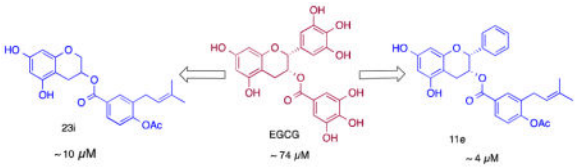
Published in final edited form as:
J Org Chem. 2013 August 16; 78(16): 7859–7884. doi:10.1021/jo401027r.

Synthesis and Structure activity relationships of EGCG Analogues, A Recently Identified Hsp90 Inhibitor

Anuj Khandelwal, **Jessica Hall**, and **Brian S. J. Blagg**
Department of Medicinal Chemistry, 1251 Wescoe Hall Drive, Malott 4070, The University of Kansas, Lawrence, Kansas 66045-7563, United States

Brian S. J. Blagg: bblagg@ku.edu

Abstract



Epigallocatechin-3-gallate (EGCG), the principal polyphenol isolated from green tea, was recently shown to inhibit Hsp90, however structure-activity relationships for this natural product have not yet been produced. Herein, we report the synthesis and biological evaluation of EGCG analogues to establish structure-activity relationships between EGCG and Hsp90. All four rings as well as the linker connecting the C- and the D-rings were systematically investigated, which led to the discovery of compounds that inhibit Hs90 and display improvement in efficacy over EGCG. Anti-proliferative activity of all the analogues was determined against MCF-7 and SKBr3 cell lines and Hsp90 inhibitory activity of four most potent analogues was further evaluated by western blot analyses and degradation of Hsp90-dependent client proteins. Prenyl substituted aryl ester of 3,5-dihydroxychroman-3-ol ring system was identified as novel scaffold that exhibit Hsp90 inhibitory activity.

INTRODUCTION

Heat shock protein 90 (Hsp90) is ubiquitously expressed and essential for the folding of many nascent polypeptides.[1–4] As a molecular chaperone, Hsp90 regulates the conformational maturation of more than 200 client proteins, including steroid hormone receptors, Akt, Raf-1 and the Src-family kinases.[5] Many of these Hsp90-dependent client proteins regulate signaling pathways associated with cell survival, cell proliferation, as well as cellular transformation and oncogenesis.[6, 7] Prior studies have shown that Hsp90 is upregulated in malignant cells and that Hsp90 inhibitors accumulate more efficiently in tumor cells than in the surrounding normal tissue.[8] Consequently, Hsp90 inhibition represents a multi-faceted approach toward the treatment of cancer. [9, 10]

Correspondence to: Brian S. J. Blagg, bblagg@ku.edu.
Supporting Information: ^{1}H and ^{13}C spectral data of all compounds is available free of charge via the Internet at http://pubs.acs.org/.

Natural products represent a class of diverse structures that contribute to clinically relevant therapeutics.[11, 12] They serve as lead compounds and/or scaffolds upon which molecules with improved efficacy and drugability can be pursued.[13] Structure-activity relationships studies on natural products have led to the identification of structurally less complex molecules that are clinically used today. (−)-Epigallocatechin-3-gallate (EGCG (**1**)) is a polyphenolic natural product that can be isolated from green tea leaves and has been shown to inhibit Hsp90's function and induce the degradation of client proteins; including telomerase, multiple kinases and the aryl hydrocarbon receptor (AhR).[14–16] Palermo and coworkers demonstrated through affinity chromatography that (−)-EGCG binds to amino acids 538-728 within the Hsp90 C-terminus and inhibits AhR-mediated transcription through interactions with Hsp90[17]. Unfortunately, the exact mechanism by which EGCG inhibits the Hsp90 protein folding machinery remains undetermined. Similar to EGCG, novobiocin (**2**) also binds Hsp90 within amino acids 538-728 and represents another naturally occurring C-terminal inhibitor (Figure 1).[4, 18] The bioavailability and lipophilicity exhibited by EGCG along with its metabolically susceptible functionalities and modest efficacy against various cancer cell lines make EGCG a poor lead compound for development.[19] However, only two natural products are known to inhibit the Hsp90 C-terminus, and therefore EGCG was pursued as a probe to further investigate the mechanism by which C-terminal inhibitors modulate the Hsp90 protein folding machinery.

EGCG is well known for its antioxidant activity both in vitro and in vivo, which also leads to epimerization and/or dimerization (Scheme 1) and contributes to its low efficacy and metabolic instability.[20, 21] Epimerization of the methine hydrogen leads to formation of the thermodynamically more stable anti product, GCG (Figure 2), whose activity against Hsp90 has not been investigated. Studies by Suzuki and co-workers have shown that incorporation of hydroxyl groups onto the B-ring can lead to epimerization at C-2, whereas O-methylated derivatives at the 4–position prevent epimerization.[22] Therefore, the design of new EGCG analogues must take into account these prior studies in an effort to produce stable derivatives that are not prone to oxidation/epimerization.[23–28] To probe EGCG's structure-activity relationships with Hsp90, three series of analogues (Scheme 2) were pursued; (I) 3′, 4′,5′-trimethoxy groups were incorporated into the B-ring, (II) compounds omitting substituents on the B-ring were prepared, and (III) compounds lacking the B-ring were also constructed. Furthermore, the phenols on the A-ring were converted to methyl ethers for biological evaluation and finally, the gallic acid moiety (D-ring) of EGCG was replaced with various aryl acids for elucidation of additional SAR trends. These aryl acids were chosen to probe the effect of substitution at the 3- and 4-position of the D-ring and to incorporate optimized novobiocin appendages to evaluate their potential for overlapping binding modes.[29–31]

RESULTS AND DISCUSSION

Synthesis of the A-, B- and D-ring modified compounds (**10a–j** & **11a–j**) are described in Scheme 3. Prior work by Li and coworkers provided rapid access towards preparation of the flavon-3-ol core, enlisting the use of a silica/sulfuric acid catalyst to couple electron rich phenols (**4a–b**) with substituted cinnamyl alcohols (**5a–b**), which worked surprisingly well and led to various substituted A- and B-ring analogues (**6a–d**).[32] Dihydroxylation of the

resulting alkenes (**6a–d**) with catalytic osmium tetroxide and excess N-methylmorpholine-N-oxide gave the corresponding diol's, **7a–d**.[33] Various methods have been reported for cyclization and construction of the benzopyran core, however, stereochemical control at the 2,3-ring junction is dependent upon substituents on the B-ring. Therefore, cylization of diol's **7a–d** to furnish the 2,3-dihydrobenzopyran core in a stereoselective manner was pursued via two steps. Treatment of **7a–d** with trimethylorthoacetate in the presence of catalytic pyridinium *p*-toluenesulfonate, led to formation of the corresponding orthoesters, which upon the addition of 10% boron trifluoride diethyl etherate produced the desired cyclic products. Without purification, the cyclized products were subjected to solvolysis conditions to furnish alcohols **8a–d** in high yields and with the anti configuration. [34] The 2,3-syn products, **9a–d**, were established by Dess-Martin oxidation of the secondary alcohols (**8a–d**) to the corresponding ketones, which underwent subsequent reduction with L–selectride to give syn products, **9a–d**, respectively.[35] These flavon-3-ol moieties (**9a–d**) served as late stage intermediates to incorporate additional substitutions onto the D-ring. Aryl acids **12–16** (Scheme 2) were chosen as replacements for the metabolically susceptible gallic ester moiety of EGCG and also represent optimized side chains identified from prior studies with the other Hsp90 C-terminal inhibitor, novobiocin.[36, 37] Coupling of the alcohols (**9a–d**) with aromatic acids **12–16** enlisting 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) and 4-dimethylaminopyrine (DMAP) gave the corresponding esters, **10a–t**.[38] Hydrogenolysis of **10k–t** with palladium/carbon and hydrogen gas gave **11a–j** in high yield.

Upon preparation of the A-, B- and the D-ring modified EGCG analogues (**10a–j** and **11a–j**), these compounds were evaluated against MCF-7 and SKBr3 breast cancer cell lines for determination of their anti-proliferative activities (Table 1). The SKBr3 (estrogen receptor negative, Her2 overexpressing) and the MCF-7 (estrogen receptor positive) cell lines were chosen due to the fact that both Her2 and the estrogen receptor are Hsp90-dependent client proteins. Four of the D-ring analogues that contain two methoxy groups on the A-ring and no substituents on the B-ring (**10a–d**) were inactive against both MCF-7 and SKBr3 cell lines and only compound **10e** manifested significant anti-proliferative activity with an IC_{50} value of 25.35 ± 5.25 μM against MCF-7 and 36.1 ± 2.51 μM against SKBr3 cell lines. Similar trends were observed for compounds (**10f–j**) containing the 3,4,5-trimethoxy substituents on the B-ring, as only **10j** was found to be potent and exhibits an IC_{50} value of 19.48 ± 2.5 μM and 24.87 ± 3.29 μM against MCF-7 and SKBr-3 cell lines, respectively.

Analogues **11a–e** that contain phenols on the A-ring were also evaluated and found to be more potent when compared to EGCG and analogues **10a–j**. Incorporation of a methoxy group at the *meta*- and the *para*- positions of the D-ring (**11b** and **11c**) did not alter activity as compared to unsubstituted analogue, **11a**. Compound **11e** was found to be the most potent of this series and displayed an IC_{50} value of 3.99 ± 1.4 μM against the MCF-7 cell line. In contrast, compounds with 3-,4-,5-trimethoxy groups on the B-ring (**11f–j**) were less active when compared to analogues without substitution on the B-ring (**11a–e**). This data suggests that substitutions on the B-ring are detrimental to activity, whereas replacement of the gallate ester moiety with prenyl benzoate enhances potency. In addition, the MCF-7 cell line was found to be more sensitive than the SKBr3 cell line upon administration of these analogues. Furthermore, the anti isomer of **11e** was synthesized and evaluated and found to

be less active (IC_{50} = 33.7 ± 1.8 against MCF-7 cell line), confirming that syn-stereochemistry is important for inhibitory activity.

Simultaneous with the above studies, synthesis of analogues that lack the B-ring were commenced by the treatment of 3,5-dibenzyloxyphenol (Scheme 4) with allyl bromide in the presence of potassium carbonate to give allyl ether **18a**.[39] 3,3-Rearrangement of the O-allylated product (**18a**) gave **19a** in high yield.[40] Dihydroxylation of the resulting olefin afforded diol **20a**. Unfortunately, attempts to cyclize via the orthoester were unsuccessful as only the 5-membered product was formed. Therefore, an alternative strategy for the cyclization of **20a** was pursued. Treatment of the primary alcohol present in **20a** with *p*-toluenesulfonyl chloride resulted in formation of the corresponding *p*-toluenesulfonic ester, which underwent intramolecular cyclization upon exposure to potassium carbonate to give a 1:1 mixure of 5- and 6-membered rings that were separated by silica gel chromatography. Subsequent coupling of **22a** with various substituted benzoic acids produced the requisite esters, which underwent hydrogenolysis to afford **23a–i**, respectively.

Upon construction of analogues that lack the B-ring, each phenol on the A-ring was systematically investigated. Therefore, derivatives **23i–s** that contain only one hydroxyl at either the 5- or the 7-position were pursued similar to that described above. Allylation of the phenol (**17**) gave ally ether, **18b**. 3,3-Rearrangement of the allyl ether (**18b**) gave a mixture of two regioisomers, **19b** and **19c**, which upon dihydroxylation and subsequent ring closure gave **22b** and **22c,** respectively.

Results from the anti-proliferative studies with compounds **23a–s** are summarized in Table 2. In addition to previously investigated substituents, the effect of hydroxyl substitution on the D-ring was also explored. Many of the compounds were found to be more efficacious than EGCG itself. This data suggests that methoxy substitution on the D-ring is more beneficial than the naturally occurring phenols, which corresponds to an overall pattern represented by O-alkyl substitutions at the 3′-position are more active than those at the 4′-position. Data also suggests that aryl and prenyl substitution on the D-ring produce enhanced efficacy, as **23i** manifested an IC_{50} value of 10.66 ± 1.09 μM against MCF-7 cells and 23.15 ± 0.25μM against SKBr3 cells. The IC_{50} values of compounds containing only one phenolic group at the 7-position on the A-ring resulted in decreased activity, except for **23n.** Similarly, compounds with 5-hydroxyl substitution on the A-ring also resulted in decreased activity with the exception of **23r**, which manifested enhanced activity and an IC_{50} value of 21.6 ± 2.55 against the MCF-7 cell line. Similar to the most active analogue produced from the B-ring series, **11e**, the most active analogue identified in this series was **23i** (IC_{50} = 10 μM in MCF-7 cell line), which also incorporates the prenylated benzoate side chain.

In an effort to further investigate the A-ring, the free phenols were replaced with methyl ethers. 5,7-Dimethoxychroman-3-ol (**26**) was synthesized in two steps using a gold(III)-mediated procedure as described by Zhangjie and coworkers (Scheme 5).[41] Commencing with commercially available 3,5-dimethoxyphenol and enlistment of epichlorohydrin and sodium hydride, produced oxirane **25**, which underwent 6-endo cyclization to yield **26** upon treatment with a gold(III) chloride/silver trifluormethanesulfonate catalyst. Upon

construction of the chroman-3-ol core (**26**), subsequent coupling with various substituted aryl acids to furnish the corresponding esters, **27a–m**. The final products **28a–e** were prepared via hydrogenolysis of **27i–m**.

In addition, investigation of the linker connecting the B- and D-rings was pursued. The ester linker was replaced with an amide functionality. These amide-based analogues were prepared from previously synthesized alcohol **26**, which was transformed into azide **29** via Mitsunobu conditions with diisopropyl azodicarboxylate, triphenylphosphine and diphenylphosphoryl azide, followed by Staudinger reduction with triphenylphosphine to afford amine **30** (Scheme 6).[42] Subsequent coupling of amine **30** with the optimal aryl acids gave the corresponding amides, **31a–d**. [37]

Results from anti-proliferative studies for compounds lacking the B-ring are summarized in Table 3. The 3-methoxy substituted compound **28b** was found to be the most active compound against the MCF-7 and the SKBr3 cell lines, and manifested IC_{50} values 0.775 ± .02 μM and 0.88 ± 0.06 μM, respectively. Increasing the length of side chain resulted in decreased activity for compound **27h**. The hydroxyl group was found to be more beneficial at the 4′-position in lieu of the 3′-position. Unfortunately, the combination of 3-methoxy and 4-hydroxyl substitutions on the D-ring (**28e**) did not improve anti-proliferative activity. Once again, MCF-7 cells exhibited greater sensitivity to these compounds. The IC_{50} values for **27d** and **27e** (Table 4) correlate directly with prior studies using novobiocin, suggesting a beneficial effect for inclusion of aryl or prenyl group on the D-ring. The linker between the B- and D-ring was also evaluated and replacement of the ester with an amide (**31a–d**) was found detrimental.

After determination of anti-proliferative activity for EGCG analogues, four representative examples were chosen for subsequent western blot analyses to confirm Hsp90 inhibition, based on each class of scaffold investigated. Since Hsp90 inhibition results in the induction of client protein degradation via the ubiquitin-proteasome pathway, immunoblots are used to confirm Hsp90 inhibitory activity. As shown in Figure 2, 11e, 27e and 10e induced the degradation of Hsp90 client proteins Her2, Raf and pAkt at concentrations that mirror the concentration needed to exhibit anti-proliferative activity, thereby linking Hsp90 inhibition to cell viability. Analog **27b** failed to induce client protein degradation, demonstrating that this compound manifests anti-proliferative activity through a mechanism independent of Hsp90 inhibition. However a related compound containing the prenylated benzoate side chain, **27e**, was shown to exhibit Hsp90 inhibitory activity. Further investigation of **11e** at increasing concentrations demonstrated client protein degradation in a dose-dependent manner, while actin levels remained the same. Actin is not an Hsp90-dependent protein and is therefore unaffected by Hsp90 inhibition. Similar to other Hsp90 C-terminal inhibitors, the level of Hsp90 was unaffected.

CONCLUSIONS

In summary, we have synthesized and evaluated the first structure-activity relationships between EGCG and Hsp90 (Figure 3). The results obtained suggest that phenolic groups on the A-ring are beneficial for Hsp90 inhibition, while phenolic substituents on the D-ring are

detrimental. The inclusion of a novobiocin-derived prenyl benzoate was found to be a suitable replacement for the gallic acid moiety present on EGCG, and suggests that both novobiocin and the EGCG may bind similarly to the Hsp90 C-terminus. Results from these studies have led to the development of analogue **11e**, which exhibits a 18-fold improvement over EGCG and can serve as a probe for further biological investigations.

EXPERIMENTAL SECTION

All reactions were performed in oven-dried glassware under argon atmosphere unless otherwise stated. Dichloromethane (DCM), tetrahydrofuran (THF), and toluene were passed through a column of activated alumina prior to use. Anhydrous methanol, acetonitrile, dimethylformamide (DMF), and dimethoxyethane (DME) were purchased and used without further purification. (−)-EGCG (≥95%) was purchased from Sigma-Aldrich and used as obtained. Flash column chromatography was performed using silica gel (40 – 63 μm particle size). The ^{1}H (500 MHz and 400 MHz) and ^{13}C-NMR (proton 125 MHz and 100 MHz) spectra were recorded on 500 MHz and 400 MHz spectrometer. Data are reported as p = pentet, q = quartet, t = triplet, d = doublet, s = singlet, bs = broad singlet, m = multiplet; coupling constant (s) in Hz. Infrared spectra were obtained using FT/IR spectrometer. High resolution mass spectral data were obtained on a Electrospray Ionization spectra were acquired on a LCT Premier, time of flight mass spectrometer. The purity of all compounds was determined to be >95% by ^{1}H and ^{13}C NMR spectra, unless otherwise noted.

3,5-Bis(benzyloxy)phenol (**4b**) and (E)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-ol (**5b**) and 3-(benzyloxy)phenol (**17**) were prepared following literature procedures.[32, 43–44] Reactions of phenols (**4a–b**) with cinnamyl alcohols (**5a–b**) to yield compounds **6a–d** were accomplished via the protocol described by Li et. al. [32]

2-Cinnamyl-3,5-dimethoxyphenol (6a)

A solution of 3,5-dimethoxy phenol (2.3 g, 14.91 mmol) and cinnamyl alcohol (2.0 g, 14.91 mmol) in a solvent mixture of dichloromethane (30 mL) and carbon disulfide (30 mL) was treated with 25% H_2SO_4/SiO_2 catalyst (2.4 g, 5.96 mmol) at rt. The resulting mixture was stirred for 4 h and then filtered through a plug of SiO_2 (40 – 63 μm particle size). Solvent was removed and the residue purified by flash chromatography (SiO_2, 1:9 EtOAc/Hexanes) to give **6a** (1.735 g, 43.15 %) as an amorphous light yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 2H), 7.30 (dd, *J* = 7.2, 1.7 Hz, 2H), 7.23 – 7.17 (m, 1H), 6.48 (dt, *J* = 16.0, 1.7 Hz, 1H), 6.34 (dt, *J* = 15.9, 6.3 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 6.11 (d, *J* = 2.3 Hz, 1H), 5.06 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.56 (d, *J* = 1.6 Hz, 1H), 3.55 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 159.0, 155.9, 137.4, 130.6, 128.6 (2), 128.6, 128.5, 127.3, 126.3, 106.1, 93.9, 91.8, 56.0, 55.5, 26.4; IR (KBr)ν_{max} 3367, 1614, 1596, 1454, 1423, 1201, 1147, 1097, 1053, 811, 736, 692 cm^{-1}; HRMS (ESI+) *m/z* [M+H^{+}] calcd for $C_{17}H_{19}O_3$, 271.1334, found 271.1336.

3,5-Bis(benzyloxy)-2-cinnamylphenol (6b)

A solution of 3,5-bis(benzyloxy)phenol (3.3 g, 9.98 mmol) and cinnamyl alcohol (1.34 g, 9.98 mmol) in a solvent mixture of dichloromethane (20 mL) and carbon disulfide (20 mL)

was treated with 25% H_2SO_4/SiO_2 catalyst (1.59g, 3.99 mmol) at rt. The resulting mixture was stirred for 4 h and then filtered through a plug of SiO_2 (40 – 63 μm particle size). Solvent was removed and the residue purified by flash chromatography (SiO_2, 1:8 EtOAc/ Hexanes) to give **6b** (1.425 g, 33.7 %) as amorphous light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 15H), 6.53 – 6.44 (m, 1H), 6.39 – 6.30 (m, 1H), 6.29 (d, *J* = 2.2 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 1H), 5.03 (m, 5H), 3.60 (dd, *J* = 6.5, 1.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 158.1, 155.9, 137.5, 137.2, 137.0 (2), 128.8 (2), 128.7 (2), 128.6 (3), 128.5, 128.2, 128.0, 127.8, 127.5 (2), 127.3, 126.3 (2), 107.0, 95.3, 93.9, 70.5, 70.3, 26.7; IR (KBr)ν_{max} 3419, 3028, 2925, 1618, 1596, 1452, 1436,1375, 1147, 1091, 734, 696 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{29}H_{27}O_3$, 423.1960, found 423.1966.

(E)-3,5-Dimethoxy-2-(3-(3,4,5-trimethoxyphenyl)allyl)phenol (6c)

A solution of 3,5-dimethoxy phenol (2.06 g, 13.4 mmol) and (E)-3,4,5-trimethoxycinnamyl (3.0 g, 13.4 mmol) in a solvent mixture of dichloromethane (26 mL) and carbon disulfide (26 mL) was treated with 25% H_2SO_4/SiO_2 catalyst (2.2g, 5.36 mmol) at rt. The resulting mixture was stirred for 4 h and then filtered through a plug of SiO_2 (40 – 63 μm particle size). Solvent was removed and the residue purified by flash chromatography (SiO_2, 1:2 EtOAc/Hexanes) to give **6c** as an amorphous light yellow solid: (1.660 g, 39.4 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, 2H), 6.38 (dt, *J* = 15.8, 1.7 Hz, 1H), 6.23 (dt, *J* = 15.8, 6.2 Hz, 1H), 6.14 (d, *J* = 2.4 Hz, 1H), 6.10 (d, *J* = 2.3 Hz, 1H), 5.09 (s, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.54 (dd, *J* = 6.2, 1.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 159.0, 155.9, 153.4 (2), 137.6, 133.2, 130.4, 128.1, 106.1, 103.3 (2), 93.9, 91.7, 61.1, 56.2 (2), 56.0, 55.5, 26.2; IR (KBr)ν_{max} 3379, 3379, 2937, 1620, 1593, 1506, 1421, 1361, 1330, 1201, 1147, 1053, 817, 707 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{20}H_{25}O_6$, 361.1651, found 361.1657.

(E)-3,5-Bis(benzyloxy)-2-(3-(3,4,5-trimethoxyphenyl)allyl)phenol (6d)

A solution 3,5-bis(benzyloxy)phenol (5.2 g, 6.97 mmol) and (E)-3,4,5 trimethoxycinnamyl alcohol (3.81 g, 16.97 mmol) in a solvent mixture of dichloromethane (33 mL) and carbon disulfide (33 mL) was treated with 25% H_2SO_4/SiO_2 catalyst (1.11 g, 2.8 mmol) at rt. The resulting mixture was stirred for 4 h and then filtered through a plug of SiO_2 (40 – 63 μm particle size). Solvent was removed and the residue purified by flash chromatography (SiO_2, 1:3 EtOAc/Hexanes) to give **6d** (1.970 g, 22.6 %) as an amorphous light yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 10H), 6.54 (s, 2H), 6.39 (dt, *J* = 15.8, 1.7 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 6.24 (dt, *J* = 15.8, 6.3 Hz, 1H), 6.19 (d, *J* = 2.3 Hz, 1H), 5.05 (s, 2H), 5.03 (s, 1H), 5.02 (s, 2H), 3.90 – 3.80 (m, 9H), 3.65 – 3.56 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 158.2, 155.9, 153.5 (2), 137.6, 137.3, 137.1, 133.3, 130.7, 128.9 (2), 128.8 (2), 128.7, 128.3 (2), 128.1 (2), 127.8 (2), 127.5, 107.0, 103.4, 95.3, 93.9, 70.6, 70.4, 61.2, 56.3 (2), 26.6. IR (KBr)ν_{max} 3400, 2937, 1614, 1585, 1454, 1328, 1238, 1126, 1001, 736, 696 cm^{-1}. HRMS (ESI+) *m/z* [M+Na$^+$] calcd for $C_{32}H_{32}NaO_6$, 535.2097, found 535.2100.

3-(2-Hydroxy-4,6-dimethoxyphenyl)-1-phenylpropane-1,2-diol (7a)

N-methylmorpholine-N-oxide (1.26g, 10.76 mmol) was added to a solution of **6a** (1.7g, 6.33 mmol) in a solvent mixture of tetrahydrofuran (18 mL) and H_2O (12 mL). The resulting solution was stirred for 15 min at rt before the addition osmium tetraoxide (0.1 mmol, 4% solution in water). The mixture was stirred for 14 h at rt before quenching with 20% of sodium metabisulphite (15 mL). The aqueous layer was extracted with ethyl acetate (3 × 25 mL) and the combined organic layers were washed with saturated sodium chloride solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:2 EtOAc/Hexanes) to afford **7a** (1.55 g, 81 %) as a colorless oil: ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.98 (brs, 1H), 7.43 – 7.37 (m, 2H), 7.37 – 7.32 (m, 3H), 6.17 (d, *J* = 2.4 Hz, 1H), 6.03 (d, *J* = 2.4 Hz, 1H), 4.55 (d, *J* = 6.6 Hz, 1H), 4.04 (ddd, *J* = 7.4, 6.5, 3.8 Hz, 1H), 3.77 (s, 3H), 3.59 (s, 3H), 3.23 (brs, 1H), 2.84 (dd, *J* = 14.8, 3.8 Hz, 1H), 2.74 (dd, *J* = 14.8, 7.4 Hz, 1H), 2.46 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 158.9, 157.5, 140.6, 128.7 (2), 128.5 (2), 127.2, 105.5, 76.9, 76.5, 94.6, 91.5, 55.5 (2), 26.2; IR (KBr)ν_{max} 3348, 2837, 1622, 1593, 1496, 1456, 1338, 1199, 1147, 1105, cm^{-1}; HRMS (ESI−) *m/z* [M−H$^-$] calcd for $C_{17}H_{19}O_5$, 303.1233, found 303.1227.

3-(2,4-Bis(benzyloxy)-6-hydroxyphenyl)-1-phenylpropane-1,2-diol (7b)

N-methylmorpholine-N-oxide (393 mg, 3.36 mmol) was added to a solution of **6a** (0.9g, 2.1 mmol) in a solvent mixture of tetrahydrofuran (9 mL) and H_2O (6 mL). The resulting solution was stirred for 15 min at rt before the addition osmium tetraoxide (0.02 mmol, 4% solution in water). The mixture was stirred for 14 h at rt before quenching with 20% of sodium metabisulphite (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with saturated sodium chloride solution (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:3 EtOAc/Hexanes) to afford **7b** (0.78g, 80.1 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.46 – 7.36 (m, 5H), 7.36 – 7.29 (m, 6H), 7.27 – 7.25 (m, 2H), 7.19 – 7.06 (m, 2H), 6.29 (d, *J* = 2.3 Hz, 1H), 6.21 (d, *J* = 2.4 Hz, 1H), 5.01 (s, 2H), 4.90 – 4.82 (m, 2H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.04 (ddd, *J* = 8.5, 6.7, 3.5 Hz, 1H), 3.32 (s, 1H), 2.93 (dd, *J* = 14.7, 3.5 Hz, 1H), 2.75 (dd, *J* = 14.6, 8.4 Hz, 1H), 2.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 158.0, 157.7, 140.4, 137.1, 137.0, 128.8 (5), 128.7 (2), 128.6, 128.2, 127.8 (4), 127.2 (2), 127.0 (2), 106.3, 96.1, 93.6, 70.3 (2), 26.6; IR (KBr)ν_{max} 3363, 3330 3087, 3031, 1701, 1620, 1598, 1452, 1375, 1147, 1099, 815, 698 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{29}H_{29}O_5$, 457.2015, found 457.2028.

