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Original article

Synthesis and evaluation of double bond substituted combretastatins

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Dedicated to Professor David Crout to mark the occasion of his retirement

Abstract

A series of combretastatins substituted with epoxides, amides and small alkyl groups has been synthesised and evaluated for cytotoxicity and their ability to inhibit the assembly of tubulin. The methyl and ethyl substituted phenols **36**, **44** have shown potent antimitotic effects whilst exhibiting reduced cytotoxicity.

Keywords: Combretastatin; Tubulin; Antimitotic

1. Introduction

The combretastatins are a group of compounds isolated [1–3] from the bark and stemwood of the South African tree *Combretum caffrum*. Combretastatin A-4 (**1**) (Fig. 1) is the most potent antimitotic agent isolated from *C. caffrum* and interacts with the colchicine site on tubulin [2]. Also combretastatin A-4 (**1**) has the ability to damage tumour vasculature at 10% of its maximum tolerated dose whilst leaving normal vasculature intact [4].

The structural features of the combretastatins, which are thought to play an important role in their antimitotic activities, have previously been published [5–7]. These features include: a *cis* double bond, a trimethoxylated A ring, a small substituent on the B ring 4-position. Recently it has been shown [8] that a trimethylated A ring combretastatin is less cytotoxic to K562 human leukaemia cells but a more potent antimitotic agent than combretastatin A-4. This suggests that a trimethoxy unit is not essential for antimitotic activity.

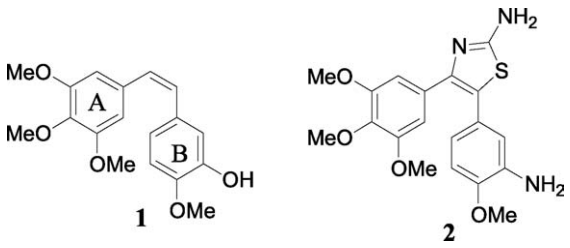

Fig. 1. Structures of antimitotic agents combretastatin A-4 (**1**) and heterocycle (**2**).

Several combretastatins (e.g. **2**) (Fig. 1) which have the olefinic bond incorporated into a heterocyclic ring have shown [9] potent antimitotic properties. This suggested that modification of the double bond could produce effective antimitotic agents. The chalcones are another group [3,10–13] of antimitotic agents, which are similar in structure to the combretastatins and also possess a double bond. With the chalcones their biological activities are enhanced when the double bond is substituted with a small alkyl group. Having noted this, our group has synthesised several combretastatin derivatives which have the double bond possessing substituents or incorporated into a ring system. The syntheses and biological activities of these compounds are described herein.

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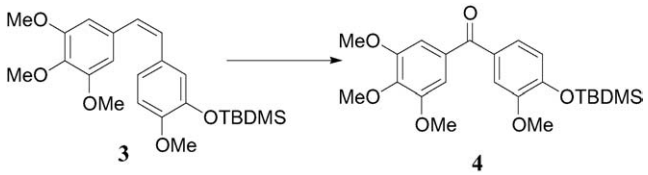
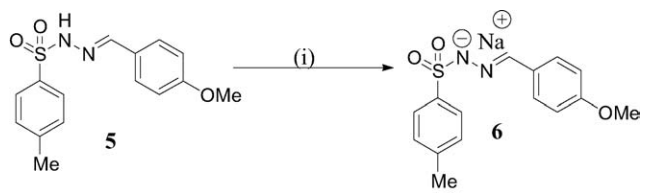
2. Chemistry

We first explored replacing the double bond with an epoxide ring. A previous attempt [14] by Pettit et al. at the formation of an oxirane using Jacobsen oxidation from TBDMS protected combretastatin A-4 resulted in the formation of the diaryl ketone **4** (Scheme 1). Cope et al. have described [15] the epoxidation of both *cis* and *trans* stilbene using peracetic acid and sodium acetate. However, our attempts to oxidise combretastatins using this method yielded only starting materials.

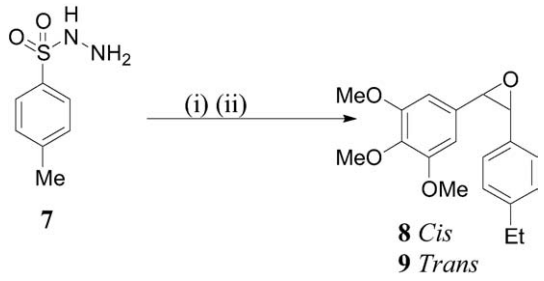
As an alternative strategy we next attempted to create the desired epoxide bond at the same time as forming the two-carbon bridge between the two aryl rings. Aggarwal et al. have investigated [16–19] the enantioselective synthesis of epoxides using the reaction of enantiopure sulphur ylides with aldehydes and ketones. As the potential bioactivities of *cis* or *trans* epoxidised combretastatins were unknown, we used tetrahydrothiophene as the ylide in an attempt to isolate both isomers (each in racemic form) for testing. The tosyl hydrazone salt **6** was synthesised (Scheme 2) and reacted with 3,4,5-trimethoxybenzaldehyde. However, only the hydrazone **5** precursor could be isolated from this reaction. Using a one-pot procedure 3,4,5-trimethoxybenzaldehyde and 4-toluenesulfonylhydrazide **7** were treated with sodium hydride followed by rhodium(II) acetate dimer, tetrahydrothiophene, benzyltriethylammonium chloride and 4-ethylbenzaldehyde. This reaction afforded, after chromatography, the *cis* epoxide **8** in moderate yield along with a small amount of the *trans* isomer **9** (Scheme 3). The stereochemistry of the isomers could be determined using NMR spectroscopy. The epoxide ring protons for the *cis* isomer **8** appear ca. 1 ppm downfield from those of the *trans* compound **9**. The assignment is supported by the Karplus equation which predicts that the *cis* epoxide **8**, in which the protons have a dihedral angle of ca. 0°, would have a greater coupling constant than the *trans* isomer **9** where the dihedral angle is 120°. In the NMR spectra, these protons in the *cis* **8** and *trans* **9** isomers showed coupling constants of 4.5 and 1.9 Hz respectively.



Scheme 1. Formation of the phenstatin (**4**) from stilbene (**3**).



Scheme 2. Preparation of sodium salt (**6**). *Reagents and conditions* (i) NaOMe.

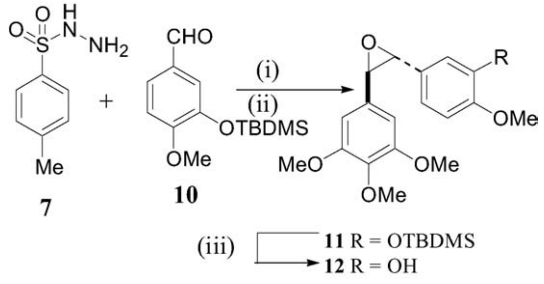


Scheme 3. Synthesis of oxiranes (**8**, **9**). *Reagents and conditions* (i) NaH, 3,4,5-trimethoxybenzaldehyde; (ii) benzyltriethylammonium chloride, tetrahydrothiophene, 4-ethylbenzaldehyde, $Rh_2(OAc)_2$.

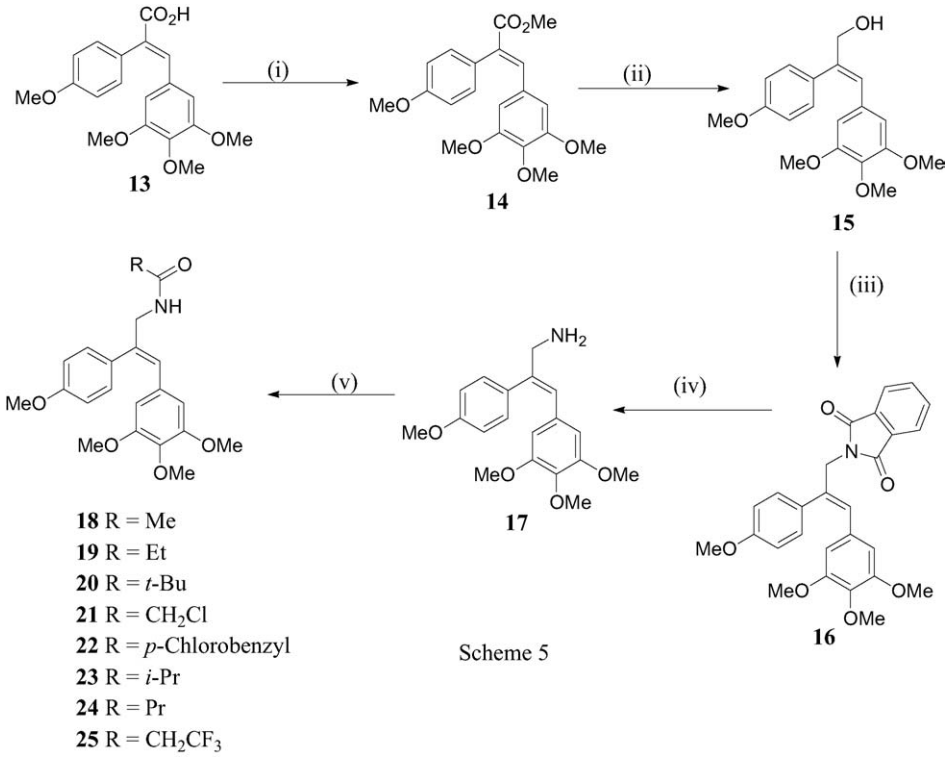
Replacing 4-ethylbenzaldehyde with isovanillin in the above procedure failed to yield any epoxides. However, when the reaction was carried out using silyl-protected isovanillin **10** [20] the *trans* epoxide **11** alone was isolated. Desilylation using fluoride (Scheme 4) gave the required epoxide **12**. The stereochemistry of these epoxides was again elucidated using NMR spectroscopy. The epoxide ring protons showed a coupling constant of 1.9 Hz in both cases.

Colchicine is an antimitotic agent [3,10], which is water soluble owing to its amide group. This led us to synthesise a series of combretastatins with amide substituents on the double bond. Reaction of 4-methoxyphenylacetic acid with 3,4,5-trimethoxybenzaldehyde under Perkin conditions afforded [6] the propenoic acid **13**. Esterification to **14** followed by reduction using lithium aluminium hydride afforded alcohol **15** in good yield. Treatment of this alcohol **15** under Mitsunobu conditions gave phthalimide **16** which then yielded methylamine **17** after treatment with hydrazine. The desired combretastatins **18**–**25** with amide groups on the side of the double bond distal to the trimethoxy aryl ring were synthesised by treating amine **17** with either an acid chloride or with a carboxylic acid in the presence of 1-hydroxybenzotriazole (HOBt) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (Scheme 5). Similarly, starting from the known [21] amine **26**, a series of combretastatins **27**–**32** with the amide group on the side of the double bond proximal to the trimethoxy aryl ring were prepared (Scheme 6).

