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Synthesis and biological evaluation of 4'-substituted kaempfer-3-ols

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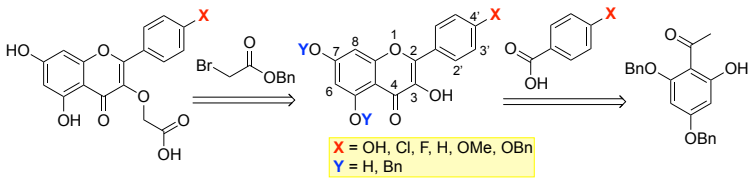
Supporting Information Placeholder



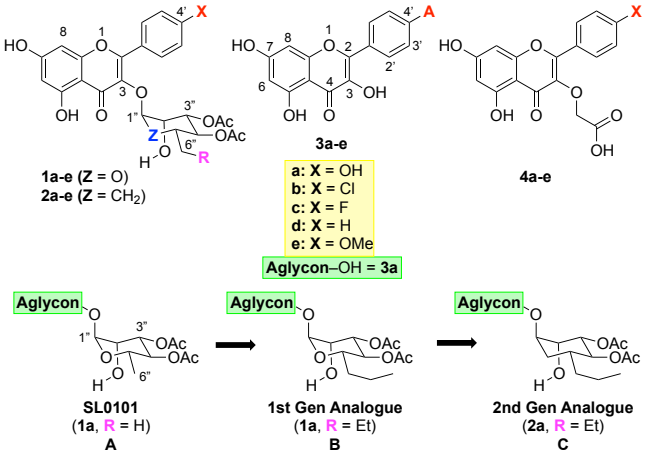
ABSTRACT: The synthesis of two series of five kaempfer-3-ols was described. The first set all have a *C*-3 hydroxyl group and the second has a carboxymethoxy ether at the *C*-3 position. Both series have variable substitution at the *C*-4' position (*i.e.*, OH, Cl, F, H, OMe). Both kaempferols and carboxymethoxy ethers were evaluated for their ability to inhibit RSK kinase activity and cancer cell proliferation.

As part of an effort to find selective inhibitors of the p90 ribosomal s6 kinases (RSK), the glycosylated kaempfer-3-ol natural product, SL0101 (**A**) was identified as a relatively selective inhibitor for RSK1/2 (Ki ~ 1 μm).[1,2] In a combination of molecular modeling and structure activity relationship studies (Figure 1),[3, 4] we identified carbohydrate (**1a-e**) and cyclitol analogues (**2a-e**) of SL0101 (**A**) with improved kinase and cancer cell inhibitory activity.[5, 6] These efforts focused on the synthesis of stereoisomers and analogues with substitution at the aglycone (*e.g.*, *C*-4'of the kaempfer-3-ol)[7] and carbohydrate (*e.g.*, C-6" of the rhamnose ring) portions of the natural product. These efforts focused on the synthesis of non-hydrolyzable alternatives to the pyranose (*e.g.*, carbasugar)[5] and *C*-3'/4' acetate groups (*e.g.*, amide and carbamate substitution at *C*-3' and/or *C*-4').[8] These efforts culminated in the discovery of a pyranose

analogue **B** (**1a**, R = Et) and a carbasugar analogue **C** (**2a**, R = Et) of SL0101 (**A**) that showed improved efficacy in the *in vitro* kinase assays.

There have been several natural[9] and unnatural kaempferol type flavonoids reported with anticancer activity. For instance, the alvocidib, cyclin-dependent kinase (CDK) inhibitor,[10] is currently under development for the treatment of acute myeloid leukemia.[11] In an effort to differentiate the effects of the sugar/cyclitol from the kaempferol aglycon, we decide to make and test a series of substituted kaempfer-3-ols (**3a-e**) with variable substitution at the *C*-4' position of the B-ring. In addition, we planned to prepare a related series of *C*-3 alkylated analogues (**4a-e**) with a polar carboxylic acid to add polarity to the molecule and to prevent metabolic oxidation of **3a** to a vinylogous quinone.[8,12]

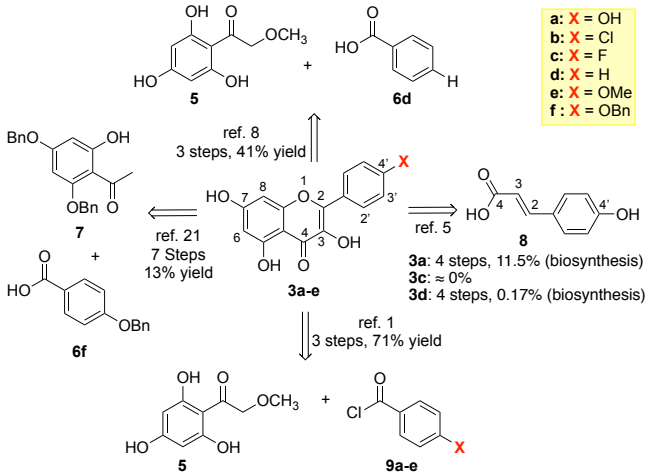
Figure 1. SL0101 and related flavan-3-ols



The list of desired aglycones **3a-e**,[13] **3a**,[14] **3d**,[15] and **3e**[16] are either part of a class of naturally occurring compounds kaempferols or related congeners[17] that have been evaluated over the years for their anti-cancer, anti-inflammatory and antioxidant properties. There have been several other approaches to the kaempfer-3-ol ring system and variants with substitution at the *C*-4' position (Scheme 1). These include direct condensations between α-methoxyacetophenone **5** with free phenols and carboxylic acids **6d** and **9a-e**,[18,19] as well as, biosynthetic routes from 4'-hydroxycinnanic acid **8**.[20] In addition, the naturally occurring kaempfer-3-ols, aka kaempferol, **3a** has been prepared from the benzyl protected acetophenone **7** and 4'-hydroxycinnanic acid **6f**.[21] Of these approaches, our approach most similarly matches the work

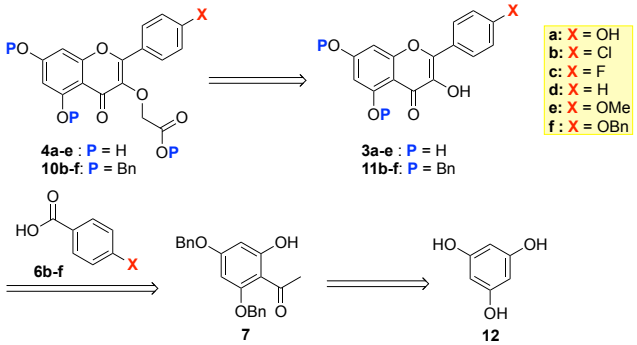
by Yu which was most compatible with our synthetic and structure activity relationship (SAR) design needs to access **3a-e** and **4a-e**. Key to their approach is the use of bis-benzyl protected acetophenone **7**.

Scheme 1. Previous approaches to substituted flavan-3-ols



Retrosynthetically, we envisioned that methylcarboxylic acids **4a-c** could be prepared from the per-benzylated material **10b-f**, which in turn could be prepared by the alkylation of enols **11b-f** (Scheme 2). The also desired aglycons **3a-e** could similarly be prepared from the same intermediates **11b-f**. The common intermediate **11b-f** could be prepared from carboxylic acids **6b-f** and acetophenone **7** by an acylation Claisen cyclization/dehydration reaction sequence. Finally, acetophenone **7** can be prepared by a bis-benzylation/acylation of phloroglucinol **12**.

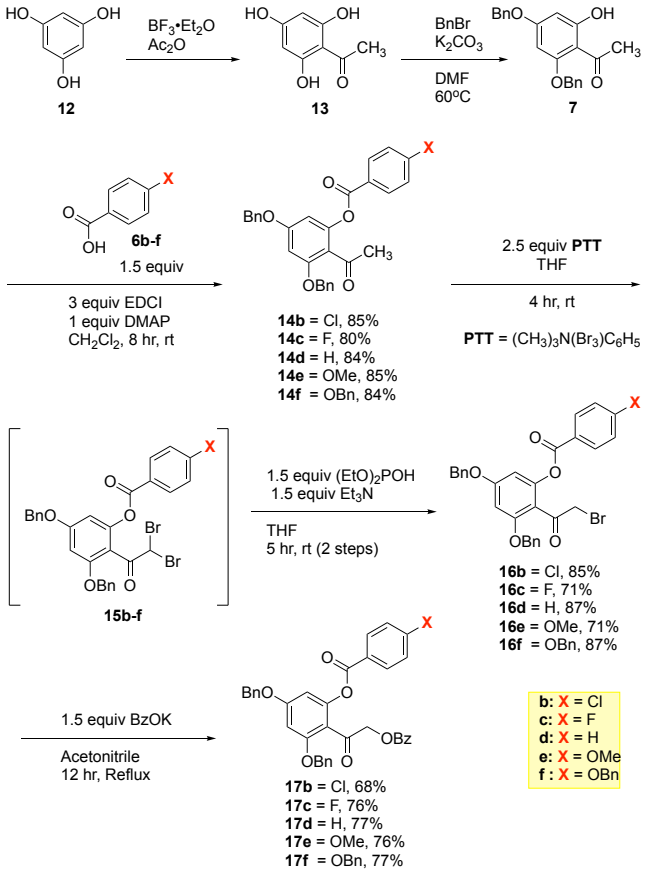
Scheme 2. Our retrosynthetic approach to the flavan-3-ols



Our synthetic efforts began with the synthesis of key intermediate **17b-f** from phloroglucinol **12** (Scheme 3). A Lewis acid catalyzed acylation of phloroglucinol **12** gave 2,4,6-trihydroxyacetophenone **13**, which can be bis-benzylated to give acetophenone **7**. At this point the diversification is introduced by means of

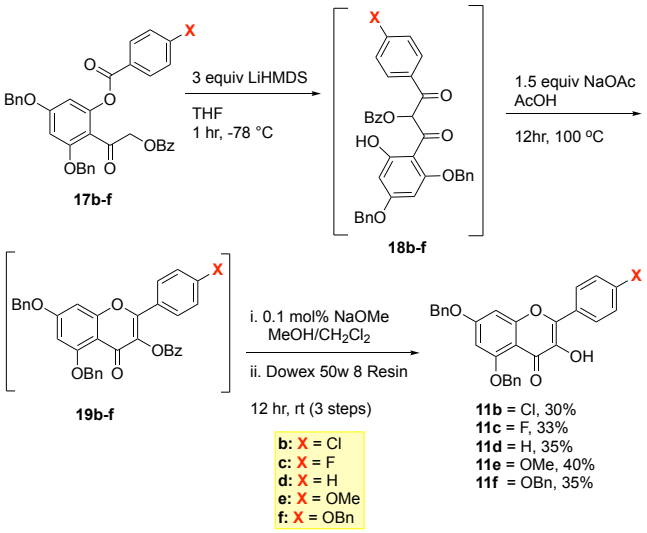
an EDCI coupling between **7** and carboxylic acids **6b-f** to form phenol esters **14b-f**. We next tuned to the alpha-bromination of methylketone **14b-f** to form **16b-f**. To our surprise this was most easily accomplished by a bis-bromination to form **15b-f** and then selective reduction with diethylphosphite to form mono-bromide **16b-f**. Finally, the mono-bromide **16b-f** can be displaced with potassium benzoate to form esters **17b-f**.

