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Synthesis and biological evaluation of vinylogous combretastatin A-4 derivatives

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Stereospecific syntheses of the *Z*–*E* and *E*–*Z* vinylogues of combretastatin A-4, and two B-ring related analogues, were achieved through a Suzuki–Miyaura coupling. As compared to CA4, the derivative with a phenyl moiety has shown increased potency in its ability to inhibit tubulin polymerisation.

Introduction

Combretastatin A-4 (CA4), a natural product isolated[1] by Pettit *et al.* in 1989 from the South African willow tree, *Combretum caffrum*, strongly inhibits the polymerisation of tubulin by binding to the colchicine site.[2] It has been shown that tumour vessels are more susceptible to the disruptive effect of CA4 than normal vasculature. The result, for the tumour's blood vessels, is a morphological change in their endothelial cells leading to increased permeability and rapid vascular shutdown.[3–5] In experimental tumours, anti-vascular effects of CA4, which are observed at 10% of its maximum tolerated dose, rapidly lead to extensive ischemic necrosis in areas that are often resistant to conventional anti-cancer treatments. A disodium phosphate prodrug form (CA4P) has already entered clinical trials for the treatment of solid tumours.[6] AVE8062, a water-soluble analogue of CA4,[7,8] is currently under clinical evaluation as tumour vascular targeting agent.[9]

Given the encouraging antivascular/anticancer activity of CA4P, the syntheses of numerous analogues have been reported in order to have a better understanding of the structure–activity relationships.[10] A key structural factor for tubulin affinity is the presence of the double bond (or of a suitable linker) forcing the two aromatic rings to be within an appropriate distance.[2,11] In order to evaluate the influence of the length of the bridge between both aromatic rings of CA4, the syntheses of analogues with a *E*,*Z*-dienic moiety were undertaken. Herein are described the preparation and biological activities of a series of vinylogues of CA4 (Fig. 1).

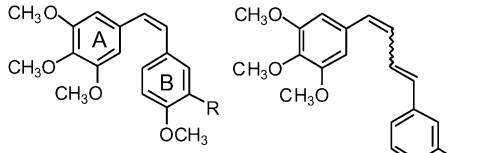
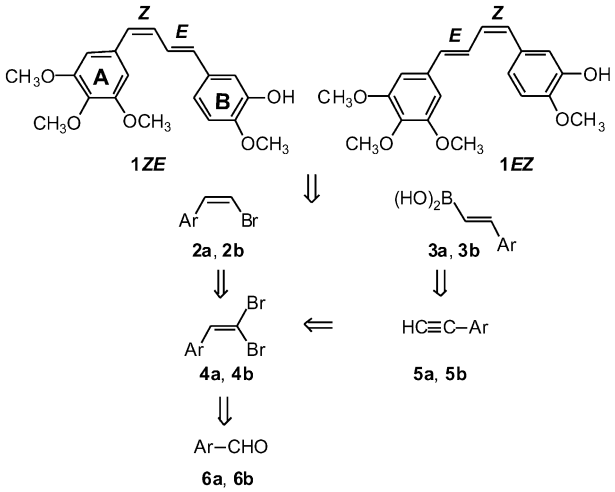


Fig. 1

Results and discussion

The route adopted to prepare these dienes (Scheme 1) was based on the Suzuki–Miyaura cross-coupling[12] of stereodefined alkenyl boron derivatives with stereodefined haloalkenes. Diene **1*ZE*** was constructed from the (*Z*)-vinylbromide **2a** and the (*E*)-vinylboronic acid **3b**, diene **1*EZ*** from derivatives **2b** and **3a**. These four requisite olefin partners were elaborated from two common intermediates, 1,1-dibromoalkenes **4a**–**b**. The required (*Z*)-vinylbromides **2a**–**b** and (*E*)-vinylboronic acids



Scheme 1 Retrosynthetic analysis of *ZE* and *EZ* vinylogues of CA4 (derivatives **a**: Ar = 3,4,5-trimethoxyphenyl, **b**: Ar = 3-hydroxy-4-methoxyphenyl).

