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The concise synthesis of chalcone, indanone and indenone analogues of combretastatin A4

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Abstract—A series of aryl- and aroyl-substituted chalcone analogues of the tubulin binding agent combretastatin A4 (**1**) were prepared, using a recently introduced one-pot palladium-mediated hydrostannylation-coupling reaction sequence. These chalcones were converted to indanones by Nazarov cyclisation, followed by oxidation to give the corresponding indenones. Indenones were also prepared using a palladium-mediated formal [3+2]-cycloaddition process between *ortho*-halobenzaldehydes and diarylpropynones. All compounds were assessed as inhibitors of tubulin polymerisation, but only ***E*-31** had activity similar to that of **1**. However, compound ***E*-31** did not exhibit antiproliferative activity against the MCF-7 cell line.

1. Introduction

Combretastatin A4 (CA4) **1** is a *cis*-stilbene natural product from the South African tree *Combretum caffrum*, originally isolated by Pettit and coworkers 20 years ago (Fig. 1).[1] Studies into the anticancer properties of this compound by Hamel and Pettit revealed that it binds to the colchicine binding site on the β-tubulin subunit of α,β-tubulin heterodimers.[1,2] This binding inhibits the polymerisation of these heterodimers into microtubules.[2] Interference of tubulin/microtubule polymerisation dynamics has two key anticancer effects: (i) inhibition of cancer cell proliferation through disturbance of mitotic spindle function, which leads to cell apoptosis;[3] and (ii) disruption of cell signalling pathways involved in regulating and maintaining the cytoskeleton of endothelial cells in tumour vasculature, leading to selective shutdown of blood flow through tumours.[4] Due to its poor solubility in aqueous media, CA4 is administered as a disodium phosphate pro-drug CA4P **2**, which is soluble in saline solutions (for intravenous administration) and that, when cleaved, yields **1** due to the action of non-specific phosphatases.[5] Whilst

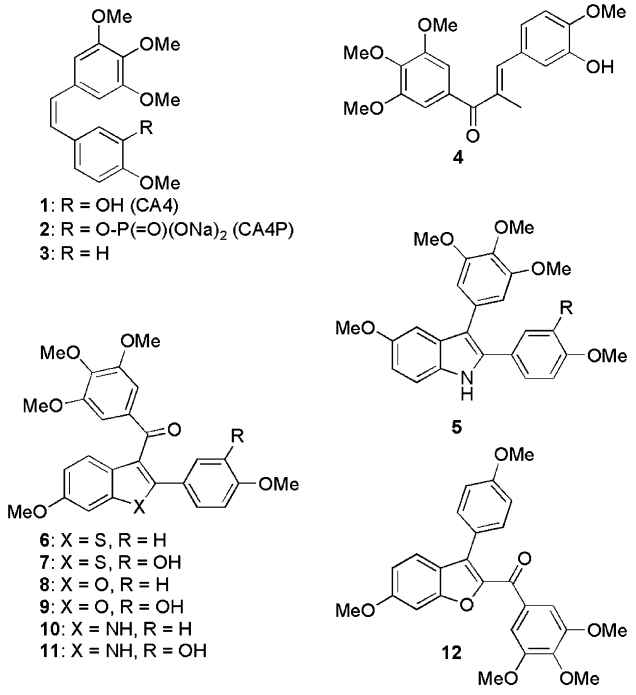

Figure 1. Combretastatin A4 and selected synthetic analogues.

combretastatin A4 is a powerful antimitotic compound, its dominant mode of action in tumour growth inhibition probably results from vasculature shutdown.[4] The

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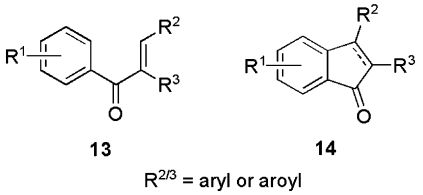


Figure 2. New CA4 analogues.

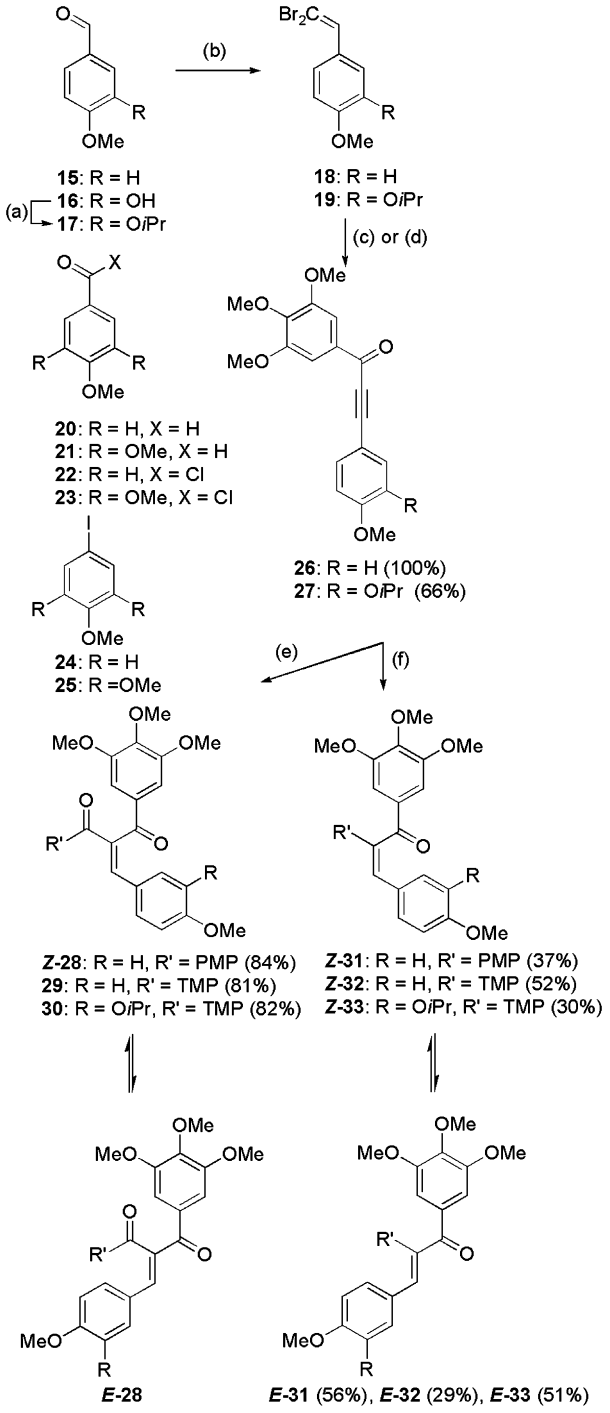
vascular disrupting properties of CA4 and related compounds represent a new approach to cancer therapy.[4] CA4 is currently in phase II and III clinical trials based on the vascular shutdown mechanism of action.[6]

