Identification of membrane PAINS via an optimized computational protocol

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Membrane Pan-Assay INterference compoundS (PAINS) are a subcategory of molecules that interact with lipid membranes in a nonspecific way and alter their physicochemical properties [1]. A prompt detection of these compounds in the drug discovery process is therefore crucial, as it avoids wasting precious time and resources chasing after false leads. Here we present an optimized umbrella sampling/molecular dynamics-based computational protocol to identify compounds with varying degrees of membrane PAINS behavior. We observed that the method was extremely susceptible to fluctuations in membrane thickness, which we were able to alleviate by changing the US-reference position from the membrane center to the closest interacting monolayer. The computational performance was further improved by adjusting the number, strength and position of the umbrellas. The membrane permeability coefficients calculated using the inhomogeneous solubility diffusion model were able to accurately assess the membrane PAINS character of both curcumin and resveratrol [2], but indicated a possible misclassification of notophagin in a previous work [3].

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