3-(2-Hydroxy-4,6-dimethoxyphenyl)-1-(3,4,5-trimethoxyphenyl)propane-1,2-diol (7c)

N-methylmorpholine-N-oxide (702 mg, 6 mmol) was added to a solution of **6c** (1.350 g, 3.75 mmol) in a solvent mixture of tetrahydrofuran (12 mL) and H_2O (8 mL). The resulting solution was stirred for 15 min at rt before the addition osmium tetraoxide (0.04 mmol, 4% solution in water). The mixture was stirred for 14 h at rt before quenching with 20% of sodium metabisulphite (12 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with saturated sodium chloride solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:10 Acetone/Dichloromethane) to afford **7c** (1.33 g, 90.4 %)

as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 6.54 (s, 2H), 6.14 (d, *J* = 2.4 Hz, 1H), 6.03 (d, *J* = 2.4 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 1H), 3.98 (ddd, *J* = 8.0, 6.1, 3.8 Hz, 1H), 3.84 (s, 6H), 3.82 (s, 3H), 3.75 (s, 3H), 3.62 (s, 3H), 3.44 (brs, 1H), 3.10 – 2.92 (m, 1H), 2.85 (dd, *J* = 14.7, 3.8 Hz, 1H), 2.73 (dd, *J* = 14.7, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 159.0, 157.3, 153.4 (2), 137.6, 136.5, 105.6, 103.9 (2), 94.6, 91.4, 76.9, 76.7, 61.0, 56.3 (2), 55.7, 55.5, 26.5; IR (KBr)ν_{max} 3405, 2932, 1620, 1591, 1498, 1439, 1379, 1218, 1146, 1029, 817 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{20}H_{27}O_8$, 395.1706, found 395.1719.

3-(2,4-Bis(benzyloxy)-6-hydroxyphenyl)-1-(3,4,5-trimethoxyphenyl)propane-1,2-diol (7d)

N-methylmorpholine-N-oxide (444 mg, 3.79 mmol) was added to a solution of **6c** (1.0 g, 2.36 mmol) in a solvent mixture of tetrahydrofuran (7.5 mL) and H_2O (5 mL). The resulting solution was stirred for 15 min at rt before the addition osmium tetraoxide (0.02 mmol, 4% solution in water). The mixture was stirred for 14 h at rt before quenching with 20% of sodium metabisulphite (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with saturated sodium chloride solution (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:10 Acetone/Dichloromethane) to afford **7d** (595 g, 56.7 %) as an amorphous light yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (brs, 1H), 7.47 – 7.28 (m, 10H), 6.54 (s, 2H), 6.28 (d, *J* = 2.3 Hz, 1H), 6.22 (d, *J* = 2.3 Hz, 1H), 5.06 – 4.95 (m, 4H), 4.91 (d, *J* = 3.0 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 1H), 3.77 (d, *J* = 10.2 Hz, 9H), 3.25 (brs, 1H), 3.01 – 2.95 (m, 1H), 2.83 (dd, *J* = 14.6, 8.3 Hz, 1H), 2.74 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 158.1, 157.6, 153.5 (2), 137.1, 137.0, 136.4, 129.0, 128.8, 128.7, 128.5, 128.4, 128.3 (2), 128.1, 127.8, 127.5, 127.4, 127.3, 126.9, 106.3, 103.8 (2), 96.2, 93.7, 70.3 (2), 61.0, 56.3, 56.3, 27.0; IR (KBr)ν_{max} 3446, 2935, 2837, 1591, 1498, 1456, 1328, 1232, 1126, 1004, 736 cm^{-1}; HRMS (ESI−) *m/z* [M−H$^-$] calcd for $C_{32}H_{33}O_8$, 547.2332, found 547.2347.

5,7-Dimethoxy-2-phenylchroman-3-ol (8a)

Trimethyl orthoacetate (2.50 mmol, 300 μl) and pyridinium *p*-toluenesulfonate (9 mg, 0.036 mmol) were added to a solution of **7a** (600 mg, 1.92 mmol) in dichloromethane (36 mL) at rt. The resulting mixture was stirred for 30 min at rt and then cooled to 0 °C before the dropwise addition of borontrifluoride diethyletherate (25 μl, 0.192 mmol). The reaction mixture was warmed to rt and stirred for another 15 min before quenching with aqueous acetone (4 mL). Solvent was removed and the residue was dissolved methanol (32 mL). Potassium carbonate (225 mg, 1.84 mmol) was added and mixture stirred for 6 h at rt. Methanol was removed, water (25 mL) was added and the products extracted with ethyl acetate (2 × 30 mL). Organic layers were combined and washed with saturated sodium chloride solution (60 mL). The organic phase was dried over anhydrous Na_2SO_4 and filtered. Solvent was removed and residue was purified via flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to yield compound **8a** (422 mg, 77.7 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.34 (m, 5H), 6.16 (d, *J* = 2.3 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 1H), 4.79 (d, *J* = 7.8 Hz, 1H), 4.11 (td, *J* = 8.1, 5.5 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.00 (dd, *J* = 16.4, 5.5 Hz, 1H), 2.63 (dd, *J* = 16.4, 8.4 Hz, 1H), 1.71 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 158.8, 155.1, 138.1, 128.8, 128.6, 127.1, 101.4, 93.0, 91.9, 81.7, 68.2, 55.5,

55.4, 27.2; IR (KBr)ν_{max} 3446, 2937, 2839, 1618, 1593, 1496, 1213, 1143, 1120, 1051, 1022, 813, 761, 689 cm^{-1}; HRMS (ESI+) *m/z* [M+H^+] calcd for $C_{17}H_{19}O_4$, 287.1283, found 287.1270.

5,7-Bis(benzyloxy)-2-phenylchroman-3-ol (8b)

Trimethyl orthoacetate (1.48 mmol, 188 μl) and pyridinium p-toluenesulfonate (6 mg, .012 mmol) were added to a solution of **7b** (560 mg, 1.22 mmol) in dichloromethane (24 mL) at rt. The resulting mixture was stirred for 30 min and cooled to 0 °C before the addition of borontrifluoride diethyletherate (18 μl, 0.24 mmol) dropwise. The reaction mixture was warmed to rt and stirred for another 15 min before quenching with aqueous acetone (4 mL). Solvent was removed and the residue was dissolved methanol (18 mL). Potassium carbonate (185 mg, 1.34 mmol) was added and mixture stirred for 6 h at rt. Methanol was removed, water (20 mL) was added and the products extracted with ethyl acetate (2 × 25 mL). The combined organic layers and washed with saturated sodium chloride solution (60 mL). The organic phase was dried over anhydrous Na_2SO_4 and filtered. Solvent was removed and the residue was purified via flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to yield compound **8b** (420 mg, 78.2 %) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.23 (m, 15H), 6.28 – 6.09 (m, 2H), 5.09 – 4.76 (m, 4H), 4.73 (d, *J* = 7.9 Hz, 1H), 4.07 (td, *J* = 8.4, 5.6 Hz, 1H), 3.05 (dd, *J* = 16.5, 5.5 Hz, 1H), 2.65 (dd, *J* = 16.4, 8.6 Hz, 1H); IR (KBr)ν_{max} 3460, 2912, 1617, 1592, 1375, 1145, 1126, 1076, 973, 813, 696 cm^{-1}; HRMS (ESI+) *m/z* [M+H^+] calcd for $C_{29}H_{27}O_4$, 439.1909, found 439.1897.

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-ol (8c)

Trimethyl orthoacetate (1.92 mmol, 250 μl) and pyridinium *p*-toluenesulfonate (10 mg, 0.032 mmol) were added to a solution of **7c** (620 mg, 1.6 mmol) in dichloromethane (32 mL) at rt. The resulting mixture was stirred for 30 min at rt and then cooled to 0 °C before the dropwise addition of borontrifluoride diethyletherate (20 μl, 0.16 mmol). The reaction mixture was warmed to rt and stirred for another 15 min before quenching with aqueous acetone (4 mL). Solvent was removed and the residue dissolved in methanol (32 mL). Potassium carbonate (240 mg, 1.76 mmol) was added and mixture stirred for 6 h at rt. Methanol was removed, water (25 mL) was added and the products extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with saturated sodium chloride solution (50 mL). The organic phase was dried over anhydrous Na_2SO_4 and filtered. Solvent was removed and the residue was purified via flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to yield compound **8c** (460 mg, 77.8) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (s, 2H), 6.15 (d, *J* = 2.3 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 1H), 4.63 (d, *J* = 8.5 Hz, 1H), 4.07 (ddd, *J* = 9.3, 8.5, 5.8 Hz, 1H), 3.87 (s, 6H), 3.85 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.11 (dd, *J* = 16.3, 5.8 Hz, 1H), 2.60 (dd, *J* = 16.3, 9.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 158.9, 155.4, 153.7 (2), 138.2, 133.6, 104.3 (2), 101.9, 93.2, 92.2, 82.4, 68.5, 61.0, 56.3 (2), 55.7, 55.6, 28.0; IR (KBr)ν_{max} 3438, 3001, 2916, 2848, 1622, 1593, 1496, 1622, 2593, 1456, 1361, 1215, 1145, 1120, 810, 667 cm^{-1}; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{20}H_{24}NaO_7$, 399.1420, found 399.1414.

5,7-Bis(benzyloxy)-2-(3,4,5-trimethoxyphenyl)chroman-3-ol (8d)

Trimethyl orthoacetate (0.94 mmol, 120 μl) and pyridinium *p*-toluene sulfonate (4 mg, 0.016 mmol) were added to a solution of **7d** (425 mg, 0.78 mmol) in dichloromethane (16 mL) at rt. The resulting mixture was stirred for 30 min at rt and then cooled to 0 °C before the dropwise addition of borontrifluoride diethyletherate (11 μl, 0.08 mmol) dropwise. The reaction mixture was warmed to rt and stirred for another 15 min before quenching with aqueous acetone (3 mL). Solvent was removed and the residue dissolved in methanol (16 mL). Potassium carbonate (118 mg, 0.85 mmol) was added and mixture stirred for 6 h at rt. Methanol was removed, water (20 mL) was added and the products extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with saturated sodium chloride solution (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and filtered. Solvent was removed and the residue was purified via flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to afford **8d** (265 mg, 63.3 %) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.37 (m, 8H), 7.37 – 7.30 (m, 2H), 6.69 (s, 2H), 6.30 (d, *J* = 2.3 Hz, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 5.11 – 4.96 (m, 4H), 4.65 (d, *J* = 8.5 Hz, 1H), 4.10 (td, *J* = 8.9, 5.8 Hz, 1H), 3.88 (s, 6H), 3.86 (s, 3H), 3.22 (dd, *J* = 16.3, 5.8 Hz, 1H), 2.69 (dd, *J* = 16.4, 9.3 Hz, 1H), 1.82 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 157.9, 155.4, 153.7 (2), 137.1, 137.0 (2), 133.5, 128.8 (2), 128.7 (2), 128.2, 128.1, 127.7, 127.3 (3), 104.3 (2), 102.6, 94.5, 94.1, 82.4, 70.3, 70.1, 68.5, 61.0, 56.3 (2), 28.2; IR (KBr)ν_{max} 3481, 2935, 1618, 1593, 1498, 1460, 1421, 1346, 1145, 1128, 1022, 829, 752, 734 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{32}H_{33}O_7$, 529.2226, found 529.2234.

Transformations of anti-alcohols to syn-alcohols was accomplished via following the procedure described by Tuckmantel et. al.[26]

5,7-Dimethoxy-2-phenylchroman-3-ol (9a)

Obtained as a colorless oil (232 mg, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.45 (dd, *J* = 8.4, 6.7 Hz, 2H), 7.43 – 7.33 (m, 1H), 6.23 (d, *J* = 2.3 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 5.05 (s, 1H), 4.34 (s, 1H), 3.82 (s, 3H), 3.80 (d, *J* = 0.7 Hz, 3H), 3.04 – 2.82 (m, 2H), 1.73 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 159.5, 155.4, 138.4, 129.0, 128.8, 128.3, 126.5, 126.4, 100.4, 93.5, 92.4, 78.8, 66.6, 55.7, 55.6, 28.3. IR (KBr)ν_{max} 3451, 1952, 2923, 2854, 1618, 1593, 1203, 1145, 1118, 1058, 968, 811, 746, 700 cm^{-1}. HRMS (ESI+) *m/z* [M+H$^+$] $C_{17}H_{19}O_4$, 287.1283, found 287.1277.

5,7-Bis(benzyloxy)-2-phenylchroman-3-ol (9b)

Obtained as a pale yellow oil (198 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.65 – 7.31 (m, 15H), 6.23 (d, *J* = 2.3 Hz, 1H), 6.16 (d, *J* = 2.3 Hz, 1H), 5.62 (dt, *J* = 7.6, 4.9 Hz, 1H), 5.13 (d, *J* = 5.3 Hz, 1H), 4.99 (d, *J* = 1.9 Hz, 4H), 3.25 (dd, *J* = 14.6, 4.9 Hz, 1H), 2.89 (dd, *J* = 14.6, 8.0 Hz, 1H); IR (KBr)ν_{max} 3449, 2954, 2842, 1618, 1593, 1498, 1458, 1198, 1145, 1120, 1080, 729 cm^{-1}; HRMS (ESI+) *m/z* [M+Na$^+$] calcd for $C_{29}H_{26}NaO_4$, 461.1729, found 461.1724.

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-ol (9c)

Obtained as a colorless oil (175 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 2H), 6.21 (d, *J* = 2.3 Hz, 1H), 6.12 (d, *J* = 2.4 Hz, 1H), 4.93 (s, 1H), 4.44 – 4.23 (m, 1H), 3.89 (s, 6H), 3.85 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.00 – 2.93 (m, 1H), 2.89 (dd, *J* = 17.3, 4.4 Hz, 1H), 1.88 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 159.4, 155.2, 153.6 (2), 137.5, 134.2, 103.4 (2), 100.4, 93.5, 92.4, 78.8, 66.6, 61.0, 56.3 (2), 55.6, 55.5, 28.2; IR (KBr)ν_{max} 3460, 2997, 2939, 2839, 1620, 1593, 1498, 1456, 1419, 1357, 1330, 1317, 1236, 1197, 1145, 1120, 1081, 939, 815, 729 cm^{-}; HRMS (ESI+) *m/z* [M+H^{+}] calcd for $C_{20}H_{25}O_7$, 377.1600, found 377.1593.

5,7-Bis(benzyloxy)-2-(3,4,5-trimethoxyphenyl)chroman-3-ol (9d)

Obtained as an amorphous pale yellow solid (72 mg, 68 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 10H), 6.75 (s, 2H), 6.32 (d, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 5.06 – 5.00 (m, 4H), 4.97 (s, 1H), 4.30 (d, *J* = 4.3 Hz, 1H), 3.91 (s, 6H), 3.87 (s, 3H), 3.07 (dd, *J* = 17.4, 2.5 Hz, 1H), 2.98 (dd, *J* = 17.3, 4.5 Hz, 1H), 1.78 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 158.5, 155.3, 153.7 (2), 137.2 (2), 137.1, 134.1, 128.8 (2), 128.7 (2), 128.2, 128.1, 127.8 (2), 127.4 (2), 103.4 (2), 101.1, 94.9, 94.4, 78.9, 70.4, 70.2, 66.8, 61.1, 56.4 (2), 28.5; IR (KBr)ν_{max} 3461, 2925, 2834, 1593, 1458, 1375, 1236, 1145, 1126, 1078, 1010, 813, 738, 696 cm^{-1}; HRMS (ESI+) *m/z* [M+H^{+}] calcd for $C_{32}H_{33}O_7$, 529.2226, found 529.2234.

5,7-Dimethoxy-2-phenylchroman-3-yl benzoate (10a)

Benzoyl chloride (8 μl, 0.07 mmol) in dichloromethane (0.5 mL) was added to a solution of **9a** (10 mg, 0.035 mmol) and 4-dimethylaminopyridine (11 mg, 0.08 mmol) in dichloromethane (1mL) at 0 °C. The resulting mixture was stirred for 6 h at rt. Solvent was removed and the residue purified via flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to give the desired ester, **10a**, as an amorphous white solid: (11 mg, 88.8%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 7.56 – 7.47 (m, 3H), 7.41 – 7.28 (m, 5H), 6.27 (d, *J* = 2.3 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 1H), 5.69 (ddd, *J* = 4.1, 3.2, 1.4 Hz, 1H), 5.21 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.15 – 3.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 159.9, 159.1, 155.7, 138.0, 133.1, 130.2, 129.9 (2), 128.5 (3), 128.3 (2), 126.7, 100.4, 93.5, 92.1, 78.0, 68.8, 55.6 (2), 26.1; IR (KBr)ν_{max} 2956, 1935, 2839, 1714, 1593, 1458, 1419, 1361, 1257, 1147, 1124, 1101, 1029, 1006, 846, 813, 769 cm^{-1}; HRMS (ESI+) *m/z* [M+H^{+}] calcd for $C_{24}H_{23}O_5$, 391.1545, found 391.1538.

5,7-Dimethoxy-2-phenylchroman-3-yl 3-methoxybenzoate (10b)

A solution of **9a** (8 mg, 0.027 mmol) in dichloromethane (0.5 mL) was added to a solution of 3-methoxybenzoic acid (8 mg, 0.05 mmol), N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (9.5 mg, 0.05 mmol) and 4-dimethylaminopyridine (6 mg, 0.05 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt and then diluted with dichloromethane (5 mL). The organic phase was washed with saturated sodium bicarbonate solution (2 × 4 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and solvent removed. The residue was purified via flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to give the desired ester, **10a** (9 mg, 76.9%), as

a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.46 (m, 3H), 7.42 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.29 (t, *J* = 2.6 Hz, 1H), 7.27-7.21 (m, 1H), 7.04 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 1H), 5.67 (ddd, *J* = 4.1, 3.2, 1.4 Hz, 1H), 5.21 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.10 – 3.04 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 159.9, 159.6, 159.1, 155.7, 138.0, 131.5, 129.5 (2), 128.5 (2), 128.3, 126.7, 122.3, 119.6, 114.4, 100.3, 93.5, 92.1, 77.9, 69.0, 55.6 (3), 26.0. IR (KBr)ν_{max} 2925, 2837, 1718, 1618, 1593, 1319, 1274, 1220, 1147, 1105, 1041, 958, 910, 811, 752, 696 cm^{-1}. HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{25}H_{25}O_6$, 421.1651, found 421.1642

5,7-Dimethoxy-2-phenylchroman-3-yl 4-methoxybenzoate (10c)

A solution of **9a** (10 mg, 0.035 mmol) in dichloromethane (0.5 mL) was added to a solution 4-methoxybenzoic acid (18 mg, 0.07 mmol), N-(3-Dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (13.5 mg, 0.07 mmol) and 4-dimethylaminopyridine (9 mg, 0.07 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt and then diluted with dichloromethane (5 mL). The organic phase was washed saturated sodium bicarbonate solution (2 × 4 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed. The residue was purified via flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to give the desired ester, **10c**, as a colorless oil (9.5 mg, 81.1%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 2H), 7.57 – 7.49 (m, 2H), 7.36 – 7.30 (m, 2H), 7.28 (d, *J* = 7.0 Hz, 1H), 6.87 – 6.82 (m, 2H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 1H), 5.66 (td, *J* = 3.7, 1.5 Hz, 1H), 5.20 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.08 – 3.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 163.5, 159.8, 159.1, 155.7, 138.1, 131.9 (2), 128.5 (2), 128.2 (2), 126.7, 122.6, 113.7 (2), 100.5, 93.5, 92.1, 78.0, 68.4, 55.6 (3), 26.1; IR (KBr)ν_{max} 2958, 2935, 2839, 1716, 1618, 1255, 1203, 1147, 1101, 1029, 906, 846, 700 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{25}H_{25}O_6$, 421.1651, found 421.1644.

(5,7-Dimethoxy-2-phenylchroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (10d)

A solution of **9a** (10 mg, 0.035 mmol) in dichloromethane (0.5 mL) was added to a solution of 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylic acid (18 mg, 0.07 mmol), N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (13.5 mg, 0.07 mmol) and 4-dimethylaminopyridine (9 mg, 0.07 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt and then diluted with dichloromethane (5 mL). The organic phase was washed with saturated sodium bicarbonate solution (2 × 4mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (SiO_2, 1:7 EtOAc/Hexanes) to give desired ester, **10d** (14 mg, 76%), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.84 (m, 2H), 7.58 – 7.48 (m, 2H), 7.38 – 7.31 (m, 3H), 7.31 – 7.28 (m, 1H), 7.05 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 7.01 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.96 – 6.87 (m, 2H), 6.24 (d, *J* = 2.3 Hz, 1H), 6.11 (d, *J* = 2.3 Hz, 1H), 5.65 (td, *J* = 3.7, 1.5 Hz, 1H), 5.21 (s, 1H), 3.84 (d, *J* = 0.7 Hz, 6H), 3.80 (s, 3H), 3.78 (s, 3H), 3.11 – 3.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 160.2, 159.6, 159.3, 158.9, 155.5, 138.8, 137.9, 132.5, 131.0, 130.2, 129.0 (2), 128.3, 128.1 (2), 126.5, 122.5, 122.0, 115.2, 112.9, 110.5, 100.2, 93.3, 91.9, 77.8, 68.5, 55.8, 55.4 (2), 55.3, 25.8; IR (KBr)ν_{max} 2933,

1716, 1616, 1595, 1298, 1245, 1205, 1147, 1108, 1027, 918, 813, 696, 649 cm^{-1}; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{32}H_{30}NaO_7$, 549.1889, found 549.1863.

5,7-Dimethoxy-2-phenylchroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (10e)

A solution of **9a** (20 mg, 0.07 mmol) in dichloromethane (0.5 mL) was added to a solution of 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoic acid (35 mg, 0.14 mmol), N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (27 mg, 0.14 mmol) and 4-dimethylaminopyridine (25 mg, 0.21 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt, diluted with dichloromethane (5 mL) and washed saturated sodium bicarbonate solution (2 × 4 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed. The residue was purified via flash chromatography (SiO_2, 1:7 EtOAc/Hexanes) to give desired ester, **10e** (20 mg, 55.5 %), as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 2.1 Hz, 1H), 7.76 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.50 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.34 (m, 3H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.11 (d, *J* = 2.3 Hz, 1H), 5.68 – 5.57 (m, 1H), 5.22 – 5.15 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.21 (d, *J* = 7.3 Hz, 2H), 3.05 (d, *J* = 3.5 Hz, 2H), 2.31 (s, 3H), 1.75 (d, *J* = 1.5 Hz, 3H), 1.71 – 1.62 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.10, 155.48, 154.11, 151.35, (2), 136.7 (2), 128.39 (5), 128.30(5), 126.14, 111.17 (2), 104.62, 102.86, 78.23, 66.5, 60.7, 60.4 (2), 31.0, 29.7, 26.8, 20.7; IR (KBr)ν_{max} 2925, 1760, 1716, 1593, 1369, 1201, 1147, 1108, 813 cm^{-1}; HRMS (ESI+) *m/z* [M+H^+] calcd for $C_{31}H_{33}O_7$, 517.2226, found 517.2215.

(2R,3R)-5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl benzoate (10f)

Benzoyl chloride (14 μl, 0.12 mmol) in dichloromethane (0.5 mL) was added to a solution of **9c** (15 mg, 0.04 mmol) and 4-dimethylaminopyridine (24 mg, 0.2 mmol) in dichloromethane 1 (mL) at 0 °C and stirred for 6 h at rt. The solvent was removed and the residue purified via flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to give desired ester, **10f** (17 mg, 89.4%), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.89 (m, 2H), 7.59 – 7.47 (m, 1H), 7.42 – 7.33 (m, 2H), 6.72 (s, 2H), 6.27 (d, *J* = 2.3 Hz, 1H), 6.14 (d, *J* = 2.3 Hz, 1H), 5.69 (td, *J* = 3.5, 1.3 Hz, 1H), 5.09 (t, *J* = 1.0 Hz, 1H), 3.82 (s, 3H), 3.80 (d, *J* = 1.7 Hz, 6H), 3.71 (s, 6H), 3.10 – 3.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 159.6, 158.9, 155.5, 153.1 (2), 137.7, 133.3, 133.1, 130.0, 129.7 (3), 128.3 (2), 103.8 (2), 100.2, 93.4, 92.0, 78.0, 68.5, 60.8, 55.9, 55.4 (2), 26.1; IR (KBr)ν_{max} 2910, 2848, 1718, 1595, 1461, 1271, 1118 cm^{-1}; HRMS (ESI+) *m/z* [M+H^+] calcd for $C_{27}H_{29}O_8$, 481.1862 found 481.1863.

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 3-methoxybenzoate (10g)

A solution of **9c** (12 mg, 0.03mmol) in dichloromethane (0.5 mL) was added to a solution of 3-methoxybenzoic acid (10 mg, 0.06 mmol), N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (13 mg, 0.06 mmol) and 4-dimethylaminopyridine (8 mg, . 06 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt, diluted with dichloromethane (5 mL) and washed with saturated $NaHCO_3$ (2 × 4 mL) solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (SiO_2, 1:3 EtOAc/ Hexanes) to give desired ester product **10g** as a colorless oil (13 mg, 80.4%): ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.56 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.48 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.30 – 7.26 (m, 1H) 7.05 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 6.72 (s, 2H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.13 (d, *J* = 2.4 Hz, 1H), 5.67 (td, *J* = 3.6, 1.3 Hz, 1H), 5.08 (s, 1H), 3.81 (s, 3H), 3.81 – 3.78 (m, 9H), 3.73 (s, 6H), 3.07 (d, *J* = 3.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 159.6, 158.9, 155.5, 153.1 (2), 137.7, 133.3, 131.3, 129.3 (2), 122.0, 119.1, 114.7, 103.8 (2), 100.1, 93.4, 92.0, 78.0, 68.6, 60.8, 55.9 (2), 55.4 (3), 26.0; IR (KBr)ν_{max} 2937, 1718, 1622, 1593, 1498, 1456, 1274, 1218, 1124, 1047, 754 cm^{-1}; HRMS (ESI+) *m/z* [$M+H^+$] calcd for $C_{28}H_{31}O_9$, 511.1968, found 511.1977.