The poor solubility of CA4 in vehicles suitable for drug administration, its potential to isomerise to the thermodynamically more stable and essentially inactive *trans*-isomer and the desire to find even more potent and selective compounds have prompted a number of groups to design more soluble, stable and/or active analogues. Accordingly, a large number of different structures containing a trimethoxyphenyl group and a 3-hydroxy-4-methoxyphenyl group in close proximity to each other (1–3 atom tether) have been prepared and evaluated as tubulin polymerisation inhibitors.[7] Active analogues of CA4 that have been prepared include benzo[*b*]thiophenes,[8] benzo[*b*]furans,[9] indoles[9,10] and chalcones.[11] Specific examples include compounds **4**–**12**. Some of these analogues are more potent inhibitors of tubulin polymerisation than CA4 and are amongst the most potent inhibitors yet reported, particularly for compounds that bind to the colchicine site (e.g., compound **8**, see Table 1). Furthermore, these analogues do not share the thermodynamic instability of CA4.

A number of compounds encompassed in structures **4**–**12** are triaryl analogues of the simple *cis*-stilbene CA4 and/or analogues that include a carbonyl unit in a 2- or 3-atom tether connecting the aryl groups. In view of the apparent importance of these additional structural features (carbonyl in the tether and, possibly, the presence of an additional aryl unit),[12] we decided to investigate the activity of compounds containing three aryl groups, as represented by chalcone **13** and indanone and indenone **14** analogues of CA4 (Fig. 2).[13,14]

2. Synthetic studies

Since Cushman et al.[15] had shown that the replacement of the OH group in CA4 with a H group, as in **3**, had little effect on the ability of this class of compound to inhibit tubulin polymerisation, we did not seek to incorporate this group in all our analogues. To prepare a variety of triaryl chalcone type systems **28**–**33**, we utilised our recently developed palladium-mediated hydrostannylation-coupling protocol (Scheme 1).[13b] This involved initial conversion of aldehydes **15** and **17** into the *gem*-dibromostyrenes **18** and **19**, respectively. Conversion of these *gem*-dibromostyrenes into the corresponding lithium phenylacetylides provided efficient access to the 1,3-diarylpropynones **26** and **27**.



Scheme 1. Reagents: (a) *i*-PrBr, K_2CO_3, DMF; (b) Ph_3P, CBr_4, Zn, CH_2Cl_2; (c) *n*-BuLi (2 equiv), THF then **21** and then protic work-up and MnO_2; (d) *n*-BuLi (2 equiv), **23**, THF; (e) $Pd(dba)_2$, PPh_3, *n*-Bu_3SnH, THF then **22** or **23**; (f) same as (e) except use **24** or **25**.

This was accomplished by treating **18** and **19** with 2 equiv of *n*-butyllithium followed by reaction with either 3,4,5-trimethoxybenzoylchloride or the corresponding benzaldehyde and subsequent MnO_2 oxidation. Diarylpropynones **26** and **27** were then used as substrates in the palladium-mediated hydrostannylation-coupling with benzoylchlorides **22** and **23** to give 2-aroylchalcones (2-benzylidene-1,3-diarylpropan-1,3-diones) **28**–**30**. Similar

hydrostannylation-couplings of diarylpropynones **26** and **27** with aryliodides **24** and **25** gave the 2-arylchalcones (1,2,3-triarylpropenones) **31**–**33**.

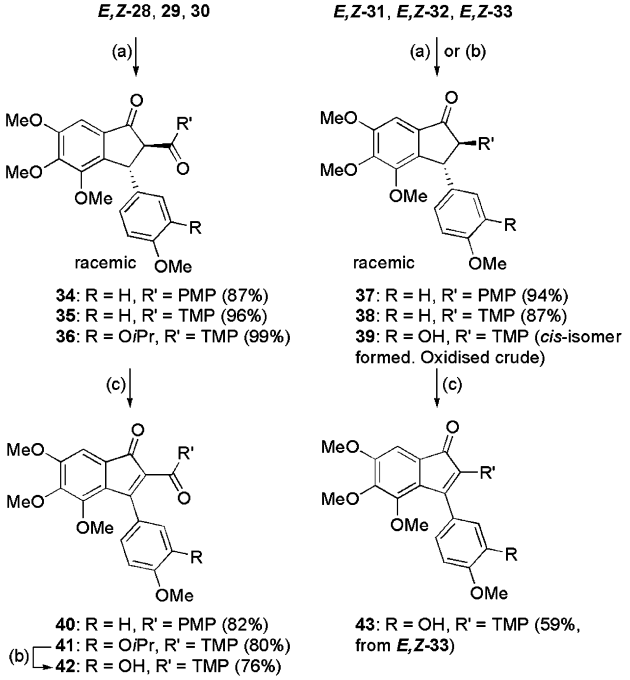
Although the palladium-mediated hydrostannylation-coupling protocol typically proceeds through a *syn*-addition of the tin-hydride, followed by coupling with stereochemical retention, all of the products were obtained as mixtures of *E*,*Z*-stereoisomers of **28**–**33**. This isomerism may be promoted by the presence of catalytic amounts of uncoordinated triphenylphosphine. In other work, we avoided such isomerism by reducing the PPh_3:Pd ratio, but we did not seek to do this here as both isomers were desired for testing as inhibitors of tubulin polymerisation.[16] Separation of the *E*,*Z*-isomeric mixtures of the triarylpropenones **31**–**33** gave stable *E*- and *Z*-isomers. The determination of *E*,*Z*-stereochemistry of triarylpropenones has previously been based on the infrared absorption of the carbonyl, where *E*-isomers are expected to absorb at lower wavenumbers (1640–1650 cm^{-1}) than *Z*-isomers (1650–1660 cm^{-1}).[17] All the triarylpropenones **31**–**33** had isomers with carbonyl IR absorptions that fell into either of these two ranges, and their stereochemistry was assigned on this basis. We also observed that the chemical shift of the vinylic hydrogen in each *Z*-isomer fell 0.2 ppm further downfield than the corresponding *E*-isomer, as might be expected for a hydrogen *cis* to a carbonyl (*Z*-isomer) relative to that *cis* to an aryl group (*E*-isomer).[18] Further support for these assignments was gained from performing a NOESY 2D NMR on ***Z*-31**, which showed a strong NOE interaction between the vinylic hydrogen and both 4-methoxyphenyl groups, which is not possible for an *E*-isomer. Additionally, both 4-methoxyphenyl rings exhibited a strong NOE with the aroyl unit, also impossible for an *E*-isomer.[18]

