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Synthesis of structurally diverse biflavonoids

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ABSTRACT

Synthetic biflavonoids are associated with interesting biological activities, yet they remain poorly explored within drug discovery. Recent years have witnessed a growing interest in synthetic approaches that can provide access to structurally novel biflavonoids so that the biological usefulness of this compound class can be more fully investigated. Herein, we report upon the exploration of strategies based around Suzuki-Miyaura cross-coupling and alcohol methylenation for the synthesis of two classes of biflavonoids: (i) rare 'hybrid' derivatives containing flavonoid monomers belonging to different subclasses, and (ii) homodimeric compounds in which the two flavonoid monomers are linked by a methylenedioxy group. Application of these strategies enabled the preparation of a structurally diverse collection of novel biflavonoids from readily-available starting materials, thereby facilitating the probing of uncharted regions of biologically interesting chemical space.

1. Introduction

Biflavonoids are a class of compounds characterized by the presence of two flavonoid monomers conjoined through an alkyl or an alkoxy-based linker [1,2]. Natural biflavonoids, ubiquitous in plants, fruits and vegetables, have been found to display a diverse range of useful biological activities [1–3]. Flavonoids themselves, which fall into a number of different subclasses (for example, aurones, chalcones, flavonols and isoflavones) also exhibit a variety of biological activities [4–6]; in a number of cases the biological activity of a biflavonoid has been found to be greater than that of the constituent flavonoid monomer(s) [2,7,8]. *Synthetic* biflavonoids are also associated with interesting biological activities [1,2,7–11]; however, they remain poorly explored within drug discovery [1,2]. In principle, there is considerable structural diversity possible within the biflavonoid compound class, since the type of flavonoid units present and the nature and the position of the linker moiety can all be varied, and large swathes of potentially biologically relevant biflavonoid chemical space still remain untapped or underexplored by current syntheses [1,2]. This has stimulated a growing interest in the exploration of synthetic approaches that can provide convenient access to collections of novel and structurally diverse biflavonoids [1,2,7].

The biological properties of biflavonoids can be affected by the structures of the flavonoid sub-units and the linker system [2]. We have previously reported a strategy for generation of a library of biflavonoids which contain a carbon-carbon linkage between identical flavonoid subunits [2]. Herein, we report studies on the synthesis of two alternative types of biflavonoid. Firstly, 'hybrid' biflavonoids containing flavonoid monomers belonging to different subclasses, which we aimed to access using a Suzuki-Miyaura cross-coupling approach. The generation of species that integrate two pharmacophoric entities is common in drug discovery [12–14], and synthetic flavonoid dimer systems (both homo- and heterodimers) have been reported to exhibit useful biological properties [12]. However, examples of synthetic *biflavonoid* hybrids of the sort described herein are extremely rare. The second type of biflavonoids targeted in this study are characterized by the presence of a methylenedioxy linker group, which we envisaged could be generated via methylenation of the hydroxyl functional groups of the different flavonoid monomers. Although more commonly occurring than the hybrid-type, there are relatively few reported examples of libraries of such methylene-bridged compounds and the diversity of flavonoid monomers present within these is generally limited. Overall, application of synthetic strategies based around Suzuki-Miyaura cross-coupling and alcohol methylenation enabled access to a collection of 34 structurally diverse biflavonoids from readily available starting materials.

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2. Results and discussion

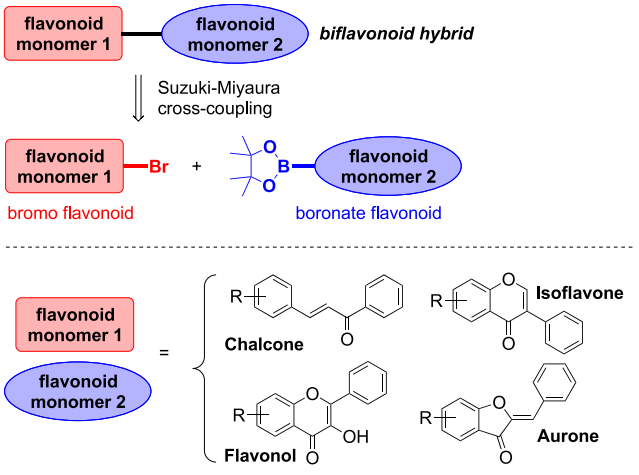
2.1. Synthesis of biflavonoid hybrids via a Suzuki-Miyaura cross-coupling strategy

The Suzuki-Miyaura cross-coupling reaction is of proven utility for the synthesis of a variety of symmetrical and unsymmetrical biflavonoids [1,4,15]. However, examples of biflavonoid hybrids (those that contain flavonoid monomers from different subclasses) generated using this reaction appear to be extremely scarce. We envisaged that the Suzuki-Miyaura process could be exploited to provide an underexplored yet convenient, modular and inherently flexible route to this rare class of compound through the use of appropriate pairs of boronate- and bromo-functionalized flavonoid monomers (Scheme 1).

As a proof-of-principle, we targeted the generation of isoflavone-aurone biflavonoid **7,** isoflavone-chalcone biflavonoid **8,** heteroaromatic isoflavone-chalcone biflavonoid **9** and isoflavone-flavonol biflavonoid **10** (Fig. 1).

2.1.1. Synthesis of isoflavone-aurone biflavonoid 7

The construction of the isoflavone-aurone biflavonoid **7** commenced with the syntheses of the isoflavone boronate **16** and bromoaurone **23** (Scheme 2). Acylation of commercially available resorcinol **11** with 4-bromophenylacetic acid **12** in the presence of boron trifluoride diethyl etherate afforded deoxybenzoin **13** in 77% yield [16]. Treatment of **13** with methanesulfonyl chloride [16] in DMF afforded bromoisoflavone **14**. Subsequent Miyaura borylation [17] with bis(pinacolato)diboron **15** gave the isoflavone boronate **16**. Bromoaurone **23** was prepared in five steps from commercially available phloroglucinol **17**. Reaction of **17** with chloroacetonitrile in the presence of $ZnCl_2$ gave the imine intermediate **18** [18]. Subsequent hydrolysis under acidic conditions afforded ketone **19** and treatment with methanolic sodium methoxide gave hydroxybenzofuranone **20** [18]. Methylation of the free hydroxyl groups afforded benzofuranone **21** which was then condensed with 4-bromobenzaldehyde **22** to yield the desired bromoaurone **23** [18]. Subsequent cross-coupling of isoflavone boronate **16** and bromoaurone **23** under Suzuki conditions [17,19] afforded the desired isoflavone-aurone biflavonoid **7** in a low yield as a 1:1 inseparable mixture of (*E*)- and (*Z*)- isomers. The generation of the (*E*)-isomer of **7** could potentially be attributed to isomerization of the alkene in **23** (due to *syn*-β-hydride elimination by the Pd catalyst) followed by cross-coupling with **16**.



Scheme 1. Strategy for the construction of biflavonoid hybrids containing flavonoid monomers from different subclasses.

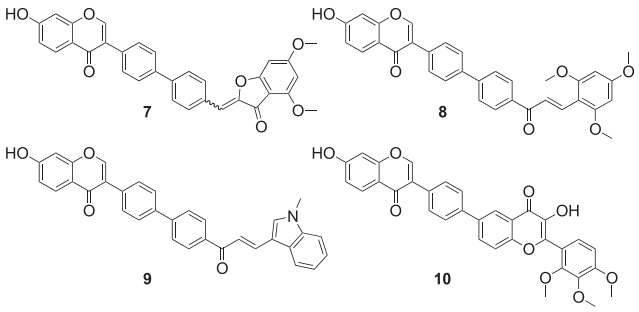
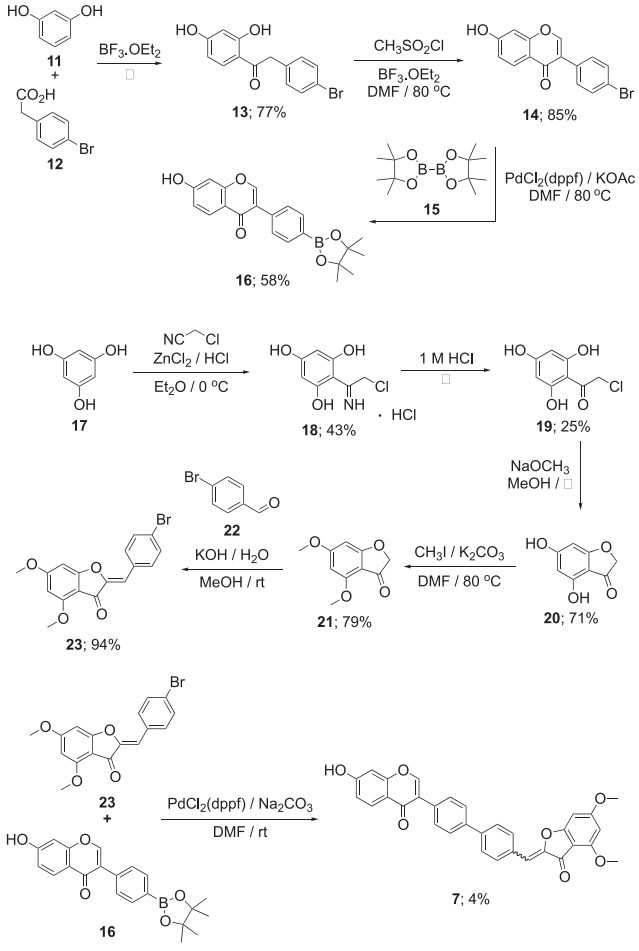


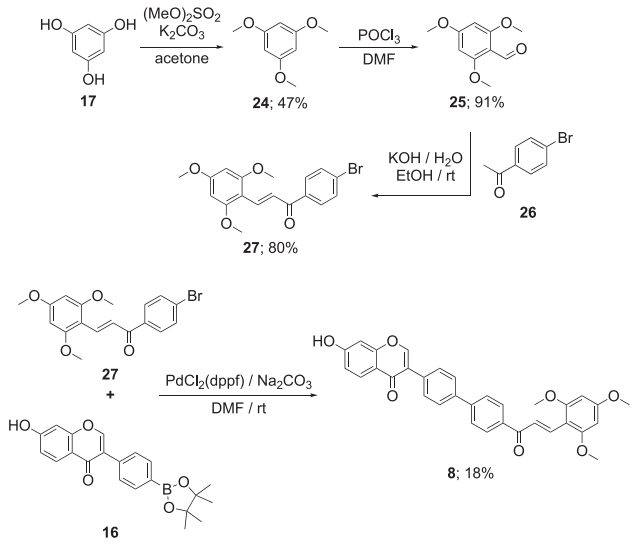
Fig. 1. Target biflavonoid hybrids.



Scheme 2. Synthesis of isoflavone-aurone biflavonoid **7**.

2.1.2. Synthesis of isoflavone-chalcone biflavonoid 8

With the successful synthesis of **7**, we moved on to investigate the construction of different hybrid biflavonoids using isoflavone boronate **16** and other bromoflavonoids. Bromochalcone **27** was readily prepared from commercially available phloroglucinol **17** in three steps (Scheme 3). Methylation of **17** with dimethyl sulfate in the presence of potassium carbonate gave trimethoxybenzene **24** [20]. Subsequent Vilsmeier-Haack formylation [21] afforded the corresponding trimethoxybenzaldehyde **25** in an excellent yield [20]. Base-catalyzed Claisen-Schmidt condensation [22] of **25** with 4-bromoacetophenone **26** generated **27** and subsequent cross-

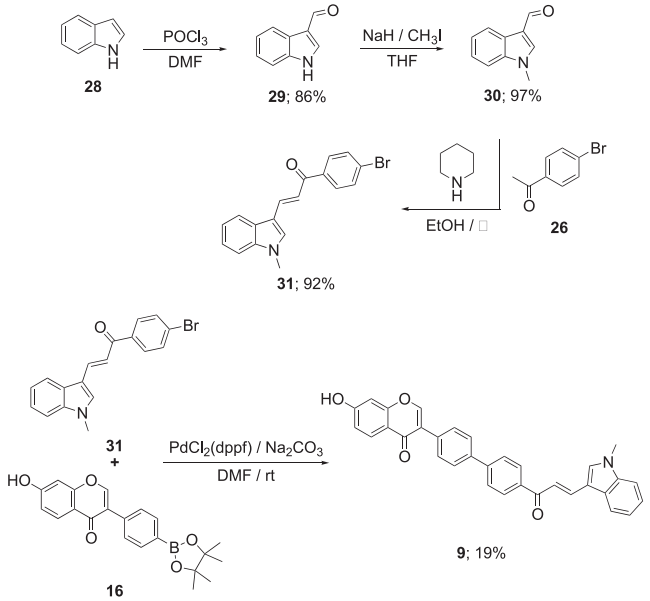


Scheme 3. Synthesis of isoflavone-chalcone biflavonoid **8**.

coupling with **16** using the previously employed Suzuki protocol afforded the target isoflavone-chalcone biflavonoid **8.**

2.1.3. *Synthesis of heteroaromatic isoflavone-chalcone biflavonoid **9***

Isoflavone-chalcone biflavonoid **9** was targeted in order to explore the potential to generate biflavonoids with heteroaromatic moieties such as indoles which are known to be associated with interesting biological properties [23]. Preparation of the required indole bromochalcone **31** commenced with Vilsmeier-Haack formylation of indole **28** to give aldehyde **29** [24]. (Scheme 4). Methylation of **29** afforded indole-aldehyde **30** [25]. and Claisen-Schmidt aldol condensation with bromoacetophenone **26** furnished indole bromochalcone **31**. Application of the previously employed Suzuki conditions enabled the successful cross-coupling of **31** with **16** to afford the desired heteroaromatic biflavonoid **9** (Scheme 4).



