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Note

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C(sp^3)-H Bond Functionalization of Benzo[*c*]oxepines via C-O bond Cleavage: Formal [3+3] Synthesis of Multi-Substituted Chromans

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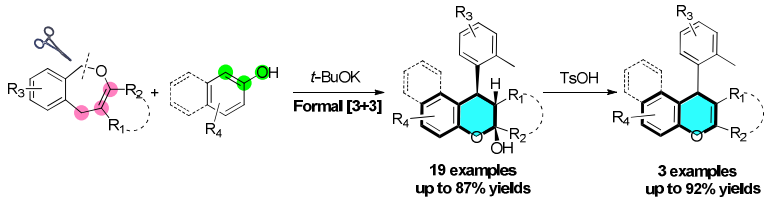
Supporting Information Placeholder



ABSTRACT: An efficient base-promoted C(sp^3)–H bond functionalization strategy for the synthesis of multi-substituted chromans from the formal [3+3] cycloaddition of benzo[*c*]oxepines and electron-rich phenols has been developed. The corresponding 4H-chromenes can be easily obtained in excellent yields by simple filtration from chromans. Preliminary mechanistic studies indicate that the C-O bond cleavage is the key step for the C(sp^3)–H bond functionalization and this reaction could have occurred through a tandem C–O bond cleavage/ Michael addition/ annulation reactions.

Chroman constitutes one of the widely used and important classes of heterocycles, and presents as key structural unit in many natural products with a range of pharmaceutical activities[1]. For example, centchroman (**I**)[2] acts as an estrogen antagonist with antifertility properties, and myristinin A (**II**)[3] is a potent polymerase beta inhibitor (Fig. 1).

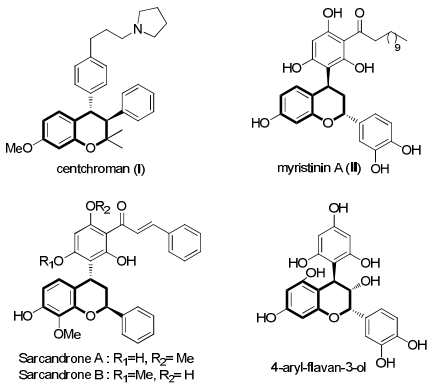
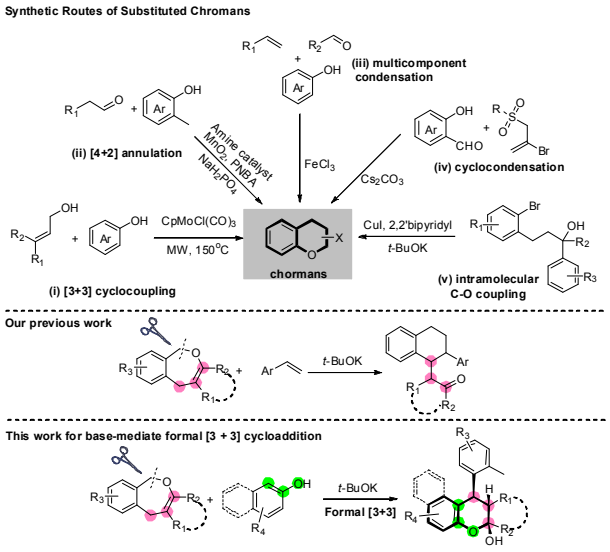


Fig. 1. Representative examples of natural products containing chroman scaffolds

Owing to their great value, the synthesis of chromans has gained much attention.[4] One of the most straightforward routes to the chroman framework is the cyclocoupling of phenol derivatives with 1,3-dienes

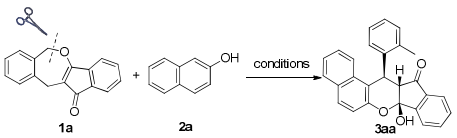
reported by Claisen in 1920s.[5] Over the past decades, considerable research has been devoted to constructing multi-substituted chromans and their analogues.[6-8] As shown in Scheme 1, the representative approaches include: (i) the [3 + 3] cyclocoupling of phenols and allylic alcohols in a Mo/*o*-chloranil catalyst system;[6a] (ii) the formal [4 + 2] cycloaddition of *in situ* oxidation-generated *ortho*-Quinone methides (*o*-QMs) and aldehydes;[6b] (iii) the multicomponent condensation of phenols, aldehydes, and styrenes under the Fe-mediated condition;[6c] (iv) the cyclocondensation of 2-hydroxybenzaldehydes and 2-bromoallyl sulfones in the aid of Cs_2CO_3;[6d] (v) the intramolecular C-O coupling of multi-step prepared substrate.[6e] Despite these significant advances up to the date, the development of a highly efficient method to access multi-substituted chromans especially involving novel reaction pathway to achieve relatively unreactive C–H bond functionalization still remained challenging. Recently, we developed a novel method for the *in situ* generation of *o*-QDM *via* C–O bond cleavage of benzo[*c*] oxepines and successfully constructed the naphthalene and tetrahydronaphthalene skeleton.[9, 10] In conjunction with our ongoing research into developing benzo[*c*]oxepine-based tandem C-O bond cleavage/ cyclization methodologies for valuable heterocycle, herein we reported a facile and efficient approach to the formation of multi-substituted chromans *via* a formal [3+3] cycloaddition of benzo[*c*]oxepines and electron-rich phenols.



