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One-Step Synthesis of New Derivatives of 4-Arylcoumarins and Neolignans

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Abstract Coupling reaction of iodovanillin or vanillin with methyl cinnamate derivatives catalysed by palladium(II) acetate yield five new compounds including three neolignans and two 4-arylcoumarins along with two known lignans and two known neolignans. Structures of all synthesized lignans, neolignans and coumarins were elucidated on the basis of various spectroscopic data (1D-NMR, 2D-NMR, IR and MS), melting point and by comparison with reported data.

Keywords Coupling reaction; palladium; arylcoumarin; neolignan; lignan

Introduction

Coumarins are the most successful class of heterocyclic compounds as they amenable a wide range of structural features due to substitution of different groups to their benzene or pyrone rings. Among coumarin derivatives, 4-arylcoumarins are biologically active molecules have been associated with various pharmacological activities such as antimicrobial [1, 2], anticancer [3, 4], antimalarial [5], anti-HIV [6-8] and insecticidal [9,10]. Several methods have been developed to synthesize 4-arylcoumarin such as Pechmann reaction [11-15], metal-catalysed reaction: Pd [2, 16-20], Ni [21], Cu [22], Pt/Ag [23, 24], Wittig reaction [25-27], Michael reaction [28, 29], Knoevenagel reaction [30], Kostanecki reaction [31] and Pechmann-Duisberg condensation [10].

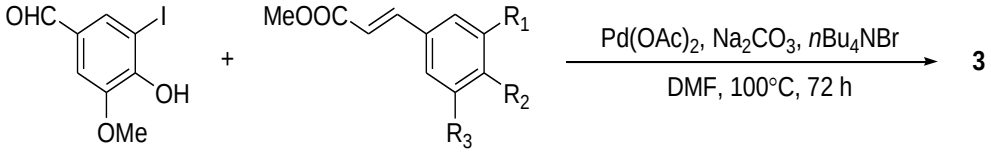
Lignans and neolignans are categorized as dimeric phenylpropanoids which are commonly found in plant origin and play an important role in medicinal field. For instance, arylbenzofuranneolignans were reported to show remarkable bioactivity such as anti-inflammatory [32-35], anticancer [36-39], antimicrobial [40, 41], pesticidal [42], antimycobacterial [38], antileishmanial [43-45] and insecticidal [46,47]. Meanwhile, the 8-O-4'-neolignan exhibited potent activity as antidepression [48], antiatherogenic and antiplasmodial [49], antitumour and anti-inflammatory [50], antifungal [51, 52], anti-HIV-1 and anticancer [53]. Some works has been providing routes to synthesize aryl substituted benzofuran neolignans including metal catalysed coupling reaction [35, 54-57], photolysis [58], Wittig reaction [59] and Lewis acid catalysed cyclisation [60, 61].Similarly, synthesis of 8-O-4'-neolignans were studied through Mitsunobu reaction [50, 62], Jacobsen epoxidation [63], and Wittig reaction [64].

The aim of this paper is to synthesisearylcoumarin, arylbenzofuranneolignan, 8-O-4'-neolignan and lignan compounds *via* one-step of Pd-catalysed coupling reaction between iodovanillin(**1**) or vanillin (**4**) and methyl ester of cinnamic acid and its derivatives (**2**).

Results and Discussion

Iodovanillin (**1**) and a series of methyl cinnamate derivatives (**2**) were obtained from vanillin (**4**) and cinnamic acid derivatives based on pioneering work of Gallo [65] and Maussouni [66], respectively. Iodination and esterification reactions gave an excellence yield of **1** (90%) and esters **2** (93-98%).

The cross-coupling reactions between iodovanillin (**1**) and methyl esters (**2**) were performed in the presence of Na_2CO_3 and nBu$_4$NBr as the phase transfer agent. The reaction of **1** with methyl 3-methoxycinnamate (**2b**), methyl 4-methoxycinnamate (**2c**) and methyl sinapate (**2f**) gave benzofuran neolignan (**3b)**, phenylcoumarin (**3c)** and lignin (**3f)** as a single product, respectively. Meanwhile, the reaction involving **1** and methyl ferulate (**2e**) gave a mixture of phenylcoumarin (**3e-1**), 8-O-4'-neolignan (**3e-2**) and lignan (**3e-3**). Compounds **3b**, **3c** and **3e-1** were identified as new benzofuran neolignan and phenylcoumarins have been synthesized from this method (Scheme 1 and Table 1). However, treatment of **1** with **2a** and **2d** was unsuccessful and led to recovery of starting materials.