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 4-methoxybenzoate (10h)

4-methoxybenzoyl chloride (10 μl, 0.07 mmol) in dichloromethane (0.5 mL) was added to a solution of **9c** (13 mg, 0.035 mmol) and 4-dimethylaminopyridine (13 mg, 0.1 mmol) in dichloromethane 0.7 (mL)-pyridine (0.3 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt, solvent was removed and the residue purified via flash chromatography (SiO_2, 1:3 EtOAc/Hexanes) to give desired ester, **10h**, (15 mg, 87.4 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.55 (m, 2H), 6.66 – 6.53 (m, 2H), 6.46 (s, 2H), 6.01 (d, *J* = 2.3 Hz, 1H), 5.88 (d, *J* = 2.3 Hz, 1H), 5.41 (td, *J* = 3.5, 1.3 Hz, 1H), 4.82 (s, 1H), 3.58 (s, 3H), 3.57 (s, 3H), 3.55 (s, 3H), 3.54 (s, 3H), 3.48 (s, 6H), 2.80 (d, *J* = 3.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 163.4, 159.6, 158.9, 155.5, 153.1 (2), 133.4, 131.8 (2), 122.4, 113.5 (2), 103.9 (2), 100.3, 93.4, 91.9, 78.1, 68.0, 60.8, 55.9 (2), 55.4 (4), 26.1; IR (KBr)ν_{max} 2927, 1731, 1604, 1591, 1508, 1458, 1458, 1419, 1373, 1326, 1255, 1234, 1126, 1099, 846, 763 cm^{-1}; HRMS (ESI+) *m/z* [$M+H^+$] calcd for $C_{28}H_{31}O_9$, 511.1968, found 511.1961.

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (10i)

A solution of **9c** (15 mg, 0.04 mmol) in dichloromethane (0.5 mL) was added to a solution of 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylic acid (21 mg, 0.08 mmol), N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (16 mg, 0.08 mmol) and 4-dimethylaminopyridine (9.6 mg, .08 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt, diluted with dichloromethane (5 mL) and washed saturated sodium bicarbonate (2 × 4 mL) solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (SiO_2, 1:3 EtOAc/Hexanes) to give desired ester, **10i** (15 mg, 62.5 %), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.92 (d, *J* = 2.2 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.02 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 6.99 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 6.90 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.75 (s, 2H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.13 (d, *J* = 2.3 Hz, 1H), 5.65 (ddd, *J* = 4.2, 2.9, 1.3 Hz, 1H), 5.16 – 5.02 (m, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.69 (s, 6H), 3.07 (t, *J* = 3.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 160.3, 159.6, 159.3, 158.9, 155.5, 153.1 (2), 138.7, 133.4, 132.4, 131.0, 130.4 (2), 129.1, 122.5, 121.9, 115.1, 113.0, 110.5, 103.8 (2), 100.3, 93.4, 92.0, 78.0, 68.4, 60.8, 55.9 (2), 55.8, 55.4 (2), 55.3, 26.1; IR (KBr)ν^{max} 2927,2848, 1716, 1593, 1496, 1456, 1361, 1238, 1126, 771 cm^{-1}; HRMS (ESI+) *m/z* [$M+H^+$] calcd for $C_{35}H_{37}O_{10}$, 617.2387, found 617.2382.

5,7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (10j)

A solution of **9c** (24 mg, 0.064 mmol) in dichloromethane (0.5 mL) was added to a solution of 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoic acid (32 mg, 0.13 mmol), N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (26 mg, 0.13 mmol) and 4-dimethylaminopyridine (15 mg, 0.13 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt, diluted with dichloromethane (5 mL) and washed saturated sodium bicarbonate solution (2 × 4 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to give desired ester, **10j** (28 mg, 72.5%), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 2.1 Hz, 1H), 7.81 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.69 (s, 2H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.13 (d, *J* = 2.4 Hz, 1H), 5.67 (td, *J* = 3.4, 1.2 Hz, 1H), 5.14 (dddd, *J* = 7.3, 5.8, 2.9, 1.4 Hz, 1H), 5.08 (brs, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.71 (s, 6H), 3.21 (d, *J* = 7.2 Hz, 2H), 3.05 (d, *J* = 3.3 Hz, 2H), 2.30 (s, 3H), 1.72 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 164.9, 159.6, 158.9, 155.4, 153.1 (2), 152.7, 137.8, 134.0, 133.9, 133.3, 131.8, 128.6, 127.8, 122.4, 120.7, 103.8 (2), 100.0, 93.3, 92.0, 77.9, 68.4, 60.8, 56.0, 55.4 (3), 28.6, 25.7 (2), 20.9, 17.8; IR (KBr)ν_{max} 2921, 2850, 1716, 1593, 1458, 1282, 1201, 1142, 1010, 948, 813 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{34}H_{39}O_{10}$, 607.2543, found 607.2541.

5,7-Bis(benzyloxy)-2-phenylchroman-3-yl benzoate (10k)

A solution of **9b** (20 mg, 0.046 mmol) in dichloromethane (0.5 mL) was added to a solution of 3-methoxybenzoic acid (14 mg, 0.09 mmol), N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and 4-dimethylaminopyridine (12 mg, 0.09 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt, diluted with dichloromethane (5 mL) and washed with saturated sodium bicarbonate (2 × 4 mL) solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (SiO_2, 1:7 EtOAc/ Hexanes) to give the desired ester, **10k** (23 mg, 93 %), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.91 (m, 2H), 7.55 – 7.51 (m, 3H), 7.50 – 7.44 (m, 2H), 7.42 – 7.30 (m, 13H), 6.38 (d, *J* = 2.3 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 5.72 (ddd, *J* = 4.4, 2.9, 1.4 Hz, 1H), 5.22 (s, 1H), 5.06 (d, *J* = 4.9 Hz, 2H), 5.02 (d, *J* = 2.6 Hz, 2H), 3.21 – 3.08 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 158.8, 158.0, 155.6, 137.7, 136.9, 136.8, 133.0, 129.9 (2), 129.7 (2), 128.6 (2), 128.5 (2), 128.3 (4), 128.1, 128.0, 127.9, 127.6 (2), 127.2 (2), 126.5, 100.9, 94.7, 93.9, 77.8, 70.2, 70.0, 68.6, 26.1; IR (KBr)ν_{max} 2952, 2923, 2852, 1716, 1616, 1269, 1147, 1107, 1027, 1002, 906, 811, 739 cm^{-1}; HRMS (ESI+) *m/z* [M+Na$^+$] calcd for $C_{36}H_{30}NaO_5$, 565.1991, found 565.1998.

5,7-Bis(benzyloxy)-2-phenylchroman-3-yl 3-methoxybenzoate (10l)

A solution of **9b** (20 mg, 0.046 mmol) in dichloromethane (0.5 mL) was added to a solution of 3-methoxybenzoic acid (14 mg, 0.09 mmol), N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and 4-dimethylaminopyridine (12 mg, 0.09 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt, diluted with dichloromethane (5 mL) and washed with saturated sodium bicarbonate (2 ×

4 mL) solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (SiO_2, 1:7 EtOAc/ Hexanes) to give the desired ester, **10l** (23.5 mg, 90 %), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 3H), 7.48 – 7.44 (m, 2H), 7.44 – 7.28 (m, 13H), 7.06 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 5.69 (ddd, *J* = 4.4, 2.8, 1.5 Hz, 1H), 5.22 (s, 1H), 5.05 (d, *J* = 4.2 Hz, 2H), 5.02 (d, *J* = 2.4 Hz, 2H), 3.80 (s, 3H), 3.20 – 3.09 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 159.4, 158.8, 158.0, 155.6, 137.8, 136.9, 136.8, 131.3, 129.3, 128.6 (2), 128.5 (2), 128.4 (2), 128.3, 128.1 (2), 128.0, 127.9, 127.6, 127.2 (2), 126.5, 122.2, 119.4, 114.2, 100.9, 94.7, 93.9, 77.7, 70.2, 70.0, 68.8, 55.4, 26.0; IR (KBr)ν_{max} 2960, 2927, 2854, 1716, 1652, 1496, 1436, 1205, 1153, 1095, 1068, 1024, 798, 754, 684 cm^{-1}. HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{37}H_{33}O_6$, 573.2277, found 573.2263.

5,7-Bis(benzyloxy)-2-phenylchroman-3-yl 4-methoxybenzoate (10m)

A solution of **9b** (20 mg, 0.046 mmol) in dichloromethane (0.5 mL) was added to a solution of 4-methoxybenzoic acid (14 mg, 0.09 mmol), N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (18 mg, 0.09 mmol) and 4-dimethylaminopyridine (12 mg, 0.09 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt and then diluted with dichloromethane (5 mL). The organic phase was washed with saturated sodium bicarbonate solution (2 × 4 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (SiO_2, 1:7 EtOAc/Hexanes) to give desired ester, **10m** (22 mg, 85%), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 2.0 Hz, 1H), 7.89 – 7.85 (m, 1H), 7.53 – 7.49 (m, 2H), 7.49 – 7.44 (m, 2H), 7.44 – 7.30 (m, 11H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 5.69 (ddd, *J* = 4.5, 2.9, 1.5 Hz, 1H), 5.21 (brs, 1H), 5.06 (d, *J* = 4.8 Hz, 2H), 5.04 – 5.00 (m, 2H), 3.83 (s, 3H), 3.19 – 3.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 163.4, 158.8, 158.0, 155.6, 137.8, 136.9, 136.8, 131.8, 128.6, 128.5 (3), 128.3 (3), 128.1 (2), 128.0, 127.9 (2), 127.6 (2), 127.2, 126.5, 122.4, 113.5 (2), 101.0, 94.7, 93.8, 77.9, 70.2, 69.9, 68.2, 55.4, 26.1; IR (KBr)ν_{max} 2925, 2852, 1716, 1147, 1095, 1026, 798, cm^{-1}; HRMS (ESI+) *m/z* [M+Na$^+$] calcd for $C_{37}H_{32}NaO_6$, 595.2097, found 595.2109.

5,7-Bis(benzyloxy)-2-phenylchroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (10n)

A solution of **9b** (20 mg, 0.045 mmol) in dichloromethane (0.5 mL) was added to a solution of 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylic acid (25 mg, 0.09 mmol), N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (18 mg, 0.00 mmol) and 4-dimethylaminopyridine (11 mg, 0.09mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt and the diluted with dichloromethane (5 mL). The organic phase was washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to give desired ester, **10n** (27 mg, 90 %), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 2H), 7.55 – 7.52 (m, 2H), 7.48 – 7.44 (m, 2H), 7.42 – 7.29 (m, 12H), 7.09 – 7.04 (m, 1H), 7.03 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.36 (d, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H),

5.68 (ddd, *J* = 4.3, 3.1, 1.5 Hz, 1H), 5.22 (brs, 1H), 5.04 (d, *J* = 3.5 Hz, 2H), 5.02 (d, *J* = 2.2 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.20 – 3.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 160.2, 159.2, 158.7, 157.9, 155.6, 138.8, 137.9, 136.9, 136.8, 132.5, 131.0, 130.2, 129.0, 128.6 (3), 128.5 (2), 128.3, 128.1, 128.0, 127.9 (2), 127.6 (2), 127.2, 126.5, 122.4, 122.0, 115.2 (2), 112.9, 110.5, 101.0, 94.7, 93.8, 77.8, 70.2, 69.9, 68.5, 55.8, 55.3, 26.0; IR (KBr)ν_{max} 2952, 2923, 2852, 1716, 1558, 1456, 1245, 1145, 1101, 1026, 798 cm^{-1}; HRMS (ESI+) *m*/*z* [M+H^+] calcd for $C_{44}H_{39}O_7$, 679.2696, found 679.2682.

5,7-Bis(benzyloxy)-2-phenylchroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (10o)

A solution of 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoic acid (34 mg, 0.138 mmol) in THF (5 mL) was treated with thionyl chloride (20 μl, 0.276 mmol). The resulting solution was heated at 70 0 °C for 3 h, cooled to rt and concentrated. The residue was dissolved in dichloromethane (0.5 mL) and added to a solution of **9b** (20 mg, 0.046 mmol) and 4-dimethylaminopyridine (22 mg, 0.184 mmol) in dichloromethane 1 (mL) at 0 °C. The resulting mixture was stirred for 6 h at rt. The solvent was removed and the residue was purified via flash chromatography (SiO_2, 1:7 EtOAc/Hexanes) to give the ester **10o** (22.5 mg, 83.5 %), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 2.2 Hz, 1H), 7.69 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.46 – 7.35 (m, 5H), 7.34 – 7.22 (m, 11H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.28 (d, *J* = 2.3 Hz, 1H), 6.21 (d, *J* = 2.3 Hz, 1H), 5.58 (ddd, *J* = 4.3, 3.1, 1.5 Hz, 1H), 5.17 – 5.06 (m, 2H), 5.00 – 4.89 (m, 4H), 3.13 (d, *J* = 7.5 Hz, 2H), 3.04 (t, *J* = 2.6 Hz, 2H), 2.23 (s, 3H), 1.67 (q, *J* = 1.3 Hz, 3H), 1.60 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 165.1, 158.8, 158.0, 155.5, 152.5, 137.8, 136.9, 136.8, 134.0, 133.7, 131.9, 128.7, 128.6 (2), 128.5 (2), 128.4 (2), 128.1, 128.0, 127.9 (2), 127.8 (2), 127.6 (2), 127.2, 126.4, 122.3, 120.8, 100.8, 94.6, 93.8, 77.7, 70.2, 70.0, 68.7, 29.7, 28.5, 26.1, 20.9, 17.84; IR (KBr)ν_{max} 2921, 2852, 1760, 1716, 1616, 1373, 1257, 1201, 1149, 1114, 1027, 736 cm^{-1}; HRMS (ESI+) *m*/*z* [M+Na^+] calcd for $C_{43}H_{40}NaO_7$, 691.2672, found 691.2682.

5,7-Bis(benzyloxy)-2-(3,4,5-trimethoxyphenyl)chroman-3-yl benzoate (10p)

Benzoyl chloride (8 μl, 0.064 mmol) in dichloromethane (0.5 mL) was added to a solution of **9d** (17 mg, 0.032 mmol) and 4-dimethylaminopyridine (12 mg, 0.092 mmol) in dichloromethane 0.7 (mL) with pyridine (0.3 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt. The resulting mixture was stirred for 6 h at rt. The solvent was removed and the residue purified via flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to give desired ester, **10p** (16 mg, 83.5%), as an amorphous white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.96 (m, 2H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.53 – 7.34 (m, 12H), 6.72 (s, 2H), 6.38 (d, *J* = 2.3 Hz, 1H), 6.32 (d, *J* = 2.3 Hz, 1H), 5.71 (ddd, *J* = 4.1, 3.0, 1.3 Hz, 1H), 5.10 (d, *J* = 3.8 Hz, 1H), 5.08 – 5.01 (m, 4H), 3.80 (s, 3H), 3.71 (s, 6H), 3.18 – 3.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 165.5, 158.8, 158.0, 155.6, 153.1, 137.7, 136.9, 136.8, 133.8, 133.3, 133.2, 130.2, 130.0, 129.8 (2), 129.3, 128.6 (2), 128.6, 128.5, 128.3 (2), 128.0, 127.9 (2), 127.6, 127.2, 100.9, 94.8, 94.0, 78.1, 70.2, 70.0, 68.5, 60.8, 55.9 (2), 26.3; IR (KBr)ν_{max} 2929, 2839, 1716, 1616, 1591, 1506, 1456, 1361, 1226, 1149, 1126, 1041, 811, 754 cm^{-1}; HRMS (ESI+) *m*/*z* [M+Na^+] calcd for $C_{39}H_{36}NaO_8$, 655.2308, found 655.2307.

5,7-Bis(benzyloxy)-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 3-methoxybenzoate (10q)

3-methoxybenzoyl chloride (9 μl, 0.064 mmol) in dichloromethane (0.5 mL) was added to a solution of **9d** (17 mg, 0.032 mmol) and 4-dimethylaminopyridine (12 mg, 0.092 mmol) in dichloromethane 0.7 (mL) with pyridine (0.3 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt. The resulting mixture was stirred for 6 h at rt. The solvent was removed and the residue purified via flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to give desired ester, **10q** (16 mg, 85.1%), as an amorphous white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.50 – 7.30 (m, 12H), 7.07 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 6.72 (s, 2H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 5.68 (ddd, *J* = 4.2, 3.0, 1.3 Hz, 1H), 5.17 – 5.03 (m, 4H), 5.03 (s, 1H), 3.80 (s, 6H), 3.73 (s, 6H), 3.17 – 3.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 159.5, 158.8, 158.0, 155.6, 153.1 (2), 137.7, 136.9, 136.8, 133.3, 131.3, 129.3, 128.6 (3), 128.5, 128.0, 127.9 (3), 127.6, 127.2 (2), 122.1, 119.1, 114.7, 103.8 (2), 100.8, 94.8, 94.0, 78.0, 70.2, 70.0, 68.6, 60.8, 55.9, 55.4, 26.2; IR (KBr)ν_{max} 2931, 2664, 1716, 1593, 1506, 1456, 1361, 1269, 1217, 1126, 1070. 1008 cm^{-1}; HRMS (ESI+) *m*/*z* [M+Na+] calcd for $C_{40}H_{38}NaO_9$, 685.2414, found 685.2401.

5,7-Bis(benzyloxy)-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 4-methoxybenzoate (10r)

4-methoxybenzoyl chloride (9 μl, 0.064 mmol) in dichloromethane (0.7 mL) was added to a solution of **9d** (17 mg, 0.032 mmol) and 4-dimethylaminopyridine (12 mg, 0.092 mmol) in dichloromethane 0.7 (mL) with pyridine (0.3 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt. The solvent was removed and the residue purified via flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to give desired ester product **10r** (17 mg, 87.4%) as an amorphous white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.89 (m, 2H), 7.49 – 7.44 (m, 2H), 7.44 – 7.31 (m, 8H), 6.88 – 6.84 (m, 2H), 6.71 (s, 2H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 5.68 (tt, *J* = 3.1, 1.2 Hz, 1H), 5.08 (s, 1H), 5.08 – 5.01 (m, 4H), 3.84 (s, 3H), 3.80 (s, 3H), 3.72 (s, 6H), 3.12 (t, *J* = 3.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 163.5, 158.7, 158.0, 155.6, 153.1, 137.7, 136.9, 136.8, 133.3 (2), 131.8, 128.6 (2), 128.5 (2), 128.0 (2), 127.9 (2), 127.6 (2), 127.2, 122.4, 113.5 (2), 103.9 (2), 101.0, 94.8, 93.9, 78.1, 70.2, 70.0, 68.0, 60.8, 60.0, 55.9, 55.5, 26.4; IR (KBr)ν_{max} 3348, 2952, 2927, 1716, 1506, 1417, 1257, 1168, 1126, 1035, 821 cm^{-1}; HRMS (ESI+) *m*/*z* [$M+H^+$] calcd for $C_{40}H_{39}O_9$, 663.2594, found 663. 2608.

5,7-Bis(benzyloxy)-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (10s)

A solution of 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylic acid (35 mg, 0.135 mmol) in THF (5 mL) was treated with thionyl chloride (20 μl, 0.27 mmol). The resulting solution was heated at reflux for 3 h, cooled to rt before the solvent was removed. The crude was dissolved in dichloromethane (0.5 mL) and added to a solution of **9d** (18 mg, 0.045 mmol) and 4-dimethylaminopyridine (22 mg, 0.18 mmol) in dichloromethane (0.7 mL) with pyridine (0.3 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt, the solvent was removed and the residue purified via flash chromatography (SiO_2, 1:3 EtOAc/Hexanes) to give desired ester, **10s** (28 mg, 83%), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.93 (d, *J* = 2.2 Hz, 1H), 7.44 (d, *J* = 1.3 Hz, 1H), 7.43 – 7.29 (m, 10H), 7.03 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.00 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H),

6.91 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.71 (s, 2H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 5.67 (td, *J* = 3.6, 1.4 Hz, 1H), 5.10 (s, 1H), 5.07 – 5.01 (m, 4H), 3.86 – 3.79 (m, 9H), 3.69 (s, 6H), 3.15 (d, *J* = 3.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 160.6, 159.5, 159.0, 158.2, 155.8, 153.3 (2), 138.9, 137.1, 137.1, 133.6, 132.6, 131.3, 130.7, 129.3, 128.9, 128.8 (2), 128.3 (2), 128.2 (2), 127.8 (2), 127.4 (2), 122.7, 122.1, 115.4, 113.2, 110.7, 104.0 (2), 101.3, 95.0, 94.2, 78.3, 70.4, 70.2, 68.6, 61.1, 56.2, 56.1 (2), 55.5, 26.5; IR (KBr)ν_{max} 3434, 2929, 1712, 1616, 1593, 1500, 1456, 2440, 2303, 1238, 1149, 1126, 1027, 821, 736,698 cm^{-1}; HRMS (ESI+) m/z [M+Na^+] calcd for $C_{47}H_{44}NaO_{10}$, 791.2832, found 791.2766.

5,7-Bis(benzyloxy)-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (10t)

A solution of 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoic acid (33.5 mg, 0.135 mmol) in THF (5 mL) was treated with thionyl chloride (20 μl, 0.27 mmol). The resulting solution was heated at 70 0 °C for 3 h and cooled to rt and concentrated. The residue was dissolved in dichloromethane (0.5 mL) and added to a solution of **9d** (18 mg, 0.045 mmol) and 4-dimethylaminopyridine (22 mg, 0.18 mmol) in dichloromethane (0.7 mL) with pyridine (0.3 mL) at 0 °C. The resulting mixture was stirred for 6 h at rt. The solvent was removed and the residue purified via flash chromatography (SiO_2, 1:3 EtOAc/Hexanes) to give desired ester, **10t** (26.6 mg, 78%), as colorless a oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 2.1 Hz, 1H), 7.74 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.44 – 7.36 (m, 2H), 7.39 – 7.28 (m, 6H), 7.01 (d, J = 8.4 Hz, 1H), 6.79 (s, 2H), 6.29 – 6.37 (m, 2H), 5.76 (ddd, J = 4.3, 2.9, 1.4 Hz, 1H), 5.22 (m, 1H), 5.15 (m, 3H), 5.00 (s, 2H), 3.81 (s, 3H), 3.77 (s, 6H), 3.20 (d, *J* = 7.4 Hz, 2H), 3.19 – 3.06 (m, 2H), 2.31 (s, 3H), 1.71 (d, 1.6 Hz, 3H), 1.66 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 165.1, 156.7, 155.1, 153.3, 152.9 (2), 152.1, 137.7, 136.9, 136.6, 134.3, 134.1, 133.0, 132.0, 128.9, 128.8 (2), 128.3 (2), 128.2 (2), 127.8 (2), 127.4 (2), 127.3 (2), 122.6, 120.8, 103.5 (2), 102.6, 93.0, 92.9, 78.2, 71.5, 70.5, 68.0, 61.0, 56.2 (2), 28.8, 26.5, 25.9, 21.0, 18.0; IR (KBr)ν_{max} 2960, 2925, 1714, 1604, 1456, 1353, 1261, 1236, 1174, 1126, 1012, 819 cm^{-1}; HRMS (ESI+) *m/z* [M+H^+] calcd for $C_{46}H_{47}O_{10}$, 759.3169, found 759.3195.

5,7-Dihydroxy-2-phenylchroman-3-yl benzoate (11a)

10k (20 mg, 0.036 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, Acetone/Dichloromethane 1:12) to give **11a** (12 mg, 90 %) as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 7.87 – 7.79 (m, 2H), 7.56 – 7.47 (m, 3H), 7.43 – 7.34 (m, 2H), 7.31 – 7.19 (m, 3H), 6.01 (d, *J* = 2.3 Hz, 1H), 5.98 (d, *J* = 2.3 Hz, 1H), 5.66 (ddd, *J* = 4.6, 2.4, 1.3 Hz, 1H), 5.23 (s, 1H), 3.08 (dd, *J* = 17.5, 4.6 Hz, 1H), 2.93 (ddd, *J* = 17.6, 2.5, 0.9 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 167.1, 158.0, 157.9, 157.1, 139.9, 134.2, 131.2, 130.5, 129.5 (2), 129.1 (2), 128.8 (2), 127.5 (2), 99.1, 96.7, 95.8, 78.6, 70.6, 26.7; IR (KBr)ν_{max} 3427, 2921, 2848, 1701, 1560, 1473, 1271, 1097 cm^{-1}; HRMS (ESI+) *m/z* [M+H^+] calcd for $C_{22}H_{19}O_5$, 363.1232, found 363.1241.

5,7-Dihydroxy-2-phenylchroman-3-yl 3-methoxybenzoate (11b)

10l (20 mg, 0.034 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, Acetone/Dichloromethane 1:10) to give **11b** (20 mg, 89%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dt, *J* = 7.7, 1.2 Hz, 3H), 7.41 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.31 – 7.27 (m, 2H), 7.05 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 6.17 (d, *J* = 2.4 Hz, 1H), 5.99 (d, *J* = 2.4 Hz, 1H), 5.67 (ddd, *J* = 4.4, 2.9, 1.5 Hz, 1H), 5.21 (brs, 1H), 5.18 (brs, 1H), 5.05 (brs, 1H), 3.79 (s, 3H), 3.22 – 3.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 159.6, 156.2, 155.5, 155.3, 137.8, 131.3, 129.6, 128.5, 128.4 (2), 126.6 (2), 122.3, 119.7, 114.4, 99.1, 96.5, 96.2, 77.8, 68.9, 55.6, 25.7; IR (KBr)ν_{max} 3359, 2923, 2852, 1714, 1631, 1461, 1274, 1103, 754, cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{23}H_{19}O_6$, 391.1182, found 391.1181.

5,7-Dihydroxy-2-phenylchroman-3-yl 4-methoxybenzoate (11c)

10m (16 mg, 0.027 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, Acetone/Dichloromethane 1:10) to afford **11c** (10 mg, 91%) as a colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.20 (d, *J* = 1.3 Hz, 1H), 8.00 (d, *J* = 1.2 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.51 – 7.41 (m, 2H), 7.25 – 7.16 (m, 2H), 7.16 – 7.08 (m, 1H), 6.84 – 6.79 (m, 2H), 5.95 (s, 2H), 5.53 (ddd, *J* = 4.7, 2.4, 1.4 Hz, 1H), 5.21 (s, 1H), 3.71 (s, 3H), 2.99 (dd, *J* = 17.7, 4.4 Hz, 1H), 2.87 (ddd, *J* = 17.4, 2.4, 0.9 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 165.7, 164.6, 158.0, 157.6, 156.9, 139.9, 132.3 (2), 129.0 (2), 128.6 (2), 127.5, 123.4, 114.7 (2), 98.9, 96.7, 95.9, 78.2, 69.6, 56.0, 26.6; IR (KBr)ν_{max} 3369, 2925, 2852, 1714, 1604, 1512, 1456, 1257, 1168, 1101, 1029, 667 cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{23}H_{19}O_6$, 391.1182, found 391.1175.

