An US-CpHMD protocol to calculate pH-dependent membrane permeability coefficients of antitumor drugs

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Many antitumor drugs cross the lipid membrane by passive diffusion to enter tumor cells. In the case of Lewis Base drugs, which are charged in water (pK_a values are generally between 8 and 9), a transient deprotonation is required to cross the lipid bilayer [1,2]. Since the Tumor MicroEnvironment (TME) is slightly more acidic than normal cells, it has been proposed that this increased acidity can significantly decrease the antitumor efficiency of these Lewis Bases by impairing the transient deprotonation process [1].

To quantify the impact of the TME in the membrane permeability of some chemotherapeutics, we propose a new protocol based on Constant-pH Molecular Dynamics [2] coupled with an Umbrella Sampling scheme (US-CpHMD) and applied it to two well-known drugs, sunitinib and nintedanib, interacting with a POPC lipid bilayer. The membrane permeability coefficients were calculated using the inhomogeneous-solubility diffusion model (ISDM) [3]. The calculations were performed at different pH values, namely 7.5 to mimic a healthy cell, 6.0 to model the TME acidity, and 4.5 to capture the strong acidity of the lysosomes lumen. The latter can provide some insights on the lysosomal sequestration phenomenon, which has been proposed as a drug resistance mechanism [1]. We have calculated the impact of acidity in the bioavailability of both sunitinib and nintedanib, which helped us design a new compound as a proof of concept that is able to circumvent these limitations.

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