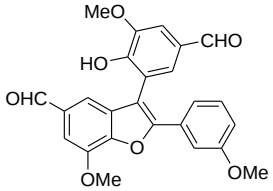
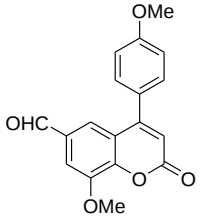
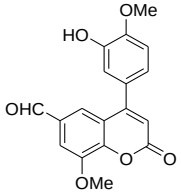


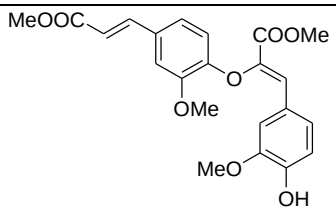
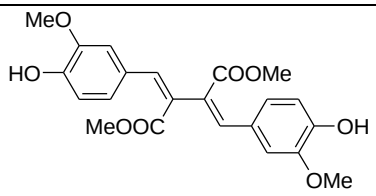
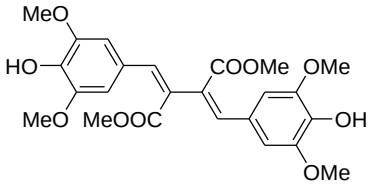
1 **2a-f**

Iodovanillin

a: R_1=R_2=R_3=H (methyl cinnamate)
b: R_1=R_2=H, R_3=OMe (methyl 3-methoxycinnamate)
c: R_1=R_3=H, R_2=OMe (methyl 4-methoxycinnamate)
d: R_1=H, R_2=R_3=OH (methyl caffieate)
e: R_1=H, R_2=OH, R_3=OMe (methyl ferulate)
f : R_1=R_3=OMe, R_2=OH (methyl sinapate)

Table 1: Coupling product of iodovanillin and methyl cinamate derivatives

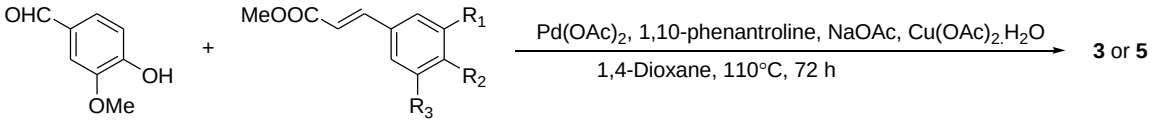
Ester	Product 3	Class of Product	Yield (%)
2b	**3b** 	2,3-Diarylbenzofuran neolignan	8
2c	**3c** 	4-Arylcoumarin	14
2e	**3e-1** 	4-Arylcoumarin	22

	3e-2		8-O-4'-Neolignan	10
	3e-3		Lignan	9
2f	**3f**		Lignan	37

Further investigations were carried out to study the coupling reaction between vanillin (**4**) and methyl cinnamate derivatives (**2**) using ligand, 1,10-phenantroline and oxidant, $Cu(OAc)_2.H_2O$. As expected from the coupling of iodovanillin (**1**) and methyl ester derivatives (**2**), the reaction of **4** with methyl 4-methoxycinnamate (**2c**) and methyl ferulate (**2e**) yield coumarin **3c** and mixture of coumarin **3e-1**, neolignan**3e-2** and lignan**3e-3**.In addition, reaction between **4** with methyl caffieate (**2d**) and methyl sinapate (**2f**) exhibited positive result with production of two new compounds, neolignans**5d** and **5f** (Scheme 2 and Table 2). Unfortunately, the coupling between **4** with **2a** and **2b** did not yield any products and considered as unsuccessful.

As shown in Table 1, cross-coupling between iodovanillin (**1**) and cinnamate derivatives (**2**) led to **3b**, **3c** and **3e-1** in approximate yield of 8%, 14% and 22%, respectively. On the other hand, homo-coupling of cinnamate units gave lignans**3e-2** (10%), **3e-3** (9%) and **3f** (37%). The results indicate that halogen and hydroxyl group iniodovanillin (**1**) initiate the coupling withalkene of methyl 3-methoxycinnamate (**2b**)and cyclized to form furan ring. Furthermore, an extra equivalence of **1** led to another coupling reaction at C3 by removal of the ester group to produce 2,3-diarylbenzofuran neolignan **3b**.

Compounds **3c**, **3e-1** and **5f** have been synthesized in moderate to high yield from the cross-coupling reaction between vanillin (**4**) and cinnamates (**2**) while **3e-2**, **3e-3**, **3f** and **5d** were obtained from homo-coupling between cinnamate units (Table 2).These findings suggest that methoxy group in cinnamates lead to corresponding cross-coupling reaction whereas the presence of hydroxyl group in cinnamates promotes homo-coupling reaction. Both methods indicate that methyl sinapate (**2f**) is considered as the best cinnamate to produce lignan**3f** (37%) and 8-O-4'-neolignan **5f** (55%).



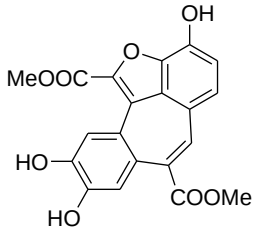
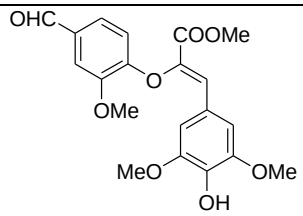
4 **2a-f**

