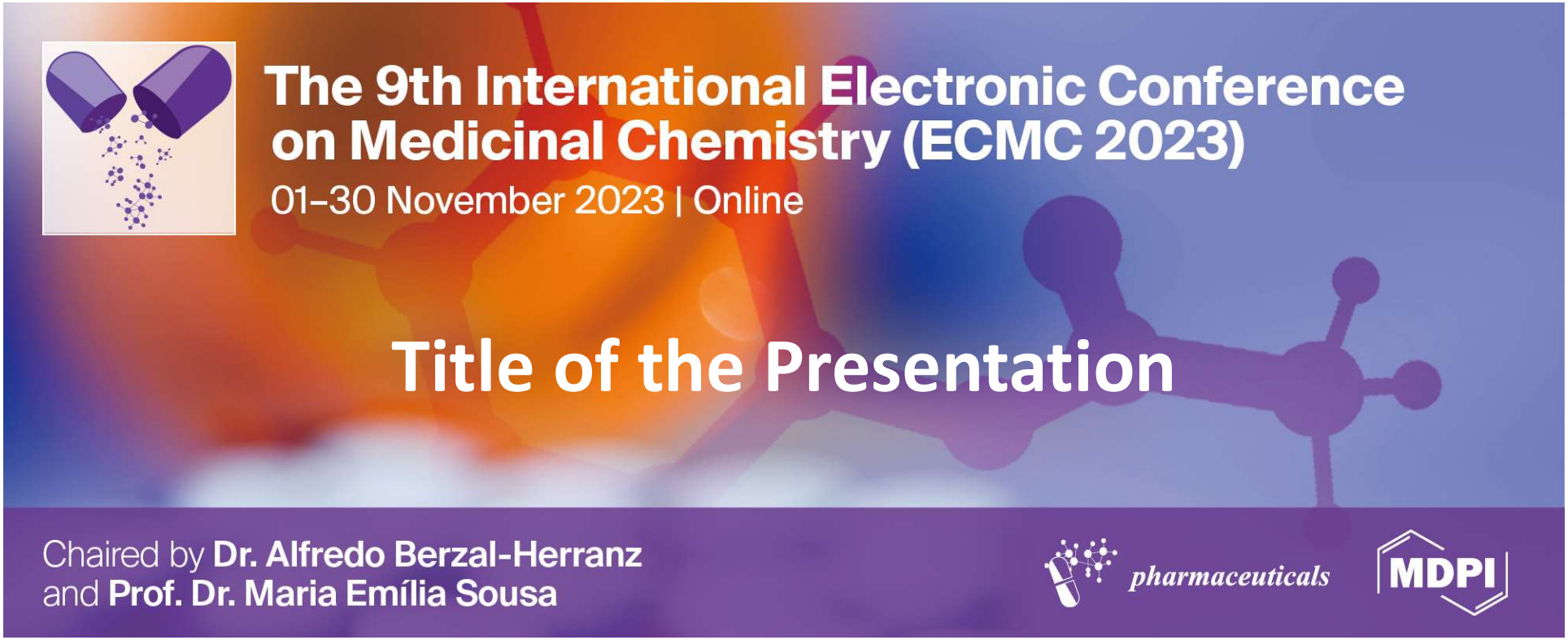

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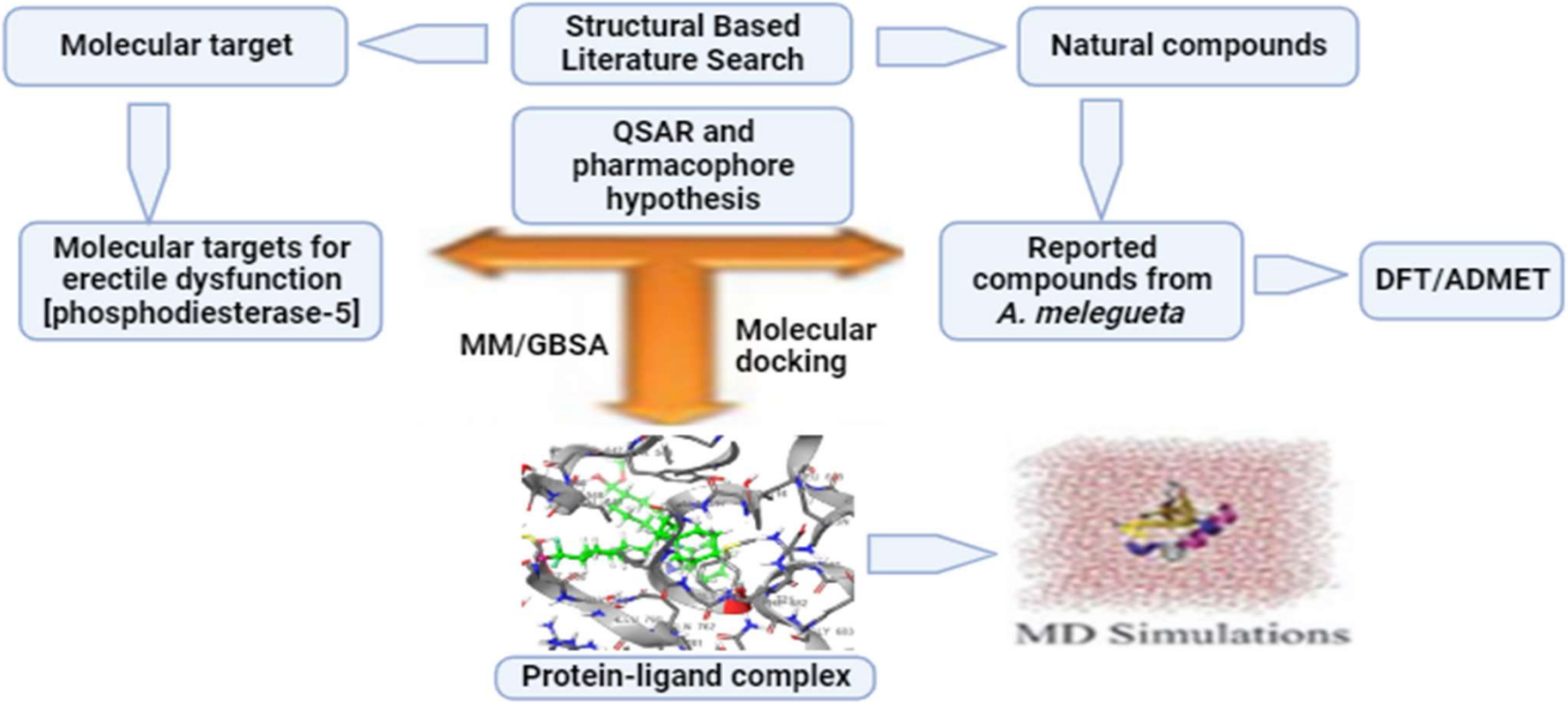
Computational Analysis of Phosphodiesterase-5 antagonists from *Aframomum melegueta* against Erectile Dysfunction



Abstract

Erectile dysfunction is a condition of insufficient ability of man to maintain erection for sexual performance.

Active molecules from *Aframomum melegueta* were docked against the target via maestro suite, 2017-1. The hit molecules in comparison with sildenafil were validated by MD-simulation at 100 ns with Desmond tool.

The result of this study revealed nine (9) hit molecules as potent antagonists of PDE-5 with 1,7-bis(3,4-dihyroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate (-11.522 kcal/mol) having the best binding affinity comparable with standard drug (sildenafil = -11.872 Kcal/mol).

The result of the QSAR and pharmacophore models validation confirmed the hit molecules as inhibitors of the target with pIC50 range of 3.835 to 7.976 µM and fitness score of 0.754 to 2.605 respectively.

The hit molecules obeyed Lipinski's rule of five with good pharmacokinetic profile. The stability of the hit molecule complex with PDE-5 was confirmed by MD-simulation analysis which was comparable with sildenafil-PDE-5 complex.

Overall, this study predicted phytochemicals from *A. melegueta* as inhibitors of PDE-5 for further experimentally validation for erectile dysfunction management.

