Application of *ortho*-acylated phenylacetic acid esters to the synthesis of 1-substituted isochromanes

Iliyan Ivanov,* Stoyanka Nikolova, Ekaterina Kochovska, and Stela Statkova-Abeghe

University of Plovdiv, Department of Organic Chemistry, 24, Tsar Assent str., 4000 Plovdiv, Bulgaria
E-mail: ivanov@argon.acad.bg

Abstract
A series of 1-substituted isochromanes has been synthesized from the corresponding alkyl 2-acylphenylacetates **3**, by reduction and cyclization with a catalytic amount of *p*-toluenesulfonic acid monohydrate (PTSA), as compounds with potential antitumor activity and N-bearing heterocycle analogues.

Keywords: Isochromanes, synthesis, alkyl 2-acylphenylacetates, reduction, sodium borohydride

Introduction

The biological activity of some isochromane derivatives has provided a great deal of interest in the synthesis. The isochromane fragment is the core of various natural compounds, which exhibit a wide variety of pharmacological activities.[1]

Many isochromanes have been synthesized as intermediates of the synthesis of anxiolytic 2,3-benzodiazepines, which are known as 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) receptor antagonists.[2-4] Recently, Nergardh *et al*. reported that isochroman A 68930 is a selective dopamine D1 antagonist.[5] Some isochromanes are pharmacologically active compounds in anti-migraine therapy. For example, PNU-109291 is selective 5-HT1D receptor agonist with anti-migraine potential, like sumatriptan.[6] Isochromane derivatives are synthesized as aromatic analogues of Stavudine, an approved anti-Human Immunodeficiency Virus (HIV) drug.[7] The isochromane analogues of the naphthylisoquinoline alkaloids michellamines and korupensamines have been synthesized because of their activity against HIV.[8]

Some isochromane analogues are part of complex natural products such as stephaoxocanine[9] and glucoside B.[10] Isochromane derivatives also exhibit plant-growth regulatory and herbicidal activities;[11,12] they are estrogen receptors,[13] dopamine receptor ligands,[14] and fragrances, such as galaxolide.[15] 6,7-Dimethoxyisochromanes substituted at C-1 *via* a one- to three- carbon chain

with arylpiperazines, *p*-trifluoromethylphenyl, *etc.,* are hypotensives, which lower blood pressure presumably by both peripheral and central α-adrenoreceptor blockade.[14] 1-Phenyl- and 1-(3-methoxy-4-hydroxy)phenyl-6,7-dihydroxyisochromans have been identified in extra-virgin olive oil and have been shown to exhibit beneficial antioxidant effects[16,17] and antiplatelet activity.[18] 1-Aryl-6,7-dimethoxyisochromanes have shown a wide range of biological activities such as analgesic, muscle relaxant, antidepressant, anti-inflammatory, antihistaminic and anticoagulant, hypotensive with peripheral and central activities, and are adrenergic antagonists.[19-21] Heterocyclic anthracyclines, as idarubicin's analogues, include the isochromane nucleus, have been reported to possess a potent and broad spectrum of antitumor activity.[22] 1,6,8-Trihydroxy-3-heptyl-7-carboxyisochroman, an isochromane derivative from *Penicillium sp*. is an antibiotic and a topoisomerase II inhibitor.[23] Another derivative, pseudoflectusin, is a selective human cancer cytotoxin found in nature from *Aspergillus pseudodeflectus*.[24]

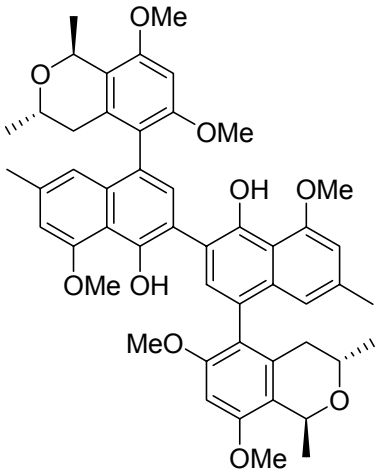


Figure 1. Structure of a synthetic analog of a korupensamine

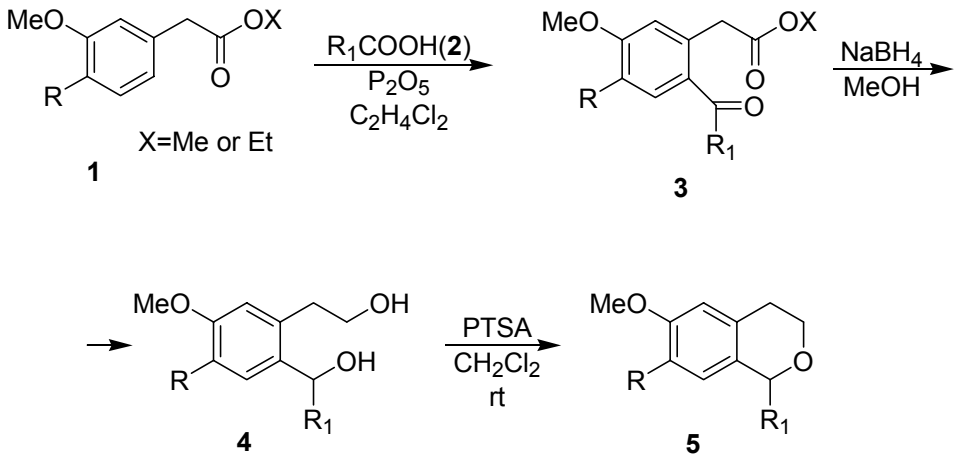
Results and Discussion

Isochroman derivatives are structural analogues of tetrahydroisoquinolines and have been repeatedly recognized as such.[25,26] This analogy has been exploited and several studies report on the use of isochromans as starting materials or intermediates for the synthesis of *iso*-quinoline derivatives and *vice versa* , as well as for the preparation of other nitrogen-containing heterocycles.[26] Numerous methods have been developed to synthesize isochromanes by intramolecular C-O [7, 27-29] or C-C bond [30,31] cyclization. Recently, the synthesis of isochromanes containing hydroxy substituents has been achieved. The key step for the synthesis of the isochromane nucleus is an oxidative mercury- mediated ring closure of phenylmethanol derivatives or the ozonolysis of the corresponding phenylmethanol derivative.[32,33] The hydroxyisochromanes were prepared also by saponification of 5-formylmellein,[34] reduction of

isocoumarins with hydrides,[35,36] reaction of benzocyclobutenols and aromatic aldehydes in the presence of lithium 2,2,6,6-tetramethylpiperidide,[37] photo-induced hetero- Diels-Alder reaction of 2-methylbenzldehydes,[38] oxidation of 2-(2-hydroxyethyl)-5-isopropylbenzyl alcohol,[39] 2-hydroxymethyl-1-(2'-hydroxyphenyl)naphthalene[40] with non-activated manganese dioxide or pyridinium chlorochromate, or by reaction of an alcohol and triethyl orthoformate catalyzed by aluminum chloride followed by catalytic hydrogenation.[41] Other authors also prepared isochroman derivatives by refluxing diols in 50% aq. H_3PO_4 [42] or 85% H_3PO_4 [43] in toluene in good- to very good yields.

