Metalloproteins Investigation for the Development of new Inhibitors

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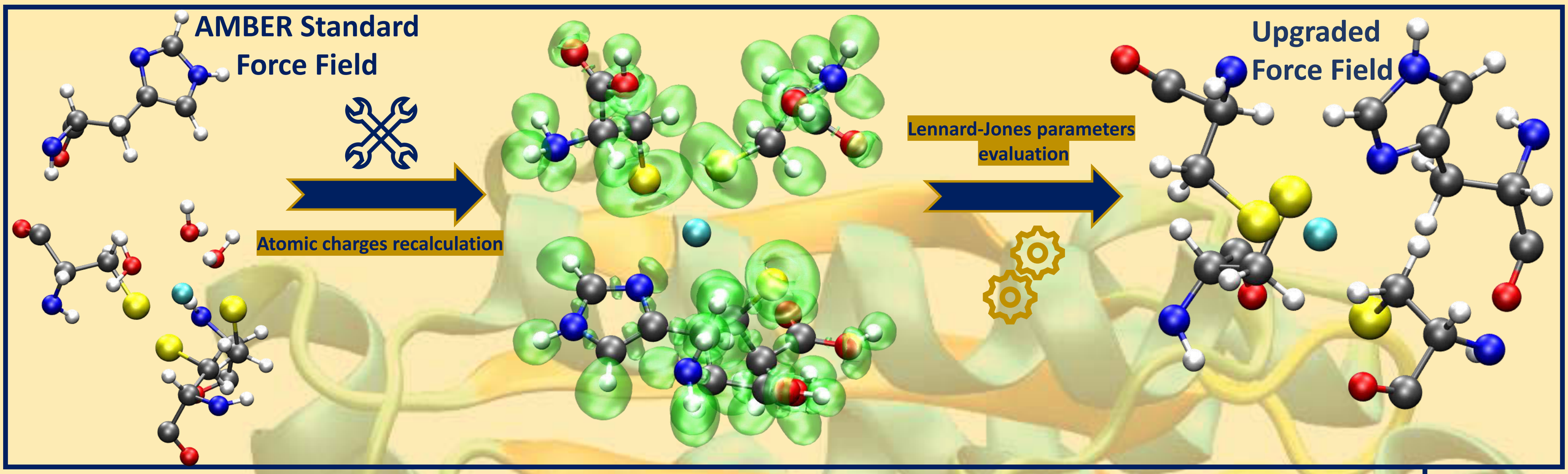
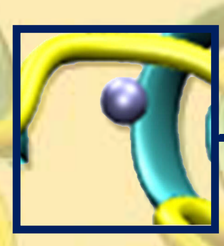
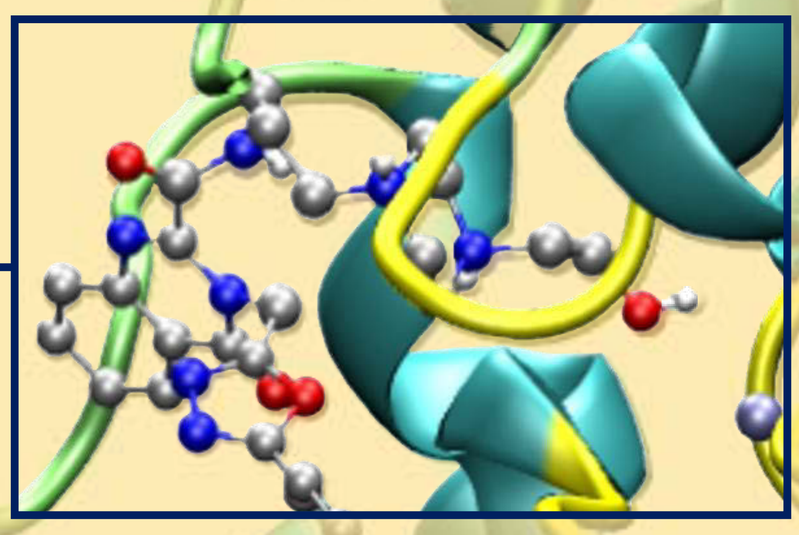
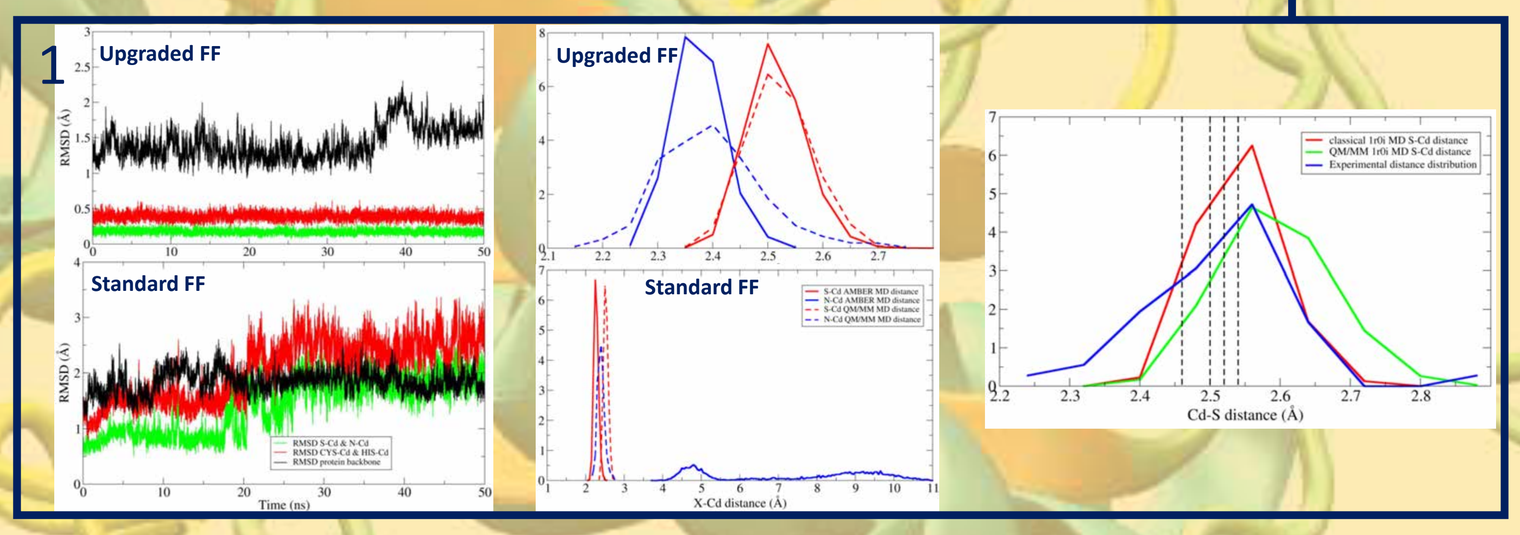


