**A 2-step synthesis of Combretastatin A-4 and derivatives as potent tubulin assembly inhibitors**

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Abstract



A series of combretastatin derivatives were designed and synthesised by a two-step stereoselective synthesis by use of Wittig olefination followed by Suzuki cross-coupling. Interestingly, all new compounds (2a-2i) showed potent cell-based antiproliferative activities in nanomolar concentrations. Among the compounds, 2a, 2b and 2e were the most active across three cancer cell lines. In addition, these compounds inhibited the polymerisation of tubulin *in vitro* more efficiently than CA-4. They caused cell cycle arrest in G2/M phase further confirming their ability to inhibit tubulin polymerisation.

1. Introduction

Microtubules are critical for cellular functions such as mitosis and cell structure. Mitosis is a key stage of cell division in which chromosomes are separated producing genetically identical daughter cells; the mitotic spindle is the cytoskeletal structure of cells that forms to separate these daughter cells. Interference with microtubule formation hinders the formation of this mitotic spindle required for cell division leading to mitotic arrest and eventual apoptosis (cell death). A number of microtubule targeting agents have been clinically successful in the treatment of cancer, making microtubules a significant target for anticancer drugs.1–4 Microtubule agents either inhibit or accelerate microtubule formation causing disruption to the formation of the mitotic spindle. A number of both natural and synthetic compounds target microtubule polymerisation with most of the antimitotic agents in use today being plant derivatives.5,6 Taxoids bind to tubulin, stabilizing the microtubules by accelerating polymerisation. Taxol (or paclitaxel) is routinely used in the treatment of a number of cancers including ovarian, breast, lung and pancreatic cancer. 7 Vinca alkaloids and colchicine (1) induce depolymerisation of microtubules. Vinca alkaloids are used in clinical practice to treat solid tumours mainly of the lung, testicle and breast. A number of natural ligands bind to the colchicine binding site of tubulin including combretastatin A-4 (CA-4, 2),8 and podophyllotoxin (3)9 (figure 1). These agents comprise *cis*-locked aryl groups one of which is 3,4,5-trimethoxyphenyl.



**Figure 1.** Structure of natural ligands that bind at the colchicine site of tubulin.

Tumour vasculature is a known therapeutic target for cancer treatment. A number of preclinical *in vivo* investigations and clinical trials have evaluated the toxicity of vascular disrupting agents (VDAs).10–12 However in several cases, VDAs have been shown to cause detrimental effects to the cardiovascular system due to long term dosing.13 Recently, VDAs have been investigated to overcome these effects as a glutamic acid conjugate14 and to induce the aggregation of gold nanoparticles.15

Combretastatins are a group of natural products isolated from the bark of the South African willow *Combretum caffrum*.16 Combretastatins are of increasing interest due to their simple structures and easy synthesis.17 The most active combretastatin known to date CA-4 (2) binds to the colchicine site of tubulin, disrupting microtubule polymerisation and eventually induces apoptosis.18–20 CA-4 disrupts endothelial cell structure in tumour capillaries, limiting blood flow and causing cell death21–23 and so can be classed as a VDA. CA-4 is a poorly water-soluble compound and so a number of water-soluble prodrugs have been developed including combretastatin A4 disodium phosphate (CA4-4P) which is converted into Z-CA4 by cellular phosphatases in the body.24 Preclinical and clinical trials of the water soluble phosphate prodrug CA4-P identified resistance at the tumour periphery;25–30 to overcome this combretastatins have been investigated as a combination therapy to complement traditional anticancer approaches.23,31–38 Limited advancement of these combination trials could be attributed to cardiovascular adverse events of CA4P.39 More recently, combretastatin A-1 diphosphate (OXi4503) has been in clinical trials for patients with relapsed or refractory acute myeloid leukemia40 or myelodysplastic syndromes.41 Combretastatins are also being investigated for photodynamic therapy as a means to overcome the acute toxic effects of the *cis*-isomers and provide a more targeted treatment through photoactivated isomerisation of the non toxic *trans-*form.42,43

Combretastatins continue to be compounds of interest with an increasing number of structurally modified combretastatin derivatives synthesized to exploit their properties for targeted therapeutic applications as VDAs. Modifications of combretastatins tended to retain the more cytotoxic *cis-*conformation which included restriction of the *cis-* configuration by replacement of the olefinic bond with heterocyclic rings such as imidazole 44, pyrazole 45, triazole 46 etc. There are a number of studies involving both modification on the olefinic bond and aromatic rings of CA-4.47–49 Modifications to the A-50 and B-51,52 rings have also been investigated to try and improve activity and solubility.

Synthetic routes for *cis*-stilbenes include the Wittig reaction,53 alkyne hydroboration,54 selective reduction of alkynes using a Lindlar catalyst,55 Perkin condensation,56 Kumada-Corriu cross-coupling57, Negishi coupling58 and Ramberg–Bäcklund reaction.59 A very useful reaction for the stereoselective synthesis of *cis-*stilbenes is the Suzuki cross-coupling. The Suzuki cross-coupling reaction has a broad application in the formation of carbon-carbon bonds owing to the mild reaction conditions and broad functional group toleration.60

1. **Results and Discussion**

**2.1 Chemistry results**

Our designed combretastatin derivatives possess a 3,4,5-trimethoxyphenyl A-ring and electron withdrawing groups at the 2- and 4- position of the B-ring (table 1). There are several syntheses of combretastatins in the literature.53–60 Most of these methods failed to provide the required combretastatin derivatives, however a Suzuki cross coupling method proved successful.

The general synthetic route for combretastatin derivatives 2a-m is illustrated in Scheme 1. 3,4,5-Trimethoxy-β-iodostyrene (6) was readily prepared using Stork-Zhao olefination methodology61 from iodomethylenetriphenylphosphonium iodide (4) (1.3 equivalents) and 3,4,5-trimethoxybenzaldehyde (5) in the presence of NaHMDS (1.3 equivalents) in 72% yield. *Z*-Combretastatins were synthesised following the Suzuki-coupling of this *Z*-iodostyrene compound with appropriately substituted aryl boronic acids (Scheme 1).



Scheme 1. Synthesis of target compounds 2a-m Reagents and conditions: (a) NaHMDS, THF, -20 to -78 °C, 2 h; (b) arylboronic acids or pinacol esters, Pd(PPh3)4, DME, Na2CO3, 80 °C, 20 h.

To further investigate the scope of this method and to extend the compound library, we synthesised 3-hydroxy substituted combretastatins. The boronic acids required for this synthesis were not commercially available. Although boronic acids react more efficiently, we chose to synthesise the corresponding boronic pinacol esters as they are easier to isolate and purify.62 The boronic pinacol esters were synthesised by Miyaura borylation;63 bis(pinacolato)diboron (B2pin2) was reacted with aryl halides in the presence of a palladium catalyst and potassium acetate. Z-Combretastatins were then synthesised as described above from 6 and appropriately substituted pinacol esters. We synthesised a small library of both known and unknown compounds with a variety of substituents including CHO (2a), CN (2h), NO2 (2j, 2k) and 3,4,5-trimethoxy (2l) in order to show the broad functional group toleration of this method (table 1). Novel synthesised compounds were characterised by 1H and 13C NMR as well as High Resolution Mass Spectrometry.

## Application of this 2-step method to the synthesis of combretastatin A-4 gave an overall yield of 56% following purification by column chromatography and recrystallisation from methanol (scheme 2). This was a huge improvement to the previously reported Suzuki cross-coupling synthesis. Gaukroger *et al* reported a 5-step process with an overall yield of 16%.63 Further to this, we avoided the use of highly toxic carbon tetrabromide and tin. Malysheva and co-workers reported a 2-step synthesis of combretastatin derivatives by Negishi cross-coupling of 6 with overall yields of 25-45%.58 Negishi coupling however requires phenol protection; they synthesised combretastatin A-4 in 39% overall yield. Our method provides a higher yielding synthesis of combretastatin derivatives without the need to protect functional groups.



**Scheme 2.**  **New synthesis of Combretastatin A-4**

* 1. **Biological results**
		1. **Antiproliferative activities of compounds 2a-2i**

We determined thecytotoxicity of these new analogues across three human cancer cell lines (table 1). The half-maximal inhibitory concentration (IC50)for all new compounds (2a−2i) tested against HepG2 hepatic carcinoma, HCT-116 colon cancer and HeLa human epithelial cervical cancer cells is shown in Table 1. We chose cell lines previously used for CA-4;64–67 CA-4 was used as a control to compare the potency of the synthesized combretastatin analogues.

As shown in table 1 most of the combretastatin derivatives show antiproliferative activity in the micromolar range, although not as active as CA-4. The most active compounds were 2b (HeLa, HCT-116) and 2e (HepG2) with IC50 values of less than 100 nanomolar.

Generally, the presence of an electron withdrawing carbonyl group in the 4-position of the B-ring provided potent anti-proliferative activities. Based on the binding determined for CA-4,68 it can be presumed this is due to hydrophobic interactions in the colchicine binding site of tubulin at the 4-position of these derivatives. Further to this, compounds lacking a 4-substitution pattern or with a nitrile group (2h, 2i) showed limited cytotoxicity. 3-Hydroxy substitution was not essential for anti-proliferative activity but increased the activity when combined with a 4-carbonyl substitution (2b).

