

Modular Approach for the Synthesis and Bioactivity Profiling of 8,8'-Biflavones

Moritz K. T. Klischan, Flaminia Mazzone,[#] Lena Berning,[#] Julian Greb,[#] Max Schlamkow, Mona Haase, Wolfgang Frey, Björn Stork, Klaus Pfeffer, and Jörg Pietruszka*



Cite This: *ACS Omega* 2023, 8, 41816–41834



Read Online

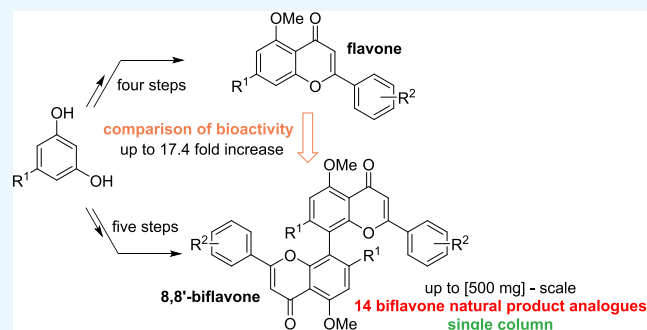
ACCESS |

Metrics & More

Article Recommendations

Supporting Information

ABSTRACT: In this work, we report the scalable and modular synthesis of a library of 55 monomeric and dimeric flavonoids including 14 8,8'-biflavones. The sterically demanding tetra-*ortho*-substituted axis of an acetophenone dimer key intermediate was constructed in a regioselective manner using Fe-mediated oxidative coupling. This step was systematically optimized and performed on up to multigram scale. The biological activities of this compound library were evaluated, including cytotoxicity against healthy and malignant human cell lines, antimicrobial activity against the apicomplexan parasite *Toxoplasma gondii*, and antioxidant capacity. A marked increase in activity for the 8,8'-dimeric structures compared to that of their monomeric counterparts was observed. Several biflavones were identified with high selectivity indices (low cytotoxicity and high antiprotazoal activity), showing that this class of natural products may serve as lead structures for further investigations.



INTRODUCTION

Biflavones are naturally occurring biaryl-based compounds present among a range of gymnosperms.^{1–4} First isolated in 1966 from *Cupressus torulosa* where its name is derived from,¹ the naturally occurring 8,8'-biflavone cupressuflavone (CUF) was subsequently also isolated from plants of the genus *Araucaria cunninghamii*.⁵ So far, very few structural modifications with the exception of glycosylations have been observed in nature.⁶ While biological activities of non-*C*₂-symmetrical biflavones are reported comprehensively in the literature (Figure 1A),^{7–13} 8,8'-biflavones are a more elusive subclass of flavonoid natural products. CUF has thus far only been investigated in some limited capacity regarding pharmacological effects.^{14–19}

In many cases, dimeric natural products show higher activities than their monomeric counterparts.^{20–22} Apigenin—the monomeric unit of CUF—exerts similar activities in some cases;¹⁹ in others, they are exclusively found for CUF,²³ highlighting the importance of comparing the activity of dimers to monomers. Additionally, 8,8'-biflavones can also, in some cases, be thought of as structurally simplified analogues of polyketides such as gonytolid A as was proposed and successfully shown by Kikuchi et al. in their synthesis of Me,Me'-CUF (Figure 1B).²⁴ This exemplifies a key strategy in the natural product-inspired drug design by simplifying complex natural structures to leverage the ease of synthesis but retain bioactivity.²⁵ Further, the merging of spherical shapes of *ortho*-substituted-biaryl-based natural products²⁶

with a biologically relevant flavone scaffold²⁷ qualifies this compound class as potent drug candidates.

Total syntheses of CUF are established since the late 1960s via different methods.^{28–34} However, only singular examples of 8,8'-biflavones were synthesized to this date, showing the lack of a systematic and diversity-oriented approach (Figure 1B). The construction of these sterically demanding tetra-*ortho*-substituted biaryls poses a synthetic challenge.^{35,36} Syntheses of these biaryl-based natural products often suffer from a narrow substrate scope involving the coupling of highly functionalized monomers^{37,38} or involve multistep functionalization or coupling under harsh reaction conditions.^{39–42} We herein report the first modular synthesis of a dedicated library of 8,8'-biflavones (Figure 1C) and the systematic investigation of their biological activity.

RESULTS AND DISCUSSION

To ensure scalability, which is highly desirable in natural product synthesis,⁴³ a synthesis route was chosen that allowed for the diversification of target structures and isolation by recrystallization. We chose the protocol developed by Li et al.

Received: August 30, 2023

Revised: September 20, 2023

Accepted: September 25, 2023

Published: October 27, 2023



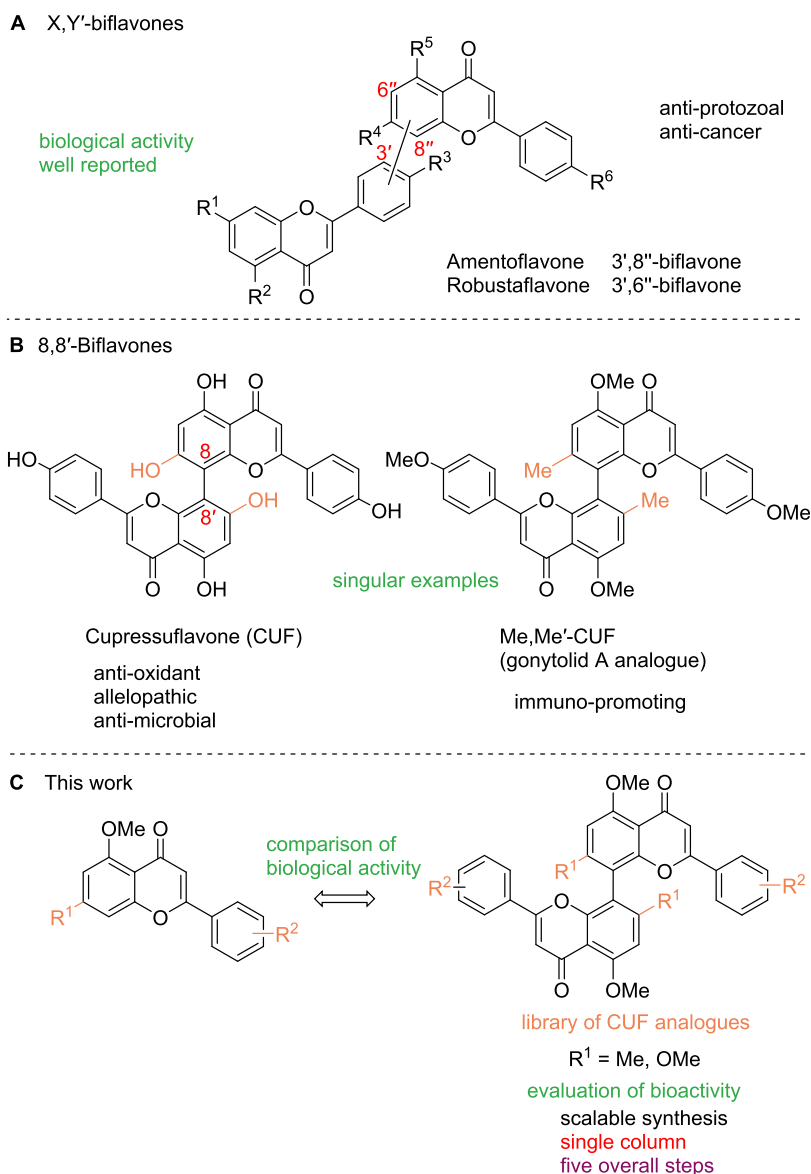


Figure 1. Biflavones as bioactive natural products with 8,8'-biflavones as a subclass.

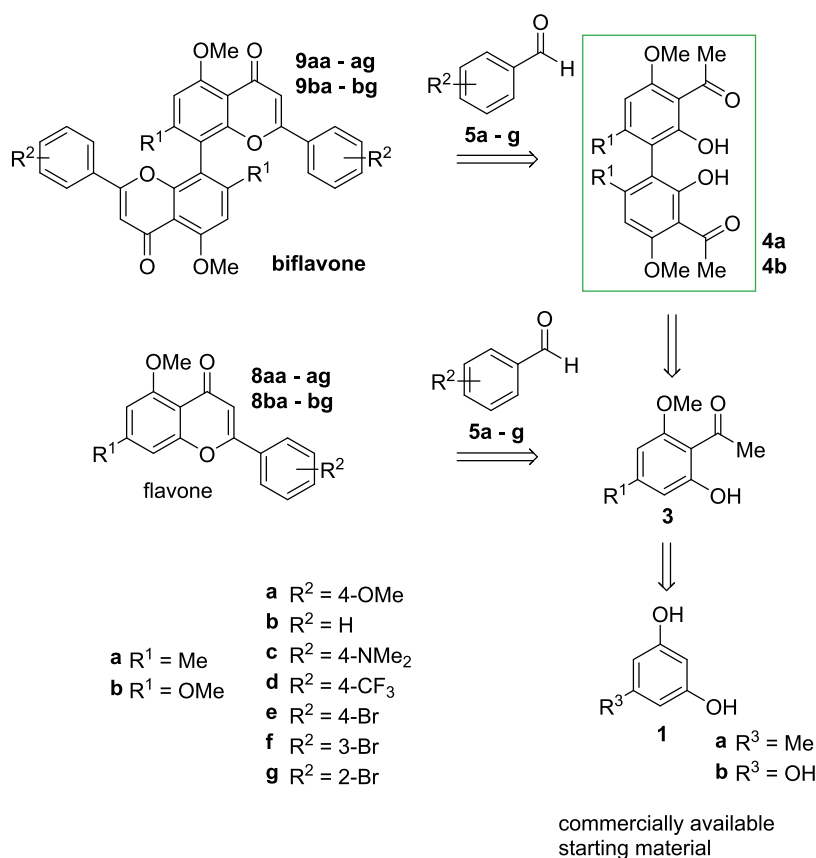
as the basis for our investigations.³⁰ Starting from commercially available phenols **1a** and **1b**, all monomeric and dimeric target compounds should be accessible. After acylation to acetophenones **2**, the key intermediates **3** and **4** should be accessible: while acetophenones **3a** and **3b** will be available based on the modified literature-known procedures (Scheme 1),^{30,44,45} the acetophenone dimers **4a** and **4b** were to be synthesized by the oxidative coupling without the involvement of toxicologically relevant transition metals. Finally, the Claisen–Schmidt condensation using aldehydes **5** provides chalcones **6** and bichalcones **7**. Subsequent I₂-catalyzed oxidation to synthesize flavones **8** and biflavones **9** was to be conducted. A variety of aldehydes were chosen to obtain the natural substitution pattern of CUF in addition to various more electron-rich and electron-deficient 8,8'-biflavones. Overall, a multigram scale synthesis route for the key intermediates **4** is outlined that avoids the use of column purification.

We initiated our studies with the synthesis of the acetophenone starting materials **3a** and **3b**, employed for

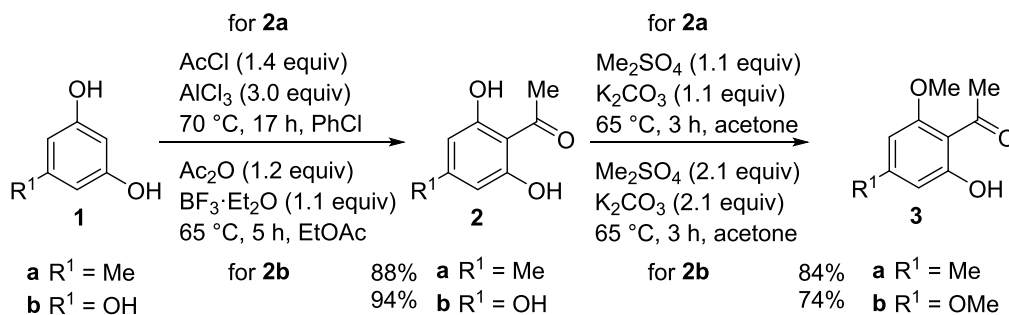
both the oxidative coupling and the synthesis of the monomers. Acetylation and subsequent selective monomethylation of commercially available phenols **1a** and **1b** proceeded smoothly on decagram-scale, with yields of 74% (**3a**) and 70% (**3b**) over two steps, respectively (Scheme 2).

Starting from acetophenones **3a** and **3b**, the corresponding chalcone monomers **6** were synthesized via the typical Claisen–Schmidt condensations under alkaline conditions in ethanol with seven different benzaldehyde derivatives **5a–g** (Scheme 2). In some cases, conversions were incomplete. This was mitigated by the addition of an additional 0.6 equiv of the corresponding aldehyde after 6 h, which led to full conversion overnight. With the synthesis of the chalcones **6** in place, we continued with the synthesis of the target flavone monomers **8**. Following literature-known conditions, the oxidative cyclization using catalytic amounts of I₂ in DMSO proceeded smoothly.⁴⁶ All flavones were obtained in yields ranging from 36 to 93%. Thus, starting from phenols **1a** and **1b**, the procedure yielded 14 monomeric flavones **8aa–g** and **8ba–g**

Scheme 1. Retrosynthesis of Flavones and Biflavones Starting from Commercially Available Phenols 1 via the Key Intermediates 4



Scheme 2. Synthesis of Acetophenones 3a and 3b via Acetylation and Subsequent Methylation

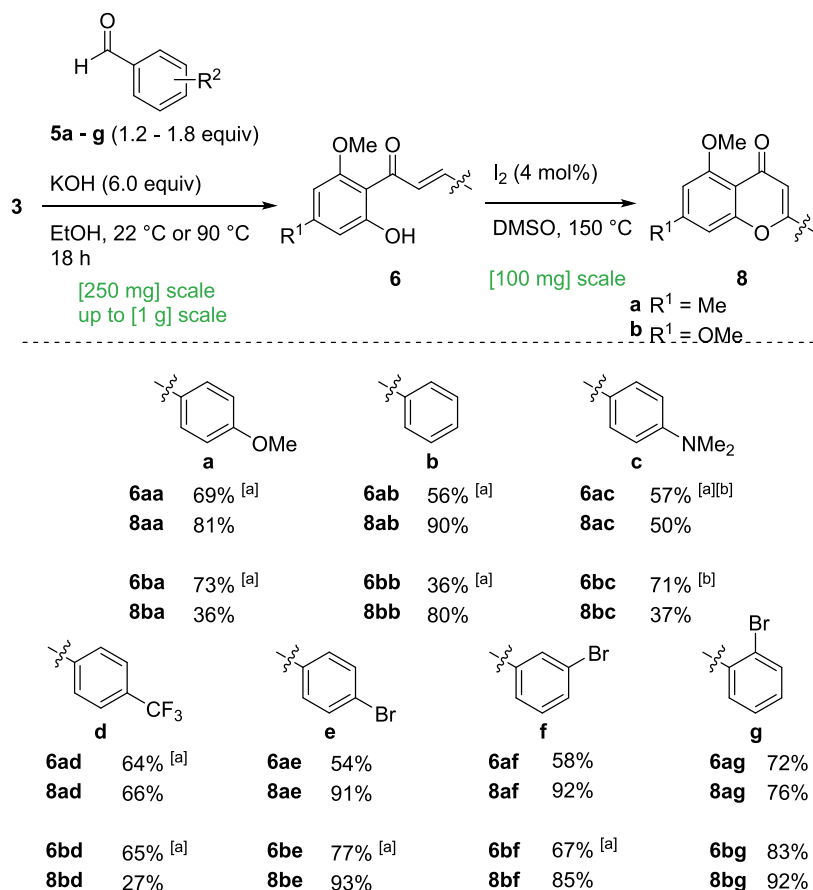


in four steps, requiring only a single column chromatographic purification step each (Scheme 3).

With a satisfactory synthesis of the monomeric flavones 8 in place, we directed our efforts toward the synthesis of acetophenone dimers 4a and 4b to ultimately provide the target biflavones 9. The oxidative coupling of naphthol using FeCl_3 to form BINOL is known since the 1870s⁴⁷ and was later improved upon by solid-phase synthesis.⁴⁸ The first application of FeCl_3 on silica ($\text{FeCl}_3/\text{SiO}_2$) was the elimination of water from alcohols.⁴⁹ Jemphy et al. conducted the first oxidative coupling of arenes using $\text{FeCl}_3/\text{SiO}_2$.⁵⁰ In their total synthesis, Li et al. used silica-bound FeCl_3 to synthesize hexamethyl-CUF,³⁰ in addition to the application of this method in the subsequent total syntheses of a variety of natural products.^{24,40,51,52} While naphthol is well-known to form radicals in the *ortho* position to the hydroxy-group in the presence of oxidative transition metals,⁴⁸ phenols tend to form

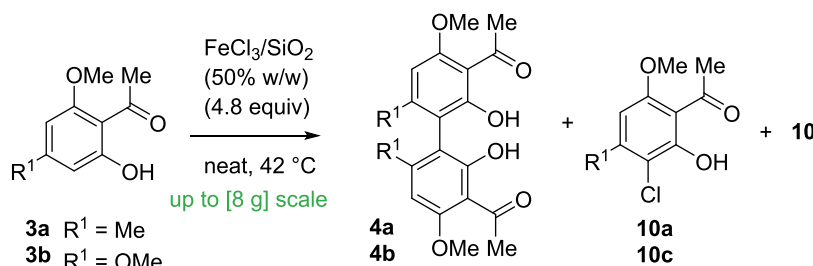
less localized radicals. The regioselectivity of Fe-based oxidative homocouplings has to the best of our knowledge hardly been investigated.^{53–58}

We next directed our efforts toward the oxidative coupling of acetophenone 3a. A variety of recent catalytic methods were evaluated for the synthesis of 4a and 4b (Table S7). After extensive efforts, we concluded that the use of stoichiometric amounts of oxidant is crucial for the conversion of 2'-hydroxy acetophenones 3a and 3b. As such, the use of classic oxidative systems such as $\text{FeCl}_3/\text{SiO}_2$ as was shown by Li et al. seemed more promising.³⁰ $\text{FeCl}_3/\text{SiO}_2$ was prepared using Et_2O as a solvent at 40 °C. When conducting solid-phase oxidative couplings using $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ on SiO_2 (50% w/w), we observed the formation of small amounts of product 4a. However, we also noted a major side product that was subsequently identified as chlorinated acetophenone 10a among other minor chlorinated side products 10. This regioselective

Scheme 3. Synthesis of Flavones 8^a

^aYields of isolated products; [a] with 1.8 equiv of aldehyde **5** and [b] at 90 °C.

