



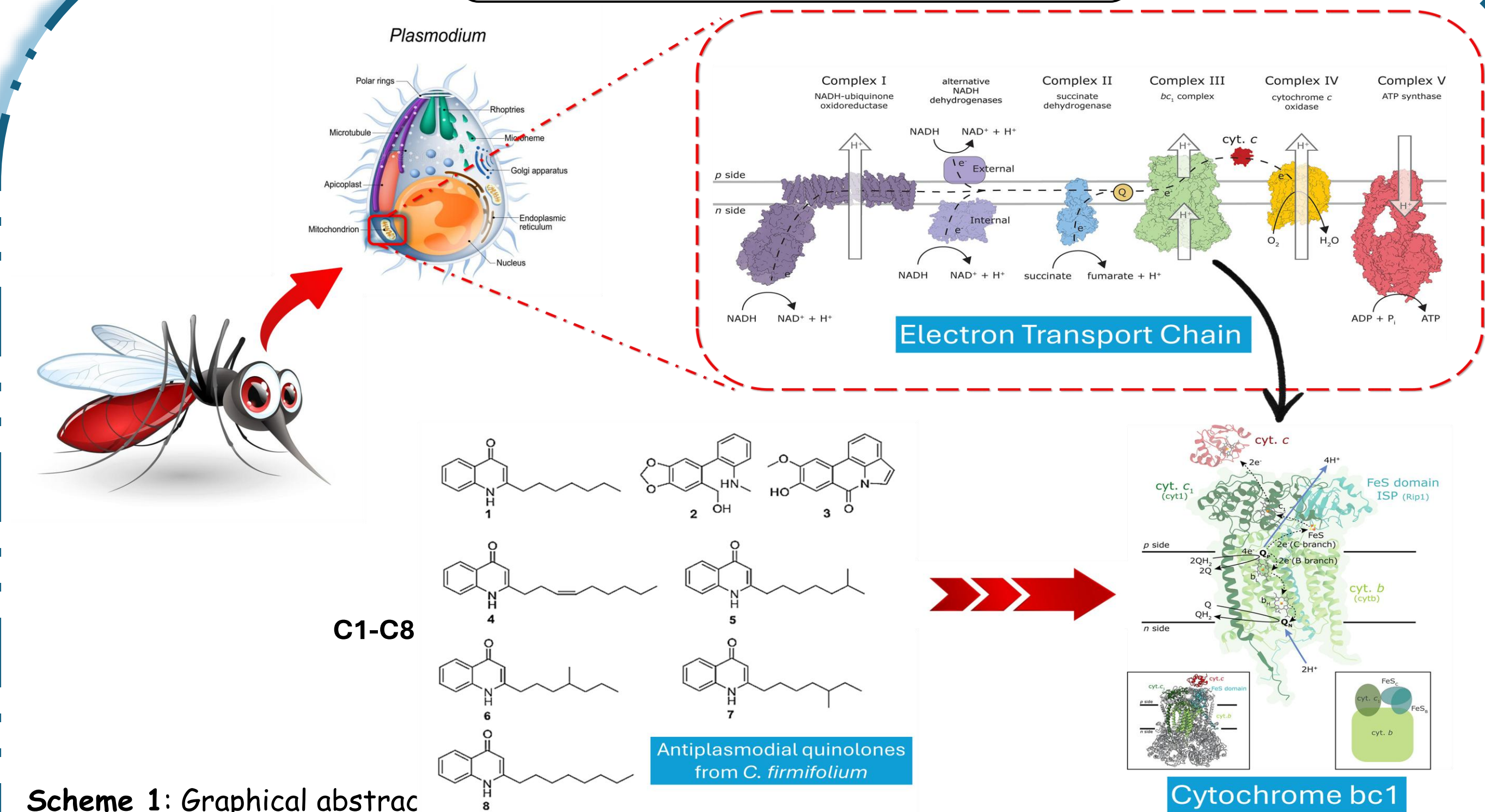
In silico Evaluation of *Crinum firmifolium*-Derived Quinolones as Potent Inhibitors of *Plasmodium falciparum* Cytochrome bc1

Philip Teye Thompson¹, Michael Konney Laryea¹, Mercy Badu¹, and Lawrence Sheringham Borquaye^{1,2}

¹Department of Chemistry, Kwame Nkrumah University of Science and Technology, Kumasi

²Central Laboratory, Kwame Nkrumah University of Science and Technology, Kumasi

1. Introduction



Malaria remains one of humanity's toughest battles, made harder by the parasite's relentless ability to develop **resistance** against existing drugs. To stay ahead, researchers are seeking novel drug targets that can unlock new therapeutics.

