

De Novo Molecular Design and Bioactivity Prediction of Novel Hexahydroquinolines as *Plasmodium falciparum* Calcium-dependent Protein Kinase 4 (PfCDPK4) Inhibitors

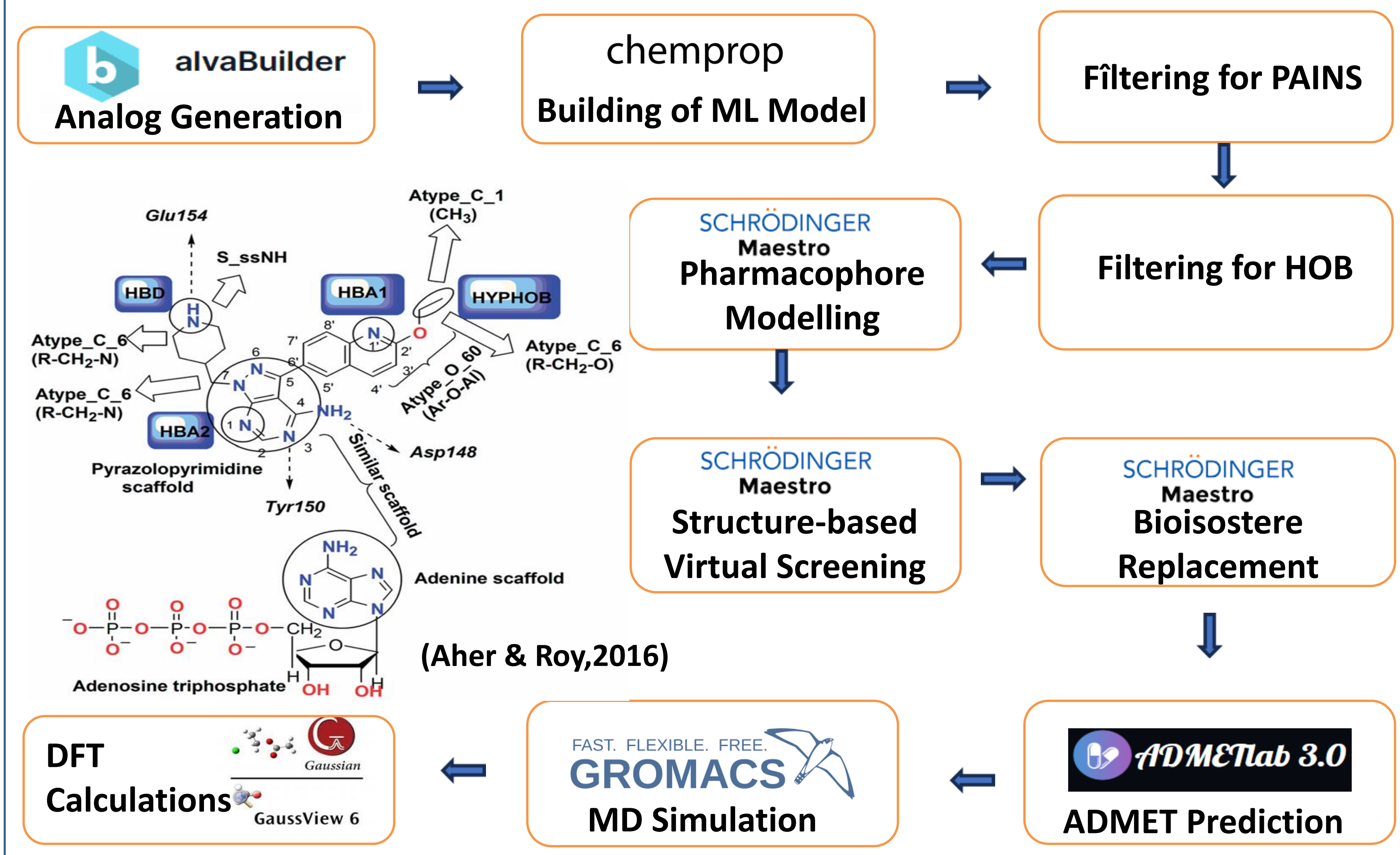
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BACKGROUND

