Chaper 7. Conclusion

Eleven paclitaxel or docetaxel analogs with a cyanonilutamide moiety linked at the C7, C10 or C3' position through linkers of various lengths were designed and synthesized. Among them, the C7 paclitaxel analogs all showed significantly reduced activity in the A2780 bioassay and tubulin assembly bioassays compared with paclitaxel, but all C10 docetaxel analogs preserved the tubulin assembly activities or even show enhanced activities in comparison with docetaxel. This result suggests that the C7 position in paclitaxel or docetaxel is more sensitive to the influence of bulky substituents on tubulin assembly and antiproliferative activity than the C10 position. Additionally, the C3' docetaxel analog was not as active as we had been expected, indicating the limitation of modifications at this position.

In androgen-dependent prostate cancer cells, the C10 docetaxel analogs displayed similar activity to that of paclitaxel or docetaxel in agreement with the results from the A2780 and tubulin assembly bioassays. However, it was disappointing that none of them were as active as paclitaxel or docetaxel against androgen-independent prostate cancer cells, although the C10 docetaxel analogs did show much better activity than the other analogs. This result may be due to fact that paclitaxel or docetaxel bind to the inner surface of microtubules, which would require a longer linker to allow the cyanonilutamide moiety to reach outside the microtubule tube, making the crosslinking of

microtubules and androgen receptor extremely difficult. Therefore, a docetaxel analog with the cyanonilutamide moiety connected to the C10 position through a much longer PEG linker could be the next candidate in further work.

One simplified fluorescently labeled discodermolide analog was designed and synthesized to help understand the bioactive conformation of discodermolide. The dimethylaminobenzoate fluorophore was introduced to replace the δ-lactone, since the previous SAR studies indicated that the replacement of the δ-lactone by aromatic ring could preserve the cytotoxicity of discodermolide if it maintained the appropriate orientation. The terminal diene was replaced with saturated alkyl group, since the diene is not essential for the activity. This analog was submitted to the A2780 bioassay and the tubulin assembly bioassay. The analog was active in both assays, but it was nearly 400 times less active than paclitaxel in A2780 bioassay. Fortunately, it showed much better activity in the tubulin assembly bioassay, only 10 times less active than paclitaxel, indicating that the analog bound to tubulin in a similar way to that of discodermolide. Further biological investigations are currently in progress.

To better understand the bioactive conformation of discodermolide, a conformationally constrained discodermolide was designed, according to the computational study conducted by James P. Snyder at Emory University. The synthetic efforts were made, but failed during the final steps. Several key intermediates were accumulated, and the further synthetic plan was proposed.