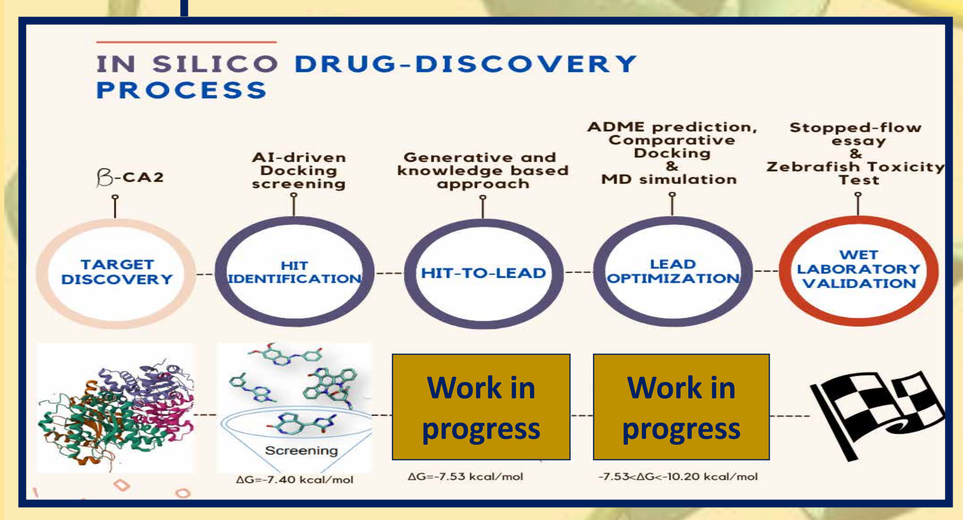
Metalloproteins Modelling

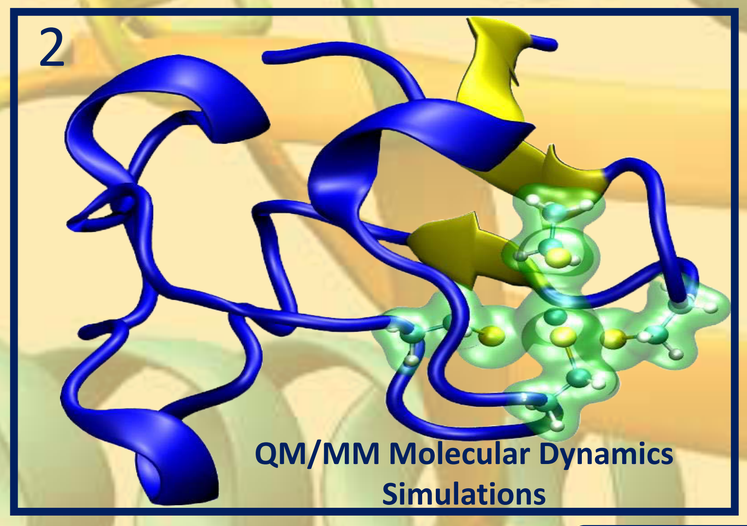
Molecular Dynamics (MD) simulations are a pivotal tool in computational chemistry and biophysics that allow to study the behavior of molecules at the atomic level. The accuracy of these simulations heavily relies on the force fields used to model the interactions between particles. We focused on the development of tailored Force Fields (**Fig. 1**)[1] for the metal-ligand interactions to simulate more accurately the behavior of metalloproteins as potential drug targets and to computationally design innovative and effective inhibitors for these targets. Simulating metal-containing systems with MD is inherently challenging due to the complex electronic and bonding properties of metals. For example, we focused on capturing the polarization effect induced by the cations on the ligands surrounding through accurate QM/MM MD (**Fig. 2**) simulations (CP2K/GROMACS interface) to reparameterize their atomic charges and Lennard-Jones parameters.

