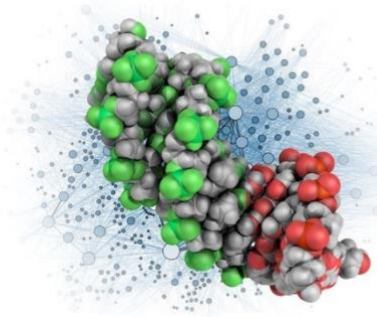

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Characterization of the membrane permeability of different proteasome inhibitors using molecular dynamics methods

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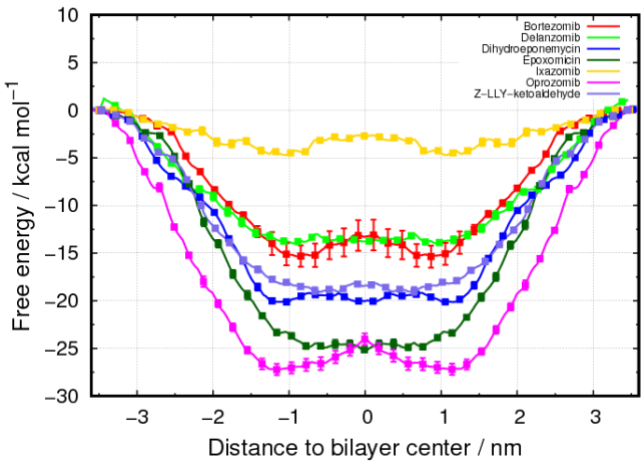
Graphical Abstract *(mandatory)*



Abstract. *(mandatory)*

Protein degradation is a key function developed by organisms to remove damaged and abnormal proteins, preventing their accumulation, and serving at the same time to regulate cellular processes by removing enzymes and regulatory proteins that are no longer needed.[1] This regulatory process can be achieved through two independent pathways: proteolysis in lysosome, or a ubiquitin-dependent process targeting unwanted proteins to proteasome. Due to its shattering function, proteasome has constituted an important therapeutic target to the control of different diseases such as malaria, cancer, multiple sclerosis, psoriasis, among others.[2] Since this protein can be found both on the cell cytoplasm and nucleus, inhibitors developed to target it, must be able to cross the membrane lipidic barrier. Until now, it is unclear if transport involves simple passive diffusion or occurs via a yet unidentified transport system. In both scenarios, associations with the cell wall and the membrane are to be expected. Modeling the interaction of different inhibitors derivatives with the cell wall is not feasible because of its complicated and variable structure. However, it is possible to model and compare the interactions of different proven proteasome inhibitors with a lipid bilayer.

In this work, by using restrained (Potential of Mean Force - PMF) and unrestrained Molecular Dynamics simulations at

	the water/membrane interface, we have evaluated the membrane permeability rates of different proteasome inhibitors (available on the market and identified in our lab) and their configurational and positional preference in this mixed medium. Our results will allow us to compare the trafficking of the evaluated compounds through the cell membrane and to relate it with the proteasome inhibition efficiency. *Acknowledgements:* We thank the Fundação para a Ciência e a Tecnologia for financial support through PTDC/QEQ-MED/7042/2014, UID/DTP/04138/2013, and SAICTPAC/0019/2015.

References *(mandatory)*

1. Sommer, T.; Wolf, D.H.; *Biochim. Biophys. Acta – Mol. Cell Res.*, **2014**, f843 (1), 1.

2. Napela, G.; Rolfe, M.; Harper, J. W.; *Nat. Rev. Drug Discov.*, **2006**, 5 (7), 596-613