Scheme 3. Synthesis of acetophenone 17b-f



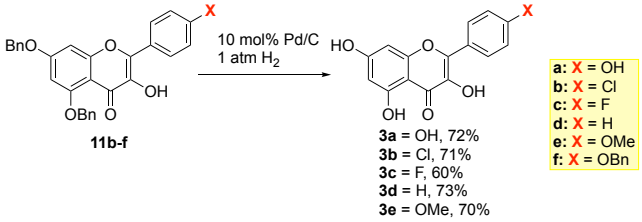
With the series of α-benzoates **17b-f** in hand, we next explored its dehydrative cyclization to form the desired series of protected kaempferols **11b-f** (Scheme 4). This began with a LiHMDS promoted intramolecular Claisen condensation to form 1,3-diketone **18b-f**. The crude THF solutions of **18b-f** could then be dehydrated upon heating in the presence of a slight excess of NaOAc/HOAc. Finally, the benzoate esters **19b-f** can be hydrolyzed to form the per-benzyl protected enol kaempferols **11b-f**.

Scheme 4. Synthesis of protected 4'-substitued flavan-3-ols

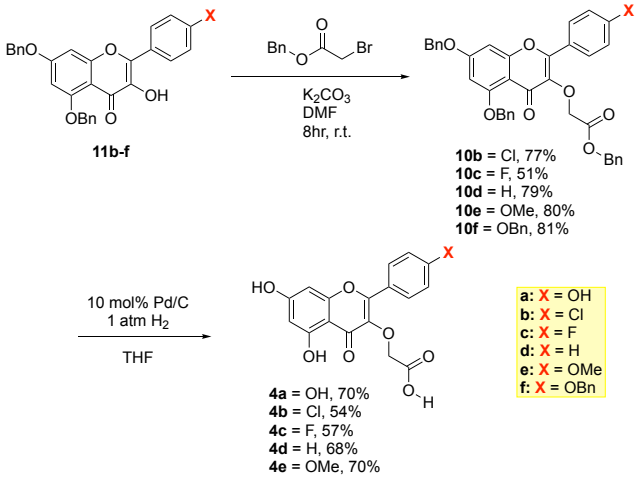


The desired kaempferol aglycons **3a-e** can be easily prepared from kaempferols **11b-f**, by a hydrogenolysis/global deprotection (Scheme 5). In a related two-step process, kaempferols **11b-f** can be converted into the series of desired carboxylic acids by an alkylation of the phenol with benzyl bromoacetate and K_2CO_3 to form benzyl esters **10b-f**, which in turn can be per-deprotected by a similar hydrogenolysis reaction to give carboxylic acids **4a-e** (Scheme 6).

Scheme 5. Synthesis of 4'-substituted flavan-3-ols



Scheme 6. Synthesis of flavan-3-ols carboxylic acids



The five SL0101 aglycons **3a-e** and the five variants with carboxymethyl groups at the *C*-3 position **4a-e** were evaluated as RSK inhibitors and for inhibition of proliferation using a breast cancer cell line, MCF-7 (Table 1). The aglycons and variants demonstrated reduced efficacy to inhibit RSK2 kinase activity in an *in vitro* kinase assay compared to SL0101 (**A**) and its more potent analogue (**C**). However, the aglycons were more effective at inhibiting proliferation than SL0101 (**A**) even though their efficacy to inhibit RSK2 *in vitro* kinase activity was diminished in comparison to SL0101 (**A**). However, the aglycons were less effective at inhibiting MCF-7 proliferation than **C**. These results suggest that the aglycons inhibit MCF-7 proliferation through a mechanism distinct from RSK. The variants with the carboxymethyl group at the *C*-3 position did not inhibit MCF-7 proliferation and a possible explanation is that these compounds are less cell permeable. These results further demonstrate that the rhamnose moiety present in SL0101 provides specificity in targeting RSK1/2.

Table 1. Inhibition of *in vitro* kinase activity and MCF-7 cell proliferation

Compound	% kinase activity (30 μM)	% proliferation (50 μM)
A	10.5 ± 1.35	50%[1]
C	3.1 ± 0.69	–2.51 ± 3.2
3a	36.4 ± 2.18	89.6 ± 4.58
3b	40.6 ± 2.19	7.6 ± 3.67
3c	25.7 ± 6.11	9.24 ± 3.22
3d	60.3 ± 1.36	40.4 ± 3.62
3e	89.2 ± 1.93	12.9 ± 2.19
4a	70.2 ± 1.54	99.0 ± 6.01
4b	69.1 ± 1.81	91.3 ± 4.49
4c	83.1 ± 1.7	90.2 ± 2.46
4d	76.8 ± 1.78	90.1 ± 4.33
4e	38.0 ± 1.39	93.1 ± 3.87

Conclusions

In summary, a route to five kaempferols **3a-e** and five variants **4a-e** with carboxymethyl groups at the *C*-3 position has been described. The route readily allows for variable *C*-4' substitution of the kaempferol substitution and provides material for biological activity (*i.e.*, the ability to inhibit RSK kinase activity and MCF-7 cell proliferation). This strategy and study will inform our further studies of the SAR of SL0101. Efforts along these lines will be reported in due course.

Experimental Section

General Methods

RSK2 in vitro kinase assay

Kinase activity in the presence or absence of inhibitors was determined using the LanthaScreen® Eu kinase binding assay for RPS6KA3 according to the manufacturer's instructions (Invitrogen). Inhibitors were pre-incubated with purified kinase before addition of kinase tracer 236 for two h. Excitation fluorescence was 330 ± 80 nm, background emission from Eu tag 620 ± 10 nm and fluorescence resonance energy transfer (FRET) emission 665 ± 8 nm. Fluorescence was measured using a Synergy Neo (BioTek Instruments). FRET was calculated as the ratio of emission at 665 divided by emission at 620.

Cell proliferation assay

The MCF-7 line was obtained and cultured as direct by ATCC. Stocks were authenticated based on growth rate, morphology, molecular markers and absence of mycoplasma. For proliferation assays 10^3 cells/well were plated in a 96-well. Inhibitor or vehicle was added, and luciferase measured at 42 h using CellTiterGlo reagent (Promega Corp.) with a GLoMax Discover luminometer (Promega Corp.).

1-(2,4,6-trihydroxyphenyl)ethan-1-one (13)[22]

To the flask of mixture of phloroglucinol **12** (125 g, 0.99 mol) and acetic anhydride (95 mL, 1.09 mol) was added dropwise boron trifluoride etherate (375 mL, 1.49 mol) over 1 h at 0 °C. The resulting mixture was stirred at room temperature for 48 h. The reaction was quenched with 10% NaOAc solution and extracted with ethyl acetate, the aqueous layers were extracted with ether. The combined organic layers were washed with brine and dried over sodium sulfate. After concentrating in vacuo, the crude product was loaded onto a silica gel column and flash with solvent (hexanes : ethyl acetate = 2 : 1) give acetyl triol **13** light a yellow solid (128 g, 78%): R_f = 0.3 (hexanes : ethyl acetate = 1 : 1); ^{1}H NMR (400 MHz, DMSO-d6) δ 12.23 (s), 10.39 (s), 5.78 (s, 2H), 2.52 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d6) δ 203.2, 165.4, 165.0, 104.7, 95.2, 33.1

1-(2,4-bis(benzyloxy)-6-hydroxyphenyl)ethan-1-one (7)[23]

To a solution of triol **13** (28 g, 0.17 mol) in 100 mL DMF, K_2CO_3 (97.2 g, 0.7 mol) was added portion wise followed by the dropwise addition of benzyl bromide (84 mL, 0.7 mol) over 1 h period at 0 °C. The

resulting mixture was heated to 65 °C for 72 h. Then the reaction was washed with water and the aqueous layers were extracted with ether. The combined organic layers were washed with brine and dried over sodium sulfate. After concentrating in vacuo, the crude product was loaded onto a silica gel column and flash with solvent (Hexanes : CH_2Cl_2 = 2 : 1) to give **7** as a white solid (20 g, 35%): R_f = 0.12 (Hexane : CH_2Cl_2= 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.27 (m, 10H), 6.18 (d, *J* = 1.7 Hz, 1H), 6.12 (d, *J* = 1.7 Hz, 1H), 5.06 (s, 2H), 5.06 (s, 2H), 2.57 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.4, 167.8, 165.3, 162.2, 136.1, 135.9, 129.0, 129.0, 128.7, 128.6, 128.3, 127.9, 106.6, 95.0, 92.6, 71.3, 70.5, 33.6.