5,7-Dihydroxy-2-phenylchroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (11d)

10n (20 mg, 0.029 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under hydrogen atmosphere. The suspension was filtered through plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, Acetone/Dichloromethane 1:9) to give **11d** (13 mg, 89%) as a colorless oil: (500 MHz, $CDCl_3$) ^{1}H NMR δ 7.83 – 7.78 (m, 2H), 7.45 – 7.39 (m, 2H), 7.31 – 7.22 (m, 3H), 7.23 – 7.20 (m, 1H), 6.98 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 6.93 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.88 – 6.80 (m, 2H), 6.08 (d, *J* = 2.2 Hz, 1H), 5.91 (d, *J* = 2.4 Hz, 1H), 5.57 (tt, *J* = 3.3, 1.5 Hz, 1H), 5.13 (s, 1H), 5.01 (s, 1H), 4.91 (s, 1H), 3.76 (d, *J* = 1.4 Hz, 6H), 3.08 – 2.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 160.5, 159.4, 156.2, 155.5, 155.3, 138.9, 137.9, 132.7, 131.2, 130.5, 129.2, 128.5 (2), 128.3 (2), 126.7, 122.5, 122.2, 115.5, 113.1, 110.7, 99.2, 96.6, 96.2, 77.9, 68.6, 56.0, 55.5, 25.7; IR (KBr)ν_{max} 3374, 2952, 2852, 1714, 1558, 1456, 1271, 1101, 1026 cm^{-1}; HRMS (ESI+) *m*/*z* [M+H$^+$] calcd for $C_{30}H_{27}O_7$, 499.1757, found 499.1744.

5,7-Dihydroxy-2-phenylchroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (11e)

A solution of palladium acetate (2 mg, 0.008 mmol), triethylamine (13μL, 0.09 mmol), triethylsilane (64μL, 0.405) in dichloromethane (0.8 mL) was stirred for 15 min before the addition of **10j** (30 mg, 0.045 mmol) in dichloromethane (0.4 mL). The resulting mixture was stirred for 15 h, quenched with saturated ammonium chloride (2 mL), and extracted with diethyl ether (3 × 4 mL). The combined organic layers were washed with saturated sodium chloride solution and dried over anhydrous Na_2SO_4. The solvent was removed and residue purified via flash chromatography (SiO_2, 5:95 MeOH/DCM) to give **11e** (4 mg, 18.9 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.63 (m, 2H), 7.51 – 7.45 (m, 2H), 7.33 – 7.25(m, 3H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.22 (d, *J* = 2.2 Hz, 1H), 5.68 – 5.56 (m, 2H), 5.26 (m, 2H), 5.13 (d, *J* = 1.2 Hz, 1H), 3.32 (d, *J* = 7.2 Hz, 2H), 3.06 (t, *J* = 3.2 Hz, 2H), 2.30 (s, 3H), 1.81 – 1.72 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 165.8, 158.9, 156.0, 154.9, 150.0, 137.7, 135.9, 132.2, 130.0 (2), 128.5 (2), 128.3 (2), 126.9, 126.6, 122.2, 121.1, 115.7, 104.7, 103.0, 101.9, 78.0, 67.9, 29.6, 26.1 (2), 21.4, 18.1; IR (KBr)ν_{max} 3432, 2922, 1701, 1562, 1471, 1101, 1271, 1093 cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{29}H_{27}O_7$, 487.1757, found 487.1755.

5,7-Dihydroxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl benzoate (11f)

10p (15 mg, 0.023 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, Acetone/Dichloromethane 1:8) to give the desired product **11f** (9.5 mg, 88.5 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.86 (m, 2H), 7.53 (ddt, *J* = 8.7, 7.2, 1.3 Hz, 1H), 7.45 – 7.33 (m, 2H), 6.70 (s, 2H), 6.19 (d, *J* = 2.3 Hz, 1H), 5.98 (d, *J* = 2.3 Hz, 1H), 5.70 (ddd, *J* = 4.3, 2.8, 1.3 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 6H), 3.15 – 3.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 156.1, 155.3 (2), 155.1 (2), 153.1, 137.7, 133.3, 129.8(2), 129.7 (3), 128.4, 103.8 (2), 98.9, 96.5, 96.1, 77.9, 68.3, 60.9, 55.9 (2), 25.8 cm^{-1}; IR (KBr)ν_{max} 3421, 2931, 2850, 1717, 1596, 1465, 1276, 1126, 756 cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{25}H_{23}O_8$, 451.1393, found 451.1412.

5,7-Dihydroxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 3-methoxybenzoate (11g)

10q (14 mg, 0.021 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, Acetone/Dichloromethane 1:8) to afford **11g** (9 mg, 89%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.45 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.06 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 1H), 5.94 (d, *J* = 2.3 Hz, 1H), 5.68 (ddd, *J* = 4.2, 2.8, 1.3 Hz, 1H), 5.43 (s, 1H), 5.29 (s, 1H), 5.15 – 5.05 (m, 1H), 3.15 – 3.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 159.5, 156.0, 155.4, 155.2, 153.1 (2), 137.6, 133.4, 131.1, 129.4, 122.0, 119.4, 114.6, 103.8 (2), 98.8, 96.3, 96.1, 77.9, 68.6, 60.8, 55.9, 55.4 (2), 25.7; IR (KBr)ν_{max} 3419, 3404, 3010, 2927, 2852, 1716, 1596, 1463, 1274, 1128,1105, 754 cm^{-1}; HRMS (ESI+) *m*/*z* [M-H$^-$] calcd for $C_{26}H_{25}O_9$, 481.1499, found 481.1509.

5,7-Dihydroxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 4-methoxybenzoate (11h)

10r (14 mg, 0.021 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, Acetone/Dichloromethane 1:8) to give **11h** (9 mg, 89 %) as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 7.93 – 7.76 (m, 2H), 6.98 – 6.90 (m, 2H), 6.79 (s, 2H), 6.00 (q, *J* = 2.3 Hz, 2H), 5.63 (ddd, *J* = 4.7, 2.3, 1.2 Hz, 1H), 5.14 (s, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 3.67 (s, 6H), 3.07 (dd, *J* = 17.4, 4.6 Hz, 1H), 2.95 – 2.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 163.8, 156.2, 155.5, 155.3, 153.3, 137.3, 133.5, 132.0 (3), 122.4, 113.8 (2), 104.0 (2), 99.2, 96.6, 96.2, 78.2, 68.1, 63.0, 56.1, 55.7 (2), 26.0; IR (KBr)ν_{max} 3419, 2931, 2842, 1701, 1604, 1506, 1458, 1361, 1257, 1166, 1126, 1101, 1018 cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{26}H_{25}O_9$, 481.1499, found 481.1518.

5,7-dihydroxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (11i)

10r (25 mg, 0.032 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, Acetone/Dichloromethane 1:8) to give the **11g** (17.4 mg, 91 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 2H), 7.45 – 7.39 (m, 2H), 7.31 – 7.22 (m, 3H), 7.23 – 7.20 (m, 1H), 6.98 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H), 6.93 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.88 – 6.80 (m, 2H), 6.08 (d, *J* = 2.2 Hz, 1H), 5.91 (d, *J* = 2.4 Hz, 1H), 5.57 (tt, *J* = 3.3, 1.5 Hz, 1H), 5.13 (s, 1H), 5.01 (s, 1H), 4.91 (s, 1H), 3.76 (d, *J* = 1.4 Hz, 6H), 3.08 – 2.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 160.6, 159.4, 156.2, 155.6, 155.4, 153.3 (2), 138.8, 133.6, 132.6, 131.2, 130.6, 129.3 (2), 122.5, 122.1, 115.3, 113.2, 110.7, 103.9 (2), 99.2, 96.6, 96.3, 78.1, 68.5, 61.0, 56.1, 56.0, 55.5, 53.6, 29; IR (KBr)ν_{max} 3429, 2931, 2851, 1699, 1604, 1508, 1476, 1248, 1166, 1145, 1098, cm^{-1}; HRMS (ESI+) *m*/*z* [M+H$^+$] calcd for $C_{33}H_{33}O_{10}$, 589.2074 found 589.2057.

5,7-Dihydroxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (11j)

A solution of palladium acetate (1 mg, 0.004 mmol), triethylamine (7 μL, 0.047 mmol), triethylsilane (34 μL, 0.208 in dichloromethane (0.5 mL) was stirred for 15 minutes before the addition of **10t** (20 mg, 0.026 mmol) in dichloromethane (0.4 mL). The resulting mixture was stirred for 15 h, quenched with saturated ammonium chloride (2 mL) and extracted with diethyl ether (3 × 4 mL). The combined organic layers were washed with saturated sodium chloride solution and dried over anhydrous Na_2SO_4. Solvent was removed and residue was purified via flash chromatography (SiO_2, 5:95 MeOH/DCM) to give **11j** (4 mg, 18.9 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 6.4, 2.4 Hz, 2H), 6.67 (s, 3H), 6.43 (d, *J* = 2.2 Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 5.74 (s, 1H), 5.66 – 5.59 (m, 1H), 5.36 (brs, 1H), 5.22 (dddt, *J* = 7.3, 5.8, 2.9, 1.5 Hz, 1H), 4.97 (s, 1H), 3.32 (d, *J* = 7.4 Hz, 2H), 3.07 – 2.99 (m, 2H), 2.30 (d, *J* = 5.3 Hz, 3H), 1.80 – 1.64 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 165.6, 159.2, 156.0, 155.0, 153.3 (2), 150.0, 137.9, 136.0, 133.2, 132.2, 130.0, 127.1 (2), 122.2, 121.0, 115.7, 104.8, 103.9 (2), 103.1, 102.1, 78.2, 67.7, 61.0, 56.2,

29.7, 26.0 (2), 21.4, 18.1; IR (KBr)ν_{max} 3412, 2937, 2843, 1715, 1693, 1562, 1473, 1126 cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{32}H_{33}O_{10}$, 577.2074, found 577.2079.

(((5-(Allyloxy)-1,3-phenylene)bis(oxy))bis(methylene))dibenzene (18a)

A solution of **4b** (1.2 g, 3.9 mmol), potassium carbonate (2.17g, 15.7 mmol) and ally bromide (0.44 mL, 5.1 mmol) in dimethyl formamide (40 mL) was heated at 90 °C for 12 h. The reaction mixture was cooled to rt, diluted with ethyl acetate (200 mL), washed with water (3 × 100 mL) and then saturated sodium chloride solution (100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2 1:9 EtOAc/Hexanes) to give **18a** (1.62 g, 89%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.29 (m, 10H), 6.27 (t, *J* = 2.2 Hz, 1H), 6.21 (d, *J* = 2.1 Hz, 2H), 6.04 (ddt, *J* = 17.2, 10.6, 5.4 Hz, 1H), 5.40 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.29 (dq, *J* = 10.5, 1.4 Hz, 1H), 5.01 (s, 4H), 4.49 (dt, *J* = 5.4, 1.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8 (2), 160.6, 137.0 (2), 133.3, 128.8 (4), 128.2 (2), 127.8 (4), 118.0, 95.0, 94.9 (2), 70.3 (2), 69.1; IR (KBr)ν_{max} 3390, 2975, 2908, 2864, 1622, 1591, 1506, 1434, 1213, 1159, 1110, 1066, 1043, 933, 810, 703 cm^{-1}; HRMS (ESI+) *m*/*z* [M+H$^+$] calcd for $C_{23}H_{23}O_3$, 347.1647, found 347.1647.

1-(Allyloxy)-3-(benzyloxy)benzene (18b)

A solution of **17** (2.45g, 12.3 mmol), potassium carbonate (6.62g, 49.2 mmol) and ally bromide (1.34 mL, 16 mmol)) dimethylformamide (60 mL) was stirred for 12 h at 90 °C. The reaction mixture was cooled to rt, diluted with EtOAc (200 mL), washed with water (3 × 100 mL times) and saturated sodium chloride solution (100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:9 EtOAc/Hexanes) to give **18b** (2.8g, 95.2 %) as light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 2H), 7.42 – 7.38 (m, 2H), 7.37 – 7.32 (m, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 6.06 (ddt, *J* = 17.2, 10.6, 5.3 Hz, 1H), 5.42 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.29 (dq, *J* = 10.5, 1.4 Hz, 1H), 5.06 (s, 2H), 4.53 (dt, *J* = 5.3, 1.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 160.0, 137.3, 133.4, 130.1, 128.8 (2), 128.2 (2), 127.7, 117.9, 107.5, 107.4, 102.3, 70.2, 69.0; IR (KBr)ν_{max} 3031, 2866, 1591, 1490, 1454, 1379, 1288, 1261, 1178, 1149, 1039, 1027, 927, 835, 734, 696 cm^{-1}; HRMS (ESI+) *m*/*z* [M+Na$^+$] calcd for $C_{16}H_{16}NaO_2$, 263.1048, found 263.1053.

2-Allyl-3,5-bis(benzyloxy)phenol (19a)

18a (1.62 g, 4.66 mmol) was dissolved in N,N-diethylaniline (23 mL) and heated at 210 °C for 12 h. Reaction mixture was cooled to rt, diluted with ethyl acetate (200 mL), washed with 1N HCl (3 × 100mL), and then saturated sodium chloride solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to afford **19a** (1.215g, 75%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.32 (m, 11H), 6.27 (d, *J* = 2.3 Hz, 1H), 6.19 (d, *J* = 2.3 Hz, 1H), 5.98 (ddt, *J* = 16.3, 10.0, 6.1 Hz, 1H), 5.18 (q, *J* = 1.8 Hz, 1H), 5.13 (dq, *J* = 5.0, 1.7 Hz, 1H), 5.07 (s, 1H), 5.02 (s, 2H), 5.01 (s, 2H), 3.46 (dt, *J* = 6.2, 1.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 160.5, 158.3, 137.0 (2), 136.9, 128.8 (4), 128.2 (2), 127.8 (4), 116.0, 106.3, 95.0, 92.9, 70.3, 69.1, 26.3; IR (KBr)ν_{max} 2925, 2867,

1596, 1456, 1375, 1213, 1153, 1058, 927, 817, 736 cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{23}H_{21}O_3$, 345.1491, found 345.1503.

3-(2,4-Bis(benzyloxy)-6-hydroxyphenyl)propane-1,2-diol (20a)

A mixture of **19a** (1.062g, 3.1 mmol) in tetrahydrofuran-water (13mL-9mL), 4% aqueous solution of osmium tetraoxide in water (0.03 mmol) and N-methyl morphline-N-oxide (575 mg, 4.9 mmol) was stirred for 12 h before quenching with 10 % aqueous sodium metabisulfite. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers washed with saturated sodium chloride solution (100 mL). The solvent was removed and the residue purified by flash chromatography (SiO_2, 2:5 EtOAc/ Hexanes) to afford **20a** (744 mg, 64 %) as a colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.77 (s, 1H), 7.50 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.48 – 7.44 (m, 2H), 7.39 (td, *J* = 7.9, 7.5, 1.5 Hz, 4H), 7.36 – 7.30 (m, 2H), 6.32 (d, *J* = 2.3 Hz, 1H), 6.20 (d, *J* = 2.3 Hz, 1H), 5.10 (s, 2H), 5.05 (s, 2H), 4.65 (d, *J* = 5.2 Hz, 1H), 3.91 (brs, 1H), 3.81 (d, *J* = 6.1 Hz, 1H), 3.53 (brs, 1H), 3.41 (dd, *J* = 11.3, 6.4 Hz, 1H), 2.96 (dd, *J* = 14.1, 5.0 Hz, 1H), 2.79 (dd, *J* = 14.1, 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 159.9, 159.1 (2), 138.7 (2), 129.4 (2), 129.3 (2), 128.9, 128.7, 128.6, 128.5, 128.2, 107.6, 96.8, 96.8, 93.6, 74.1, 70.9, 70.5, 66.6, 27.8; IR (KBr)ν_{max} 3298, 1616, 1598, 1452, 1436, 1375, 1217, 1147, 1105, 1045, 1027, 908, 813, 736, 696, 649 cm^{-1}; HRMS (ESI−) *m*/*z* [M+H$^+$] calcd for $C_{23}H_{25}O_5$, 381.1702, found 381.1709.

3-(4-(Benzyloxy)-2-hydroxyphenyl)propane-1,2-diol (20b)

18b (2.7g, 11.23 mmol) was dissolved in N,N-diethylaniline (70 mL) and heated at 210 °C for 12 h. The reaction mixture was cooled to rt, diluted with ethyl acetate (200 mL), washed with 1N HCl (3 × 100mL), and then with saturated sodium chloride solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to give a mixture of **19b** and **19c.** The mixture of **19b** & **19c** (2.02g, 8.41 mmol) in tetrahydrofuran-water (18mL-12mL), 4% aqueous solution osmium tetraoxide in water (0.168mmol) and N-methyl morphline-N-oxide (1.67g, 14.29 mmol) was stirred 12 h before quenching with 10 % aqueous sodium metabisulfite. The aqueous phase was extracted with ethyl acetate (3 × 200 mL), the combined organic layers were washed with saturated sodium chloride solution and solvent was removed. The residue was purified by flash chromatography (1:5 Acetone-DCM) to afford **20b** (1.24g) as a colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.49 – 7.43 (m, 2H), 7.427.35 (m, 2H), 7.34 – 7.27 (m, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.49 (d, *J* = 2.6 Hz, 1H), 6.45 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.90 (tt, *J* = 6.9, 4.4 Hz, 1H), 3.54 – 3.49 (m, 1H), 3.47 – 3.40 (m, 1H), 2.83 – 2.75 (m, 1H), 2.74 – 2.66 (m, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 159.6, 157.7, 138.6, 132.6, 129.2, 129.1, 128.4 (2), 128.2, 118.8, 106.7, 103.8, 74.2, 70.2, 66.2, 35.3; IR (KBr)ν_{max} 3311, 2931, 1618, 1585, 1506, 1454, 1279, 1286, 1166, 1108, 1024, 842, 736, 696 cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{16}H_{17}O_4$, 273.1127, found 273.1129.

3-(2-(Benzyloxy)-6-hydroxyphenyl)propane-1,2-diol (20c)

The mixture of **19b** & **19c** (2.02g, 8.41 mmol) in tetrahydrofuran-water (18mL-12mL), 4% aqueous solution osmium tetraoxide in water (0.168mmol) and N-methyl morphline-N-oxide ((1.67g, 14.29 mmol) was stirred 12 h before quenching with 10 % aqueous sodium metabisulfite. The aqueous phase was extracted with ethyl acetate (3 × 200 mL, and the combined organic layers washed with saturated sodium chloride solution. The solvent was removed and the residue purified by flash chromatography (1:5 Acetone-DCM) to afford **20c** (0.8 g) as a colorless oil was used as is in the next step: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.70 (s, 1H), 7.53 – 7.48 (m, 2H), 7.42 – 7.35 (m, 2H), 7.35 – 7.29 (m, 1H), 7.02 (t, *J* = 8.2 Hz, 1H), 6.59 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.52 (dd, *J* = 8.1, 1.0 Hz, 1H), 5.10 (s, 2H), 4.86 – 4.48 (m, 1H), 3.97 (tdd, *J* = 6.7, 5.3, 4.0 Hz, 1H), 3.83 (brs, 1H), 3.55 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.43 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.04 (dd, *J* = 13.8, 5.3 Hz, 1H), 2.89 (dd, *J* = 13.8, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.47, 156.58, 136.82, 128.69 (2), 128.10 (2), 127.40 (2), 112.99, 110.56, 104.13, 72.83, 70.54, 65.24, 26.59; IR (KBr)ν_{max} 3334, 2929, 1618, 1583, 1506, 1454, 1279, 1286, 1217, 1166, 1045, 1025, 849 cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{16}H_{17}O_4$, 273.1127, found 273.1127.

3-(2,4-Bis(benzyloxy)-6-hydroxyphenyl)-2-hydroxypropyl 4-methylbenzenesulfonate (21a)

Pyridine (0.46mL, 5.8 mmol) was added to a solution of **19a** (500 mg, 1.37 mmol) and *p*-toluenesulfonyl chloride (282 mg, 1.5 mmol) in dichloromethane (14 mL) at 0 °C. The resulting mixture was stirred for 12 h at rt before quenching with 2N HCl (20mL). The aqueous layer was extracted with dichloromethane (2 × 30mL). The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 2:5 EtOAc/Hexanes) to give **21a** (427 mg, 58%) as a pale yellow oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.51 (s, 1H), 7.72 – 7.67 (m, 2H), 7.50 – 7.44 (m, 4H), 7.43 – 7.37 (m, 6H), 7.37 – 7.30 (m, 2H), 6.31 (d, *J* = 2.4 Hz, 1H), 6.19 (d, *J* = 2.3 Hz, 1H), 5.07 (s, 2H), 5.04 (s, 2H), 4.84 (d, *J* = 4.5 Hz, 1H), 4.11 – 3.94 (m, 2H), 3.95 – 3.70 (m, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 160.0, 159.1, 158.0, 145.7, 138.4 (2), 130.8 (2), 129.4 (2), 129.3 (2), 128.6 (5), 128.5 (2), 128.1 (2), 106.1, 96.2, 93.3, 75.2, 70.6, 70.4, 70.2, 28.0, 21.5; IR (KBr)ν_{max} 3334, 2925, 1625, 1506, 1361, 1174, 1108, 1095, 975 cm^{-1}; HRMS (ESI+) *m*/*z* [M+H$^+$] calcd for $C_{30}H_{31}O_7S$, 535.1790, found 535.1773.

3-(4-(Benzyloxy)-2-hydroxyphenyl)-2-hydroxypropyl 4-methylbenzenesulfonate (21b)

Pyridine (0.46mL, 5.8 mmol) was added to a solution of **19b** (500 mg, 1.37 mmol) and *p*-toluenesulfonyl chloride (282 mg, 1.5 mmol) in dichloromethane (14 mL) at 0 °C. The resulting mixture was stirred for 12 h at rt before quenching with 2N HCl (20mL). The aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with saturated sodium chloride solution (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 2:5 EtOAc/Hexanes) to give **21b** (.97g, 58.6 %) as a pale yellow oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.82 – 7.74 (m, 3H), 7.50 – 7.43 (m, 5H), 7.43 – 7.28 (m, 4H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.48 (d, *J* = 2.5 Hz, 1H), 6.42 (dd, *J* = 8.3, 2.5 Hz, 1H), 4.17 – 3.97 (m, 3H), 3.89 (dd, *J* = 9.9, 6.7 Hz, 1H), 2.76 – 2.67 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz,

$(CD_3)_2CO$) δ 159.8 (2), 145.8, 138.6, 134.1, 132.8, 130.9, 130.8, 129.3 (2), 128.8, 128.7, 128.6 (2), 128.4, 106.8, 103.5, 74.3, 70.4, 70.3, 34.9, 21.5; IR (KBr)ν_{max} 3348, 2928, 1627, 1361, 1174, 1108, 1096 cm^{-1}; HRMS (ESI+) *m*/*z* [M+H^+] calcd for $C_{23}H_{25}O_6S$, 429.1372, found 429.1383.

3-(2-(Benzyloxy)-6-hydroxyphenyl)-2-hydroxypropyl 4-methylbenzenesulfonate (21c)

Pyridine (0.47 mL, 15.4 mmol) was added to a solution of **20c** (410 mg, 1.5 mmol) and *p*-toluenesulfonyl chloride (310 mg, 1.7 mmol) in dichloromethane (14 mL) at 0 °C. The resulting mixture was stirred for 12 h at rt before quenching with 2N HCl (20mL). The aqueous layer was extracted with dichloromethane (2 × 30mL). The combined organic layers were washed with saturated sodium chloride solution (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 2:5 EtOAc/Hexanes) to give **21c** (367 mg, 57 %) as a pale yellow oil and was used as is in the next step.

5,7-Bis(benzyloxy)chroman-3-ol (22a)

Potassium carbonate (115 mg, 0.83 mmol) was added to a solution of **21a** (277 mg, 0.58 mmol) in methanol (2.6 mL) and the resulting mixture was stirred for 6 h at rt. Methanol was removed, the residue was partitioned between water (5 mL) and dichloromethane (5 mL) The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:5 EtOAc/Hexanes) to give **22a** (86 mg, 46%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 8H), 7.34 (ddt, *J* = 7.4, 4.0, 1.7 Hz, 2H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 1H), 5.02 (s, 2H), 5.01 (s, 2H), 4.33 – 4.15 (m, 1H), 4.15 – 3.97 (m, 2H), 2.93 (dd, *J* = 17.0, 5.0 Hz, 1H), 2.75 (dd, *J* = 17.0, 4.5 Hz, 1H), 1.89 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 158.4, 155.2, 137.1, 137.1, 128.8 (2), 128.7, 128.7, 128.2, 128.1, 127.8, 127.7, 127.4 (2), 101.6, 94.8, 94.0, 70.3, 70.1, 69.8, 63.2, 28.4; IR (KBr)ν_{max} 3392, 2925, 2871, 1616, 1591, 1496, 1456, 1145, 1122, 1062, 1027, 811, 696 cm^{-1}; HRMS (ESI+) *m*/*z* [M+H^+] calcd for $C_{23}H_{23}O_4$, 363.1596, found 363.1596.

7-(Benzyloxy)chroman-3-ol (22b)

Potassium carbonate (440 mg, 3.18 mmol) was added to a solution of **21a** (830 mg, 1.98 mmol) in methanol (5 mL) and the resulting solution was stirred for 6 h at rt. Methanol was removed, the residue was partitioned between water 105 mL) and dichloromethane (10 mL) The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:5 EtOAc/Hexanes) to give desire product **22b** (200 mg, 40 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.30 (m, 5H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.52 – 6.45 (m, 2H), 5.03 (s, 2H), 4.98 – 4.80 (m, 1H), 3.84 (dd, *J* = 12.0, 3.3 Hz, 1H), 3.74 (dd, *J* = 12.0, 6.4 Hz, 1H), 3.19 (dd, *J* = 15.1, 9.4 Hz, 1H), 2.94 (ddd, *J* = 15.1, 7.2, 1.2 Hz, 1H), 2.07 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 137.2, 128.8 (2), 128.1 (2), 127.6, 125.2, 118.9,

107.3, 97.5, 84.3, 70.5, 65.2, 30.8; IR (KBr)ν_{max} 3382, 2927, 1614, 1494, 1145, 1029 cm^{-1}; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{16}H_{16}NaO_3$, 279.0097, found 279.1002.

5-(Benzyloxy)chroman-3-ol (22c)

Potassium carbonate **21c** (262 mg, 0.61 mmol), potassium carbonate (135 mg, 0.98 mmol) in methanol (2 mL) and the resulting solution was stirred for 6 h at rt. Methanol was removed, the residue was partitioned between water (5 mL) and dichloromethane (5 mL) The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:5 EtOAc/Hexanes) to give desire product **22c** (70 mg, 45 %) as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 7.49 – 7.43 (m, 2H), 7.37 (ddd, *J* = 7.7, 6.4, 1.2 Hz, 2H), 7.30 (td, *J* = 7.1, 1.4 Hz, 1H), 7.01 (t, *J* = 8.2 Hz, 1H), 6.55 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.43 (dd, *J* = 8.1, 1.1 Hz, 1H), 5.07 (s, 2H), 3.88 (ddd, *J* = 10.7, 6.4, 1.5 Hz, 1H), 2.99 (ddd, *J* = 17.3, 5.3, 1.6 Hz, 1H), 2.66 (dd, *J* = 17.1, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 158.8, 156.3, 139.0, 129.5, 128.8, 128.3, 128.1 (2), 110.5, 110.3, 104.8 (2), 71.0, 70.3, 63.7, 29.3; IR (KBr)ν_{max} 3388, 2928, 1616, 1591, 1496, 1146, 1061, 1027 cm^{-1}; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{16}H_{16}NaO_3$, 279.0997, found 279.0993.