Table 1. Oxidative Coupling of Acetophenones **3a and **3b** by Solid-Phase Synthesis, with the Main Side Product **10a** Formation under Varying Conditions for the Preparation of FeCl₃/SiO₂**

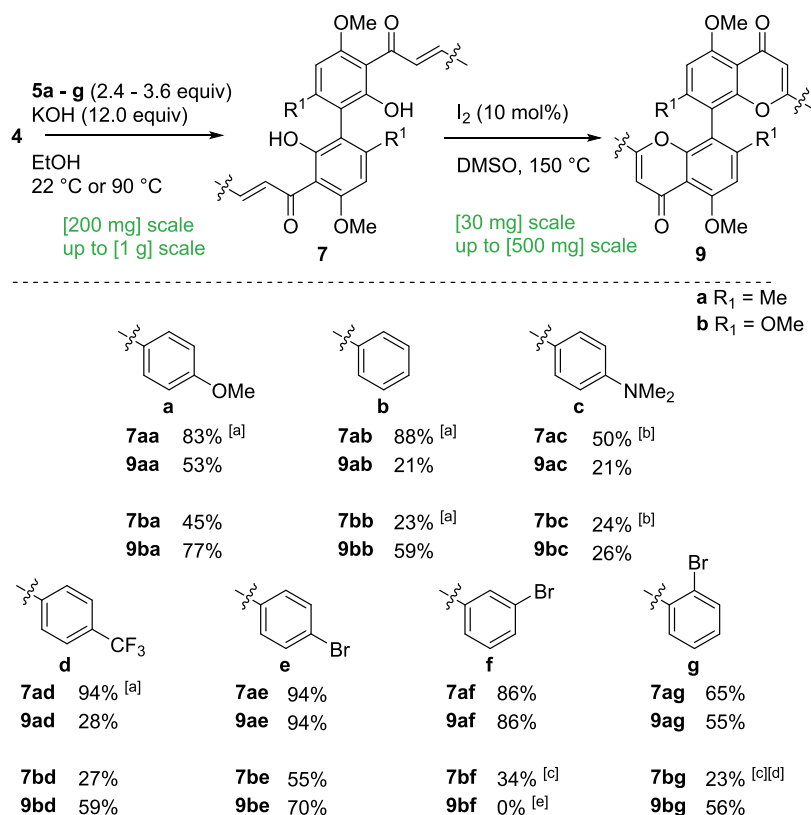


entry	4	FeCl ₃ /SiO ₂	conversion ^a [%]	10a/c [%]	yield ^b [%]
1	4a	I	21	45	
2	4a	II	6	94	
3	4a	III	76	18	39
4	4a	IV	50	7	23
5	4a	V	51	43	
6 ^c	4a	III	88	9	58
7 ^c	4b	I	81	4	52

^aConversion to main product **4a/4b** relative to **10** and **3** according to ¹H NMR. ^bIsolated yield. ^cg scale, improved workup; I: FeCl₃/SiO₂ prepared at 40 °C in Et₂O using FeCl₃·6H₂O; II: FeCl₃/SiO₂ prepared at 40 °C in Et₂O/MeOH (9:1) using FeCl₃·6H₂O; III: FeCl₃/SiO₂ prepared at 40 °C, then 60 °C in anhydr. Et₂O/MeOH (9:1) using FeCl₃; IV: FeCl₃/SiO₂ prepared at 40 °C, then 60 °C in (nonanhydr.) Et₂O/MeOH (9:1) using FeCl₃; V: FeCl₃/SiO₂ prepared at 40 °C, then 60 °C in anhydr. Et₂O/MeOH (9:1) using newly purchased FeCl₃·6H₂O (refer to Supporting Information Table S4).

formation of the chlorinated side product has already been reported in the literature.³⁰

To address this lack of chemoselectivity, we first conducted a full factorial screening⁵⁹ regarding the %weight/weight (%w/w) composition of FeCl₃/SiO₂, equivalents, and reaction time

Scheme 4. Synthesis of a Library of Bichalcones **8** and Biflavones **9**^a

^aYields of isolated products: [a] with 3.6 equiv of aldehyde **5**; [b] at 90 °C; [c] presumed mixture of chalcone and flavanones and monoaddition product; [d] 1 h reaction time; and [e] complex mixture according to ¹H NMR.

(Table S5). More equivalents of FeCl₃·6H₂O gave a higher conversion of acetophenone **3a**. A higher %w/w FeCl₃·6H₂O/SiO₂ resulted not only in an increase in the conversion of **3a** but also in a significant increase in the side product formation **10a**. A longer reaction time resulted in a higher conversion of acetophenone **3a** but an increase in the chlorinated side product formation **10a** (Table S6).

With these assessments in place, we resumed our preparative screening efforts. The use of methanol as a cosolvent during the FeCl₃/SiO₂ preparation did not increase selectivity (procedure II, Table 1 entry 2). To our delight, the use of anhydrous FeCl₃ instead of FeCl₃·6H₂O in combination with anhydrous solvents resulted in the formation of less chlorinated side product (preparation III, Table 1 entry 3). The use of anhydrous solvents and by effect the method of FeCl₃/SiO₂ preparation proved crucial in increasing the selectivity as the use of nonanhydrous solvents gave lower selectivity (preparation IV, Table 1 entry 4). Again, we observed an increase in the formation of side product **10a** over time. FeCl₃ may deteriorate over time, and thus a fast reaction may be beneficial for the selective conversion of the starting material. We also considered that the exposure to moisture might have deteriorated the FeCl₃·6H₂O. FeCl₃/SiO₂ prepared under otherwise anhydrous conditions using the newly purchased FeCl₃·6H₂O gave better conversion and selectivity (procedure V, Table 1 entry 4) albeit still with significant side product formation. Ultimately, 4.8 equiv of anhydrous FeCl₃ with 50% w/w of SiO₂ in combination with anhydrous solvents resulted in the most selective conversion to acetophenone dimer **4a** in 2.5 h with a conversion of >95% (according to ¹H

NMR) and an isolated yield of 58%. We obtained the complementary acetophenone dimer **4b** in a yield of 52% on a scale of 8 g, further underlining the utility of this reaction. We attribute the remaining mass balance to polymerization side products. This is in accordance with the previous observation of a fast reaction being more selective, whereas a long reaction time resulted in complex reaction mixtures and low yields. With the optimized protocol established, the sterically demanding products could be obtained without protecting groups and without selective functionalization of the monomeric acetophenones **3**. We were able to adapt the protocol by Li et al.³⁰ to synthesize acetophenone **4a** via this route and synthesize **4b** accordingly, lowering the literature-reported reaction time significantly. The X-ray structure of the acetophenone dimer **4a** supports the regioselectivity of the coupling in addition to the NMR 2D data (Figure 1 and Figures S71–S73).

With a scalable and robust synthesis of the acetophenone dimers in hand, we commenced the synthesis of the biflavone library (Scheme 4). It is noteworthy that again for some reactions, under the appropriately modified conditions of the chalcone **6** synthesis, the addition of a further 1.2 equiv of aldehyde after 6 h gave full conversion of acetophenone **4** (2.4–3.6 equiv aldehyde **5** in total). The use of an ionic liquid as a solvent to address low solubility gave chalcone dimer **7ac** in comparable yield but appeared less generally applicable (Table S7). During the reaction, a complex mixture of side products and intermediates could form and as such the isolation of these highly insoluble compounds proved difficult. However, scaleup and purification by recrystallization gave

chalcone dimers **7** in acceptable yield and purity. Only for **7bf** and **7bg**, the isolation of bichalcone in acceptable purity proved to not be possible. These compounds were obtained as a mixture of bichalcone and flavanone side products and significant amounts of an additional side product, presumably the monoaddition product.

With a scalable synthesis of bichalcones **7** with yields of up to 94% on a 0.2–1 g scale established, we proceeded with the synthesis of biflavones **9**. Modified conditions of the monomer synthesis were successfully transferred to the chalcone dimers. Only biflavone **9bf** was not obtained under the given conditions attributed to the difficulty in isolation of chalcone **7bf** in sufficient purity. Overall, we were able to obtain a library of 13 8,8'-biflavones with up to 38% yield (**9ae**) over five steps in a scalable fashion on up to 500 mg scale in the final step, with only a single column chromatographic purification over the full synthesis route.

BIOLOGICAL DATA

With a dedicated library at hand, we initiated the biological evaluation of flavones and biflavones (Figure 2). Bioactivity

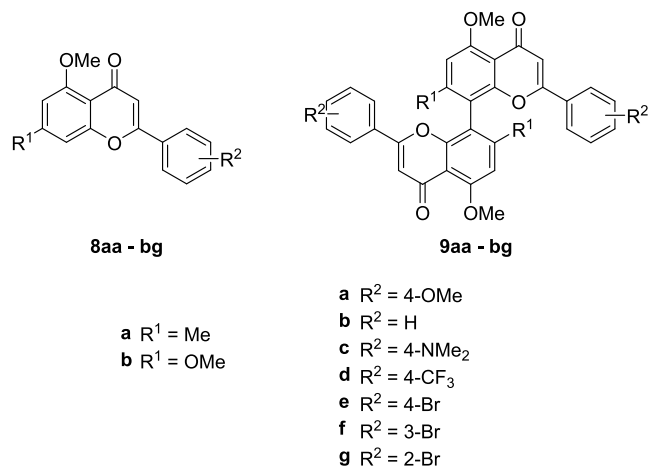


Figure 2. Structure of flavones **8** and biflavones **9** and the associated library evaluated regarding their bioactivity against *T. gondii* proliferation and against human cell lines.

assays against *Toxoplasma gondii* (*T. gondii*) proliferation and the viability of healthy and malignant human cell lines were performed. Overall, this allowed for a systematic comparison of the natural product 8,8'-biflavone analogues **9** with the corresponding monomers **8**.

T. gondii, the causative agent of toxoplasmosis, is an obligate intracellular protozoan parasite member of the phylum Apicomplexa.⁶⁰ It is referred to as one of the most successful parasites due to its ability to infect and persist in virtually all warm-blooded animals as intermediate hosts, including humans.⁶¹ According to the World Health Organization (WHO), it is estimated that up to a third of the world's human population is infected with this parasite.⁶² This unmet medical need has yet to be resolved. As biflavones such as the structurally related 3',8''-biflavone amentoflavone are known to exert activity against kinetoplastid parasites, we wished to investigate the activity of our compound library (Table 2 and Figure 3).¹³

First, the cytotoxicity of this compound library was assessed by in vitro screening against Hs27 fibroblasts used as hosts in

Table 2. IC₅₀ (HeLa), IC₅₀ (*T. gondii*), and IC₅₀ (Hs27) and Selectivity Index (SI) of Flavones (**8**) and Biflavones (**9**) against *T. gondii* Proliferation^a

	IC ₅₀ (HeLa) [μM]	IC ₅₀ (<i>T. gondii</i>) [μM]	IC ₅₀ (Hs27) [μM]	SI ^[a]
8aa	28.4	13.7	>200	>14.6
8ab	82.5	6.68	>200	>29.9
8ac	24.2	7.98	140.6	19.1
8ad	>100	> 50	>200	-
8ae	>100	2.33	>200	>85.6
8af	32.9	4.09	104.0	25.4
8ag	76.3	7.46	130.0	17.4
8ba	33	4.86	>200	>41.1
8bb	73.7	4.61	>200	>43.3
8bc	55.7	22.9	>200	>8.7
8bd	>100	4.03	>200	>49.5
8be	85.8	3.44	>200	>58.0
8bf	72	8.10	128.1	15.6
8bg	>100	6.02	>200	>33.2
9aa	41.4	3.20	>200	>62.5
9ab	11.8	5.12	>200	> 39.0
9ac	1.4	1.58	179.9	113.4
9ad	>100	10.4	>200	>19.2
9ae	35.8	2.21	>200	>90.4
9af	>100	12.3	>200	> 16.2
9ag	18.5	39.6	>200	> 5.0
9ba	39.5	3.33	>200	>59.9
9bb	22.1	2.28	>200	>87.5
9bc	43.8	12.3	>200	>16.3
9bd	>100	4.16	>200	>48.0
9be	96.1	2.29	>200	>87.1
9bf	N/A	-	-	-
9bg	10.4	11.4	>200	>17.6

^aSI ≥ 50 (Highlighted in Gray). [a] SI = (IC₅₀ (Hs27))/(IC₅₀ (*T. gondii*)). For Confidence Intervals of IC₅₀, refer to Tables S1 and S2

the *T. gondii* proliferation assay. Comparison of the activities against *T. gondii* proliferation revealed that in many cases biflavones **9** exerted higher bioactivity (lower IC₅₀) than their respective flavone counterpart **8** (Table 2). Overall, biflavone **9ac** was the most active compound regarding the inhibition of *T. gondii* proliferation with an IC₅₀ of 1.6 μM. By dividing the cytotoxicity (IC₅₀ (Hs27) value against fibroblasts; Table S1) by the IC₅₀ (*T. gondii*) value (*T. gondii* proliferation inhibition), we obtained the selectivity index (SI) for each tested compound, giving us a measure of the therapeutic potential (Table 2). Of the seven compounds with the highest SI, six are biflavones, one of which is hexa-O-methyl-CUF (**9ba**). Five of these most active non-natural analogues have higher SIs than hexa-O-methyl-CUF (**9ba**).

Next, the cytotoxicity toward malignant human cells [HeLa cells (IC₅₀ (HeLa))] was assessed (Table 2). Broadly speaking, biflavones **9** again display higher activities compared to flavones **8**, the most active compound again being biflavone **9ac**. Compounds with 4-CF₃ substituents **8ad**, **8bd**, **9ad**, and **9bd** appeared to be noncytotoxic against either human cell line while exhibiting moderate to good activity against *T. gondii* proliferation. 4-NMe₂-substituted biflavone **9ac** exerted the highest bioactivity (IC₅₀ (HeLa) = 1.4 μM and IC₅₀ (*T. gondii*) =

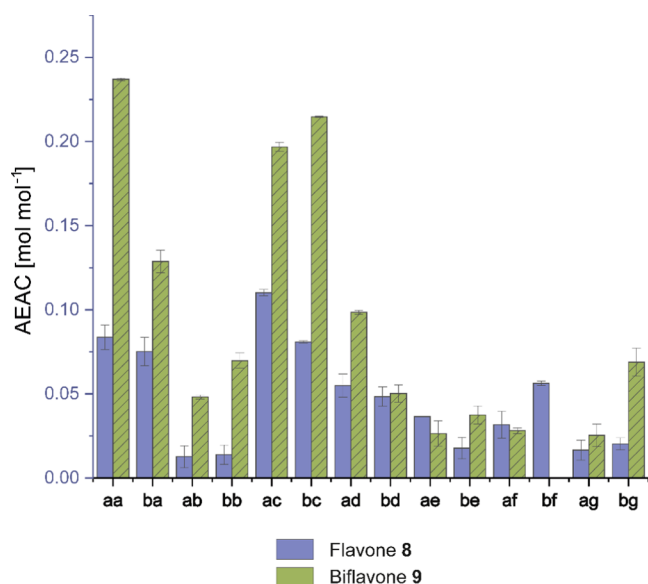


Figure 3. Ascorbic acid equivalent antioxidant capacity (AEAC) of flavones **8** and biflavones **9** relative to ascorbic acid (mol mol^{-1}) determined by the ABTS decolorization assay with standard deviation.⁶³ For absolute values, refer to Table S3.

1.58 μM) as well as the highest SI (113.4) of all tested compounds (Figure 4). Additionally, biflavone **9be** exerts high

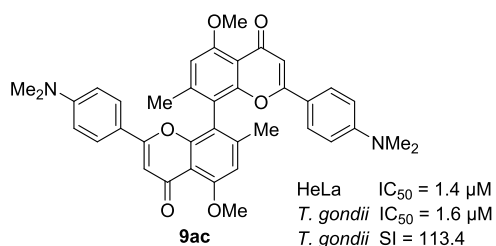


Figure 4. Most overall active compound biflavone **9ac**.

activity against *T. gondii* while exhibiting little activity against HeLa cells ($\text{IC}_{50} (\text{Hs27}) > 200 \mu\text{M}$, $\text{IC}_{50} (\text{HeLa}) 96.1 \mu\text{M}$, $\text{IC}_{50} (T. gondii) 2.3 \mu\text{M}$). Biflavone **9ag** exerts moderate activity against HeLa cells, while no cytotoxicity and little activity against *T. gondii* is observed ($\text{IC}_{50} (\text{Hs27}) > 200 \mu\text{M}$, $\text{IC}_{50} (\text{HeLa}) 18.5 \mu\text{M}$, $\text{IC}_{50} (T. gondii) 39.6 \mu\text{M}$). Overall, all tested compounds and particularly biflavones **9** that show moderate to high cytotoxicity against malignant HeLa cells exert little to no cytotoxicity against healthy fibroblasts Hs27.

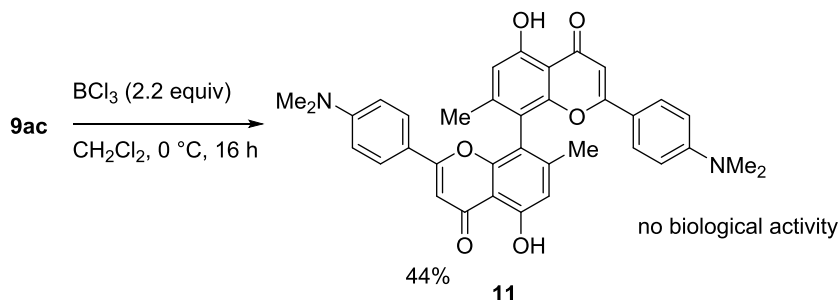
Additionally, electron-rich arenes such as flavones are known to exhibit antioxidant properties.⁶⁴ Therefore, we assessed the ascorbic acid equivalent antioxidant capacity (AEAC) of our dedicated library using an ABTS decolorization assay.⁶³ We found that electron-rich biflavone **9aa** (0.25 equiv ascorbic acid [mol mol^{-1}]) exerts the highest antioxidant activity with similarly electron-rich **9bc**, **9ac**, and **9ba** following suit (Figure 3).

To show the usefulness of our synthesis route, we scaled-up the reaction to gram-scale. Biflavone **9ac** was chosen as it exerted the lowest IC_{50} regarding HeLa cells while also having one of the highest selectivity indices (SI) toward *T. gondii* proliferation inhibition. We found that slightly lower yields were obtained, which we attribute to the necessity for an intermediate workup as no further conversion was observed after adding additional 1.2 equiv of aldehyde **5c**. Following the procedure of the chalcone synthesis, we performed the flavone synthesis on a 575 mg scale. The pure biflavone was isolated in a yield of 21%. This scaleup allowed for additional modification of the biflavone by cleavage of the methoxy groups using BCl_3 (Scheme 5). This was to showcase the potential for further functionalization. The obtained biflavone **11** was isolated in a 44% yield and showed no biological activity ($\text{IC}_{50} (\text{HeLa}) > 100 \mu\text{M}$, $\text{IC}_{50} (T. gondii) > 50 \mu\text{M}$, $\text{IC}_{50} (\text{Hs27}) > 200 \mu\text{M}$) and less antioxidant capacity (0.037 equiv (**11**) vs 0.197 equiv (**9ac**) ascorbic acid (mol mol^{-1})) compared to the protected biflavones **9ac**.

CONCLUSIONS

In summary, we were able to establish a scalable synthesis of a library of non-natural 8,8'-biflavones. The lack of a diversity-oriented approach for the synthesis of 8,8'-biflavones was addressed, and synthesis protocols were set in place that allow for further investigations. To provide the necessary acetophenone dimer key intermediates, we investigated a one-step oxidative coupling procedure. By doing so, we were able to overcome chemoselectivity issues by investigating the chlorinated side product formation. The reaction was then performed on a scale of up to 8 g without the need for column chromatographic isolation. Using our established protocols, we managed to synthesize a library of 14 flavones and 13 biflavones. Further, we were able to show the antiproliferative biological activity of the said library against *T. gondii* as well as selective cytotoxicity against malignant human cell lines (HeLa) and antioxidant capacity. Most biflavones **9** were more active than their respective monomeric flavone counterparts **8**. The most potent biflavone **9ac** showed the strongest activity against both *T. gondii* proliferation and

Scheme 5. Selective Deprotection of the Methoxy Groups of Biflavone **9ac** for the Synthesis of Biflavone **11**. Yield of Isolated Product



HeLa viability while exerting low cytotoxicity against healthy fibroblasts ($SI = 113.4$, IC_{50} (*T. gondii*) = $1.6 \mu M$, IC_{50} (HeLa) = $1.4 \mu M$), making it a lead structure in further studies. The synthesis of this compound was scaled up to 500 mg scale to show the viability of our approach. While this study highlights the potential use of flavones and biflavones as novel anti-*Toxoplasma* agents, further research is needed to assess their efficacy and safety in humans. The modes of action are undergoing further investigations.