Medicines for Malaria Venture (MMV) provides Target Product Profiles (TPPs) and Target Candidate Profiles (TCPs) as guidelines for antimalarial development. TCP 5 addresses transmission-blocking by targeting gametocyte stages. While most existing drugs act on blood-stage parasites, complementary transmission-blocking drugs are urgently needed. *Plasmodium falciparum* Calcium Dependent Protein Kinase 4 (PfCDPK4), a Ca^{2+} signaling kinase absent in humans, is a selective TCP 5 target. Inhibiting PfCDPK4 disrupts male gametocyte exflagellation and sexual stage development. Bumped kinase inhibitors (BKIs) are the main reported PfCDPK4 inhibitors, but limitations in bioavailability and safety restrict their clinical potential. This study aims to design novel antimalarial hexahydroquinoline (HHQ) derivatives with improved predicted bioactivity, enhanced bioavailability and reduced toxicity compared to existing BKIs. By doing so, it contributes to SDG 3 (Good Health and Well-being), Target 3.3, which calls for ending the malaria epidemic by 2030.

METHODOLOGY



RESULTS

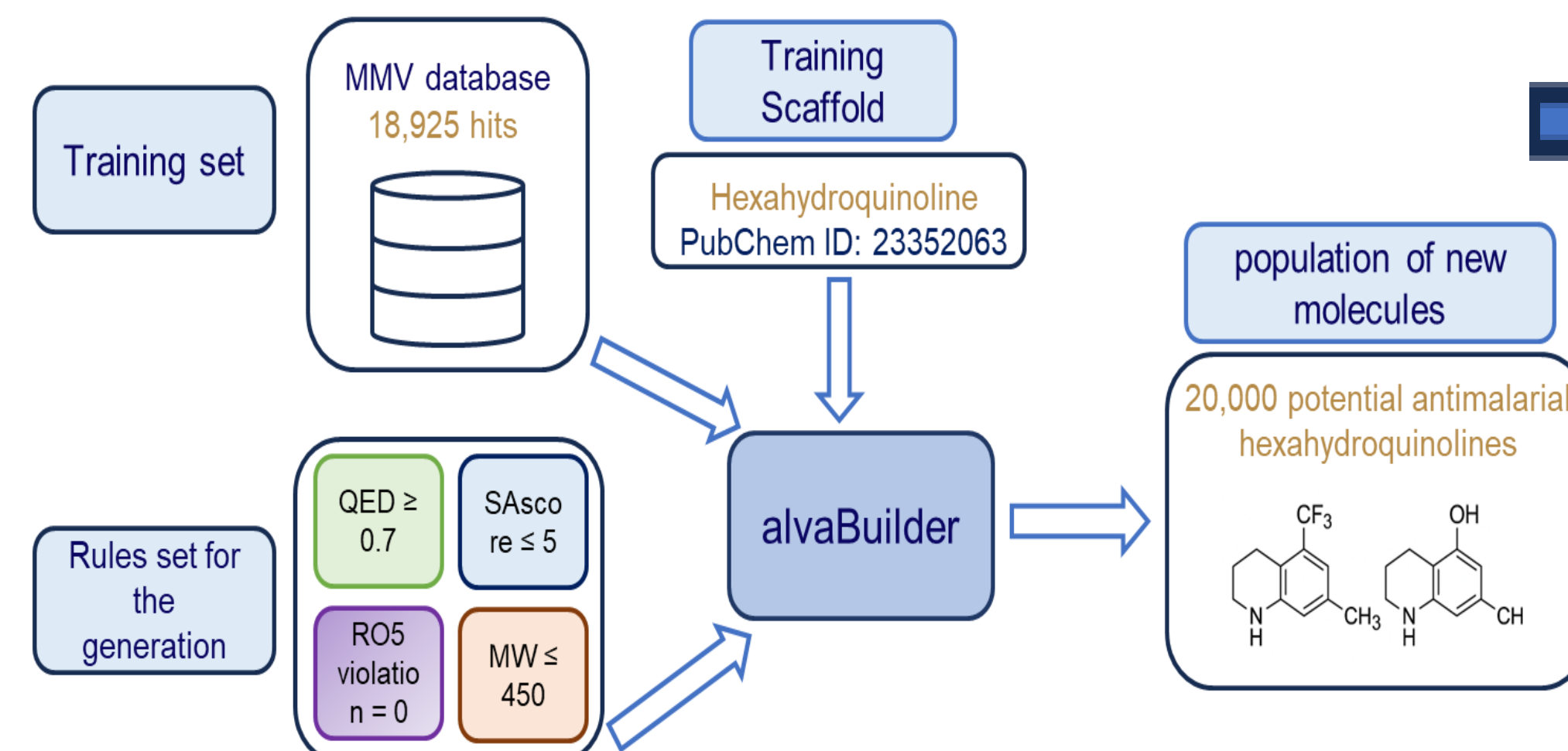


Fig 1. Generation Of Novel HHQ Analogs

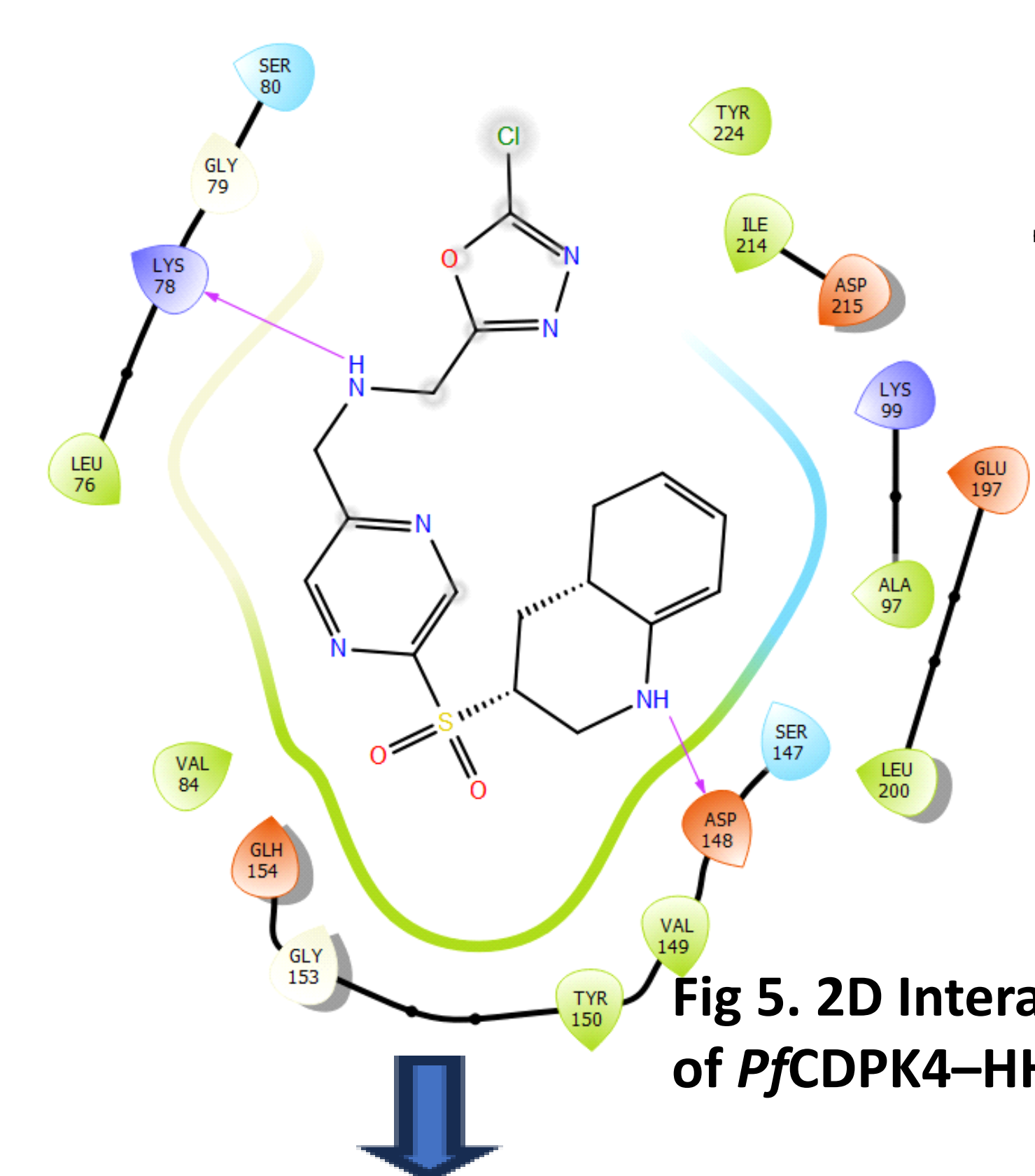


Fig 5. 2D Interaction Diagram of PfCDPK4-HHQ 1a

Table 1. Classification Metrics of the Machine Learning Model

Data set	Accuracy	Precision	Recall	F1 Score	Specificity
Train	0.90	0.95	0.85	0.90	0.96
Test	0.82	0.82	0.76	0.79	0.86
Val	0.75	0.81	0.67	0.73	0.84

