Quantum Mechanics/Molecular Mechanics Optimizations of Zinc Metallo-β-Lactamase Inhibitor

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Introduction, Specific Aims, and Hypothesis

Problem: A major public health challenge to β-lactam antibacterial treatment is the resistance mechanism developed by the bacteria, rendering the treatment ineffective.

- Resistance by the expression of metallo-β-lactamase (MBL), a Zn(II) dependent enzyme
- MBL cleaves the 4 membered β-lactam ring structure, integral to the mechanism of action
- No approved MBL inhibitor yet

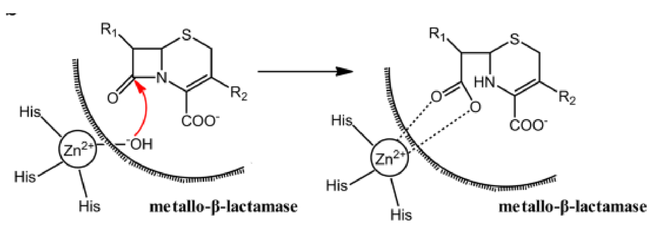

Figure 1: Mode of action by metallo-β-lactamase[1]

Literature Review: Sham Lab has discovered analogues of 8-hydroxyquinoline (8-HQ) as a low cytotoxic, nanomolar, MBL inhibitor through fragment – based screening of zinc chelators.[2]

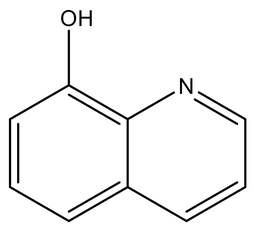

Figure 2: 8-hydroxquinoline

Docking to metallo-enzymes is challenging, as it only accounts for electrostatic interactions and no quantum mechanical effects involving charge transfer from the metal chelate to the zinc. Hence, **the objective is to optimize the mode of ligand binding and to account for quantum mechanical (QM) effect on the binding affinity**.

Specific Aim 1: Create a workflow and utilize the molecular dynamics and micromodel simulations to determine ideal coordination of 8-HQ analogues

Specific Aim 1: Introducing the electron distribution to determine ligand binding affinity to New Delhi metallo-β-Lactamase – Type 1 (NDM-1)

Hypothesis: Incorporating the Quantum Mechanical effects will improve the accuracy of determining and optimizing the ligand binding affinity, providing insight for designing the potent MBL inhibitor.

Methodology and Results

Aim 1: A combinatorial library was created using a sorted reagent file of various functional groups

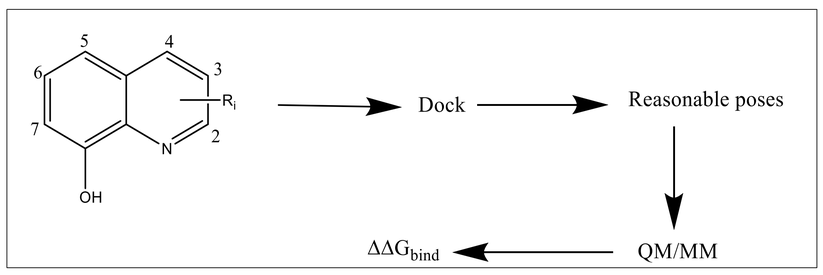

Figure 3: The workflow for designing potent MBL inhibitors

Aim 1: Coordination Profile, Protein RMSD and torsion angle profile created for docked 8-HQ analogues to determine reasonable poses

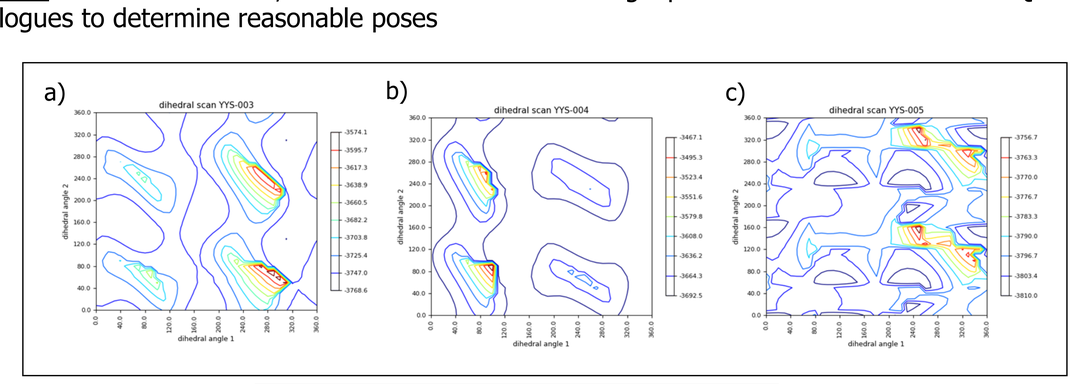

Figure 4: a-c) coordination profile generated for three potent analogues of 8-HQ using dihedral angle scan, d) Cα-RMSD with 8-HQ analogue (YYS-003) and e) torsion angle scans for the 8-HQ analogue (YYS-003)

Methodology and Results

Aim 2: QM/MM was modeled to the protein structure with the 8-HQ and its analogues as ligands.