Keywords: Sildenafil; Erection; Schrodinger; Phosphodiesterase-5; Inhibitors

Introduction

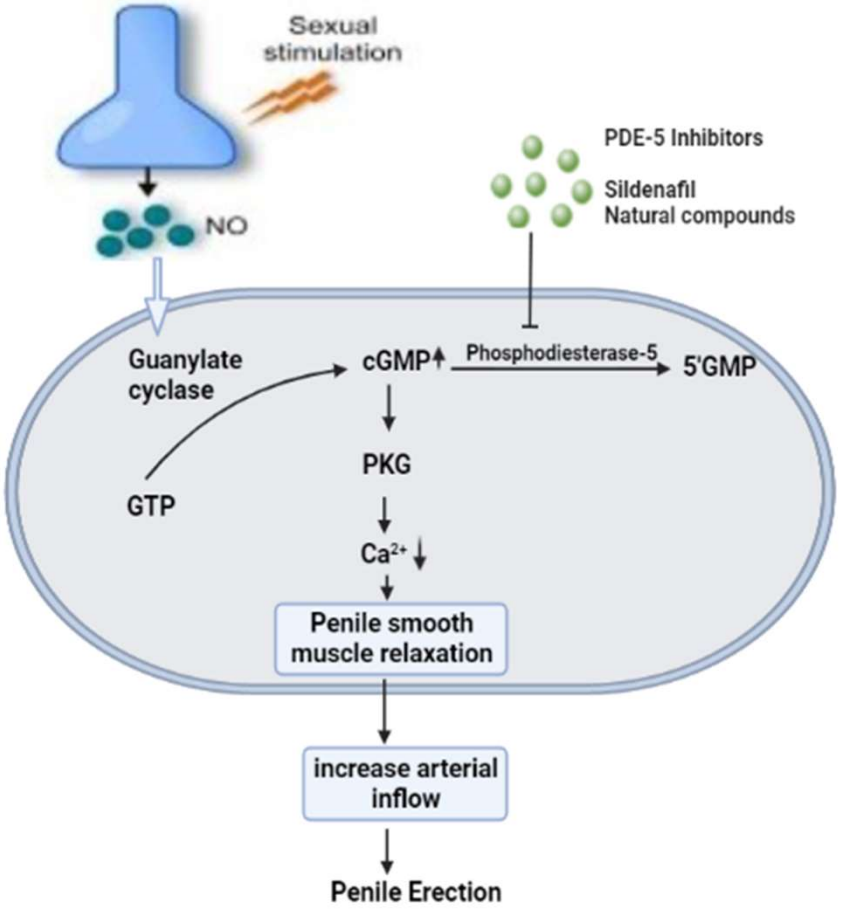


Fig. 1: Signaling mechanism of erectile process with inhibitors