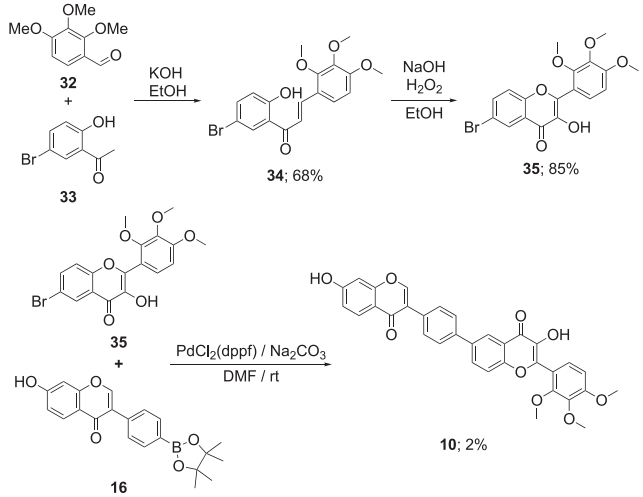
Scheme 4. Synthesis of heteroaromatic isoflavone-chalcone biflavonoid **9**.

2.1.4. *Synthesis of isoflavone-flavonol biflavonoid **10***

Finally, attention was directed towards the synthesis of the isoflavone-flavonol biflavonoid **10** (Scheme 5). Aldol condensation of trimethoxybenzaldehyde **32** and bromoacetophenone **33** gave bromochalcone **34** which was converted to the required bromoflavonol coupling partner **35** by an Algar-Flynn-Oyamada (AFO) oxidation [22]. Cross-coupling of bromoflavonol **35** and isoflavone boronate **16** under the previously employed conditions gave the final isoflavone-flavonol biflavonoid **10** in a low isolated yield.

2.1.5. *Summary*

The Suzuki-Miyaura cross-coupling strategy outlined in Scheme 1 was successfully applied to the synthesis of four target hybrid biflavonoids **7**–**10**. The yields of all the Suzuki-Miyaura coupling reactions were disappointingly low. This can be attributed to several factors. Firstly, there was incomplete consumption of both the bromo-flavonoid and boronoate-flavonoid starting materials (as indicated by TLC and/or LCMS analysis of the reaction mixtures) and recovery of these materials could not be achieved. In addition, LCMS analysis of the crude reaction mixtures prior to purification indicated the presence of several unidentifiable (possibly including polymeric) side products. Any attempts to improve the efficiency of these reactions were unsuccessful. For example, in the case of the coupling of **16** and **23**, a variety of different combinations of solvents (DMF, THF and DMSO), reaction temperatures (room temperature, gentle heating and heating at reflux), bases (sodium carbonate and sodium hydroxide) and palladium catalysts ($PdCl_2(dppf)\cdot CH_2Cl_2$, $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$) were investigated but there was no improvement in the isolated yield of the desired product. Analytically pure samples of all the target biflavonoids could be isolated by column chromatography on silica gel. However, in all cases this process was practically extremely challenging and laborious; significant streaking was observed on silica and there may have been decomposition of both the target biflavonoids and residual starting materials during chromatographic elution. Although the yields of the Suzuki-Miyaura coupling reactions were disappointingly low, it is worth noting that milligram quantities of all target biflavonoids were successfully obtained; this should be sufficient material for screening in a wide variety of biological assays. This work establishes the general feasibility of our approach for the synthesis of this structurally rare and biologically interesting compound class; it is anticipated that a larger range of functionalized flavonoid monomer building blocks could be



Scheme 5. Synthesis of isoflavone-flavonol biflavonoid **10**.

employed in order to access a highly structurally diverse library of such compounds in a step-efficient fashion.

2.2. Synthesis of a library of biflavonoids that contain a methylenedioxy linker

Attention was next turned towards the generation of a library of unnatural homodimeric biflavonoids that contain a methylenedioxy linker between the flavonoid monomers (Scheme 6). It was envisaged that such derivatives could be conveniently accessed via treatment of hydroxyl-substituted flavonoid monomers with diiodomethane [26]. It was anticipated that a variety of functionalized flavonoid building blocks belonging to different flavonoid structural classes could be employed in order to access a structurally diverse library of methylenedioxy-linked biflavonoids. This study examined building blocks from six different flavonoid subclasses: aurone, chalcone, dihydrochalcone, flavone, flavonol and isoflavone.

2.2.1. Synthesis of a methylenedioxy-bridged bidihydrochalcone *40*

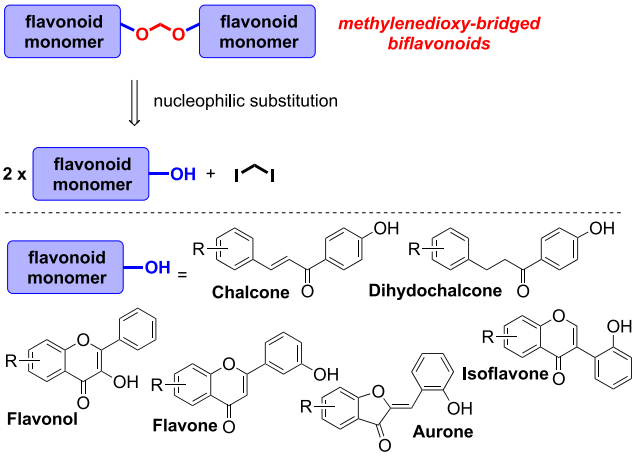
The preparation of the methylenedioxy-bridged biflavonoid library commenced with the synthesis of bidihydrochalcone **40** (Scheme 7). Acetophenone **37** was prepared in good yield from **36** by the Eaton's reagent-induced Fries rearrangement of 2-methoxyphenylacetate **36** [28]. Base-catalyzed Claisen-Schmidt condensation [22] of **25** and **37** generated chalcone **38** and subsequent hydrogenation furnished dihydrochalcone **39** [27]. Methylenation [26] of **39** gave the desired bidihydrochalcone **40** in a moderate yield.

2.2.2. Synthesis of methylenedioxy-bridged bichalcones *59–69* and *72*

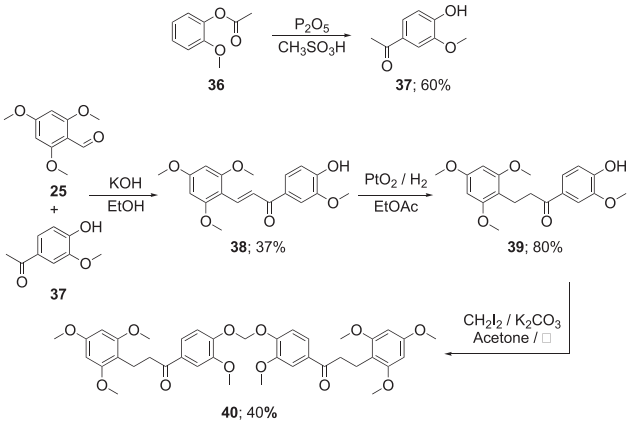
Methylenedioxy-bridged bichalcones **59**–**69** and **72** were generated by the route shown in Scheme 8. Claisen-Schmidt condensation [22] of various aromatic and heteroaromatic aldehyde building blocks with acetophenones **37** or **70** yielded chalcone precursors **38**, **49**–**58** and **71**. Subsequent methylenation [26] in the presence of diiodomethane and potassium carbonate afforded the final bichalcone dimers **59**–**69** and **72**.

2.2.3. Synthesis of methylenedioxy-bridged biflavones *96–104* and *114*

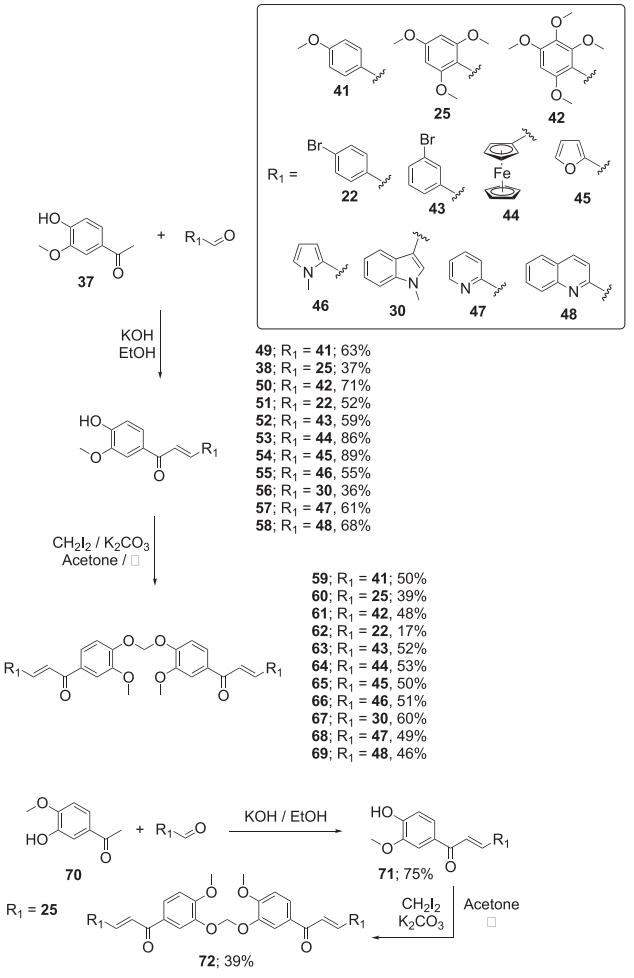
Claisen-Schmidt condensation [29] of acetophenones **73**–**75** and **33** with various aromatic and heteroaromatic aldehyde building blocks yielded chalcones **78**–**86** (Scheme 9). Subsequent AFO oxidation [22] generated the respective flavonols **87**–**95** (Scheme 9). Dimerization under the common methylenation conditions [26] afforded the desired biflavones **96**–**104**. Concurrently, biflavone **114** was synthesized by the route shown in Scheme 10, building upon our previous work on flavone synthesis [27]. Pyrogallol **105** was acylated in the presence of glacial acetic acid and boron trifluoride diethyl etherate under reflux conditions to afford gallacetophenone **106** [30]. Selective methylation of **106** with iodomethane and anhydrous potassium carbonate in dry acetone



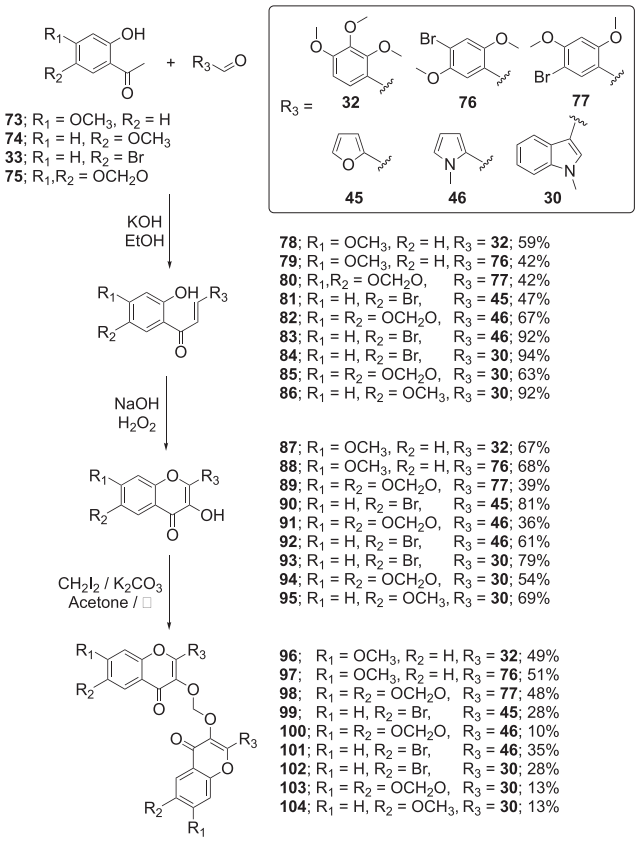
Scheme 6. Outline of the strategy towards diverse methylenedioxy-bridged biflavonoids.



