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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.

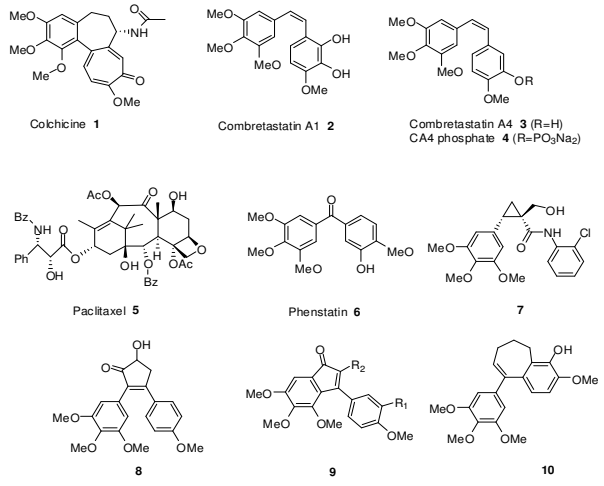

Figure 1. Structures of colchicinoid antimitotics **1**-**4**, paclitaxel **5** and a selection of synthetic stilbenoid modifications **6** to**10 .**

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