5,7-Dihydroxychroman-3-yl benzoate (23a)[45]

A solution of alcohol (14 mg, 0.04 mmol) in dichloromethane (0.5 mL) was added to a stirred solution of benzoic acid (10 mg, 0.08 mmol), N,N′-dicyclohexylcarbodiimide (17 mg, 0.08 mmol) and 4-dimethylaminopyridine (4.8 mg, 0.04 mmol) in dichloromethane (1 mL) at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered concentrate. The residue was purified by flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to afford give 5,7-bis(benzyloxy)chroman-3-yl benzoate (16.2 mg, 90%) as a colorless oil, which was used as for hydrogenolysis. 5,7-Bis(benzyloxy)chroman-3-yl benzoate (16.2 mg, 0.034 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23a** (8 mg, 81.6 %) as a colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.32 (s, 1H), 8.05 (s, 1H), 8.02 – 7.91 (m, 2H), 7.71 – 7.59 (m, 1H), 7.57 – 7.44 (m, 2H), 6.05 (d, *J* = 2.3 Hz, 1H), 5.91 (d, *J* = 2.3 Hz, 1H), 5.60 – 5.41 (m, 1H), 3.02 (ddd, *J* = 17.1, 5.3, 1.2 Hz, 1H), 2.90 – 2.83 (m, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 166.4, 157.9, 157.5, 156.5, 134.1, 131.3 (2), 130.3 (2), 129.5, 99.2, 96.5, 95.8, 67.4, 67.3, 25.6; IR (KBr)ν_{max} 3385, 2933, 2840, 1716, 1622, 1593, 1496, 1452, 1272, 1201, 1145, 1056, 813, 711 cm^{-1}; HRMS (ESI+) *m/z* [M+H^+] calcd for $C_{16}H_{14}O_5$, 287.0919, found 287.0912.

5,7-Dihydroxychroman-3-yl 3-methoxybenzoate (23b)

A solution of alcohol (14 mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 3-methoxybenzoic acid (12 mg, 0.08 mmol), N,N′-dicyclohexylcarbodiimide (17 mg, 0.08 mmol) and 4-dimethylaminopyridine (4.8 mg, 0.04 mmol) in dichloromethane (1 mL) at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to afford give 5,7-bis(benzyloxy)chroman-3-yl 3-methoxybenzoate (18 mg, 89%) as a colorless oil, which was used as for hydrogenolysis. 5,7-bis(benzyloxy)chroman-3-yl 3-methoxybenzoate (18 mg) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23b** (11 mg, 96 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (ddd, *J* = 7.7, 1.5, 1.0 Hz, 1H), 7.53 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.09 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 6.03 (d, *J* = 2.3 Hz, 1H), 5.99 (d, *J* = 2.4 Hz, 1H), 5.54 – 5.45 (m, 1H), 5.43 – 5.33 (m, 1H), 5.24 (s, 1H), 4.29 (ddd, *J* = 11.4, 5.0, 1.8 Hz, 1H), 4.20 (ddd, *J* = 11.4, 2.3, 1.0 Hz, 1H), 3.04 (ddd, *J* = 16.9, 5.4, 1.2 Hz, 1H), 2.88 (ddd, *J* = 16.9, 4.5, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 159.7, 155.7, 155.4, 155.3, 131.3, 129.7, 122.4, 119.8, 114.6, 99.5, 96.3, 96.1, 66.9, 66.2, 55.7, 24.9; IR (KBr)ν_{max} 3404, 2960, 1716, 1596, 1469, 1278, 1224, 1099, 933, 752 cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{17}H_{15}O_6$, 315.0869, found 315.0830.

5,7-Dihydroxychroman-3-yl 4-methoxybenzoate (23c)

A solution of **22a** (13 mg, 0.036 mmol) in dichloromethane (0.5 mL) was added to a stirred solution of 4-methoxybenzoic acid (11 mg, 0.072 mmol), N,N′-dicyclohexylcarbodiimide (17 mg, 0.08 mmol) and 4-dimethylaminopyridine (4.8 mg, 0.04 mmol) in dichloromethane (1 mL) at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to afford 5,7-bis(benzyloxy)chroman-3-yl 4-methoxybenzoate (16.7 mg, 93.8%) as a colorless oil, which was used as for hydrogenolysis. 5,7-bis(benzyloxy)chroman-3-yl 4-methoxybenzoate (16.2 mg, 0.033 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23c** (10 mg, 98 %) as colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.30 (s, 1H), 8.04 (s, 1H), 7.99 – 7.88 (m, 2H), 7.03 – 6.94 (m, 2H), 6.05 (d, *J* = 2.3 Hz, 1H), 5.90 (d, *J* = 2.3 Hz, 1H), 5.42 (dtd, *J* = 5.4, 4.5, 2.2 Hz, 1H), 4.24 (ddd, *J* = 11.4, 4.7, 1.9 Hz, 1H), 4.19 (ddt, *J* = 11.5, 1.9, 0.9 Hz, 1H), 3.86 (s, 3H), 3.00 (ddd, *J* = 17.2,

5.3, 1.2 Hz, 1H), 2.83 (ddd, *J* = 17.2, 4.4, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 166.1 (2), 164.6, 157.8, 157.5, 156.5, 132.4 (2), 123.5, 114.7, 99.2, 96.5, 95.7, 67.3, 66.9, 56.0, 25.6; IR (KBr)ν_{max} 3404, 2958, 1716, 1596, 14266, 1284 1224, 1098 cm^{-1}; HRMS (ESI+) *m*/*z* [M+H$^+$] calcd for $C_{17}H_{17}O_6$, 317.1025, found 317.1029.

5,7-Dihydroxychroman-3-yl 3,4-dimethoxybenzoate (23d)

A solution of **22a** (12 mg, 0.033 mmol) in dichloromethane (0.5 mL) was added to a stirred solution of 4-methoxybenzoic acid 3,4-methoxybenzoic acid (14 mg, 0.066 mmol), N,N′-dicyclohexylcarbodiimide (14 mg, 0.066 mmol) and 4-dimethylaminopyridine (4.8 mg, 0.04 mmol) in dichloromethane (1 mL) at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed. The residue was purified by flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to afford 5,7-bis(benzyloxy)chroman-3-yl 3,4-methoxybenzoate (17 mg, 95%) as colorless oil which was used as for hydrogenolysis. 5,7-bis(benzyloxy)chroman-3-yl 3,4-methoxybenzoate (17 mg, 0.032 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23d** (9.5 mg, 86 %) as colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.30 (s, 1H), 8.04 (s, 1H), 7.58 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.05 (d, *J* = 2.3 Hz, 1H), 5.90 (d, *J* = 2.3 Hz, 1H), 5.41 (qd, *J* = 4.7, 2.5 Hz, 1H), 4.21 (td, *J* = 4.2, 3.5, 1.4 Hz, 2H), 3.87 (s, 4H), 3.83 (s, 3H), 3.01 (ddd, *J* = 17.1, 5.3, 1.1 Hz, 1H), 2.88 – 2.73 (m, 1H); ^{13}C NMR (125 MHz $(CD_3)_2CO$) δ 166.2, 157.9, 157.5, 156.6, 154.7, 150.0, 124.4, 123.5, 113.2, 111.8, 99.3, 96.5, 95.7, 78.1, 67.1, 56.3, 56.2, 25.7; IR (KBr)ν_{max} 3404, 2921, 1699, 1515, 1271, 1145, 1022, 761, 667 cm^{-1}; HRMS (ESI+) *m*/*z* [M+H+] calcd for $C_{18}H_{19}O_7$, 347.1131, found 347.1128.

5,7-Dihydroxychroman-3-yl 3,5-dimethoxybenzoate (23e)

A solution of **22a** (13 mg, 0.036 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 4-methoxybenzoic acid 3,5-dimethoxybenzoic acid (13 mg, 0.072 mmol), N,N′-dicyclohexylcarbodiimide (17 mg, 0.08 mmol)and 4-dimethylaminopyridine (4.8 mg, 0.04 mmol) in dichloromethane (1 mL) at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to afford 5,7-bis(benzyloxy)chroman-3-yl 3,5-dimethoxybenzoate (17.8 mg, 94.6%) as a colorless oil, which was used as for hydrogenolysis. 5,7-bis(benzyloxy)chroman-3-yl 3,5-methoxybenzoate (17 mg, 0.032 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23e** (9.5 mg, 86 %) as colorless

oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.31 (s, 1H), 8.04 (s, 1H), 7.10 (d, *J* = 2.4 Hz, 2H), 6.72 (t, *J* = 2.4 Hz, 1H), 6.05 (d, *J* = 2.3 Hz, 1H), 5.90 (d, *J* = 2.3 Hz, 1H), 5.53 – 5.35 (m, 1H), 4.32 – 4.16 (m, 2H), 3.15 – 2.95 (m, 1H), 2.86 – 2.82 (m, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 166.1, 161.8 (2), 157.8, 157.4, 156.4, 133.2, 108.1 (2), 105.6, 99.1, 96.4, 95.6, 77.1, 67.5, 67.2, 55.9, 25.5; IR (KBr)ν_{max} 1916, 2848, 1702, 1683, 1558, 1244, 1145, 1103, cm^{-1}; HRMS (ESI+) *m*/*z* [M+Na$^+$] calcd for $C_{18}H_{18}NaO_7$, 369.0950, found 369.0962.

5,7-Dihydroxychroman-3-yl 3-hydroxybenzoate (23f)[45]

A solution of **22a** (14 mg, 0.039 mmol) in dichloromethane (0.5 mL) was added to a stirred solution of 4-(benzyloxy)benzoic acid (13 mg, 0.072 mmol), N,N′-dicyclohexylcarbodiimide (16 mg, 0.077 mmol)and 4-dimethylaminopyridine (4.8 mg, 0.04 mmol) in dichloromethane (1 mL) at 0 °C. The resulting solution was stirred for 6 h at rt then filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to afford 5,7-bis(benzyloxy)chroman-3-yl 3-(benzyloxy)benzoate (19 mg, 86.3 %), which was used further as obtained. 5,7-bis(benzyloxy)chroman-3-yl 3-(benzyloxy)benzoate (18 mg, 0.031 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:9 Acetone/ Dichloromethane) to give **23f** (8.6 mg, 92.6 %) as a colorless oil: ^{1}H NMR (500 MHz, MeOD) δ 7.83 (d, *J* = 8.8 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 5.94 (d, *J* = 2.3 Hz, 1H), 5.84 (d, *J* = 2.3 Hz, 1H), 5.37 (ddd, *J* = 5.3, 4.5, 2.7 Hz, 1H), 4.19 (ddd, *J* = 11.4, 4.9, 1.8 Hz, 1H), 4.14 (dd, *J* = 11.4, 2.1 Hz, 1H), 2.95 (ddd, *J* = 17.1, 5.4, 1.1 Hz, 1H), 2.77 (ddd, *J* = 17.1, 4.5, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 166.2, 158.3, 157.7, 157.4, 156.4, 132.6, 130.5, 121.5, 121.0, 116.7, 99.1, 96.3, 95.6, 67.6, 67.2, 25.5; IR (KBr)ν_{max} 3384, 2910, 1848, 1699, 1436, 1290, 1145 cm^{-1}; HRMS (ESI−) *m*/*z* [M−H$^-$] calcd for $C_{16}H_{13}O_6$, 301.0712, found 301.0717.

5,7-Bis(benzyloxy)chroman-3-yl 4-(benzyloxy)benzoate (23g)[36]

A solution of **22a** (14 mg, 0.039 mmol) in dichloromethane (0.5 mL) was added to a stirred solution of 4-(benzyloxy)benzoic acid (13 mg, 0.072 mmol), N,N′-dicyclohexylcarbodiimide (16 mg, 0.077 mmol)and 4-dimethylaminopyridine (4.8 mg, 0.04 mmol) in dichloromethane (1 mL) at 0 °C. The resulting solution was stirred for 6 h at rt and filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to afford 5,7-bis(benzyloxy)chroman-3-yl 4-(benzyloxy)benzoate (20 mg, 90.4 %) as a colorless oil, which was used as for hydrogenolysis. 5,7-bis(benzyloxy)chroman-3-yl 3-(benzyloxy)benzoate (18 mg, 0.031 mmol) and palladium/ carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm

particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23g** (9.8 mg, 97%) as a colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 9.15 (s, 1H), 8.29 (s, 1H), 8.03 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 6.97 – 6.83 (m, 2H), 6.05 (d, *J* = 2.3 Hz, 1H), 5.90 (d, *J* = 2.3 Hz, 1H), 5.57 – 5.28 (m, 1H), 4.23 (ddd, *J* = 11.4, 4.7, 1.8 Hz, 1H), 4.18 (ddt, *J* = 11.4, 2.1, 0.9 Hz, 1H), 2.99 (ddd, *J* = 17.0, 5.4, 1.1 Hz, 1H), 2.82 (ddd, *J* = 17.0, 4.4, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 166.2, 160.7, 159.8, 159.4, 156.1, 133.1, 108.7, 108.1, 101.1, 94.2, 92.2, 67.3, 66.8, 55.8, 55.5, 25.3; IR (KBr)ν_{max} 3363, 2962, 2927, 1683, 1608, 1355, 1272, 1166, 1143, 1099, 1014, 769 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{16}H_{15}O_6$, 303.0869, found 303.0878.

5,7-Dihydroxychroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (23h)

A solution of **22a** (11 mg, 0.03 mmol) in dichloromethane (0.5 mL) was added to a stirred solution of 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylic acid (16 mg, 0.06 mmol), N,N′-dicyclohexylcarbodiimide (13 mg, 0.06 mmol) and 4-dimethylaminopyridine (4.8 mg, 0.04 mmol) in dichloromethane (1 mL) 0 °C. The resulting solution was stirred for 6 h at rt and filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc/Hexanes) to afford 5,7-bis(benzyloxy)chroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (17.5 mg, 96.1%) as a colorless oil, which was used as for hydrogenolysis. 5,7-bis(benzyloxy)chroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (17 mg, 0.028 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23h** (11.1 mg, 93.2 %) as a colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.97 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.92 (d, *J* = 2.2 Hz, 1H), 7.37 – 7.29 (m, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.10 – 7.00 (m, 2H), 6.91 (ddd, *J* = 8.3, 2.6, 1.1 Hz, 1H), 6.04 (d, *J* = 2.3 Hz, 1H), 5.89 (d, *J* = 2.3 Hz, 1H), 5.50 – 5.35 (m, 1H), 4.33 – 4.23 (m, 1H), 4.22 – 4.18 (m, 1H), 3.89 (s, 4H), 3.81 (s, 3H), 3.01 (ddd, *J* = 17.1, 5.3, 1.2 Hz, 1H), 2.92 – 2.80 (m, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 166.0, 161.4, 160.4, 157.8, 157.4, 156.5, 139.9, 132.7, 131.7, 131.3, 129.9, 123.5, 122.5, 116.0, 113.6, 112.1, 99.2, 96.4, 95.7, 67.3, 67.0, 55.5 (2), 25.6; IR (KBr)ν_{max} 3355, 2923, 1701, 1606,1458, 1251, 1145, 1031, 752, 667 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{24}H_{23}O_7$, 423.1444, found 423.1454.

5,7-Dihydroxychroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (23i)

4-Acetoxy-3-(3-methylbut-2-en-1-yl)benzoic acid (34 mg, 0.137 mmol) and thionyl chloride (33 μL, 0.27 mmol) in tetrahydrofuran (5 mL) was heated at reflux for 3 h, cooled to rt and concentrated. The residue was dissolved in dichloromethane (0.5 mL) and added to a stirred solution of **22a** (25 mg, 0.069 mmol) in dichloromethane (0.7 mL) with triethylamine (0.3 mL) under at 0°C. The resulting mixture was stirred for 6 h, concentrated and the residue was purified by flash chromatography (SiO_2, 1:4 EtOAc/Hexanes) to give 5,7-bis(benzyloxy)chroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (34 mg, 85 %) as

colorless a oil, which was used as for hydrogenolysis. A solution of palladium acetate (5 mg, 0.023 mg), triethylamine (15μL, 0.108 mmol), triethylsilane (82μL, 0.108) in dichloromethane (0.8 mL) was stirred for 15 minutes before the slow addition of a solution of bis(benzyloxy)chroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (34 mg, 0.057 mmol) in dichloromethane (0.4 mL). The resulting mixture was stirred for 15 h, quenched with saturated ammonium chloride (2 mL) and extracted with ether (3 × 4 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica, 5:95 MeOH/DCM) to afford **23i** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 13.7, 2.2 Hz, 1H), 7.86 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.03 – 5.99 (m, 1H), 5.96 (d, *J* = 2.4 Hz, 1H), 5.50 (ddt, *J* = 7.2, 4.8, 2.4 Hz, 1H), 5.18 (dddd, *J* = 7.3, 5.8, 2.9, 1.5 Hz, 1H), 4.29 (ddd, *J* = 11.5, 4.9, 1.9 Hz, 1H), 4.24 – 4.14 (m, 1H), 3.25 (d, *J* = 7.2 Hz, 2H), 3.07 – 2.98 (m, 1H), 2.87 (ddd, *J* = 16.9, 4.4, 1.8 Hz, 1H), 2.32 (s, 3H), 1.72 (q, *J* = 1.3 Hz, 2H), 1.68 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 165.7, 155.4, 155.3 (2), 152.9, 134.2, 134.1, 132.2, 129.0, 127.9, 122.6, 121.0, 99.4, 96.3, 96.0, 66.9, 65.9, 28.9, 25.9, 24.9, 21.1, 18.1; IR (KBr)ν_{max} 3363, 2921, 1703, 1606, 1252, 1146 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{23}H_{25}O_7$, 413.1600, found 413.1617.

7-Hydroxychroman-3-yl 4-methoxybenzoate (23j)

A solution of **22b** (15 mg, 0.06 mmol) in dichloromethane (0.5 mL) was added to a stirred solution benzoic acid (14 mg, 0.12 mmol), N,N′-dicyclohexylcarbodiimide (24 mg, 0.12 mmol) and 4-dimethylaminopyridine (7.2 mg, 0.06 mmol) at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to afford 7-(benzyloxy)chroman-3-yl benzoate as a colorless oil (21 mg, 90%), which was used as for hydrogenolysis. 7-(benzyloxy)chroman-3-yl benzoate (14 mg, 0.04 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23j** (11.1 mg, 90.4 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.93 (m, 2H), 7.54 (ddt, *J* = 8.7, 7.7, 1.3 Hz, 1H), 7.40 (ddt, *J* = 7.3, 6.3, 1.0 Hz, 2H), 6.92 (dt, *J* = 8.1, 0.9 Hz, 1H), 6.42 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 5.49 (qd, *J* = 4.8, 2.2 Hz, 1H), 4.71 (s, 1H), 4.32 (ddd, *J* = 11.5, 4.8, 1.9 Hz, 1H), 4.23 (dtd, *J* = 11.5, 1.5, 0.8 Hz, 1H), 3.18 (ddt, *J* = 16.6, 5.1, 1.1 Hz, 1H), 3.02 – 2.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 155.3, 154.8, 133.4, 130.8 (2), 130.1, 130.0, 128.6 (2), 111.4, 108.9, 103.5, 67.1, 66.4, 29.8; IR (KBr)ν_{max} 3392, 2925, 1716, 1699, 1519, 1456, 1272, 1145, 1027, 1016, 821, 711cm^{-1}; HRMS (ESI−) *m/z* [M+H$^+$] calcd for $C_{16}H_{15}O_4$, 271.0970, found 271.0966.

7-Hydroxychroman-3-yl 3-methoxybenzoate (23k)

A solution of **22b** (11 mg, 0.04 mmol) in dichloromethane (0.5 mL) was added to a stirred solution 3-methoxybenzoic acid (12 mg, 0.08 mmol), N,N′-dicyclohexylcarbodiimide (17 mg, 0.08 mmol)and 4-dimethylaminopyridine (5 mg, 0.04 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to afford 7-(benzyloxy)chroman-3-yl 3-methoxybenzoate (15 mg, 89.5) as a colorless oil, which was used as for hydrogenolysis. 7-(benzyloxy)chroman-3-yl 3-methoxybenzoate (11 mg, 0.028 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23k** (7.5 mg, 89.4 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.52 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.09 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 6.92 (dt, *J* = 8.2, 1.0 Hz, 1H), 6.43 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.39 (d, *J* = 2.5 Hz, 1H), 5.49 (qd, *J* = 4.9, 2.3 Hz, 1H), 4.81 (brs, 1H), 4.32 (ddd, *J* = 11.5, 4.9, 1.9 Hz, 1H), 4.24 (ddt, *J* = 11.4, 1.8, 1.0 Hz, 1H), 3.19 (ddt, *J* = 16.7, 5.2, 1.2 Hz, 1H), 3.03 – 2.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 159.7, 155.3, 154.8, 131.4, 130.9, 129.6, 122.4, 119.8, 114.5, 111.3, 108.9, 103.5, 67.1, 66.5, 55.7, 29.9; IR (KBr)ν_{max} 3384, 2910, 2848, 1701, 1635, 1508, 1259, 1164, 1116, 667 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{17}H_{17}O_5$, 301.1076, found 301.1076.

7-Hydroxychroman-3-yl 4-methoxybenzoate (23l)

A solution of **22b** (11 mg, 0.04 mmol) in dichloromethane (0.5 mL) was added to a stirred solution 4-methoxybenzoic acid (12 mg, 0.08 mmol), N,N′-dicyclohexylcarbodiimide (17 mg, 0.08 mmol) and 4-dimethylaminopyridine (4.8 mg, 0.04 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to afford 7-(benzyloxy)chroman-3-yl 4-methoxybenzoate (15.5 mg, 79.2 %) as a colorless oil, which was used as for hydrogenolysis. 7-(Benzyloxy)chroman-3-yl 4-methoxybenzoate (11 mg, 0.028 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23l** (8 mg, 94.3 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.88 (m, 2H), 6.93 (dt, *J* = 8.3, 0.9 Hz, 1H), 6.91 – 6.87 (m, 2H), 6.43 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.39 (d, *J* = 2.5 Hz, 1H), 5.48 (qd, *J* = 4.8, 2.2 Hz, 1H), 4.78 (brs, 1H), 4.32 (ddd, *J* = 11.5, 4.9, 1.9 Hz, 1H), 4.23 (dtd, *J* = 11.5, 1.5, 0.8 Hz, 1H), 3.85 (s, 3H), 3.18 (ddt, *J* = 16.5, 5.0, 1.2 Hz, 1H), 2.95 (dtd, *J* = 16.7, 2.4,

1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 163.7, 155.3, 154.8, 132.0, 130.9 (2), 122.5 (2), 113.8, 111.5, 108.8, 103.5, 67.2, 66.0, 55.7, 29.9; IR (KBr)ν_{max} 3392, 2918, 2848, 1701, 1606, 1510, 1458, 1259, 1164, 1108, 1022 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{17}H_{17}O_5$, 301.1076, found 301.1071.

7-Hydroxychroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (23m)

A solution of **22b** (10 mg, 0.039 mmol)in dichloromethane (0.5 mL) was added to a stirred solution 4-methoxybenzoic acid (12 mg, 0.08 mmol), N,N′-dicyclohexylcarbodiimide (17 mg, 0.08 mmol)a nd 4-dimethylaminopyridine (4.8 mg, 0.04 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL) dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to afford 7-(benzyloxy)chroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (17 mg, 87.4 %) as a colorless oil, which was used further as for hydrogenolysis. 7-(benzyloxy)chroman-3-yl 3′, 6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (12 mg, 0.024 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23m** (9 mg, 91.4 %) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 2H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.10 – 7.05 (m, 1H), 7.03 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.95 – 6.88 (m, 2H), 6.42 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 4.73 (brs, 1H), 4.31 (ddd, *J* = 11.4, 5.1, 1.8 Hz, 1H), 4.24 (ddd, *J* = 11.5, 2.4, 1.1 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.19 (ddt, *J* = 16.6, 5.0, 1.2 Hz, 1H), 3.03 – 2.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 160.6, 159.5, 155.3, 154.8, 138.9, 132.7, 131.3, 130.9, 130.6, 129.3, 122.5, 122.2, 115.5, 113.1, 111.5, 110.8, 108.9, 103.5, 67.2, 66.2, 56.0, 55.5, 30.0; IR (KBr)ν_{max} 3411, 2921, 1701, 1598, 1510, 1278, 1224, 1155, 1116, 1043, 754 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{24}H_{23}O_6$, 407.1495, found 407.1475.

7-Hydroxychroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (23n)

4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoic acid (39 mg, 0.156 mmol) and thionyl chloride (38 μL, 0.312 mmol) in THF (5 mL) were heated at reflux for 3 h under argon, cooled to rt and concentrated. The residue was dissolved in dichloromethane (0.5 mL) and added drop wise to a stirred solution of **22b** (20 mg, 0.078) in dichloromethane (0.7 mL) with triethylamine (0.3 mL) under argon at 0 °C. The resulting mixture was stirred for and stirred for 6 h at rt before solvent was removed. The residue was purified by flash chromatography (SiO_2 1:4 EtOAc/Hexanes) to give 7-benzyloxychroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (26 mg, 84 %) as q colorless oil, which was used as for hydrogenolysis. A solution of palladium acetate (1.3 mg, 0.006 mg), triethylamine (4μL, 0.03 mmol), triethylsilane (24 μL, 0.15) in dichloromethane (0.8 mL) was stirred for 15 minutes under argon before the addition of a solution of 7-benzyloxychroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (15 mg, 0.03 mmol) in dichloromethane (0.4 mL). The resulting mixture was stirred for 15 h, quenched with saturated ammonium chloride (2 mL)

and extracted with ether (3 × 4 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, filtered and concentrated solvent. The residue was purified by flash chromatography (SiO_2, 1:2 EtOAc/Hexanes) to give **23n** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 2.1 Hz, 1H), 7.84 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.92 (dt, *J* = 8.3, 0.9 Hz, 1H), 6.46 – 6.40 (m, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 5.49 (qd, *J* = 4.7, 2.2 Hz, 1H), 5.17 (dddt, *J* = 7.3, 5.9, 2.9, 1.4 Hz, 1H), 4.63 (s, 1H), 4.32 (ddd, *J* = 11.5, 4.8, 1.9 Hz, 1H), 4.22 (dt, *J* = 11.4, 1.6 Hz, 1H), 3.24 (d, *J* = 7.2 Hz, 2H), 3.18 (ddt, *J* = 16.7, 5.1, 1.2 Hz, 1H), 2.94 (ddd, *J* = 16.5, 4.7, 1.8 Hz, 1H), 2.32 (s, 3H), 1.72 (q, *J* = 1.3 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 164.4, 154.0, 153.6, 151.7, 132.9, 130.9, 129.6 (2), 127.7, 126.7 (2), 121.4, 119.7, 110.1, 107.6, 102.2, 65.8, 65.1, 28.7, 27.7, 24.6, 19.8, 16.8; IR (KBr)ν_{max} 3419, 2823, 2854, 1716, 1596, 1456, 1286, 1201, 1163, 1054, 796 cm^{-1}; HRMS (ESI−) *m/z* [M+H$^+$] calcd for $C_{23}H_{25}O_6$, 397.1651, found 397.1642.