Results and discussion

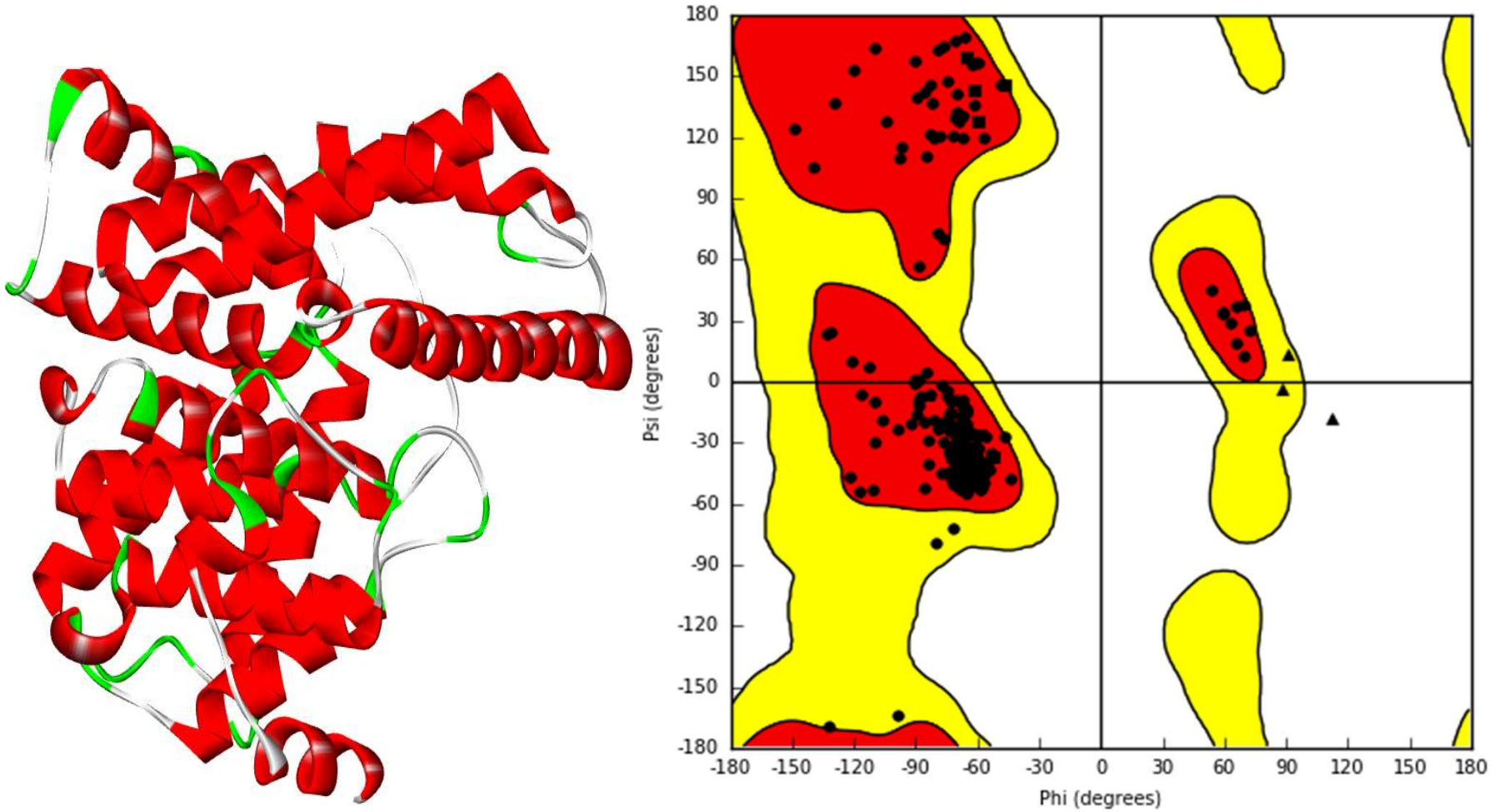


Fig. 2: Crystal structure of PDE-5 and Ramachandran plot of residues distribution

