



# Synthesis of isochromans via Fe(OTf)<sub>2</sub>-catalyzed Oxa-Pictet–Spengler cyclization

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## ABSTRACT

Fe(OTf)<sub>2</sub> has been found to be an efficient catalyst for the Oxa-Pictet–Spengler cyclization reaction leading to isochromans. A series of substituted isochromans were obtained with good to excellent isolated yields by coupling β-arylethanol with aldehydes or ketals under the catalysis of 1 mol% of Fe(OTf)<sub>2</sub> at 70 °C. Using a cheap, less-toxic catalyst with water as the only byproduct, this iron-catalyzed Oxa-Pictet–Spengler reaction can be considered environmentally-friendly and atom-economic.

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## 1. Introduction

Isochromans are one of most interesting structure units, as they are present in a great number of natural products and possess a wide range of biological activities. Examples are found in DMHI, a plant growth regulator isolated from *Penicillium steckii* of terrestrial and marine origin, [1], and glucoside B, an aphid insect pigment derivative [2] (Fig. 1). Furthermore, the synthetic tricyclic etodolac [3] bearing an indole ring is an isochroman with commercial importance in the drug industry. Therefore, the synthesis of isochromans may lead to compounds of potential application in the pharmaceutical industry.

Indeed, the synthesis of substituted isochromans has received considerable attention, and significant progress has been made in the past years [4]. Direct C–H functionalization of benzopyran with coupling reagents in the presence of an oxidant is one of most efficient synthetic methods to synthesize 1-substituted

isochromans [5]. However, the developed coupling procedures are not very practical, owing to toxic oxidants being required to finish the reaction, and a lot of waste generated after the reaction (Scheme 1a). A more practical, less-toxic, and atom economic method is desired in the synthesis of substituted isochromans [4].

Alcohols and carbonyl compounds are rich in variety and quantity and are easily commercially available. Thus, catalytic synthesis of substituted isochromans by coupling of alcohols with aldehydes is a straightforward, atom economic, and practical pathway to obtain isochromans. In the Oxa-Pictet–Spengler reaction, a β-arylethanol is condensed with a carbonyl compound to form a hemiacetal intermediate as an electrophile, which then undergoes intramolecular electrophilic aromatic substitution yielding an isochroman compound. Wünsch and Zott firstly reported the reaction by using ZnCl<sub>2</sub> and HCl gas, 2–3 equivalents of *p*-toluenesulfonic acids or Lewis acids (TiCl<sub>4</sub>, AlCl<sub>3</sub>, SnCl<sub>4</sub>) as catalyst under high temperature and long reaction time (24–66 h) [6]. A milder and more economic method made use of catalytic *p*-toluenesulfonic acids, [7], oleic acid, or molecular sieves and anhydrous Na<sub>2</sub>SO<sub>4</sub> to improve the yield; but the reaction could take up to 48 h to completion [8]. When using HCl gas as catalyst for the Oxa-Pictet–Spengler reaction, a much shorter time is possible [9]. Considering the cost of catalyst, Hegedüs and Hell used a solid acid, zeolite E4a, as a heterogeneous catalyst, which could be recycled

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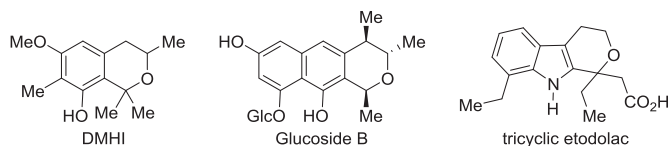
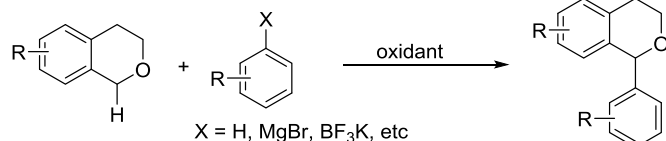
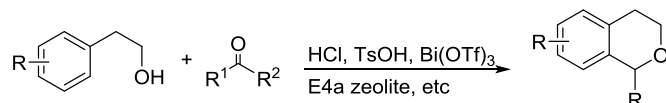


Fig. 1. Representative examples of isochromans with biological activities.

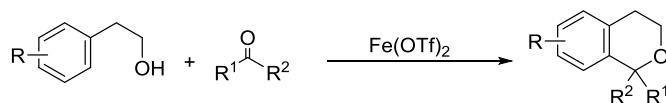
### a) Synthesis of isochromans via C(sp<sup>3</sup>)-H bond arylation



### b) Synthesis of isochromans via Oxa-Pictet-Spengler cyclization



### c) This work



Scheme 1. Methods for the synthesis of substituted isochromans.

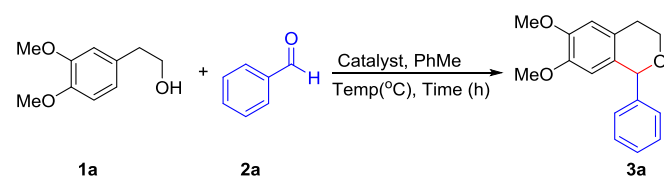
without loss of any activity in the reaction [10]. Lherbet and co-worker reported Bi(OTf)<sub>3</sub> as a nontoxic and easy-to-handle catalyst for the synthesis of substituted isochromans [11]. They observed that the product yields were increased by trace amount of water and decreased by dehydrating agents such as 4 Å molecular sieves and MgSO<sub>4</sub> [11]. Therefore, in the Bi(OTf)<sub>3</sub> catalyzed Oxa-Pictet-Spengler reaction, the real catalyst appears to be the triflic acid TfOH. The triflate salts of In, Sc, Yb, and Y have also been studied, which showed a similar catalytic activity for the reaction (Scheme 1b) [12].

