IN-SILICO STUDY OF ADMET PROPERTIES, MOLECULAR DOCKING AND MOLECULAR DYNAMICS OF POTENTIAL INHIBITORS OF NEW DELHI METALLO-Β-LACTAMASE (NDM-1)

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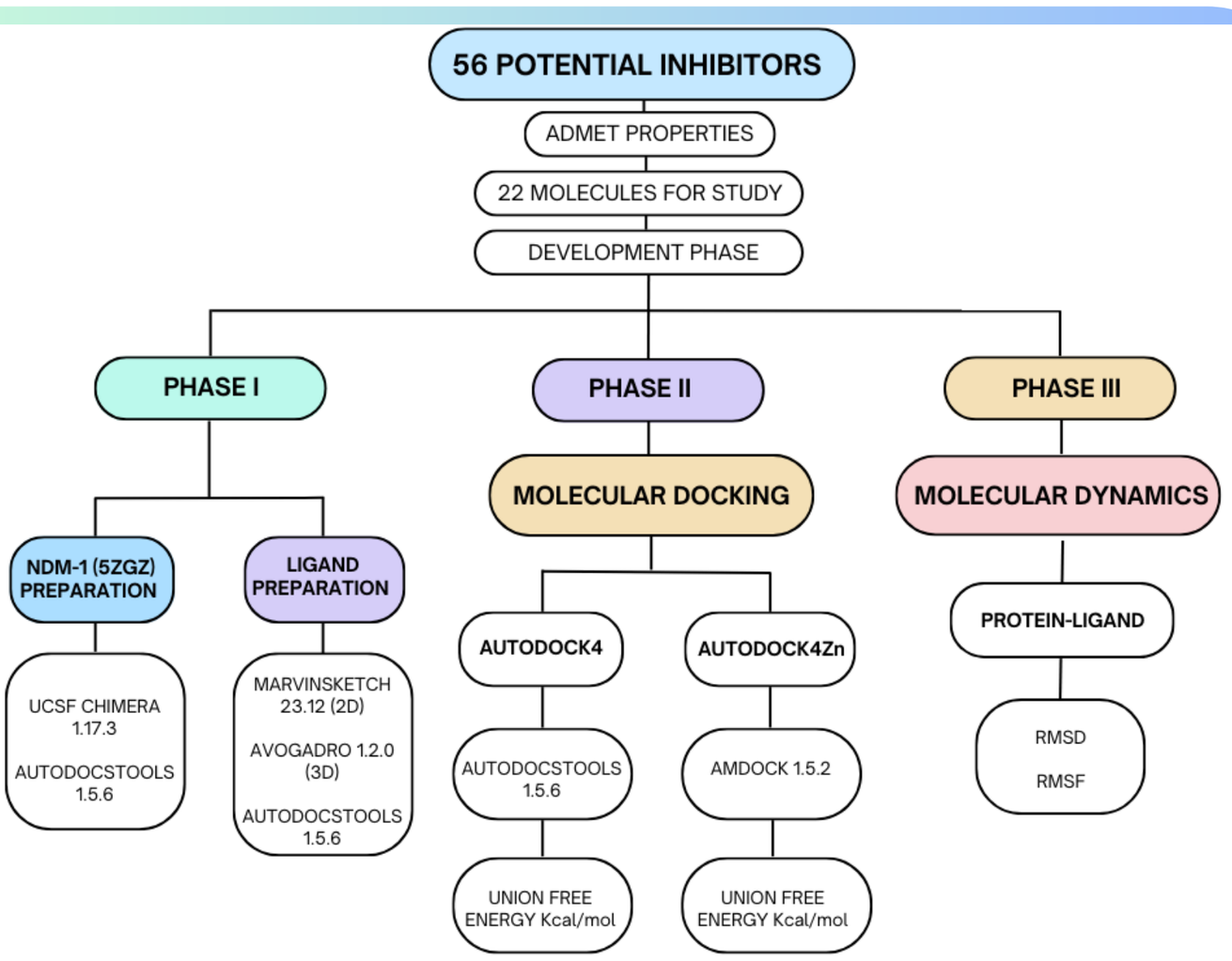
ABSTRACT