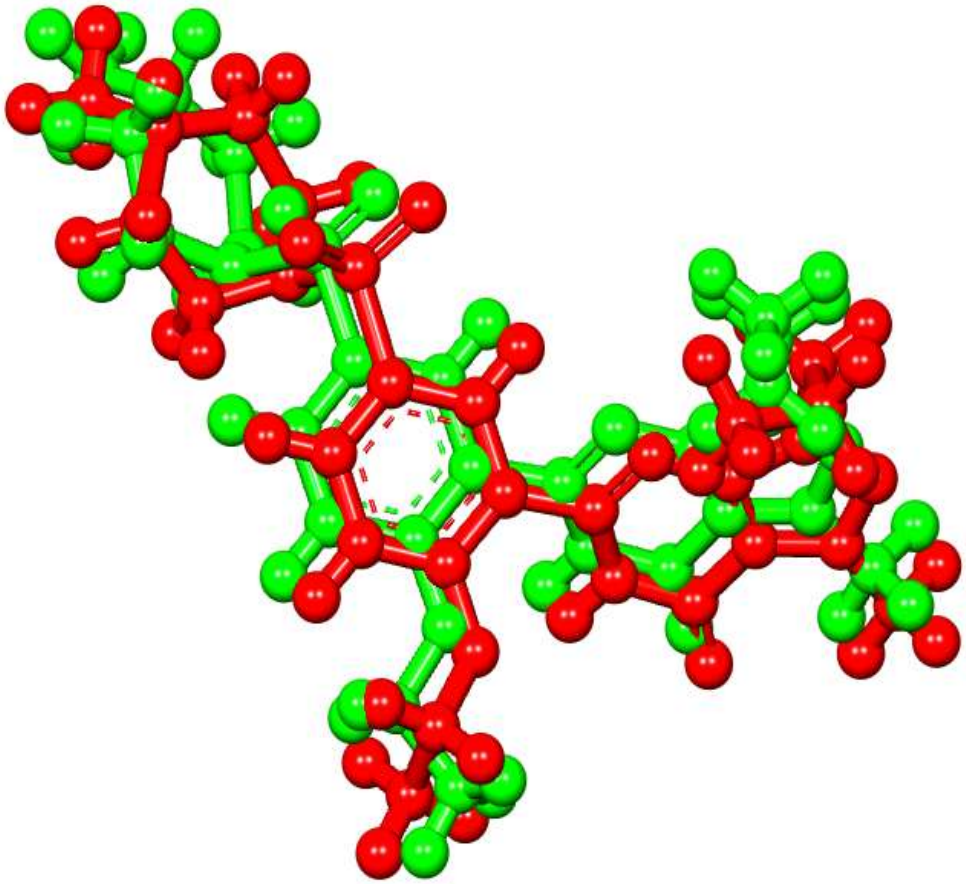


Figure 3: Superimposition of sildenafil at the active site of PDE-5

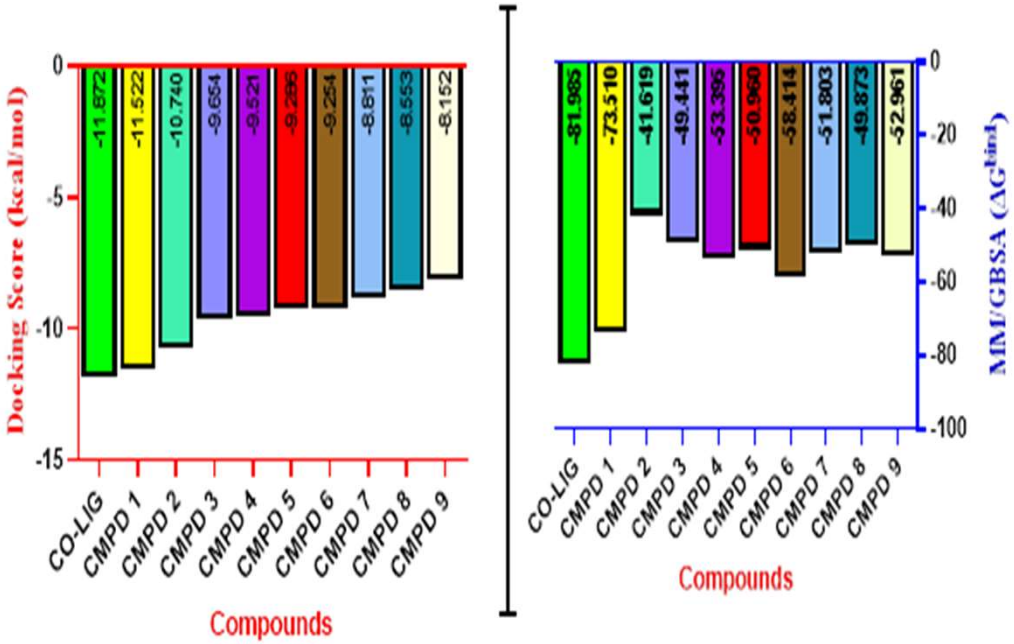


Fig. 4: Binding affinity and Binding Energies of the hit compound

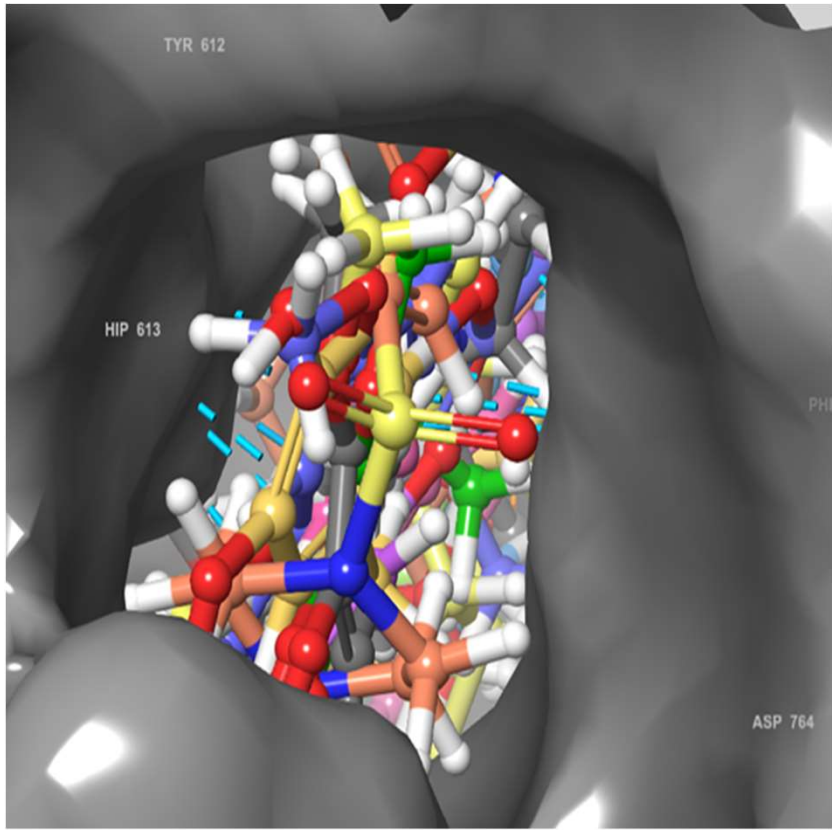


Fig. 5: presentation of extra precision binding of all hit compounds

