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Colchicine site ligands with indole B rings are potent tubulin polymerization inhibitors. Structural modifications at the indole 3-position of 1-methyl-5-indolyl-based isocombretastatins (1,1-diarylethenes) and phenstatins endowed them with anchors for further derivatization and resulted in highly potent compounds. The substituted derivatives displayed potent cytotoxicity against several human cancer cell lines due to tubulin inhibition, as shown by cell cycle analysis, confocal microscopy, and tubulin polymerization inhibitory activity studies and promoted cell killing mediated by caspase-3 activation. Binding at the colchicine site was confirmed by means of fluorescence measurements of MTC displacement. Molecular modeling suggests that the tropolone-binding region of the colchicine site of tubulin can adapt to hosting small polar substituents. Isocombretastatins accepted substitutions better than phenstatins, and the highest potencies were achieved for the cyano and hydroxyiminomethyl substituents, with TPI values in the submicromolar range and cytotoxicities in the subnanomolar range. A 3,4,5-trimethoxyphenyl ring usually afforded more potent derivatives than a 2,3,4-trimethoxyphenyl ring.