Fragment-based virtual screening identifies novel leads against Plasmepsin IX (PlmIX) of *Plasmodium falciparum*: Homology modeling, molecular docking, and simulation approaches	
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Abstract: Despite continuous efforts to develop safer and efficient medications, malaria remains a major threat posing great challenges for new drug discovery. The emerging drug resistance, increased toxicities, and impoverished pharmacokinetic profiles exhibited by conventional drugs have hindered the search for new entities. Plasmepsins, a group of *Plasmodium*-specific, aspartic acid protease enzymes, are involved in many key aspects of parasite biology, and this makes them interesting targets for antimalarial chemotherapy. Among different isoforms, PlmIX serves as an unexplored antimalarial drug target that plays a crucial role along with PlmV and X in the parasite's survival by digesting hemoglobin in the host's erythrocytes. In this study, fragment-based virtual screening was performed by modeling the three-dimensional structure of PlmIX and predicting its ligand-binding pocket by using the Sitemap tool. Screening identified the fragments with the XP docking score ≤ −3 kcal/mol from the OTAVA General Fragment Library (≈16,397 fragments), and the selected fragments were chosen for ligand breeding. The resulting ligands (≈69,858 ligands) were subsequently subjected to filtering based on the QikProp properties along with carcinogenicity testing performed using CarcinoPred-EL and then docked in the SP (≈14,078 ligands) as well as XP mode (≈3,104 ligands), and compared with that of control ligands 49C and I0L. The top-ranked ligands were taken further for the calculation of the free energy of binding using Prime MM–GBSA. Overall, a total of six complexes were taken further for MD simulation studies performed at 100 ns to attain a better understanding of the binding mechanisms, and compounds **3** and **4** were found to be the most efficient ones *in silico*. The analysis of compound **3** revealed that the carbonyl group present in position 1 on the isoindoline moiety (Arg554) was responsible for inhibitory activity against PlmIX. However, the analysis of compound **4** revealed that the amide linkage sandwiched between the phenyl ring and isoquinoline moiety (Lys555 and Ser226) as well as carbonyl oxygen of the carbamoyl group present at position 2 of the pyrazole ring (Gln222) were responsible for PlmIX inhibitory activity, owing to their crucial interactions with key amino acid residues.