2-acetyl-3,5-bis(benzyloxy)phenyl 4-(benzyloxy)benzoate (14f)[21]

To a solution of phenol **7** (3.17 g, 9.1 mmol) and benzoic acid **6f** (3.12 g, 13.6 mmol) in CH_2Cl_2 (74 mL) at 0 °C was added EDCI (5.25 g, 27.3 mmol) and DMAP (1.11 g, 9.1 mmol). After stirring for 4 h at rt, the mixture was diluted with EtOAc, and then washed with saturated $NaHCO_3$ solution. The organic phase was washed with brine, dried over Na2SO4 and then concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexanes : Ethyl Acetate = 1 : 1) to give **14f** (4.27 g, 84%) as a white solid: R_f= 0.32 (Hexanes : Ethyl Acetate = 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 2H), 7.48 – 7.31 (m, 15H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.54 (d, *J* = 1.5 Hz, 1H), 6.47 (d, *J* = 1.4 Hz, 1H), 5.15 (s, 2H), 5.08 (s, 2H), 5.04 (s, 2H), 2.47 (d, *J* = 0.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.4, 164.6, 163.1, 161.1, 158.1, 149.8, 136.1, 136.0, 135.9, 132.5, 128.7, 128.3, 128.2, 127.6, 127.4, 127.4, 121.7, 118.1, 114.7, 101.4, 98.4, 70.9, 70.4, 70.2, 32.0.

3,5-bis(benzyloxy)-2-(2-bromoacetyl)phenyl 4-(benzyloxy)benzoate (16f)[21]

To a solution of ester **14f** (4.18 g, 7.5 mmol) in dry THF (15 mL) was added PTT (7.03 g, 18.7 mmol, 2.5 equiv) in portions at 0 °C. The reaction mixture was stirred for 4 h at rt, monitored by crude NMR. When the reaction was completed, it was cooled down at 0 °C and treated with diethyl phosphate (1.44 mL, 11.3 mmol, 1.5 equiv) and Et_3N (1.49 mL, 11.3 mmol, 1.5 equiv) dropwise. The resulting mixture was stirred for 6 h at rt until complete. Then the reaction was washed with water and the aqueous layers were extracted with dichloromethane. The combined organic layers were washed with brine and dried over sodium

sulfate. After concentrating in vacuo, the crude product was loaded onto a silica gel column and flash with solvent (Hexanes : CH_2Cl_2 = 1 : 2) to give **16f** (4.1 g, 87%): R_f = 0.34 (Hexanes : Ethyl Acetate = 4: 1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.47 – 7.35 (m, 15H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.55 (s, 2H), 5.15 (s, 2H), 5.10 (s, 2H), 5.05 (s, 2H), 4.37 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 192.0, 164.6, 163.2, 162.1, 158.3, 151.1, 136.1, 135.7, 135.4, 132.6, 128.8, 128.7, 128.7, 128.5, 128.4, 128.2, 127.7, 127.6, 127.5, 121.4, 114.8, 114.1, 102.1, 98.3, 77.3, 77.0, 76.8, 71.3, 70.6, 70.2, 36.7

2-(2-(benzoyloxy)acetyl)-3,5-bis(benzyloxy)phenyl 4-(benzyloxy)benzoate (17f)[21]

A mixture of **16f** (2.79 g, 4.4 mmol) and BzOK (1.1 g, 6.6 mmol) was stirred in CH_3CN (30 mL) at 82 °C in a sand bath for 24 h. The reaction was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, then concentrated in vacuo. The resulting crude was purified by silica gel chromatography and flash with solvent (Hexane: Ethyl Acetate = 10 : 1) to afford the product **17f** as a light yellow solid (2.3 g, 77%): R_f = 0.40 (Hexane: Ethyl Acetate = 4: 1); mp 161 – 163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.6 Hz, 2H), 7.99 (d, *J* = 7.7 Hz, 2H), 7.53 (dd, *J* = 7, 7 Hz, 1H), 7.46 – 7.31 (m, 17H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.54 (d, *J* = 5.8 Hz, 2H), 5.23 (s, 2H), 5.12 (s, 2H), 5.10 (s, 2H), 5.05 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.9, 166.0, 164.9, 163.3, 162.3, 159.0, 151.5, 136.4, 136.1, 135.8, 133.2, 132.9, 130.1, 129.9, 129.0, 129.0, 128.9, 128.7, 128.6, 128.5, 128.5, 127.9, 127.8, 127.7, 121.9, 114.9, 114.5, 102.5, 98.5, 71.5, 70.8, 70.4, 69.9

5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-3-hydroxy-4H-chromen-4-one (11f)[21]

To a solution of benzoate **17f** (2.19 g, 3.2 mmol) in THF (30 mL) added LiHMDS in hexanes (9.4 mL, 9.6 mmol) at −78 °C. The mixture was stirred at −78 °C for 1 h until the crude NMR confirmed completion of the reaction. The cooled mixture was poured into water and was then extracted with Ethyl Acetate (3 x 80 mL). The combined organic layers were then washed with brine, dried over sodium sulfate and concentrated in vacuo. Resulting residue was dissolved in AcOH (30 mL), then AcONa (0.34 g, 4.8 mmol) was added. After being stirred at 100 °C for 12 h, the mixture was cooled to rt and then diluted with CH_2Cl_2. The mixture was washed with water, saturated $NaHCO_3$ solution and brine, successively. The

organic phases were combined and concentrated in vacuo to give a solid residue, which was dissolved in MeOH/ CH_2Cl_2 (12 mL, v/v1:1). After being stirred for 10 h in the presence of a catalytic amount of NaOMe at rt, the mixture was neutralized with Dowex 50W-X 8 (H^+) resin. The resins were filtered, solvent was removed. The resulting solid was recrystallized from methanol to provide **11f** (630 mg, 35%) as a yellow solid. mp 167 – 169 °C; R_f = 0.41 (Hexane: Ethyl Acetate = 2: 1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.46 – 7.33 (m, 13H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.62 (s, 1H), 6.47 (s, 1H), 5.22 (s, 2H), 5.13 (s, 2H), 5.11 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.7, 163.2, 159.8, 159.3, 158.7, 142.4, 137.6, 136.5, 136.2, 135.6, 128.9, 128.8, 128.7, 128.6, 128.5, 128.1, 127.8, 127.7, 127.5, 126.6, 123.8, 114.9, 106.7. 97.6, 93.7, 70.7, 70.6, 70.0.

2-acetyl-3,5-bis(benzyloxy)phenyl 4-chlorobenzoate (14b)

To a suspension of phenol **7** (3.51 g, 0.01 mol), 4-chlorobenzoic acid **7b** (2.37 g, 0.015 mol) in CH_2Cl_2 (50 mL) at 0 °C was added EDCI (5.79 g, 0.03 mol) and DMAP (1.23 g, 0.01 mol). After stirring for 4 h at rt, the mixture was diluted with EtOAc, and then washed with saturated $NaHCO_3$ solution. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc-petroleum ether, 1 : 1) to give **14b** (4.17 g, 85%) as a white solid: R_f = 0.5 (Hexanes : Ethyl Acetate = 4: 1), mp 100 – 102 °C; IR (thin film, cm^{-1}) 3063, 3010, 1736, 1683, 1608, 1573, 1497, 1487, 1454, 1431, 1400, 1377, 1352, 1327, 1254, 1150, 1088, 1012, 977, 910, 876, 845, 733, 695, 612, 524, 475; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 2H), 7.52 – 7.29 (m, 10H), 6.56 (s, 1H), 6.47 (d, *J* = 1.2 Hz, 1H), 5.09 (s, 2H), 5.05 (s, 2H), 2.48 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.3, 164.5, 161.6, 158.7, 150.0, 140.4, 136.2, 136.0, 132.0, 129.2, 129.0, 128.6, 128.6, 128.0, 127.9, 127.8, 117.8, 101.7, 98.8, 71.3, 70.7, 32.4; HRMS (MALDI-TOF/CCA) calcd. $[C_{29}H_{23}ClO_5+Na]^+$; 509.1126, found: 509.1096.

3,5-bis(benzyloxy)-2-(2-bromoacetyl)phenyl 4-chlorobenzoate (16b)

To a solution of ester **14b** (5.70 g, 0.012 mol) in dry THF (40 mL) was added PTT (11 g, 0.03 mol, 2.5 equiv) in portions at 0 °C. The reaction mixture was stirred at rt for 4 h, the reaction progress was

monitored by crude NMR. When the reaction was completed, it was cooled down to 0 °C and dropwise treated with diethyl phosphate (2.27 mL, 0.018 mol, 1.5 equiv) and Et3N (2.45 mL, 0.018 mol, 1.5 equiv), the resulting mixture was stirred for 6 h at rt until complete, the mixture was poured into water and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over $NaSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexanes : CH_2Cl_2= 1 : 2) to give **16b** (4.81 g, 85%) as a light yellow solid: R_f = 0.47 (Hexanes : Ethyl Acetate = 4: 1), mp 98 -100 °C; IR (thin film, cm-1) 3064, 1933, 1740, 1691, 1690, 1574, 1497, 1487, 1454, 1435, 1400, 1380, 1330, 1257, 1153, 1089, 1058, 1013, 846, 828, 750, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 8H), 6.57 (d, *J* = 9.1 Hz, 2H), 5.10 (s, 2H), 5.06 (s, 2H), 4.36 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.0, 164.4, 162.5, 158.8, 151.3, 140.5, 135.9, 135.5, 132.0, 129.2, 129.1, 129.0, 128.9, 128.7, 127.9, 127.7, 114.0, 102.3, 98.7, 71.6, 70.9, 37.0; HRMS (MALDI-TOF/CCA) calcd. $[C_{29}H_{22}BrClO_5+Na]^+$; 587.0231, found: 587.0238.

