Synthesis and Biological Evaluation of Small Molecular Compounds as Potent Antimitotic/Vascular Disrupting Agents

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A series of aroylquinoline derivatives ([6,6]-fused heterocycle) were synthesized and evaluated for anticancer activity. 5-Amino-6-methoxy-2-aroylquinoline **15** showed more potent antiproliferative activity (IC_{50} values ranging from 0.2 to 0.4 nM) as compared to combretastatin A-4 (CA4, IC_{50} = 1.9-835 nM) against various human cancer cell lines and a MDR-resistant cancer cell line. Compound **15** (IC_{50} = 1.6 μM) exhibited more potent inhibition of tubulin polymerization than CA4 (IC_{50} = 2.1 μM) and showed strong binding property to the colchicine binding site of microtubules.

In an attempt to mimic the 3,4,5-trimethoxyphenyl-Z-stilbene moiety of combretastatin A-4, a series of N-aryl-5,6,7-trimethoxyindoles ([6,5]-fused heterocycle) were synthesized via copper-catalyzed Ullmann-type N-arylation through corresponding 5,6,7-trimethoxyindole and aryl halides. These synthesized compounds demonstrated potent antiproliferative activity providing a novel skeleton for potent tubulin polymerization inhibitors. Compound **6** demonstrated substantial vascular disrupting activity (VDA), which was capable to disrupt formed capillaries in concentration-dependent manner without affecting cell viability.