**Table 1. Structures of synthesised compounds 2a-m and antiproliferative activities of compounds 2a-i against human cancer cell lines *in vitro***



|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Comp. | R1 | R2 | R3 | *In vitro* cytotoxicity (IC50 ± SD, μM) |
| HepG2 | HeLa | HCT-116 |
| **2a** | H | H | CHO | 0.25 ± 0.05 | 0.28 ± 0.06 | 0.27 ± 0.15 |
| **2b** | H | OH | CHO | 0.23 ± 0.05 | 0.07 ± 0.01 | 0.09 ± 0.03 |
| **2c** | CHO | H | OMe | 0.14 ± 0.03 | 0.15 ± 0.03 | 0.14 ± 0.09 |
| **2d** | CHO | H | H | 1.06 ± 0.38 | 1.21 ± 0.31 | 2.61 ± 1.51 |
| **2e** | H | H | C(=O)Me | 0.06 ± 0.03 | 0.14 ± 0.02 | 0.25 ± 0.12 |
| **2f** | H | OH | C(=O)Me | 0.37 ± 0.09 | 0.34 ± 0.10 | 0.35 ± 0.23 |
| **2g** | C(=O)Me | H | H | 0.46 ± 0.12 | 0.14 ± 0.08 | 0.45 ± 0.12 |
| **2h** | H | H | CN | 0.96 ± 0.35 | 0.46 ± 0.10 | 1.42 ± 0.40 |
| **2i** | H | OH | CN | 0.53 ± 0.24 | 0.58 ± 0.13 | 0.79 ± 0.21 |
| **2j** | H | H | NO2 | n.d | n.d | n.d |
| **2k** | NO2 | H | H | n.d | n.d | n.d  |
| **2l** | OMe | OMe | OMe | n.d | n.d | n.d |
| **2m** | H | H | H | n.d | n.d | n.d |
| **CA-4** | H | OH | OMe | 0.006 ± 0.001 | 0.007 ± 0.002 | 0.010 ± 0.003 |

IC50 was determined after 72 h of drug exposure. Each experiment was carried out in triplicate at least two times. SD represents standard deviation.

**2.2.2 Effect on microtubules**

 CA-4 is a microtubule-destabilising agent that binds with tubulin at the same site as that of colchicine.69,70 Combretastatins are known to depolymerize cellular microtubules. The inhibition of tubulin polymerisation by the combretastatin derivatives was tested using bovine brain tubulin.

We analyzed the effect of compounds 2a-2i on the assembly kinetics of tubulin *in vitro* using a fluorescence-based assay. Combretastatins 2a, 2b and 2e inhibited tubulin polymerisation almost completely at 1 µM (Figure 2a); interestingly, these compounds were also the most cytotoxic. Compounds 2c, 2f and 2h slowed the rate of tubulin polymerisation with maximum polymerisation below that of untreated tubulin (figure 2b). These compounds showed a similar trend in cytotoxicity; they effected cell proliferation but were not as potent as 2a, 2b and 2e. Although compounds 2d, 2g and 2i didn’t inhibit the final proportion of tubulin polymerised at a concentration of 1 µM (figure 2c), these compounds appeared to slow down the rate of tubulin polymerisation.

Compounds 2d and 2g displayed tubulin polymerisation curves comparable to that of untreated tubulin with a clear growth phase. The rate of tubulin polymerisation was estimated by fitting the early times of the curve to a pseudo-first order rate equation (table 2). Values for compound 2i were not determined as the one–phase association was ambiguous. The rate constant (k) of microtubule formation under normal conditions was 0.0208 min-1 with a half-life of 33 min. Incubation with compounds 2d and 2g decreased the rate of microtubule formation with k values of 0.0116 min-1, 0.0123 min-1 respectively. The half-life of tubulin formation also increased upon treatment with compounds 2d and 2g confirming that although the final volume of microtubules did not appear to be inhibited, these compounds slowed down the rate of tubulin polymerisation (k) and thus expected to disrupt the cell signalling pathways, as demonstrated by the cell toxicity results, Table 1.17

An IC50 of the tubulin polymerisation was determined from the Vmax of the polymerisation curves at varying concentrations for 2a, 2b and 2e (Figure 2d). These combretastatin derivatives had IC50 values of 0.39, 0.32 and 0.28 μM respectively. This is almost a 10-fold increase in inhibition of tubulin polymerisation than that of colchicine (2.68 μM).71 Further to this, CA-4 is reported as one of the most potent tubulin polymerisation inhibitors with IC50 values reported to range from 0.53 to 2.4 μM.71–74 The inhibition of tubulin polymerisation correlated with the cytotoxicity towards cancer cell lines suggesting the main mode of action of these combretastatin derivatives is the inhibition of tubulin polymerisation.73–76



**Figure 2.** Combretastatin derivatives (1 μM) inhibited the assembly of tubulin *in vitro.* Normal tubulin polymerisation is shown as the control. Paclitaxel (3 μM) and CA-4 (1 μM) were used as positive controls and experiments were repeated three times. Data is shown for one of these repeats. (a) Compounds 2a, 2b, 2e; (b) 2c, 2f, 2h; (c) 2d, 2g, 2i; (d) example of dose curves for compound 2a 1 µM, 0.5 µM, 0.1 µM.

**Table 2. Rate (k) and half-life (t1/2) of tubulin polymerisation after treatment with compounds 2d and 2g**

|  |  |  |
| --- | --- | --- |
| Conditions | k (min‑1) | t1/2 (min) |
| No drug control | 0.0208 | 33 |
| 2d (1 μM) | 0.0116 | 59 |
| 2g (1 μM) | 0.0123 | 56 |

**2.2.3 Effect on Cell Cycle Arrest**

During mitosis, the microtubule is critical for the separation of chromosomes. Exposure to microtubule targeting agents leads to damaged mitotic spindles resulting in mitotic arrest and subsequent apoptosis; it is widely accepted that the G2/M cell cycle arrest is strongly associated with inhibition of tubulin polymerisation.77–79 To investigate the effect of the combretastatin derivatives on cell cycle arrest, flow cytometry was used to analyse the cell cycle distribution of HepG2 cells following treatment with compounds 2a, 2b and 2e at 1 μM. Untreated cells showed a fairly even spread across the growth stages; the percentage of cells in the G0/G1 and G2/M phase were 45.6 % and 44.8% respectively (table 3). After treatment with 2a, 2b and 2e, the percentage of cells in the G2/M phase drastically increased to 91.6%, 94.6% and 94.7% respectively.

After incubation for 48 hours with 2a, the percentage of apoptotic cells (sub-G1) increased (43.3%) and the percentage of G2/M arrested cells decreased (46.7%). The increased sub-G1 population, suggested extensive DNA fragmentation indicating apoptosis as a direct result of mitotic arrest.80 We observed a similar trend for compounds 2b and 2e after 48 hours; the percentage of apoptotic cells increased to 43.3% and 43.5% respectively. This cell cycle arrest in the G2/M phase and subsequently sub-G1 suggests compounds 2a, 2b and 2e inhibit tubulin polymerisation causing a mitotic block that leads to apoptosis.

**Table 3. Effect of compounds 2a, 2b and 2e on the cell cycle in HepG2 cells**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | 2a | 2b | 2e | No drug control |
|  | 24 h  | 48 h | 24 h | 48 h | 24 h | 48 h | 24 h | 48 h |
| Sub G1 | 3.3 | 44.2 | 1.2 | 43.3 | 2.7 | 43.5 | 1.2 | 5.9 |
| G0/G1 | 3.5 | 5.6 | 2.8 | 21.5 | 1.6 | 11.4 | 45.6 | 56.2 |
| S | 1.6 | 3.5 | 1.3 | 4.1 | 1.0 | 4.1 | 8.4 | 12.5 |
| G2/M | 91.6 | 46.7 | 94.6 | 31.1 | 94.7 | 41.0 | 44.8 | 25.4 |

Number of cells arrested in each stage of the cell cycle are expressed as a percentage (%).

1. **Conclusion**

In conclusion, a series of combretastatin analogues were synthesised using a new two-step reaction by use of a Wittig olefination followed by the Suzuki cross-coupling. Fourteen compounds were synthesised using this new route including the biologically active CA-4 in a 56% overall yield. This two-step synthesis is an improved synthesis of CA-4 which allowed for a library of combretastatins with B-ring modifications to be synthesised.

New compounds (2a-2i) exhibited antiproliferative activities in nanomolar concentrations. 4-Formyl-3',4',5'-trimethoxy-(Z)-stilbene (2a), 4-formyl-3-hydroxy-3',4',5'-trimethoxy-(Z)-stilbene (2b) and 4-Acetyl-3',4',5'-trimethoxy-(Z)-stilbene (2e) were the most potent across all three cell lines. Like CA-4, compounds 2a, 2b and 2e inhibited the rate and extent of an *in vitro* assembly of purified tubulin with IC50s of 0.39, 0.32 and 0.28 μM respectively.Additionally, compounds 2a, 2b and 2e appear to cause a mitotic block and eventual apoptosis in HepG2 cells, further confirming their ability to inhibit tubulin polymerisation.

1. **Experimental**

**4.1 Chemistry**

**General Considerations**

All reactants and reagents were obtained from the commercial source and used without further purification. The NMR spectra were recorded on a Bruker Avance DPX 400 MHz spectrometer in CDCl3 unless stated otherwise using TMS as an internal standard. J values are given in Hz. HRMS (ESI) were recorded with Bruker−Maxis mass spectrometers. The purity of synthesized compounds was analyzed by HPLC (Shimadzu LC-6AD system), Phenomenex RP-C18 column (250 mm × 4.60 mm), particle size 5 μm, flow rate 1 mL/min, using water−acetonitrile. Purity of tested compounds was >95%.