2-(2-(benzoyloxy)acetyl)-3,5-bis(benzyloxy)phenyl 4-chlorobenzoate (17b)

A mixture of **16b** (3 g, 5.3 mmol) and BzOK (1.27 g, 8.0 mmol) was stirred in CH_3CN (53 mL) at 82 °C in a sand bath for 24 h. The reaction was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, then concentrated in vacuo. The resulting crude was purified by a silica gel chromatography and flash with solvent (Hexane: Ethyl Acetate = 10 : 1) to afford the product **17b** as a light yellow solid (2.19 g, 68%): m. 118 – 120 °C; R_f = 0.40 (Hexane: Ethyl Acetate = 4: 1); IR (thin film, cm^{-1}) 3064, 3033, 2932, 1724, 1692, 1607, 1488, 1452, 1434, 1401, 1365, 1329, 1315, 1265 ,1152, 1089, 1014, 973, 939, 911, 878, 845, 738, 710, 699, 525; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 7.5 Hz, 2H), 7.54 (dd, *J* = 7, 7 Hz, 1H), 7.44 – 7.34 (m, 14H), 6.56 (s, 2H), 5.22 (s, 2H), 5.11 (s, 2H), 5.06 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.6, 166.1, 164.5, 162.4, 159.3, 151.4, 140.2, 135.9, 135.6, 133.3, 132.1, 130.0, 129.8, 129.1, 129.1, 129.0, 128.8, 128.7, 128.6, 127.9, 127.9, 114.1, 102.6, 98.7, 71.5, 70.8, 70.0; HRMS (MALDI-TOF/CCA) calcd. $[C_{36}H_{27}ClO_7+Na]^+$; 629.1338, found: 629.1321.

5,7-bis(benzyloxy)-2-(4-chlorophenyl)-3-hydroxy-4H-chromen-4-one (11b)

To a solution of benzoate **17b** (1.54 g, 2.5 mmol) in THF (25 mL) added LiHMDS in hexanes (7.6 mL, 7.5 mmol). The mixture was stirred at −78 °C for 1 h until crude NMR analysis confirmed the reaction was complete. The cooled reaction mixture was poured into water and then extracted with Ethyl Acetate (3 x 80 mL). Combined organic layers were then washed with brine, dried over sodium sulfate and concentrated in vacuo. Resulting residue was dissolved in AcOH (25 mL), then AcONa (0.52 g, 6.25 mmol) was added. After stirring at 100 °C for 12 h, the mixture was cooled to rt and then diluted with CH_2Cl_2. The reaction mixture was washed with water, saturated $NaHCO_3$ solution and brine, successively. The combined organic phases were and concentrated to give a solid residue, which was dissolved in MeOH/CH_2Cl_2 (20 mL, v/v1:1). After being stirred for 10 h in the presence of a catalytic amount of NaOMe at rt, the mixture was neutralized with Dowex 50W-X 8 (H^+) resin. The resins were filtered off, the solvent was removed in vacuo. The resulting solid was recrystallized from methanol to provide **11b** (330 mg, 30%) as a yellow solid. mp 178 – 180 °C; R_f = 0.48 (Hexane: Ethyl Acetate = 2: 1); IR (thin film, cm^{-1}) 3407–3190 (br), 2923, 2853, 1615, 1491, 1452, 1401, 1332, 1213, 1170, 1135, 1092, 1050, 1013, 832, 801, 735, 697, 596; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.50 – 7.39 (m, 9H), 7.34 (dd, *J* = 8, 8 Hz, 1H), 6.64 (s, 1H), 6.49 (s, 1H), 5.23 (s, 2H), 5.13 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.1, 163.8, 159.7, 159.1, 140.9, 138.7, 136.3, 135.7, 129.8, 129.0, 129.0, 128.9, 128.9, 128.8, 128.7, 128.6, 128.1, 127.9, 126.9, 106.9, 97.9, 94.7, 93.9, 71.0, 70.9; HRMS (MALDI-TOF/CCA) calcd. $[C_{29}H_{21}ClO_5+Na]^+$: 507.0970, found: 507.0955

2-acetyl-3,5-bis(benzyloxy)phenyl 4-fluorobenzoate (14c)

To a solution of phenol **7** (5.03 g, 0.014 mol) and 4-fluorobenzoic acid **6c** (3.03 g, 0.02 mol) in CH_2Cl_2 (30 mL) at 0 °C added EDCI (8.30 g, 0.04 mol) and DMAP (1.76 g, 0.014 mol). After stirring for 4 h at rt, the mixture was diluted with EtOAc, and then washed with saturated $NaHCO_3$ solution. The organic phases were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc-petroleum ether, 1 : 1) to give **14c** (5.80 g, 83%) as a white

solid: R_f = 0.24 (Hexanes : Ethyl Acetate = 6 : 1); mp 115 – 117 °C; IR (thin film, cm-1) 2953, 1739, 1686, 1610, 1577, 1506, 1433, 1413, 1377, 1352, 1329, 1257, 1204, 1153, 1100, 1053, 1028, 1013, 912, 878, 852, 828, 758, 740, 697, 630, 612; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.44 – 7.31 (m, 10H), 7.16 (dd, *J* = 9, 9 Hz, 2H), 6.56 (d, *J* = 1.8 Hz, 1H), 6.47 (d, *J* = 1.8 Hz, 1H), 5.09 (s, 2H), 5.05 (s, 2H), 2.48 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 199.2, 166.2 (d, *J* = 203.1 Hz, 1C), 164.2, 161.3, 158.4, 149.7, 135.9, 135.8, 133.0, 132.9, 128.7, 128.4, 128.3, 127.6, 127.5, 125.5, 125.4, 117.7, 115.8 (d, *J* = 17.6 Hz, 2C), 101.4, 101.4, 98.6, 71.0, 70.5, 32.1; HRMS (MALDI) calcd for $[C_{29}H_{23}FO_5+Na]^+$: 493.1422, found: 493.1433.

3,5-bis(benzyloxy)-2-(2-bromoacetyl)phenyl 4-fluorobenzoate (16c)

To a solution of ester **14c** (5.80 g, 0.012 mol) in dry THF (25 mL) was added PTT (11.6 g, 0.03 mol, 2.5 equiv) in portions at 0 °C. The reaction mixture was stirred at rt for 4 h, the reaction was monitored by crude NMR. When the reaction was completed, it was cooled down to 0 °C and dropwise treated directly with diethyl phosphate (2.39 mL, 0.018 mol, 1.5 equiv) and Et_3N (2.58 mL, 0.018 mol, 1.5 equiv), the resulting mixture was stirred for 6 h at rt until complete, then mixture was poured into water and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over $NaSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexanes : CH_2Cl_2 = 1 : 2) to give **16c** (4.81 g, 71%) as a light yellow solid: R_f = 0.47 (Hexanes : Ethyl Acetate = 4: 1), mp : 122 – 124 °C; IR (thin film, cm^{-1}) 3065, 2932, 1739, 1691, 1605, 1576, 1506, 1454, 1435, 1413, 1379, 1330, 1294, 1255, 1152, 1098, 1056, 1028, 1013, 851, 828, 756, 738, 698, 630, 612, 574; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.2, 5.6 Hz, 2H), 7.47 – 7.32 (m, 11H), 7.17 (dd, *J* = 9, 9 Hz, 2H), 6.58 (s, 1H), 6.56 (s, 1H), 5.11 (s, 2H), 5.07 (s, 2H), 4.37 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 191.8, 166.2 (d, *J* = 203.1 Hz, 1C), 164.0, 162.3, 158.5, 151.1, 135.6, 135.2, 133.1, 133.0, 128.9, 128.8, 128.6, 128.5, 127.7, 127.7, 125.2, 125.2, 115.8 (d, *J* = 17.6 Hz, 2C), 113.8, 102.1, 98.4, 71.4, 70.6, 36.7; HRMS (MALDI) calcd for $[C_{29}H_{22}BrFO_5+Na]^+$: 571.0527, found: 571.0532.

2-(2-(benzoyloxy)acetyl)-3,5-bis(benzyloxy)phenyl 4-fluorobenzoate (17c)

A mixture of **16c** (3.79 g, 6.9 mmol) and BzOK (1.66 g, 10.3 mmol) was stirred in CH_3CN (40 mL) at 82 ^oC in a sand bath for 24 h. The reaction was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate and brine. The combined organic layers were dried over sodium sulfate, and then concentrated in vacuo. The resulting crude was purified by a silica gel chromatography and flash with solvent (Hexane: Ethyl Acetate = 10 : 1) to afford the product **17c** as a light yellow solid (3.08 g, 76%): mp 104 – 106 °C; R_f = 0.40 (Hexane: Ethyl Acetate = 4: 1); IR (thin film, cm^{-1}) 2921, 2852, 1743, 1644, 1611, 1508, 1498, 1451, 1439, 1349, 1288, 1238, 1173, 1112, 1097, 1044, 1021, 840, 823, 736, 699, 624, 508, 488, 454; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.8, 5.5 Hz, 2H), 8.04 – 7.97 (m, 2H), 7.55 (dd, *J* = 7, 7 Hz, 1H), 7.44 – 7.35 (m, 12H), 7.12 (dd, *J* = 9, 9 Hz, 2H), 6.59 (d, *J* = 1.1 Hz, 2H), 5.26 (s, 2H), 5.12 (s, 2H), 5.06 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 193.4, 166.1 (d, *J* = 253.8 Hz, 1C), 165.8, 164.1, 162.2, 159.0, 151.2, 135.8, 135.4, 133.2, 133.1, 133.1, 129.8, 129.7, 128.8, 128.7, 128.5, 128.4, 128.3, 127.7, 127.7, 127.6, 125.5, 125.5, 115.8 (d, *J* = 22 Hz, 2C), 114.0, 102.5, 98.4, 71.3, 70.6, 69.8; HRMS (MALDI) calcd for $[C_{36}H_{27}FO_7+Na]^+$: 613.1633, found: 613.1612.

