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Diastereoselective construction of 4-indole substituted chromans bearing a ketal motif through a three-component Friedel–Crafts alkylation/ketalization sequence†

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The first TfOH-catalyzed three-component Friedel–Crafts alkylation/ketalization sequence of indoles, alcohols and *ortho*-hydroxychalcones was developed to afford a wide range of 4-indole substituted chromans bearing a ketal motif in 77–99% yields. Notably, only a simple filtration was needed to purify them. By altering methanol to CHCl₃, 2,4-bisindole substituted chroman with the same indole substituent at the C2 and C4 positions was afforded. Moreover, 2,4-bisindole substituted chromans with different indole substituents could be obtained by treatment of 4-indole monosubstituted chromans with another indole molecule.

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Introduction

Multi-component reactions (MCRs), which show apparent advantages over conventional reactions with respect to operational simplicity, synthetic efficiency and convergence as well as atom- and step-economy, have emerged as an appealing and versatile synthetic tool to access bioactive heterocycles with structural and functional complexity and diversity.¹ Chroman represents a kind of unique and privileged structural unit with wide occurrence in natural products and pharmaceuticals, and exhibit significant biological activities (Fig. 1).² Thus, establishing convenient and practical strategies for assembly of this skeleton has been the focus of many chemists. On the other hand, indole is another one attractive structural motif prevalent in nature.³ Given the medicinal relevance and the intriguing scaffolds of chroman and indole, integration of them into one complex molecule would contribute greatly to medicinal chemistry, which not only inherit the structures and properties of both biologically active skeletons, but may grant a few new bioactivities. However, only limited methods were available for the synthesis of indole-substituted chromans and the developed approaches mainly involved cycloaddition of 2-vinyl-1H-indole with 3-nitro-2H-chromenes,⁴ substitution,⁵ domino Knoevenagel-hetero-Diels–Alder reactions,⁶ Friedel–Crafts alkylation of

indoles with 3-nitro-2H-chromenes,⁷ Friedel–Crafts alkylation-inspired cyclizations,⁸ and others.⁹ Despite these elegant works, many of these methodologies suffer from limitations of substrate availability, synthetic efficiency and product diversity, which may limit their applicability in synthetic chemistry. As a result, development of an efficient and robust method for the rapid synthesis of indole-substituted chromans with diverse and complex structures is highly desirable and challenging.

Recently, we have realized a TfOH-catalyzed highly diastereoselective Michael addition/ketalization sequence of 3-hydroxyoxindoles and *ortho*-hydroxychalcones, where 3-hydroxyoxindoles served as a bisnucleophile to react with competent biselectrophile *ortho*-hydroxychalcone by Michael addition-initiated tandem reaction (Scheme 1).¹⁰ Based on this, we envisioned that a three-component reaction among indole, *ortho*-hydroxychalcone and alcohol may also take place under suitable conditions, in which both indole and alcohol served as the nucleophiles. As shown in Scheme 1, this domino reaction was proposed to be initiated by a Friedel–Crafts alkylation between indole and *ortho*-hydroxychalcone to yield intermediate A. Followed by hemiketalization and sequential dehydration, an oxocarbenium ion C was afforded, which was trapped by an alcohol molecule to give the 4-indole substituted chromans bearing a ketal motif. However, there was a competition

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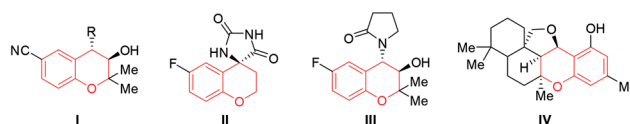
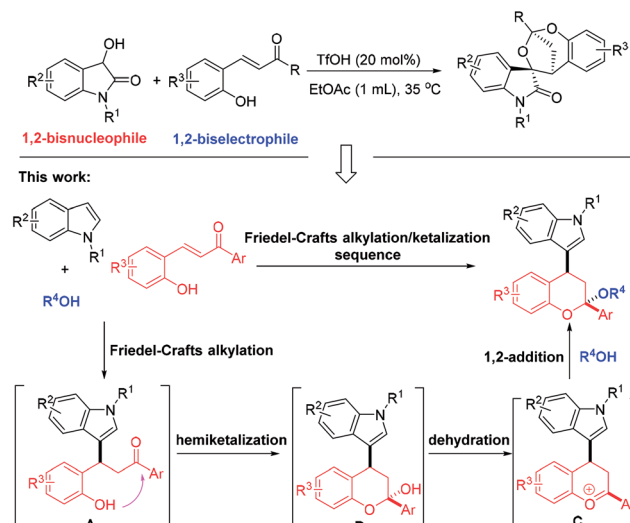


Fig. 1 Selected biologically active compounds containing a chroman motif.



Scheme 1 Our synthetic design for the construction of 4-indole substituted chromans bearing a ketal motif.

between indole and alcohol because the oxocarbenium ion **C** could also be captured by indole to deliver 2,4-bisindole substituted chromans. Thus, extra effort should be paid to control the chemoselectivity.

As part of our continuous interest in indole- and spirooxindole-related chemistry,¹¹ herein, we wish to report a TfOH-catalyzed three-component reaction of indoles, *ortho*-hydroxychalcones and alcohols, which afforded a wide range of 4-indole substituted chromans bearing a ketal motif. In this transformation, the alcohol not only acted as a reactant, but served as a solvent. Notably, all of the products were

precipitated from the homogeneous reaction system, and only a filtration was needed to purify them. These characteristics conferred our system with a prominent feature on meeting the requirement of green organic synthesis. Additionally, by switching the solvent to CHCl_3 , a novel 2,4-bisindole substituted chroman with the same indole substituents was afforded. Also, chromans with different 2,4-indole substituents could be obtained by reacting 4-indole substituted chromans with another distinct indole molecule.

Results and discussion

To test the feasibility of our synthetic design, *N*-benzyl indole **1a** and *ortho*-hydroxychalcone **2a** were initially chosen as the model substrates to react in methanol under the catalysis of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$. Gratifyingly, this reaction worked well to give the desired 4-indole substituted chroman with a ketal skeleton **3a** in 54% yield (Table 1, entry 1). The ketal skeleton was also important structural unit, which not only exhibited significant bioactivities, but also served as a useful synthetic handle for various transformations.¹² It should be mentioned that before our work Yin's group reported a similar reaction with iodine as catalyst under refluxing, but totally different products 4-indole chromenes were obtained in moderate yields with limited substrate scope.¹³ To improve the synthetic efficiency, some other catalysts, including Lewis acids and protonic acids, were examined (Table 1, entries 1–7). Generally, much better results were obtained when conducting the reactions in protic acids

Table 2 Substrate scope with respect to various substituted indoles^{a,b}

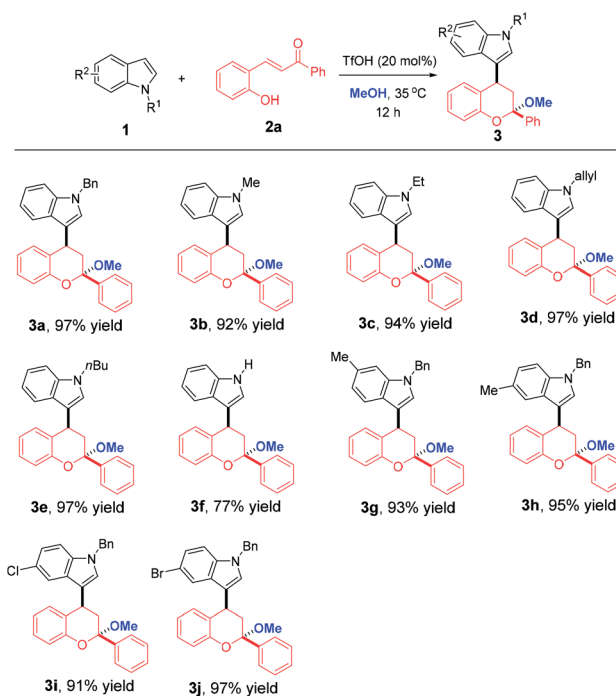
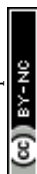


Table 1 Optimization of reaction conditions^a

Entry	Cat.	Ratio (1a : 2a)	Yield (%)
1	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	1.2 : 1	54 ^b
2	$\text{Fe}(\text{OTf})_3$	1.2 : 1	25 ^b
3	$\text{Cu}(\text{OTf})_2$	1.2 : 1	n.r.
4	<i>p</i> -TSA	1.2 : 1	59 ^c
5	TFA	1.2 : 1	78 ^c
6	MsOH	1.2 : 1	70 ^c
7	TfOH	1.2 : 1	97 ^c
8	TfOH	1.5 : 1	96 ^c
9	TfOH	1.8 : 1	92 ^c
10	TfOH	1 : 1.2	89 ^c

^a Unless otherwise noted, the reaction was carried out with 0.20 mmol of **2a** and specified amount of **1a** in 1.0 mL MeOH at 35 °C. ^b Isolated yield obtained by column chromatography. ^c Isolated yield obtained by filtration of the precipitate.

^a Unless otherwise noted, the reactions were conducted with 0.24 mmol of substituted indole **1** and 0.20 mmol of *ortho*-hydroxychalcone **2a** in the presence of 20 mol% TfOH in 1.0 mL MeOH at 35 °C for 12 h. ^b Isolated yields obtained by filtration of the precipitate.



and TfOH turned out to be the catalyst of choice, in which the yield of **3a** could increase to 97% (Table 1, entry 7). Then, the substrate ratios were evaluated and the results indicated that the ratios of **1a** to **2a** had some influence on the yield. When an excess of **1a** or **2a** were used, inferior yields were obtained (Table 1, entries 7 vs. 8–10). As a consequence, the following optimal conditions were recommended: 0.24 mmol **1a** and 0.20 mmol **2a** with 20 mol% TfOH in 1.0 mL MeOH at 35 °C for 12 h.

