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Dynamics and Binding Behavior in Light-Responsive HDAC Inhibitors

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Conventional anticancer therapies are known for damaging not only tumorous cells but also the surrounding tissue. This poor spatial selectivity leads to adverse effects that significantly compromise patient well-being. Photoswitchable therapy offers an alternative by enabling external, light controlled activation and localized drug activity, thereby reducing systemic toxicity. Histone deacetylases (HDACs) are well-established anticancer targets due to their involvement in gene expression regulation. Azobenzene-modified derivatives from the FDA-approved inhibitor vorinostat have demonstrated reversible, light dependent inhibition. Notably, the Z isomer shows roughly 50 fold greater potency toward HDAC1 than its E counterpart, as reported in in situ assays[1]. Computational studies have mapped binding poses and proposed intermediates associated with the switching behavior, but the direct photoisomerization process within the enzyme environment is not yet fully characterized[2]. In this study, we perform classical molecular dynamics simulations complemented by MM/GBSA calculations to evaluate the stability and energetics of enzyme–inhibitor interactions[3]. The next stage will incorporate non-adiabatic molecular dynamics to follow excited-state evolution and the photoisomerization pathway in real time[4]. Together, these approaches elucidate the mechanistic basis for the experimentally observed differences in isomer stability inside the HDAC active site and provide computational insights that may guide the rational design of photoswitchable HDAC inhibitors with enhanced photochemical performance.

References:

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