Vanillin

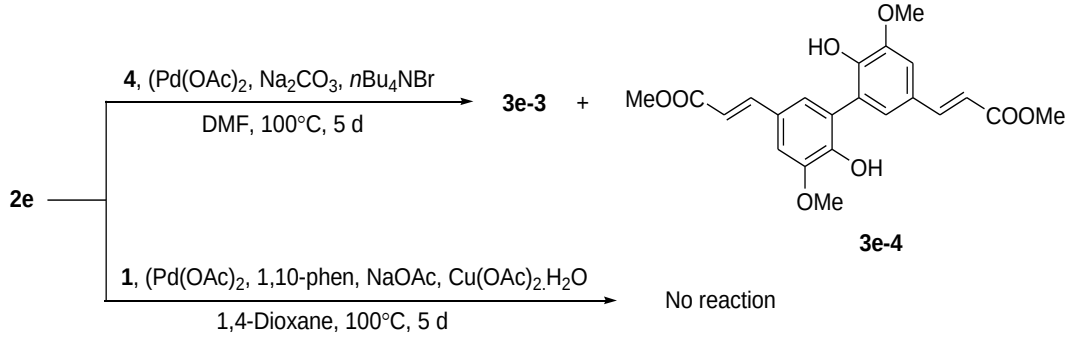
a: $R_1=R_2=R_3=H$ (methyl cinnamate)
b: $R_1=R_2=H$, $R_3=OMe$ (methyl 3-methoxycinnamate)
c: $R_1=R_3=H$, $R_2=OMe$ (methyl 4-methoxycinnamate)
d: $R_1=H$, $R_2=R_3=OH$ (methyl caffieate)
e: $R_1=H$, $R_2=OH$, $R_3=OMe$ (methyl ferulate)
f : $R_1=R_3=OMe$, $R_2=OH$ (methyl sinapate)

Scheme 2: Pd-catalysed coupling reaction of vanillin and methyl cinnamate derivatives

Table 2: Coupling product of vanillin and methyl cinamate derivatives

Ester	Product 3 or 5	Class of Product	Yield (%)
2c	**3c**	4-Arylcoumarin	2
2d	**5d** 	8,3'-Epoxy-2,8'-cyclolignan-7'-ene	2
2e	**3e-1**	4-Arylcoumarin	12
	3e-2	8-O-4'-Neolignan	20
	3e-3	Lignan	14
2f	**3f**	Lignan	12
	5f 	8-O-4'-Neolignan	55

Production of several interesting compounds using these methods prompted us to extend the strategy by swapping iodovanillin (**1**) or vanillin (**4**). Using phase transfer catalyst nBu$_4$NBr, reaction between **4** and methyl ferulate (**2e**) leads to lignans**3e-3** and **3e-4**. In contrast, the reaction between iodovanillin**1** with **2e** was unsuccessful after five days of continuous reaction (Scheme 3).



Scheme 3: Pd-catalysed coupling reaction between methyl ferulate with iodovanillin and vanillin

Neolignan **3b** was isolated as orange oil and the HRMS spectrum gave a molecular ion peak at *m/z* 432.1216 (calcd 432.1209) for M^+ which corresponds to the molecular formula $C_{25}H_{20}O_7$. In the ^{1}H NMR spectrum, appearance of two singlets corresponded to two aldehyde protons at δ 9.95 and δ 9.99 ppm further support the presence of two vanilyl units in the structure. Another three singlets were observed at δ 4.09, 3.96 and 3.75 ppm attributed to three methoxy groups in the structure. Eight aromatic protons appear as three singlets at δ 7.81, 7.60 and 7.43 ppm, three doublets at δ 7.44, 7.00 and 6.97 ppm, one triplet at δ 7.31 ppm as well as one doublet of doublet at δ 6.89 ppm. A total of 25 carbons in the molecule including two aldehyde carbons at δ 191.7 and 190.4 ppm were deduced from the ^{13}C NMR spectrum. All the protonated carbons of this molecule were assigned by HMQC spectrum. The installment of the aryl in cinnamate unit at C2 was confirmed by HMBC correlation between H5' and C2 (Figure 1).

Phenylcoumarins**3c** and **3e-1** can be distinguished by the presence of hydroxyl group at C-3 in coumarin **3e-1** (4'-O*H* at δ 5.81 ppm). The IR spectra of **3c** and **3e-1** showed typical signals of coumarins absorptions at 1725 and 1712, 1597 and 1593 cm^{-1}. The ^{1}H NMR of **3c** showed two sets of identical aromatic protons at δ 7.06 ppm (H3'and

H5') and 7.40 ppm (H2'and H6') which were assigned to 4-phenyl moiety. The olefinic proton and carbon of both **3c** and **3e-1** (H3 and C3) appeared at δ 6.42 ppm and δ 115.5 ppm respectively. The HMBC correlation between H3 with C2, C4a and C1' justify the formation of coumarin. The attachment of phenyl group to C-4 was rationalised by correlation between H2' to C4, H3 to C1' as well as correlation between H5' to C4 (Figure 1).