Scheme 1. Synthetic Routes to multi-substituted chromans

We initiated our investigation by utilizing benzo[*c*]oxepine (**1a**) and 2-naphthol (**2a**) as model substrates to produce the corresponding multi-substituted chroman **3aa** (Table 1), this benzo[*c*]oxepine could be easily prepared from 1,3-dicarbonyl compounds and 1,2-bis(halomethyl)benzene compounds.[10a, 10c] To our delight, the desired compound **3aa** was obtained in 62% yield when a DMSO solution of **1a** was dropped into a mixture of **2a** and Cs_2CO_3 in DMSO at 90°C (entry 1). Other bases were also tested, and *t*-BuOK was found to be the best choice (entries 2–7). The desired product **3aa** was not obtained in the absence of a base (entry 8). The reaction was also carried out in different solvents (entries 9–11), but all resulted in lower yields than those obtained in DMSO. A range of temperatures were screened to improve the yield (entries 12–16), and 90 °C was identified as the optimal temperature for this cascade reaction. Finally, the dose of *t*-BuOK was varied (entries 17 and 18); 1.0 equiv gave the best yield of **3aa**.

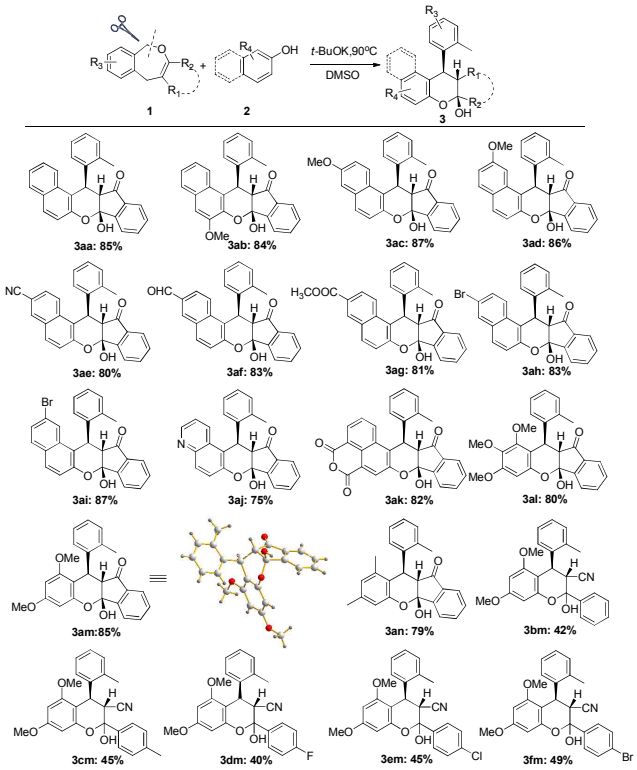
Table 1. Optimization of the Reaction Conditions[a].



entry	solvent	base (eq.)	temp (°C)	yield[b] (%)
1	DMSO	Cs_2CO_3 (1.0)	90	62
2	DMSO	$NaHCO_3$ (1.0)	90	68
3	DMSO	NaOH (1.0)	90	64
4	DMSO	KOH (1.0)	90	58
5	DMSO	DBU (1.0)	90	82
6	**DMSO**	***t*-BuOK (1.0)**	**90**	**85**
7	DMSO	K_3PO_4 (1.0)	90	75
8	DMSO	-	90	trace
9	DMF	*t*-BuOK (1.0)	90	72
10	MeOH	*t*-BuOK (1.0)	90	10
11	THF	*t*-BuOK (1.0)	90	16
12	DMSO	*t*-BuOK (1.0)	r.t.	20
13	DMSO	*t*-BuOK (1.0)	50	35
14	DMSO	*t*-BuOK (1.0)	70	60
15	DMSO	*t*-BuOK (1.0)	80	80
16	DMSO	*t*-BuOK (1.0)	100	84
17	DMSO	*t*-BuOK (0.5)	90	50
18	DMSO	*t*-BuOK (1.5)	90	24

[a]Reaction conditions: **1a** (1.0 mmol) in solvent (2.0 mL) was added dropwise to a mixture of **2a** (1.0 mmol) and base in solvent (2 mL) at different temperatures. The reaction was performed for 1.0 h. [b]isolated yields based on **1a**.

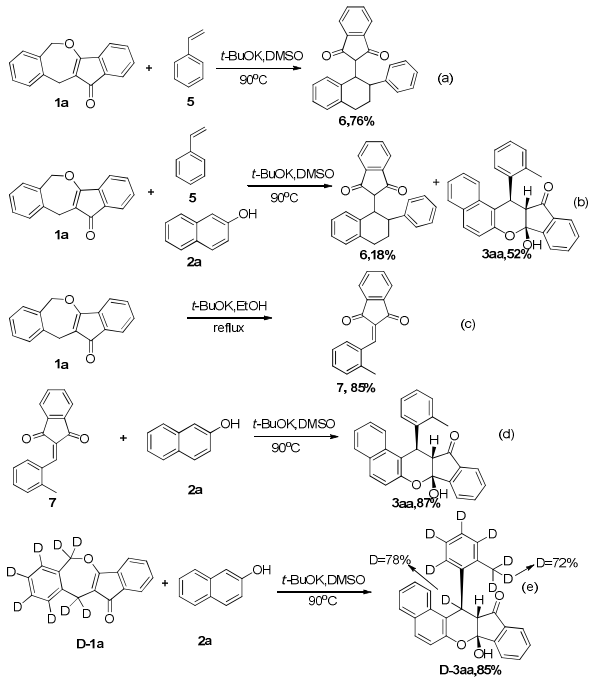
Investigation of the substrate scope of this cascade reaction showed that the optimal reaction conditions were applicable to a broad range of substrates. Scheme 2 shows that substituted naphthols bearing electronically neutral (4-H), electron-donating (3-OMe, 6-OMe, 7-OMe), and electron-withdrawing (6-CN, 6-CHO, 4-CO_2CH_3) substituents reacted smoothly to afford the corresponding multi-substituted chromans in moderate to excellent yields (81–87%, **3aa**–**3ag**). The conditions were mild enough to be compatible with halogenated (6-Br, 7-Br) substrates (83–87% yields, **3ah** and **3ai**), which provides the potential for further functionalization. Reactions of heteroaryl-naphthols under the optimal conditions delivered the corresponding products in good yields (75–82%, **3aj** and **3ak**). The reactions of various substituted phenols under the optimal conditions gave the corresponding products **3al**–**3an** in 79–85% yields. Encouraged by these results, we further investigated the scope of this cascade reaction using various substituted benzo[*c*]oxepines **1** under the standard conditions. The reaction tolerated 4-carbonitrile-benzo[*c*]oxepines, providing the corresponding products in moderate yields (40–49%, **3bm**–**3fm**). The structures of **3ai** and **3am** were identified by single-crystal X-ray diffraction (see the Supporting Information).



