CASE STUDIES: AI & Computational Chemistry for BioPharma R&D

CASE STUDY 3: Enhanced Ligand Selectivity via Advanced Molecular Dynamics

- **Context:** Lead molecular candidates identified in a *de novo* NCE project needed to be assessed in depth for selectivity and specificity in binding and off-target effects
- **Objective:** To enhance the selectivity and reduce off-target effects of a ligand towards a target protein's binding site through the application of advanced-physics based MD simulations and Free Nergy methods

Method

Classical Molecular Dynamics (cMD) simulations to understand the natural dynamics and conformational flexibility of both the ligand and the target protein

Using Free Energy Perturbation (FEP) with restraints to assess changes in free energy from ligand modifications and predict their impact on selectivity

Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA) scoring to evaluate the binding energy contributions and identify the most favorable ligand-protein interactions.

Flow

Dynamic Interaction Profiling

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Selective Binding Assessment

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Energetic Scoring (Utilize MMPBSA)

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Selective Optimization (FEP)

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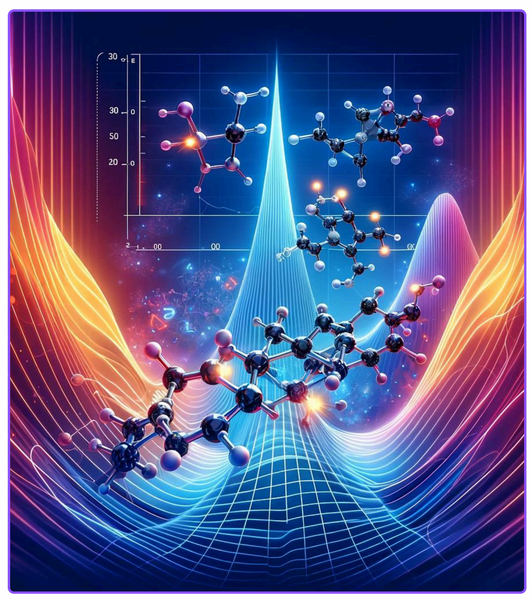
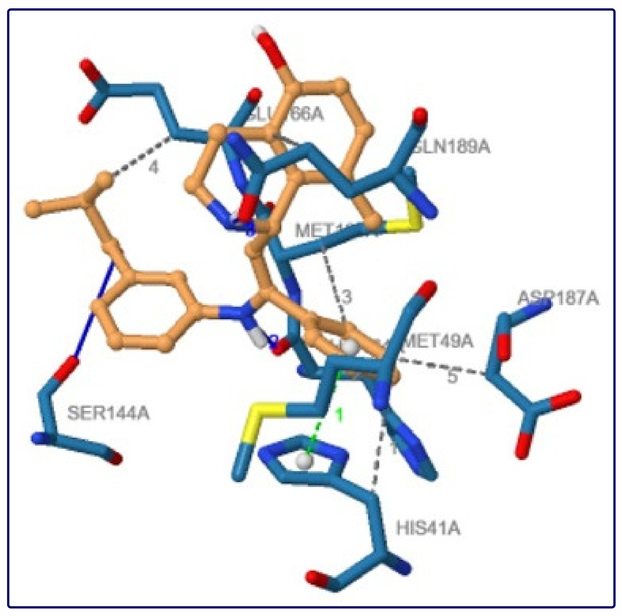
Robust Validation

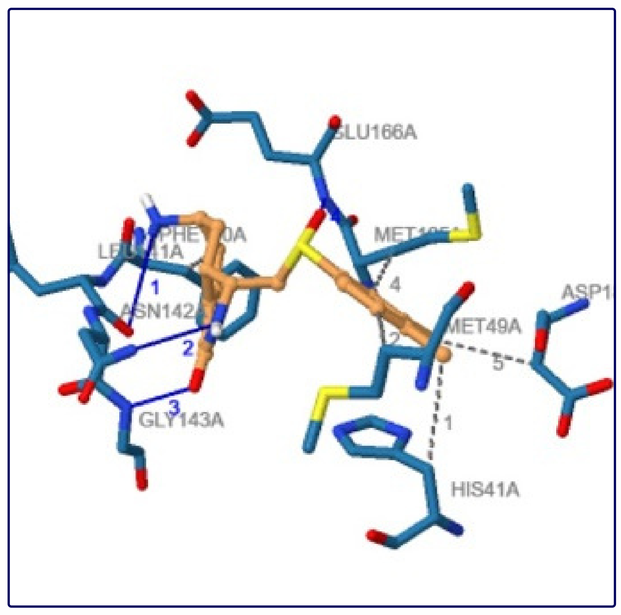


Results

- cMD pinpointed potential off-target interactions, directing efforts to improve selectivity
- FEP with restraints enabled accurate energy landscape mapping, guiding rational ligand tweaks
- MMPBSA detailed interaction energies, verifying the optimized ligand's enhanced binding
- Follow-up simulations showed significant gains in ligand selectivity and stability at the protein's binding site



mv_20278



mv_19171

Compounds	cMD	Umbrella sampling	FEP Score
mv_19171	Completed	-7.8 kcal/mol	-14.3 kcal/mol
mv_20278	Completed	-14.7 kcal/mol	-16.9 kcal/mol
mv_17030	Completed	-18.1 kcal/mol	-19.01 kcal/mol
mv_18313	Completed	-8.7 kcal/mol	-12.1 kcal/mol