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Antimitotic activity of structurally simplified biaryl analogs of the anticancer agents colchicine and combretastatin A4

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Abstract – Two substituted biaryl analogues of colchicine and combretastatin A4, readily available through a one-step, protecting group free Suzuki-Miyaura reaction were discovered to exhibit anticancer activity while simultaneously being of low cytotoxicity to noncancerous cell lines. The compounds were shown to initiate apoptosis selectively via a mechanism involving inhibition of tubulin polymerization.

Since their isolation from the African bush willow *Combretum caffrum* by Pettit and co-workers in 1982,[1] the combretastatin phenolic-stilbenes have attracted considerable attention in view of the potent anticancer activity demonstrated.[2] Colchicine **1**, as well as the combretastatin **2-4** (see Figure 1) antimitotics share obvious structural similarities and have been collectively referred to as colchicinoids.[2b] Their potent antimitotic activity is attributed to microtubule-destabilization through inhibition of tubulin polymerization, acting at a site distinct from the vinca-alkaloid tubulin destabilizing agents (vinblastine, vincristine etc). Disruption of the microtubule assembly process results in the induction of apoptosis in actively dividing cells. The combretastatins are distinct in their mode of activity from other tubulin-active agents, such as paclitaxel (taxol) **5**, that act directly on assembled microtubules enhancing tubulin polymerization. Both classes of tubulin-interactive compounds ultimately interfere with the normal cellular vascalature[2d] resulting in apoptosis induction. The combretastatins are also highly distinctive by comparison with paclitaxel and other taxoids in view of their relative structural simplicity.

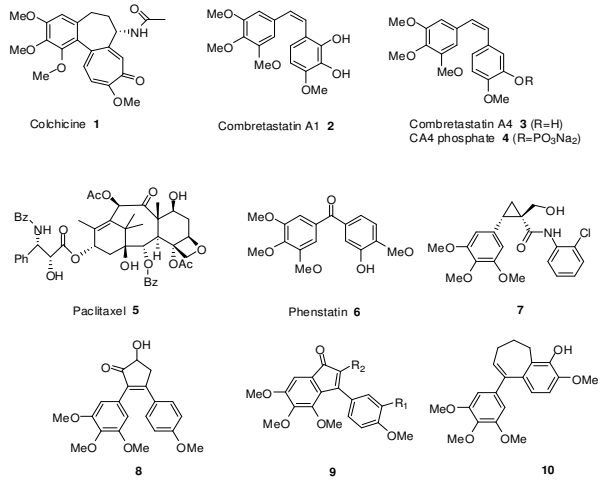

Figure 1. Structures of colchicinoid antimitotics **1**-**4**, paclitaxel **5** and a selection of synthetic stilbenoid modifications **6** to**10 .**

The synthesis and biological evaluation of many structural analogues of the combretastatins has been carried out over the last two decades.[2,3] As select examples, Pettit and co-workers reported the synthesis of phenstatin **6**, its phosphate derivative and analogs some of which exhibited nanomolar potencies to human tumor cell lines.[3d] Chen and co-workers synthesized a series of analogs containing a cyclopropylamide bridge **7** that showed micromolar activity to select human cancer cell lines.[3e] Gurjar and co-workers synthesized a series of analogs with hydroxycyclopentenone or hydroxycyclopentenone oxime bridges based on **8,** examples of which exhibited nanomolar activity towards human cell cancer lines (oral, larynx, ovary, colon, lung, pancreas) and anti-tubulin activity of 1.75

μM.[3f] Flynn and co-workers synthesized a series of combretastatin A4 (CA-4) indenone derivatives **9** that showed tubulin inhibition properties but no cytotoxicity to MCF-7 breast cancer cells,[3g] while Pinney et al. synthesized a library of benzosuberene analogs **10** that showed nM activity to some cancer cell lines.[3h]

These varied structure-activity studies have allowed development of a relatively clear view of the anticancer pharmacophore, outlined in Figure 2. Three preferred embodiments (circled) include a 3,4,5-trimethoxyaryl motif in ring-A, a *cis*-configured stilbene or analog thereof linking ring-A to a 3,4-substituted methoxyphenol as ring-B.[2b] Small deviations from these requirements often result in total loss of apoptosis-inducing and anticancer activity. Currently, CA-4 **3** and its disodium-phosphate prodrug **4** are the most investigated compounds in the series having advanced to Phase II and III clinical trials in a variety of human cancers[4a] as well as treatment of diabetic retinopathy,[4b] the most common cause of blindness, in view of the potent vascular disrupting activity demonstrated.