One promising target is **cytochrome bc1**, a key enzyme in the parasite's mitochondrial electron transport chain. Unlike its human counterpart, this enzyme exhibits structural differences that make it a particularly attractive target. Blocking its function disrupts the parasite's energy production, ultimately threatening its survival.

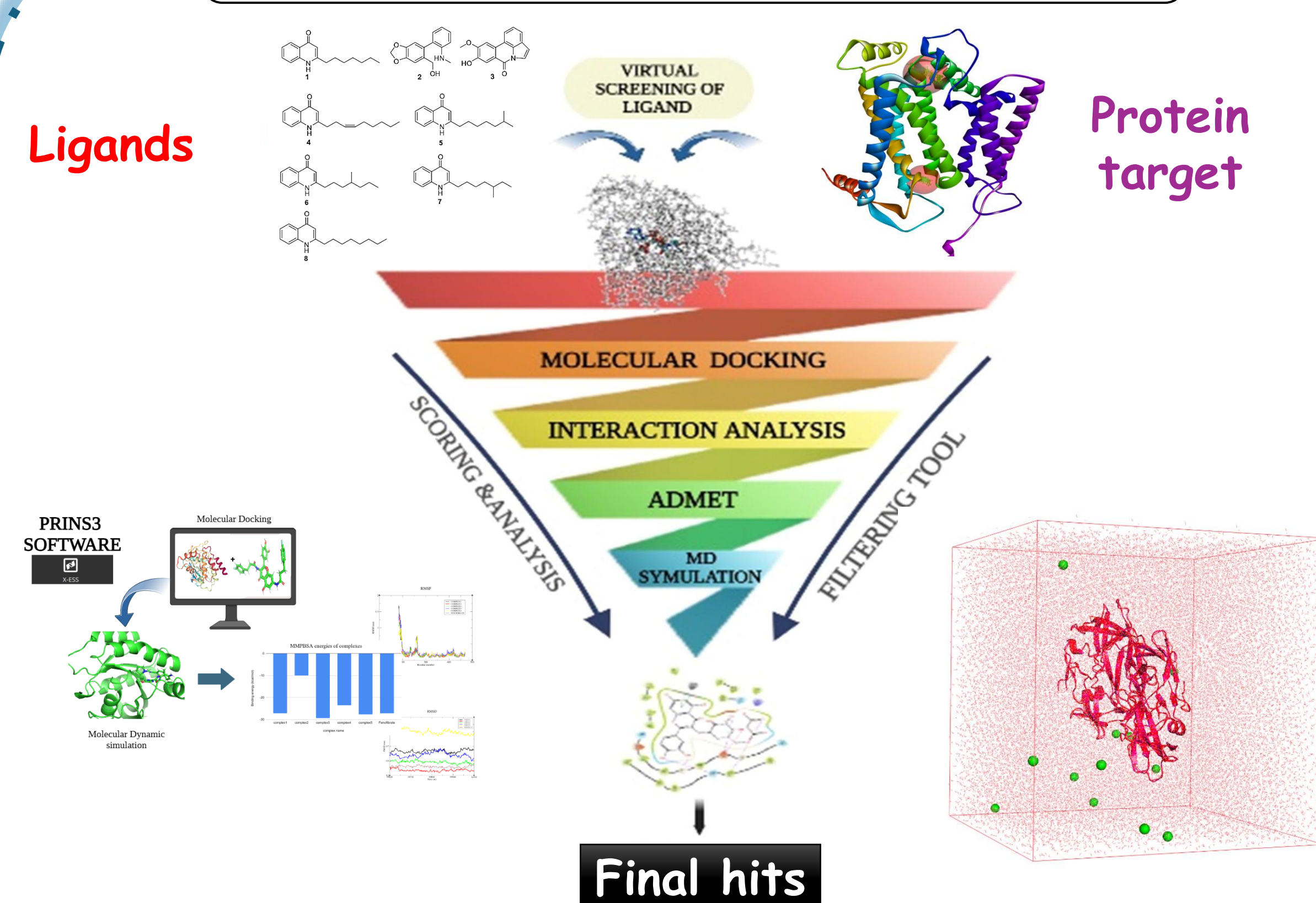
Evidence from the literature points to **quinolones** as inhibitors of cytochrome bc1. Interestingly, ***Crinum firmifolium***, a plant long used in traditional medicine for treating malaria, contains compounds with antiparasitic activity. Some of its isolates have already shown *in vitro* activity against Plasmodium strains, hinting at the potential for novel therapeutic development from natural sources.

