*Title:* **Molecular Dynamics with many ligands: Allosteric inhibition of the antiapoptotic Mcl-1 and Bcl-xL proteins**

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The purpose of the present work is the study and selection of allosteric inhibitors of the Mcl-1 and Bcl-$x_L$, Bcl-2 protein family members, involved in the regulation of the programmed cell death called apoptosis. Given that the over-expression of these antiapoptotic proteins is related to the development of some types of cancer, both proteins are considered potential therapeutic targets for the development of effective cancer treatment. However, the similarity of the Mcl-1 and Bcl-xL active sites leads to undesirable side effects of cancer treatment. Due to the lack of selectivity in compounds that targets the active site of these proteins, the aim of this work is the selection of two drug candidate fragments capable of selectively regulate the apoptotic mechanism of the proteins Mcl-1 and Bcl-$x_L$ by means of their selective inhibition.

For this purpose, six different fragments have been studied in order to predict their binding affinity and selectivity towards both proteins. To accomplish this purpose, four independent Gaussian accelerated Molecular Dynamics and their respective trajectory analysis have been performed for each studied system. Through the evaluation of the obtained results, the identification of the different allosteric binding sites for both proteins has been possible.

As the knowledge of the binding poses is important to determine the correct growth of the fragments, a first proposal of the binding mode has been made. To correctly discern the binding site of each selected fragment, it has been suggested the necessity of extending the study of their binding modes by an increase of the Molecular Dynamics simulation time. Therefore, more precise and reliable results will be obtained to develop larger ligands in further studies.