In the case of the 2-aroylchalcones, *E*,*Z*-isomerism is likely to be spontaneous since the 2-aroylchalcone ***Z*-28** could not be separated from its stereoisomer ***E*-28**, these isomers existed as a 1:1 equilibrium mixture at ambient temperature. Due to their greater symmetry, there are no double bond stereoisomers for **29** and **30**.

Nazarov cyclisation of the 2-aryl and 2-aroylchalcones **28**–**32** was readily achieved using either cupric triflate or methanesulfonic acid to give indanones **34**–**38**. Similar results were obtained irrespective of whether a specific *E*- or *Z*-isomer or an isomeric mixture of the 2-arylchalcones was used. All indanones **34**–**39** were isolated as *trans*-isomers. In the case of the 2-aroylchalcone **28**, where cyclisation could proceed through either one of two aroyl units, cyclisation is favoured through the most electron rich aroyl unit to give exclusively **34**. Indanones **34** and **36** were readily converted to indenones **40** and **41** through oxidation with 2,3-dichloro-5,6-dicyanoquinone (DDQ). In the case of isopropyl protected system **33**, deprotection and Nazarov cyclisation were achieved in a single step using $AlCl_3$ to give *cis*-**39**, which was oxidised as the crude product to give **43** in an overall 59% yield.

The three steps of (i) coupling of a lithium acetylide to an acid chloride; (ii) palladium-mediated hydrostannylation-coupling and (iii) Nazarov cyclisation can be achieved as a one-pot procedure, as exemplified in the formation of **44** from **18**, **22** and methylchloroformate.

To access additional indenones of interest we, decided to employ a procedure first developed by Heck[19] and later generalised by Larock and Cacchi.[20] These groups showed that 2-bromo or 2-iodobenzaldehydes could be reacted with alkynes in a formal [3+2]-cycloaddition process under palladium catalysis.[18,20] When 2-bromo-5-methoxybenzaldehyde (**45**) underwent cycloaddition to 1,3-diarylpropynone **26**, a 1:1 mixture of separable regioisomers **46** and **47** was formed in a moderate yield (45% combined yield). Similarly, when 2-iodo-5-isopropoxy-4-methoxybenzaldehyde (**48**)[21] underwent cycloaddition to 1,3-diarylpropynone **27**, a 1:1 mixture of separable regioisomers **49** and **50** was formed in low yield (20% combined yield). Of these two regioisomers, only **50** was deprotected to give **51** and a small amount of the monodemethylated compound **52**. The relative regiochemistry of the indenones was based on the chemical shift of the carbonyl carbons, with 3-aroyl-2-arylindenones having carbonyl resonances at around 193 and 196 ppm and 2-aroyl-3-arylindenones having carbonyl resonances at around 193 and 191 ppm. This pattern has been seen repeatedly with our other 2-aroyl-3-arylindenones **40**–**42** and with literature examples of 2-aroyl-3-arylindenones[22] (Scheme 2).



Scheme 2. Reagents: (a) $MeSO_3H$ or $CuOTf_2$, CH_2Cl_2; (b) $AlCl_3$, CH_2Cl_2 (***E*,*Z*-33**, gives **39**); (c) DDQ, CH_2Cl_2.

3. Biological studies

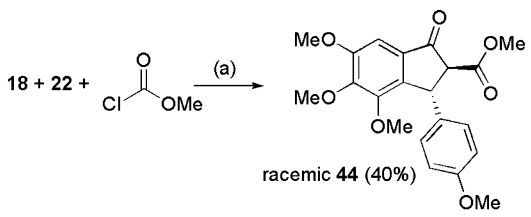
All chalcones, indanones and indenones prepared above were evaluated for their capacity to inhibit tubulin polymerisation (except for the isopropyl ethers, which were only tested as the corresponding deprotected phenols). Those that inhibited the reaction by over 50% at concentrations <20 μM (***Z*-31** and ***E*-31**) were also examined for inhibitory effects on the proliferation of MCF-7 breast cancer cells (Table 1). The newly synthesized compounds were compared in contemporaneous experiments to the potent tubulin polymerisation inhibitor combretastatin A4 (**1**). Of the active compounds, only triarylpropenone ***E*-31** exhibited activity comparable to that of CA4 as an inhibitor of tubulin polymerisation. However, none of the new compounds inhibited growth of the MCF-7 cells at the highest concentration used (1 μM), whereas CA4 exhibited a GI_{50} of 26 nM against this cancer cell line (Scheme 3).

