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SYNTHESIS OF NEW BIHETEROCYCLES BY A ONE-POT SONOGASHIRA COUPLING REACTION

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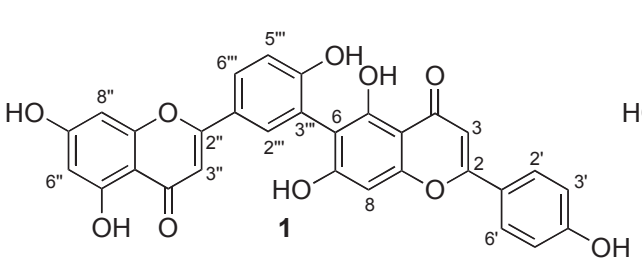
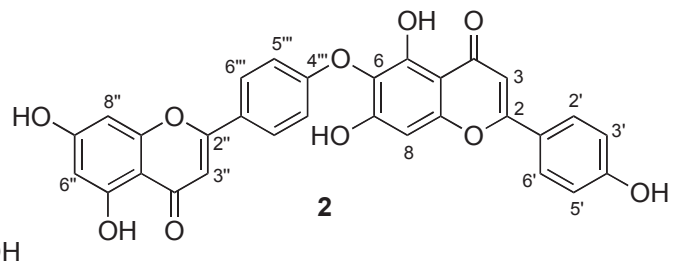
Dedicated to Prof. Albert Eschenmoser on the occasion of his 85th birthday

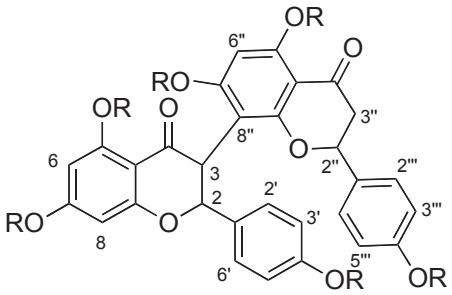
Abstract – Halogenated flavones, isoflavones and indoles were subjected to a one-pot Sonogashira coupling reaction to generate a series of new biheterocyclic compounds. The methodology can be readily adapted to the synthesis of a wide variety of substituted biheterocycles.

Biflavonoids are naturally occurring compounds that include two flavonoid molecules attached to each other either directly or *via* a linker. So far, more than 100 biflavonoid compounds have been isolated from various plants and a variety of biological activities have been associated with them.[1,2] For example robustaflavone **1** and hinoidflavone **2** are examples of novel non-nucleoside natural products which possess impressive activity against hepatitis B virus (HBV) replication.





In robustaflavone **1** two apigenin molecules are directly attached to each other *via* C6-C3''' linkage, whereas in hinoidflavone **2**, the C6 and C4''' carbons are linked *via* an oxygen atom. Biflavonoid **3** and its hexamethyl ether **4** in which two naringenin molecules are attached *via* a C3-C8'' linkage show potent antitubercular activity.[3]



3 R = H
4 R = Me

Although there are several examples of naturally occurring biflavonoids and biisoflavonoids, biheterocyclic compounds containing one flavone and one isoflavone component have not been reported in the literature. Moreover, the use of naturally occurring dimeric flavonoids as medicaments has been severely limited due to their low abundance in the plant material, tedious methods of extraction and purification, and unavailability of appropriate biological data.

Intrigued by the wide range of useful properties associated with biheterocycles, and in continuation of our interest in the synthesis of novel bis-heterocyclic systems,[4,5] we set out to synthesize biflavones, biisoflavones and mixed flavone-isoflavone dimers.

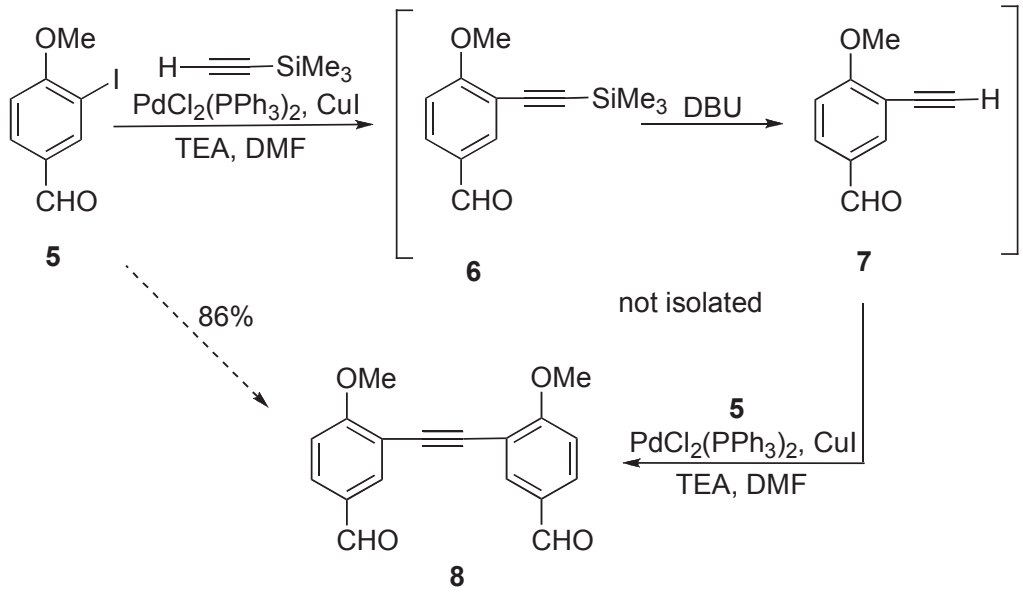
The acetylenic group is frequently present in bioactive natural products such as enediyne antibiotics, e.g. neocarzinostatin and dynemicin[6] as well as pharmaceuticals e.g. terbinafine (Lamisil)® and tazarotene. Therefore, synthesis of bis-flavonoids linked *via* an acetylenic bridge was undertaken.