Specific Objectives

To use *in silico* tools to:

1. Study the interactions between the isolates and cytochrome bc1 at the molecular level
2. Study the mechanism of action of the isolates
3. Study the drug-likeness and toxicity of the isolates

2. Experimental Design



4. Conclusion

- *In silico* results suggest that the isolates are good binders of the cytochrome bc1 protein and, as such, can inhibit the normal function of the enzyme
- The isolates can keep the loop G195-L206 in the closed conformation, which prevents the transportation of protons from the matrix to the intermembrane space

5. References

- Presley, C. C., Du, Y., Dalal, S., Merino, E. F., Butler, J. H., Rakotonandrasana, S., Rasamison, V. E., Cassera, M. B., & Kingston, D. G. I. (2017). Isolation, structure elucidation, and synthesis of antiparasitic quinolones from *Crinum firmifolium*. *Bioorganic & Medicinal Chemistry*, 25(15), 4203–4211. <https://doi.org/10.1016/j.bmc.2017.06.017>
- Kumar, S., Bhardwaj, T. R., Prasad, D. N., & Singh, R. K. (2018). Drug targets for resistant malaria: Historic to future perspectives. *Biomedicine & Pharmacotherapy*, 104, 8–27. <https://doi.org/10.1016/j.biopha.2018.05.009>

3. Results and Discussion

Table 1: Molecular Docking Binding Energy Scores for C1-8, Inhibitors and Substrates against CYT bc1

Quinolones	Binding Energy (kcal/mol)	Substrates and Known Inhibitors	Binding Energy (kcal/mol)
C1	-6.2	Ubiquinol	-7.0
C2	-7.2	Ubiquinone	-8.1
C3	-8.4	Antimycin A	-7.2
C4	-8.7	Atovaquone	-9.7
C5	-6.8	Decoquinone	-7.9
C6	-9.0	ELQ-300	-10.0
C7	-8.2	GSK932121	-10.4
C8	-8.3		

B. E. = Binding Energy (kcal/mol); C1-8 = Compounds 1 - 8; CYT bc1 = Cytochrome bc1

2

Compound	Physicochemical						Medicinal		Absorption		Excretion		Solubility	
	MW (g/mol)	n HA	n HD	n Rot	TPSA	logP	Lipinski Rule	Pfizer Rule	HIA	Pgp- sub	Cl (mL/mi n/kg)	T _{1/2} (hrs)	ESOL log S	Class
C1	243.16	2	1	6	32.86	4.4	Accepted	Rejected	High	No	3.3	0.3	-4.44	MS
C2	257.11	4	2	3	50.72	2.7	Accepted	Accepted	High	No	10.1	0.7	-3.25	S
C3	265.07	4	1	1	50.94	2.4	Accepted	Accepted	High	No	8.2	1.0	-3.81	S
C4	269.18	2	1	7	32.86	4.3	Accepted	Rejected	High	No	6.2	0.4	-4.71	MS
C5-C8	257.18	2	1	6	32.86	4.1	Accepted	Rejected	High	No	5.8	0.3	-4.67	MS

Key: **MW**: Molecular weight, **nHA**: number of hydrogen bond acceptors (Optimal: 0-12), **nHD**: number of hydrogen bond donors (Optimal: 0-7), **nRot**: number of rotatable bonds (Optimal: 0-11), **TPSA**: Topological Polar Surface Area (Optimal: 0-40), **logP**: logarithm of the n-octanol/water distribution coefficient at pH 7.4 (Optimal: -1 to 3).