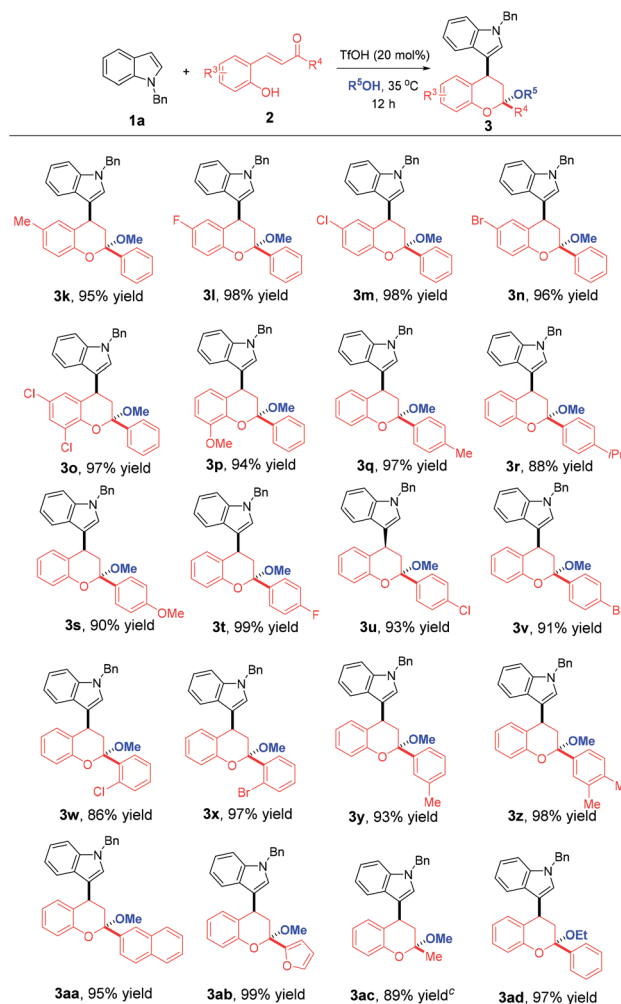
With the optimized reaction conditions in hand, the substrate scope with respect to indoles **1** bearing different substituents was initially explored. As shown in Table 2, the reaction tolerated a wide range of indoles, delivering **3a–j** in 77–97% yields. At the outset, the effect of *N*-substituents was investigated and the results revealed that it had minimal impact on the yield. Remarkably, *N*-H indole was also a suitable reaction partner, delivering **3f** in 77% yield. Subsequently, we turned our attention to study the effect of R^2 substituents on the phenyl ring of indoles. When the R^2 substituents were varied, irrespective of substitution positions and electronic nature, excellent yields (91–97%) were achieved for products **3g–j**.

Then, a wide array of *ortho*-hydroxychalcones with various substitution patterns were employed to further extend the generality of this reaction. As highlighted in Table 3, all reactions proceeded smoothly, leading to the desired products **3k–ad** in good to excellent yields. Firstly, *ortho*-hydroxychalcones with different R^3 substitution patterns were examined. All of them participated in this multi-component domino reaction successfully with the formation of **3k–p** in 94–98% yields. Afterwards, the R^4 substituents effect was evaluated and the results implied that this reaction was amendable to a wide range of *ortho*-hydroxychalcones bearing different R^4 substituents, regardless of the substitution positions and electronic nature, affording **3q–z** in 86–99% yields. 2-Naphthyl and 2-furyl substituted *ortho*-hydroxychalcones were also compatible to generate **3aa** and **3ab** in 95% and 99% yields, respectively. Not only aromatic rings were tolerated in these reactions, but also a methyl group was successful, allowing the assembly of **3ac** in 89% yield.

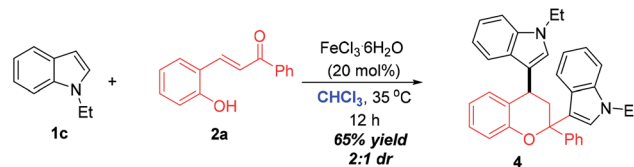
Besides methanol, ethanol could also participate in this reaction perfectly and the synthesis of **3ad** was achieved in 97% yield. However, as the length of chain increases, *n*-propanol and *n*-butanol failed to give the desired products due to the more steric hindrance. It was worthy to note that all of the products were precipitated from the original homogeneous reaction system and only a filtration was needed to separate them, which not only greatly simplifies the purification procedure, but also reduces the synthetic cost. Furthermore, the reactions proceeded in a highly diastereoselective manner. Only one diastereoisomer was observed for all cases although the products contained two stereocenters. The structure and the relative configuration of **3o** were definitely assigned by X-ray crystallization diffraction.¹⁴

The synthesis of 2,4-bisindole substituted chroman was achieved by performing the reaction of *N*-ethyl indole **1c** and *ortho*-hydroxychalcone **2a** in CHCl_3 under the catalysis of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (Scheme 2). This reaction worked well and went

Table 3 Substrate scope with respect to various *ortho*-hydroxychalcones and alcohols^{a,b}



^a Unless otherwise specified, the reactions were conducted with 0.24 mmol **1a** and 0.20 mmol **2** in the presence of 20 mol% TfOH in 1.0 mL MeOH at 35 °C for 12 h. ^b Isolated yields obtained by filtration of the precipitate. ^c For 36 h.

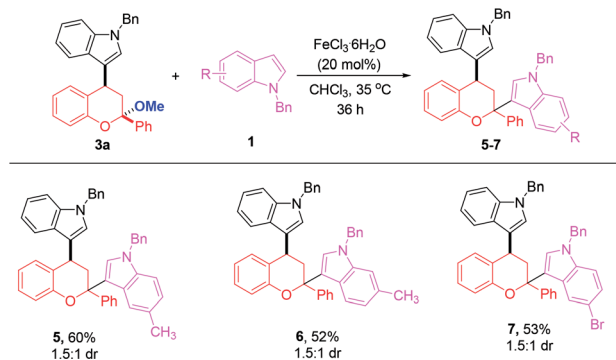


Scheme 2 Synthesis of 2,4-bisindole substituted chroman **4** with the same indole substituents.

completion within 12 h, delivering **4** in 65% yields with 2 : 1 dr value.

With monoindole substituted chromans bearing a ketal moiety **3**, we could also convert them into chromans with two different indole substituents at the C2 and C4 positions. This work not only provides a supplement to the one-pot reaction in



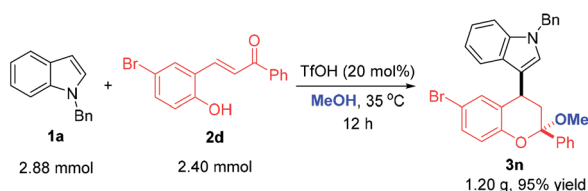


Scheme 3 Assembly of chromans with two different indole substituents.

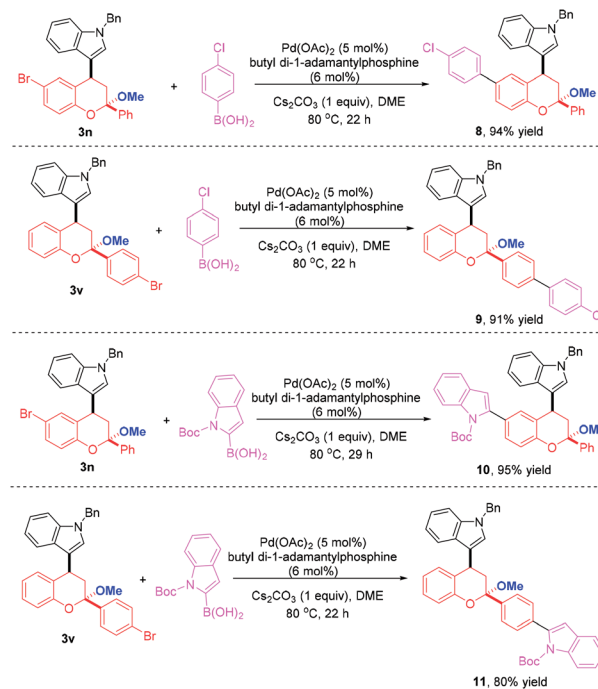
CHCl_3 system, but also allows access to a highly congested quaternary carbon center linking with an oxygen atom and two aromatic rings. For instance, **3a** could react with 5-Me, 6-Me and 5-Br substituted *N*-benzyl indoles, thus affording the products **5–7** in moderate yields (Scheme 3).

To highlight the synthetic applicability of this method, a gram-scale experiment was carried out with 2.88 mmol **1a** and 2.40 mmol **2d**. This reaction proceeded successfully to afford **3n** in comparable yield (95% yield, Scheme 4). In addition, the presence of a bromide atom in **3n** and **3v** offer an opportunity for further decoration to generate molecules with more complex and diverse structures. Therefore, derivations of **3n** and **3v** with 4-chlorophenyl boronic acid were conducted under the condition of a palladium-catalyzed Suzuki coupling and a 4-chlorophenyl group was introduced to afford **8** and **9** in 94% and 91% yields, respectively. Likewise, an indole moiety could also be incorporated by reacting **3n** and **3v** with 2-indolyl boronic acid, thus giving **10** and **11** in 95% and 80% yields, which not only largely enriches the types of chromans, but provides more novel compounds for bioassay (Scheme 5).