The metalloenzyme New Delhi Metallo-β-lactamase-1 (NDM-1), as well as its reported variants, present multidrug resistance to different antibiotics for the treatment of infectious diseases, due to its ability to hydrolyze a large number of β-lactam compounds such as carbapenems, a factor that has an impact on microbial resistance, which is a worldwide concern. The present work is based on a previous study of the ADMET properties of 56 potential inhibitors of the NDM-1 enzyme, of which 22 compounds showed promising oral bioavailability and toxicity values; These compounds present in their structure ethylenediamine derivatives, N,N',N''-triacetate-1,4,7-triazacyclonane, phosphonic acid mercapto esters, sulfur-containing carboxylic acids, dipicolinic acid, cyclic borate, chromones, natural compounds and their thioamide derivatives. For this group of selected molecules, molecular docking was performed with AutoDock4 and AutoDock4Zn, finding small differences between the force fields applied by each program whose docking energy results were (kcal/mol): AutoDock4 of -12.88 for M26 and -10.6 for M25, as well as -12.84 for M26 and -11.21 for M25 with AutoDock4Zn. Finally, 10ns molecular dynamics was performed for the best docking found (M26), with GROMACS software, obtaining acceptable ranges of RMSD and RMSF determining the best approximation to the possible real behavior of the molecular complex analyzed.

INTRODUCTION

Computer-aided drug design remains one of the most commonly performed forms of analysis in drug discovery and development, in order to reduce costs and obtain results in less time (Etruri et al., 2021). Through in-silico assays, it is possible to predict values or estimates of descriptors or properties of interest, through approximations and probabilities, modeling with values already published in the literature, and analyzing the structure of the molecule (Etruri, et al., 2021). Such data give us an idea of the bioavailability and biosafety profile in a rational way, and discarding those compounds that may show undesirable values, although one has to be very intuitive when filtering such compounds as many molecules may have values within the optimal ranges and yet be orally inactive, while others are active despite deviating in some of these physicochemical parameters (Xiong, et al., 2021). The computational approaches needed to design potential inhibitors of β-metalloid β-lacatamases against NDM-1 protein may improve the success of the project and reduce the cost of developing new lead molecules, as mentioned above (Salih, T., & Ali, P. G., 2023)

METHOD



RESULTS

MOLECULAR DOCKING

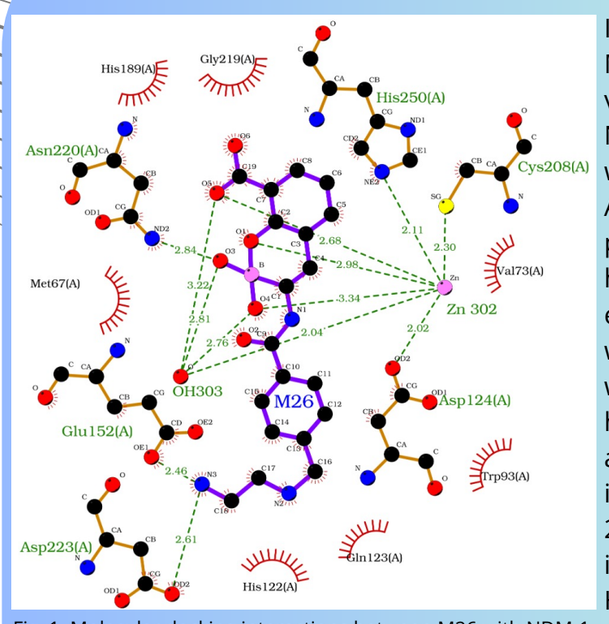


Fig. 1. Molecular docking interactions between M26 with NDM-1.

