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Potential therapeutic antioxidants that combine the radical scavenging ability of myricetin and the lipophilic chain of vitamin E to effectively inhibit microsomal lipid peroxidation

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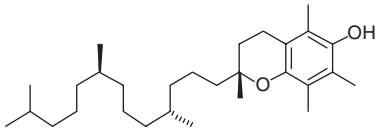
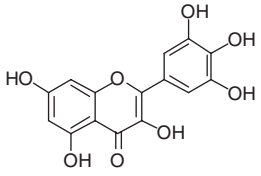
Abstract—The flavonol myricetin, reacts with oxygen-centred galvinoxyl radicals 28 times faster than d-α-tocopherol (vitamin E), the main lipid-soluble antioxidant in biological membranes. Moreover, each myricetin molecule reduces twice as many such radicals as vitamin E. However, myricetin fails to protect vitamin E-deficient microsomes from lipid peroxidation as assessed by the formation of thiobarbituric acid reactive substances (TBARS). Novel and potentially therapeutic antioxidants have been prepared that combine the radical-scavenging ability of a myricetin-like head group with a lipophilic chain similar to that of vitamin E. C_6–C_{12} alkyl chains are attached to the A-ring of either a 3,3′,4′,5′-tetrahydroxyflavone or a 3,2′,4′,5′-tetrahydroxyflavone head group to give lipophilic flavonoids ($C\log P = 4$ to 10) that markedly inhibit iron-ADP catalysed oxidation of microsomal preparations. Orientation of the head group as well as total lipophilicity are important determinants of antioxidant efficacy. MM2 models indicate that our best straight chain 7-alkylflavonoids embed to the same depth in the membrane as vitamin E. The flavonoid head groups are prepared by aldol condensation followed by Algar–Flynn–Oyamada (AFO) oxidation or by Baker–Venkataraman rearrangement. The alkyl tails are introduced by Suzuki or Negishi palladium-catalysed cross-coupling or by cross-metathesis catalysed by first generation Grubbs catalyst, which tolerate phenolic hydroxyl and ketone groups.

1. Introduction

The damage caused by reactive oxygen species (ROS) such as hydroxyl radicals, peroxyl radicals and superoxide radical anions to the lipid components of cell membranes is implicated in the development of many clinical conditions including ischaemia-reperfusion injury, cancers, heart disease, arthritis, neurological disorders and autoimmune diseases.[1] The human body protects itself from excessive lipid peroxidation in part by sequestering the vitamin E homologue, d-α-tocopherol (Fig. 1) from the diet and incorporating it into cell and organelle membranes.[2] Vitamin E **1** has two key structural features: a phenolic component that reacts with ROS, by donating the hydrogen atom from the phenolic hydroxyl to generate a more stable tocopheroxyl radical; and a hydrophobic chain that anchors the molecule to the membrane.[3]



1 d-α-Tocopherol (Vitamin E)



2 Myricetin

Figure 1. Natural antioxidants.

Many flavonoids, plant secondary metabolites ubiquitous in the diet, also possess phenolic structures capable of hydrogen donation to reactive radicals.[4] For example, the flavonol myricetin **2** is a particularly powerful

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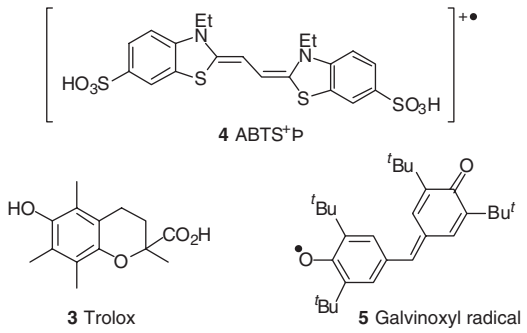


Figure 2. Components of antioxidant assays.

antioxidant in vitro. It is more readily reduced than vitamin E (one-electron reduction potential at pH 7 of 0.36 and 0.48 V, respectively),[5] and is almost fourfold more effective than Trolox **3**, a water soluble vitamin E analogue, in scavenging the radical cation 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{\circ+}$) **4** at physiological pH (Fig. 2).[6] Furthermore, myricetin reacts 28 times as fast as vitamin E with galvinoxyl radicals **5** (second-order rate constants are 14463 ± 1767 and $524 \pm 48\ mol^{-1}\ L\ s^{-1}$, respectively) and has a better reaction stoichiometry reducing four galvinoxyl radicals while vitamin E reduces only two.[7] This reflects the ability of myricetin to be oxidised to two different B-ring orthoquinones and an extended para-quinone.

However, the potent in vitro antioxidant ability of flavonoids such as myricetin is less apparent in vivo due in part to a relatively poor bioavailability[8] and low solubility in cell membranes compared with vitamin E.[9] The hydrophobic chain of vitamin E is vital for its uptake from the gut, systemic transportation and orientation in cell membranes for optimum antioxidant function. Increasing lipophilicity of water soluble antioxidants such as myricetin may therefore have therapeutic potential to treat a range of clinical conditions such as stroke, diabetic complications and neurodegenerative conditions where membrane lipid peroxidation has pathogenetic consequences. In addition such compounds may improve the prevention of rancidity and markedly prolong the shelf life of food products. For example, results from recent studies with lipophilic analogues of gibbilimbols,[10] phaffiaol,[11] chromanols,[12] polyprenylated hydroquinones,[13] dihydrobenzofurans[14] and esters of gallic[15] and ferulic acids[16] emphasise the importance of increased lipophilicity in the prevention of lipid oxidation. As myricetin **2** is a much more powerful antioxidant than all these classes of compounds, we have attempted to generate potent antioxidants **6** capable of inhibiting lipid peroxidation within biological membranes by combining the B and C ring substituents of myricetin **2** with lipophilic chains similar to that of vitamin E **1** (Fig. 3). Compounds **6**–**11** were synthesised to determine the effect of chain length, position and branching, and one variation in the head group on lipid peroxidation in a microsomal system (Fig. 4).

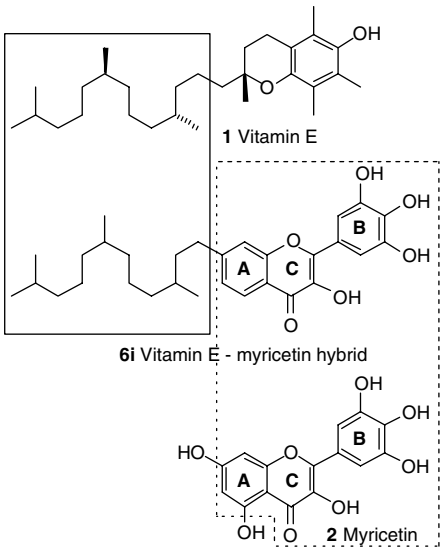


Figure 3. Novel design of therapeutic antioxidant.

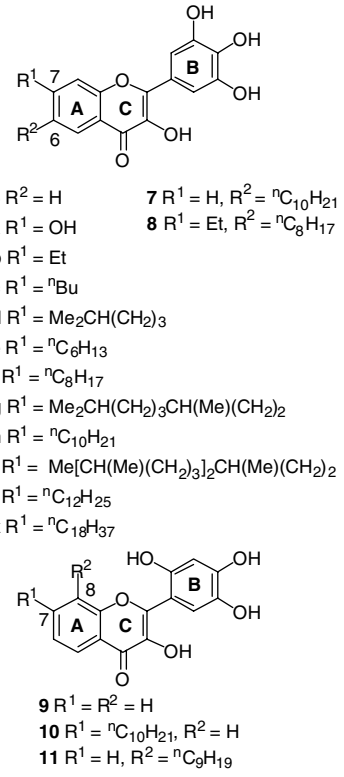
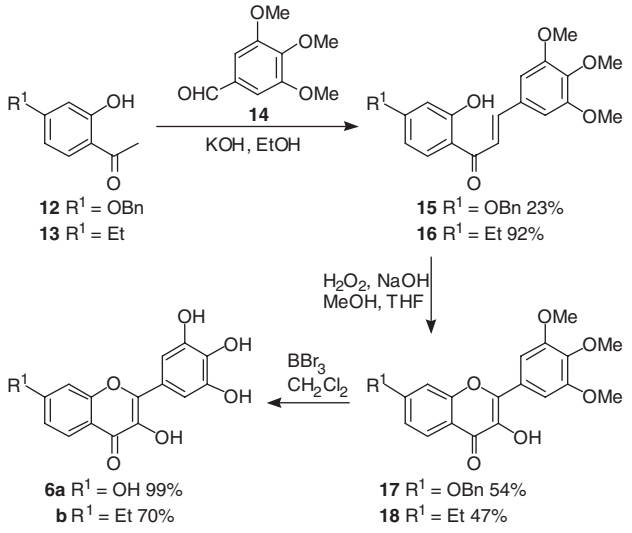


Figure 4.

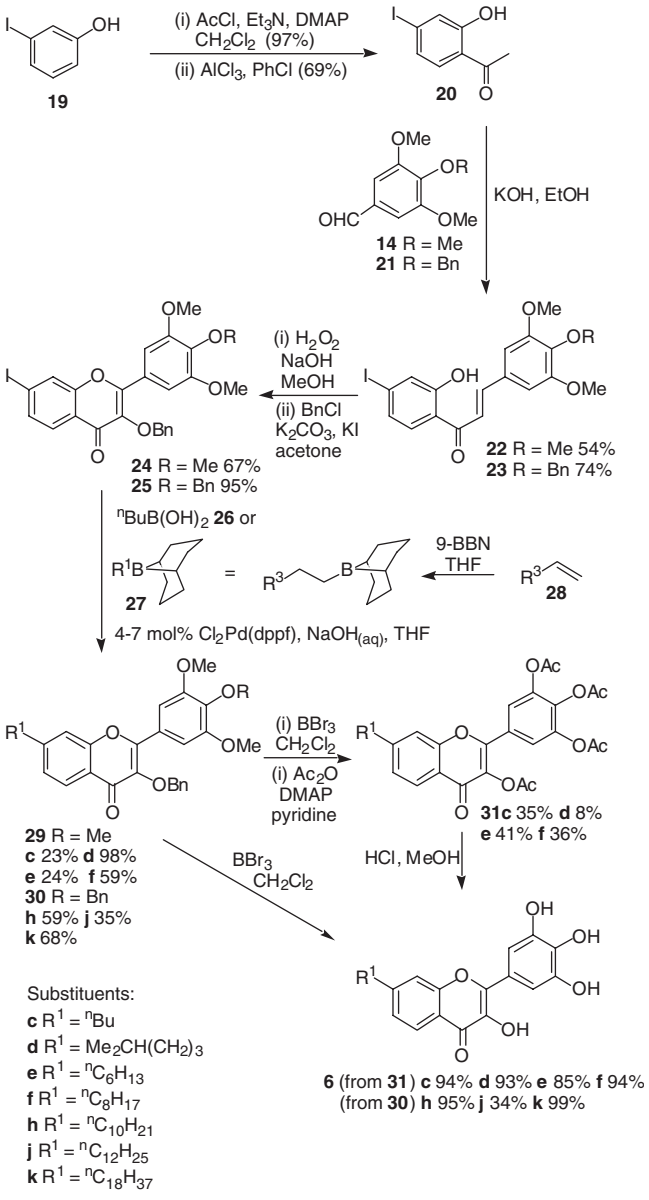
2. Synthetic chemistry

Flavonols **6a** and **6b** were synthesised from the corresponding acetophenones **12** and **13** (Scheme 1). Aldol condensation with trimethoxybenzaldehyde **14** gave chalcones **15** and **16**, then Algar–Flynn–Oyamada (AFO) oxidation[17] gave flavonols **17** and **18** and finally, deprotection gave the desired flavonols **6a** and **6b**. Flavonol **9** was synthesised in much the same way.



Scheme 1. Synthesis of modified flavonoids.

Straight chain 7-alkylflavonols **6c**, **6e**, **6f**, **6h**, **6j** and **6k** and short branched chain 7-alkylflavonol **6d** were synthesised from 3-iodophenol (Scheme 2). Acetophenone **20** was prepared following the literature procedure by acetylation of 3-iodophenol **19** and Fries rearrangement.[18] Aldol condensation with benzaldehydes **14** and **21** gave chalcones **22** and **23**. These underwent Algar–Flynn–Oyamada (AFO) oxidation[17] and benzyl protection to give flavonoids **24** and **25**. Suzuki cross-coupling[19] with alkylboronic acid **26** or alkylboranes **27**, prepared by hydroboration of 1-alkenes **28**,[20] gave 7-alkyl-flavonoids **29** and **30** in modest to excellent yield. The mild conditions required for coupling tolerate the C-ring ketone. Surprisingly, although alkyl–aryl Suzuki couplings can be catalysed by a variety of palladium and nickel complexes,[21–24] they have rarely been employed in target-based synthesis previously.[25–28] Generally, deprotection with boron tribromide proceeded in high yield, but acetylation and recrystallisation of the tetra-acetates **31** followed by deprotection proved to be the best way to purify flavonoids **6c**, **6e** and **6f**.

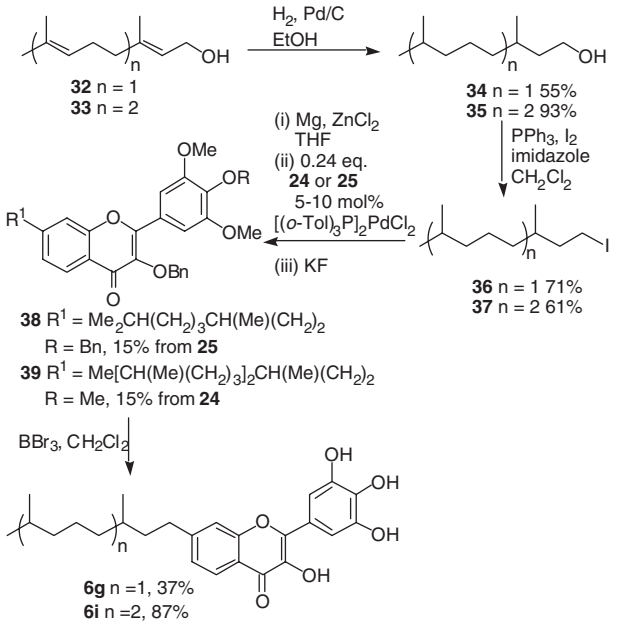


Scheme 2. Synthesis of 7-alkyl myricetin analogues.

In a related approach, the branched tetrahydrogeranyl and hexahydrofarnesyl chains of flavonoids **6g** and **6i** were introduced by Negishi cross-coupling[29] (Scheme 3). Geraniol **32** and farnesol **33** were hydrogenated to give saturated alcohols **34** and **35**, respectively, as 1:1 mixtures of diastereomers. These were converted into iodides **36** and **37**. Iodo-flavonoid **25** reacted with excess organozinc derived from iodide **36** in the presence of a catalyst that is designed to avoid β-elimination during alkyl–aryl couplings,[30] but gave a poor yield of 7-alkyl-flavonoid **38**. 7-Hexahydrofarnesyl-flavonoid **39** was made in similarly poor yield from iodo-flavonoid **24** and an organozinc derived from iodide **37**. Deprotection then gave the desired flavonoids **6g** and **6i**.

6-Alkyl-flavonoid **7** and 6,7-dialkyl flavonoids **8** were prepared by a similar approach (Scheme 4). Friedel–Crafts acylation of acetamide **40**, followed by deprotection, diazotisation and iodination gave aryl iodide **41**. While bromination of acetophenone **13** gave aryl bromide **42**. Aldol condensation with aldehyde **21** and AFO reaction of the resulting chalcones **43** and **44** gave 6-haloflavonols **45** and **46**, respectively. Suzuki cross-coupling proceeded without the need to protect the 3-hydroxyls to give 6-alkyl-flavonoids **47** and **48**. Deprotection and purification via the tetra-acetates **49** and **50** then gave the target flavonoids **7** and **8**.