As mentioned earlier, the chalcones which have an ∝-alkyl group attached to the double bond show greater antimotic activities than those which are unsubstituted. This led us to synthesise a series of stilbenes where the side of the olefinic

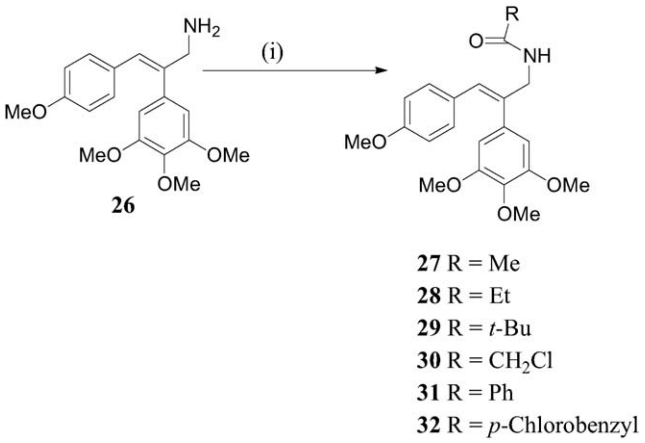


Scheme 4. Synthesis of oxiranes (**11**) and (**12**). *Reagents and conditions*: (i) NaH; (ii) tetrahydrothiophene, 3,4,5-trimethoxybenzaldehyde, benzyltriethylammonium chloride, $Rh_2(OAc)_2$, (iii) tetrabutylammonium fluoride.

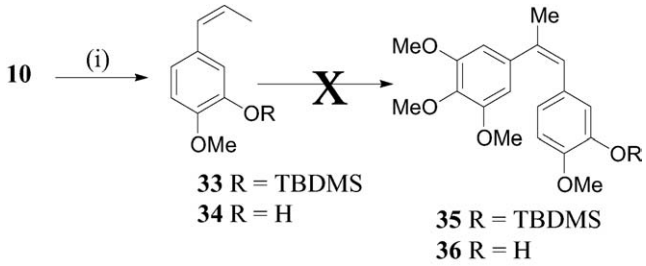


Scheme 5

Scheme 5. Synthesis of amides (**18**–**25**). *Reagents and conditions*: (i) $MeOH/H_2SO_4$; (ii) $LiAlH_4$; (iii) diisopropyl azodicarboxylate, phthalimide, Ph_3P; (iv) N_2H_2; (v) RCOCl/pyridine or RCOOH/EDC/HOBt/*N*-ethyldiisopropylamine.



Scheme 6. *Reagents and conditions*: (i) RCOCl/pyridine or RCOOH/EDC/HOBt/*N*-ethyldiisopropylamine.

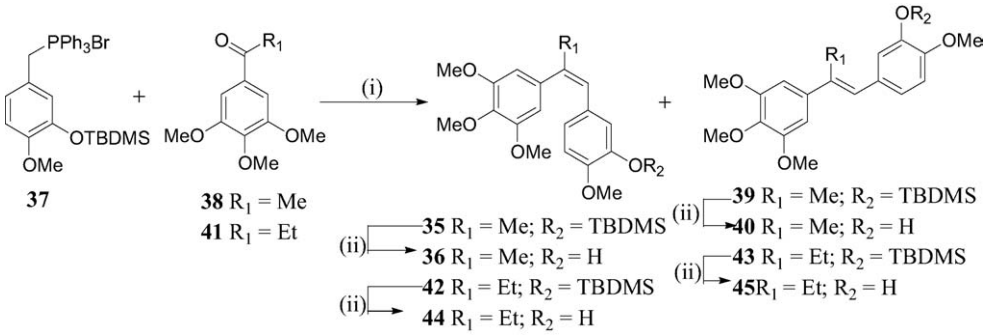


Scheme 7. Attempted preparation of stilbenes (**35**, **36**). *Reagents and conditions*: (i) $EtPPh_3Br$, $KN(Me_3Si)_2$.

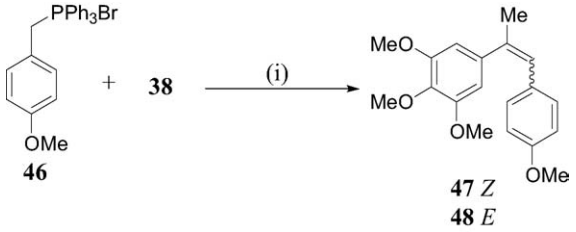
bond proximal to the trimethoxy group was substituted with a small alkyl group (Scheme 7).

The first attempt to synthesise a combretastatin with a methyl group on the olefinic bond utilised Heck chemistry. Treatment of aldehyde **10** with ethyltriphenylphosphonium bromide afforded an inseparable isomeric mixture of predominantly *cis* alkene **33** *cis*/*trans* (15:1). Treatment of this alkene mixture **33** with 3,4,5-trimethoxyiodobenzene under Heck conditions using triphenylphosphine and palladium(II) acetate failed to produce the desired stilbene **35**. Using the free phenol **34** in place of **33** also failed to give stilbene **36** under these conditions. However, reaction of phosphonium bromide **37** with acetophenone **38** successfully provided a separable mixture of the desired *Z*- and *E*-stilbenes **35**, **39**. Silyl group deprotection using fluoride provided the desired phenols **36**, **40**. Similarly the reaction of acetophenone **41** with phosphonium bromide **37** yielded a mixture of the desired *Z*- and *E*-ethyl substituted stilbenes **42**, **43**. Again treatment with fluoride yielded the free phenols **44**, **45** (Scheme 8). Wittig chemistry was also successful in the synthesis of the tetramethoxy stilbenes **47**, **48** from the reaction of 4-methoxybenzyltriphenylphosphonium bromide **46** and acetophenone **38** (Scheme 9).

The stereochemistry of these methyl and ethyl substituted stilbenes was elucidated using UV and NMR spectroscopy. Stilbenes with the aryl rings *cis* to each other have extinction coefficients in their UV spectra of lower magnitude (ca. 10,000–20,000) compared to their *trans* isomers and have maximum absorptions at 20–30 nm lower than their *trans* counterparts. For these stilbenes all the designated stereochemistries are in agreement with the above criteria. Also



Scheme 8. Synthesis of stilbenes (**35**, **36**, **39**–**45**). *Reagents and conditions*: (i) *n*-BuLi, (ii) Bu_4NF.



Scheme 9. Synthesis of stilbenes (**47**, **48**). *Reagents and conditions*: (i) *n*-BuLi.

the signals corresponding to the methyl group (or CH_2 protons of the ethyl group) and the olefinic proton in the *E* isomers appear downfield to those in the *Z* equivalents. In ^1H NOESY spectra (spectra not shown) of the *Z* isomers the CH_3 protons of the methyl group and CH_2 protons of the ethyl group form crosspeaks with both the olefinic proton and 2′, 6′ aromatic protons on the A ring (Fig. 2). In the spectra of the *E* isomers the CH_2 protons form crosspeaks with both the 2′, 6′ aromatic protons of ring A and the 2″, 6″ aromatic protons of ring B. For the *E* compounds no crosspeaks are seen for the olefinic proton. These spectra again confirm the stereochemistry of these stilbenes (Fig. 3).

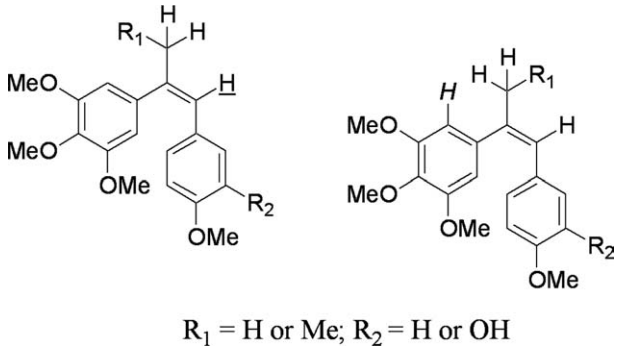


Fig. 2. Idealised conformers of the *Z* isomer to illustrate the formation of NOESY crosspeaks between the CH_2 protons, and both the olefinic proton, shown underlined, and aromatic protons, 2′ and 6′, (2′ shown in italics).

3. Biological results and discussion

The stilbenes were tested for cytotoxicity against the human leukaemia K562 cell line and for their ability to inhibit the assembly of tubulin and to displace colchicine from its binding site on tubulin. For the epoxides the biochemical data is shown in Table 1. Although the stilbene equivalent of ethyl-substituted epoxides shows good cytotoxicity and the ability to inhibit the assembly of tubulin, these epoxides **8**, **9** are non-cytotoxic and do not interact with tubulin. However, it is noteworthy that the *cis* epoxide **8** is ca. 20 times more cytotoxic than the *trans* equivalent **9**. The *trans* epoxide **11** of combretastatin A-4 shows good cytotoxicity in K562 cells (IC_{50} = 90 nM). Although epoxides in general are poor drugs this suggests that the *cis* isomer of **11** may be a good target for SAR studies. However, this agent **11** (*trans*) was ineffective in the tubulin assays.

The data for the amines (**17**, **26**) and amides (**18**–**25**, **27**–**32**) is depicted in Table 2. For these amides only the chloroethyl **21**, chlorobenzyl **30** and trifluoroethyl **25** compounds showed less than μM IC_{50}s. The amine **26** showed the most potent cytotoxicity (0.23 μM) of these compounds. This is a 200-fold less potent than combretastatin A-4 (**1**). Also these agents were not able to inhibit the assembly of tubulin (data not shown).

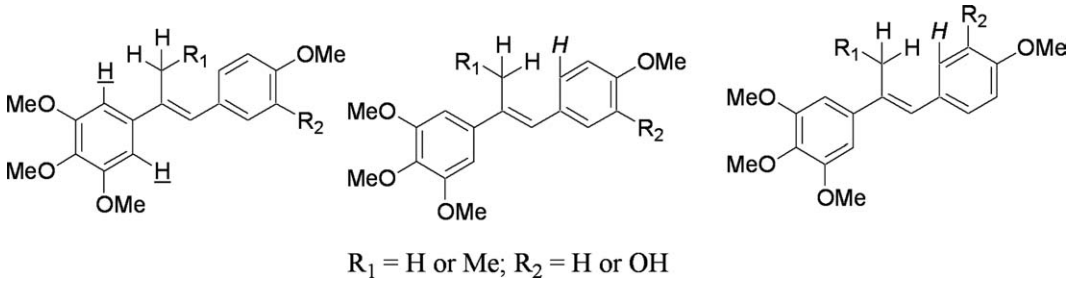


Fig. 3. Idealised conformers of the *E* isomer to illustrate the formation of NOESY crosspeaks between the CH_2 protons, and both the aromatic protons (underlined), 2′ and 6′ on the A ring, and the aromatic protons on the B ring, 2″ and 6″, 2″ shown in italics.

Table 1

Compound	IC_{50} (K562)	IC_{50} MA	IC_{50} CD
1	0.001	0.175	3
8	0.54	>10	>25
9	10	>10	>25
11	0.09	>10	>25

Table 2

Compound	IC_{50} (K562)
17	2.95
26	0.23
18	2.3
19	3.3
20	27.0
21	0.6
22	0.7
23	22.4
24	20.6
25	0.6
27	11.3
28	1.5
29	4.8
30	1.0
31	3.1
32	4.5

The biochemical data for the agents with methyl or ethyl groups **35**, **36**, **39**–**48** on the double bond is shown in Table 3. As expected all the *Z*-stilbenes **35**, **36**, **42**, **44**, **47** showed greater potencies in the cytotoxicity assay and the tubulin assay than their *E*-counterparts **39**, **40**, **43**, **45**, **48**. The tetramethoxycombretastatin **47** possessing a methyl group on the double bond (but without a hydroxy group on the B ring) showed some cytotoxicity (IC_{50} = 100 nM) and moderate ability to inhibit the assembly of tubulin. More significantly the phenolic compounds **36**, **44** with both methyl and ethyl groups on the double bond showed more potent abilities in inhibiting the assembly of tubulin than combretastatin A-4 (**1**). Moreover, both the agents **36**, **44** were 40 and 120 times less cytotoxic (IC_{50}s 40 and 120 nM respectively) than combretastatin A-4 (**1**) (IC_{50} = 1 nM).

