



Novel Combretastatin A-4 Analogues with Potent Cytotoxicity and Anti-Tubulin Polymerization Activities (*William J. Welsh, RWJ 04-29*) Therapeutic

Background

The microtubule system of eukaryotic cells is considered to be a target for the development of anti-cancer agents. The α - and β -tubulin heterodimer is the building block of microtubules and, as such, is the biochemical target for several clinically used chemotherapeutics. Colchicine, paclitaxel and other clinically used anti-tubulin drugs often face limitations such as neural and systemic toxicity, poor water solubility and bioavailability, and complex synthetic pathways and isolation procedures. The present invention describes five novel small-molecule compounds that exhibit anti-tubulin polymerization and anti-cancer activity.

Description of the Technology

The present invention describes the rational design, synthesis and biological evaluation of a series of novel small-molecule compounds that exhibit strong *in vitro* anti-tubulin polymerization activity as well as cytotoxicity in the low nM range against four cancer cell lines isolated from cervical, breast and colon tumors. Moreover, these compounds show significant cytotoxicity in human cervix epithelial adenocarcinoma and colon carcinoma cells which overexpress multiple drug resistance. Furthermore, these novel inhibitors are water soluble and predicted to exhibit good bioavailability. These compounds and their analogues are also attractive from the standpoint of medicinal chemistry and large-scale chemical synthesis, by virtue of the absence of chiral (stereochemical) centers and the efficient 5-step reaction scheme which renders the desired product in high yield employing inexpensive starting materials.

Applications

Compounds of this invention can be used as anti-cancer agents

Patent Status

PCT patent application filed

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