Abstract

Prostate cancer is the most common non-skin cancer for men in America. The androgen receptor exerts transcriptional activity and plays an important role for the proliferation of prostate cancer cells. Androgen receptor ligands bind the androgen receptor and inhibit its transcriptional activity effectively. However, prostate cancer can progress to hormone refractory prostate cancer (HRPC) to avoid this effect. Chemotherapies are currently the primary treatments for HRPC. Unfortunately, none of the available chemotherapies are curative. Among them, paclitaxel and docetaxel are two of the most effective drugs for HRPC. More importantly, docetaxel is the only form of chemotherapy known to prolong survival in the HRPC patients. We hypothesized that the conjugation of paclitaxel or docetaxel with an androgen receptor ligand will overcome the resistance mechanism of HRPC. Eleven conjugates were designed, synthesized and biologically evaluated. Some of them were active against androgen-independent prostate cancer, but they were all less active than paclitaxel and docetaxel.

Discodermolide is a microtubule interactive agent, and has a similar mechanism of action to paclitaxel. Interestingly, discodermolide is active against paclitaxel-resistant cancer cells and can synergize with paclitaxel, which make it an attractive anticancer drug candidate. Understanding the bioactive conformation of discodermolide is important for drug development, but this task is difficult due to the linear and flexible structure of discodermolide. Indirect evidence for the orientation of discodermolide in the tubulin binding pocket can be obtained from fluorescence spectroscopy of the discodermolide tubulin complex. For this purpose, we designed and synthesized a simplified fluorescently labeled discodermolide analog, and it was active in the tubulin assembly bioassay. In addition, a conformationally constrained discodermolide was designed to mimic the bioactive conformation according to computational modeling. The synthetic effort was made, but failed during one of the final steps.