An alternative approach was employed in the synthesis of 7-alkyl-flavonol **10**, which has a head group with a different hydroxy substitution pattern from myricetin (Scheme 5). Here the alkyl chain was introduced by Suzuki cross-coupling prior to construction of the flavonol by Baker–Venkataraman rearrangement.[17] Thus, resorcinol **51** was converted into acetophenone **52** by the Houben–Hoesch reaction and selective trifluoromethanesulfonation of the unchelated hydroxyl. Suzuki



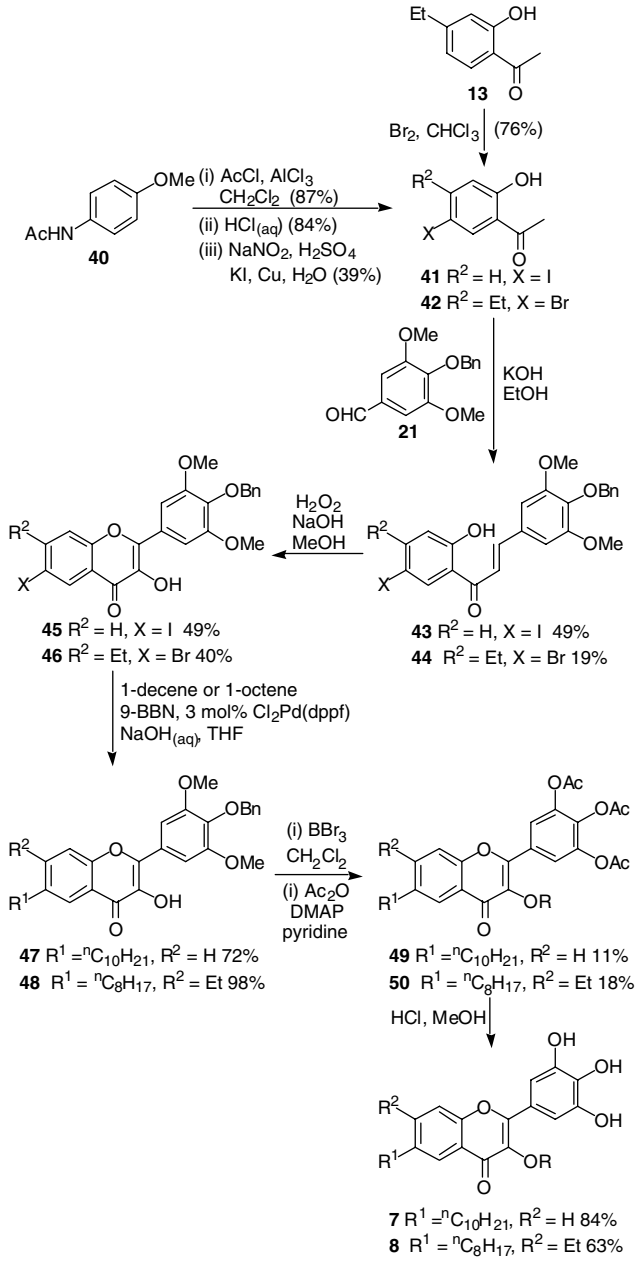
Scheme 3. Route to branched-chain compounds.

cross-coupling proceeded without the need to protect the free phenolic hydroxyl to give phenol **53**. Esterification with 2,4,5-trimethoxybenzoic acid gave ester **54**, which underwent base-induced Baker–Venkataraman rearrangement to give diketone **55**. Cyclisation[31] gave the flavone **56**, which was then deprotected to give the 7-alkylflavonol **10** in good yield.

Finally, the side chain of 8-nonyl-flavonoid **11** was introduced by C-allylation using microwave-assisted[32] Claisen rearrangement followed by chain extension using alkene metathesis (Scheme 6).[33] O-allylation of acetophenone **57** followed by Claisen rearrangement gave C-allylated acetophenone **58** with complete regiocontrol.[34] Aldol condensation with aldehyde **59** and AFO oxidation of the resulting chalcone **60** produced flavonol **61** in good yield. Chain extension by cross-metathesis[35] using first generation Grubbs catalyst[36] yielded non-2-enyl derivative **62**. Until recently, cross-metathesis of alkenes had rarely been applied to target-based synthesis because of the problem of homo-coupling.[37] However, it is becoming increasingly popular since it tolerates a wide range of polar functionality, in this case both a ketone and a phenolic hydroxyl group are unaffected. Hydrogenation of alkene **62** gave 8-nonyl-flavonoid **63** and deprotection gave the desired flavonol, following purification by recrystallisation of the tetra-acetate derivative **64**.

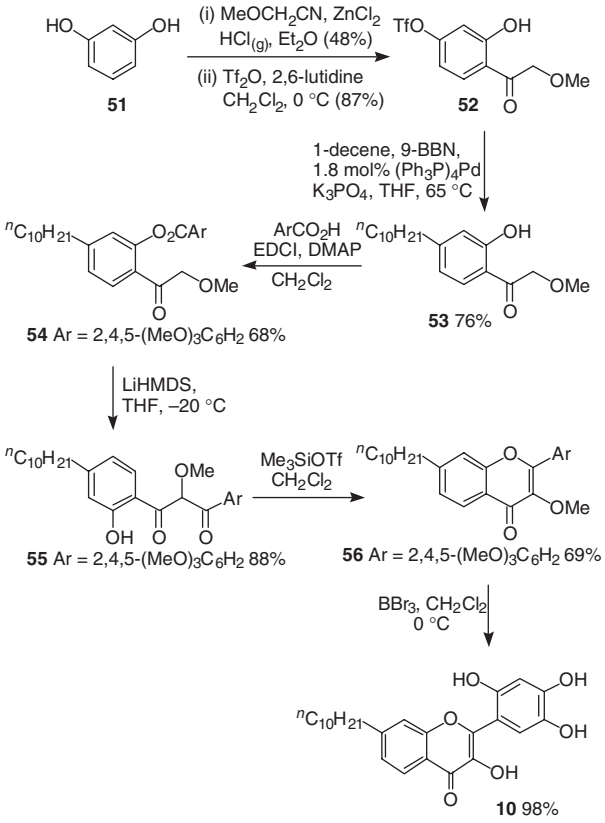
3. Inhibition of microsomal peroxidation

Free radical-mediated peroxidation of the polyunsaturated fatty acids within the membrane lipid bilayer can be initiated by addition of Fe(II)-ADP chelate and ascorbate. The extent of peroxidation after a given period of time can be measured by adding thiobarbituric

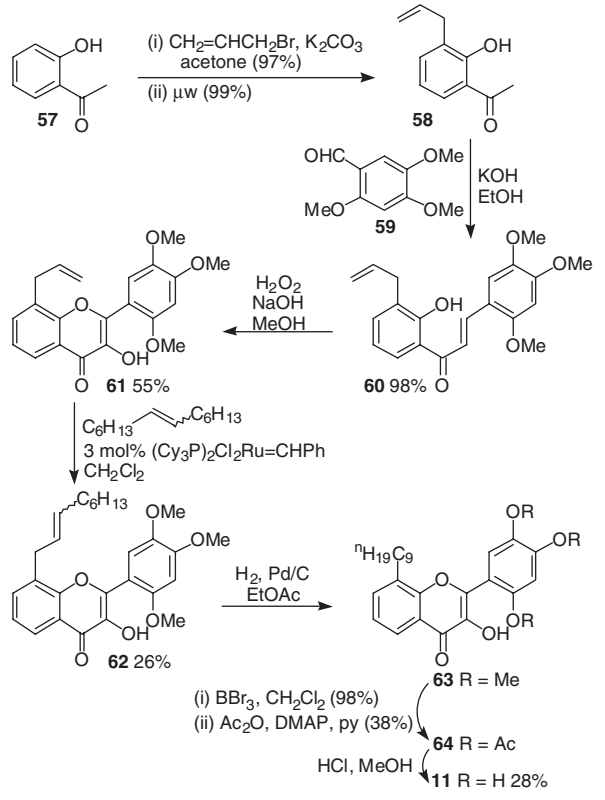


Scheme 4. Route to 6-alkyl myricetin analogues.

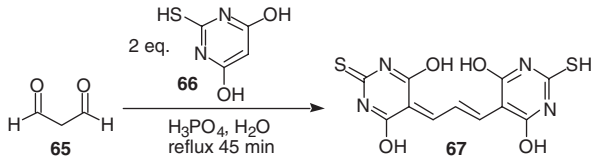
acid **66** and quantifying the thiobarbituric acid reactive substances (TBARS e.g., **67**) formed from oxidative-degradation products such as malondialdehyde **65** (Scheme 7).[1] Therefore, following the protocol of Mitchell et al.[9] (see experimental for details), each candidate compound **6**–**11** was incubated with hepatic microsomes[38] (membrane-bound vesicles that result from the fragmentation of the endoplasmic reticulum of liver cells) prior to 20 min of oxidative stress induced by Fe(II)-ADP chelate and ascorbate. The oxidative damage was then measured by TBARS formation: the less TBARS formed, the better the membrane protectant. Microsomes derived from vitamin E deficient rats were employed as this increases discrimination of protective effects and allows the ability of the candidate compounds to suppress peroxidation to be compared to that



Scheme 5. Synthesis of analogues with different head groups.



Scheme 6. Synthesis of 8-alkyl flavonoid **11**.



Scheme 7.

of vitamin E **1** (d-α-tocopherol), which is the major lipid soluble antioxidant in biological membranes.[39]

First, we investigated the effect of varying chain length and chain methylation, while maintaining the same head group and chain attachment site. The resulting TBARS data from compounds **6** with vitamin E **1** and myricetin **2** as controls is presented in Figure 5. In the absence of vitamin E and with no added candidate compound (-E), lipid-peroxidation was greatest. Confirming previous studies,[9] increased peroxidation of microsomes from vitamin E-deficient rats (-E) was strongly suppressed by preincubation with d-α-tocopherol **1** but not with myricetin **2**. Compound **6a** that lacks a 5-OH showed similarly poor protection. However, when the 7-OH is replaced by an alkyl chain, significant suppression of lipid peroxidation is observed and this is strongly dependent on chain-length. Compounds **6e**–**j** with chain lengths in the range C6–C12 protect the membrane well. Indeed, 7-(3,7-dimethyloctyl)flavonoid **6g** and 7-decylflavonoid **6h** are almost as effective as vitamin E **1** itself. Methylation appears to improve membrane protection at both ends of the range: thus, 7-(3,7-dimethyloctyl)flavonoid **6g** is a better protectant than 7-octylflavonoid **6f**, while 7-(3,7,11-trimethyldodecyl)flavonoid **6i** is better than 7-dodecylflavonoid **6j**. This argues against a simple correlation of activity with lipophilicity, although it is clear from Figure 6 that a $C\log P$ in the range 4–10 is good for 7-alkylflavonoids **6** (note that vitamin E **1** has a $C\log P$ of 12). Although slightly less effective, straight-chain flavonoid **6h** is a better drug candidate than **6g** as it is achiral.

Next we briefly investigated the effect of changing the position of the alkyl chain and of changing the head group (Figs. 7 and 8). 7-Decylflavonoid **6h**, 6-decylflavonoid **7** and 6-ethyl-7-octylflavonoid **8** have the same head group and almost identical lipophilicities ($C\log P$ values) but suppress lipid peroxidation to different degrees. Thus, there appears to be an orientation effect that means that there is an optimum chain length for a particular site of attachment of the chain to a particular head group. Compounds **9**–**11** have the 3,2′,4′,5′-tetrahydroxy-flavone head group, which should act as a good scavenger of ROS as it can form an orthoquinone, a paraquinone, an extended orthoquinone and an extended paraquinone when it donates two phenolic hydrogen atoms. As expected flavonoid **9** is a poor membrane protectant, but 7-decylflavonoid **10** is similar to vitamin E in its potency. Again 8-alkylflavonoid **11** that has a similar lipophilicity to 7-alkylflavonoid **10** is less effective at suppressing lipid peroxidation indicating that orientation in the membrane is important.

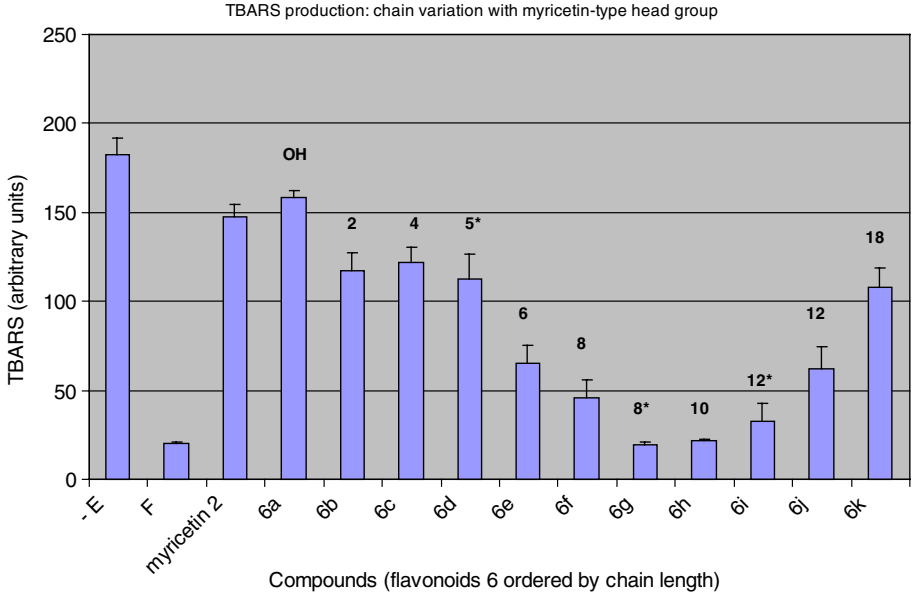


Figure 5. Note: The number above each bar indicates the chain length of the 7-alkyl chain (an asterisk implies that there are methyl groups attached to the chain).

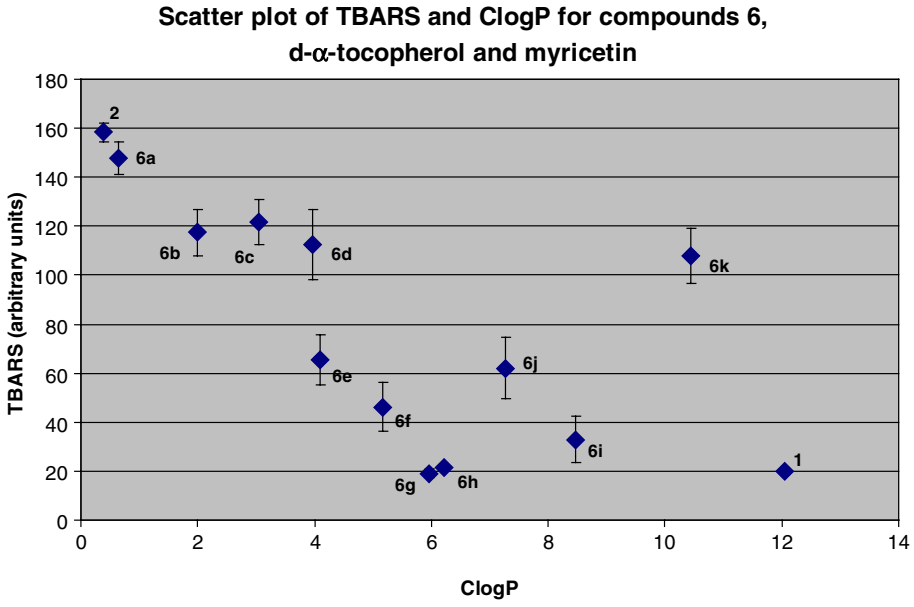


Figure 6.

4. Conclusions

We have prepared novel flavonoids that combine the radical-scavenging ability of myricetin with vitamin E's ability to embed itself in membranes. Unlike myricetin, these potential therapeutic antioxidants effectively protect vitamin E-deficient microsomes from lipid peroxidation. Membrane protection depends not only on lipophilicity but also on orientation determined by chain position and length. When we set out on this work, we believed that an alkyl chain of similar length to that of α-d-tocopherol would be required (Fig. 3). However, our best straight chain flavonols **6h** and **10** have a shorter chain length. Interestingly, aligning the 4′-OH (which is believed to be the best hydrogen atom donor) of flavonoids **6h** and **10** with the OH of vitamin E gives an excellent molecular match (Fig. 9). These are both 7-alkylflavonols and putting the chain at any other position does not allow such a straight forward match. We believe that this is clear evidence for the importance of orientation within the membrane, both for our compounds and vitamin E itself.

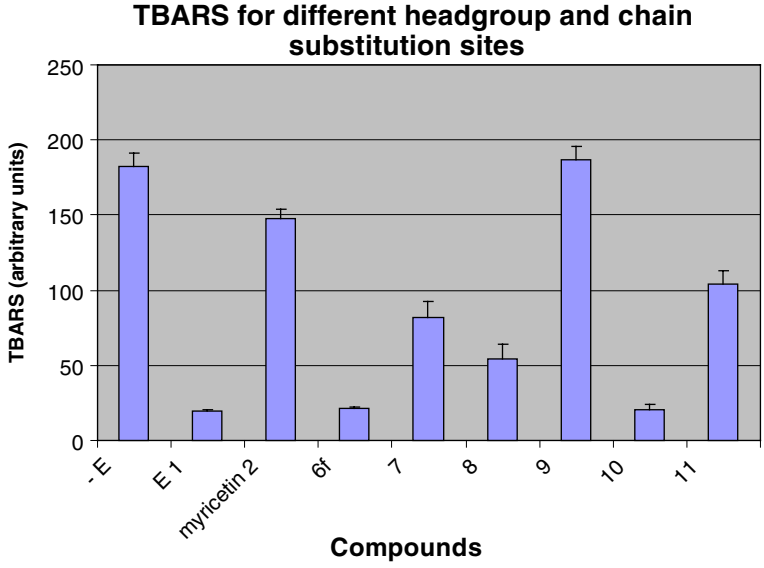


Figure 7.

