Computational Docking Screen: Omeprazole Against Neisseria gonorrhoeae Resistance-Associated Proteins

An exploratory in silico screen - preliminary, hypothesis-generating, not validated

Status: Preliminary computational screen only. No wet-lab, cell-based, or functional data exists for this hypothesis at this time.

Purpose of this document: to report exactly what the docking simulation does and does not show, so the result can be cited accurately in any external or investor-facing context.

1. Summary

This report describes an exploratory molecular docking screen assessing whether omeprazole, a widely used and approved proton pump inhibitor, shows any predicted binding interaction with two proteins associated with antimicrobial resistance in *Neisseria gonorrhoeae*: the PorB outer membrane porin and the MtrD multidrug efflux transporter. Ceftriaxone, a clinically active antibiotic against *N. gonorrhoeae*, was docked against the same targets as a reference comparator.

The screen found that omeprazole produces moderate predicted binding scores against both targets, weaker than ceftriaxone's scores, but present. This is a preliminary computational signal only. It identifies omeprazole as a candidate worth further investigation; it does not demonstrate antibacterial activity, efflux inhibition, or any other biological effect.

2. Methods

Docking was performed using AutoDock Vina following standard receptor preparation (removal of crystallographic waters/ligands, addition of polar hydrogens) and ligand preparation (generation of a 3D conformer with standard protonation state). Two N. gonorrhoeae targets were selected based on their established roles in antimicrobial resistance:

- PorB outer membrane porin (PDB ID: 4AUI) - docking focused on the channel lumen
- MtrD multidrug efflux transporter (PDB ID: 4MT1) - docking focused on the periplasmic substrate-binding cleft

Ceftriaxone was docked against both targets under the same conditions as a reference point, since it is a clinically active antibiotic against *N. gonorrhoeae* and provides a useful (though imperfect) benchmark for what a stronger predicted interaction looks like in this system.

3. Results

3.1 Binding affinity scores for best poses (out of 10 models)

Target	Omeprazole (kcal/mol)	Ceftriaxone (kcal/mol)
PorB porin (4AUI)	-5.448	-6.339
MtrD efflux pump (4MT1)	-5.770	-6.805

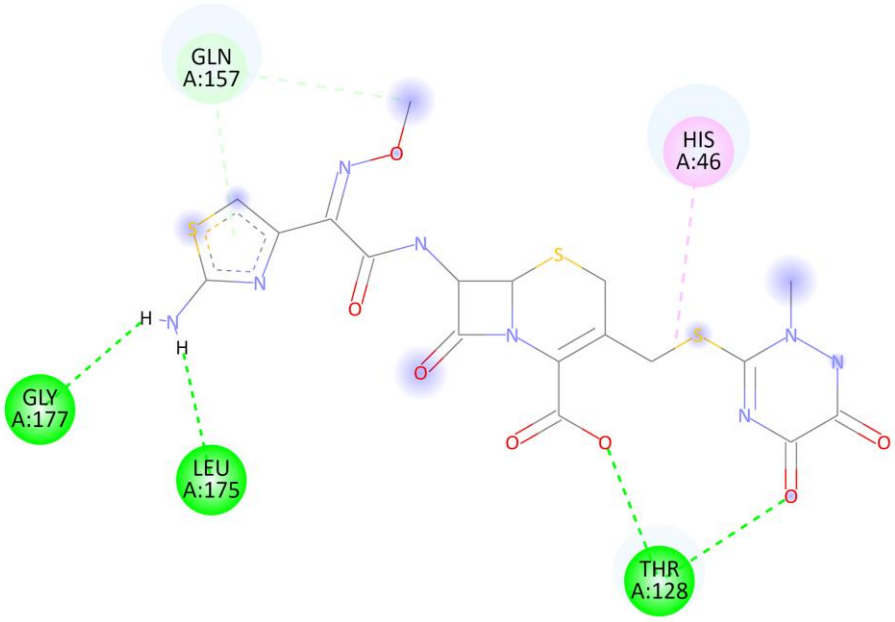

Fig 1. 2D protein-ligand interaction diagram of Ceftriaxone bound to the MtrD efflux pump (PDB: 4MT1) of *Neisseria gonorrhoeae*. Hydrogen bonds were observed with Gly177, Leu175, Gln157, and Thr128, while an additional interaction involved His46. These interactions indicate stable accommodation of Ceftriaxone within the MtrD binding pocket.

