Molecular dynamics study of the anticancer drug dioxadet transfer across the lipid membrane DOPC

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Dioxadet is a drug used in chemotherapy for abdominal cancer developed at the Petrov Research Institute of Oncology in St Petersburg. To identify the mechanism of dioxadet transport across the cell membrane we performed molecular dynamic simulation with free energy and permeability calculations.

In a previous step of the study, we created several models of dioxadet and showed that dioxadet readily dissolves in water and forms associates. In this study, we used a model with a DOPC lipid bilayer as a membrane. The Gibbs free energy profile at different temperatures of 300, 305 and 310 K was calculated to estimate its permeability. Since the ΔG sign in the membrane is negative, therefore the dioxadet prefers to be inside the membrane. In the middle of the membrane, in the gap between the lipid tails, there is a small energy barrier whose height increases with increasing temperature. The enthalpy and entropy contribution profiles to the free energy say that the system loses in entropy, but gains in enthalpy when the drug is transferred to the membrane. The large enthalpy is caused by the large partial charges on the atoms of the aromatic ring of the dioxadet, which interact with the polar heads of the lipids. The diffusion coefficient profile and the resistivity profile were also calculated, see our similar calculations for other molecules in [1, 2]. It is shown that when a dioxadet molecule passively diffuses across the membrane, its near-surface region offers the greatest resistance. The barrier in the central non-polar region practically does not play a role. The membrane permeability for dioxadet was found to be $P = (0.6 \pm 0.1)\cdot 10^{-3}$ cm/s at T=300 K. When a second dioxadet molecule is added to the membrane, its permeability is almost doubled due to a decrease in the resistance of the bilayer surface.

[1] A.V. Kim, E.A. Shelepova, O.Yu. Selyutina, E.S. Meteleva, A.V. Dushkin, N.N. Medvedev, N.E. Polyakov, N.Z. Lyakhov, *Molecular Pharmaceutics* **2019**, *16/7*, pp. 3188-3198.

[2] A.V. Kim, E.A. Shelepova, V.I. Evseenko, A.V. Dushkin, N.N. Medvedev, N.E. Polyakov, *Journal of Molecular Liquids* **2021**, *344*, pp. 117759.