3a–**b** were elaborated from two common intermediates, the 1,1-dibromoalkenes **4a**–**b** which have been previously synthesised[13,14] from the commercially available aldehydes **6a**–**b**.

(*E*)-3,4,5-Trimethoxystyryl boronic acid **3a**, required for the synthesis of diene **1*EZ*** (Scheme 2), was prepared by hydroboration[15] of the appropriate acetylenic precursor. The known arylacetylene **5a** was synthesized, *via* the dibromide **4a**, by Corey–Fuchs conversion[16] of 3,4,5-trimethoxybenzaldehyde **6a**. Hydroboration of **5a** with catecholborane (1 equiv.) in refluxing THF, followed by *in situ* hydrolysis of the intermediate adduct, stereoselectively afforded the (*E*)-vinylboronic acid **3a** in 60% yield. The other partner, (*Z*)-β-styrylbromide **2b**, was prepared from isovanillin **6b** (60% yield) according to Gaukroger *et al.*,[14] by stereoselective hydrogenolysis of the dibromide **4b** with tributyltin hydride in the presence of a catalytic amount of $Pd(PPh_3)_4$.[17] The cross-coupling of vinylbromide **2b** and boronic acid **3a**, in the presence[18] of $Pd(PPh_3)_4$ and EtONa as a base, afforded the desired diene **1*EZ*** in 80% yield with retention of configuration.

The synthesis of the isomeric diene **1*ZE*** by the same approach (Scheme 3) required the (*E*)-alkenylboron derivative **3b** and the (*Z*)-3,4,5-trimethoxystyrylbromide **2a** which was prepared from dibromide **4a**.[19] Reaction of dibromostyrene **4c** with *n*-butyllithium, followed by hydrolysis, afforded arylacetylene **5c** (93% yield). Difficulties were encountered for hydroboration of compound **5c**; three equivalents of catecholborane were necessary for completion of the reaction. Moreover, after *in situ* hydrolysis of the boronate, the corresponding boronic acid proved to be very difficult to separate from the catechol

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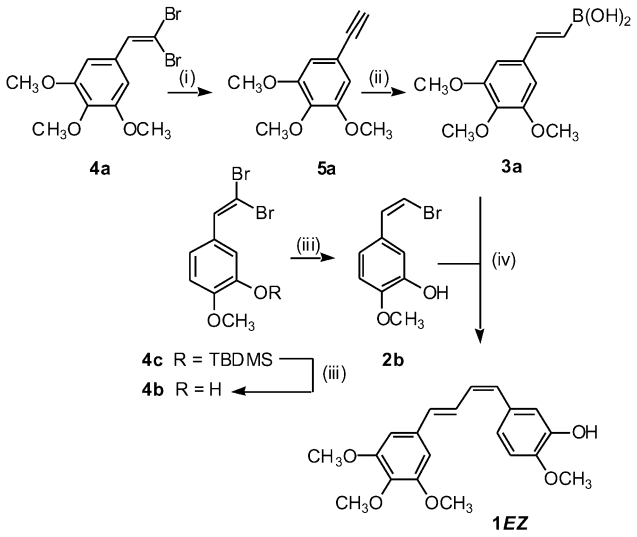
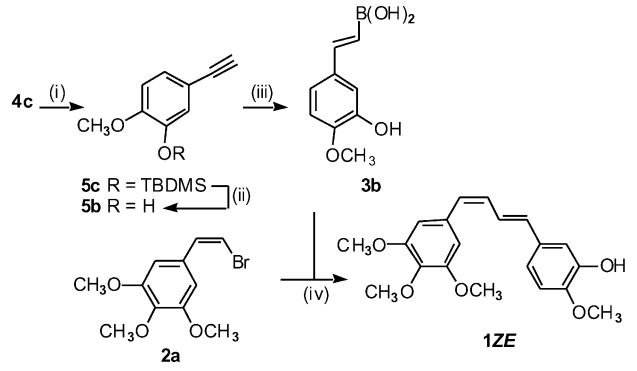


Scheme 2 Synthesis of vinylogue **1*EZ***. Reagents and conditions: (i) ref. 13: *n*-BuLi (2 equiv.), THF, 0 °C to rt; (ii) catecholborane, THF, reflux then H_2O; (iii) ref 14: Bu_3SnH, $Pd(PPh_3)_4$, benzene, 0 °C to rt; (iv) $Pd(PPh_3)_4$, EtONa, THF, reflux.