EXPERIMENTAL SECTION

Experimental Synthesis Procedures. *General Information.* All chemicals not synthesized or present in the group were purchased from Sigma-Aldrich Co., Alfa Aesar GmbH & Co. KG, Merck KGaA, or Fluorochem Ltd. All reactants were used without any further purification unless stated otherwise. Methanol was dried using the activated molecular sieve (3 Å). DMSO was degassed via freeze–pump–thaw. Anhyd. diethyl ether and dichloromethane were taken from the solvent purifier MB SPS-800 by MBraun. Silica gel 60 (0.040–0.063 mm, 230–400 mesh) by Merck used for synthesis was dried in an oven at $110^\circ C$ overnight. Anhyd. solid reagents were stored in a desiccator under an atmosphere of N_2 . All glassware and stirring bars used for reactions under anhyd. or inert conditions were put in an oven at $110^\circ C$ for at least 12 h. When removing glassware from the oven, it was sealed airtight using septa and stopcocks. It was then attached to a Schlenk line and left to cool under nitrogen gas, which was itself dried over SICAPENT, for several minutes. Glassware was then dried using the Schlenk technique by heating the glassware under vacuum for several minutes and then letting it cool to room temperature under a N_2 flow. This process was repeated three times. Septa were only opened briefly during the addition of reactants under a N_2 countercurrent. Liquid reactants, solvents, and solutions of reactants were transferred using syringes flushed three times with N_2 . Solvents were removed using rotary evaporators at a bath temperature of $40^\circ C$ under reduced pressure. Analytical balance AE 163 by Mettler Toledo was used to determine and weigh yields and reactants. Sonication of reactions was conducted using an ultrasonic cleaning bath T310 by Elma Schmidbauer GmbH. Distillations of liquid aldehydes were conducted using Kugelrohrföfen Glass Oven B-580 and Glass Oven B-585 by Büchi under reduced pressure. For thin-layer chromatography (TLC), silica gel plates (Polygram SIL G/UV 254) by Machery-Nagel with a fluorescent indicator were used. Spots were made visible under UV light, using aqueous potassium permanganate solution, CAM, Molydip, anisaldehyde. Column chromatographic purification was conducted using the appropriate solvent mixture and silica gel 60 (0.040–0.063 mm, 230–400 mesh) by Merck in cylindrical glass columns by applying pressure with compressed air. IR spectra were recorded using a SpectrumTwo FT-IR by PerkinElmer with attenuated total reflection (ATR). The absorption bands were given in units of wave numbers (cm^{-1}). 1H -, ^{13}C -, $^{13}SDEPT$ -, COSY-, HSQC-, and HMBC-NMR spectra were measured on the spectrometer Bruker Avance/DRX 600 at a frequency of 600 MHz (1H) and 151 MHz (^{13}C). ^{19}F - and select 1H - and ^{13}C NMR spectra were measured on the spectrometer Bruker Avance/DRX 300 at a frequency of 282 MHz (^{19}F), 300 MHz (1H), and 75 MHz (^{13}C). Deuterated chloroform with 0.03 vol % of TMS ($CDCl_3$) or deuterated d^6 -DMSO was used as a solvent. The 1H - and ^{13}C -spectra were referenced to the

solvent peak ($CDCl_3$, $\delta = 7.26$ ppm (1H), $\delta = 77.16$ ppm (^{13}C); $DMSO-d^6$, $\delta = 2.50$ ppm (1H), $\delta = 39.52$ ppm (^{13}C)). Data was evaluated using the software MNova (MestReNova) version 14.1 by Mestrelab Research. Coupling constants J were given in Hz, and chemical shifts δ were given in ppm (parts per million). Multiplicities are abbreviated as the following: singlet (s), broad singlet (brs), doublet (d), triplet (t), quartet (q), and multiplet (m).

General Procedures. *General Procedure A Chalcone Monomer (6).* A vial with a stir bar was charged with acetophenone (3) (250 mg, 1.0 equiv), ethanol (2.50 mL), and aq. KOH solution (3 M, 6.0 equiv, 2.78 mL). The mixture was stirred for 5 min until all solids were dissolved. Aldehyde (5) (1.2 equiv) was added at once. The reaction was stirred at room temperature unless stated otherwise. If stated, after 6 h, another portion of aldehyde was added (0.6 equiv). The reaction mixture was left to stir overnight. After the completion of the reaction, aq. HCl (1 M, 10 mL) was added and solids precipitated. The suspension was filtered, and the filtrate was washed with some methanol. The filtrate was then dissolved in CH_2Cl_2 (10 mL), MeOH (10% v/v) was added, and the solvent was removed in vacuo. The crude product was washed with MeOH (4 mL) at $70^\circ C$ and left to cool to room temperature, and the solids were filtered off to isolate the title compound.

General Procedure B Chalcone Dimer (7). A vial with a stir bar was charged with acetophenone (4) (200 mg, 1.0 equiv), ethanol (2.50 mL), and aq. KOH solution (3 M, 12.0 equiv). The mixture was stirred for 5 min until all solids were dissolved. Aldehyde (5) (2.4 equiv) was added at once. The reaction was stirred at room temperature unless stated otherwise. If stated, after 6 h, another portion of aldehyde was added (1.2 equiv). The reaction mixture was left to stir overnight unless stated otherwise. After the completion of the reaction, aq. HCl (1 M, 10 mL) was added unless stated otherwise, and solids precipitated. The suspension was filtered, and the filtrate was washed with some methanol. The filtrate was then dissolved in CH_2Cl_2 , MeOH (10% v/v) was added, and the solvent was removed in vacuo. The crude product was washed with MeOH (10 mL) at $22^\circ C$ and filtered off to isolate the title compound.

General Procedure C Flavone Monomer (8). A 10 mL microwave vial with a stir bar was charged with chalcone (6) (100 mg, 1.00 equiv) and capped with a septum. The degassed DMSO (1.70 mL) and a solution of I_2 in degassed DMSO (78.8 mM, 4 mol %) were added. The reaction solution was then heated to $150^\circ C$ and stirred for 3 h. After complete conversion, sat. aq. Na_2SO_3 solution (4 mL) was added. The aq. phase was extracted with ethyl acetate (3×20 mL). The combined org. layers were washed with cold water (3×20 mL) and sat. NaCl solution (2×20 mL), and the solvent was removed in vacuo. The product was isolated by filtration over a plug of silica (CH_2Cl_2 /MeOH, 9:1 v/v).

General Procedure D Flavone Dimer (9). A 10 mL microwave vial with a stir bar was charged with bichalcone (7) (30 mg, 1.00 equiv) and capped with a septum. Degassed DMSO (0.24 mL) and a solution of I_2 in degassed DMSO (78.8 mM, 10 mol %) were added. The reaction solution was then heated to $150^\circ C$ and stirred for 3 h unless stated otherwise. After complete conversion, sat. aq. Na_2SO_3 solution (4 mL) was added. The aq. phase was extracted with ethyl acetate (3×20 mL). The combined org. layers were washed with cold water (3×20 mL) and sat. NaCl solution (2×20 mL).

mL), and the solvent was removed in vacuo. The product was isolated by column chromatography unless otherwise stated.

(E)-1-(2-Hydroxy-6-methoxy-4-methylphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (6aa). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3a** (250 mg, 1.39 mmol, 1.0 equiv) and 4-methoxybenzaldehyde (**5a**) (0.30 mL, 2.50 mmol, 1.2 + 0.6 equiv). The product was isolated as orange solids (286 mg, 0.96 mmol, 69%). ¹H NMR (600 MHz, CDCl₃): δ 2.33 (s, 3H), 3.86 (s, 3H), 3.94 (s, 3H), 6.24 (d, *J* = 1.5 Hz, 1H), 6.44 (dd, *J* = 1.5, 0.8 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.80 (s, 2H), 13.49 (s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 22.53, 55.56, 56.01, 103.00, 110.01, 111.52, 114.56, 125.51, 128.43, 130.34, 142.87, 147.51, 161.02, 161.64, 165.33, 193.94. IR (ATR film): 3003, 2838, 1627, 1605, 1561, 1511, 1483, 1457, 1422, 1410, 1305, 1289, 1255, 1223, 1207, 1172, 1113, 1035, 982, 828, 814, 768, 742, 722, 662, 557, 539. HR-MS (ESI): *m/z* calcd for [C₁₈H₁₉O₄]⁺ ([M + H⁺]): 299.1278, found: 299.1284. **Melting point:** 113–114 °C.

(E)-1-(2-Hydroxy-6-methoxy-4-methylphenyl)-3-phenylprop-2-en-1-one (6ab). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3a** (250 mg, 1.39 mmol, 1.0 equiv) and benzaldehyde (**5b**) (0.26 mL, 2.50 mmol, 1.2 + 0.6 equiv). The product was isolated as orange solids (209 mg, 0.78 mmol, 56%). ¹H NMR (600 MHz, CDCl₃): δ 2.33 (s, 3H), 3.94 (s, 3H), 6.24 (s, 1H), 6.45 (s, 1H), 7.40–7.61 (m, 5H), 7.80 (d, *J* = 15.6 Hz, 1H), 7.89 (d, *J* = 15.6 Hz, 1H), 13.37 (s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 22.59, 56.01, 102.97, 109.89, 111.46, 127.83, 128.56, 129.04, 130.31, 135.61, 142.72, 147.89, 161.04, 165.31, 194.02. IR (ATR film): 3091, 3036, 2980, 2951, 1641, 1576, 1495, 1459, 1418, 1378, 1344, 1284, 1232, 1216, 1168, 1124, 1082, 985, 954, 878, 853, 824. HR-MS (ESI): *m/z* calcd for [C₁₇H₁₇O₃]⁺ ([M + H⁺]): 269.1172, found: 269.1173. **Melting point:** 169.6–170.2 °C.

(E)-3-(4-(Dimethylamino)phenyl)-1-(2-hydroxy-6-methoxy-4-methylphenyl)prop-2-en-1-one (6ac). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3a** (250 mg, 1.39 mmol, 1.0 equiv) and 4-(dimethylamino)benzaldehyde (**5c**) (373 mg, 2.50 mmol, 1.2 + 0.6 equiv) at 90 °C. The product was isolated as red solids (264 mg, 0.85 mmol, 61%). ¹H NMR (600 MHz, CDCl₃): δ 2.31 (s, 3H), 3.04 (s, 6H), 3.93 (s, 3H), 6.22 (d, *J* = 1.6 Hz, 1H), 6.43 (d, *J* = 1.6 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 2H), 7.50–7.55 (m, 2H), 7.74 (d, *J* = 15.4 Hz, 1H), 7.84 (d, *J* = 15.4 Hz, 1H), 13.72 (s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 22.47, 40.28, 55.93, 102.90, 110.06, 111.40, 112.00, 122.40, 123.41, 130.59, 144.39, 146.89, 152.02, 160.88, 165.24, 193.67. IR (ATR film): 3121, 3009, 2968, 2808, 2645, 2169, 2052, 1628, 1593, 1525, 1476, 1462, 1435, 1413, 1375, 1336, 1296, 1257, 1223, 1198, 1168, 1113, 1069, 1031, 984, 948, 883, 838, 819, 807, 768, 732, 711, 680, 665, 638, 600, 546, 529, 514, 501, 470. HR-MS (ESI): *m/z* calcd for [C₁₉H₂₂O₃N]⁺ ([M + H⁺]): 312.1594, found: 312.1596. **Melting point:** 182–183 °C.

(E)-1-(2-Hydroxy-6-methoxy-4-methylphenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (6ad). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3a** (250 mg, 1.39 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzaldehyde (**5d**) (0.34 mL, 2.50 mmol, 1.2 + 0.6 equiv). The product was isolated as orange solids (299 mg, 0.89 mmol, 64%). ¹H NMR (600 MHz, CDCl₃): δ 2.36 (s, 3H), 3.97 (s, 3H), 6.27 (s, 1H), 6.48 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.78 (d, *J* = 15.7 Hz, 1H),

7.94 (d, *J* = 15.7 Hz, 1H), 13.26 (d, *J* = 2.3 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 22.63, 56.05, 103.00, 109.77, 111.53, 124.05 (q, *J* = 272.1 Hz), 125.98 (q, *J* = 3.8 Hz), 128.53, 130.21, 131.62 (q, *J* = 32.6 Hz), 139.06, 140.37, 148.42, 161.03, 165.40, 193.63. ¹⁹F NMR (282 MHz, CDCl₃): δ –62.77. IR (ATR film): 3746, 3123, 3051, 2974, 1635, 1614, 1565, 1487, 1456, 1410, 1368, 1317, 1287, 1266, 1223, 1169, 1066, 1031, 1015, 983, 909, 843, 813, 768, 747, 732, 683, 666, 626, 593, 558, 530, 506, 492. HR-MS (ESI): *m/z* calcd for [C₁₈H₁₆O₃F₃]⁺ ([M + H⁺]): 337.1046, found: 337.1050. **Melting point:** 124–126 °C.

(E)-3-(4-Bromophenyl)-1-(2-hydroxy-6-methoxy-4-methylphenyl)prop-2-en-1-one (6ae). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3a** (250 mg, 1.39 mmol, 1.0 equiv) and 4-bromobenzaldehyde (**5e**) (309 mg 1.66 mmol, 1.2 equiv). The product was isolated as yellow solids (261 mg, 0.75 mmol, 54%). ¹H NMR (600 MHz, CDCl₃): δ 2.33 (s, 3H), 3.93 (s, 3H), 6.23 (d, *J* = 1.6 Hz, 1H), 6.45 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 15.6 Hz, 1H), 7.85 (d, *J* = 15.6 Hz, 1H), 13.30 (s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 22.60, 56.04, 102.98, 109.82, 111.51, 124.48, 128.43, 129.88, 132.28, 134.56, 141.20, 148.13, 161.00, 165.36, 193.74. IR (ATR film): 2970, 2850, 1632, 1571, 1486, 1454, 1402, 1369, 1331, 1270, 1222, 1206, 1159, 1114, 1072, 1031, 1009, 979, 945, 874, 820, 790, 764, 712, 595, 572, 557, 529. HR-MS (ESI): *m/z* calcd for [C₁₇H₁₆O₃Br]⁺ ([M + H⁺]): 347.0277, found: 347.0279. **Melting point:** 122–124 °C.

(E)-3-(3-Bromophenyl)-1-(2-hydroxy-6-methoxy-4-methylphenyl)prop-2-en-1-one (6af). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3a** (250 mg, 1.39 mmol, 1.0 equiv) and 3-bromobenzaldehyde (**5f**) (0.20 mL, 1.66 mmol, 1.2 equiv). The product was isolated as yellow solids (279 mg, 0.81 mmol, 58%). ¹H NMR (600 MHz, CDCl₃): δ 2.33 (s, 3H), 3.94 (s, 3H), 6.24 (d, *J* = 1.5 Hz, 1H), 6.43–6.46 (m, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.51 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.67 (d, *J* = 15.6 Hz, 1H), 7.74 (t, *J* = 1.8 Hz, 1H), 7.84 (d, *J* = 15.6 Hz, 1H), 13.27 (s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 22.61, 56.09, 102.99, 109.79, 111.49, 123.15, 127.21, 129.18, 130.53, 131.03, 132.97, 137.80, 140.70, 148.23, 161.03, 165.35, 193.65. IR (ATR film): 2918, 2850, 1633, 1571, 1454, 1410, 1368, 1329, 1307, 1276, 1222, 1204, 1159, 1114, 1072, 1031, 978, 945, 898, 863, 815, 787, 760, 699, 667, 626, 606, 583, 557, 529, 485. HR-MS (ESI): *m/z* calcd for [C₁₇H₁₆O₃Br]⁺ ([M + H⁺]): 347.0277, found: 347.0278. **Melting point:** 123–124 °C.

(E)-3-(2-Bromophenyl)-1-(2-hydroxy-6-methoxy-4-methylphenyl)prop-2-en-1-one (6ag). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3a** (250 mg, 1.39 mmol, 1.0 equiv) and 2-bromobenzaldehyde (**5g**) (0.19 mL, 1.66 mmol, 1.2 equiv). The product was isolated as yellow solids (347 mg, 1.00 mmol, 72%). ¹H NMR (600 MHz, CDCl₃): δ 2.33 (s, 3H), 3.92 (s, 3H), 6.23 (s, 1H), 6.45 (s, 1H), 7.23 (td, *J* = 7.6, 1.6 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.80 (d, *J* = 15.4 Hz, 1H), 8.11 (d, *J* = 15.5 Hz, 1H), 13.29 (s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 22.61, 56.03, 102.95, 109.80, 111.50, 126.07, 127.77, 128.03, 130.45, 131.10, 133.69, 135.66, 140.78, 148.17, 161.02, 165.38, 193.65. IR (ATR film): 3065, 1629, 1577, 1487, 1466, 1451, 1438, 1367, 1334, 1278, 1225, 1208, 1191, 1159, 1113, 1049, 1025, 996, 966, 944, 893, 858, 839, 813, 768, 745, 713, 656, 625, 606, 561, 530, 511, 489. HR-MS (ESI): *m/z* calcd for

$[\text{C}_{17}\text{H}_{16}\text{O}_3\text{Br}]^+$ ($[\text{M} + \text{H}^+]$): 347.0277, found: 347.0281. **Melting point:** 162–164 °C.