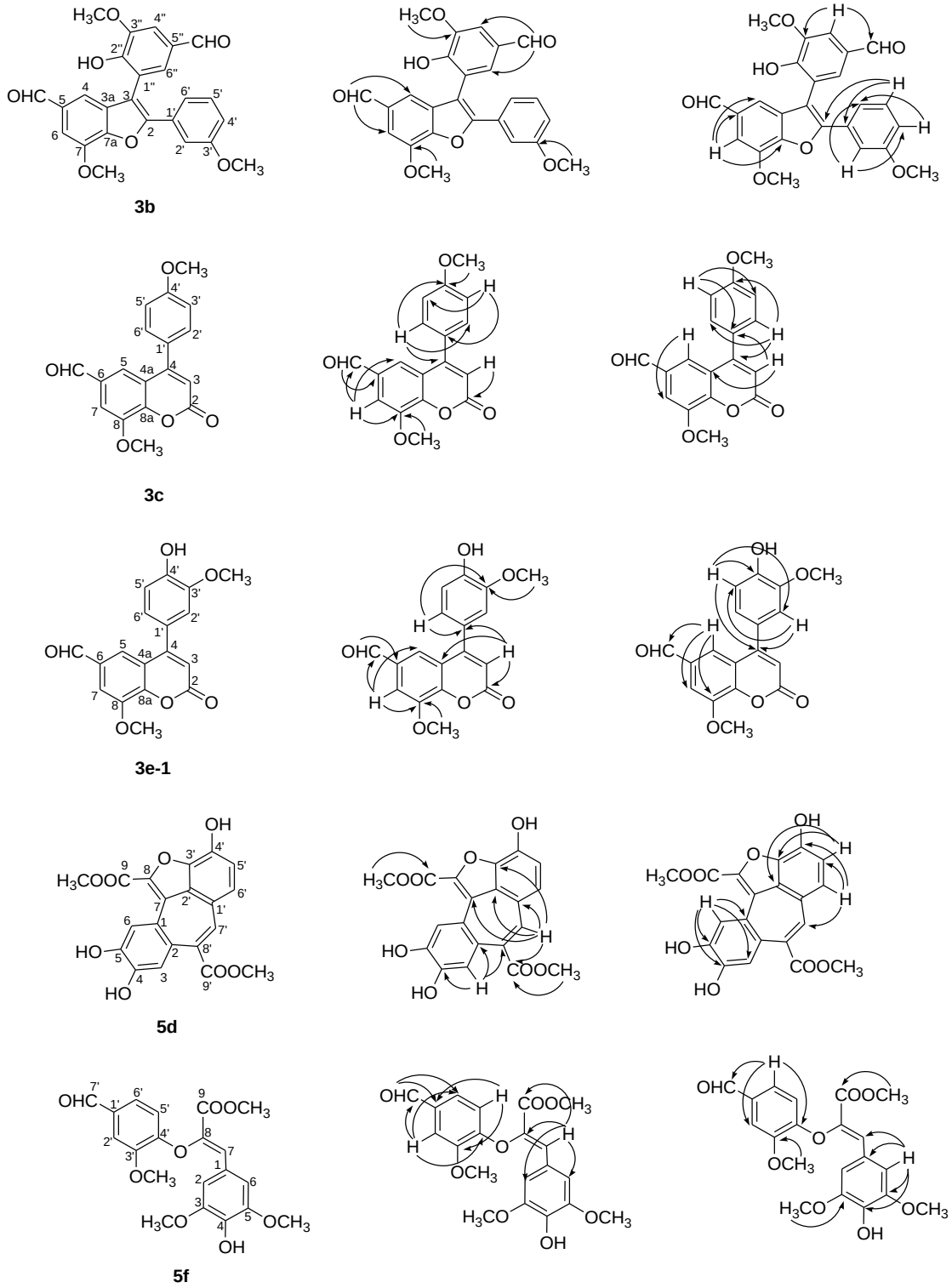


Figure 1: HMBC correlation of new synthesized neolignans and arylcoumarins

New compound **5d** was isolated as pale brown solid with melting point of 267-268 °C. The HRMS spectrum gave a molecular ion peak at *m/z* 382.0682 which was in agreement to the molecular formula, $C_{20}H_{14}O_8$ (calcd 382.0689). The proposed structure of **5d** was supported by the ^{1}H NMR analysis which showed a broad singlet attributed to 4'-O*H* at the non-shielded area (δ 8.59 ppm) indicating that the hydrogen was chelated to the nearest oxygen of furan ring. A sharp singlet was observed at δ 8.15 ppm represents the proton of octane ring, H7'. Another two singlets appeared at δ 3.86 and δ 3.95 ppm were assigned to two methyl ester groups meanwhile the remaining two singlet peaks and two doublet peaks were attributed to four aromatic protons (δ 6.70, 7.17, 7.31 and 7.51 ppm). Two peaks at the downfield region (δ 166.8 and 171.1 ppm) in ^{13}C NMR spectrum proved the presence of two ester groups rationalised the reaction between two units of methyl caffeate (**2d**). The HMBC analysis on **5d** showed the correlation between H7' with C9', C1', C2', C3' and C7 justify the octane ring was fused to benzofuran ring whereas ^2J correlations between H3 with C2 and H6 with C7 along with ^3J correlation of H3 with C8' also proved the fused of octane ring and benzene through C2-C7 bond (Figure 1). Based on these spectral data and comparison with related compound, the class of this new lignan was established as 8,3'-epoxy-2,8'-cyclolignan-7'-ene and given the trivial name as fadinosin (**5d**).