Palladium catalyzed coupling of terminal alkynes with a vinyl or aryl halide, also known as the Sonogashira coupling, has become one of the most attractive and powerful tools for the synthesis of aryl-alkynes and vinyl-alkynes.[7-14] This reaction has been extensively studied and numerous modifications have been reported. These include the use of various solvents,[15,16] phase-transfer catalysts,[17] new catalyst systems,[18-21] copper free versions,[3,22,23] biphasic versions,[24] use of hydrogen atmosphere to suppress the homocoupling of the terminal alkynes,[25] polymer supported Pd-triazine complex[26] and solid supported Pd-catalyst.[27]

A number of one-pot Sonogashira processes have been reported,[28-31] however, an application of these methods for the synthesis of biflavonoids has not been reported yet. Grieco *et al.* have reported a one-pot synthesis of biarylethynes[32] which involves refluxing a mixture of an aryl halide with ethynyltrimethylsilane, CuI and palladium catalyst in benzene, followed by addition of 0.4 equivalents of water and 6.0 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for *in situ* deprotection of the TMS group. One more equivalent of aryl halide is then added and the reaction is continued to give the dimeric product**.** A one-pot synthesis of biflavones was investigated using similar conditions. However, benzene was replaced with DMF because of the high solubility of flavonoids in this solvent. It has been reported that the presence of residual oxygen in the reaction mixture can deactivate the catalyst and also

give rise to higher amounts of the homocoupled by-products.[33] Therefore, degassing of the reaction mixture is crucial for the success of the reaction. The degassing was done by heating the reactants and the solvent for 30 min while sweeping the headspace with argon prior to the addition of catalyst.[33]

In our work, the reaction conditions were optimized using 3-iodo-4-methoxybenzaldehyde **5** as the substrate by treating it with ethynyltrimethylsilane, CuI and palladium catalyst in a mixture of triethylamine and DMF. Upon complete conversion of the aryl halide into intermediate trimethylsilylated derivative **6** (TLC analysis), DBU and another equivalent of iodobenzaldehyde **5** was added. After work-up and chromatographic purification, the dimeric compound **8** was obtained in 86% yield (Scheme 1).

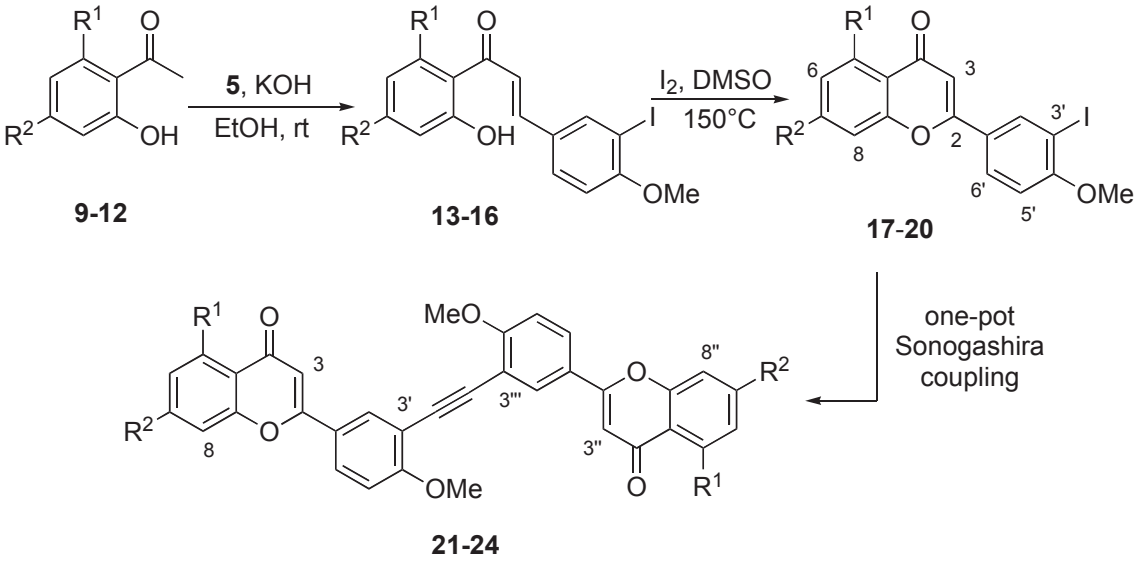


Scheme 1. One-pot synthesis of 1,2-Bis-(2-methoxy-5-formylphenyl)ethyne **8**

Encouraged by this result, the same methodology was applied for the preparation of symmetrical biflavones (Scheme 2).

Iodoflavones required for the dimerization reaction were synthesized in two steps from their respective acetophenones. In the first step, appropriately substituted acetophenones (**9-12**) were reacted with 3-iodo-4-methoxybenzaldehyde **5** in the presence of excess KOH to give chalcones (**13-16**) in 50-64% yield. Oxidative cyclization was then carried out by heating the chalcones in DMSO in the presence of a catalytic amount of iodine to give flavones **17-20** (Scheme 2) in 91-95% yield. When 3'-Iodo-4'-methoxyflavone **17** was subjected to one-pot reaction conditions described above, the resulting biflavone **21** was obtained in 80% yield. In the ^{1}H NMR spectrum of compound **21** the olefinic protons (H3 and H3''') appear as a singlet at δ 6.84 ppm, while in the ^{13}C NMR spectrum the two alkyne carbons appear at δ 89.6 ppm. In iodoflavone **17**, C3' attached to iodine appears at δ 86.4 ppm, whereas in compound **21** the corresponding C3' and C3''' attached to alkyne carbons move downfield to δ 113.2 ppm. The structure of

the compound **21** was further confirmed by the presence of the molecular ion peak at m/z 549.13 $(M + Na)^+$ in the mass spectrum. The coupling reaction of other iodoflavones **18-20** proceeded in a similar manner to yield the corresponding biflavones **22-24** in 84-90% yield. The yields and the nature of R^1 and R^2 substituents are depicted in Table 1.