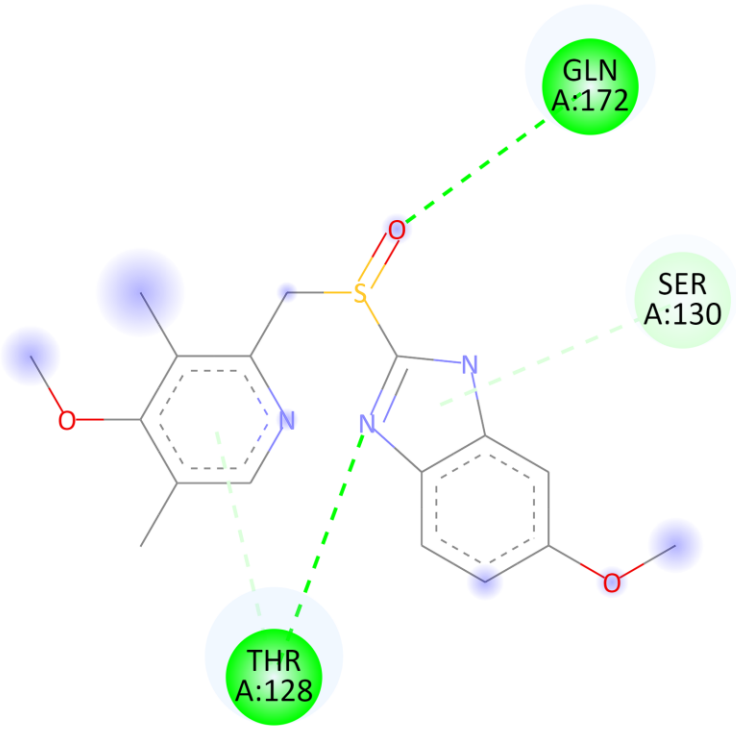

Fig 2. 2D protein-ligand interaction diagram of Omeprazole bound to the MtrD efflux pump (PDB: 4MT1) of *Neisseria gonorrhoeae*. Hydrogen bonds were observed with Gln172 and Thr128, while weaker contacts involved Ser130. These interactions contribute to the stabilization of Omeprazole within the MtrD binding pocket.