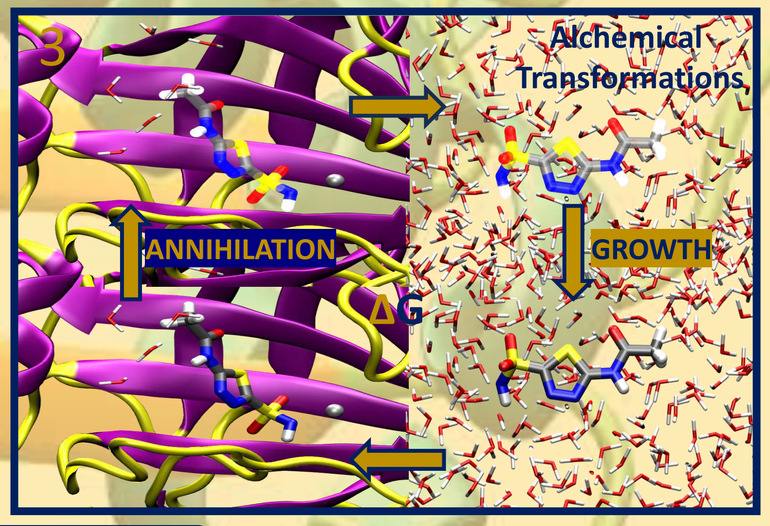


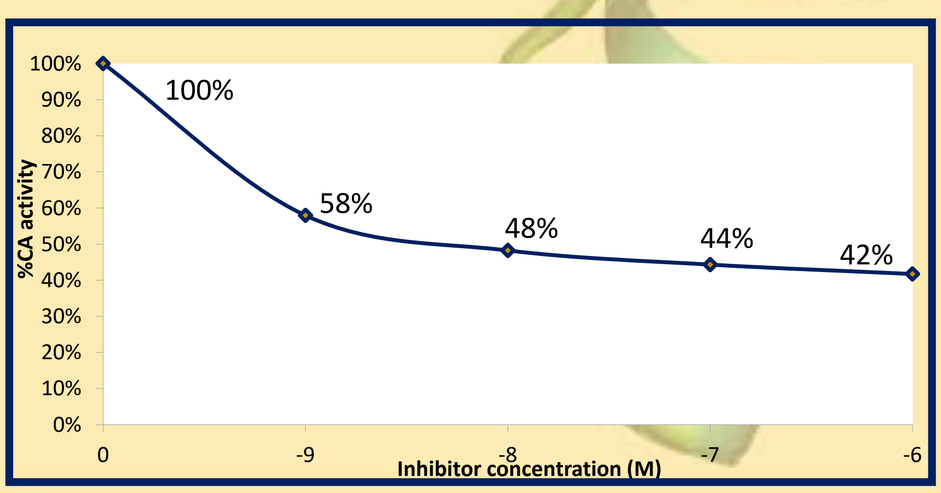












Drug Design

The drug discovery pipeline involves a multifaceted process, spanning from the validation of biological targets to in vivo testing. Computational chemistry tools play a crucial role in accelerating drug development. Their focus lies in minimizing false positive hits and lead compounds that may progress to in vivo experimentation, ultimately mitigating economic losses for the pharmaceutical industry. We focused on the design of a new class of antitubercular drugs effective against the **β Carbonic Anhydrases** of drug-resistant *Mycobacterium tuberculosis*[2]. To develop the new chemical entities both *deep learning generative models*[3] and chemical intuition were exploited. Binding affinities calculation schemes (**Fig. 3**) were also tuned on metalloproteins complex, since the modeling complexity of these systems poses arduous challenges in the feasibility of accurate predictions.

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