Table 3

Compound	IC_{50} (K562)	IC_{50} MA	IC_{50} CD
1	0.001	0.175	3
35	0.2	1.5	>25
39	6	>10	>25
36	0.04	0.13	6
40	0.7	>10	>25
42	0.5	>10	>25
43	3.4	>10	>25
44	0.12	0.13	>25
45	4	>10	>25
46	0.1	1.3	>25
47	0.8	>10	>25

Cells treated with antimitotic agents accumulate their DNA in the G_2/M phase of the cell cycle and several of the above tubulin active agents were subjected to cell cycle analysis. These results are depicted in Table 4. Of the epoxides only the *cis* ethyl-substituted stilbene **8** showed potent ability to cause cells to accumulate in the G_2/M phase. This perhaps indicates the requirement for the two aryl rings to be *cis*. The three tubulin active alkyl substituted stilbenes **36**, **44**, **47** also showed potent ability to cause cells to accumulate in the G_2/M phase.

4. Conclusions

Stilbenes possessing heterocyclic rings on the double bond (e.g. **2**) have previously shown potent antimitotic effects. The simple epoxides **8**, **9** showed only moderate cytotoxicity to K562 cells, but failed to interact with tubulin (Table 1). The *trans* isomer **9** of the epoxide of combretastatin A-4 (**1**) did show potent cytotoxicity (IC_{50} = 90 nM) although this agent also failed to inhibit the assembly of tubulin.

Of the amides the choroethyl and trifluoroethyl agents **21**, **25** showed the best cytotoxicities (IC_{50} = 600 nM) (Table 2). However, these agents did not inhibit the assembly of tubulin.

The phenolic *Z*-stilbenes **36**, **44** and the tetramethoxystilbene **47** possessing alkyl groups on the double bond all showed potent ability to block cells in the G_2/M phase of the cell cycle. The phenolic stilbenes **36**, **44** were more potent (ca. 25%) in inhibiting the assembly of tubulin than combretastatin A-4 (**1**). However, these agents **36**, **44** were considerably less cytotoxic to K562 cells than combretastatin A-4 (**1**) (40- and 120-fold, respectively).

All the data here are consistent with the known pharmacophore [5–8] for the combretastatins [(*Z*) double bond, small group on the 4-position of ring B, trimethoxy/trimethyl substitution on ring A]. What is particularly significant is the potent ability of phenols **36**, **44** to inhibit the assembly of tubulin whilst showing considerably less cytotoxicity in comparison with combretastatin A-4. This may suggest that an agent able to cause vascular damage (via microtubule disruption) may be designed to possess minimal cytotoxicity. The

Table 4

Compound	% of cells with DNA content <2*n*	% of cells with DNA content ≥ 2*n*		
		% of cells in G_0–G_1 phase	% of cells in S phase	% of cells in G_2–M phase
8	16	4	20	76
9	27	10	40	50
11	3	19	55	27
36	23	5	22	73
44	24	7	19	74
47	23	5	22	73

antivascular activity of **36** and **44** is currently being assessed and these results will be reported in due course.

5. Experimental protocols

5.1. Chemistry

General: All reagents and chromatography grade solvents were obtained from commercial sources and used without further purification unless indicated. Flash column chromatography was performed on silica gel [Fluka Silica gel 60 220–440 mesh (35–70 μm)] and TLC was carried out using silica (0.2 mm, 60 F_{254}) pre-coated, aluminium backed plates. Mass spectra were recorded on VG70-70 Eq. (FAB, CI^+, EI^+) and MS50 (FAB) spectrometers, with only major peaks being reported. Melting points (m.p.) were determined on a Gallenkamp m.p. apparatus and are uncorrected. The UV/VIS spectra were determined using a Hewlett–Packard HP8452 diode-array spectrophotometer. Elemental analyses were carried out by the Microanalytical Department at UMIST and Manchester University and are within 0.3% of theoretical values. GC was carried out using a Perkin–Elmer 8500 Gas Chromatograph analyser with a CW20 M column, 25 m × 0.31 mm (film thickness 0.17 μM). ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC-300 instrument or at 400 MHz on a Bruker AC-400 MHz instrument. ^{13}C NMR spectra were recorded at either 75.5 MHz on a Bruker AC-300 instrument or at 100 MHz on a Bruker AC-400 instrument. Chemical shifts (δ) are quoted in ppm, relative to TMS and are referenced to the $CDCl_3$ unless otherwise stated. Coupling constants (J) are reported to 1 decimal place. For 1,4-disubstituted compounds, only J_{A-B} is given.

5.1.1. 4-Methoxybenzaldehyde tosyl hydrazone sodium salt (*6*)

To a solution of sodium methoxide (0.6 g, 26.1 mmol) in MeOH (20 ml) was added 4-methoxybenzaldehyde tosyl hydrazone 5 (8 g, 26.3 mmol) and the mixture stirred until the solid had dissolved. After stirring for a further 15 min the methanol was removed under reduced pressure to give the title salt **6** [19] as a fine white powder (7.11 g, 72%). δ_H (300 MHz, D_2O) 2.19 (3 H, s, CH_3), 3.63 (3 H, s, OCH_3), 6.76 (2 H, d, J = 8.3, H-3″,5″), 7.19 (2 H, d, J = 8.3, H-3′,5′), 7.33 (2 H, d, J = 8.3, H-2″,6″), 7.57 (2 H, d, J = 8.3, H-2′,6′), 7.77 (1 H, s, CH).

5.1.2. *Cis and* trans *2-(3′,4′,5′-trimethoxyphenyl)-3-(4″-ethylphenyl) oxirane (**8**, **9**)*

3,4,5-Trimethoxybenzaldehyde (2.51 g, 12.8 mmol) was added to a solution of 4-toluenesulfonylhydrazide **7** (2.5 g, 13.4 mmol) in dry 1,4-dioxane (30 ml) at room temperature. The solution was stirred for 30 min after which sodium hydride (510 mg of 60% dispersion in oil, 12.8 mmol) was added. The mixture was stirred for 1 h and rhodium(II) acetate dimer (54 mg, 0.122 mmol), benzyltriethylammonium chloride (557 mg, 2.25 mmol), tetrahydrothiophene (198 mg, 198 μl, 2.25 mmol) and 4-ethylbenzaldehyde (1.64 g, 1.67 ml, 12.2 mmol) were added sequentially. The reaction mixture was stirred vigorously at 40 °C for 6 h and quenched by the addition of water (20 ml) and EtOAc (20 ml). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 ml), the combined organic phases dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (petroleum ether/EtOAc 9:1) afforded *trans* epoxide **9** as a clear oil (1.10 g, 29%). R_f 0.24 (petroleum ether/EtOAc 3:1). δ_H (300 MHz) 1.27 (3 H, t, J = 7.5, CH_3), 2.68 (2 H, q, J = 7.5, CH_2), 3.81 (1 H, d, J = 1.9, CH), 3.85 (1 H, d, J = 1.9, CH), 3.87 (3 H, s, OCH_3), 3.89 [6 H, s, $(CH_3)_2$], 6.59 (2 H, s, H-2′,6′), 7.14 (2 H, d, J = 8.3, H-3″,5″), 7.19 (2 H, d, J = 8.3, H-2″,6″). δ_C (100 MHz) 16.1 (CH_3), 29.1 (CH_2), 56.5 (CH_3), 61.3 (CH_3), 63.2 (CH), 63.4 (CH), 102.4 (CH), 126.0 (CH), 128.6 (CH), 133.4 (C), 134.6 (C), 138.3 (C), 145.1 (C), 154.0 (C). *m/z* (FAB) 315 [$(MH)^+$, 100%]. (Found: M^+ 314.1512; C, 72.7; H, 7.0%. $C_{19}H_{22}O_4$ requires M^+ 314.1518; C, 72.7; H, 7.05%). Further elution afforded *cis* isomer **8** as a white solid (94 mg, 2%). M.p. 54–56 °C. R_f 0.19 (petroleum ether/EtOAc 3:1). δ_H (300 MHz) 1.18 (3 H, t, J = 7.5, CH_3), 2.59 (2 H, q, J = 7.5, CH_2), 3.71 [6 H, s, $(CH_3)_2$], 3.78 (3 H, s, OCH_3), 4.26 (1 H, d, J = 4.5, CH), 4.35 (1 H, d, J = 4.5, CH), 6.37 (2 H, s, H-2′,6′), 7.07 (2 H, d, J = 8.3, H-3″,5″), 7.15 (2 H, d, J = 8.3, H-2″,6″). δ_C (100 MHz) 16.0 (CH_3), 28.9 (CH_2), 56.4 (CH_3), 60.1 (CH_3), 60.5 (CH), 61.2 (CH), 104.5 (CH), 127.4 (CH), 127.8 (CH), 130.5 (C), 132.0 (C), 137.6 (C), 144.1 (C), 153.1 (C). *m/z* (FAB) 315 [$(MH)^+$, 45%], 135 (100%). (Found: M^+ 314.1516; C, 72.7; H, 7.2. $C_{19}H_{22}O_4$ requires M^+ 314.1518; C, 72.7; H, 7.05%).

5.1.3. Trans-*2-(3′,4′,5′-Trimethoxyphenyl)-3-(3″-t-butyldimethylsilyloxy-4″-methoxy-phenyl)oxirane (**11**)*

Oxirane **11** was prepared from 3,4,5-trimethoxybenzaldehyde and 3-*t*-butyldimethylsilyloxy-4-methoxybenzaldehyde (**10**) according to the procedure described above for compounds **8**, **9**. Flash column chromatography (petroleum ether/EtOAc 9:1) afforded oxirane **11** as a colourless oil (274 mg, 9%). R_f 0.65 (petroleum ether/EtOAc 1:1). δ_H (300 MHz) 0.18 [6 H, s, $(CH_3)_2$], 1.02 [9 H, s, $(CH_3)_3$], 3.73 (1 H, d, J = 1.9, CH), 3.80 (1 H, d, J = 1.9, CH), 3.84 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 3.89 [6 H, s, $(OCH_3)_2$], 6.59 (2 H, s, H-2′,6′), 6.83 (1 H, d, J = 1.9, H-2″), 6.86 (1 H, d, J = 8.3, H-5″), 6.92 (1 H, dd, J = 8.3, 1.9, H-6″). δ_C (100 MHz) –4.2 (CH_3), 18.9 (C), 26.1 (CH_3), 56.0 (CH_3), 56.5 (CH_3), 61.3 (CH_3), 63.1 (CH), 63.2 (CH), 102.5 (CH), 112.4 (CH), 118.4 (CH), 119.4 (CH), 129.8 (C), 133.3 (C), 138.3 (C), 145.7 (C), 151.7 (C), 154.0 (C). *m/z* (FAB) 447 [$(MH)^+$, 50%], 417 {$[M-(CH_3)_2]^+$ 60%}, 73 (100%).