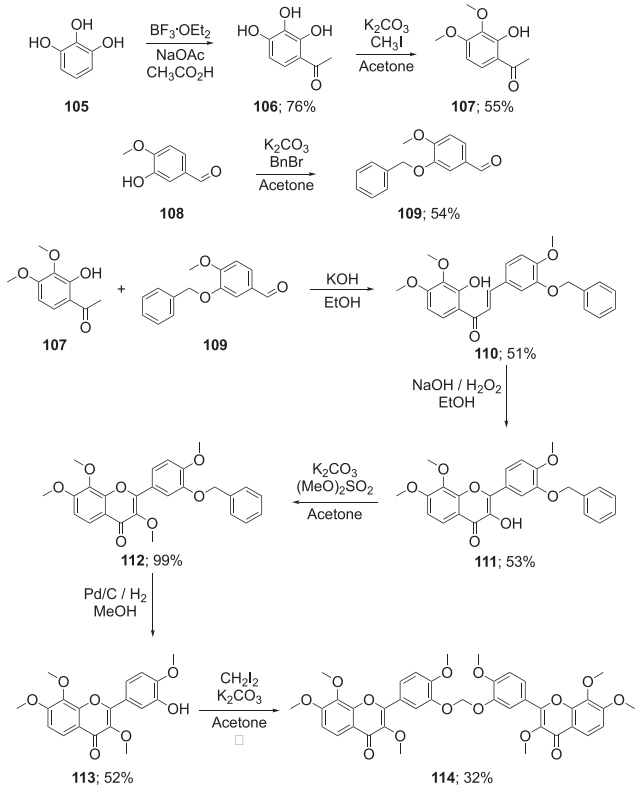
Scheme 7. Synthesis of methylenedioxy-bridged bidihydrochalcone **40**.



Scheme 8. Synthesis of methylenedioxy-bridged bichalcones.



Scheme 9. Synthesis of methylenedioxy-bridged biflavones.



Scheme 10. Synthesis of methylenedioxy-bridged biflavone 114.

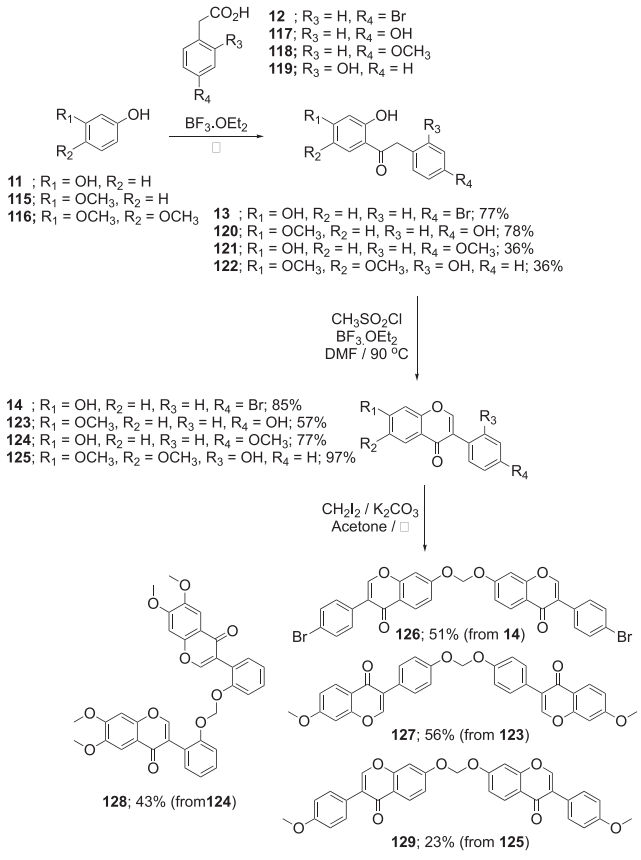
afforded acetophenone **107** [31]. Benzaldehyde **109** was acquired in 54% yield through benzylation of the phenol functionality of isovanillin **108** under basic conditions [32]. Condensation of **107** and **109** in ethanolic KOH solution at room temperature afforded the chalcone **110** and subsequent intramolecular AFO oxidative cyclization [22] proceeded smoothly to produce the intermediate 3-hydroxyflavonoid **111**. Selective methylation of the 3-hydroxyl group of the flavone ring provided the corresponding tetramethoxyflavone **112** in quantitative yield and subsequent debenzylation by hydrogenolysis furnished the 5-deoxyflavone **113** [27]. Methylenation [26] of **113** afforded the desired biflavone **114** in a moderate yield.

2.2.4. Synthesis of methylenedioxy-bridged biisoflavones

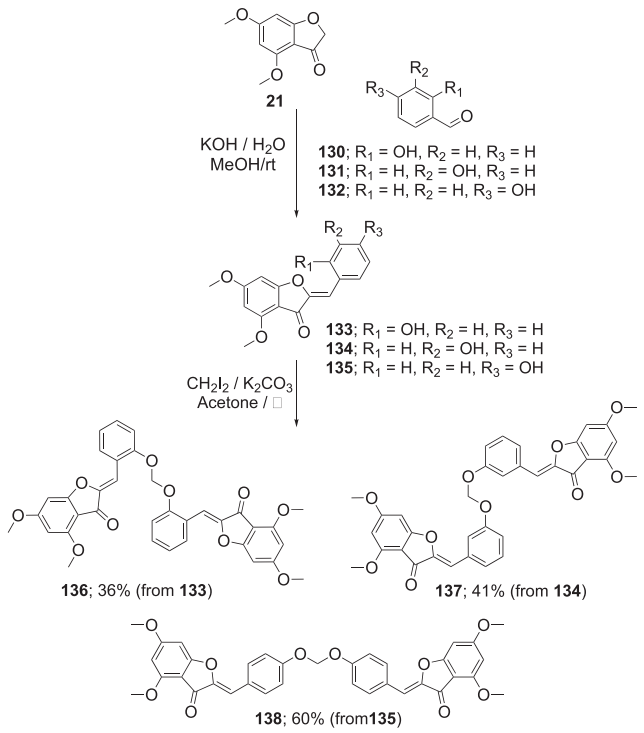
The isoflavone dimerization precursors were synthesized by the route shown in Scheme 11. Acylation of phenols **11**, **115** and **116** with phenylacetic acids **12** and **117**–**119** in the presence of boron trifluoride diethyl etherate gave deoxybenzoins **13, 120**–**122** [16]. Heating with methanesulfonyl chloride and DMF effected cyclization to generate dimerization precursors **14** and **123**–**125** [16]. Reaction under the standard methylenation conditions [26] afforded the desired biisoflavones **126**–**129** in moderate-to-good yields.

2.2.5. Synthesis of methylenedioxy-bridged biaurones

Finally, we turned our attention towards the synthesis of methylenedioxy-bridged biaurones. The required hydroxyuaurone precursors **133**–**135** were readily prepared by the condensation [18] of benzofuranone **21** with various hydroxybenzaldehydes **130**–**132** (Scheme 12). Methylenation under the standard conditions [26] furnished the targeted biaurones **136**–**138**.



Scheme 11. Synthesis of methylenedioxy-bridged biisoflavones.



Scheme 12. Synthesis of methylenedioxy-bridged biaurones.

2.2.6. Summary

A range of flavonoid building blocks were successfully employed in the methylenation strategy (Scheme 6) to generate a library of 30 diverse methylenedioxy-bridged biflavonoids. Six different biologically-relevant flavonoid subclasses were incorporated into the library (aurone, chalcone, dihydrochalcone, flavone, flavonol and isoflavone), and many of the compounds feature additional structural motifs associated with biological activity (for example, heterocyclic ring systems and hydrogen-bonding motifs) as well as an aryl bromide group, which could conceivably serve as a synthetic handle for further modification via metal-catalyzed cross-coupling processes.

3. Conclusions

In conclusion, we have reported strategies based around Suzuki-Miyaura cross-coupling and alcohol methylenation for synthesis of two types of biologically interesting biflavonoid derivatives: (i) 'hybrid' compounds containing flavonoid monomers belonging to different subclasses, and (ii) homodimeric compounds featuring a methylenedioxy linker group between the flavonoid monomers. A structurally diverse library of 34 biflavonoids (4 hybrid compounds and 30 methylenedioxy-bridged dimers) was successfully generated using these strategies. All final compounds were isolated in milligram quantities, providing ample material for their biological evaluation. Notable results from these screening studies will be reported in due course.

4. Experimental section

4.1. General information

All reagents and solvents were purchased from commercial sources and used without further purification unless otherwise stated. All the experiments were carried out under a nitrogen atmosphere unless otherwise stated. Melting points were measured using a Büchi B545 melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on precoated Merck silica gel GF254 plates. IR spectra were recorded on a PerkinElmer Spectrum One (FT-IR) spectrophotometer. Flash column chromatography was performed on silica gel (230–400 mesh). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 500 MHz instrument in $CDCl_3$ and DMSO-d_6. HRMS was recorded on a Micromass Q-TOF mass spectrometer or a Waters LCT Premier Time of Flight mass spectrometer. LCMS setup: Waters ACQUITY H-Class UPLC with an ESCi Multi-Mode Ionisation Waters SQ Detector 2 spectrometer using MassLynx 4.1 software; LC system: solvent A: 2 mM NH_4OAc in water/acetonitrile (95:5); solvent B: acetonitrile; solvent C: 2% formic acid; column: ACQUITY UPLC CSH C18 (2.1 mm × 50 mm, 1.7 μm, 130 Å) at 40 °C; gradient: 5–95% B with constant 5% C over 1 min at flow rate of 0.6 mL·min-1; detector: PDA eλ Detector 220 nm - 800 nm, interval 1.2 nm.

4.2. General procedures

4.2.1. General procedure A: Synthesis of non-identical biflavonoids via Suzuki-Miyaura cross-coupling strategy (GP-A)

To a stirred solution of boronate flavonoid (1.0 equiv) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (1.0 equiv) in dry DMF (10 mL) were added aqueous Na_2CO_3 solution (1 M, 5.0 equiv) and the corresponding bromo flavonoid (1.0 equiv). The reaction mixture was stirred at room temperature for 72 h under nitrogen or until LCMS analysis indicated complete consumption of starting material. The resulting suspension was then poured into H_2O (50 mL) and the aqueous solution was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layer was washed with H_2O (2 × 50 mL), brine (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography over silica to afford the corresponding biflavonoids.

4.2.2. General procedure B: Synthesis of identical biflavonoids via methylenation strategy (GP-B)

To a stirred solution of the corresponding flavonoid (1.0 equiv) in dry acetone or DMF (20 mL) were added CH_2I_2 (3.0 equiv) and anhydrous K_2CO_3 (3.0 equiv). The reaction mixture was heated at reflux under a nitrogen atmosphere for 24 h or until TLC analysis indicated complete consumption of starting material. The resulting mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The crude residue was redissolved in $CHCl_3$ (50 mL), washed with H_2O (2 × 50 mL), brine (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography over silica and/or recrystallized from MeOH, EtOAc or $CHCl_3$ to afford the corresponding biflavonoids.

4.3. Experimental details and characterization data

*4.3.1. Synthesis of 3-(4′-((4,6-dimethoxy-3-oxobenzofuran-2(3H)-ylidene)methyl)-[1,1′-biphenyl]-4-yl)-7-hydroxy-4H-chromen-4-one (isoflavone-aurone biflavonoid) (**7**)*

A mixture of boronate isoflavone **16** (304 mg, 0.835 mmol), bromoaurone **23** (299 mg, 0.829 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (136 mg, 0.166 mmol) and aq. Na_2CO_3 (1 M, 5.0 mL, 5.00 mmol) in dry DMF (30 mL) was reacted according to GP-A. The crude residue was purified by flash column chromatography (SiO_2, 0.5–10% $MeOH/CH_2Cl_2$) to afford biflavonoid **7** (19.1 mg, 4%) as a bright yellow powdery solid in a 1:1 inseparable mixture of (*E*)- and (*Z*)-isomers. **m.p.** >300 °C. **TLC** R_f = 0.33 (5% $MeOH/CH_2Cl_2$). **IR** ν_{max} (neat)/cm^{-1}: 3242 m(br) (O–H str), 2922w (C–H str), 2850w (C–H

str), 1668 m (C=O str), 1627s (C=C str), 1584s (C=C str), 1505 m (C=C str), 1457 m, 1422w, 1363 m, 1246 m, 1217s, 1158s, 1122 m, 1077s, 1047w, 1017w, 1005w. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.89 (1.5H, s, −OCH_3), 3.91 (3H, s, −OCH_3 and −OCH_3′, overlap), 3.94 (1.5H, s, −OCH_3′), 6.31 (0.5H, d, *J* 1.6 Hz, ArH_a), 6.37 (0.5H, d, *J* 1.6 Hz, ArH_b), 6.54 (0.5H, d, *J* 1.2 Hz, ArH_a'), 6.75 (0.5H, d, *J* 1.6 Hz, ArH_b'), 6.79 (0.5H, s, −C=CH_c), 6.91 (1H, d, *J* 2.4 Hz, ArH), 6.97 (1H, dd, *J* 8.8, 2.0 Hz, ArH), 7.08 (0.5H, s, −C=CH_c'), 7.70–7.73 (2H, m, ArH), 7.79–7.87 (4H, m, ArH), 8.01 (1H, d, *J* 8.8 Hz, ArH), 8.04 (1H, d, *J* 8.4 Hz, ArH), 8.30 (1H, d, *J* 8.8 Hz, ArH), 8.48 (1H, s, −C=CH), 10.85 (1H, s, OH). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 56.1, 56.2, 56.5, 56.6, 89.1, 90.0, 93.8, 94.5, 102.2, 104.0, 105.9, 109.1, 115.4, 116.6, 119.1, 123.0, 126.3, 126.4, 126.5, 127.0, 127.4, 129.5, 131.1, 131.5, 131.6, 131.8, 131.9, 138.4, 138.5, 140.5, 140.7, 147.5, 148.5, 154.0, 157.5, 159.0, 159.2, 162.7, 167.4, 168.2, 168.9, 169.0, 174.4, 177.7, 179.0. **LCMS** (ES-) *m*/*z* = 517.1 ([M-H]$^-$, t_r = 1.65 min). **HRMS** (ESI+) *m*/*z* = 519.1436 $[M+H]^+$ found, $C_{32}H_{23}O_7^+$ required 519.1438.

