.10 (s, 2H); ESI-MS: *m/z* 443.14 $[M + H]^+$.

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