Isochromanes have been synthesized from acetals of phenethyl alcohols, followed by cyclization utilizing a Lewis acid or *via* oxa-Pictet-Spengler reaction from 2-phenylethanol and an aldehyde or ketone with a fatty acid as catalyst.[26,44,45] In addition, some authors used reduction of oximes followed by intramolecular cyclization,[46] condensation of 3,4-dimethoxyphenethyl alcohol with aromatic aldehydes,[2-4] or cyclization with *p*-toluenesulfonic acid.[47]

In a search for new approaches to the synthesis of isochromanes, we found that they can be obtained from the corresponding ethyl- (or methyl-) 2-acylphenylacetates **3** in very good yields. In our previous reports, we have shown that different ethyl 2-acyl-4,5-dimethoxyphenylacetates can be obtained from ethyl 3,4-dimethoxyphenylacetate and carboxylic acids in the presence of P_2O_5.[48] We found that the acylation reaction in phenylacetic acid esters takes place if electron-donating groups exist on a third position of the aromatic ring in order to activate it. According to this procedure, we obtained the corresponding alkyl 2-acylphenylacetates from esters of 3-methoxy- and 3,4-dimethoxyphenylacetic acid, with very good yields (Scheme 1, Table 1).



Scheme 1

Table 1. Synthesis of alkyl 2-acylphenyl acetates

No	R	R1	Yield* %	mp °C	No.	R	R1	Yield * %	mp °C
3a	OMe	Me	84	94a	3i	OMe	2,4- Cl2C6H3	82	98-99.5
3b	H	Me	77	84-87	3j	OMe	Bn	62	73-75a
3c	OMe	Et	79	90-94	3k	OMe	p-MeOC6H4CH2	75	83-86
3d	OMe	i-Bu	86	71-74a	3l	OMe	3,4-(MeO)2C6H3CH2	80	127-129b
3e	OMe	n-C15H31	90	82-83	3m	OMe	naphth-2-yl	80	54-55
3f	OMe	Ph	90	78-79a	3n	OMe	CHPh2	60	111.5-116
3g	OMe	3,4-(MeO)2C6H3	83	113-114	3o	H	CHPh2	65	117.5-119
3h	OMe	3,4,5-(MeO)3C6H2	74	128-130					

* The yields were for products isolated after recrystallization.
[a] mp and spectroscopic data are given in ref. 48. [b] mp 125-129°C in ref. 46.

The next step in this synthesis of isochromanes was the reduction of the alkyl 2-acylphenylacetates, **3**. We reduced the alkyl 2-acylphenylacetates to the corresponding diols using sodium borohydride-methanol system. Sodium borohydride under normal conditions does not reduce ester groups but reduces (in moderate- to good yields) double bonds in compounds, where the double bond is cross-conjugated with two carboxylic groups or where the double bond is conjugated with one carboxylic and one phenyl group.[49] In these cases the reduction was carried out by using equimolar quantities of sodium borohydride and the ester in ethanol or isopropyl alcohol to react first at 0-5ºC and then at RT.

We found that the reduction of the alkyl 2-acylphenylacetates **3** with sodium borohydride in methanol easily led to the corresponding 2-hydroxy-4,5-dimethoxyphenyl-ethanols **4** with 85-90% yields (Table 2). Their cyclization in the presence of a catalytic amount of PTSA for 30 min at RT in dichloromethane afforded the corresponding isochromanes **5** (Table 2).

Table 2. Reduction of alkyl 2-acylphenylacetates to 2-hydroxy-4,5-dimethoxyphenyl-ethanols followed by cyclization with PTSA to isochromanes

2-Hydroxy-4,5-dimethoxyphenyl ethanols					Isochromanes		
No.	**R**	**R[1]**	**Yield %**	**mp °C**	**No.**	**Yield %**	**mp °C**
4a	OMe	Me	94	105-105.5	**5a**	92	Oil
4b	H	Me	97	87-88	**5b**	93	Oil
4c	OMe	Et	95	Oil	**5c**	90	Oil
4d	OMe	i-Bu	92	49-50	**5d**	90	118-120
4e	OMe	n-$C_{15}H_{31}$	95	72-75	**5e**	92	73-75
4f	OMe	Ph	90	110-110.5	**5f**	88	73-75[a]
4g	OMe	3,4-$(MeO)_2C_6H_3$	92	100-105	**5g**	85	80-82[b]
4h	OMe	3,4,5-$(MeO)_3C_6H_2$	93	86-90	**5h**	85	99-101
4i	OMe	2,4- $Cl_2C_6H_3$	95	151-153	**5i**	87	Oil
4j	OMe	Bn	89	107-108	**5j**	90	Oil
4k	OMe	*p*-$MeOC_6H_4CH_2$	88	78-79	**5k**	92	Oil
4l	OMe	$(MeO)_2C_6H_3CH_2$	85	134-136	**5l**	90	69-72[c]
4m	OMe	2-naphthyl	85	124-125	**5m**	90	128-129
4n	OMe	$CHPh_2$	88	107-109	**5n**	88	144-154
4o	H	$CHPh_2$	92	112.5-114	**5o**	90	91-91.5

[a] mp 74-75°C in ref. 40; [b] mp 80-81°C in ref. 16; [c] mp 69-71°C in refs. 25,46

In conclusion, six-membered oxygen-containing heterocycles with the isochromane skeleton were synthesized, as a type of compound found in nature and among bioactive compounds of interest. We have developed a convenient method for their synthesis by simple reduction of ethyl (or methyl) 2-acylphenylacetates in a sodium borohydride-methanol system, followed by cyclization in a less acidic medium with a catalytic amount of PTSA. A variety of substituents at the 1-position of the isochromane skeleton was introduced readily by changing the carboxylic acids. Some of the so-obtained isochromanes are O-analogues of isoquinoline alkaloids: **5l,** the O-analogue of papaverine, **5g** and **5h** of cryptostiline II and III, **5a** of salsolidine.

Experimental Section

General Procedures. Melting points were determined on a Boetius hot-stage apparatus and are uncorrected. IR spectra were measured (KBr pellets or film) with a Perkin-Elmer 1750 IFTS. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker Avance DRX250 or Bruker Avance II+ 600 instrument, using $CDCl_3$ as solvent. Chemical shifts (δ, ppm) were referenced to TMS (δ=0.00 ppm) as an internal standard and coupling constants are indicated in Hz. All the NMR spectra were taken at RT (295 K). MS were recorded on a Jeol JMS-D300 spectrometer (70 eV). Elemental analyses were performed in the analytical laboratory at the Faculty of Chemistry, University of Plovdiv. TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates, using chloroform/diethyl ether/*n*-hexane: 6/3/1 as chromatographic system. Merck silica gel 60 (0.063-0.2mm) was used for chromatographic filtration.