Key: MW: Molecular weight, nHA: number of hydrogen bond acceptors (Optimal: 0–12), nHD: number of hydrogen bond donors (Optimal: 0–7), nRot: number of rotatable bonds (Optimal: 0–11), TPSA: Topological Polar Surface Area (Optimal: 0–40), logP: logarithm of the n-octanol/water distribution coefficient at pH = 7.4, HIA: human intestinal absorption (High/Low), Pgp-sub: Pgp-substrate (Yes/No), Cl: clearance (plasma penetration), T_{1/2}: Half-life, MS: Moderately soluble, S: Soluble.

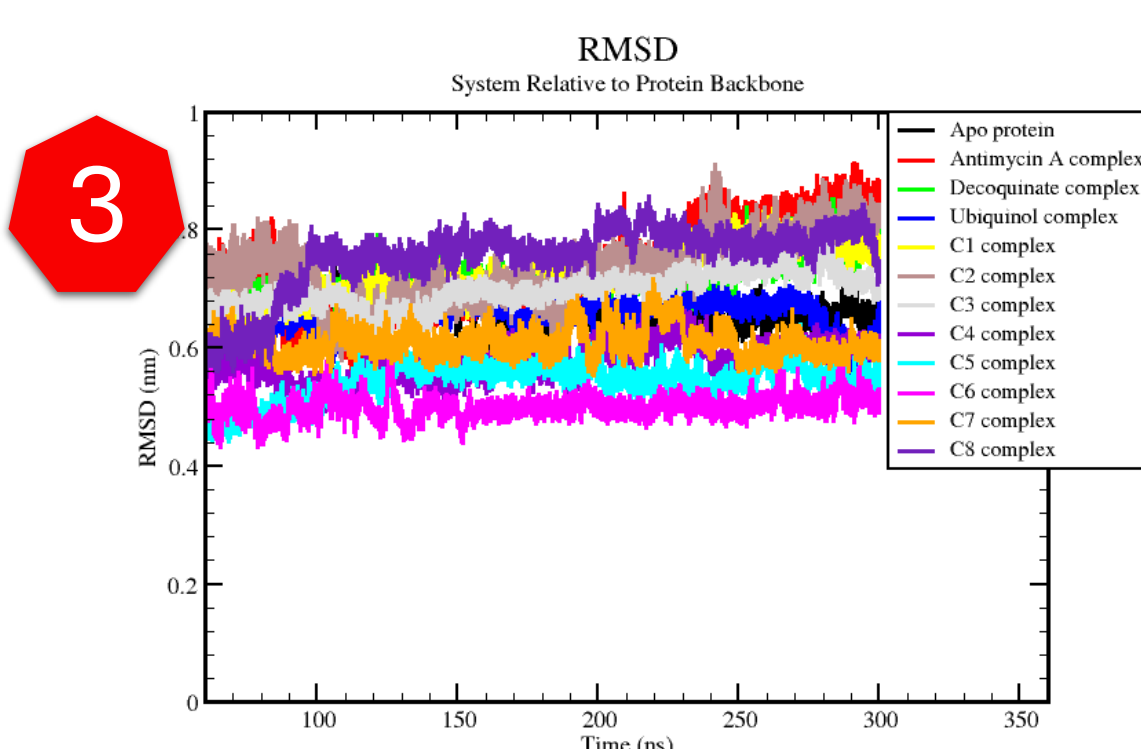