In continuing our search for cheap and environmentally benign base metal catalysts for organic synthesis, [4], herein we report that Fe(OTf)<sub>2</sub> is a highly efficient catalyst for the synthesis of isochroman derivatives via the Oxa-Pictet-Spengler reaction (Scheme 1c). To the best of our knowledge, no iron salts have been reported to catalyze the Oxa-Pictet-Spengler reaction.

## 2. Results and discussion

In a preliminary study, we screened various reaction conditions with focus on Brønsted and Lewis acids as potential catalysts for the model reaction of 3,4-dimethoxyphenylethanol with benzaldehyde (Table 1). As can be seen, there was no Oxa-Pictet-Spengler reaction at all in the absence of a catalyst (entry 1, Table 1). In line with the literature reports, [11], the reaction took place in the presence of the Brønsted acid TfOH (10 mol%), affording the coupled product **3a** in 77% isolated yield (entry 2, Table 1). Increasing the amount of TfOH to 30 mol% brought about no significant effect on the yield (entry 3, Table 1). Using the Lewis acid FeCl<sub>2</sub> as a catalyst, a lower yield of 28% was obtained (entry 4, Table 1). Delightfully, changing FeCl<sub>2</sub> to the more Lewis acidic Fe(OTf)<sub>2</sub> as a catalyst, a much faster reaction was observed, affording almost quantitative yield of **3a** in 4 h (entry 5, Table 1). Using carefully dried toluene as solvent, the same product yield was obtained (entry 5, 6, Table 1), indicating

Table 1  
Screening catalysts for the Oxa-Pictet-Spengler reaction.<sup>a</sup>



Entry	Catalyst	(mol%)	Temp (°C)	Time (h)	Yield (%)
1	None	/	70	4	no
2	TfOH	10	70	4	77
3	TfOH	30	70	4	78
4	FeCl <sub>2</sub>	10	70	4	28
5	Fe(OTf) <sub>2</sub>	10	70	4	99
6	Fe(OTf) <sub>2</sub>	10	70	4	99 <sup>b</sup>
7	Fe(OTf) <sub>2</sub>	1	70	4	98
8	Fe(OTf) <sub>2</sub>	1	70	4	99 <sup>c</sup>
9	Fe(OTf) <sub>3</sub>	1	70	4	99
10	Fe(OTf) <sub>2</sub>	1	70	3	85
11	Fe(OTf) <sub>2</sub>	1	60	5	82

<sup>a</sup> General reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst (1–30 mol %), toluene (2 mL), in a reaction tube, isolated yield. See SI for more details.

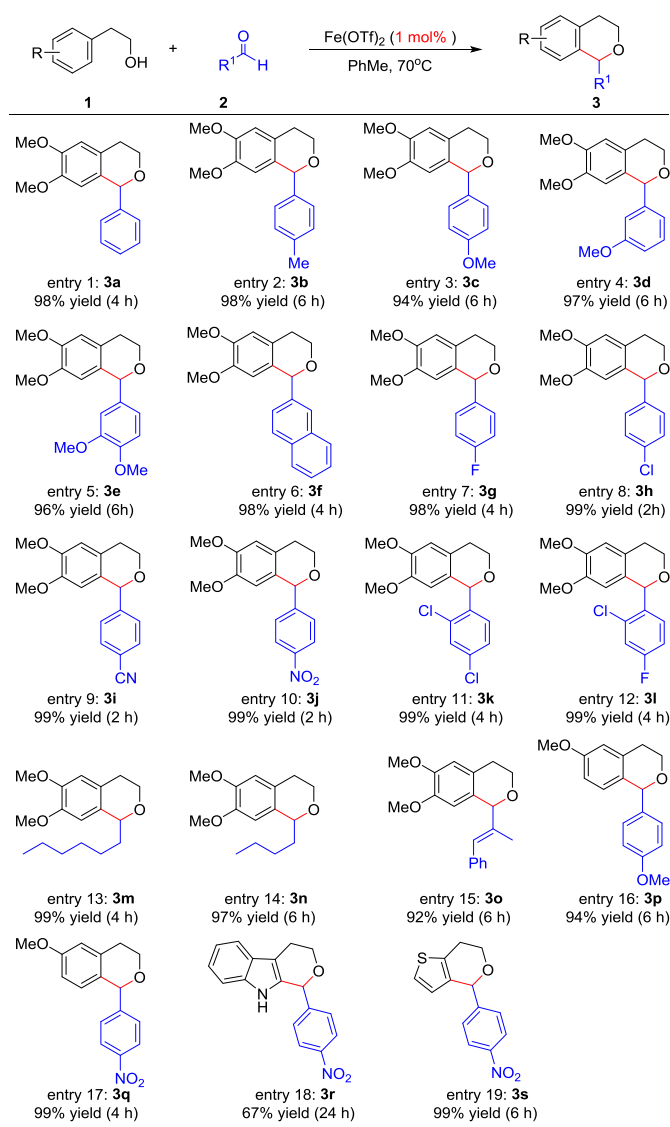
<sup>b</sup> Dry toluene.

