Synthesis of Taxol™ Analogs as Conformational Probes

by

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Abstract

Taxol™, isolated from the bark of *Taxus brevifolia* in the late 1960s, and the semisynthetic analog Taxotere™ have proven clinical importance for the treatment of ovarian and breast cancer. Taxol™ exerts its biological effect by binding to polymerized tubulin and stabilizing the resulting microtubules. Studies aimed at understanding the biologically active conformation of taxol and its binding environment on β–tubulin are described. This knowledge is important because it could lead to the design of structurally less complicated drugs with better efficacy and better bioavailability. Moreover, the information can be extended to other natural products that possess microtubule–stabilizing properties similar to Taxol™. In this work, the synthesis of a triply labeled taxol analog is described as well as REDOR studies of this compound complexed to tubulin are in progress. Macrocyclic analogs of taxol have been prepared and their biological activities were evaluated. Chemical modeling of these analogs and their activities agrees with the hypothesis that Taxol™ adopts T–shaped conformation. Difficulties were encountered with the key ring–closing metathesis strategy, suggesting that a more flexible and efficient macrocyclization method will be needed to synthesize additional macrocyclic analogs.