[a]Reaction conditions: **1** (1.0 mmol) in DMSO (2.0 mL) was added dropwise to a mixture of **2** (1.0 mmol) and *t*-BuOK (1.0 mmol) in DMSO (2 mL) at 90℃ for 1.0 h. [b]isolated yields based on **1**.

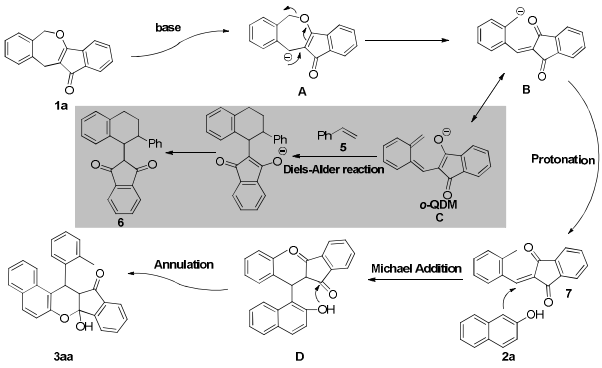
Scheme 2. Scope of Substrates[ab].

With the scope of the method established, the reaction mechanism was then investigated. The reaction of benzo[*c*]oxepine (**1a**) with styrene (**5**) was performed under the standard reaction conditions and the Diels–Alder reaction product **6** was obtained in 76% yield (Scheme 3a). When **1a** was added dropwise to a mixture of 2-naphthol (**2a**) and styrene (**5**) under the standard conditions, **3aa** and **6** were obtained in 52% and 18% yields, respectively (Scheme 3b). These results indicated that the intermediate *o*-QDM could be formed under these conditions. Further experiments showed that **6** could be obtained from **1a** in EtOH[11] (Scheme 3c), and **3aa** with 87% yield (Scheme 3d) could be derived when **7** and 2-naphthol (**2a**) were subjected to the standard reaction condition. These results confirmed that **7** could be a key intermediate in this transformation. Furthermore, the reaction of benzo[*c*]oxepine-d_8 (D-**1a**) and 2-naphthol (**2a**) under the standard conditions delivered the deuterated product D-**3aa** in 85% yield with 72% deuterated methyl group (this means 0.16 D was obtained) (Scheme 3e). This result suggested that an intramolecular H shift might involve in this transformation, but it was not the main pathway.



Scheme 3. Control Experiments

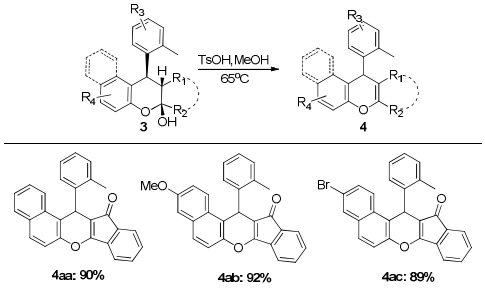
On the basis of the above results and related reports, a preliminary proposed mechanism is presented in Scheme 4 (**3aa** as an example). Initially, in the presence of base, proton at the benzylic position will be removed to generate carbanion intermediate **A**. Then, the tautomerism and C–O bond cleavage of **A** occurs to form intermediate **B**. Subsequently, the protonation of **B** will give the key intermediate **7**. Finally, a sequence of Michael addition and cyclization reactions of **2a** with **7** produces the desired **3aa**. And for the formation of **6**, the resonance of **B** gives the intermediate *o*-QDM **C**, which then undergoes a Diels–Alder reaction to form **6** in the presence of olefin. Moreover, in view of the above control experiment (Scheme 3e) and some works about the [1, 5]-H shift of *o*-QDM,[12] an intramolecular H shift pathway cannot be overlooked for this reaction. (See the Supporting Information, Scheme S1).



Scheme 4. A possible mechanism.

We next investigated the functionalization of **3** to the corresponding 4H-chromene, which represents an important class of scaffolds and is found in many naturally occurring and synthetic molecules with

biological and pharmacological activities.[13, 14] We treated compounds **3** with 1 equiv of TsOH in MeOH at 65 °C. The reaction proceeded smoothly to deliver the corresponding 4H-chromenes **4a**–**4c** in 85–92% yields after simple filtration (Scheme 5).



Scheme 5. Synthesis of 4H-chromenes derivatives.

In summary, we have developed a novel base-promoted C(sp^3)–H bond functionalization strategy for the synthesis of multi-substituted chromans from the formal [3+3] cycloaddition of benzo[*c*]oxepines and electron-rich phenols. Initial studies of the mechanism suggest that this reaction could involve a self-sequenced C–O bond cleavage/Michael addition/annulation cascade reaction. This method is facile and highly efficient, and has a broad scope. The corresponding 4H-chromenes can be easily obtained in excellent yields by simple filtration from multi-substituted chromans. Further exploration of this base-promoted C(sp^3)–H bond functionalization strategy is currently underway in our laboratory and the results will be reported in due course.