5-Hydroxychroman-3-yl benzoate (23o)

A solution of **22c** (9 mg, 0.035 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of benzoic acid (8.6 mg, 0.07 mmol), N,N′-dicyclohexylcarbodiimide (23 mg, 0.11 mmol) and 4-dimethylaminopyridine (4.2 mg, 0.035 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:9 EtOAc/Hexanes) to afford give 5-(benzyloxy)chroman-3-yl benzoate (21 mg, 90%) as a colorless oil, which was used as for hydrogenolysis. obtained. 5-(benzyloxy)chroman-3-yl benzoate (5 mg, 0.014 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23o** (3 mg, 93 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 7.92 (m, 2H), 7.62 – 7.47 (m, 1H), 7.47 – 7.35 (m, 2H), 7.01 (t, *J* = 8.1 Hz, 1H), 6.52 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.38 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.55 (tdd, *J* = 5.2, 4.4, 2.2 Hz, 1H), 4.84 (brs, 1H), 4.33 (ddd, *J* = 11.4, 4.9, 1.9 Hz, 1H), 4.22 (dt, *J* = 11.6, 1.5 Hz, 1H), 3.12 (dd, *J* = 17.4, 5.5 Hz, 1H), 2.97 (ddd, *J* = 17.5, 4.3, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 155.3, 154.5, 133.4, 130.1, 130.0, 128.6 (2), 127.7 (2), 109.4, 107.4, 107.2, 66.8, 65.9, 25.3. IR (KBr)ν_{max} 3374, 2921, 1703, 1681,1476, 1098, 770 cm^{-1}; HRMS (ESI−) *m/z* [M−H$^-$] calcd for $C_{16}H_{13}O_4$, 269.0814, found 269.0804.

5-Hydroxychroman-3-yl 3-methoxybenzoate (23p)

A solution of **22c** (14 mg, 0.055 mmol) in dichloromethane (0.5 mL) was added to a stirred solution of 3-methoxybenzoic acid (17 mg, 0.11 mmol), N,N′-dicyclohexylcarbodiimide (23 mg, 0.11 mmol) and 4-dimethylaminopyridine (8 mg, 0.11mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The eluent was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated

sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed. The residue was purified by flash chromatography (SiO_2, 1:9 EtOAc/Hexanes) to afford give give 5-(benzyloxy)chroman-3-yl 3-methoxybenzoate (19 mg, 90%) as a colorless oil, which was used as for hydrogenolysis. 5-(benzyloxy)chroman-3-yl 3-methoxybenzoate (18 mg, 0.044 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23p** (12.9 mg, 92.4 %) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.46 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.02 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 6.93 (t, *J* = 8.1 Hz, 1H), 6.44 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.31 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.54 – 5.43 (m, 1H), 4.87 (s, 1H), 4.27 – 4.21 (m, 1H), 4.15 (dt, *J* = 11.4, 1.6 Hz, 1H), 3.75 (s, 3H), 3.06 (dd, *J* = 17.4, 5.5 Hz, 1H), 2.90 (ddd, *J* = 17.4, 4.6, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 159.7, 155.3, 154.5, 131.4, 129.6, 127.7, 122.4, 119.8, 114.5, 109.4, 107.4, 107.2, 66.8, 66.1, 55.7, 25.3. IR (KBr)ν_{max} cm^{-1}; HRMS (ESI−) *m/z* [M−H$^-$] calcd for $C_{17}H_{15}O_5$, 299.0920, found 299.0934.

5-Hydroxychroman-3-yl 4-methoxybenzoate (23q)

A solution of **22c** (11 mg, 0.042 mmol) in dichloromethane (0.5 mL) was added to a stirred solution of 4-methoxybenzoic acid (13 mg, 0.09 mmol), N,N′-dicyclohexylcarbodiimide (18 mg, 0.085 mmol) and 4-dimethylaminopyridine (5 mg, 0.05mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:9 EtOAc/Hexanes) to give 5-(benzyloxy)chroman-4-yl 3-methoxybenzoate (15 mg, 91.5%) as a colorless oil, which was used as for hydrogenolysis. 5-(Benzyloxy)chroman-3-yl 4-methoxybenzoate (5 mg, 0.014 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23q** (3.5 mg, 93 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 7.92 (m, 2H), 7.64 – 7.49 (m, 1H), 7.49 – 7.38 (m, 2H), 7.02 (t, *J* = 8.1 Hz, 1H), 6.53 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.40 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.56 (tdd, *J* = 5.2, 4.4, 2.2 Hz, 1H), 4.86 (s, 1H), 4.35 (ddd, *J* = 11.4, 4.9, 1.9 Hz, 1H), 4.23 (dt, *J* = 11.6, 1.6 Hz, 1H), 3.14 (dd, *J* = 17.4, 5.5 Hz, 1H), 2.99 (ddd, *J* = 17.5, 4.3, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 155.3, 154.5 (2), 133.4 (2), 130.1, 130.0, 128.6, 127.7, 109.4 (2), 107.4, 107.2, 66.8, 65.9, 25.3; IR (KBr)ν_{max} 3384, 2921, 1701, 1683, 1606, 1471, 1259, 1168, 1099, 771 cm^{-1}; HRMS (ESI−) *m/z* [M−H$^-$] calcd for $C_{17}H_{15}O_5$, 299.0920, found 299.0928.

5-hydroxychroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (23r)

A solution of **22c** (11 mg, 0.042 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylic acid (22 mg, 0.085 mmol),, N,N′-dicyclohexylcarbodiimide (18 mg, 0.085 mmol) and 4-dimethylaminopyridine (5 mg,

0.0042mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to afford 7-(benzyloxy)chroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (18 mg, 85 %) as a colorless oil, which was used further as obtained. 7-(benzyloxy)chroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (18 mg, 0.036 mmol) and palladium/carbon (10%) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **23r** (13 mg, 88.2 %) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 2H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.00 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.96 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.94 – 6.87 (m, 2H), 6.83 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.44 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.31 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.55 – 5.34 (m, 1H), 4.86 (brs, 1H), 4.22 (ddd, *J* = 11.3, 5.2, 1.7 Hz, 1H), 4.16 (ddd, *J* = 11.4, 2.4, 1.2 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.06 (dd, *J* = 17.3, 5.6 Hz, 1H), 2.92 – 2.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 160.6, 159.4, 155.3, 154.5, 138.9, 132.7, 131.3, 130.7, 129.3, 127.6, 122.5, 122.2, 115.4, 113.2, 110.7, 109.4, 107.4, 107.3, 66.9, 65.7, 56.0, 55.5, 25.4; IR (KBr)ν_{max} 3396, 2933, 2837, 1712, 1598, 1469, 1440, 1249, 1031, 771, 711 cm^{-1}; HRMS (ESI−) *m/z* [M+H$^+$] calcd for $C_{24}H_{23}O_6$, 407.1495, found 407.1482.

5-Hydroxychroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (23s)

A solution of **22c** (10 mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoic acid (20 mg, 0.08 mmol), N,N′-dicyclohexylcarbodiimide (16 mg, 0.08 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and solvent was removed. The residue was purified by flash chromatography (SiO_2, 1:8 EtOAc/Hexanes) to give 5-(benzyloxy)chroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (13 mg, 72.2 %) as a colorless oil, which was used as in the next step. For benzyl group removal, a solution of palladium acetate (1 mg, 0.004 mmol), triethylamine (4μL, .025 mmol), triethylsilane (19μL, 0.0112) in DCM (0.8 mL) was stirred for 15 minutes under argon before the addition of a solution of 5-(benzyloxy)chroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (12 mg, 0.025mmol) in dichloromethane (0.2 mL) was added and reaction was stirred for 15 hours. Then reaction was quenched with saturated ammonium chloride (2 mL) and extracted with ether (3 × 4 mL). The combined organic layers were washed with saturated sodium chloride solution, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:2 EtOAc/Hexanes) to afford **23s** as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.67 (m, 2H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.03 – 6.98 (m, 1H), 6.53 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.43 (dd, *J* = 8.1, 1.0 Hz, 1H), 5.52 (tdd, *J* = 5.1, 4.2, 2.1 Hz, 1H), 5.17 (dddt, *J* = 7.3, 5.8, 2.9, 1.4 Hz, 1H), 4.31 (ddd, *J* = 11.5, 4.8, 2.0 Hz, 1H), 4.24 – 4.12 (m, 1H), 3.24 (d, *J* = 7.2 Hz, 2H), 3.05 (dd, *J* = 17.6,

5.3 Hz, 1H), 2.94 (ddd, *J* = 17.5, 4.4, 1.8 Hz, 1H), 2.32 (s, 3H), 1.71 (q, *J* = 1.3 Hz, 3H), 1.69 – 1.65 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 165.4, 155.0, 154.6, 152.7, 133.9, 131.9, 128.8, 127.8 (2), 127.1, 122.4, 120.8, 110.8, 110.5, 109.5, 66.4, 66.0, 28.7, 25.8, 25.7, 20.9, 17.8; IR (KBr)ν_{max} 3429, 2854, 1716, 1595, 1458, 1286, 1161, 1054 cm^{-1}; HRMS (ESI−) *m/z* [M+H$^+$] calcd for $C_{23}H_{25}O_6$, 397.1651, found 397.1662.

5,7-Dimethoxychroman-3-yl benzoate (27a)

A solution of **26** (10 mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of benzoic acid (12 mg, 0.1 mmol), N,N′-dicyclohexylcarbodiimide (20.6 mg, 0.1 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:7 EtOAc/Hexanes) to afford **27a** (13 mg, 90 %) as a colorless oil ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 7.91 (m, 2H), 7.55 (ddt, *J* = 7.6, 6.8, 1.1 Hz, 1H), 7.47 – 7.37 (m, 2H), 6.11 (s, 2H), 5.52 (tdt, *J* = 5.5, 4.5, 1.9 Hz, 1H), 4.32 (dddd, *J* = 11.4, 4.9, 1.9, 0.9 Hz, 1H), 4.21 (ddd, *J* = 11.5, 2.2, 1.2 Hz, 1H), 3.79 (dd, *J* = 2.9, 0.9 Hz, 6H), 3.09 – 2.94 (m, 1H), 2.88 (ddd, *J* = 17.4, 4.3, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 159.8, 159.1, 155.3, 133.4, 130.3, 130.1 (2), 128.6 (2), 100.8, 93.4, 92.0, 67.1, 66.2, 55.7, 55.6, 25.1; IR (KBr)ν_{max} 2931, 1716, 1620, 1591, 1499, 1456, 1145, 1045, 754 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{18}H_{19}O_5$, 315.1232, found 315.1239.

5,7-Dimethoxychroman-3-yl 3-methoxybenzoate (27b)

A solution of **26** (10 mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 3-methoxybenzoic acid (15 mg, 0.1 mmol), N,N′-dicyclohexylcarbodiimide (20.6 mg, 0.1 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:6 EtOAc/Hexanes) to afford **27b** (13 mg, 80 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.54 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.09 (ddd, *J* = 8.3, 2.7, 1.1 Hz, 1H), 6.10 (d, *J* = 1.2 Hz, 2H), 5.69 – 5.42 (m, 1H), 4.30 (ddd, *J* = 11.4, 5.1, 1.8 Hz, 1H), 4.24 – 4.16 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.02 (ddd, *J* = 17.5, 5.6, 1.3 Hz, 1H), 2.86 (ddd, *J* = 17.4, 4.5, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 159.8, 159.7, 159.0, 155.3, 131.5, 129.6, 122.4, 119.6, 114.5, 100.7, 93.4, 92.0, 67.0, 66.3, 55.7, 55.6, 55.6, 25.1; IR (KBr)ν_{max} 2935, 2839, 1716, 1622, 1593, 1498, 1456, 1276, 1145, 1045, 754 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{19}H_{21}O_6$, 345.1338, found 345.1347.

5,7-Dimethoxychroman-3-yl 4-methoxybenzoate (27c)

A solution of **26** (10 mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 4-methoxybenzoic acid (15 mg, 0.1 mmol), N,N′-dicyclohexylcarbodiimide (20.6 mg, 0.1 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:6 EtOAc/Hexanes) to afford **27c** (14 mg, 86 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (ddd, *J* = 10.7, 5.1, 2.6 Hz, 2H), 7.27 (td, *J* = 4.5, 1.5 Hz, 1H), 6.89 (ddd, *J* = 8.5, 5.7, 2.6 Hz, 2H), 6.10 (m, 2H), 5.56 – 5.37 (m, 1H), 4.29 (m, 1H), 4.26 – 4.12 (m, 1H), 3.88 – 3.81 (s, 3H), 3.78 (s, 6H), 3.10 – 2.93 (m, 1H), 2.85 (dddd, *J* = 17.5, 5.7, 4.3, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 163.7, 159.8, 159.0, 155.3, 132.1 (2), 122.7, 113.8 (2), 100.9, 93.3, 91.9, 67.1, 65.8, 55.6, 55.6 (2), 25.1; IR (KBr)ν_{max} 2935, 1716, 1620, 1593, 1499, 1456, 1145, 1043 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{19}H_{21}O_6$, 345.1338, found 345.1347.

5,7-Dimethoxychroman-3-yl 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylate (27d)

A solution of **26** (10 mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxylic acid (15 mg, 0.1 mmol), N,N′-dicyclohexylcarbodiimide (20.6 mg, 0.1 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:6 EtOAc/Hexanes) to afford **27d** (18.4 mg, 82 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 7.97 (m, 2H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.08 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.04 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.91 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.10 (s, 2H), 5.54 – 5.42 (m, 1H), 4.28 (ddd, *J* = 11.3, 5.2, 1.7 Hz, 1H), 4.21 (ddd, *J* = 11.2, 2.3, 1.1 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.02 (ddd, *J* = 17.4, 5.6, 1.2 Hz, 1H), 2.85 (ddd, *J* = 17.2, 4.6, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 160.5, 159.7, 159.4, 159.0, 155.3, 139.0, 132.6, 131.3, 130.6, 129.2, 122.7, 122.2, 115.4, 113.1, 110.7, 100.9, 93.3, 91.9, 67.1, 66.0, 56.0, 55.62, 55.6, 55.5, 25.2. IR (KBr)ν_{max} 2954, 2931, 1712, 1595, 1498, 1456, 1436, 1247, 1215, 1052, 813, 756 cm^{-1}; HRMS (ESI+) *m/z* [M+Na$^+$] calcd for $C_{26}H_{26}NaO_7$, 473.1576, found 473.1566.

5,7-Dimethoxychroman-3-yl 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoate (27e)

A solution of **26** (20 mg, 0.08 mmol), in dichloromethane (1 mL) was added to a stirred solution of 4-acetoxy-3-(3-methylbut-2-en-1-yl)benzoic acid (48 mg, 0.19 mmol), N,N′-dicyclohexylcarbodiimide (40 mg, 0.19 mmol) and 4-dimethylaminopyridine (12 mg, 0.084 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (10 mL), washed with 0.5N HCl (2 × 8 mL) and then with saturated sodium bicarbonate (2 × 8 mL) solution. The combined organic

layers were washed with saturated sodium chloride solution (8 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:7 EtOAc/Hexanes) to afford **27e** (17 mg, 53%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 2.1 Hz, 1H), 7.86 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.18 (s, 2H), 5.57 – 5.44 (m, 1H), 5.18 (dddd, *J* = 7.2, 5.8, 2.8, 1.4 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.25 (d, *J* = 7.2 Hz, 2H), 2.99 (ddd, *J* = 17.3, 5.4, 1.2 Hz, 1H), 2.86 (ddd, *J* = 17.4, 4.4, 1.8 Hz, 1H), 2.32 (s, 3H), 1.72 (q, *J* = 1.2 Hz, 3H), 1.69 – 1.63 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 165.7, 159.8, 159.0, 155.2, 152.9, 134.1 (2), 132.1, 129.0, 128.1, 122.6, 121.1, 100.7, 93.3, 91.9, 66.9, 66.2, 55.6, 55.6, 28.9, 25.9, 25.1, 21.1, 18.1; IR (KBr)ν_{max} 2937, 2844, 1737, 1622, 2595, 1242, 1218, 1201, 1145, 1128, 1058, 811 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{25}H_{29}O_7$, 441.1913, found 441.1894.

5,7-Dimethoxychroman-3-yl 3,4-dimethoxybenzoate (27f)

A solution of **26** (5 mg, 0.025mmol) in dichloromethane (0.5 mL) was added to a stirred solution of 3,4-dimethoxybenzoic acid (9mg, 0.05 mmol), N,N′-dicyclohexylcarbodiimide (10mg, 0.05 mmol) and 4-dimethylaminopyridine (3mg, 0.025 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:6 EtOAc/Hexanes) to afford **27f** (10 mg, 71.4 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.10 (s, 2H), 5.57 – 5.41 (m, 1H), 4.28 (ddd, *J* = 11.3, 5.1, 1.8 Hz, 1H), 4.21 (ddd, *J* = 11.3, 2.2, 1.1 Hz, 1H), 3.92 (d, *J* = 8.3 Hz, 6H), 3.79 (d, *J* = 4.1 Hz, 6H), 3.02 (ddd, *J* = 17.2, 5.5, 1.2 Hz, 1H), 2.86 (ddd, *J* = 17.3, 4.5, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9 (2), 159.5 (2), 155.4 (2), 138.5, 128.8, 128.3, 126.5, 100.5, 93.5, 92.4, 78.9, 66.6, 55.7 (2), 55.6 (2), 28.4; IR (KBr)ν_{max} 2931, 1701, 1558, 1458, 1419, 1271, 732 cm^{-1}; HRMS (ESI+) *m/z* [M+Na$^+$] calcd for $C_{20}H_{22}NaO_7$, 397.1263, found 397.1269.

5,7-Dimethoxychroman-3-yl 3,5-dimethoxybenzoate (27g)

A solution of **26** (5 mg, 0.025mmol) in dichloromethane (0.5 mL) was added to a stirred solution of 3,4-dimethoxybenzoic acid (9mg, 0.05 mmol), N,N′-dicyclohexylcarbodiimide (10mg, 0.05 mmol) and 4-dimethylaminopyridine (3mg, 0.025 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 ×4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:6 EtOAc/Hexanes) to afford **27g** (11.9mg, 85 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 2.4 Hz, 2H), 6.64 (t, *J* = 2.4 Hz, 1H), 6.10 (s, 2H), 5.57 – 5.43 (m, 1H), 4.28 (ddd, *J* = 11.3, 5.2, 1.7 Hz, 1H), 4.21 (ddd, *J* = 11.3, 2.4, 1.1 Hz, 1H), 3.85 – 3.73 (m, 13H), 3.02 (ddd, *J* = 17.3, 5.5, 1.2 Hz, 1H), 2.85 (ddd, *J* = 17.4, 4.7, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9 (2), 159.5 (2), 155.4 (2), 138.5, 128.8, 128.3, 126.5, 100.5 (2), 93.5, 92.4, 78.9, 66.6, 55.7, 55.6

(2), 28.4. IR (KBr)ν_{max} 2931, 1701, 1558, 1458, 1419, 1271, 732 cm^{-1}; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{20}H_{22}NaO_7$, 397.1263, found 397.1269.

5,7-Dimethoxychroman-3-yl 3-ethoxybenzoate (27h)

A solution of **26** (10 mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 3-ethoxybenzoic acid (17 mg, 0.1 mmol), N,N′-dicyclohexylcarbodiimide (20.6 mg, 0.1 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h and filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:6 EtOAc/Hexanes) to afford **27h** (14 mg, 82.3 %) as a colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 7.52 (ddd, *J* = 7.7, 1.5, 1.0 Hz, 1H), 7.46 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.16 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 6.14 (d, *J* = 2.4 Hz, 1H), 6.06 (d, *J* = 2.4 Hz, 1H), 5.50 – 5.41 (m, 1H), 4.32 (ddd, *J* = 11.5, 4.5, 2.0 Hz, 1H), 4.22 (ddt, *J* = 11.5, 1.9, 0.9 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 2.99 (ddd, *J* = 17.3, 5.2, 1.1 Hz, 1H), 2.89 – 2.78 (m, 1H), 1.36 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 166.2, 160.7, 160.0, 159.8, 156.1, 132.5, 130.5, 122.3, 120.1, 115.9, 101.1, 94.2, 92.2, 67.3, 67.1, 64.3, 55.8, 55.5, 25.4, 15.0; IR (KBr)ν_{max} 2910, 1718, 1622, 1593, 1498, 1423, 1274, 1217, 1145, 1051, 754 cm^{-1}; HRMS (ESI+) *m/z* [M+H^+] calcd for $C_{20}H_{23}O_6$, 359.1495, found 359.1483.

5,7-Dimethoxychroman-3-yl 3-(benzyloxy)benzoate (27i)

A solution of **26** (10 mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 3-(benzyloxy)benzoic acid (23 mg, 0.1 mmol) (17 mg, 0.1 mmol), N,N′-dicyclohexylcarbodiimide (20.6 mg, 0.1 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt then filterd. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:5 EtOAc/Hexanes) to afford **27i** (18 mg, 90 %) as a pale yellow amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.2, 1.5 Hz, 2H), 7.48 – 7.36 (m, 4H), 7.37 – 7.27 (m, 3H), 7.19 – 7.12 (m, 1H), 6.11 (s, 2H), 5.50 (ddt, *J* = 5.3, 4.2, 2.5 Hz, 1H), 5.09 (s, 2H), 4.31 (ddd, *J* = 11.3, 4.9, 1.9 Hz, 1H), 4.20 (ddd, *J* = 11.4, 2.2, 1.2 Hz, 1H), 3.02 (ddd, *J* = 17.4, 5.5, 1.2 Hz, 1H), 2.87 (ddd, *J* = 17.4, 4.3, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 159.8, 159.0, 158.8, 155.3, 136.7, 131.6, 129.6 (2), 128.9 (2), 128.3 (2), 127.8, 122.7, 120.4, 115.6, 100.7, 93.4, 92.0, 70.4, 67.0, 66.3, 55.6, 55.6, 25.1; IR (KBr)ν_{max} 2918, 1701, 1683, 1558, 15036, 1458, 1203, 1145, cm^{-1}; HRMS (ESI+) *m/z* [M+H^+] calcd for $C_{25}H_{25}O_6$, 421.1651, found 421.1637.

5,7-Dimethoxychroman-3-yl 4-(benzyloxy)benzoate (27j)

A solution of **26** (10 mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 4-(benzyloxy)benzoic acid (23 mg, 0.1 mmol) (23 mg, 0.1 mmol) (17 mg, 0.1

mmol), N,N′-dicyclohexylcarbodiimide (20.6 mg, 0.1 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:5 EtOAc/Hexanes) to afford **27j** (17 mg, 85%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.2, 1.5 Hz, 2H), 7.46 – 7.37 (m, 4H), 7.36 – 7.29 (m, 2H), 7.21 – 7.04 (m, 1H), 6.11 (s, 2H), 5.50 (ddt, *J* = 5.3, 4.2, 2.5 Hz, 1H), 5.09 (s, 2H), 4.31 (ddd, *J* = 11.3, 4.9, 1.9 Hz, 1H), 4.20 (ddd, *J* = 11.4, 2.2, 1.2 Hz, 1H), 3.81 – 3.78 (m, 6H), 3.02 (ddd, *J* = 17.4, 5.5, 1.2 Hz, 1H), 2.87 (ddd, *J* = 17.4, 4.3, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 162.8, 159.7, 159.0, 155.3, 136.4, 132.1 (2), 128.9 (2), 128.4, 127.7, 122.9, 114.6 (2), 100.8, 93.3, 91.9, 70.3, 67.1, 65.8, 55.6, 55.6, 25.1. IR (KBr)ν_{max}, 2918, 2817, 1701, 1683, 1558, 1503, 1458, 1203, 1145, 729 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{25}H_{25}O_6$, 421.1651, found 421.1666.

5,7-Dimethoxychroman-3-yl 3,5-bis(benzyloxy)benzoate (27k)

A solution of **26** (10 mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 3,5-bis(benzyloxy)benzoic acid (33.4 mg, 0.1 mmol) N,N′-dicyclohexylcarbodiimide (20.6 mg, 0.1 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:5 EtOAc/Hexanes) to afford **27k** (22 mg, 88%) as an amorphous pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.27 (m, 12H), 6.79 (t, *J* = 2.3 Hz, 1H), 6.11 (s, 2H), 5.47 (qd, *J* = 5.0, 2.2 Hz, 1H), 5.04 (s, 4H), 4.29 (ddd, *J* = 11.4, 5.0, 1.8 Hz, 1H), 4.25 – 4.12 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.01 (ddd, *J* = 17.4, 5.5, 1.1 Hz, 1H), 2.85 (ddd, *J* = 17.4, 4.5, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 159.9 (2), 159.8, 159.0, 155.3, 136.6 (2), 132.1, 128.9 (4), 128.4 (4), 127.9 (2), 108.8 (2), 107.3, 100.7, 93.4, 92.0, 70.5 (2), 66.9, 66.5, 55.6, 55.6, 25.1; IR (KBr)ν_{max} 2955, 2852, 1697, 1596, 1456, 1145, 1251, 1009, 769, cm^{-1}. HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{32}H_{31}O_7$, 527.2070, found 527.2087.

5,7-Dimethoxychroman-3-yl 3,4-bis(benzyloxy)benzoate (27l)

A solution of **26** (9mg, 0.04 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 3,4-bis(benzyloxy)benzoic acid (33.4 mg, 0.1 mmol) N,N′-dicyclohexylcarbodiimide (20.6 mg, 0.1 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:5 EtOAc/Hexanes) to afford **27l** (20.8 mg, 92%) as an amorphous pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.0 Hz, 1H), 7.58 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.48 –

7.40 (m, 4H), 7.40 – 7.29 (m, 6H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.11 (s, 2H), 5.56 – 5.39 (m, 1H), 5.22 (s, 2H), 5.17 (s, 2H), 4.27 (ddd, J = 11.3, 4.9, 1.8 Hz, 1H), 4.22 – 4.14 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.98 (ddd, *J* = 17.3, 5.5, 1.2 Hz, 1H), 2.83 (ddd, *J* = 17.4, 4.3, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 159.8, 159.0, 155.3, 153.1, 148.4, 137.0, 136.7, 128.8 (3), 128.7, 128.2, 128.1, 127.7 (2), 127.3 (2), 124.4, 123.1, 115.8, 113.3, 100.8, 93.3, 91.9, 71.3, 71.0, 67.0, 65.9, 55.6, 55.6, 25.1. IR (KBr)ν_{max} 2921, 2848, 1699, 1618, 1510, 1454, 1290, 1203, 1058 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{32}H_{31}O_7$, 527.2070, found 527.2081.

5,7-Dimethoxychroman-3-yl 4-(benzyloxy)-3-methoxybenzoate (27m)

A solution of **26** (20 mg, 0.1 mmol), in dichloromethane (0.5 mL) was added to a stirred solution of 4-(benzyloxy)-3-methoxybenzoic acid (49 mg, 0.19 mmol) N,N′-dicyclohexylcarbodiimide (39 mg, 0.19 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) under argon at 0 °C. The resulting solution was stirred for 6 h at rt and then filtered. The filtrate was diluted with dichloromethane (5 mL), washed with 0.5N HCl (2 × 4 mL) and then with saturated sodium bicarbonate (2 × 4 mL) solution. The combined organic layers were washed with saturated sodium chloride solution (4 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:5 EtOAc/Hexanes) to afford **27m** (34 mg, 81%) as an amorphous pale yellow solid. IR (KBr)ν_{max} 2921, 2848, 1699, 1618, 1510, 1454, 1290, 1203, 1058 cm−1. HRMS (ESI+) m/z [M+H$^+$] calcd for $C_{26}H_{27}O_7$, 451.1757, found 451.1668.