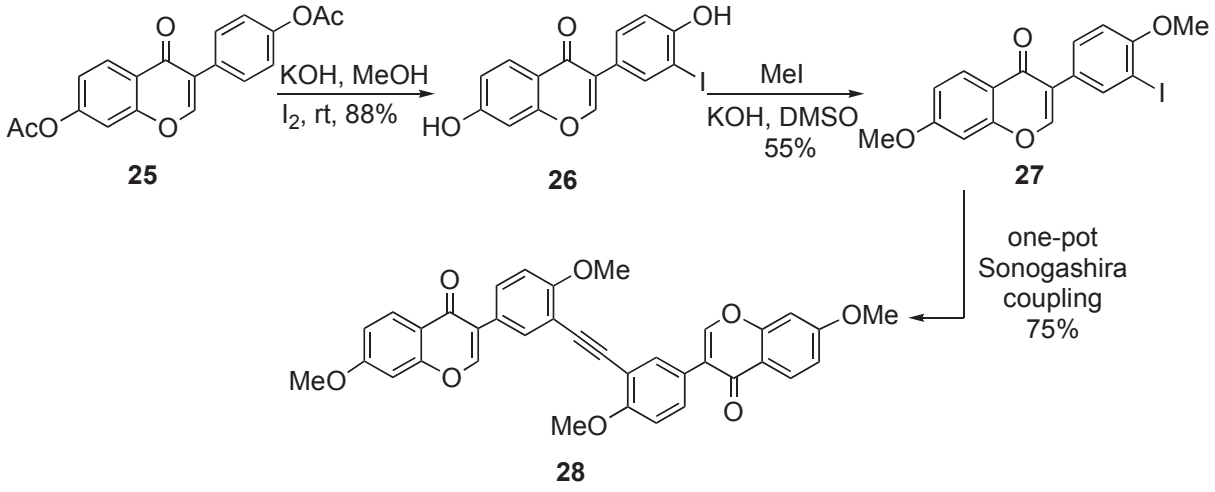
Scheme 2. Synthesis of biflavones **21-24** *via* a one-pot Sonogashira coupling reaction

Substrate	R^1	R^2	Product (% yield)	Product (% yield)	Product (% yield)
9	H	H	**13** (60)	**17** (91)	**21** (80)
10	MeO	H	**14** (64)	**18** (92)	**22** (90)
11	H	MeO	**15** (50)	**19** (95)	**23** (90)
12	MeO	MeO	**16** (50)	**20** (95)	**24** (84)

Table 1

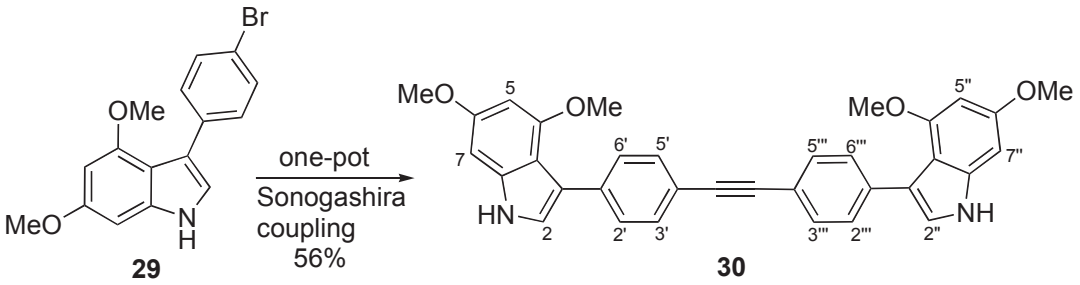
3'-Iodo-4',7-dimethoxyisoflavone **27** was synthesized from diacetyldaidzein **25** in three steps. First, isoflavone **27** was hydrolysed using methanolic KOH and then *in situ* iodinated by addition of iodine crystals to the reaction mixture. This was followed by methylation using methyl iodide in the presence of

KOH in DMSO. Isoflavone **27** after one-pot Sonogashira coupling gave biheterocycle **28** in 75% yield (Scheme 3).



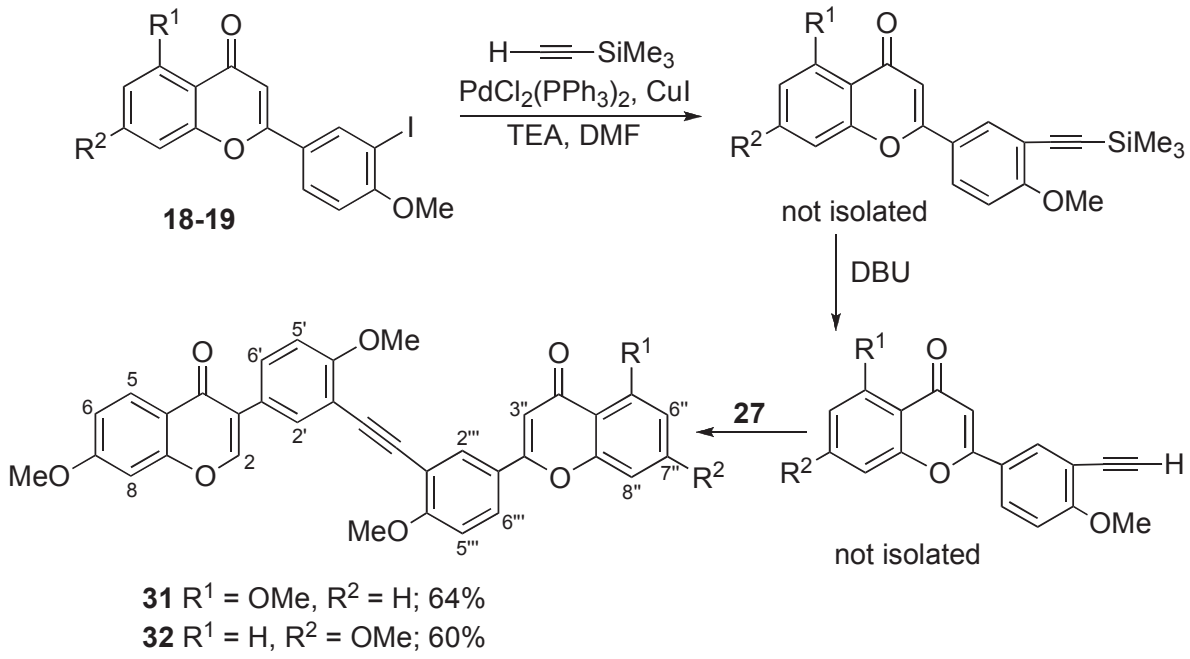
Scheme 3. Synthesis of biisoflavone *via* a one-pot Sonogashira coupling reaction

With these results in hand, we decided to investigate whether this methodology could be applied to the synthesis of biheterocycles using brominated heterocyclic substrates. When 3-(4-bromophenyl)-4,6-dimethoxyindole[34] **29** was subjected to the one-pot reaction conditions described above, the reaction was found to be sluggish and the resulting dimer **30** was obtained in 56% yield (Scheme 4).