***Z*-3,4,5-Trimethoxy-β-iodostyrene (6)** 58

A suspension of iodomethylenetriphenylphosphonium iodide (3.53 g, 6.67 mmol, 1.3 eq) in anhydrous THF (30 ml) was cooled to -20 °C and sodium bis(trimethylsilyl)amide in THF (3.33 ml of a 2 M solution, 1.3 eq) was added dropwise. The resulting mixture was stirred at -20 °C for 15 min, then cooled to -78 °C and 3,4,5-trimethoxybenzaldehyde (1 g, 1.45 mmol, 1 eq) in THF (10 ml) was added over 1 h with good stirring. The reaction was stirred for a further 2 h, quenched with saturated aq. NH4Cl (10 ml) and extracted with diethyl ether (3 x 10 ml). The combined organic layers were filtered to remove triphenylphosphine oxide, dried over MgSO4 and concentrated *in vacuo. ­*The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 4:1) to give **6** (1.2 g, 72%) as a yellow oil. 1H δ ppm: 7.20 (d, J = 8.6 Hz, 2h), 6.91 (s, 2H), 6.48 (d, J = 8.6 Hz, 2h), 3.86 (s, 6H), 3.85 (s, 3H).

**General synthesis of boronic pinacol esters**81

Into a thick walled screw top flask containing a solution of appropriately substituted aryl halide (2.49 mmol, 1 eq) in dry 1,4-dioxane (10 ml) were added *bis*(pinacolato)diboron (0.632 g, 2.49 mmol, 1 eq) [1,1'-*Bis*(diphenylphosphino)ferrocene]palladium(II) dichloride (0.03 eq) and potassium acetate (3 eq). The flask was cooled to 0 °C under argon for 30 min. The reaction mixture was gradually warmed to room temperature, and stirred at 80 °C for 16 h. After cooling to room temperature, the solvent was evaporated to dryness under reduced pressure. The residue was dissolved in *n*-hexane, and the solution was washed with H2O, brine and dried (MgSO4), further purification was by recrystallization from hexane.

**2-Hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (7a)**81

From 4-bromosalicylaldehyde (0.500 g, 2.49 mmol, 1 eq). **7a** was isolated as a white solid (0.482 g, 1.94 mmol, 78%). 1H δ:1.28 (12 H, s, 4 x CH3), 7.35 (2 H, m), 7.48 (1 H, d, *J* = 8.16), 9.86 (1 H, s, CHO), 10.76 (1 H, s, OH).

**2-Hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acetophenone (7b)**

From 1-(4-bromo-2-hydroxyphenyl)ethanone (0.535 g, 2.49 mmol, 1 eq) **7b** was isolated as a white solid (0.451 g, 1.72 mmol, 69%). 1H δ:1.28 (12 H, s, 4 x CH3), 2.58 (3 H, s, CH3), 7.22 (1 H, dd, *J* = 7.87, 0.97, *para* to OH), 7.35 (1 H, d, *J* = 0.97, *ortho* to OH), 7.64 (1 H, d, *J* = 7.87, *meta* to OH), 11.99 (1 H, s, OH); 13Cδ:24.9 (4 C, CH3), 26.9 (1 C, CH3­), 84.3 (2 C, C-O), 114.5 (1 C, C-COCH3), 119.9 (1 C, Ar C), 124.6 (1 C, Ar C), 124.8 (1 C, C-B), 129.6 (1 C, Ar C), 158.8 (1 C, C-OH), 201.2 (1 C, C=O)

##### **2-Hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (7c)**

From 4-bromo-2-hydroxybenzonitrile (0.493 g, 2.49 mmol, 1 eq). **7c** was isolated as a white solid (0.464 g, 1.89 mmol, 76%).1Hδ:1.27 (12 H, s, 4 x CH3), 7.14 (1 H, dd, *J* = 7.71, 1.28, *para* to OH), 7.35 (1 H, d, *J* = 1.28, *ortho* to OH), 7.36 (1 H, d, *J* = 7.71, *meta* to OH), 10.49 (1 H, s, OH); 13Cδ:24.9 (4 C, CH3), 84.5 (2 C, C-O), 94.6 (1 C, C-CN), 105.2 ( 1 C, C-B), 116.4 (1 C, CN), 120.1 (1 C Ar C), 127.9 (1 C, Ar C), 132.8 (1 C, Ar C), 158.2 (1 C, Ar C-OH).

# Synthesis of Combretastatin A-4 and analogues (2a-i)

## General synthesis of combretastatins

## 3,4,5-Trimethoxy-β-iodostyrene (0.22 g, 0.68 mmol, 1 eq) and *tetrakis* (triphenylphosphine) palladium(0) (0.04 g, 0.034 mmol, 5 mol %) were stirred in 1,2-dimethoxyethane (50 ml) under argon for 20 min. Aryl boronic acid (or ester) (1.02 mmol, 1.5 eq) (for 1 0.168 g, 2a 0.150 g, 2b 0.248 g, 2c 0.180 g, 2d 0.150 g, 2e 0.164 g, 2f 0.262 g, 2g 0.164 g, 2h 0.147 g, 2i 0.245 g, 2j 0.167 g, 2k 0.167 g, 2l 0.212 g, 2m 0.122 g) and aqueous sodium carbonate (1 ml of a 2 M solution, 3 eq) were added and the mixture heated at reflux for 20 h. The reaction mixture was allowed to cool to room temperature, passed through a plug of celite and the DME was removed *in vacuo*. DCM (20 ml) was added and washed with saturated brine, water, dried (MgSO4), and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 10:1) and recrystallised from methanol.

## Combretastatin A-4 (1)53

## From 3-methoxy-4-hydroxyphenyl boronic acid (0.168 g, 1 mmol, 1.5 eq). Following purification 1 was isolated as a white solid (0.168 g, 78%); Mp 117-118 (lit. mp42 116-118). 1H δ: 3.70 (6 H, s, 2 x OMe), 3.85, 3.87 (6 H, 2 s, 2 x OMe), 5.55 (1 H, s, OH), 6.43, 6.49 (2 H, 2 d, J = 12.2 Hz, olefinic Hs), 6.67 (2 H, s, ArH ortho to OMe), 6.85 (1 H, d, J = 8 Hz, ArH meta to OH), 6.80 (1 H, dd, J = 8, 2 Hz, ArH para to OH), 6.93 (1 H, d, J = 2 Hz, ArH ortho to OH).

## 4-Formyl-3',4',5'-trimethoxy-(Z)-stilbene (2a)82

From 4-formylphenyl boronic acid (0.15 g, 1 mmol, 1.5 eq). Following purification **2a** was isolated as yellow crystals (0.171 g, 84%); Mp 98-100°C; 1H δ: 3.57 (3 H, s, 4’-OMe), 3.70 (6 H, s, 3’,5’-OMe), 6.37 (2 H, s, 2’,6’-CH), 6.51 (1 H, d, *J* = 12.3, olefinic CH), 6.58 (1 H, d, *J* = 12.3, olefinic CH), 7.37 (2 H, d, *J* = 8.2, 2, 6-CH), 7.69 (2 H, d, *J* = 8.2, 3, 5-CH), 9.08 (1 H, s, CHO). 13C (100 MHz) δ 55.9, (2 x OCH3), 60.9 (OCH3), 106.1 (2,6-C), 125.5 (2’,6’-C), 128.6, 129.6 (2 x olefinic CH), 130.1 (3’,5’-C), 131.8 (1-C), 135.0 (4’-C), 137.7 (1’-C), 140.0 (4-C), 153.0 (3,5-C), 191.5 (CHO). HRMS calcd for C18H19O4 [M+H+]: 299.1278; found: 299.1278.

**4-Formyl-3-hydroxy-3',4',5'-trimethoxy-(Z)-stilbene (2b)**

From2-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (0.248 g, 1.00 mmol). Following purification **2b** was isolated as a pale yellow solid (0.113 g, 54%); Mp 89 °C. 1H δ: 3.71 (3 H, s, OCH3), 3.87 (6 H, s, 2 x OCH3), 6.50 (2 H, s, Ar H), 6.51 (1 H, d, *J* = 12.3, CH), 6.53 (1 H, d, *J* = 12.3, CH), 6.68 (1 H, dd, *J* = 7.7, 1.8, *para* to OH), 6.69 (1 H, d, *J* = 1.8, *ortho* to OH), 7.43 (1 H, d, *J* = 7.7, *meta* to OH), 9.83 (1 H, s, CHO), 11.06 (1 H, s, OH).13C (100 MHz) δ 56.2 (2 C, 2 x OCH3), 61.0 (1 C, OCH3), 104.2 (1 C, o-OH), 106.2 (2 C, o-C-OCH3), 114.8 (1 C, C-CHO), 126.6 ( 1 C, o-CHO), 128.3 (1 C, p-OH) 131.6 (1 C, ArC), 132.0 (2 C, CH), 138.9 (1 C, C-O CH3), 153.0 (2 C, C-O CH3), 153.5 (1 C, C-OH), 195.7 (1 C, C=O). HRMS calcd for C18H19O5 315.1230, found 315.1227.