Figure 1: Protein Stability

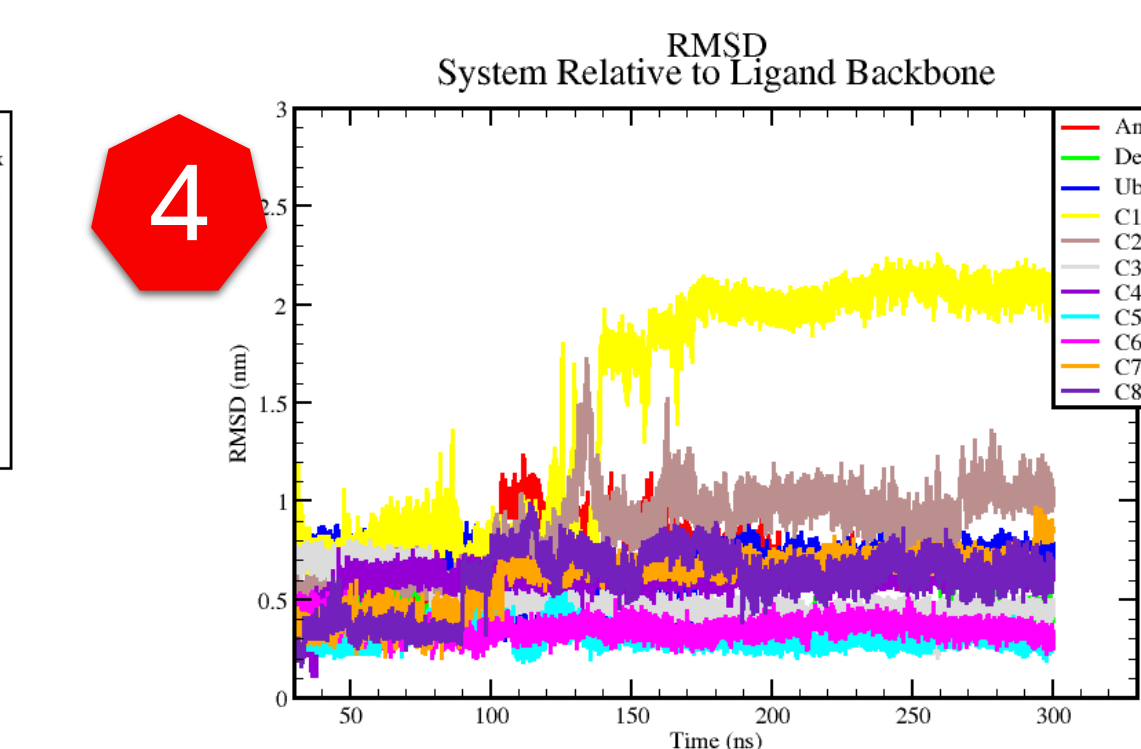


Figure 2: Ligand Stability

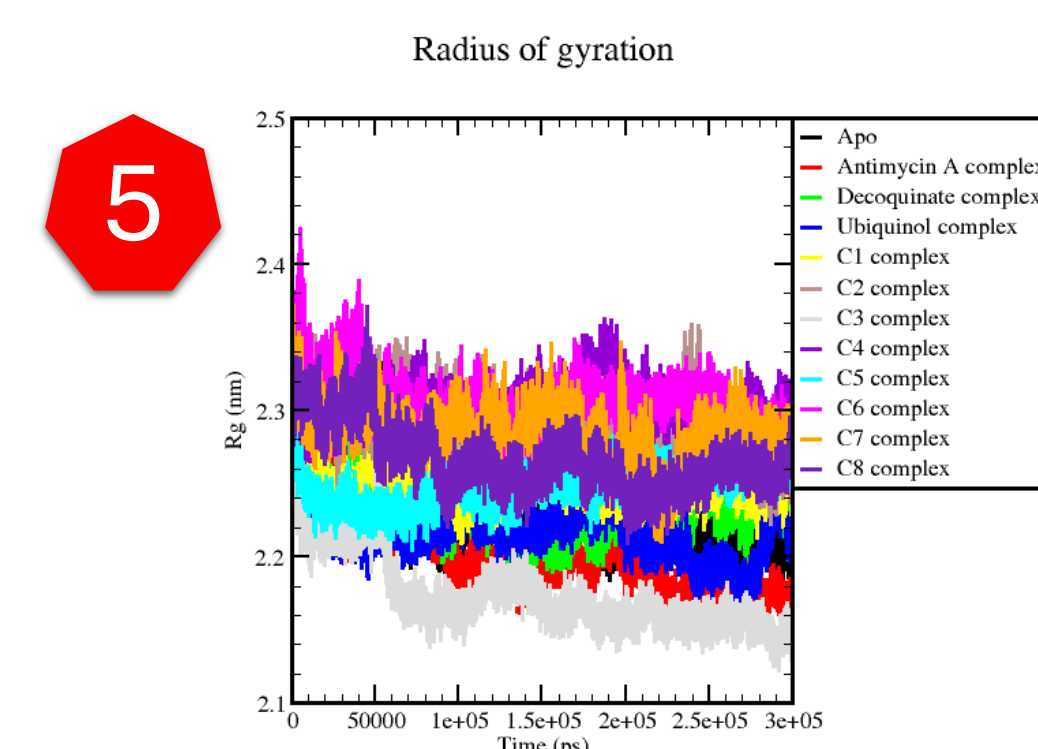


Figure 3: Protein Flexibility

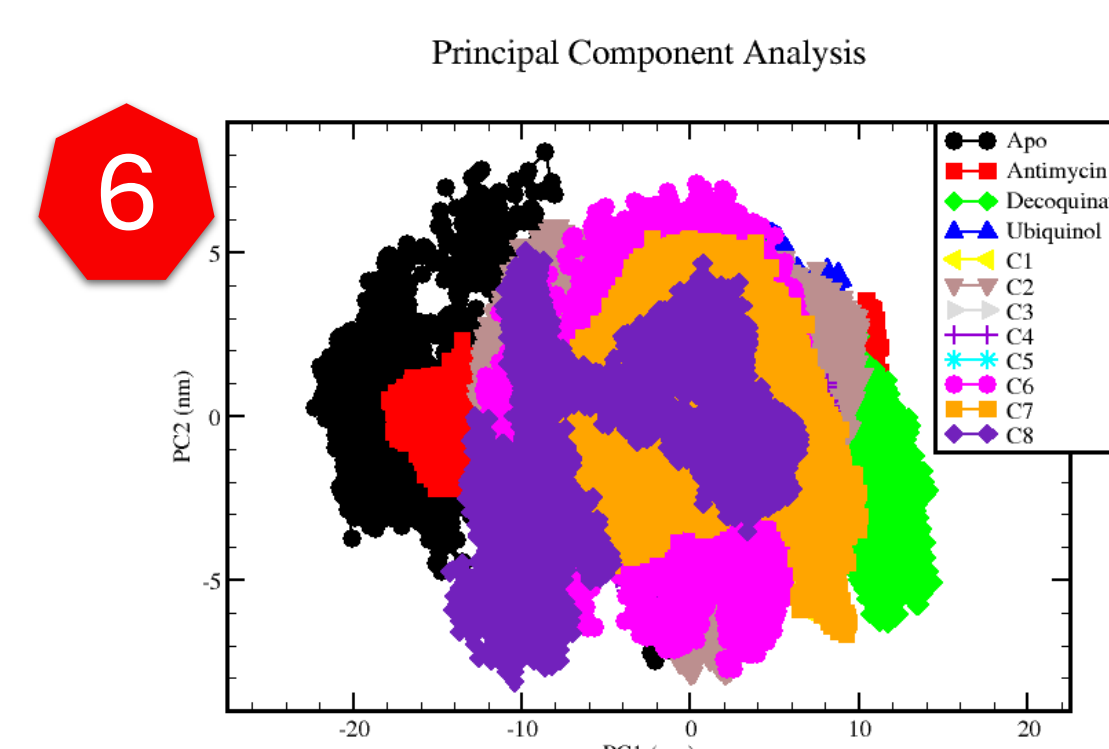


Figure 4: Complex Compactness