Scheme 3 Synthesis of vinylogue **1*ZE***. Reagents and conditions: (i) *n*-BuLi (2 equiv.), THF, 0 °C to rt; (ii) TBAF, THF, rt; (iii) catecholborane, THF, reflux then chromatography; (iv) $Pd(PPh_3)_4$, EtONa, THF, reflux.

by-product. Consequently, the reaction was repeated using arylacetylene **5b** bearing a free phenol (obtained in 75% yield after TBAF treatment). Flash chromatography of the crude boronate was performed, but concomitant hydrolysis of the product occurred, so boronic acid **3b** was isolated in only modest yield (35% yield). Finally, subsequent Suzuki coupling of the free phenol derivative **3b** with the (*Z*)-vinylbromide **2a** produced isomerically pure diene **1*ZE*** in an unoptimized 37% yield after chromatography.

A molecular modelling study of vinylogue **1*ZE*** and CA4, using HyperChem software,[20] suggested close geometric similarities (Fig. 2). Nevertheless, for the dienic derivative, substituents of the B-ring were out of the conformational space of CA4. These results prompted us to synthesize dienic derivatives (Scheme 4) with no substituent at the 4-position of the B-ring. So, using the afore-mentioned procedure, vinylbromide **2a** was coupled to commercially available (*E*)-vinylboronic acids **7** and **8**, giving dienes **9** and **10** in 75 and 54% yields, respectively.

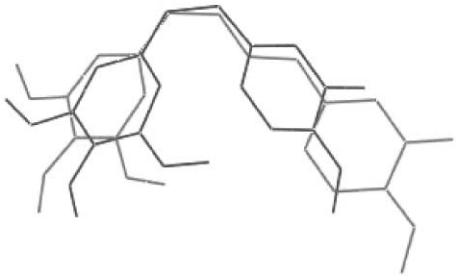
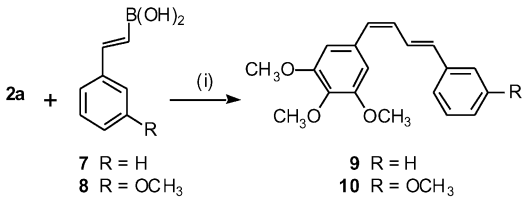


Fig. 2 Superimposition of diene 1*ZE* (gray) with CA4 (black).

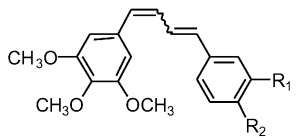


Scheme 4 Synthesis of dienes **9** and **10**. Reagents and conditions: (i) $Pd(PPh_3)_4$, EtONa, THF, reflux.

The synthesized diarylbutadienes were evaluated (Table 1) for their antitubulin polymerisation activities and for their *in vitro* cytotoxicity against the human colon carcinoma cell line (HCT116).

Vinylogues **1*ZE*** and **1*EZ*** inhibit tubulin polymerisation with IC_{50} values of 2.3 and 2.0 μM, respectively, values comparable to that of CA4, but both these compounds, in acidic media, are prone to isomerise into the more stable (*EE*)-butadiene.[21] This isomerisation resulted in a marked loss in antitubulin activity (>10-fold) that confirms, in this series, the necessity of a *cis*-double bond for bioactivity. Derivative **9**, with no substituent on the B-ring, is 4-fold more potent than vinylogue **1*ZE*** (IC_{50} = 0.5 μM), whereas compound **10** (IC_{50} = 3.5 μM), possessing a *meta*-methoxy group, is slightly less potent.