5,7-bis(benzyloxy)-2-(4-fluorophenyl)-3-hydroxy-4H-chromen-4-one (11c)

To a solution of benzoate **17c** (2.32 g, 3.9 mmol) in THF (39 mL) was added LiHMDS in hexanes (11.8 mL, 11.8 mmol) at – 78 °C. The mixture was stirred at – 78 °C for 1 h until the crude NMR analysis confirmed the reaction was completed. The cooled mixture was poured into water and was then extracted with Ethyl Acetate (3 x 80 mL). The combined organic layers were then washed with brine, dried over sodium sulfate and concentrated in vacuo. Resulting residue was dissolved in AcOH (38 mL), then AcONa (0.81 g, 9.8 mmol) was added. After stirring at 100 °C for 12 h, the mixture was cooled to rt and then diluted with CH_2Cl_2. The mixture was washed with water, saturated $NaHCO_3$ solution and brine, successively. The organic phase was combined and concentrated in vacuo to give a solid residue, which was then dissolved in MeOH/CH_2Cl_2 (20 mL, v/v1:1). After stirring for 10 h in the presence of a catalytic amount of NaOMe at rt, the mixture was neutralized with Dowex 50W-X 8 (H^+) resin. The resins were

filtered off, the solvent was removed. The resulting solid was recrystallized from methanol to provide **11c** (600 mg, 33%) as a yellow solid. mp 179 – 181 °C; R_f = 0.45 (Hexane: Ethyl Acetate = 2: 1); IR (thin film, cm^{-1}) 2946, 1754, 1617, 1507, 1453, 1375, 1258, 1234, 1214, 1198, 1163, 1030, 736, 702, 471, 410; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.49 – 7.36 (m, 7H), 7.33 (dd, *J* = 7, 7 Hz, 1H), 7.19 (dd, *J* = 9, 9 Hz, 2H), 6.64 (d, *J* = 1.8 Hz, 1H), 6.50 (d, *J* = 1.8 Hz, 1H), 5.24 (s, 2H), 5.13 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.9, 163.5, 163.3 (d, *J* = 250.1 Hz, 1C), 159.5, 158.8, 141.0, 138.1, 136.1, 135.5, 129.4, 129.3, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 127.8, 127.6, 127.3, 127.3, 126.7, 126.7, 126.6, 115.6 (d, *J* = 21.6 Hz, 2C), 106.7, 97.7, 93.7, 70.8, 70.6; HRMS (MALDI-TOF/CCA) calcd. $[C_{29}H_{21}FO_5+Na]^+$: 491.1265, found: 491.1257

2-acetyl-3,5-bis(benzyloxy)phenyl benzoate (14d)

To a solution of phenol **7** (7.81 g, 0.022 mol) and benzoic acid **6d** (4.10 g, 0.034 mol) in CH_2Cl_2 (30 mL) at 0 °C was added EDCI (12.90 g, 0.066 mol) and DMAP (2.74 g, 0.022 mol). After stirring for 4 h at rt, the mixture was diluted with EtOAc, and then washed with saturated $NaHCO_3$ solution. The organic phases were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc-Hexanes, 1 : 1) to give **14d** (8.5 g, 84%) as a white solid: R_f = 0.32 (Hexanes : Ethyl Acetate = 4 : 1); mp 108 – 110 °C; IR (thin film, cm^{-1}) 3063, 2922, 1737, 1686, 1610, 1576, 1497, 1452, 1432, 1377, 1351, 1327, 1289, 1250, 1204, 1153, 1096, 1069, 1027, 1002, 827, 738, 703; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.9 Hz, 2H), 7.62 (dd, *J* = 7, 7 Hz, 1H), 7.50 (dd, *J* = 7, 7 Hz, 2H), 7.43 – 7.31 (m, 10H), 6.56 (s, 1H), 6.49 (s, 1H), 5.10 (s, 2H), 5.05 (s, 2H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 199.3, 165.0, 161.2, 158.2, 149.8, 135.9, 135.8, 133.7, 130.3, 129.2, 128.7, 128.7, 128.6, 128.3, 128.3, 127.6, 127.5, 117.9, 101.4, 98.5, 71.0, 70.5, 32.1; HRMS (MALDI-TOF/CCA) calcd. $[C_{29}H_{24}O_5+Na]^+$: 475.1516, Found: 475.1494.

3,5-bis(benzyloxy)-2-(2-bromoacetyl)phenyl benzoate (16d)

To a solution of ester **14d** (8.47 g, 0.019 mol) in dry THF (40 mL) was added PTT (17.6 g, 0.047 mol, 2.5 equiv) in portions at 0 °C. The reaction mixture was stirred at rt for 4 h, and monitored by crude NMR.

When the reaction completed, it was cooled down to 0 °C and dropwise treated directly with diethyl phosphate (3.62 mL, 0.028 mol, 1.5 equiv) and Et3N (3.91 mL, 0.028 mol, 1.5 equiv), the resulting mixture was stirred for 6 h at rt until complete, then mixture was poured into water and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over $NaSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexanes : Ethyl Acetate = 10 : 1) to give **16d** (8.6 g, 87%) as a light yellow solid: R_f = 0.45 (Hexanes : Ethyl Acetate = 4: 1), mp 106 – 108 °C; IR (thin film, cm^{-1}) 3064, 3032, 1738, 1693, 1608, 1574, 1497, 1452, 1434, 1379, 1329, 1257, 1150, 1091, 1056, 1026, 827, 737, 699, 613, 590; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.4 Hz, 2H), 7.63 (dd, *J* = 7, 7 Hz, 1H), 7.50 (dd, *J* = 8, 8 Hz, 2H), 7.48 – 7.33 (m, 10H), 6.56 (d, *J* = 2.0 Hz, 1H), 6.55 (d, *J* = 2.0 Hz, 1H), 5.11 (s, 2H). 5.06 (s, 2H). 4.36 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 191.8, 165.0, 162.2, 158.4, 151.1, 135.7, 135.3, 133.8, 130.4, 129.0, 128.9, 128.8, 128.6, 128.6, 128.5, 127.7, 127.7, 114.0, 110.0, 102.1, 98.4, 71.3, 70.6, 36.7; HRMS (MALDI-TOF/CCA) calcd. $[C_{29}H_{23}BrO_5+H]^+$: 553.0621, Found: 553.0607.

2-(2-(benzoyloxy)-4,6-bis(benzyloxy)phenyl)-2-oxoethyl benzoate (17d)

A mixture of **16d** (8 g, 15 mmol) and BzOK (3.62 g, 22.5 mmol) was stirred in CH_3CN (30 mL) at 82 °C in a sand bath for 24 h. Reaction was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, then concentrated in vacuo. The resulting crude was purified by silica gel chromatography and flash with solvent (Hexane: Ethyl Acetate = 10 : 1) to afford the product **17d** as a light yellow solid (8.6 g, 77%): mp 114 – 116 °C; R_f = 0.48 (Hexane: Ethyl Acetate = 5 : 1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.5 Hz, 2H), 8.01 – 7.95 (d, *J* = 7.5 Hz, 2H), 7.59 (dd, *J* = 8, 8 Hz, 1H), 7.53 (dd, *J* = 7, 7 Hz, 1H), 7.47 (d, *J* = 8, 8 Hz, 2H), 7.44 – 7.32 (m, 13H), 6.56 (dd, *J* = 5.3, 1.9 Hz, 2H), 5.23 (s, 2H), 5.11 (s, 2H), 5.06 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.6, 165.8, 165.0, 162.1, 158.9, 151.2, 135.7, 135.4, 133.5, 133.0, 130.5, 129.8, 129.6, 129.2, 128.8, 128.7, 128.5, 128.4, 128.3, 127.7, 127.6, 114.1, 112.5, 102.3, 98.4, 71.3, 70.5, 69.7; IR (thin film, cm^{-1}) 1724, 1606, 1582, 1497,

1451, 1434, 1413, 1364, 1329, 1315, 1258, 1176, 1151, 1092, 1071, 1024, 1001, 972, 938, 911, 826, 797, 735, 699; HRMS (MALDI-TOF/CCA) calcd. $[C_{36}H_{28}O_7+H]^+$: 595.1727, Found: 595.1707.

5,7-bis(benzyloxy)-3-hydroxy-2-phenyl-4H-chromen-4-one (11d)

To a solution of benzoate **17d** (2.5 g, 4.4 mmol) in THF (30 mL) was added LiHMDS in hexanes (13 mL, 13.2 mmol) at – 78 °C. The mixture was stirred at – 78 °C for 1 h until crude NMR analysis confirmed the reaction was completed. The cooled mixture was then poured into water and then extracted with Ethyl Acetate (3 x 80 mL). The combined organic layers were then washed with brine, dried over sodium sulfate and concentrated in vacuo. Resulting residue was dissolved in AcOH (13 mL), then AcONa (0.54 g, 6.6 mmol) was added. After stirring at 100 °C for 12 h, the mixture was cooled to rt and then diluted with CH_2Cl_2. The mixture was washed with water, saturated $NaHCO_3$ solution and brine, successively. The organic phases were combined and concentrated in vacuo to give a solid residue, which was dissolved in MeOH/CH_2Cl_2 (12 mL, v/v1:1). After stirring for 10 h in the presence of a catalytic amount of NaOMe at rt, the mixture was neutralized with Dowex 50W-X 8 (H^+) resin. The resins were filtered off, the solvent was removed. The resulting solid was recrystallized from methanol to provide **11d** (650 mg, 35%) as a yellow solid. mp 167 – 169 °C; R_f = 0.41 (Hexane: Ethyl Acetate = 2: 1); IR (thin film, cm^{-1}) 3266, 1740, 1615, 1495, 1452, 1375, 1303, 1264, 1213, 1169, 1134, 1109, 1097, 821, 736, 695; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.7 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.51 (dd, *J* = 8, 8 Hz, 2H), 7.47 – 7.37 (m, 8H), 7.32 (dd, *J* = 7, 7 Hz, 1H), 6.65 (d, *J* = 1.9 Hz, 1H), 6.48 (d, *J* = 1.9 Hz, 1H), 5.23 (s, 2H), 5.12 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.9, 163.4, 159.4, 158.9, 141.8, 138.4, 136.1, 135.6, 131.1, 129.6, 128.8, 128.7, 128.5, 128.5, 127.8, 127.6, 127.2, 126.6, 106.8, 97.6, 93.7, 70.7, 70.6; HRMS (MALDI-TOF/CCA) calcd. $[C_{29}H_{22}O_5+H]^+$: 473.1359, Found: 473.1348.

