1, 6-Diaryl-3(Z)-hexen-1, 5-diynes as Antitumor Agents

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A series of 1,5-diaryl-3(Z)-hexen-1,5-diynes have been synthesized and the growth inhibition activity against various human tumor cell lines have also been evaluated. 2-(6-(2-Trifluoromethylphenyl))-3(Z)-hexen-1,5-diynylaniline (1) was found to show high potency of growth inhibition activity. After a 24 h treatment with compound 1, a strong ability to induce a massive accumulation of cells in the G2/M phase was observed. After 72 h treatment with compound 1, some of the cells undergo apoptosis via activation of caspase-3, -8 and -9. A brief exposure of the MDA-MB-231/ATCC cells to compound 1 is sufficient to produce sustained de-polymerization of the microtubules in a concentration-dependent manner. The disruption of microtubule is reversible when the drug is removed, which indicates a lower toxicity of this compound. The ligand docking experiment shows that compound 1 binds to the α- and β-tubuline in the same manner as colchicine. The trifluoromethylphenyl group of 1 coincides with the trimethoxyphenyl subsunit of colchicine and the amino group of 1 serves a hydrogen bond acceptor with α-tubulin (179-Thr and 181-Val), similar to the carbonyl group of colchicine. Replacing the ortho-trifluoromethylphenyl ring of compound 1 to 3,4,5-trimethoxyphenyl group gave compound 2. Compound 2 was found to exhibit even higher potency of growth inhibition activity against some human cancer cell lines.