Table 1 Inhibition of tubulin polymerisation and cellular proliferation for dienes **1**, **9** and **10**



Compound	R_1	R_2	IC_{50} Antitubulin activity/μM[a]	IC_{50} HCT116/μM[b]
1*ZE*	OH	OCH_3	2.3	0.163
1*EZ*	OH	OCH_3	2.0	0.062
1*EE*	OH	OCH_3	24.9	ND
9	H	H	0.5	0.503
10	OCH_3	H	3.5	6.32
CA4	—	—	1.2	0.016[c]

[a] Drug concentration that inhibits tubulin polymerisation by 50%. [b] Drug concentration that inhibits cancer cells growth by 50%. [c] Reference 10*h*.

From the cellular tests, it appears that cytotoxicities are not well correlated with the inhibitory ability of tubulin polymerisation. Against HCT116, vinylogue **1*EZ*** showed good antiproliferative effect (IC_{50} = 62 nM), while the unsubstituted derivative **9** showed a 8-fold reduction in potency. This reduced cytotoxicity was presumed to be due to its poor cellular permeability. Adding a methoxy group at the C-3 position of the phenyl ring decreased the observed activity.

Conclusion

We have demonstrated that replacement of the *cis* double bond between the two aromatic rings of CA4, by an (*E*,*Z*)butadiene moiety, gave compounds with equal or greater depolymerising microtubule activity than CA4. Surprisingly however, this does not correlate with the cytotoxicities observed. Nevertheless, separating the cytotoxic activity from the ability to inhibit the polymerisation of tubulin represents an interesting goal in the search for potent antivascular agents.

Experimental

General

NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 MHz (^{1}H) and at 75 MHz (^{13}C) using $CDCl_3$ as the solvent. The residual proton-solvent peak is used as the internal standard [(δ 7.25 (^{1}H) and 77.0 ppm (^{13}C)] and *J* values are given in Hz. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, dd = doublet of doublets, br = broad, m = multiplet. Chemical ionization (CI) mass spectra were recorded on a Nermag R10-10-C spectrometer. High-resolution mass spectra (HRMS) were obtained on a Jeol-700 spectrometer. Melting points were determined using an Electrothermal 9200 apparatus and are uncorrected. Elemental analyses were performed by the "Service de Microanalyses du CNRS" (Vernaison-Lyon, France). The thin-layer chromatographic analyses were performed using pre-coated silica gel (Merck, 60F254) plates and the spots were examined with UV light and phosphomolybdic acid spray. Preparative column chromatographies were carried out on Merck silica gel (230–240 mesh). THF was distilled from sodium benzophenone ketyl prior to use. Derivatives **2b**,[14] **4a**[19] and **5a**[13] were prepared according to published procedures.

2-(3-*t*-Butyldimethylsilyloxy-4-methoxyphenyl)ethyne (5c). Following the method of Corey and Fuchs,[16] a solution of the dibromoalkene **4c** (2.50 g, 5.9 mmol) in anhydrous THF (35 mL) at −78 °C under argon was treated with *n*-butyllithium (7.8 mL, 1.6 M in hexane, 12.5 mmol). The reaction mixture was stirred at −78 °C for 1 h then warmed slowly to rt and stirred for a further 1 h. Saturated aqueous NH_4Cl solution was added and the mixture extracted with ether. The combined organic fractions were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a brown oil. After column chromatography on silica gel (cyclohexane–EtOAc 99 : 1), ethyne **5c** was isolated as a clear oil (1.44 g, 93%); δ_H (300 MHz, $CDCl_3$) 7.08 (1H, dd, *J* 8.3, 2.0, H-6), 6.98 (1H, d, *J* 2.0, H-2), 6.77 (1H, d, *J* 8.3, H-5), 3.81 (3H, s, OCH_3), 2.97 (1H, s, CH), 0.99 [9H, s, $C(CH_3)_3$], 0.15 [6H, s, $Si(CH_3)_2$].