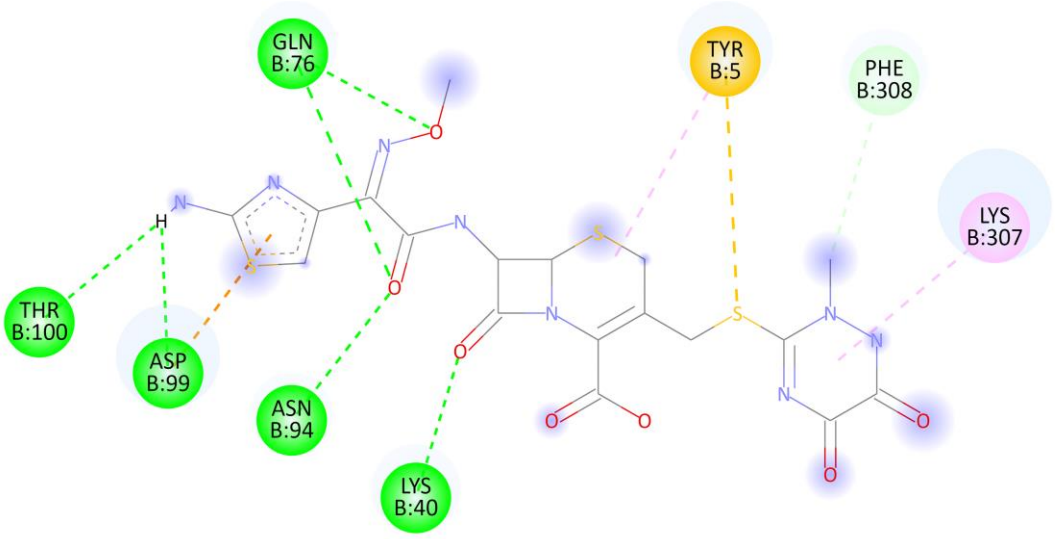

Fig 3. 2D interaction map of Ceftriaxone docked to the PorB porin (PDB: 4AUI) of *Neisseria gonorrhoeae*. Hydrogen bonding interactions were observed with Lys40, Asn94, Gln76, Asp99, and Thr100, while hydrophobic/π interactions involved Tyr5, Lys307, and Phe308.

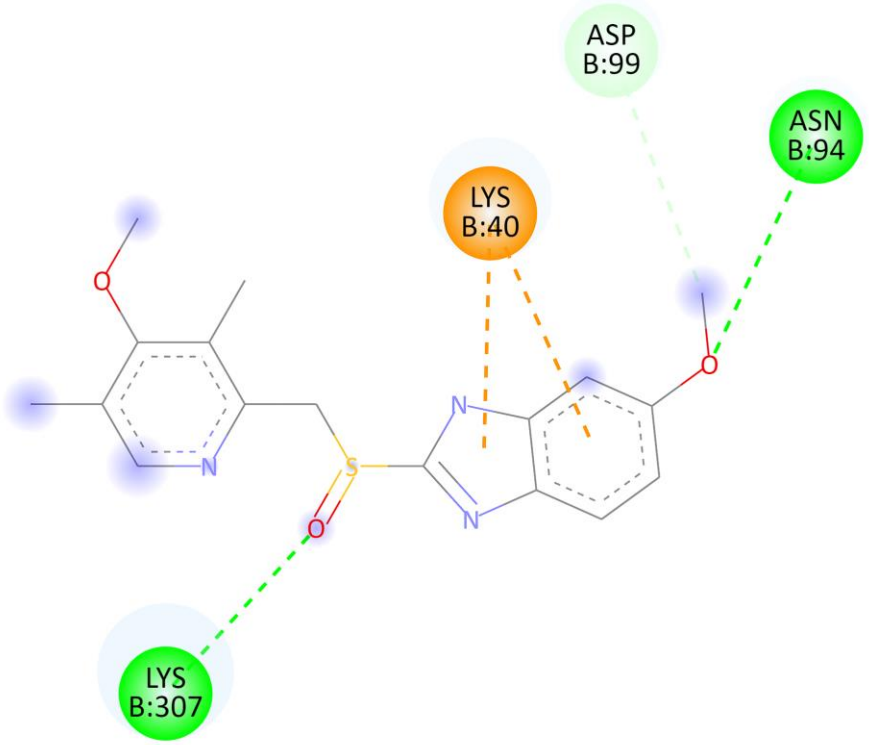

Fig 4. 2D protein-ligand interaction diagram of Omeprazole bound to PorB (PDB: 4AUI) of *Neisseria gonorrhoeae*. Hydrogen bonds were formed with Lys307 and Asn94, while hydrophobic interactions involved Lys40. A weak interaction with Asp99 was also observed.

Table1. Molecular docking interactions of ceftriaxone and omeprazole with PorB porin (4AUI) and MtrD efflux pump (4MT1) of *Neisseria gonorrhoeae*.