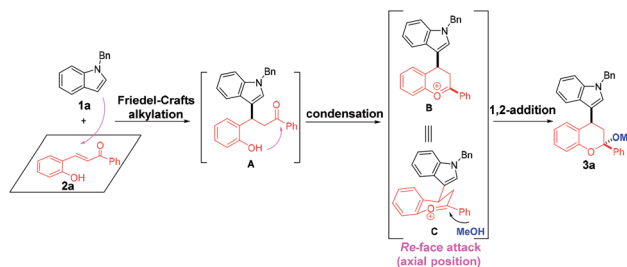
On the basis of the experimental results and previous reports,^{8,10,11g,h} a possible reaction mechanism was proposed to explain the reaction pathway and the stereochemistry (Scheme 6, taking the formation of **3a** as an example). First, a Friedel-Crafts alkylation between *N*-benzyl indole **1a** and *ortho*-hydroxychalcone **2a** took place to deliver the intermediate **A**. Then, an intramolecular condensation occurred with the formation of oxocarbenium **B**, which was equal with intermediate **C**. Finally, methanol served as a nucleophile to attack the oxocarbenium from the re-face due to that axial position has more thermodynamic preference, thus affording the corresponding product **3a** with more stable structure.



Scheme 4 Gram-scale preparation of **3n**.



Scheme 5 Chemical conversions of **3n** and **3v**.



Scheme 6 Plausible reaction mechanism.

Conclusions

In summary, we have established the first TfOH-catalyzed highly diastereoselective three-component domino Friedel-Crafts alkylation/ketalization reaction of indoles, alcohols and *ortho*-hydroxychalcones, which provides an efficient and versatile approach for the construction of 4-indole substituted chromans bearing a ketal motif at the C2 position. In this transformation, the alcohol played dual roles: one was a reactant, and the other was a solvent. Moreover, the assembly of 2,4-bisindole substituted chromans and some chemical transformations were accomplished. The salient features of this reaction, including easily available starting materials, mild reaction conditions, simple procedures, broad scope, high yields and excellent diastereoselectivity, rendered our system possible for green synthesis. Further studies to extend the applicability of this method are ongoing in our lab.



Experimental

General procedure for the synthesis of 4-indole substituted chromans 3a–ad

To a 5.0 mL vial were successively added indole **1** (0.24 mmol), *ortho*-hydroxychalcone **2** (0.20 mmol), TFOH (6.0 mg, 0.04 mmol) and 1.0 mL alcohol. The resulting mixture was stirred at 35 °C for 12 h. For all cases, the precipitate was generated from the homogenous reaction system, and only a simple filtration was needed to purify them.

1-Benzyl-3-(2-methoxy-2-phenylchroman-4-yl)-1H-indole (3a)

White solid; 86.2 mg, 97% yield; reaction time = 12 h; mp 148.5–149.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.42–7.32 (m, 4H), 7.26–6.96 (m, 12H), 6.82 (t, *J* = 8.0 Hz, 1H), 5.25 (s, 2H), 4.82 (dd, *J*₁ = 8.0 Hz, *J*₂ = 4.0 Hz, 1H), 3.17 (s, 3H), 2.52 (dd, *J*₁ = *J*₂ = 5.6 Hz, 1H), 2.31 (t, *J* = 13.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 152.1, 141.2, 137.6, 137.1, 129.1, 128.8, 128.4, 128.2, 127.6, 127.5, 127.4, 126.8, 126.7, 126.5, 126.3, 121.8, 121.3, 120.0, 119.1, 117.1, 117.0, 109.9, 100.7, 50.4, 50.0, 42.8, 30.2. IR (KBr) ν 3441, 3060, 3029, 2958, 2935, 2826, 1608, 1580, 1487, 1456, 1365, 1335, 1154, 1045, 1019, 908, 737, 699 cm^{−1}. HRMS (ESI) calcd for C₂₈H₂₉NNaO₂ [M + Na]⁺ 468.1934, found 468.1936.

3-(2-Methoxy-2-phenylchroman-4-yl)-1-methyl-1H-indole (3b)

White solid; 68.3 mg, 92% yield; reaction time = 12 h; mp 71.9–73.9 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.57–7.55 (m, 2H), 7.31–7.28 (m, 2H), 7.25–7.22 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.07–7.00 (m, 3H), 6.95–6.86 (m, 2H), 6.81 (s, 1H), 6.72–6.70 (s, 1H), 4.74–4.70 (m, 1H), 3.59 (s, 3H), 3.08 (s, 3H), 2.44–2.39 (m, 1H), 2.24–2.17 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 152.1, 141.2, 137.4, 129.2, 128.5, 128.2, 127.6, 127.4, 127.2, 126.7, 126.3, 121.6, 121.3, 119.9, 118.9, 117.2, 116.4, 109.4, 100.7, 50.4, 42.9, 32.7, 30.2. IR (KBr) ν 3425, 3058, 2935, 2831, 1721, 1612, 1582, 1483, 1452, 1236, 1155, 1045, 1019, 907, 743, 701 cm^{−1}. HRMS (ESI) calcd for C₂₅H₂₃NNaO₂ [M + Na]⁺ 392.1621, found 392.1607.

1-Ethyl-3-(2-methoxy-2-phenylchroman-4-yl)-1H-indole (3c)

White solid; 72.2 mg, 94% yield; reaction time = 12 h; mp 113.7–115.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.39–7.27 (m, 5H), 7.18–7.09 (m, 3H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.97–6.95 (m, 2H), 6.80 (t, *J* = 8.0 Hz, 1H), 4.83 (dd, *J*₁ = *J*₂ = 5.6 Hz, 1H), 4.05 (q, *J* = 6.4 Hz, 2H), 3.17 (s, 3H), 2.52 (dd, *J*₁ = *J*₂ = 5.6 Hz, 1H), 2.31 (t, *J* = 12.0 Hz, 1H), 1.38 (t, *J* = 8.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 152.2, 141.3, 136.5, 129.3, 128.5, 128.3, 127.6, 127.5, 126.8, 126.4, 125.6, 121.6, 121.4, 120.1, 118.9, 117.2, 116.5, 109.5, 100.8, 50.5, 43.0, 40.9, 30.3, 15.6. IR (KBr) ν 3426, 3056, 2965, 2935, 2832, 1732, 1612, 1582, 1483, 1452, 1233, 1155, 1047, 1019, 908, 743, 703 cm^{−1}. HRMS (ESI) calcd for C₂₆H₂₅NNaO₂ [M + Na]⁺ 406.1778, found 406.1777.

1-Allyl-3-(2-methoxy-2-phenylchroman-4-yl)-1H-indole (3d)

White solid; 76.6 mg, 97% yield; reaction time = 12 h; mp 136.1–138.4 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 8.0 Hz,

2H), 7.33–7.17 (m, 5H), 7.11–7.06 (m, 2H), 7.02 (t, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.89 (t, *J* = 8.0 Hz, 2H), 6.72 (t, *J* = 8.0 Hz, 1H), 5.91–5.81 (m, 1H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.95 (d, *J* = 16.0 Hz, 1H), 4.73 (dd, *J*₁ = *J*₂ = 5.6 Hz, 1H), 4.55 (d, *J* = 5.2 Hz, 2H), 3.09 (s, 3H), 2.43 (dd, *J*₁ = *J*₂ = 5.6 Hz, 1H), 2.22 (t, *J* = 13.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 152.1, 141.2, 136.9, 133.6, 129.2, 128.5, 128.2, 127.6, 127.4, 126.6, 126.4, 126.3, 121.7, 121.3, 120.0, 119.0, 117.3, 117.1, 116.8, 109.8, 100.7, 50.4, 48.8, 42.8, 30.1. IR (KBr) ν 3431, 3059, 2962, 2935, 2832, 1582, 1485, 1455, 1337, 1155, 1048, 1020, 912, 760, 738 cm^{−1}. HRMS (ESI) calcd for C₂₇H₂₅NNaO₂ [M + Na]⁺ 418.1778, found 418.1776.

1-Butyl-3-(2-methoxy-2-phenylchroman-4-yl)-1H-indole (3e)

White solid; 80.2 mg, 97% yield; reaction time = 12 h; mp 145.1–146.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.27–7.20 (m, 3H), 7.11–7.00 (m, 3H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.89–6.86 (m, 2H), 6.72 (t, *J* = 8.0 Hz, 1H), 4.73 (dd, *J*₁ = *J*₂ = 8.0 Hz, 1H), 3.95 (t, *J* = 8.0 Hz, 2H), 3.09 (s, 3H), 2.42 (dd, *J*₁ = *J*₂ = 5.6 Hz, 1H), 2.21 (t, *J* = 13.2 Hz, 1H), 1.72–1.64 (m, 2H), 1.26–1.14 (m, 2H), 0.82 (t, *J* = 4.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 152.1, 141.2, 136.7, 129.2, 128.4, 128.2, 127.5, 127.3, 126.7, 126.3, 121.4, 121.3, 119.9, 118.7, 117.1, 116.2, 109.6, 100.7, (one carbon missing in the aromatic region), 50.4, 46.1, 42.9, 32.4, 30.1, 20.3, 13.8. IR (KBr) ν 3431, 3058, 2964, 2933, 2830, 1580, 1482, 1451, 1342, 1154, 1050, 1015, 906, 758, 736 cm^{−1}. HRMS (ESI) calcd for C₂₈H₂₉NNaO₂ [M + Na]⁺ 434.2091, found 434.2098.

3-(2-Methoxy-2-phenylchroman-4-yl)-1H-indole (3f)

White solid; 55.0 mg, 77% yield; reaction time = 12 h; mp 188.3–189.4 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.0 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.41–7.35 (m, 3H), 7.17–7.08 (m, 3H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.87–6.77 (m, 3H), 4.70 (dd, *J*₁ = *J*₂ = 8.0 Hz, 1H), 3.05 (s, 3H), 2.42 (dd, *J*₁ = 8.0 Hz, *J*₂ = 4.0 Hz, 1H), 2.28 (t, *J* = 13.2 Hz, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 151.8, 140.9, 137.2, 129.0, 128.9, 128.8, 128.0, 127.1, 126.5, 126.4, 124.3, 121.6, 121.4, 119.2, 118.9, 117.4, 115.8, 112.2, 100.6, 50.2, 42.0, 30.1. IR (KBr) ν 3455, 3061, 3030, 2961, 2936, 2833, 1581, 1487, 1451, 1234, 1155, 1046, 1018, 907, 745, 702 cm^{−1}. HRMS (ESI) calcd for C₂₄H₂₁NNaO₂ [M + Na]⁺ 378.1465, found 378.1456.