4.3.2. Synthesis of (E)-7-hydroxy-3-(4'-(3-(2,4,6-trimethoxyphenyl)acryloyl)-[1,1′-biphenyl]-4-yl)-4H-chromen-4-one (isoflavone-chalcone biflavonoid) (**8**)

A mixture of boronate isoflavone **16** (306 mg, 0.839 mmol), bromochalcone **27** (317 mg, 0.841 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (108 mg, 0.133 mmol) and aq. Na_2CO_3 (1 M, 5.0 mL, 5.00 mmol) in dry DMF (20 mL) was reacted according to GP-A. The crude residue was purified by flash column chromatography (SiO_2, 0.5–1% MeOH/CH_2Cl_2) and further recrystallized from MeOH to afford biflavonoid **8** (82.4 mg, 18%) as a pale yellow-brown powdery solid. **m.p.** >300 °C. **TLC** R_f = 0.43 (5% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3227 m(br) (O–H str), 2940w (C–H str), 2847w (C–H str), 1653 m (C=O str), 1620s, 1603s (C=C str), 1581s (C=C str), 1566s (C=C str), 1455 m, 1417w, 1337s, 1300 m, 1267 m, 1222s, 1204s, 1157 m, 1121s, 1098 m, 1054 m, 1029 m, 1005w. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.87 (3H, s, −OCH_3), 3.94 (6H, s, 2 × −OCH_3), 6.35 (2H, s, ArH), 6.91 (1H, d, *J* 1.6 Hz, ArH), 6.97 (1H, dd, *J* 8.4, 1.6 Hz, ArH), 7.74 (2H, d, *J* 8.4 Hz, ArH), 7.84 (2H, d, *J* 8.4 Hz, ArH), 7.93 (2H, d, *J* 8.8 Hz, ArH), 7.93 (1H, d, *J* 16.0 Hz, −CH=CHCO−), 8.01 (1H, d, *J* 8.8 Hz, ArH), 8.08 (2H, d, *J* 8.4 Hz, ArH), 8.14 (1H, d, *J* 16.0 Hz, −CH=CHCO−), 8.50 (1H, s, −C=CH), 10.85 (1H, s, OH). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 55.6, 56.1, 91.1, 102.2, 105.1, 115.3, 116.6, 120.3, 122.9, 126.6, 126.9, 127.4, 128.8, 129.5, 132.2, 135.2, 137.4, 138.3, 143.5, 154.1, 157.5, 161.5, 162.7, 163.4, 174.4, 189.4. **LCMS** (ES+) *m*/*z* = 535.2 ($[M+H]^+$, t_r = 1.65 min). **HRMS** (ESI+) *m*/*z* = 535.1751 $[M+H]^+$ found, $C_{33}H_{27}O_7^+$ required 535.1757.

4.3.3. Synthesis of (E)-7-hydroxy-3-(4'-(3-(1-methyl-1H-indol-3-yl)acryloyl)-[1,1′-biphenyl]-4-yl)-4H-chromen-4-one (isoflavone-indole chalcone biflavonoid) (**9**)

A mixture of boronate isoflavone **16** (305 mg, 0.837 mmol), indole bromochalcone **31** (283 mg, 0.833 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (107 mg, 0.131 mmol) and aq. Na_2CO_3 (1 M, 5.0 mL, 5.00 mmol) in dry DMF (30 mL) was reacted according to GP-A. The crude residue was purified by flash column chromatography (SiO_2, 0.5–1% MeOH/CH_2Cl_2) to afford biflavonoid **9** (79.9 mg, 19%) as a bright yellow powdery solid. **m.p.** 280–282 °C. **TLC** R_f = 0.30 (5% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3244w(br) (O–H str), 2925w (C–H str), 1718w (C=O str), 1620 m, 1602s (C=C str), 1581s (C=C str), 1566s (C=C str), 1526 m (C=C str), 1465 m, 1375s, 1281s, 1264s, 1219s, 1180s, 1133w, 1097w, 1042 m, 1013w. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.87 (3H, s, −NCH_3), 6.91 (1H, d, *J* = 2.0 Hz, ArH-8), 6.97 (1H, dd, *J* = 8.8, 2.0 Hz, ArH-6), 7.28–7.35 (2H, m, ArH-25 and ArH-26), 7.57 (1H, d, *J* = 7.6 Hz, ArH-24), 7.70 (1H, d, *J* = 15.2 Hz, −CH=CHCO−), 7.74 (2H, d, *J* = 8.4 Hz, ArH-11 and ArH-13), 7.85 (2H, d, *J* = 8.4 Hz, ArH-10 and ArH-14), 7.91 (2H, d, *J* = 8.4 Hz, ArH-16 and ArH-20), 8.02 (1H, d, *J* = 9.2 Hz, ArH-5), 8.05 (1H, d, *J* = 15.6 Hz, −CH=CHCO−), 8.13–8.14 (2H, m, ArH-22 and ArH-27), 8.23 (2H, d, *J* = 8.4 Hz, ArH-17 and ArH-19), 8.49 (1H, s, −C=CH), 10.87 (1H, s, OH). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 33.1, 102.2, 110.9, 111.8, 115.3, 116.6, 120.5, 121.5, 122.8, 122.9, 125.6, 126.7, 126.8, 127.4, 128.9, 129.5, 132.1, 136.7, 137.4, 138.0, 138.3, 138.4, 143.4, 154.1, 157.5, 162.7, 174.4, 188.1. **LCMS** (ES-) *m*/*z* = 496.3 ([M-H]$^-$, t_r = 1.82 min). **HRMS** (ESI+) *m*/*z* = 498.1702 $[M+H]^+$ found, $C_{33}H_{24}NO_4^+$ required 498.1705.

4.3.4. Synthesis of 3-hydroxy-6-(4-(7-hydroxy-4-oxo-4H-chromen-3-yl)phenyl)-2-(2,3,4-trimethoxyphenyl)-4H-chromen-4-one (isoflavone-flavonol biflavonoid) (**10**)

A mixture of boronate isoflavone **16** (269 mg, 0.738 mmol), bromoflavonol **35** (304 mg, 0.747 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (110 mg, 0.134 mmol) and aq. Na_2CO_3 (1 M, 5.0 mL, 5.00 mmol) in dry DMF (20 mL) was reacted according to GP-A. The crude residue was purified by flash column chromatography (SiO_2, 1–10% MeOH/CH_2Cl_2) and further purified by preparative HPLC (60–100% B) to afford biflavonoid **10** (7.10 mg, 2%) as an off-white powdery solid. **m.p.** >300 °C. **TLC** R_f = 0.44 (10% MeOH/CH_2Cl_2). **HPLC** t_r = 7.89 min (60–100% B), peak area 90%. **IR** ν_{max} (neat)/cm^{-1}: 3285w(br) (O–H str), 2924 m (C–H str), 2851w (C–H str), 1680 m (C=O str), 1622s, 1600s (C=C str), 1569 m (C=C str), 1453s, 1301 m, 1272 m, 1294 m, 1272 m, 1198s, 1190s, 1142s, 1124s, 1098s, 1027 m. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.81 (3H, s, −OCH_3), 3.87 (3H, s, −OCH_3), 3.88 (3H, s, −OCH_3), 6.91 (1H, d, *J* 2.0 Hz, ArH), 6.97 (2H, dd, *J* 8.8, 2.0 Hz, ArH), 7.30 (1H, d, *J* 8.8 Hz, ArH), 7.75 (2H, d, *J* 8.4 Hz, ArH), 7.77 (1H, d, *J* 8.8 Hz, ArH), 7.86 (2H, d, *J* 8.4 Hz, ArH), 8.02 (1H, d, *J* 8.8 Hz, ArH), 8.15 (1H, dd, *J* 8.8, 1.6 Hz, ArH), 8.38 (1H, d, *J* 2.0 Hz, ArH), 8.50 (1H, s, −C=CH), 9.07 (1H, s, OH), 10.87 (1H, s, OH). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 56.1, 60.5, 61.2, 102.2, 107.8, 115.4, 116.6, 117.6, 119.2, 121.9, 122.2, 123.0, 125.9, 126.6, 127.4, 129.6, 131.7, 132.1, 136.0, 137.9, 139.1, 142.0, 147.0, 151.8, 154.0, 154.4, 155.2, 157.5, 162.7, 172.7, 174.4. **LCMS** (ES+) *m*/*z* = 565.2 ($[M+H]^+$, t_r = 1.84 min). **HRMS** (ESI+) *m*/*z* = 565.1477 $[M+H]^+$ found, $C_{33}H_{25}O_9^+$ required 565.1493.

4.3.5. Synthesis of 1,1'-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(2,4,6-trimethoxyphenyl)propan-1-one) (**40**)

A mixture of dihydrochalcone **39** (150 mg, 0.434 mmol), CH_2I_2 (0.12 mL, 1.49 mmol) and anhydrous K_2CO_3 (207 mg, 1.50 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford bidihydrochalcone **40** (124 mg, 40%) as a white powdery solid. **m.p.** 198–200 °C. **TLC** R_f = 0.23 (1% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2987w (C–H str), 2950w (C–H str), 2840w (C–H str), 1684s (C=O str), 1609 m, 1589s (C=C str), 1514 m (C=C str), 1504 m (C=C str), 1452 m, 1418s, 1363w, 1277 m, 1254s, 1150s, 1108s, 1033 m, 1014s, 1001s. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 2.78 (4H, t, *J* 8.5 Hz, 2 × −$CH_2$$CH_2$CO−), 2.96 (4H, t, *J* 8.5 Hz, 2 × −$CH_2$$CH_2$CO−), 3.73 (12H, s, 4 × −OCH_3), 3.75 (6H, s, 2 × −OCH_3), 3.80 (6H, s, 2 × −OCH_3), 5.96 (2H, s, −OCH_2O-), 6.21 (4H, s, ArH), 7.29 (2H, d, *J* 8.0 Hz, ArH), 7.47 (2H, d, *J* 2.0 Hz, ArH), 7.62 (2H, dd, *J* 8.5, 2.0 Hz, ArH). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 18.2, 38.0, 55.2, 55.6, 55.6, 90.6, 90.7, 108.4, 111.1, 115.3, 122.0, 131.4, 149.2, 158.3, 159.4, 198.6. **LCMS** (ES+) *m*/*z* = 705.3 ($[M+H]^+$, t_r = 1.85 min). **HRMS** (ESI+) *m*/*z* = 705.2886 $[M+H]^+$ found, $C_{39}H_{45}O_{12}^+$ required 705.2906.

4.3.6. Synthesis of (2E,2′E)-1,1'-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(4-methoxyphenyl)prop-2-en-1-one) (**59**)

A mixture of chalcone **49** (306 mg, 1.08 mmol), CH_2I_2 (0.26 mL, 3.18 mmol) and anhydrous K_2CO_3 (449 mg, 3.25 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford bichalcone **59**

(314 mg, 50%) as a pale yellow powdery solid. **m.p.** 228–230 °C. **TLC** R_f = 0.21 (1% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2978w (C–H str), 2845w (C–H str), 1659 m (C=O str), 1601s (C=C str), 1582s (C=C str), 1572 m (C=C str), 1508s (C=C str), 1465 m, 1448 m, 1416 m, 1334w, 1293 m, 1250s, 1165s, 1133s, 1055w, 1010s. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.82 (6H, s, 2 × −OCH_3), 3.87 (6H, s, 2 × −OCH_3), 6.04 (2H, s, −OCH_2O-), 7.02 (4H, d, *J* 8.4 Hz, ArH), 7.36 (2H, d, *J* 8.4 Hz, ArH), 7.66 (2H, d, *J* 2.0 Hz, ArH), 7.70 (2H, d, *J* 15.6 Hz, 2 × −*CH*=CHCO−), 7.81 (2H, d, *J* 15.6 Hz, 2 × −CH=*CH*CO−), 7.86 (4H, d, *J* 8.8 Hz, ArH), 7.89 (2H, dd, *J* 8.4, 1.6 Hz, ArH). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 55.4, 55.8, 90.6, 111.6, 114.4, 115.2, 119.4, 122.6, 127.4, 130.8, 132.8, 143.5, 149.4, 149.4, 161.3, 187.4. **LCMS** (ES+) *m/z* = 581.2 ($[M+H]^+$, t_r = 1.84 min). **HRMS** (ESI+) *m/z* = 619.1730 $[M+K]^+$ found, $C_{35}H_{32}O_8K^+$ required 619.1729.