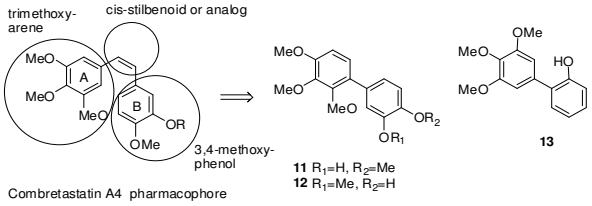

Figure 2. Depiction of the 3-component combretastatin A4 pharmacophore and reduction to simplified biaryl analogs **11** and **12**.

In view of the structural requirements of the CA-4 pharmacophore and the biaryl linkage found within colchicine **1**, we postulated that complete removal of the double bond and re-connection of the two aryl rings as direct biaryl derivatives, leading to structures **11** and **12** (Figure 2), might lead to structurally simplified analogs retaining anticancer activity. We recently disclosed that the styryl-double bond in the anticancer natural product narciclasine was detrimental to further development of this compound due to the interaction of human cytochrome P450 enzymes at this site.[5] Removal of the double bond, as in CA4 analogues **11** and **12**, could also lead to more metabolically stable analogs. A successful outcome of this biaryl strategy is not obvious given that many biaryl natural products are known in particular being commonly found as antifungal phytoalexins in plants of the Rosaceae family. The closest examples recorded include biaryl compounds such as **13** (Scheme 2), which were reported to be devoid of anticancer activity.[6] Nonetheless, we considered pursuit of **11** and **12** worthwhile given the known peculiarities of the combretastatin A4 pharmacophore.

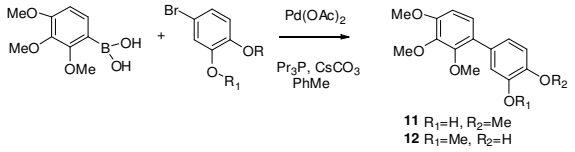

Figure 3. Suzuki-Miyaura cross coupling as a direct synthesis of biaryl analogs **11** and **12**.

As part of our research program investigating the apoptosis-inducing activity of natural products and structural analogs,[7] we have amassed a large collection of variously substituted biaryl[8] and stilbenoid[9] derivatives. Compounds **11** and **12** were prepared[8] as part of this program (McMaster) and included in a library consisting of 600 compounds, which was screened blind (Windsor) against an osteocarcoma cell line (U-2 OS). Each of the compounds was tested at a concentration of 10 μM for 48 hours. Compounds that significantly reduced the proliferation of these cancer cells were further studied allowing identification of four efficient inducers of apoptosis. Two of these compounds were positive controls (pancratistatin and narciclasine) randomly seeded in the library, while the other two compounds proved to be the biaryl derivatives **11** and **12**. The two compounds were readily accessed on scale-up of the original synthesis[8] and were readily prepared in one step, without requirement of phenol protection, using a standard Suzuki-Miyaura cross-coupling reaction (Figure 3). As a result, large amounts of **11** and **12** were prepared for further study.

Screening of analogs **11** and **12** for anti-proliferative properties was conducted in leukemia and osteocarcoma cell lines, as well as in noncancerous colon epithelial cells (Table. 1). The half-maximal inhibitory concentration (IC_{50}) was calculated for CA-4 and the biarly analogs and in each cell line, without exception, CA-4 had an IC_{50} at least two orders of magnitude lower than that of analogues **11** and **12**.

	IC_{50} (μM)				
	MV-4-11	E6-1	Saos-2	U-2 OS	NCM460
11	2.76 ± 0.26	0.965 ± 0.085	5.43 ± 1.2	> 20	> 20
12	1.25 ± 0.052	0.486 ± 0.044	1.77 ± 0.42	> 20	> 20
CA-4	0.00627 ± 0.00078	0.00608 ± 0.0014	0.0114 ± 0.0019	0.0141 ± 0.00143	> 20

Table 1. IC_{50} values of structures **11**, **12**, and CA-4 were determined at the 48 hour time point in several cancerous and noncancerous cell lines. MV-4-11 = myelocytic leukemia; E6-1 = acute T-cell leukemia; Saos-2 & U-2 OS = osteocarcoma; NCM460 = normal colon epithelial cells. Values are represented as mean of quadruplicates ± SD of three independent trials.