1-Benzyl-3-(2-methoxy-2-phenylchroman-4-yl)-6-methyl-1H-indole (3g)

White solid; 85.5 mg, 93% yield; reaction time = 12 h; mp 142.9–144.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.30–7.16 (m, 5H), 7.10–7.04 (m, 5H), 6.95 (s, 1H), 6.82 (t, *J* = 4.0 Hz, 2H), 5.23 (s, 2H), 4.78 (dd, *J*₁ = *J*₂ = 4.0 Hz, 1H), 3.17 (s, 3H), 2.50 (dd, *J*₁ = 4.0 Hz, *J*₂ = 8.0 Hz, 1H), 2.39 (s, 3H), 2.30 (t, *J* = 12.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 152.0, 141.1, 137.8, 137.5, 131.6, 129.1, 128.8, 128.4, 128.2, 127.5, 127.4, 126.7, 126.6, 126.3, 126.1, 125.2, 121.2, 120.8, 119.7, 117.1, 116.9, 109.8, 100.7, 50.4, 49.8, 42.8, 30.2, 21.9. IR (KBr) ν 3433, 3064, 3028, 2937, 2828, 1607, 1580, 1488, 1448, 1233, 1184, 1155, 1045,



1023, 762, 702 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{29}\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 482.2091, found 482.2067.

1-Benzyl-3-(2-methoxy-2-phenylchroman-4-yl)-5-methyl-1H-indole (3h)

White solid; 87.2 mg, 95% yield; reaction time = 12 h; mp 181.4–182.8 °C; ^1H NMR (400 MHz, CDCl_3), δ 7.68–7.65 (m, 2H), 7.42–7.34 (m, 3H), 7.27–7.20 (m, 6H), 7.15–7.07 (m, 5H), 6.97 (d, J = 4.0 Hz, 1H), 6.84 (t, J = 8.0 Hz, 1H), 5.24 (s, 2H), 4.82–4.79 (m, 1H), 3.18 (d, J = 4.0 Hz, 3H), 2.55–2.49 (m, 1H), 2.36 (d, J = 4.0 Hz, 3H), 2.28 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.0, 141.1, 137.7, 135.4, 129.0, 128.7, 128.4, 128.3, 128.2, 127.8, 127.5, 127.4, 126.7, 126.6, 126.3, 123.4, 121.2, 119.4, 117.0, 116.5, 116.4, 109.6, 100.6, 50.3, 50.0, 42.7, 29.9, 21.5. IR (KBr) ν 3425, 3063, 3031, 2933, 1616, 1582, 1487, 1450, 1230, 1162, 1045, 1024, 760, 702 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{29}\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 482.2091, found 482.2100.

1-Benzyl-5-chloro-3-(2-methoxy-2-phenylchroman-4-yl)-1H-indole (3i)

White solid; 87.1 mg, 91% yield; reaction time = 12 h; mp 163.9–165.6 °C; ^1H NMR (400 MHz, CDCl_3), δ 7.66 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.35 (t, J = 8.0 Hz, 2H), 7.27 (t, J = 8.0 Hz, 3H), 7.20 (t, J = 8.0 Hz, 1H), 7.15–7.04 (m, 6H), 7.00 (d, J = 8.0 Hz, 1H), 6.84 (t, J = 8.0 Hz, 1H), 5.24 (s, 2H), 4.77 (dd, J_1 = J_2 = 8.0 Hz, 1H), 3.17 (s, 3H), 2.49 (dd, J_1 = 8.0 Hz, J_2 = 4.0 Hz, 1H), 2.24 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.6, 138.8, 137.6, 137.1, 135.2, 129.8, 129.0, 128.8, 127.6, 127.5, 127.3, 126.8, 126.5, 121.8, 121.3, 120.7, 120.1, 119.1, 117.0, 116.8, 109.8, 100.8, one carbon missing in the aromatic region, 50.4, 50.0, 38.9, 29.7. IR (KBr) ν 3429, 3065, 3031, 2960, 2938, 2831, 1580, 1458, 1347, 1236, 1156, 1024, 908, 758, 701 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{ClNNaO}_2$ $[\text{M} + \text{Na}]^+$ 502.1544, found 502.1553.

1-Benzyl-5-bromo-3-(2-methoxy-2-phenylchroman-4-yl)-1H-indole (3j)

White solid; 101.8 mg, 97% yield; reaction time = 12 h; mp 163.8–165.4 °C; ^1H NMR (400 MHz, CDCl_3), δ 7.58 (d, J = 4.0 Hz, 2H), 7.43 (s, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.28 (d, J = 4.0 Hz, 1H), 7.20–7.11 (m, 5H), 7.02 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 4.0 Hz, 2H), 6.92 (d, J = 8.0 Hz, 2H), 6.77 (t, J = 8.0 Hz, 1H), 5.15 (s, 2H), 4.70 (dd, J_1 = J_2 = 4.0 Hz, 1H), 3.09 (s, 3H), 2.42 (dd, J_1 = J_2 = 5.6 Hz, 1H), 2.15 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.0, 140.9, 137.1, 135.6, 129.3, 128.9, 128.8, 128.4, 128.2, 127.9, 127.8, 127.7, 126.7, 126.3, 126.0, 124.7, 122.3, 121.3, 117.3, 116.8, 112.6, 111.4, 100.5, 50.3, 50.2, 42.7, 29.9. IR (KBr) ν 3430, 3067, 3031, 2936, 2835, 1608, 1581, 1477, 1450, 1355, 1308, 1157, 1046, 1022, 907, 759, 701 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{BrNNaO}_2$ $[\text{M} + \text{Na}]^+$ 546.1039, found 546.1036.

1-Benzyl-3-(2-methoxy-6-methyl-2-phenylchroman-4-yl)-1H-indole (3k)

White solid; 87.6 mg, 95% yield; reaction time = 12 h; mp 175.0–176.3 °C; ^1H NMR (400 MHz, CDCl_3), δ 7.66 (t, J = 8.0 Hz, 2H), 7.43–7.38 (m, 3H), 7.35–7.23 (m, 5H), 7.17–7.08 (m, 3H), 7.02 (q, J = 8.0 Hz, 4H), 6.87 (d, J = 8.0 Hz, 1H), 5.27 (d, J = 4.0 Hz, 2H), 4.83–4.76 (m, 1H), 3.17 (d, J = 4.0 Hz, 3H), 2.54–2.47 (m, 1H), 2.33–2.24 (m, 1H), 2.14 (d, J = 8.0 Hz, 3H); ^{13}C NMR

(100 MHz, CDCl_3) δ 149.9, 141.2, 137.6, 137.0, 130.4, 129.3, 128.8, 128.4, 128.2, 128.1, 127.6, 127.5, 126.8, 126.7, 126.3, 126.2, 121.7, 120.0, 119.1, 117.3, 116.9, 109.8, 100.5, 50.3, 50.0, 43.1, 30.1, 20.8. IR (KBr) ν 3402, 3029, 2930, 2835, 1608, 1490, 1456, 1341, 1237, 1157, 1045, 927, 736, 708 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{29}\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 482.2091, found 482.2100.

1-Benzyl-3-(6-fluoro-2-methoxy-2-phenylchroman-4-yl)-1H-indole (3l)

White solid; 90.7 mg, 98% yield; reaction time = 12 h; mp 148.1–149.6 °C; ^1H NMR (400 MHz, CDCl_3), δ 7.55 (d, J = 8.0 Hz, 2H), 7.32–7.10 (m, 8H), 7.05–6.89 (m, 6H), 6.77 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 5.16 (s, 2H), 4.67 (s, 1H), 3.06 (s, 3H), 2.42–2.39 (m, 1H), 2.24–2.17 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.5 (d, J = 237.0 Hz, 1C), 148.0 (d, J = 2.0 Hz, 1C), 140.8, 137.5, 132.2, 128.9, 128.5, 128.3, 128.1 (d, J = 7.0 Hz, 1C), 127.7, 127.1, 126.8, 126.7, 126.3, 122.0, 119.9, 119.3, 118.4 (d, J = 8.0 Hz, 1C), 116.4, 115.2 (d, J = 23.0 Hz, 1C), 114.35 (d, J = 24.0 Hz, 1C), 110.0, 100.7, 50.4, 50.2, 42.4, 30.5. IR (KBr) ν 3429, 3038, 2936, 2832, 1615, 1488, 1249, 1187, 1153, 1020, 933, 739, 700 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{FNNaO}_2$ $[\text{M} + \text{Na}]^+$ 486.1840, found 486.1850.

1-Benzyl-3-(6-chloro-2-methoxy-2-phenylchroman-4-yl)-1H-indole (3m)

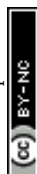
White solid; 93.6 mg, 98% yield; reaction time = 12 h; mp 145.3–147.2 °C; ^1H NMR (400 MHz, CDCl_3), δ 7.63 (d, J = 8.0 Hz, 2H), 7.43–7.34 (m, 4H), 7.31–7.25 (m, 4H), 7.17–7.09 (m, 4H), 7.04–7.02 (m, 4H), 5.29 (s, 2H), 4.78 (dd, J_1 = J_2 = 4.0 Hz, 1H), 3.16 (s, 3H), 2.53–2.47 (m, 1H), 2.29 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.7, 140.6, 137.5, 137.1, 128.8, 128.7, 128.4, 128.3, 127.7, 127.6, 127.1, 126.8, 126.7, 126.2, 126.1, 121.9, 119.7, 119.2, 118.5, 116.2, 109.9, 100.9, 50.4, 50.0, 42.4, 30.2. IR (KBr) ν 3429, 3058, 3029, 2938, 2836, 1475, 1342, 1247, 1155, 1039, 1019, 909, 742, 705 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{ClNNaO}_2$ $[\text{M} + \text{Na}]^+$ 502.1544, found 502.1546.