<sup>c</sup> At nitrogen atmosphere.

that the Oxa-Pictet-Spengler reaction was not affected by the trace amount of water present in the solvent and hence probably not catalyzed by triflic acid. Indeed, replacing Fe(OTf)<sub>2</sub> with TfOH led to inferior results under similar conditions (Entry 2 and 5, Table 1). This is in contrast to the reaction catalyzed by Bi(OTf)<sub>3</sub>, which is promoted by water. As indicated above, water hydrolyzes Bi(OTf)<sub>3</sub>, affording triflic acid, the real catalyst. However, since water is a byproduct of the Oxa-Pictet-Spengler reaction, we cannot exclude the possibility of the reaction in question being catalyzed by triflic acid in situ produced from Fe(OTf)<sub>2</sub>. Lower the amount of Fe(OTf)<sub>2</sub> from 10 mol% to 1 mol%, an excellent isolated yield of **3a** was still obtained (entry 7, Table 1). Under the conditions employed, performing the reaction under a nitrogen atmosphere or changing to the more Lewis acidic Fe(OTf)<sub>3</sub>, excellent yields were still obtained (entry 8, 9, Table 1). Upon shortening the reaction time or lowering the temperature, the yield of the product decreased (entry 10, 11, Table 1). Taken together, the optimized conditions for the Oxa-Pictet-Spengler reaction are as follows: Fe(OTf)<sub>2</sub> (1 mol%) as catalyst, un-distilled toluene as solvent, reaction temperature 70 °C, 4 h reaction time.

Under the optimized conditions, the Fe(OTf)<sub>2</sub> catalyst is shown to be effective for the Oxa-Pictet-Spengler reaction, furnishing various isochroman derivatives in the reaction of electron-rich β-arylethanol with a variety of aldehydes, ketones, and ketals, in excellent isolated yields in general (Tables 2 and 3). Thus, in addition to forming 6,7-dimethoxy-1-phenylisochroman **3a**, 2-(3,4-dimethoxyphenyl)ethanol reacted with arylaldehydes bearing either electron-donating groups, such as methyl and methoxy, or electron-withdrawing ones, such as fluoro, chloro, cyano and nitro, affording the corresponding isochroman products in up to 99% isolated yield (entries 1–4, 7–10, Table 2). Arylaldehydes containing electron-donating or withdrawing di-substituents, such as 3,4-dimethoxy, 2,4-dichloro and 2-chloro-4-fluoro, are also suitable substrates for the reaction (Table 2, entries 5, 11, 12). Beside substituted benzaldehydes, 2-naphthaldehyde also worked. Of particular note is that aliphatic and unsaturated aldehydes, such as cyclohexanecarbaldehyde, butyraldehyde and *E*-cinnamaldehyde, proved to be equally viable, affording isochromans in high isolated

**Table 2**  
Iron triflate-catalyzed Oxa-Pictet–Spengler reaction to access 1-substituted isochromans.<sup>a</sup>



<sup>a</sup> General reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), Fe(OTf) (1 mol%), toluene (2 mL), at 70 °C in a reaction tube, isolated yield. See SI for more details.

yields (entries 6, 13, 14 and 15, Table 2).

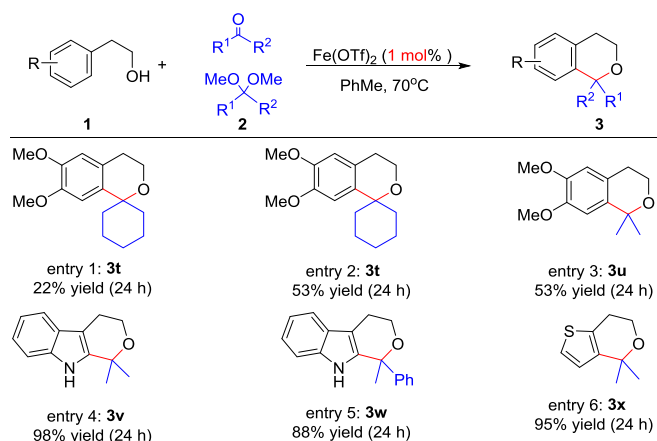
The presence of the dimethoxy substituents on the arylethanol is not essential. As an example, 2-(3-methoxyphenyl)ethanol was reacted with two electronically-different aromatic aldehydes, one bearing a methoxy and the other a nitro substituent. As can be seen, both reactions led to the expected isochromans with excellent isolated yields (Table 2, entries 16, 17). Changing  $\beta$ -arylethanol to the electron rich, unprotected 2-(1H-indol-3-yl)ethan-1-ol, the isochroman derivative was isolated in 67% yield in 24 h (Table 2, entries 18). A further example is seen in 2-(thiophen-3-yl)ethan-1-ol, which coupled with *p*-nitrobenzaldehyde to afford the corresponding product in almost quantitative yield in 6 h. However, non-substituted, less-electron-rich phenylethanol failed to react with aldehyde under the current conditions.

To explore further the scope of this iron-catalyzed Oxa-Pictet–Spengler reaction, the substrate was extended to ketones,

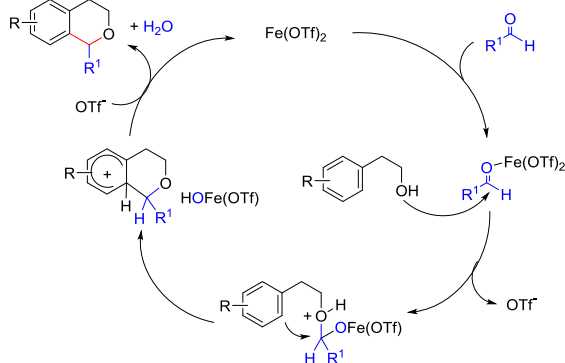
which could lead to 1,1-disubstituted isochromans, a class of products that are more difficult to access. The results obtained varied with the carbonyl derivatives used (Table 3). Thus, starting with cyclohexane, **3t** was obtained in only 24% yield in 24 (Table 3, entries 1). Changing the ketone to a ketal, **3t** was obtained in a higher yield of 53% (Table 3, entries 2). Following this lead, ketals were used to couple with arylethanols, affording a range of 1,1-disubstituted isochromans in good to excellent isolated yield (Table 3, entries 3–6).