5.1.4. Trans-*2-(3′,4′,5′-Trimethoxyphenyl)-3-(3″-hydroxy-4″-methoxyphenyl)oxirane (**12**)*

To a stirred solution of TBDMS ether **11** (500 mg, 1.12 mmol) in dry THF (20 ml) was added tetra-*n*-butylammonium fluoride (2 ml of 1 M solution in THF,

2 mmol). The resulting yellow solution was stirred for 20 min and treated with water (30 ml). The aqueous layer was separated, extracted with chloroform (3 × 25 ml) and the combined organic layers were washed with water (2 × 25 ml), brine (25 ml), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (petroleum ether/EtOAc 9:1) afforded phenolic oxirane **12** as a colourless oil (272 mg, 73%). R_f 0.34 (petroleum ether/EtOAc 1:1). δ_H (300 MHz) 3.76 (1 H, d, J = 1.9, CH), 3.82 (1 H, d, J = 1.9, CH), 3.87 (3 H, s, OCH_3), 3.89 [6 H, s, $(OCH_3)_2$], 3.93 (3 H, s, OCH_3), 5.73 (1 H, s, OH), 6.59 (2 H, s, H-2′,6′), 6.86–6.92 (3 H, m, H-2″,5″,6″). δ_C (100 MHz) 55.0 (CH_3), 55.1 (CH_3), 59.9 (CH_3), 61.6 (CH), 61.8 (CH), 101.1 (CH), 109.6 (CH), 110.4 (CH), 116.6 (CH), 129.1 (C), 131.8 (C), 136.8 (C), 144.9 (C), 145.8 (C), 152.5 (C). *m/z* (FAB) 333 [$(MH)^+$, 25%], 303 (75%).

5.1.5. E-*2-(4′-Methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)acrylic acid (**13**)*

A mixture of 3,4,5-trimethoxybenzaldehyde (11.8 g, 0.06 mol), 4-methoxyphenylacetic acid (20 g, 0.12 mol), triethylamine (25 ml) and acetic anhydride (50 ml) was heated under reflux for 3 h After acidification with concentrated hydrochloric acid (150 ml), the solid formed was removed by filtration and recrystallised from ethanol to afford the cinnamic acid **13** as a yellow solid (20.1 g, 97%). M.p. 200–203 °C (lit. [21] m.p. 207–8 °C) R_f 0.56 (petroleum ether/EtOAc 1:1). ν_{max} 2967 (b, OH), 1676 (s, C=O), 1612 (s, C=C), 1499 (s, C=C). δ_H (DMSO-d_6) 3.48 (6 H, s, 2 × OCH_3), 3.61 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 6.42 (2 H, s, H-2″ and H-6″), 6.99 (2 H, d, J = 8.7, H-3′ and H-5′), 7.11 (2 H, d, J = 8.7, H-2′ and H-6′), 7.67 (1 H, s, C=CH). δ_C (DMSO-d_6) 54.9 (OCH_3), 55.8 (OCH_3), 59.7 (OCH_3), 107.7, 113.8, 128.3, 129.6, 130.5, 131.7, 137.9, 138.7, 152.0, 158.5 (CH and C), 168.3 (CO_2H). *m/z* (EI) 345 [$(M + H)^+$, 100%]. (Found: M^+, 344.1267; C, 66.0; H, 5.8%. $C_{19}H_{20}O_6$ requires M^+, 344.1259; C, 66.2; H, 5.8%).

5.1.6. E-*2-(4′-Methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)acrylic acid methyl ester (**14**)*

Concentrated sulphuric acid (40 ml) was added to a solution of acid **13** (21.6 g, 0.063 mol) in methanol (320 ml) and the mixture was heated under reflux conditions for 45 min. Upon cooling some ester **14** was formed as a solid and was removed by filtration. The methanol solution was concentrated under reduced pressure, the residue dissolved in diethyl ether and washed with water (20 ml) and sodium bicarbonate (40 ml). The organics were dried over magnesium sulphate before concentration under reduced pressure. The crude product obtained was recrystallised from methanol to give the title ester **14** as fine yellow crystals (14.4 g, 64%). M.p. 65–67 °C. R_f 0.80 (petroleum ether/EtOAc 1:1). ν_{max} 2950 (s, CH), 2838 (s, CH), 1709 (s, C=O), 1618 (s, C=C), 1508 (s, C=C). δ_H 3.48 (6 H, s, 2 × OCH_3), 3.60 (3 H, s, OCH_3), 3.77 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 6.44 (2 H, s, H-2″ and H-6″), 6.99 (2 H, d, J = 8.7, H-3′ and H-5′), 7.09 (2 H, d, J = 8.7, H-2′ and H-6′), 7.71 (1 H, s, C=CH). δ_C (DMSO-d_6) 52.3 (OCH_3), 55.3 (OCH_3), 55.6 (OCH_3), 60.8 (OCH_3), 108.0, 114.2, 128.2, 130.0, 131.0, 138.7, 140.2, 152.5, 159.2 (CH and C), 168.4 (CO_2Me). *m/z* (EI) 359 [$(M+H)^+$, 100%]. (Found: M^+, 358.1420; C, 67.1; H, 6.0. $C_{20}H_{22}O_6$ requires M^+, 358.1416; C, 67.0; H, 6.1%).

5.1.7. E-*2-(4′-Methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)prop-2-en-1-ol (**15**)*

To a stirred solution of cinnamic ester **14** (10 g, 0.028 mol) in dry THF (100 ml) at –20 °C was added $LiAlH_4$ powder (4.25 g, 0.112 mol). The reaction mixture was stirred at room temperature for 1 h before the careful addition of aqueous solutions of THF, followed by the addition of water (the solution went from grey to white). The lithium salts were removed by filtration. Water was added to the filtrate and the product extracted with diethyl ether (3 × 50 ml). The organics were washed with water (2 × 100 ml), brine (1 × 100 ml) and dried over magnesium sulphate before concentrating under reduced pressure to furnish the alcohol **15** as a yellow oily solid (8.88 g, 96%). R_f 0.62 (petroleum ether/EtOAc 1:1). ν_{max} 3474 (b, OH), 1581 (s, C=C), 1509 (s, C=C), 1126 (s, CO). δ_H (DMSO) 3.47 (6 H, s, 2 × OCH_3), 3.57 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), 4.18 (2 H, dd, J = 5.7 and 1.6, CH_2), 6.25 (2 H, s, H-2″ and H-6″), 6.54 (1 H, d, J = 1.6, C=CH), 6.95 (2 H, d, J = 8.8, H-3′ and H-5′), 7.11 (2 H, d, J = 8.8, H-2′ and H-6′). δ_C 55.0 (OCH_3), 55.3 (OCH_3), 60.5 (OCH_3), 68.2 (CH_2), 106.0, 114.0, 125.6, 128.7, 129.7, 130.5, 131.7, 140.4, 152.0, 158.5 (CH and C). *m/z* (EI) 331 [$(M + H)^+$, 100%]. (Found: M^+, 330.1464; C, 69.1; H, 6.8. $C_{19}H_{22}O_5$ requires M^+, 330.1467; C, 69.0; H, 6.7%).

5.1.8. E-*2-[2-(4′-Methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)allyl]isoindole-1,3-dione (**16**)*

Following a similar method to Hammerschmidt and Hanbauer [22], diisopropyl azodicarboxylate (4.9 ml, 0.025 mol), phthalimide (3.85 g, 0.025 mol) and triphenylphosphine (5.60 g, 0.021 mol) were added to a solution of alcohol **15** (6.93 g, 0.021 mol) in THF (30 ml). The reaction mixture was stirred at room temperature for 45 min, the THF removed under reduced pressure and the residue purified by flash column chromatography (petroleum ether/EtOAc 2:1). The solid obtained was further purified by recrystallisation from ethanol to yield the phthalimide **16** as white crystals (2.78 g, 30%). M.p. 140–142 °C. R_f 0.67 (petroleum ether/EtOAc 1:1). ν_{max} 1771 (s, C=C), 1716 (s, C=O), 1244 (s, CN). δ_H 3.45 (6 H, s, 2 × OCH_3), 3.65 (6 H, s, 2 × OCH_3), 4.60 (2 H, s, CH_2), 6.15 (2 H, s, H-2″ and H-6″), 6.45 (1 H, s, C=CH), 6.75 (2 H, d, J = 8.8, H-3′ and H-5′), 7.11 (2 H, d, J = 8.8, H-2′ and H-6′), 7.70 (2 H, dd, J = 5.4 and 5.6, phthalimide H), 7.82 (2 H, dd, J = 5.4 and 5.6, phthalimide H). δ_C 45.4 (CH_2), 55.5 (OCH_3), 56.4 (2 × OCH_3), 61.3 (OCH_3), 106.2, 113.9, 125.6, 128.7, 129.5, 130.7, 131.9, 133 7, 134.3, 134.6, 137.8, 153.6 (CH and C), 158.9, 168.3 (C=O). *m/z* (EI) 460 [$(M + H)^+$ 100%]. (Found: M^+, 459.1681; C, 70.4; H, 5.7; N, 3.1. $C_{27}H_{25}NO_6$ requires M^+, 459.1681; C, 70.5; H, 5.5; N, 3.1%).

5.1.9. E-*2-(4′-Methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)allylamine (**17**)*

A solution of phthalimide **16** (1.69 g, 3.68 mmol) and hydrazine hydrate (4.00 g, 12.14 mmol) in ethanol (25 ml) was heated at 100 °C for 1.25 h The solid phthalimide by-product formed was removed by filtration and the solution remaining was washed with ethanol, concentrated and refiltered. Evaporation of the solvent afforded the amine **17** (857 mg, 71%) as a yellow oily solid. R_f 0.12 (MeOH/EtOAc 1:9). ν_{max} 3378 (m, NH), 1605 (s, C=C), 1506 (s, C=C), 1242 (s, CN). δ_H (DMSO-d_6) 3.44 (2 H, d, J = 1.6, CH_2), 3.46 (6 H, s, 2 × OCH_3), 3.57 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), 6.22 (2 H, s, H-2″ and H-6″), 6.50 (1 H, d, J = 1.6, C=CH), 6.95 (2 H, d, J = 8.7, H-3′ and H-5′), 7.05 (2 H, d, J = 8.7, H-2′ and H-6′). δ_C 50.7 (CH_2), 55.0 (OCH_3), 56.5 (2 × OCH_3), 106.0, 114.0, 125.6, 129.7, 130.5, 135.7, 137.4, 153.9, 158.5 (CH and C). *m/z* (EI) 329 [$(M)^+$ 40%]. (Found M^+, 329.1624. $C_{19}H_{23}NO_4$ requires M^+, 329.1627).

5.1.10. E-N-*[2-(4-Methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)allyl]acetamide (**18**)*

Procedure A: To a solution of aminostilbene **17** (158 mg, 0.480 mmol) and pyridine (2.4 mmol) in chloroform (15 ml) was added acetyl chloride (41 μl, 0.576 mmol. After stirring for 1 h the solution was washed with aqueous hydrochloric acid (0.1 M, 2 × 30 ml), water (10 ml) and brine (10 ml). After drying ($MgSO_4$) and removal of the solvent the followed by purification by flash column chromatography (petroleum ether/EtOAc 1:1) the target compound **18** was isolated as a brown oil (100 mg, 56%). R_f 0.24 (petroleum ether/EtOAc 1:2); ν_{max} (neat) 3294 (s, NH), 2938 (s), 1663 (s, C=O), 1581 (s), 1513 (s), 1416 (s), 1243 (s), 1123 (s). δ_H 1.95 (3 H, s, CH_3), 3.56 (6 H, s, 2 × OCH_3), 3.77 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 4.23 (2 H, d, J = 5.7, CH_2), 5.51 (1 H, t J = 5.7, NH), 6.21 (2 H, s, H-2′ and H-6′), 6.46 (1 H, s, C=CH), 6.88 (2 H, d, J = 8.8, H-3″ and H-5″), 7.15 (2 H, d, J = 8.8, H-2″and H-6″). δ_C 23.6 (CH_3), 47.7 (CH_2), 55.7 (OCH_3), 56.0 (2 × OCH_3), 61.2 (OCH_3), 106.7 (CH), 114.4 (CH), 127.9 (CH), 130.4 (CH), 131.1, 132.3, 137.2, 137.9, 153.2, 159.5, 170.3 (C=O) ppm. *m/z* (EI) 372 [$(M+H)^+$, 25%]. (Found: M^+, 371.1726. $C_{21}H_{25}NO_5$ requires M^+, 371.1727).