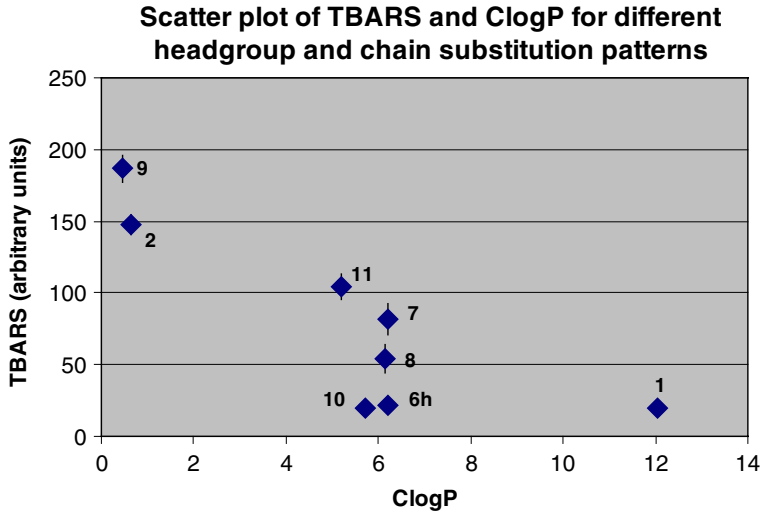


Figure 8.

5. Experimental

5.1. Microsomal peroxidation and TBARS

Microsomes were prepared[38] from the perfused livers of male rats of the Rowett Hooded Lister strain maintained on a vitamin E-deficient semi-synthetic diet for 12 weeks by which time vitamin E concentrations were below the limits of detection by HPLC. Incubations were carried out as described in Mitchell et al.[9] In brief, protein concentration of the microsomal suspension was adjusted to 10 mg/mL with 0.05 M potassium phosphate buffer (pH 7.4) prior to incubation at 25 °C for 30 min with constant gentle mixing with ethanolic solutions of the compounds to give a final concentration of 0.05 mM. Peroxidation was then initiated by addition of Fe-ADP/ascorbate (final concentrations: Ascorbate, 0.5 mM; Fe(II), 0.006 mM; ADP, 2 mM) and after 20 min, the reaction was stopped by addition of TCA (20%). Following addition of thiobarbituric acid (0.67%), samples were boiled for 30 min and TBARS measured by HPLC.

5.2. Synthetic chemistry

All reactions were carried out under an inert atmosphere unless otherwise stated, using oven-dried or flame-dried glassware. Solutions were added via syringe unless otherwise stated. Reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Where dry solvents were used: THF, was freshly distilled from sodium–benzophenone; dichloromethane, toluene and pyridine were distilled from CaH_2 prior to use. Purification by column chromatography was carried out using Fisher

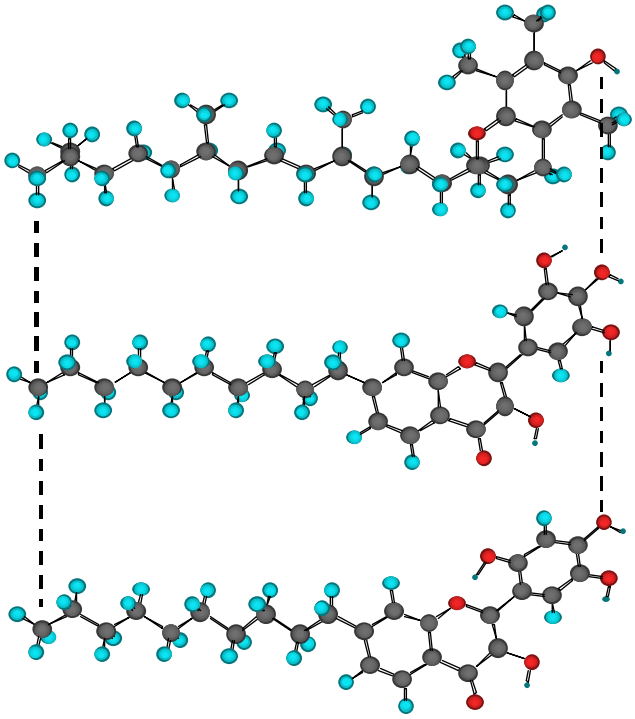


Figure 9. Chem3D molecular mechanics (MM2) force field model of d-α-tocopherol (top) and flavonoids **6h** (middle) and **10** (bottom). The model suggests that if the terminal carbon atoms of the alkyl chains embed at the same depth in a membrane, then the dominant hydrogen atom donor group of the flavonoids (4′-OH) will occupy a similar spatial distribution at the membrane surface as the tocopherol counterpart.

Matrex TM silica gel, mesh size 35–70 μm, as the stationary phase. Melting points are uncorrected. IR spectra were recorded using a Nicolet Impact 410 FTIR or JASCO FT/IR spectrometer. NMR spectra were recorded using a Bruker DPX-400. All NMR *J* values are given in Hz. Mass spectra were recorded on a JEOL JMS700 spectrometer.

5.3. 3,7-Dihydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 6a

To a stirring solution of **17** (79 mg, 0.2 mmol) in dichloromethane (10 mL) under Ar at 0 °C was added boron tribromide in dichloromethane (1.0 M, 2 mL, 2 mmol). The mixture was warmed to room temperature and then stirred for 22 h. The reaction mixture was then cooled to 0 °C and methanol (10 mL) added. The reaction mixture was heated to reflux for 2 h, then concentrated in vacuo to give a yellow solid. Water (10 mL) was added and sonicated then left to stand overnight then **6a** (55 mg, 99%) was collected as a yellow solid.[40] δ_H (400 MHz, d-6 pyridine) 6.82–6.87 (m, 2H) 7.96 (s, 2H) 8.07 (d, 1H, 10 Hz) δ_C (100 MHz, D5 pyridine) 97.18, 102.95, 109.65, 109.84, 121.59, 132.12, 133.67, 140.75, 142.27, 151.89, 158.06, 167.79. LRMS (FAB): 303 ($M^{+\cdot}$, 40%), 86 (100). HRMS: calcd for $C_{15}H_{11}O_7$ 303.0505 found, 303.0505.

5.4. 7-Ethyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 6b

In the same way, **18** (0.504 g, 1.4 mmol) added boron tribromide (10 mmol) in dichloromethane (60 mL) gave flavonol **6b** (0.313 g, 70%) as a black solid. δ_H (400 MHz, acetone-d_6) 1.32 (t, 3H, 7.5 Hz), 2.81–2.89 (m, 2H), 7.33 (d, 1H, 8.0 Hz), 7.48 (s, 2H), 7.53 (s, 1H), 8.04 (d, 1H, 8.0 Hz). δ_C (100 MHz, DMSO-d_6) 15.23, 28.53, 107.56, 116.64, 119.58, 121.58, 124.97, 125.15, 135.99, 138.19, 146.07, 146.13, 150.59, 154.89, 172.61. LRMS (FAB): 315 ($[M+H]^+$, 100%), 314 (M^+, 73%). HRMS: calcd for $C_{17}H_{15}O_6$ 315.0869 found, 315.0869.

5.5. 7-Butyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 6c

To a stirring suspension of **31c** (19 mg, 0.04 mmol) in methanol (1 mL) was added concentrated hydrochloric acid (1 drop). The mixture was heated to reflux for 1 h then cooled and water (10 mL) added. The precipitated solid was collected, washed with water and dried under vacuum to give **6c** (12 mg, 94%) as a yellow powder. δ_H (400 MHz, DMSO-d_6) 0.92 (t, 3H, 7.3 Hz) 1.34 (m, 2H) 1.65 (m, 2H) 2.76 (t, 2H, 7.3 Hz) 7.29–7.31 (m, 3H) 7.48 (s, 1H) 8.00 (d, 1H, 8.1 Hz). LRMS (FAB): 343 ($[M+H]^+$, 10%), 86 (100). HRMS: calcd for $C_{19}H_{19}O_6$ 343.1182 found, 343.1184.

5.6. 7-(4-Methyl-pentyl)-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 6d

In the same way, **31d** (11 mg, 0.02 mmol) and concentrated hydrochloric acid (1 drop) in methanol (0.75 mL) gave **6d** (7 mg, 93%) as a yellow powder. δ_H (400 MHz, DMSO-d_6) 0.86 (d, 6H, 6.6 Hz) 1.18–1.24 (m, 2H) 1.51–1.67 (m, 3H) 2.74 (t, 2H, 7.5 Hz) 7.30–7.33 (m, 3H) 7.48 (s, 1H) 7.99 (d, 1H, 8.0 Hz) 8.80 (s, 1H) 9.22 (s, 3H). δ_C (100 MHz, DMSO-d_6) 22.82, 27.64, 28.26, 35.66, 38.29, 107.56, 117.24, 119.59, 121.56, 124.92, 125.54, 135.98, 138.20, 146.07, 146.07, 149.29, 154.81, 172.61. LRMS (EI): 370 ($M^{+\cdot}$, 100%). HRMS: calcd for $C_{21}H_{22}O_6$ 370.1416 found, 370.1411.

5.7. 7-Hexyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 6e

In the same way, **31e** (24 mg, 0.04 mmol) and concentrated hydrochloric acid (1 drop) in methanol (1 mL) gave **6e** (14 mg, 85%) as a yellow powder. δ_H (400 MHz, DMSO-d_6) 0.86 (t, 3H, 6.0 Hz) 1.27–1.33 (m, 6H) 1.61–1.68 (m, 2H) 2.75 (t, 2H, 7.5 Hz) 7.28–7.33 (m, 3H) 7.48 (s, 1H) 7.99 (d, 1H, 8.1 Hz) 8.79 (s, 1H) 9.21 (m, 3H). δ_C (100 MHz, DMSO-d_6) 14.29, 22.35, 28.60, 30.64, 31.39, 35.42, 107.56, 117.24, 119.57, 121.56, 124.91, 125.56, 135.98, 138.18, 146.06, 146.06, 149.298, 154.81, 172.62. LRMS (EI): 370 ($M^{+\cdot}$, 100%). HRMS: calcd for $C_{21}H_{22}O_6$ 370.1416 found, 370.1414.

5.8. 7-Octyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 6f

In the same way, **31f** (92 mg, 0.2 mmol) and concentrated hydrochloric acid (2 drops) in methanol (8 mL) gave **6f** (61 mg, 94%) as a yellow powder. δ_H (400 MHz, DMSO-d_6) 0.85 (t, 3H, 6.5 Hz) 1.24–1.30 (m, 10H) 1.63–1.87 (m, 2H) 2.75 (t, 2H, 7.6 Hz) 7.28–7.34 (m, 3H) 7.48 (s, 1H) 7.99 (d, 1H, 8.2 Hz) 8.79 (s, 1H) 9.20 (s, 3H). δ_C (100 MHz, DMSO-d_6) 14.29, 22.41, 28.95, 29.13, 29.13, 30.66, 31.60, 35.42, 107.56, 117.24, 119.58, 121.57, 124.91, 125.53, 135.98, 138.19, 146.06, 146.06, 149.27, 154.80, 172.61. LRMS (EI): 398 ($M^{+\cdot}$, 7%) 134 (100). HRMS: calcd for $C_{23}H_{26}O_6$ 398.1729 found, 398.1733.

5.9. 7-(3,7-Dimethyl-octyl)-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 6g

In the same way as for flavonol **6a**, a solution of **38** (28 mg, 0.05 mmol) and boron tribromide (0.7 mmol) in dichloromethane (1.7 mL) gave **6g** (8 mg, 37%) as a yellow solid following chromatography (silica gel, dichloromethane–methanol, 19:1). δ_H (400 MHz, acetone-d_6) 0.73 (d, 6.6 Hz, 6H) 0.86 (d, 7.6 Hz, 3H) 1.00–1.11 (m, 4H) 1.15–1.30 (m, 4H) 1.36–1.47 (m, 2H) 2.61–2.82 (m, 2H) 7.19 (dd, 1H, 1.1 and 7.0 Hz) 7.35 (s, 2H) 7.39 (s, 1H) 7.90 (d, 1H, 8.0 Hz). δ_C (100 MHz, acetone-d_6) 20.26, 23.28, 23.36, 25.78, 29.03, 33.58, 34.54, 38.17, 39.52, 40.40, 108.63, 118.41, 120.19, 123.60, 125.98, 126.55, 136.38, 138.99, 146.13, 146.66, 151.20, 156.60, 173.66. LRMS (EI): 426 ($M^{+\cdot}$, 100%). HRMS: calcd for $C_{25}H_{30}O_6$ 426.2042 found, 426.2043.

5.10. 7-Decyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 6h

In the same way as for flavonol **6a**, a solution of **30h** (0.335 g, 0.5 mmol) and boron tribromide (5 mmol) in dichloromethane (30 mL) gave **6h** (0.213 g, 95%) as a yellow solid. δ_H (400 MHz, acetone-d_6) 0.88 (m, 3H) 1.26–1.47 (m, 14H) 1.75 (m, 2H) 2.78 (m, 2H) 7.34 (d, 1H, 8.0 Hz) 7.49 (s, 2H) 7.54 (s, 1H) 7.87 (br s, 1H) 7.93 (br s, 1H) 8.05 (d, 1H, 8.0 Hz) 8.19 (s, 2H). δ_C (100 MHz, DMSO-d_6) 14.28, 22.43, 28.90, 29.02, 29.14, 29.28, 29.30, 30.64, 31.62, 35.42, 107.56, 117.23, 119.59, 121.58, 124.90, 125.52, 135.98, 138.20, 146.06, 146.11, 149.25, 154.81, 172.60. LRMS (FAB): 427 ($[M+H]^+$, 100%). HRMS: calcd for $C_{25}H_{31}O_6$ 427.2121 found, 427.2122.

5.11. 3-Hydroxy-2-(3,4,5-trihydroxy-phenyl)-7-(3,7,11-trimethyl-dodecyl)-chromen-4-one 6i

In the same way as for flavonol **6a**, a solution of **39** (48 mg, 0.08 mmol) and boron tribromide (2.5 mmol) in dichloromethane (5 mL) gave **6i** (33 mg, 87%) as a waxy solid following chromatography (silica gel, chloroform–methanol, 9:1). δ_H (400 MHz, acetone-d_6) 0.67–1.61 (m, 29H), 2.52–2.75 (m, 2H), 6.91–6.98 (m, 1H), 7.18 (d, 8.1 Hz, 1H), 7.35–7.38 (m, 2H), 7.91 (d, 1H, 8.2 Hz). δ_C (100 MHz, acetone-d_6) 14.94, 20.29, 20.36, 23.33, 23.41, 25.43, 25.89, 29.05, 29.73, 29.92, 30.12, 30.31, 30.50, 30.69, 30.89, 31.06, 33.56, 33.86, 34.58, 38.40, 38.45, 38.47, 40.47, 60.98, 108.74, 118.40, 120.13, 123.54, 126.02, 126.64, 128.93, 129.47, 146.67, 151.26, 156.58, 172.04. LRMS (EI): 496 ($M^{+\cdot}$, 100%). HRMS: calcd for $C_{30}H_{40}O_6$ 496.2825, obs. 496.2823.

5.12. 3-Hydroxy-2-(3,4,5-trihydroxy-phenyl)-7-dodecyl-chromen-4-one 6j

In the same way as for flavonol **6a**, a solution of **30j** (58 mg, 0.09 mmol) and boron tribromide (2.25 mmol) in dichloromethane (4.75 mL) gave **6j** as a waxy solid (30 mg, 69%) following chromatography (silica gel, dichloromethane–methanol, 9:1). δ_H (400 MHz, DMSO-d_6) 0.84 (t, 3H, 6.4 Hz) 1.18–1.34 (m, 18H) 1.62–1.71 (m, 2H) 2.75 (t, 2H, 7.4 Hz) 7.27–7.30 (m, 3H) 7.47 (s, 1H) 7.99 (d, 1H, 8.1 Hz). δ_C (100 MHz, DMSO-d_6) 14.28, 22.42, 28.87, 29.02, 29.11, 29.24, 29.33, 30.63, 31.61, 35.41, 107.56, 117.24, 119.58, 121.57, 124.90, 125.53, 135.99, 138.20, 146.06, 149.27, 154.81, 172.62. LRMS (EI): 454 ($M^{+\cdot}$, 28%), 44 (100). HRMS: calcd for $C_{27}H_{34}O_6$ 454.2355 found, 454.2353. LRMS (FAB): 455 ($[M+H]^+$, 55%), 56 (100). HRMS: calcd for $C_{27}H_{35}O_6$ 455.2434 found, 455.2438.

5.13. 3-Hydroxy-7-octadecyl-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 6k

In the same way as for flavonol **6a**, a solution of **30k** (0.455 g, 0.6 mmol) and boron tribromide (6 mmol) in dichloromethane (31 mL) gave **6k** (0.325 g, 99%) as a yellow solid. δ_H (400 MHz, DMSO-d_6) 0.84 (t, 3H, 6.2 Hz) 1.18–1.33 (m, 30H) 1.62–1.70 (m, 2H) 2.73 (d, 2H, 6.9 Hz) 7.23–7.30 (m, 3H) 7.46 (s, 1H) 7.99 (d, 1H, 8.1 Hz) 9.18 (s, 3H). δ_C (100 MHz, DMSO-d_6) 14.28, 22.43, 28.92, 29.04, 29.14, 29.26, 29.33, 30.67, 31.63, 35.43, 107.56, 117.22, 119.59, 121.58, 124.90, 125.48, 135.97, 138.20, 146.06, 146.10, 149.22, 154.81, 172.59. LRMS (FAB): 539 ($[M+H]^+$, 100%). HRMS: calcd for $C_{33}H_{47}O_6$ 539.3373 found, 539.3367.