## 2-Formyl-3',4,4',5'-tetramethoxy-(Z)-stilbene (2c)

From 2-formylphenyl boronic acid (0.18 g, 1 mmol, 1.5 eq). Following purification **2c** was isolated as a pale yellow solid (0.176 g, 79%); Mp 88-91 °C; 1H δ: 3.60 (3 H, s, 4’-OMe), 3.82 (6 H, s, 3’,5’-OMe), 3.88 (3 H, s, 4-OMe), 6.31 (2 H, s, 2’,6’-CH), 6.72 (1 H, d, *J* = 12.2, olefinic CH), 6.88 (1 H, d, *J* = 12.2, olefinic CH), 7.13 (1 H, dd, *J* = 2.9, 8.6, 5-CH), 7.28 (1 H, d, *J* = 8.6, 6-CH), 7.43 (1 H, d, *J* = 2.9, 3-CH), 10.25 (1 H, s, CHO). 13C (100 MHz) δ 55.6, 55.8 (4, 4’-OMe), 60.9 (3’,5’-OMe), 106.4 (2,6-C), 110.9 (3’-C), 114.6 (5’-C), 121.7 (6’-C), 125.2, 131.3 (2 x olefinic Cs), 131.9 (1-C), 133.3 (2’-C), 134.2 (2’-C), 134.4 (1’-C), 139.4 (4-C), 152.9 (3,5-Cs), 159.1 (4’-C), 191.7 (CHO). HRMS calcd for C19H21O5 [M+H+]: 329.1384; found: 329.1385.

## 2-Formyl-3',4',5'-trimethoxy-(Z)-stilbene (2d)

## From 2-formylphenyl boronic acid (0.15 g, 1 mmol, 1.5 eq). Following purification 2d was isolated as a yellow solid (0.162 g, 80%); Mp 91-93 °C; 1H δ: 3.48 (3 H, s, 4’-OMe), 3.71 (6 H, s, 3’,5’-OMe), 6.15 (2 H, s, 1’,6’-CHs), 6.66 (1 H, d, *J* = 12.5, olefinic CH), 6.86 (1 H, d, *J* = 12.5, olefinic CH), 7.27 (1 H, d, *J* = 7.5, 4-CH), 7,34 (1 H t, *J* = 7.5, 6-CH), 7.47 (1 H, m, 5-CH), 7.85 (1 H, d, *J* = 7.5, 3-CH). 13C (100 MHz) δ 56.2 (2 x OCH3), 60.9 (OCH3), 104.1 (2,6-Cs), 125.8 (6’-C), 127.2, 127.7 (2 x olefinic CH), 128.9 (3’-C), 130.6 (4’-C), 131.1 (5’-C), 133.3 (1-C), 134.0 (1’-C), 137.6 (2’-C), 141.5 (4-C), 153.5 (3,5-Cs), 192.0 (CHO). HRMS calcd for C18H19O4 [M+H+]:299.1278; found: 299.1278.

## 4-Acetyl-3',4',5'-trimethoxy-(Z)-stilbene (2e)

## From 4-acetylphenylboronic acid (0.164 g, 1 mmol, 1.5 eq). Following purification 2e was isolated as a white solid (0.157 g, 74%); Mp 79-81 °C; 1H δ: 2.51 (3 H, s, OCMe), 3.59 (6 H, s, 3’,5’-OMes), 3.77 (3 H, s, 4’-OMe), 6.38 (2 H, s, 2’,6’-CH), 6.51 (1 H, d, *J* = 12.3, olefinic CH), 6.57 (1 H, d, *J* = 12.3, olefinic CH), 7.31 (2 H, d, *J* = 8.1, 2, 6-CH), 7.78 (2 H, d, *J* = 8.2, 3,5-CH); 13C (100 MHz) δ 26.4 (4’-OC*Me*), 55.9 (3’,5’-OMes), 61.0 (4-OMe), 106.1 (2,6-C), 128.3 (olefinic C), 128.4 (2’,6’-C),, 128.8 (olefinic C), 129.1 (3’,5’-C), 132.3 (1-C), 137.4 (4’-C), 139.5 (4-C), 143.5 (1’-C), 153.0 (3,5-C), 193.5 (CHO). HRMS calcd for C19H21O4 [M+H+]: 313.1431; found: 313.1434.

## 4-Acetyl-3-hydroxy-3',4',5'-trimethoxy-(Z)-stilbene (2f)

From and 2-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acetophenone (0.262 g, 1.00 mmol)**.** Following purification **2f** was isolated as a pale yellow solid (0.122 g, 56%). Mp 73 °C.1H δ: 2.62 (3 H, CH3), 3.72 (6 H, s, 2 x OCH3), 3.87 (3 H, s, OCH3), 6.51 (2 H, s, Ar H), 6.52 (1 H, d, *J* = 12.5, CH), 6.66 (1 H, d, *J* = 12.5, CH), 6.83 (1 H, dd, *J* = 8.2, 1.6, *para* to OH), 6.97 (1 H, d, *J* = 1.6, *ortho* to OH), 7.60 (1 H, d, *J* = 8.2, *meta* to OH), 12.27 (1 H, s, OH). 13C (100 MHz) δ 26.6 (1 C, CH3), 56.0 (2 C, 2 x OCH3), 61.0 (1 C, OCH3), 106.2 (2 C, o-C-OCH3), 118.3 (C-COCH3), 128.5 (1 C, o-COCH3), 130.3 (1 C, p-OH), 131.8 (1 C, ArC), 132.9 (1 C, Ar C), 146.0 (1 C, C-OCH3), 153.0 (2 C, C-O CH3), 162.4 (1 C, C-OH), 203.8 (1 C, C=O). HRMS calcd for C19H21O5 [M+H]: 329.1384; found: 329.1385.

## 2-Acetyl-3',4',5'-trimethoxy-(Z)-stilbene (2g)

From 5-[(Z)-2-bromovinyl]-1,2,3-trimethoxybenzene (0.164 g, 1 mmol, 1.5 eq).) and 2-acetylphenylboronic acid (0.169 g, 1.03 mmol). Following purification **2g** was isolated as a yellow solid (0.182 g, 0.58 mmol, 85%).1H δ:2.56 (3 H, s, CH3), 3.60 (6 H, s, 2 x OCH3),3.82 (3 H, s, OCH3), 6.28 (2 H, s, Ar H), 6.56 (1 H, d, *J* = 12.3, CH), 6.92 (1 H, d, *J* = 12.3, CH), 7.33 (2 H, d, *J* = 7.4, Ar H) 7.36 (t, *J*= 1.58, 8.99, 1 H*,* Ar H), 7.79 (d, J=7,4 , 1 H, Ar H); 13C (100 MHz) δ 29.5 (CH3), 55.7 (2 C, OCH3), 60.9 (OCH3), 106.4 (olefinic C), 126.7 (Ar C), 127.7 (Ar C), 129.1 (olefinic C), 129.9 (olefinic C), 130.0 (Ar C), 131.2 (Ar C), 131.6 (Ar C), 132.0 (Ar C), 137.2 (Ar C), 138.0 (Ar C). 152.7 (olefinic C), 200.7 (carbonyl C). HRMS calcd for C19H21O4 [M+H]: 313.1431, found: 313.1434

## 4-Cyano-3',4',5'-trimethoxy-(Z)-stilbene (2h)

## From 4-cyanophenylboronic acid (0.147 g, 1 mmol, 1.5 eq). Following purification 2h was isolated as a white solid (0.156 g, 78%); Mp 89-91 °C. 1H δ: 3.60 (s, 6 H), 3.78 (s, 3 H), 6.33 (s, 2 H), 6.47 (d, *J* = 12.2, 1 H), 6.60 (d, *J* = 12.2, 1 H), 7.31 (d, *J* = 8.4, 2 H), 7,47 (d, *J* = 8.4, 2 H). 13C (100 MHz) 55.9 (3’,5’ OMe), 61.0 (4’-OMe), 106. 0 (2’, 6’-C), 110.5 (1-C), 118.9 (1’-C), 128.0, 129.7 (2 x olefinic C), 131.5 (CN), 132.4 (2, 6-C), 133.10 (3,5-C), 137.8 (4’-C), 142.3 (aromatic 4-C), 153.1 (3’, 5’-C). HRMS calcd for C18H18NO3 [M+H+]: 296.1287; found: 296.1281.

## 4-Cyano-3-hydroxy-3',4',5'-trimethoxy-(Z)-stilbene (2i)

 From 2-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (0.245 g, 2.00 mmol**.** Following purification, **2i** was isolated as a dark yellow solid (0.100 g, 48%). Mp 95 °C. 1H δ: 3.70 (6 H, s, 2 x OCH3), 3.85 (3 H, s, OCH3), 6.45 (2 H, s, Ar H), 6.48 (1 H, d, *J* = 12.2, CH), 6.63 (1 H, d, *J* = 12.2, CH), 6.88 (1 H, dd, *J* = 9.0, 1.2, *para* to OH), 6.98 (1 H, d, *J* = 1.2, *ortho* to OH), 7.39 (1 H, d, *J* = 9.0, *meta* to OH). 13C (100 MHz) δ 55.9 (2 C, 2 x OCH3), 61.2 (1 C, OCH3),99.8 (1 C, C-CN), 106.0 (2 C, o-C-OCH3), 121.4 (CN), 128.1 (1 C, o-COCH3), 1331.5 (1 C, p-OH), 132.8 (1 C, ArC), 132.9 (1 C, Ar C), 143.9 (1 C, C-OCH3), 153.1 (2 C, C-O CH3), 159.4 (1 C, C-OH). HRMS calcd for C18H16NO4 3[M-H]:10.33, found 310.00.