(*E*)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one or Flavokavain A (**6ba**). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3b** (250 mg, 1.27 mmol, 1.0 equiv) and 4-methoxybenzaldehyde (**5a**) (0.28 mL, 2.29 mmol, 1.2 + 0.6 equiv). The product was isolated as yellow solids (292 mg, 0.93 mmol, 73%). The analytical data was in accordance with the literature.⁶⁵ ^1H NMR (600 MHz, CDCl_3): δ 3.84 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 5.97 (dd, $J = 5.1, 2.4$ Hz, 1H), 6.11 (d, $J = 2.3$ Hz, 1H), 6.93 (d, $J = 8.8$ Hz, 2H), 7.57 (d, $J = 8.7$ Hz, 2H), 7.80 (m, 2H), 14.43 (s, 1H). ^{13}C NMR (151 MHz, CDCl_3): δ 55.39, 55.56, 55.84, 91.26, 93.86, 106.41, 114.38, 125.19, 128.37, 130.10, 142.45, 161.38, 162.48, 166.03, 168.38, 192.61. IR (ATR film): 3005, 2838, 1622, 1580, 1559, 1511, 1488, 1455, 1440, 1421, 1391, 1344, 1304, 1289, 1255, 1216, 1172, 1158, 1112, 984, 939, 870, 828, 766, 721, 697, 674, 615, 559, 539, 520. HR-MS (ESI): m/z calcd for $[\text{C}_{18}\text{H}_{19}\text{O}_5]^+$ ($[\text{M} + \text{H}^+]$): 315.1227, found: 315.1230. **Melting point:** 113–114 °C (110 °C).⁶⁶

(*E*)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-phenylprop-2-en-1-one (**6bb**). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3b** (250 mg, 1.27 mmol, 1.0 equiv) and benzaldehyde (**5b**) (0.23 mL, 2.29 mmol, 1.2 + 0.6 equiv) at 50 °C. The product was isolated as yellow solids (130 mg, 0.46 mmol, 36%). The analytical data was in accordance with the literature.⁶⁵ ^1H NMR (600 MHz, CDCl_3): δ 3.84 (s, 3H), 3.92 (s, 3H), 5.97 (d, $J = 2.4$ Hz, 1H), 6.11 (d, $J = 2.4$ Hz, 1H), 7.36–7.44 (m, 3H), 7.58–7.63 (m, 2H), 7.79 (d, $J = 15.6$ Hz, 1H), 7.91 (d, $J = 15.6$ Hz, 1H), 14.31 (s, 1H). ^{13}C NMR (151 MHz, CDCl_3): δ 55.59, 55.87, 91.31, 93.86, 106.41, 127.60, 128.36, 128.88, 130.04, 135.64, 142.32, 162.55, 166.27, 168.43, 192.67. IR (ATR film): 3082, 3059, 3025, 3004, 2969, 2940, 2849, 1615, 1558, 1494, 1415, 1340, 1284, 1211, 1155, 1112, 1072, 1055, 1033, 984, 939, 888, 869, 818, 788, 742, 691, 673, 647, 623, 577, 562, 534, 495, 459. HR-MS (ESI): m/z calcd for $[\text{C}_{17}\text{H}_{17}\text{O}_4]^+$ ($[\text{M} + \text{H}^+]$): 285.1121, found: 285.1122. **Melting point:** 83–84 °C (85–86 °C).⁶⁵

(*E*)-3-(4-(Dimethylamino)phenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**6bc**). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3b** (250 mg, 1.27 mmol, 1.0 equiv) and 4-(dimethylamino)benzaldehyde (**5c**) (228 mg, 1.53 mmol, 1.2 equiv) at 90 °C. The product was isolated as red solids (296 mg, 0.91 mmol, 71%). The analytical data was in accordance with the literature.⁶⁷ ^1H NMR (600 MHz, CDCl_3): δ 3.03 (s, 6H), 3.82 (s, 3H), 3.91 (s, 3H), 5.95 (d, $J = 2.4$ Hz, 1H), 6.10 (d, $J = 2.4$ Hz, 1H), 6.69 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.7$ Hz, 2H), 7.75 (d, $J = 15.3$ Hz, 1H), 7.83 (d, $J = 15.4$ Hz, 1H), 14.66 (s, 1H). ^{13}C NMR (151 MHz, CDCl_3): δ 40.16, 55.52, 55.78, 91.12, 93.83, 106.45, 111.90, 122.09, 123.40, 130.37, 143.99, 151.84, 162.39, 165.63, 168.31, 192.47. IR (ATR film): 3004, 2962, 2850, 1621, 1587, 1528, 1481, 1436, 1415, 1379, 1346, 1296, 1209, 1172, 1154, 1111, 1031, 1001, 986, 941, 920, 864, 810, 765, 711, 677, 638, 616, 547, 516, 503, 461. HR-MS (ESI): m/z calcd for $[\text{C}_{19}\text{H}_{22}\text{O}_4]^+$ ($[\text{M} + \text{H}^+]$): 328.1543, found: 328.1546. **Melting point:** 203–204 °C (153 °C).⁶⁶

(*E*)-1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**6bd**). Synthesized in accordance with **General Procedure A**. Starting from

acetophenone **3b** (250 mg, 1.27 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzaldehyde (**5d**) (0.31 mL, 2.29 mmol, 1.2 + 0.6 equiv). The product was isolated as yellow solids (293 mg, 0.83 mmol, 65%). ^1H NMR (600 MHz, CDCl_3): δ 3.84 (s, 3H), 3.92 (s, 3H), 5.97 (d, $J = 2.4$ Hz, 1H), 6.11 (d, $J = 2.4$ Hz, 1H), 7.65 (d, $J = 8.3$ Hz, 2H), 7.68 (d, $J = 8.3$ Hz, 2H), 7.74 (d, $J = 15.6$ Hz, 1H), 7.93 (d, $J = 15.6$ Hz, 1H), 14.14 (s, 1H). ^{13}C NMR (151 MHz, CDCl_3): δ 55.78, 56.05, 91.53, 94.00, 106.43, 124.07 (q, $J = 272.1$ Hz), 125.96 (q, $J = 3.8$ Hz), 128.47, 130.12, 131.51 (q, $J = 32.6$ Hz), 139.19, 140.13, 162.65, 166.72, 168.66, 192.32. ^{19}F NMR (282 MHz, CDCl_3): δ –62.76. IR (ATR film): 3022, 2980, 2948, 1633, 1613, 1579, 1488, 1456, 1438, 1414, 1342, 1324, 1287, 1216, 1101, 1067, 1030, 1016, 955, 936, 906, 872, 838, 827, 815, 768, 750, 732, 693, 676, 605, 590, 535, 504, 461. HR-MS (ESI): m/z calcd for $[\text{C}_{18}\text{H}_{16}\text{O}_4\text{F}_3]^+$ ($[\text{M} + \text{H}^+]$): 353.0995, found: 353.0997. **Melting point:** 148–149 °C.

(*E*)-3-(4-Bromophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**6be**). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3b** (250 mg, 1.27 mmol, 1.0 equiv) and 4-bromobenzaldehyde (**5e**) (423 mg, 2.29 mmol, 1.2 + 0.6 equiv). The product was isolated as a yellow solid (356 mg, 0.98 mmol, 77%). The analytical data was in accordance with the literature.⁶⁵ ^1H NMR (600 MHz, CDCl_3): δ 3.82 (s, 3H), 3.90 (s, 3H), 5.94 (d, $J = 2.4$ Hz, 1H), 6.09 (d, $J = 2.4$ Hz, 1H), 7.44 (d, $J = 8.2$ Hz, 2H), 7.52 (d, $J = 8.2$ Hz, 2H), 7.67 (d, $J = 15.6$ Hz, 1H), 7.85 (d, $J = 15.6$ Hz, 1H), 14.23 (s, 1H). ^{13}C NMR (151 MHz, CDCl_3): δ 55.72, 55.99, 91.42, 93.95, 106.39, 124.30, 128.26, 129.78, 132.20, 134.63, 140.88, 162.58, 166.49, 168.57, 192.40. IR (ATR film): 3016, 2996, 2978, 1627, 1586, 1564, 1484, 1440, 1420, 1336, 1303, 1289, 1272, 1215, 1158, 1114, 1069, 1029, 1007, 986, 973, 936, 891, 818, 792, 758, 709, 666, 604, 564, 534, 505, 483, 460. HR-MS (ESI): m/z calcd for $[\text{C}_{17}\text{H}_{16}\text{O}_4\text{Br}]^+$ ($[\text{M} + \text{H}^+]$): 363.0226, found: 363.0231. **Melting point:** 169–170 °C (166 °C)⁶⁸ (150–151 °C).⁶⁵

(*E*)-3-(3-Bromophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**6bf**). Starting from acetophenone **3b** (250 mg, 1.27 mmol, 1.0 equiv) and 3-bromobenzaldehyde (**5f**) (0.27 mL, 2.29 mmol, 1.2 + 0.6 equiv). The product was isolated as a yellow solid (310 mg, 0.85 mmol, 67%). The analytical data was in accordance with the literature.⁶⁹ ^1H NMR (600 MHz, CDCl_3): δ 3.83 (s, 3H), 3.92 (s, 3H), 5.96 (d, $J = 2.4$ Hz, 1H), 6.10 (d, $J = 2.4$ Hz, 1H), 7.27 (t, $J = 7.9$ Hz, 1H), 7.49 (dd, $J = 7.9, 1.8$ Hz, 2H), 7.66 (d, $J = 15.6$ Hz, 1H), 7.72 (t, $J = 1.8$ Hz, 1H), 7.85 (d, $J = 15.6$ Hz, 1H), 14.18 (s, 1H). ^{13}C NMR (151 MHz, CDCl_3): δ 55.75, 56.07, 91.47, 93.96, 106.42, 123.12, 127.12, 129.05, 130.49, 130.99, 132.84, 137.90, 140.43, 162.63, 166.59, 168.59, 192.35. IR (ATR film): 2942, 2852, 1619, 1578, 1469, 1454, 1440, 1416, 1392, 1340, 1319, 1303, 1262, 1216, 1158, 1114, 1072, 1055, 1030, 983, 939, 911, 863, 819, 787, 758, 688, 670, 647, 624, 582, 564, 533, 492. HR-MS (ESI): m/z calcd for $[\text{C}_{17}\text{H}_{16}\text{O}_4\text{Br}]^+$ ($[\text{M} + \text{H}^+]$): 363.0226, found: 363.0230. **Melting point:** 115–116 °C.

(*E*)-3-(2-Bromophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (**6bg**). Synthesized in accordance with **General Procedure A**. Starting from acetophenone **3b** (250 mg, 1.27 mmol, 1.0 equiv) and 2-bromobenzaldehyde (**5g**) (0.18 mL, 1.53 mmol, 1.2 equiv). The product was isolated as yellow solids (385 mg, 1.06 mmol, 83%). The analytical data was in accordance with the

literature.⁷⁰ ¹H NMR (600 MHz, CDCl₃): δ 3.83 (s, 3H), 3.89 (s, 3H), 5.95 (d, *J* = 2.4 Hz, 1H), 6.10 (d, *J* = 2.4 Hz, 1H), 7.21 (td, *J* = 7.6, 1.6 Hz, 1H), 7.34 (td, *J* = 7.6, 1.3 Hz, 1H), 7.62 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.81 (d, *J* = 15.5 Hz, 1H), 8.09 (d, *J* = 15.5 Hz, 1H), 14.21 (s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 55.73, 56.01, 91.41, 93.96, 106.41, 125.96, 127.75, 127.99, 130.32, 130.98, 133.62, 135.73, 140.51, 162.62, 166.55, 168.60, 192.34. IR (ATR film): 3005, 2976, 1627, 1579, 1565, 1490, 1464, 1437, 1416, 1343, 1321, 1307, 1269, 1216, 1160, 1113, 1048, 1027, 971, 939, 874, 814, 797, 770, 744, 695, 663, 646, 622, 586, 535, 507. HR-MS (ESI): *m/z* calcd for [C₁₇H₁₆O₄Br]⁺ ([M + H]⁺): 363.0226, found: 363.0233. Melting point: 147–148 °C (146–147 °C).⁷⁰

5-Methoxy-2-(4-methoxyphenyl)-7-methyl-4H-chromen-4-one (8aa). Synthesized in accordance with General Procedure C. Starting from chalcone 6aa (100 mg, 0.34 mmol, 1.0 equiv) and I₂ (78.8 mM, 173 μL, 0.01 mmol, 4 mol %). The product was isolated as white solids (81.0 mg, 0.28 mmol, 81%). ¹H NMR (600 MHz, CDCl₃): δ 2.46 (s, 3H), 3.88 (s, 3H), 3.98 (s, 3H), 6.62 (d, *J* = 1.4 Hz, 1H), 6.63 (s, 1H), 6.94 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.00 (d, *J* = 8.9 Hz, 2H), 7.83 (d, *J* = 8.9 Hz, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 22.42, 55.63, 56.59, 107.88, 110.39, 112.60, 114.54, 124.13, 127.86, 145.01, 158.44, 159.67, 161.04, 162.28, 178.34. IR (ATR film): 2840, 1639, 1606, 1575, 1512, 1483, 1423, 1377, 1340, 1300, 1220, 1180, 1115, 1050, 955, 903, 833, 611, 586. HR-MS (ESI): *m/z* calcd for [C₁₈H₁₇O₄]⁺ ([M + H]⁺): 297.1121, found: 297.1126. Melting point: 173–174 °C.

5-Methoxy-7-methyl-2-phenyl-4H-chromen-4-one (8ab). Synthesized in accordance with General Procedure C. Starting from chalcone 6ab (100 mg, 0.38 mmol, 1.0 equiv) and I₂ (78.8 mM, 192 μL, 0.02 mmol, 4 mol %). The product was isolated as white solids (90.3 mg, 0.34 mmol, 90%). ¹H NMR (600 MHz, CDCl₃): δ 2.45 (s, 3H), 3.98 (s, 3H), 6.62 (s, 1H), 6.70 (s, 1H), 6.95 (s, 1H), 7.49 (m, 3H), 7.87 (dd, *J* = 7.5, 2.3 Hz, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 22.40, 56.55, 107.93, 109.17, 110.39, 112.62, 126.14, 129.05, 131.34, 131.77, 145.26, 158.45, 159.65, 160.97, 178.28. IR (ATR film): 3068, 2914, 2851, 2236, 1637, 1610, 1577, 1566, 1482, 1463, 1449, 1410, 1375, 1337, 1298, 1263, 1219, 1188, 1163, 1118, 1079, 1049, 1014, 1001, 973, 956, 919, 901, 848, 825, 769, 729, 691, 676, 610, 566, 545, 528, 488. HR-MS (ESI): *m/z* calcd for [C₁₇H₁₅O₃]⁺ ([M + H]⁺): 267.1016, found: 267.1020. Melting point: 162–163 °C.

2-(4-(Dimethylamino)phenyl)-5-methoxy-7-methyl-4H-chromen-4-one (8ac). Synthesized in accordance with General Procedure C. Starting from chalcone 6ac (100 mg, 0.32 mmol, 1.0 equiv) and I₂ (78.8 mM, 162 μL, 0.01 mmol, 4 mol %). The product was isolated as orange solids (50.0 mg, 0.16 mmol, 50%). ¹H NMR (600 MHz, CDCl₃): δ 2.44 (s, 3H), 3.05 (s, 6H), 3.97 (s, 3H), 6.57 (s, 1H), 6.60 (s, 1H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.92 (s, 1H), 7.76 (d, *J* = 8.9 Hz, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 22.38, 40.24, 56.54, 106.13, 107.60, 110.36, 111.76, 112.55, 118.36, 127.49, 144.54, 152.37, 158.38, 159.53, 161.89, 178.42. IR (ATR film): 2924, 2853, 2235, 1629, 1597, 1523, 1481, 1463, 1445, 1412, 1366, 1339, 1300, 1253, 1223, 1197, 1170, 1118, 1092, 1049, 1015, 972, 947, 914, 776, 758, 728, 677, 643, 611, 577, 541, 528, 510, 480. HR-MS (ESI): *m/z* calcd for [C₁₉H₂₀NO₃]⁺ ([M + H]⁺): 310.1438, found: 310.1441. Melting point: 198 °C (decomposition).

5-Methoxy-7-methyl-2-(4-(trifluoromethyl)phenyl)-4H-chromen-4-one (8ad). Synthesized in accordance with General Procedure C. Starting from chalcone 6ad (100 mg, 0.30 mmol, 1.0 equiv) and I₂ (78.8 mM, 152 μL, 0.01 mmol, 4 mol %). The product was isolated as white solids (65.7 mg, 0.20 mmol, 66%). ¹H NMR (600 MHz, CDCl₃): δ 2.46 (s, 3H), 3.98 (s, 3H), 6.64 (s, 1H), 6.74 (s, 1H), 6.96 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.98 (d, *J* = 8.1 Hz, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 22.44, 56.59, 108.19, 110.34, 112.63, 122.91 (q, *J* = 271.2 Hz), 126.07 (q, *J* = 3.8 Hz), 126.48, 132.97 (q, *J* = 32.8 Hz), 135.23, 145.73, 158.35, 159.23, 159.73, 177.89. ¹⁹F NMR (282 MHz, CDCl₃): δ –62.95. IR (ATR film): 3074, 2920, 1645, 1612, 1567, 1518, 1486, 1466, 1417, 1379, 1319, 1295, 1257, 1219, 1202, 1159, 1114, 1071, 1049, 1016, 958, 902, 889, 849, 823, 776, 731, 702, 677, 649, 635, 612, 585, 566, 551, 530, 497. HR-MS (ESI): *m/z* calcd for [C₁₈H₁₄O₃F₃]⁺ ([M + H]⁺): 335.0890, found: 335.0895. Melting point: 226–228 °C.

2-(4-Bromophenyl)-5-methoxy-7-methyl-4H-chromen-4-one (8ae). Synthesized in accordance with General Procedure C. Starting from chalcone 6ae (100 mg, 0.29 mmol, 1.0 equiv) and I₂ (78.8 mM, 147 μL, 0.01 mmol, 4 mol %). The product was isolated as white solids (90.5 mg, 0.26 mmol, 91%). ¹H NMR (600 MHz, CDCl₃): δ 2.46 (s, 3H), 3.98 (s, 3H), 6.64 (s, 1H), 6.69 (s, 1H), 6.94 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 22.48, 56.60, 108.05, 109.29, 110.35, 112.54, 126.02, 127.61, 130.71, 132.39, 145.53, 158.34, 159.67, 159.95, 178.13. IR (ATR film): 3072, 2236, 1612, 1588, 1567, 1483, 1463, 1404, 1375, 1334, 1300, 1265, 1218, 1188, 1164, 1120, 1074, 1048, 1008, 956, 828, 776, 731, 677, 644, 566, 550, 529, 495, 475. HR-MS (ESI): *m/z* calcd for [C₁₇H₁₄O₃Br]⁺ ([M + H]⁺): 345.0121, found: 345.0121. Melting point: 203–206 °C.

2-(3-Bromophenyl)-5-methoxy-7-methyl-4H-chromen-4-one (8af). Synthesized in accordance with General Procedure C. Starting from chalcone 6af (100 mg, 0.29 mmol, 1.0 equiv) and I₂ (78.8 mM, 147 μL, 0.01 mmol, 4 mol %). The product was isolated as white solids (92.1 mg, 0.27 mmol, 92%). ¹H NMR (600 MHz, CDCl₃): δ 2.39 (s, 3H), 3.91 (s, 3H), 6.57 (d, *J* = 8.3 Hz, 2H), 6.86 (t, *J* = 1.1 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.54 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.68 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.92 (t, *J* = 1.9 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 22.28, 56.37, 107.88, 109.44, 110.17, 112.29, 123.08, 124.44, 128.84, 130.40, 133.49, 133.99, 145.44, 158.03, 158.97, 159.40, 177.71. IR (ATR film): 2921, 1644, 1613, 1560, 1483, 1465, 1417, 1375, 1301, 1266, 1217, 1165, 1121, 1098, 1077, 1050, 998, 977, 956, 846, 825, 791, 744, 721, 693, 612, 566, 529, 487. HR-MS (ESI): *m/z* calcd for [C₁₇H₁₄O₃Br]⁺ ([M + H]⁺): 345.0121, found: 345.0125. Melting point: 165–166 °C.

2-(2-Bromophenyl)-5-methoxy-7-methyl-4H-chromen-4-one (8ag). Synthesized in accordance with General Procedure C. Starting from chalcone 6ag (100 mg, 0.29 mmol, 1.0 equiv) and I₂ (78.8 mM, 147 μL, 0.01 mmol, 4 mol %). The product was isolated as white solids (76.4 mg, 0.22 mmol, 76%). ¹H NMR (600 MHz, CDCl₃): δ 2.45 (s, 3H), 3.99 (s, 3H), 6.45 (s, 1H), 6.64 (s, 1H), 6.88 (s, 1H), 7.35 (td, *J* = 7.7, 1.7 Hz, 1H), 7.43 (td, *J* = 7.5, 1.2 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.1 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 22.43, 56.58, 108.06, 110.45, 112.62, 114.33, 122.05, 127.70, 130.98, 131.81, 134.02, 134.05, 145.50, 158.71, 159.75, 161.65, 177.90. IR (ATR film): 2931, 1650, 1616, 1483, 1466, 1436, 1411, 1332, 1298, 1267, 1217, 1164, 1117,

1061, 1040, 1026, 854, 764, 727, 683, 567, 545, 500. **HR-MS (ESI)**: m/z calcd for $[C_{17}H_{14}O_3Br]^+$ ($[M + H^+]$): 345.0121, found 345.0125. **Melting point**: 146–148 °C.