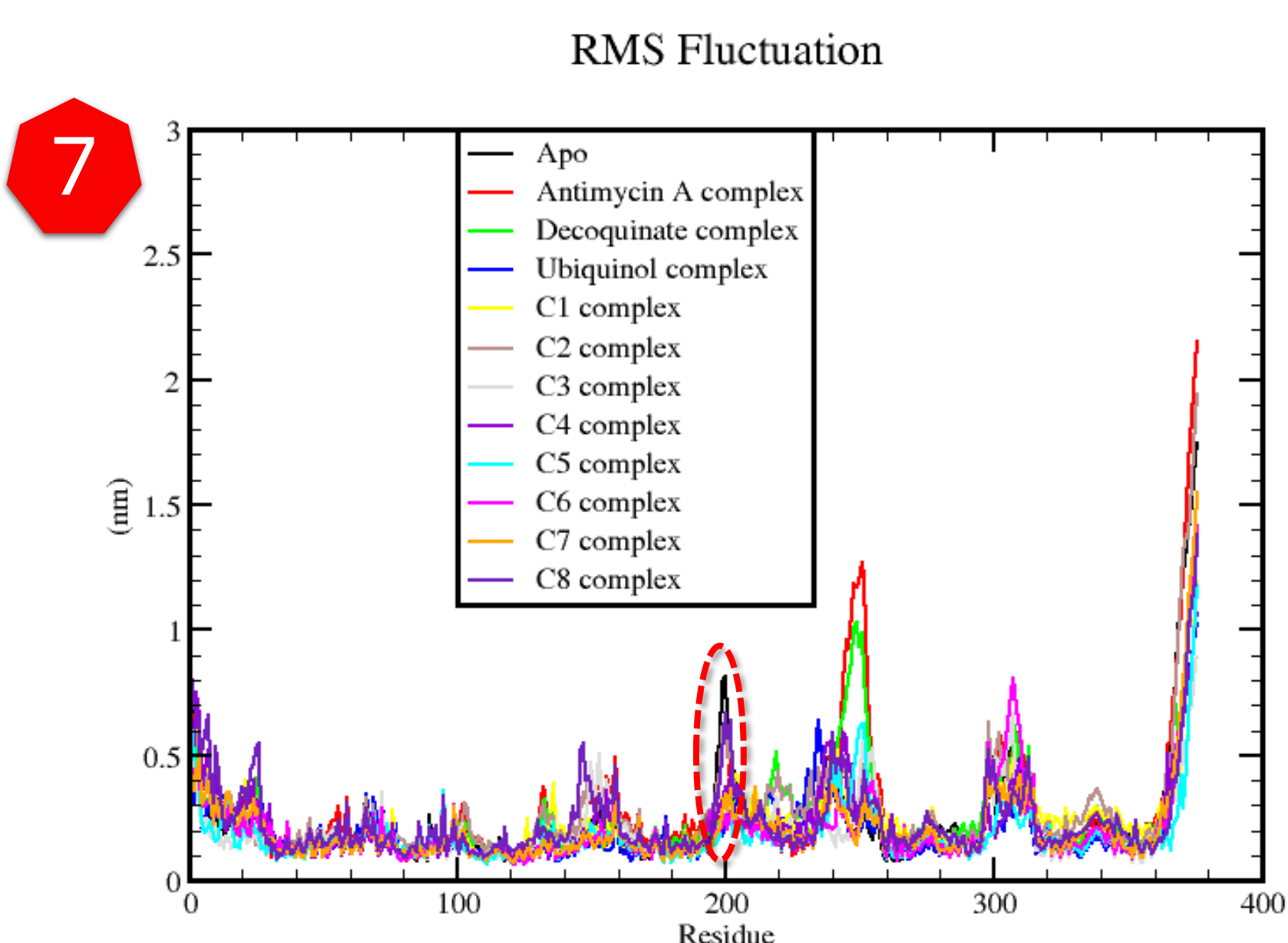


Figure 5: Protein Residues Fluctuations

Fluctuations at loop G195-L206 are indicative of the 'open' and 'closed' states of the loop, which allow or prevent the movement of protons, respectively, through the enzyme