## 4-Nitro-3',4',5'-trimethoxy-(Z)-stilbene (2j)83

## From 4-nitrophenyl boronic acid (0.167 g, 1 mmol, 1.5 eq). Following purification 2j was isolated as a yellow solid (0.167 g, 78%); Mp 142-143 °C. (Lit. Mp 210-212 °C). 1H δ: 3.70 (6 H, s, 3’,5’-OMe), 3.88 (3 H, s, 4-OMe), 6.51 (1 H, d, *J* = 12.0, olefinic H), 6.25 (1 H, d, *J* = 12.0, olefinic H), 6.45 (2 H, s, 2’, 6’-CHs), 7.48 (2 H, d, *J* = 8.1, 2,6-CHs), 8.15 (2 H, d, *J* = 8.1, 3,5-CHs).

## 2-Nitro-3',4',5'-trimethoxy-(Z)-stilbene (2k)84

## From 2-nitrophenyl boronic acid (0.167 g, 1 mmol, 1.5 eq). Following purification 2k was isolated as a yellow solid (0.158 g, 74%); Mp 126-129 °C. 1H δ: 3.60 (6 H, s, 3’, 5’-OMe), 3.82 (3 H, s, 4’-OMe), 6.38 (2 H, s, 2’,6’-CHs), 6.69 (d, *J* = 12.1, olefinic H), 6.90 (d, *J* = 12.1, olefinic H), 7.38 (1 H, d, *J* = 8.2, 3-CH), 7.42 (1 H, m, 4-CH), 7.48 (1 H, m, 5-CH), 8.10 (1.0, d, *J* = 8.2, 6-CH).

## 3,3',4,4',5,5'-Hexamethoxy-(Z)-stilbene (2l)85

## From 3,4,5-trimethoxyphenyl boronic acid (0.212 g, 1 mmol, 1.5 eq). Following purification 2l was isolated as a white solid (0.181 g, 0.5 mmol, 74%); Mp 173-175 °C. (Lit. Mp 173°C). 1H δ: 3.72 (12 H, s, 3,3’,5,5’-OMe), 3.85 (6 H, s, 4,4’-OMe), 6.52 (2 H, s, 2 x olefinic Hs) 2 H), 6.53 (4 H, s, 2,2’,6,6’-CHs)).

## 3,4,5-Trimethoxy-(Z)-stilbene (2m)86

From phenylboronic acid (0.122 g, 1 mmol, 1.5 eq). Following purification **2m** was isolated as a yellow solid (0.149 g, 81%); Mp 105-107 °C. (Lit. mp 106-8 °C. 1H δ: 3.69 (3 H, s, 4-OMe), 3.85 (6 H, s, 3,5-OMes), 6.47 (2 H, s, 2,6-Hs), 6.54 (1 H, d, *J* = 12.2, olefinic H), 6.62 (1 H, d, *J* = 12.2, olefinic H), 7.22 - 7.32(5 H, m, 2’,3’,4’,5,,6’-Hs).

**4.2 Biology**

**4.2.1 Cell culture.**

HepG2, HeLa and HCT-116 cells were cultured in Dulbecco’s Modified Eagle’s Medium (DMEM) supplemented with FCS (10 %), penicillin (100 units/ml), streptomycin (100 μg/ml) and L-glutamine (2 mM). Cell lines were cultured at 37 °C in a humidified incubator with 5% carbon dioxide.

**4.2.2 Cell-Based Screening Assay**. Synthesized combretastatin analogues, (**2a**-**2i**) and CA-4 used in the study were dissolved in 100% cell culture grade DMSO. The compounds were serially diluted in DMEM to maintain the final concentration of DMSO as <0.1% for testing on cancer cell lines. A concentration of 50 μM of synthesized combretastatin analogues (**2a**-**2i**) and CA-4 were initially used for screening the potency of compounds in cell lines.

**4.2.3 Half-Maximal Inhibition of Tumour Cell Growth by Combretastatin Analogues.** HepG2, HeLa and HCT-116 cells (1 × 105 cells/mL) were seeded in 96-well plates and incubated for 24 h for attachment. The cells were then incubated with different concentrations of synthesized combretastatin analogues and incubated for 24 h. Following incubation, MTT solution (50 μl; 3 mg/ml in PBS) was added to each well and incubated for a further 3 h. The half-maximal inhibitory concentration (IC50) for the respective compounds were determined using a known method. In short, formazan crystals were dissolved in DMSO (100 μl) and optical densities of the wells were read on a spectrophotometer platereader (Multiskan Ascent, Thermo Labsystems) at 540 nm with 690 nm as a background reading.The no drug control sample was normalised to 100 % cell growth (no inhibition of cell growth). CA-4 was used as a control for comparing the potencies of the synthesized combretastatin analogues. Data was analysed using GraphPad. 6 sets of experiments were performed.

### 4.2.4 Assembly Kinetics of Tubulin *in vitro*. A fluorescence-based tubulin polymerisation assay was performed according to the manufacturer’s protocol (cat # BK011P, Cytoskeleton, Inc.). Tubulin (10 mg ml-1) was resuspended in a premixed buffer containing PIPES, EGTA, MgCl2 and fluorescent reporter (243 μl), glycerol buffer (112 μl) and GTP (100 mM, 4.4 μl). The tubulin reaction mix (50 μl) was added to 1 μM of test compounds and subsequently the assembly kinetics of tubulin was monitored using excitation wavelength 355 nm at 37 °C using Spectramax M2. CA4 and paclitaxel were tested as controls and three independent experiments were performed for each compound.

### 4.2.5 Cell Cycle Analysis by Flow Cytometry. HepG2 cells were incubated in the absence and presence of compounds 2a, 2b, 2e and CA-4 for 24 h or 48 h. Subsequently, the cells were fixed with 70% ethanol. The fixed cells were then incubated with RNase (50 μl; 100 μg/ml in PBS) and propidium iodide (300 μl; 50 μg/ml in PBS) for 1 h. Flow cytometry analysis was performed using BD FACSVerse flow cytometer.

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1. **References**

(1) Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. Tubulin as a Target for Anticancer Drugs: Agents Which Interact with the Mitotic Spindle. *Med. Res. Rev.* **1998**, *18* (4), 259–296.

(2) Hadfield, J. a; Ducki, S.; Hirst, N.; McGown, A. T. Tubulin and Microtubules as Targets for Anticancer Drugs. *Prog. Cell Cycle Res.* **2003**, *5*, 309–325.

(3) Jordan, M. A.; Wilson, L. Microtubules as a Target for Anticancer Drugs. *Nat. Rev. Cancer* **2004**, *4* (4), 253–265. https://doi.org/10.1038/nrc1317.

(4) Mukhtar, E.; Adhami, V. M.; Mukhtar, H. Targeting Microtubules by Natural Agents for Cancer Therapy. *Molecular Cancer Therapeutics*. **2014,** 13 (2), 275–284. https://doi.org/10.1158/1535-7163.MCT-13-0791.

(5) Lin, C. M.; Ho, H. H.; Pettit, G. R.; Hamel, E. Antimitotic Natural Products Combretastatin A-4 and Combretastatin A-2: Studies on the Mechanism of Their Inhibition of the Binding of Colchicine to Tubulin. *Biochemistry* **1989**, *28* (17), 6984–6991. https://doi.org/10.1021/bi00443a031.

(6) Uppalapati, M.; Huang, Y.; Aravamuthan, V.; Jackson, T. N.; Hancock, W. O. Integrative Biology ‘“ Artificial Mitotic Spindle ”’ Generated by Dielectrophoresis and Protein Micropatterning Supports Bidirectional Transport of Kinesin-Coated Beadsw. **2011**, 57–64. https://doi.org/10.1039/c0ib00065e.

(7) Weaver, B. A. How Taxol/Paclitaxel Kills Cancer Cells. *Mol. Biol. Cell* **2014**, *25* (18), 2677–2681. https://doi.org/10.1091/mbc.E14-04-0916.

(8) Nam, N.-H. Combretastatin A-4 Analogues as Antimitotic Antitumor Agents. *Curr. Med. Chem.* **2003**, *10* (17), 1697–1722.

(9) Liu, Y. Q.; Tian, J.; Qian, K.; Zhao, X. B.; Morris-Natschke, S. L.; Yang, L.; Nan, X.; Tian, X.; Lee, K. H. Recent Progress on C-4-Modified Podophyllotoxin Analogs as Potent Antitumor Agents. *Med. Res. Rev.* **2015**, *35* (1), 1–62. https://doi.org/10.1002/med.21319.

(10) Sessa, C.; Lorusso, P.; Tolcher, A.; Farace, F.; Lassau, N.; Delmonte, A.; Braghetti, A.; Bahleda, R.; Cohen, P.; Hospitel, M.; et al. Phase I Safety, Pharmacokinetic and Pharmacodynamic Evaluation of the Vascular Disrupting Agent Ombrabulin (AVE8062) in Patients with Advanced Solid Tumors. *Clin. Cancer Res.* **2013**, *19* (17), 4832–4842. https://doi.org/10.1158/1078-0432.CCR-13-0427.

(11) Ho, Y. J.; Wang, T. C.; Fan, C. H.; Yeh, C. K. Current Progress in Antivascular Tumor Therapy. *Drug Discovery Today*, **2017,** *22* (10), 1503–1515. https://doi.org/10.1016/j.drudis.2017.06.001.