Experimental Section

General

All substrates and reagents were commercially available and used without further purification. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using silica gel (200–300 mesh). IR spectra were recorded on a Perkin-Elmer PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on 400/600 MHz NMR spectrometers and resonances (δ) are given in parts per million relative to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quadruple), coupling constants (Hz) and integration. ^{13}C spectra were recorded in $CDCl_3$ or DMSO-*d6* on 100/150 MHz NMR spectrometers and resonances (δ) are given in ppm. HRMS were obtained on a Bruker 7-tesla FT-ICR MS equipped with an electrospray source. The X-ray crystal structure determinations of **3ai** and **3am** were obtained on a Bruker SMART APEX CCD system. Melting points were determined using XT-4 apparatus and not corrected.

General procedure for the synthesis of 3 (3aa as an example)

The benzo[*c*]oxepine **1a** (1.0 mmol, 1.0 eq. in 2 mL DMSO) was added dropwise to a mixture of 2-naphthol 2a (1.0 mmol, 1.0 eq) and *t*-BuOK (1.0mmol, 1.0 eq.) in DMSO (2mL) upon stirred at 90 ^oC for 1.0h after disappearance of the reactant (monitored by TLC). The resulting mixture was dropped into 100 mL 1 M HCl (aq) and extracted with EtOAc 3 times (3 ×50 mL). The organic extract was dried with anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc = 8/1) to afford the product **3aa**.

General procedure for the synthesis of 4 (4aa as an example)

The 2-chromanols **3aa** (0.5 mmol, 1.0 eq), TsOH(0.5 mmol, 1.0 eq) in MeOH upon stirred at 65°C for 1.0h after disappearance of the reactant (monitored by TLC). The product **4aa** was precipitated out, and **4aa** were easily obtained after a simple filtration.

Analytical Data for Compounds 3 and 4

7a-hydroxy-13-(o-tolyl)-12a,13-dihydrobenzo[f]indeno[1,2-b]chromen-12(7aH)-one: (3aa)

Yield: 85% (167 mg), white solid; mp: 245.1- 248.4°C; IR (KBr) νmax: 2551, 1710, 1633, 1394, 1222, 1121, 999, 745, 601 cm^{-1}; ^1H NMR (600 MHz, DMSO-$_{d6}$) δ =8.12 (d, *J* = 7.2 Hz, 1H), 8.05 (s, 1H), 7.87 (s, 1H), 7.81 (d, *J* = 6.6 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.61 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.42 (s, 1H), 7.32 (s, 1H), 7.29 (d, *J* = 6.0 Hz, 1H), 7.09-7.05 (m, 2H), 6.94 (s, 1H), 6.78 (d, *J* = 7.2 Hz, 1H), 5.48 (s, 1H), 3.51 (s, 1H), 2.73 (s, 3H); ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ= 200.3, 153.6, 150.3, 140.4, 136.2, 135.1, 133.4, 131.4, 130.7, 130.5, 130.3, 129.4, 128.5, 127.9, 127.1, 126.5, 125.8, 125.7, 124.0, 123.8, 123.5, 123.4, 122.4, 122.2, 118.8, 116.2, 101.8, 58.1, 33.3, 33.2, 19.2; HRMS (ESI): m/z $[M + Na]^+$ calcd for: $C_{27}H_{20}NaO_3$: 415.1305; found: 415.1304.

7a-hydroxy-6-methoxy-13-(o-tolyl)-12a,13-dihydrobenzo[f]indeno[1,2-b]chromen-12(7aH)-one: (3ab)

Yield: 84% (177 mg), yellow solid; mp: 245.6- 248.7°C; IR (KBr) νmax: 1705, 1602, 1471, 1242, 1133, 1112, 1082, 834, 605, cm^{-1};^1H NMR (600 MHz, DMSO-$_{d6}$) δ=8.20 (s, 1H), 8.15 (d, *J* = 7.2 Hz, 1H), 7.88 (t, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 6.6Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.27 (m, 4H), 7.12 (t, *J* = 6.6 Hz, 1H), 6.97 (t, *J* = 7.2Hz, 1H), 6.80 (d, *J* = 7.2 Hz, 1H), 5.47 (s, 1H), 3.85 (s, 3H), 3.50 (s, 1H), 2.74(s, 3H); ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ=200.3, 153.5, 148.4, 142.4, 140.1, 136.1, 135.0, 133.5, 130.6, 130.3, 129.6, 127.9, 127.1, 126.5, 126.1, 125.7, 124.5, 124.4, 123.7, 122.2, 121.9, 117.4, 106.6, 102.1, 58.0, 55.4, , 33.6, 19.1; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{28}H_{22}NaO_4$: 445.1410; found: 445.1412.

7a-hydroxy-3-methoxy-13-(o-tolyl)-12a,13-dihydrobenzo[f]indeno[1,2-b]chromen-12(7aH)-one: (3ac)

Yield: 87% (183 mg), gray solid; mp: 185.5-187.8°C; IR (KBr) νmax: 1708, 1602, 1514, 1278, 1124, 984, 803, 541, cm^{-1};^1H NMR (600 MHz, DMSO-$_{d6}$) δ= 8.11 (d, *J* = 6.6Hz, 1H), 7.98 (s, 1H), 7.84 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 6.6 Hz, 1H), 7.52 (s, 1H), 7.48 (d, *J* =9.0Hz, 1H), 7.24 (d, *J* = 9.0 Hz, 2H), 7.11 – 7.07 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.93 (s, 1H), 6.78 (d, *J* = 6.6 Hz, 1H), 5.45 (s, 1H), 3.75 (s, 3H), 3.48 (s, 1H), 2.70 (s, 3H); ^{13}C NMR (150MHz, DMSO-$_{d6}$) δ =200.4, 155.9, 153.7, 148.7, 140.5, 136.2, 135.1, 133.5, 130.7, 130.5, 130.2, 128.2, 126.4, 125.8, 123.7, 123.5, 123.4, 122.3, 119.2, 116.8, 107.4, 107.1, 101.8, 58.3, 55.1, 33.7, 33.6, 19.1; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{28}H_{22}NaO_4$: 445.1410; found: 445.1407.