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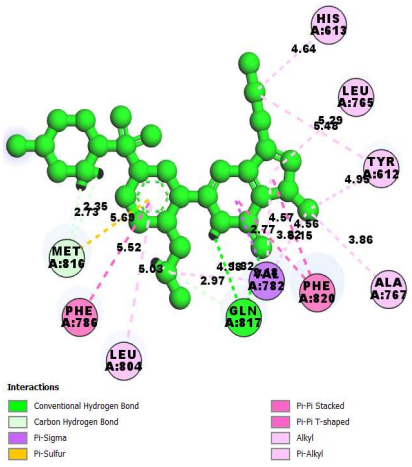
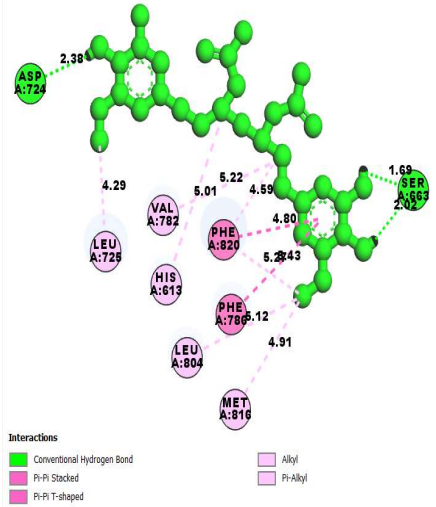
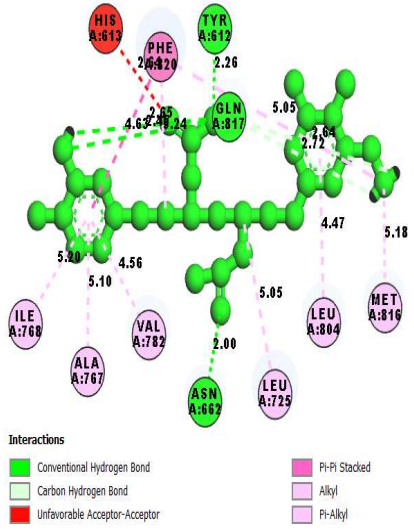


CO-LIGAND



CMPD 1



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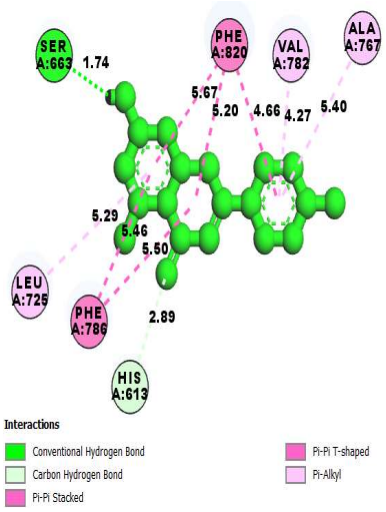

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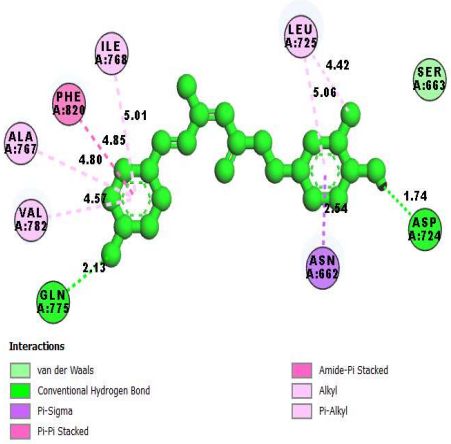