(12) Nishio, M.; Satouchi, M.; Horiike, A.; Horio, Y.; Sunaga, Y.; Ecstein-Fraisse, E.; Hida, T. Phase 1 Study of Ombrabulin in Combination with Docetaxel and Cisplatin in Japanese Patients with Advanced Solid Tumors. *JJCO Japanese J. Clin. Oncol. Japanese J. Clin. Oncol.* **2018**, *48* (4), 322–328. https://doi.org/10.1093/jjco/hyy026.

(13) Gill, J. H.; Rockley, K. L.; De Santis, C.; Mohamed, A. K. Vascular Disrupting Agents in Cancer Treatment: Cardiovascular Toxicity and Implications for Co-Administration with Other Cancer Chemotherapeutics. *Pharmacology and Therapeutics*, **2019**, *202,*18–31. https://doi.org/10.1016/j.pharmthera.2019.06.001.

(14) Qin, H.; Yu, H.; Sheng, J.; Zhang, D.; Shen, N.; Liu, L.; Tang, Z.; Chen, X. PI3Kgamma Inhibitor Attenuates Immunosuppressive Effect of Poly(L‐Glutamic Acid)‐Combretastatin A4 Conjugate in Metastatic Breast Cancer. *Adv. Sci.* **2019**, *6* (12), 1900327. https://doi.org/10.1002/advs.201900327.

(15) Hong, S.; Zheng, D. W.; Zhang, C.; Huang, Q. X.; Cheng, S. X.; Zhang, X. Z. Vascular Disrupting Agent Induced Aggregation of Gold Nanoparticles for Photothermally Enhanced Tumor Vascular Disruption. *Sci. Adv.* **2020**, *6* (23), 1-12. https://doi.org/10.1126/sciadv.abb0020.

(16) Pettit, G. R.; Cragg, G. M.; Herald, D. L.; Schmidt, J. M.; Lohavanijaya, P. Isolation and Structure of Combretastatin. *Can. J. Chem.* **1982**, *60* (11), 1374–1376. https://doi.org/10.1139/v82-202.

(17) Nasir, S.; Bukhari, A.; Kumar, G. B.; Revankar, H. M.; Qin, H.-L. Development of Combretastatins as Potent Tubulin Polymerization Inhibitors. **2017**, *72,* 130-147. https://doi.org/10.1016/j.bioorg.2017.04.007.

(18) Ley, C. D.; Horsman, M. R.; Kristjansen, P. E. G. Early Effects of Combretastatin-A4 Disodium Phosphate on Tumor Perfusion and Interstitial Fluid Pressure. *Neoplasia* **2007**, *9* (2), 108–112. https://doi.org/10.1593/NEO.06733.

(19) Ahmed, B.; Van Eijk, L. I.; Bouma-ter Steege, J. C.; Van Der Schaft, D. W.; Van Esch, A. M.; Joosten-achjanie, S. R.; Lambin, P.; Landuyt, W.; Griffioen, A. W. Vascular Targeting Effect of Combretastatin A-4 phosphate Dominates the Inherent Angiogenesis Inhibitory Activity, *Int. J. Cancer,* **2003,** *105* (1), 20-25. https://doi.org/10.1002/ijc.11010.

(20) Böhle, A. S.; Leuschner, I.; Kalthoff, H.; Henne-Bruns, D. Combretastatin A-4 Prodrug: A Potent Inhibitor of Malignant Hemangioendothelioma Cell Proliferation. *Int. J. Cancer* **2000**, *87* (6), 838–843. https://doi.org/10.1002/1097-0215(20000915)87:6<838::AID-IJC13>3.0.CO;2-7.

(21) Jain, R. K.; Carmeliet, P. F. Vessels of Death or Life. *Scientific American*. 2001, pp 38–45.

(22) Patterson, D. M.; Rustin, G. J. S. Vascular Damaging Agents. *Clin. Oncol.* **2007**, *19* (6), 443-456. https://doi.org/10.1016/j.clon.2007.03.014.

(23) Chaplin, D. J.; Horsman, M. R.; Siemann, D. W. Current Development Status of Small-Molecule Vascular Disrupting Agents. *Curr. Opin. Investig. Drugs* **2006**, *7* (6), 522–528.

(24) Hadimani, M. B.; Hua, J.; Jonklaas, M. D.; Kessler, R. J.; Sheng, Y.; Olivares, A.; Tanpure, R. P.; Weiser, A.; Zhang, J.; Edvardsen, K.; et al. Synthesis, in Vitro, and in Vivo Evaluation of Phosphate Ester Derivatives of Combretastatin A-4. *Bioorganic Med. Chem. Lett.* **2003**, *13* (9), 1505–1508. https://doi.org/10.1016/S0960-894X(03)00206-3.

(25) Nathan, P.; Zweifel, M.; Padhani, A. R.; Koh, D.-M.; Ng, M.; Collins, D. J.; Harris, A.; Carden, C.; Smythe, J.; Fisher, N.; et al. Phase I Trial of Combretastatin A4 Phosphate (CA4P) in Combination with Bevacizumab in Patients with Advanced Cancer. *Clin. Cancer Res.* **2012**, *18* (12), 3428–3439. https://doi.org/10.1158/1078-0432.CCR-11-3376.

(26) Griggs, J.; Metcalfe, J. C.; Hesketh, R. Targeting Tumour Vasculature : The Development of Combretastatin A4. *Lancet* **2001**, *2*, 0–5.

(27) Griggs, J.; Hesketh, R.; Smith, G. A.; Brindle, K. M.; Metcalfe, J. C.; Thomas, G. A.; Williams, E. D. Combretastatin-A4 Disrupts Neovascular Development in Non-Neoplastic Tissue. *Br. J. Cancer* **2001**, *84*, 832–835.

(28) Grosios, K.; Holwell, S. E.; McGown, A. T.; Pettit, G. R.; Bibby, M. C. In Vivo and in Vitro Evaluation of Combretastatin A-4 and Its Sodium Phosphate Prodrug. *Br. J. Cancer* **1999**, *81*, 1318–1327.

(29) Patterson, D. M.; Rustin, G. J. S. Vascular Damaging Agents. *Clin. Oncol. (R. Coll. Radiol).* **2007**, *19* (6), 443–456. https://doi.org/10.1016/j.clon.2007.03.014.

(30) Cancer Research UK. A trial looking at immunotherapy and combretastatin for advanced bowel and pancreatic cancer (A5B7-CA4P; PH1/092).

(31) Chaplin, D. J.; Hill, S. a. The Development of Combretastatin A4 Phosphate as a Vascular Targeting Agent. *Int. J. Radiat. Oncol. Biol. Phys.* **2002**, *54* (5), 1491–1496. https://doi.org/10.1016/S0360-3016(02)03924-X.

(32) Grosios, K.; Loadman, P. M.; Swaine, D. J.; Pettit, G. R.; Bibby, M. C. Combination Chemotherapy with Combretastatin A-4 Phosphate and 5-Fluorouracil in an Experimental Murine Colon Adenocarcinoma. *Anticancer Res.* **2000**, *20* (1A), 229–233.

(33) Siemann, D. W.; Mercer, E.; Lepler, S.; Rojiani, A. M. Vascular Targeting Agents Enhance Chemotherapeutic Agent Activities in Solid Tumor Therapy. *Int. J. cancer* **2002**, *99* (1), 1–6.

(34) Morinaga, Y.; Suga, Y.; Ehara, S.; Harada, K.; Nihei, Y.; Suzuki, M. Combination Effect of AC-7700, a Novel Combretastatin A-4 Derivative, and Cisplatin against Murine and Human Tumors in Vivo. *Cancer Sci.* **2003**, *94* (2), 200–204. https://doi.org/10.1111/j.1349-7006.2003.tb01419.x.

(35) Yeung, S.-C. J.; She, M.; Yang, H.; Pan, J.; Sun, L.; Chaplin, D. Combination Chemotherapy Including Combretastatin A4 Phosphate and Paclitaxel Is Effective against Anaplastic Thyroid Cancer in a Nude Mouse Xenograft Model. *J. Clin. Endocrinol. Metab.* **2007**, *92* (8), 2902–2909. https://doi.org/10.1210/jc.2007-0027.

(36) Horsman, M. R.; Murata, R.; Breidahl, T.; Nielsen, F. U.; Maxwell, R. J.; Stødkiled-Jørgensen, H.; Overgaard, J. Combretastatins Novel Vascular Targeting Drugs for Improving Anti-Cancer Therapy. Combretastatins and Conventional Therapy. *Adv. Exp. Med. Biol.* **2000**, *476*, 311–323.

(37) Horsman, M. R.; Murata, R. Combination of Vascular Targeting Agents with Thermal or Radiation Therapy. *Int. J. Radiat. Oncol.* **2002**, *54* (5), 1518–1523. https://doi.org/10.1016/S0360-3016(02)03926-3.

(38) Zweifel, M.; Jayson, G. C.; Reed, N. S.; Osborne, R.; Hassan, B.; Ledermann, J.; Shreeves, G.; Poupard, L.; Lu, S.; Balkissoon, J.; et al. Carboplatin , and Paclitaxel in Patients with Platinum-Resistant Ovarian Cancer. **2011**. https://doi.org/10.1093/annonc/mdq708.