7a-hydroxy-2-methoxy-13-(o-tolyl)-12a,13-dihydrobenzo[f]indeno[1,2-b]chromen-12(7aH)-one: (3ad)

Yield: 86% (181 mg), yellow solid; mp: 249.4-251.6°C; IR (KBr) νmax: 2251, 1654, 1512, 1220, 1027, 825, 764, 625 cm^{-1}; ^1H NMR (600 MHz, DMSO-$_{d6}$) δ= 8.13 (d, J = 6.0 Hz, 1H), 8.08 (s, 1H), 7.88 (s, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.69 – 7.66 (m, 2H), 7.58 (s, 1H), 7.31 (s, 1H), 7.11 (s, 1H), 7.01 – 6.97 (m, 2H), 6.91-6.87 (m, 2H), 6.74 (s, 1H), 5.36 (s, 1H), 3.67 (s, 3H), 3.50 (s, 1H), 2.74 (s, 3H); ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ =200.1, 157.9, 153.5, 150.7, 140.8, 136.1, 135.0, 133.4, 132.8, 130.2, 129.0, 128.1, 126.4, 125.9, 124.6, 123.3, 122.5, 116.2, 116.0, 115.1, 114.6, 101.9, 101.1, 57.9, 54.7, 33.0, 32.9, 19.2; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{28}H_{22}NaO_4$: 445.1410; found: 445.1416.

7a-hydroxy-12-oxo-13-(o-tolyl)-7a,12,12a,13-tetrahydrobenzo[f]indeno[1,2-b]chromene-3-carbonitrile: (3ae)

Yield: 80% (166 mg), yellow solid; mp: 201.4-205.2°C; IR (KBr) νmax: 2225, 1718, 1645, 1381, 1218, 998, 824, 762, 530, cm^{-1}; ^1H NMR (400 MHz, DMSO-$_{d6}$) δ =8.45 (s, 1H), 8.23 (s, 1H), 8.13 (d, *J* = 7.2 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 3H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 6.4 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.09 (t, *J* = 6.6 Hz 1H), 6.94 (t, *J* = 6.8 Hz 1H), 6.71 (d, *J* = 6.8 Hz, 1H), 5.48 (s, 1H), 3.61 (s, 1H), 2.73 (s, 3H);^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ= 199.3, 152.8, 152.6, 139.8, 136.0, 134.9, 134.5, 133.0, 130.5, 130.2, 130.0, 128.2, 127.7, 127.5, 126.4, 125.6, 123.5, 123.2, 122.3, 120.4, 119.0, 115.7, 106.0, 101.7, 57.5, 32.8, 19.2; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{28}H_{19}NNaO_3$: 440.1257; found: 440.1260.

7a-hydroxy-12-oxo-13-(o-tolyl)-7a,12,12a,13-tetrahydrobenzo[f]indeno[1,2-b]chromene-3-carbaldehyde: (3af)

Yield: 83% (174 mg), yellow solid; mp: 172.3-175.6°C; IR (KBr) νmax: 2554, 1647, 1385, 999, 826, 765, 626 cm^{-1}; ^1H NMR (600 MHz, DMSO-$_{d6}$) δ= 10.05 (s, 1H), 8.48 (s, 1H), 8.21 (s, 1H), 8.13 (d, *J* = 6.0 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.89 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.67 – 7.64 (m, 2H), 7.60 (d, *J* = 5.4 Hz, 1H), 7.31 (d, *J* = 6.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.11 (s, 1H), 6.95 (s, 1H), 6.72 (s, 1H), 5.49 (s, 1H), 3.58 (s, 1H), 2.73 (s, 3H); ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ= 199.8, 153.2, 153.0, 140.2, 136.2, 135.2, 134.8, 133.3, 132.0, 131.3, 130.8, 130.5, 128.6, 128.0, 126.7, 125.7, 124.0, 123.4, 122.6, 120.2, 120.0, 116.3, 101.9, 57.6, 33.0, 32.9, 19.2; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{28}H_{20}NaO_4$: 443.1254; found: 443.1249.

3-acetyl-7a-hydroxy-13-(o-tolyl)-12a,13-dihydrobenzo[f]indeno[1,2-b]chromen-12(7aH)-one: (3ag)

Yield: 81% (175 mg), yellow solid; mp: 219.4-221.8°C; IR (KBr) νmax: 1710, 1623, 1469, 1280, 1122, 989, 720, 557 cm^{-1}; ^1H NMR (600 MHz, DMSO-$_{d6}$) δ= 8.54 (s, 1H), 8.17 (s, 1H), 8.13 (d, *J* = 7.2Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.92– 7.89 (m, 2H), 7.64 (d, *J* = 6.6 Hz, 2H), 7.59 (s, 1H), 7.30 (d, *J* = 6.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.11 (s, 1H), 6.95 (s, 1H), 6.74 (d, *J* = 6.6 Hz, 1H), 5.49 (s, 1H), 3.86 (s, 3H), 3.57 (s, 1H), 2.74 (s, 3H); ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ= 199.9, 166.2, 153.3, 152.4, 140.2, 136.2, 135.1, 133.8, 133.3, 131.0, 130.9, 130.6, 128.5, 128.0, 126.6, 126.1, 124.8, 123.4, 122.8, 122.4, 119.7, 116.0, 101.9, 57.7, 52.1, 33.0, 32.9, 19.1; HRMS (ESI) m/z calcd for $C_{29}H_{23}O_5^+$ $(M+H)^+$ 451.1540, found 451.1534.