2-(3-Hydroxy-4-methoxyphenyl)ethyne (5b). To a solution of **5c** (2.90 g, 11 mmol) in THF (25 mL) was added Bu_4NF (11 mL, 1.0 M in THF). After stirring at rt for 1 h, water was added and the mixture was extracted with ether. The combined organic fractions were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane–EtOAc 8 : 2), to yield phenol **5b** as a white solid which was recrystallized in ether–hexane (1.23 g, 75%); mp 62–64 °C (Found: C, 73.3; H, 5.1. $C_9H_8O_2$ requires C, 73.0; H, 5.4%);δ_H (300 MHz, $CDCl_3$) 7.05 (2H, m, H-2,6), 6.78 (1H, d, *J* 8.1, H-5), 5.60 (1H, s, OH), 3.90 (3H, s, OCH_3), 2.97 (1H, s, CH); MS (CI/NH_3) *m*/*z* 166 $(M + NH_4)^+$.

(*E*)-2-(3,4,5-Trimethoxyphenyl)vinylboronic acid (3a). To a solution of trimethoxyphenylacetylene **5a** (250 mg, 1.3 mmol) in dry THF (1 mL) under argon at rt was added dropwise catecholborane (140 µL, 1.3 mmol). The mixture was heated under reflux for 3 h, then partially concentrated *in vacuo*. Cold water (2 mL) was added and the white suspension was stirred for 2 h at 0 °C to hydrolyze the ester. The resulting solid was filtered, and rinsed with cold water. Recrystallization from diethylether afforded acid **3a** as a white solid (185 mg, 60% yield); mp 136–138 °C; δ_H (300 MHz, $CDCl_3$) 7.23 (1H, d, *J* 16.6, ArCH), 6.70 (2H, s, H-2,6), 6.04 (1H, d, *J* 16.6, CHB), 3.83 (6H, s, OCH_3 × 2), 3.81 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 153.0 (C × 2), 146.9 (C), 138.3 (C), 133.5 (C), 120.7 (CH), 103.8 (CH × 2), 60.7 (CH_3), 55.9 (CH_3 × 2).

(*E*)-2-(3-Hydroxy-4-methoxyphenyl)vinylboronic acid (3b). To a solution of alkyne **5b** (665 mg, 4.49 mmol) in dry THF (10 mL) under argon at rt was added dropwise catecholborane (1.43 mL, 13.45 mmol). The mixture was heated under reflux for 5 h then evaporated *in vacuo*. Column chromatography on silica gel (cyclohexane–EtOAc 7 : 3) of the crude ester afforded boronic acid **3b** as a foam (305 mg, 35%);δ_H (300 MHz, $CDCl_3$) 7.21 (1H, d, *J* 18.0, ArCH), 7.02 (1H, d, *J* 1.8, H-2), 6.94 (1H, dd, *J* 8.1, 1.8, H-6), 6.87 (1H, d, *J* 8.1, H-5), 6.14 (1H, d, *J* 18.0, CHB), 3.86 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 149.9 (C), 149.5 (C), 147.7 (CH), 132.7 (CH), 120.9 (CH), 113.9 (CH), 112.4 (CH), 56.3 (CH_3).