Despite the lower potency of biaryls **11** and **12**, both compounds still possessed strong anticancer properties, clearly exhibited in the Saos-2 osteocarcoma cell line and the leukemia cells lines, MV-4-11 and E6-1. In these cells lines, while CA-4 possessed a lower IC_{50} value, all three compounds, including **11** and **12**, reduced the proliferation of the cancer cells to the same low level (Figure 4). This is important when considering the lack of anti-proliferative properties exhibited in the noncancerous NCM460 cells. With doses as large as 20 µM not bringing the proliferation of the cells below 50%, it may be concluded that all compounds tested were effective at reducing the proliferation of cancer cells selectively in the *in-vitro* model used.

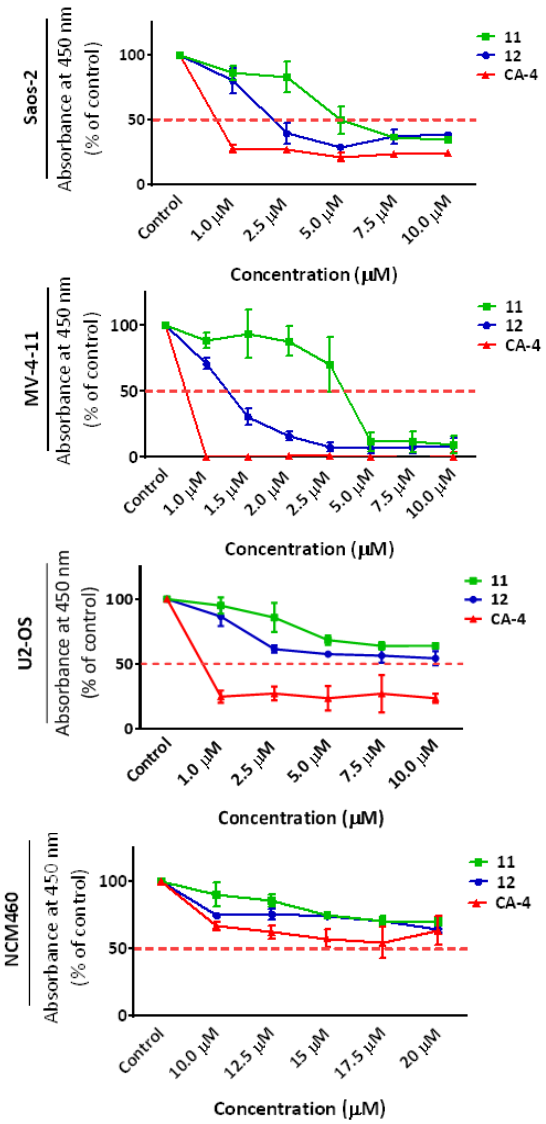

Figure 4. Dose-response curves of **11**, **12**, and combretastatin A4 at 48 hours in various cancerous and noncancerous cell lines. Values are represented as mean of quadruplicates ± SD of three independent trials.

The one outlier appeared to be the U-2 OS cell line, in which **11** and **12** appeared to have little effect when considering that its IC_{50} was above 20 µM, while CA-4 retained its typically low IC_{50} value. However, at a range consistent with the other reported IC_{50} values (2.5-5.0 µM), **11** and **12** succeeded at reducing the proliferation of the U-2 OS osteocarcoma cells to approximately 60% (Figure 4). It was because of this reduction in proliferation that compounds **11** and **12** were first identified in the blind screen. In the same dose range of 2.5-5.0 µM, C-A4 reduced cell proliferation to approximately 30%, suggesting that the large difference in IC_{50} values did not mirror a similarly disproportionate difference in overall anticancer activity towards the U-2 OS osteocarcoma cell line.

The ability of **11** and **12** to induce apoptosis in cancer cells was evaluated and compared to that of CA-4 (Figure 5). Apoptotic induction was monitored by observing phosphatidylserine externalization, which is a characteristic feature of apoptosis that leads to identification and consumption of apoptotic cells by surrounding macrophages.[10] To do so, Annexin V, a molecule with natural affinity for phosphatidylserine, conjugated to Alexa Fluor 488 (green fluorescent probe) was utilized. Additionally, propidium iodide (red fluorescent probe) uptake by cells with permeabalized membranes (i.e. necrotic cells) was monitored. Cell populations exhibiting green and/or red fluorescence were quantified using image-based cytometry. Paralleling the data obtained with the proliferation screen, CA-4 was effective at inducing apoptosis at lower doses than both **11** and **12**. This was the case with both Saos-2 osteocarcoma cell line and the MV-4-11 leukemia cell line. However, at higher doses, **11** and **12** approached the level of activity seen with CA-4, particularly structure **12**, which at 5.0 µM in both the Saos-2 and MV-4-11 cancer cells matched the anticancer activity witnessed with CA-4 at the same dose. Lastly, and most importantly, all three treatments did not cause an increase in apoptotic/necrotic cell populations in the noncancerous model (NCM460 cells) studied.