Scheme 4. Synthesis of biindole **30** *via* a one-pot Sonogashira coupling reaction

Finally, we investigated the use of this methodology for synthesis of unsymmetrical biheterocycles. Interestingly, it was found that two different heteroaromatic substances could successfully be reacted under these conditions to give unsymmetrical biheterocycles. In this case iodoflavones **14** or **15** were first reacted with trimethylsilyl acetylene as described previously. Once the trimethylsilylated compound was formed, DBU and one equivalent of an iodoisoflavone **27** were added. The unsymmetrical biheterocycles **31** and **32** were obtained in 64 and 60% yields respectively.



Scheme 5. Syntheses of unsymmetrical biheterocycles *via* a one-pot Sonogashira coupling reaction

The formation of the coupling products was confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR and mass spectrometry and elemental analyses.

In conclusion, we have described a one-pot synthesis of symmetrical and unsymmetrical biflavonoids and a biindolyl linked *via* an acetylenic linker. The process involves Sonogashira coupling of halogenated heterocycles with a protected alkyne, *in situ* removal of the protecting group followed by another Sonogashira coupling reaction with one equivalent of the same or a different heterocycle without the addition of any additional catalyst. The described methodology represents an efficient access to afford a range of biheterocycles and their analogues with potentially interesting biological activities.

EXPERIMENTAL

All reactions were performed under an argon atmosphere. Melting points are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyzer EA 1108. NMR spectra were recorded in the designated solvents on a Bruker Avance DPX300 (300 MHz) spectrometer and were internally referenced to the solvent peaks. Low resolution mass spectrometric analysis was carried out on a Q-Star Pulsar API (Applied Biosystems) mass spectrometer. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR spectrometer. Column chromatography was carried out using Merck 230-400 mesh ASTM silica gel.

General procedure for synthesis of chalcones: To a solution of hydroxyacetophenone (15 mmol) and 3-iodo-4-methoxybenzaldehyde **5** (3.9 g, 15 mmol) in 95% EtOH (150 mL) was added a solution of KOH (30.0 g, 535 mmol) in water (20 mL). The mixture was stirred at ambient temperature for 30 min and then

left at rt for 3 days. The mixture was cooled to 15 °C and acidified to pH 4 by addition of 2M hydrochloric acid. The precipitated product was filtered, washed with water (50 mL) and air dried. An analytical sample was prepared by recrystallization from EtOH.

2'-Hydroxy-3-iodo-4-methoxychalcone (13): A yellow solid (60%). Mp 165-167 °C (from EtOH), (lit.,[35] 169 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (3H, s, CH_3O), 6.85 (1H, d, *J* = 8.3 Hz, H5), 6.95 (1H, t, *J* = 7.9 Hz, H5'), 7.03 (1H, d, *J* = 8.7 Hz, H3'), 7.50 (1H, ddd, *J* = 1.1, 7.9, 8.7 Hz, H4'), 7.53 (1H, d, *J* = 15.5 Hz, H_α), 7.59 (1H, dd, *J* = 1.9, 8.3 Hz, H6), 7.79 (1H, d, *J* = 15.5 Hz, H_β), 7.92 (1H, dd, *J* = 1.1, 7.9 Hz, H6'), 8.14 (1H, d, *J* = 1.9 Hz, H2), 12.82 (1H, s, OH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 56.5, 86.7, 110.7, 118.5, 118.6, 118.8, 119.9, 129.2, 129.5, 131.1, 136.3, 139.0, 143.4, 160.1, 163.5, 193.3.

2'-Hydroxy-3-iodo-4,6'-dimethoxychalcone (14): A yellow solid (64%). Mp 148-150 °C; IR (KBr): ν_{max} 1628, 1608, 1578, 1548, 1487, 1474, 1453, 1237, 1204, 1088, 1045, 863, 810, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (3H, s, CH_3O), 3.95 (3H, s, CH_3O), 6.42 and 6.61 (2H, 2 × d, *J* = 8.3 Hz, H3' and H5'), 6.83 (1H, d, *J* = 8.7 Hz, H5), 7.35 (1H, t, *J* = 8.3 Hz, H4'), 7.55 (1H, dd, *J* = 1.9, 8.7 Hz, H6), 7.69 (1H, d, *J* = 15.4 Hz, H_α), 7.72 (1H, d, *J* = 1.5 Hz, H_β), 8.06 (1H, d, *J* = 1.9 Hz, H2); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.9, 56.4, 86.5, 101.5, 110.7, 110.9, 111.9, 126.3, 130.0, 130.5, 135.8, 139.1, 141.0, 159.6, 160.8, 164.8, 194.0; HRMS (ESI) m/z $C_{17}H_{15}O_4INa$ $(M + Na)^+$ 432. 9914; Anal. Calcd for $C_{17}H_{15}IO_4$: C, 49.78; H, 3.69. Found: C, 49.58; H 3.64.

2'-Hydroxy-3-iodo-4,4'-dimethoxychalcone[36] **(15):** A yellow solid (50%). Mp 238 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (3H, s, CH_3O), 3.93 (3H, s, CH_3O), 6.46 (1H, d, *J* = 2.3 Hz, H3'), 6.48 (1H, dd, *J* = 2.3, 8.7 Hz, H5'), 6.84 (1H, d, *J* = 8.3 Hz, H5), 7.43 (1H, d, *J* = 15.5 Hz, H_α), 7.57 (1H, dd, *J* = 2.3, 8.3 Hz, H6), 7.75 (1H, d, *J* = 15.5 Hz, H_β), 7.83 (1H, d, *J* = 8.7 Hz, H6'), 8.11 (1H, d, *J* = 2.3 Hz, H2), 13.43 (1H, s, OH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.5, 56.5, 86.6, 101.0, 107.7, 110.7, 114.0, 118.8, 129.4, 130.9, 131.1, 138.8, 142.4, 159.9, 166.1, 166.6, 191.4.