2-acetyl-3,5-bis(benzyloxy)phenyl 4-methoxybenzoate (14e)

To a suspension of phenol **7** (7.92 g, 0.023 mol) and 4-methoxybenzoic acid **6e** (5.68 g, 0.034 mol) in CH_2Cl_2 (120 mL) at 0 °C was added EDCI (13.07 g, 0.069 mol) and DMAP (2.78 g, 0.023 mol). After stirring for 8 h at rt, the mixture was diluted with EtOAc, and then washed with saturated NaHCO3

solution. The organic phases were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexanes : Ethyl Acetate = 1 : 1) to give **14e** (9.34 g, 85 %) as a white solid: R_f = 0.27 (Hexanes : Ethyl Acetate = 4 : 1), mp 100 – 102 °C; IR (thin film, cm^{-1}) 2872, 1729, 1687, 1605, 1578, 1510, 1454, 1433, 1421, 1377, 1351, 1329, 1252, 1204, 1165, 1153, 1095, 1028, 845, 827, 760, 738, 696, 612; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.7 Hz, 2H), 7.50 – 7.28 (m, 10H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 1.7 Hz, 1H), 6.49 (d, *J* = 1.7 Hz, 1H), 5.09 (s, 2H), 5.04 (s, 2H), 3.88 (s, 3H), 2.48 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.4, 164.6, 164.0, 161.1, 158.0, 149.8, 136.0, 135.9, 132.4, 132.4, 132.4, 128.9, 128.9, 128.8, 128.8, 128.8, 128.8, 128.8, 128.7, 128.3, 128.2, 127.6, 127.4, 127.3, 121.5, 118.1, 113.9, 113.8, 101.5, 98.4, 70.9, 70.4, 55.5, 32.0; HRMS (MALDI-TOF/CCA) calcd. $[C_{30}H_{26}O_6+Na]^+$:505.1622, found: 505.1652.

3,5-bis(benzyloxy)-2-(2-bromoacetyl)phenyl 4-methoxybenzoate (16e)

To a solution of ester **14e** (9.34 g, 0.019 mol) in dry THF (50 mL) was added PTT (18.2 g, 0.048 mol, 2.5 equiv) in portions at 0 °C. The reaction mixture was stirred at rt for 4 h. The reaction was monitored by crude NMR. When the reaction was complete, it was cooled down to 0 °C and dropwise treated directly with diethyl phosphate (3.75 mL, 0.029 mol, 1.5 equiv) and Et3N (4.05 mL, 0.029 mol, 1.5 equiv), the resulting mixture was stirred for 6 h at rt until complete, then mixture was poured into water and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried over $NaSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexanes : CH_2Cl_2 = 1 : 2) to give **16e** (4.81 g, 71%) as a light yellow solid: R_f = 0.34 (Hexanes : Ethyl Acetate = 4: 1), mp 141 – 143 °C; IR (thin film, cm^{-1}) 3064, 2910, 1731, 1694, 1605, 1577, 1510, 1498, 1435, 1422, 1381, 1331, 1252, 1166, 1152, 1092, 1028, 845, 759, 739, 697, 639, 613, 580; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.9 Hz, 2H), 7.46 – 7.31 (m, 10H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.56 (dd, *J* = 4.1, 1.9 Hz, 2H), 5.10 (s, 2H), 5.06 (s, 2H), 4.37 (s, 2H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 191.9, 164.6, 164.1, 162.1, 158.3, 151.1, 135.7, 135.4, 132.5, 128.8, 128.7, 128.5, 128.4, 127.7, 127.6, 121.2, 114.2, 113.9, 102.1, 98.3, 71.2, 70.6, 55.5, 36.8; HRMS (MALDI-TOF/CCA) calcd. $[C_{30}H_{25}BrO_6+Na]^+$:583.0727, found: 583.0715

2-(2-(benzoyloxy)acetyl)-3,5-bis(benzyloxy)phenyl 4-methoxybenzoate (17e)

A mixture of **16e** (9.11 g, 0.016 mol) and BzOK (3.90 g, 0.024 mol) was stirred in CH_3CN (100 mL) at 82 °C in a sand bath for 24 h. Reaction was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, the combined organic layers were concentrated in vacuo. The resulting crude was purified by silica gel column chromatography and flash with solvent (Hexane: Ethyl Acetate = 10 : 1) to afford product **17e** as a light yellow solid (7.40 g, 76%): mp 116 – 118 °C; R_f = 0.40 (Hexane: Ethyl Acetate = 4: 1); IR (thin film, cm^{-1}) 3033, 2935, 1724, 1602, 1577, 1510, 1452, 1434, 1364, 1330, 1315, 1249, 1150, 1089, 1024, 971, 939, 911, 878, 826, 793, 758, 734, 695, 642, 578, 506; ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.7 Hz, 2H), 8.01 (d, *J* = 7.4 Hz, 2H), 7.54 (dd, *J* = 7, 7 Hz, 1H), 7.48 – 7.31 (m, 12H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 1.8 Hz, 1H), 6.55 (d, *J* = 1.8 Hz, 1H), 5.26 (s, 2H), 5.11 (s, 2H), 5.05 (s, 2H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.7, 165.8, 164.7, 163.9, 162.1, 158.8, 151.3, 135.8, 135.5, 133.0, 132.6, 129.8, 129.7, 128.8, 128.7, 128.4, 128.4, 128.3, 127.7, 127.6, 121.5, 114.2, 113.8, 102.4, 98.2, 71.2, 70.5, 69.7, 55.5; HRMS (MALDI-TOF/CCA) calcd. $[C_{37}H_{30}O_8+Na]^+$: 625.1833, found: 625.1815

5,7-bis(benzyloxy)-3-hydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one (11e)

To a solution of benzoate **17e** (2.52 g, 0.004 mol) in THF (30 mL) was added LiHMDS in hexanes (12.5 mL, 0.012 mol) at – 78 °C. The mixture was stirred at – 78 °C for 1 h until the crude NMR analysis confirmed the reaction was complete. The cooled mixture was poured into water and was then extracted with Ethyl Acetate (3 x 80 mL). The combined organic layers were then washed with brine, dried over sodium sulfate and concentrated in vacuo. Resulting residue was dissolved in AcOH (30 mL), then AcONa (0.51 g, 6.27 mmol) was added. After stirring at 100 °C for 12 h, the mixture was cooled to rt and then diluted with CH_2Cl_2. The mixture was washed with water, saturated $NaHCO_3$ solution and brine, successively. The organic phases were combined and concentrated to give a solid residue, which was dissolved in MeOH/CH_2Cl_2 (20 mL, v/v1:1). After being stirred for 10 h in the presence of a catalytic amount of NaOMe at rt, the mixture was neutralized with Dowex 50W-X 8 (H^+) resin. The resins were

filtered off, solvent was concentrated in vacuo. The resulting solid was recrystallized from methanol to provide **11e** (800 mg, 40%) as a yellow solid. mp 188 – 190 °C; R_f= 0.42 (Hexane: Ethyl Acetate = 2: 1); IR (thin film, cm^{-1}) 3309 – 3234 (br), 2873, 1605, 1571, 1511, 1452, 1374, 1334, 1300, 1255, 1212, 1179, 1135, 1099, 1030, 976, 911, 8334, 819, 736, 696, 624; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.0 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.46 – 7.36 (m, 9H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.63 (d, *J* = 1.9 Hz, 1H), 6.48 (d, *J* = 1.9 Hz, 1H), 5.23 (s, 2H), 5.12 (s, 2H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.7, 163.2, 160.6, 159.3, 158.7, 142.4, 137.5, 136.2, 135.6, 130.0, 128.9, 128.8, 128.7, 128.7, 128.6, 128.5, 127.8, 127.7, 126.6, 123.6, 114.0, 106.7, 97.6, 93.7, 70.7, 70.6, 55.4; HRMS (MALDI-TOF/CCA) calcd. $[C_{30}H_{24}O_6+Na]^+$: 503.1465, found: 503.1442.

3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one (3a)

To a solution of compound **11f** (14 mg, 0.025 mmol) in 0.3 mL of a solvent mixture of THF and methanol (1 : 1) was added Pd/C (2.6 mg, 10 mol%) and the resulting mixture was stirred under a H_2 atmosphere for 12 h. The reaction mixture was flashed through a celite column and crystalized by the addition of acetone to give product **3a** (5 mg, 72%) as a yellow solid. IR (thin film, cm^{-1}) 3510 – 3060 (br), 1658, 1616, 1568, 1508, 1456, 1378, 1314, 1256, 1224, 1174, 1090, 1007, 977, 883, 797, 736, 641; ^{1}H NMR (500 MHz, DMSO-d6) δ 12.43 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.43 (s, 1H), 6.18 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d6) δ 176.3, 164.3, 161.1, 159.6, 156.6, 147.2, 136.1, 129.9, 122.1, 115.9, 103.5, 98.7, 93.9; HRMS (MALDI-TOF/CCA) calcd. $[C_{15}H_{10}O_6+Na]^+$: 309.0370, Found: 309.0378.

2-(4-chlorophenyl)-3,5,7-trihydroxy-4H-chromen-4-one (3b)

To a solution of compound **11b** (6.7 mg, 0.014 mmol) in 0.3 mL of a solvent mixture of THF and CH_2Cl_2 (1 : 1) was added Pd/C (0.7 mg, 5 mol%) and resulting mixture was stirred under a H_2 atmosphere for 6 h. The reaction mixture was flashed through a celite column and crystalized by the addition of acetone to give product **3b** (3 mg, 71%) as a yellow solid. mp > 200 °C; IR (thin film, cm^{-1}) 3407 – 3178(br), 2366, 2342, 1653, 1624, 1599, 1559, 1541, 1507, 1490, 1371, 1308, 1218, 1167, 1088, 1013, 878, 862, 831; ^{1}H

NMR (500 MHz, methanol-d4) δ 8.20 (d, *J* = 4.0 Hz, 2H), 7.51 (d, *J* = 4.0 Hz, 2H), 6.42 (s, 1H), 6.19 (s, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, methanol-d4) δ 176.2, 164.9, 161.3, 157.0, 144.2, 137.4, 135.3, 130.0, 128.9, 128.3, 128.1, 127.4, 103.2, 98.1, 93.2; HRMS (MALDI-TOF/CCA) calcd. $[C_{15}H_9ClO_5+Na]^+$:305.0211, found: 305.0217.