5.1.11. E-N-*[2-(4′-Methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)allyl]propionamide (**19**)*

Prepared according to procedure A from amine **17** (60 mg, 0.18 mmol) and propionyl chloride (19 μl, 0.22 mmol). Purification by flash column chromatography (petroleum ether/EtOAc 1:1) provided the title amide **19** as a cream solid (48 mg, 69%). M.p. 115–117 °C. R_f 0.2 (petroleum ether/EtOAc 1:1). ν_{max} 3295 (b, NH), 1642 (s, C=O), 1510 (s, C=C), 1245 (s, CN). δ_H 1.10 (3 H, t, J = 7.6, CH_3), 2.16 (2 H, q, J = 7.6, CH_2CH_3), 3.57 (6 H, s, 2 × OCH_3), 3.78 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 4.26 (2 H, dd, J = 5.7 and 1.2, CH_2), 5.49 (1 H, s, NH), 6.22 (2 H, s, H-2″ and H-6″), 6.45 (1 H, d, J = 1.2, C=CH), 6.88 (2 H, d, J = 8.8, H-3′ and H-5′), 7.15 (2H, d, J = 8.8, H-2′ and H-6′). δ_C 10.4 (CH_3), 30.1 (CH_2), 47.2 (CH_2), 55.5 (OCH_3), 56.1 (2 × OCH_3), 61.2 (OCH_3), 106.8, 114.7, 127.6, 130.5, 131.2, 132.4, 137.4, 138.1, 152.9, 159.5 (CH and C), 173.8 (C=O). *m/z* (EI) 386 [$(M + H)^+$, 100%]. (Found: M^+ 385.1893. $C_{22}H_{27}NO_5$ requires M^+ 385.1889).

5.1.12. E-N-*[2-(4′-Methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenylallyl]-2,2-dimethyl-propionamide (**20**)*

Prepared according to procedure A from amine **17** (60 mg, 0.18 mmol) and trimethylacetyl chloride (27 μl, 0.22 mmol). Purification by flash column chromatography (petroleum ether/EtOAc 2:1) provided the title amide **20** as a cream coloured solid (51 mg, 67%). M.p. 96–97 °C. R_f 0.41 (petroleum ether/EtOAc 1:1). ν_{max} 3352 (b, NH), 1645 (s, C=O), 1510 (s, C=C). δ_H 1.10 (12 H, s, 3 × CH_3), 3.57 (6 H, s, 2 × OCH_3), 3.78 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 4.24 (2 H, dd, J = 5.7 and 1.2, CH_2), 5.39 (1 H, t, J = 5.7, NH), 6.23 (2 H, s, H-2″ and H-6″), 6.45 (1 H, d, J = 1.2, C=CH), 6.88 (2 H, d, J = 8.8, H-3′ and H-5′), 7.14 (2 H, d, J = 8.8, H-2′ and H-6′). δ_C 27.9 (CH_3), 39.1 (CH_2), 55.7 (OCH_3), 56.1 (2 × OCH_3), 61.2 (OCH_3), 98.5, 106.8, 114.7, 130.5, 131.2, 132.3, 152.9, 159.5 (CH and C), 173.5 (C=O). *m/z* (EI) 414 [$(M + H)^+$, 100%]. (Found: M^+ 413.2199; C, 69.8; H, 7.6; 3.7. $C_{24}H_{31}NO_5$ requires M^+ 413.2202; C, 69.7; 7.5; 3.4%).

5.1.13. E-*2-Chloro*-N-*[2-(4′-methoxyphenyl)-3-(3″,4″,5″-trimethoxy-phenyl)-allyl]-acetamide (**21**)*

Prepared according to procedure A from amine **17** (60 mg, 0.18 mmol) and chloroacetyl chloride (17 μl, 0.22 mmol). Purification by flash column chromatography (petroleum ether/EtOAc 2:1) provided the title amide **21** as a pale yellow solid (18 mg, 24%). M.p. 115–117 °C. R_f 0.35 (petroleum ether/EtOAc 1:1). ν_{max} 3309 (b, NH), 1665 (s, C=O), 1511 (s, C=C), 1244 (s, CN), 733 (w, CCl). δ_H 3.57 (6 H, s, 2 × OCH_3), 3.78 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 4.03 (2 H, s, CH_2Cl), 4.28 (2 H, d, J = 5.7, CH_2), 6.23 (2 H, s, H-2″ and H-6″), 6.48 (1 H, s, C=CH), 6.68 (1 H, t, J = 5.7, NH), 6.89 (2 H, d, J = 8.7, H-3′ and H-5′), 7.16 (2 H, d, J = 8.7, H-2′ and H-6′). δ_C 35.1 (CH_2), 47.2 (CH_2), 55.7 (OCH_3), 56.1 (2 × OCH_3), 61.2 (OCH_3), 100.0, 106.8, 114.7, 130.8, 131.2, 132.4, 137.4, 138.1, 152.9, 159.5, 166.0 (CH and C), 173.5 (C=O). *m/z* (EI) 406 [$(M + H)^+$, 100%]. (Found: M^+ 405.1342; C, 62.0; H, 6.1; N, 3.5. $C_{21}H_{24}ClNO_5$ requires M^+ 405.1343; C, 62.0; H, 5.9; N, 3.5%).

5.1.14. E-*2-(4-Chlorophenyl)*-N-*[2-(4′-methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)-allyl]acetamide (**22**)*

Prepared according to procedure A from amine **17** (86 mg, 0.26 mmol) and 4-chlorophenylacetyl chloride (60 mg, 0.31 mmol). Purification by flash column chromatography (petroleum ether/EtOAc 1:1) provided amide **22** as a yellow solid (84 mg, 67%). M.p. 128–130 °C. R_f 0.22 (petroleum ether/EtOAc 1:1). ν_{max} 3292 (b, NH), 1648 (s, C=O), 1509 (s, C=C), 1244 (s, CN). δ_H 3.47 (2 H, CH_2Ar), 3.55 (6 H, s, 2 × OCH_3), 3.77 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 4.22 (2 H, d, J = 5.4, CH_2), 5.35 (1 H, t, J = 5.4, NH), 6.17 (2 H, s,

H-2″ and H-6″), 6.36 (1 H, s, C=CH), 6.83 (2 H, d, J = 8.7, H-3′ and H-5′), 7.01 (2 H, d, J = 8.2, H-2, and H-6), 7.02 (2 H, d, J = 8.7, H-2′ and H-6′), 7.23 (2 H, d, J = 8.2, H-3 and H-5). δ_C 42.8 (CH_2), 46.9 (CH_2), 55.3 (OCH_3), 56.1 (2 × OCH_3), 60.5 (OCH_3), 99.3, 106.0, 113.9, 127.2, 128.7, 129.6, 130.3, 131.4, 136.9, 152.2, 158.8 (CH and C), 169.7 (C=O). *m/z* (EI) 482 [(M + H)$^+$, 100%]. (Found: M$^+$ 481.1664; C, 67.2; H, 6.2; N, 3.2; Cl, 7.2. $C_{27}H_{28}ClNO_5$ requires M$^+$ 481.1656; C, 67.2; H, 5.8; N, 2.9; Cl, 7.3%).

5.1.15. E-N-*[2-(4′-Methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)allyl]isobutyramide (**23**)*

Procedure B: To a solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (35 mg, 0.18 mmol), 1-hydroxybenzotriazole (25 mg, 0.18 mmol) and isobutyric acid (17 μl, 0.18 mmol) in DMF, amine **17** (60 mg, 0.18 mmol) and *N*-ethyldiisopropylamine (95 μl, 0.55 mmol) were added. The solution was stirred overnight, ethyl acetate (10 ml) added and washed with water (10 ml), hydrochloric acid (0.1 M, 10 ml) and saturated sodium bicarbonate solution (10 ml). The organics were dried over magnesium sulphate and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether/EtOAc 1:1) gave amide **23** as a cream coloured solid (49 mg, 67%). M.p. 122–124 °C. R_f 0.28 (petroleum ether/EtOAc 1:1). ν_{max} 3307 (b, NH), 1657 (s, C=O), 1601 (s, C=C), 1245 (s, CN). λ_{max} = 278 (ϵ = 9380). δ_H 1.06 (6 H, d, J = 6.9, 2 × CH_3), 2.29 (1 H, septet, J = 6.9, CH), 3.57 (6 H, s, 2 × OCH_3), 3.74 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 4.25 (2 H, dd, J = 5.7 and 1.2, CH_2), 5.53 (1 H, t, J = 5.7, NH), 6.22 (2 H, s, H-2″ and H-6″), 6.46 (1 H, d, J = 1.2, C=CH), 6.87 (2 H, d, J = 8.8, H-3′ and H-5′), 7.14 (2 H, d, J = 8.8, H-2′ and H-6′). δ_C 19.9 (3 × CH_3), 36.1 (CH), 47.5 (CH_2), 55.7 (OCH_3), 56.2 (2 × OCH_3), 61.2 (OCH_3), 106.9, 112.0, 114.7, 127.3, 128.0, 130.5, 131.1, 132.3, 137.4, 138.2, 152.9, 159.5 (CH and C), 177.3 (C=O). *m/z* (EI) 400 [(M + H)$^+$, 100%]. (Found: M$^+$ 399.2044. $C_{23}H_{29}NO_5$ requires M$^+$ 399.2046).

5.1.16. E-N-*[2-(4′-Methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)allyl]butyramide (**24**)*

Prepared according to procedure B from amine **17** (60 mg, 0.18 mmol) and butyric acid (17 μl, 0.18 mmol). Purification by flash column chromatography (petroleum ether/EtOAc 1:1) gave amide **24** as a yellow crystalline solid (55 mg, 75%). M.p. 79–80 °C. R_f 0.18 (petroleum ether/EtOAc 1:1). ν_{max} 3287 (b, NH), 1650 (s, C=O), 1510 (s, C=C), 1245 (s, CN). δ_H 0.87 (3 H, t, J = 7.4, CH_3), 1.58 (2 H, m, CH_2CH_3), 2.11 (2 H, t, J = 7.5, $COCH_2$), 3.57 (6 H, s, 2 × OCH_3), 3.78 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 4.26 (2 H, dd, J = 5.7 and 1.2, CH_2), 5.52 (1 H, t, J = 5.7, NH), 6.22 (2 H, s, H-2″ and H-6″), 6.45 (1 H, d, J = 1.2, C=CH), 6.87 (2 H, d, J = 8.7, H-3′ and H-5′), 7.15 (2 H, d, J = 8.7, H-2′ and H-6′). δ_C19.7 (CH_3), 39.3 (CH_2), 43.5 (CH_2), 55.5 (OCH_3), 56.2 (2 × OCH_3), 61.2 (OCH_3), 100.2, 107.0, 114.7, 127.8, 128.0, 130.4, 138.1, 152.9, 155.5 (CH and C), 173.3 (C=O). *m/z* (EI) 400 [(M + H)$^+$, 100%]. (Found: M$^+$ 399.2046. $C_{23}H_{29}NO_5$ requires M$^+$ 399.2046).