2'-Hydroxy-3-iodo-4,4',6'-trimethoxychalcone (16): A yellow solid (0.50 g, 50%). Mp 152-154 °C, (lit.,[37] 154-155 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (3H, s, CH_3O), 3.92 (6H, s, 2 × CH_3O), 5.96 and 6.10 (2H, 2 × d, *J* = 2.6 Hz, H3', H5'), 6.83 (1H, d, *J* = 8.3 Hz, H5), 7.53 (1H, dd, *J* = 2.3, 8.3 Hz, H6), 7.65 (1H, d, *J* = 15.5 Hz, H_α), 7.75 (1H, d, *J* = 15.5 Hz, H_β), 8.04 (1H, d, *J* = 2.3 Hz, H2); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.5, 55.8, 56.4, 86.4, 91.2, 93.7, 106.2, 110.7, 126.2, 130.27, 130.29, 139.0, 140.4, 159.4, 162.4, 166.1, 168.3, 192.2.

General procedure for synthesis of iodoflavones: A suspension of chalcone (10.0 mmol) and DMSO (38 mL) under an argon atmosphere was immersed in an oil bath preheated at 160 °C. After 5 min iodine crystals (0.15 g, 0.6 mmol) were added and heating was continued further for 45 min. The mixture was cooled to 60 °C and potassium metabisulfite solution (5 mL, 10% w/v) was added to the mixture. The stirring was continued for 2 min and the mixture was diluted with water (100 mL). The resulting solid

was filtered, washed with water (50 mL) and air dried.

3'-Iodo-4'-methoxyflavone (17): Off-white crystals (91%). Mp 189-191 °C, (lit.,[35] 192 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.95 (3H, s, CH_3O), 6.71 (1H, s, H3), 6.91 (1H, d, *J* = 8.6 Hz, H5'), 7.40 (1H, t, *J* = 7.5 Hz, H6), 7.55 (1H, d, *J* = 8.3 Hz, H8), 7.69 (1H, dd, *J* = 7.5, 8.3 Hz, H7), 7.86 (1H, dd, *J* = 1.5, 8.6 Hz, H6'), 8.20 (1H, d, *J* = 7.5 Hz, H5), 8.34 (1H, d, *J* = 1.5 Hz, H2'); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 56.6, 86.4, 106.6, 110.7, 118.0, 123.8, 125.2, 125.6, 125.8, 128.0, 133.7, 137.4, 156.0, 160.2, 161.7, 178.2.

3'-Iodo-4',5-dimethoxyflavone (18): Off-white crystals (92%). Mp 210-212 °C; IR (KBr): ν_{max} 1650, 1594, 1474, 1396, 1276, 1261, 1102, 1046, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.95 (3H, s, CH_3O), 3.99 (3H, s, CH_3O), 6.61 (1H, s, H3), 6.82 and 7.12 (2H, 2 × d, *J* = 8.3 Hz, H6 and H8), 6.90 (1H, d, *J* = 8.7 Hz, H5'), 7.56 (1H, t, *J* = 8.3 Hz, H7), 7.82 (1H, dd, *J* = 2.3, 8.7 Hz, H6'), 8.30 (1H, d, *J* = 2.3 Hz, H2'); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 56.4, 56.5, 86.3, 106.4, 108.1, 110.0, 110.6, 114.4, 125.5, 127.6, 133.6, 137.2, 158.1, 159.4, 159.7, 160.4, 178.0; HRMS (ESI) m/z $C_{17}H_{13}O_4INa$ $(M + Na)^+$ 430.9745; Anal. Calcd for $C_{17}H_{13}O_4I$: C, 50.0; H, 3.18. Found: C, 50.12; H, 3.28.

3'-Iodo-4',7-dimethoxyflavone (19): An off-white solid (95%). Mp 219-221 °C, (lit.,[38] 219 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (3H, s, 7 CH_3O), 3.96 (3H, s, 4' CH_3O), 6.66 (1H, s, H3), 6.91 (1H, d, *J* = 8.7 Hz, H5'), 6.96 (1H, d, *J* = 2.3 Hz, H8), 6.98 (1H, dd, *J* = 2.3, 9.4 Hz, H6), 7.84 (1H, dd, *J* = 2.3, 8.6 Hz, H6'), 8.11 (1H, d, *J* = 9.4 Hz, H5), 8.34 (1H, d, *J* = 2.3 Hz, H2'); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.8, 56.5, 86.3, 100.3, 106.5, 110.7, 114.4, 117.6, 125.9, 127.0, 127.8, 137.2, 157.8, 160.5, 161.4, 164.1, 177.5.

3'-Iodo-5,7,4'-trimethoxyflavone (20): An off-white solid (380 mg, 95%). Mp 206-208 °C, (lit.,[37] 206-208 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (3H, s, CH_3O), 3.95 (6H, s, 2 × CH_3O), 6.37 and 6.58 (1H, 2 × d, *J* = 2.3 Hz, H6, H8), 6.68 (1H, s, H3), 6.90 (1H, d, *J* = 8.7 Hz, H5'), 7.81 (1H, dd, *J* = 2.3, 8.7 Hz, H6'), 8.30 (1H, d, *J* = 2.3 Hz, H2').