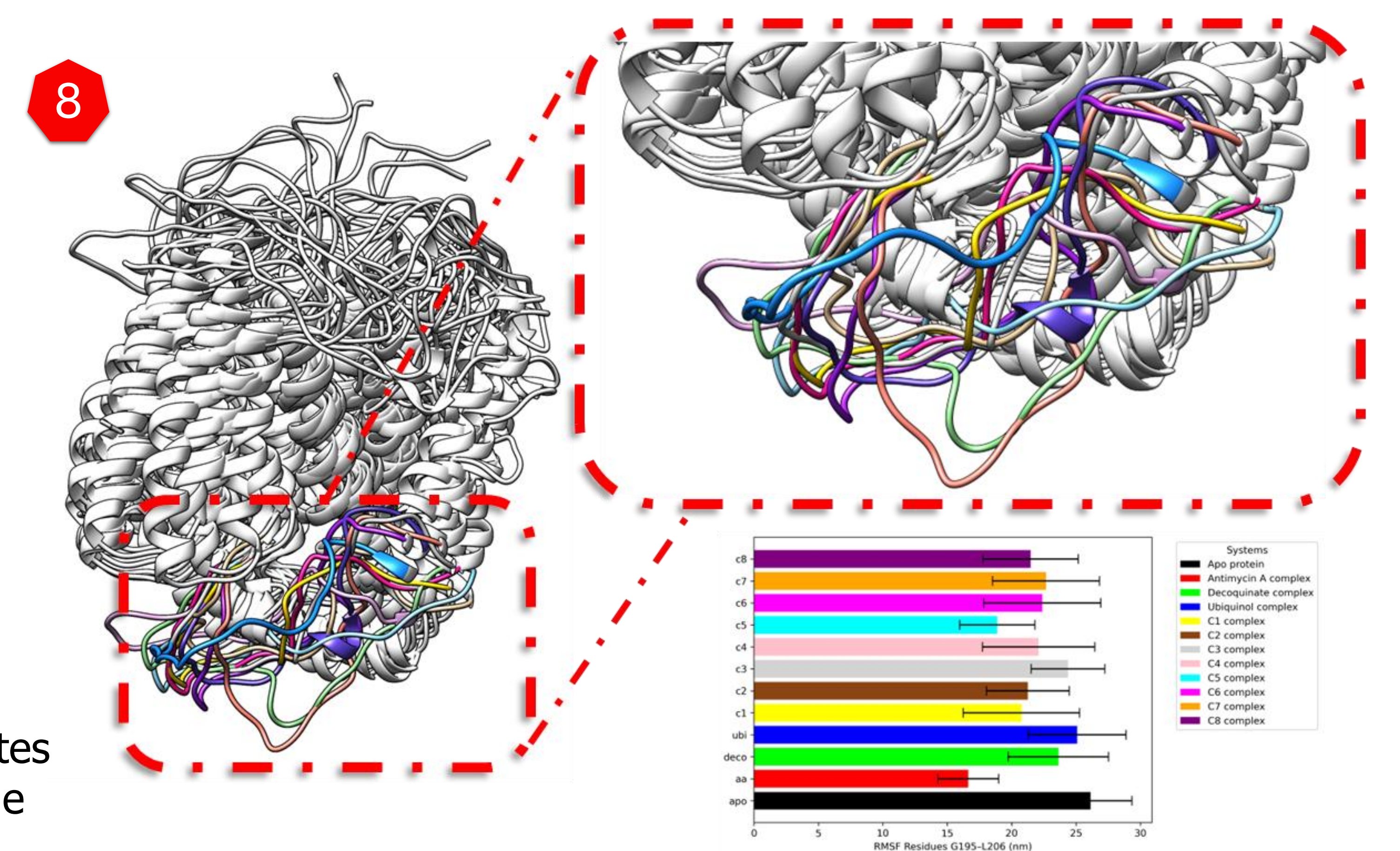


Figure 6: Loop G195-L206 Fluctuations of Complexes