3-bromo-7a-hydroxy-13-(o-tolyl)-12a,13-dihydrobenzo[f]indeno[1,2-b]chromen-12(7aH)-one: (3ah)

Yield: 83% (195 mg), white solid; mp: 221.7-224.2°C; IR (KBr) νmax: 1708, 1589, 1221, 1122, 1084, 753, 688, 567 cm^{-1}; ^1H NMR (600 MHz, DMSO-$_{d6}$) δ= 8.18 (d, *J* =7.8 Hz 1H), 8.11 (s, 1H), 7.89 (t, *J* = 7.2 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.59-7.53 (m, 3H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 6.6 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.50 (s, 1H), 3.59 (s, 1H), 2.75 (s, 3H); `^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ= 200.0, 153.4, 150.7, 140.3, 136.2, 135.1, 133.4, 130.8, 130.3, 130.2, 130.1, 128.7, 128.0, 127.9, 126.6, 123.5, 123.4, 122.5, 122.4, 120.2, 120.0, 117.0, 116.2, 101.8, 57.9, 33.2, 33.1, 19.2; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{27}H_{19}BrNaO_3$: 493.0410; found: 493.0419.

2-bromo-7a-hydroxy-13-(o-tolyl)-12a,13-dihydrobenzo[f]indeno[1,2-b]chromen-12(7aH)-one: (3ai)

Yield: 87% (204 mg), yellow solid; mp: 161.7-164.0°C; IR (KBr) νmax: 1708, 1619, 1338, 1123, 1080, 825, 748, 602cm^{-1}; ^1H NMR (600 MHz, DMSO-$_{d6}$) δ= 8.09 (s, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.74 (s, 2H), 7.59 (s, 2H), 7.54 (s, 1H), 7.41 (d, *J* =7.2 Hz, 1H), 7.29 (s, 1H), 7.11 (s, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.95 (s,

1H), 6.78(d, *J* = 6.0 Hz, 1H), 5.35 (s, 1H), 3.45 (s, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ= 199.9, 153.3, 151.2, 139.9, 136.2, 134.9, 133.3, 132.7, 130.8, 130.7, 130.3, 129.5, 127.9, 126.8, 126.7, 125.9, 124.0, 123.4, 122.4, 120.7, 119.5,115.2, 101.7, 57.8, 33.0, 19.0; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{27}H_{19}BrNaO_3$: 493.0410; found: 493.0409.

7a-hydroxy-13-(o-tolyl)-12a,13-dihydroindeno[2',1':5,6]pyrano[3,2-f]quinolin-12(7aH)-one: (3aj)

Yield: 75% (147 mg), red solid; mp: 243.6-246.1°C; IR (KBr) νmax: 1718, 1601, 1277, 1240, 1134, 1024, 923, 614, cm^{-1}; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ= 8.77 (d, *J* = 3.6 Hz, 1H), 8.34 (s, 1H), 8.25 (d, *J* = 7.2 Hz, 1H), 8.06 (d, *J* =9.0 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.92 (t, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 3.69 (s, 1H), 2.79 (s, 3H); ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ= 199.9, 153.3, 150.5, 148.0, 144.4, 140.3, 136.3, 136.1, 135.2, 133.4, 130.9, 130.3, 128.1, 126.6, 125.9, 123.4, 123.0, 122.5, 122.2, 115.9, 101.9, 57.8, 32.8. 32.7, 19.2; HRMS (ESI): m/z $[M+H]^+$ calcd for: $C_{26}H_{20}NO_3$: 394.1438; found: 394.1433.

8a-hydroxy-14-(o-tolyl)-13a,14-dihydroindeno[1,2-b]isochromeno[5,4-fg]chromene-4,6,13(8aH)-trione: (3ak)

Yield: 82% (189 mg), yellow solid; mp: 195.7-199.1°C; IR (KBr) νmax: 1777, 1734, 1709, 1414, 1241, 1138, 1007, 756 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ= 8.41 (s, 1H), 8.34 (s, 1H), 8.18 (d, *J* = 7.2 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 2H), 7.81 (t, *J* = 7.2 Hz, 1H), 7.64-7.60 (m, 2H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.2 Hz, 1H), 5.61 (s, 1H), 3.70 (s, 1H), 2.77 (s, 3H); ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ= 199.6, 160.5, 160.0, 152.8, 151.3, 139.2, 136.5, 135.4, 133.4, 131.1, 130.8, 130.4, 130.1, 130.0, 129.7, 129.6, 128.7, 127.9, 126.2, 125.7, 123.7, 122.6, 120.5, 119.8, 102.9, 57.5, 34.0, 33.9, 19.2; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{29}H_{18}NaO_6$: 485.0996; found: 485.1000.

4b-hydroxy-7,8,9-trimethoxy-10-(o-tolyl)-10,10a-dihydroindeno[1,2-b]chromen-11(4bH)-one: (3al)

Yield: 80% (172 mg), brown solid; mp: 198.7-201.2°C; IR (KBr) νmax: 1706, 1605, 1457, 1124, 1043, 931, 884, 731 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ= 7.99 (d, *J* = 7.6 Hz, 1H), 7.86-7.80 (m, 2H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.07 – 7.03 (m, 2H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.23 (s, 1H), 5.02 (s, 1H), 3.67 (s, 3H), 3.57 (s, 3H), 3.40 (s, 3H), 3.23 (s, 1H), 2.55 (s, 3H); ^{13}C NMR (150 MHz, DMSO-$_{d6}$) δ= 200.8, 153.5, 153.3, 152.9, 150.3, 148.4, 141.7, 136.6, 136.2, 134.9, 133.6, 130.3, 130.1, 123.6, 111.2, 102.5, 97.4, 60.4, 60.3, 58.2, 55.7, 32.0, 31.9, 19.1; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{26}H_{24}NaO_6$: 455.1465; found: 455.1463.