4',7-Dimethoxy-3'-iodoisoflavone (27): To a suspension of 4',7-diacetoxyisoflavone **25** (2.0 g, 5.91 mmol) in MeOH (100 mL) was added powdered KOH (6.0 g, 107 mmol) and the mixture was stirred under argon for 30 min. A solution of iodine (2.3 g, 10 mmol) in MeOH (40 mL) was added dropwise over 1 h and the mixture was stirred at ambient temperature for 1 h. Again a solution of iodine (0.22 g, 0.86 mmol) in MeOH (20 mL) was added over 30 min and stirring was continued further for 30 min. The mixture was poured into water (400 mL) and acidified to pH 2 using conc. hydrochloric acid. The precipitated solid was filtered, washed with water and air dried (2.0 g). This was suspended in DMSO (6 mL) and a solution of a solution of KOH (0.9 g, 16 mmol) in water (1 mL) was added under an argon atmosphere. The mixture was stirred for 15 min and then methyl iodide (3.0 g, 21.1 mmol) was added in one lot. Stirring was continued further for 2 h. The mixture was poured into water (200 mL) and the solid was filtered, washed with water and air dried. Iodoisoflavone **27** was obtained as a white solid (1.2 g,

55%). Mp 190-192 °C (from CH_2Cl_2/hexane); IR (KBr) ν_{max}: 1626, 1593, 1491, 1439, 1283, 1254, 1044, 802 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.91 (6H, s, 2 × CH_3O), 6.85 (1H, d, *J* = 2.6 Hz, H8), 6.88 (1H, d, *J* = 8.7 Hz, H5'), 6.99 (1H, dd, *J* = 2.6, 9.1 Hz, H6), 7.57 (1H, dd, *J* = 1.9, 8.7 Hz, H6'), 7.91 (1H, s, H2), 7.94 (1H, d, *J* = 9.0 Hz, H2'), 8.19 (1H, d, *J* = 9.1 Hz, H5); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.8, 56.4, 85.7, 100.1, 110.6, 114.6, 118.2, 123.5, 126.1, 127.7, 130.3, 139.4. 152.2, 157.9, 158.0, 164.0, 175.4; HRMS (ESI) m/z $C_{17}H_{13}O_4INa$ $(M + Na)^+$ 430.9752; Anal. Calcd for $C_{17}H_{13}IO_4$: C, 50.02; H, 3.21. Found: C, 50.10; H, 3.30.

General procedure for one-pot synthesis of biheterocycles: A solution of aryl halide (0.6 mmol) in triethylamine (3 mL) and DMF (3 mL) was deoxygenated by heating at 80 °C for 30 min with the headspace being purged continuously with argon. The mixture was cooled to rt and ethynyltrimethylsilane (0.1 mL, 0.7 mmol), $PdCl_2(PPh_3)_2$ (20 mg, 0.03 mmol) and CuI (7 mg, 0.5 mmol) were added. Heating was continued at 80 °C for 1.5 h. DBU (0.54 mL, 3.6 mmol) and another equivalent of aryl halide (0.6 mmol) were added and the heating was continued further for 1.5 h. The mixture was cooled to rt and poured into hydrochloric acid (2M, 50 mL) and stirred for 10 min. The solid was filtered, washed with water, air dried and purified by silica gel column chromatography.

1,2-Bis-(2-methoxy-5-formylphenyl)ethyne (8): An off-white solid (86%). This was purified by silica gel column chromatography [eluted with hexane/CH_2Cl_2 (30:70)]. Mp 209-211 °C (from MeOH); IR (KBr): ν_{max} 2842, 2752, 1674, 1597, 1500, 1290, 1273, 1244, 1170, 1139, 1019, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.02 (6H, s, 2 × CH_3O), 7.03 (2H, d, *J* = 8.7 Hz, H3, H3'), 7.86 (2H, dd, *J* = 2.3, 8.7 Hz, H4, H4'), 8.05 (2H, d, *J* = 2.3 Hz, H6, H6'), 9.89 (2H, s, 2 × CHO); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 56.3, 89.3, 110.7, 113.2, 129.5, 131.9, 135.5, 164.4, 190.1; HRMS (ESI) m/z $C_{18}H_{14}O_4Na$ $(M + Na)^+$ 317.0782; Anal. Calcd for $C_{18}H_{14}O_4 \cdot {}^1/_3H_2O$: C, 72.0; H, 4.88. Found: C, 72.11; H, 4.73.

1,2-Bis-(4'-methoxyflavon-3'-yl)ethyne (21): A pale yellow solid (80%). An analytical sample was prepared by flash chromatography (SiO_2, 2% MeOH/CH_2Cl_2). Mp 262-264 °C; IR (KBr): ν_{max} 1640, 1602, 1499, 1466, 1369, 1279, 1153, 1128, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.05 (6H, s, 4' CH_3O, 4''' CH_3O), 6.84 (2H, s, H3, H3''), 7.06 (2H, d, *J* = 8.6 Hz, H5', H5'''), 7.43 (2H, t, *J* = 7.9 Hz, H6, H6''), 7.92 (2H, d, *J* = 7.9 Hz, H8, H8''), 7.69 (2H, td, *J* = 1.5, 7.9 Hz, H7, H7''), 7.91 (2H, dd, *J* = 1.9, 8.6 Hz, H6', H6'''), 8.16 (2H, d, *J* = 1.9 Hz, H2', H2'''), 8.24 (2H, dd, *J* = 1.5, 7.9 Hz, H5, H5''); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 56.3, 89.6, 106.4, 111.0, 113.2, 118.0, 123.8, 124.0, 125.2, 125.6, 128.2, 131.6, 133.7, 156.1, 162.4, 162.6, 178.2; HRMS (ESI) m/z $C_{34}H_{22}O_6Na$ $(M + Na)^+$ 549.1304; Anal. Calcd for $C_{34}H_{22}O_6$: C, 77.56; H, 4.18. Found: C, 77.45; H, 4.23.

1,2-Bis-(4',5-dimethoxyflavon-3'-yl)ethyne (22): An off-white solid (90%). An analytical sample was prepared by flash chromatography (SiO_2, 2% MeOH/CH_2Cl_2). Mp 277-279 °C; IR (KBr): ν_{max} 1637, 1602, 1476, 1439, 1404, 1278, 1264, 1099, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.00 (6H, s, 2 × CH_3O),

4.03 (6H, s, 2 × CH_3O), 6.64 (2H, s, H3, H3''), 6.82 and 7.15 (4H, 2 × d, *J* = 8.3 Hz, H6, H6'', H8, H8''), 7.03 (2H, d, *J* = 9.0 Hz, H5', H5'''), 7.57 (2H, t, *J* = 8.3 Hz, H7, H7''), 7.85 (2H, dd, *J* = 2.3, 9.0 Hz, H6', H6'''), 8.10 (2H, d, *J* = 2.3 Hz, H2', H2'''); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 56.2, 56.4, 89.6, 106.4, 108.1, 110.1, 110.9, 113.2, 114.5, 123.8, 127.9, 131.4, 133.6, 158.2, 159.7, 160.2, 162.2, 178.1; HRMS (ESI) m/z $C_{36}H_{26}O_8Na$ $(M + Na)^+$ 609.1520; Anal. Calcd for $C_{36}H_{26}O_8 \cdot {}^1/_2H_2O$: C, 72.60; H, 4.53. Found: C, 72.62; H, 4.57.