In combination with our earlier studies,[8b,9a] this provides valuable structure–activity relationship (SAR) information with respect to the role of X in the closely related triaryl arrangements **6**, **8**, **10**, **47** and ***E*-31**

Table 1. The effects of arylchalcones, indanones and indenones on tubulin polymerisation and MCF-7 cancer cell growth

Compound	Inhibition of tubulin polymerisation[a] (μM)	Inhibition of cell growth (μM)
CA4	2.0 ± 0.3[b]	0.026 ± 0.008[d]
***E*-31**	2.5 ± 0.1	>1.0[d]
***Z*-31**	6.6 ± 3.0	>1.0[d]
42	20 ± 1	ND[e]
52	36 ± 1	ND[e]
6	>40*[,c]	ND[e,f]
8	0.41 ± 0.1[c]	ND[e,f]
10	1.6[c]	ND[e,f]

[a] The tubulin concentration was 10 μM. Inhibition of extent of assembly was the parameter measured.
[b] Value same as that obtained in Ref. 9a.
[c] Value from Ref. 8b, the asterisk indicates that the rate but not the extent of assembly was inhibited by compound concentrations as high as 40 mM.
[d] MCF-7 human breast cancer cells were exposed to a concentration range of each compound for 48 h. Cell growth was quantitated by measuring protein with sulforhodamine B. The GI_{50} value is the graphically determined compound concentration at which the increase in cell protein is 50% of the increase in untreated control cells.[27]
[e] ND, not done.
[f] Against the Burket Lymphoma CA46 cell line the compounds **6**, **8** and **10** have been shown to have GI_{50} values of 0.63, 0.034 and 0.045 μM, respectively.



Scheme 3. Reagents: (a) **18**, *n*-BuLi (2 equiv), THF, then ClC(O)OMe, then $Pd(dba)_2$, PPh_3, *n*-Bu_3SnH and **22**, then $MeSO_3H$.

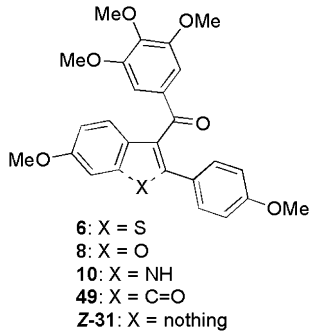
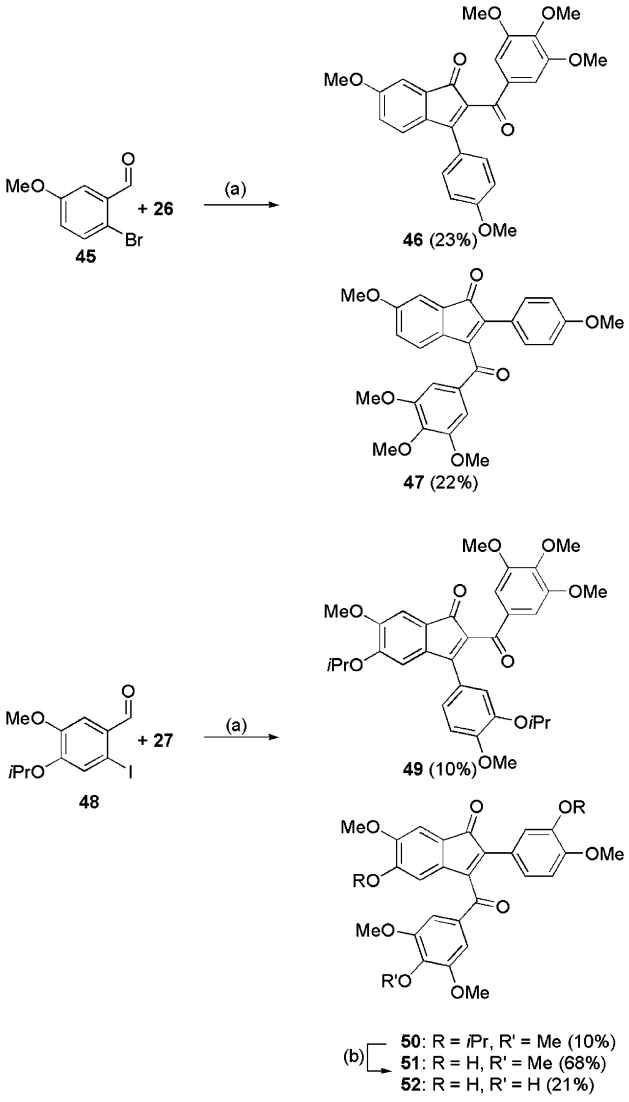


Figure 3. Summary of tubulin polymerisation inhibitors.

(Fig. 3; Schemes 1 and 4). The benzo[*b*]furan **8** is one of the most potent tubulin polymerisation inhibitors yet reported (entry 7, Table 1), particularly for compounds that interact at the colchicine binding site of β-tubulin.[9a] As has been previously shown, when the oxygen atom X in **8** is replaced with a NH group, as



Scheme 4. Reagents: (a) $Pd(OAc)_2$, NaOAc, *n*-Bu_4NCl, DMF; (b) $AlCl_3$, CH_2Cl_2.

in **10** (entry 8, Table 1), some activity is lost.[9a] In contrast, replacing the oxygen atom with a sulfur atom group, as in **6** (entry 6, Table 1), leads to a much larger loss of activity. In this work, it has been shown that when X = C=O, as in **47**, all activity is lost.[8b] When the X group is removed altogether, as in ***E*-31** and ***Z*-31** (entries 2 and 3, Table 1), the compound retains activity as a tubulin polymerisation inhibitor (similar to CA4), but antiproliferative activity is lost (at least in the MCF-7 line).

Compounds such as ***E*-31** that inhibit tubulin polymerisation at low concentrations, but that do not exhibit an antimitotic or cytotoxic effect, may prove useful as selective vascular disrupting agents. Such agents interfere with microtubules responsible for regulating endothelial cell shape and intercellular adhesion.[4a] In principle it should be desirable to maximise the difference between the dose required to affect cell proliferation and/or viability and the dose required to disrupt other cellular cytoskeletal functions.[23] Further examination of ***E*-31** and its congeners, in particular more configurationally stable arrangements, for this role is ongoing.

4. Experimental

Melting points were recorded with a Kofler hot-stage apparatus and are uncorrected. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded with a Varian Gemini 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon, unless otherwise stated. All NMR spectra were recorded in (D)chloroform ($CDCl_3$) at 20 °C. The protonicities of the carbon atoms observed in the carbon NMR were determined using attached proton test (APT) experiments. Infrared spectra (IR) were obtained as KBr discs or as films on NaCl plates and were recorded on a Perkin-Elmer *Spectrum One* Fourier-transform infrared spectrophotometer. Low-resolution electron impact mass spectra (MS) were recorded at 70 eV on either a VG micromass 7070F instrument or a JEOL AX-505H mass spectrometer, unless otherwise stated. High-resolution mass spectra (HRMS) were recorded on a VG micromass 7070F instrument. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. All experiments were performed under an anhydrous atmosphere of N_2 (g) except as indicated. Flash chromatography was performed on Merck Kieselgel 60.