1-Benzyl-3-(6-bromo-2-methoxy-2-phenylchroman-4-yl)-1H-indole (3n)

White solid; 100.9 mg, 96% yield; reaction time = 12 h; mp 171.1–172.4 °C; ^1H NMR (400 MHz, CDCl_3), δ 7.62 (d, J = 8.0 Hz, 2H), 7.42–7.25 (m, 10H), 7.14 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.03–6.97 (m, 2H), 5.28 (s, 2H), 4.78 (dd, J_1 = J_2 = 4.0 Hz, 1H), 3.15 (s, 3H), 2.50 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H), 2.28 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.3, 140.6, 137.5, 137.1, 131.6, 130.5, 129.0, 128.8, 128.4, 128.3, 127.7, 127.1, 126.8, 126.8, 126.2, 121.9, 119.7, 119.3, 119.0, 116.2, 113.6, 109.9, 100.9, 50.4, 50.0, 42.5, 30.2. IR (KBr) ν 3427, 3057, 3029, 2938, 2836, 1473, 1342, 1247, 1156, 1039, 1019, 908, 741, 703 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{BrNNaO}_2$ $[\text{M} + \text{Na}]^+$ 546.1039, found 546.1045.

1-Benzyl-3-(6,8-dichloro-2-methoxy-2-phenylchroman-4-yl)-1H-indole (3o)

White solid; 100.0 mg, 97% yield; reaction time = 12 h; mp 186.2–187.7 °C; ^1H NMR (400 MHz, CDCl_3), δ 7.70–7.67 (m, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.38–7.25 (m, 7H), 7.16 (t, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.03 (t, J = 8.0 Hz, 2H), 6.93–6.90 (m,



1H), 5.29 (s, 2H), 4.79 (dd, $J_1 = J_2 = 4.0$ Hz, 1H), 3.15 (s, 3H), 2.60–2.54 (m, 1H), 2.37–2.31 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.6, 139.9, 137.4, 137.1, 129.7, 128.8, 128.5, 128.4, 127.9, 127.7, 127.3, 126.9, 126.8, 126.3, 126.2, 125.7, 123.1, 122.0, 119.7, 119.4, 115.7, 110.0, 101.4, 50.5, 50.0, 42.0, 30.5. IR (KBr) ν 3427, 3032, 2938, 2832, 1452, 1341, 1255, 1154, 1021, 974, 922, 741, 699 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{25}\text{Cl}_2\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 536.1155, found 536.1156.

1-Benzyl-3-(2,8-dimethoxy-2-phenylchroman-4-yl)-1H-indole (3p)

White solid; 89.7 mg, 94% yield; reaction time = 12 h; mp 155.1–156.8 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, $J = 8.0$ Hz, 2H), 7.33–7.12 (m, 8H), 7.01 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 3H), 6.90 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 2H), 6.72 (d, $J = 8.0$ Hz, 1H), 6.67 (t, $J = 8.0$ Hz, 1H), 6.58 (d, $J = 8.0$ Hz, 1H), 5.15 (s, 2H), 4.74 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 1H), 3.84 (s, 3H), 3.10 (s, 3H), 2.45 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 1H), 2.24 (t, $J = 12.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.8, 140.5, 140.0, 136.5, 135.9, 127.7, 127.3, 127.1, 126.5, 126.3, 125.7, 125.6, 125.3, 120.7, 119.9, 119.3, 118.9, 117.9, 116.1, 109.2, 108.7, 99.5, one carbon missing in the aromatic region, 55.3, 49.3, 48.9, 41.6, 29.2. IR (KBr) ν 3431, 3036, 2936, 2833, 1586, 1467, 1339, 1264, 1212, 1158, 1045, 1023, 945, 738, 704 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{29}\text{NNaO}_3$ $[\text{M} + \text{Na}]^+$ 498.2040, found 498.2054.

1-Benzyl-3-(2-methoxy-2-(*p*-tolyl)chroman-4-yl)-1H-indole (3q)

White solid; 88.8 mg, 97% yield; reaction time = 12 h; mp 168.2–169.3 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.22–7.07 (m, 8H), 7.05–7.00 (m, 3H), 6.98–6.89 (m, 3H), 6.74 (t, $J = 8.0$ Hz, 1H), 5.19 (s, 2H), 4.73 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 3.09 (s, 3H), 2.43 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 2.29 (s, 3H), 2.22 (t, $J = 12.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.0, 137.1, 136.8, 136.5, 135.9, 128.0, 127.9, 127.7, 127.4, 126.8, 126.5, 126.4, 125.7, 125.6, 125.5, 125.1, 120.7, 120.1, 118.9, 118.0, 116.0, 108.7, 99.6, 49.2, 48.9, 41.7, 29.0, 20.1. IR (KBr) ν 3431, 3030, 2927, 1615, 1453, 1343, 1264, 1222, 1154, 1103, 1023, 977, 908, 812, 732 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{29}\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 482.2091, found 482.2086.

1-Benzyl-3-(2-(4-isopropylphenyl)-2-methoxychroman-4-yl)-1H-indole (3r)

White solid; 85.4 mg, 88% yield; reaction time = 12 h; mp 173.5–174.4 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.48 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 1H), 7.17 (t, $J = 8.0$ Hz, 6H), 7.12–6.90 (m, 8H), 6.74 (t, $J = 8.0$ Hz, 1H), 5.18 (s, 2H), 4.73 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 3.11 (s, 3H), 2.88–2.81 (m, 1H), 2.43 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 1H), 2.23 (t, $J = 12.0$ Hz, 1H), 1.18 (d, $J = 8.0$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.1, 148.8, 138.5, 137.6, 137.0, 129.1, 128.8, 128.7, 127.6, 127.5, 127.4, 126.8, 126.7, 126.6, 126.4, 126.2, 121.8, 121.2, 120.0, 119.0, 117.1, 109.8, 100.7, 50.3, 50.0, 42.8, 33.9, 30.1, 24.1. IR (KBr) ν 3435, 3033, 2963, 1582, 1480, 1456, 1340, 1264, 1220, 1156, 1107, 1025, 968, 908, 834, 736 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{34}\text{H}_{33}\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 510.2404, found 510.2407.

1-Benzyl-3-(2-methoxy-2-(4-methoxyphenyl)chroman-4-yl)-1H-indole (3s)

White solid; 85.8 mg, 90% yield; reaction time = 12 h; mp 81.1–82.9 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (t, $J = 8.0$ Hz, 2H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.19–6.84 (m, 14H), 6.74 (t, $J = 8.0$ Hz, 1H), 5.19 (s, 2H), 4.74 (s, 1H), 3.74 (d, $J = 4.0$ Hz, 3H), 3.09 (d, $J = 8.0$ Hz, 3H), 2.47–2.41 (m, 1H), 2.27–2.18 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.5, 152.1, 137.6, 137.0, 133.3, 129.1, 128.8, 127.6, 127.5, 127.5, 127.4, 126.8, 126.7, 126.6, 121.8, 121.2, 120.0, 119.1, 117.1, 113.7, 109.9, 100.6, 55.3, 50.2, 50.0, 42.9, 30.2. IR (KBr) ν 3424, 3032, 2933, 2834, 1609, 1582, 1485, 1458, 1337, 1306, 1252, 1171, 1024, 970, 905, 835, 741 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{29}\text{NNaO}_3$ $[\text{M} + \text{Na}]^+$ 498.2040, found 498.2030.

1-Benzyl-3-(2-(4-fluorophenyl)-2-methoxychroman-4-yl)-1H-indole (3t)

White solid; 91.7 mg, 99% yield; reaction time = 12 h; mp 137.9–139.6 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.53 (t, $J = 8.0$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 1H), 7.17 (t, $J = 8.0$ Hz, 4H), 7.12–6.88 (m, 10H), 6.74 (t, $J = 8.0$ Hz, 1H), 5.16 (s, 2H), 4.72 (dd, $J_1 = J_2 = 4.0$ Hz, 1H), 3.07 (s, 3H), 2.41 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 1H), 2.20 (t, $J = 12.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.7 (d, $J = 245.0$ Hz, 1C), 151.9, 137.6, 137.1, 129.1, 128.8, 128.3, 128.2, 127.7, 127.6, 127.4, 126.8, 126.7, 126.4, 121.9, 121.4, 120.0, 119.1, 117.1, 116.9, 115.3 (d, $J = 21.0$ Hz, 1C), 109.9, 100.4, 50.3, 50.0, 42.9, 30.2. IR (KBr) ν 3427, 3061, 3032, 2935, 2834, 1607, 1507, 1485, 1457, 1337, 1264, 1225, 1155, 1106, 1044, 1021, 908, 838, 809, 738, 698 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{FNNaO}_2$ $[\text{M} + \text{Na}]^+$ 486.1840, found 486.1839.