5,7-Dimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one or Apigenin Trimethyl Ether (8ba). Synthesized in accordance with **General Procedure C**. Starting from chalcone **6ba** (100 mg, 0.32 mmol, 1.0 equiv) and I_2 (78.8 mM, 162 μ L, 0.01 mmol, 4 mol %). The product was isolated as white solids (35.7 mg, 0.12 mmol, 36%). The analytical data was in accordance with the literature.⁷¹ **¹H NMR** (600 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 6.37 (d, J = 2.3 Hz, 1H), 6.56 (d, J = 2.3 Hz, 1H), 6.60 (s, 1H), 7.00 (d, J = 8.9 Hz, 2H), 7.82 (d, J = 8.9 Hz, 2H). **¹³C NMR** (151 MHz, $CDCl_3$): δ 55.62, 55.87, 56.59, 93.02, 96.25, 107.92, 109.46, 114.53, 124.09, 127.76, 160.03, 160.83, 161.12, 162.22, 164.07, 177.75. **IR** (ATR film): 2941, 1640, 1605, 1513, 1491, 1460, 1422, 1347, 1301, 1259, 1218, 1202, 1180, 1161, 1114, 1057, 1032, 908, 833, 773, 620, 599, 559. **HR-MS (ESI)**: m/z calcd for $[C_{18}H_{17}O_5]^+$ ($[M + H^+]$): 313.1071, found: 313.1075. **Melting point**: 155–157 °C (155–157 °C).⁷¹

5,7-Dimethoxy-2-phenyl-4H-chromen-4-one or Dimethylchrysin (8bb). Synthesized in accordance with **General Procedure C**. Starting from chalcone **6bb** (100 mg, 0.35 mmol, 1.0 equiv) and I_2 (78.8 mM, 178 μ L, 0.01 mmol, 4 mol %). The product was isolated as white solids (80.1 mg, 0.28 mmol, 80%). The analytical data was in accordance with the literature.⁷² **¹H NMR** (600 MHz, $CDCl_3$): δ 3.91 (s, 3H), 3.95 (s, 3H), 6.37 (d, J = 2.3 Hz, 1H), 6.57 (d, J = 2.3 Hz, 1H), 6.68 (s, 1H), 7.47–7.52 (m, 3H), 7.84–7.90 (m, 2H). **¹³C NMR** (151 MHz, $CDCl_3$): δ 55.89, 56.57, 93.02, 96.35, 109.26, 109.52, 126.09, 129.06, 131.29, 131.75, 160.08, 160.78, 161.12, 164.22, 177.69. **IR** (ATR film): 3017, 2948, 2922, 2844, 2326, 2226, 2015, 1646, 1605, 1491, 1465, 1451, 1422, 1392, 1348, 1302, 1268, 1215, 1204, 1189, 1161, 1120, 1104, 1079, 1058, 1035, 1022, 1000, 962, 949, 915, 851, 819, 803, 766, 723, 689, 642, 614, 556, 530, 483. **HR-MS (ESI)**: m/z calcd for $[C_{17}H_{15}O_4]^+$ ($[M + H^+]$): 283.0965, found: 283.0969. **Melting point**: 80.0 °C (brown discoloration), 141–142 °C (145–146 °C).⁷²

2-(4-(Dimethylamino)phenyl)-5,7-dimethoxy-4H-chromen-4-one (8bc). Synthesized in accordance with **General Procedure C**. Starting from chalcone **6bc** (100 mg, 0.31 mmol, 1.0 equiv) and I_2 (78.8 mM, 157 μ L, 0.01 mmol, 4 mol %). The product was isolated as orange solids (37.1 mg, 0.11 mmol, 37%). **¹H NMR** (600 MHz, $CDCl_3$): δ 3.06 (s, 6H), 3.91 (s, 3H), 3.95 (s, 3H), 6.36 (d, J = 2.3 Hz, 1H), 6.55 (s, 2H), 6.74 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H). **¹³C NMR** (151 MHz, $CDCl_3$): δ 40.25, 55.83, 56.57, 93.03, 96.03, 106.23, 111.83, 112.16, 118.48, 127.44, 152.39, 160.00, 161.04, 161.72, 163.79, 177.87. **IR** (ATR film): 2943, 1635, 1601, 1525, 1489, 1458, 1369, 1347, 1303, 1253, 1217, 1200, 1161, 1117, 1057, 1029, 1002, 908, 819, 729, 674, 642, 618, 592, 511, 467. **HR-MS (ESI)**: m/z calcd for $[C_{19}H_{20}NO_4]^+$ ($[M + H^+]$): 326.1387, found: 326.1388. **Melting point**: 211–214 °C.

5,7-Dimethoxy-2-(4-(trifluoromethyl)phenyl)-4H-chromen-4-one (8bd). Synthesized in accordance with **General Procedure C**. Starting from chalcone **6bd** (100 mg, 0.29 mmol, 1.0 equiv) and I_2 (78.8 mM, 147 μ L, 0.01 mmol, 4 mol %). The product was isolated as white solids (26.8 mg, 0.08 mmol 27%). The analytical data was in accordance with the literature.⁷³ **¹H NMR** (600 MHz, $CDCl_3$): δ 3.91 (s, 3H), 3.95 (s, 3H), 6.38 (d, J = 2.3 Hz, 1H), 6.57 (d, J = 2.3 Hz, 1H),

6.70 (s, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.97 (d, J = 8.1 Hz, 2H). **¹³C NMR** (151 MHz, $CDCl_3$): δ 55.80, 56.45, 92.88, 96.41, 109.36, 110.30, 123.68 (q, J = 272.2 Hz), 125.91 (q, J = 3.8 Hz), 126.26, 132.77 (q, J = 32.8 Hz), 135.02, 158.87, 159.84, 161.04, 164.34, 177.11. **¹⁹F NMR** (282 MHz, $CDCl_3$): δ –62.93. **IR** (ATR film): 2945, 2240, 1645, 1574, 1491, 1459, 1416, 1386, 1322, 1295, 1264, 1218, 1203, 1161, 1070, 1057, 1027, 1016, 908, 841, 807, 731, 675, 635, 616, 586, 564, 528, 514, 493, 468. **HR-MS (ESI)**: m/z calcd for $[C_{18}H_{14}F_3O_4]^+$ ($[M + H^+]$): 351.0839, found: 351.0843. **Melting point**: 185–186 °C.

2-(4-Bromophenyl)-5,7-dimethoxy-4H-chromen-4-one (8be). Synthesized in accordance with **General Procedure C**. Starting from chalcone **6be** (100 mg, 0.28 mmol, 1.0 equiv) and I_2 (78.8 mM, 142 μ L, 0.01 mmol, 4 mol %). The product was isolated as white solids (92.6 mg, 0.26 mmol, 93%). The analytical data was in accordance with the literature.⁷⁴ **¹H NMR** (600 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.94 (s, 3H), 6.36 (d, J = 2.3 Hz, 1H), 6.54 (d, J = 2.3 Hz, 1H), 6.63 (s, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 8.6 Hz, 2H). **¹³C NMR** (151 MHz, $CDCl_3$): δ 55.91, 56.57, 92.93, 96.40, 109.33, 109.38, 125.88, 127.47, 130.60, 132.33, 159.64, 159.91, 161.06, 164.28, 177.44. **IR** (ATR film): 2842, 1644, 1607, 1572, 1488, 1459, 1422, 1404, 1380, 1341, 1277, 1217, 1202, 1161, 1118, 1105, 1073, 1057, 1008, 905, 827, 773, 738, 718, 674, 635, 616, 529, 491, 475. **HR-MS (ESI)**: m/z calcd for $[C_{17}H_{14}O_4Br]^+$ ($[M + H^+]$): 361.0070, found: 361.0073. **Melting point**: 194–195 °C (197–198 °C).⁷⁴

2-(3-Bromophenyl)-5,7-dimethoxy-4H-chromen-4-one (8bf). Synthesized in accordance with **General Procedure C**. Starting from chalcone **6bf** (100 mg, 0.28 mmol, 1.0 equiv) and I_2 (78.8 mM, 142 μ L, 0.01 mmol, 4 mol %). The product was isolated as white solids (84.9 mg, 0.24 mmol, 85%). The analytical data was in accordance with the literature.⁷⁵ **¹H NMR** (600 MHz, $CDCl_3$): δ 3.92 (s, 3H), 3.96 (s, 3H), 6.39 (d, J = 2.3 Hz, 1H), 6.58 (d, J = 2.3 Hz, 1H), 6.65 (s, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.63 (dd, J = 8.0, 1.5 Hz, 1H), 7.77 (dt, J = 7.9, 1.4 Hz, 1H), 8.03 (d, J = 1.9 Hz, 1H). **¹³C NMR** (151 MHz, $CDCl_3$): δ 55.82, 56.46, 92.85, 96.41, 109.35, 109.75, 123.16, 124.50, 128.93, 130.45, 133.66, 134.00, 158.95, 159.84, 161.00, 164.26, 177.21. **IR** (ATR film): 2949, 1649, 1609, 1571, 1489, 1421, 1384, 1268, 1201, 1160, 1115, 1099, 1063, 1024, 910, 854, 825, 764, 728, 636, 611, 566, 554, 531, 504, 480. **HR-MS (ESI)**: m/z calcd for $[C_{17}H_{14}O_4Br]^+$ ($[M + H^+]$): 361.0070, found: 361.0077. **Melting point**: 134–136 °C (278–280 °C).⁷⁵ The melting point deviated strongly from the literature-reported value.

2-(2-Bromophenyl)-5,7-dimethoxy-4H-chromen-4-one (8bg). Synthesized in accordance with **General Procedure C**. Starting from chalcone **6bg** (100 mg, 0.28 mmol, 1.0 equiv) and I_2 (78.8 mM, 142 μ L, 0.01 mmol, 4 mol %). The product was isolated as white solids (92.3 mg, 0.26 mmol, 92%). **¹H NMR** (600 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.96 (s, 3H), 6.39 (d, J = 2.3 Hz, 1H), 6.43 (s, 1H), 6.50 (d, J = 2.3 Hz, 1H), 7.35 (td, J = 7.7, 1.7 Hz, 1H), 7.43 (td, J = 7.5, 1.2 Hz, 1H), 7.54 (dd, J = 7.6, 1.7 Hz, 1H), 7.70 (dd, J = 8.1, 1.2 Hz, 1H). **¹³C NMR** (151 MHz, $CDCl_3$): δ 55.89, 56.59, 92.99, 96.51, 109.48, 114.41, 122.05, 127.71, 130.98, 131.80, 133.97, 134.02, 160.35, 161.20, 161.34, 164.35, 177.28. **IR** (ATR film): 2843, 1644, 1607, 1489, 1459, 1421, 1383, 1334, 1306, 1269, 1217, 1202, 1161, 1119, 1101, 1079, 1057, 1028, 997, 965, 953, 916, 876, 846, 824, 790, 772, 754, 726, 692, 674, 643, 616, 566, 529, 483. **HR-MS (ESI)**: m/z calcd for $[C_{17}H_{14}O_4Br]^+$ ($[M +$

H⁺]): 361.0070, found: 361.0074. **Melting point:** 162–163 °C.

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4'-dimethoxy-6,6'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(3-(4-methoxyphenyl)prop-2-en-1-one) (**7aa**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4a** (200 mg, 0.56 mmol, 1.0 equiv) and 4-methoxybenzaldehyde (**5a**) (0.24 mL, 2.01 mmol, 2.4 equiv +1.2 equiv). The product was isolated as orange solids (278 mg, 0.46 mmol, 83%). ¹H NMR (600 MHz, CDCl₃): δ 2.11 (s, 6H), 3.86 (s, 6H), 3.99 (s, 6H), 6.43 (s, 2H), 6.94 (d, *J* = 8.7 Hz, 4H), 7.58 (d, *J* = 8.7 Hz, 4H), 7.79 (d, *J* = 15.6 Hz, 2H), 7.84 (d, *J* = 15.6 Hz, 2H), 13.80 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 20.87, 55.40, 55.77, 103.30, 109.96, 114.38, 117.73, 125.66, 128.37, 130.16, 142.50, 147.05, 160.12, 161.41, 162.70, 194.03. **IR** (ATR film): 2970, 2839, 1623, 1603, 1558, 1510, 1464, 1422, 1363, 1327, 1304, 1291, 1256, 1216, 1170, 1114, 1037, 908, 871, 828, 770, 647, 619, 559, 536, 521, 487. **HR-MS** (ESI): *m/z* calcd for [C₃₆H₃₅O₈]⁺ ([M + H⁺]): 595.2327, found: 595.2335. **Melting point:** 212–214 °C.

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4'-dimethoxy-6,6'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(3-phenylprop-2-en-1-one) (**7ab**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4a** (200 mg, 0.56 mmol, 1.0 equiv) and benzaldehyde (**5b**) (0.20 mL, 2.01 mmol, 2.4 + 1.2 equiv). The product was isolated as orange solids (263 mg, 0.49 mmol, 88%). ¹H NMR (600 MHz, CDCl₃): δ 2.12 (s, 6H), 4.00 (s, 6H), 6.44 (s, 2H), 7.37–7.45 (m, 6H), 7.59–7.65 (m, 4H), 7.80 (d, *J* = 15.6 Hz, 2H), 7.94 (d, *J* = 15.6 Hz, 2H), 13.71 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 21.06, 55.96, 103.50, 110.07, 117.82, 128.16, 128.56, 129.04, 130.24, 135.76, 142.55, 147.57, 160.38, 162.89, 194.30. **IR** (ATR film): 3104, 3026, 2970, 2942, 2250, 1628, 1609, 1564, 1448, 1388, 1361, 1329, 1272, 1214, 1179, 1115, 1073, 1038, 976, 948, 907, 869, 817, 789, 758, 725, 688, 647, 565, 534, 494. **HR-MS** (ESI): *m/z* calcd for [C₃₄H₃₁O₆]⁺ ([M + H⁺]): 535.2115, found: 535.2122. **Melting point:** 213–215 °C.

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4'-dimethoxy-6,6'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(3-(4-(dimethylamino)phenyl)prop-2-en-1-one) (**7ac**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4a** (200 mg, 0.56 mmol, 1.0 equiv) and 4-(dimethylamino)benzaldehyde (**5c**) (200 mg, 1.34 mmol, 2.4 equiv) at 90 °C. The product was isolated as red solids (175 mg, 0.28 mmol, 50%).

Scaleup: in a 50 mL round-bottom flask, acetophenone **4a** (1.00 g, 2.80 mmol, 1.0 equiv) and 4-(dimethylamino)benzaldehyde (**5c**) (1.00 g, 6.70 mmol, 2.4 equiv) were given in EtOH (10 mL). Aq. KOH solution was added (3 M, 11 mL, 33.5 mmol, 12.0 equiv). The reaction mixture was stirred at 90 °C. After 24 h, 4-(dimethylamino)benzaldehyde (**5c**) (500 mg, 3.40 mmol, 1.2 equiv) was added. After an additional 24 h heating was stopped, KPi-buffer (1 M, pH 7, 20 mL) was added. The organic phases were extracted using CH₂Cl₂ (3x 100 mL). The combined organic phases were washed with sat. aq. NaCl solution (50 mL) and dried over MgSO₄. The solvent was removed in vacuo. The mixture was then resuspended in MeOH (10 mL). Aq. KOH solution was added (3 M, 11.0 mL, 33.5 mmol, 12.0 equiv). Then, 4-(dimethylamino)benzaldehyde (**5c**) (500 mg, 3.40 mmol, 1.2 equiv) was added and the mixture was stirred at 90 °C for 16 h. The reaction was stopped, and KPi-buffer (1 M, pH 7, 20 mL) was

added. The organic phases were extracted using CH₂Cl₂ (3 × 100 mL). The combined organic phases were washed with sat. aq. NaCl solution (50 mL) and dried over MgSO₄. MeOH (15 mL) was added to the solution, and the solvent was carefully removed in vacuo. The resulting mixture was macerated with MeOH (15 mL). The solids were filtered off and washed with copious amounts of MeOH. The product was obtained as red solids (607 mg, 0.98 mmol, 35%). ¹H NMR (600 MHz, CDCl₃): δ 2.10 (s, 6H), 3.04 (s, 12H), 3.98 (s, 6H), 6.41 (s, 2H), 6.70 (d, *J* = 8.6 Hz, 4H), 7.53 (d, *J* = 8.5 Hz, 4H), 7.78 (d, *J* = 15.4 Hz, 2H), 7.84 (d, *J* = 15.5 Hz, 2H), 13.96 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 20.98, 40.30, 55.87, 103.40, 110.29, 112.07, 118.01, 122.95, 123.69, 129.01, 130.54, 144.05, 146.58, 152.03, 160.15, 162.83, 193.97. **IR** (ATR film): 1602, 1543, 1525, 1472, 1445, 1414, 1364, 1316, 1298, 1228, 1211, 1167, 1113, 1067, 979, 947, 866, 815, 732, 703, 651, 613, 569, 541, 469. **HR-MS** (ESI): *m/z* calcd for [C₃₈H₄₁N₂O₆]⁺ ([M + H⁺]): 621.2959, found: 621.2962. **Melting point:** 265 °C (decomposition).

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4'-dimethoxy-6,6'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one) (**7ad**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4a** (200 mg, 0.56 mmol, 1.0 equiv) and 4-(trifluoromethyl)benzaldehyde (**5d**) (0.25 mL, 2.01 mmol, 2.4 + 1.2 equiv). The product was isolated as orange solids (232 mg, 0.35 mmol, 62%). ¹H NMR (600 MHz, CDCl₃): δ 2.12 (s, 6H), 4.00 (s, 6H), 6.45 (s, 2H), 7.67 (d, *J* = 8.2 Hz, 4H), 7.71 (d, *J* = 8.1 Hz, 4H), 7.76 (d, *J* = 15.6 Hz, 2H), 7.97 (d, *J* = 15.7 Hz, 2H), 13.59 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 21.10, 56.03, 103.55, 109.97, 117.77, 124.09 (q, *J* = 271.5), 126.00 (q, *J* = 3.8 Hz), 128.54, 130.49, 131.65 (q, *J* = 33.4 Hz), 139.17, 140.30, 148.08, 160.41, 162.94, 193.93. ¹⁹F NMR (282 MHz, CDCl₃): δ −62.76. **IR** (ATR film): 2946, 2852, 1609, 1570, 1481, 1452, 1414, 1389, 1362, 1321, 1288, 1273, 1216, 1180, 1116, 1068, 1034, 1017, 979, 954, 834, 734, 716, 673, 652, 593, 571, 535. **HR-MS** (ESI): *m/z* calcd for [C₃₆H₂₉F₆O₆]⁺ ([M + H⁺]): 671.1863, found: 671.1866. **Melting point:** 208–209 °C.

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4'-dimethoxy-6,6'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(3-(4-bromophenyl)prop-2-en-1-one) (**7ae**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4a** (200 mg, 0.56 mmol, 1.0 equiv) and 4-bromobenzaldehyde (**5e**) (248 mg, 1.34 mmol, 2.4 equiv). The product was isolated as orange solids (364 mg, 0.53 mmol, 94%). ¹H NMR (600 MHz, CDCl₃): δ 2.11 (s, 6H), 3.99 (s, 6H), 6.43 (s, 2H), 7.47 (d, *J* = 8.5 Hz, 4H), 7.54 (d, *J* = 8.4 Hz, 3H), 7.71 (d, *J* = 15.6 Hz, 2H), 7.90 (d, *J* = 15.6 Hz, 2H), 13.65 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 21.06, 56.00, 103.51, 110.00, 117.80, 124.43, 128.73, 129.88, 132.29, 134.68, 141.07, 147.79, 160.35, 162.90, 194.02. **IR** (ATR film): 2970, 2941, 2848, 2251, 1627, 1605, 1559, 1485, 1389, 1359, 1323, 1213, 1178, 1141, 1114, 1072, 1035, 1009, 979, 946, 908, 875, 819, 801, 786, 731, 648, 632, 604, 571, 535, 507, 491. **HR-MS** (ESI): *m/z* calcd for [C₃₄H₂₉O₆Br₂]⁺ ([M + H⁺]): 691.0325, found: 691.0324. **Melting point:** 230–236 °C.

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4'-dimethoxy-6,6'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(3-(3-bromophenyl)prop-2-en-1-one) (**7af**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4a** (200 mg, 0.56 mmol, 1.0 equiv) and 3-bromobenzaldehyde (**5f**) (0.16 mL, 1.34 mmol, 2.4 equiv). The product was isolated as orange

solids (335 mg, 0.48 mmol, 86%). ¹H NMR (600 MHz, CDCl₃): δ 2.11 (s, 6H), 4.00 (s, 6H), 6.44 (s, 2H), 7.29 (t, J = 7.8 Hz, 2H), 7.51 (dt, J = 8.1, 1.5 Hz, 4H), 7.68 (d, J = 15.6 Hz, 2H), 7.74 (t, J = 1.8 Hz, 2H), 7.89 (d, J = 15.6 Hz, 2H), 13.63 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 21.09, 56.04, 103.51, 109.92, 117.71, 123.15, 127.20, 129.43, 130.53, 131.06, 132.94, 137.88, 140.62, 147.92, 160.37, 162.90, 193.93. IR (ATR film): 2922, 1630, 1469, 1389, 1323, 1274, 1180, 1116, 1035, 907, 864, 795, 778, 730, 648. HR-MS (ESI): *m/z* calcd for [C₃₄H₂₉O₆Br₂]⁺ ([M + H]⁺): 691.0325, found: 691.0324. **Melting point:** 110 °C (decomposition).