4.3.7. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(2,4,6-trimethoxyphenyl)prop-2-en-1-one) (**60**)

A mixture of chalcone **38** (302 mg, 0.877 mmol), CH_2I_2 (0.25 mL, 3.11 mmol) and anhydrous K_2CO_3 (382 mg, 2.77 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford bichalcone **60** (239 mg, 39%) as a pale yellow-white powdery solid. **m.p.** 230–232 °C. **TLC** R_f = 0.35 (2% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2940w (C–H str), 2839w (C–H str), 1657 m (C=O str), 1598s (C=C str), 1576s (C=C str), 1510 m (C=C str), 1468 m, 1418 m, 1337 m, 1300 m, 1259 m, 1200 m, 1124s, 1065 m, 1031 m, 1012s. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.86 (6H, s, 2 × −OCH_3), 3.86 (6H, s, 2 × −OCH_3), 3.92 (12H, s, 4 × −OCH_3), 5.99 (2H, s, −OCH_2O-), 6.32 (4H, s, ArH), 7.34 (2H, d, *J* 8.5 Hz, ArH), 7.54 (2H, d, *J* 2.0 Hz, ArH), 7.66 (2H, dd, *J* 8.5, 2.0 Hz, ArH), 7.89 (2H, d, *J* 16.0 Hz, 2 × −CH=CHCO−), 8.07 (2H, d, *J* 15.5 Hz, 2 × −CH=CHCO−). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 55.6, 56.1, 90.9, 91.0, 105.1, 111.2, 115.5, 120.2, 121.9, 133.4, 134.7, 149.0, 149.4, 161.4, 163.2, 188.5. **LCMS** (ES+) *m/z* = 701.1 ($[M+H]^+$, t_r = 1.75 min). **HRMS** (ESI+) *m/z* = 701.2564 $[M+H]^+$ found, $C_{39}H_{41}O_{12}^+$ required 701.2593.

4.3.8. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(2,3,4,6-tetramethoxyphenyl)prop-2-en-1-one) (**61**)

A mixture of chalcone **50** (253 mg, 0.674 mmol), CH_2I_2 (0.20 mL, 2.49 mmol) and anhydrous K_2CO_3 (280 mg, 2.02 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1% MeOH/CH_2Cl_2) and recrystallized from MeOH to afford bichalcone **61** (249 mg, 48%) as a yellow powdery solid. **m.p.** 182–184 °C. **TLC** R_f = 0.31 (2% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2943w (C–H str), 2837w (C–H str), 1654 m (C=O str), 1598 m (C=C str), 1564s (C=C str), 1504 m (C=C str), 1467 m, 1401 m, 1341 m, 1309 m, 1259s, 1170 m, 1135 m, 1111s, 1067 m, 1011s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.85 (6H, s, 2 × −OCH_3), 3.93 (6H, s, 2 × −OCH_3), 3.94 (6H, s, 2 × −OCH_3), 3.95 (6H, s, 2 × −OCH_3), 3.96 (6H, s, 2 × −OCH_3), 5.93 (2H, s, −OCH_2O-), 6.31 (2H, s, ArH), 7.37 (2H, d, *J* 8.0 Hz, ArH), 7.65 (2H, dd, *J* 8.4, 2.0 Hz, ArH), 7.67 (2H, d, *J* 1.6 Hz, ArH), 7.96 (2H, d, *J* 16.0 Hz, 2 × −CH=CHCO−), 8.13 (2H, d, *J* 16.0 Hz, 2 × −CH=CHCO−). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 56.0, 56.0, 61.1, 61.2, 92.0, 92.3, 111.0, 111.8, 116.0, 122.4, 122.8, 134.4, 135.6, 136.5, 149.5, 149.9, 154.7, 155.6, 156.6, 190.3. **LCMS** (ES+) *m/z* = 761.3 ($[M+H]^+$, t_r = 1.88 min). **HRMS** (ESI+) *m/z* = 761.2834 $[M+H]^+$ found, $C_{41}H_{45}O_{14}^+$ required 761.2809.

4.3.9. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(4-bromophenyl)prop-2-en-1-one) (**62**)

A mixture of chalcone **51** (305 mg, 0.915 mmol), CH_2I_2 (0.25 mL, 3.11 mmol) and anhydrous K_2CO_3 (382 mg, 2.76 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, CH_2Cl_2) and recrystallized from MeOH to afford bichalcone **62** (104 mg, 17%) as an off-white powdery solid. **m.p.** 206–208 °C. **TLC** R_f = 0.47 (1% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2939w (C–H str), 1660 m (C=O str), 1607 m (C=C str), 1584s (C=C str), 1510 m (C=C str), 1487 m, 1467w, 1419s, 1322w, 1258s, 1220 m, 1169 m, 1136s, 1073w, 1031 m, 1007s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.96 (6H, s, 2 × −OCH_3), 5.95 (2H, s, −OCH_2O-), 7.38 (2H, d, *J* 8.8 Hz, ArH), 7.51 (4H, d, *J* 8.8 Hz, ArH), 7.52 (2H, d, *J* 15.6 Hz, 2 × −*CH*=CHCO−), 7.57 (4H, d, *J* 8.8 Hz, ArH), 7.64–7.66 (4H, m, ArH), 7.75 (2H, d, *J* 15.6 Hz, 2 × −CH=*CH*CO−). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 56.1, 92.0, 111.7, 115.9, 122.1, 122.5, 124.7, 129.8, 132.2, 133.4, 133.8, 143.0, 150.0, 150.2, 188.5. **LCMS** (ES+) *m/z* = 676.9 ($[M+H]^+$ for $^{79}Br_2$, t_r = 2.09 min). **HRMS** (ESI+) *m/z* = 698.9968 $[M+Na]^+$ found, $C_{33}H_{26}O_6^{79}Br_2Na^+$ required 698.9988.

4.3.10. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(3-bromophenyl)prop-2-en-1-one) (**63**)

A mixture of chalcone **52** (306 mg, 0.919 mmol), CH_2I_2 (0.22 mL, 2.74 mmol) and anhydrous K_2CO_3 (419 mg, 3.03 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1% MeOH/CH_2Cl_2) to afford bichalcone **63** (321 mg, 52%) as a pale yellow-white powdery solid. **m.p.** 118–120 °C. **TLC** R_f = 0.39 (1% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2941w (C–H str), 1708w, 1657 m (C=O str), 1605 m (C=C str), 1584s (C=C str), 1563 m (C=C str), 1509s (C=C str), 1469 m, 1419s, 1312 m, 1254s, 1221w, 1169 m, 1135s, 1007s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.95 (6H, s, 2 × −OCH_3), 5.95 (2H, s, −OCH_2O-), 7.29 (2H, t, *J* 8.0 Hz, ArH), 7.37 (2H, dd, *J* 8.0, 0.5 Hz, ArH), 7.50–7.55 (4H, m, ArH), 7.51 (2H, d, *J* 15.5 Hz, 2 × −*CH*=CHCO−), 7.64–7.66 (2H, m, ArH), 7.72 (2H, d, *J* 16.0 Hz, 2 × −CH=*CH*CO−), 7.79 (2H, t, *J* 1.5 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 56.1, 91.9, 111.6, 115.9, 122.6, 122.7, 123.0, 127.2, 130.4, 130.7, 133.1, 133.2, 137.0, 142.5, 150.0, 150.1, 188.2. **LCMS** (ES+) *m/z* = 677.1 ($[M+H]^+$ for $^{79}Br_2$, t_r = 1.99 min). **HRMS** (ESI+) *m/z* = 677.0144 $[M+H]^+$ found, $C_{33}H_{27}O_6^{79}Br_2^+$ required 677.0169.

4.3.11. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(ferrocenyl)prop-2-en-1-one) (**64**)

A mixture of chalcone **53** (308 mg, 0.850 mmol), CH_2I_2 (0.20 mL, 2.49 mmol) and anhydrous K_2CO_3 (357 mg, 2.58 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 0.5% MeOH/CH_2Cl_2) to afford bichalcone **64** (329 mg, 53%) as a dark purple microcrystalline solid. **m.p.** 124–126 °C. **TLC** R_f = 0.32 (1% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3011w (C–H str), 2842w (C–H str), 1697w (C=O str), 1654 m (C=C str), 1596s (C=C str), 1575s (C=C str), 1510 m (C=C str), 1463 m, 1419 m, 1342w, 1296 m, 1259s, 1196 m, 1132s, 1106 m, 1029 m, 1002s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.97 (6H, s, 2 × −OCH_3), 4.19 (10H, s, 2 × −C_5H_5), 4.50 (4H, t, *J* 2.0 Hz, 2 × −C_5H_4), 4.61 (4H, t, *J* 2.0 Hz, 2 × −C_5H_4), 5.94 (2H, s, −OCH_2O-), 7.13 (2H, d, *J* 15.5 Hz, 2 × −*CH*=CHCO−), 7.37 (2H, d, *J* 8.5 Hz, ArH), 7.60 (2H, dd, *J* 8.5, 2.0 Hz, ArH), 7.64 (2H, d, *J* 2.0 Hz, ArH), 7.76 (2H, d, *J* 15.5 Hz, 2 × −CH=*CH*CO−). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 56.1, 69.0, 69.8, 71.3, 79.3, 92.1, 111.7, 116.0, 118.7, 122.2, 134.0, 146.4, 150.0, 150.1, 188.2. **LCMS** (ES+) *m/z* = 736.1 ($[M+H]^+$, t_r = 2.06 min). **HRMS** (ESI+) *m/z* = 737.1259 $[M+H]^+$ found, $C_{41}H_{37}O_6Fe_2^+$ required 737.1283.

4.3.12. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(furan-2-yl)prop-2-en-1-one) (**65**)

A mixture of chalcone **54** (636 mg, 2.60 mmol), CH_2I_2 (0.30 mL,

3.74 mmol) and anhydrous K_2CO_3 (540 mg, 3.91 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford bichalcone **65** (645 mg, 50%) as a pale brown-white powdery solid. **m.p.** 258–260 °C. **TLC** $R_f = 0.35$ (1% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3115w (C–H str), 2949w (C–H str), 2910w (C–H str), 1740w, 1650 m (C=O str), 1596s (C=C str), 1577s (C=C str), 1552s (C=C str), 1508 m (C=C str), 1479 m, 1467 m, 1420s, 1311 m, 1293 m, 1259s, 1210s, 1163s, 1138s, 1023s. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.86 (6H, s, 2 × −OCH_3), 6.02 (2H, s, −OCH_2O-), 6.69–6.70 (2H, m, ArH), 7.10 (2H, d, *J* 3.2 Hz, ArH), 7.35 (2H, d, *J* 8.4 Hz, ArH), 7.56 (4H, s, 2 × −C*H*=CHCO− and 2 × −CH=C*H*CO−), 7.61 (2H, d, *J* 1.6 Hz, ArH), 7.79 (2H, dd, *J* 8.4, 1.6 Hz, ArH), 7.92 (2H, d, *J* 1.2 Hz, ArH). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 55.7, 90.6, 111.5, 113.1, 115.3, 116.9, 118.6, 122.5, 130.1, 132.4, 146.1, 149.5, 151.2, 187.0. **LCMS** (ES-) *m/z* = 500.3 ([M-H]$^-$, t_r = 2.04 min). **HRMS** (ESI+) *m/z* = 501.1532 $[M+H]^+$ found, $C_{29}H_{25}O_8^+$ required 501.1549.

4.3.13. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one) (**66**)

A mixture of chalcone **55** (202 mg, 0.786 mmol), CH_2I_2 (0.20 mL, 2.49 mmol) and anhydrous K_2CO_3 (331 mg, 2.39 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1% MeOH/CH_2Cl_2) to afford bichalcone **66** (210 mg, 51%) as a bright yellow powdery solid. **m.p.** 228–230 °C. **TLC** $R_f = 0.48$ (2% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2926w (C–H str), 2833w (C–H str), 1648 m (C=O str), 1597 m (C=C str), 1575s (C=C str), 1512 m (C=C str), 1481 m, 1459 m, 1409 m, 1380w, 1329 m, 1260s, 1249s, 1188 m, 1140s, 1092w, 1059 m, 1001s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.78 (6H, s, 2 × −NCH_3), 3.96 (6H, s, 2 × −OCH_3), 5.93 (2H, s, −OCH_2O-), 6.23–6.24 (2H, m, ArH), 6.82 (2H, t, *J* 2.5 Hz, ArH), 6.85 (2H, dd, *J* 4.0, 1.0 Hz, ArH), 7.30 (2H, d, *J* 15.0 Hz, 2 × −CH=CHCO−), 7.36 (2H, d, *J* 8.0 Hz, ArH), 7.63 (2H, dd, *J* 8.5, 2.0 Hz, ArH), 7.65 (2H, d, *J* 2.0 Hz, ArH), 7.81 (2H, d, *J* 15.0 Hz, 2 × −CH=CHCO−). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 34.4, 56.1, 92.1, 109.7, 111.6, 112.3, 116.0, 116.3, 122.0, 127.7, 130.3, 131.9, 134.1, 149.6, 150.0, 188.3. **LCMS** (ES+) *m/z* = 527.3 ([M+H]$^+$, t_r = 1.74 min). **HRMS** (ESI+) *m/z* = 527.2163 $[M+H]^+$ found, $C_{31}H_{31}O_6N_2^+$ required 527.2177.

