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Computational campaign to discover novel human 20S proteasome

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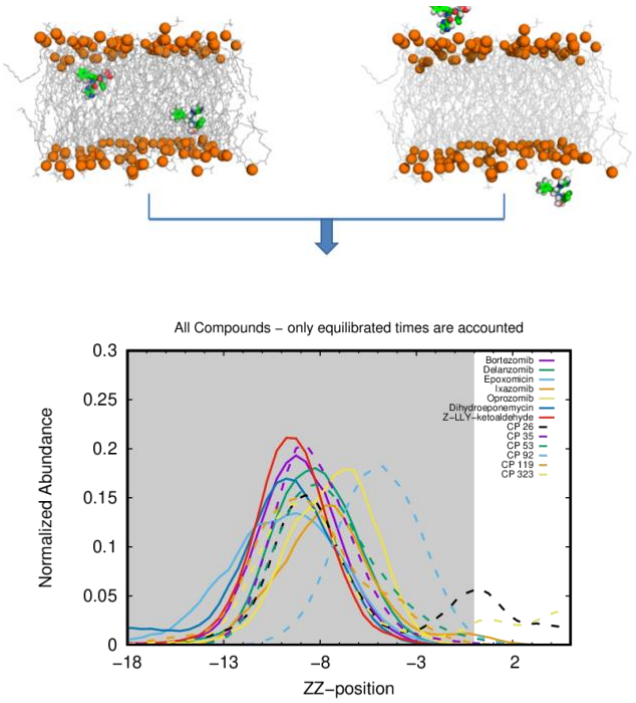
Graphical Abstract



Abstract.

The Ubiquitin Proteasome Pathway (UPP) plays a pivotal role in intracellular protein degradation and turnover in eukaryotic cells. [1] Therefore, modulation of the UPP emerged as a rational therapeutic approach in cancer, neurodegenerative diseases, among others. [2] During the last two decades academia and pharmaceutical industry made huge efforts to develop natural and synthetic proteasome inhibitors (PI). However, despite the enormous potential of PI, their use is still limited to certain types of blood cancer and shows severe side effects, limited activity in solid tumor and innate or acquired drug resistance. [3] This work encompasses a computational drug discover campaign to find new small molecules that inhibit proteasomal activity, with the goal of obtaining new anti-cancer drugs. A set of several compounds were identified in our lab as PIs obtained from virtual screening procedure. Since the proteasome can be found both on the cell cytoplasm and nucleus, inhibitors developed to target it, must be able to cross the membrane barrier. To acquire more information on how they interact with the lipid bilayer restrained (PMF) and unrestrained MD simulations at the water/membrane interface. The results showed

that our compounds have similar permeability rates and behavior in the lipid bilayer when compared with known proteasome inhibitors. Furthermore, one of the major challenges with the approved PIs is acquired resistance, possibly from point mutations in the catalytic subunits of the proteasome. We have used MD simulations to focused our analysis on three different point mutations in the □5 catalytic subunit, with recognized importance in PI's resistance: Ala49Thr, Ala50Val and Cys52Phe. Hopefully, our studies will be able to shed the light on the structural key determinants that regulate the observed PI's resistance in the different mutations, and ultimately use the acquired knowledge in the development of new alternative and efficient proteasome inhibitors.

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