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4'-dimethoxy-6,6'-dimethyl-[1,1'-biphenyl]-3,3'-diyl)bis(3-(2-bromophenyl)prop-2-en-1-one) (**7ag**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4a** (200 mg, 0.56 mmol, 1.0 equiv) and 2-bromobenzaldehyde (**5g**) (0.16 mL, 1.34 mmol, 2.4 equiv). The product was isolated as orange solids (253 mg, 0.36 mmol, 65%). ¹H NMR (600 MHz, CDCl₃): δ 2.11 (s, 6H), 3.98 (s, 6H), 6.43 (s, 2H), 7.24 (td, J = 7.7, 1.6 Hz, 2H), 7.36 (td, J = 7.4, 1.0 Hz, 2H), 7.64 (dd, J = 8.0, 1.3 Hz, 2H), 7.70 (dd, J = 7.8, 1.6 Hz, 2H), 7.85 (d, J = 15.5 Hz, 2H), 8.11 (d, J = 15.6 Hz, 2H), 13.61 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 20.93, 55.83, 103.33, 109.85, 117.63, 125.88, 127.62, 127.96, 130.69, 130.86, 133.54, 135.70, 140.43, 147.70, 160.21, 162.79, 193.76. IR (ATR film): 2851, 1610, 1573, 1465, 1361, 1214, 1180, 1117, 1027, 907, 730, 535. HR-MS (ESI): *m/z* calcd for [C₃₄H₂₉O₆Br₂]⁺ ([M + H]⁺): 691.0325, found: 691.0323. TLC (petroleum ether/EtOAc, 6:4 v/v): R_f = 0.44 **Melting point:** 220–221 °C.

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-3,3'-diyl)bis(3-(4-methoxyphenyl)prop-2-en-1-one) (**7ba**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4b** (200 mg, 0.56 mmol, 1.0 equiv) and 4-methoxybenzaldehyde (**5a**) (0.15 mL, 1.23 mmol, 2.4 equiv). The product was isolated as yellow solids (145 mg, 0.25 mmol, 45%). The analytical data is in accordance with the literature.²⁹ ¹H NMR (600 MHz, CDCl₃): δ 3.86 (s, 12H), 4.01 (s, 6H), 6.14 (s, 2H), 6.93 (d, J = 8.6 Hz, 4H), 7.56 (d, J = 8.5 Hz, 4H), 7.76 (d, J = 15.5 Hz, 2H), 7.82 (d, J = 15.6 Hz, 2H), 14.20 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 55.55, 55.98, 56.08, 87.20, 103.27, 106.93, 114.50, 125.90, 128.69, 130.18, 142.07, 161.40, 162.93, 164.02, 164.78, 193.18. IR (ATR film): 1739, 1622, 1604, 1510, 1466, 1407, 1371, 1290, 1255, 1215, 1171, 1122, 829, 801, 776, 603, 559, 539, 520. HR-MS (ESI): *m/z* calcd for [C₃₆H₃₅O₁₀]⁺ ([M + H]⁺): 627.2225, found: 627.2227. **Melting point:** 284–285 °C (282–285 °C).²⁹

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-3,3'-diyl)bis(3-phenylprop-2-en-1-one) (**7bb**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4b** (200 mg, 0.51 mmol, 1.0 equiv) and benzaldehyde (**5b**) (0.19 mL, 1.85 mmol, 2.4 + 1.2 equiv). The product was isolated as yellow solids (65.8 mg, 0.13 mmol, 23%). ¹H NMR (600 MHz, CDCl₃): δ 3.86 (s, 6H), 4.02 (s, 6H), 6.15 (s, 2H), 7.37–7.44 (m, 6H), 7.61 (d, J = 7.1 Hz, 4H), 7.77 (d, J = 15.6 Hz, 2H), 7.91 (d, J = 15.6 Hz, 2H), 14.11 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 56.00, 56.10, 87.20, 103.20, 106.90, 128.25, 128.47, 129.00, 130.04, 135.94, 141.97, 163.06, 164.25, 164.80, 193.25. IR (ATR film): 2918, 2850, 1737, 1617, 1560, 1470, 1450, 1435, 1373, 1331, 1287, 1217, 1179, 1155, 1122, 1037, 870, 804, 762, 726, 703, 685, 662, 633, 576, 532, 477. HR-MS (ESI): *m/z* calcd for

[C₃₄H₃₁O₈]⁺ ([M + H]⁺): 567.2013, found: 567.2020. **Melting point:** 272 °C (decomposition).

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-3,3'-diyl)bis(3-(4-(dimethylamino)phenyl)prop-2-en-1-one) (**7bc**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4b** (200 mg, 0.51 mmol, 1.0 equiv) and 4-(dimethylamino)-benzaldehyde (**5c**) (183.4 mg, 1.23 mmol, 2.4 equiv) at 90 °C. The product was isolated as red solids (80.2 mg, 0.13 mmol, 24%). (Due to poor solubility in CDCl₃, and *d*₆-DMSO, only a ¹H NMR spectrum could be obtained.) ¹H NMR (600 MHz, CDCl₃): δ 3.04 (s, 12H), 3.84 (s, 6H), 4.00 (s, 6H), 6.13 (s, 2H), 6.70 (d, J = 8.6 Hz, 4H), 7.52 (d, J = 8.5 Hz, 4H), 7.76 (d, J = 15.4 Hz, 2H), 7.81 (d, J = 15.4 Hz, 2H), 14.37 (s, 2H). IR (ATR film): 2850, 1598, 1542, 1527, 1467, 1434, 1411, 1370, 1334, 1295, 1214, 1168, 1114, 1038, 996, 982, 970, 863, 818, 776, 722, 702, 662, 605, 543. HR-MS (ESI): *m/z* calcd for [C₃₈H₄₁N₂O₈]⁺ ([M + H]⁺): 653.2857, found: 653.2851. **Melting point:** 302 °C (decomposition).

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-3,3'-diyl)bis(3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one) (**7bd**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4b** (200 mg, 0.51 mmol, 1.0 equiv) and 4-(trifluoromethyl)-benzaldehyde (**5d**) (0.17 mL, 1.23 mmol, 2.4 equiv). The product was isolated as yellow solids (95.0 mg, 0.15 mmol, 27%). ¹H NMR (600 MHz, CDCl₃): δ 3.87 (s, 6H), 4.02 (s, 6H), 6.15 (s, 2H), 7.66 (d, J = 8.2 Hz, 4H), 7.69 (d, J = 8.2 Hz, 4H), 7.73 (d, J = 15.7 Hz, 2H), 7.94 (d, J = 15.7 Hz, 2H), 13.99 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 56.05, 56.12, 87.21, 103.14, 106.80, 124.12 (q, J = 271.3 Hz), 125.96 (q, J = 3.8 Hz), 128.45, 130.61, 131.46 (q, J = 32.7 Hz), 139.36, 139.75, 163.13, 164.57, 164.83, 192.79. ¹⁹F NMR (282 MHz, CDCl₃): δ –62.74. IR (ATR film): 2921, 2852, 1731, 1611, 1566, 1467, 1405, 1321, 1286, 1215, 1122, 1067, 1032, 1016, 954, 907, 834, 775, 732, 649, 597, 531. HR-MS (ESI): *m/z* calcd for [C₃₆H₂₉F₆O₈]⁺ ([M + H]⁺): 703.1761, found: 703.1767. **Melting point:** 251 °C (decomposition).

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-3,3'-diyl)bis(3-(4-bromophenyl)prop-2-en-1-one) (**7be**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4b** (200 mg, 0.56 mmol, 1.0 equiv) and 4-bromobenzaldehyde (**5e**) (227 mg, 1.23 mmol, 2.4 equiv). The product was isolated as yellow solids (202 mg, 0.31 mmol, 55%). ¹H NMR (600 MHz, CDCl₃): δ 3.86 (s, 6H), 4.01 (s, 6H), 6.14 (s, 2H), 7.45 (d, J = 8.4 Hz, 4H), 7.53 (d, J = 8.3 Hz, 4H), 7.67 (d, J = 15.6 Hz, 2H), 7.88 (d, J = 15.6 Hz, 2H), 14.05 (s, 2H). ¹³C NMR (151 MHz, CDCl₃): δ 56.03, 56.10, 87.20, 103.17, 106.83, 124.19, 128.83, 129.79, 132.24, 134.86, 140.51, 163.05, 164.38, 164.80, 192.92. IR (ATR film): 2918, 2850, 1738, 1628, 1556, 1486, 1471, 1436, 1399, 1372, 1328, 1291, 1214, 1180, 1154, 1090, 1073, 1033, 1009, 974, 820, 648, 631. HR-MS (ESI): *m/z* calcd for [C₃₄H₂₉Br₂O₈]⁺ ([M + H]⁺): 723.0220, found: 723.0224. **Melting point:** 274 °C (decomposition).

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-3,3'-diyl)bis(3-(3-bromophenyl)prop-2-en-1-one) (**7bf**). Synthesized in accordance with **General Procedure B**. Starting from acetophenone **4b** (200 mg, 0.56 mmol, 1.0 equiv) and 3-bromobenzaldehyde (**5f**) (0.14 mL, 1.23 mmol, 2.4 equiv). The product was obtained as yellow solids (124 mg). A 3:1 mix of chalcone:flavanone with monoaddition product present (according to ¹H NMR). ¹H

NMR reported for the major chalcone product. ^1H NMR (600 MHz, CDCl_3): δ 3.86 (d, 6H), 4.03 (s, 6H), 6.15 (s, 2H), 7.29 (t, J = 7.9 Hz, 2H), 7.50 (d, J = 7.8 Hz, 4H), 7.65 (d, J = 15.5 Hz, 2H), 7.73 (s, 2H), 7.87 (d, J = 15.6 Hz, 2H), 14.03 (s, 2H). HR-MS (ESI): m/z calcd for $[\text{C}_{34}\text{H}_{29}\text{Br}_2\text{O}_8]^+$ ($[\text{M} + \text{H}^+]$): 723.0221, found: 723.0224.

rac-(2*E*,2'*E*)-1,1'-(2,2'-Dihydroxy-4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-3,3'-diyl)bis(3-(2-bromophenyl)prop-2-en-1-one) (7bg). Synthesized in accordance with General Procedure B. Starting from acetophenone 4b (200 mg, 0.56 mmol, 1.0 equiv) and 2-bromobenzaldehyde (5g) (0.14 mL, 1.23 mmol, 2.4 equiv), 1.5 h reaction time. The product was obtained as yellow solids (84.7 mg). A 5:1 mix of chalcone:flavanone with monoaddition product present (according to ^1H NMR). ^1H NMR reported for the major chalcone product. ^1H NMR (600 MHz, CDCl_3): δ 3.86 (s, 6H), 4.00 (s, 6H), 6.13 (s, 2H), 7.22 (t, J = 7.7 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 7.6 Hz, 3H), 7.82 (d, J = 15.6 Hz, 2H), 8.07 (d, J = 15.6 Hz, 2H), 13.96 (s, 1H). HR-MS (ESI): m/z calcd for $[\text{C}_{34}\text{H}_{29}\text{Br}_2\text{O}_8]^+$ ($[\text{M} + \text{H}^+]$): 723.0216, found: 723.0224.

rac-5,5'-Dimethoxy-2,2'-bis(4-methoxyphenyl)-7,7'-dimethyl-4*H*,4'*H*-[8,8'-bichromene]-4,4'-dione (9aa). Synthesized in accordance with General Procedure D. Starting from bichalcone 7ab (30.0 mg, 50.7 μmol , 1.00 equiv) and I_2 (78.8 mM, 63 μL , 5.1 μmol , 10 mol %) in 1 h. The product was isolated by column chromatography (EtOAc/MeOH, 95:5 v/v) and was obtained as white solids (15.8 mg, 30.2 μmol , 53%). The analytical data was in accordance with the literature.²⁴ ^1H NMR (600 MHz, CDCl_3): δ 2.18 (s, 6H), 3.79 (s, 6H), 4.11 (s, 6H), 6.64 (s, 2H), 6.78 (d, J = 8.9 Hz, 4H), 6.88 (s, 2H), 7.23 (d, J = 8.9 Hz, 4H). ^{13}C NMR (151 MHz, CDCl_3): δ 20.76, 55.63, 56.72, 107.23, 108.34, 112.96, 114.66, 116.56, 123.48, 127.32, 144.67, 155.77, 159.28, 160.94, 162.32, 178.62. IR (ATR film): 2844, 2238, 1605, 1576, 1512, 1496, 1478, 1464, 1442, 1423, 1371, 1335, 1301, 1207, 1116, 1062, 1031, 976, 956, 909, 730, 644, 590. TLC (EtOAc/MeOH, 95:5 v/v): R_f = 0.26 HR-MS (ESI): m/z calcd for $[\text{C}_{36}\text{H}_{31}\text{O}_8]^+$ ($[\text{M} + \text{H}^+]$): 591.2013, found: 591.2020. Melting point: 295–296 $^\circ\text{C}$.

rac-5,5'-Dimethoxy-7,7'-dimethyl-2,2'-diphenyl-4*H*,4'*H*-[8,8'-bichromene]-4,4'-dione (9ab). Synthesized in accordance with General Procedure D. Starting from bichalcone 7ab (30.0 mg, 56.5 μmol , 1.00 equiv) and I_2 (78.8 mM, 72 μL , 5.7 μmol , 10 mol %). The product was isolated by column chromatography (EtOAc/MeOH, 98:2 v/v) and was obtained as white solids (6.2 mg, 12 μmol , 21%). ^1H NMR (600 MHz, CDCl_3): δ 2.19 (s, 6H), 4.11 (s, 6H), 6.73 (s, 2H), 6.89 (s, 2H), 7.26–7.33 (m, 8H), 7.34–7.40 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3): δ 20.65, 56.57, 108.28, 108.50, 112.92, 116.35, 125.44, 129.01, 131.09, 131.29, 144.81, 155.66, 159.20, 160.64, 178.44. IR (ATR film): 3005, 2848, 1640, 1597, 1578, 1495, 1479, 1464, 1450, 1370, 1333, 1307, 1281, 1258, 1207, 1189, 1122, 1062, 976, 955, 908, 850, 771, 730, 689, 665, 645, 612, 551, 531. TLC (EtOAc/MeOH, 98:2 v/v): R_f = 0.28 HR-MS (ESI): m/z calcd for $[\text{C}_{34}\text{H}_{27}\text{O}_6]^+$ ($[\text{M} + \text{H}^+]$): 531.1802, found: 531.1805. Melting point: 296 $^\circ\text{C}$.

rac-2,2'-Bis(4-(dimethylamino)phenyl)-5,5'-dimethoxy-7,7'-dimethyl-4*H*,4'*H*-[8,8'-bichromene]-4,4'-dione (9ac). Synthesized in accordance with General Procedure D. Starting from bichalcone 7ac (30.0 mg, 48.6 μmol , 1.00 equiv) and I_2 (78.8 mM, 62 μL , 4.9 μmol , 10 mol %). The product was isolated by column chromatography and was

obtained as orange solids (6.3 mg, 10 μmol , 21%). The reaction was repeatedly scaled up with bichalcone 7ac (575 mg, 0.93 mmol, 1.00 equiv). The product was isolated as orange solids (123 mg, 0.20 μmol , 21%). The purity of biflavone 9ac was assessed by reverse-phase HPLC (97.3%) and was in accordance with purity determined by ^1H NMR (96.9%). Stability experiments revealed that biflavone 9ac was stable in DMSO at up to 40 $^\circ\text{C}$ over 24 h. ^1H NMR (600 MHz, CDCl_3): δ 2.17 (s, 3H), 2.97 (s, 6H), 4.10 (s, 3H), 6.51 (d, J = 9.1 Hz, 4H), 6.58 (s, 1H), 6.86 (s, 1H), 7.16 (d, J = 9.0 Hz, 4H). ^{13}C NMR (151 MHz, CDCl_3): δ 20.71, 40.17, 56.64, 105.38, 108.02, 111.79, 112.83, 116.66, 117.70, 127.05, 144.20, 152.28, 155.70, 159.00, 161.92, 178.80. IR (ATR film): 2923, 2237, 1731, 1604, 1591, 1524, 1495, 1364, 1335, 1302, 1284, 1251, 1197, 1171, 1120, 1063, 908, 819, 761, 728, 662, 642, 582, 570, 544, 531, 512. TLC (EtOAc/ CH_2Cl_2 /MeOH, 7:2.5:0.5 v/v): R_f = 0.16 HR-MS (ESI): m/z calcd for $[\text{C}_{38}\text{H}_{37}\text{N}_2\text{O}_6]^+$ ($[\text{M} + \text{H}^+]$): 617.2646, found: 617.2653. Melting point: 196–197 $^\circ\text{C}$.

rac-5,5'-Dimethoxy-7,7'-dimethyl-2,2'-bis(4-(trifluoromethyl)phenyl)-4*H*,4'*H*-[8,8'-bichromene]-4,4'-dione (9ad). Synthesized in accordance with General Procedure D. Starting from bichalcone 7ad (30.0 mg, 45.0 μmol , 1.00 equiv) and I_2 (78.8 mM, 57 μL , 4.5 μmol , 10 mol %) for 2 h. The product was isolated by column chromatography (petroleum ether/EtOAc/isopropanol, 6:3:1 v/v) and was obtained as a white viscous semisolid (8.5 mg, 13 μmol , 28%). ^1H NMR (600 MHz, CDCl_3): δ 2.21 (s, 6H), 4.12 (s, 6H), 6.78 (s, 2H), 6.93 (s, 2H), 7.40 (d, J = 8.2 Hz, 4H), 7.56 (d, J = 8.3 Hz, 4H). ^{13}C NMR (151 MHz, CDCl_3): δ 20.83, 56.78, 108.68, 109.89, 113.06, 116.21, 123.61 (q, J = 272.1 Hz), 125.84, 126.22 (q, J = 3.7 Hz), 133.12 (q, J = 33.1 Hz), 134.59, 145.37, 155.68, 159.03, 159.52, 178.08. ^{19}F NMR (282 MHz, CDCl_3): δ -63.13. IR (ATR film): 2854, 1817, 1646, 1600, 1579, 1497, 1480, 1466, 1445, 1417, 1323, 1295, 1207, 1125, 1063, 1015, 977, 957, 909, 844, 777, 731, 625, 557, 532, 518. TLC (petroleum ether/EtOAc/isopropanol, 6:3:1 v/v): R_f = 0.21 HR-MS (ESI): m/z calcd for $[\text{C}_{36}\text{H}_{25}\text{F}_6\text{O}_6]^+$ ($[\text{M} + \text{H}^+]$): 667.1555, found: 667.1550. Melting point: 263–265 $^\circ\text{C}$.