4b-hydroxy-7,9-dimethoxy-10-(o-tolyl)-10,10a-dihydroindeno[1,2-b]chromen-11(4bH)-one: (3am)

Yield: 85% (164 mg), yellow solid; mp: 208.6-211.8°C; IR (KBr) νmax: 1725, 1618, 1463, 1231, 1107, 930, 833, 523 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-$_{d6}$) δ= 8.00 (d, *J* = 7.8 Hz, 1H), 7.85-7.82 (m, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 6.6 Hz, 1H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.10 (s, 1H), 5.99 (s, 1H), 5.02 (s, 1H), 3.64 (s, 3H), 3.58 (s, 3H), 3.20 (s, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ= 200.7, 159.6, 157.1, 153.6, 153.3, 141.3, 136.0, 134.8, 133.5, 130.1, 127.4, 125.9, 125.5, 123.5, 121.9, 106.1, 102.6, 94.5, 92.5, 58.5, 55.6, 55.1, 31.7, 19.1; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{25}H_{22}NaO_5$: 425.1359; found: 425.1356.

4b-hydroxy-7,9-dimethyl-10-(o-tolyl)-10,10a-dihydroindeno[1,2-b]chromen-11(4bH)-one: (3an)

Yield: 79% (146 mg), yellow solid; mp: 254.4-257.2°C; IR (KBr) νmax: 1706, 1639, 1123, 1205, 999, 766, 570 cm^{-1}; ^1H NMR (400 MHz, DMSO-$_{d6}$) δ=7.96 (d, *J* = 7.6 Hz, 1H), 7.82 – 7.78 (m, 2H), 7.57-7.49 (m, 2H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.53 (s, 1H), 6.42 (s, 1H), 4.87 (s, 1H), 3.26 (s, 1H), 2.55 (s, 3H), 2.10 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ= 200.7, 153.5, 152.3, 139.6, 137.2, 136.0, 135.8, 135.0, 133.4, 130.1, 130.0, 127.7, 126.2, 125.6, 124.4, 123.4, 121.9, 121.1, 115.5, 102.4, 58.4, 35.0, 20.6, 19.0, 18.2; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{25}H_{22}NaO_3$: 393.1461; found: 393.1455.

2-hydroxy-5,7-dimethoxy-2-phenyl-4-(o-tolyl)chroman-3-carbonitrile: (3bm)

Yield: 42% (84mg), white solid; mp: 158.6-162.1°C; IR (KBr) νmax: 1616, 1587, 1454, 1199, 982, 817, 756, 573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 7.71 (d, *J* = 7.2 Hz, 2H), 7.38 (d, *J* = 6.0 Hz, 3H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.03-6.98 (m, 2H), 6.86 (s, 1H), 6.13 (d, *J* = 2.0 Hz, 1H), 6.01 (s, 1H), 4.79 (d, *J* = 10.8 Hz, 1H), 3.68 (s, 3H), 3.47 (s, 1H), 3.27 (s, 3H), 3.14 (d, *J* = 11.2 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 159.9, 158.0, 152.3, 141.0, 139.7, 136.4, 130.0, 129.4, 128.4, 126.2, 126.0, 125.9, 117.7, 106.4, 96.3, 94.7, 94.1, 55.5, 55.4, 47.5, 36.2, 36.1, 19.9; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{25}H_{23}NNaO_4$: 424.1519; found: 424.1512.

2-hydroxy-5,7-dimethoxy-4-(o-tolyl)-2-(p-tolyl)chroman-3-carbonitrile: (3cm)

Yield: 45% (93mg), white solid; mp: 157.7-160.0°C; IR (KBr) νmax: 1616, 1585, 1456, 1199, 1149, 982, 816, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 7.60 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.04-6.97 (m, 2H), 6.86 (s, 1H), 6.14 (d, *J* = 2.0 Hz, 1H), 6.01 (d, *J* = 2.0 Hz, 1H), 4.78 (d, *J* = 10.8 Hz, 1H), 3.71 (s, 3H), 3.52 (s, 1H), 3.29 (s, 3H), 3.14 (d, *J* = 11.2 Hz, 1H), 2.52 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 159.9, 158.0, 152.4, 141.1, 139.4, 136.9, 136.5, 130.0, 129.1, 128.8, 126.2, 126.0, 125.7, 117.8, 106.4, 96.3, 94.6, 94.1, 55.5, 55.4, 47.6, 36.1, 21.3, 20.0; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{26}H_{25}NNaO_4$: 438.1676; found: 438.1680.

2-(4-fluorophenyl)-2-hydroxy-5,7-dimethoxy-4-(o-tolyl)chroman-3-carbonitrile: (3dm)

Yield: 40% (83mg), yellow solid; mp: 143.6-146.5 °C; IR (KBr) νmax: 1614, 1585, 1492, 1199, 1149, 819, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 7.71 – 7.67 (m, 2H), 7.10 – 6.98 (m, 5H), 6.84 (s, 1H), 6.12 (s, 1H), 6.01 (s, 1H), 4.77 (d, *J* = 11.2 Hz, 1H), 3.75 (s, 1H), 3.69 (s, 3H), 3.28 (s, 3H), 3.10 (d, *J* = 10.8 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 164.3, 161.9, 159.9, 158.0, 152.1, 140.9, 136.4, 135.7, 130.0, 128.1, 126.9, 126.3, 126.0, 117.6, 115.4, 115.2, 106.3, 96.0, 94.7, 94.2, 55.5, 55.4, 47.7, 36.2, 36.0, 19.9; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{25}H_{22}FNNaO_4$: 442.1425; found: 442.1433.

