ABSTRACT

The thesis titled "**Total synthesis of (−)-hygrophorone A[12], 4-*epi*-2,3-dihydrohygrophorone H[12] and discovering potent quorum sensing inhibitors through insilico studies"** presents the work carried out on the total synthesis (−)-hygrophorone A[12], 4-*epi*-2,3-dihydrohygrophorone H[12] and using insilico tools to discover potent quorum sensing inhibitors

Chapter 1 describes the stereoselective total synthesis of anti-fungal cyclopentenone (−)-hygrophorone A[12] and cyclopentanone 4-*epi*-2,3-dihydrohygrophorone H[12] in high overall yields from D-ribose. The key step of this syntheses is an aqueous KOH mediated diastereoselective intramolecular aldol reaction to form *β*-hydroxy ketone with three contiguous chiral centres, which was further elaborated to (−)-hygrophorone A[12] and (+)-hygrophorone B[12].

Chapter 2 This chapter consists of three subsections discussing three classes of molecules namely, hygrophorones, pentenomycins, and crown ethers to be potential inhibitors for the LasR protein in the QS pathway of *P. aeuriginosa* bacteria. In the hygrophorone class, we found 8 molecules from a pool of 64 different molecules, while from the crown ethers only 5 out of 54 molecules have shown promising results. Hygrophorones seem to be the structural analog of autoinducer AHL (natural ligand for LasR). Most of the top scored molecules of hygrophorone series reflect higher binding energy than the rest of the molecules of different classes. On the contrary, the pentenomycin class molecules have poor binding efficiency due to their small size and the lack of the alkyl chain. However, previous literature reports and our simulations results confirm that the addition of an alkyl chain to the pentenomycin molecules will enhance their interaction with the LasR active site residues (coherence with in-vitro studies reported).

Crown ethers seem to be the intermediate candidate for LasR inhibition. C5-5, C5-10, and C5-11 are some of the best candidates among 54 chosen ligands. This macrocyclic crown moiety of the crown ethers gets stabilized in the polar pocket of the LasR protein, while the aromatic or alkyl chain gets stabilised in the non-polar pocket of LasR. In summary, comparable and higher binding energies of the lead compounds obtained from our study from that of naturally occurring autoinducer AHL reflect these molecules to be potential candidates as inhibitors for the LasR target. We hope our work will spur further experimental studies that would lead to the discovery of new antibiotics for *P. aeruginosa* infections.

Chapter 3 This chapter unravels the molecular level insights and the binding mechanism for pentenomycin to behave as a broad range antibiotic. In our computational study, we found that pentenomycin binds with the LuxP enzyme and can even bind with the LuxP homologue, LsrB. Based on molecular docking, molecular dynamics simulations, and MMPBSA calculations, it was observed that pentenomycin induces conformational changes of LsrB/LuxP from its closed to open state. Pentenomycin ligand prevents domain closure (as seen in the cases of 1TJY, 3EJW, 3T95) thereby blocking PBP signals and ultimately shutting down the QS cascade and virulence factors. For other proteins, it was observed that pentenomycin occupies the active binding site without causing much of the structural change in protein and preventing may prevent binding with AI-2, hence again shutting QS cascade (as seen in the cases of 5BQ3, 5BRA, 5GTA, 6DSP). Through these computational studies, we predict that pentenomycin would prove to be a better antibiotic in the case of bacteria having periplasmic binding proteins (such as LuxP or LsrB). Because PBPs share a common architecture and hinge motion upon opening and closing and we anticipate that pentenomycin takes the exact binding site and prevents domain closure in some while in others it may occupy active site thereby preventing the binding of AI-2.