1,2-Bis-(4',7-dimethoxyflavon-3'-yl)ethyne (23): A pale yellow solid (90%). An analytical sample was prepared by flash chromatography (SiO_2, 2% MeOH/CH_2Cl_2). Mp 274-276 °C; IR (KBr): ν_{max} 1646, 1628, 1603, 1496, 1440, 1280, 1164, 1018, 832 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (6H, s, 2 × CH_3O), 4.04 (6H, s, 2 × CH_3O), 6.73 (2H, s, H3, H3''), 6.98 (2H, dd, *J* = 2.3, 9.4 Hz, H6, H6''), 6.99 (2H, d, *J* = 2.3 Hz, H8, H8''), 7.05 (2H, d, *J* = 9.0 Hz, H5', H5'''), 7.88 (1H, dd, *J* = 2.3, 9.0 Hz, H6', H6'''), 8.12 (2H, d, *J* = 2.3 Hz, H2', H2'''), 8.13 (2H, d, *J* = 9.4 Hz, H5, H5''); ^{13}C NMR (150 MHz, DMSO-d_6, 60 °C): δ 57.0, 57.3, 90.5, 102.0, 106.8, 113.2, 113.4, 115.5, 118.1, 124,6, 127.1, 129.7, 131.7, 158.4, 162.4, 163.3, 164.9, 177.2 (C=O); HRMS (ESI) m/z $C_{36}H_{26}O_8Na$ $(M + Na)^+$ 609.1530; Anal. Calcd for $C_{36}H_{26}O_8$: C, 73.72; H, 4.43. Found: C, 73.74; H 4.52.

1,2-Bis-(4',5,7-trimethoxyflavon-3'-yl)ethyne (24): A pale yellow solid (84%). An analytical sample was prepared by flash chromatography (SiO_2, 1.5% MeOH/CH_2Cl_2). Mp 308-310 °C; IR (KBr): ν_{max} 1639, 1605, 1494, 1342, 1164, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (6H, s, 2 × CH_3O), 3.96 (6H, s, 2 × CH_3O), 4.03 (6H, s, 2 × CH_3O), 6.38 (2H, d, *J* = 2.3 Hz, H6, H6''), 6.60 (2H, d, *J* = 2.3 Hz, H8, H8''), 6.64 (2H, s, H3, H3''), 7.02 (2H, d, *J* = 9.0 Hz, H5', H5'''), 7.83 (2H, dd, *J* = 2.3, 9.0 Hz, H6', H6'''), 8.09 (2H, d, *J* = 2.3 Hz, H2', H2'''); ^{13}C NMR (Due to very low solubility of compound **19** a ^{13}C NMR spectrum could not be obtained); HRMS (ESI) m/z $C_{38}H_{30}O_{10}Na$ $(M + Na)^+$ 669.1746; Anal. Calcd for $C_{38}H_{30}O_{10} \cdot H_2O$: C, 69.61; H, 4.73. Found: C, 69.41; H, 4.73.

1,2-Bis-(4',7-dimethoxyisoflavone-3'-yl)ethyne (28): A grey solid (75%) which was purified by leaching with THF. M.p. 320-321 °C; UV spectrum could not be obtained due to extremely low solubility. IR (KBr): ν_{max} 3076, 2832, 1629, 1604, 1508, 1440, 1273, 1240, 1153, 1020, 856, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 6H, 2 × CH_3O), 3.88 (s, 6H, 2 × CH_3O), 7.08 (dd, *J* = 2.6, 9.0 Hz, 2H, H6, H6''), 7.15 (d, *J* = 8.7 Hz, 2H, H5', H5'''), 7.16 (d, *J* = 2.6 Hz, 2H, H8, H8''), 7.59 (dd, *J* = 2.3, 8.7 Hz, 2H, H6', H6'''), 7.67 (d, *J* = 2.3 Hz, 2H, H2', H2'''), 8.02 (d, *J* = 9.0 Hz, 2H, H5, H5''), 8.51 (s, 2H, H2, H2''); ^{13}C NMR (150 MHz, DMSO-d_6, 26000 scans): δ 56.8 (CH_3O), 57.0 (CH_3O), 101.5 (ArCH), 112.3 (ArCH), 115.8 (ArC), 116.9 (ArC), 118.4 (ArCH), 123.4 (ArC), 124.0 (ArC), 125.0 (ArC), 127.8 (ArCH), 131.6 (ArCH), 134.1 (ArCH), 154.9 (ArCH), 158.4 (ArC), 160.1 (ArC), 164.7 (ArC), 175.5 (C=O); HRMS (ESI) m/z Calcd for $C_{36}H_{26}O_8Na$ $(M + Na)^+$ 609.1511. Found 609.1524; Anal. Calcd. for $C_{36}H_{26}O_8 \cdot H_2O$: C, 71.52; H, 4.67. Found: C, 72.26; H, 4.58.