rac-2,2'-Bis(4-bromophenyl)-5,5'-dimethoxy-7,7'-dimethyl-4*H*,4'*H*-[8,8'-bichromene]-4,4'-dione (9ae). Synthesized in accordance with General Procedure D. Starting from bichalcone 7ae (30.0 mg, 43.6 μmol , 1.00 equiv) and I_2 (78.8 mM, 55 μL , 4.4 μmol , 10 mol %). The product was obtained as white solids (27.7 mg, 40.1 μmol , 94%). ^1H NMR (600 MHz, CDCl_3): δ 2.18 (s, 6H), 4.10 (s, 6H), 6.69 (s, 2H), 6.89 (s, 2H), 7.14 (d, J = 8.7 Hz, 4H), 7.42 (d, J = 8.7 Hz, 4H). ^{13}C NMR (151 MHz, CDCl_3): δ 20.82, 56.74, 108.49, 108.77, 112.94, 116.23, 126.19, 126.93, 130.08, 132.49, 145.14, 155.62, 159.37, 159.72, 178.26. IR (ATR film): 3005, 2931, 2851, 2240, 1773, 1638, 1597, 1562, 1479, 1464, 1403, 1368, 1329, 1303, 1275, 1260, 1207, 1187, 1167, 1122, 1061, 1030, 1008, 977, 955, 907, 830, 794, 681, 645, 626, 573, 557, 532, 499, 478. HR-MS (ESI): m/z calcd for $[\text{C}_{34}\text{H}_{25}\text{O}_4\text{Br}_2]^+$ ($[\text{M} + \text{H}^+]$): 687.0012, found: 687.0017. Melting point: 245 $^\circ\text{C}$ (decomposition).

rac-2,2'-Bis(3-bromophenyl)-5,5'-dimethoxy-7,7'-dimethyl-4*H*,4'*H*-[8,8'-bichromene]-4,4'-dione (9af). Synthesized in accordance with General Procedure D. Starting from bichalcone 7af (30.0 mg, 43.6 μmol , 1.00 equiv) and I_2 (78.8 mM, 55 μL , 4.4 μmol , 10 mol %) for 1 h. The product was isolated by column chromatography (EtOAc 100%) and

was obtained as white solids (25.4 mg, 37.5 μmol , 86%). ^1H NMR (600 MHz, CDCl_3): δ 2.24 (s, 6H), 4.11 (s, 6H), 6.70 (s, 2H), 6.94 (s, 2H), 7.18 (t, J = 7.9 Hz, 2H), 7.31 (dt, J = 8.0, 1.4 Hz, 2H), 7.34 (t, J = 1.9 Hz, 2H), 7.49 (ddd, J = 8.0, 2.0, 1.0 Hz, 2H). ^{13}C NMR (151 MHz, CDCl_3): δ 20.84, 56.73, 108.62, 109.16, 113.03, 116.16, 123.38, 123.91, 128.77, 130.58, 133.21, 134.18, 145.20, 155.49, 158.77, 159.50, 178.11. IR (ATR film): 2851, 2241, 1642, 1598, 1561, 1496, 1478, 1442, 1417, 1367, 1299, 1266, 1206, 1124, 1062, 998, 956, 917, 847, 790, 730, 692, 646, 619, 571, 551, 532. TLC (EtOAc 100%): R_f = 0.26 HR-MS (ESI): m/z calcd for $[\text{C}_{34}\text{H}_{25}\text{O}_4\text{Br}_2]^+$ ($[\text{M} + \text{H}^+]$): 687.0012, found: 687.0005. Melting point: 276–278 $^\circ\text{C}$.

rac-2,2'-Bis(2-bromophenyl)-5,5'-dimethoxy-7,7'-dimethyl-4H,4'H-[8,8'-bichromene]-4,4'-dione (9ag). Synthesized in accordance with General Procedure D. Starting from bichalcone **7ag** (30.0 mg, 43.6 μmol , 1.00 equiv) and I_2 (78.8 mM, 55 μL , 4.4 μmol , 10 mol %) for 2 h. The product was obtained as white solids (16.5 mg, 24.0 μmol , 55%). ^1H NMR (600 MHz, CDCl_3): δ 2.12 (s, 6H), 4.02 (s, 6H), 6.46 (s, 2H), 6.78 (s, 2H), 7.20 (td, J = 7.4, 6.9, 2.0 Hz, 2H), 7.21–7.29 (m, 4H), 7.51 (dd, J = 7.8, 1.5 Hz, 2H). ^{13}C NMR (151 MHz, CDCl_3): δ 20.93, 56.54, 108.54, 113.00, 114.33, 116.56, 121.57, 127.67, 130.73, 131.78, 133.49, 134.22, 144.91, 156.39, 159.23, 161.62, 178.19. IR (ATR film): 3300, 2924, 2869, 2852, 1733, 1653, 1600, 1562, 1496, 1464, 1437, 1370, 1327, 1279, 1263, 1206, 1115, 1065, 976, 954, 912, 855, 763, 733, 703, 680, 645, 612. HR-MS (ESI): m/z calcd for $[\text{C}_{34}\text{H}_{25}\text{O}_4\text{Br}_2]^+$ ($[\text{M} + \text{H}^+]$): 687.0012, found: 687.0011. Melting point: 250 $^\circ\text{C}$ (decomposition).

rac-5,5',7,7'-Tetramethoxy-2,2'-bis(4-methoxyphenyl)-4H,4'H-[8,8'-bichromene]-4,4'-dione or Hexa-O-methylcupressuflavone (9ba). Synthesized in accordance with General Procedure D. Starting from bichalcone **7ba** (30.0 mg, 48.2 μmol , 1.00 equiv) and I_2 (78.8 mM, 61 μL , 4.8 μmol , 10 mol %). The product was isolated by column chromatography (EtOAc/MeOH, 9:1 v/v) and was obtained as white solids (23.1 mg, 37.1 μmol , 77%). The analytical data was in accordance with the literature.²⁹ ^1H NMR (600 MHz, CDCl_3): δ 3.77 (s, 6H), 3.86 (s, 6H), 4.12 (s, 6H), 6.58 (s, 2H), 6.59 (s, 2H), 6.77 (d, J = 8.9 Hz, 4H), 7.29 (d, J = 8.9 Hz, 4H). ^{13}C NMR (151 MHz, CDCl_3): δ 55.47, 56.13, 56.60, 91.78, 102.13, 106.80, 109.05, 114.39, 123.54, 127.15, 156.57, 160.66, 161.29, 161.74, 162.03, 178.14. IR (ATR film): 1637, 1593, 1465, 1424, 1388, 1338, 1304, 1180, 1111, 1033, 919, 834, 588, 567. TLC (EtOAc/MeOH, 9:1 v/v): R_f = 0.22 HR-MS (ESI): m/z calcd for $[\text{C}_{36}\text{H}_{31}\text{O}_{10}]^+$ ($[\text{M} + \text{H}^+]$): 623.1912, found: 623.1912. Melting point: 240.0 $^\circ\text{C}$ (brown discoloration) 285–286 $^\circ\text{C}$ (294–295 $^\circ\text{C}$).²⁹

rac-5,5',7,7'-Tetramethoxy-2,2'-diphenyl-4H,4'H-[8,8'-bichromene]-4,4'-dione (9bb). Synthesized in accordance with General Procedure D. Starting from **7bb** (30.0 mg, 53.3 μmol , 1.00 equiv) and I_2 (78.8 mM, 68 μL , 5.3 μmol , 10 mol %) for 2 h. The product was isolated by column chromatography (EtOAc/MeOH, 98:2 v/v) and was obtained as white solids (17.6 mg, 31.4 μmol , 59%). The analytical data was in accordance with the literature.³⁴ ^1H NMR (600 MHz, CDCl_3): δ 3.85 (s, 6H), 4.12 (s, 6H), 6.59 (s, 2H), 6.68 (s, 2H), 7.28 (d, J = 7.4 Hz, 4H), 7.33–7.40 (m, 6H). ^{13}C NMR (151 MHz, CDCl_3): δ 56.25, 56.72, 91.92, 102.19, 108.36, 109.29, 125.56, 129.01, 131.23, 131.42, 156.77, 160.62, 161.51, 161.99, 178.19. IR (ATR film): 3067, 2844, 2238, 1635, 1590, 1508, 1491, 1465, 1450, 1435, 1388, 1333, 1299, 1265, 1214, 1190, 1172,

1125, 1109, 1087, 1036, 1022, 957, 917, 849, 812, 771, 728, 689, 672, 644, 618, 570, 546, 514. TLC (EtOAc/MeOH, 98:2 v/v): R_f = 0.12 HR-MS (ESI): m/z calcd for $[\text{C}_{34}\text{H}_{27}\text{O}_8]^+$ ($[\text{M} + \text{H}^+]$): 563.1700, found: 563.1707. Melting point: 312–313 $^\circ\text{C}$ (318–319 $^\circ\text{C}$).³⁴

rac-2,2'-Bis(4-(dimethylamino)phenyl)-5,5',7,7'-tetramethoxy-4H,4'H-[8,8'-bichromene]-4,4'-dione (9bc). Synthesized in accordance with General Procedure D. Starting from **7bc** (30.0 mg, 46.3 μmol , 1.00 equiv) and I_2 (78.8 mM, 59 μL , 4.6 μmol , 10 mol %). The product was isolated by column chromatography (CH_2Cl_2 /EtOAc/MeOH, 5:4.5:0.5 v/v) and obtained as orange solids (7.7 mg, 12 μmol , 26%). ^1H NMR (600 MHz, CDCl_3): δ 2.95 (s, 12H), 3.86 (s, 6H), 4.11 (s, 6H), 6.50 (d, J = 8.9 Hz, 4H), 6.53 (s, 2H), 6.56 (s, 2H), 7.21 (d, J = 9.0 Hz, 4H). ^{13}C NMR (151 MHz, CDCl_3): δ 40.19, 56.24, 56.71, 91.82, 102.44, 105.21, 109.21, 111.78, 118.11, 127.09, 152.25, 156.70, 161.21, 161.61, 161.82, 178.44. IR (ATR film): 2942, 2234, 1630, 1601, 1586, 1524, 1487, 1465, 1434, 1387, 1366, 1336, 1305, 1253, 1214, 1198, 1171, 1124, 1064, 1030, 1001, 947, 917, 840, 819, 783, 766, 729, 664, 643, 582, 563, 513, 486. TLC (CH_2Cl_2 /EtOAc/MeOH, 5:4.5:0.5 v/v): R_f = 0.14 HR-MS (ESI): m/z calcd for $[\text{C}_{38}\text{H}_{37}\text{N}_2\text{O}_8]^+$ ($[\text{M} + \text{H}^+]$): 649.2544, found: 649.2546.

rac-5,5',7,7'-Tetramethoxy-2,2'-bis(4-(trifluoromethyl)phenyl)-4H,4'H-[8,8'-bichromene]-4,4'-dione (9bd). Synthesized in accordance with General Procedure D. Starting from **7bd** (30.0 mg, 42.9 μmol , 1.00 equiv) and I_2 (78.8 mM, 54 μL , 4.3 μmol , 10 mol %) for 2 h. The product was isolated by column chromatography (petroleum ether/EtOAc/*i*PrOH, 2:7:1 v/v) and obtained as white solids (17.7 mg, 25.3 μmol , 59%). ^1H NMR (600 MHz, CDCl_3): δ 3.89 (s, 6H), 4.15 (s, 6H), 6.62 (s, 2H), 6.73 (s, 2H), 7.46 (d, J = 8.2 Hz, 4H), 7.56 (d, J = 8.3 Hz, 4H). ^{13}C NMR (151 MHz, CDCl_3): δ 56.32, 56.77, 92.04, 101.94, 109.24, 109.63, 123.64 (q, J = 271.8 Hz), 125.80, 126.09 (q, J = 3.6 Hz), 132.92 (q, J = 32.9 Hz), 134.79, 156.67, 158.84, 161.72, 162.24, 177.67. ^{19}F NMR (282 MHz, CDCl_3): δ –63.08. IR (ATR film): 1622, 1594, 1416, 1388, 1324, 1216, 1170, 1128, 1070, 1027, 958, 919, 843, 812. TLC (petroleum ether/EtOAc/*i*PrOH, 2:7:1 v/v): R_f = 0.35 HR-MS (ESI): m/z calcd for $[\text{C}_{36}\text{H}_{25}\text{N}_2\text{O}_8]^+$ ($[\text{M} + \text{H}^+]$): 699.1448, found: 699.1450. Melting point: 261–262 $^\circ\text{C}$.

rac-2,2'-Bis(4-bromophenyl)-5,5',7,7'-tetramethoxy-4H,4'H-[8,8'-bichromene]-4,4'-dione (9be). Synthesized in accordance with General Procedure D. Starting from **7be** (30.0 mg, 41.6 μmol , 1.00 equiv) and I_2 (78.8 mM, 53 μL , 4.2 μmol , 10 mol %) for 2 h. The product was isolated by column chromatography (petroleum ether/EtOAc/*i*PrOH, 2:7:1 v/v) and obtained as white solids (20.9 mg, 29.1 μmol , 70%). ^1H NMR (600 MHz, CDCl_3): δ 3.86 (s, 6H), 4.12 (s, 6H), 6.58 (s, 2H), 6.64 (s, 2H), 7.20 (d, J = 8.4 Hz, 4H), 7.42 (d, J = 8.5 Hz, 4H). ^{13}C NMR (151 MHz, CDCl_3): δ 56.28, 56.74, 91.93, 101.96, 108.51, 109.17, 125.95, 126.92, 130.30, 132.35, 156.60, 159.53, 161.60, 162.07, 177.85. IR (ATR film): 2885, 2239, 1638, 1590, 1508, 1487, 1465, 1435, 1403, 1388, 1331, 1302, 1274, 1215, 1190, 1171, 1127, 1107, 1073, 1027, 1009, 958, 828, 782, 730, 687, 644, 626, 572, 545, 517, 477. TLC (petroleum ether/EtOAc/*i*PrOH, 2:7:1 v/v): R_f = 0.21 HR-MS (ESI): m/z calcd for $[\text{C}_{34}\text{H}_{25}\text{O}_8\text{Br}_2]^+$ ($[\text{M} + \text{H}^+]$): 718.9911, found: 718.9915. Melting point: 251–255 $^\circ\text{C}$.

rac-2,2'-Bis(2-bromophenyl)-5,5',7,7'-tetramethoxy-4H,4'H-[8,8'-bichromene]-4,4'-dione (9bg). Synthesized in accordance with General Procedure D. Starting from **7bg** (30.0 mg, 41.6 μmol , 1.00 equiv) and I_2 (78.8 mM, 53 μL , 4.2

μmol , 10 mol %) for 1 h. The product was isolated by column chromatography (EtOAc/MeOH, 9:1 v/v) and obtained as white solids (16.7 mg, 23.3 μmol , 56%). ^1H NMR (600 MHz, CDCl_3): δ 3.84 (s, 6H), 4.06 (s, 6H), 6.47 (s, 2H), 6.50 (s, 2H), 7.23 (ddd, J = 7.8, 4.0, 2.4 Hz, 4H), 7.27–7.29 (m, 2H), 7.53–7.57 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3): δ 56.20, 56.58, 91.98, 102.18, 109.12, 114.04, 121.57, 127.62, 130.63, 131.65, 133.50, 134.24, 157.33, 161.14, 161.41, 162.13, 177.82. IR (ATR film): 3493, 2940, 2842, 2244, 1646, 1593, 1472, 1434, 1389, 1336, 1214, 1109, 1025, 730. TLC (EtOAc/MeOH, 9:1 v/v): R_f = 0.32 HR-MS (ESI): m/z calcd for $[\text{C}_{34}\text{H}_{25}\text{O}_8\text{Br}_2]^+$ ($[\text{M} + \text{H}^+]$): 718.9911, found: 718.9916 Melting point: 260 $^\circ\text{C}$ (decomposition).

rac-2,2'-Bis(4-(dimethylamino)phenyl)-5,5'-dihydroxy-7,7'-dimethyl-4H,4'H-[8,8'-bichromene]-4,4'-dione (**11**). A dry 25 mL Schlenk round-bottom flask was charged with biflavone **9ac** (40.0 mg, 0.06 mmol, 1.0 equiv) and anhyd. CH_2Cl_2 (2.5 mL). The solution was cooled to -78°C , and BCl_3 (1 M in CH_2Cl_2 , 0.14 mL, 0.14 mmol, 2.2 equiv) was added dropwise. The cooling bath was left to warm up overnight. After 16 h of reaction time, KPi-buffer ($\text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$, 1 M, pH 7, 10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), and the combined organic phases were washed with sat. aq. NaCl solution (20 mL). The crude product was isolated by column chromatography (EtOAc/MeOH, 9:1 v/v) and obtained as orange crystals (16.9 mg, 0.03 μmol , 44%). ^1H NMR (600 MHz, CDCl_3): δ 2.15 (s, 6H), 3.01 (s, 12H), 6.56 (s, 2H), 6.58 (d, J = 9.0 Hz, 4H), 6.87 (s, 2H), 7.28 (d, J = 9.0 Hz, 4H), 12.99 (s, 2H). ^{13}C NMR (151 MHz, CDCl_3): δ 20.78, 40.17, 102.04, 109.12, 111.85, 112.58, 113.33, 117.29, 127.63, 146.42, 152.81, 153.79, 160.16, 165.32, 183.41. IR (ATR film): 2923, 1649, 1588, 1520, 1482, 1360, 1246, 1201, 1163, 1110, 1034, 814. TLC (petroleum ether/EtOAc, 55:45 v/v): R_f = 0.3 HR-MS (ESI): m/z calcd for $[\text{C}_{36}\text{H}_{33}\text{N}_2\text{O}_6]^+$ ($[\text{M} + \text{H}^+]$): 589.2333, found: 589.2340 Melting point: 280–283 $^\circ\text{C}$.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.3c06503>

Coordinates of the X-ray structure of compound **4a**; bioactivity data; additional synthesis procedures; computational details including all coordinates; copies of all ^1H and ^{13}C spectral data; HPLC chromatograms; and material and methods for biological assays as well as biological activity graphs (PDF)

Compound **4a** piet13 (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Jörg Pietruszka – Institute of Bioorganic Chemistry, Heinrich Heine University Düsseldorf, Forschungszentrum Jülich, 52426 Jülich, Germany; Institut für Bio- und Geowissenschaften (IBG-1: Bioorganische Chemie) Forschungszentrum, 52428 Jülich, Germany; orcid.org/0000-0002-9819-889X; Email: j.pietruszka@fz-juelich.de

Authors

Moritz K. T. Klischan – Institute of Bioorganic Chemistry, Heinrich Heine University Düsseldorf, Forschungszentrum Jülich, 52426 Jülich, Germany

Flaminia Mazzone – Institute of Medical Microbiology and Hospital Hygiene, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany; orcid.org/0000-0003-1429-230X

Lena Berning – Institute of Molecular Medicine I, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany

Julian Greb – Institute of Bioorganic Chemistry, Heinrich Heine University Düsseldorf, Forschungszentrum Jülich, 52426 Jülich, Germany

Max Schlammkow – Institute of Bioorganic Chemistry, Heinrich Heine University Düsseldorf, Forschungszentrum Jülich, 52426 Jülich, Germany; Institut für Bio- und Geowissenschaften (IBG-1: Bioorganische Chemie) Forschungszentrum, 52428 Jülich, Germany

Mona Haase – Institute of Bioorganic Chemistry, Heinrich Heine University Düsseldorf, Forschungszentrum Jülich, 52426 Jülich, Germany

Wolfgang Frey – Institute of Organic Chemistry, University of Stuttgart, 70569 Stuttgart, Germany

Björn Stork – Institute of Molecular Medicine I, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany; orcid.org/0000-0002-4167-7806

Klaus Pfeffer – Institute of Medical Microbiology and Hospital Hygiene, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany

Complete contact information is available at:

<https://pubs.acs.org/doi/10.1021/acsomega.3c06503>

■ Author Contributions

#F.M., L.B. and J.G. contributed equally to this work.

■ Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the DFG (GRK2158), the Forschungszentrum Jülich GmbH, and the Heinrich Heine University (HHU) for their generous support. The authors thank Ruth Ganardi, Sebastian Myllek, Karin Buchholz, Daniel Degrandi, and Ursula Sorg for their scientific consultation, Birgit Henßen for HPLC support, and Vera Ophoven for synthesis support.