4.1. 3-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (26)

This material was prepared in three steps from anisaldehyde **15** by converting it first to *gem*-dibromostyrene **18**, which was converted to the corresponding lithium acetylide and reacted with 3,4,5-trimethoxybenzaldehyde. The resulting alcohol was oxidised with MnO_2.[24] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.3 Hz, 2H), 7.48 (s, 2H), 6.92 (d, J = 8.3 Hz, 2H), 3.95 (s, 6H), 3.93 (s, 3H), 3.84 (s, 3H).

4.2. 3-(3-Isopropoxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (27)

n-Butyllithium (9.4 mL, 2.0 M in hexanes, 19 mmol) was added dropwise to a stirred solution of *gem*-dibromostyrene **19**[23] (3.29 g, 9.39 mmol) in THF (50 mL) at −78 °C, and the solution was allowed to warm to 18 °C over 1 h. The solution was recooled to −78 °C, and 3,4,5-trimethoxybenzoyl chloride **22** was added (2.27 g, 9.86 mmol, dissolved in 10 mL THF). The solution was rewarmed to 18 °C, and 100 mL of ethyl acetate was added. After washing with distilled water (2× 50 mL), the organic phase was dried over $MgSO_4$ and concentrated onto silica gel (10 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, 2% diethyl ether in dichloromethane), yielding the product as a white solid (2.27 g, 66%, mp = 130–1 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 2H), 7.28 (dd, J = 8.3 Hz, 1.8 Hz, 1H), 7.16 (d, J = 1.8 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 4.54 (septet, J = 6.1 Hz, 1H), 3.96 (s, 6H), 3.94 (s, 3H), 3.90 (s, 3H), 1.38 (d, J = 6.1 Hz, 6H).^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 176.8 (C), 153.0 (C), 152.9 (C), 147.1 (C), 143.3 (C), 132.3 (C,), 127.3 (CH), 119.3 (CH), 111.7 (C), 111.6 (CH), 106.7 (CH), 94.4 (C), 86.3.4 (C), 71.6 (CH), 61.0 (CH_3), 56.2 (CH_3), 56.0 (CH_3), 21.9 (CH_3). IR (KBr disc, cm^{-1}): 3011, 2976, 2938, 2838, 2187, 1637, 1586, 1510, 1460, 1413, 1328, 1248, 1127. LRMS (70 eV) *m/z* (%): 384 ($M^{+\bullet}$, 80), 342 (100), 299 (55), 175 (30). HRMS calcd for $C_{22}H_{24}O_6$: 384.1573. Found: 384.1570.

4.3. (*E*,*Z*)-2-(4-Methoxybenzylidine)-3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-1,3-propadione (*E*,*Z*-28)

$Pd(dba)_2$ (32 mg, 0.06 mmol) was added to a solution of PPh_3 (60 mg, 0.24 mmol) in THF (14 mL) and stirred for 0.25 h at 18 °C. After this time, **26** (560 mg, 1.72 mmol) was added and the reaction mixture cooled to 0 °C. Bu_3SnH (0.48 mL, 1.72 mmol) was then added dropwise and the mixture allowed to warm to room temperature over 1 h. 4-Methoxybenzoyl chloride **22** (352 mg, 2.06 mmol) and CuCl (150 mg, 1.5 mmol) were then added and the reaction mixture stirred at 18 °C for 16 h. Then $KF_{(aq)}$ (30%, 20 mL) was added and the reaction mixture stirred for 2 h. The triphasic (organic, aqueous and solid) mixture was filtered through Celite and the retained solid washed with ethyl acetate (25 mL). The aqueous and organic phases were separated and the latter dried over $MgSO_4$ and concentrated onto silica gel (2 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, hexanes/dichloromethane/diethyl ether 1:1:0.27) giving the product as a light yellow solid (667 mg, 84%, mp = 107–110 °C). ^{1}H NMR analysis indicated that this material, ***E,Z*-28**, exists as an equilibrium mixture of double bond stereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ Isomer A: 7.95 (d, J = 8.8 Hz, 2 H), 7.56 (s, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.08 (s, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.82 (s, 9H), 3.75 (s, 3H). Isomer B: 7.88 (d, J = 8.7 Hz, 2H), 7.45 (s, 1H), 7.27 (d, J = 8.7 Hz, 2H), 7.25 (s, 2H), 6.95 (d, J = 8.7 Hz, 2H), 6.78

(d, J = 8.7 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.80 (s, 6H), 3.76 (s, 3H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 196.0 (C), 195.9 (C), 193.4 (C), 193.3 (C), 164.1 (C), 163.2 (C), 161.3 (C), 161.2 (C), 153.1 (C), 152.8 (C), 143.0 (CH), 142.5 (CH), 141.6 (C), 137.24 (C), 137.17 (C), 132.8 (C), 132.2 (CH), 131.9 (CH), 131.85 (CH), 131.81 (CH), 131.5 (C), 130.0 (C), 129.6 (C), 125.72 (C), 125.68 (C), 114.2 (CH), 114.0 (CH), 113.7 (CH), 106.8 (CH), 106.6 (CH), 60.8 (CH_3), 56.12 (CH_3), 56.06 (CH_3), 55.4 (CH_3), 55.2 (CH_3). IR (KBr disc, cm^{-1}): 3072, 3004, 2936, 2838, 1656, 1642, 1599, 1582, 1507, 1460, 1414, 1331, 1258, 1167, 1123, 1025, 848, 831. LRMS (70 eV) m/z (%): 462 ($M^{+\bullet}$, 50), 327 (25), 195 (45), 135 (100). HRMS calcd for $C_{27}H_{26}O_7$: 462.1679. Found: 462.1677.