5,7-Dimethoxychroman-3-yl 3-hydroxybenzoate (28a)

Palladium/carbon (10%) and **27i** (18 mg, 0.03 mmol) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give flash chromatography (SiO_2, 1:3 EtOAc/Hexanes) to give **28a** (8.8 mg, 92.6%) as a colorless oil: ^{1}H NMR (500 MHz, CD_3CN) δ 7.41 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H), 7.33 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.03 (ddd, *J* = 8.1, 2.6, 1.1 Hz, 1H), 6.14 (d, *J* = 2.3 Hz, 1H), 6.07 (d, *J* = 2.3 Hz, 1H), 5.52 – 5.36 (m, 1H), 4.30 (ddd, *J* = 11.7, 4.2, 2.1 Hz, 1H), 4.15 (ddt, *J* = 11.6, 1.9, 1.0 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.92 (ddd, *J* = 17.4, 5.2, 1.1 Hz, 1H), 2.86 – 2.71 (m, 1H). ^{13}C NMR (125 MHz, CD_3CN) δ 166.5, 160.7, 159.9, 157.9, 156.1, 132.6, 130.8, 122.5, 121.9, 118.3, 117.0, 94.2, 92.4, 67.4, 67.0, 56.2, 55.9, 25.1. IR (KBr)ν_{max} 3335, 2918, 1701, 1683, 1558, 15036, 1458, 1203, 1145, cm^{-1}. HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{18}H_{19}O_6$, 331.1182, found 331.1188.

5,7-Dimethoxychroman-3-yl 4-hydroxybenzoate (27b)

Palladium/carbon (10%) and **27j** (12 mg, 0.028 mmol) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:3 EtOAc/Hexanes) to give the **28b** (9 mg, 90 %) as a colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 9.16 (s, 1H), 7.88 – 7.80 (m, 2H), 6.94 – 6.86 (m, 2H), 6.14 (d, *J* = 2.3 Hz, 1H), 6.05 (d, *J* = 2.3 Hz, 1H), 5.49 – 5.36 (m, 1H), 4.29

(ddd, *J* = 11.5, 4.6, 2.0 Hz, 1H), 4.24 – 4.14 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.97 (ddd, *J* = 17.3, 5.3, 1.1 Hz, 1H), 2.80 (ddd, *J* = 17.3, 4.0, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 166.1, 162.7, 160.7, 159.8, 156.1, 132.5 (2), 122.4, 116.0 (2), 101.2, 94.2, 92.2, 67.4, 66.4, 55.8, 55.5, 25.5. IR (KBr)ν_{max} 3365, 2956, 2852, 1701, 1596, 1456, 1214, 1145, 1051, 767cm^{-1}; HRMS (ESI+) *m/z* [M+Na$^+$] calcd for $C_{18}H_{18}NaO_6$, 353.1001, found 353.0991.

5,7-Dimethoxychroman-3-yl 3,5-dihydroxybenzoate (28c)

Palladium/carbon (10%) and **27k** (12 mg, 0.028 mmol) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:1 EtOAc/Hexanes) to give **28c** (12 mg, 91 %) as a colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.58 (s, 2H), 6.96 (d, *J* = 2.3 Hz, 2H), 6.56 (t, *J* = 2.3 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 6.05 (d, *J* = 2.3 Hz, 1H), 5.43 (dtd, *J* = 5.5, 4.1, 1.9 Hz, 1H), 4.31 (ddd, *J* = 11.6, 4.3, 2.1 Hz, 1H), 4.19 (ddt, *J* = 11.7, 1.9, 1.0 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.97 (ddd, *J* = 17.6, 5.4, 1.2 Hz, 1H), 2.82 – 2.74 (m, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 166.2, 160.7, 159.8 (2), 159.4, 156.1, 133.1, 108.7, 108.1, 101.1, 94.2, 92.2, 67.3, 66.8, 55.8, 55.5 (2), 25.3. IR (KBr)ν_{max} 3365, 3330, 2956, 2850, 1697, 1596, 1456, 1361, 1145, 1054, 1004, 769, cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{18}H_{19}O_7$, 347.1131, found 347.1134.

5,7-Dimethoxychroman-3-yl 3,4-dihydroxybenzoate (28d)

Palladium/carbon (10%) and **27l** (18 mg, 0.034 mmol) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:3 EtOAc/Hexanes) to give the desired product **28d** (11 mg, 92 %) as a colorless oil: ^{1}H NMR (500 MHz, $(CD_3)_2$ CO) δ 7.45 (d, *J* = 2.1 Hz, 1H), 7.41 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 6.10 – 6.04 (m, 1H), 5.49 – 5.38 (m, 1H), 4.29 (ddd, *J* = 11.5, 4.4, 2.0 Hz, 1H), 4.22 – 4.14 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 2.97 (ddd, *J* = 17.4, 5.5, 1.2 Hz, 1H). ^{13}C NMR (125 MHz, $(CD_3)_2$ CO)) δ 159.9, 160.2 (2), 158.1 (2), 123.6 (2), 122.85, 117.21, 115.9, 101.3, 94.3, 92.3, 67.47, 66.4, 55.9, 55.6, 25.5; IR (KBr)ν_{max} 3381, 3321, 2924, 2839, 1698, 16120, 1510, 1456, 1203, 1056, 728 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{18}H_{19}O_7$, 347.1131, found 347.1125:

5,7-Dimethoxychroman-3-yl 4-hydroxy-3-methoxybenzoate (28e)

Palladium/carbon (10%) and **27l** (24 mg, 0.053 mmol) were suspended in tetrahydrofuran (2 mL) and stirred for 18 h under a hydrogen atmosphere. The suspension was filtered through a small plug of SiO_2 (40 – 63 μm particle size). The eluent was concentrated and the residue purified by flash chromatography (SiO_2, 1:3 EtOAc/Hexanes) to give the desired product **28e** (17 mg, 91 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.52 (d, *J* = 1.9 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.10 (s, 2H), 6.07 (s, 1H), 5.47 (dq, *J* = 7.5, 2.6 Hz, 1H), 4.28 (ddd, *J* = 11.3, 5.1, 1.8 Hz, 1H), 4.24 – 4.16 (m, 1H), 3.92 (s, 3H), 3.78 (d, *J* = 3.5 Hz, 6H), 3.01 (ddd, *J* = 17.5, 5.6, 1.2 Hz, 1H), 2.85 (ddd, *J* = 17.3, 4.6,

1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 159.6, 158.2, 155.2, 150.2, 146.1, 124.5, 122.1, 114, 111.8, 100.6, 93.1, 91.7, 66.9, 65.8, 56.1, 55.4, 55.3, 24.9; IR (KBr)ν_{max} 3385, 2939, 2841, 1699, 1612, 1508, 1214, 1145, 729 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{19}H_{21}O_7$, 361.1287, found 361.1278.

3-Azido-5,7-dimethoxychroman (29)

A solution of **26** (75, 0.36 mmol) and triphenylphosphine (161 mg, 0.61) in tetrahydrofuran (2.5 ml) at 0 °C was treated with diisopropyl azodicarboxylate (120 μl, 0.61 mmol) and diphenylphosphoryl azide (130 μl, 0.61 mmol). The resulting mixture was stirred for 15 h at 25°C before the solvent was removed. The residue was purified by flash chromatography (SiO_2, 1:20 EtOAc/Hexanes) to give **29** (75 mg, 83.9 %) as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (d, *J* = 2.4 Hz, 1H), 6.06 (d, *J* = 2.4 Hz, 1H), 4.15 (ddd, *J* = 10.8, 2.6, 1.3 Hz, 1H), 4.02 (ddd, *J* = 10.9, 6.4, 1.5 Hz, 1H), 3.96 (qd, *J* = 6.0, 2.6 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 2.95 (ddd, *J* = 16.7, 5.5, 1.4 Hz, 1H), 2.71 (ddd, *J* = 16.7, 6.0, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 157.9, 154.1, 99.3, 92.3, 91.2, 66.3, 54.7, 54.6, 52.4, 23.8; IR (KBr)ν_{max} 2931, 2847, 2113, 1558, 1456, 1276,811 cm^{-1};HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{11}H_{14}N_3O_3$, 236.1035, found 236.1028.

5,7-Dimethoxychroman-3-amine (30)

To a solution of **29** and triphenylphosphine in water in THF (3 mL), water (22 μl, 0.93 mmol) was added and stirred for 30 h at rt. The solvent was removed and the residue purified via flash chromatography (silica gel 3:97 MeOH/$CHCl_3$) to give **30** (55 mg, 83%) as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 – 5.87 (m, 2H), 4.09 (ddd, *J* = 10.5, 2.8, 1.5 Hz, 1H), 3.84 – 3.79 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.34 (tdd, *J* = 6.8, 5.5, 2.9 Hz, 1H), 2.88 (ddd, *J* = 16.5, 5.5, 1.5 Hz, 1H), 2.36 (ddd, *J* = 16.4, 6.6, 1.2 Hz, 1H), 2.04 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 159.1, 155.3, 101.7, 93.2, 91.8, 71.3, 55.6, 55.5, 44.0, 28.9; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{11}H_{16}NO_3$, 210.1130, found 210.1133.

N-(5,7-Dimethoxychroman-3-yl)benzamide (31a)

Benzoic acid (15 mg, 0.12 mmol) and N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (19 mg, 0.14 mmol) were added to a solution of alcohol **30** (12 mg, 0.057 mmol) in dichloromethane (0.7 mL) with pyridine (0.3 mL). The resulting mixture was stirred for 16 h and then the reaction mixture was diluted with dichloromethane (2 mL). The organic phase was washed with saturated $NaHCO_3$ (2 × 2 mL) and saturated sodium chloride solution (3 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:2 Hexanes/EtOAc) to give **31a** (12 mg, 81%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.66 (m, 2H), 7.54 – 7.46 (m, 1H), 7.41 (tt, *J* = 6.6, 1.4 Hz, 2H), 6.39 (d, *J* = 8.0 Hz, 1H), 6.17 – 5.90 (m, 2H), 4.70 (ddtd, *J* = 7.5, 5.5, 3.5, 1.8 Hz, 1H), 4.26 (ddd, *J* = 10.9, 3.8, 2.1 Hz, 1H), 4.15 (dd, *J* = 10.9, 1.8 Hz, 1H), 3.78 (d, *J* = 1.1 Hz, 6H), 2.91 (dd, *J* = 17.2, 5.7 Hz, 1H), 2.78 (ddd, *J* = 17.1, 3.2, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 159.9, 159.4, 155.3, 134.5, 131.8, 128.7 (2), 127.2 (2), 101.0, 93.5, 92.2, 68.3, 55.6, 55.6, 42.6, 25.6; IR

(KBr)ν_{max} 3307, 2925, 2850, 1645, 1635, 1622, 1539, 1521, 1145, 1122, 813, 756cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{18}H_{20}NO_4$, 314.1392, found 314.1391.

N-(5,7-Dimethoxychroman-3-yl)-3-methoxybenzamide (31b)

3-Methoxybenzoic acid (15 mg, 0.12 mmol) and N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (19 mg, 0.14 mmol) were added to a solution of alcohol **30** (12 mg, 0.057 mmol) in dichloromethane (0.7 mL) with pyridine (0.3 mL). The resulting mixture was stirred for 16 h and then the reaction mixture was diluted with dichloromethane (2 mL). The organic phase was washed with saturated sodium bicarbonate (2 × 2 mL) and saturated sodium chloride solution (3 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:2 Hexanes/EtOAc) to give **31b** (12 mg, 70%) as pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.14 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.94 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 6.30 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 2.4 Hz, 1H), 6.01 (d, *J* = 2.4 Hz, 1H), 4.60 (dtt, *J* = 7.7, 3.8, 1.8 Hz, 1H), 4.17 (ddd, *J* = 10.9, 3.9, 2.1 Hz, 1H), 4.11 – 4.01 (m, 1H), 3.77 (s, 3H), 3.70 (s, 6H), 2.83 (dd, *J* = 17.1, 5.7 Hz, 1H), 2.69 (ddd, *J* = 17.2, 3.4, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 160.0, 159.9, 159.4, 155.3, 136.0, 129.7, 119.0, 117.9, 112.7, 100.9, 93.5, 92.2, 68.2, 55.7, 55.6 (2), 42.6, 25.5; IR (KBr)ν_{max} 3363, 2921, 2850, 1712, 1681, 1498, 1454, 1272, 1145, 771 cm^{-1}; HRMS (ESI+) *m/z* [M+H$^+$] calcd for $C_{19}H_{22}NO_5$, 344.1498, found 344.1498.

N-(5,7-dimethoxychroman-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (31c)

3-3′,6-Dimethoxy-[1,1′-biphenyl]-3-carboxylic acid (25 mg, 0.1 mmol) and N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (19 mg, 0.12 mmol) were added to a solution of alcohol **30** (10 mg, 0.048 mmol) in dichlormethane (0.7 mL) with pyridine (0.3 mL). The resulting mixture was stirred for 16 h and then the reaction mixture was diluted with dichloromethane (2 mL) and organic phase was washed with saturated $NaHCO_3$ (2 × 2 mL) and saturated sodium chloride solution (2 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:2 Hexanes/EtOAc) to give **31c** (19.3 mg, 90%) as an amorphous light yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.08 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.04 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.91 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.32 (d, *J* = 7.9 Hz, 1H), 6.09 (d, *J* = 2.4 Hz, 1H), 6.08 (d, *J* = 2.4 Hz, 1H), 4.68 (ddt, *J* = 7.8, 3.9, 1.9 Hz, 1H), 4.24 (ddd, *J* = 10.8, 4.0, 2.0 Hz, 1H), 4.15 (dd, *J* = 10.7, 1.9 Hz, 1H), 3.84 (s, 6H), 3.77 (s, 6H), 2.92 (dd, *J* = 17.1, 5.7 Hz, 1H), 2.76 (ddd, *J* = 17.2, 3.5, 1.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 159.8, 159.5, 159.3 (2), 155.3, 139.1, 130.7, 129.8, 129.3, 128.4, 126.9, 122.2, 115.4, 113.1, 110.9, 101.1, 93.5, 92.2, 68.3, 56.0, 55.6, 55.6, 55.5, 42.6, 25.6; IR (KBr)ν_{max} 3315, 2931 1620, 1596, 1531, 1498, 1249, 1201, 1249, 1215, 1145, 1051, 752 cm^{-1}; HRMS (ESI+) *m/z* [M+Na$^+$] calcd for $C_{26}H_{27}NaNO_6$, 472.1736, found 472.1738.

4-((5,7-dimethoxychroman-3-yl)carbamoyl)-2-(3-methylbut-2-en-1-yl)phenyl acetate (31d)

4-Acetoxy-3-(3-methylbut-2-en-1-yl)benzoic acid (47mg, 0.19 mmol) and N-(3-dimethylamino-propyl)-N′-ethylcarbodiimide hydrochloride (37 mg, 0.24 mmol) were

added to a solution of alcohol **30** (20 mg, 0.096 mmol), in dichlormethane (1.4 mL) with pyridine (0.6 mL). The resulting mixture was stirred for 16 h and then the reaction mixture was diluted with dichloromethane (4 mL). The organic phase was washed with saturated $NaHCO_3$ (2 × 4 mL) and saturated sodium chloride solution (4 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, 1:2 Hexanes/EtOAc) to give **31c** (33 mg, 77%) as an amorphous light yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.2 Hz, 1H), 7.54 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.34 (d, *J* = 8.0 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 1H), 6.10 (d, *J* = 2.3 Hz, 1H), 5.20 (dddd, *J* = 7.2, 5.8, 2.9, 1.4 Hz, 1H), 4.68 (dtt, *J* = 7.6, 3.6, 1.7 Hz, 1H), 4.26 (ddd, *J* = 10.9, 3.8, 2.1 Hz, 1H), 4.15 (dd, *J* = 10.8, 1.8 Hz, 1H), 3.80 (s, 6H), 3.27 (d, *J* = 7.2 Hz, 2H), 2.91 (dd, *J* = 17.1, 5.6 Hz, 1H), 2.86 – 2.71 (m, 1H), 2.33 (s, 3H), 1.74 (s, 3H), 1.72 – 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 166.9, 159.9, 159.4, 155.3, 151.5, 134.4, 134.0, 132.5, 129.6, 125.7, 122.6, 121.1, 100.9, 93.5, 92.2, 68.2, 55.6, 55.6, 42.6, 29.0, 25.9, 25.5, 21.1, 18.1; IR (KBr)ν_{max} 3325, 2932 1623, 1602, 1596, 1531, 1496, 1249, 1201, 1251, 1215, 1145, 749 cm^{-1}; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{25}H_{29}NaNO_6$, 462.1893, found 462.1872

4. Anti-proliferation Assay

MCF-7 and SKBr3 cells were maintained in a 1:1 mixture of advanced DMEM/F12 (Gibco) containing non-essential amino acids, L-glutamine (2 mM), streptomycin (500 μg/mL), penicillin (100 units/mL), and 10% FBS as supplements. Cells were grown to confluence in a humidified atmosphere (37 °C, 5% CO2) and seeded (2000/well, 100 μL) in 96-well plates, and allowed to attach for 24 hr. Compounds or geldanamycin at 6 increasing concentrations in DMSO (1% DMSO final concentration) were added, and cells were returned to the incubator for 72 h. At 72 h, the number of viable cells was determined using an MTS/PMS cell proliferation kit (Promega) per the manufacturer's instructions. Cells incubated in 1% DMSO were used as 100% proliferation, and values were adjusted accordingly. IC_{50} values were calculated from minimum two separate experiments performed in triplicate using GraphPad Prism program.

5. Western Blot Analysis

MCF-7 cells were cultured as described previously and treated with various concentrations of the compound to be tested, Geldanamycin in DMSO (1% DMSO final concentration), or vehicle (DMSO) for 24 h. Cells were harvested in cold PBS and lysed in RIPA lysis buffer containing 1 mM PMSF, 2 mM sodium orthovanadate, and protease inhibitors on ice for 1 h. Lysates were clarified at 1400 g for 10 min at 4 °C. Protein concentrations were determined by using the Pierce BCA assay kit per the manufacturer's instructions. Equal amounts of proteins (4 μg) were electrophoresed under reducing conditions, transferred to a nitrocellulose membrane, and immunoblotted with the corresponding specific antibodies. Membranes were incubated with an appropriate horseradish peroxidase-labeled secondary anti-body, developed with chemiluminescent substrate, and visualized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank to NIH (CA109265) for providing financial support and Matthew Axtman for preliminary studies.

References

1. Chaudhury S, Welch TR, Blagg BS. Chem Med Chem. 2006; 1:1331–40. [PubMed: 17066389]
2. Peterson LB, Blagg BS. Future med chem. 2009; 1:267–83. [PubMed: 20161407]
3. Whitesell L, Lindquist SL. Nature reviews Cancer. 2005; 5:761–72.
4. Yu XM, Shen G, Neckers L, Blake H, Holzbeierlein J, Cronk B, Blagg BSJ. J Am Chem Soc. 2005; 127:12778–12779. [PubMed: 16159253]
5. Bishop SC, Burlison JA, Blagg BS. Cur cancer drug targets. 2007; 7:369–88.
6. Jolly C, Morimoto RI. J Nat Cancer Inst. 2000; 92:1564–72. [PubMed: 11018092]
7. Wegele H, Muller L, Buchner J. Rev of physiology, biochemistry and pharmacology. 2004; 151:1–44.
8. Chiosis G, Huezo H, Rosen N, Mimnaugh E, Whitesell L, Neckers L. Mol Can Ther. 2003; 2:123–9.
9. Adams J, Elliott PJ. Oncogene. 2000; 19:6687–92. [PubMed: 11426656]
10. Vries EG, Verweij J. Reviews and commentaries in antimicrobial and anticancer chemotherapy. 2000; 3:197–201.
11. Newman DJ. J Med Chem. 2008; 51:2589–99. [PubMed: 18393402]
12. Newman DJ, Cragg GM. J Nat Prod. 2012; 75:311–335. [PubMed: 22316239]
13. Ojima I. J Med Chem. 2008; 51:2587–8. [PubMed: 18393400]
14. Cox MB, Miller CA. Mol Pharmacol. 2003; 64:1549–56. [PubMed: 14645686]
15. Palermo CM, Westlake CA, Gasiewicz TA. Biochemistry. 2005; 44:5041–52. [PubMed: 15794642]
16. Tran PL, Kim SA, Choi HS, Yoon JH, Ahn SG. BMC cancer. 2010; 10:276. [PubMed: 20537126]
17. Yin Z, Henry EC, Gasiewicz TA. Biochemistry. 2009; 48:336–45. [PubMed: 19113837]
18. Matts RL, Dixit A, Peterson LB, Sun L, Voruganti S, Kalyanaraman P, Hartson SD, Verkhivker GM, Blagg BSJ. ACS Chem Biol. 2011; 6:800–807. [PubMed: 21548602]
19. Huo C, Wan SB, Lam WH, Li L, Wang Z, Landis-Piwowar KR, Chen D, Dou QP, Chan TH. Inflammopharmacology. 2008; 16:248–52. [PubMed: 18815735]
20. Ishino N, Yanase E, Nakatsuka S. Biosci, Biotechnol, Biochem. 2010; 74:875–7. [PubMed: 20378961]
21. Sang S, Lee MJ, Hou Z, Ho CT, Yang CS. J Agric Food Chem. 2005; 53:9478–84. [PubMed: 16302765]
22. Suzuki M, Sano M, Yoshida R, Degawa M, Miyase T, Maeda-Yamamoto M. J Agric Food Chem. 2003; 51:510–4. [PubMed: 12517118]
23. For previously made EGCG analogues see refrences 23–28. Osanai K, Milacic V, Dou QP, Chan TH. Heterocycles. 2008; 76:485–505.
24. Wan SB, Landis-Piwowar KR, Kuhn DJ, Chen D, Dou QP, Chan TH. Bioorg Med Chem. 2005; 13:2177–2185. [PubMed: 15727870]
25. Osanai K, Landis-Piwowar KR, Dou QP, Chan TH. Bioorg Med Chem. 2007; 15:5076–5082. [PubMed: 17544279]
26. Osanai K, Huo C, Landis-Piwowar KR, Dou QP, Chan TH. Tetrahedron. 2007; 63:7565–7570. [PubMed: 21152270]
27. Huo C, Shi G, Lam WH, Chen D, Cui QC, Dou QP, Chan TH. Can J Chem. 2008; 86:495–502.
28. Kazi A, Wang Z, Kumar N, Falsetti SC, Chan TH, Dou QP. Anticancer Res. 2004; 24:943–954. [PubMed: 15161048]
29. Burlison JA, Avila C, Vielhauer G, Lubbers DJ, Holzbeierlein J, Blagg BSJ. J Org Chem. 2008; 73:2130–2137. [PubMed: 18293999]

30. Zhao H, Donnelly AC, Kusuma BR, Brandt GEL, Brown D, Rajewski RA, Vielhauer G, Holzbeierlein J, Cohen MS, Blagg BSJ. J Med Chem. 2011; 54:3839–3853. [PubMed: 21553822]
31. Zhao H, Reddy Kusuma B, Blagg BSJ. ACS Med Chem Lett. 2010; 1:311–315. [PubMed: 21904660]
32. Li L, Chan TH. Org Lett. 2001; 3:739–41. [PubMed: 11259050]
33. Nicolaou KC, Adsool VA, Hale CR. Org Lett. 2010; 12:1552–5. [PubMed: 20192259]
34. Zheng T, Narayan RS, Schomaker JM, Borhan B. J Am Chem Soc. 2005; 127:6946–6947. [PubMed: 15884926]
35. Tückmantel W, Kozikowski AP, Romanczyk LJ. J Am Chem Soc. 1999; 121:12073–12081.
36. Donnelly A, Blagg BSJ. Curr Med Chem. 2008; 15:2702–2717. [PubMed: 18991631]
37. Donnelly AC, Mays JR, Burlison JA, Nelson JT, Vielhauer G, Holzbeierlein J, Blagg BSJ. J Org Chem. 2008; 73:8901–8920. [PubMed: 18939877]
38. Yoshida A, Hirooka Y, Sugata Y, Nitta M, Manabe T, Ido S, Murakami K, Saha RK, Suzuki T, Ohshima M, Yoshida A, Itoh K, Shimizu K, Oku N, Furuta T, Asakawa T, Wakimoto T, Kan T. Chem Commun (Camb). 2011; 47:1794–6. [PubMed: 21132166]
39. Chen W, Yang XD, Li Y, Yang LJ, Wang XQ, Zhang GL, Zhang HB. Org Biomol Chem. 2011; 9:4250–4255. [PubMed: 21505704]
40. Van TN, Debenedetti S, De Kimpe N. Tetrahedron Lett. 2003; 44:4199–4201.
41. Shi Z, He C. J Am Chem Soc. 2004; 126:5964–5965. [PubMed: 15137751]
42. Klepper F, Jahn EM, Hickmann V, Carell T. Angew Chem Int Ed Engl. 2007; 46:2325–7. [PubMed: 17310487]
43. Sagrera G, Seoane G. Synthesis. 2009; 24:4190.
44. Sagrera G, Seoane G. Synthesis. 2010; 16:2776.
45. Tillekeratne LM, Sherette A, Fulmer JA, Hupe L, Hupe D, Gabbara S, Peliska JA, Hudson RA. Bioorg Med Chem Lett. 2002; 12:525. [PubMed: 11844664]

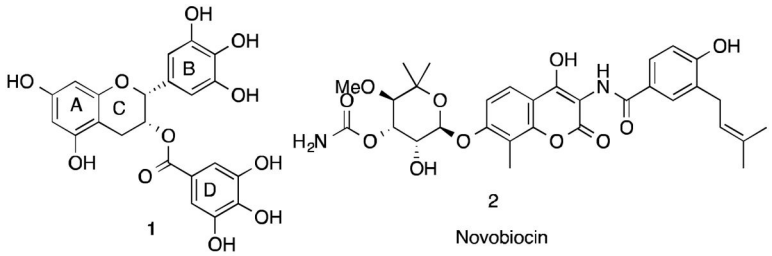


Figure 1.
Hsp 90 C-terminal inhibitors

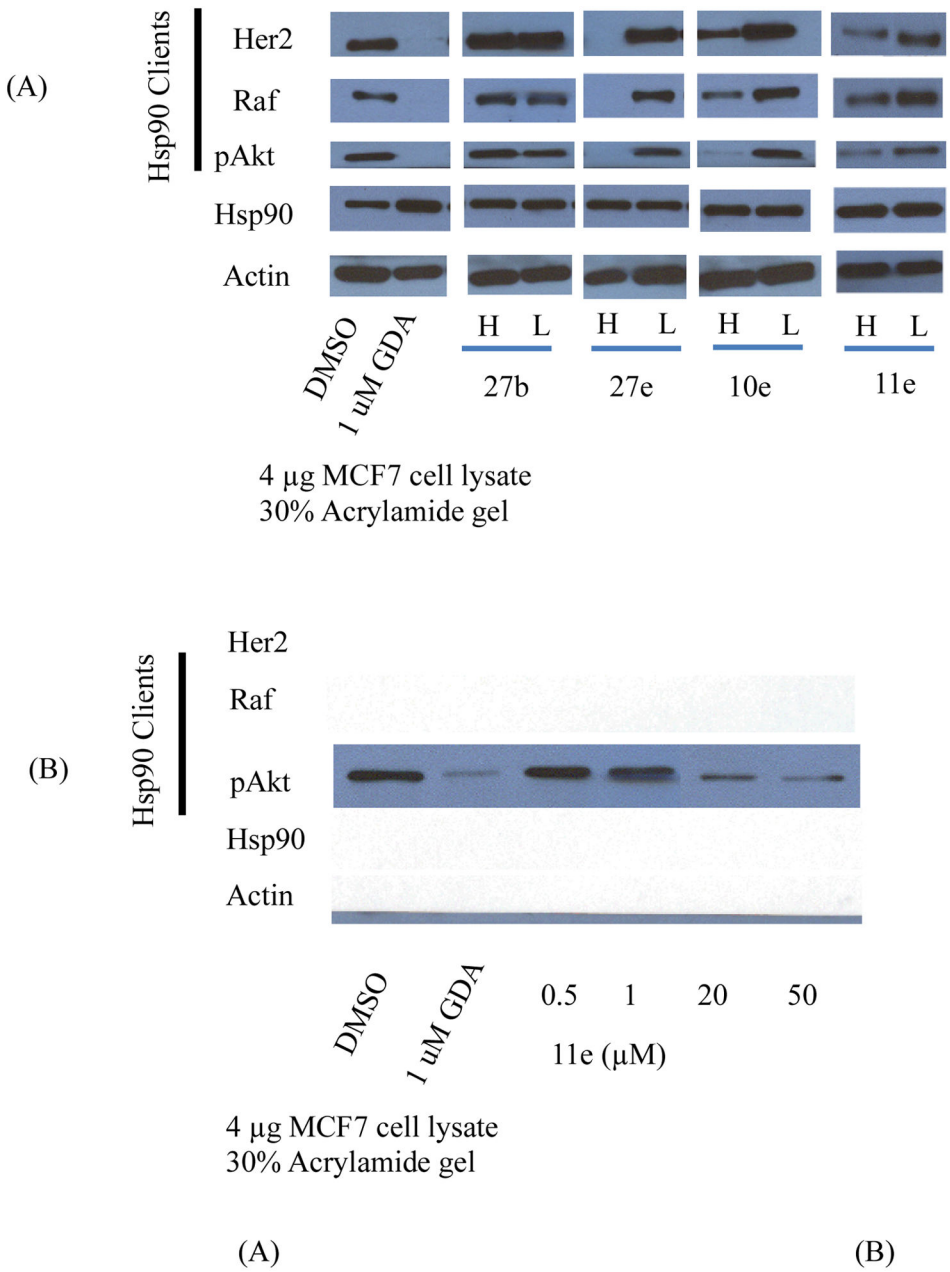


Figure 2.