Preparation of alkyl 2-acyl-phenylacetates (Table 1, 3a-o). General procedure.[48]
To a solution of ethyl (or methyl) 3,4-dimethoxyphenylacetate (10 mmol) and the corresponding carboxylic acid **2** (10 mmol) in 1,2-dichloroethane (30 mL) was added P_2O_5 (5g). The suspension was stirred vigorously for 8-10 h at RT, then water was added dropwise to the cooled mixture. The organic layer was washed with water (50 ml), Na_2CO_3 (30 ml), water (50 ml) and dried (Na_2SO_4), then the combined extracts were dried (Na_2SO_4) and filtered through a short column with neutral Al_2O_3. The products, after the removal of the solvent, were purified by recrystallization with MeOH. Compounds **3a,d,f,j,l** were previously characterized.[46,48] The spectroscopic data of new compounds follow.
Methyl 2-(2-acetyl-5-methoxyphenyl)acetate (3b). ^{1}H-NMR (600 MHz): 2.55 (s, 3H), 3.71 (s, 3H), 3.86 (s, 3H), 3.93 (s, 2H), 6.76 (d, 1H, *J*=2.2), 6.87 (dd, 2H, *J*=8.6, 2.3), 7.86 (d, 1H, *J*=8.7); ^{13}C-NMR (150.9 MHz): 199.1, 171.8, 162.1, 139.6, 132.8, 118.8, 111.9, 60.7, 55.4, 51.9, 40.9. MS *m/z*: 236 (M+).
Ethyl 2-(4,5-dimethoxy-2-propionylphenyl)acetate (3c). ^{1}H-NMR (600 MHz): 1.18 (t, 3H, *J*=7.2), 1.28 (t, 3H, *J*=7.2), 2.95 (q, 2H, *J*=7.3), 3.89 (s, 2H), 3.93 (s, 6H), 4.17 (q, 2H, *J*=7.1), 6.73 (s, 1H), 7.32 (s, 1H); ^{13}C-NMR (150.9 MHz): 202.0, 171.8, 151.5, 147.3, 129.3, 129.1, 115.3, 112.8, 60.7, 56.2, 55.9, 40.3, 33.6, 14.3, 8.5. MS *m/z*: 280 (M^+).
Methyl 2-(4,5-dimethoxy-2-palmitoylphenyl)acetate (3e). ^{1}H-NMR (600 MHz): 0.88 (t, 3H, *J*=7.1), 1.21-1.36 (m, 24H), 1.67-1.71 (m, 2H), 2.89 (t, 2H, *J*=7.5), 3.71 (s, 3H), 3.92 (s, 2H), 3.94 (s, 6H), 6.73 (s, 1H), 7.32 (s, 1H); ^{13}C-NMR (150.9 MHz): 201.8, 172.3, 151.6, 147.4, 129.3, 129.1, 115.4, 112.9, 56.2, 55.9, 51.9, 40.5, 40.2, 31.9, 29.7, 29.6, 29.4, 24.5, 22.7, 14.2. MS *m/z*: 462 (M^+).
Ethyl 2-(2-(3,4-dimethoxybenzoyl)-4,5-dimethoxyphenyl)acetate (3g). ^{1}H-NMR (250 MHz): 3.68 (s, 3H), 3.85 (s, 3H), 3.87 (s, 6H), 3.94 (s, 3H), 4.12 (s, 2H), 6.94 (s, 1H), 7.06 (s, 1H), 7.10-7.20 (m, 3H); ^{13}C-NMR (62.9 MHz): 196.3, 171.2, 152.8, 149.5, 148.3, 142.2, 133.4, 130.6, 130.3, 128.1, 114.6, 113.4, 107.8, 61.3, 56.2, 56.1, 38.3, 14.1. MS *m/z*: 388 (M^+).

Ethyl 2-(4,5-dimethoxy-2-(3,4,5-trimethoxybenzoyl)phenyl)acetate (3h). ^{1}H-NMR (600 MHz): 1.18 (t, 3H, *J*=7.1), 3.78 (s, 2H), 3.83 (s, 3H), 3.86 (s, 6H), 3.94 (s, 3H), 3.97 (s, 3H), 4.08 (q, 2H, *J*=7.1), 6.87 (s, 1H), 6.98 (s, 1H), 7.06 (s, 2H); ^{13}C-NMR (150.9 MHz): 196.1, 171.5, 152.9, 150.9, 146.9, 142.2, 133.4, 130.3, 128.0, 114.5, 113.4, 107.7, 60.9, 56.3, 56.2, 56.1, 38.7, 14.2. MS *m/z*: 418 (M^+).

Ethyl 2-(2-(2,4-dichlorobenzoyl)-4,5-dimethoxyphenyl)acetate (3i). ^{1}H-NMR (250 MHz): 1.25 (t, 3H, *J*=7.2), 3.71 (s, 3H), 3.95 (s, 3H), 3.96 (s, 2H), 4.15 (q, 2H, *J*=7.1), 6.82 (d, 2H, *J*=6.1), 7.26-7.46 (m, 3H); ^{13}C-NMR (62.9 MHz): 194.2, 171.4, 152.4, 147.2, 137.7, 136.6, 132.6, 130.8, 130.5, 130.0, 128.3, 127.1, 115.5, 115.3, 60.8, 56.1, 39.8, 14.2. MS *m/z*: 397 (M^+).

Ethyl 2-(4,5-dimethoxy-2-(2-(4-methoxyphenyl)acetyl)phenyl)acetate (3k). ^{1}H-NMR (250 MHz): 1.25 (t, 3H, *J*=7), 3.77 (s, 3H), 3.86 (s, 3H), 3.87 (s, 2H), 3.91 (s, 3H), overlapped with 4.15 (s, 2H), 4.14 (q, 2H, *J*=7), 6.71 (s, 1H), 6.83-6.87 (m, 2H), 7.14-7.17 (m, 2H), 7.36 (s, 1H); ^{13}C-NMR (62.9 MHz): 199.0, 171.6, 158.4, 151.5, 147.1, 130.3, 129.7, 128.7, 127.0, 115.2, 114.1, 113.3, 60.6, 56.1, 55.9, 55.2, 46.8, 40.2, 14.2. MS *m/z*: 372 (M^+).

Ethyl 2-(2-(2-naphthoyl)-4,5-dimethoxyphenyl)acetate (3m). ^{1}H-NMR (250 MHz): 1.09 (t, 3H, *J*=7.1), 3.77 (s, 3H), 3.84 (s, 2H), 3.98 (s, 3H), overlapped with 4.00 (q, 2H, *J*=7.1), 6.90 (s, 1H), 7.01 (s, 1H), 7.53-7.63 (m, 2H), 7.88-7.94 (m, 4H), 8.23 (s, 1H); ^{13}C-NMR (62.9 MHz): 197.2, 171.5, 150.9, 146.9, 135.6, 135.3, 132.3, 132.2, 130.5, 129.5, 128.4, 128.2, 128.1, 127.7, 126.7, 125.6, 114.5, 113.7, 60.7, 56.1, 55.8, 38.7, 14.1. MS *m/z*: 378 (M^+).