4.4. (*E* and *Z*)-2,3-Bis-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (*E*-31 and *Z*-31)

$Pd(dba)_2$ (27 mg, 0.05 mmol) was added to a solution of PPh_3 (50 mg, 0.20 mmol) in THF (7 mL) and stirred for 0.25 h at 18 °C. After this time, **26** (326 mg, 1.00 mmol) was added and the reaction mixture cooled to 0 °C. Bu_3SnH (0.28 mL, 1.00 mmol) was then added dropwise and the mixture warmed to room temperature over 1 h. 4-Iodoanisole **24** (281 mg, 1.20 mmol) and CuCl (200 mg, 2.0 mmol) were then added and the reaction mixture stirred at 18 °C for 72 h. Then $KF_{(aq)}$ (30%, 20 mL) was added and the reaction mixture stirred for 2 h. The triphasic (organic, aqueous and solid) mixture was filtered through Celite, and the retained solid was washed with ethyl acetate (25 mL). The aqueous and organic phases were separated and the latter dried over $MgSO_4$ and concentrated onto silica gel (1 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, hexanes/dichloromethane/diethyl ether 1:1:0.1/1:1:0.15) giving the product as two separable tan solids (combined mass 404 mg, 93%). Higher R_f isomer ***Z*-31**, (160 mg, 37%, mp = 136–7 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.9 Hz, 2H), 7.28 (s, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.05 (s, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.79 (s, 6H), 3.74 (s, 3H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 198.7 (C), 159.4 (C), 159.2 (C), 153.0 (C), 142.7 (C), 138.1 (C), 131.4 (C), 131.1 (C), 130.0 (CH), 128.4 (C), 128.1 (CH), 127.4 (CH), 114.2 (CH), 113.9 (CH), 106.9 (CH), 60.9 (CH_3), 56.1 (CH_3), 55.3 (CH_3), 55.2 (CH_3). IR (KBr disc, cm^{-1}): 3003, 2940, 2836, 1654, 1606, 1578, 1512, 1501, 1462, 1412, 1325, 1246, 1176, 1158, 1123, 1028, 999, 852, 763, 564. LRMS (70 eV) m/z (%): 424 ($M^{+\bullet}$, 100), 287 (70), 239 (35), 195 (100). HRMS calcd for $C_{26}H_{26}O_6$: 434.1729. Found: 434.1731. Lower R_f Isomer (***E*-31**), (244 mg, 56%, mp = 112–4 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.20 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.9 Hz, 2H), 7.05 (s, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.82 (s, 6H), 3.78 (s, 3H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 196.5 (C), 160.0 (C), 159.1 (C), 152.6 (C), 141.2 (C), 139.3 (CH), 138.2 (C), 133.3 (C), 132.0 (CH), 130.9 (CH), 129.3 (C), 127.5 (C), 114.3 (CH), 113.7 (CH), 107.2 (CH), 60.9 (CH_3), 56.1 (CH_3), 55.2 (CH_3). IR (KBr disc, cm^{-1}): 3003, 2968, 2941, 2838, 1647, 1602, 1579, 1507, 1468, 1414, 1330, 1256, 1156, 1124, 1031, 1006, 920, 833, 810, 765. LRMS (70 eV) m/z (%): 434 ($M^{+\bullet}$, 100), 287 (85), 239 (55), 195 (90). HRMS calcd for $C_{26}H_{26}O_6$: 434.1729, Found: 434.1734.

4.5. (±)-4,5,6-Trimethoxy-2-(4-methoxybenzoyl)-3-(4-methoxyphenyl)indan-1-one (34)

Methanesulfonic acid (30 μL, 0.44 mmol) was added to a solution of ***E,Z*-28** (185 mg, 0.40 mmol) in dry dichloromethane (5 mL). After stirring for 20 min, the solution was diluted with diethyl ether (20 mL), washed with distilled water (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield **34** as a light brown solid (161 mg, 87%, mp = 131–3 °C). ^{1}H NMR analysis indicated that the product **34** exists as an equilibrium mixture of an enol tautomer and the *trans*-keto tautomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ *trans*-Keto tautomer: 8.00 (d, J = 8.9 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 7.03 (s, 1H), 6.94 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.10 (d, J = 2.4 Hz, 1H), 4.61 (d, J = 2.4 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H), 3.45 (s, 3H). Enol tautomer: 7.68 (d, J = 8.9 Hz, 2H), 7.20 (s, 1H), 6.99 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 5.23 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H), 3.68 (s, 3H), 3.28 (s, 3H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 199.2 (C), 195.8 (C), 192.2 (C), 170.7 (C), 163.9 (C), 161.7 (C), 158.5 (C), 157.9 (C), 155.0 (C), 154.6 (C), 150.1 (C), 149.7 (C), 149.2 (C), 147.5 (C), 144.3 (C), 140.1 (C), 135.2 (C), 132.8 (C), 132.2 (CH), 132.0 (C), 130.5 (C), 130.4 (CH), 129.2 (CH), 129.1 (C), 128.5 (CH), 126.2 (C), 115.2 (C), 114.0 (CH), 113.7 (CH), 113.33 (CH), 113.27 (CH), 100.8 (CH), 100.6 (CH), 67.1 (CH), 60.9 (CH_3), 60.8 (CH_3), 60.14 (CH_3), 60.08 (CH_3), 56.2 (CH_3, 2C), 55.5 (CH_3), 55.3 (CH_3), 55.2 (CH_3), 55.0 (CH_3), 45.6 (CH), 45.2 (CH). IR (KBr disc, cm^{-1}): 2942, 2837, 1708, 1664, 1602, 1512, 1466, 1421, 1343, 1315, 1265, 1175, 1123, 1092, 1031, 835, 821, 792, 570. LRMS (70 eV) m/z (%): 462 ($M^{+\bullet}$, 35), 327 (95), 135 (100). HRMS calcd for $C_{27}H_{26}O_7$: 462.1679. Found: 462.1676.