5.1.17. E-*3,3,3-Trifluoro*-N-*[2-(4′-methoxyphenyl)-3-(3″,4″,5″-trimethoxyphenyl)allyl]propionamide (**25**)*

Prepared according to procedure B from amine **17** (90 mg, 0.27 mmol) and 3,3,3-trifluoropropionic acid (24 μl, 0.27 mmol). Purification by flash column chromatography (petroleum ether/EtOAc 2:1) gave amide **25** as a cream coloured solid (39 mg, 49%). M.p. 132–135 °C. R_f 0.45 (petroleum ether/EtOAc 1:1). ν_{max} 3309 (b, NH), 1665 (s, C=O), 1510 (s, C=C), 1243 (s, CN), 665 (m, CF). δ_H 3.57 (6 H, s, 2 × OCH_3), 3.78 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.86 (2 H, s, CH_2), 4.30 (2 H, dd, J = 5.9 and 1.2, CH_2), 5.82 (1 H, t, J = 5.9, NH), 6.22 (2 H, s, H-2″ and H-6″), 6.48 (1 H, d, J = 1.2, C=CH), 6.88 (2 H, d, J = 8.9, H-3′ and H-5′), 7.15 (2 H, d, J = 8.9, H-2′ and H-6′). δ_C 13.8 (CF_3), 20.4 (CH_2), 47.2 (CH_2), 55.5 (OCH_3), 56.1 (2 × OCH_3), 61.3 (OCH_3), 127.9, 128.5, 130.5, 130.6, 132.0, 136.9, 152.9. *m/z* (EI) 440 [(M+H)$^+$, 100%]. (Found: M$^+$ 439.1893; C, 60.2; H, 5.8; N, 3.4; F, 12.6%. $C_{22}H_{24}F_3NO_5$ requires M$^+$ 439.1889; C, 60.1; H, 5.5; N, 3.2; F, 12.9%).

5.1.18. E-N-*[3-(4′-Methoxyphenyl)-2-(3″,4″,5″-trimethoxyphenyl)allyl]acetamide (**27**)*

Acetamide **27** was prepared according to procedure A from amine **26** [21] (110 mg, 0.33 mmol) and acetyl chloride (24 μl, 0.33 mmol) as a cream coloured solid (25 mg, 20%) from diethyl ether. Product decomposition before m.p. reached. R_f 0.23 (petroleum ether/EtOAc 1:1). 3294 (b, NH), 1652 (s, C=O), 1510 (s, C=C), 1249 (s, CN), 1032 (m, CN). δ_H 1.98 (3 H, s, CH_3), 3.71 (6 H, s, 2 × OCH_3), 3.75 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 4.25 (2 H, d, J = 5.7 Hz, CH_2), 5.48 (1 H, t, J = 5.7, NH), 6.38 (2 H, s, H-2″ and H-6″), 6.45 (1 H, s, C=CH), 6.68 (2 H, d, J = 8.8, H-3′ and H-5′), 6.92 (2 H, d, J = 8.8, H-2′ and H-6′). δ_C 23.8 (CH_3), 47.5 (CH_2), 55.6 (OCH_3), 56.5 (2 × OCH_3), 61.3 (OCH_3), 106.2, 114.1, 127.8, 129.2, 130.8, 134.4, 136.4, 137.8, 153.7, 158.9 (CH and C), 170.2 (C=O). *m/z* (EI) 371 [(M)$^+$ 100%]. (Found M$^+$, 371.1736. $C_{21}H_{25}NO_5$ requires M$^+$, 371.1733).

5.1.19. E-N-*[3-(4′-Methoxyphenyl)-2-(3″,4″,5″-trimethoxyphenyl)allyl]propionamide (**28**)*

Prepared according to procedure A from amine **26** (60 mg, 0.18 mmol) and propionyl chloride (21 μl, 0.24 mmol). Recrystallisation from ethanol yielded the title amide **28** as a white solid (18 mg, 26%). M.p. 141–144 °C. R_f 0.13 (petroleum ether/EtOAc 1:1). ν_{max} 3307 (b, NH), 1647 (s, C=O), 1510 (s, C=C), 1249 (s, CN), 1032 (m, CN). δ_H 1.10 (3 H, t, J = 7.6, CH_3), 2.17 (2 H, q, J = 7.6, CH_2CH_3), 3.73 (6 H, s, 2 × OCH_3), 3.78 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 4.27 (2 H, dd, J = 5.7 and 1.2, CH_2), 5.48 (1 H, t, J = 5.7, NH), 6.42 (2 H, s, H-2″ and H-6″), 6.49 (1 H, s, C=CH), 6.68 (2 H, d, J = 8.7, H-3′ and H-5′), 6.95 (2 H, d, J = 8.7, H-2′ and H-6′). δ_C 10.3 (CH_3), 30.2 (CH_2), 47.3 (CH_2), 55.5 (OCH_3), 56.5 (2 × OCH_3), 61.3 (OCH_3), 106.2, 113.8, 127.6, 129.3, 130.8, 134.4, 136.6, 137.8, 153.8, 158.9 (CH and C), 173.8 (C=O). *m/z* (EI) 386 [(M+H)$^+$, 100%]. (Found: M$^+$ 385.1887; C, 68.4; H, 7.2; N, 3.6. $C_{22}H_{27}NO_5$ requires M$^+$ 385.1889; C, 68.4; H, 7.0; N, 3.6%).

5.1.20. E-N-*[3′-(4-Methoxyphenyl)-2-(3″,4″,5″-trimethoxyphenyl)-2,2-dimethyl-propionamide (**29**)*

Prepared according to procedure A from amine **26** (60 mg, 0.18 mmol) and trimethylacetyl chloride (29 μl, 0.24 mmol). Flash column chromatography (petroleum ether/EtOAc 2:1) provided the title amide **29** as a pale yellow solid (38 mg, 50%). M.p. 128–129 °C. R_f 0.27 (petroleum ether/EtOAc 2:1). ν_{max} 3355 (b, NH), 1645 (s, C=O), 1510 (s, C=C), 1249 (s, CN), 1030 (m, CN). δ_H 1.10 (12 H, s, 3 × CH_3), 3.73 (6 H, s, 2 × OCH_3), 3.78 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 4.26 (2 H, dd, J = 5.9 and 0.9, CH_2), 5.67 (1 H, t, J = 5.9, NH), 6.42 (2 H, s, H-2″ and H-6″), 6.47 (1 H, d, J = 0.9, C=CH), 6.68 (2 H, d, J = 8.7, H-3′ and H-5′), 6.96 (2 H, d, J = 8.7, H-2′ and H-6′). δ_C 27.9 (CH_3), 39.1 (CH_2), 55.6 (OCH_3), 56.5 (2 × OCH_3), 61.4 (OCH_3), 100.0, 106.2, 113.8, 127.3, 129.3, 130.8, 134.5, 137.1, 153.9, 159.9 (CH and C), 178.4 (C=O). *m/z* (EI) 414 [(M + H)$^+$, 100%]. (Found: M$^+$ 413.2207; C, 69.4; H, 7.7; N, 3.4%. $C_{24}H_{31}NO_5$ requires M$^+$ 413.2202; C, 69.6; H, 7.5; N, 3.4%).

5.1.21. E-*2-Chloro*-N-*[3-(4′-methoxyphenyl)-2-(3″,4″,5″-trimethoxyphenyl)-allyl]acetamide (**30**)*

Prepared according to procedure A from amine **26** (56 mg, 0.17 mmol) and chloroacetyl chloride (20 μl, 0.22 mmol). Flash column chromatography (petroleum ether/EtOAc 2:1) provided the title amide **30** as pale yellow crystals (18 mg, 25%). M.p. 120–121 °C. R_f 0.36 (petroleum ether/EtOAc 1:1). ν_{max} 3316 (b, NH), 1671 (s, C=O), 1509 (s, C=C), 1250 (s, CN), 736 (w, CCl). δ_H 3.75 (6 H, s, 2 × OCH_3), 3.78 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.04 (2 H, s, CH_2Cl), 4.28 (2 H, d, J = 5.4, CH_2), 5.34 (1 H, t, J = 5.4, NH), 6.41 (2 H, s, H-2″ and H-6″), 6.52 (1 H, s, C=CH), 6.68 (2 H, d, J = 8.7, H-3′ and H-5′), 6.95 (2 H, d, J = 8.7, H-2′ and H-6′). δ_C 43.0 (CH_2), 47.8 (CH_2), 55.5 (OCH_3), 56.4 (2 × OCH_3), 61.3 (OCH_3), 105.9, 113.8, 128.3, 128.8, 130.7, 135.5, 154.0, 159.0, 165.9 (CH and C), 173.5 (C=O). *m/z* (EI) 406 [(M + H)$^+$, 50%]. (Found M$^+$ 405.1346; C, 62.0; H, 6.2; N, 3.4. $C_{21}H_{24}ClNO_5$ requires M$^+$ 405.1343; C, 62.0; H, 5.9; N, 3.4%).

5.1.22. E-N-*[3-(4′-Methoxyphenyl)-2-(3″,4″,5″-trimethoxyphenyl)allyl]benzamide (**31**)*

Prepared according to procedure A from amine **26** (56 mg, 0.17 mmol) and benzoyl chloride (28 μl, 0.22 mmol). Flash column chromatography (petroleum ether/EtOAc 2:1) provided the title amide **31** as a yellow solid (51 mg, 32%). M.p. 147–149 °C. R_f 0.48 (petroleum ether/EtOAc 1:1). ν_{max} 3325 (b, NH), 1640 (m, C=O), 1510 (s, C=C), 1249 (s, CN). λ_{max} 270 (ϵ = 15,900). δ_H 3.71 (6 H, s, 2 × OCH_3), 3.75 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 4.47 (2 H, d, J = 5.9, CH_2), 6.18 (1 H, t, J = 5.9, NH), 6.47 (2 H, s, H-2″ and H-6″), 6.59 (1 H, s, C=CH), 6.69 (2 H, d, J = 8.8, H-3′ and H-5′), 6.96 (2 H, d, J = 8.8, H-2′ and H-6′), 7.41 (2 H, dd, J = 7.1 and 7.5, H-3 and H-5), 7.49 (1 H, t, J = 7.5, H-4), 7.67 (2 H, d, J = 7.1, H-2 and H-6). δ_C 48.0 (CH_2), 55.6 (OCH_3), 56.5 (2 × OCH_3), 61.4 (OCH_3), 106.2, 113.8, 127.2, 128.0, 129.0, 129.2, 130.8, 131.9, 134.5, 135.0, 136.4, 154.0, 159.0 (CH and C), 167.7 (C=O). *m/z* (EI) 434 [(M + H)$^+$, 100%]. (Found M$^+$ 433.1892; C, 72.1; H, 6.3; N, 3.1. $C_{26}H_{27}NO_5$ requires M$^+$ 433.1889; C, 72.0; H, 6.2; N, 3.2%).