4.3.14. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(1-methyl-1H-indol-3-yl)prop-2-en-1-one) (**67**)

A mixture of chalcone **56** (207 mg, 0.674 mmol), CH_2I_2 (0.20 mL, 2.49 mmol) and anhydrous K_2CO_3 (330 mg, 2.17 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from $CHCl_3$ to afford bichalcone **67** (253 mg, 60%) as a pale yellow-brown powdery solid. **m.p.** >300 °C. **TLC** $R_f = 0.26$ (2% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2922w (C–H str), 2841w (C–H str), 1651 m (C=O str), 1597s (C=C str), 1568s (C=C str), 1531 m (C=C str), 1514 m (C=C str), 1474 m, 1377s, 1335 m, 1283s, 1262s, 1252s, 1200 m, 1177 m, 1117s, 1074 m, 1016s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.87 (6H, s, 2 × −NCH_3), 3.98 (6H, s, 2 × −OCH_3), 5.96 (2H, s, −OCH_2O-), 7.31–7.36 (4H, m, ArH), 7.40 (4H, d, *J* 8.8 Hz, ArH), 7.50 (2H, s, ArH), 7.56 (2H, d, *J* 15.6 Hz, 2 × −CH=CHCO−), 7.70–7.71 (4H, m, ArH), 8.03 (2H, d, *J* 6.8 Hz, ArH), 8.10 (2H, d, *J* 15.2 Hz, 2 × −CH=CHCO−). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 33.3, 56.1, 92.3, 110.1, 111.7, 113.1, 116.1, 116.7, 120.8, 121.6, 122.1, 123.2, 126.2, 134.4, 134.5, 138.3, 148.2, 149.4, 150.0, 189.2. **LCMS** (ES+) *m/z* = 627.2 ([M+H]$^+$, t_r = 1.86 min). **HRMS** (ESI+) *m/z* = 627.2472 $[M+H]^+$ found, $C_{39}H_{35}O_6N_2^+$ required 627.2490.

4.3.15. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(pyridin-2-yl)prop-2-en-1-one) (**68**)

A mixture of chalcone **57** (303 mmg, 1.19 mmol), CH_2I_2 (0.28 mL, 3.49 mmol) and anhydrous K_2CO_3 (509 mg, 3.68 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 0.5% MeOH/CH_2Cl_2) to afford bichalcone **68** (303 mg, 49%) as an off-white powdery solid. **m.p.** 248–250 °C. **TLC** $R_f = 0.39$ (5% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2943w (C–H str), 2843w (C–H str), 1658 m (C=O str), 1582s (C=C str), 1565 m (C=C str), 1509s (C=C str), 1460 m, 1415s, 1323s, 1303 m, 1258s, 1206 m, 1163 m, 1137s, 1026 m. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.95 (6H, s, 2 × −OCH_3), 5.94 (2H, s, −OCH_2O-), 7.29–7.30 (2H, m, ArH), 7.36 (2H, d, *J* 8.4 Hz, ArH), 7.47 (2H, d, *J* 7.6 Hz, ArH), 7.68 (2H, d, *J* 1.6 Hz, ArH), 7.71–7.77 (4H, m, ArH), 7.77 (2H, d, *J* 15.2 Hz, 2 × −C*H*=CHCO−), 8.11 (2H, d, *J* 15.2 Hz, 2 × −CH=C*H*CO−), 8.68 (2H, d, *J* 4.0 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 56.1, 91.9, 111.7, 115.9, 123.1, 124.4, 125.1, 125.4, 133.2, 136.9, 142.4, 150.1, 150.1, 153.2, 188.7. **LCMS** (ES+) *m/z* = 523.3 ([M+H]$^+$, t_r = 1.65 min). **HRMS** (ESI+) *m/z* = 523.1844 $[M+H]^+$ found, $C_{31}H_{27}O_6N_2^+$ required 523.1864.

4.3.16. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(3-methoxy-4,1-phenylene))bis(3-(quinolin-2-yl)prop-2-en-1-one) (**69**)

A mixture of chalcone **58** (310 mmg, 1.01 mmol), CH_2I_2 (0.25 mL, 3.11 mmol) and anhydrous K_2CO_3 (447 mg, 3.23 mmol) in dry DMF (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford bichalcone **69** (291 mg, 46%) as a pale brown powdery solid. **m.p.** 238–240 °C. **TLC** $R_f = 0.37$ (3% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3056w (C–H str), 2952w (C–H str), 1655 m (C=O str), 1592 m (C=C str), 1577s (C=C str), 1510 m (C=C str), 1461w, 1447w, 1416s, 1349 m, 1293s, 1262s, 1219 m, 1191 m, 1166 m, 1140s, 1037 m. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.90 (6H, s, 2 × −OCH_3), 6.09 (2H, s, −OCH_2O-), 7.43 (2H, d, *J* 8.8 Hz, ArH), 7.66 (2H, t, *J* 8.0 Hz, ArH), 7.70 (2H, d, *J* 2.0 Hz, ArH), 7.82 (2H, t, *J* 7.2 Hz, ArH), 7.84 (2H, d, *J* 15.6 Hz, 2 × −C*H*=CHCO−), 7.96 (2H, dd, *J* 8.4, 1.6 Hz, ArH), 8.02 (2H, d, *J* 8.0 Hz, ArH), 8.09 (2H, d, *J* 8.4 Hz, ArH), 8.24 (2H, d, *J* 8.4 Hz, ArH), 8.34 (2H, d, *J* 15.6 Hz, 2 × −CH=C*H*CO−), 8.49 (2H, d, *J* 8.8 Hz, ArH). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 55.8, 90.5, 111.7, 115.3, 120.8, 123.1, 126.9, 127.5, 127.8, 127.9, 129.2, 130.2, 132.1, 136.9, 143.1, 147.6, 149.6, 149.8, 153.7, 187.7. **LCMS** (ES+) *m/z* = 623.2 ([M+H]$^+$, t_r = 1.90 min). **HRMS** (ESI+) *m/z* = 623.2161 $[M+H]^+$ found, $C_{39}H_{31}O_6N_2^+$ required 623.2177.

4.3.17. Synthesis of (2E,2′E)-1,1′-((methylenebis(oxy))bis(4-methoxy-3,1-phenylene))bis(3-(2,4,6-trimethoxyphenyl)prop-2-en-1-one) (**72**)

A mixture of chalcone **71** (301 mg, 0.873 mmol), CH_2I_2 (0.21 mL, 2.61 mmol) and anhydrous K_2CO_3 (404 mg, 3.15 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford bichalcone **72** (241 mg, 39%) as a pale yellow powdery solid. **m.p.** 248–250 °C. **TLC** $R_f = 0.21$ (2% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2939w (C–H str), 2837w (C–H str), 1648 m (C=O str), 1598 m (C=C str), 1566s (C=C str), 1513 m (C=C str), 1457 m, 1415 m, 1336 m, 1319 m, 1258 m, 1222 m, 1148 m, 1113s, 1059 m, 1005s. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.85 (6H, s, 2 × −OCH_3), 3.86 (6H, s, 2 × −OCH_3), 3.89 (12H, s, 4 × −OCH_3), 5.91 (2H, s, −OCH_2O-), 6.31 (4H, s, ArH), 7.17 (2H, d, *J* 8.4 Hz, ArH), 7.77 (2H, dd, *J* 8.4, 1.6 Hz, ArH), 7.86 (2H, d, *J* 1.6 Hz, ArH), 7.89 (2H, d, *J* 16.0 Hz, 2 × −CH=CHCO−), 8.07 (2H, d, *J* 15.6 Hz, 2 × −CH=CHCO−). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 55.5, 55.8, 56.0, 91.0, 92.3, 105.1, 111.9, 116.4, 120.1, 124.4, 131.3, 134.5, 145.4, 153.5, 161.3, 163.2, 188.0. **LCMS** (ES+) *m/z* = 701.3 ([M+H]$^+$,

$t_r = 1.67$ min). **HRMS** (ESI+) m/z = 701.2587 $[M+H]^+$ found, $C_{39}H_{41}O_{12}^+$ required 701.2593.

*4.3.18. Synthesis of 3,3'-(methylenebis(oxy))bis(7-methoxy-2-(2,3,4-trimethoxyphenyl)-4H-chromen-4-one) (**96**)*

A mixture of flavonol **87** (301 mg, 0.841 mmol), CH_2I_2 (0.20 mL, 2.51 mmol) and anhydrous K_2CO_3 (362 mg, 2.62 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1–5% MeOH/CH_2Cl_2) to afford biflavone **96** (299 mg, 49%) as a pale yellow-brown powdery solid. **m.p.** 228–230 °C. **TLC** $R_f = 0.32$ (3% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2941w (C–H str), 2844w (C–H str), 1735w, 1611s (C=O str), 1574 m (C=C str), 1495 m, 1463 m, 1443s, 1412 m, 1395w, 1364w, 1245s, 1202 m, 1168 m, 1097s, 1056w. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.77 (6H, s, 2 × −OCH_3), 3.81 (6H, s, 2 × −OCH_3), 3.85 (6H, s, 2 × −OCH_3), 3.90 (6H, s, 2 × −OCH_3), 6.03 (2H, s, −OCH_2O-), 6.39 (2H, d, *J* 8.4 Hz, ArH), 6.80 (2H, d, *J* 2.0 Hz, ArH), 6.95 (2H, dd, *J* 8.8, 2.0 Hz, ArH), 7.12 (2H, d, *J* 8.8 Hz, ArH), 8.06 (2H, d, *J* 8.8 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 55.8, 60.8, 61.3, 94.5, 99.9, 106.5, 114.1, 117.5, 118.2, 125.8, 127.1, 137.4, 142.0, 152.2, 155.1, 155.3, 157.1, 163.7, 173.6. **LCMS** (ES+) m/z = 729.1 ($[M+H]^+$, $t_r = 1.66$ min). **HRMS** (ESI+) m/z = 729.2160 $[M+H]^+$ found, $C_{39}H_{37}O_{14}^+$ required 729.2178.

*4.3.19. Synthesis of 3,3'-(methylenebis(oxy))bis(2-(4-bromo-2,5-dimethoxyphenyl)-7-methoxy-4H-chromen-4-one) (**97**)*

A mixture of flavonol **88** (506 mg, 1.24 mmol), CH_2I_2 (0.30 mL, 3.68 mmol) and anhydrous K_2CO_3 (512 mg, 3.71 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1–5% MeOH/CH_2Cl_2) to afford biflavone **97** (520 mg, 51%) as a pale yellow-white powdery solid. **m.p.** 242–244 °C. **TLC** $R_f = 0.56$ (3% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2941w (C–H str), 2843w (C–H str), 1734w, 1627s (C=O str), 1613s, 1577w (C=C str), 1493s, 1441 m, 1390w, 1376w, 1246s, 1216s, 1199s, 1163 m, 1103 m, 1050 m, 1023s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.70 (6H, s, 2 × −OCH_3), 3.72 (6H, s, 2 × −OCH_3), 3.92 (6H, s, 2 × −OCH_3), 6.04 (2H, s, −OCH_2O-), 6.80 (2H, d, *J* 2.5 Hz, ArH), 6.97–6.99 (4H, m, ArH), 7.13 (2H, s, ArH), 8.04 (2H, d, *J* 9.0 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 55.8, 56.6, 56.7, 95.2, 100.0, 114.4, 114.6, 114.9, 117.0, 117.9, 119.0, 126.9, 137.6, 149.4, 151.5, 154.2, 157.2, 164.0, 173.5. **LCMS** (ES+) m/z = 827.0 ($[M+H]^+$, $t_r = 2.14$ min). **HRMS** (ESI+) m/z = 825.0151 $[M+H]^+$ found, $C_{37}H_{31}O_{12}Br_2^+$ required 825.0177.

*4.3.20. Synthesis of 7,7'-(methylenebis(oxy))bis(6-(5-bromo-2,4-dimethoxyphenyl)-8H-[1,3]dioxolo[4,5-g]chromen-8-one) (**98**)*

A mixture of flavonol **89** (204 mg, 0.484 mmol), CH_2I_2 (0.11 mL, 1.42 mmol) and anhydrous K_2CO_3 (209 mg, 1.51 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1–5% MeOH/CH_2Cl_2) to afford biflavone **98** (200 mg, 48%) as a pale yellow-brown powdery solid. **m.p.** 198–200 °C. **TLC** $R_f = 0.34$ (3% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2922w (C–H str), 2850w (C–H str), 1620s (C=O str), 1598s (C=C str), 1568w (C=C str), 1500 m (C=C str), 1461s, 1348 m, 1303w, 1256s, 1205s, 1186w, 1177 m, 1158 m, 1148w, 1057w, 1025s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.78 (6H, s, 2 × −OCH_3), 3.86 (6H, s, 2 × −OCH_3), 6.11 (6H, s, 3 × −OCH_2O-), 6.30 (2H, s, ArH), 6.79 (2H, s, ArH), 7.43 (2H, s, ArH), 7.53 (2H, s, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 56.1, 56.2, 93.7, 96.2, 97.8, 101.5, 102.1, 102.3, 113.4, 119.2, 134.4, 137.2, 145.7, 152.4, 152.7, 152.9, 158.0, 158.2, 173.0. **LCMS** (ES+) m/z = 855.0 ($[M+H]^+$, $t_r = 1.74$ min). **HRMS** (ESI+) m/z = 852.9783 $[M+H]^+$ found, $C_{37}H_{27}O_{14}Br_2^+$ required 852.9762.