2-(4-chlorophenyl)-2-hydroxy-5,7-dimethoxy-4-(o-tolyl)chroman-3-carbonitrile: (3em)

Yield: 45% (97mg), yellow solid; mp: 143.6-146.5 °C; IR (KBr) νmax: 2928, 1618, 1493, 1461, 1149, 1095, 1018, 818, 751 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ= 7.70 (d, J = 7.8 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 7.2 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 7.02 (t, J = 6.6 Hz, 1H), 6.86 (s, 1H), 6.16 (s, 1H), 6.05 (s, 1H), 4.80 (d, J = 10.2 Hz, 1H), 3.74 (s, 3H), 3.55 (s, 1H), 3.32 (s, 3H), 3.12 (d, J = 11.4 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 160.3, 158.1, 152.1, 140.8, 138.3, 136.5, 135.6, 130.1, 128.6, 127.5, 126.3,

126.1, 117.6, 106.3, 96.0, 94.6, 94.3, 55.4, 47.5, 36.3, 36.0, 19.9; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{25}H_{22}ClNNaO_4$: 458.1130; found: 458.1135.

2-(4-bromophenyl)-2-hydroxy-5,7-dimethoxy-4-(o-tolyl)chroman-3-carbonitrile: (3fm)

Yield: 49% (117mg), red solid; mp: 197.8-200.5 °C; IR (KBr) νmax: 2941, 1596, 1495, 1460, 1352, 1199, 1152, 1009, 822 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ= 7.58 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 7.2 Hz, 1H), 7.05-6.97 (m, 2H), 6.84 (s, 1H), 6.12 (d, J = 2.0 Hz, 1H), 6.01 (d, J = 2.2 Hz, 1H), 4.77 (d, J = 11.2 Hz, 1H), 3.71 (s, 3H), 3.29 (s, 3H), 3.09 (d, J = 11.6 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=160.0, 158.1, 152.1, 140.8, 138.8, 136.4, 131.6, 130.1, 127.8, 126.3, 126.1, 124.0, 117.5, 106.3, 96.1, 94.6, 94.3, 55.5, 47.4, 36.3, 36.0, 20.0; HRMS (ESI): m/z $[M+Na]^+$ calcd for: $C_{25}H_{22}BrNNaO_4$: 502.0624; found: 502.0621.

13-(o-tolyl)benzo[f]indeno[1,2-b]chromen-12(13H)-one: (4aa)

Yield: 90% (84mg), yellow solid; mp: 249.0-252.6 °C; IR (KBr) νmax: 1703, 1650, 1591, 1397, 1187, 735, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 7.78 – 7.73 (m, 2H), 7.57 – 7.54 (m, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.33 – 7.29 (m, 4H), 7.24 –7.21 (m, 2H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.96 – 6.92 (m, 1H), 6.89 – 6.85 (m, 2H), 5.57 (s, 1H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 192.3, 167.2, 148.8, 142.5, 137.0, 135.2, 132.3, 132.2, 131.9, 130.5, 130.0, 129.5, 129.0, 128.5, 127.2, 126.5, 126.4, 125.2, 123.8, 121.5, 118.2, 118.0, 117.7, 32.9, 20.1; HRMS (ESI): m/z $[M+H]^+$ calcd for: $C_{27}H_{19}O_2$: 375.1380; found:375.1403.

3-methoxy-13-(o-tolyl)benzo[f]indeno[1,2-b]chromen-12(13H)-one: (4ab)

Yield: 92% (92mg), yellow solid; mp: 273.4-275.6 °C; IR (KBr) νmax: 1700, 1623, 1393, 1187, 1151, 1122, 812, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 7.67 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.35 – 7.32 (m, 3H), 7.23 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.07 (s, 1H), 7.00 (d, J = 9.2 Hz, 1H), 6.97 (t, J = 7.2 Hz, 1H), 6.90 – 6.85 (m, 2H), 5.57 (s, 1H), 3.83 (s, 3H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 192.3, 167.2, 157.0, 147.4, 142.5, 137.0, 135.1, 133.1, 132.4, 132.1, 130.5, 130.0, 129.0, 128.1, 126.9, 126.5, 126.4, 125.3, 121.4, 119.3, 118.1, 118.0, 111.3, 107.0, 55.2, 29.3, 20.0; HRMS (ESI): m/z $[M+H]^+$ calcd for: $C_{28}H_{21}O_3$: 405.1485; found: 405.1481.

3-bromo-13-(o-tolyl)benzo[f]indeno[1,2-b]chromen-12(13H)-one: (4ac)

Yield: 89% (100mg), yellow solid; mp: 294.3-297.0°C; IR (KBr) νmax: 1702, 1647, 1389, 1186, 1150, 1124, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 7.91 (d, J = 2.0 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.48 – 7.42 (m, 3H), 7.36 – 7.33 (m, 3H), 7.27 –7.25 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.00 – 6.95 (m, 1H), 6.89 (t, J = 7.2 Hz, 1H), 6.83 (s, 1H), 5.61 (s, 1H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 192.1, 167.1, 149.0, 136.9, 135.1, 133.0, 132.3, 132.2, 130.7, 130.5, 130.4, 130.2, 129.0, 128.6, 126.7, 126.6, 125.6, 121.6, 119.3, 118.9, 118.4, 118.3, 29.7, 20.0; HRMS (ESI): m/z $[M+H]^+$ calcd for: $C_{27}H_{17}BrO_2$: 453.0485; found: 453.0473.

ASSOCIATED CONTENT

Supporting Information

Crystallographic data and copies of the ^1H and ^{13}C NMR spectra are involved. This material is available free

of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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