A possible mechanistic pathway for the iron-catalyzed Oxa-Pictet–Spengler reaction is shown in Scheme 2. The aldehyde is activated by the Lewis acid Fe(OTf)<sub>2</sub>, prompting the attack of the arylethanol. A subsequent Friedel–Crafts reaction closes the ring, affording the target isochroman. As aforementioned, however, the possibility of catalysis by triflic acid cannot be excluded.

**Table 3**  
Iron triflate-catalyzed synthesis of 1,1-disubstituted isochromans.<sup>a</sup>



<sup>a</sup> General reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), Fe(OTf)<sub>2</sub> (1 mol%), toluene (2 mL), at 70 °C in a reaction tube, isolated yield. See SI for more details.



**Scheme 2.** Suggested mechanism for the Fe(OTf)<sub>2</sub>-catalyzed Oxa-Pictet-Spengler cyclization. Redraw and Make it look better.

### 3. Conclusions

In summary, we have developed an efficient and practical method for the synthesis of 1-substituted isochromans through iron-catalyzed oxa-Pictet-Spengler cyclization. Under the catalysis of Fe(OTf)<sub>2</sub>, electron-rich β-arylethanol react with various aldehydes and ketals to give 1-substituted isochromans with high yields in general. Catalyzed by a cheap iron catalyst under mild conditions with water as the only byproduct, this protocol may find applications in the synthesis of isochroman derivatives.

## 4. Experimental section

### 4.1. General methods

Unless otherwise specified, all reagents were obtained commercially and used without further purification. Iron salts were purchased from commercial suppliers and used without further purification. Toluene was used without further purification. All reactions were carried out under air atmosphere. All glassware was oven-dried before use. Solvents (ethyl acetate, petroleum ether) used for column chromatography were of technical grade and used after distillation. Analytical thin-layer chromatography (TLC) was conducted with TLC plates (Silica gel 60 F254, Qingdao Haiyang).

Flash column chromatography was performed on silica gel 200–300 mesh with freshly distilled solvents. <sup>1</sup>H NMR spectra were recorded on a Bruker Advance 400 (400 MHz) NMR spectrometer and reported in units of parts per million (ppm) relative to tetramethyl silane (δ 0 ppm) or CDCl<sub>3</sub> (δ 7.26 ppm). Multiplicities are given as: brs (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), dd (doublets of doublet), dt (doublets of triplet), td (triplets of doublet) or m (multiplet). <sup>13</sup>C NMR spectra were recorded on a Bruker Advance 400 (100 MHz) NMR spectrometer and reported in ppm relative to tetramethyl silane (δ 0 ppm) or CDCl<sub>3</sub> (δ 77.0 ppm). Coupling constants were reported as J value in Hz. HRMS data was recorded on Bruker Apex IV FTMS (ESI). IR spectra were recorded on a Bruker Tensor 27 spectrometer. Infrared spectra were prepared as KBr pellets and recorded on a Bruker spectrometer.

### 4.2. Experimental details and characterization data

#### 4.2.1. Typical procedure for the synthesis of 1-substituted isochromans **3a–3x**

β-Arylethanol **1** (1 mmol) and Fe(OTf)<sub>2</sub> (0.01 mmol) were added sequentially to a solution of aldehyde, ketone, or ketal (1 eq, 1 mmol) in toluene (2 mL). The reaction mixture was warmed up slowly to the 70 °C and stirred for a few hours with monitoring by TLC plate. After completion the reaction, the mixture was cooled to room temperature. Then, the reaction mixture was washed with saturated NaHCO<sub>3</sub> solution (5 mL), and the organic layer extracted with DCM (2 × 5 mL), dried over MgSO<sub>4</sub>, filtered and evaporated in vacuo. The residue was purified by silica gel column chromatography using PE-EtOAc mixture as eluent to afford the desired product.

#### 4.2.2. 6,7-Dimethoxy-1-phenylisochroman (**3a**) [5f]

White solid, 265 mg, 98% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ2.72–2.76 (m, 1H), 3.03–3.07 (m, 1H), 3.66 (s, 3H), 3.88 (s, 3H), 3.88–3.89 (m, 1H), 4.13–4.16 (m, 1H), 5.69 (s, 1H), 6.23 (s, 1H), 6.66 (s, 1H), 7.26–7.34 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ28.4, 56.0, 63.6, 79.2, 109.8, 111.2, 126.1, 128.2, 128.4, 129.0, 142.2, 147.3, 147.9; IR (KBr) 3071, 2918, 2861, 1505, 1453, 1261, 1214, 1095 cm<sup>-1</sup>; HRMS (ESI) *m/z* calc. for C<sub>17</sub>H<sub>18</sub>O<sub>3</sub> [M+Na]<sup>+</sup>: 293.1154; found: 293.1147.

#### 4.2.3. 6,7-Dimethoxy-1-(*p*-tolyl)isochroman (**3b**) [11]

White solid, 278 mg, 98% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ2.35 (s, 3H), 2.75–2.76 (m, 1H), 2.97–3.05 (m, 1H), 3.66 (s, 3H), 3.86–3.88 (m, 1H), 3.88 (s, 3H), 4.10–4.13 (m, 1H), 5.65 (s, 1H), 6.26 (s, 1H), 6.65 (s, 1H), 7.13–7.20 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ21.0, 28.2, 55.7, 63.2, 78.7, 109.6, 111.0, 125.9, 128.7, 128.9, 129.0, 137.5, 139.1, 147.1, 147.7; IR (KBr) 3074, 2962, 2929, 2837, 1606, 1512, 1457, 1257, 1091 cm<sup>-1</sup>; HRMS (ESI) *m/z* calc. for C<sub>18</sub>H<sub>20</sub>O<sub>3</sub> [M+Na]<sup>+</sup>: 307.1310; found: 307.1295.