2-(4-fluorophenyl)-3,5,7-trihydroxy-4H-chromen-4-one (3c)

To a solution of compound **11c** (14.4 mg, 0.03 mmol) in 0.3 mL of a solvent mixture of THF and methanol (1 : 1) was added Pd/C (3.3 mg, 10 mol%) and resulting mixture was stirred under a H_2 atmosphere for 12 h. The reaction mixture was flashed through a celite column and crystalized by the addition of acetone to give product **3c** (60%) as a yellow solid. mp 196 – 198 °C; IR (thin film, cm^{-1}) 3393 – 3201 (br), 2367, 2313, 1655, 1627, 1601, 1508, 1473, 1437, 1418, 1375, 1314, 1243, 1216, 1167, 1124, 1087, 1007, 978, 899, 882, 835; ^{1}H NMR (500 MHz, acetone-d6) δ 12.06 (s, 1H), 8.31 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.34 (dd, *J* = 8.7 Hz, 2H), 6.57 (s, 1H), 6.29 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, acetone-d6) δ 176.0, 164.5, 163.4 (d, *J* = 248.6 Hz, 1C), 161.5, 157.0, 144.4, 136.8, 130.1, 130.0, 127.6, 115.5 (d, *J* = 21.9 Hz, 2C), 103.4, 98.5, 93.7; HRMS (MALDI-TOF/CCA) calcd. $[C_{15}H_9FO_5+Na]^+$: 289.0507, found: 289.0518.

3,5,7-trihydroxy-2-phenyl-4H-chromen-4-one (3d)

To a solution of compound **11d** (12.7 mg, 0.028 mmol) in 0.3 mL of a solvent mixture of THF and CH_2Cl_2 (1 : 1) was added Pd/C (3 mg, 10 mol%) and resulting mixture was stirred under a H_2 atmosphere for 6 h. The reaction mixture was flashed through a celite column and crystalized by the addition of acetone to give product **3d** (5.4 mg, 73%) as a yellow solid. mp > 200 °C; IR (thin film, cm^{-1}) 3412 – 3157(br), 2924, 2359, 2331, 1636, 1601, 1558, 1506, 1497, 1472, 1465, 1457, 1448, 1373, 1313, 1254, 1217, 1163, 1088, 1073, 1005, 990, 689; ^{1}H NMR (500 MHz, acetone-d6) δ 8.25 (d, *J* = 7.9 Hz, 2H), 7.57 (dd, *J* = 7, 7 Hz, 2H), 7.51 (d, *J* = 7.1 Hz, 1H), 6.58 (s, 1H), 6.30 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, acetone-d6) δ 205.3, 176.1, 164.5, 161.5, 157.1, 145.2, 137.1, 131.2, 129.9, 128.5, 127.6, 103.4, 98.4, 93.7, 29.3, 29.1, 28.9, 28.7, 28.5; HRMS (MALDI-TOF/CCA) calcd. $[C_{15}H_{10}O_5+H]^+$: 271.0601, Found: 271.0574.

3,5,7-trihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one (3e)

To a solution of compound **11e** (10 mg, 0.014 mmol) in 0.3 mL of a solvent mixture of THF and CH_3OH (1 : 1) was added Pd/C (2 mg, 10 mol%) and the resulting mixture was stirred under a H_2 atmosphere for 6 h. The reaction mixture was flashed through a celite column and crystalized by the addition of acetone to give product **3e** (4 mg, 70%) as a yellow solid. mp > 200 °C; IR (thin film, cm^{-1}) 3648 – 3274(br), 2251, 2125, 1653, 1618, 1598, 1541, 1510, 1398, 1372, 1310, 1258, 1223, 1175 ,1052, 1003, 882, 821, 758, 622; ^1H NMR (500 MHz, DMSO-d6) δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.43 (s, 1H), 6.18 (s, 1H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d6) δ 176.4, 164.5, 161.2, 160.9, 156.7, 146.7, 136.5, 129.8, 123.7, 114.5, 103.5, 98.7, 94.0, 55.8; HRMS (MALDI-TOF/CCA) calcd. $[C_{16}H_{12}O_6+Na]^+$: 323.0526, Found: 323.0518.

benzyl 2-((5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yl)oxy)acetate (10f)

To a solution of OBn-aglycon **11f** (25 mg, 0.045 mmol) in DMF at 0 °C was added K_2CO_3 (8 mg, 0.058 mmol) portion-wise and dropwise of benzyl bromoacetate (7.9 μL, 0.049 mmol). The resulting solution was stirred at rt for 6 h. The reaction solution was washed with water (3 x 4 mL) and extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with CH_2Cl_2 and hexanes (CH_2Cl_2 : Hexanes = 5 : 1) to give benzyl ester **10f** (25 mg, 81%) as a yellow solid: mp 165 – 167 °C. R_f = 0.21 (CH_2Cl_2); IR (thin film, cm^{-1}) 2955, 2922, 2852, 1749, 1627, 1603, 1508, 1497, 1454, 1437, 1375, 1351, 1295, 1254, 1176, 1124, 1107, 1038, 1026, 1015, 967, 835, 824, 736, 696, 406; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.39 (m, 18H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.59 (s, 1H), 6.47 (s, 1H), 5.25 (s, 2H), 5.15 (s, 2H), 5.11 (s, 2H), 5.10 (s, 2H), 4.93 (s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.4, 169.1, 162.8, 160.4, 159.7, 158.6, 152.8, 139.1, 136.5, 136.3, 135.6, 135.4, 130.3, 128.8, 128.7, 128.6, 128.5, 128.5, 128.3, 128.3, 128.2, 127.7, 127.6, 127.5, 126.6, 123.2, 114.6, 109.8, 98.1, 93.9, 70.8, 70.5, 70.0, 68.4, 66.5; HRMS (MALDI-TOF/CCA) calcd. $[C_{45}H_{36}O_8+Na]^+$: 727.2302, Found: 727.2274.

benzyl 2-((5,7-bis(benzyloxy)-2-(4-chlorophenyl)-4-oxo-4H-chromen-3-yl)oxy)acetate (10b)

To a solution of chloro-aglycon **11b** (16 mg, 0.033 mmol) in 0.3 mL of DMF at 0 °C added K_2CO_3 (5.9 mg, 0.043 mmol) portion-wise and benzyl bromoacetate (5.8 μL, 0.036 mmol) dropwise. The resulting solution was stirred at rt overnight. The reaction solution was washed with water (3 x 4 mL) and extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with CH_2Cl_2 and hexanes (CH_2Cl_2 : Hexanes = 5 : 1) to give benzyl ester **10b** (16 mg, 77%) as a white solid; mp 132 – 134 °C. R_f = 0.21 (CH_2Cl_2); IR (thin film, cm^{-1}) 2923, 1754, 1634, 1605, 1488, 1442, 1362, 1301, 1174, 1120, 1093, 1030, 749, 697, 455; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.27 (m, 15H), 6.59 (d, *J* = 1.9 Hz, 1H), 6.48 (d, *J* = 1.9 Hz, 1H), 5.24 (s, 2H), 5.13 (s, 2H), 5.11 (s, 2H), 4.97 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.2, 168.9, 163.1, 159.8, 158.6, 151.5, 139.9, 136.4, 136.2, 135.6, 135.3, 129.9(2C), 129.1, 128.8(2C), 128.6(2C), 128.6(2C), 128.5(2C), 128.5, 128.4, 128.3(2C), 127.7, 127.6 (2C), 126.7, 126.6, 109.9, 98.3, 93.8, 70.8, 70.5, 68.3, 66.6; HRMS (MALDI-TOF/CCA) calcd. $[C_{38}H_{29}ClO_7+Na]^+$:655.1494, found: 655.1467

benzyl 2-((5,7-bis(benzyloxy)-2-(4-fluorophenyl)-4-oxo-4H-chromen-3-yl)oxy)acetate (10c)

To a solution of fluoro-aglycon **11c** (31.1 mg, 0.066 mmol) in DMF at 0 °C was added K_2CO_3 (11.9 mg, 0.86) portion-wise and benzyl bromoacetate (11.6 μL, 0.073 mmol) dropwise. The resulting solution was stirred at rt for 6 h. The reaction solution was washed with water (3 x 4 mL) and extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. The crude product was purified by flash silica gel chromatography column with CH_2Cl_2 and hexanes (CH_2Cl_2 : Hexanes = 5 : 1) to give a yellow solid, 10c (20 mg, 51%), mp 132 – 134 °C. R_f = 0.21 (CH_2Cl_2); IR (thin film, cm^{-1}) 2920, 1778, 1755, 1634, 1605, 1507, 1498, 1488, 1453, 1432, 1379, 1255, 1237, 1175, 1114, 736, 697, 454, 414; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.4, 5.7 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 2H), 7.46 – 7.28 (m, 14H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.59 (s, 1H), 6.48 (s, 1H), 5.25 (s, 2H), 5.13 (s, 2H), 5.11 (s, 2H), 4.96 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 169.0, 163.0, 163.7 (d, *J* = 251.0 Hz, 1C), 159.8, 158.6, 151.7, 139.5, 136.2, 135.6, 135.3, 130.9, 130.8, 128.9, 128.8, 128.8, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3,

128.3, 127.7, 127.7, 127.6, 126.8, 126.8, 126.7, 126.6, 115.4 (d, J = 21.6 Hz, 2C), 109.9, 98.2, 93.8, 70.8, 70.5, 68.3, 66.6; HRMS (MALDI-TOF/CCA) calcd. $[C_{38}H_{29}FO_7+Na]^+$: 639.1790, found: 639.1790.

benzyl 2-((5,7-bis(benzyloxy)-4-oxo-2-phenyl-4H-chromen-3-yl)oxy)acetate (10d)