4.6. (±)-*trans*-4,5,6-Trimethoxy-2,3-bis(4-methoxyphenyl)-indan-1-one (37)

Cupric triflate (78 mg, 0.216 mmol) was added to a solution of ***E,Z*-31** (78 mg, 0.180 mmol) in dry dichloromethane (2 mL). After stirring for 4 h, the solution was concentrated directly onto silica gel (0.5 g). Flash chromatography (silica gel, hexanes/dichloromethane/diethyl ether 1:1:0.1/1:1:0.15) yielded **37** as a tan solid (74 mg, 94%, mp = 128 °C), as well as oxidised material (3 mg, 3%) and impure *cis*-isomer (2 mg, 2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.01 (d, J = 8.7 Hz, 4H), 6.84 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.48 (d, J = 3.2 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.66 (d, J = 3.2 Hz, 1H), 3.38 (s, 3H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 205.0 (C), 158.6 (C), 158.3 (C), 155.0 (C), 150.2 (C), 149.0 (C), 143.2 (C), 135.7 (C), 131.5 (C), 131.3 (C), 128.8 (CH), 128.2 (CH), 114.2 (CH), 113.9 (CH), 100.8

(CH), 64.0 (CH), 60.8 (CH_3), 60.0 (CH_3), 56.2 (CH_3), 55.1 (CH_3), 51.6 (CH). IR (KBr disc, cm^{-1}): 3084, 3067, 3037, 3011, 2938, 2836, 1709, 1612, 1599, 1584, 1512, 1466, 1417, 1344, 1306, 1249, 1175, 1127, 1102, 1028, 974, 835, 801. LRMS (70 eV) *m/z* (%): 434 ($M^{+\bullet}$, 100), 135 (20), 91 (25). HRMS calcd for $C_{26}H_{26}O_6$: 434.1729. Found: 434.1732.

4.7. 4,5,6-Trimethoxy-2-(4-methoxybenzoyl)-3-(4-methoxyphenyl)-1*H*-inden-1-one (40)

Indanone **34** (62 mg, 0.132 mmol) and 2,3-dichloro-5,6-dicyanoquinone (45 mg, 0.198 mmol) were dissolved in dry 1,2-dichloroethane (2 mL) and stirred at reflux for 7 days. After this time, the solution was decanted from the precipitate (dihydro-DDQ), concentrated onto silica gel (0.5 g) and flash chromatographed (silica gel, 5:5:1, hexanes/dichloromethane/diethyl ether) to yield **40** as a red/orange solid (50 mg, 82%, mp = 164–5 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.9 Hz, 2H), 7.47 (d, J = 8.9 Hz, 2H), 7.08 (s, 1H), 6.78 (d, J = 8.9 Hz, 4H), 3.93 (s, 3H), 3.91 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.41 (s, 3H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 192.4 (C), 190.9 (C), 163.6 (C), 162.1 (C), 160.9 (C), 155.4 (C), 150.3 (C), 147.3 (C), 131.9 (C), 131.7 (CH), 130.1 (CH), 130.0 (C), 127.2 (C), 126.4 (C), 124.8 (C), 113.4 (CH), 112.9 (CH), 104.8 (CH), 61.3 (CH_3), 61.1 (CH_3), 56.4 (CH_3), 55.3 (CH_3), 55.1 (CH_3). IR (KBr disc, cm^{-1}): 3073, 3010, 2962, 2843, 1694, 1648, 1594, 1503, 1468, 1407, 1362, 1310, 1243, 1169, 1122, 1045, 1024, 837. LRMS (70 eV) *m/z* (%): 460 ($M^{+\bullet}$, 100), 445 (15), 432 (20), 353 (20), 327 (15), 135 (35), 105 (30). HRMS calcd for $C_{27}H_{24}O_7$: 460.1522. Found: 460.1511.

4.8. 3-(3-Hydroxy-4-methoxyphenyl)-4,5,6-trimethoxy-2-(3,4,5-trimethoxyphenyl)-1*H*-inden-1-one (43)

$AlCl_3$ (41 mg, 0.304 mmol) was added to a stirred solution of propenone ***E,Z*-33** (42 mg, 0.076 mmol) in dry dichloromethane (2 mL). After 30 min, the reaction was quenched with aqueous ammonium chloride (10%, 10 mL). This mixture was extracted with diethyl ether (3 × 10 mL) and the combined organic fractions dried over $MgSO_4$ and concentrated under reduced pressure. This crude material was dissolved in dry dichloromethane, and 2,3-dichloro-5,6-dicyanoquinone (18 mg, 0.080 mmol) was added. This solution was then refluxed for 2 days. After this time, the solution was decanted from the precipitate (dihydro-DDQ), concentrated onto silica gel (0.5 g) and flash chromatographed (silica gel, 7% diethyl ether in dichloromethane) to yield **43** as a dark red solid (23 mg, 59%, mp = 175–8 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 7.02 (d, J = 1.9 Hz, 1H), 6.82–6.86 (m, 2H), 6.46 (s, 2H), 5.65 (s, 1H), 3.91 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H,), 3.81 (s, 3H), 3.64 (s, 6H), 3.41 (s, 3H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 195.7 (C), 156.0 (C), 154.2 (C), 152.5 (C), 149.3 (C), 147.5 (C), 146.7 (C), 145.1 (C), 137.2 (C), 131.4 (C), 128.7 (C), 127.8 (C), 126.7 (C), 126.4 (C), 120.6 (CH), 114.8 (CH), 110.0 (CH), 107.0 (CH), 104.6 (CH), 61.3 (CH_3), 61.1 (CH_3), 60.8 (CH_3), 56.5 (CH_3), 55.9 (CH_3), 55.7 (CH_3). IR (KBr disc, cm^{-1}): 3369, 3080, 2925, 2853, 1697, 1607, 1581, 1501, 1467, 1412, 1351, 1296, 1123, 1023. LRMS (70 eV) *m/z* (%): 508 ($M^{+\bullet}$, 100), 493 (35). HRMS calcd for $C_{28}H_{28}O_9$: 508.1733. Found: 508.1727.