#### 4.2.4. 6,7-Dimethoxy-1-(4-methoxyphenyl)isochroman (**3c**) [11]

White solid, 282 mg, 94% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ2.71–2.75 (m, 1H), 3.00–3.06 (m, 1H), 3.67 (s, 3H), 3.81 (s, 3H), 3.86–3.88 (m, 1H), 3.88 (s, 3H), 4.11–4.13 (m, 1H), 5.65 (s, 1H), 6.23 (s, 1H), 6.65 (s, 1H), 6.87 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ28.4, 55.3, 55.9, 63.4, 78.7, 109.8, 111.1, 113.8, 126.2, 129.2, 130.2, 134.5, 147.2, 147.8, 159.4; IR (KBr) 3062, 2975, 2923, 2837, 1605, 1519, 1254, 1207, 1095 cm<sup>-1</sup>; HRMS (ESI) *m/z* calc. for C<sub>18</sub>H<sub>20</sub>O<sub>4</sub> [M+Na]<sup>+</sup>: 323.1259; found: 323.1248.

#### 4.2.5. 6,7-Dimethoxy-1-(3-methoxyphenyl)isochroman (**3d**) [7b]

White solid, 291 mg, 97% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ2.71–2.75 (m, 1H), 3.00–3.05 (m, 1H), 3.67 (s, 3H), 3.78 (s, 3H), 3.86–3.89 (m, 1H), 3.88 (s, 3H), 4.12–4.15 (m, 1H), 5.65 (s, 1H), 6.26



(s, 1H), 6.65 (s, 1H), 6.85–6.90 (m, 3H), 7.24–7.28 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 28.3, 55.2, 55.9, 63.5, 79.0, 109.7, 111.2, 113.7, 114.4, 121.3, 126.0, 128.8, 129.4, 143.7, 147.3, 147.9, 159.7; IR (KBr) 3069, 3008, 2956, 2837, 1605, 1505, 1247, 1095  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{18}\text{H}_{20}\text{O}_4$   $[\text{M}+\text{Na}]^+$ : 323.1259; found: 323.1245.

#### 4.2.6. 1-(3,4-Dimethoxyphenyl)-6,7-dimethoxyisochroman (**3e**) [7b]

White solid, 317 mg, 96% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.70–2.75 (m, 1H), 3.00–3.07 (m, 1H), 3.67 (s, 3H), 3.83 (s, 3H), 3.86–3.89 (m, 1H), 3.88 (s, 6H), 4.11–4.15 (m, 1H), 5.62 (s, 1H), 6.25 (s, 1H), 6.65 (s, 1H), 6.83 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 28.3, 55.9, 55.9, 63.6, 79.1, 109.8, 110.6, 111.1111.7, 121.6, 126.1, 129.1, 134.7, 147.2, 147.9, 148.9, 149.0; IR (KBr) 3075, 2996, 2949, 2843, 1605, 1505, 1460, 1261, 1155, 1082  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{19}\text{H}_{22}\text{O}_5$   $[\text{M}+\text{Na}]^+$ : 353.1365; found: 353.1360.

#### 4.2.7. 6,7-Dimethoxy-1-(naphthalen-2-yl)isochromane (**3f**) [13]

White solid, 321 mg, 98% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.76–2.80 (m, 1H), 3.06–3.13 (m, 1H), 3.60 (s, 3H), 3.90 (s, 3H), 3.90–3.94 (m, 1H), 4.17–4.19 (m, 1H), 5.85 (s, 1H), 6.26 (s, 1H), 6.70 (s, 1H), 7.41 (d,  $J = 8.4$  Hz, 1H), 7.49 (t,  $J = 6.4$  Hz, 2H), 7.77 (s, 1H), 7.82 (d,  $J = 6.6$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 28.3, 55.8, 63.5, 79.2, 109.7, 111.2, 125.9, 126.0, 126.1, 126.5, 127.6, 128.0, 128.1, 128.3, 128.7, 133.0, 133.2, 139.5, 147.3, 147.9; IR (KBr) 3069, 2956, 2916, 2837, 1612, 1505, 1460, 1353, 1261, 1207, 1088  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{21}\text{H}_{20}\text{O}_3$   $[\text{M}+\text{Na}]^+$ : 343.1310; found: 343.1296.

#### 4.2.8. 1-(4-Fluorophenyl)-6,7-dimethoxyisochroman (**3g**) [7b]

White solid, 290 mg, 98% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.70–2.74 (m, 1H), 3.03 (m, 1H), 3.66 (s, 3H), 3.86–3.88 (m, 1H), 3.88 (s, 3H), 4.11–4.14 (m, 1H), 5.66 (s, 1H), 6.18 (s, 1H), 6.65 (s, 1H), 7.03 (t,  $J = 8.0$  Hz, 2H), 7.28 (t,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 28.4, 56.0, 63.7, 78.5, 109.7, 111.3, 115.3 (d,  $^2J_{\text{C-F}} = 21.3$  Hz), 126.2, 128.8, 130.7 (d,  $^3J_{\text{C-F}} = 8.2$  Hz), 138.2 (d,  $^4J_{\text{C-F}} = 3.0$  Hz), 147.4, 148.0, 162.6 (d,  $^1J_{\text{C-F}} = 245.0$  Hz); IR (KBr) 3073, 2971, 2917, 2847, 1600, 1514, 1467, 1257, 1218, 1086  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{17}\text{H}_{17}\text{FO}_3$   $[\text{M}+\text{Na}]^+$ : 311.1059; found: 311.1050.