To a solution of aglycon **11d** (15.7 mg, 0.035 mmol) in 0.3 mL of DMF at 0 °C was added K_2CO_3 (6.3 mg, 0.046 mmol) portion-wise and benzyl bromoacetate (6.1 μL, 0.039 mmol) dropwise. The resulting solution was stirred at rt for 6 h. Reaction solution was washed with water (3 x 4 mL) and extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. The crude product was purified by flash silica gel column chromatography with CH_2Cl_2 and hexanes (CH_2Cl_2 : Hexanes = 5 : 1) to give a yellow solid, benzyl ester **10d** (16 mg, 79%), mp 50 – 52 °C. R_f = 0.21 (CH_2Cl_2); IR (thin film, cm^{-1}) 1758, 1632, 1605, 1559, 1517, 1496, 1446, 1375, 1351, 1276, 1260, 1174, 1116, 1030, 822, 736, 695; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, J = 3.0, 3.0 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.44 – 7.30 (m, 16H), 6.61 (d, J = 0.9 Hz, 1H), 6.48 (d, J = 1.0 Hz, 1H), 5.25 (s, 2H), 5.13 (s, 2H), 5.11 (s, 2H), 4.94 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.4, 169.0, 163.0, 159.8, 158.7, 152.8, 139.8, 136.3, 135.6, 135.4, 130.6, 130.4, 128.8, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.3, 127.7, 127.6, 126.6, 109.9, 98.2, 93.9, 70.8, 70.5, 68.3, 66.5; HRMS (MALDI-TOF/CCA) calcd. $[C_{38}H_{30}O_7+Na]^+$: 621.1884, Found: 621.1907.

benzyl 2-((5,7-bis(benzyloxy)-2-(4-methoxyphenyl)-4-oxo-4H-chromen-3-yl)oxy)acetate (10e)

To a solution of methoxyl-aglycon **11e** (17.7 mg, 0.037 mmol) in 0.4 mL of DMF at 0 °C added K_2CO_3 (6.6 mg, 0.048 mmol) portion-wise and benzyl bromoacetate (6.4 μL, 0.041 mmol) dropwise. The resulting solution was stirred at rt for 6 h. The reaction solution was washed with water (3 x 4 mL) and extracted with ethyl acetate, dried over sodium sulfate and concentrated in vacuo. Crude was purified by flash silica gel chromatography with CH_2Cl_2 and hexanes (CH_2Cl_2 : Hexanes = 5 : 1) to give yellow solid, benzyl ester **10e** (20 mg, 80%), mp 120 – 122 °C. R_f = 0.20 (CH_2Cl_2); IR (thin film, cm^{-1}) 1757, 1604, 1509, 1487, 1453, 1440, 1351, 1298, 1258, 1178, 1123, 1106, 1062, 1029, 836, 737, 697; ^1H NMR (500

MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.9 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.44 – 7.30 (m, 13H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 1.8 Hz, 1H), 6.47 (d, *J* = 1.7 Hz, 1H), 5.24 (s, 2H), 5.15 (s, 2H), 5.10 (s, 2H), 4.93 (s, 2H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 169.0, 162.8, 161.2, 159.7, 158.6, 152.8, 139.1, 136.3, 135.7, 135.5, 130.3, 128.7, 128.7, 128.7, 128., 128.5, 128.4, 128.3, 128.3, 128.3, 127.7, 127.6, 126.6, 123.0, 113.8, 109.9, 98.1, 93.9, 70.8, 70.5, 68.3, 66.5, 55.3; HRMS (MALDI-TOF/CCA) calcd. $[C_{39}H_{32}O_8+Na]^+$: 651.1989, Found: 651.1969.

2-((5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yl)oxy)acetic acid (4a)

To a solution of alkylated aglycon **10f** (12.4 mg, 0.018 mmol) in 0.2 mL of a mixture of CH_2Cl_2 and MeOH (1 : 1) was added Pd/C (1.9 mg, 10 mol%) under H_2 atmosphere and resulting solution was stirred for 12 h. The resulting suspension solution was filtered by flashing through a celite column and then concentrated in vacuo to give a yellow solid, acid **4a** (4.5 mg, 70%), mp > 200 °C; IR (thin film, cm^{-1}) 3316 – 3188(br), 2928, 1732, 1651, 1604, 1566, 1497, 1438, 1360, 1284, 1261, 1203, 1175, 1090, 1038, 1015, 999, 966, 844, 840, 732, 709, 691, 636, 581, 569, 517; ^1H NMR (500 MHz, DMSO-d6) δ 8.16 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.41 (d, *J* = 0.7 Hz, 1H), 6.15 (s, 1H), 4.36 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 178.0, 171.3, 164.5, 161.5, 160.3, 156.9, 156.4, 136.2, 130.3, 121.0, 115.1, 104.3, 98.5, 93.4, 68.3; HRMS (MALDI-TOF/CCA) calcd. $[C_{17}H_{12}O_8+Na]^+$: 367.0424, Found: 367.0413.

2-((2-(4-chlorophenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)acetic acid (4b)

To a solution of alkylated aglycon **10b** (13.2 mg, 0.021 mmol) in a mixture of CH_2Cl_2 and THF (1 : 1) was added Pd/C (1.1 mg, 5 mol%) under H_2 atmosphere and resulting solution was stirred for 12 h. The resulting suspension solution was filtered through a celite column and then concentrated in vacuo to give a yellow solid, acid **4b** (4 mg, 54%), mp > 200 °C; IR (thin film, cm^{-1}) 3421 – 3157(br), 2953, 2854, 1652, 1609, 1557, 1488, 1419, 1364, 1307, 1256, 1205, 1180, 1090, 1052, 1026, 1011, 837, 822, 807; ^1H NMR (500 MHz, DMSO-d6) δ 12.37 (s, 1H), 8.16 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 6.47 (d, *J* = 1.5 Hz, 1H), 6.21 (d, *J* = 1.6 Hz, 1H), 4.74 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d6) δ 178.1,

170.3, 165.0, 161.6, 156.8, 153.6, 137.7, 136.1, 130.8, 129.0, 112.5, 104.7, 99.3, 94.3, 68.4; HRMS (MALDI-TOF/CCA) calcd. $[C_{17}H_{11}ClO_7+Na]^+$:385.0086, found: 385.0102.

2-((2-(4-fluorophenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl) oxy) acetic acid (4c)

To a solution of alkylated aglycon **10c** (7.4 mg, 0.012 mmol) in a mixture of CH_2Cl_2 and MeOH (1 : 1) was added Pd/C (1.3 mg, 10 mol%) under H_2 atmosphere and resulting solution was stirred for 12 h. The resulting suspension solution was filtered through a celite column and then concentrated in vacuo to give a yellow solid, acid **4c** (2.2 mg, 57%), mp 188 – 190 °C; IR (thin film, cm^{-1}) 3212 – 3084 (br), 2923, 2366, 2342, 1741, 1698, 1653, 1559, 1506, 1473, 1416, 1397, 1364, 1340, 1310, 1238, 1167, 1090, 1073, 1050, 1040, 1024, 843, 776; ^1H NMR (500 MHz, CD_3OD) δ 8.31 – 8.16 (m, 2H), 7.25 (dd, J = 8.4, 8.4 Hz, 2H), 6.41 (s, 1H), 6.20 (s, 1H), 4.62 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d6) δ 178.4, 170.8, 164.9, 163.8 (d, J = 274.8 Hz, 1C), 161.6, 156.8, 153.5, 137.7, 131.7, 131.6, 127.3, 127.3, 115.9 (d, J = 21.6 Hz, 2C), 104.6, 99.3, 94.2, 69.4; HRMS (MALDI-TOF/CCA) calcd. $[C_{17}H_{11}FO_7+Na]^+$: 369.0381, found: 369.0386.

2-((5,7-dihydroxy-4-oxo-2-phenyl-4H-chromen-3-yl) oxy) acetic acid (4d)

To a solution of alkylated aglycon **10d** (16.4 mg, 0.027 mmol) in 0.3 mL mixture of CH_2Cl_2 and THF (1 : 1) added Pd/C (3 mg, 10 mol%) under H_2 atmosphere and resulting solution was stirred for 12 h. Suspension solution was filtered through a celite column and then concentrated in vacuo. The product was crystallized from acetone to give yellow solid, acid **4d** (6 mg, 68%), mp 160 – 162 °C; IR (thin film, cm^{-1}) 3308 – 3099 (br), 1732, 1651, 1606, 1567, 1491, 1447, 1363, 1306, 1256, 1203, 1175, 1092, 1075, 1039, 1000, 961, 881, 774, 690; ^1H NMR (500 MHz, Methanol-d4) δ 8.12 (dd, J = 6.6, 2.8 Hz, 2H), 7.53 (m, 3H), 6.43 (d, J = 1.6 Hz, 1H), 6.22 (d, J = 1.7 Hz, 1H), 4.69 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, Methanol-d4) δ 178.22, 170.99, 164.77, 161.67, 157.13, 155.74, 137.27, 130.77, 130.15, 128.32, 104.56, 98.62, 93.48, 68.11; HRMS (MALDI-TOF/CCA) calcd. $[C_{17}H_{12}O_7+Na]^+$: 351.0475, Found: 351.0452.

2-((5,7-dihydroxy-2-(4-methoxyphenyl)-4-oxo-4H-chromen-3-yl)oxy)acetic acid (4e)

To a solution of alkylated aglycon **10e** (14.2 mg, 0.023 mmol) in 0.3 mL of a mixture of CH_2Cl_2 and THF (1 : 1) was added Pd/C (2.4 mg, 10 mol%) under H_2 atmosphere and resulting solution was stirred for 12 h. The resulting suspension solution was filtered by flashing through celite column and concentrated in vacuo. The product was crystallized from acetone to give a yellow solid, acid **4e** (5.6 mg, 70%), mp 192 – 194 °C; IR (thin film, cm^{-1}) 2357, 2149, 1603, 1541, 1520, 1507, 1435, 1361, 1339, 1303, 1261, 1202, 1179, 1125, 1074, 1026, 996; ^1H NMR (500 MHz, DMSO-d6) δ 8.27 (d, J = 7.4 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 6.43 (s, 1H), 6.16 (s, 1H), 4.35 (s, 2H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d6) δ 178.5, 171.1, 165.3, 161.6, 161.5, 156.7, 154.3, 137.5, 130.8, 123.2, 114.3, 104.3, 99.1, 94.1, 70.9, 55.8; HRMS (MALDI-TOF/CCA) calcd. $[C_{18}H_{14}O_8+Na]^+$: 381.0581, Found: 381.0554.

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Supporting Information

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^1H and ^{13}C NMR spectra (PDF)

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