Systematic Modeling of Drug P-Glycoprotein Interactions via Combined Docking/QM Approach

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Abstract

Introduction: The overexpression of P-gp in cancer tumor cells result in increased efflux of chemotherapeutic compounds. This phenomenon leads tothe wide-spectrum resistance of cancer cells to variant drugs or multi drug resistance (MDR). Regarding the important biological role of P-gp with regard to cancer therapy, *in silico* analysis of binding affinity/mode of diverse anticancer drugs toward P-gp may be an active area of research since it provides more insight into the binding interactions and key amino acid residues that were involved.

Methods and Results: Ligand-flexible docking studies were performed using the molecular docking software, AutoDock 4.2. To elucidate the interactions of selected anticancer drugs, all the related structures were docked into the active site of validated P-gptarget (4XWK). Quantum mechanical calculations were applied to intermolecular binding energy analysis in terms of drug-residue binding interactions via functional B3LYP in association with split valence basis set using polarization functions (Def2-SVP).

Mitomycin was found to be the weakest binder with -7.29 kcal/mol energy. Bisantrenewas the top-ranked binder(-10.59 kcal/mol)with H-bond and lipophilic interaction patterns. To explain more, Asn838 participated in bidentate H-bonding with nitrogen atom of imidazole ring. Another H-bond interaction was detected in the case of Ser725 within the same ring but different nitrogen atom of the drug molecule. Besides hydrogen bonding, it was revealed that 12 hydrophobic residues interacted with Bisantrene. Within the evaluated drugs, unlike EpothiloneE and F, no H-bondscould be detected for Epothilone A, B, C& D. Such observation was pertained to the presence of hydroxymethyl moiety on the thiazole ring of EpothiloneE and F which provided well-oriented H-bonds with Ala307. Despite observed interactive residues, lower binding affinity of Epothilone F persuaded us to run QM job in terms ofdrug-residue binding interactions. It was interestingly concluded that a few residues made repulsive forces with the drug, a result that might explain lower affinity of this molecule toward P-gp.

Conclusions: Collective *in silico* exploration of a few anticancer drugs provided some insights into the binding mode toward P-gp as an interfering target in chemotherapeutic strategies. On the basis of obtained results, structure binding relationship pattern for studied anticancer drugs were developed.

Key words: Cancer, MDR, P-gp, Docking, B3LYP

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