Ethyl 2-(2-(2,2-diphenylacetyl)-4,5-dimethoxyphenyl)acetate (3n). ^{1}H-NMR (600 MHz): 1.19 (t, 3H, *J*=7.1), 3.66 (s, 3H), 3.89 (s, 3H), 3.91 (s, 2H), 4.10 (q, 2H, *J*=7.1), 5.89 (s, 1H), 6.69 (s, 1H), 7.23-7.33 (m, 11H); ^{13}C-NMR (150.9 MHz): 199.1, 171.7, 151.5, 147.0, 139.5, 130.3, 129.2, 128.8, 128.7, 127.1, 115.2, 113.7, 61.7, 60.7, 56.0, 55.8, 40.3, 14.2. MS *m/z*: 418 (M^+).

Methyl 2-(2-(2,2-diphenylacetyl)-5-methoxyphenyl)acetate (3o). ^{1}H-NMR (600 MHz): 3.59 (s, 3H), 3.80 (s, 3H), 3.94 (s, 2H), 5.96 (s, 1H), 6.74 (d, 1H, *J*=2.4), 6.76 (dd, 1H, *J*=8.7, 2.6), 7.23-7.25 (m, 6H), 7.29-7.31 (m, 4H), 7.88 (d, 1H, *J*=8.7); ^{13}C-NMR (150.9 MHz): 199.1, 171.8, 162.1, 139.6, 138.5, 132.8, 129.3, 129.2, 128.6, 127.0, 118.8, 111.9, 60.7, 55.4, 51.9, 40.9. MS *m/z*: 374 (M^+).

Preparation of 2-hydroxy-phenyl ethanols (Table 2, 4a-o). Typical procedure

To solution of 1 mmol of the corresponding ethyl (methyl) 2-acyl-4,5-dimethoxy-phenylacetates **3** in 15 mL methanol, $NaBH_4$ (2 mmol, 0.1 g) was added portionwise. The solution was stirred 30 min at room temperature, than the solvent was removed under vacuum. Water (30 mL) was added to the residue and the solution was extracted with CH_2Cl_2 (3x20 mL), then the combined extracts were dried (Na_2SO_4) and filtered through a short column with silica gel. The products, after evaporation of the solvent, were obtained with 85-90 % yields.

2-(2-(1-Hydroxyethyl)-4,5-dimethoxyphenyl)ethanol (4a). IR ν (KBr, cm^{-1}): 3410, 3248 (OH), 1608 (ArH); ^{1}H-NMR (600 MHz): 1.48 (dd, 1H, *J*=6.4), 2.75 (dt, 1H, *J*=14.2, 5.1), 2.94 (ddd, 1H, *J*=14.2, 8.6, 5.8), 3.31 (br s, 2H, OH), 3.69 (ddd, 1H, *J*=10.3, 8.7, 5.1), 3.82-3.85 (m, 1H), overlapped with 3.85 (s, 3H, OCH_3), 3.87 (s, 3H), 5.05 (q, 1H, *J*=6.4), 6.65 (s, 1H), 6.99 (s,

1H); ^{13}C-NMR (150.9 MHz): 148.2, 147.7, 136.0, 128.5, 112.8, 108.6, 65.4, 63.5, 55.9 (2 OCH_3), 34.6, 23.3. MS *m/z*: 208 (M^+-H_2O).

1-(2-(2-Hydroxyethyl)-4-methoxyphenyl)ethanol (4b). IR ν (KBr, cm^{-1}): 3276 (br, OH), 1608 (ArH); ^{1}H-NMR (600 MHz): 1.49 (d, 3H, *J*=6.5), 2.80 (dt, 1H, *J*=14.0, 5.1), 2.99 (ddd, 1H, *J*=14.2, 8.7, 5.7), 3.16 (br s, 1H, OH), 3.31 (br s, 1H, OH), 3.74 (ddd, 1H, *J*=10.3, 8.8, 5.0), 3.78 (s, 3H), 3.87-3.90 (m, 1H), 5.05 (q, 1H, *J*=6.5), 6.71 (d, 1H, *J*=2.7), 6.78 (dd, 1H, *J*=8.6, 2.7), 7.38 (d, 1H, *J*=8.6); ^{13}C-NMR (150.9 MHz): 158.9, 138.3, 135.8, 126.7, 115.4, 112.0, 65.2, 63.6, 55.2, 35.0, 23.0. MS *m/z*: 178 (M^+-H_2O).

1-(2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl)propan-1-ol (4c). IR ν (film, cm^{-1}): 3260 (br, OH), 1606 (ArH); ^{1}H-NMR (250 MHz): 0.93 (t, 3H, *J*=7.4), 1.69-1.96 (m, 2H), 2.03 (br s, 1H, OH), 2.75 (dt, 1H, *J*=14.1, 5.4), 2.96 (ddd, 1H, *J*=14.0, 8.1, 5.9), 3.02 (br s, 1H, OH), 3.70 (ddd, 1H, *J*=10.3, 8.2, 5.3), 3.79-3.88 (m, 1H) overlapped with 3.86 (s, 6H, 2xOCH_3), 4.75 (dd, 1H, *J*=7.3, 6.4), 6.65 (s, 1H), 6.94 (s, 1H); ^{13}C-NMR (62.9 MHz): 148.2, 147.7, 135.0, 128.8, 112.8, 109.1, 71.3, 63.6, 55.9, 34.7, 30.4, 10.7. MS *m/z*: 222 (M^+-H_2O).

1-(2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl)-3-methylbutan-1-ol (4d). IR ν (KBr, cm^{-1}): 3333 (br, OH), 1608 (ArH); ^{1}H-NMR (250 MHz): 0.95 (dd, 6H, *J*=6.4, 2.8), 1.43-1.54 (m, 1H), 1.69-1.84 (m, 1H), 2.02 (br s, 1H, OH), 2.75 (dt, 1H, *J*=14.2, 5.2), 2.82 (br s, 1H, OH), 2.97 (ddd, 1H, *J*=14.1, 8.3, 5.8), 3.71 (ddd, 1H, *J*=10.3, 8.4, 5.1), overlapped with 3.85 (s, 3H, OCH_3), 3.87 (s, 3H), 4.93 (dd, 1H, *J*=8.4, 5.0), 6.65 (s, 1H), 6.95 (s, 1H); ^{13}C-NMR (62.9 MHz): 148.1, 147.7, 135.6, 128.4, 112.8, 109.1, 67.8, 63.6, 55.9, 46.6, 34.6, 25.1, 23.4, 22.3. MS *m/z*: 250 (M^+-H_2O).