5.1.23. E-*2-(4-Chlorophenyl)*-N-*[3-(4′-methoxyphenyl)-2-(3″,4″,5″-trimethoxyphenyl)-allyl]acetamide (**32**)*

Prepared according to procedure A from amine **26** (60 mg, 0.18 mmol) and 4-chlorophenylacetyl chloride (34 mg, 0.22 mmol). Recrystallisation from ethanol afforded the title amide **32** as a white solid (30 mg, 35%). M.p. 114–116 °C. R_f 0.41 (petroleum ether/EtOAc 1:1). ν_{max} 3292 (b, NH), 1647 (s, C=O), 1509 (s, C=C), 1250 (s, CN), 1016 (m, CN), 735 (m, CCl). δ_H 3.47 (2 H, CH_2Ar), 3.69 (6 H, s, 2 × OCH_3), 3.74 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 4.24 (2 H, d, J = 5.4, CH_2), 5.34 (1 H, t, J = 5.4, NH), 6.31 (2 H, s, H-2″ and H-6″), 6.38 (1 H, s, C=CH), 6.66 (2 H, d, J = 8.9, H-3′ and H-5′), 6.90 (2 H, d, J = 8.9, H-2′ and H-6′), 6.99 (2 H, d, J = 8.5, H-2 and H-6), 7.23 (2 H, d, J = 8.5, H-3 and H-5). δ_C 43.5 (CH_2), 47.5 (CH_2), 55.6 (OCH_3), 56.5 (2 × OCH_3), 61.4 (OCH_3), 99.4, 106.1, 113.8, 127.8, 129.0, 129.4, 130.8, 131.1, 133.5, 136.1, 153.9, 159.0 (CH and C), 170.5 (C=O). *m/z* (EI) 482 [(M + H)$^+$, 100%]. (Found: M$^+$ 481.1653; C, 67.2; H, 5.8; N, 2.9; Cl, 7.5. $C_{27}H_{28}ClNO_5$ requires M$^+$ 481.1656, C, 67.2; H, 5.8; N, 2.9; Cl, 7.4%).

*5.1.24. 1-(3′-*t*-Butyldimethylsilyloxy-4′-methoxyphenyl)propene (**33**)*

Potassium bis(trimethylsilyl)amide (34 ml of 0.5 M solution in toluene, 17 mmol) was added to ethyltriphenylphosphonium bromide (6.31 g, 17 mmol) in THF (150 ml) under argon at 0 °C. The mixture was stirred at 0 °C for 2 h, cooled to –78 °C and 3-*t*-butyldimethylsilyloxy-4-methoxybenzaldehyde **10** (2.74 g, 17 mmol) added. The resulting mixture was stirred at –78 °C for 2 h and allowed to warm to room temperature. Water (50 ml) was carefully added and the aqueous layer separated and extracted with ether (3 × 50 ml). The combined organic layers were washed with water (2 × 50 ml), brine (50 ml), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (petroleum ether/EtOAc 9:1) afforded a mixture of the two isomers, **33Z** and **33E**, as a colourless oil (2.88 g, 63%). R_f 0.76 (petroleum ether/EtOAc 8:3). δ_H (300 MHz) 0.17 [6 H, s, $(CH_3)_2$ **33E**], 0.18 [6 H, s, $(CH_3)_2$ **33Z**], 1.01 [9H, s $(CH_3)_3$ **33E**], 1.02 [9H, s $(CH_3)_3$ **33Z**], 1.86 (3 H, dd, J = 6.4, 1.5, CH_3 **33E**), 1.91 (3 H, dd, J = 6.4, 1.5, CH_3 **33Z**), 3.80 (3 H, s, OCH_3 **33E**), 3.83 (3 H, s, OCH_3 **33Z**), 5.70 (1 H, dq, J = 12.1, 6.4, olefinic H **33Z**), 6.07 (1 H, dq, J = 16.1, 6.4, olefinic H **33E**), 6.27 (1 H, dd, J = 16.1, 1.5, olefinic H **33E**), 6.34 (1 H, dd, J = 12.1, 1.5, olefinic H **33Z**), 6.85–7.24 (6 H, m, H-2′,5′,6′ **33Z** and **33E**). Ratio **33Z/33E**, 15:1. *m/z* (FAB) 279 [(MH)$^+$, 20%], 73 {[$C(CH_3)_3H$]$^+$ 100%}. (Found: (MH)$^+$ 279.1774. $C_{16}H_{26}O_2Si$ requires (MH)$^+$ 279.1780).

*5.1.25. 1-(3′-Hydroxy-4′-methoxyphenyl)propene (**34**)*

Phenols **34Z** and **34E** were prepared from the TBDMS ethers, **34Z** and **34E**, (1 g, 3.6 mmol) as in the procedure

described for phenol **12**. Flash column chromatography (petroleum ether/EtOAc 4:1) afforded the mixture of the two isomers (**34Z** and **34E**) as a colourless oil (381 mg, 65%). R_f 0.80 (petroleum ether/EtOAc 1:1). δ_H (300 MHz) 1.87 (3 H, dd, J = 6.4, 1.5, CH_3 **34E**), 1.92 (3 H, dd, J = 6.4, 1.5, CH_3 **34Z**), 3.90 (3 H, s, OCH_3 **34E**), 3.92 (3 H, s, OCH_3 **34Z**), 5.58 (1 H, d, J = 1.1, OH **34E**), 5.60 (1 H, d, J = 1.1, OH **34Z**), 5.72 (1 H, dq, J = 12.1, 6.4, olefinic H **34Z**), 6.11 (1 H, dq, J = 16.1, 6.4, olefinic H **34E**), 6.29 (1 H, dd, J = 16.1, 1.5, olefinic H **34E**), 6.35 (1 H, dd, J = 12.1, 1.5, olefinic H **34Z**), 6.83 (4 H, m, H-5′,6′ **34Z** and **34E**), 6.95 (2 H, d, J = 1.9, H-2′ **34Z**), 6.98 (2 H, d, J = 1.9, H-2′ **34E**); Ratio **34Z/34E**, 16:1. m/z (FAB) 164 (M^+, 100%). (Found: M^+ 164.0839. $C_{10}H_{12}O_2$ requires M^+ 164.0837).

5.1.26. Z- and E-*2-(3′,4′,5′-Trimethoxyphenyl)-3-(3″-t-butyldimethylsilyloxy-4″-methoxyphenyl)prop-2-ene (**35**, **39**)*

To a slurry of phosphonium bromide **37** [23] (1 g, 1.69 mmol) in THF (15 ml) under argon was added *n*-butyllithium (1.25 ml of 1.6 M solution, 2 mmol) at –15 °C. The resulting red anion was stirred for 20 min and 3,4,5-trimethoxyacetophenone (**38**) (355 mg, 1.69 mmol) added. The resultant solution was stirred at room temperature for 1 h and water (5 ml) carefully added. The aqueous layer was separated and extracted with ether (3 × 10 ml). The combined organic layers were washed with water (2 × 10 ml), brine (10 ml), dried ($MgSO_4$) and concentrated in vacuo. Following flash column chromatography (petroleum ether/EtOAc 19:1), *Z* stilbene **35** was isolated as a colourless oil (109 mg, 15%). R_f 0.72 (petroleum ether/EtOAc 1:1). λ_{max} (MeOH) 270 (ϵ = 7607). δ_H (300 MHz) 0.01 [6 H, s, $(CH_3)_2$], 0.92 [9 H, s, $(CH_3)_3$], 2.17 (3 H, d, J = 1.5, CH_3), 3.75 [6 H, s, $(OCH_3)_2$], 3.76 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 6.35 (1 H, d, J = 1.5, olefinic H), 6.42 (2 H, s, H-2′,6′) 6.52 (1 H, d, J = 1.9, H-2″), 6.62 (1 H, dd, J = 8.3, 1.9, H-6″), 6.67 (1 H, d, J = 8.3, H-5″); δ_C (100 MHz) –4.5 (CH_3), 18.6 (C), 26.0 (CH_3), 27.6 (CH_3), 55.8 (CH_3), 56.4 (CH_3), 61.2 (CH_3), 105.4 (CH), 111.8 (CH), 121.4 (CH), 123.1 (CH), 126.4 (CH), 130.9 (C), 137.1 (C), 137.2 (C), 138.4 (C), 144.7 (C), 150.4 (C), 153.6 (C). m/z (FAB) 445 [(MH^+), 40%], 73 (100%). (Found: M^+ 444.2329; C, 67.3; H, 8.4. $C_{25}H_{36}O_5Si$ requires M^+ 444.2332; C, 67.5; H, 8.2%). Further elution afforded *E* stilbene **39** as a colourless oil (258 mg, 34%). R_f 0.67 (petroleum ether/EtOAc 1:1). λ_{max} (MeOH) = 296 (ϵ = 16,541). δ_H (300 MHz) 0.20 [6 H, s, $(CH_3)_2$], 1.03 [9 H, s, $(CH_3)_3$], 2.28 (3 H, d, J = 1.1, CH_3), 3.85 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 3.93 [6 H, s, $(OCH_3)_2$], 6.69 (1 H, d, J = 1.1, olefinic H), 6.72 (2 H, s, H-2′,6′) 6.87 (1 H, d, J = 8.3, H-5″), 6.91 (1 H, d, J = 2.3, H-2″), 6.95 (1 H, dd, J = 8.3, 2.3, H-6″); δ_C (100 MHz) –4.2 (CH_3), 18.3 (CH_3), 18.9 (C), 26.2 (CH_3), 55.9 (CH_3), 56.6 (CH_3), 61.3 (CH_3), 103.7 (CH), 112.1 (CH), 122.2 (CH), 123.3 (CH), 127.6 (CH), 131.6 (C), 136.4 (C), 137.6 (C), 140.7 (C), 144.9 (C), 150.2 (C), 153.4 (C). m/z (FAB) 445 [(MH^+), 20%], 73 (100%). (Found: M^+ 444.2333; C, 67.3; H, 8.4. $C_{25}H_{36}O_5Si$ requires M^+ 444.2332; C, 67.5; H, 8.2%).

*5.1.27. Z-2-(3′,4′,5′-Trimethoxyphenyl)-3-(3″-hydroxy-4″-methoxyphenyl)prop-2-ene (**36**)*

Z-Phenol **36** was prepared from TBDMS ether **35** (111 mg, 0.250 mmol) by the method used to make phenol **12** from silylether **11**. Flash column chromatography (petroleum ether/EtOAc 2:1) and recrystallisation from EtOAc afforded phenol **36** as a fine white powder (49 mg, 60%). M.p. 156–158 °C. R_f 0.36 (petroleum ether/EtOAc 2:1). λ_{max} (MeOH) 270 (ϵ = 11,524). δ_H (300 MHz) 2.18 (3 H, d, J = 1.5, CH_3), 3.75 [6 H, s, $(OCH_3)_2$], 3.84 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 5.42 (1 H, s, OH), 6.36 (1 H, d, J = 1.5, olefinic H), 6.43 (2 H, s, H-2′,6′) 6.48 (1 H, dd, J = 8.3, 2.3, H-6″), 6.62 (1 H, d, J = 8.3, H-5″), 6.63 (1 H, d, J = 2.3, H-2″); δ_C (100 MHz) 27.4 (CH_3), 56.3 (CH_3), 56.5 (CH_3), 61.4 (CH_3), 105.7 (CH), 110.5 (CH), 115.4 (CH), 121.3 (CH), 126.4 (CH), 131.5 (C), 137.3 (C), 137.4 (C), 138.0 (C), 145.3 (C), 145.5 (C), 153.6 (C). m/z (FAB) 330 (M^+, 95%). (Found: M^+ 330.1469; C, 68.9; H, 7.0. $C_{19}H_{22}O_5$ requires M^+ 330.1467 C, 69.1; H, 6.7%).