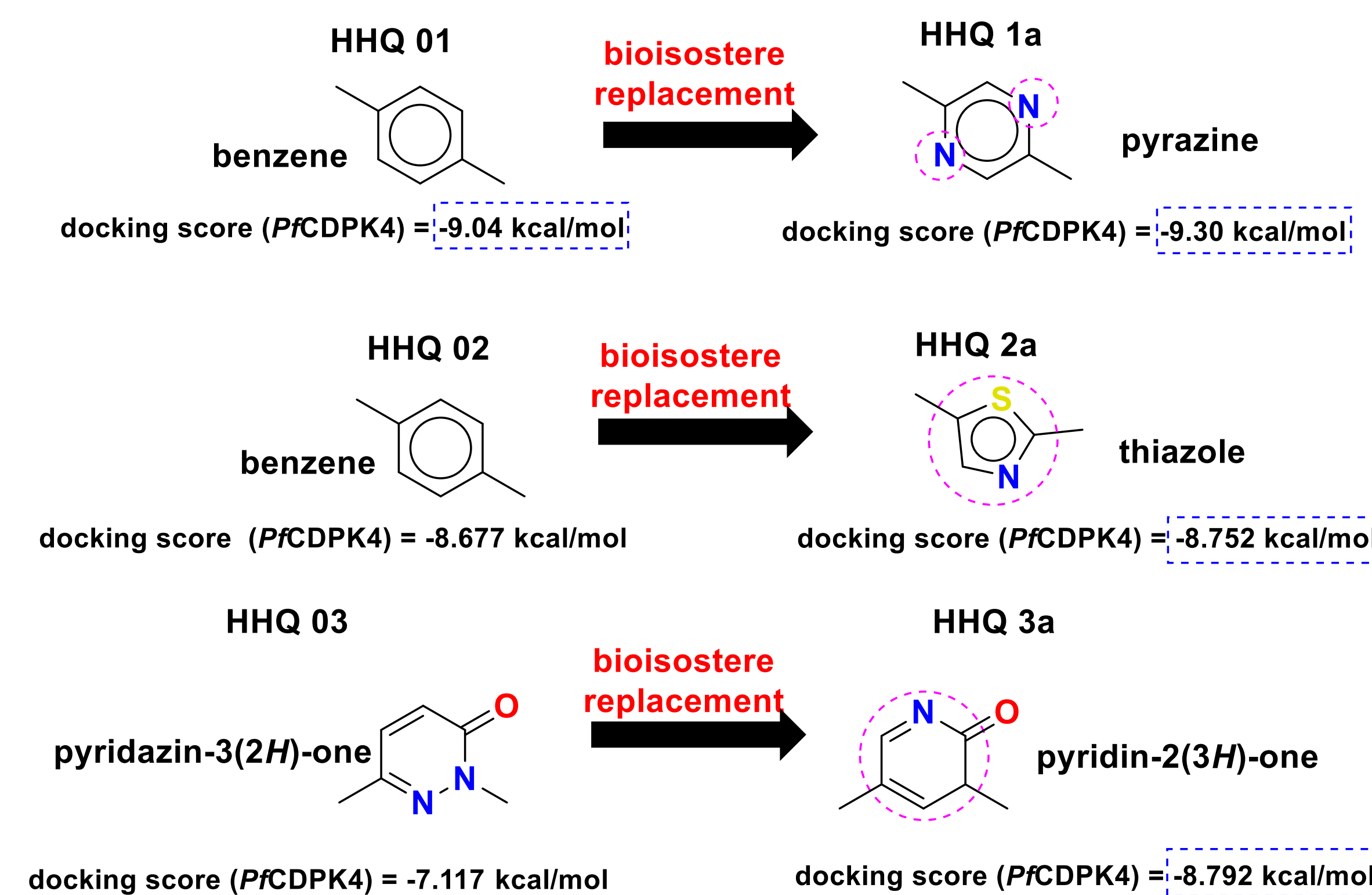


Fig 4. Bioisosteric Replacement for top HHQ hits

Table 2. ADMET profiles of the top HHQ hits

S/N	Name	HHQ 01	HHQ 1a	HHQ 2a	HHQ 3a	BKI-1	Optimal range
1	LogS	-2.684	-2.684	-3.818	-2.194	-3.152	-4 to 0.5 log mol/L
2	LogD	1.829	1.829	2.802	1.085	2.564	1 to 3 log mol/L
3	LogP	1.586	1.586	2.874	1.503	1.342	0 to 3 log mol/L
4	F(30%)	0.155	0.155	0.028	0.007	0.039	0-0.3
5	Caco-2	-4.601	-4.601	-5.134	-4.762	-5.645	>-5.15 log cm/s
6	MDCK	6.48E-06	6.48E-06	8.69E-06	8.91E-06	3.96E-06	>2 × 10 ⁻⁶ cm/s
7	hERG	0.061	0.061	0.018	0.033	0.949	0-0.3
8	Ames	0.012	0.012	0.046	0.013	0.957	0-0.3
9	QED	0.721	0.721	0.817	0.765	0.525	>0.67
10	Synth	4.136	4.136	4.522	4.642	3.738	≤ 6