1-Benzyl-3-(2-(4-chlorophenyl)-2-methoxychroman-4-yl)-1H-indole (3u)

White solid; 89.1 mg, 93% yield; reaction time = 12 h; mp 157.4–158.8 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, $J = 8.0$ Hz, 2H), 7.27 (dd, $J_1 = J_2 = 8.0$ Hz, 4H), 7.20–7.14 (m, 4H), 7.12–6.88 (m, 9H), 6.74 (t, $J = 8.0$ Hz, 1H), 5.16 (s, 2H), 4.72 (dd, $J_1 = J_2 = 4.0$ Hz, 1H), 3.06 (s, 3H), 2.39 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 2.19 (t, $J = 12.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.7, 138.6, 136.5, 136.0, 133.0, 128.0, 127.7, 127.5, 127.4, 126.8, 126.5, 126.2, 125.7, 125.6, 125.3, 120.8, 120.3, 118.8, 118.0, 116.0, 115.7, 108.8, 99.2, 49.2, 48.9, 41.6, 29.0. IR (KBr) ν 3431, 3059, 3032, 2931, 2834, 1607, 1585, 1484, 1455, 1341, 1263, 1219, 1156, 1099, 1050, 1019, 969, 910, 815, 731 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{ClNNaO}_2$ $[\text{M} + \text{Na}]^+$ 502.1544, found 502.1555.

1-Benzyl-3-(2-(4-bromophenyl)-2-methoxychroman-4-yl)-1H-indole (3v)

White solid; 95.7 mg, 91% yield; reaction time = 12 h; mp 163.4–164.6 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.44 (s, 4H), 7.25 (d, $J = 8.0$ Hz, 1H), 7.21–7.14 (m, 4H), 7.10–6.88 (m, 8H), 6.75 (t, $J = 8.0$ Hz, 1H), 5.18 (s, 2H), 4.72 (dd, $J_1 = J_2 = 4.0$ Hz, 1H), 3.07 (s, 3H), 2.39 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 2.19 (t, $J = 12.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.7, 139.2, 136.5, 136.0, 130.5, 128.0, 127.7, 127.1, 126.6, 126.5, 126.2, 125.7, 125.6, 125.3, 121.3, 120.8, 120.3, 118.8, 118.0, 116.0, 115.7, 108.8, 99.2, 49.2, 48.9, 41.5, 29.0. IR (KBr) ν 3433, 3033, 2963, 1585, 1481,



1457, 1339, 1262, 1206, 1158, 1101, 1040, 805, 745 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{BrNNaO}_2$ $[\text{M} + \text{Na}]^+$ 546.1039, found 546.1052.

1-Benzyl-3-(2-(2-chlorophenyl)-2-methoxychroman-4-yl)-1H-indole (3w)

White solid; 82.8 mg, 86% yield; reaction time = 12 h; mp 179.3–180.8 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.89 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 4.0 Hz, 1H), 7.27–7.13 (m, 7H), 7.11–6.97 (m, 7H), 6.91 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 4.0 Hz, 1H), 5.19 (s, 2H), 4.74 (dd, $J_1 = J_2$ = 4.0 Hz, 1H), 3.14 (s, 3H), 2.87 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 1H), 2.31–2.23 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.6, 137.6, 137.3, 137.1, 132.1, 131.6, 129.7, 129.6, 129.0, 128.8, 127.6, 127.5, 126.9, 126.8, 126.6, 121.8, 121.3, 120.1, 119.1, 117.0, 116.9, 109.9, 100.5, 50.4, 50.0, 38.8, 29.7. IR (KBr) ν 3420, 3060, 2934, 1583, 1486, 1458, 1338, 1264, 1235, 1158, 1043, 1015, 906, 758, 744 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{ClNNaO}_2$ $[\text{M} + \text{Na}]^+$ 502.1544, found 502.1558.

1-Benzyl-3-(2-(2-bromophenyl)-2-methoxychroman-4-yl)-1H-indole (3x)

White solid; 101.6 mg, 97% yield; reaction time = 12 h; mp 125.5–127.1 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.96 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.41–7.36 (m, 2H), 7.31–7.24 (m, 4H), 7.20–7.18 (m, 2H), 7.12 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 4H), 7.06 (t, J = 8.0 Hz, 2H), 6.99 (t, J = 8.0 Hz, 1H), 6.83 (t, J = 8.0 Hz, 1H), 5.28 (s, 2H), 4.81 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 3.22 (s, 3H), 2.92 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 2.38 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.0, 140.9, 137.1, 135.4, 128.9, 128.8, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 126.7, 126.3, 126.0, 124.9, 122.1, 121.3, 119.2, 117.2, 116.8, 110.9, 100.5, 50.3, 50.2, 42.7, 30.0. IR (KBr) ν 3440, 3061, 3030, 2961, 2933, 2829, 1584, 1487, 1458, 1337, 1265, 1235, 1207, 1157, 1117, 1038, 1012, 966, 906, 813, 744 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{26}\text{BrNNaO}_2$ $[\text{M} + \text{Na}]^+$ 546.1039, found 546.1020.

1-Benzyl-3-(2-methoxy-2-(*m*-tolyl)chroman-4-yl)-1H-indole (3y)

White solid; 85.5 mg, 93% yield; reaction time = 12 h; mp 149.0–150.9 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 4.0 Hz, 2H), 7.17–7.10 (m, 6H), 7.03–6.95 (m, 5H), 6.91 (d, J = 12.0 Hz, 2H), 6.72 (t, J = 8.0 Hz, 1H), 5.15 (s, 2H), 4.73 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 1H), 3.08 (s, 3H), 2.42 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 2.27 (s, 3H), 2.21 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.0, 137.1, 136.8, 136.5, 135.9, 128.0, 127.9, 127.7, 127.4, 126.7, 126.6, 126.5, 126.4, 125.7, 125.6, 125.5, 125.1, 123.6, 120.7, 120.1, 118.9, 118.0, 116.0, 108.7, 99.6, 49.2, 48.9, 41.7, 29.0, 20.1. IR (KBr) ν 3431, 3032, 2932, 1730, 1611, 1481, 1457, 1340, 1264, 1235, 1157, 1107, 1042, 1023, 971, 906, 816, 742 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{29}\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 482.2091, found 482.2072.

1-Benzyl-3-(2-(3,4-dimethylphenyl)-2-methoxychroman-4-yl)-1H-indole (3z)

White solid; 92.9 mg, 98% yield; reaction time = 12 h; mp 123.7–125.6 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.34 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.22–7.14 (m, 4H), 7.10–6.89 (m, 9H), 6.72 (t, J = 8.0 Hz, 1H), 5.19 (s, 2H), 4.73 (dd, $J_1 = J_2$ = 4.0 Hz, 1H), 3.10 (s, 3H), 2.43 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 2.25–2.18 (m, 7H);

^{13}C NMR (100 MHz, CDCl_3) δ 151.1, 137.5, 136.5, 135.9, 135.5, 135.4, 128.6, 128.0, 127.7, 126.5, 126.4, 126.3, 125.7, 125.6, 125.5, 122.6, 120.7, 120.1, 118.9, 117.9, 116.1, 116.0, 115.9, 108.7, 99.6, 49.2, 48.9, 41.8, 29.0, 18.9, 18.5. IR (KBr) ν 3431, 3057, 3029, 2957, 2930, 2832, 1610, 1580, 1483, 1454, 1337, 1264, 1232, 1156, 1048, 1029, 909, 806, 737 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{33}\text{H}_{31}\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 496.2247, found 496.2248.

1-Benzyl-3-(2-methoxy-2-(naphthalen-2-yl)chroman-4-yl)-1H-indole (3aa)

White solid; 94.0 mg, 95% yield; reaction time = 12 h; mp 169.4–170.9 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.21 (s, 1H), 7.91–7.82 (m, 3H), 7.69 (d, J = 8.0 Hz, 1H), 7.51–7.46 (m, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.25–7.17 (m, 6H), 7.13–6.96 (m, 6H), 6.84 (t, J = 8.0 Hz, 1H), 5.23 (s, 2H), 4.88 (dd, $J_1 = J_2$ = 4.0 Hz, 1H), 3.21 (s, 3H), 2.63 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 2.37 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.1, 138.6, 137.6, 137.1, 133.2 (2C), 129.2, 128.8, 128.5, 128.3, 127.7, 127.6, 127.5, 126.8, 126.7, 126.6, 126.4, 126.3, 125.8, 124.0, 121.8, 121.4, 120.0, 119.1, 117.2, 117.0, 109.9, 100.8, one carbon missing in the aromatic region, 50.5, 50.0, 42.7, 30.2. IR (KBr) ν 3435, 3056, 3029, 2932, 2835, 1609, 1581, 1452, 1342, 1271, 1226, 1157, 1044, 907, 862, 823, 741, 699 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{30}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 496.2271, found 496.2281.

1-Benzyl-3-(2-(furan-2-yl)-2-methoxychroman-4-yl)-1H-indole (3ab)

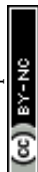
White solid; 86.4 mg, 99% yield; reaction time = 12 h; mp 192.7–194.1 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.41 (s, 1H), 7.32–7.21 (m, 5H), 7.16–7.03 (m, 7H), 6.97 (t, J = 8.0 Hz, 1H), 6.81 (t, J = 8.0 Hz, 1H), 6.63 (d, J = 4.0 Hz, 1H), 6.39 (s, 1H), 5.27 (s, 2H), 4.76 (dd, $J_1 = J_2$ = 4.0 Hz, 1H), 3.23 (s, 3H), 2.73 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.0$ Hz, 1H), 2.40 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.7, 151.4, 142.5, 137.6, 137.1, 129.2, 128.8, 127.6 (2C), 127.3, 126.9, 126.8, 126.4, 121.8, 121.5, 120.1, 119.1, 117.1, 116.8, 110.2, 109.9, 108.5, 97.5, 50.8, 50.0, 39.5, 29.5. IR (KBr) ν 3434, 3038, 2940, 1609, 1584, 1456, 1343, 1265, 1233, 1157, 1039, 1007, 905, 815, 747, 698 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{26}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 436.1907, found 436.1901.

