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Evaluation of the effect of the chiral centers of Taxol on binding to β-tubulin: A docking and molecular dynamics simulation study

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ABSTRACT

Taxol is one of the most important anti-cancer drugs. The interaction between different variants of Taxol, by altering one of its chiral centers at a time, with β-tubulin protein has been investigated. To achieve such goal, docking and molecular dynamics (MD) simulation studies have been performed. In docking studies, the preferred conformers have been selected to further study by MD method based on the binding energies reported by the AutoDock program. The best result of docking study which shows the highest affinity between ligand and protein has been used as the starting point of the MD simulations. All of the complexes have shown acceptable stability during the simulation process, based on the RMSDs of the backbone of the protein structure. Finally, MM-GBSA calculations have been carried out to select the best ligand, considering the binding energy criteria. The results predict that two of the structures have better affinity toward the mentioned protein, in comparison with Taxol. Three of the structures have affinity similar to that of the Taxol toward the β-tubulin.

1. Introduction

Paclitaxel (trade name Taxol®) is playing a great role in cancer chemotherapy (Martello et al., 2001). It was found that the Taxol acting via binding to the β-tubulin (Stiles and Nelson, 2005; Yang et al., 2009). The binding conformation of Taxol in β-tubulin has been investigated by different groups. As an example, Snyder et al. used electron crystallographic density method; they found that the T-shaped Taxol or butterfly structure is optimized within the β-tubulin site (Snyder et al., 2001). Tubulin-bound paclitaxel conformation was used extensively as a model to inspect new drugs for cancer treatment. Geney et al. utilized such a method and their designed and synthesized compounds showed activities similar to Taxol (Geney et al., 2005). Serum proteins are important in effectiveness of drugs because binding of drugs to these proteins affect their activity as well as their disposition. It has been known that the albumin and globulin of the serum accumulate in tumor tissues because of enhanced tumor vascular permeability. Trynda-Lemiesz has investigated the binding of paclitaxel to the human serum albumin (HSA). The result showed that the paclitaxel–HSA interaction results in the helical stability of HSA via changing the conformation of the protein (Trynda-Lemiesz, 2004). Nowadays docking studies are playing a great role to investigate the interaction between ligands and proteins and these methods are extensively in use (da Cunha et al., 2010; Hanessian et al., 2001; Josa et al., 2008; Ligabue-Braun et al., 2012; Seeliger and de Groot, 2010; Taylor et al., 2002). As an example, Paal et al. used docking method to analyze the interaction of the Taxol with HSA. The results showed that the baccatin core of the Taxol and the C13 side chain were playing uniformly to the binding energy (Paal et al., 2007). In another work, the same research group investigated binding of the Taxol to the HSA in the presence of long-chain fatty acid. They reported that the effect of the baccatin core is more than the C13 side chain on the binding energy (Paul and Shkarupin, 2007). Rao et al. employed the photoaffinity labeling method to explore the binding of the Taxol to the β-tubulin. Their results were in good agreement with electron crystallography data (Rao et al., 1999). Xu et al. have performed molecular dynamic (MD) simulation and density functional studies to inspect interaction between the active pocket of the β-tubulin and the Taxol. Their results are indicative of the fact that ten amino acids of the protein play role in the interaction with the Taxol (Xu et al., 2012). Xiao et al. have investigated the mechanism of the microtubule stabilization by the Taxol. Their data suggest that the microtubule depolymerization is inhibited by the Taxol-induced changes in the tubulin conformation (Xiao et al., 2006).

Paclitaxel is naturally extracted from the bark of yew trees (*Taxus brevifolia*) which grows very slowly. Therefore, obtaining

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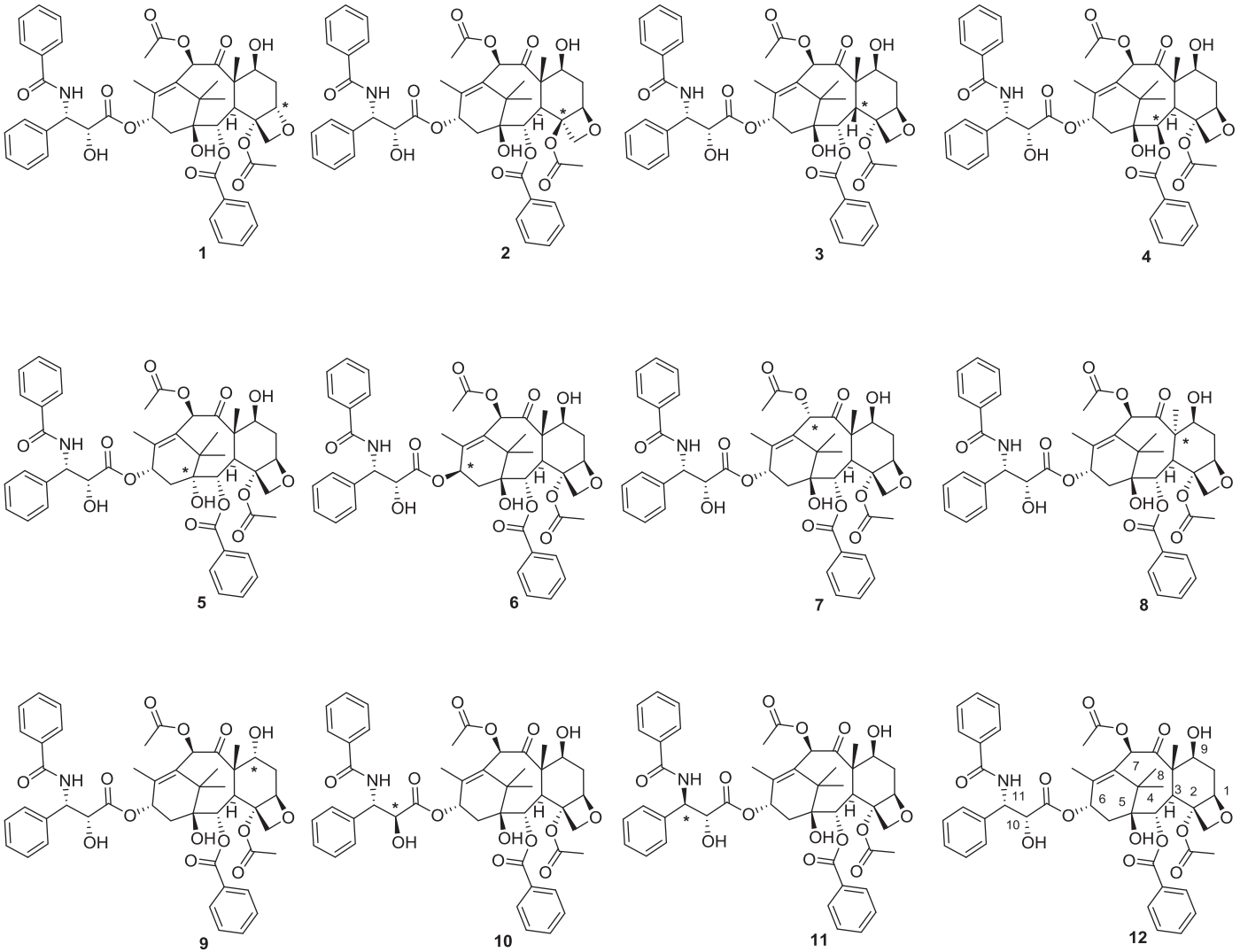

Fig. 1. The investigated chiral centers (shown with asterisks) of Paclitaxel (Taxol®). In structure 12 the chiral centers were not changed.