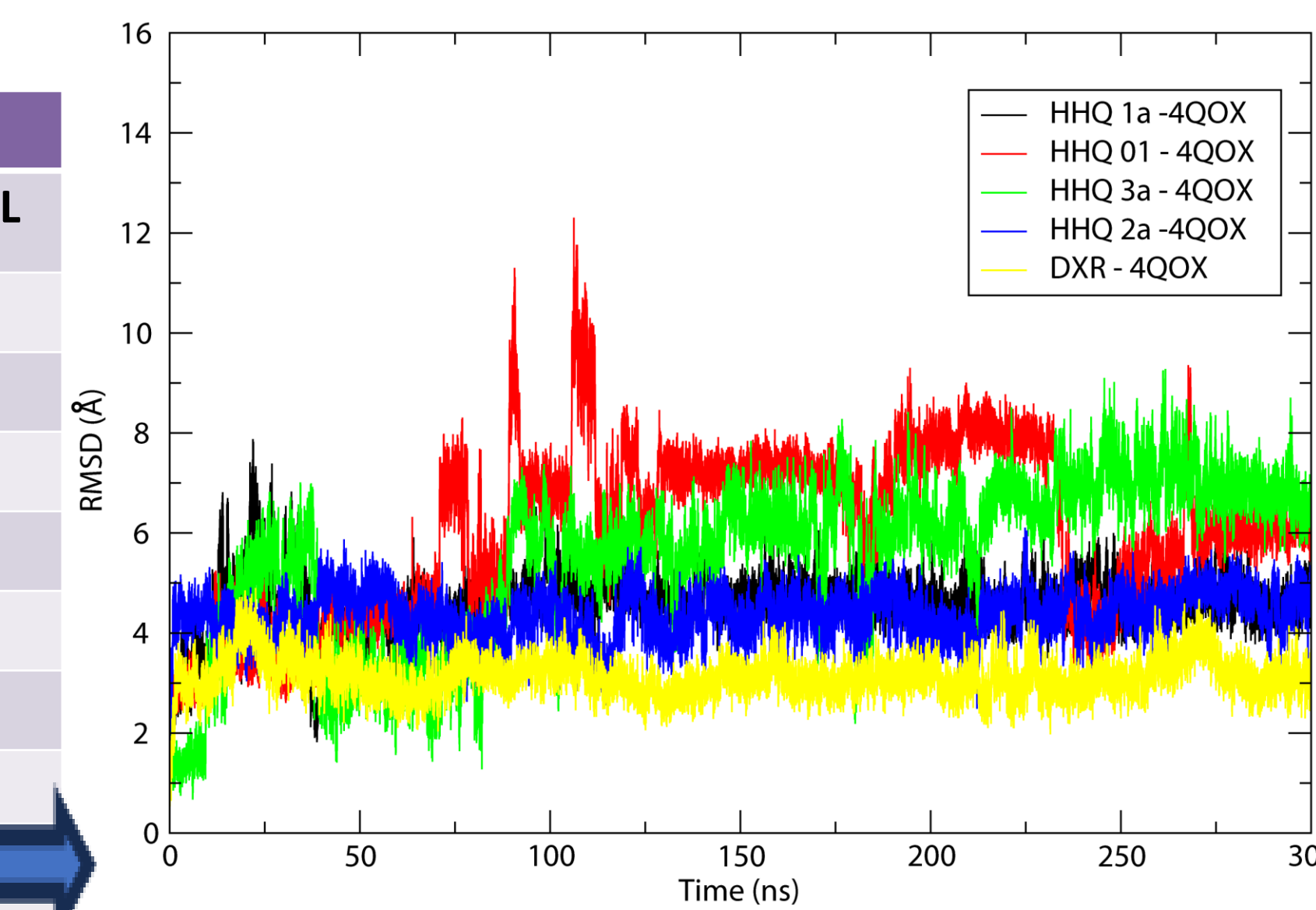


Fig 6. RMSD of the top hits

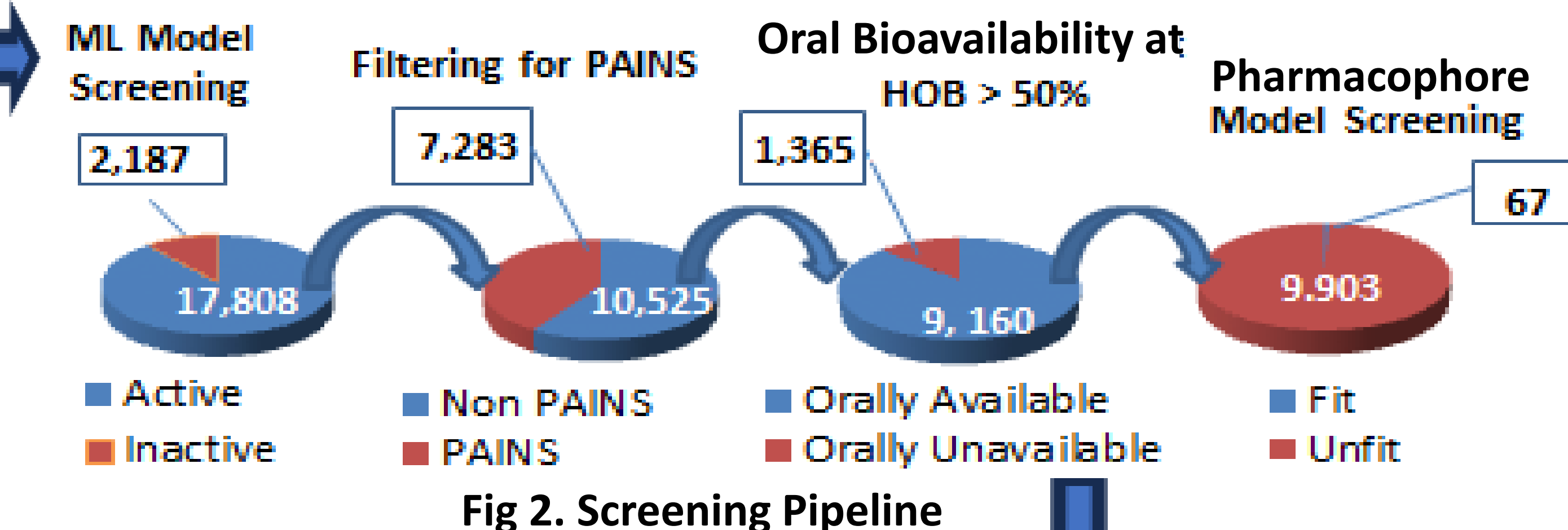


Fig 2. Screening Pipeline

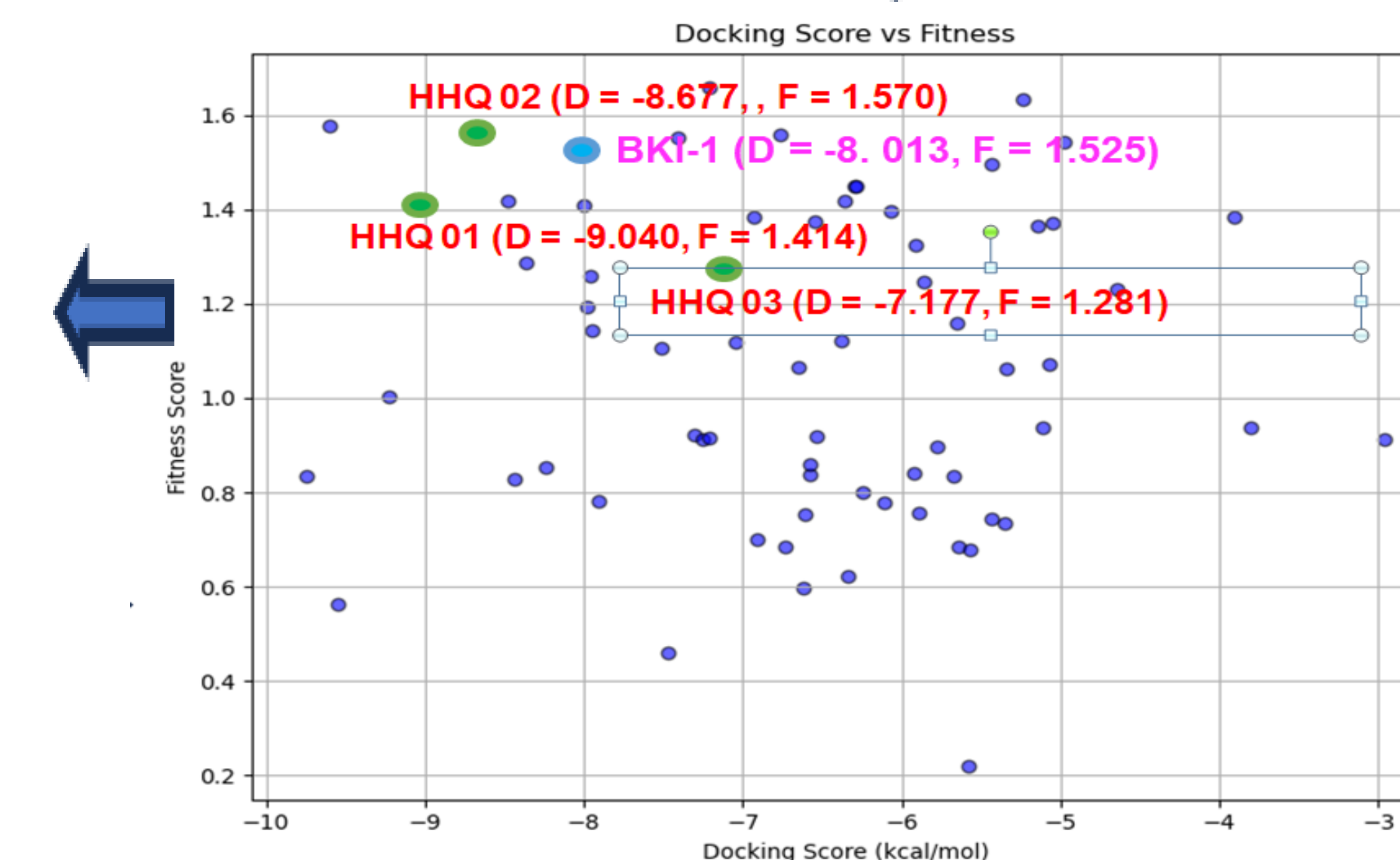


Fig 3. Docking and Fitness scores for the top HHQ hits compared to BKI-1

CONCLUSION

This study successfully developed novel HHQ analogs as potential PfCDPK4 inhibitors for malaria transmission blocking. Four lead compounds (HHQ 01, HHQ 1a, HHQ 2a, and HHQ 3a) outperformed the reference inhibitor BKI-1, showing stronger binding affinity and improved predicted oral bioavailability and safety. These findings represent an important step toward new malaria therapeutics, supporting global efforts to combat drug resistance and advance SDG 3.3—to end the malaria epidemic.