5.14. 6-Decyl-3-hydroxy-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 7

In the same way as for **31d**, a solution of **47** (0.369 g, 0.7 mmol) and boron tribromide (3.4 mmol) in dichloromethane (23.4 mL) gave **7** (0.318 g) as a brown oil. A solution of crude of **7** (0.318 g, 0.7 mmol), *N*,*N*-dimethyl-4-aminopyridine (4 mg) and acetic anhydride (0.42 mL, 4 mmol) in pyridine (3.6 mL) was then stirred for 3 h to give **49** (58 mg, 13%) as a grey solid after recrystallisation in methanol. In the same way as for **6c**, a solution of acetate **49** (58 mg, 0.1 mmol) and concentrated hydrochloric acid (5 drops) in methanol (5 mL) gave **7** (35 mg, 84%) as a yellow solid. δ_H (400 MHz, DMSO-d_6) 1.25 (t, 3H, 6.4 Hz) 1.62–1.72 (m, 14H) 1.99–2.04 (m, 2H) 3.13 (t, 2H, 7.5 Hz) 7.72 (s, 2H) 7.98–8.04 (m, 2H) 8.28 (s, 1H) 9.21 (s, 1H) 9.61 (s, 3H). δ_C

(100 MHz, DMSO-d_6) 14.28 (CH_3) 22.43 (CH_2) 28.86 (CH_2) 29.01 (CH_2) 29.15 (CH_2) 29.15 (CH_2) 29.30 (CH_2) 31.20 (CH_2) 31.62 (CH_2) 34.75 (CH_2) 107.59 (CH) 118.27 (CH) 121.31 (C) 121.54 (C) 123.50 (CH) 134.30 (CH) 136.04 (C) 138.30 (C) 138.97 (C) 146.06 (C) 146.34 (C) 153.14 (C) 172.69 (C). LRMS (FAB) 427 ($[M+H]^+$, 100%). HRMS: calcd for $C_{25}H_{31}O_6$ 427.2122 found, 427.2123.

5.15. 7-Ethyl-3-hydroxy-6-octyl-2-(3,4,5-trihydroxy-phenyl)-chromen-4-one 8

In the same way as for flavonol **6c**, **50** (11 mg, 0.02 mmol) and concentrated hydrochloric acid (1 drop) in methanol (0.5 mL) gave **8** (5 mg, 63%) as a yellow powder. δ_H (400 MHz, DMSO-d_6) 0.91 (m, 3H) 1.29–1.40 (m, 13H) 1.61–1.65 (m, 2H) 2.75–2.88 (m, 4H) 7.35 (s, 2H) 7.49 (s, 1H) 7.86 (s, 1H) 8.81 (s, 1H) 9.16–9.30 (m, 3H). δ_C (100 MHz, DMSO-d_6) 14.30, 14.70, 22.43, 25.33, 29.00, 29.18, 29.34, 30.71, 31.62, 31.69, 108.53, 116.80, 119.40, 121.66, 123.96, 135.91, 137.42, 138.14, 146.06, 146.06, 148.83, 153.38, 172.52. LRMS (FAB): 427 ($[M+H]^+$, 100%). HRMS: calcd for $C_{25}H_{31}O_6$ 427.2121 found, 427.2125.

5.16. 7-Decyl-3,2′,4′,5′-tetrahydroxy-flavone 10

In the same way as for flavonol **6a**, a solution of flavone **56** (392 mg, 0.81 mmol) and boron tribromide (4.06 mmol) in dry dichloromethane (7 mL) gave flavonol **10** as a red/brown amorphous solid (338 mg, 98%). mp decomp >90 °C. δ_H (400 MHz: DMSO-d_6): 0.84 (3H, t, J 6.7 Hz, CH_2CH_3), 1.22–1.28 (14H, m, $7\times CH_2$), 1.60–1.64 (2H, m, $ArCH_2CH_2$), 2.72 (2H, t, J 7.5 Hz, $ArCH_2CH_2$), 6.43 (1H, s, H-3′), 6.87 (1H, s, H-6′), 7.28 (1H, d, J 8.2 Hz, H-6), 7.39 (1H, s, H-8), 8.00 (1H, d, J 8.2 Hz, H-5). δ_C (100 MHz: DMSOd_6): 14.28 (CH_3), 22.42 (CH_2), 28.91 (CH_2), 29.01 (CH_2), 29.13 (CH_2), 29.30 (CH_2), 29.31 (CH_2), 30.70 (CH_2), 31.62 (CH_2), 35.37 (CH_2), 104.55 (CH), 108.65 (C), 116.77 (CH), 117.45 (CH), 120.26 (C), 124.94 (CH), 125.38 (CH), 138.07 (C), 138.28 (C), 148.14 (C), 148.90 (C), 149.05 (C), 149.10 (C), 155.43 (C), 172.59 (C). m/z (FAB): 427.4 [$(M+H)^+$, 100%]. Found: 427.2120 $C_{25}H_{31}O_6$ requires [$(M+H)^+$] 427.2121. υ_{max} (golden gate)/cm^{-1}: 3226 (OH), 2919 (CH_2), 1558 (C=O).

5.17. 8-Nonyl-3-hydroxy-2-(2,4,5-trihydroxy-phenyl)-chromen-4-one 11

In the same way as for flavonol **6c**, **64** (96 mg, 0.17 mmol) and concentrated hydrochloric acid (3 drops) in methanol (5 mL) gave **11** (19 mg, 28%) as a yellow powder following crystallisation in chloroform. δ_H (400 MHz, DMSO-d_6) 0.83 (t, 3H, 6.7 Hz) 1.17–1.29 (m, 12H) 1.61–1.65 (m, 2H) 2.84 (t, 2H, 7.4 Hz) 7.01 (s, 1H) 7.37 (t, 1H, 1.6 Hz) 7.60 (d, 1H, 7.1 Hz) 7.96 (dd, 1H, 1.4 and 8.0 Hz) 9.45 (s, 1H) 9.65 (s, 1H). δ_C (100 MHz, DMSO-d_6) 14.31, 22.42, 28.94, 28.98, 29.02, 29.07, 29.26, 29.43, 31.61, 101.53, 109.72, 114.69, 122.27, 122.78, 124.31, 132.25, 133.39, 138.01, 138.79, 146.10, 146.88, 153.54, 173.09. LRMS (FAB): 413 ($[M+H]^+$, 1%), 86 (100%).

5.18. 4′-Benzyloxy-2′-hydroxy-acetophenone 12

To a stirring suspension of 2′,4′-dihydroxy-acetophenone (10.02 g, 66 mmol) and potassium carbonate (9.93 g, 72 mmol) in acetone (250 mL) was added benzyl bromide (7.9 mL, 66 mmol). The reaction was heated to reflux for 18 h and then filtered and concentrated in vacuo to give a pink solid. This was recrystallised from ethanol to give **12** (27 g, 87%) as a pink solid.[41] δ_H (400 MHz, $CDCl_3$) 2.55 (s, 3H) 5.09 (s, 2H) 6.49–6.53 (m, 2H) 7.31–7.43 (m, 5H) 7.63 (dd, 1H, 2 and 8 Hz) 12.72 (s, 1H). δ_C (100 MHz, $CDCl_3$) 26.62, 70.61, 102.27, 108.53, 114.49, 127.92, 128.71, 129.10, 132.73, 136.27, 165.58, 202.98. LRMS (EI): 242 ($M^{+\cdot}$, 73%) 91 (Bn^+, 100). HRMS: calcd for $C_{15}H_{14}O_3$ 242.0943 found, 242.0943.

5.19. 4′-Ethyl-2′-hydroxy-acetophenone 13

To a stirring solution of 3-ethyl-phenol (9.95 g, 81 mmol) and triethylamine (14 mL, 100 mmol) in dichloromethane (100 mL) under nitrogen at 0 °C was added acetyl chloride (7 mL, 98 mmol) dropwise. The reaction was allowed to stir at room temperature for 3 h and then washed with saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo to give 3-ethyl-phenyl acetate (13.3 g, 97%) as a pale yellow solid.[42] δ_H (400 MHz, $CDCl_3$) 1.21 (t, 3H, 7.6 Hz) 2.28 (s, 3H) 2.65 (q, 2H, 7.6 Hz) 6.88–6.92 (m, 2H) 7.06 (d, 1H, 7 Hz) 7.25–7.30 (m, 1H). δ_C (100 MHz, $CDCl_3$) 15.64, 21.58, 29.01, 119.04, 121.31, 125.84, 129.60, 146.35, 151.09, 170.06. To aluminium chloride (23 g, 172 mmol) was added 3-ethyl-phenyl acetate (14.82 g, 90 mmol) dropwise. The mixture was heated to 130 °C for 150 min then cooled. HCl (2 M, 50 mL) was added slowly and the mixture stirred for 45 min, then poured into 2 M HCl (85 mL) and extracted into diethyl ether (2x). The combined organic layers were washed with water, 1% sodium carbonate, water then dried ($MgSO_4$) and concentrated in vacuo to give **13** (10.8 g, 97%) as a brown oil.[43] δ_H (400 MHz, $CDCl_3$) 1.81 (t, 3H, 7.6 Hz) 2.60–2.63 (m, 5H) 6.74 (dd, 1H, 1.5 and 8 Hz) 6.79 (br s, 1H) 7.63 (d, 1H, 8 Hz) 12.28 (s, 1H). δ_C (100 MHz, $CDCl_3$) 15.12, 26.87, 29.53, 117.55, 118.12, 119.46, 131.09, 154.62, 163.01, 204.28. LRMS (EI): 164 ($M^{+\cdot}$, 30%) 149 ($[M-Me]^+$, 100). HRMS: calcd for $C_{10}H_{12}O_2$ 164.0837 found, 164.0836.

5.20. 1-(4-Benzyloxy-2-hydroxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-propenone 15

To a stirring suspension of **12** (0.617 g, 2.5 mmol) and 3,4,5-trimethoxybenzaldehyde (0.501 g, 2.6 mmol) in ethanol (25 mL) was added potassium hydroxide (0.384 g, 6.9 mmol). The reaction mixture was stirred for 144 h then acidified (2 N HCl) and extracted with ethyl acetate (2x). The combined organic layers were then

washed with brine, 10% sodium bisulfite solution (3x) and then saturated aqueous sodium bicarbonate again. The organic layer was then dried ($MgSO_4$) and concentrated in vacuo to give a yellow solid (31 g). This solid was heated in ethanol, and the undissolved solid, **15** (0.244 g, 23%), collected. This was used without further purification.

5.21. 1-(4-Ethyl-2-hydroxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-propenone 16

In the same way, a solution of ketone **13** (5.00 g, 30 mmol), 3,4,5-trimethoxy benzaldehyde (7.20 g, 37 mmol) and potassium hydroxide (4.21 g, 7.5 mmol) in ethanol (145 mL) were stirred for 200 h and gave chalcone **16** (9.62 g, 92%) as a brown tar following work-up and solvent evaporation. LRMS (EI): 342 ($M^{+\cdot}$, 100%). HRMS: calcd for $C_{20}H_{22}O_5$ 342.1467 Found, 342.1467.

5.22. 7-Benzyloxy-3-hydroxy-2-(3,4,5-trimethoxy-phenyl)-chromen-4-one 17

To a stirring solution of **15** (0.15 g, 0.4 mmol) in methanol (5 mL), THF (3 mL) and 16% aqueous sodium hydroxide solution (0.5 mL, 2 mmol) at 0 °C was added 15% aqueous hydrogen peroxide (0.5 mL, 0.5 mmol) dropwise. The solution was stirred at 0 °C for the 1 h then sealed and place in a refrigerator for 46 h. The reaction was acidified (2 N HCl) and extracted into dichloromethane (2x). The combined organic layers was then dried ($MgSO_4$) and concentrated to give a yellow solid, which was recrystallised from ethanol to give **17** (84 mg, 54%) as a yellow solid. δ_H (400 MHz, $CDCl_3$) 3.94 (s, 3H) 3.97 (s, 6H) 5.20 (s, 2H) 7.05–7.09 (m, 2H) 7.26 (s, 2H) 7.38–7.50 (m, 5H) 8.15 (d, 1H, 9 Hz). δ_C (100 MHz, $CDCl_3$) 56.73, 61.39, 71.04, 101.46, 105.62, 115.56, 127.29, 127.98, 128.89, 129.18, 135.99, 138.14, 144.73, 153.61, 157.87, 164.11, 173.27. LRMS (EI): 434 ($M^{+\cdot}$, 63%) 343.1 ($[M-Bn]^+$, 100). HRMS: calcd for $C_{25}H_{22}O_7$ 434.1366 found, 434.1365.

5.23. 7-Ethyl-3-hydroxy-2-(3,4,5-trimethoxy-phenyl)-chromen-4-one 18

In the same way, a solution of **16** (1.60 g, 4.7 mmol), sodium hydroxide (6.5 mL of a 16% solution in water, 26 mmol) and hydrogen peroxide (6.5 mL of a 15% solution in water, 29 mmol) in methanol (45 mL) gave **18** (0.777 g, 47%) as a yellow solid after 26 h at 0 °C. This was used without further purification.

5.24. 2-Hydroxy-4-iodo-acetophenone 20

To a stirring solution of 3-iodophenol **19** (26.06 g, 118 mmol), triethylamine (18 mL, 129 mmol) and *N*,*N*-dimethyl-4-amino-pyridine (0.62 g, 5 mmol) in dichloromethane (250 mL) under nitrogen was added acetyl chloride (9 mL, 127 mmol) dropwise over 5 min. The reaction was allowed to stir for 2 h and then washed with water (200 mL) and saturated aqueous sodium bicarbonate solution (200 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo to give 3-iodo-phenyl acetate[44] (30.20 g, 97%) as a pale yellow solid. mp 32.4–34.6 °C. IR (film) 3062, 1765, 1578, 1468, 1369, 1201, 1011, 924 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.29 (s, 3H) 7.06–7.12 (m, 2H) 7.46 (m, 1H) 7.55–7.58 (m, 1H). δ_C (100 MHz, $CDCl_3$) 20.99, 93.50, 121.14, 130.66, 130.77, 134.94, 150.89, 168.99. LRMS (EI) 262 ($M^{+\cdot}$, 34%) 220 ($M^{+\cdot}$–CH_2CO, 100). HRMS: calcd for $C_8H_7O_2I$, 261.9491; found, 261.9489. To a stirring solution of 3-iodo phenyl acetate (32.20 g, 123 mmol) in chlorobenzene (250 mL) under nitrogen was added aluminium chloride (31.00 g, 232 mmol). The reaction mixture was heated to 140 °C for 90 h then allowed to cool. The reaction mixture was poured onto ice/water and then filtered, and the residue washed with dichloromethane. The filtrate was then extracted with dichloromethane and the combined organic layers extracted with 10% potassium hydroxide solution (3×100 mL). The combined aqueous layers were then acidified with 6 N hydrochloric acid and extracted with dichloromethane (3×75 mL). This organic layer was then dried ($MgSO_4$) and concentrated in vacuo to give **20** (22.3 g, 69%) as a brown solid.[18] mp 51.5–52 °C. IR (GG) 1699, 1558, 1205 cm^{-1}. δ_H (400 MHz, $CDCl_3$). 2.60 (s, 3H) 7.26–7.28 (m, 2H) 7.42 (s, 1H) 12.26 (s, 1H). δ_C (100 MHz, $CDCl_3$) 26.60, 103.77, 118.99, 127.83, 128.33, 131.25, 162.19, 204.21. LRMS (CI): 263 ($M+H^+$, 98%) 262 (M^+, 100). HRMS: calcd for $C_8H_8O_2I$ (M+H), 262.9569 found, 262.9568.

5.25. 4-Benzyloxy-3,5-dimethoxy-benzaldehyde 21

To a stirring suspension of syringaldehyde (25.19 g, 138 mmol) and potassium carbonate (38.14 g, 276 mmol) in *N*,*N*-dimethyl formamide (500 mL) was added benzyl bromide (20 mL, 168 mmol). The reaction was stirred for 25 h, then poured into dichloromethane. The organic solvent was washed with water (5x) then dried ($MgSO_4$) and concentrated in vacuo to give a pink oil. This was recrystallised from hexane to give **21** (32.9 g, 87%). Mp 56–57 °C (lit.[45] 59–60 °C) δ_H (400 MHz, $CDCl_3$) 3.92 (s, 6H) 5.15 (s, 2H) 7.13 (s, 2H) 7.28–7.38 (m, 3H) 7.48 (dd, 2H, 7.4 and 1.5 Hz) 9.91 (s, 1H). δ_C (100 MHz, $CDCl_3$) 56.64, 75.43, 105.09, 128.48, 128.62, 128.80, 132.29, 137.59, 142.79, 154.38, 191.49. LRMS (EI): 272 ($M^{+\cdot}$, 17%), 91.1 (Bn^+, 100). HRMS: calcd for $C_{16}H_{16}O_4$ 272.1049, obs. 272.1053.

