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Molecular dynamics simulations of aqueous systems of inhibitor candidates for adenosine-5'-phosphosufate reductase

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A combination of molecular docking and molecular dynamics (MD) methods were used to evaluate some chelating agents (**Fig. 1**) as potential candidates for inhibitors for dissimilatory adenosine-5'-phosphosulfate reductase (APSrAB), an enzyme present in the metabolic pathway of sulfate-reducing bacteria (SRB), which responsible by the generating of H_2S in oil production well.[1-3] Molecular docking methods were used to evaluate the best binding modes of the molecules to the enzyme at two binding sites: of the substrate (enzyme active site) by mean of the redocking protocol of substrate with VINA; and of one of the $[Fe_4S_4]^{2+}$ groups by mean of the clusterization protocol with AutoDock4. The best docking poses were selected due to low energy and RMSD (redocking), and the cluster with the higher number of similar poses (clusterization) which were submitted to MD simulations in GROMACS 2019 using the forcefield parametrized for $[Fe_4S_4(Cys)_4]^{2-}$ developed by our group.[4] The protein-ligant binding energy (E_{bin}) was calculated with mmPBSA.
RMSD, RDF, and hydrogen bonds results revealed that all ligands left the cube site, while in the active site, HXA (hydroxamic acid), AHA (2-Hydroxyisobutyric acid), and CAT (catechol) remained in their docking region, pointing to the enzyme active site as the best target for the selected ligands. The binding energy results of ligands HXA and CAT (Table 1) showed that they bonded favorably to the enzyme, and key residues of the active site (such as Asn74, Glu141, Gln145, Trp234, Arg265, and His398) contributed significantly to the protein-ligand bind. The ligands HAX and CAT demonstrated that they could compete with the substrate for interactions with essential residues of the active site and display potential as candidates for experimental studies about APSrAB inhibitors.

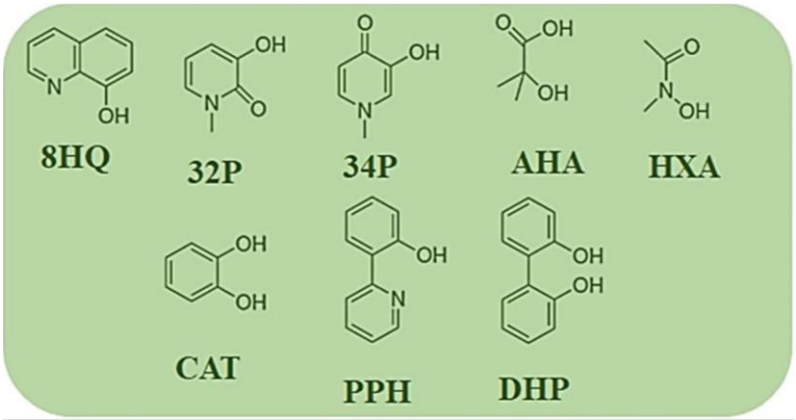

Fig. 1. Structures of the studied ligands

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