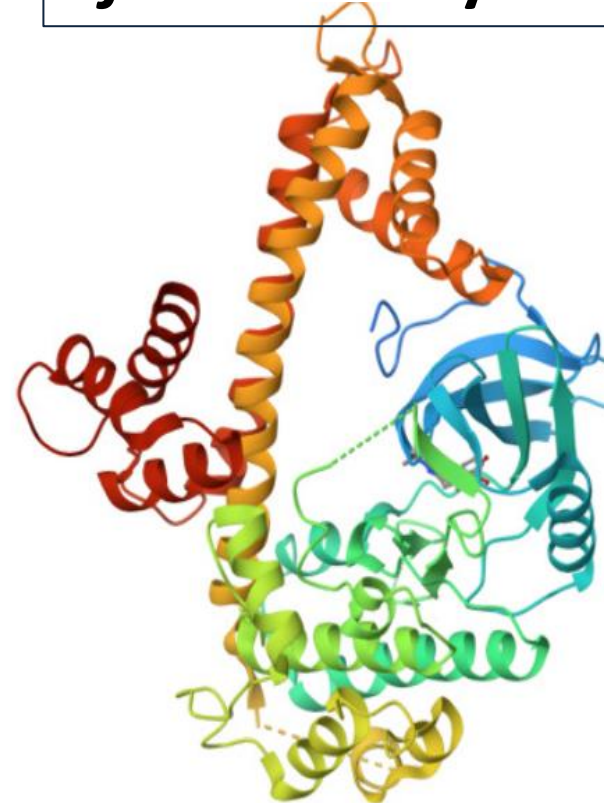


INTRODUCTION

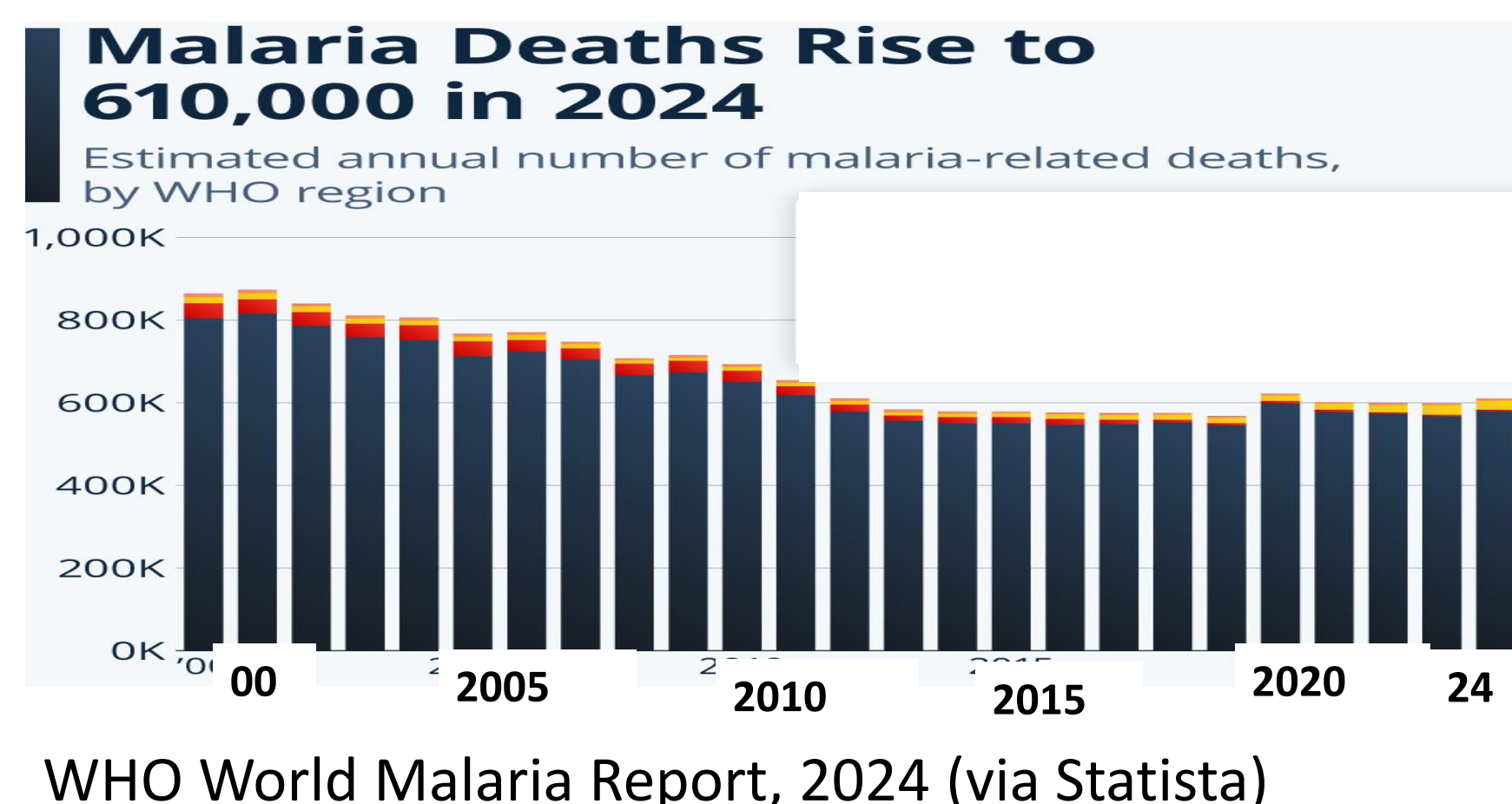
The rising burden of antimalarial drug resistance has slowed progress made toward malaria eradication over the past two decades. This challenge necessitates diversified treatment strategies beyond the currently predominant curative therapies. One promising approach is human-to-mosquito transmission blockade, as recognised through Target Candidate Profile 5 (TCP5) by Medicines for Malaria Venture (MMV).