1-(2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl)hexadecan-1-ol (4e). IR ν (KBr, cm^{-1}): 3517, 3357 (OH), 1607 (ArH); ^{1}H-NMR (600 MHz): 0.88 (t, 3H, *J*=7.1), 1.25 (br s, 26H), 1.28-1.39 (m, 1H), 1.42-1.48 (m, 1H), 1.68-1.73 (m, 1H), 1.80 (br s, 1H, OH), 1.82-1.88 (m, 1H), 2.71 (br s, 1H, OH), 2.77 (dt, 1H, *J*=14.1, 5.3), 2.97 (ddd, 1H, *J*=14.1, 8.3, 5.8), 3.73 (ddd, 1H, *J*=10.3, 8.3, 5.2), 3.84-3.89 (m, 1H), overlapped with 3.86 (s, 3H, OCH_3) and 3.87 (s, 3H, OCH_3), 4.84 (dd, 1H, *J*=7.9, 5.8), 6.65 (s, 1H), 6.95 (s, 1H); ^{13}C-NMR (150.9 MHz): 148.2, 147.8, 135.4, 128.6, 112.8, 109.1, 69.9, 63.7, 55.9, 37.6, 34.7, 31.9, 29.7, 29.4, 26.4, 22.7, 14.2. MS *m/z*: 404 (M^+-H_2O).

2-(2-(Hydroxy(phenyl)methyl)-4,5-dimethoxyphenyl)ethanol (4f). IR ν (KBr, cm^{-1}): 3495, 3317 (OH), 1608 (ArH); ^{1}H-NMR (600 MHz): 2.73 (dt, 1H, *J*=14.3, 5.3) 2.92 (ddd, 1H, *J*=13.8, 8.2, 5.3), 3.69 (s, 3H), 3.64-3.68 (m, 1H), overlapped with 3.69 (s, 3H, OCH_3), 3.77-3.80 (m, 1H), 3.84 (s, 3H), 5.96 (s, 1H), 6.65 (s, 1H), 6.66 (s, 1H), 7.23-7.33 (m, 5H); ^{13}C-NMR (150.9 MHz): 148.5, 147.4, 134.9, 129.6, 128.2, 127.1, 126.5, 112.8, 111.5, 72.2, 63.5, 55.9, 55.8, 34.7. MS *m/z*: 270 (M^+-H_2O).

2-(2-((3,4-Dimethoxyphenyl)(hydroxyl)methyl)-4,5-dimethoxyphenyl)ethanol (4g). IR ν (KBr, cm^{-1}): 3536, 3485 (OH), 1607 (ArH); ^{1}H-NMR (600 MHz): 1.85 (br s, 1H, OH), 2.77 (dt, 1H, *J*=14.2, 5.1), 2.81 (br s, 1H, OH), 2.96 (ddd, 1H, *J*=13.9, 8.4, 5.3), 3.69-3.74 (m, 1H), overlapped with 3.72 (s, 3H, OCH_3), 3.82-3.88 (m, 1H), overlapped with 3.83 (s, 3H, OCH_3) and 3.86 (s, 3H, OCH_3) and 3.87 (s, 3H, OCH_3), 5.95 (s, 1H), 6.69 (s, 1H), 6.7 (s, 1H), 6.81-6.83 (m,

3H); ^{13}C-NMR (150.9 MHz): 148.8, 148.5, 148.0, 147.4, 136.0, 135.0, 129.5, 118.8, 112.8, 111.3, 110.8, 109.9, 71.9, 63.6, 56.1, 55.9, 55.8, 34.7. MS *m/z*: 330 (M^+-H_2O).

2-(2-(Hydroxy(3,4,5-trimethoxyphenyl)methyl)-4,5-dimethoxyphenyl)ethanol (4h). IR ν (KBr, cm^{-1}): 3495, 3322 (OH), 1592 (ArH); ^{1}H-NMR (600 MHz): 1.72 (br s, 1H, OH), 2.40 (br s, 1H, OH), 2.72 (dt, 1H, *J*=16.1, 3.6), 3.05 (ddd, 1H, *J*=15.4, 8.8, 6.0), 3.69 (s, 3H), 3.80-3.85 (m, 1H) overlapped with 3.82 (s, 6H, 2xOCH_3) and 3.84 (s, 3H, OCH_3), 3.88-3.92 (m, 1H) overlapped with 3.91 (s, 3H, OCH_3), 5.60 (s, 1H), 6.29 (s, 1H), 6.53 (s, 2H), 6.66 (s, 1H); ^{13}C-NMR (150.9 MHz): 153.2, 147.9, 147.2, 137.8, 128.6, 126.1, 111.2, 109.7, 106.0, 103.6, 79.6, 60.9, 56.2, 56.1, 56.0, 55.9, 28.3. MS *m/z*: 360 (M^+-H_2O).

2-(2-((2,4-Dichlorophenyl)(hydroxyl)methyl)-4,5-dimethoxyphenyl)ethanol (4i). IR ν (KBr, cm^{-1}): 3506, 3347 (OH), 1608 (ArH); ^{1}H-NMR (600 MHz): 2.78 (dt, 1H, *J*=14.4, 3.9), 2.82 (br s, 1H, OH), 3.20 (ddd, 1H, *J*=14.8, 10.2, 5.0), 3.62 (s, 3H), 3.74 (td, 1H, *J*=10.1, 3.7), 3.85 (s, 3H), 3.99 (tt, 1H, *J*=8.3, 4.1), 4.54 (br s, 1H, OH), 6.15 (s, 1H), 6.32 (s, 1H), 6.69 (s, 1H), 7.32 (dd, 1H, *J*=8.3, 2.1), 7.34 (d, 1H, *J*=2.1), 7.70 (d, 1H, *J*=8.3); ^{13}C-NMR (150.9 MHz): 148.8, 147.6, 139.2, 133.5, 133.0, 130.2, 129.3, 128.9, 127.0, 112.7, 110.3, 68.5, 63.6, 55.9, 55.8, 34.5. MS *m/z*: 338 (M^+-H_2O).

1-(2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl)-2-phenylethanol (4j). IR ν (KBr, cm^{-1}): 3305 (br, OH), 1608 (ArH); ^{1}H-NMR (600 MHz): 2.21 (s, 1H, OH), 2.69 (dt, 1H, *J*=14.1, 5.8), 2.82 (ddd, 1H, *J*=13.9, 7.7, 6.1), 2.88 (br s, 1H, OH), 3.03 (dq, 1H, *J*=13.6, 6.7), 3.64 (ddd, 1H, *J*=10.4, 7.7, 5.8), 3.71 (dt, 1H, *J*=11.6, 4.6), 3.85 (s, 3H), 3.86 (s, 3H), 5.06 (dd, 1H, *J*=8.1, 5.3), 6.62 (s, 1H), 7.00 (s, 1H), 7.17 (d, 1H, *J*=6.9), 7.23-7.19 (m, 1H), 7.27 (dd, 1H, *J*=10.6, 4.0); ^{13}C-NMR (150.9 MHz): 148.2, 147.7, 138.4, 134.3, 129.5, 128.5, 128.2, 126.5, 112.7, 109.3, 71.2, 63.6, 56.0, 55.9, 44.7, 34.6. MS *m/z*: 284 (M^+-H_2O).