8-O-4'-Neolignan **5f** was obtained as white solid. The melting point was recorded at 69-70°C and its molecular ion peak (HRMS) at *m/z* 388.1120 matched the molecular formula of $C_{20}H_{20}O_8$ (calcd 388.1158). The 1D NMR spectrum of **5f** demonstrated the presence of olefinic proton and carbon peaks at δ 7.38 and δ 128.9 attributed to H7 and C7, respectively. Another singlet peak occurred at δ 5.77 ppm corresponded to hydroxyl group at C4. The cross-coupling between vanillin (**4**) and methyl sinapate (**2f**) was proven to be a success by the appearance of a sharp singlet at δ 9.82 due to the resonance of aldehyde proton. In addition, three sharp singlet peaks corresponded to two methoxy and one methyl of ester groups (δ 3.98, 3.77 and 3.76 ppm) were noted. The HMBC analysis showed all the aromatic protons (H2', H5', H6' and H6) were correlated to their aromatic carbons, suggests that the coupling does not involve C-C bond between the vanillin (**4**) and methyl sinapate (**2f**) moiety. The HMBC measurement also showed long range ^2J correlation of H7 with C8 and ^3J correlations between H7 with C2, C6 and C9, as well as H6 to C7 further support the argument (Figure 1).

The structures of the known synthesised compounds, 3e-2[49], 3e-3[31],3f[67] and 3e-4[68] were elucidated and compared with published data.

Experimental

General

All chemicals and solvents are commercially available as analytical grades and used without purification unless otherwise stated. The reactions were monitored by thin layer chromatography (TLC), using Silica gel 60 F245 (Merck KGaA) precoated aluminium backed plates, visualized under ultraviolet light (UVP, UV Lamp UVGL-58) and stained with $KMnO_4$ solution. Column chromatography was performed with 100-150 mesh of Silica gel 60 (0.040 mm - 0.063 mm). The organic extracts were dried over sodium sulfate (Na_2SO_4) and evaporated using rotavapor (Buchi R-215, Switzerland).

The melting points were measured by using digital Electrothermal IA9000 Series and repeated three times for each compound. The infrared spectra were measured by using the Fourier Transform Infrared Spectroscopy, Perkin-Elmer FT-IR Model Spectrum 100 series spectrophotometer. The 1D and 2D NMR spectra were run on JEOL machine at 500 MHz. Chemical shift, δ was recorded in ppm relative to TMS signal. The exact molecular weights (HRMS) were obtained by AGILENT 6550 iFunnel Q-TOF.

Iodination

Vanillin (1 mmol) and I_2 (2 mmol) were dissolved in H_2O (5 mL). 30% of H_2O_2 (4 mmol) was then added dropwise with constant stirring at 50°C for 24 hours. Saturated $Na_2S_2O_3$ solution (5 mL) was added to the reaction mixture followed by extraction with EtOAc (3×10 mL). The combined organic layer was dried, evaporated and purified by column chromatography (hexane:EtOAc, 3:2).

Iodovanillin (1)

White solid; 45-90%; mp 179-181°C (Lit. [69] 179-182°C); IR (UATR) 3421, 3158, 2918, 1735, 1664, 1570, 1410, 1153 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.75 (1H, s, C*H*O), 7.80 (1H, s, *H*-Ar), 7.35 (1*H*, s, *H*-Ar), 6.67 (1H, br. s, O*H*), 3.95 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 189.5, 151.4, 146.5, 136.2, 131.1, 108.7, 80.5, 56.6; *m/z* (EIMS) 278 (M^+, $C_8H_7O_3I$ requires 278).

Esterification

A reflux apparatus was charged with concentrated H_2SO_4 (0.025 mL) and cinnamic acid derivatives (1 mmol) in MeOH (10 mmol) and refluxed for 3 hours. The reaction mixture was cooled to room temperature and ice-cold water (5 mL) was added. The organic phase was extracted with Et_2O (3×10 mL) and the combined organic layer was washed with saturated $NaHCO_3$ solution (3×30 mL), brine (3×30 mL), dried over Na_2SO_4, evaporated and purified by column chromatography (**2a** - hexane:EtOAc, 7:3; **2b** and **2c** - petroleum ether:EtOAc, 7:2; **2d**, **2e** and **2f** - petroleum ether: EtOAc, 3:2).

Methyl cinnamate (2a)

Yellow oil; 98%; IR (UATR) 3024, 2949, 1710, 1634, 1441 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.67 (1H, d, *J* 16.0 Hz, C=C*H*) 7.49 (2H, t, *J* 3.4 Hz, *H*-Ar), 7.34 (3H, dd, *J* 3.4 5 7 Hz, *H*-Ar), 6.42 (1H, d, *J* 16.0 Hz, C=C*H*), 3.77 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 167.3, 144.8, 134.2, 130.2, 128.8, 127.9, 117.7, 51.5; *m/z* (EIMS) 162 (M^+, $C_{10}H_{10}O_2$ requires 162).

Methyl 3-methoxycinnamate (2b)

Yellow oil; 97%; IR (UATR) 2947, 1710, 1590, 1445, 1166 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.62 (1H, d, *J* 16.0 Hz, C=C*H*), 7.23 (1H, t, *J* 8.0 Hz, *H*-Ar), 7.06 (1H, d, *J* 6.9 Hz, *H*-Ar), 6.99 (1H, s, *H*-Ar), 6.88 (1H, dd, *J* 2.3, 8.0 Hz, *H*-Ar), 6.39 (1H, d, *J* 16.0 Hz, C=C*H*), 3.77 (3H, s, CH_3), 3.76 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 167.1, 159.7, 144.6, 135.6, 129.7, 120.6, 117.9, 115.9, 112.8, 55.0, 51.5; *m/z* (EIMS) 192 (M^+, $C_{11}H_{12}O_3$ requires 192).