PfCDPK4 enzyme



PDB ID : 4QOX

Plasmodium falciparum Calcium-Dependent Protein Kinase 4 (PfCDPK4) is a validated target for malaria transmission-blocking drug development. Its inhibition disrupts phosphorylation events required for exflagellation of male gametocytes, preventing parasite sexual development in the mosquito vector. Because the current curative antimalarial therapies are not effective against this sexual stage responsible for onward transmission of the parasites to humans, there is a need to explore novel transmission-blocking approaches. This study aimed to identify potential PfCDPK4 inhibitors with favourable predicted bioactivity, pharmacokinetic, and safety profiles for malaria transmission blockade from ChemDiv. This compound library, selected for structural diversity and synthetic accessibility, was subjected to a rigorous multi-stage computational pipeline to identify viable PfCDPK4 inhibitors.



IDENTIFICATION OF PfCDPK4 INHIBITORS

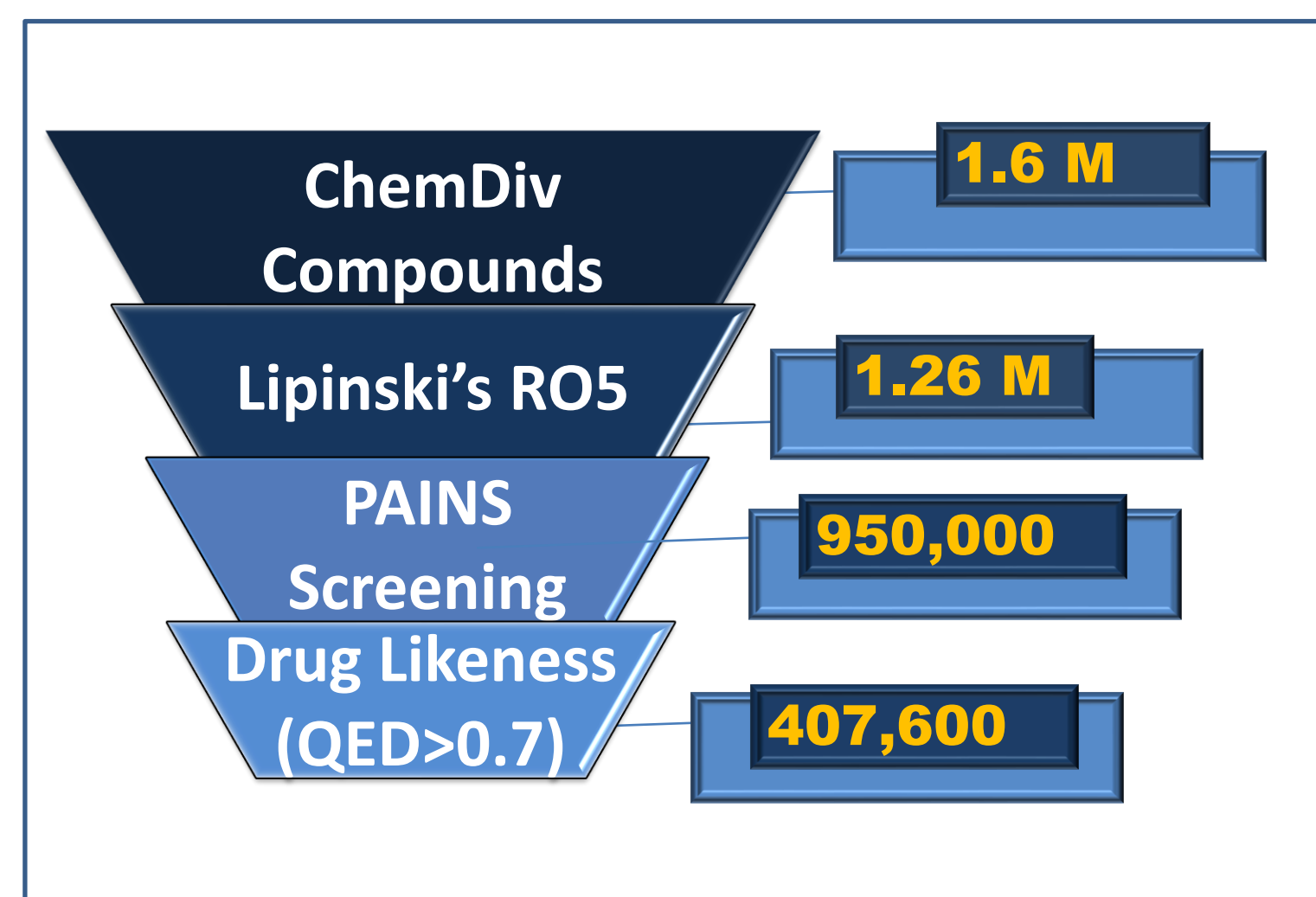