It was also seen that the levels of apoptotic cells (those exhibiting green fluorescence above base levels observed in the control) exceeded the levels of necrotic cells (those exhibiting red fluorescence above basal levels). Cells that exhibited elevated red and green fluorescence were considered both apoptotic and necrotic. Overall, the data suggested that treatment with **11**, **12**, and CA-4 resulted in cell suicide that progressed towards necrosis in our *in-vitro* model that lacked macrophages.

From the data gathered on the ability of **11** and **12** to halt cancer proliferation and induce cell death, it was clearly discerned that structure **12** is a more effective anticancer compound than **11**, considering that both compounds did not have a deleterious impact on the noncancerous NCM460 cells. Not only did **12** have a lower IC_{50} in all of the cancerous cell lines tested for which a concrete IC_{50} value could be obtained, it was also more effective at inducing apoptosis. This evidence suggests that phenyl substitution in ring-B of the biaryl having the hydoxyl group in the para position and the methoxy group in the meta position, is more effective than the reverse constitution. This evidence is in accord with the body of knowledge obtained around the CA-4 pharmacophore, the structure of which most closely overlaps with the biaryl **12**. These data illuminate the subtleties of this new biaryl apoptosis-inducing pharmacophore, particularly given the inactivity of many known biaryl derivatives such as **13**,[6] for further development of leads in the series.[11]

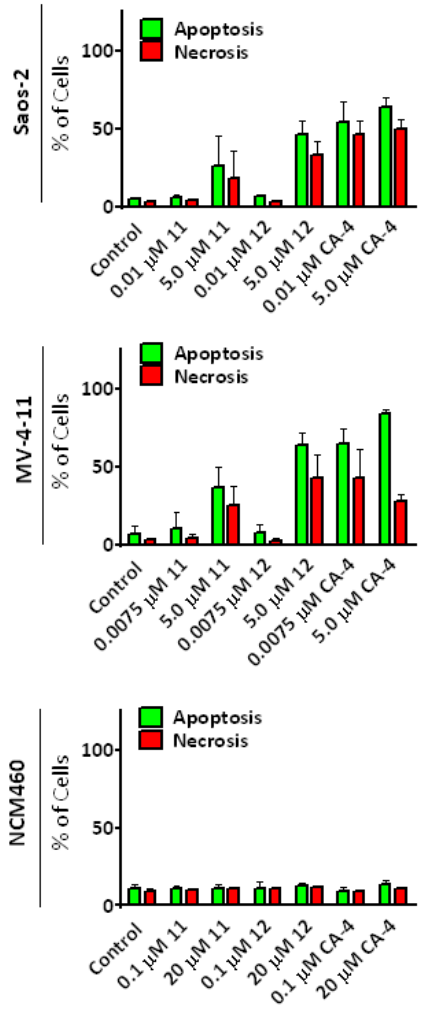

Figure 5. Apoptotic induction was selectively induced by **11**, **12**, and CA-4 at 48 hours. Values are represented as mean ± SD of three independent trials.

Finally, we wished to obtain evidence that the primary mechanism of action of CA-4, that of mitotic suppression via inhibition of tubulin polymerization, was still present with **11** and **12** (Figure. 6). Using an *in vitro* assay, microtubule polymerization was monitored kinetically for one hour, either in the presence of DMSO vehicle control or studied compound. The extent of microtubule polymerization was determined fluorometrically based on the incorporation of a fluorescent reporter. Tubulin polymerization was completely abolished by 3 μM CA-4, in a manner similar to positive control colchicine. Conversely, 3 μM **11** had no impact on tubulin dynamics and 3 μM **12** had only a moderate effect. With 10 μM of **11,** a similarly moderate effect was noticed while 10 μM of **12** was almost as effective as the lower dose of CA-4. Thus, a clear relationship between the anticancer effect and impact on tubulin dynamics was discerned. **11** was least effective at inhibiting tubulin polymerization and similarly, was least effective at inhibiting cancer proliferation and inducing apoptosis. **12** was more effective than **11** at both the inhibition of tubulin polymerization and the induction of cell death in cancer cells. Lastly, CA-4 was the most effective at halting tubulin polymerization and causing the cancer cells to commit suicide. Thus, a correlation can be drawn between the ability of these colchicinoids to disrupt tubulin dynamics and cause cell death.