Methyl 4-methoxycinnamate (2c)

White solid; 96%; mp 87-88°C (Lit. [70] 86-88°C); IR (UATR) 2936, 1708, 1602, 1506, 1436, 1177 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.60 (1H, d, *J* 16.0 Hz, C=C*H*), 7.41 (2H, d, *J* 8.0 Hz, *H*-Ar), 6.84 (2H, d, *J* 8.0 Hz, *H*-Ar), 6.26 (1H, d, *J* 16.0 Hz, C=C*H*), 3.77 (3H, s, CH_3), 3.74 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 167.3, 161.1, 144.2, 129.4, 126.8, 115.0, 114.0, 55.0, 51.2; *m/z* (EIMS) 192 (M^+, $C_{11}H_{12}O_3$ requires 192).

Methyl caffieate (2d)

White solid; 93%; mp 154-156°C (Lit. [71] 152-153°C); IR (UATR) 2924, 1704, 1524, 1451 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.56 (1H, d, *J* 16.0 Hz, C=C*H*), 7.06 (1H, s, *H*-Ar), 6.98 (1H, d, *J* 8.0 Hz, *H*-Ar), 6.85 (1H, d, *J* 8.0 Hz, *H*-Ar), 6.24 (1H, d, *J* 16.0 Hz, *H*-Ar), 5.91 (1H, br. s, O*H*), 3.78 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 168.0, 146.2, 144.9, 143.8, 127.6, 122.5, 115,5, 115.4, 114.3, 51.7; *m/z* (EIMS) 194 (M^+, $C_{10}H_{10}O_4$ requires 194).

Methyl ferulate (2e)

White solid; 98%; mp 64-65°C (Lit. [72] 65°C); IR (UATR) 3402, 2949, 1700, 1597, 1514, 1440, 1169 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.58 (1H, d, *J* 16.0 Hz, C=C*H*), 7.02 (1H, dd, *J* 2.3, 8.0 Hz, *H*-Ar) 6.98 (1H, s, *H*-Ar), 6.88 (1H, d, *J* 9.2 Hz, *H*-Ar), 6.25 (1H, d, *J* 16.0 Hz, C=C*H*), 6.15 (1H, br. s, O*H*), 3.86 (3H, s, CH_3), 3.76 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 167.7, 148.0, 146.8, 144.9, 126.7, 122.9, 114.9, 114.8, 109.4, 55.8, 51.5 *m/z* (EIMS) 208 (M^+, $C_{11}H_{12}O_4$ requires 208).

Methyl sinapate (2f)

White solid; 98%; mp 90-92°C (Lit. [73] 89.9-90.7°C); IR (UATR) 3409, 2946, 2846, 1702, 1604, 1512, 1450, 1110 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.58 (1H, d, *J* 16.0 Hz, C=C*H*), 6.74 (2H, s, *H*-Ar), 6.28 (1H, d, *J* 16.0 Hz, C=C*H*), 5.78 (1H, br. s, O*H*), 3.89 (6H, s, CH_3), 3.77 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 167.6, 147.2, 145.1, 137.1, 125.8, 115.5, 105.0, 56.3, 51.6; *m/z* (EIMS) 238 (M^+, $C_{12}H_{14}O_5$ requires 238).

Coupling reaction between iodovanillin (1) and methyl cinnamate derivatives (2a-f)

Iodovanillin (1.0 mmol), methyl cinnamate derivatives (2.0 mmol), $Pd(OAc)_2$ (0.05 mmol), Na_2CO_3 (1.0 mmol) and *n*Bu_4NBr (0.15 mmol) were dissolved in DMF (2.3 mL) and heated to 100°C for 72 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with saturated NH_4Cl (3×30 mL) and brine (3×30 mL), dried over Na_2SO_4, concentration in vacuo and purified by

column chromatography (**3b** - hexane: EtOAc, 7:3; **3c** - hexane: EtOAc, 1:1; **3e-1**, **3e-2** and **3e-3** - hexane: EtOAc, 2:3; **3f** - petroleum ether: EtOAc, 2:3).

3-(5-Formyl-2-hydroxy-3-methoxyphenyl)-7-methoxy-2-(3-methoxy phenyl) benzofuran-5-carbaldehyde (3b)

Orange oil; 8%; IR (UATR) 3368, 2932, 1684, 1593, 1139 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.99 (1H, s, C*H*O), 9.95 (1H, s, C*H*O), 7.81 (1H, s, *H*-Ar), 7.60 (1H, s, *H*-Ar), 7.44 (1H, d, *J* 2.3 Hz, *H*-Ar), 7.43 (1H, s, *H*-Ar), 7.31 (1H, t, *J* 8.0 Hz, *H*-Ar), 7.00 (1H, d, *J* 8.0 Hz, *H*-Ar), 6.97 (1H, d, *J* 2.0 Hz, *H*-Ar), 6.89 (1H, dd, *J* 2.3, 8.0 Hz, *H*-Ar), 4.09 (3H, s, CH_3), 3.96 (3H, s, CH_3), 3.75 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 191.7, 190.4, 159.9, 149.8, 148.6, 147.7, 147.6, 146.3, 133.6, 133.0, 130.4, 130.0, 129.33, 129.27, 121.2, 120.8, 118.9, 116.3, 114.6, 113.1, 108.7, 104.9, 56.5, 56.3, 55.3; *m/z* (HRMS) 432.1216 $[M]^+$ (Calcd for $C_{25}H_{20}O_7$ requires 432.1209),455.1112 $[M+Na]^+$ (Calcd for $C_{25}H_{20}O_7Na$ requires 455.1107).