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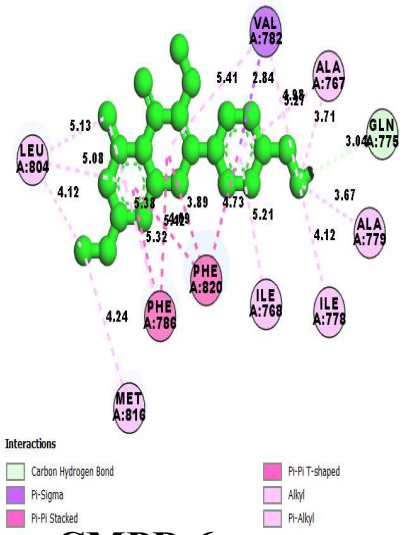
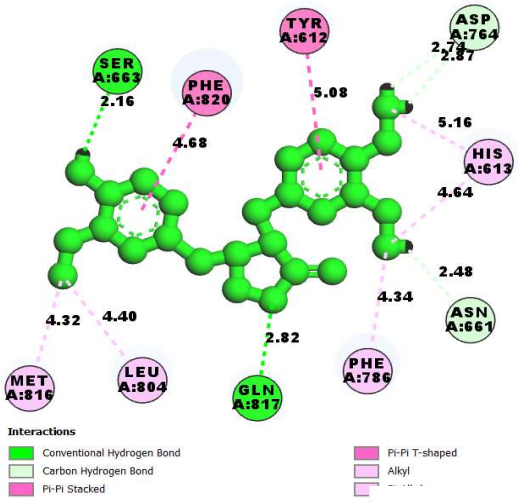


CMPD 6



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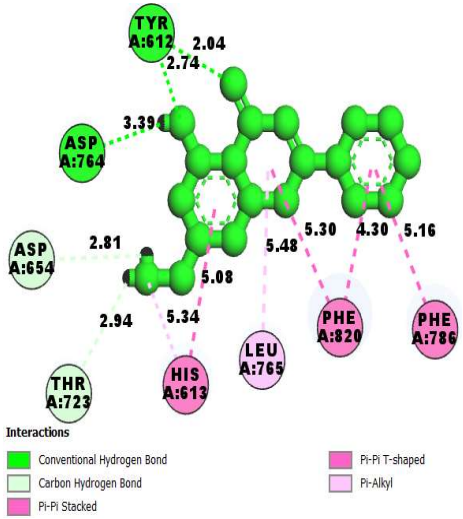
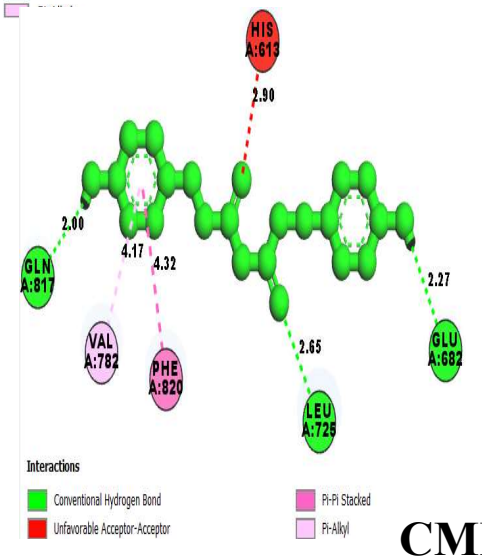