5.26. 2′-Hydroxy-4′-iodo-3,4,5-trimethoxy-chalcone 22

In the same way as for the synthesis of chalcone **15**, a solution of ketone **20** (0.55 g, 2.1 mmol) and 3,4,5-trimethoxybenzaldehyde (0.66 g, 3.4 mmol) and potassium hydroxide (0.25 g, 4.5 mmol) in ethanol (10 mL) was stirred for 119 h to give a yellow solid (1.17 g) following work-up and solvent removal. This solid was heated in methanol, and the undissolved solid collected. The filtrate was concentrated and then heated in methanol

again. More undissolved solid was collected. Undissolved solid is **22** (0.50 g, 54%). mp 140.5–140.9 °C. IR (GG) 1716, 1684 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 3.92 (s, 3H) 3.94 (s, 6H) 6.88 (s, 2H) 7.30 (dd, 1.6 and 8 Hz, 1H) 7.42–7.47 (m, 2H) 7.59 (d, 8 Hz, 1H) 7.86 (d, 15 Hz, 1H) 12.89 (s, 1H). δ_C (100 MHz, $CDCl_3$) 56.27, 61.02, 103.70, 103.70, 106.05, 118.68, 119.32, 128.01, 128.13 129.80, 130.13, 146.27, 153.52, 163.38, 193.15. LRMS (EI): 440 ($M^{+\cdot}$, 100%). HRMS: calcd for $C_{18}H_{17}O_5I$, 440.0121, found, 440.0118.

5.27. 2′-Hydroxy-4′-iodo-4-benzyloxy-3,5-dimethoxy-chalcone 23

In the same way, a solution of ketone **20** (0.73 g, 2.8 mmol), aldehyde **21** (0.911 g, 3.3 mmol) and potassium hydroxide (0.42 g, 7.5 mmol) in ethanol (10 mL) was stirred for 46 h to give a brown oil following work-up and solvent removal. Chalcone **23** (1.06 g, 74%) was crystallised from methanol as yellow crystals. mp 123.6–124.6 °C (MeOH). δ_H (400 MHz, $CDCl_3$) 3.89 (s, 6H) 5.09 (s, 2H) 6.85 (s, 2H) 7.25–7.49 (m, 7H) 7.57 (d, 1H, 8.5 Hz) 7.83 (d, 1H, 15 Hz) 12.91 (s, 1H). δ_C (100 MHz, $CDCl_3$) 56.67, 75.53, 104.10, 106.54, 119.06, 119.76, 128.42, 128.55, 128.61, 128.84, 130.36, 130.55, 137.79, 140.34, 146.75, 154.26, 163.81, 193.58. LRMS (EI): 516 ($M^{+\cdot}$, 42%), 425.0 ($[M-Bn]^+$, 100) 91.0 (Bn^+). HRMS: calcd for $C_{24}H_{21}IO_5$ 516.0434, obs. 516.0433.

5.28. 3-Benzyloxy-7-iodo-2-(3,4,5-trimethoxyphenyl)-chromen-4-one 24

In the same way as for flavonol **15**, a solution of **22** (0.165 g, 0.4 mmol), sodium hydroxide (0.6 mL of a 16% solution in water, 2.4 mmol), and hydrogen peroxide (0.6 mL of a 15% solution in water, 2.6 mmol) in methanol (4.4 mL) gave 3-hydroxy-7-iodo-2-(3,4,5-trimethoxyphenyl)-chromen-4-one (0.130 g, 76%) as a yellow solid after 24 h at 0 °C. Mp 151–153 °C. IR (GG) 3749, 1734, 1265, 740 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 3.95 (s, 3H) 3.97 (s, 6H) 7.03 (br s, 1H) 7.51 (s, 2H) 7.72 (dd, 1.4 and 8 Hz, 1H) 7.93 (d, 8 Hz, 1H) 8.05 (d, 1.4 Hz, 1H). δ_C (100 MHz, $CDCl_3$) 56.30, 61.01, 100.11, 105.37, 119.95, 125.79, 126.52, 127.35, 133.87, 138.33, 140.16, 144.70, 153.23, 154.78, 172.83. LRMS (EI): 454 ($M^{+\cdot}$, 100%). HRMS: calcd for $C_{18}H_{15}O_6I$, 453.9913, found, 453.9916. A stirring suspension of 3-hydroxy-7-iodo-2-(3,4,5-trimethoxyphenyl)-chromen-4-one (0.257 g, 0.6 mmol), potassium carbonate (1.48 g, 11 mmol), potassium iodide (60 mg, 0.3 mmol) and benzyl chloride (0.16 mL, 1.3 mmol) in acetone (12 mL) under nitrogen was heated to reflux for 1 h. The reaction was filtered and the filtrate concentrated in vacuo to give an orange solid. This solid was recrystallised from isopropanol to give **24** (0.270 g, 88%) as a white solid. Mp 142 °C. IR (GG) 1734, 1558, 1265, 744 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 3.79 (s, 6H) 3.95 (s, 3H) 5.15 (s, 2H) 7.28–7.30 (m, 5H) 7.35–7.37 (m, 2H) 7.76 (d, 8 Hz, 1H) 7.99–8.01 (m, 2H). δ_C (100 MHz, $CDCl_3$) 56.11, 60.97, 74.49, 99.72, 106.33, 123.52, 125.57, 126.99, 127.10, 128.28, 128.83, 134.03, 136.54, 140.98, 141.23, 152.86, 154.80, 155.73, 174.56. LRMS (EI): 544 ($M^{+\cdot}$, 30%), 453 ($M^{+\cdot}-Bn\cdot$, 47%), 425 (100). HRMS: calcd for $C_{25}H_{21}O_6I$, 544.0383 found, 544.0385.

5.29. 3-Benzyloxy-7-iodo-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-chromen-4-one 25

In the same way as for flavonol **15**, a solution of **23** (0.85 g, 1.6 mmol), sodium hydroxide (2.2 mL of a 16% solution in water, 8.8 mmol), and hydrogen peroxide (2.2 mL of a 15% solution in water, 9.7 mmol) in methanol (17 mL) gave 3-hydroxy-7-iodo-(4-benzyloxy-3,5-dimethoxyphenyl)-chromen-4-one (0.84 g, 96%) as a yellow solid after 24 h at 0 °C, work-up and trituration with ethanol. Mp 169–171 °C. δ_H (400 MHz, $CDCl_3$) 3.93 (s, 6H) 5.12 (s, 2H) 7.04 (br s, 1H) 7.28–7.38 (m, 3H) 7.49–7.52 (m, 4H) 7.72 (dd, 1H, 1.4 and 8.4 Hz) 7.92 (d, 1H, 8.4 Hz) 8.03 (d, 1H 1.4 Hz). LRMS (EI): 530.0 ($M^{+\cdot}$, 22%), 439 ($M^{+\cdot}-Bn\cdot$, 100). HRMS: calcd for $C_{24}H_{19}IO_6$ 530.0226, obs. 530.0234. A stirring suspension of 3-hydroxy-7-iodo-(4-benzyloxy-3,5-dimethoxy-phenyl)-chromen-4-one (5 g, 9 mmol), potassium carbonate (6.2 g, 45 mmol), potassium iodide (0.64 g, 4 mmol) and benzyl chloride (1.7 mL, 15 mmol) in acetone (150 mL) under nitrogen was heated to reflux for 19 h. The reaction was filtered and the filtrate concentrated in vacuo to give an cream solid. This solid was recrystallised from isopropanol to give **25** (5.77 g, 99%) as a white solid. Mp 131–133 °C. δ_H (400 MHz, $CDCl_3$) 3.73 (s, 6H) 5.11 (s, 2H) 7.21 (s, 2H) 7.26–7.37 (m, 8H) 7.49 (d, 2H, 7 Hz) 7.73 (d, 1H, 8 Hz) 7.97 (m, 2H). δ_C (100 MHz, $CDCl_3$) 56.51, 74.87, 75.44, 100.10, 106.78, 123.93, 126.10, 127.40, 127.51, 128.60, 128.68, 128.69, 128.88, 129.27, 134.42, 136.93, 137.83, 139.59, 140.46, 153.60, 155.21, 156.22, 174.97. LRMS (EI): 620 ($M^{+\cdot}$, 20%), 91 (Bn^+, 100). HRMS: calcd for $C_{31}H_{25}IO_6$ 620.0696, obs. 620.0695.

5.30. 3-Benzyloxy-7-butyl-2-(3,4,5-trimethoxy-phenyl)-chromen-4-one 29c

To a stirring solution of *n*-butane boronic acid **26** (0.133 g, 1.3 mmol) and dichloropalladium (dppf) (50 mg) in tetrahydrofuran (7 mL) and 3 M NaOH solution (1.1 mL) was added **24** (0.500 g, 0.9 mmol) added and the reaction heated to reflux for 21 h. The reaction was then quenched with water and diethyl ether. The organic layer was collected and the aqueous layer extracted with diethyl ether (2x). The combined organic layers were washed with 1 M HCl and brine then dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. A silica plug (dichloromethane) yielded **29c** (99 mg, 23%) as an orange oil. LRMS (EI): 474 ($M^{+\cdot}$, 15%), 299 (100). HRMS: calcd for $C_{29}H_{30}O_6$ 474.2042 found, 474.2041.

5.31. 3-Benzyloxy-7-(4-methyl-pentyl)-2-(3,4,5-trimethoxy-phenyl)-chromen-4-one 29d

To a stirring solution of 4-methyl-pent-1-ene (0.110 g, 1.3 mmol) in tetrahydrofuran (2 mL) under argon at 0 °C was added 9-BBN in tetrahydrofuran (0.5 M, 2.7 mL,

1.4 mmol). The reaction was allowed to warm to room temperature then stirred for 6 h then **24** (0.499 g, 0.9 mmol) in tetrahydrofuran (5 mL), 3 M NaOH solution (1.1 mL) and dichloropalladium (dppf) (28 mg, 0.03 mmol) were added and the reaction heated to reflux for 14 h. The reaction was then quenched with water and diethyl ether. The organic layer was collected and the aqueous layer extracted with diethyl ether (2x). The combined organic layers were washed with 1 M HCl and brine then dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. A silica plug (dichloromethane) yielded **29d** (0.197 g, 49%) as a yellow oil. LRMS (EI): 502 ($M^{+\cdot}$, 6%), 299 (100). HRMS: calcd for $C_{31}H_{34}O_6$ 502.2355 found, 502.2358.

5.32. 3-Benzyloxy-7-hexyl-2-(3,4,5-trimethoxy-phenyl)-chromen-4-one 29e

In the same way, a solution of 1-hexene (0.109 g, 1.3 mmol) and 9-BBN (1.35 mmol) in tetrahydrofuran (4.7 mL) was stirred for 8 h then **24** (0.505 g, 0.9 mmol) in tetrahydrofuran (5 mL), 3 M aqueous NaOH solution (1.1 mL) and dichloropalladium (dppf) (32 mg) were added and the mixture was heated to reflux for 15 h. Work-up and column chromatography (silica gel, dichloromethane) then yielded **29e** (0.112 g, 24%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 0.89 (t, 3H, 6.5 Hz) 1.30–1.42 (m, 6H) 1.66–1.73 (m, 2H) 2.76 (t, 2H, 7.5 Hz) 3.78 (s, 6H) 3.93 (s, 3H) 5.13 (s, 2H) 7.23–7.37 (m, 9H) 8.19 (d, 1H, 8.1 Hz). δ_C (100 MHz, $CDCl_3$) 14.45, 22.94, 29.30, 31.35, 32.03, 32.44, 36.50, 56.52, 61.35, 74.87, 106.76, 117.38, 122.48, 125.98, 126.11, 126.58, 128.55, 128.64, 129.25, 137.23, 140.30, 140.48, 150.22, 153.23, 155.75, 155.92, 175.38. LRMS (EI): 503 ($M^{+\cdot}$, 35%), 412 ($[M-Bn]^+$, 42), 383 (100). HRMS: calcd for $C_{31}H_{34}O_6$ 502.2355 found, 502.2354.

5.33. 3-Benzyloxy-7-octyl-2-(3,4,5-trimethoxy-phenyl)-chromen-4-one 29f

In the same way, a solution of 1-octene (0.148 g, 1.3 mmol) and 9-BBN (1.35 mmol) in tetrahydrofuran (4.7 mL) was stirred for 9 h then **24** (0.504 g, 0.9 mmol) in tetrahydrofuran (5 mL), 3 M aqueous NaOH solution (1.1 mL) and dichloropalladium (dppf) (31 mg) were added and the mixture was heated to reflux for 15 h. Work-up and column chromatography (silica gel, dichloromethane) then yielded **29f** (0.290 g, 59%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 0.88 (t, 3H, 7.0 Hz) 1.25–1.41 (m, 10H) 1.62–1.74 (m, 2H) 2.76 (t, 2H, 7.5 Hz) 3.78 (s, 6H) 3.89 (s, 3H) 5.13 (s, 2H) 7.21–7.37 (m, 9H) 8.19 (d, 1H, 8.2 Hz). δ_C (100 MHz, $CDCl_3$) 14.48, 23.03, 29.59, 29.65, 29.80, 31.40, 32.30, 36.51, 56.52, 61.35, 74.87, 106.76, 117.38, 122.48, 125.98, 126.11, 126.58, 128.55, 128.64, 129.25, 137.23, 140.30, 140.49, 150.22, 153.23, 155.75, 155.91, 175.37. LRMS (CI): 531 ($[M+H]^+$, 22%), 419 (100). HRMS: calcd for $C_{33}H_{39}O_6$ 531.2747 found, 531.2744.

5.34. 3-Benzyloxy-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-7-decyl-chromen-4-one 30h

In the same way, a solution of 1-decene (0.176 g, 1.3 mmol) and 9-BBN (1.35 mmol) in tetrahydrofuran (4.7 mL) was stirred for 6 h, then **25** (0.560 g, 0.9 mmol) in tetrahydrofuran (5 mL), 3 M aqueous NaOH solution (1.1 mL) and dichloropalladium (dppf) (27 mg) were added and the mixture was heated to reflux for 15 h. Work-up and column chromatography (silica gel, dichloromethane) gave **30h** (0.339 g, 59%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) 0.88 (t, 3H, 7 Hz) 1.26–1.42 (m, 14H) 1.65–1.74 (m, 2H) 2.75 (t, 2H, 7 Hz) 3.74 (s, 6H) 5.10 (s, 2H) 5.11 (s, 2H) 7.20–7.38 (m, 12H) 7.49–7.51 (m, 2H) 8.18 (d, 1H, 8 Hz). δ_C (100 MHz, $CDCl_3$) 14.11, 22.68, 29.27, 29.31, 29.46, 29.55, 29.60, 31.01, 31.89, 36.13, 56.14, 74.46, 75.06, 106.41, 117.00, 122.09, 125.60, 125.72, 126.31, 128.00, 128.17, 128.21, 128.26, 128.51, 128.90, 136.82, 137.52, 138.24, 139.99, 149.82, 153.16, 155.37, 155.60, 175.01. LRMS (FAB): 635 ($[M+H]^+$, 25%) 91.5 (Bn^+, 100%). HRMS: calcd for $C_{41}H_{47}O_6$ 635.3373 found, 635.3370.

5.35. 3-Benzyloxy-7-dodecyl-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-chromen-4-one 30j

In the same way, a solution of 1-dodecene (0.214 g, 1.27 mmol) and 9-BBN (1.35 mmol) in tetrahydrofuran (4.7 mL) was stirred for 6 h, then **25** (0.565 g, 0.9 mmol) in tetrahydrofuran (5 mL), 3 M aqueous NaOH solution (1.1 mL) and dichloropalladium (dppf) (24 mg) were added and the mixture was heated to reflux for 15 h. Work-up and column chromatography (silica gel, dichloromethane to dichloromethane–MeOH 99:1) yielded **30j** (0.210 g, 35%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) 0.85–0.89 (m, 3H) 1.20–1.37 (m, 16H) 1.51–1.56 (m, 2H) 1.62–1.71 (m, 2H) 2.75 (t, 2H, 7.4 Hz) 3.74 (s, 6H) 5.11 (s, 2H) 5.11 (s, 2H) 7.23–7.38 (m, 13H) 7.50 (dd, 1H, 1.5 and 6.7 Hz) 8.19 (d, 1H, 8.2 Hz). δ_C (100 MHz, $CDCl_3$) 14.12, 22.69, 25.75, 27.43, 29.28, 29.35, 29.47, 29.56, 29.64, 31.02, 31.92, 36.14, 56.15, 74.46, 75.06, 106.42, 118.00, 122.10, 125.60, 125.73, 126.32, 128.01, 128.16, 128.21, 128.27, 128.51, 128.90, 136.83, 137.53, 138.94, 139.88, 149.82, 153.17, 155.37, 155.61, 175.00. LRMS (EI): 662 ($M^{+\cdot}$, 8%) 571 ($[M-Bn]^+$, 12) 91 (Bn^+, 100). HRMS: calcd for $C_{43}H_{50}O_6$ 662.3607 found, 662.3600. HRMS: calcd for $C_{42}{}^{13}CH_{50}O_6$ 663.3641 found, 663.3636.