8-Methoxy-4-(4-methoxyphenyl)-2-oxo-2*H*-chromene-6-carbaldehyde (3c)

Brown solid; 14%; mp 239-240°C; IR (UATR) 2920, 1725, 1597, 1219 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.86 (1H, s, C*H*O), 7.61 (1H, d, J 2.3 Hz, *H*-Ar), 7.58 (1H, d, J 2.3 Hz, *H*-Ar), 7.40 (2H, d, J 8.0 Hz, *H*-Ar), 7.06 (2H, d, J 8.0 Hz, *H*-Ar) 6.42 (1H, s, C*H*=C), 4.04 (3H, s, CH_3), 3.89 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 190.4, 161.2, 159.3, 157.6, 155.1, 148.7, 132.1, 129.9, 126.9, 123.3, 119.9, 115.5, 114.6, 110.6, 56.5, 55.5; *m/z* (HRMS) 310.0844 $[M]^+$ (Calcd for $C_{18}H_{14}O_5$ requires 310.0841), 333.0738 $[M+Na]^+$ (Calcd for $C_{18}H_{14}O_5Na$ requires 333.0739).

4-(4-Hydroxy-3-methoxyphenyl)-8-methoxy-2-oxo-2*H*-chromene-6carbaldehyde (3e-1)

Yellow solid; 22%; mp 218-219°C; IR (UATR) 3492, 3404, 2946, 2851, 1712, 1593, 1428, 1135 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.86 (1H, s, C*H*O), 7.65 (1H, s, *H*-Ar), 7.58 (1H, s, *H*-Ar), 7.06 (1H, d, J 8.0 Hz, *H*-Ar), 6.99 (1H, dd, J 2.3, 8.0 Hz, *H*-Ar), 6.93 (1H, d, J 2.3 Hz, *H*-Ar), 6.42 (1H, s, C*H*=C), 5.91 (1H, s, O*H*), 4.03 (3H, s, CH_3), 3.93 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 190.4, 159.3, 155.2, 148.7, 148.3, 147.5, 147.0, 132.2, 126.6, 123.3, 122.1, 119.9, 115.5, 115.0, 110.9, 110.6, 56.5, 56.2;*m/z* (HRMS) 326.0790 $[M]^+$ (Calcd for $C_{18}H_{14}O_6$ requires 326.0790), 349.0684 $[M+Na]^+$(Calcd for $C_{18}H_{14}O_6Na$ requires 349.0688).

Methyl-3-(4-hydroxy-3-methoxyphenyl)-2-{2-methoxy-4[(*E*)-3-methoxy-3-oxoprop-1-enyl]phenoxy}-prop-2-enoate (3e-2)

Yellow solid; 20%; mp 187-189°C (Lit. [49] 186-188°C);IR (UATR) 3420, 2947, 1710, 1634, 1506, 1251 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.60 (1H, d, *J* 16.0 Hz, C*H*=C), 7.37 (1H, s, *H*-Ar), 7.35 (1H, s, C*H*=C), 7.12 (1H, d, *J* 6.9 Hz, *H*-Ar), 7.11 (1H, s, *H*-Ar), 6.96 (1H, d, *J* 6.9 Hz, *H*-Ar), 6.84 (1H, d, *J* 8.0 Hz, *H*-Ar), 6.37 (1H, d, *J* 8.0 Hz, *H*-Ar), 6.30 (1H, d, *J* 16.0 Hz, C*H*=C), 5.79(1H, s, O*H*), 3.96 (3H, s, CH_3), 3.77 (3H, s, CH_3), 3.75 (3H, s, CH_3), 3.74 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 167.5, 163.9, 149.0, 147.6, 147.5, 146.4, 144.4, 137.1, 129.4, 128.4, 125.7, 124.5, 122.2, 116.3, 114.5, 113.8, 112.0, 111.1, 56.2, 55.5, 52.4, 51.7; *m/z* (HRMS) 414.1335 $[M]^+$ (Calcd for $C_{22}H_{22}O_8$ requires 414.1315), 437.1229 $[M+Na]^+$ (Calcd for $C_{22}H_{22}O_8Na$ requires 437.1212).

(2*E*,3*E*)- Dimethyl 2,3-bis(4-hydroxy-3-methoxybenzylidene)succinate (3e-3)

Yellow solid; 5-37%; mp 72-74°C; IR (UATR) 3389, 2943, 1695, 1591, 1509, 1248 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.84 (2H, s, C*H*=C), 7.10 (2H, d *J* 2.3 Hz, *H*-Ar), 7.04 (2H, dd, *J* 2.3, 8.0 Hz, *H*-Ar), 6.82 (2H, d, *J* 9.2 Hz, *H*-Ar), 5.81 (2H, s, O*H*) 3.73 (6H, s, CH_3), 3.68 (6H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 167.8, 147.4, 146.4, 142.5, 127.1, 125.1, 124.2, 114.5, 111.4, 55.7, 52.4; *m/z* (EIMS) 414 (M^+, $C_{22}H_{22}O_8$ requires 414).