- QM : Ligand and Zn (II) ions
- MM : Protein
- Calculation carried out using Qsite from Schrodinger Modeling package

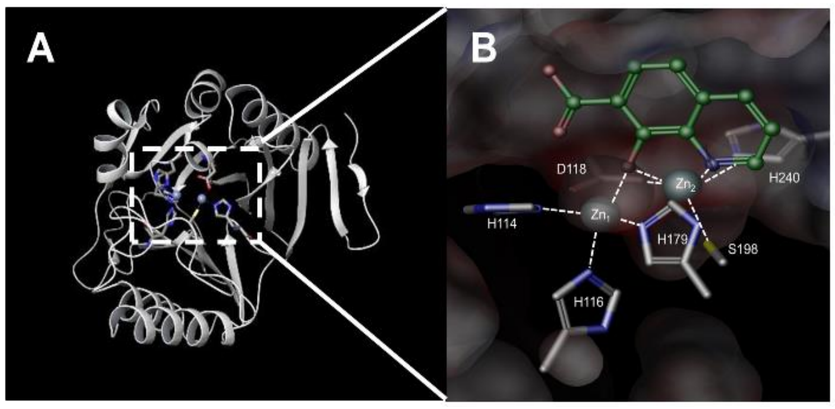

Figure 5: A) Structure of NDM-1 (PDB : 4EXS) and B) Ligand binding site with 8-HQ-7-COOH

Aim 2: MMGBSA was used to determine the binding affinity of the ligand to the protein structure. MMGBSA utilizes the protein ligand thermodynamic cycle to determine binding affinity.

- The atomic partial charges generated by Qsite were utilized
- Calculations carried out using PRIME-MMGBSA by from Schrodinger modeling package

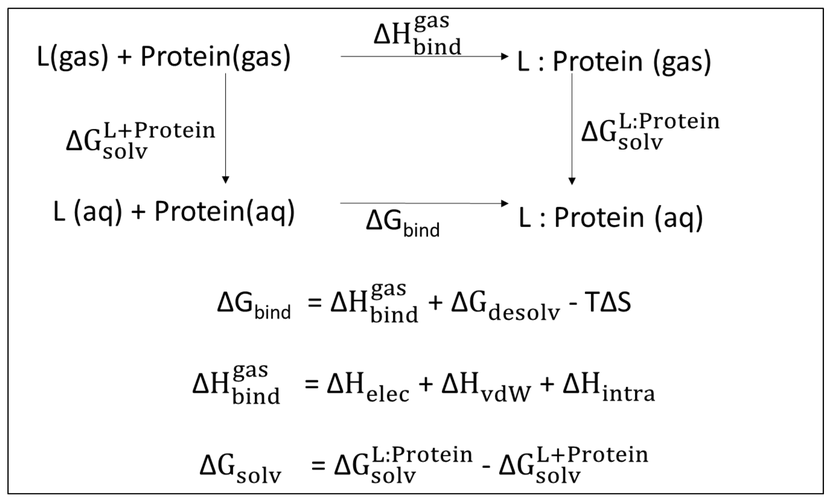

Figure 6: Thermodynamic cycle used by MMGBSA to determine ligand binding affinity[3]

Table 1: Binding Energy (Kcal/mol) determined by MMGBSA using MM A) classical OPLS 2005 force field and B) QM/MM (Qsite) along with experimental values

Comp.	OPLS 2005	Qsite	K_i	$\Delta\Delta G_{bind}$ (exp.)
8-HQ	-15.18	-7.51	6.70E-07	-8.52
8-HQ-7COOH	-13.17	-13.83	2.80E-07	-9.04

Conclusion and Future Work

Conclusion:

- The combinatorial library provided potent compounds to be optimized as an MBL inhibitor.
- The molecular dynamics simulation and coordinate scan allowed to determine the reasonable poses for 8-HQ analogues
- QM/MM improved the binding affinity when compared to experimental values

Future Work:

- Repeat the QM/MM experiments for potent 8-HQ analogues, YYS-003, YYS-004, and YYS-005
- Synthesize optimized compounds to determine experimental binding affinity

Acknowledgements

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References

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