5.36. 3-Benzyloxy-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-7-octadecyl-chromen-4-one 30k

In the same way, a solution of 1-octadecene (0.322 g, 1.3 mmol) and 9-BBN (1.35 mmol) in tetrahydrofuran (4.7 mL) was stirred for 6 h, then **25** (0.558 g, 0.9 mmol) in tetrahydrofuran (5 mL), 3M aqueous NaOH solution (1.1 mL) and dichloropalladium (dppf) (25 mg) were added and the mixture was heated to reflux for 18 h. Work-up and column chromatography (silica gel, dichloromethane) yielded **30k** (0.455 g, 68%) as a white solid. δ_H (400 MHz, $CDCl_3$) 0.88 (t, 3H, 7 Hz) 1.25–1.39

(m, 30H) 1.69–1.70 (m, 2H) 2.75 (t, 2H, 7.3 Hz) 3.74 (s, 6H) 5.10 (s, 2H) 5.11 (s, 2H) 7.21–7.38 (m, 12H) 7.50 (d, 2H, 6.7 Hz) 8.18 (d, 1H, 8 Hz). δ_C (100 MHz, $CDCl_3$) 14.12, 22.70, 29.30, 29.37, 29.48, 29.57, 29.67, 29.70, 31.03, 31.93, 36.14, 56.14, 74.46, 75.06, 106.40, 117.00, 122.20, 125.60, 125.81, 126.33, 128.01, 128.17, 128.21, 128.26, 128.51, 128.90, 140.00, 149.96, 153.16, 155.74, 174.93. LRMS (FAB): 747 ($[M+H]^+$, 22%) 91.5 (Bn^+, 100). HRMS: calcd for $C_{49}H_{63}O_6$ 747.4625 Found, 747.4622.

5.37. 3-Acetoxy-7-butyl-2-(3,4,5-triacetoxy-phenyl)-chromen-4-one 31c

In the same way as for acetate **31d**, a solution of **29c** (0.389 g, 1 mmol) and boron tribromide (5 mmol) in dichloromethane (20 mL) gave crude **6c** (0.302 g, 77%) as a brown solid (no precipitation occurred in water so extraction with ethyl acetate was employed). A solution of crude **6c** (0.302 g, 0.9 mmol), *N*,*N*-dimethyl-4-aminopyridine (5 mg) and acetic anhydride (0.50 mL, 5.3 mmol) in pyridine (3 mL) was then stirred for 1 h to give **31c** (0.302 g, 67%) as a white solid after crystallisation in methanol. δ_H (400 MHz, $CDCl_3$) 0.95 (t, 3H, 7.3 Hz) 1.32–1.42 (m, 2H) 1.60–1.70 (m, 2H) 2.33 (s, 9H), 2.39 (s, 3H), 2.75 (t, 2H, 7.8 Hz) 7.21–7.28 (m, 1H) 7.34 (s, 1H) 7.68 (s, 2H) 8.14 (d, 1H, 7.9 Hz).

5.38. 3-Acetoxy-7-(4-methyl-pentyl)-2-(3,4,5-triacetoxy-phenyl)-chromen-4-one 31d

To a stirring solution of **29d** (0.184 g, 0.4 mmol) in dichloromethane (20 mL) under argon at 0 °C was added boron tribromide in dichloromethane (1.0 M, 1.8 mL, 1.8 mmol). The mixture was warmed to room temperature and then stirred for 15 h. Methanol (10 mL) was then added. The reaction was heated to reflux for 2 h, then concentrated in vacuo to give a brown solid. Water (20 mL) was added and the mixture sonicated then left to stand overnight. Crude **6d** (0.124 g, 91 %) was then collected as a yellow solid. To a stirring solution of crude **6d** (88 mg, 0.2 mmol) and *N*,*N*-dimethyl-4-aminopyridine (2 mg, 0.02 mmol) in pyridine (0.8 mL) under argon was added acetic anhydride (0.20 mL, 2 mmol). The reaction was stirred for 23 h then poured into ethyl acetate and washed with 2 M HCl, sodium hydrogen carbonate solution and brine, then dried ($MgSO_4$) and concentrated in vacuo to give an off-white solid. Recrystallisation (methanol) yielded **31d** (11 mg, 9%) as a white solid. δ_H (400 MHz, $CDCl_3$) 0.89 (d, 6H, 6.6 Hz) 1.20–1.26 (m, 1H) 1.54–1.72 (m, 4H), 2.33 (s, 6H), 2.34 (s, 3H), 2.39 (s, 3H), 2.73 (t, 2H, 7.6 Hz) 7.25–7.27 (m, 1H) 7.34 (s, 1H) 7.68 (s, 2H) 8.14 (d, 1H, 8.2 Hz). LRMS (FAB): 539 ($M^{+\cdot}$, 7%), 136 (100). $C_{29}H_{31}O_{10}$ calcd 539.1917 found, 539.1919.

5.39. 3-Acetoxy-7-hexyl-2-(3,4,5-triacetoxy-phenyl)-chromen-4-one 31e

In the same way, a solution of **29e** (96 mg, 0.2 mmol) and boron tribromide (1.0 mmol) in dichloromethane (11 mL) gave crude **6e** (66 mg, 93%) as a yellow solid. A solution of crude **6e** (47 mg, 0.1 mmol), *N*,*N*-dimethyl-4-aminopyridine (2 mg) and acetic anhydride (0.11 mL, 1 mmol) in pyridine (0.50 mL) was then stirred for 18 h to give **31e** (30 mg, 44%) as a white solid after crystallisation in methanol. δ_H (400 MHz, $CDCl_3$) 0.89 (t, 3H, 6.8 Hz) 1.32–1.41 (m, 6H) 1.63–1.69 (m, 2H) 2.33 (s, 6H) 2.34 (s, 3H) 2.39 (s, 3H) 2.75 (t, 2H, 7.6 Hz) 7.24–7.27 (m, 1H) 7.34 (s, 1H) 7.68 (s, 2H) 8.14 (d, 1H, 8.2 Hz). δ_C (100 MHz, $CDCl_3$) 14.45, 20.60, 20.88, 21.10, 22.93, 29.21, 31.22, 32.00, 36.49, 117.54, 121.26, 121.88, 126.32, 126.73, 128.37, 134.44, 136.96, 143.94, 151.10, 153.77, 156.08, 166.98, 167.90, 168.57, 172.32. LRMS (FAB): 539 [$(M+H)^+$, 100%). $M+H^+$ requires $C_{29}H_{31}O_{10}$ calcd 539.1917 found, 539.1917.

5.40. 3-Acetoxy-7-octyl-2-(3,4,5-triacetoxy-phenyl)-chromen-4-one 31f

In the same way, a solution of **29f** (0.290 g, 0.5 mmol) and boron tribromide (2.7 mmol) in dichloromethane (12.7 mL) gave crude **6f** (0.155 g, 71 %) as a yellow solid. A solution of crude **6f** (0.133 g, 0.3 mmol), *N*,*N*-dimethyl-4-aminopyridine (2 mg) and acetic anhydride (0.20 mL, 2 mmol) in pyridine (1 mL) was then stirred for 5 h to give **31f** (97 mg, 51%) as a white solid after crystallisation in methanol. δ_H (400 MHz, $CDCl_3$) 0.88 (t, 3H, 6.6 Hz) 1.22–1.48 (m, 10H) 1.65–1.70 (m, 2H) 2.33 (s, 6H) 2.34 (s, 3H) 2.39 (s, 3H) 2.74 (t, 2H, 7.5 Hz) 7.24–7.26 (m, 1H) 7.34 (s, 1H) 7.68 (s, 2H) 8.14 (d, 1H, 8.2 Hz). δ_C (100 MHz, $CDCl_3$) 14.48, 20.60, 20.88, 21.10, 23.03, 29.55, 29.57, 29.78, 31.26, 32.22, 36.50, 117.54, 121.27, 121.88, 126.32, 126.74, 128.37, 134.44, 136.96, 143.94, 151.10, 153.76, 156.08, 166.98, 167.90, 168.57, 172.32. LRMS (FAB): 567 [$(M+H)^+$, 100%]. $M+H^+$ requires $C_{31}H_{35}O_{10}$ calcd 567.2230 found, 567.2228.

5.41. 3,7-Dimethyl-octan-1-ol 34

A flask containing a stirring suspension of geraniol (10 mL, 58 mmol) and palladium on carbon (10% Pd, 0.494 g) in ethanol (70 mL) was evacuated, and then filled with hydrogen. The reaction mixture was then stirred under an atmosphere of hydrogen for 21 h. After this time the mixture was filtered and the filtrate concentrated in vacuo to give **34** (5 g, 55%) as a colourless oil.[46] δ_H (400 MHz, $CDCl_3$) 0.86–0.90 (m, 10H) 1.11–1.42 (m, 6H) 1.49–1.68 (m, 3H) 3.63–3.73 (m, 2H). δ_C (100 MHz, $CDCl_3$) 20.01, 22.96, 23.06, 25.05, 28.34, 29.89, 37.75, 39.63, 40.36, 61.60.

5.42. 3,7,11-Trimethyl-dodecan-1-ol 35

In the same way, farnesol (5.7 mL, 22.5 mmol) gave a mixture of diastereomers **35** (4.81 g, 93%) as a colourless oil.[47] IR (film) 2925, 1715, 1459 cm^{-1}. δ_H (400 MHz, $CDCl_3$) mixture of diastereoisomers. 0.84–0.90 (m, 12H) 1.05–1.38 (m, 13H) 1.49–1.62 (m, 4H) 3.63–3.73 (m, 2H). δ_C (100 MHz, $CDCl_3$) 11.78, 11.80, 19.59, 19.64, 20.07, 20.13, 23.00, 23.09, 24.75, 24.88, 25.18, 58.36,

29.85, 29.95, 33.16, 33.18, 34.80, 37.33, 37.37, 37.68, 37.76, 37.79, 37.84, 39.75, 40.36, 61.65. LRMS (CI): 246 ($M+NH_4^+$, 100%). LRMS (EI): 210 ($M^{+\cdot}-H_2O$, 11%), 18 (100). HRMS: calcd for $C_{15}H_{32}O$, ($M-H_2O$), 210.2348 found, 210.2346.

5.43. 1-Iodo-3,7-dimethyl-octane 36

To a stirring solution of **34** (5 g, 32 mmol), imidazole (2.59 g, 38 mmol) and triphenylphosphine (9.11 g, 35 mmol) in toluene (100 mL) under nitrogen was added iodine (10.44 g, 41 mmol). The reaction mixture was stirred for 18 h then filtered. The filtrate was washed with 5% sodium thiosulfate solution (3×100 mL) then dried (Na_2SO_4) and concentrated in vacuo to give a white solid. This solid was taken up in hexane (20 mL), cooled and filtered. The filtrate was then concentrated in vacuo to give **36** (6 g, 71%) as a colourless oil.[48] δ_H (400 MHz, $CDCl_3$) 0.86–0.90 (m, 9H) 1.10–1.32 (m, 6H) 1.49–1.69 (m, 3H) 1.84–1.90 (m, 1H) 3.14–3.28 (m, 2H). δ_C (100 MHz, $CDCl_3$) 5.77, 19.12, 22.97, 24.91, 28.33, 34.27, 36.86, 39.56, 41.37.

5.44. 3,7,11-Trimethyl-1-dodecyl iodide 37

In the same way, a solution of alcohol **35** (1.5 g, 6.6 mmol), imidazole (1.13 g, 16.6 mmol) and triphenylphosphine (4.40 g, 16.8 mmol) and iodine (3.26 g, 12.8 mmol) in toluene (250 mL) gave a mixture of diastereomers **37** (1.1 g, 61%) as a colourless oil. IR (film) 2955 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 0.84–0.88 (m, 12H), 0.95–1.38 (m, 11H), 1.49–1.57 (m, 4H), 1.61–1.67 (m, 1H) 1.86–1.89 (m, 1H) 3.13–3.28 (m, 2H). δ_C (100 MHz, $CDCl_3$) 5.73, 11.80, 11.82, 19.17, 19.60, 20.09, 20.15, 23.02, 23.11, 24.60, 24.89, 25.20, 28.38. 29.86, 33.17, 33.20, 34.81, 37.34, 37.38, 37.63, 37.65, 37.69, 37.78, 37.80, 37.85, 39.77. LRMS (EI): 338 ($M^{+\cdot}$, 2%) 211 ($M^{+\cdot}-I\cdot$, 24) 57 (100). HRMS: calcd for $C_{15}H_{31}I$, 338.1471 found, 338.1472.

5.45. 3-Benzyloxy-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-7-(3,7-dimethyl-octyl)-chromen-4-one 38

To a stirring suspension of zinc chloride (0.302 g, 2.2 mmol) and magnesium (86 mg, 3.5 mmol) in tetrahydrofuran (2 mL) under argon was added **36** (0.879 g, 3.3 mmol) in tetrahydrofuran (2 mL). The reaction was heated to 50 °C for 20 h then cooled. **25** (0.465 g, 0.8 mmol) in tetrahydrofuran (6 mL) and dichlorobis-[tri-(o-tolyl)-phosphinyl]palladium (33 mg, 0.04 mmol) were added and the reaction stirred for 25 h. The reaction was then quenched with 3 N HCl (10 mL), diluted with water and extracted into dichloromethane, washed with brine (2x), dried ($MgSO_4$) and concentrated in vacuo to give a brown oil. Column chromatography (silica gel, dichloromethane–MeOH 1:0 to 19:1) yielded **38** (0.143 g, 30%) as a yellow oil. LRMS (FAB): 635 ($[M+H]^+$, 18%) 545 ($[M-Bn]^+$, 75) 91.5 (Bn^+, 100). HRMS: calcd for $C_{41}H_{47}O_6$ 635.3373 found, 635.3374.

5.46. 3-Benzyloxy-2-(3,4,5-trimethoxy-phenyl)-7-(3,7,11-trimethyl-dodecyl)-chromen-4-one 39

In the same way, the organozinc derived from iodide **37** (1.268 g, 3.8 mmol) was coupled with iodoflavonoid **24** (0.481 g, 0.8 mmol) using dichlorobis-[tri-(o-tolyl)-phosphinyl]palladium (63 mg, 0.08 mmol) to give flavonoid **39** (82 mg, 15%) as a pale yellow oil after column chromatography (silica gel, petrol–EtOAc 9:1 to 2:1). IR (film) 2928, 1457, 908, 734 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 0.84–0.92 (m, 7H), 0.96 [d, 6 Hz, 2H (3H of one diastereomer)], 1.05–1.42 (m, 8H), 1.48–1.70 (m, 12H) 2.68–2.83 (m, 2H) 3.78 (s, 6H) 3.93 (s, 3H) 5.13 (s, 2H) 7.21–7.37 (m, 9H) 8.19 (d, 8 Hz, 1H). δ_C (100 MHz, $CDCl_3$) 19.56, 19.63, 19.68, 19.75, 22.63, 22.72, 24.38, 24.80, 27.98, 32.60, 32.78, 33.74, 37.22, 37.28, 37.37, 38.45, 38.55, 39.36, 56.15, 60.99, 74.51, 106.39, 116.94, 122.08, 125.65, 126.20, 128.18, 128.27, 128.88, 136.84, 139.92, 150.18, 152.86, 155.41, 175.02. LRMS (EI): 628 ($M^{+\cdot}$, 20%) 509 (100). HRMS: calcd for $C_{40}H_{52}O_6$, 628.3764 found, 628.3768.

5.47. *N*-(4-Methoxy-phenyl)-acetamide 40

To a stirring suspension of *p*-anisidine (6.036 g, 49 mmol) in dichloromethane (20 mL) was added acetic anhydride (5 mL, 53 mmol) over 1 h. The reaction was stirred for 1 h then poured into hexane (60 mL) and stirred for 1 h. The solid was collected and washed with hexane to give **40** (7.717 g, 95%) as a pale grey solid.[49] δ_H (400 MHz, $CDCl_3$) 2.13 (s, 3H) 3.78 (s, 3H) 6.83 (d, 2H, 9 Hz) 7.38 (d, 2H, 9 Hz). δ_C (100 MHz, $CDCl_3$) 24.66, 55.85, 114.49, 122.37, 131.41, 156.82, 168.79. LRMS (EI): 165 ($M^{+\cdot}$, 71%), 108 ($[NH_2C_6H_4O]^+$, 100). HRMS: calcd for $C_9H_{11}NO_2$ 165.0790 Found, 165.0789.