Fig 1. Preliminary virtual screening pipeline

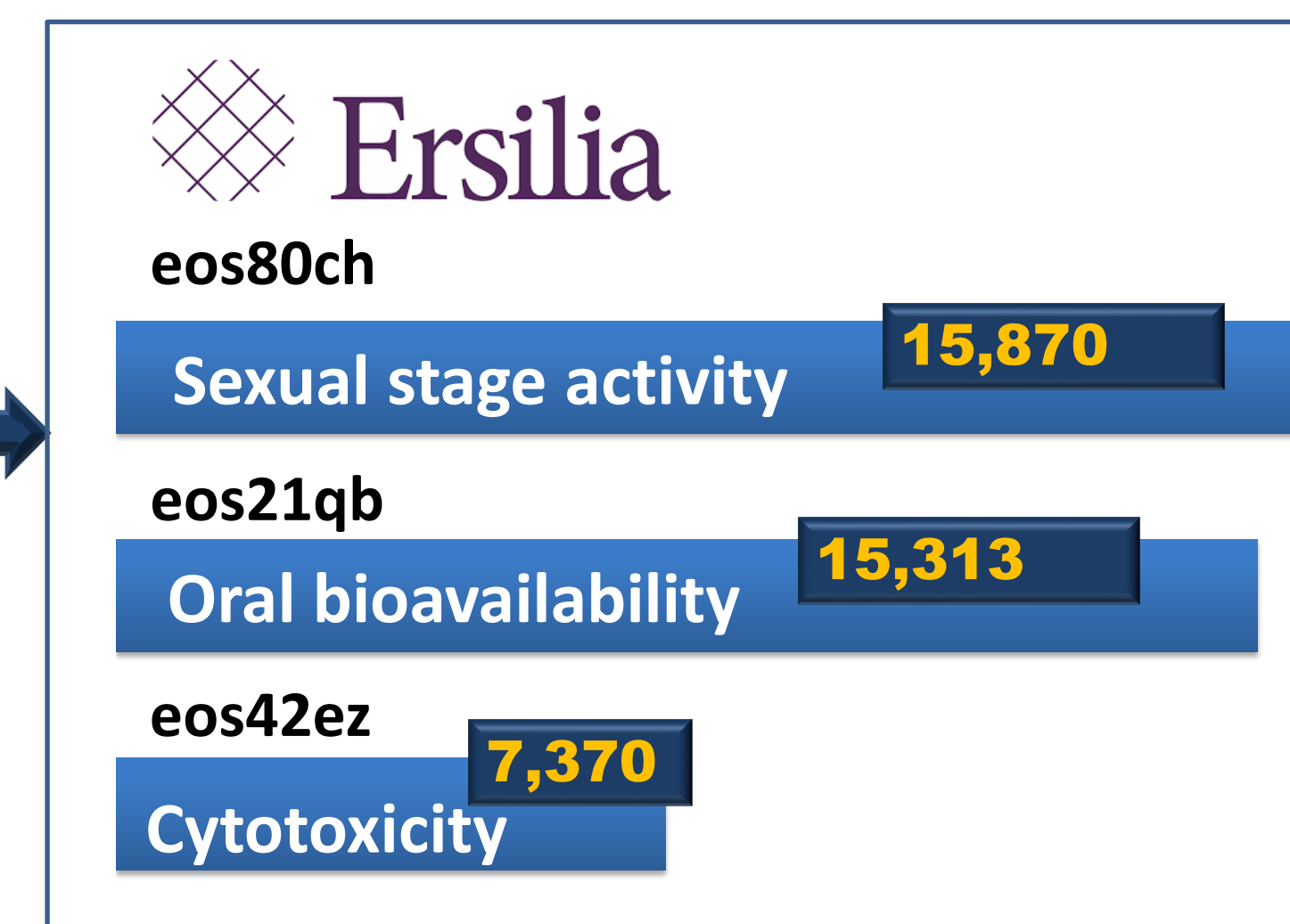


Fig 2. Ersilia machine learning model-based screening

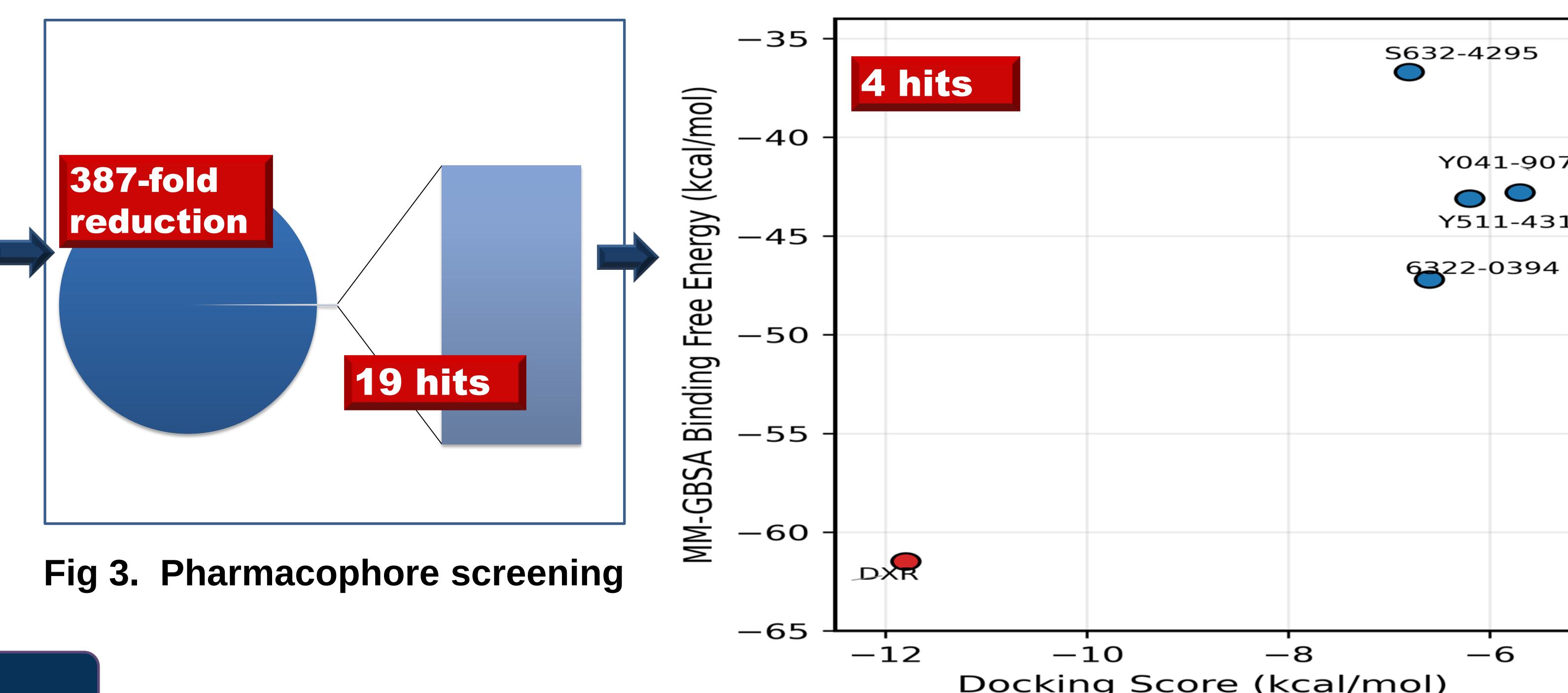


Fig 4. Docking and fitness scores for the top hits compared to the DXR co-ligand

