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Computational prediction of interaction of lumefantrine with human topoisomerase II beta complexed to DNA

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Lumefantrine (LF) is used in artemisinin-based combination therapies against malaria worldwide. It is genotoxic and mutagenic to human lymphocytes *in vitro* and may interact non-covalently with DNA minor groove surface. Considering that DNA binders are often topoisomerase inhibitors; in this study, we investigated the potential non-covalent interaction of LF with human topoisomerase II beta (hTOP2β) complexed to DNA by molecular docking study. Computer-assisted molecular analyses have been performed for predicting the possible interactions between hTOP2β-DNA complex and LF. The hTOP2β-DNA complex bound to LF was then assessed for interactions, energetic contributions, and for identification of the best correlation between the LF conformations and their associated scores. The fused-tricyclic 9*H*-fluorene rings in the LF chemical structure promote the intercalative binding into cleaved DNA sites present in hTOP2β-DNA complex. Since this is a polycyclic aromatic moiety, it gives the LF molecule the necessary planarity and aromaticity for intercalative binding to DNA base pairs in the cleavage sites, which showed aromatic interactions of -8.6 kcal/mol in the binding computational analysis for predicted binding affinity energy. The N-dibutyl moiety and hydroxyl group from LF accommodate into the major groove and hydrogen bond to nitrogen and oxygen atoms on the base-pair in the DNA segment. The N-dibutyl moiety also interacts with residues on the major groove side. The (4-chlorophenyl) methylidene moiety protrudes into the DNA minor groove side facing nearby residues from this protein–DNA interface. The hypothesis on the interaction of LF with topoisomerase II needs to be investigated using other approaches.

Biography

Carmen Lucia Bassi Branco has completed her PhD at São Paulo University in 2004 and Post-doctoral studies at the same university in 2007. She is Professor at the Federal University of Mato Grosso since 2009, where she develops research in the mutagenesis area.

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