(39) Grisham, R.; Ky, B.; Tewari, K. S.; Chaplin, D. J.; Walker, J. Clinical Trial Experience with CA4P Anticancer Therapy: Focus on Efficacy, Cardiovascular Adverse Events, and Hypertension Management. *Gynecol. Oncol. Res. Pract.* **2018**, *5* (1). https://doi.org/10.1186/s40661-017-0058-5.

(40) Uckun, F. M.; Cogle, C. R.; Lin, T. L.; Qazi, S.; Trieu, V. N.; Schiller, G.; Watts, J. M. A Phase 1B Clinical Study of Combretastatin A1 Diphosphate (OXI4503) and Cytarabine (ARA-C) in Combination (OXA) for Patients with Relapsed or Refractory Acute Myeloid Leukemia. *Cancers (Basel).* **2020**, *12* (1), 11. https://doi.org/10.3390/cancers12010074.

(41) Cogle, C. R.; Collins, B.; Turner, D.; Pettiford, L. C.; Bossé, R.; Hawkins, K. E.; Beachamp, Z.; Wise, E.; Cline, C.; May, W. S.; et al. Safety, Feasibility and Preliminary Efficacy of Single Agent Combretastatin A1 Diphosphate (OXi4503) in Patients with Relapsed or Refractory Acute Myeloid Leukemia or Myelodysplastic Syndromes. *Br. J. Haematol.* **2020**, *189* (5), e211–e213. https://doi.org/10.1111/bjh.16629.

(42) Scherer, K. M.; Bisby, R. H.; Botchway, S. W.; Hadfield, J. A.; Parker, A. W. Anticancer Phototherapy Using Activation of E -Combretastatins by Two-Photon–Induced Isomerization. *J. Biomed. Opt.* **2014**, *20* (5), 051004. https://doi.org/10.1117/1.jbo.20.5.051004.

(43) M. Scherer, K.; H. Bisby, R.; W. Botchway, S.; W. Parker, A. New Approaches to Photodynamic Therapy from Types I, II and III to Type IV Using One or More Photons. *Anticancer. Agents Med. Chem.* **2017**, *17* (2), 171–189. https://doi.org/10.2174/1871520616666160513131723.

(44) Romagnoli, R.; Baraldi, P. G.; Prencipe, F.; Oliva, P.; Baraldi, S.; Tabrizi, M. A.; Lopez-Cara, L. C.; Ferla, S.; Brancale, A.; Hamel, E.; et al. Design and Synthesis of Potent in Vitro and in Vivo Anticancer Agents Based on 1-(3′,4′,5′-Trimethoxyphenyl)-2-Aryl-1H-Imidazole. *Sci. Rep.* **2016**, *6* (1), 26602. https://doi.org/10.1038/srep26602.

(45) Brown, A. W.; Fisher, M.; Tozer, G. M.; Kanthou, C.; Harrity, J. P. A. Sydnone Cycloaddition Route to Pyrazole-Based Analogs of Combretastatin A4. *J. Med. Chem.* **2016**, *59* (20), 9473–9488. https://doi.org/10.1021/acs.jmedchem.6b01128.

(46) Madadi, N. R.; Penthala, N. R.; Howk, K.; Ketkar, A.; Eoff, R. L.; Borrelli, M. J.; Crooks, P. A. Synthesis and Biological Evaluation of Novel 4,5-Disubstituted 2H-1,2,3-Triazoles as Cis-Constrained Analogues of Combretastatin A-4. *Eur. J. Med. Chem.* **2015**, *103*, 123–132. https://doi.org/10.1016/j.ejmech.2015.08.041.

(47) Ashraf, M.; Shaik, T. B.; Malik, M. S.; Syed, R.; Mallipeddi, P. L.; Vardhan, M. V. P. S. V.; Kamal, A. Design and Synthesis of Cis-Restricted Benzimidazole and Benzothiazole Mimics of Combretastatin A-4 as Antimitotic Agents with Apoptosis Inducing Ability. *Bioorg. Med. Chem. Lett.* **2016**, *26* (18), 4527–4535. https://doi.org/10.1016/J.BMCL.2016.06.044.

(48) Kamal, A.; Shaik, A. B.; Polepalli, S.; Kumar, G. B.; Reddy, V. S.; Mahesh, R.; Garimella, S.; Jain, N. Synthesis of Arylpyrazole Linked Benzimidazole Conjugates as Potential Microtubule Disruptors. *Bioorg. Med. Chem.* **2015**, *23* (5), 1082–1095. https://doi.org/10.1016/j.bmc.2015.01.004.

(49) Mahal, K.; Biersack, B.; Schruefer, S.; Resch, M.; Ficner, R.; Schobert, R.; Mueller, T. Combretastatin A-4 Derived 5-(1-Methyl-4-Phenyl-Imidazol-5-Yl)Indoles with Superior Cytotoxic and Anti-Vascular Effects on Chemoresistant Cancer Cells and Tumors. *Eur. J. Med. Chem.* **2016**, *118*, 9–20. https://doi.org/10.1016/j.ejmech.2016.04.045.

(50) Simoni, D.; Romagnoli, R.; Baruchello, R.; Rondanin, R.; Grisolia, G.; Eleopra, M.; Rizzi, M.; Tolomeo, M.; Giannini, G.; Alloatti, D.; et al. Novel A-Ring and B-Ring Modified Combretastatin A-4 (CA-4) Analogues Endowed with Interesting Cytotoxic Activity. *J. Med. Chem.* **2008**, *51* (19), 6211-6215. https://doi.org/10.1021/jm8005004.

(51) Kamal, A.; Shaik, B.; Nayak, V. L.; Nagaraju, B.; Kapure, J. S.; Shaheer Malik, M.; Shaik, T. B.; Prasad, B. Synthesis and Biological Evaluation of 1,2,3-Triazole Linked Aminocombretastatin Conjugates as Mitochondrial Mediated Apoptosis Inducers. *Bioorg. Med. Chem.* **2014**, *22* (19), 5155–5167. https://doi.org/10.1016/j.bmc.2014.08.008.

(52) Gerova, M. S.; Stateva, S. R.; Radonova, E. M.; Kalenderska, R. B.; Rusew, R. I.; Nikolova, R. P.; Chanev, C. D.; Shivachev, B. L.; Apostolova, M. D.; Petrov, O. I. Combretastatin A-4 Analogues with Benzoxazolone Scaffold: Synthesis, Structure and Biological Activity. *Eur. J. Med. Chem.* **2016**, *120,* 121-133. https://doi.org/10.1016/j.ejmech.2016.05.012.

(53) Petit, G. R.; Singh, S. B.; Boyd, M. R.; Hamel, E.; Pettit, R. K.; Schmidt, J. M.; Hogan, F. Antineoplastic Agents. 291. Isolation and Synthesis of Combretastatins A-4, A-5, and A-6. *J. Med. Chem.* **1995**, *38*, 1666–1672.

(54) Lawrence, N. J.; Ghani, F. A.; Hepworth, L. A.; Hadfield, J. A.; McGown, A. T.; Pritchard, R. G. The Synthesis of (E) and (Z)-Combretastatins A-4 and a Phenanthrene from Combretum Caffrum. *Synthesis (Stuttg).* **1999**, *9*, 1656–1660.

(55) Fürstner, A.; Nikolakis, K. Ethynylation of Aryl Halides by a Modified Suzuki Reaction. Application to the Syntheses of Combretastatin A-4, A-5, and Lunularic Acid. *Liebigs Ann.* **1996**, *12*, 2107–2113. https://doi.org/10.1002/jlac.199619961224.

(56) Gaukroger, K.; Hadfield, J. A.; Hepworth, L. A.; Lawrence, N. J.; McGown, A. T. Novel Syntheses of Cis and Trans Isomers of Combretastatin A-4. *J. Org. Chem.* **2001**, *66*, 8135–8138.

(57) Camacho-Dávila, A. A. Kumada–Corriu Cross Coupling Route to the Anti-Cancer Agent Combretastatin A-4. *Synth. Commun.* **2008**, *38* (21), 3823–3833. https://doi.org/10.1080/00397910802238692.

(58) Malysheva, Y. B.; Combes, S.; Fedorov, A. Y.; Knochel, P.; Gavryushin, A. E. New Method of Synthesis and Biological Evaluation of Some Combretastatin A-4 Analogues. *Synlett* **2012**, *23* (08), 1205–1208. https://doi.org/10.1055/s-0031-1290899.

(59) Robinson, J. E.; Taylor, R. J. K. A Ramberg-Bäcklund Route to the Stilbenoid Anti-Cancer Agents Combretastatin A-4 and DMU-212. *Chem. Commun. (Camb).* **2007**, No. 16, 1617–1619. https://doi.org/10.1039/b702411h.

(60) Ishiyama, T.; Murata, M.; Miyaura, N. Palladium(0)-Catalyzed Cross-Coupling Reaction of Alkoxydiboron with Haloarenes: A Direct Procedure for Arylboronic Esters. *J. Org. Chem.* **1995**, *60* (23), 7508–7510. https://doi.org/10.1021/jo00128a024.

(61) Stork, G.; Zhao, K. A Stereoselective Synthesis of (Z)-1-Iodo-1-Alkenes. *Tetrahedron Lett.* **1989**, *30* (17), 2173–2174. https://doi.org/10.1016/S0040-4039(00)99640-0.