Western blot analyses of MCF-7 cell lysates for Hsp90 client protein degradation after 24h of incubation. (a) Compounds **27b**, **27e**, **10e** and **11e** at two different concentrations. “H” (high) represents a concentration 5 × IC_{50} value, whereas and “L” (low) represents a concentration at one half the IC_{50} value as determined by anti-proliferative studies; (b) Compound **11e** at increasing concentrations.

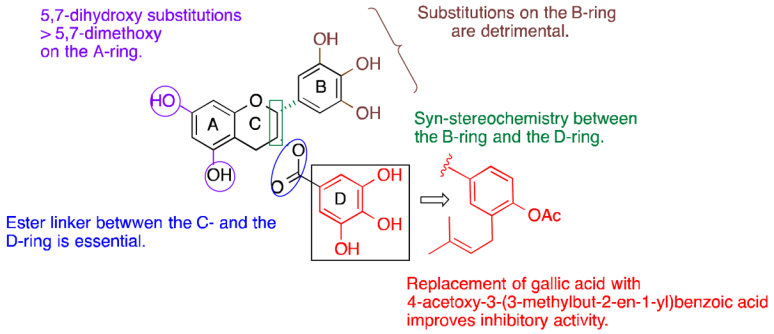
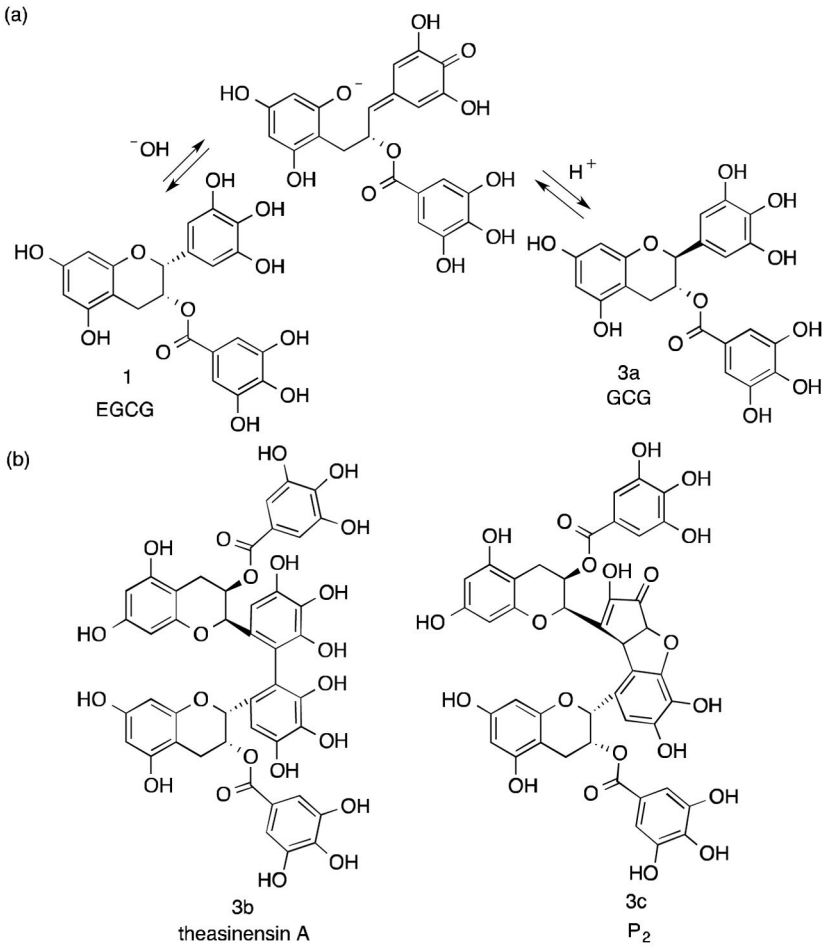
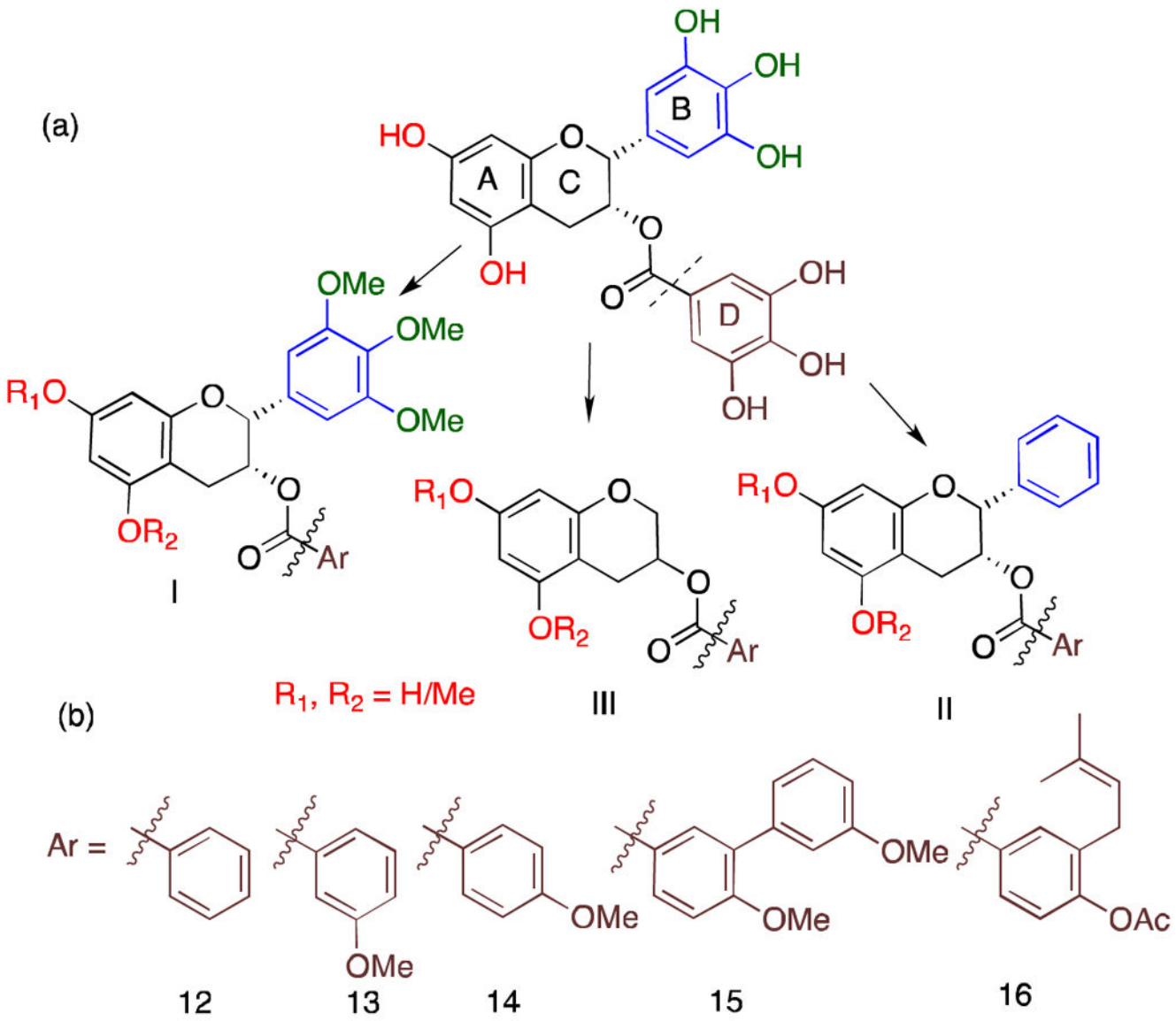


Figure 3.
Summary of EGCG structure-activity relationships.



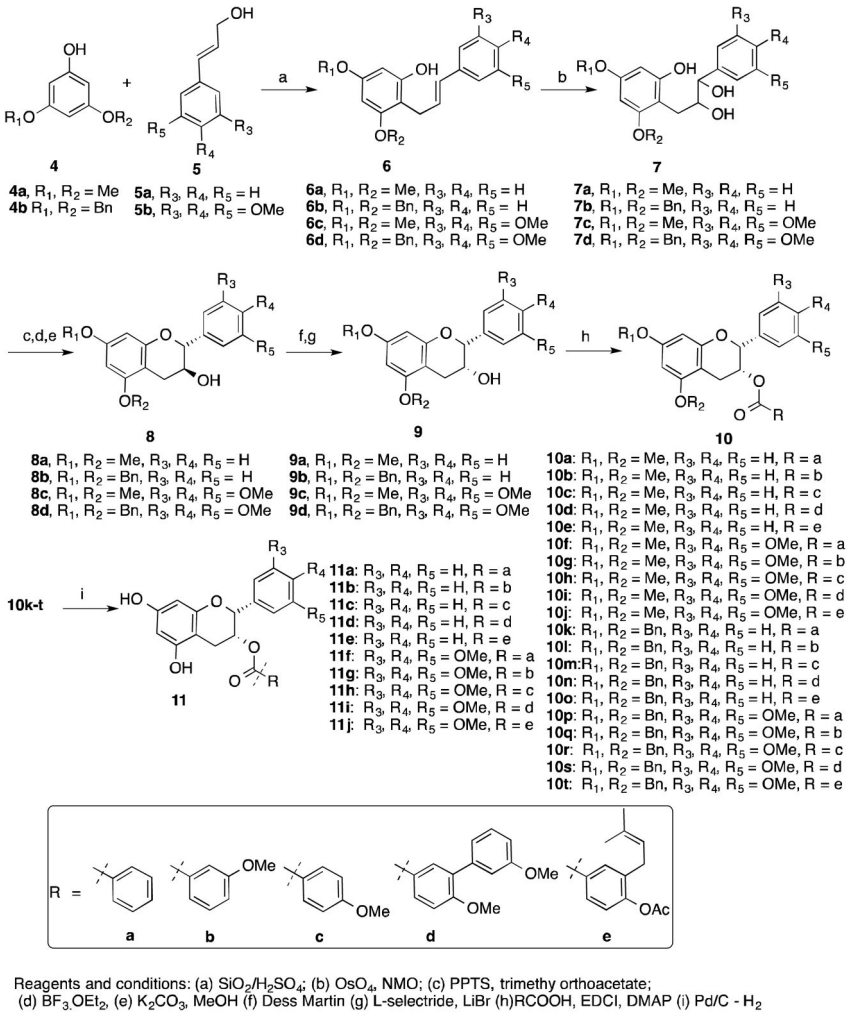
Scheme 1.

(a) Epimerization of EGCG to GCC**,** (b) Auto-oxidation products of EGCG.



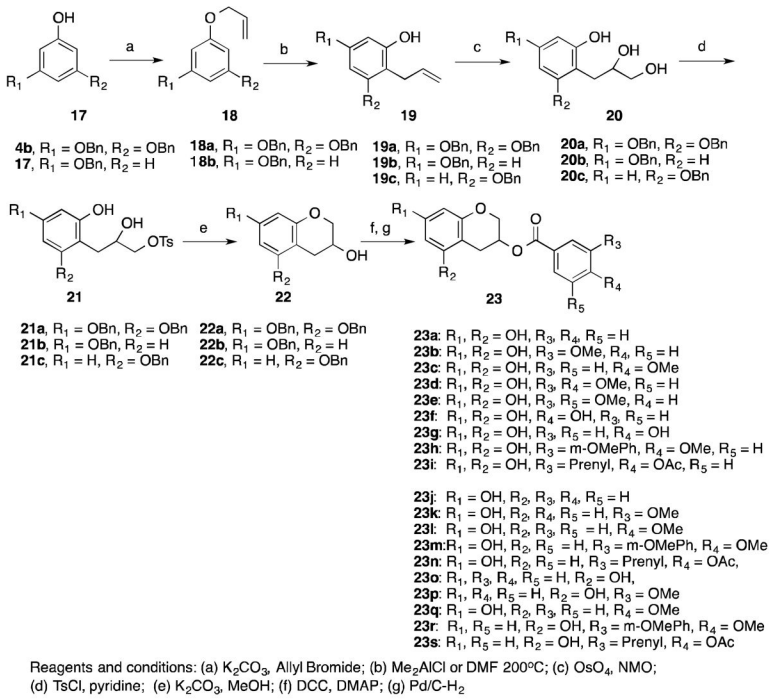
Scheme 2.

(a) Scaffolds derived from EGCG for Hsp90 inhibition, (b) Aryl acids used to replace the gallic acid moiety.



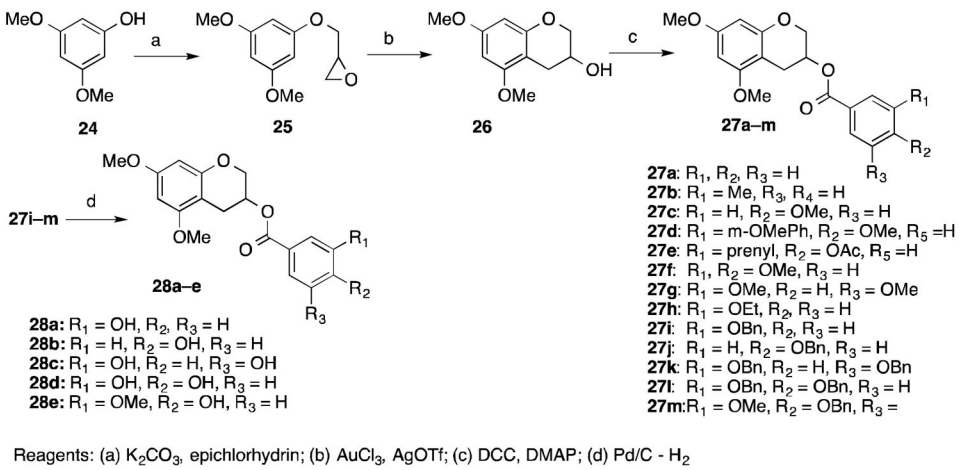
Scheme 3.

Synthesis of EGCG analogues containing modifications to the A-, B- and D-rings



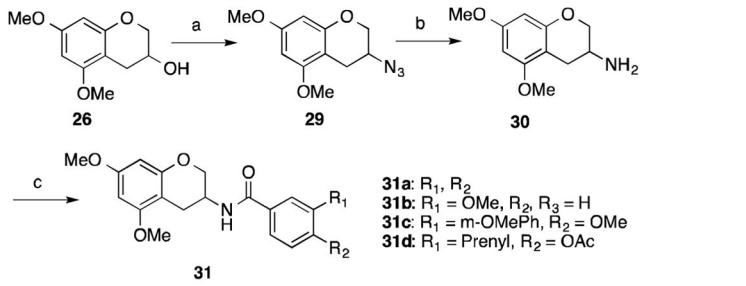
Scheme 4.

Synthesis of esters of 3,5-dihydroxychroman-3-ol.



Scheme 5.

Synthesis of 3,5-dimethoxychroman-3-ol esters.



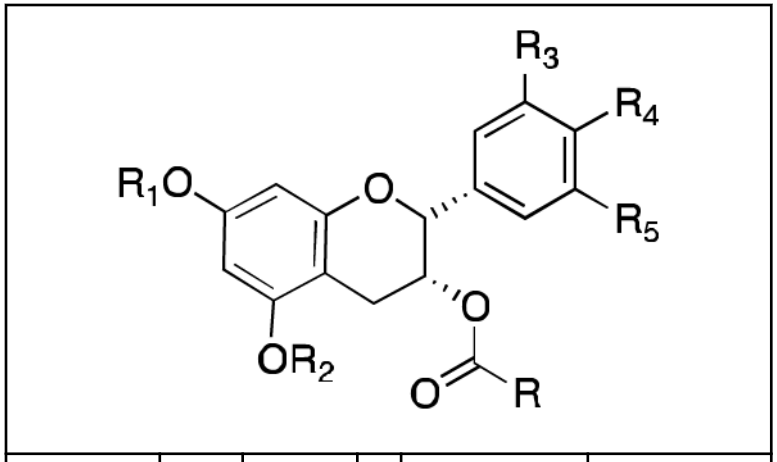
Reagents and conditions : (a) DPPA, PPh_3, DIAD; (b) PPh_3, H_2O; (c) EDCI.HCl, pyridine, aryl acid; (d) Pd/C - H_2

Scheme 6.

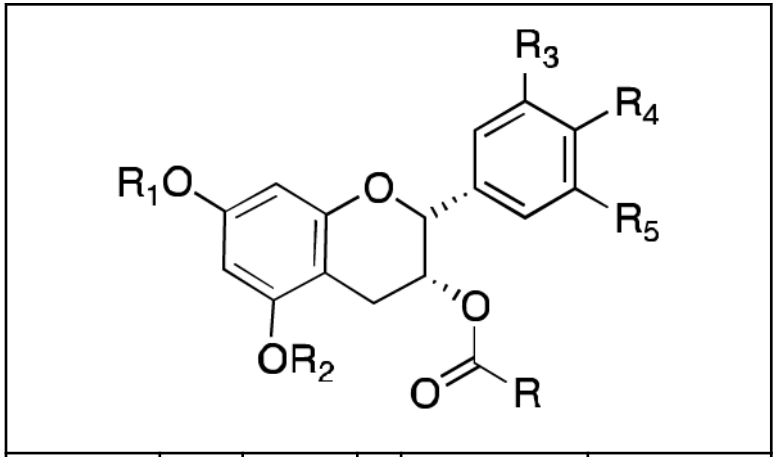
Synthesis of 3,5-dimethoxychroman-3-ol amides.

Table 1

Anti-proliferative activities produced by A-, B- and the D-ring modified EGCG analogues



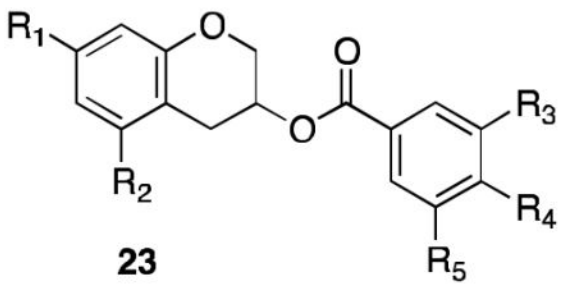
Entry	R_1, R_2	R_3, R_4, R_5	R	MCF-7 (IC_{50}, μM)	SKBr3 (IC_{50}, μM)
(−)-EGCG	7-	-	-	74.4 ± 2.19	100.16 ± 0.03
Geldanamycin	-	-	-	0.05 ± 0.03	0.008 ± 0.02
10a	Me	H	a	>100	>100
10b	Me	H	b	>100	>100
10c	Me	H	c	>100	>100
10d	Me	H	d	>100	>100
10e	Me	H	e	25.35 ± 5.25	36.1 ± 2.51
10f	Me	OMe	a	>100	>100
10g	Me	OMe	b	91.18 ± 0.76	>100
10h	Me	OMe	c	>100	>100
10i	Me	OMe	d	88.7 ± 11.3	>100
10j	Me	OMe	e	19.48 ± 2.5	24.87 ± 3.29
11a	OH	H	a	15.26 ± 0.57	18.67 ± 0.82
11b	OH	H	b	13.10 ± 0.86	15.42 ± 1.04
11c	OH	H	c	13.12 ± 0.54	17.26 ± 2.27



Entry	R_1, R_2	R_3, R_4, R_5	R	MCF-7 (IC_{50}, μM)	SKBr3 (IC_{50}, μM)
11d	OH	H	d	14.14 ± 0.7	19.88 ± 3.22
11e	OH	H	e	3.99 ± 1.4	21.45 ± 4.75
11f	OH	OMe	a	65.88 ± 2.1	>100
11g	OH	OMe	b	45.72 ± 0.4	37.92 ± 4.08
11h	OH	OMe	c	42.80 ± 7.30	62.90 ± 0.70
11i	OH	OMe	d	47.31 ± 3.39	71.9 ± 2.76
11j	OH	OMe	e	42.08 ± 1.85	50.4 ± 1.39

Table 2

Anti-proliferative activities produced by 3,5-dihydroxychroman-3-ol esters.



23

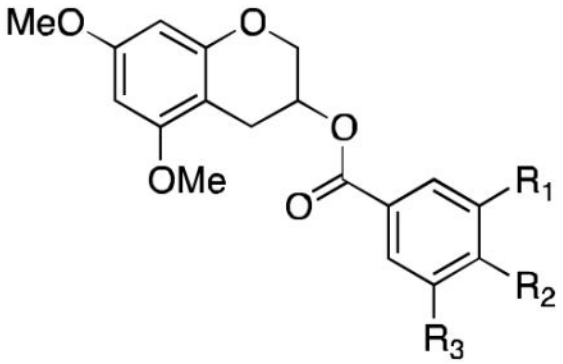
Entry	R_1	R_2	R_3	R_4	R_5	MCF-7 (IC_{50}, μM)	SKBr3 (IC_{50}, μM)
23a	OH	OH	H	H	H	98.24 ± 1.76	>100
23b	OH	OH	OMe	H	H	57.75 ± 3.12	50
23c	OH	OH	H	OMe	H	>100	>100
23d	OH	OH	OMe	OMe	H	>100	>100
23e	OH	OH	OMe	H	OMe	96.50 ± 3.51	>50
23f	OH	OH	OH	H	H	61.94 ± 6.85	85.30 ± 5.36
23g	OH	OH	H	OH	H	>100	>100
23h	OH	OH	m OMePh	OMe	H	21.93 ± 2.27	34.84 ± 16.29
23i	OH	OH	Prenyl	OAc	H	10.66 ± 1.09	23.15 ± 0.25
23j	OH	H	H	H	H	>100	>100
23k	OH	H	OMe	H	H	>100	>100
22l	OH	H	H	OMe	H	>100	>100
23m	OH	H	m-OMePh	OMe	H	55.09 ± 5.53	57.73 ± 4.28
23n	OH	H	Prenyl	OAc	H	15.94 ± 1.86	25.25 ± 4.05
23o	H	OH	H	H	H	>100	>100
23p	H	OH	OMe	H	H	>100	>100
22q	H	OH	H	OMe	H	>100	>100
23r	H	OH	m-OMePh	OMe	H	21.6 ± 2.55	41.72 ± 0.34

23

Entry	R_1	R_2	R_3	R_4	R_5	MCF-7 (IC_{50}, μM)	SKBr3 (IC_{50}, μM)
23s	H	OH	Prenyl	OAc	H	60 ± 7.38	>100

Table 3

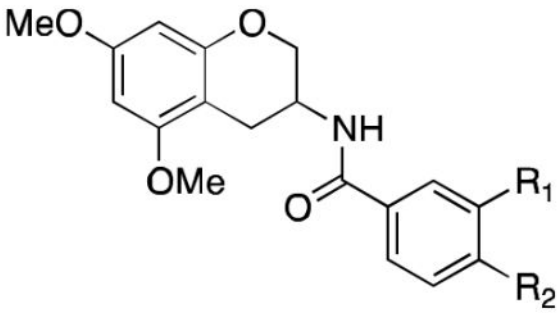
Anti-proliferative activity produced by 3,5-dimethoxychroman-3-ol esters.



Entry	R_1	R_2	R_3	MCF-7 (IC_{50}, μM)	SKBr3 (IC_{50}, μM)
27a	H	H	H	14.02 ± 0.91	44.605 ± 5.40
27b	OMe	H	H	0.77 ± .02	0.88 ± 0.06
27c	H	OMe	H	32.89 ± 2.05	50.40 ± 1.39
27d	m-OMePh	OMe	H	31.20 ± 18.17	80.13 ± 9.67
27e	Prenyl	OAc	H	38.66 ± 7.71	47.90 ± 0.71
27f	OMe	OMe	H	10.89 ± 0.27	36.98 ± 5.24
27g	OMe	H	OMe	21.8 ± 3.08	29.5 ± 1.5
27h	OEt	H	H	8.19 ± 0.16	33.35 ± 4.81
28a	OH	H	H	37.72 ± 6.75	64.11 ± 13.95
28b	H	OH	H	17.51 ± 0.86	17.73 ± 5.97
28c	OH	H	OH	>100	>100
28d	OH	OH	H	22.12 ± 1.01	30.63 ± 11.89
28e	OMe	OH	H	51.29 ± 1.13	76.50 ± 1.10

Table 4

Anti-proliferative activity produced by analogues containing amide linkers.



Entry	R_1	R_2	MCF-7 (IC_{50}, μM)	SKBr3 (IC_{50}, μM)
31a	H	H	>100	>100
31b	OMe	H	>100	>100
31c	m-OMePh	OMe	>100	>100
31d	Prenyl	OAc	54.5 ± 0.6	55.2 ± 1.2