In the molecular docking study, molecule M26 obtained the lowest affinity energy value for the pharmacological target NDM-1, with a value of -12.88 kcal/mole with Autodock and -12. 84 with AutodockZn, on the other hand, it presented an approximate of 6 hydrogen bonds, highlighting those established with the water molecule 303, which coordinates with zinc atoms, widely studied for being related to the hydrolysis mechanism of NDM-1, as well as with Zn 302. It also presents interactions with Glu 125, Asp 124, Asn 220 and Lys 211. It also presents important hydrophobic interactions with His 122, Gln 123, Trp93, Val 73, Gly 219, His 189 and Met 67 (Figure 1).

MOLECULAR DYNAMICS

IIn Figure 2, it can be observed that the protein backbone showed an initial deflection during the first 2 ns, which may be due to the stabilization of the initial metalloenzymatic structure. Subsequently, the system stabilized and showed a dynamic steady-state trend specifically from 4ns onwards. The RMSD of the backbone of NDM-1 fluctuated at values no larger than 0.25 nm. On the other hand, the RMSD of M26, which corresponds to the backbone of NDM-1, fluctuated between 0.05nm and 0.275nm. The variation in the RMSD of compound M26 matched to the backbone of NDM-1 could be due to ligand entry into the active site cavity of NDM- 1.

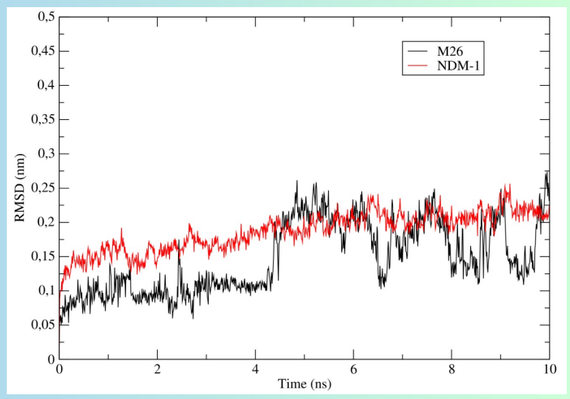


Fig. 2. Molecular dynamics (MD) simulation of M26 with NDM-1 shows the root mean square deviations (RMSD) of NDM-1 alone and the NDM-1_M26 complex.

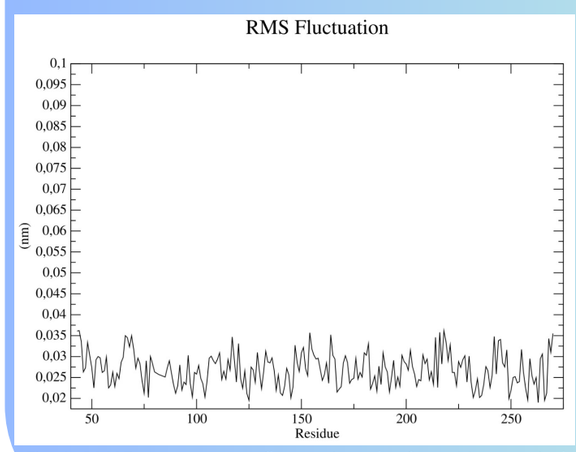


Fig. 3. RMSF mean square fluctuation plot for a 10 ns period of MD simulations for NDM-1 protein residues.

In the RMSF calculation and diagram, the conformational flexibility of the NDM-1 protein was evaluated, where an approximate average variation during the trajectory from 0.02nm to 0.035nm is observed. In Figure 3, it is clearly evident that the fluctuations were minimal. No considerable peaks are observed in the area related to the active site (residues 120 to 250), this because the energy minimization process was efficient. This observation suggests that the protein was able to maintain its structural flexibility during the simulation.

CONCLUSION

- Out of a total of 22 initial compounds, the best molecular docking values were presented by molecules M26, M25, M27 and M35, respectively. It could be established that the extended force field included in AutodockZn, produces some variations in the coupling values compared to Autodock4, in some cases, allowing to obtain even lower coupling results, i.e., it can improve the affinity values.
- RMSD trajectory analysis suggested the formation of a complex with relative stability. Similarly, RMSF analysis showed that the protein was able to maintain its structural flexibility during the simulation thanks to its low fluctuations, especially in the area related to the active site.

REFERENCES

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