(62) Lennox, A. J. J.; Lloyd-Jones, G. C. Selection of Boron Reagents for Suzuki–Miyaura Coupling. *Chem. Soc. Rev.* **2014**, *43* (1), 412–443. https://doi.org/10.1039/C3CS60197H.

(63) Ishiyama, T.; Murata, M.; Miyaura, N. Palladium (0)-Catalyzed Cross-Coupling Reaction of Alkoxydiboron with Haloarenes: A Direct Procedure for Arylboronic Esters. *J Org Chem* **1995**, *60* (23), 7508–7510. https://doi.org/10.1021/jo00128a024.

(64) Qi, Z.-Y.; Hao, S.-Y.; Tian, H.-Z.; Bian, H.-L.; Hui, L.; Chen, S.-W. Synthesis and Biological Evaluation of 1-(Benzofuran-3-Yl)-4-(3,4,5-Trimethoxyphenyl)-1H-1,2,3-Triazole Derivatives as Tubulin Polymerization Inhibitors. **2019**. https://doi.org/10.1016/j.bioorg.2019.103392.

(65) Quan, Y. P.; Cheng, L. P.; Wang, T. C.; Pang, W.; Wu, F. H.; Huang, J. W. Molecular Modeling Study, Synthesis and Biological Evaluation of Combretastatin A-4 Analogues as Anticancer Agents and Tubulin Inhibitors. *Medchemcomm* **2018**, *9* (2), 316–327. https://doi.org/10.1039/c7md00416h.

(66) Assali, M.; Kittana, N.; Qasem, S. A.; Adas, R.; Saleh, D.; Arar, A.; Zohud, O. Combretastatin A4-Camptothecin Micelles as Combination Therapy for Effective Anticancer Activity. *RSC Adv.* **2019**, *9* (2), 1055–1061. https://doi.org/10.1039/C8RA08794F.

(67) Shen, Y. N.; Lin, L.; Qiu, H. Y.; Zou, W. Y.; Qian, Y.; Zhu, H. L. The Design, Synthesis, in Vitro Biological Evaluation and Molecular Modeling of Novel Benzenesulfonate Derivatives Bearing Chalcone Moieties as Potent Anti-Microtubulin Polymerization Agents. *RSC Adv.* **2015**, *5* (30), 23767–23777. https://doi.org/10.1039/c4ra12108b.

(68) Gaspari, R.; Prota, A. E.; Bargsten, K.; Cavalli, A.; Steinmetz, M. O. Structural Basis of Cis- and Trans-Combretastatin Binding to Tubulin. *Chem,* **2017**, *2* (1), 102-113. https://doi.org/10.1016/j.chempr.2016.12.005.

(69) Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendall, D. Isolation and Structure of the Strong Cell Growth and Tubulin Inhibitor Combretastatin A-4. *Experientia* **1989**, *45* (2), 209–211.

(70) Pettit, G. R.; Temple, C.; Narayanan, V. L.; Varma, R.; Simpson, M. J.; Boyd, M. R.; Rener, G. A.; Bansal, N. Antineoplastic Agents 322. Synthesis of Combretastatin A-4 Prodrugs. *Anticancer. Drug Des.* **1995**, *10* (4), 299–309.

(71) Lu, Y.; Chen, J.; Xiao, M.; Li, W.; Miller, D. D. An Overview of Tubulin Inhibitors That Interact with the Colchicine Binding Site. *Pharm. Res.* **2012**, *29* (11), 2943–2971. https://doi.org/10.1007/s11095-012-0828-z.

(72) Wang, T. C.; Cheng, L. P.; Huang, X. Y.; Zhao, L.; Pang, W. Identification of Potential Tubulin Polymerization Inhibitors by 3D-QSAR, Molecular Docking and Molecular Dynamics. *RSC Adv.* **2017**, *7* (61), 38479–38489. https://doi.org/10.1039/C7RA04314G.

(73) Sriram, M.; Hall, J. J.; Grohmann, N. C.; Strecker, T. E.; Wootton, T.; Franken, A.; Trawick, M. L.; Pinney, K. G. Design, Synthesis and Biological Evaluation of Dihydronaphthalene and Benzosuberene Analogs of the Combretastatins as Inhibitors of Tubulin Polymerization in Cancer Chemotherapy. *Bioorg. Med. Chem.* **2008**, *16* (17), 8161–8171. https://doi.org/10.1016/j.bmc.2008.07.050.

(74) Wu, M.; Sun, Q.; Yang, C.; Chen, D.; Ding, J.; Chen, Y.; Lin, L.; Xie, Y. Synthesis and Activity of Combretastatin A-4 Analogues: 1,2,3-Thiadiazoles as Potent Antitumor Agents. *Bioorg. Med. Chem. Lett.* **2007**, *17* (4), 869–873. https://doi.org/10.1016/j.bmcl.2006.11.060.

(75) Mangiatordi, G. F.; Trisciuzzi, D.; Alberga, D.; Denora, N.; Iacobazzi, R. M.; Gadaleta, D.; Catto, M.; Nicolotti, O. Novel Chemotypes Targeting Tubulin at the Colchicine Binding Site and Unbiasing P-Glycoprotein. *Eur. J. Med. Chem.* **2017**, *139*, 792–803. https://doi.org/10.1016/j.ejmech.2017.07.037.

(76) Mikstacka, R.; Stefański, T.; Rózański, J. Tubulin-Interactive Stilbene Derivatives as Anticancer Agents. *Cell. Mol. Biol. Lett.* **2013**, *18* (3), 368–397. https://doi.org/10.2478/s11658-013-0094-z.

(77) Kanthou, C.; Greco, O.; Stratford, A.; Cook, I.; Knight, R.; Benzakour, O.; Tozer, G. The Tubulin-Binding Agent Combretastatin A-4-Phosphate Arrests Endothelial Cells in Mitosis and Induces Mitotic Cell Death. *Am. J. Pathol.* **2004**, *165* (4), 1401–1411. https://doi.org/10.1016/S0002-9440(10)63398-6.

(78) Wang, L. G.; Liu, X. M.; Kreis, W.; Budman, D. R. The Effect of Antimicrotubule Agents on Signal Transduction Pathways of Apoptosis: A Review. *Cancer Chemother. Pharmacol.* **1999**, *44* (5), 355–361. https://doi.org/10.1007/s002800050989.

(79) Zhu, M.-L.; Horbinski, C. M.; Garzotto, M.; Qian, D. Z.; Beer, T. M.; Kyprianou, N. Tubulin-Targeting Chemotherapy Impairs Androgen Receptor Activity in Prostate Cancer. *Cancer Res.* **2010**, *70* (20), 7992–8002. https://doi.org/10.1158/0008-5472.CAN-10-0585.

(80) Gerova, M. S.; Stateva, S. R.; Radonova, E. M.; Kalenderska, R. B.; Rusew, R. I.; Nikolova, R. P.; Chanev, C. D.; Shivachev, B. L.; Apostolova, M. D.; Petrov, O. I. Combretastatin A-4 Analogues with Benzoxazolone Scaffold: Synthesis, Structure and Biological Activity. *Eur. J. Med. Chem.* **2016**, *120*, 121–133. https://doi.org/10.1016/j.ejmech.2016.05.012.

(81) Mamiya, F.; Ousaka, N.; Yashima, E. Remote Control of the Planar Chirality in Peptide-Bound Metallomacrocycles and Dynamic-to-Static Planar Chirality Control Triggered by Solvent-Induced 3 10 -to-α-Helix Transitions. *Angew. Chemie Int. Ed.* **2015**, *54* (48), 14442–14446. https://doi.org/10.1002/anie.201507918.

(82) Luo, Z.; Guo, Q.; Liu, X.; Ye, X.; Hongru, L.; Gao, F. Novel Two-Photon Singlet Oxygen Photosensitizers: Experimental and Theoretical Studies of Numbers of Bromine Atoms Effect. *Curr. Org. Chem.* **2013**, *17* (3), 1–13.

(83) Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraborti, A. K.; Lin, C. M.; Hamel, E. Synthesis and Evaluation of Stilbene and Dihydrostilbene Derivatives as Potential Anticancer Agents That Inhibit Tubulin Polymerization. *J. Med. Chem.* **1991**, *34* (8), 2579–2588.

(84) Motoshima, K.; Ishikawa, M.; Hashimoto, Y.; Sugita, K. Inhibition of Restriction Enzymes EcoRI, BamHI and HindIII by Phenethylphenylphthalimides Derived from Thalidomide. *Chem. Pharm. Bull.* **2011**, *59* (7), 880–884. https://doi.org/10.1248/cpb.59.880.

(85) Fischer, F.; Schmutzler, F.; Haak, E. Kondensation von Verbindungen Des Vollacetal-Typs Mit C-H aciden Verbindungen I. Kondensation von Bromacetaldehyddiathylacetal Mit Phenolathern Und von Benzaldehyd-Bisaminalen Des Piperidins Und Morpholins Mit Ketonen. *J. Prakt. Chemie* **1964**, *24* (3–4), 216–225. https://doi.org/10.1002/prac.19640240313.

(86) Liu, Y. Q.; Li, X. J.; Zhao, C. Y.; Lu, Y.; Li, W. Q.; Liu, Z. L.; Feng, G.; Yang, L. Synthesis and Insect Antifeedant Activity of Stilbene Derivatives against Brontispa Longissima Larvae. *Med. Chem. Res.* **2013**, *22* (5), 2196–2206. https://doi.org/10.1007/s00044-012-0212-x.