1-Benzyl-3-(2-methoxy-2-methylchroman-4-yl)-1H-indole (3ac)

White solid; 68.3 mg, 89% yield; reaction time = 36 h; mp 158.7–160.1 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.19 (m, 5H), 7.17–7.09 (m, 4H), 6.99 (q, J = 8.0 Hz, 3H), 6.91 (d, J = 8.0 Hz, 1H), 6.75 (t, J = 8.0 Hz, 1H), 5.26 (s, 2H), 4.63 (dd, $J_1 = J_2$ = 4.0 Hz, 1H), 3.34 (s, 3H), 2.32–2.23 (m, 2H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.2, 137.7, 137.2, 129.1, 128.8, 127.7, 127.4, 127.3, 126.9, 126.8, 126.3, 121.8, 120.9, 120.1, 119.1, 117.5, 116.8, 109.9, 98.7, 50.0, 49.2, 40.7, 29.6, 23.2. IR (KBr) ν 3433, 3055, 3032, 2985, 2935, 1609, 1582, 1480, 1456, 1345, 1225, 1191, 1065, 885, 806, 742 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{26}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 384.1958, found 384.1957.

1-Benzyl-3-(2-ethoxy-2-phenylchroman-4-yl)-1H-indole (3ad)

White solid; 89.1 mg, 97% yield; reaction time = 12 h; mp 154.5–155.9 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.67 (t, J = 8.0 Hz, 2H), 7.41–6.98 (m, 16H), 6.82 (d, J = 8.0 Hz, 1H), 5.27 (s, 2H),



4.86 (s, 1H), 3.54 (d, $J = 8.0$ Hz, 1H), 3.39 (d, $J = 8.0$ Hz, 1H), 2.51–2.25 (m, 2H), 1.09 (t, $J = 8.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.3, 142.1, 137.6, 137.1, 129.0, 128.8, 128.4, 128.1, 127.6, 127.5, 127.4, 126.8, 126.7, 126.5, 126.2, 121.8, 121.1, 120.1, 119.0, 117.1, 117.0, 109.8, 100.6, 58.5, 50.0, 42.9, 30.2, 15.4. IR (KBr) ν 3428, 3062, 3031, 2975, 2929, 2886, 1611, 1581, 1487, 1456, 1337, 1264, 1233, 1161, 1058, 1018, 931, 896, 748, 702 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{29}\text{NNaO}_2$ $[\text{M} + \text{Na}]^+$ 482.2089, found 482.2091.

General procedure for the synthesis of 4 bearing two same indole substituents

To a 5.0 mL vial were successively added indole **1c** (0.44 mmol), *ortho*-hydroxychalcone **2a** (0.20 mmol), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (10.8 mg, 0.04 mmol) and 1.0 mL CHCl_3 . The resulting mixture was stirred at 35 °C till almost full consumption of **2a** monitored by thin layer chromatography, and then the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate = 100 : 1 to 80 : 1) to afford the corresponding products **4** in 65% yield with 2 : 1 dr.

3,3'-(2-Phenylchromane-2,4-diyl)bis(1-ethyl-1H-indole) (4)

White solid; 64.5 mg, 65% yield; reaction time = 12 h; dr = 2 : 1; mp 87.8–88.9 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.75–7.61 (m, 1H), 7.50–7.45 (m, 2H), 7.25–6.81 (m, 14H), 6.73–6.60 (m, 2H), 4.32–3.90 (m, 5H), 3.24–3.09 (m, 1H), 2.93–2.77 (m, 1H), 1.33–1.24 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.2, 144.9, 135.7, 135.2, 128.1, 127.3, 126.9, 126.6, 126.3, 125.8, 125.2, 125.1, 124.9, 124.6, 124.2, 124.0, 120.5, 120.0, 119.5, 119.0, 118.8, 118.3, 117.7, 116.1, 115.9, 108.3, 79.5, 39.8, 39.7, 30.6, 29.7, 14.4, 14.3. IR (KBr) ν 3428, 3055, 2975, 2932, 2878, 1610, 1581, 1546, 1477, 1456, 1346, 1232, 906, 742, 706 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{32}\text{N}_2\text{NaO}$ $[\text{M} + \text{Na}]^+$ 519.2407, found 519.2402.

General procedure for the synthesis of 5–7 bearing two different indole substituents

To a 5.0 mL vial were successively added mono-indole substituted chroman **3a** (0.10 mmol), substituted indole (0.11 mmol), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (5.4 mg, 0.02 mmol) and 1.0 mL CHCl_3 . The resulting mixture was stirred at 35 °C for 36 h, and then the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate = 100 : 1 to 80 : 1) to afford the corresponding products **5–7**. Among them, the two isomers of **7** could be separated by gel column chromatography, while for **5–6**, they could not be separated. The dr value was determined by ^1H NMR.

1-Benzyl-3-(4-(1-benzyl-1H-indol-3-yl)-2-phenylchroman-2-yl)-5-methyl-1H-indole (5)

White solid; 38.3 mg, 60% yield; reaction time = 36 h; dr = 1.5 : 1; mp 107.3–108.9 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 8.0$ Hz, 2H), 7.24–6.80 (m, 25H), 6.63 (t, $J = 8.0$ Hz, 1H), 5.12 (dd, $J_1 = 12.0$ Hz, $J_2 = 16.0$ Hz, 4H), 4.34–3.98 (m, 1H), 3.28–3.07 (m, 1H), 2.94–2.74 (m, 1H), 2.28 (dd, $J_1 = J_2 = 4.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.4, 142.9, 136.9, 136.7, 136.6, 136.4,

128.3, 127.8, 127.7, 127.5, 127.2, 126.8, 126.6, 126.5, 126.3, 126.0, 125.8, 125.7, 125.6, 125.5, 125.4, 125.2, 124.8, 124.6, 122.7, 122.5, 120.3, 119.9, 116.2, 116.0, 108.9, 108.7, 119.3, 118.2, 80.2, 57.6, 49.1, 39.3, 30.8, 20.7. IR (KBr) ν 3432, 3058, 3030, 2923, 2860, 1610, 1582, 1485, 1451, 1302, 1234, 1176, 1102, 1030, 907, 799, 739, 701 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{46}\text{H}_{38}\text{N}_2\text{NaO}$ $[\text{M} + \text{Na}]^+$ 657.2876, found 657.2871.

1-Benzyl-3-(4-(1-benzyl-1H-indol-3-yl)-2-phenylchroman-2-yl)-6-methyl-1H-indole (6)

White solid; 32.9 mg, 52% yield; reaction time = 36 h; dr = 1.5 : 1; mp 106.6–108.1 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.63–7.49 (m, 3H), 7.24–6.73 (m, 24H), 6.63 (dd, $J_1 = J_2 = 4.0$ Hz, 1H), 5.17–5.07 (m, 4H), 4.34–3.94 (m, 1H), 3.22–3.03 (m, 1H), 2.92–2.74 (m, 1H), 2.30 (dd, $J_1 = J_2 = 4.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.3, 146.0, 143.9, 137.8, 137.7, 137.4, 136.9, 131.9, 131.7, 129.2, 128.8, 128.4, 128.1, 127.7, 127.6, 127.3, 127.1, 126.9, 126.8, 126.7, 126.6, 126.3, 126.1, 125.6, 123.9, 121.9, 121.8, 121.5, 120.9, 120.2, 119.8, 117.7, 117.0, 109.8, 80.6, 58.5, 49.8, 40.4, 30.8, 21.9. IR (KBr) ν 3433, 3059, 3030, 2923, 2861, 1612, 1583, 1478, 1454, 1300, 1235, 1174, 1106, 1029, 906, 802, 736, 702 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{46}\text{H}_{38}\text{N}_2\text{NaO}$ $[\text{M} + \text{Na}]^+$ 657.2876, found 657.2866.

1-Benzyl-3-(4-(1-benzyl-1H-indol-3-yl)-2-phenylchroman-2-yl)-5-bromo-1H-indole (7)

White solid; 37.5 mg, 53% yield; reaction time = 36 h; dr = 1.5 : 1; mp 215.7–212.3 °C (major isomer), 219.8–221.1 °C (minor isomer); ^1H NMR (400 MHz, CDCl_3) for major isomer δ 7.88 (s, 1H), 7.49 (d, $J = 8.0$ Hz, 2H), 7.28–7.01 (m, 17H), 6.92 (t, $J = 8.0$ Hz, 5H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.73 (s, 1H), 6.65 (d, $J = 4.0$ Hz, 1H), 5.17 (s, 2H), 5.06 (s, 2H), 4.01 (t, $J = 4.0$ Hz, 1H), 3.13 (t, $J = 12.0$ Hz, 1H), 2.92 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) for major isomer δ 154.0, 143.4, 137.6, 137.0, 136.8, 136.0, 129.2, 128.9, 128.8, 128.6, 127.9, 127.8, 127.7, 127.6, 127.2, 127.1, 126.8, 126.7, 126.6, 126.5, 126.2, 125.4, 125.0, 124.1, 121.9, 121.1, 120.5, 119.9, 119.2, 117.4, 117.1, 113.2, 111.5, 109.9, 80.3, 58.6, 50.3, 40.4, 30.7. ^1H NMR (400 MHz, CDCl_3) for minor isomer δ 7.81 (s, 1H), 7.46 (d, $J = 8.0$ Hz, 2H), 7.18–7.11 (m, 12H), 7.08–6.98 (m, 6H), 6.96–6.92 (m, 2H), 6.89–6.86 (m, 3H), 6.81 (s, 1H), 6.63 (t, $J = 8.0$ Hz, 1H), 5.15 (d, $J = 4.0$ Hz, 4H), 4.35 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 3.01 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 1H), 2.73 (t, $J = 12.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) for minor isomer δ 153.1, 144.5, 136.5, 135.8, 134.7, 128.1, 127.9, 127.8, 127.7, 127.5, 127.2, 126.9, 126.7, 126.6, 126.5, 126.3, 125.7, 125.5, 125.4, 125.3, 124.8, 124.2, 123.9, 122.6, 120.8, 119.4, 118.5, 118.2, 116.6, 116.4, 116.1, 112.2, 110.3, 108.8, 79.6, 57.4, 48.9, 41.0, 30.6. IR (KBr) for major isomer ν 3429, 3059, 3031, 2924, 2860, 1610, 1548, 1457, 1346, 1232, 1178, 1103, 1035, 906, 797, 735, 698 cm^{-1} . IR (KBr) for minor isomer ν 3434, 3060, 3031, 2958, 2926, 2861, 1723, 1608, 1582, 1546, 1456, 1389, 1340, 1298, 1260, 1234, 1179, 1075, 1025, 800, 736, 698 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{45}\text{H}_{36}\text{BrN}_2\text{O}$ $[\text{M} + \text{H}]^+$ 699.2006, found 699.1997.



