Three-dimensional Pharmacophore Modelling Of 4-Quinolinyl and 9-Acrydinylhydrazone Analogues as Potential Inhibitors of *Plasmodium Falciparum*

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Malaria is a mosquito-borne infectious disease of humans caused by eukaryotic protists of the genus *Plasmodium*. Four species of *Plasmodium* can infect and be transmitted by humans. Severe disease is largely caused by *Plasmodium falciparum*. Symptoms that typically include in malaria are fever and headache, in severe cases progressing to coma, and death.1 The emergence of resistance to the cheapest and most commonly used drugs, such as chloroquine and sulfadoxine-pyrimethamine, represents a major obstacle in controlling malaria.2 Chloroquine may have a more rapid effect on lowering parasitemia than either quinine or quinidine, but it also has a more profound hypotensive side effect. Thus, there is great interest in developing potent and less toxic inhibitors of *Plasmodium falciparum* glutathione reductase (*P. falciparum* GR). Pharmacophore based methods provide a way of establishing a structure–activity relationship for a series of known active ligands. A ligand-based pharmacophore model using Catalyst HypoGen algorithm was developed for set of 4-quinolinyl and 9-acrydinylhydrazone analogues3 as *P. falciparum* GR inhibitors with an aim to obtain rational hypothetical image of the primary chemical features responsible for activity and this pharmacophore model was used as an in silico screening tool to retrieve novel and potential inhibitors against *P. falciparum* GR from various databases. The best pharmacophore model for selective *P. falciparum* GR inhibitors (Hypo-1) was obtained through a Cat-Scramble validation process. The best pharmacophore model (Hypo-1) for *P. falciparum* GR are shown in Fig. 1, consisting of one hydrogen bond donor (HBD), three hydrophobic (HY) and one ring aromatic (RA) features, as well as three exclude volumes with highest correlation coefficient (0.88), cost difference (46.2), low RMS (0.85), as well as it shows a high goodness of fit and predictive factor. Hydrophobic interactions are essential for ligand pharmacophore interaction. Highly active compounds share up to three hydrophobic features that allow the ligand to occupy large areas of the predominantly hydrophobic binding pocket. Pharmacophore models have been validated toward a test set containing 12 molecules. To further evaluate the model external test set comprising of known *P. falciparum* GR inhibitors were mapped on to developed pharmacophoric model which also showed five point mapping and estimated values in close range to actual values. The results of our study will act as a valuable tool for retrieving potent compounds with desired biological activities and designing novel and less toxic *P. falciparum* GR inhibitors.