4.9. (±)-(*trans*)-Methyl-4,5,6-trimethoxy-3-(4-methoxyphenyl)indan-1-one-2-carboxylate (44)

n-Butyllithium (1.2 mL, 1.7 M in hexanes, 2.0 mmol) was added dropwise to a stirred solution of *gem*-dibromostyrene **18** (292 mg, 1.00 mmol) in THF (7 mL) at −78 °C. The solution was warmed to 18 °C over 1 h. The solution was recooled to −78 °C, and methyl chloroformate (84 μL, 1.05 mmol) was added. The solution was rewarmed to 18 °C and PPh_3 (50 mg, 0.20 mmol) and $Pd(dba)_2$ (27 mg, 0.05 mmol) were added. This solution was stirred for 0.5 h. Bu_3SnH (0.29 mL, 1.04 mmol) was added dropwise, followed 0.5 h later by 3,4,5-trimethoxybenzoyl chloride **23** (282 mg, 1.2 mmol) and CuCl (100 mg, 1.0 mmol). After stirring for 24 h, the solvent was removed under the flow of a stream of nitrogen, followed by evacuation. The residue was dissolved in dichloromethane (7 mL), and methanesulfonic acid (325 μL, 5.0 mmol) was added. After 0.5 h, KF (30% w/v in H_2O, 15 mL) was added, and the triphasic mixture was stirred for 12 h. To this mixture, H_2O (50 mL) and diethyl ether (50 mL) were added and the phases separated. The aqueous phase was re-extracted with ether (2× 30 mL), and the combined organic fractions were dried over $MgSO_4$ and concentrated onto silica gel (2 g) under reduced pressure. The solid residue was subjected to flash chromatography (silica gel, hexanes/dichloromethane/diethyl ether 20:20:3), and **44** was obtained as a light brown oil (155 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 7.03 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 4.91 (d, J = 3.2 Hz, 1H), 3.91 (s, 6H), 3.80 (s, 3H), 3.78 (s, 3H), 3.61 (d, J = 3.2 Hz, 1H), 3.38 (s, 3H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 197.8 (C), 168.7 (C), 158.4 (C), 155.0 (C), 150.1 (C), 149.3 (C), 143.5 (C), 134.5 (C), 130.2 (C), 128.2 (CH), 113.9 (CH), 100.8 (CH), 63.6 (CH), 60.7 (CH_3), 59.9 (CH_3), 56.1 (CH_3), 55.0 (CH_3), 52.7 (CH_3), 45.3 (CH). IR (neat, cm^{-1}): 2998, 2949, 2838, 1738, 1709, 1600, 1512, 1471, 1313, 1248, 1126, 1032, 837. LRMS (70 eV) *m/z* (%): 386 ($M^{+\bullet}$, 85), 354 (40), 326 (100), 297 (15). HRMS calcd for $C_{21}H_{22}O_7$: 386.1366. Found: 386.1362.

4.10. 6-Methoxy-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxybenzoyl)-1*H*-inden-1-one (46) and 6-methoxy-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxybenzoyl)-1*H*-inden-1-one (47)

Palladium(II) acetate (12 mg, 0.05 mmol), sodium acetate (164 mg, 2.00 mmol), tetrabutylammonium chloride (150 mg, 0.540 mmol), 2-bromo-5-methoxybenzaldehyde **45**(108 mg, 0.500 mmol) and propynone **26** (326 mg, 1.00 mmol) were added to degassed *N*,*N*-dimethylformamide (10 mL). This mixture was heated at 100 °C until disappearance of the aldehyde, which

was confirmed by TLC. The mixture was then taken up in diethyl ether (50 mL) and washed with aqueous ammonium chloride (10%, 3× 30 mL), followed by distilled water (30 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure onto silica gel (0.5 g). Two isomers were isolated in similar yields after flash chromatography (silica gel, 1:1:0.075/1:1:0.18 hexanes/dichloromethane/diethyl ether). Lower $R_f$isomer (**46**), 52 mg, 23%, mp = 143–5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 2.5 Hz, 1H), 7.06 (s, 2H), 6.87 (dd, J = 8.2, 2.5 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.76 (s, 6H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 192.9 (C), 191.2 (C), 162.21 (C), 162.16 (C), 161.7 (C), 152.7 (C), 142.6 (C), 134.5 (C), 133.5 (C), 131.9 (C), 130.1 (CH), 129.4 (C), 124.3 (CH), 124.0 (C), 116.5 (CH), 114.2 (CH), 110.7 (CH), 106.9 (CH), 60.8 (CH_3), 56.1 (CH_3), 55.8 (CH_3), 55.3 (CH_3). IR (KBr disc, cm^{-1}): 3064, 2997, 2938, 2838, 1707, 1629, 1604, 1581, 1508, 1447, 1415, 1349, 1255, 1123, 1020, 839, 797. LRMS (70 eV) *m/z* (%): 460 ($M^{+\bullet}$, 100), 417 (35), 293 (45), 195 (30). HRMS calcd for $C_{27}H_{24}O_7$: 460.1522. Found: 460.1523. Higher R_f isomer (**47**), 50 mg, 22%, mp = 104–5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.7 Hz, 2H), 7.18 (s, 2H), 7.16 (d, J = 2.3 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.78 (dd, J = 8.1, 2.3 Hz, 1H), 6.75 (d, J = 8.7 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.74 (s, 9H). ^{13}C NMR + APT (75 MHz, $CDCl_3$) δ 196.4 (C), 193.3 (C), 160.9 (C), 159.9 (C), 153.0 (C), 149.0 (C), 143.5 (C), 136.0 (C), 133.0 (C), 131.5 (C), 130.5 (CH), 129.8 (C), 122.5 (C), 122.4 (CH), 117.2 (CH), 113.9 (CH), 111.4 (CH), 106.6 (CH), 60.9 (CH_3), 56.1 (CH_3), 55.7 (CH_3), 55.1 (CH_3). IR (KBr disc, cm^{-1}): 3098, 2994, 2938, 2831, 1712, 1637, 1607, 1578, 1509, 1470, 1413, 1349, 1312, 1250, 1126, 1027, 835, 794, 768. LRMS (70 eV) *m/z* (%): 460 ($M^{+\bullet}$, 100), 195 (25). HRMS calcd for $C_{27}H_{24}O_7$: 460.1522. Found: 460.1519.

4.11. Biological materials and methods

Bovine brain tubulin was prepared as described previously,[25] and MCF-7 human breast cancer cells were provided by the Screening Technologies Branch, National Cancer Institute. The tubulin assembly procedure[26] and techniques used to culture the MCF-7 cells and quantitate their growth[27] have been described in detail elsewhere.

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Supplementary data

Preparative procedures and spectral data for compounds **29**, **30**, **32**, **35**, **36**, **38**, **41**, **42**, **50**, **51** and **52**. NOESY NMR for compound ***Z*-31**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.02.006.

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