5.48. 5′-Iodo-2′-hydroxy-acetophenone 41

To a stirring suspension of **40** (5.253 g, 32 mmol) and acetyl chloride (6.6 mL, 93 mmol) in dichloromethane (55 mL) was added aluminium trichloride (14.55 g, 109 mmol) in portions over 90 min. The reaction was then heated to reflux for 4.5 h and cooled overnight. The mixture was poured onto ice then extracted into dichloromethane (5x), dried ($MgSO_4$) and concentrated in vacuo to give *N*-(3-acetyl-4-hydroxy-phenyl)-acetamide[50] (5.336 g, 87%) as a pale green solid. δ_H (400 MHz, $CDCl_3$) 2.19 (s, 3H) 2.63 (s, 3H) 6.94 (d, 1H, 9 Hz) 7.12 (br s, 1H, NH) 7.33 (dd, 1H, 2.6 and 9 Hz) 8.17 (d, 1H, 2.6 Hz) 12.12 (s, 1H). δ_C (100 MHz, $CDCl_3$) 24.71, 27.16, 119.08, 119.60, 122.94, 129.58, 159.62, 168.86, 204.84. LRMS (EI): 193 ($M^{+\cdot}$, 100%). HRMS: calcd for $C_{10}H_{11}NO_3$ 193.0739 Found, 193.0740. A suspension of *N*-(3-acetyl-4-hydroxy-phenyl)-acetamide (1.029 g, 5.3 mmol) in 15% HCl (1.5 mL, 6.2 mmol) was heated to reflux for 40 min, then cooled and neutralised with 10% aqueous ammonia. The precipitated solid was collected by filtration as 5′-amino-2′-hydroxy-acetophenone[50] (0.677 g, 84%) a green solid. δ_H (400 MHz, $CDCl_3$) 2.58 (s, 3H) 3.47 (br s, 2H) 6.83 (d, 1H, 8.8 Hz) 6.91 (dd, 1H, 2.8 and 8.8 Hz) 7.02 (d, 1H, 2.8 Hz). δ_C (100 MHz,

$CDCl_3$) 27.12, 115.71, 119.40, 119.87, 125.737, 138.40, 156.03, 204.48. LRMS (EI): 151 ($M^{+\cdot}$, 100%). HRMS: calcd for $C_8H_9NO_2$ 151.0633 found, 151.0632. To a stirring solution 5′-amino-2′-hydroxy-acetophenone (6.856 g, 46 mmol) in 98% sulfuric acid (24 mL) and water (19 mL) was added sodium nitrite (3.30 g, 48 mmol) in water (5.5 mL). The reaction was stirred for 35 min, then sulfuric acid (4 mL), copper powder (0.17 g, 0.3 mmol) and potassium iodide (8.80 g, 53 mmol) in water (5.5 mL) added. The mixture was then heated slowly to 65 °C and maintained at 65 °C for 2 h. The reaction was then cooled, water (25 mL) and sodium hydrogen carbonate added. More water was added, then extracted into a mixture of ethyl acetate and dichloromethane, then ethyl acetate (2x). The combined organic layers were washed with brine then concentrated in vacuo. This mixture was then taken up in ethyl acetate and 2 M HCl, filtered and the organic layer dried ($MgSO_4$) and concentrated in vacuo to give **41** (1.339 g, 39%) as a purple oil.[50] This was then used in the next reaction.

5.49. 1-(5-Bromo-4-ethyl-2-hydroxy-phenyl)-ethanone 42

To a stirring solution of **13** (1.002 g, 6.1 mmol) in chloroform (10 mL) under argon at −12 °C was added bromine (0.32 mL, 6.2 mmol) in chloroform (5 mL) over 20 min. The reaction was stirred at −12 °C for 50 min, then poured into water (20 mL). The organic layer was washed with water (10 mL), 10% sodium thiosulfate (2 × 10 mL) and water (10 mL), dried ($MgSO_4$) then concentrated in vacuo to give **42** (1.132 g, 76%) as a brown solid. LRMS (EI): 242(+244) ($M^{+\cdot}$, 16%) 227(+229) ($[M-Me]^+$, 40), 191 (100). HRMS: calcd for $C_{10}H_{11}BrO_2$ 241.9942+243.9923, found, 241.9941+243.9916.

5.50. 1-(2-Hydroxy-5-iodo-phenyl)-3-(4-benzyloxy-3,5-dimethoxy-phenyl)-propenone 43

In the same way as for the synthesis of chalcone **15**, a solution of ketone **41** (4.243 g, 16 mmol), aldehyde **21** (4.51 g, 17 mmol) and potassium hydroxide (1.839 g, 33 mmol) in ethanol (100 mL) was stirred for 191 h to give a black oil following work-up and solvent evaporation. This was taken up in ethanol (50 mL), potassium hydroxide (1.97 g) added and stirred for 169 h. The reaction was then acidified with 6 M HCl and diluted with water then extracted into ethyl acetate (3x) washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a black foam. Crystallisation (ethanol) yielded chalcone **43** (4.122 g, 49%). LRMS (EI): 516 ($M^{+\cdot}$) 425 ($[M-Bn]^+$, 32%) 91 (Bn^+, 100). HRMS: calcd for $C_{24}H_{21}IO_5$ 516.0434 found, 516.0435.

5.51. 1-(5-Bromo-4-ethyl-2-hydroxy-phenyl)-3-(4-benzyloxy-3,5-dimethoxy-phenyl)-propenone 44

In the same way as for the synthesis of chalcone **15**, a solution of ketone **42** (1.132 g, 4.7 mmol), aldehyde **21** (0.918 g, 4.7 mmol) and added potassium hydroxide (0.545 g, 9.7 mmol) in ethanol (30 mL) was stirred for 26 h to give a brown oil following work-up and solvent evaporation. Crystallisation (ethanol) yielded chalcone **44** (0.368 g, 19%). δ_H (400 MHz, $CDCl_3$) 1.26 (t, 3H, 7.5 Hz) 2.76 (q, 2H, 7.5 Hz) 3.92 (s, 6H) 5.10 (s, 2H) 6.88 (s, 2H) 6.94 (s, 1H) 7.28–7.42 (m, 4H) 7.48–7.50 (m, 2H) 7.85 (d, 1H, 15 Hz) 8.03 (s, 1H) 12.78 (s, 1H). δ_C (100 MHz, $CDCl_3$) 13.89, 30.25, 56.74, 75.53, 106.61, 113.24, 119.01, 119.54, 119.89, 128.41, 128.61, 128.86, 130.38, 133.16, 137.81, 140.31, 146.77, 152.75, 154.25, 163.24, 192.47. LRMS (EI): 496(+498) ($M^{+\cdot}$, 18%) 405(+407) ($[M-Bn]^+$, 35) 91.1 (Bn^+, 100). HRMS: calcd for $C_{26}H_{25}BrO_5$ 496.0855+498.0869 found, 496.0884+498.0863.

5.52. 3-Hydroxy-6-iodo-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-chromen-4-one 45

In the same way as for flavonol **17**, chalcone **43** (4.155 g, 8 mmol) gave flavonol **45** (2.106 g, 49%) as a grey solid following crystallisation in ethanol. δ_H (400 MHz, $CDCl_3$) 3.93 (s, 6H) 5.12 (s, 2H) 7.00 (br s, 1H) 7.25–7.38 (m, 5H) 7.49–7.51 (m, 3H) 7.95 (dd, 1H, 2.2 and 8.9 Hz) 8.58 (s, 1H). δ_C (100 MHz, $CDCl_3$) 56.73, 75.71, 105.92, 120.94, 123.00, 128.39, 128.65, 128.86, 134.89, 138.10, 142.43, 154.10, 155.02, 169.89. LRMS (EI): 530 ($M^{+\cdot}$, 31%) 439 ($[M-Bn]^+$, 35) 91 (Bn^+, 100). HRMS: calcd for $C_{24}H_{19}IO_6$ 530.0226 found, 530.0226.

5.53. 6-Bromo-7-ethyl-3-hydroxy-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-chromen-4-one 46

In the same way as for flavonol **17**, chalcone **44** (0.238 g, 0.5 mmol) gave flavonol **46** (97 mg, 40%) as a yellow solid following crystallisation in ethanol. δ_H (400 MHz, $CDCl_3$) 1.34 (t, 3H, 7.5 Hz) 2.90 (q, 2H, 7.5 Hz) 3.94 (s, 6H) 5.12 (s, 2H) 6.99 (s, 1H) 6.99 (s, 1H) 7.25–7.38 (m, 4H) 7.46–7.52 (m, 4H) 8.40 (s, 1H). δ_C (100 MHz, $CDCl_3$) 14.03, 30.23, 56.70, 75.47, 105.82, 118.60, 120.19, 120.92, 126.50, 128.36, 128.60, 129.08, 137.95, 138.52, 139.35, 145.20, 150.03, 153.88, 154.66, 172.32.

5.54. 3-Hydroxy-6-decyl-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-chromen-4-one 47

In the same way as for flavonoid **29d**, a solution of 1-decene (0.189 g, 1.3 mmol) and 9-BBN (1.4 mmol) in tetrahydrofuran (4.8 mL) was stirred for 8 h then **45** (0.501 g, 0.9 mmol) in tetrahydrofuran (5 mL), 3 M aqueous NaOH solution (1.26 mL) and dichloropalladium(dppf) (21 mg) were added and the mixture was heated to reflux for 15 h. After work-up the mixture was passed through a short plug of silica, eluting with ethyl acetate to give **47** (0.369 g, 72%) as a red oil. This was used in the next step.

5.55. 7-Ethyl-3-hydroxy-6-octyl-2-(4-benzyloxy-3,5-dimethoxy-phenyl)-chromen-4-one 48

In the same way as for flavonoid **29d**, a solution of 1-octene (32 mg, 0.3 mmol) and 9-BBN (0.3 mmol) in tetrahydrofuran (1.6 mL) was stirred for 7 h then **46** (0.102 g, 0.2 mmol) in tetrahydrofuran (4 mL), 3 M aqueous NaOH solution (0.2 mL) and dichloropalladium(dppf) (5 mg) were added and the mixture was heated to reflux for 15 h. After work-up, flavonoid **47** (0.369 g, 72%) was obtained as a red oil. This was used in the next step.

5.56. 3-Acetoxy-7-ethyl-6-octyl-2-(3,4,5-triacetoxy-phenyl)-chromen-4-one 50

In the same way as for **31d**, a solution of **48** (0.125 g, 0.2 mmol) and boron tribromide (1.2 mmol) in dichloromethane (11.2 mL) gave crude **8** (88 mg, 90%) as a green solid. A solution of crude **8** (88 mg, 0.2 mmol), *N*,*N*-dimethyl-4-aminopyridine (2 mg) and acetic anhydride (0.20 mL, 2 mmol) in pyridine (0.75 mL) was then stirred for 2 h to give **50** (25 mg, 20%) as a white solid after recrystallisation in methanol. δ_H (400 MHz, $CDCl_3$) 0.79–0.88 (m, 3H) 1.20–1.36 (m, 12H) 1.50–1.63 (m, 3H) 2.26 (s, 9H) 2.32 (s, 3H) 2.60–2.74 (m, 4H) 7.19 (s, 2H) 7.27 (s, 1H) 7.35 (s) 7.60 (s, 2H) 7.91 (s, 1H) 8.31 (s). δ_C (100 MHz, $CDCl_3$) 13.09, 13.44, 19.19, 19.50, 19.70, 21.65, 24.81, 28.22, 28.46, 28.63, 28.80, 29.74, 30.85, 31.11, 115.67, 119.86, 120.29, 124.21, 127.13, 132.95, 135.48, 137.90, 142.50, 149.08, 152.22, 153.18, 165.59, 166.51, 167.22, 170.98.

5.57. 2′-hydroxy-2-methoxy-4′-trifluoromethanesulfonyl-oxy-acetophenone 52

Resorcinol **51** (154.9 g, 1.40 mol), methoxyacetonitrile (50.0 g, 703.4 mmol) and dry diethyl ether (400 mL) where placed in a three necked flask containing freshly fused zinc chloride (19.16 g, 140.7 mmol) under argon. The solution was cooled to 0 °C and the argon inlet replaced with a calcium chloride drying tube. Dry hydrochloric acid was bubbled through the solution for 2 h. The resulting precipitate was filtered off and washed with ether (2×100 mL). The hydrochloride salt was dissolved in water (300 mL) and heated under reflux for 60 min. After cooling the resulting solid was filtered off and washed with water (2×100 mL) and dried by toluene azeotrope to give 2′-4′dihydroxy-2-methoxy-acetophenone as a white solid (62.04 g, 48%). Mp 108–110 °C. δ_H (400 MHz: DMSO-d_6): 3.35 (3H, s, OCH_3), 4.66 (2H, s, OCH_2), 6.29 (1H, d, *J* 2.3 Hz, H-3′), 6.36 (1H, dd, *J* 2.3 Hz and 8.8 Hz, H-5′), 7.68 (1H, d, *J* 8.8 Hz, H-6′), 10.59 (1H, s, OH), 11.92 (1H, s, OH). δ_C (100 MHz: DMSO-d_6): 58.89 (CH_3), 74.68 (CH_2), 102.80 (CH), 108.55 (CH), 111.99 (C), 132.26 (CH), 163.77 (C), 164.95 (C), 199.52 (C). *m*/*z* (EI): 182.1 (M^+, 10%), 137.0 (100). Found: 182.0581 $C_9H_{10}O_4$ requires (M^+) 182.0579. Found: C, 59.43%; H, 5.50%. $C_9H_{10}O_4$ requires C, 59.34%, H 5.53%. υ_{max} (golden gate)/cm^{-1}: 3361 (OH), 1633 (C=O). R_f silica EtOAc 0.56. Trifluoromethanesulfonic anhydride (25.5 mL, 155.21 mmol) was added slowly over 1 h to a solution of 2′-4′-dihydroxy-2-methoxy-acetophenone (25.68 g, 141.10 mmol) and 2,6-lutidine (18.0 mL, 155.21 mmol) in dry dichloromethane (450 mL) cooled to 0 °C and under an atmosphere of argon. After 1 h. the solution was diluted with dichloromethane (200 mL) and washed with 1 M hydrochloric acid (600 mL). The organic layer was re-extracted with dichloromethane (200 mL) and the combined organics washed with 1 M hydrochloric acid (600 mL). The organics were then dried over magnesium sulfate and concentrated under vacuum to give the triflate **52** as a purple oil suitably pure for the next step (38.84 g, 87%). The product was contaminated with ~5% ditriflate. δ_H (400 MHz: $CDCl_3$): 3.53 (3H, s, OCH_3), 4.68 (2H, s, CH_2), 6.84 (1H, dd, *J* 2.5 and 8.9 Hz, H-5′), 6.94 (1H, d, *J* 2.5 Hz, H-3′), 7.85 (1H, d, *J* 8.9 Hz, H-6′), 12.14 (1H, s, OH).

5.58. 2′-hydroxy-4′-decyl-2-methoxy-acetophenone 53

9-BBN (0.5 M solution in THF, 272.0 mL, 136 mmol) was added to decene (25.75 mL, 136 mmol) at rt under argon. The solution was then stirred at rt overnight. After this time, K_3PO_4 (39.48 g, 21.8 mmol), $Pd(Ph_3P)_4$ (2.54 g, 2.20 mmol, 1.8 mol %), KBr (16.19 g, 136 mmol) and degassed H_2O (2.5 mL, 136 mmol) were added followed by a solution of triflate **52** (38.84 g, 124 mmol) in dry degassed THF (100 mL). The reaction mixture was then heated to 65 °C under argon for 2 h. **Caution!**—The reaction mixture becomes exothermic once at 65 °C. A 2 L round-bottom flask was used to contain the large expansion of reaction contents, which also occurs. After cooling the solution was acidified to pH 1 and extracted into EtOAc (400 mL). The aqueous layer was re-extracted with EtOAc (200 mL) and the combined organics washed with H_2O (2×500 mL) and brine (500 mL). The organic layer was concentrated under vacuum. The resulting residue was dissolved in Et_2O (200 mL) and 4 M NaOH (100 mL). After stirring for 15 min. the solid was filtered off and washed with Et_2O (2×500 mL). The solid was then acidified with dilute hydrochloric acid and extracted into DCM (400 mL). The organic layer was dried over MgSO4 and concentrated under vacuum to give the acetophenone **53** as a black oil (28.71 g, 76%) suitably pure for the next step. Further purification of a small sample by column chromatography on silica eluting dichloromethane gave the acetophenone as a pale yellow solid. Mp <25 °C. δ_H (400 MHz: $CDCl_3$): 0.88 (3H, t, *J* 6.7 Hz, CH_2CH_3), 1.22–1.31 (14H, m, 7×CH_2), 1.57–1.65 (2H, m, $ArCH_2CH_2$), 2.61 (2H, t, *J* 7.5 Hz, $ArCH_2CH_2$), 3.53 (3H, s, OCH_3), 4.71 (2H, s, OCH_2), 6.73 (1H, dd, *J* 1.6 Hz and 8.2 Hz, H-5′), 6.83 (1H, d, *J* 1.4 Hz, H-3′), 7.58 (1H, d, *J* 8.0 Hz, H-6′), 11.98 (1H, s, OH). δ_C (100 MHz: $CDCl_3$): 14.05 (CH_3), 22.61 (CH_2), 29.16 (CH_2), 29.25 (CH_2), 29.37 (CH_2), 29.47 (CH_2), 29.53 (CH_2), 30.53 (CH_2), 31.83 (CH_2), 36.20 (CH_2), 59.48 (CH_3), 74.19 (CH_2), 115.48 (C), 117.93 (CH), 119.69 (CH), 128.53 (CH), 153.33 (C), 162.52 (C), 200.78 (C). *m*/*z* (EI): 306.1 ($M^{+\cdot}$, 10%), 261.1 (100), 147.0 (25), 45.0 (30). Found: 306.2194 $C_{19}H_{30}O_3$ requires (M^+) 306.2195. Found: C, 74.74; H, 10.03.

$C_{19}H_{30}O_3$ requires C, 74.47, H 9.87. υ_{max} (thin film)/cm^{-1}: 3039 (OH), 2925 (CH_2), 1648 (C=O). R_f (silica DCM) 0.26.