#### 4.2.9. 1-(4-Chlorophenyl)-6,7-dimethoxyisochroman (**3h**) [7b]

White solid, 301 mg, 99% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.71–2.75 (m, 1H), 3.01–3.05 (m, 1H), 3.67 (s, 3H), 3.86–3.89 (m, 1H), 3.88 (s, 3H), 4.11–4.13 (m, 1H), 5.66 (s, 1H), 6.18 (s, 1H), 6.65 (s, 1H), 7.24 (d,  $J = 8.0$  Hz, 2H), 7.32 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 28.3, 55.9, 63.6, 78.4, 109.6, 111.3, 126.1, 128.4, 128.6, 130.3, 133.9, 140.8, 147.4, 148.0; IR (KBr) 3065, 2963, 2932, 2831, 1608, 1514, 1467, 1249, 1218, 1086  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{17}\text{H}_{17}\text{ClO}_3$   $[\text{M}+\text{Na}]^+$ : 327.0764; found: 327.0749.

#### 4.2.10. 4-(6,7-Dimethoxyisochroman-1-yl)benzotrile (**3i**) [11]

White solid, 292 mg, 99% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.73–2.77 (m, 1H), 3.00–3.07 (m, 1H), 3.66 (s, 3H), 3.87–3.89 (m, 1H), 3.88 (s, 3H), 4.10–4.12 (m, 1H), 5.71 (s, 1H), 6.15 (s, 1H), 6.67 (s, 1H), 7.43 (d,  $J = 7.6$  Hz, 2H), 7.64 (d,  $J = 7.6$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 28.2, 56.0, 56.1, 63.8, 78.4, 109.5, 111.6, 112.1, 118.8, 126.2, 127.5, 129.6, 132.3, 147.5, 147.6, 148.4; IR (KBr) 3080, 2956, 2932, 2831, 2356, 2215, 1615, 1506, 1467, 1296, 1241, 1093  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{18}\text{H}_{17}\text{NO}_3$   $[\text{M}+\text{Na}]^+$ : 318.1106; found: 318.1086.

#### 4.2.11. 6,7-Dimethoxy-1-(4-nitrophenyl)isochroman (**3j**) [11]

White solid, 315 mg, 99% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.73–2.77 (m, 1H), 3.01–3.09 (m, 1H), 3.65 (s, 3H), 3.87–3.89 (s, 1H), 3.88 (s, 3H), 4.10–4.14 (m, 1H), 5.75 (s, 1H), 6.15 (s, 1H), 6.67 (s, 1H), 7.49 (d,  $J = 8.0$  Hz, 2H), 8.19 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR

(100 MHz,  $\text{CDCl}_3$ )  $\delta$ 28.2, 55.9, 56.0, 63.8, 78.1, 109.3, 111.5, 123.7, 126.1, 127.4, 129.7, 147.6, 147.7, 148.3, 149.4; IR (KBr) 3065, 3002, 2940, 2854, 1608, 1522, 1460, 1343, 1265, 1210, 1101  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{17}\text{H}_{17}\text{NO}_5$   $[\text{M}+\text{Na}]^+$ : 338.1004; found: 338.0991.

#### 4.2.12. 1-(2,4-Dichlorophenyl)-6,7-dimethoxyisochroman (**3k**)

White solid, 335 mg, 99% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.73–2.78 (m, 1H), 3.00–3.06 (m, 1H), 3.68 (s, 3H), 3.86–3.89 (s, 1H), 3.88 (s, 3H), 4.09–4.14 (m, 1H), 6.14 (s, 1H), 6.20 (s, 1H), 6.65 (s, 1H), 7.10 (d,  $J = 8.4$  Hz, 1H), 7.17 (dd,  $J = 2.0, 8.4$  Hz, 1H), 7.46 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 28.0, 55.7, 55.8, 63.5, 74.3, 108.9, 111.2, 126.1, 127.1, 127.5, 129.1, 131.5, 134.2, 134.7, 138.4, 147.4, 148.0; IR (KBr) 3058, 2982, 2913, 2842, 1615, 1502, 1467, 1255, 1216, 1088  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{O}_3$   $[\text{M}+\text{Na}]^+$ : 361.0374; found: 361.0360.

#### 4.2.13. 1-(2-Chloro-4-fluorophenyl)-6,7-dimethoxyisochroman (**3l**)

White solid, 319 mg, 99% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.73–2.77 (m, 1H), 3.00–3.07 (m, 1H), 3.68 (s, 3H), 3.88 (s, 3H), 3.87–3.98 (m, 1H), 4.11–4.14 (m, 1H), 6.15 (s, 1H), 6.20 (s, 1H), 6.65 (s, 1H), 6.90–6.94 (m, 1H), 7.17–7.18 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  27.9, 55.5, 63.3, 74.1, 108.9, 111.1, 113.8 (d,  $^2J_{\text{C-F}} = 20.8$  Hz), 116.3 (d,  $^3J_{\text{C-F}} = 24.6$  Hz), 126.0, 127.7, 131.7 (d,  $^4J_{\text{C-F}} = 10.2$  Hz), 134.6 (d,  $^5J_{\text{C-F}} = 10.2$  Hz), 135.7 (d,  $^5J_{\text{C-F}} = 3.5$  Hz), 147.3, 147.8, 161.6 (d,  $^1J_{\text{C-F}} = 248.9$  Hz); IR (KBr) 3080, 2956, 2925, 2847, 1615, 1514, 1460, 1257, 1218, 1093  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{17}\text{H}_{16}\text{ClFO}_3$   $[\text{M}+\text{Na}]^+$ : 345.0670; found: 345.0648.