1-(2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanol (4k). IR ν (KBr, cm^{-1}): 3312 (br, OH), 1610 (ArH); ^{1}H-NMR (250 MHz): 2.51 (br s, 2H, OH), 2.68 (dt, 1H, *J*=11.9, 5.7), 2.82 (dt, 1H, *J*=13.8, 6.8), 2.96 (dd, 2H, *J*=6.5, 2.8), 3.59-3.68 (m, 1H), 3.71 (dd, 1H, *J*=10.1, 4.2), 3.76 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 5.02 (dd, 1H, *J*=7.3, 6.0), 6.62 (s, 1H), 6.80 (d, 2H, *J*=8.6), 7.03 (d, 2H, *J*=8.6), 7.10 (s, 1H); ^{13}C-NMR (62.9 MHz): 158.2, 148.1, 147.6, 134.3, 130.4, 130.3, 128.2, 113.8, 112.6, 109.2, 71.2, 63.5, 55.9, 55.8, 55.2, 43.7, 34.6. MS *m/z*: 314 (M^+-H_2O).

2-(3,4-Dimethoxyphenyl)-1-(2-(2-hydroxyethyl)-4,5-dimethoxyphenyl)ethanol (4l). IR ν (KBr, cm^{-1}): 3348 (br, OH), 1605 (ArH); ^{1}H-NMR (600 MHz): 2.20 (br s, 1H, OH), 2.69 (dt, 1H, *J*=14.1, 5.7), 2.80-2.85 (ddd, 1H, *J*=14.1, 7.5, 6.2), 2.86 (br s, 1H, OH), 2.95 (dd, 1H, *J*=13.7, 5.2), 3.01 (dd, 1H, *J*=13.7, 8.1), 3.67-3.69 (m, 1H), 3.75 (dd, 1H, *J*=11.1, 5.3), 3.80 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.05 (dd, 1H, *J*=8.1, 5.2), 6.63 (s, 1H), 6.66 (d, 1H, *J*=1.7), 6.74 (dd, 1H, *J*=8.1, 1.8), 6.78 (d, 1H, *J*=8.1), 7.02 (s, 1H); ^{13}C-NMR (150.9 MHz): 148.8, 148.3, 147.8, 147.7, 134.4, 130.9, 128.4, 121.4, 112.7, 111.2, 109.3, 71.3, 63.6, 56.0, 55.9, 55.8, 44.3, 34.7. MS *m/z*: 344 (M^+-H_2O).

2-(2-(Hydroxy-(naphth-2-yl)-methyl)-4,5-dimethoxyphenyl)ethanol (4m). IR ν (KBr, cm^{-1}): 3263 (br, OH), 1606 (ArH); ^{1}H-NMR (600 MHz): 2.76 (dt, 1H, *J*=14.3, 5.1), 2.95 (ddd, 1H,

J=13.8, 8.4, 5.1), 3.09 (br s, 1H, OH), 3.62 (s, 3H), 3.69 (ddd, 1H, *J*=10.0, 8.5, 4.6), 3.82 (s, 3H, OCH_3), overlapped with 3.80-3.84 (m, 1H), 4.42 (br s, 1H, OH), 6.10 (s, 1H), 6.65 (s, 1H), 6.66 (s, 1H), 7.30 (dd, 1H, *J*=6.7, 1.7), 7.44-7.46 (m, 2H), 7.74 (d, 1H, *J*=8.5), 7.77-7.81 (m, 2H), 7.90 (s, 1H); ^{13}C-NMR (150.9 MHz): 148.6, 147.5, 140.8, 134.7, 133.2, 132.6, 129.8, 128.1, 127.9, 127.6, 126.1, 125.8, 125.0, 124.7, 112.8, 111.7, 72.2, 63.6, 55.9, 55.8, 34.7. MS *m/z*: 320 (M^+-H_2O).

1-(2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl)-2,2-diphenylethanol (4n). IR ν (KBr, cm^{-1}): 3492, 3359 (OH), 1601 (ArH); ^{1}H-NMR (600 MHz): 1.68 (br s, 1H, OH), 2.11 (br s, 1H, OH), 2.59 (dt, 1H, *J*=14.1, 5.6), 2.83 (ddd, 1H, *J*=13.8, 7.7, 5.9), 3.61-3.65 (m, 1H), 3.67-3.71 (m, 1H), 3.74 (s, 3H), 3.81 (s, 3H), 4.36 (d, 1H, *J*=9.2), 5.61 (d, 1H, *J*=9.2), 6.53 (s, 1H), 6.82 (s, 1H), 7.04-7.12 (m, 5H), 7.25 (t, 1H, *J*=7.4), 7.35 (t, 2H, *J*=7.7), 7.44 (d, 2H, *J*=7.8); ^{13}C-NMR (150.9 MHz): 148.2, 147.3, 141.6, 141.2, 132.6, 129.1, 128.5, 128.2, 126.9, 126.3, 112.3, 110.3, 72.4, 63.6, 58.8, 55.8, 55.7, 34.6. MS *m/z*: 360 (M^+-H_2O).

1-(2-(2-Hydroxyethyl)-4-methoxyphenyl)-2,2-diphenylethanol (4o). IR ν (KBr, cm^{-1}): 3496, 3360 (OH), 1599 (ArH); ^{1}H-NMR (600 MHz): 2.07 (br s, 1H, OH), 2.15 (br s, 1H, OH), 2.65-2.69 (m, 1H), 2.88-2.93 (m, 1H), 3.61-3.65 (m, 1H), 3.67-3.71 (m, 1H), 3.80 (s, 3H), 4.41 (d, 1H, *J*=10), 5.59 (d, 1H, *J*=10), 6.74 (d, 1H, *J*=2.4), 6.76 (dd, 1H, *J*=8.7, 2.6), 7.20-7.26 (m, 7H), 7.30 (t, 3H, *J*=7.6), 7.88 (d, 1H, *J*=8.7); ^{13}C-NMR (150.9 MHz): 162.1, 139.6, 138.5, 132.8, 129.3, 129.2, 128.8, 128.6, 127.0, 126.3, 118.8, 111.9, 60.8, 55.4, 51.8, 40.9, 29.7. MS *m/z*: 330 (M^+-H_2O).

Synthesis of 1-substituted isochromanes 5. Typical procedure

A catalytic amount of *p*-toluenesulfonic acid monohydrate (PTSA) was added to a solution of 1 mmol of the corresponding 2-hydroxy-4,5-dimethoxyphenylethanols **4** in dichloromethane. The solution was stirred 30 min at room temperature. Then the solution was filtered through a short column of silica gel. The products, after evaporation of the solvent, were obtained with 88-90 % yield.