(1*E*,3*Z*)-1-(3′,4′,5′-Trimethoxyphenyl)-4-(3″-hydroxy-4″-methoxyphenyl)-1,3-butadiene (1*EZ*). To a stirred solution of boronic acid **3a** (61 mg, 0.25 mmol) and vinylbromide **2b** (59 mg, 0.25 mmol) in degassed THF (1 mL) under argon were successively added $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) then 21% sodium ethoxide in ethanol (190 µL). The reaction mixture was stirred at room temperature for 2 h then heated under reflux for 1 h. Dilution with EtOAc was followed by filtration through Celite. The filtrate was washed with a saturated NaCl solution and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (cyclohexane–EtOAc 7 : 3) provided diene **1*EZ*** as a foam (71 mg, 80%); δ_H (300 MHz, $CDCl_3$) 7.22 (1H, dd, *J* 15.4, 10.7, H-2), 7.00 (1H, d, *J* 1.6, H-2″), 6.87 (2H, m, H-5″,6″), 6.62 (2H, s, H-2′,6′), 6.59 (1H, d, *J* 15.4, H-1), 6.35 (2H, m, H-3,4), 5.63 (1H, s, OH), 3.92 (3H, s, OCH_3), 3.87 (6H, s, OCH_3 × 2), 3.85 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 153.3 (C × 2), 145.8 (C), 145.4 (C), 138.0 (C), 134.3 (CH), 133.2 (C), 131.2 (C), 129.8 (CH), 129.1 (CH), 125.0 (CH), 121.2 (CH), 115.1 (CH), 110.4 (CH), 103.7 (CH × 2), 60.9 (CH_3), 56.1(CH_3 × 2), 56.0 (CH_3); HRMS (CI/NH_3) calcd. for $C_{20}H_{23}O_5$ (MH^+): 343.1546. Found: 343.1544.

The following compounds were prepared in a similar manner.

(1*Z*,3*E*)-1-(3′,4′,5′-Trimethoxyphenyl)-4-(3″-hydroxy-4″-methoxyphenyl)-1,3-butadiene (1*ZE*). From vinylbromide **2a** (410 mg, 1.50 mmol) and boronic acid **3b** (189 mg, 0.97 mmol) was obtained, after chromatography (cyclohexane–EtOAc 8 : 2), compound **1*ZE*** as a foam (122 mg, 37%); δ_H (300 MHz, $CDCl_3$) 7.22 (1H, dd, *J* 15.4, 9.5, H-3), 7.00 (1H, d, *J* 1.9, H-2″), 6.88 (1H, dd, *J* 8.3, 1.9, H-6″), 6.79 (1H, d, *J* 8.3, H-5″), 6.61 (1H, d, *J* 15.4, H-4), 6.59 (2H, s, H-2′,6′), 6.37 (2H, m, H-1,2), 5.59 (1H, s, OH), 3.88 (9H, s, OCH_3 × 3), 3.87 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 153.0 (C × 2), 146.5 (C), 145.8 (C), 137.3 (C), 134.4 (CH), 133.4 (C), 131.1 (C), 130.2 (CH), 129.4 (CH), 123.7 (CH), 119.2 (CH), 111.8 (CH), 110.7 (CH), 106.1 (CH × 2),

61.0 (CH_3), 56.1 (CH_3 × 2), 56.0 (CH_3); HRMS (CI/NH_3) calcd. for $C_{20}H_{23}O_5$ (MH^+): 343.1546. Found: 343.1542.

(1*Z*,3*E*)-1-(3′,4′,5′-Trimethoxyphenyl)-4-phenyl-1,3-butadiene (9). From vinylbromide **2a** (250 mg, 1.68 mmol) and (*E*)-vinylboronic acid **7** (230 mg, 0.84 mmol) was obtained, after chromatography (cyclohexane–EtOAc 9 : 1) and recrystallisation from EtOAc–pentane, compound **9** as a white solid (187 mg, 75%); mp 85–87 °C; δ_H (300 MHz, $CDCl_3$) 7.40 (2H, m, H-2″,6″), 7.32 (1H, m, H-4″), 7.29 (2H, m, H-3″,5″), 7.26 (1H, m, H-3), 6.71 (1H, d, *J* 15.6, H-4), 6.60 (2H, s, H-2′,6′), 6.42 (2H, m, H-1,2), 3.89 (3H, s, OCH_3), 3.88 (6H, s, OCH_3 × 2); δ_C (75 MHz, $CDCl_3$) 153.0 (C × 2), 137.2 (C × 2), 134.7 (CH), 133.2 (C), 130.3 (CH), 130.1 (CH), 128.7 (C × 2), 127.7 (CH), 126.4 (CH × 2), 125.1 (CH), 106.1 (CH × 2), 61.0 (CH_3), 56.1 (CH_3 × 2); HRMS (CI/NH_3) calcd. for $C_{19}H_{21}O_3$ (MH^+): 297.1491. Found: 297.1483.