#### 4.2.14. 1-Hexyl-6,7-dimethoxyisochroman (**3m**) [11]

White solid, 275 mg, 99% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 0.87–0.90 (m, 3H), 1.27–1.38 (m, 6H), 1.44 (d,  $J = 8.1$  Hz, 2H), 1.75–1.84 (m, 2H), 2.58–2.62 (m, 1H), 2.86–2.94 (m, 1H), 3.72–3.74 (m, 1H), 3.86 (s, 3H), 4.09–4.14 (m, 1H), 4.67–4.69 (m, 1H), 6.55 (s, 1H), 6.59 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 14.1, 22.7, 25.3, 28.7, 29.5, 31.9, 36.2, 55.9, 56.1, 63.2, 75.6, 108.0, 111.5, 126.0, 130.5, 147.5; IR (KBr) 2925, 2854, 1686, 1506, 1452, 1249, 1101  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{17}\text{H}_{26}\text{O}_3$   $[\text{M}+\text{Na}]^+$ : 301.1780; found: 301.1770.

#### 4.2.15. 1-Butyl-6,7-dimethoxyisochroman (**3n**) [11].

White solid, 243 mg, 97% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 0.92–0.94 (m, 3H), 1.36–1.47 (m, 4H), 1.74–1.88 (m, 2H), 2.58–2.62 (m, 1H), 2.8–2.92 (m, 1H), 3.71–3.76 (m, 1H), 3.85 (s, 6H), 4.11–4.12 (m, 1H), 4.67 (d,  $J = 8.0$  Hz, 1H), 6.56 (s, 1H), 6.59 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 13.9, 22.6, 27.2, 28.5, 35.6, 55.6, 55.8, 62.9, 75.3, 107.7, 111.3, 125.8, 130.3, 147.2; IR (KBr) 2948, 2847, 1608, 1514, 1467, 1335, 1249, 1109  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{15}\text{H}_{22}\text{O}_3$   $[\text{M}+\text{Na}]^+$ : 273.1467; found: 273.1461.

#### 4.2.16. (E)-6,7-Dimethoxy-1-(1-phenylprop-1-en-2-yl)isochroman (**3o**)

White solid, 285 mg, 92% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 1.76 (s, 3H), 2.59–2.63 (m, 1H), 3.05 (m, 1H), 3.80 (s, 3H), 3.85–3.90 (m, 1H), 3.89 (s, 3H), 4.20–4.30 (m, 1H), 5.21 (s, 1H), 6.60 (s, 1H), 6.65 (d,  $J = 3.2$  Hz, 2H), 7.26 (s, 1H), 7.36 (s, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 13.7, 28.4, 55.9, 56.0, 64.1, 83.7, 108.6, 111.4, 126.6, 126.8, 127.9, 128.2, 129.1, 130.3, 137.4, 138.6, 147.6, 147.9; IR (KBr) 3065, 2963, 2925, 2847, 1608, 1506, 1467, 1350, 1249, 1218, 1086  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{20}\text{H}_{22}\text{O}_3$   $[\text{M}+\text{Na}]^+$ : 333.1467; found: 333.1461.

#### 4.2.17. 6-Methoxy-1-(4-methoxyphenyl)isochroman (**3p**) [11]

White solid, 254 mg, 94% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.77–2.81 (m, 1H), 3.10–3.17 (m, 1H), 3.80 (s, 3H), 3.89–3.95 (m, 1H), 4.18–4.20 (m, 1H), 5.68 (s, 1H), 6.66 (d,  $J = 8.4$  Hz, 1H), 6.71 (d,  $J = 8.6$  Hz, 2H), 6.89 (d,  $J = 8.6$  Hz, 2H), 6.93 (d,  $J = 7.6$  Hz, 1H), 7.28 (t,  $J = 7.7$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 29.1, 55.2, 63.8, 79.3,

112.3, 113.2, 113.6, 114.2, 121.2, 128.0, 129.3, 129.5, 135.1, 143.9, 158.2, 159.7; IR (KBr) 3041, 2963, 2932, 2839, 1693, 1600, 1499, 1452, 1312, 1241, 1156, 1031  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{17}\text{H}_{18}\text{O}_3$   $[\text{M}+\text{Na}]^+$ : 293.1154; found: 293.1145.

#### 4.2.18. 6-Methoxy-1-(4-nitrophenyl)isochroman (**3q**) [11]

White solid, 307 mg, 99% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.78–2.86 (m, 1H), 3.10–3.18 (m, 1H), 3.79 (s, 3H), 3.92–3.96 (m, 1H), 4.15–4.20 (m, 1H), 5.77 (s, 1H), 6.59 (d,  $J = 8.4$  Hz, 1H), 6.63 (d,  $J = 8.4$  Hz, 1H), 6.72 (s, 1H), 7.49 (d,  $J = 8.4$  Hz, 2H), 8.19 (d,  $J = 8.4$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 29.0, 55.3, 64.0, 78.3, 112.6, 113.6, 123.7, 127.7, 128.1, 129.6, 135.1, 147.7, 149.6, 158.5; IR (KBr) 3073, 2971, 2940, 2831, 2348, 1608, 1514, 1467, 1343, 1241, 1109  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{16}\text{H}_{15}\text{NO}_4$   $[\text{M}+\text{Na}]^+$ : 308.0899; found: 308.0895.

#### 4.2.19. 1-(2-Chloro-4-fluorophenyl)-6,7-dimethoxyisochroman (**3r**) [11]

White solid, 197 mg, 67% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.83–2.87 (m, 1H), 3.05–3.13 (m, 1H), 3.96–4.02 (m, 1H), 4.27–4.30 (m, 1H), 5.88 (s, 1H), 7.11–7.15 (m, 2H), 7.24 (d,  $J = 8.4$  Hz, 1H), 7.47 (s, 1H), 7.54 (d,  $J = 8.4$  Hz, 3H), 8.18 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 22.3, 65.0, 75.1, 109.4, 111.2, 118.6, 120.1, 122.6, 124.1, 126.9, 129.2, 132.0, 136.3, 146.8, 148.2; IR (KBr) 3330, 3065, 2940, 2917, 2371, 1717, 1608, 1514, 1436, 1343, 1265, 1047  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3$   $[\text{M}+\text{Na}]^+$ : 317.0902; found: 317.0899.