6,7-Dimethoxy-1-methylisochroman (5a). ^{1}H-NMR (250 MHz): 1.51 (d, 3H, *J*=6.5), 2.56-2.64 (m, 1H), 2.91-2.95 (m, 1H), 3.72-3.82 (m, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 4.10-4.18 (m, 1H), 4.79 (q, 1H, *J*=6.5), 6.56 (s, 1H), 6.60 (s, 1H); ^{13}C-NMR (62.9 MHz): 148.8, 146.9, 128.9, 128.2, 111.6, 107.6, 79.7, 62.3, 55.9, 55.8, 28.9, 14.6. MS *m/z*: 208 (M+); Anal. calcd. for $C_{12}H_{16}O_3$: C 69.21, H 7.74. Found: C 69.33, H 7.86.

6-Methoxy-1-methylisochroman (5b). ^{1}H-NMR (250 MHz): 1.51 (d, 3H, *J*=6.5), 2.56-2.64 (m, 1H), 2.81-2.95 (m, 1H), 3.72-3.84 (m, 1H), 3.85 (s, 3H), 4.78 (q, 1H, *J*=6.5), 6.61-7.12 (m, 3H) 3.85 (s, 3H), 3.86 (s, 3H), 4.10-4.18 (m, 1H), 4.79 (q, 1H, *J*=6.5), 6.56 (s, 1H), 6.60 (s, 1H); ^{13}C-NMR (62.9 MHz): 159.6, 136.6, 128.3, 127.2, 113.4, 110.9, 79.4, 62.3, 55.8, 28.9, 14.5. MS *m/z*: 178 (M+); Anal. Calcd. for $C_{11}H_{14}O_2$: C 74.13, H 7.92. Found: C 74.23, H 7.80.

6,7-Dimethoxy-1-ethylisochroman (5c). ^{1}H-NMR (250 MHz): 1.01 (t, 3H, *J*=7.3), 1.82 (dd, 1H, *J*=14.9, 7.3), 1.97 (ddd, 1H, *J*=14.4, 7.4, 3.3), 2.61 (dt, 1H, *J*=15.9, 3.6), 2.93 (ddd, 1H, *J*=14.9, 9.4, 5.3), 3.77 (ddd, 1H, *J*=11.2, 9.6, 3.8), 3.87 (s, 3H), 3.88 (s, 3H), 4.14 (ddd, 1H,

J=11.2, 5.3, 3.7), 4.66 (dd, 1H, *J*=7.8, 2.5), 6.58 (s, 1H), 6.62 (s, 1H); ^{13}C-NMR (62.9 MHz): 147.8, 147.3, 130.1, 126.1, 111.4, 107.8, 63.2, 55.9, 55.8, 28.8, 28.7, 9.5. MS *m/z*: 222 (M+); Anal. Calcd. for $C_{13}H_{18}O_3$: C 70.24, H 8.16. Found: C 70.36, H 8.28.

6,7-Dimethoxy-1-isobutylisochroman (5d). ^{1}H-NMR (250 MHz): 0.98 (dd, 6H, *J*=15.6, 6.6), 1.53 (ddd, 1H, *J*=14.2, 10.0, 2.9), 1.75 (ddd, 1H, *J*=14.2, 10.3, 3.8), 1.91-2.04 (m, 1H), 2.62 (dt, 1H, *J*=16.0, 4.3), 2.74-2.88 (m, 1H), 2.88-3.01 (m, 1H), 3.72 (ddd, 1H, *J*=12.4, 7.5, 4.1), 3.84 (s, 3H), 3.85 (s, 3H), 4.08 (dt, 1H, *J*=11.2, 4.8), 4.71 (dd, 1H, *J*=9.5, 1.8), 6.51 (s, 1H), 6.58 (s, 1H); ^{13}C-NMR (62.9 MHz): 147.4, 147.3, 131.0, 125.8, 111.5, 107.9, 73.6, 62.8, 56.0, 55.9, 45.3, 28.6, 24.5, 24.0, 21.5. MS *m/z*: 250 (M+); Anal. Calcd. for $C_{15}H_{22}O_3$: C 71.97, H 8.86. Found: C 72.08, H 8.98.

6,7-Dimethoxy-1-pentadecyl-isochroman (5e). ^{1}H-NMR (600 MHz): 0.88 (t, 3H, *J*=7.0), 1.25-1.31 (m, 23H), 1.32-1.39 (m, 1H), 1.43-1.51 (m, 2H), 1.73-1.79 (m, 1H), 1.85-1.89 (m, 1H), 2.60 (dt, 1H, *J*=15.8, 3.7), 2.90 (ddd, 1H, *J*=15.1, 9.4, 5.3), 3.74 (ddd, 1H, *J*=11.1, 9.5, 3.8), 3.85 (s, 3H), 3.86 (s, 3H), 4.11 (ddd, 1H, *J*=11.2, 5.2, 3.8), 4.67 (dd, 1H, *J*=8.3, 2.2), 6.55 (s, 1H), 6.59 (s, 1H); ^{13}C-NMR (150.9 MHz): 147.4, 130.5, 126.0, 111.4, 107.9, 75.6, 63.2, 56.0, 55.9, 36.2, 32.0, 29.8, 29.7, 25.4, 22.7, 14.2. MS *m/z*: 404 (M+); Anal. Calcd. for $C_{26}H_{44}O_3$: C 77.18, H 10.96. Found: C 77.28, H 11.08.

6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)isochroman (5h). ^{1}H-NMR (600 MHz): 2.72 (dt, 1H, *J*=16.0, 3.8), 3.06 (ddd, 1H, *J*=15.2, 9.2, 5.7), 3.70 (s, 3H), 3.82 (s, 6H), 3.85 (s, 3H), 3.89 (s, 3H, OCH_3), overlapped with 3.88-3.91 (m, 1H), 4.19 (ddd, 1H, *J*=11.3, 5.4, 3.9), 5.60 (s, 1H), 6.29 (s, 1H), 6.53 (s, 2H), 6.66 (s, 1H); ^{13}C-NMR (150.9 MHz): 153.2, 148.0, 147.2, 137.8, 137.7, 128.6, 126.1, 111.2, 109.7, 106.0, 79.6, 64.0, 60.8, 56.1, 56.0, 55.9, 28.4. MS *m/z*: 360 (M+); Anal. Calcd. for $C_{20}H_{24}O_6$: C 66.65, H 6.71. Found: C 66.78, H 6.82.