PROTEIN-LIGAND INTERACTION STUDIES

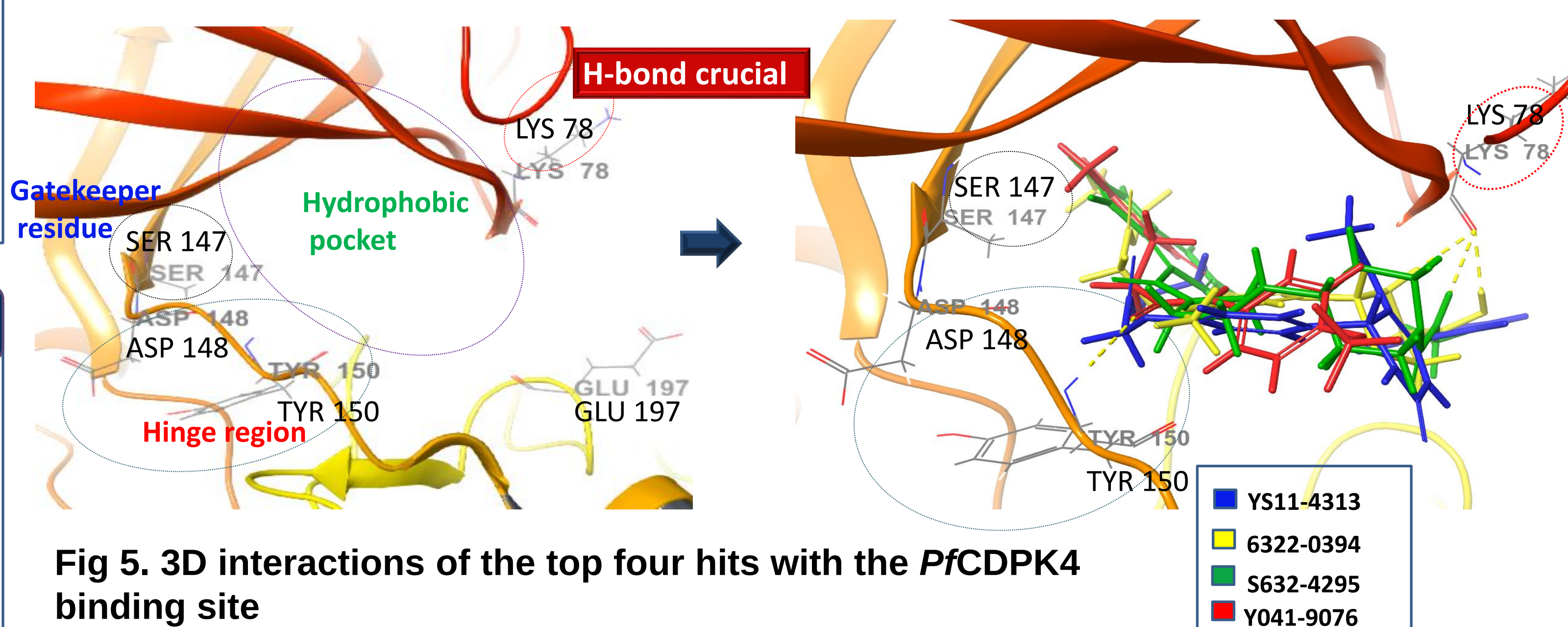


Fig 5. 3D interactions of the top four hits with the PfCDPK4 binding site

MOLECULAR DYNAMICS SIMULATION

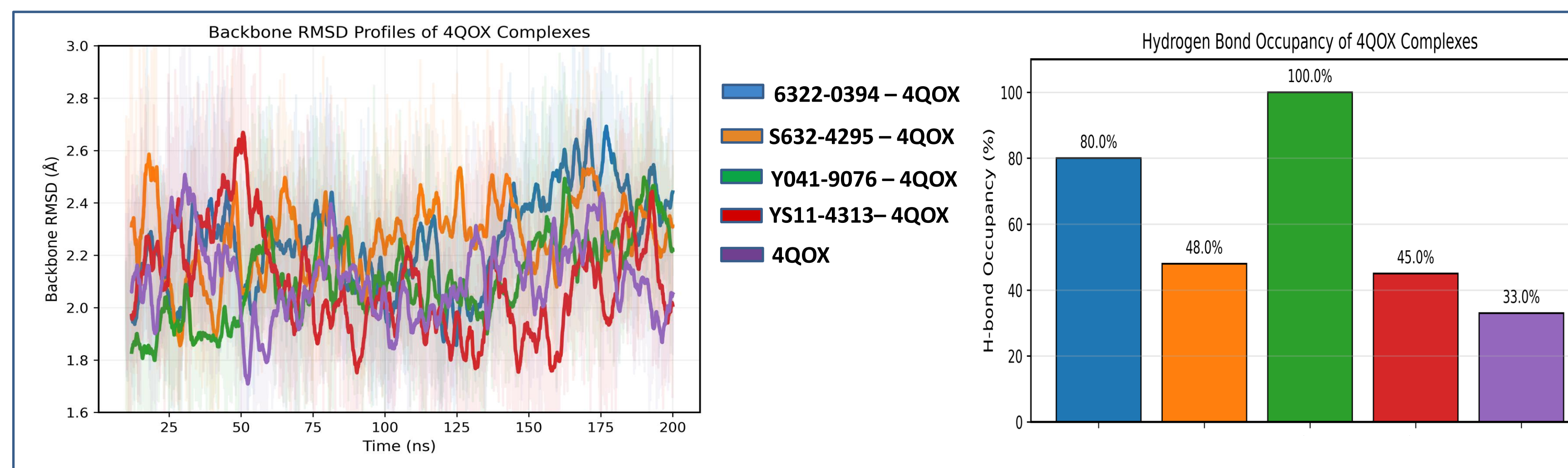
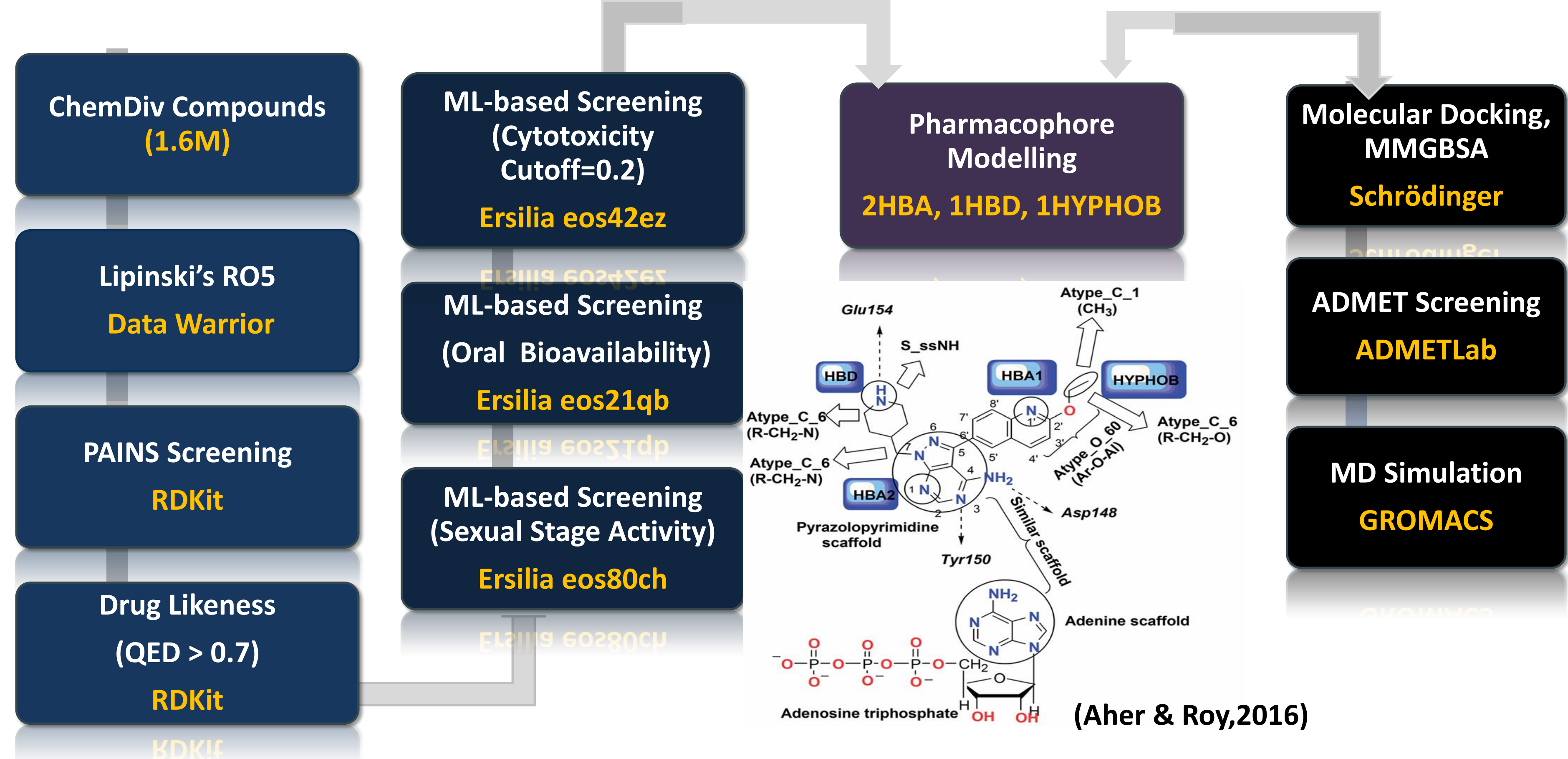