1,2-Bis[4-(4,6-dimethoxyindol-3-yl)phenyl]ethyne (30): A pale yellow solid (56%). An analytical sample was prepared by flash chromatography (SiO_2, 10% hexane/CH_2Cl_2). Mp 295 °C (from dichloroethane/hexane); IR (KBr): ν_{max} 3394, 2926, 2832, 1625, 1607, 1583, 1551, 1511, 1332, 1215, 1199, 1161, 1146, 1125, 1091, 1045, 965, 843 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 3.80 (6H, s, 2 × CH_3O), 3.83 (6H, s, 2 × CH_3O), 6.26 (2H, d, J = 1.9 Hz, H5, H5''), 6.61 (2H, d, J = 1.9 Hz, H7, H7''), 7.24 (2H, d, J = 1.5 Hz, H2, H2''), 7.49 and 7.65 (8H, 2 × d, J = 8.3 Hz, H2', H3', H5', H6', H2''', H3''', H5''', H6'''), 10.32 (2H, bs, 2 × NH); ^{13}C NMR (75.6 MHz, acetone-d_6): δ 54.3, 54.7, 87.1, 89.5, 91.9, 109.9, 117.4, 119.8, 121.5, 129.1, 130.4, 137.0, 139.1, 154.5, 157.6; HRMS (ESI) m/z $C_{34}H_{28}N_2O_4Na$ $(M + Na)^+$ 551.1936; Anal. Calcd for $C_{34}H_{28}N_2O_4 \cdot {}^1/_2H_2O$: C, 75.97; H, 5.40; N, 5.21. Found: C, 76.14; H, 5.42; N, 5.09.

1-(4',7-Dimethoxyisoflavon-3'-yl)-2-(4''',5''-dimethoxyflavon-3'''-yl)ethyne (31): A solution of iodoflavone **11** (243 mg, 0.6 mmol) in triethylamine (3 mL) and DMF (3 mL) was deoxygenated by heating at 80 °C for 30 min with the headspace being purged continuously with argon. The mixture was quickly cooled to rt and ethynyltrimethylsilane (100 μL, 0.7 mmol), $PdCl_2(PPh_3)_2$ (30 mg, 0.042 mmol) and CuI (10 mg, 0.05 mmol) were added. Heating was continued at 80 °C for 1.5 h. DBU (0.54 mL, 3.6 mmol) and iodoisoflavone **9** (243 mg, 0.6 mmol) were added and the heating was continued at 80 °C for another 1.5 h and then at 100 °C for 30 min. The mixture was cooled to rt and poured into a mixture of hydrochloric acid (2M, 50 mL) and EtOAc (25 mL) and stirred for 10 min. The solid was filtered, washed with water (25 mL) and air dried (272 mg, 76%). An analytical sample was prepared by flash chromatography (SiO_2, 2% MeOH/CH_2Cl_2). Mp. 168 °C (from CH_2Cl_2/hexane); IR (KBr): ν_{max} 3075, 2832, 1638, 1634, 1603, 1503, 1475, 1439, 1279, 1265, 1106, 1094, 1038, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.92 (3H, s, CH_3O), 3.99 (9H, 3 × s, 3 × CH_3O), 6.67 (1H, s, H3''), 6.82 (1H, d, J = 8.3 Hz, H6''), 6.86 (1H, d, J = 2.3 Hz, H8), 6.99 (3H, m, H6, H5''', H5'), 7.16 (1H, d, J = 8.3 Hz, H8''), 7.56 (1H, t, J = 8.3 Hz, H7''), 7.62 (1H, dd, J = 2.3, 8.6 Hz, H6'), 7.72 (1H, d, J = 2.3 Hz, H2'), 7.81 (1H, dd, J = 2.3, 8.7 Hz, H6'''), 7.97 (1H, s, H2), 8.09 (1H, d, J = 2.3 Hz, H2'''), 8.21 (1H, d, J = 9.0 Hz, H5); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.7, 56.1, 56.2, 56.4, 88.8, 90.6, 100.1, 106.3, 108.0, 110.1, 110.7, 110.9, 112.4, 113.6, 114.6, 118.3, 123.6, 124.1, 124.2, 127.5, 127.7, 130.8, 131.3, 133.5, 133.6, 152.2, 157.9, 158.2, 159.7, 159.9, 160.3, 162.1, 164.0, 171.3, 175.6, 178.2; HRMS (ESI) m/z $C_{36}H_{26}O_8Na$ $(M + Na)^+$ 609.1527; Anal. Calcd for $C_{36}H_{26}O_8 \cdot {}^1/_2H_2O$: C, 72.60; H, 4.53. Found: C, 71.97; H, 4.47.

1-(4',7-Dimethoxyisoflavon-3'-yl)-2-(4''',7''-dimethoxyflavon-3'''-yl)ethyne (32): The title compound was synthesized following the procedure for compound **21** using iodoflavone **12** (243 mg, 0.6 mmol) and isoflavone **9** (243 mg, 0.6 mmol). The solid was filtered, washed with water (25 mL) and air dried (270 mg, 82%). An analytical sample was prepared by flash chromatography (SiO_2, 2% MeOH/CH_2Cl_2). Mp 239-241 °C (from CH_2Cl_2/hexane); IR (KBr): ν_{max} 2929, 2835, 1626, 1630, 1604,

1502, 1440, 1278, 1201, 1162, 1095, 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.91 (3H, s, CH_3O), 3.92 (3H, s, CH_3O), 3.98 (3H, s, CH_3O), 3.99 (3H, s, CH_3O), 6.69 (1H, s, H3''), 6.85 (1H, d, *J* = 2.3 Hz, H8), 6.99 (5H, m, H5', H6, H5''', H6'', H8''), 7.59 (1H, dd, *J* = 2.3, 8.7 Hz, H6'), 7.74 (1H, d, *J* = 2.3 Hz, H2'), 7.81 (1H, dd, *J* = 2.3, 8.8 Hz, H6'''), 7.97 (1H, s, H2), 8.11 (1H, d, *J* = 8.6 Hz, H5''), 8.11 (1H, d, *J* = 2.3 Hz, H2'''), 8.21 (1H, d, *J* = 9.0 Hz, H5); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 55.7, 55.8, 56.1, 56.2, 88.8, 90.6, 100.1, 100.3, 106.3, 110.8, 110.9, 112.4, 113.7, 114.3, 114.6, 117.7, 118.3, 124.0, 124.1, 124.2, 126.9, 127.6, 127.7, 130.8, 131.3, 133.8, 152.2, 157.9, 159.8, 162.1, 162.2. 164.0, 175.6, 177.7; HRMS (ESI) m/z $C_{36}H_{26}O_8Na$ $(M + Na)^+$ 609.1515; Anal. Calcd for $C_{36}H_{26}O_8 \cdot {}^3/_4H_2O$: C, 72.05; H, 4.62. Found: C, 72.08; H, 4.50.

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