*4.3.21. Synthesis of 3,3'-(methylenebis(oxy))bis(6-bromo-2-(furan-2-yl)-4H-chromen-4-one) (**99**)*

A mixture of flavonol **90** (310 mg, 1.01 mmol), CH_2I_2 (0.24 mL, 2.93 mmol) and anhydrous K_2CO_3 (451 mg, 3.26 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1–5% MeOH/CH_2Cl_2) to afford biflavone **99** (177 mg, 28%) as a pale yellow-white powdery solid. **m.p.** 258–260 °C. **TLC** $R_f = 0.46$ (0.5% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3099w (C–H str), 2852w (C–H str), 1636s (C=O str), 1610s, 1572 m (C=C str), 1553 m (C=C str), 1483 m, 1464s, 1438s, 1360 m, 1270 m, 1250s, 1194s, 1165s, 1118 m, 1018 m. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.10–6.11 (2H, m, ArH), 6.65 (2H, s, −OCH_2O-), 7.00 (2H, dd, *J* 3.5, 0.5 Hz, ArH), 7.34 (2H, d, *J* 9.0 Hz, ArH), 7.37 (2H, dd, *J* 1.5, 1.0 Hz, ArH), 7.73 (2H, dd, *J* 9.0, 2.5 Hz, ArH), 8.33 (2H, d, *J* 2.5 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 92.7, 112.0, 117.6, 118.2, 119.7, 125.4, 128.1, 134.8, 136.3, 143.1, 145.0, 147.8, 153.1, 171.9. **LCMS** (ES+) m/z = 627.0 ($[M+H]^+$, $t_r = 2.20$ min). **HRMS** (ESI+) m/z = 646.8924 $[M+Na]^+$ found, $C_{27}H_{14}O_8Br_2Na^+$ required 646.8948.

*4.3.22. Synthesis of 7,7'-(methylenebis(oxy))bis(6-(1-methyl-1H-pyrrol-2-yl)-8H-[1,3]dioxolo[4,5-g]chromen-8-one) (**100**)*

A mixture of flavonol **91** (301 mg, 1.05 mmol), CH_2I_2 (0.25 mL, 3.16 mmol) and anhydrous K_2CO_3 (449 mg, 3.25 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1–5% MeOH/CH_2Cl_2) to afford biflavone **100** (58.8 mg, 10%) as a pale yellow-brown powdery solid. **m.p.** 222–224 °C. **TLC** $R_f = 0.28$ (3% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3107w (C–H str), 2921w (C–H str), 1627 m (C=O str), 1610 m, 1577 m (C=C str), 1559s (C=C str), 1505w (C=C str), 1462s, 1414s, 1360 m, 1306 m, 1262s, 1210s, 1163s, 1066 m, 1031s, 1017 m. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.70 (6H, s, 2 × −NCH_3), 5.88–5.89 (2H, m, ArH), 6.10 (4H, s, 2 × −OCH_2O-), 6.25 (2H, s, −OCH_2O-), 6.54 (2H, t, *J* 2.0 Hz, ArH), 6.70–6.71 (2H, m, ArH), 6.75 (2H, s, ArH), 7.46 (2H, s, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 37.1, 94.0, 97.2, 102.1, 102.4, 108.3, 116.7, 119.1, 122.1, 127.4, 135.3, 145.7, 150.1, 151.7, 152.2, 172.5. **LCMS** (ES+) m/z = 583.2 ($[M+H]^+$, $t_r = 1.81$ min). **HRMS** (ESI+) m/z = 583.1360 $[M+H]^+$ found, $C_{31}H_{23}N_2O_{10}^+$ required 583.1353.

*4.3.23. Synthesis of 3,3'-(methylenebis(oxy))bis(6-bromo-2-(1-methyl-1H-pyrrol-2-yl)-4H-chromen-4-one) (**101**)*

A mixture of flavonol **92** (262 mg, 0.819 mmol), CH_2I_2 (0.19 mL, 2.34 mmol) and anhydrous K_2CO_3 (383 mg, 2.77 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1–5% MeOH/CH_2Cl_2) to afford biflavone **101** (185 mg, 35%) as a pale yellow-brown powdery solid. **m.p.** 178–180 °C. **TLC** $R_f = 0.24$ (1% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2953w (C–H str), 2926w (C–H str), 1719w, 1626s (C=O str), 1606s, 1549s (C=C str), 1461s, 1438 m, 1408s, 1360 m, 1305 m, 1259 m, 1242w, 1190s, 1144 m, 1062 m. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.76 (6H, s, 2 × −NCH_3), 5.85–5.87 (2H, m, ArH), 6.26 (2H, s, −OCH_2O-), 6.54 (2H, t, *J* 2.0 Hz, ArH), 6.78 (2H, dd, *J* 4.0, 1.6 Hz, ArH), 7.25 (2H, d, *J* 8.8 Hz, ArH), 7.69 (2H, dd, *J* 8.8, 2.4 Hz, ArH), 8.24 (2H, d, *J* 2.4 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 37.3, 93.8, 108.7, 117.8, 117.8, 119.1, 121.8, 125.4, 128.2, 128.3, 135.5, 135.7, 151.0, 153.2, 171.9. **LCMS** (ES+) m/z = 652.9 ($[M+H]^+$, $t_r = 1.98$ min). **HRMS** (ESI+) m/z = 672.9565 $[M+Na]^+$ found, $C_{29}H_{20}O_6N_2Br_2Na^+$ required 672.9580.

*4.3.24. Synthesis of 3,3'-(methylenebis(oxy))bis(6-bromo-2-(1-methyl-1H-indol-3-yl)-4H-chromen-4-one) (**102**)*

A mixture of flavonol **93** (263 mg, 0.712 mmol), CH_2I_2 (0.16 mL, 2.03 mmol) and anhydrous K_2CO_3 (301 mg, 2.18 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue

was purified by flash column chromatography (SiO_2, 1–5% MeOH/CH_2Cl_2) to afford biflavone **102** (152 mg, 28%) as a bright yellow-green powdery solid. **m.p.** >300 °C. **TLC** R_f = 0.45 (5% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3096w (C–H str), 2942w (C–H str), 1625 m (C=O str), 1604 m, 1593 m (C=C str), 1540s (C=C str), 1516s (C=C str), 1458s, 1445s, 1342s, 1247 m, 1227 m, 1189s, 1118 m, 1078 m. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.52 (6H, s, 2 × $-NCH_3$), 6.42 (2H, d, *J* 8.8 Hz, ArH), 6.81 (2H, s, $-OCH_2O$-), 6.94 (2H, d, *J* 7.6 Hz, ArH), 7.12–7.25 (6H, m, ArH, overlain by $CDCl_3$), 7.80 (2H, s, ArH), 7.84 (2H, d, *J* 7.6 Hz, ArH), 8.06 (2H, d, *J* 1.6 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 33.2, 90.3, 104.3, 109.7, 116.6, 118.1, 121.5, 121.5, 122.7, 124.6, 125.2, 126.4, 133.0, 134.5, 135.0, 135.9, 152.0, 156.1, 171.1. **LCMS** (ES+) *m/z* = 752.9 ($[M+H]^+$, t_r = 2.16 min). **HRMS** (ESI+) *m/z* = 751.0059 $[M+H]^+$ found, $C_{37}H_{25}O_6N_2Br_2^+$ required 751.0074.

*4.3.25. Synthesis of 7,7'-(methylenebis(oxy))bis(6-(1-methyl-1H-indol-3-yl)-8H-[1,3]dioxolo[4,5-g]chromen-8-one) (**103**)*

A mixture of flavonol **94** (209 mg, 0.622 mmol), CH_2I_2 (0.14 mL, 1.79 mmol) and anhydrous K_2CO_3 (271 mg, 1.96 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1–5% MeOH/CH_2Cl_2) to afford biflavone **103** (56.1 mg, 13%) as a pale yellow-brown powdery solid. **m.p.** >300 °C. **TLC** R_f = 0.38 (5% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2920w (C–H str), 2853w (C–H str), 1728w, 1629s (C=O str), 1607s, 1575s (C=C str), 1562s (C=C str), 1518 m (C=C str), 1459s, 1339w, 1255s, 1209 m, 1157 m, 1127s, 1033s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.54 (6H, s, 2 × $-NCH_3$), 6.09 (4H, s, 2 × $-OCH_2O$-), 6.12 (2H, s, ArH), 6.82 (2H, s, $-OCH_2O$-), 7.01 (2H, d, *J* 7.6 Hz, ArH), 7.22–7.30 (4H, m, ArH, overlain by $CDCl_3$), 7.36 (2H, s, ArH), 7.87 (2H, s, ArH), 7.91 (2H, d, *J* 7.2 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 33.1, 90.5, 96.6, 100.7, 102.1, 104.6, 108.8, 118.3, 121.2, 121.7, 122.5, 125.2, 132.8, 134.4, 136.0, 145.0, 150.6, 151.2, 155.2, 171.8. **LCMS** (ES+) *m/z* = 683.2 ($[M+H]^+$, t_r = 1.91 min). **HRMS** (ESI+) *m/z* = 683.1659 $[M+H]^+$ found, $C_{39}H_{27}N_2O_{10}^+$ required 683.1666.

*4.3.26. Synthesis of 3,3'-(methylenebis(oxy))bis(6-methoxy-2-(1-methyl-1H-indol-3-yl)-4H-chromen-4-one) (**104**)*

A mixture of flavonol **95** (303 mg, 0.942 mmol), CH_2I_2 (0.23 mL, 2.80 mmol) and anhydrous K_2CO_3 (396 mg, 2.87 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1–5% MeOH/CH_2Cl_2) to afford biflavone **104** (8.10 mg, 13%) as a pale yellow-white powdery solid. **m.p.** 118–120 °C. **TLC** R_f = 0.28 (2% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2937w (C–H str), 1737s (C=O str), 1722s, 1614s, 1556s (C=C str), 1528 m (C=C str), 1487 m, 1462 m, 1436w, 1419w, 1351s, 1288w, 1216 m, 1194s, 1169w, 1147w, 1127w, 1088s, 1044 m, 1003s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.42 (3H, s, $-NCH_3$), 3.61 (3H, s, $-NCH_3$), 3.78 (3H, s, $-OCH_3$), 3.94 (3H, s, $-OCH_3$), 6.08 (2H, s, $-OCH_2O$-), 6.95–6.98 (2H, m, ArH), 7.06 (1H, d, *J* 9.6 Hz, ArH), 7.20–7.32 (7H, m, ArH), 7.54 (1H, d, *J* 9.2 Hz, ArH), 7.59 (1H, d, *J* 3.2 Hz, ArH), 7.75 (1H, s, ArH), 8.08 (1H, dd, *J* 7.6, 1.2 Hz, ArH), 8.15 (1H, s, ArH), 8.28–8.30 (1H, m, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 33.2, 33.5, 55.3, 56.0, 87.7, 104.8, 104.9, 105.8, 109.8, 109.9, 114.7, 119.0, 120.2, 121.5, 121.6, 121.9, 122.1, 122.8, 122.8, 122.9, 123.1, 124.8, 125.3, 125.9, 126.7, 135.1, 135.5, 136.0, 136.7, 137.2, 144.4, 149.6, 156.4, 156.6, 156.9, 163.0, 164.2, 171.9. **LCMS** (ES+) *m/z* = 655.1 ($[M+H]^+$, t_r = 1.67 min). **HRMS** (ESI+) *m/z* = 655.2072 $[M+H]^+$ found, $C_{39}H_{31}N_2O_8^+$ required 655.2080.

*4.3.27. Synthesis of 2,2'-((methylenebis(oxy))bis(4-methoxy-3,1-phenylene))bis(3,7,8-trimethoxy-4H-chromen-4-one) (**114**)*

A mixture of hydroxyflavone **113** (203 mg, 0.567 mmol), CH_2I_2 (0.14 mL, 1.70 mmol) and anhydrous K_2CO_3 (240 mg, 1.73 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1–5% MeOH/CH_2Cl_2) to afford biflavone **114** (133 mg, 32%) as a pale yellow-white powdery solid. **m.p.** 238–240 °C. **TLC** R_f = 0.40 (5% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2934w (C–H str), 2841w (C–H str), 1637 m (C=O str), 1598s (C=C str), 1564w (C=C str), 1510s (C=C str), 1456 m, 1432 m, 1381 m, 1288s, 1268s, 1206 m, 1175 m, 1129 m, 1087s, 1004s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.89 (6H, s, 2 × $-OCH_3$), 3.93 (6H, s, 2 × $-OCH_3$), 3.96 (6H, s, 2 × $-OCH_3$), 3.99 (6H, s, 2 × $-OCH_3$), 5.90 (2H, s, $-OCH_2O$-), 7.02 (2H, d, *J* 8.8 Hz, ArH), 7.06 (2H, d, *J* 8.8 Hz, ArH), 7.96 (2H, d, *J* 9.2 Hz, ArH), 7.99 (2H, dd, *J* 8.8, 2.4 Hz, ArH), 8.25 (2H, d, *J* 2.4 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 55.9, 56.5, 59.8, 61.5, 93.7, 109.8, 111.7, 118.5, 119.0, 120.9, 123.8, 124.6, 136.7, 140.5, 145.8, 149.5, 152.3, 154.4, 156.3, 174.7. **LCMS** (ES+) *m/z* = 729.2 ($[M+H]^+$, t_r = 4.73 min). **HRMS** (ESI+) *m/z* = 729.2153 $[M+H]^+$ found, $C_{39}H_{37}O_{14}^+$ required 729.2178.