Ligand	Target (PDB)	Hydrogen Bond Residues	Additional Interactions
Ceftriaxone	**PorB (4AUI)**	**Lys40, Asn94, Gln76, Asp99, Thr100**	**Tyr5, Lys307, Phe308**
Omeprazole	**PorB (4AUI)**	**Lys307, Asn94**	**Asp99, Lys40**
Ceftriaxone	**MtrD (4MT1)**	**Gly177, Leu175, Gln157, Thr128**	**His46**
Omeprazole	**MtrD (4MT1)**	**Gln172, Thr128**	**Ser130**

Molecular docking analysis demonstrated that both ceftriaxone and omeprazole interacted favorably with the PorB porin (PDB: 4AUI) and MtrD efflux pump (PDB: 4MT1) of *Neisseria gonorrhoeae*. Ceftriaxone exhibited a greater number of hydrogen-bonding and hydrophobic interactions within PorB, involving residues Lys40, Asn94, Gln76, Asp99, Thr100, Tyr5, Lys307, and Phe308, indicating strong stabilization within the porin channel. In contrast, omeprazole formed fewer interactions with PorB, primarily through hydrogen bonds with Lys307 and Asn94, suggesting moderate binding affinity. Within the MtrD efflux pump, ceftriaxone established multiple hydrogen-bond interactions with Gly177, Leu175, Gln157, and Thr128, along with an additional contact with His46, reflecting stable binding within the substrate-binding pocket. Omeprazole interacted with MtrD through Gln172, Thr128, and Ser130, indicating favorable accommodation within the efflux transporter. Overall, ceftriaxone demonstrated more extensive protein-ligand interactions than omeprazole across both targets, while the ability of omeprazole to bind PorB and MtrD suggests its potential as an adjuvant capable of modulating membrane permeability and efflux-mediated resistance mechanisms in *N. gonorrhoeae*.

3.2 Discussion

For both targets, ceftriaxone produced a more favorable (more negative) predicted binding score than omeprazole, which is expected given ceftriaxone is a known active antibacterial agent against this organism. Omeprazole showed weaker, moderate-range scores at both targets, a difference of roughly 0.9 and 1.0 kcal/mol respectively, which in docking terms represents a real but not large gap.

This pattern is consistent with omeprazole having some predicted affinity for these binding sites, but it is equally consistent with a range of other explanations, including that the docking scoring function used is imprecise, that the true binding mode differs from the predicted pose, or that the interaction is real but functionally irrelevant. The data cannot currently distinguish between these possibilities.

4. What Can and Cannot Be Claimed From This Data

Supportable claim	Not supportable from this data

Omeprazole shows a preliminary, moderate predicted binding interaction with two *N. gonorrhoeae* resistance-associated proteins in silico	Omeprazole blocks, inhibits, or disrupts the MtrD efflux pump
This is a hypothesis-generating result that justifies a targeted, low-cost functional follow-up experiment	Omeprazole has antimicrobial activity against *N. gonorrhoeae*
The same docking workflow can reasonably be extended to structurally related efflux systems as a separate, distinct screen	Results against *N. gonorrhoeae's* MtrD transfer directly to *E. coli's* AcrB or any other organism's efflux pump without separately verifying structural and functional homology

5. Conclusion

This docking screen provides a preliminary, exploratory computational signal suggesting omeprazole may interact with two resistance-associated proteins in *N. gonorrhoeae*, at a level weaker than the clinical comparator ceftriaxone. The result is consistent with previously reported interest in repurposing proton pump inhibitors against bacterial targets in other species, and represents a genuinely novel question for this specific organism and target pair as far as current literature searches have found.

The result should be treated strictly as hypothesis-generating. No claim of antimicrobial or efflux-inhibitory activity is supported until functional, wet-lab data exists. This framing is intentional and should be preserved in any future internal, academic, or investor-facing use of this work.

Prepared by Aman Sriadibhatla, Co-founder, Bactrix
Reviewed and revised for accuracy of claims relative to underlying data.