6,7-Dimethoxy-1-(2,4-dichlorophenyl)isochroman (5i). ^{1}H-NMR (250 MHz): 2.74 (dt, 1H, *J*=15.9, 3.7), 3.02 (ddd, 1H, *J*=8.4, 7.5, 5.5), 3.88 (s, 3H), 3.92 (s, 3H, OCH_3), overlapped with 3.90-3.96 (m, 1H), 4.11 (dt, 1H, *J*=11.2, 4.9), 6.14 (s, 1H), 6.21 (s, 1H), 6.65 (s, 1H), 7.09 (d, 1H, *J*=8.4), 7.18 (dd, 2H, *J*=8.4, 2.0), 7.46 (d, 1H, *J*=2.0); ^{13}C-NMR (62.9 MHz): 148.1, 147.5, 138.5, 134.9, 134.3, 131.6, 129.3, 127.7, 127.3, 126.2, 111.3, 109.0, 74.4, 63.7, 55.9, 55.8, 28.2. MS *m/z*: 339 (M+); Anal. Calcd. for $C_{17}H_{16}Cl_2O_3$: C 60.19, H 4.75. Found: C 60.30, H 4.87.

6,7-Dimethoxy-1-benzylisochroman (5j). ^{1}H-NMR (250 MHz): 2.64 (dt, 2H, *J*=15.8, 4.2), 2.81 (ddd, 1H, *J*=13.6, 8.4, 4.8), 3.10 (dd, 1H, *J*=14.3, 7.9), 3.15 (dd, 1H, *J*=14.2, 4.8), 3.72 (m, 1H), overlapped with 3.76 (s, 3H, OCH_3), 3.85 (s, 3H), 4.15 (dt, 1H, *J*=11.4, 4.8), 4.96 (dd, 1H, *J*=11.4, 4.8), 6.47 (s, 1H), 6.59 (s, 1H), 7.24-7.31 (m, 5H); ^{13}C-NMR (62.9 MHz): 147.6, 147.2, 138.8, 130.1, 129.6, 128.3, 126.3, 111.5, 108.3, 76.3, 62.8, 56.2, 55.9, 42.8, 28.6. MS *m/z*: 284 (M+); Anal. Calcd. for $C_{18}H_{20}O_3$: C 76.03, H 7.09. Found: C 76.14, H 7.21.

6,7-Dimethoxy-1-(4-methoxybenzyl)isochroman (5k). ^{1}H-NMR (250 MHz): 2.61 (dt, 1H, *J*=15.8, 4.2), 2.80 (ddd, 1H, *J*=13.6, 8.4, 4.9), 3.01 (dd, 1H, *J*=14.3, 7.9), 3.11 (dd, 1H, *J*=14.2, 4.8), 3.68-3.76 (m, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H), 4.14 (dt, 1H, *J*=11.3, 4.8), 4.91 (dd, 1H, *J*=7.5, 5.0), 6.49 (s, 1H), 6.59 (s, 1H), 6.82 (s, 1H), 6.86 (s, 1H), 7.17 (s, 1H), 7.20 (s, 1H); ^{13}C-NMR (62.9 MHz): 158.1, 147.5, 147.1, 130.8, 130.5, 129.6, 126.2, 113.7, 111.4, 108.3,

76.4, 62.9, 55.9, 55.2, 41.9, 28.7. MS *m/z*: 314 (M+); Anal. Calcd. for $C_{19}H_{22}O_4$: C 72.59, H 7.05. Found: C 72.71, H 7.17.

6,7-Dimethoxy-1-(naphth-2-yl)isochroman (5m). ^{1}H-NMR (600 MHz): 2.77 (dt, 1H, *J*=16.1, 4.1), 3.08 (ddd, 1H, *J*=14.9, 8.9, 5.4), 3.60 (s, 3H), 3.89 (s, 3H), 3.93 (ddd, 1H, *J*=11.3, 9.0, 4.1), 4.17 (ddd, 1H, *J*=11.2, 5.2, 4.5), 5.84 (s, 1H), 6.26 (s, 1H), 6.69 (s, 1H), 7.41 (dd, 1H, *J*=8.5, 1.6), 7.46 (t, 1H, *J*=3.4), 7.48 (t, 1H, *J*=3.4), 7.76 (s, 1H), 7.81 (s, 1H), 7.82-7.84 (m, 2H); ^{13}C-NMR (150.9 MHz): 147.9, 147.3, 139.5, 133.3, 133.1, 128.8, 128.4, 128.2, 128.1, 127.7, 126.6, 126.2, 126.1, 126.0, 111.2, 109.7, 79.3, 63.6, 55.9, 55.8, 28.4. MS *m/z*: 320 (M+); Anal. Calcd. for $C_{21}H_{20}O_3$: C 78.73, H 6.29. Found: C 78.85, H 6.40.

6,7-Dimethoxy-1-benzhydrylisochroman (5n). ^{1}H-NMR (600 MHz): 2.55 (dt, 1H, *J*=15.7, 4.3), 2.58-2.65 (m, 1H), 3.54 (s, 3H), 3.66 (ddd, 1H, *J*=11.3, 8.3, 4.2), 3.82 (s, 3H), 4.05 (dt, 1H, *J*=9.9, 4.5), 4.46 (d, 1H, *J*=6.1), 5.48 (d, 1H, *J*=6.1), 6.15 (s, 1H), 6.51 (s, 1H), 7.13 (t, 1H, *J*=7.3), 7.20 (t, 3H, *J*=7.6), 7.25-7.30 (m, 4H),7.34 (d, 2H, *J*=7.6); ^{13}C-NMR (150.9 MHz): 147.3, 146.5, 142.8, 141.2, 129.5, 129.3, 128.4, 121.9, 126.8, 126.4, 126.1, 111.1, 109.0, 77.5, 62.6, 57.3, 55.7, 55.5, 28.5. MS *m/z*: 360 (M+); Anal. Calcd. for $C_{24}H_{24}O_3$: C 79.97, H 6.71. Found: C 79.86, H 6.83.

6-Methoxy-1-benzhydrylisochroman (5o). ^{1}H-NMR (600 MHz): 2.50 (dt, 1H, *J*=15.9, 3.2), 2.62-2.67 (m, 1H), 3.64 (ddd, 1H, *J*=11.0, 10.1, 3.5), 3.74 (s, 3H), 4.06 (ddd, 1H, *J*=11.1, 5.1, 3.5), 4.52 (d, 1H, *J*=4.4), 5.48 (d, 1H, *J*=4.4), 6.53 (d, 1H, *J*=2.3), 6.63 (dd, 1H, *J*=8.6, 2.6), 6.85 (d, 1H, *J*=8.6), 7.09 (t, 1H, *J*=7.2), 7.14 (t, 2H, *J*=7.4), 7.18-7.23 (m, 3H), 7.30 (t, 2H, *J*=7.6), 7.40 (d, 2H, *J*=7.7); ^{13}C-NMR (150.9 MHz): 157.7, 143.1, 140.8, 136.3, 130.0, 129.2, 129.1, 128.2, 127.6, 126.7, 126.3, 126.0, 113.1, 112.0, 78.1, 63.3, 56.9, 55.1, 29.4. MS *m/z*: 330 (M+); Anal. Calcd. for $C_{23}H_{22}O_2$: C 83.60, H 6.71. Found: C 83.72, H 6.82.

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