(1*Z*,3*E*)-1-(3′,4′,5′-Trimethoxyphenyl)-4-(3″-methoxyphenyl)-1,3-butadiene (10). From vinylbromide **2a** (410 mg, 1.50 mmol) and boronic acid **8** (189 mg, 0.97 mmol) was obtained, after chromatography (cyclohexane–EtOAc 8 : 2), compound **10** as a foam (122 mg, 37%); δ_H (300 MHz, $CDCl_3$) 7.36 (1H, dd, *J* 15.5, 10.6, H-3), 7.22 (1H, m, H-5″), 6.99 (1H, d, *J* 7.8, H-6″), 6.92 (1H, m, H-2″), 6.79 (1H, m, H-4″), 6.68 (1H, d, *J* 15.6, H-4), 6.60 (2H, s, H-2′,6′), 6.42 (2H, m, H-1,2), 3.89 (3H, s, OCH_3), 3.88 (6H, s, OCH_3 × 2), 3,80 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 159.8 (C), 153.1 (C × 2), 138.7 (C), 137.3 (C), 134.6 (CH), 133.2 (C), 130.5 (CH), 129.9 (CH), 129.8 (CH), 125.4 (CH), 119.1 (CH), 113.3 (CH), 111.8 (CH), 106.1 (CH × 2), 61.0 (CH_3), 56.1 (CH_3 × 2), 56.0 (CH_3); HRMS (CI/NH_3) calcd. for $C_{20}H_{23}O_4$ (MH^+): 327.1596. Found: 327.1588.

(1*E*,3*E*)-1-(3′,4′,5′-Trimethoxyphenyl)-4-(3″-hydroxy-4″-methoxyphenyl)-1,3-butadiene (1*EE*). A solution of dienic derivative **1*ZE*** (28 mg, 0.081 mmol) in $CDCl_3$ was stirred, under argon, for 4 d. Compound **1*EE*** was obtained as a foam (19.5 mg, 70%) after chromatography (CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 7.07 (1H, d, *J* 1.9, H-2″), 6.90 (1H, dd, *J* 8.4,1.9, H-6″), 6.80 (3H, m, H-2, H-3, H-5″), 6.59 (2H, s, H-2′,6′), 6.58 (d, 1, *J* 14.8, H-1 or H-4), 6.55 (d, 1, *J* 14.8 H-1 or H-4), 5.60 (1H, s, OH), 3.90 (9H, s, OCH_3 × 3), 3.85 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 153.3 (C × 2), 146.4 (C), 145.7 (C), 137.7 (C), 133.3 (C), 132.4 (CH), 131.8 (CH), 131.1 (C), 129.0 (CH), 127.5 (CH), 119.2 (CH), 111.6 (CH), 110.6 (CH), 103.2 (CH × 2), 61.0 (CH_3), 56.1 (CH_3 × 2), 56.0 (CH_3); HRMS (CI/NH_3) calcd. for $C_{20}H_{23}O_5$ (MH^+): 343.1546. Found: 343.1543.

Biological test methods [22]

Tubulin polymerisation. Porcin brain tubulin was prepared as previously reported. Tubulin polymerisation was monitored by turbidimetry at 350 nM with a Uvikon 931 spectrophotometer (Kontron) equipped with a thermostatically-regulated cuvette holder. The products were dissolved at 10 mM in DMSO and added at variable concentrations (0.5 to 10 μM) to the tubulin solution before polymerisation. The IC_{50} value is defined as the concentration of product which inhibits the rate of polymerisation by 50%.

Cytotoxicity assays. Human colon carcinoma HCT116 cell line was obtained from the American Tissue Culture Collection. The cell proliferation was evaluated by measuring the incorporation of ^{14}C-thymidine. The IC_{50} value is defined as the concentration of product which reduces the radioactivity by 50% compared with an untreated control.

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