(2*E*,3*E*)-Dimethyl 2,3-bis(4-hydroxy-3,5-dimethoxybenzylidene)succinate (3f)

Yellow solid; 55%; mp 129-130°C; IR (UATR) 3413, 2944, 1705, 1598, 1510, 1234 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.81 (2H, s, C*H*=C), 6.80 (4H, s, *H*-Ar), 5.77 (2H, br. s, O*H*), 3.76 (12H, s, CH_3), 3.66 (6H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 167.7, 146.9, 142.5, 136.7, 125.9, 124.7, 107.1, 56.1, 52.4; *m/z* (EIMS) 474 (M^+, $C_{24}H_{26}O_{10}$ requires 474).

Coupling reaction between vanillin (4) and methyl cinnamate derivatives (2a-f)

Vanillin (5.0 mmol) and methyl cinnamate derivatives (1.0 mmol) were dissolved in 1,4-dioxane (8 mL) followed by addition of $Pd(OAc)_2$ (0.05 mmol), NaOAc (5.0 mmol), 1,10-phenanthroline (0.10 mmol) and $Cu(OAc)_2.H_2O$ (2.0 mmol). The reaction mixture was stirred at 100°C for 72 h and cooled to room temperature. After cooling, the resulting solid was filtered and washed with $CHCl_3$ (20 mL). The filtrate was evaporated and purified by column chromatography (**5d** - hexane:EtOAc, 1:1; **5f** and **3e-4** - hexane:EtOAc, 3:2).

Fadinosin (5d)

Brown solid; 60%; mp 267-268°C; IR (UATR) 3374, 2954, 1690, 1606, 1517, 1443, 1193 cm^{-1}; δ_H(500 MHz, $(CD_3)_2O$) 8.59 (1H, br. s, O*H*), 8.15 (1H, s, C=C*H*), 7.51 (1H, d, *J* 8.0 Hz, *H*-Ar) 7.31 (1H, d, *J* 8.0 Hz, *H*-Ar), 7.17 (1H, s, *H*-Ar), 6.70 (1H, s, *H*-Ar), 3.95 (3H, s, CH_3), 3.86 (3H, s, CH_3); δ_C (125 MHz, $(CD_3)_2O$) 171.1, 166.8, 148.9.1, 147.6, 142.6, 142.4, 137.4, 129.5, 127.4, 125.6, 124.8, 124.0, 122.1, 121.5, 120.5, 111.9, 110.7, 104.5, 52.7, 52.4; *m/z* (HRMS) 382.0682 $[M]^+$ (Calcd for $C_{20}H_{14}O_8$ requires 382.0689),405.0576 $[M+Na]^+$ (Calcd for $C_{20}H_{14}O_8Na$ requires 405.0586).

(*Z*)-Methyl 2-(4-formyl-2-methoxyphenoxy)-3-(4-hydroxy-3,5-dimethoxy phenyl) acrylate (5f)

White solid; 12-29%; mp 69-70°C; IR (UATR) 3404, 2928, 1702, 1512, 1260 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.82 (1H, s, C*H*O), 7.49 (1H, s, *H*-Ar), 7.38 (1H, s, C*H*=C), 7.32 (1H, d, *J* 8.0 Hz, *H*-Ar), 6.97 (2H, s, *H*-Ar), 6.85 (1H, d, *J* 8.0 Hz, *H*-Ar), 5.77 (1H, br. s, O*H*), 3.98 (3H, s, CH_3), 3.77 (3H, s, CH_3), 3.76 (6H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 190.7, 163.6, 150.9, 149.4, 146.9, 137.1, 136.9, 131.7, 128.9, 126.3, 123.1, 113.1, 110.2, 107.6, 56.1, 56.0, 52.6;*m/z* (HRMS) 388.1120 $[M]^+$ (Calcd for $C_{20}H_{20}O_8$ requires 388.1158),411.0996 $[M+Na]^+$ (Calcd for $C_{20}H_{20}O_8Na$ requires 411.1056).

(2*E*,2'*E*)-3,3'-[6,6'-Dihydroxy-5,5'-dimethoxy-(1,1'-biphenyl)-3,3'-diyl] diacrylate (3e-4)

White solid;6%;mp 74-76°C;IR (UATR) 3399, 2940, 1702, 1617, 1439, 1166 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.63 (1H, d, *J* 16.0 Hz, C*H*=C), 7.12 (1H, s, *H*-Ar), 7.05 (1H, s, *H*-Ar), 6.31 (1H, d, *J* 16.0 Hz, C*H*=C), 6.19 (1H, br. s, O*H*), 3.95 (3H, s, CH_3), 3.77 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 167.6, 147.2, 145.2, 144.8, 126.6, 124.8, 123.6, 115.7, 108.8, 56.2, 51.6; *m/z* (HRMS) 414.1305 $[M]^+$ (Calcd for $C_{22}H_{22}O_8$ requires 414.1315), 437.1198 $[M+Na]^+$ (Calcd for $C_{22}H_{22}O_8Na$ requires 437.1212).

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