■ REFERENCES

- (1) Murti, V.; Raman, P.; Seshadri, T. Cupressuflavone, a new biflavonyl pigment. *Tetrahedron* **1967**, *23*, 397–404.
- (2) Molyneux, R.; Waiss, A., Jr; Haddon, W. Oxidative coupling of apigenin. *Tetrahedron* **1970**, *26*, 1409–1416.
- (3) Rahman, W.; Bhatnagar, S. A new biflavonyl AC3 from *Araucaria cunninghamii*. *Tetrahedron Lett.* **1968**, *9*, 675–678.
- (4) Murti, V.; Raman, P.; Seshadri, T. Cupressuflavone, a new member of the biflavonyl group. *Tetrahedron Lett.* **1964**, *5*, 2995–2997.
- (5) Natarajan, S.; Murti, V.; Seshadri, T. Biflavones of some Cupressaceae plants. *Phytochemistry* **1970**, *9*, 575–579.
- (6) Inatomi, Y.; Iida, N.; Murata, H.; Inada, A.; Murata, J.; Lang, F. A.; Iinuma, M.; Tanaka, T.; Nakanishi, T. A pair of new atropisomeric cupressuflavone glucosides isolated from *Juniperus communis* var. *depressa*. *Tetrahedron Lett.* **2005**, *46*, 6533–6535.
- (7) Yu, S.; Yan, H.; Zhang, L.; Shan, M.; Chen, P.; Ding, A.; Li, S. F. Y. A review on the phytochemistry, pharmacology, and pharmacoki-

netics of amentoflavone, a naturally-occurring biflavonoid. *Molecules* **2017**, *22*, No. 299.

(8) Kim, H. P.; Park, H.; Son, K. H.; Chang, H. W.; Kang, S. S. Biochemical pharmacology of biflavonoids: implications for anti-inflammatory action. *Arch. Pharmacol. Res.* **2008**, *31*, 265–273.

(9) Lin, Y.-M.; Flavin, M. T.; Schure, R.; Chen, F.-C.; Sidwell, R.; Barnard, D. I.; Huffmann, J. H.; Kern, E. R. Antiviral activities of biflavonoids. *Planta Med.* **1999**, *65*, 120–125.

(10) Adnan, M.; Rasul, A.; Hussain, G.; Shah, M. A.; Zahoor, M. K.; Anwar, H.; Sarfraz, I.; Riaz, A.; Manzoor, M.; Adem, Ş.; Selamoglu, Z. Ginkgetin: A natural biflavone with versatile pharmacological activities. *Food Chem. Toxicol.* **2020**, *145*, No. 111642.

(11) Yamaguchi, L. F.; Kato, M. J.; Di Mascio, P. Biflavonoids from *Araucaria angustifolia* protect against DNA UV-induced damage. *Phytochemistry* **2009**, *70*, 615–620.

(12) Gontijo, V. S.; dos Santos, M. H.; Viegas, C., Jr Biological and chemical aspects of natural biflavonoids from plants: a brief review. *Mini Rev. Med. Chem.* **2017**, *17*, 834–862.

(13) Tasdemir, D.; Kaiser, M.; Brun, R.; Yardley, V.; Schmidt, T. J.; Tosun, F.; Rüedi, P. Antitrypanosomal and antileishmanial activities of flavonoids and their analogues: in vitro, in vivo, structure-activity relationship, and quantitative structure-activity relationship studies. *Antimicrob. Agents Chemother.* **2006**, *50*, 1352–1364.

(14) Al-Sayed, E.; Gad, H. A.; El-Shazly, M.; Abdel-Daim, M. M.; Singab, A. N. Anti-inflammatory and analgesic activities of cupressuflavone from *Cupressus macrocarpa*: Impact on pro-inflammatory mediators. *Drug Dev. Res.* **2018**, *79*, 22–28.

(15) Freitas, A.; Almeida, M.; Andrighetti-Fröhner, C.; Cardozo, F.; Barardi, C.; Farias, M.; Simões, C. Antiviral activity-guided fractionation from *Araucaria angustifolia* leaves extract. *J. Ethnopharmacol.* **2009**, *126*, 512–517.

(16) Siddiqui, J. A.; Swarnkar, G.; Sharan, K.; Chakravarti, B.; Sharma, G.; Rawat, P.; Kumar, M.; Khan, F. M.; Pierroz, D.; Maurya, R. 8, 8''-Biapigeninyl stimulates osteoblast functions and inhibits osteoclast and adipocyte functions: Osteoprotective action of 8, 8''-biapigeninyl in ovariectomized mice. *Mol. Cell. Endocrinol.* **2010**, *323*, 256–267.

(17) Al-Sayed, E.; Abdel-Daim, M. M. Protective role of Cupressuflavone from *Cupressus macrocarpa* against carbon tetrachloride-induced hepato-and nephrotoxicity in mice. *Planta Med.* **2014**, *80*, 1665–1671.

(18) Sasaki, H.; Kitoh, Y.; Tsukada, M.; Miki, K.; Koyama, K.; Juliawaty, L. D.; Hakim, E. H.; Takahashi, K.; Kinoshita, K. Inhibitory activities of biflavonoids against amyloid- β peptide 42 cytotoxicity in PC-12 cells. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2831–2833.

(19) DeForest, J. C.; Du, L.; Joyner, P. M. 4', 4'', 7, 7''-Tetra-O-methylcupressuflavone Inhibits Seed Germination of *Lactuca sativa*. *J. Nat. Prod.* **2014**, *77*, 1093–1096.

(20) Frank, M.; Niemann, H.; Böhler, P.; Stork, B.; Wesselborg, S.; Lin, W.; Proksch, P. Phomoxanthone A-from mangrove forests to anticancer therapy. *Curr. Med. Chem.* **2015**, *22*, 3523–3532.

(21) Zhang, W.; Krohn, K.; Flörke, U.; Pescitelli, G.; Di Bari, L.; Antus, S.; Kurtán, T.; Rheinheimer, J.; Draeger, S.; Schulz, B. New Mono- and Dimeric Members of the Secalonic Acid Family: Blennolides A–G Isolated from the Fungus *Blennoria* sp. *Chem. - Eur. J.* **2008**, *14*, 4913–4923.

(22) Kikuchi, H.; Isobe, M.; Sekiya, M.; Abe, Y.; Hoshikawa, T.; Ueda, K.; Kurata, S.; Katou, Y.; Oshima, Y. Structures of the dimeric and monomeric chromanones, gonytolides A–C, isolated from the fungus *Gonytrichum* sp. and their promoting activities of innate immune responses. *Org. Lett.* **2011**, *13*, 4624–4627.

(23) Sirimangalakitti, N.; Juliawaty, L. D.; Hakim, E. H.; Waliana, I.; Saito, N.; Koyama, K.; Kinoshita, K. Naturally occurring biflavonoids with amyloid β aggregation inhibitory activity for development of anti-Alzheimer agents. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1994–1997.

(24) Kikuchi, H.; Hoshikawa, T.; Kurata, S.; Katou, Y.; Oshima, Y. Design and synthesis of Structure-Simplified derivatives of Gonytolide

for the promotion of innate immune responses. *J. Nat. Prod.* **2016**, *79*, 1259–1266.

(25) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. Function-oriented synthesis, step economy, and drug design. *Acc. Chem. Res.* **2008**, *41*, 40–49.

(26) Brown, D. G.; Bostrom, J. Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? Miniperspective. *J. Med. Chem.* **2016**, *59*, 4443–4458.

(27) Singh, M.; Kaur, M.; Silakari, O. Flavones: An important scaffold for medicinal chemistry. *Eur. J. Med. Chem.* **2014**, *84*, 206–239.

(28) Ahmad, S.; Razaq, S. A new approach to the synthesis of symmetrical biflavones. *Tetrahedron Lett.* **1971**, *12*, 4633–4636.

(29) Ahmad, S.; Razaq, S. New synthesis of biflavones of cupressuflavone series. *Tetrahedron* **1976**, *32*, 503–506.

(30) Li, H.-Y.; Nehira, T.; Hagiwara, M.; Harada, N. Total Synthesis and Absolute Stereochemistry of the Natural Atropisomer of the Biflavone 4', 4'', 7, 7''-Tetra-O-methylcupressuflavone. *J. Org. Chem.* **1997**, *62*, 7222–7227.

(31) Lin, G.-Q.; Zhong, M. The first enantioselective synthesis of optically pure (R)- and (S)-5, 5''-dihydroxy-4', 4'', 7, 7''-tetramethoxy-8, 8''-biflavone and the reconfirmation of their absolute configuration. *Tetrahedron Lett.* **1997**, *38*, 1087–1090.

(32) Parthasarathy, M.; Gupta, S. Oxidative coupling of phloracetophenone dimethyl ether, resacetophenone and resacetophenone monomethyl ether using silica-bound FeCl₃. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1984**, *23*, 227–230.

(33) Lee, C. Y.; Cheon, C. H. Diastereomeric Resolution of a Racemic Biarylboronic Acid and Its Application to Divergent Asymmetric Total Syntheses of Some Axially Chiral Natural Products. *Adv. Synth. Catal.* **2016**, *358*, 549–554.

(34) Zhang, F. J.; Lin, G. Q. Synthesis of the optically pure 5, 5''-dihydroxy-7, 7''-dimethoxy-8, 8''-biflavone and its derivatives. *Chin. J. Chem.* **1997**, *15*, 464–471.

(35) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Atropselective Synthese axial-chiraler Biaryle. *Angew. Chem.* **2005**, *117*, 5518–5563.

(36) Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O.; Tasler, S. Biaryls in nature: a multi-faceted class of stereochemically, biosynthetically, and pharmacologically intriguing secondary metabolites. In *Progress in the Chemistry of Organic Natural Products*; Springer, 2001; Vol. 82, pp 1–249.

(37) Wu, X.; Iwata, T.; Scharf, A.; Qin, T.; Reichl, K. D.; Porco, J. A., Jr Asymmetric synthesis of gonytolide A: strategic use of an aryl halide blocking group for oxidative coupling. *J. Am. Chem. Soc.* **2018**, *140*, 5969–5975.

(38) Qin, T.; Skraba-Joiner, S. L.; Khalil, Z. G.; Johnson, R. P.; Capon, R. J.; Porco, J. A., Jr Atropselective syntheses of (–) and (+) rugulotrocin A utilizing point-to-axial chirality transfer. *Nat. Chem.* **2015**, *7*, 234–240.

(39) Giles, R. G.; Sargent, M. Naturally-Occurring Dibenzofurans. X. A New Synthesis of Di-O-Methylstrepsilin. *Aust. J. Chem.* **1986**, *39*, 2177–2181.

(40) Drochner, D.; Hüttel, W.; Bode, S. E.; Müller, M.; Karl, U.; Nieger, M.; Steglich, W. Dimeric orsellinic acid derivatives: Valuable intermediates for natural product synthesis. *Eur. J. Org. Chem.* **2007**, *2007*, 1749–1758.

(41) Hauser, F. M.; Gauuan, P. J. F. Total synthesis of (±)-Biphyscion. *Org. Lett.* **1999**, *1*, 671–672.

(42) Rahman, M.; Riaz, M.; Desai, U. R. Synthesis of biologically relevant biflavonoids—a review. *Chem. Biodiversity* **2007**, *4*, 2495–2527.

(43) Kuttruff, C. A.; Eastgate, M. D.; Baran, P. S. Natural product synthesis in the age of scalability. *Nat. Prod. Rep.* **2014**, *31*, 419–432.

(44) Wang, J.; Zhou, R.-G.; Wu, T.; Yang, T.; Qin, Q.-X.; Li, I.; Yang, B.; Yang, J. Total synthesis of apigenin. *J. Chem. Res.* **2012**, *36*, 121–122.

- (45) Königs, P.; Rinker, B.; Maus, L.; Nieger, M.; Rheinheimer, J.; Waldvogel, S. Structural revision and synthesis of altechromone A. *J. Nat. Prod.* **2010**, *73*, 2064–2066.
- (46) Freitas, M.; Ribeiro, D.; Tome, S. M.; Silva, A. M.; Fernandes, E. Synthesis of chlorinated flavonoids with anti-inflammatory and proapoptotic activities in human neutrophils. *Eur. J. Med. Chem.* **2014**, *86*, 153–164.
- (47) Dianin, A. About Products from the Oxidation of Naphthols with Ferric Chloride. *Zh. Russ. Fiz.-Khim. O-va.* **1874**, *6*, 183–193.
- (48) Tanaka, K.; Toda, F. Oxidative coupling reactions of phenols with FeCl₃ in the solid state. *Mol. Cryst. Liq. Cryst. Incorporating Nonlinear Opt.* **1990**, *187*, 49–52.
- (49) Keinan, E.; Mazur, Y. Reactions in dry media. Ferric chloride adsorbed on silica gel. A multipurpose, easily controllable reagent. *J. Org. Chem.* **1978**, *43*, 1020–1022.
- (50) Jempty, T. C.; Miller, L. L.; Mazur, Y. Oxidative coupling reactions using silica-bound ferric chloride. *J. Org. Chem.* **1980**, *45*, 749–751.
- (51) Drochner, D.; Hüttel, W.; Nieger, M.; Müller, M. Unselective Phenolic Coupling of Methyl 2-Hydroxy-4-methoxy-6-methylbenzoate—A Valuable Tool for the Total Synthesis of Natural Product Families. *Angew. Chem.* **2003**, *115*, 961–963.
- (52) Hüttel, W.; Nieger, M.; Müller, M. A Short and Efficient Total Synthesis of the Naturally Occurring Coumarins Siderin, Kotanin, Isokotanin A and Desertorin C. *Synthesis* **2003**, 1803–1808.
- (53) Nieves-Quinones, Y.; Paniak, T. J.; Lee, Y. E.; Kim, S. M.; Tcyrlunikov, S.; Kozlowski, M. C. Chromium-salen catalyzed cross-coupling of phenols: mechanism and origin of the selectivity. *J. Am. Chem. Soc.* **2019**, *141*, 10016–10032.
- (54) Libman, A.; Shalit, H.; Vainer, Y.; Narute, S.; Kozuch, S.; Pappo, D. Synthetic and predictive approach to unsymmetrical biphenols by iron-catalyzed chelated radical–anion oxidative coupling. *J. Am. Chem. Soc.* **2015**, *137*, 11453–11460.
- (55) Kang, H.; Herling, M. R.; Niederer, K. A.; Lee, Y. E.; Vasu Govardhana Reddy, P.; Dey, S.; Allen, S. E.; Sung, P.; Hewitt, K.; Torruellas, C.; et al. Enantioselective vanadium-catalyzed oxidative coupling: development and mechanistic insights. *J. Org. Chem.* **2018**, *83*, 14362–14384.
- (56) Lee, Y. E.; Cao, T.; Torruellas, C.; Kozlowski, M. C. Selective oxidative homo- and cross-coupling of phenols with aerobic catalysts. *J. Am. Chem. Soc.* **2014**, *136*, 6782–6785.
- (57) Shalit, H.; Libman, A.; Pappo, D. meso-Tetraphenylporphyrin iron chloride catalyzed selective oxidative cross-coupling of phenols. *J. Am. Chem. Soc.* **2017**, *139*, 13404–13413.
- (58) Shalit, H.; Dyadyuk, A.; Pappo, D. Selective oxidative phenol coupling by iron catalysis. *J. Org. Chem.* **2019**, *84*, 1677–1686.
- (59) Montgomery, D. C. *Design and Analysis of Experiments*; John Wiley & Sons, 2017.
- (60) Dardé, M.; Ajzenberg, D.; Smith, J. Population structure and epidemiology of *Toxoplasma gondii*. In *Toxoplasma Gondii*; Elsevier, 2007; pp 49–80.
- (61) Flegr, J.; Prandota, J.; Sovičková, M.; Israili, Z. H. Toxoplasmosis—a global threat. Correlation of latent toxoplasmosis with specific disease burden in a set of 88 countries. *PLoS One* **2014**, *9*, No. e90203.
- (62) EFSA, E. 2019; p e05926.
- (63) Re, R.; Pellegrini, N.; Proteggente, A.; Pannala, A.; Yang, M.; Rice-Evans, C. Antioxidant activity applying an improved ABTS radical cation decolorization assay. *Free Radical Biol. Med.* **1999**, *26*, 1231–1237.
- (64) Catarino, M. D.; Alves-Silva, J. M.; Pereira, O. R.; Cardoso, S. M. Antioxidant capacities of flavones and benefits in oxidative-stress related diseases. *Curr. Top. Med. Chem.* **2015**, *15*, 105–119.
- (65) Boeck, P.; Falcão, C. A. B.; Leal, P. C.; Yunes, R. A.; Cechinel Filho, V.; Torres-Santos, E. C.; Rossi-Bergmann, B. Synthesis of chalcone analogues with increased antileishmanial activity. *Bioorg. Med. Chem.* **2006**, *14*, 1538–1545.
- (66) Thieury, C.; Lebouvier, N.; Le Guével, R.; Barguil, Y.; Herbette, G.; Antheaume, C.; Hnawia, E.; Asakawa, Y.; Nour, M.; Guillaudeux, T. Mechanisms of action and structure-activity relationships of cytotoxic flavokawain derivatives. *Bioorg. Med. Chem.* **2017**, *25*, 1817–1829.
- (67) Mai, C. W.; Yaeghoobi, M.; Abd-Rahman, N.; Kang, Y. B.; Pichika, M. R. Chalcones with electron-withdrawing and electron-donating substituents: anticancer activity against TRAIL resistant cancer cells, structure–activity relationship analysis and regulation of apoptotic proteins. *Eur. J. Med. Chem.* **2014**, *77*, 378–387.
- (68) Sinyeue, C.; Matsui, M.; Oelgemöller, M.; Bregier, F.; Chaleix, V.; Sol, V.; Lebouvier, N. Synthesis and Investigation of Flavanone Derivatives as Potential New Anti-Inflammatory Agents. *Molecules* **2022**, *27*, No. 1781.
- (69) Akçok, İ.; Çağır, A. Synthesis of stilbene-fused 2'-hydroxychalcones and flavanones. *Bioorg. Chem.* **2010**, *38*, 139–143.
- (70) Cabrera, M.; Simoens, M.; Falchi, G.; Lavaggi, M. L.; Piro, O. E.; Castellano, E. E.; Vidal, A.; Azqueta, A.; Monge, A.; de Cerain, A. L. Synthetic chalcones, flavanones, and flavones as antitumoral agents: Biological evaluation and structure–activity relationships. *Bioorg. Med. Chem.* **2007**, *15*, 3356–3367.
- (71) Schwarz, M.; Eno, R. F.; Freitag-Pohl, S.; Coxon, C. R.; Straker, H. E.; Wortley, D. J.; Hughes, D. J.; Mitchell, G.; Moore, J.; Cummins, I.; et al. Flavonoid-based inhibitors of the Phi-class glutathione transferase from black-grass to combat multiple herbicide resistance. *Org. Biomol. Chem.* **2021**, *19*, 9211–9222.
- (72) Basilio, N.; Lima, J. C.; Cruz, L.; de Freitas, V.; Pina, F.; Ando, H.; Kimura, Y.; Oyama, K. I.; Yoshida, K. Unveiling the 6, 8-rearrangement in 8-phenyl-5, 7-dihydroxyflavylium and 8-methyl-5, 7-dihydroxyflavylium through host–guest complexation. *Eur. J. Org. Chem.* **2017**, *2017*, 5617–5626.
- (73) Zheng, X.; Cao, J.-G.; Meng, W.-D.; Qing, F.-L. Synthesis and anticancer effect of B-ring trifluoromethylated flavonoids. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3423–3427.
- (74) Shih, T.-L.; Chou, C.-E.; Liao, W.-Y.; Hsiao, C.-A. Copper-mediated trimethylsilyl azide in amination of bromoflavonoids to synthesize unique aminoflavonoids. *Tetrahedron* **2014**, *70*, 3657–3664.
- (75) Wu, C.; Dunaway-Mariano, D.; Mariano, P. S. Design, synthesis, and evaluation of inhibitors of pyruvate phosphate dikinase. *J. Org. Chem.* **2013**, *78*, 1910–1922.