General procedure for the synthesis of 8

Under nitrogen atmosphere, compound **3n** (104.9 mg, 0.20 mmol), 4-chlorophenyl boronic acid (1.5 equiv.), Cs_2CO_3 (2.0 equiv.), $\text{Pd}(\text{OAc})_2$ (0.05 equiv.) and butyl di-1-adamantylphosphine (0.06 equiv.) were successively added to a 15 mL dried tube, followed by adding 2.0 mL DME. The resulting mixture was stirred at 80 °C for 22 h till almost full consumption of **3n** monitored by thin layer chromatography, and then the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding product **8**.

1-Benzyl-3-(6-(4-chlorophenyl)-2-methoxy-2-phenylchroman-4-yl)-1H-indole (8)

White solid obtained by column chromatography (petroleum ether/ethyl acetate = 100 : 1); 104.7 mg, 94% yield; reaction time = 22 h; mp 194.8–196.1 °C; ^1H NMR (400 MHz, CDCl_3), δ 7.66 (d, J = 8.0 Hz, 2H), 7.44–7.31 (m, 5H), 7.27–7.15 (m, 10H), 7.12 (t, J = 8.0 Hz, 1H), 7.04–6.97 (m, 4H), 5.22 (s, 2H), 4.89 (dd, $J_1 = J_2$ = 8.0 Hz, 1H), 3.19 (s, 3H), 2.57 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H), 2.30 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.2, 140.9, 139.6, 137.7, 137.1, 133.0, 132.5, 128.8, 128.7, 128.5, 128.3, 128.0, 127.7, 127.4, 127.0, 126.8, 126.7, 126.3 (2C), 122.0, 119.8, 119.2, 117.8, 117.0, 109.9, 100.9, one carbon missing in the aromatic region, 50.5, 49.9, 43.1, 30.3. IR (KBr) ν 3432, 3031, 2961, 2931, 1610, 1476, 1337, 1251, 1209, 1156, 1042, 1015, 969, 909, 815, 735, 699 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{31}\text{ClNO}_2$ $[\text{M} + \text{H}]^+$ 556.2038, found 556.2041.

General procedure for the synthesis of 9

Under nitrogen atmosphere, compound **3v** (104.9 mg, 0.20 mmol), 4-chlorophenyl boronic acid (1.5 equiv.), Cs_2CO_3 (2.0 equiv.), $\text{Pd}(\text{OAc})_2$ (0.05 equiv.) and butyl di-1-adamantylphosphine (0.06 equiv.) were successively added to a 15 mL dried tube, followed by adding 2.0 mL DME. The resulting mixture was stirred at 80 °C for 22 h till almost full consumption of **3v** monitored by thin layer chromatography, and then the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding product **9**.

1-Benzyl-3-(2-(4'-chloro-[1,1'-biphenyl]-4-yl)-2-methoxychroman-4-yl)-1H-indole (9)

White solid obtained by column chromatography (petroleum ether/ethyl acetate = 100 : 1); 100.8 mg, 91% yield; reaction time = 22 h; mp 222.8–223.6 °C; ^1H NMR (400 MHz, CDCl_3), δ 7.64 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 8.0 Hz, 3H), 7.18–7.09 (m, 5H), 7.04–6.89 (m, 7H), 6.75 (t, J = 8.0 Hz, 1H), 5.17 (s, 2H), 4.76 (dd, $J_1 = J_2$ = 4.0 Hz, 1H), 3.13 (s, 3H), 2.46 (dd, J_1 = 8.0 Hz, J_2 = 4.0 Hz, 1H), 2.25 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.0, 140.6, 139.8, 139.2, 137.6, 137.1, 133.6, 129.1, 129.0, 128.8, 128.4, 127.6 (2C), 127.4, 127.0, 126.9, 126.8, 126.7, 126.5, 121.8, 121.3, 120.0, 119.1, 117.1, 117.0, 109.9, 100.6, 50.4, 50.0, 42.8, 30.2. IR (KBr) ν 3434, 3032, 2962, 2931, 1610, 1581, 1480, 1457,

1388, 1345, 1297, 1263, 1225, 1154, 1100, 1040, 1017, 967, 906, 852, 816 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{31}\text{ClNO}_2$ $[\text{M} + \text{H}]^+$ 556.2038, found 556.2042.

General procedure for the synthesis of 10

Under nitrogen atmosphere, compound **3n** (104.9 mg, 0.20 mmol), 2-indolyl boronic acid (1.7 equiv.), Cs_2CO_3 (2.0 equiv.), $\text{Pd}(\text{OAc})_2$ (0.05 equiv.) and butyl di-1-adamantylphosphine (0.06 equiv.) were successively added to a 15 mL dried tube, followed by adding 2.0 mL DME. The resulting mixture was stirred at 80 °C for 29 h till almost full consumption of **3n** monitored by thin layer chromatography, and then the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding product **10**.

tert-Butyl 2-(4-(1-benzyl-1H-indol-3-yl)-2-methoxy-2-phenylchroman-6-yl)-1H-indole-1-carboxylate (10)

White solid obtained by column chromatography (petroleum ether/ethyl acetate = 100 : 1 to 80 : 1); 124.9 mg, 95% yield; reaction time = 29 h; mp 205.4–206.9 °C; ^1H NMR (400 MHz, CDCl_3), δ 8.14 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.45–7.33 (m, 5H), 7.27–7.14 (m, 7H), 7.11–7.04 (m, 5H), 7.01 (s, 1H), 6.96 (t, J = 8.0 Hz, 1H), 6.32 (s, 1H), 5.23 (s, 2H), 4.84 (dd, $J_1 = J_2$ = 4.0 Hz, 1H), 3.17 (s, 3H), 2.55 (dd, J_1 = 8.0 Hz, J_2 = 4.0 Hz, 1H), 2.36 (t, J = 12.0 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.9, 150.3, 140.9, 140.7, 137.5, 137.3, 137.2, 129.4, 129.2, 128.8, 128.4, 128.3, 128.2, 127.9, 127.6, 127.2, 126.8, 126.7, 126.3, 126.0, 124.0, 122.8, 121.9, 120.2, 119.8, 119.1, 116.7, 116.6, 115.2, 109.9, 109.3, 100.9, 83.1, 50.3, 49.9, 42.9, 30.4, 27.7. IR (KBr) ν 3425, 3058, 2974, 2933, 1726, 1610, 1486, 1455, 1365, 1330, 1257, 1217, 1161, 1126, 1042, 1022, 907, 813, 739, 703 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{44}\text{H}_{41}\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 661.3061, found 661.3060.

General procedure for the synthesis of 11

Under nitrogen atmosphere, compound **3v** (104.9 mg, 0.20 mmol), 2-indolyl boronic acid (1.8 equiv.), Cs_2CO_3 (2.0 equiv.), $\text{Pd}(\text{OAc})_2$ (0.05 equiv.) and butyl di-1-adamantylphosphine (0.06 equiv.) were successively added to a 15 mL dried tube, followed by adding 2.0 mL DME. The resulting mixture was stirred at 80 °C for 22 h till almost full consumption of **3v** monitored by thin layer chromatography, and then the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding product **11**.

tert-Butyl 2-(4-(1-benzyl-1H-indol-3-yl)-2-methoxychroman-2-yl)phenyl-1H-indole-1-carboxylate (11)

White solid obtained by column chromatography (petroleum ether/ethyl acetate = 100 : 1 to 80 : 1); 105.8 mg, 80% yield; reaction time = 22 h; mp 229.8–230.9 °C; ^1H NMR (400 MHz, CDCl_3), δ 8.23 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.35–6.98 (m, 14H), 6.83 (t, J = 8.0 Hz, 1H), 6.56 (s, 1H), 5.26 (s,



2H), 4.85 (dd, $J_1 = J_2 = 4.0$ Hz, 1H), 3.22 (s, 3H), 2.55 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.0$ Hz, 1H), 2.32 (t, $J = 12.0$ Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.0, 150.2, 140.6, 140.1, 137.6 (2C), 137.1, 134.9, 129.3, 129.1, 128.8, 127.7, 127.6, 127.5, 126.9, 126.7, 126.6, 125.8, 124.5, 123.0, 121.9, 121.3, 120.5, 120.0, 119.1, 117.1, 117.0, 115.3, 110.3, 109.9, 100.6, one carbon missing in the aromatic region, 83.5, 50.4, 50.0, 42.8, 30.2, 27.7. IR (KBr) ν 3427, 3071, 3033, 2979, 2935, 1721, 1583, 1456, 1363, 1330, 1264, 1227, 1161, 1037, 967, 905, 849, 816, 745 cm^{-1} . HRMS (ESI) calcd for $\text{C}_{44}\text{H}_{41}\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 661.3061, found 661.3074.

Conflicts of interest

There are no conflicts to declare.

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