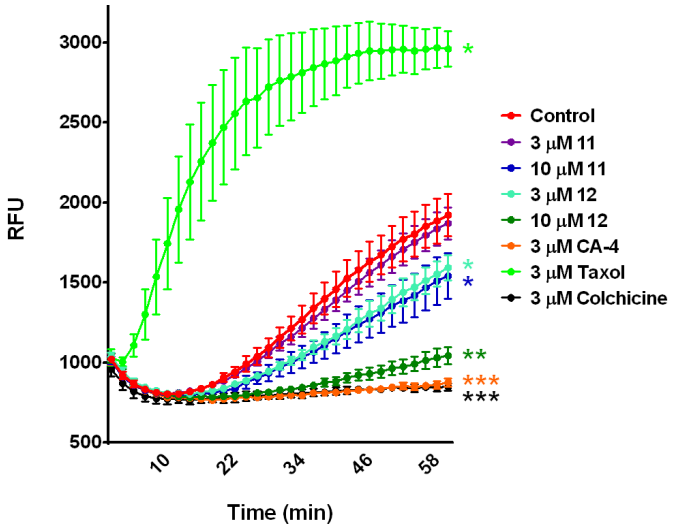

Figure 6. Tubulin polymerization *in vitro* was inhibited by the colchicinoid combretastatin A4, as well as novel biaryl analogs **11** and **12.** RFU = relative fluorescent units. Values are represented as mean of duplicates ± SEM of three independent trials. * $p < 0.05$ vs. control; ** $p < 0.005$ vs. control; *** $p < 0.0005$ vs. control.

Although the novel biaryl analogues are less effective, with a sufficient dose it can be seen that at least **12** was able to completely abolish tubulin polymerization,

presumably leading to the witnessed apoptosis. The potential advantage of analogs **11** and **12** are their simplicity, even in comparison to CA-4. Lacking the connecting stilbene group, **11** and **12** are expected to be less sensitive to cytochrome P450. Additionally, the conformation of the two aryl rings should be more stable and less prone to conformational change, as there is not an ethylene linker, isomerization of which from active *Z*-isomer to inactive *E*-isomer has been shown to abolish cytotoxic effects.[11] In fact, much research has been focused on attempting to alter the *cis*-stilbenoid pharmacophore in order to lock in a *cis* configuration, thus producing a more stable linker between the two rings. Recent examples include the replacement of the ethylene linker with a N-acylhydrazone scaffold[12] or pyridine ring.[13] While the two sets of CA-4 analogs show promise, as several of the synthesized compounds possess potent cytotoxic effects, they are relatively complicated structures. While it is true that **11** and **12** exhibit significantly less cytotoxicity in cancer cells, they are simpler structures that are easily synthesized and may possess similar stability, although it remains to be confirmed.

Additionally, the lack of cytotoxic effects in the nanomolar range for **11** and **12** may not be a large detriment as higher doses can be used moving forward as doses up to 20 μM were well tolerated in the noncancerous cells studied. However, to confirm the selectivity of **11** and **12**, further noncancerous cell lines need to be screened. To further evaluate the selectivity of **11** and **12**, they could also be tested in colon cancer cell lines, which would be a direct counterpart to the noncancerous colon cells (NCM460) tested.

The most significant aspect of this research, perhaps, is the potential for a paradigm shift, as far as the synthesis of new colchicine and CA-4 analogs is concerned. It has been seemingly established in literature that the optimal length of the linker between the two rings in CA-4 is two carbons, based on the (*Z*)-ethylene linker.[11,14] This assertion is not without a plethora of supporting evidence, summed up well by Tron et al.[11] Standing in contrast to this large body of research is the unusual case of phenstatin, which features aryl rings linked by a carbonyl group and possesses similar activity to CA-4.[3d] Building on the premise of structurally active CA-4 analogs with linkers of less than two carbons, research has been published on the great potential of *iso*CA-4 and related analogs, which are structurally similar to phenstatin, and are comprised of a 1,1-diarylethylene scaffold.[15] These unique CA-4 analogs are linked only by a single carbon, which has been otherwise thought to yield a distance between the two aryl rings that was two small for effective binding to tubulin or for cytotoxic effects. Our research extends the work on 1,1-diarylethylene analogs of CA-4 but now provides further evidence that effective CA-4 analogs can be discovered with linkers of less than two carbons. The new antimitotics **11** and **12** demonstrate that simple vascalature disrupting/apoptosis-inducing agents can be derived from directly coupled biaryl derivatives based on the CA-4 pharmacophore. In conclusion, simplified biaryl structures may now be added to the growing arsenal of colchicinoid vasculature disrupting agents in the pursuit of potent, selective anticancer agents.

Acknowledgements

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Supplementary data

Experimental procedures and characterization data are provided.

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Graphical abstract