White solid, 258.4 mg, 99% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.72–2.76 (m, 1H), 2.99–3.01 (m, 1H), 3.91–3.96 (m, 1H), 4.25–4.29 (m, 1H), 5.88 (s, 1H), 6.86 (d,  $J = 4.4$  Hz, 1H), 7.26 (s, 1H), 7.57 (d,  $J = 8.0$  Hz, 2H), 8.21 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 26.1, 64.6, 76.7, 123.8, 124.4, 127.1, 128.4, 134.0, 135.2, 147.9, 148.6; IR (KBr) 3052, 2988, 2916, 2835, 1600, 1513, 1457, 1256, 1208, 1075  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{13}\text{H}_{11}\text{NO}_3\text{S}$   $[\text{M}+\text{Na}]^+$ : 284.0357; found: 284.0345.

#### 4.2.20. 6',7'-DimethoxySpiro[cyclohexane-1,1'-isochroman (**3t**) [11]

White solid, (Table 3, entry 1: 58 mg, 22% yield; Table 3, entry 2: 139 mg, 53% yield);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 1.26–1.32 (m, 1H), 1.55–1.61 (m, 4H), 1.72–1.75 (m, 3H), 1.91–1.95 (m, 2H), 2.73 (t,  $J = 5.2$  Hz, 2H), 3.85 (s, 3H), 3.85–3.88 (m, 1H), 3.87 (s, 3H), 6.57 (s, 1H), 6.60 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 21.8, 25.6, 29.2, 37.1, 55.8, 56.1, 58.7, 74.7, 108.7, 111.4, 125.7, 135.4, 147.2, 147.3; IR (KBr) 2932, 2862, 1608, 1506, 1452, 1327, 1249, 1163, 1093  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{16}\text{H}_{22}\text{O}_3$   $[\text{M}+\text{Na}]^+$ : 285.1467; found: 285.1455.

#### 4.2.21. 6,7-Dimethoxy-1,1-dimethylisochroman (**3u**) [11]

White solid, 118 mg, 53% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 1.15 (s, 6H), 2.73 (t,  $J = 5.6$  Hz, 2H), 3.86 (s, 3H), 3.85 (s, 2H), 3.93 (t,  $J = 5.5$  Hz, 2H), 6.57 (d,  $J = 2.0$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 29.1, 29.8, 55.8, 56.1, 59.7, 74.2, 108.6, 111.3, 125.1, 134.9, 147.3, 147.4; IR (KBr) 2940, 2854, 1615, 1522, 1452, 1350, 1257, 1210, 1156, 1086  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_{13}\text{H}_{18}\text{O}_3$   $[\text{M}+\text{Na}]^+$ : 245.1154; found: 245.1145.

#### 4.2.22. 1,1-Dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (**3v**) [11]

White solid, 197 mg, 98% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 1.59 (s, 6H), 2.83 (t,  $J = 5.6$  Hz, 2H), 4.07 (t,  $J = 5.6$  Hz, 2H), 7.14–7.19 (m, 2H), 7.33 (d,  $J = 8.0$  Hz, 1H), 7.52 (d,  $J = 8.0$  Hz, 1H), 7.75 (brs, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 22.5, 27.9, 60.6, 71.9, 106.7, 110.9, 118.4, 119.7, 121.8, 127.1, 135.8, 139.0; IR (KBr) 3267, 3034, 2971, 2901, 2862, 1756, 1717, 1615, 1514, 1444, 1358, 1257, 1132, 1039  $\text{cm}^{-1}$ .

#### 4.2.23. 1-Methyl-1-phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (**3w**) [11]

White solid, 262 mg, 88% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 2.02 (s, 3H), 2.83–2.87 (m, 1H), 3.10–3.17 (m, 1H), 3.83–3.90 (m, 1H), 4.12–4.16 (m, 1H), 7.28–7.36 (m, 2H), 7.42–7.50 (m, 6H), 7.70 (d,  $J = 7.6$  Hz, 1H), 8.30 (brs, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 22.2, 27.9, 60.7, 76.2, 108.1, 111.0, 118.5, 119.6, 121.9, 126.8, 126.9, 127.8, 128.2, 136.0, 136.6, 144.2; IR (KBr) 3750, 3680, 3408, 1740, 1717, 1608, 1506, 1428, 1304  $\text{cm}^{-1}$ .

#### 4.2.24. 4,4-Dimethyl-6,7-dihydro-4H-thieno[3,2-c]pyran (**3x**) [11]

White solid, 160 mg, 95% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ 1.56 (s, 6H), 2.69 (t,  $J = 5.6$  Hz, 2H), 3.96 (t,  $J = 5.6$  Hz, 2H), 6.75 (d,  $J = 5.6$  Hz, 2H), 7.11 (d,  $J = 5.6$  Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ 26.5, 30.7, 60.0, 74.1, 122.2, 126.9, 132.2, 142.8; IR (KBr) 3735, 3665, 3423, 1740, 1701, 1608, 1522, 1428, 1366, 1234, 1163, 1086  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calc. for  $\text{C}_9\text{H}_{12}\text{OS}$   $[\text{M}+\text{Na}]^+$ : 191.0507; found: 191.0502.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tet.2018.10.028>.

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