Design of Novel Tubulin Polymerization Inhibitors Based on CA-4

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- Combretastatin A-4(CA-4), a group of polyhydroxylated stilbenes isolated from the bark of the South African tree Combretum Caffrum, is a highly effective natural tubulin-binding molecule affecting microtubule dynamics by binding to the colchicines site. Its water soluble phosphate ester (CA-4P) is under evaluation in phase 3 trials for treatment of anaplastic thyroid cancer and in phase 2 trials for non-small cell lung cancer and platinum-resistant ovarian cancer, thus stimulating significant interest in a variety of combretastatin A-4 analogues. Unfortunately, a problem have limited their use as therapeutic agents. The cis configuration is biologically active, with the trans form showing significantly inactive. The active cis double bond in CA-4 is readily converted to the more stable trans isomer during storage or metabolism by heat, light, and protic media , resulting in a dramatic decrease in antitumor activity. Thus, it is necessary to design and discover novel cis configuration inhibitors based on CA-4.
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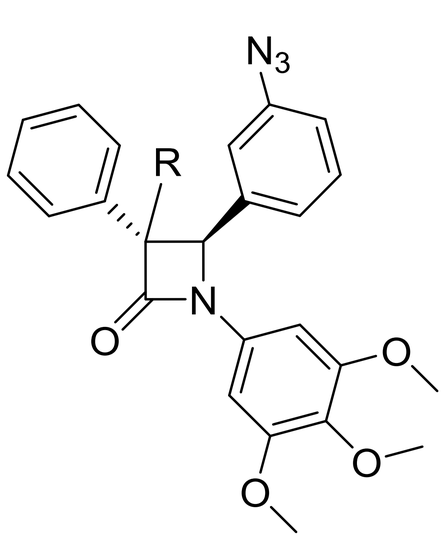
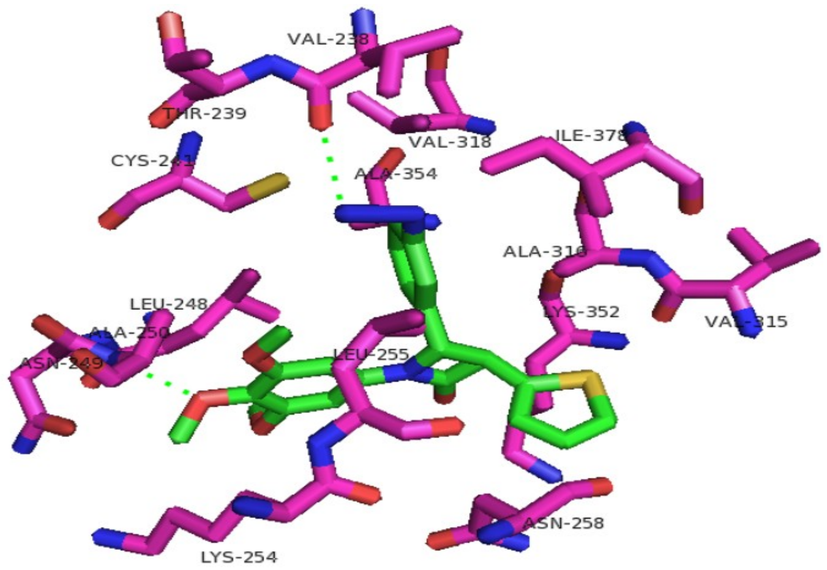
- β-Lactam skeleton has attracted much attention from medicinal chemists for many years because of their numerous biological activities, especially their antitumor activity. Importantly, some β-lactam analogues were shown to cause apoptosis in cancer cells through induction of microtubule disorganization and mitotic catastrophe. In our lab, a series of β-lactam-azide derivatives as tubulin polymerization inhibitors were synthesized and evaluated their antitumor activity in vitro and in vivo. In addition, the detailed structure activity relationships in five regions of β-lactam-azides were explored to provide further insight for developing more efficient tubulin targeting and antiproliferative agents for cancer therapy.





- **Keywords**: Combretastatin A-4; cis configuration; antitumor.

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