5.59. 4′-decyl-2-methoxy-2′-(2″, 4″,5″-trimethoxy-benzoyloxy)-acetophenone 54

EDCI (860 mg, 4.49 mmol) was added to a solution of phenol **53** (916 mg, 2.99 mmol), trimethoxybenzoic acid (634 mg, 2.99 mmol) and DMAP (36 mg, 0.30 mmol) in dry dichloromethane (10 mL) under argon at rt. The resulting solution was stirred overnight. The reaction mixture was then diluted with DCM (20 mL) and washed with brine (50 mL). The aqueous layer was re-extracted with DCM (20 mL) and the combined organics washed with brine (50 mL). The organic layer was then dried over magnesium sulfate and concentrated under vacuum. The resulting residue was purified by column chromatography (silica, EtOAc–hexane 2:1) to give the ester **54** as a pale yellow solid (1.01 g, 68%). Mp 80–81 °C. δ_H (400 MHz: $CDCl_3$): 0.88 (3H, t, *J* 6.8 Hz, CH_2CH_3), 1.26–1.31 (14H, m, 7×CH_2), 1.60–1.67 (2H, m, $ArCH_2CH_2$), 2.66 (2H, t, *J* 7.6 Hz, $ArCH_2CH_2$), 3.38 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.56 (2H, s, OCH_2), 6.58 (1H, s, H-3″), 7.08 (1H, d, *J* 1.2 Hz, H-3′), 7.15 (1H, dd, *J* 1.2 Hz and 8.0 Hz, H-5′), 7.65 (1H, s, H-6″), 7.80 (1H, d, *J* 8.0 Hz, H-6′). δ_C (100 MHz: $CDCl_3$): 14.05 (CH_3), 22.61 (CH_2), 29.21 (CH_2), 29.24 (CH_2), 29.36 (CH_2), 29.47 (CH_2), 29.53 (CH_2), 30.75 (CH_2), 31.82 (CH_2), 35.74 (CH_2), 56.09 (CH_3), 56.41 (CH_3), 56.81 (CH_3), 59.19 (CH_3), 77.18 (CH_2), 97.35 (CH), 108.85 (C), 114.77 (CH), 123.79 (CH), 125.97 (CH), 126.53 (C), 129.69 (CH), 142.71 (C), 149.79 (2×C), 154.69 (C), 156.79 (C), 163.39 (C), 196.20 (C). *m*/*z* (EI): 500.3 ($M^{+\cdot}$, 5%), 261.1 (10), 195.1 (100). Found: 500.2776 $C_{29}H_{40}O_7$ requires (M^+) 500.2774. υ_{max} (golden gate)/cm^{-1}: 2913 (CH_2), 1747 (CO_2), 1685 (C=O). R_f (silica, EtOAc–hexane 2:1) 0.31.

5.60. 1-(4′-decyl-2′-hydroxyphenyl)-2-methoxy-3-(2″,4″,5″-trimethoxyphenyl)-propan-1,3-dione 55

Lithium hexamethyldisilylazide (1.0 M solution in THF) (4.88 mL, 4.88 mmol) was added dropwise to a solution of ester **54** (814 mg, 1.63 mmol) in dry THF (6 mL) cooled to −20 °C and under argon. After 1 h. the reaction was quench with saturated $NaHCO_3$ solution (30 mL) and extracted in EtOAc (50 mL). The aqueous phase was re-extracted with EtOAc (20 mL) and the combined organics washed with brine (2×100 mL). The organic phase was then dried over magnesium sulfate and concentrated under vacuum to give the diketone **55** as an off white solid suitably pure for the next step (717 mg, 88%). Mp 99–101 °C. δ_H (400 MHz: $CDCl_3$): 0.88 (3H, t, *J* 6.8 Hz, CH_2CH_3), 1.26–1.31 (14H, m, 7×CH_2), 1.58–1.63 (2H, m, $ArCH_2CH_2$), 2.62 (2H, t, *J* 7.5 Hz, $ArCH_2CH_2$), 3.48 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 5.90 (1H, s, H-2), 6.37 (1H, s, H-3″), 6.80–6.82 (2H, m, H-3′ and H-5′), 7.62 (1H, s, H-6″), 7.78 (1H, d, *J* 8.1 Hz, H-6′), 11.65 (1H, s, OH). δ_C (100 MHz: $CDCl_3$): 14.09 (CH_3), 22.65 (CH_2), 29.23 (CH_2), 29.29 (CH_2), 29.42 (CH_2), 29.52 (CH_2), 29.57 (CH_2), 30.55 (CH_2), 31.87 (CH_2), 36.26 (CH_2), 55.29 (CH_3), 56.14 (CH_3), 56.24 (CH_3), 58.89 (CH_3), 86.83 (CH), 95.70 (CH), 112.08 (C), 116.31 (C), 116.47 (C), 117.83 (CH), 119.94 (CH), 130.45 (CH), 138.10 (C), 143.68 (C), 153.29 (C), 154.92 (C), 163.15 (C), 191.92 (C), 198.68 (C). *m*/*z* (EI): 500.3 ($M^{+\cdot}$, 1%), 261.1 (10), 195.1 (100). Found: 500.2775 $C_{29}H_{40}O_7$ requires (M^+) 500.2774. υ_{max} (golden gate)/cm^{-1}: 2915 (CH_2), 1664 (C=O), 1631 (C=O). R_f (silica, EtOAc–hexane 1:1) 0.41.

5.61. Synthesis of 3,2′,4′,5′-tetramethoxy-7-decyl-flavone 56

TMSOTf (0.245 mL, 1.35 mmol) was added slowly to a solution of diketone **55** (614 mg, 1.23 mmol) in dry DCM (4 mL) at rt under argon. The yellow solution was then stirred for 1 h and then quenched with saturated $NaHCO_3$ solution (30 mL) and extracted into DCM (20 mL). The aqueous layer was re-extracted with DCM (20 mL) and the combined organics washed with brine (50 mL). The organic layer was then dried over magnesium sulfate and concentrated under vacuum. The residue was purified by column chromatography on silica eluting EtOAc–hexane 1:1 to give the flavone **56** as a viscous yellow oil (409 mg, 69%). δ_H (400 MHz: $CDCl_3$): 0.88 (3H, t, *J* 6.8 Hz, CH_2CH_3), 1.24–1.32 (14H, m, 7×CH_2), 1.63–1.70 (2H, m, $ArCH_2CH_2$), 2.72 (2H, t, *J* 7.5 Hz, $ArCH_2CH_2$), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 6.64 (1H, s, H-3′), 7.00 (1H, s, H-6′), 7.21 (1H, dd, *J* 1.3 Hz and 8.2 Hz, H-6), 7.26 (1H, d, *J* 1.3 Hz, H-8), 8.18 (1H, d, *J* 8.2 Hz, H-5). δ_C (100 MHz: $CDCl_3$): 14.06 (CH_3), 22.63 (CH_2), 29.15 (CH_2), 29.26 (CH_2), 29.39 (CH_2), 29.49 (CH_2), 29.54 (CH_2), 30.87 (CH_2), 31.84 (CH_2), 35.98 (CH_2), 56.07 (CH_3), 56.56 (CH_3), 56.69 (CH_3), 60.28 (CH_3), 97.58 (CH), 111.42 (C), 113.62 (CH), 117.08 (CH), 122.29 (C), 125.39 (CH), 125.54 (CH), 141.73 (C), 142.93 (C), 149.39 (C), 151.68 (C), 152.38 (C), 155.41 (C), 155.86 (C), 174.75 (C). *m*/*z* (EI): 482.2 ($M^{+\cdot}$, 60%), 467.2 (75), 451.2 (100). Found: 482.2672 $C_{29}H_{38}O_6$ requires (M^+) 482.2668. υ_{max} (thin film)/cm^{-1}: 2927 (CH_2), 1644 (C=O). R_f (silica, EtOAc–hexane 1:1) 0.31.

5.62. 3′-Allyl-2′-hydroxy-acetophenone 58

To a stirring suspension of 2′-hydroxyacetophenone **57** (5 mL, 42 mmol) and potassium carbonate (6.516 g, 47 mmol) in acetone (30 mL) was added allyl bromide (4 mL, 46 mmol). The reaction was heated to reflux for 20 h. The reaction was then concentrated in vacuo, taken up in water and extracted into ethyl acetate (2x). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo to give an yellow oil. This was taken up in diethyl ether, washed with 1 M potassium hydroxide then dried ($MgSO_4$) and concentrated in vacuo to give 2′-allyloxy-acetophenone[34] (3.70 g, 51%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) 2.64 (s, 3H) 4.65 (td, 2H, 1.5 and 5.3 Hz) 5.32 (dt, 1H, 10.5 and 1.3 Hz)

5.44 (dt, 1H, 17 and 1.5 Hz) 6.04–6.14 (m, 1H) 6.93–7.02 (m, 2H) 7.44 (td, 1H, 7.3 and 1.9 Hz) 7.73 (dd, 1H, 7.7 and 1.8 Hz). δ_C (100 MHz, $CDCl_3$) 32.38, 69.78, 113.15, 118.58, 121.17, 130.81, 133.02, 133.90, 158.29, 200.32. LRMS (EI): 176 ($M^{+\cdot}$, 21%) 161 ($[M-Me]^+$, 40%) 121 ($[M-(Me \text{ and } CH_2CCH_2)]^+$). HRMS: calcd for $C_{11}H_{12}O_2$ 176.0837 found, 176.0838. ^1H and ^{13}C NMR in good agreement with literature.[34] 2′-allyloxy-acetophenone (2.518 g, 14 mmol) was heated to 200 °C for 44 h to give **58** (2.518 g, 100%).[51] Alternatively, 2′-allyloxy-acetophenone (5.959 g, 34 mmol) was irradiated in a microwave set to 230 W and 210 °C for 1 h with simultaneous air cooling to give **58** (5.959 g, 100%). δ_H (400 MHz, $CDCl_3$) 2.63 (s, 3H) 3.43 (d, 2H, 6.6 Hz) 5.06–5.11 (m, 1H) 5.95–6.06 (m, 1H) 6.85 (t, 1H, 7.7 Hz) 7.36 (d, 1H, 7.2 Hz) 7.62 (dd, 1H, 1.4 and 8 Hz). δ_C (100 MHz, $CDCl_3$) 27.17, 33.80, 116.39, 118.81, 119.63, 129.20, 129.79, 136.49, 136.87, 160.81, 205.15. LRMS (EI): 176 ($M^{+\cdot}$, 90%) 161.1 ($[M-Me]^+$, 100). HRMS: calcd for $C_{11}H_{12}O_2$ 176.0837 found, 176.0837.

5.63. 1-(2-Hydroxy-3-allyl-phenyl)-3-(2,4,5-trimethoxy-phenyl)-propenone 60

To a stirring suspension of **58** (1.779 g, 27 mmol) and 2,4,5-trimethoxy-benzaldehyde **59** (5.89 g, 30 mmol) in ethanol (50 mL) was added potassium hydroxide (3.23 g, 58 mmol). The reaction mixture was stirred for 191 h then acidified (2 M HCl) and extracted with ethyl acetate (3x). The combined organic layers were then washed with water and brine then dried ($MgSO_4$) and concentrated in vacuo to give **60** (11.165 g, 116%) as an orange solid. δ_H (400 MHz, $CDCl_3$) 3.47 (d, 2H, 6.6 Hz) 3.92 (s, 3H) 3.94 (s, 3H) 3.96 (s, 3H) 5.08–5.14 (m, 2H) 5.99–6.10 (m, 1H) 6.53 (s, 1H) 6.88 (t, 1H, 7.7 Hz) 7.13 (s, 1H) 7.36 (d, 1H, 6.5 Hz) 7.63 (d, 1H, 15.5 Hz) 7.82 (dd, 1H, 1.4 and 8.1 Hz) 8.21 (d, 1H, 15.5 Hz) 13.43 (s, 1H). δ_C (100 MHz, $CDCl_3$) 33.94, 56.49, 56.73, 57.08, 97.12, 112.20, 115.69, 116.31, 118.49, 118.57, 120.19, 128.04, 129.80, 136.29, 136.68, 138.51, 141.12, 143.71, 153.33, 155.46, 161.97, 194.66. LRMS (EI): 354 ($M^{+\cdot}$, 69%) 323 ($[M-OMe]^+$, 100). HRMS: calcd for $C_{21}H_{22}O_5$ 354.1467 found, 354.1468.

5.64. 8-Allyl-3-hydroxy-2-(2,4,5-trimethoxy-phenyl)-chromen-4-one 61

To a stirring solution of **60** (11.15 g, 31 mmol) in methanol (300 mL) and 16% aqueous sodium hydroxide solution (37 mL, 148 mmol) at 0 °C was added 15% aqueous hydrogen peroxide (37 mL, 163 mmol) dropwise. The solution was stirred at 0 °C for ten min then sealed and placed in a refrigerator for 23 h. The reaction was then acidified (2 M HCl) and extracted into chloroform (3x). The organic layer was then washed with brine, dried ($MgSO_4$) and concentrated to give an orange solid. This was taken up in methanol (300 mL) and 16% aqueous sodium hydroxide solution (37 mL, 148 mmol) at 0 °C, then 15% aqueous hydrogen peroxide (37 mL, 163 mmol) was added and the solution stirred at 0 °C for the 5 min then sealed and place in a refrigerator for 18 h. The reaction was then acidified (2 M HCl) and extracted into dichloromethane (3x). The organic layer was then dried ($MgSO_4$) and concentrated to give an orange solid. Recrystallisation (ethanol) yielded **61** (4.815 g, 42%) as a yellow solid. δ_H (400 MHz, $CDCl_3$) 3.66 (d, 2H, 6.5 Hz) 3.89 (s, 6H) 3.98 (s, 3H) 5.07–5.12 (m, 2H) 6.00–6.11 (m, 1H) 6.53 (br s, 1H) 6.67 (s, 1H) 7.19 (s, 1H) 7.34 (t, 1H, 7.7 Hz) 7.53 (dd, 1H, 1.4 and 7.1 Hz) 8.15 (dd, 1H, 1.6 and 8.0 Hz). δ_C (100 MHz, $CDCl_3$) 34.15, 56.51, 56.94, 57.14, 98.19, 111.37, 114.00, 116.98, 121.74, 124.05, 124.50, 130.13, 133.72, 135.97, 138.75, 143.49, 145.88, 152.32, 152.94, 154.26, 173.76. LRMS (EI): 368 ($M^{+\cdot}$, 100%). HRMS: calcd for $C_{21}H_{20}O_6$ 368.1260 found, 368.1259.

5.65. 3-Hydroxy-8-non-2-enyl-2-(2,4,5-trimethoxy-phenyl)-chromen-4-one 62

A mixture of 1-octene (7.15 g, 64 mmol) and Grubbs' catalyst (30 mg, 0.04 mmol, 0.06 mol%) was stirred under a static vacuum for 15 h, then passed through a plug of silica eluting with hexane. Concentration gave tetradec-7-ene (4.982 g, 80%) as a colourless liquid.[52] δ_H (400 MHz, $CDCl_3$) 0.86–0.90 (m, 6H) 1.21–1.41 (m, 16H) 1.94–2.04 (m, 4H) 5.31–5.43 (m, 2H). δ_C (100 MHz, $CDCl_3$) 14.48, 23.04, 27.60, 29.23, 29.38, 30.02, 30.13, 32.15, 32.17, 33.00, 130.28, 130.75. LRMS (EI): 196 ($M^{+\cdot}$, 9%), 84 (100). HRMS: calcd for $C_{14}H_{28}$ 196.2191 Found, 196.2191. To a stirring solution of tetradec-7-ene (0.539 g, 2.75 mmol) and Grubbs' catalyst (29 mg, 0.04 mmol, 3 mol%) in dichloromethane (13.5 mL) under argon was added **61** (0.479 g, 1.3 mmol). The reaction was heated to reflux for 5.5 h then concentrated in vacuo to give a brown solid. Recrystallisation (ethanol) yielded **62** (0.258 g, 26%) as a lilac solid, which was used for the next step.

5.66. 3-Hydroxy-8-nonyl-2-(2,4,5-trimethoxy-phenyl)-chromen-4-one 63

A stirring suspension of **62** (0.258 g, 0.6 mmol) and 10% palladium on carbon (24 mg) in ethyl acetate (30 mL) was placed under an atmosphere of hydrogen for 43 h. The reaction was filtered through celite, the residue washed with ethyl acetate and the combined filtrates concentrated in vacuo to give a grey solid. Recrystallisation (petrol–ethyl acetate 2:1) yielded **63** (0.212g, 82%) as an off-white solid. δ_H (400 MHz, $CDCl_3$) 0.87 (t, 3H, 6.7 Hz) 1.18–1.39 (m, 12H) 1.68–1.72 (m, 2H) 2.88 (t, 2H, 7.6 Hz) 3.88 (s, 3H) 3.89 (s, 3H) 3.98 (s, 3H) 6.53 (br s, 1H) 6.67 (s, 1H) 7.18 (s, 1H) 7.32 (t, 1H, 7.7 Hz) 7.50 (d, 1H, 6.2 Hz) 8.12 (d, 1H, 6.6 Hz).

5.67. 3-Acetoxy-8-nonyl-2-(2,4,5-triacetoxy-phenyl)-chromen-4-one 64

In the same way as for **31d**, a solution of **63** one (0.209 g, 0.5 mmol) and boron tribromide (2.3 mmol) in dichloromethane (17.3 mL) gave crude **11** (0.203 g, 107 %) as a brown solid. A solution of crude **11** (0.203 g, 0.5 mmol), *N*,*N*-dimethyl-4-aminopyridine (3 mg) and acetic anhydride (0.30 mL, 3 mmol) in pyridine (2.5 mL) was then

stirred for 22 h to give **64** (0.109 g, 38%) as a brown oil. This was used without further purification.

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