5.1.28. E-*2-(3′,4′,5′-Trimethoxyphenyl)-3-(3″-hydroxy-4″-methoxyphenyl)-prop-2-ene (**40**)*

E-Phenol **40** was prepared from TBDMS ether **39** (156 mg, 0.351 mmol) by the method used to make phenol **12**. Flash column chromatography (petroleum ether/EtOAc 2:1) and recrystallisation from EtOAc afforded phenol **40** as a white solid (106 mg, 91%). M.p. 116–117 °C. R_f 0.36 (petroleum ether/EtOAc 2:1). λ_{max} (MeOH) 290 (ϵ = 21,161). δ_H (400 MHz, acetone-d_6) 2.28 (3 H, d, J = 1.5, CH_3), 3.76 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 3.90 [6 H, s, $(OCH_3)_2$], 6.79 (1 H, d, J = 1.5, olefinic H), 6.85 (2 H, s, H-2′,6′), 6.87 (1 H, dd, J = 8.0, 2.0, H-6″), 6.93 (1 H, d, J = 2.0, H-2″), 6.93 (1 H, d, J = 8.0, H-5″); δ_C (100 MHz) 18.2 (CH_3), 56.4 (CH_3), 56.6 (CH_3), 61.3 (CH_3), 103.8 (CH), 110.8 (CH), 115.7 (CH), 121.7 (CH), 127.5 (CH), 132.1 (C), 136.8 (C), 137.8 (C), 140.6 (C), 145.6 (C), 145.7 (C), 153.4 (C). m/z (FAB) 330 (M^+, 65%). (Found: M^+ 330.1472; C, 69.1; H, 6.7. $C_{19}H_{22}O_5$ requires M^+ 330.1467; C, 69.3; H, 6.7%).

5.1.29. Z- and E-*3-(3′,4′,5′-Trimethoxyphenyl)-4-(3′-t-butyldimethylsilyloxy-4′-methoxyphenyl)but-3-ene (**42**, **43**)*

The stilbenes **42** and **43** were prepared from phosphonium bromide **37** (2 g, 3.37 mmol) and 1-(3′,4′,5′-trimethoxyphenyl)propan-1-one (**41**) [12] (755 mg, 3.37 mmol) by the procedure described for ethers **35**, **39**. Following flash column chromatography (petroleum ether/EtOAc 19:1), *Z* stilbene **42** was isolated as a colourless oil (170 mg, 11%). R_f 0.35 (petroleum ether/EtOAc 17:3). δ_H (300 MHz) 0.024 [6 H, s, $(CH_3)_2$], 0.93 [9 H, s, $(CH_3)_3$], 1.09 (3 H, t, J = 7.5, CH_3), 2.46 (2 H, qd, J = 7.5, 1.5, CH_2), 3.75 (3 H, s, OCH_3), 3.76 [6 H, s, $(OCH_3)_2$], 3.88 (3 H, s, OCH_3), 6.30 (1 H, d, J = 1.5, olefinic H), 6.38 (2 H, s, H-2′,6′), 6.51 (1 H, d, J = 1.9, H-2″), 6.61 (1 H, dd, J = 8.3, 1.9, H-6″), 6.67 (1 H, d, J = 8.3, H-5″). m/z (FAB) 458 (M^+, 95%), 73 (100%). (Found: $(MH)^+$ 459.2564. $C_{26}H_{38}O_5Si$ requires $(MH)^+$ 459.2566). Further elution afforded *E* stilbene **43** as a colourless oil (392 mg,

25%). R_f 0.29 (petroleum ether/EtOAc 17:3). δ_H (300 MHz) 0.20 [6 H, s, $(CH_3)_2$], 1.03 [9 H, s, $(CH_3)_3$], 1.11 (3 H, t, J = 7.5, CH_3), 2.73 (2 H, q, J = 7.5, CH_2), 3.85 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 3.91 [6 H, s, $(OCH_3)_2$], 6.57 (1 H, s, olefinic H), 6.68 (2 H, s, H-2′,6′), 6.84–6.93 (3 H, m, H-2″,5″,6″); δ_C (100 MHz) –4.2 (CH_3), 13.9 (CH_3), 18.8 (C), 24.0 (CH_2), 26.2 (CH_3), 55.9 (CH_3), 56.5 (CH_3), 61.4 (CH_3), 104.2 (CH), 112.3 (CH), 121.7 (CH), 122.8 (CH), 127.4 (CH), 131.4 (C), 137.7 (C), 139.4 (C), 143.6 (C), 145.1 (C), 150.3 (C), 153.4 (C). *m/z* (FAB) 458 (M^+, 10%), 73 (100%). (Found: $(MH)^+$ 459.2558. $C_{26}H_{38}O_5Si$ requires $(MH)^+$ 459.2566).

*5.1.30. Z-3-(3′,4′,5′-Trimethoxyphenyl)-4-(3″-hydroxy-4″-methoxyphenyl)but-3-ene (**44**)*

Phenolic stilbene **44** was prepared from TBDMS ether **42** (125 mg, 0.273 mmol) by the method used to make phenol **12**. Flash column chromatography (petroleum ether/EtOAc 2:1) and recrystallisation from EtOAc afforded *Z* phenol **44** as a white solid (77 mg, 85%). M.p. 106–108 °C. R_f 0.23 (petroleum ether/EtOAc 2:1). δ_H (300 MHz) 1.09 (3 H, t, J = 7.5, CH_3), 2.47 (2 H, qd, J = 7.5, 1.1, CH_2), 3.77 [6 H, s, $(OCH_3)_2$], 3.83 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 5.4 (1 H, s, OH), 6.30 (1 H, d, J = 1.1, olefinic H), 6.39 (2 H, s, H-2′,6′), 6.46 (1 H, dd, J = 8.3, 2.3, H-6″), 6.60 (1 H, d, J = 2.3, H-2″), 6.61 (1 H, d, J = 8.3, H-5″); δ_C (100 MHz) 13.4 (CH_3), 33.9 (CH_2), 56.3 (CH_3), 56.5 (CH_3), 61.4 (CH_3), 106.0 (CH), 110.5 (CH), 115.5 (CH), 121.3 (CH), 124.9 (CH), 131.4 (C), 137.5 (C), 143.7 (C), 145.2 (C), 145.4 (C), 148.8 (C), 153.6 (C). *m/z* (FAB) 344 (M^+, 100%). (Found: $(MH)^+$ 345.1710; C, 68.7; H, 7.3. $C_{20}H_{24}O_5$ requires $(MH)^+$ 345.1702; C, 68.6; H, 7.3%).

*5.1.31. E-3-(3′,4′,5′-Trimethoxyphenyl)-4-(3″-hydroxy-4″-methoxyphenyl)but-3-ene (**45**)*

Phenol **45** was prepared from TBDMS ether **43** (221 mg, 0.483 mmol) by the method used to make phenol **12**. Flash column chromatography (petroleum ether/EtOAc 2:1) and recrystallisation from EtOAc afforded *E*-phenol **45** as a white solid (104 mg, 65%). M.p. 89–91 °C. R_f 0.18 (petroleum ether/EtOAc 2:1). δ_H (300 MHz) 1.10 (3 H, t, J = 7.5, CH_3), 2.73 (2 H, qd, J = 7.5, 1.1, CH_2), 3.89 (3 H, s, OCH_3), 3.92 [6 H, s, $(OCH_3)_2$], 3.94 (3 H, s, OCH_3), 5.61 (1 H, s, OH), 6.58 (1 H, d, J = 1.1, olefinic H), 6.68 (2 H, s, H-2′,6′), 6.84 (1 H, dd, J = 8.3, 1.9, H-6″), 6.88 (1 H, d, J = 8.3, H-5″), 6.96 (1 H, d, J = 1.9, H-2″). δ_C (100 MHz) 13.9 (CH_3), 24.0 (CH_2), 56.4 (CH_3), 56.6 (CH_3), 61.3 (CH_3), 104.2 (CH), 111.0 (CH), 115.2 (CH), 121.1 (CH), 127.3 (CH), 132.1 (C), 137.7 (C), 139.2 (C), 144.0 (C), 145.7 (C), 145.8 (C), 153.5 (C). *m/z* (FAB) 344 (M^+, 100%). (Found: $(MH)^+$ 345.1702. $C_{19}H_{24}O_5$ requires $(MH)^+$ 345.1702).

*5.1.32. Z- and E-2-(3′,4′,5′-Trimethoxyphenyl)-3-(4″-methoxyphenyl)prop-2-ene (**47**, **48**)*

Stilbenes **47** and **48** were prepared from 4-methoxybenzyltriphenylphosphonium chloride **46** (598 mg, 1.43 mmol) and 3,4,5-trimethoxyacetophenone (**38**) (300 mg, 1.43 mmol) by the method described for the synthesis of stilbene **35**. Following flash column chromatography (petroleum ether/EtOAc 9:1) and recrystallisation from EtOAc, *Z* stilbene **47** was isolated as white needles (45 mg, 10%). M.p. 73–75 °C. R_f 0.46 (petroleum ether/EtOAc 3:1). λ_{max} (MeOH) 273 (ϵ = 14,926). δ_H (300 MHz) 2.19 (1 H, d, J = 1.5, CH_3), 3.74 [6 H, s, $(OCH_3)_2$], 3.76 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 6.40 (1 H, d, J = 1.5, olefinic H), 6.42 (2 H, s, H-2′,6′), 6.69 (1 H, d, J = 8.7, H-3″,5″), 6.93 (1 H, d, J = 8.7, H-2″,6″). δ_C (100 MHz) 18.2 (CH_3), 55.7 (CH_3), 56.4 (CH_3), 56.6 (CH_3), 103.8 (CH), 114.1 (CH), 127.6 (CH), 130.4 (CH), 130.8 (C), 131.2 (C), 136.3 (C), 140.7 (C), 153.5 (C), 158.6 (C); *m/z* (EI^+) 314 (M^+, 100%). (Found: C, 72.8; H, 6.9. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05%). Further elution and recrystallisation from EtOAc afforded *E*-stilbene **48** as an off white solid (44 mg, 10%). M.p. 80–82 °C. R_f = 0.41 (petroleum ether/EtOAc 3:1). λ_{max} (MeOH) 287 (ϵ = 21,822). δ_H (300 MHz) 2.28 (1 H, d, J = 1.5, CH_3), 3.86 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 3.94 [6 H, s, $(OCH_3)_2$], 6.74 (2 H, s, H-2′,6′), 6.75 (1 H, d, J = 1.5, olefinic H), 6.94 (1 H, d, J = 8.7, H-3″,5″), 7.34 (1 H, d, J = 8.7, H-2″,6″). *m/z* (EI^+) 314 (M^+, 100%).

5.2. Biochemistry

The stilbenes were tested for cytotoxicity using the previously published MTT assay [24]. Cell cycle analysis, measurement of the inhibition of tubulin, the colchicine displacement assays and immunohistochemistry were carried out as previously published [5].

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