*4.3.28. Synthesis of 7,7'-(methylenebis(oxy))bis(3-(4-bromophenyl)-4H-chromen-4-one) (**126**)*

A mixture of isoflavone **14** (302 mg, 0.952 mmol), CH_2I_2 (0.50 mL, 6.23 mmol) and anhydrous K_2CO_3 (502 mg, 3.63 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford biisoflavone **126** (314 mg, 51%) as a pale brown-white powdery solid. **m.p.** >300 °C. **TLC** R_f = 0.34 (1% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3082w (C–H str), 1621s (C=O str), 1599s (C=C str), 1573 m (C=C str), 1559w (C=C str), 1488 m, 1440s, 1366 m, 1332 m, 1300w, 1250w, 1233s, 1223s, 1194s, 1091w, 1075w, 1042 m, 1001s. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 6.23 (2H, s, $-OCH_2O$-), 7.27 (2H, d, *J* 8.8 Hz, ArH), 7.45 (2H, s, ArH), 7.57 (4H, d, *J* 8.0 Hz, ArH), 7.64 (4H, d, *J* 8.4 Hz, ArH), 8.11 (2H, d, *J* 8.8 Hz, ArH), 8.56 (2H, s, 2 × −C=CH). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 79.2, 103.6, 115.5, 118.9, 121.2, 122.7, 127.4, 131.0, 131.1, 132.6, 154.7, 157.0, 160.1, 174.2. **LCMS** (ES+) *m/z* = 647.3 ($[M+H]^+$, t_r = 1.99 min). **HRMS** (ESI+) *m/z* = 682.9137 $[M+K]^+$ found, $C_{31}H_{18}O_6Br_2K^+$ required 682.9113.

*4.3.29. Synthesis of 3,3'-((methylenebis(oxy))bis(4,1-phenylene))bis(7-methoxy-4H-chromen-4-one) (**127**)*

A mixture of isoflavone **123** (252 mg, 0.939 mmol), CH_2I_2 (0.30 mL, 3.74 mmol) and anhydrous K_2CO_3 (422 mg, 3.05 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford biisoflavone **127** (288 mg, 56%) as a white powdery solid. **m.p.** 248–250 °C. **TLC** R_f = 0.49 (2% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2956w (C–H str), 2893w (C–H str), 1736w, 1638s (C=O str), 1627s, 1606s (C=C str), 1570 m (C=C str), 1511 m (C=C str), 1443 m, 1375w, 1322w, 1252s, 1222s, 1184s, 1145w, 1106w, 1095w, 1050 m, 1022s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.93 (6H, s, 2 × $-OCH_3$), 5.80 (2H, s, $-OCH_2O$-), 6.87 (2H, d, *J* 2.0 Hz, ArH), 7.00 (2H, dd, *J* 8.8, 2.4 Hz, ArH), 7.20 (4H, d, *J* 8.4 Hz, ArH), 7.53 (4H, d, *J* 8.4 Hz, ArH), 7.93 (2H, s, 2 × −C=CH), 8.22 (2H, d, *J* 8.8 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 55.8, 91.0, 100.1, 114.6, 116.5, 118.4, 124.8, 126.1, 127.8, 130.2, 152.2, 156.8, 158.0, 164.0, 175.7. **LCMS** (ES+) *m/z* = 549.2 ($[M+H]^+$, t_r = 1.81 min). **HRMS** (ESI+) *m/z* = 549.1569 $[M+H]^+$ found, $C_{33}H_{25}O_8^+$ required 549.1544.

*4.3.30. Synthesis of 7,7'-(methylenebis(oxy))bis(3-(4-methoxyphenyl)-4H-chromen-4-one) (**128**)*

A mixture of isoflavone **124** (253 mg, 0.942 mmol), CH_2I_2 (0.25 mL, 3.11 mmol) and anhydrous K_2CO_3 (392 mg, 2.84 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford biisoflavone **128** (221 mg, 43%) as a pale brown-white powdery solid. **m.p.** >300 °C. **TLC** R_f = 0.42 (2% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2970w (C–H str), 2838w (C–H str), 1736w, 1639s (C=O str),

1607s (C=C str), 1578w (C=C str), 1514 m (C=C str), 1449 m, 1370 m, 1288 m, 1235s, 1195 m, 1133w, 1091w, 1050 m, 1026s, 1011s, 1002s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.85 (6H, s, 2 × −OCH_3), 5.95 (2H, s, −OCH_2O-), 6.98 (4H, d, *J* 8.8 Hz, ArH), 7.18 (2H, dd, *J* 8.8, 2.4 Hz, ArH), 7.22 (2H, d, *J* 2.0 Hz, ArH), 7.51 (4H, d, *J* 8.4 Hz, ArH), 7.96 (2H, s, 2 × −C=CH), 8.28 (2H, d, *J* 8.8 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 55.3, 90.2, 103.5, 114.0, 115.1, 120.0, 124.0, 125.1, 128.3, 130.1, 152.3, 157.5, 160.0, 160.4, 175.7. **LCMS** (ES+) *m/z* = 549.5 ($[M+H]^+$, t_r = 1.82 min). **HRMS** (ESI+) *m/z* = 549.1532 $[M+H]^+$ found, $C_{33}H_{25}O_8^+$ required 549.1544.

*4.3.31. Synthesis of 3,3′-((methylenebis(oxy))bis(2,1-phenylene)) bis(6,7-dimethoxy-4H-chromen-4-one) (**129**)*

A mixture of isoflavone **125** (307 mg, 1.03 mmol), CH_2I_2 (0.25 mL, 3.11 mmol) and anhydrous K_2CO_3 (421 mg, 3.04 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1% MeOH/CH_2Cl_2) to afford biisoflavone **129** (144 mg, 23%) as a pale yellow-brown powdery solid. **m.p.** 208–210 °C. **TLC** R_f = 0.44 (5% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2942w (C–H str), 2831w (C–H str), 1641s (C=O str), 1625 m, 1604s (C=C str), 1506s (C=C str), 1476 m, 1454 m, 1432s, 1363w, 1325w, 1271s, 1251 m, 1240s, 1198s, 1168 m, 1122 m, 1040s, 1014s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.98 (6H, s, 2 × −OCH_3), 4.00 (6H, s, 2 × −OCH_3), 5.66 (2H, s, −OCH_2O-), 6.86 (2H, s, ArH), 7.00–7.03 (2H, m, ArH), 7.18 (2H, d, *J* 1.0 Hz, ArH), 7.19–7.20 (2H, m, ArH), 7.27–7.29 (2H, m, ArH), 7.57 (2H, s, ArH), 7.80 (2H, s, 2 × −C=CH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 56.3, 56.4, 92.8, 99.6, 104.9, 116.0, 117.9, 121.6, 122.5, 122.8, 129.5, 131.8, 147.5, 152.2, 153.7, 154.2, 155.0, 175.1. **LCMS** (ES+) *m/z* = 609.1 ($[M+H]^+$, t_r = 1.61 min). **HRMS** (ESI+) *m/z* = 609.1780 $[M+H]^+$ found, $C_{35}H_{29}O_{10}^+$ required 609.1755.

*4.3.32. Synthesis of (2Z,2′Z)-2,2′-(((methylenebis(oxy))bis(2,1-phenylene))bis(methanylylidene))bis(4,6-dimethoxybenzofuran-3(2H)-one) (**136**)*

A mixture of aurone **133** (202 mg, 0.677 mmol), CH_2I_2 (0.20 mL, 2.49 mmol) and anhydrous K_2CO_3 (298 mg, 2.16 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford biaurone **136** (150 mg, 36%) as a pale yellow powdery solid. **m.p.** 248–250 °C. **TLC** R_f = 0.50 (2% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3018w (C–H str), 2938w (C–H str), 1695 m (C=O str), 1648w, 1614s (C=C str), 1595s (C=C str), 1457 m, 1419 m, 1363 m, 1348 m, 1257 m, 1210s, 1150s, 1091s, 1051w, 1006s. **^{1}H NMR** (500 MHz, DMSO-d_6): δ 3.87 (6H, s, 2 × −OCH_3), 3.89 (6H, s, 2 × −OCH_3), 6.13 (2H, s, −OCH_2O-), 6.30 (2H, d, *J* 1.6 Hz, ArH), 6.63 (2H, d, *J* 1.6 Hz, ArH), 6.83 (2H, s, 2 × −C=CH), 7.18 (2H, dt, *J* 8.0, 2.0 Hz, ArH), 7.43–7.49 (4H, m, ArH), 8.11 (2H, d, *J* 7.2 Hz, ArH). **^{13}C NMR** (500 MHz, DMSO-d_6): δ 56.1, 56.5, 89.9, 91.2, 94.4, 102.3, 103.9, 115.3, 122.0, 122.9, 131.0, 131.1, 147.6, 155.0, 158.9, 168.1, 168.9, 178.7. **LCMS** (ES+) *m/z* = 609.2 ($[M+H]^+$, t_r = 2.00 min). **HRMS** (ESI+) *m/z* = 609.1735 $[M+H]^+$ found, $C_{35}H_{29}O_{10}^+$ required 609.1761.

*4.3.33. Synthesis of (2Z,2′Z)-2,2′-(((methylenebis(oxy))bis(3,1-phenylene))bis(methanylylidene))bis(4,6-dimethoxybenzofuran-3(2H)-one) (**137**)*

A mixture of aurone **134** (204 mg, 0.684 mmol), CH_2I_2 (0.20 mL, 2.49 mmol) and anhydrous K_2CO_3 (297 mg, 2.15 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by flash column chromatography (SiO_2, 1% MeOH/CH_2Cl_2) to afford biaurone **137** (171 mg, 41%) as a pale yellow powdery solid. **m.p.** 198–200 °C. **TLC** R_f = 0.45 (3% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 2916w (C–H str), 2844w (C–H str), 1691 m (C=O str), 1659w, 1615 m (C=C str), 1585s (C=C str), 1505 m, 1423 m, 1345 m, 1216s, 1159 m, 1131w, 1091s, 1060w, 1037s. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.89 (6H, s, 2 × −OCH_3), 3.95 (6H, s, 2 × −OCH_3), 5.83 (2H, s, −OCH_2O-), 6.12 (2H, d, *J* 2.0 Hz, ArH), 6.32 (2H, d, *J* 1.6 Hz, ArH), 6.74 (2H, s, 2 × −C=CH), 7.17 (2H, dd, *J* 8.0, 2.0 Hz, ArH), 7.39 (2H, t, *J* 8.0 Hz, ArH), 7.53 (2H, t, *J* 8.0 Hz, ArH), 7.71 (2H, t, *J* 1.6 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 56.1, 56.2, 89.3, 91.5, 94.1, 105.1, 110.2, 117.6, 118.9, 125.6, 129.9, 134.1, 148.1, 157.1, 159.4, 169.0, 169.1, 180.6. **LCMS** (ES+) *m/z* = 609.2 ($[M+H]^+$, t_r = 1.91 min). **HRMS** (ESI+) *m/z* = 609.1745 $[M+H]^+$ found, $C_{35}H_{29}O_{10}^+$ required 609.1755.

*4.3.34. Synthesis of (2Z,2′Z)-2,2′-(((methylenebis(oxy))bis(4,1-phenylene))bis(methanylylidene))bis(4,6-dimethoxybenzofuran-3(2H)-one) (**138**)*

A mixture of aurone **135** (107 mg, 0.357 mmol), CH_2I_2 (0.10 mL, 1.25 mmol) and anhydrous K_2CO_3 (166 mg, 1.20 mmol) in dry acetone (20 mL) was reacted according to GP-B. The crude residue was purified by recrystallization from EtOAc to afford biaurone **138** (131 mg, 60%) as a pale yellow powdery solid. **m.p.** 238–240 °C. **TLC** R_f = 0.36 (3% MeOH/CH_2Cl_2). **IR** ν_{max} (neat)/cm^{-1}: 3101w (C–H str), 2922w (C–H str), 1699 m (C=O str), 1658w (C=C str), 1615 m (C=C str), 1586s (C=C str), 1507s, 1471w, 1424 m, 1347 m, 1254w, 1211s, 1173 m, 1158 m, 1089s, 1023 m. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.92 (6H, s, 2 × −OCH_3), 3.97 (6H, s, 2 × −OCH_3), 5.83 (2H, s, −OCH_2O-), 6.14 (2H, d, *J* 1.6 Hz, ArH), 6.39 (2H, d, *J* 1.6 Hz, ArH), 6.75 (2H, s, 2 × −C=CH), 7.18 (4H, d, *J* 8.8 Hz, ArH), 7.85 (4H, d, *J* 8.8 Hz, ArH). **^{13}C NMR** (500 MHz, $CDCl_3$): δ 56.1, 56.2, 89.2, 90.4, 94.0, 105.4, 110.4, 116.6, 127.1, 132.8, 147.2, 157.5, 159.4, 168.8, 168.9, 180.6. **LCMS** (ES+) *m/z* = 609.1 ($[M+H]^+$, t_r = 1.82 min). **HRMS** (ESI+) *m/z* = 609.1738 $[M+H]^+$ found, $C_{35}H_{29}O_{10}^+$ required 609.1755.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.05.003.

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