Fig 6. RMSD profile and hydrogen bond occupancy for the top four ChemDiv hits

METHODOLOGY – IN SILICO SCREENING PIPELINE



IN SILICO DMPK AND CYTOTOXICITY PROFILING

Table 1. Predicted DMPK and cytotoxicity profiles of the top 4 ChemDiv hit compounds

Compound s	Log S (mol/L)	Log D (mol/L)	MDCK (cm/s)	PPB (%)	Clearance (ml/min/kg)	Cytotoxicity y (HepG2)	Cytotoxicity (HSKMC)	Cytotoxicity (IMR90)
Optimal ranges	-4 to 0.5 mol/L	1 to 3 mol/L	> 2 x 10 ⁻⁶ cm/s	≤ 90%	≥ 5	0 - nontoxic 1 - toxic	0 - nontoxic 1 - toxic	0 - nontoxic 1 - toxic
S632-4295	-3.017	1.392	5.37 x 10 ⁻⁶	74.67	4.348	0.04667	0.04155	0.00968
6322-0394	-1.953	1.034	6.15 x 10 ⁻⁶	51.78	5.339	0.06591	0.10969	0.01495
Y511-4313	-3.959	2.439	38.2 x 10 ⁻⁶	96.68	3.370	0.12609	0.13020	0.03435
Y041-9076	-3.921	2.497	13.2 x 10 ⁻⁶	94.54	5.892	0.19329	0.15984	0.03121

CONCLUSION AND FUTURE DIRECTIONS

This study identified four ChemDiv compounds (Y511-4313, Y041-9076, 6322-0942, and S632-4295) as potential PfCDPK4 inhibitors. They exhibited favourable drug-likeness, ADMET profiles, and key interactions within the PfCDPK4 ATP-binding pocket, supporting their potential as malaria transmission-blockers. Future *in vitro* and *in vivo* validation will be essential to confirm their activity and advance their optimisation as novel transmission-blocking therapies. Overall, this work contributes to global efforts toward achieving SDG 3.3, aimed at ending the malaria epidemic.

Aher, R.B. and Roy, K. (2016) "Exploring structural requirements for the inhibition of: Plasmodium falciparum calcium-dependent protein kinase-4 (Pf CDPK-4) using multiple in silico approaches," *RSC Advances*, 6(57), pp. 51957–51982. Available at: <https://doi.org/10.1039/c6ra05692j>.
Seanego, T.D. *et al.* (2022) "7H-Pyrrolo[2,3-d]pyrimidine-4-amines as Potential Inhibitors of Plasmodium falciparum Calcium-Dependent Protein Kinases," *ChemMedChem*, 17(22), pp. 1–11. Available at: <https://doi.org/10.1002/cmdc.202200421>.
Fleck, A. (2026) *Infographic: Malaria Deaths Rise to 610,000 in 2024*, Statista Daily Data. Statista. Available at: <https://www.statista.com/chart/1758/estimated-number-of-deaths-caused-by-malaria-worldwide>, (Accessed: 10 June 2026).