CMPD 8



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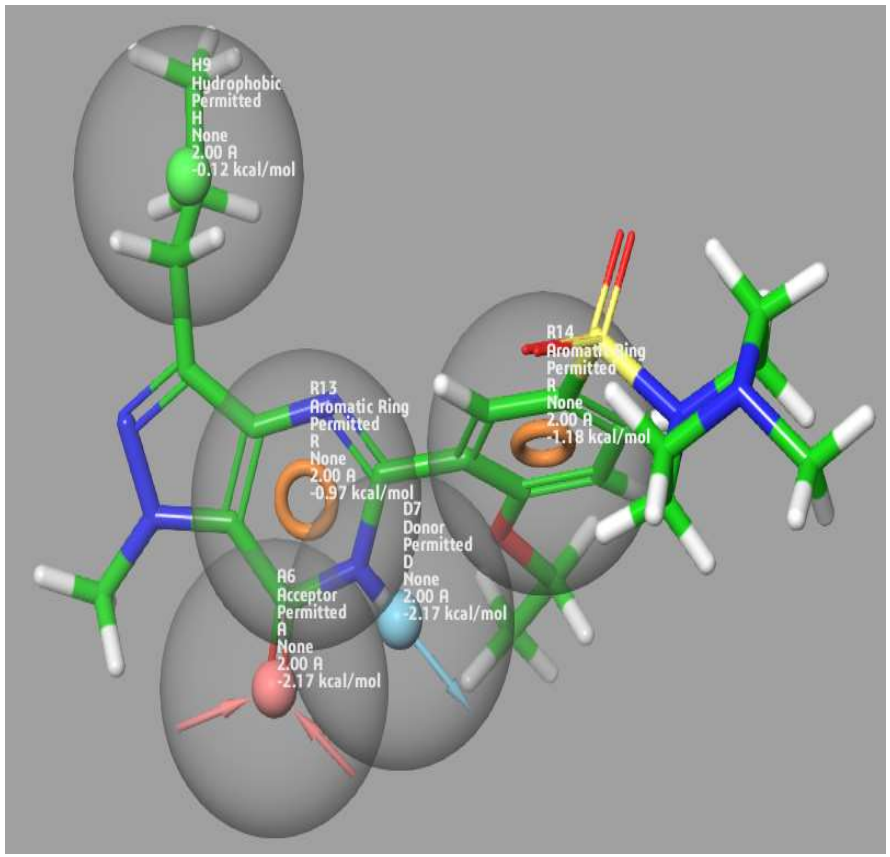


Fig. 5: Pharmacophore Hypothesis Generation

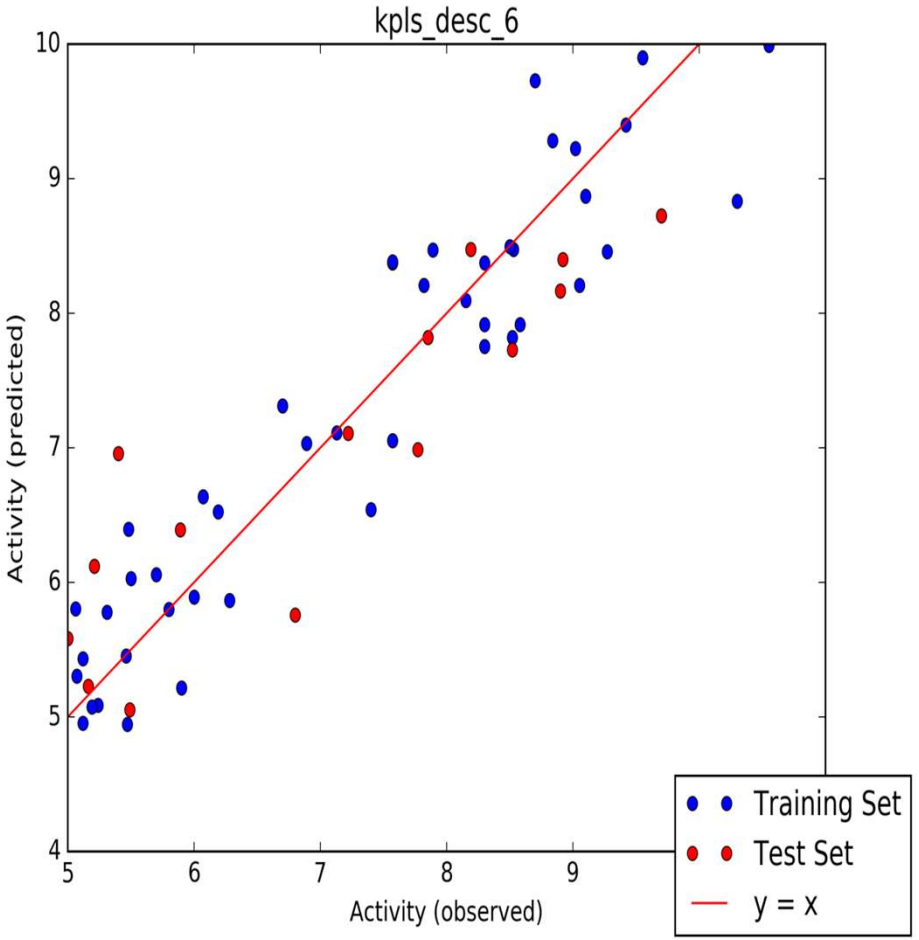
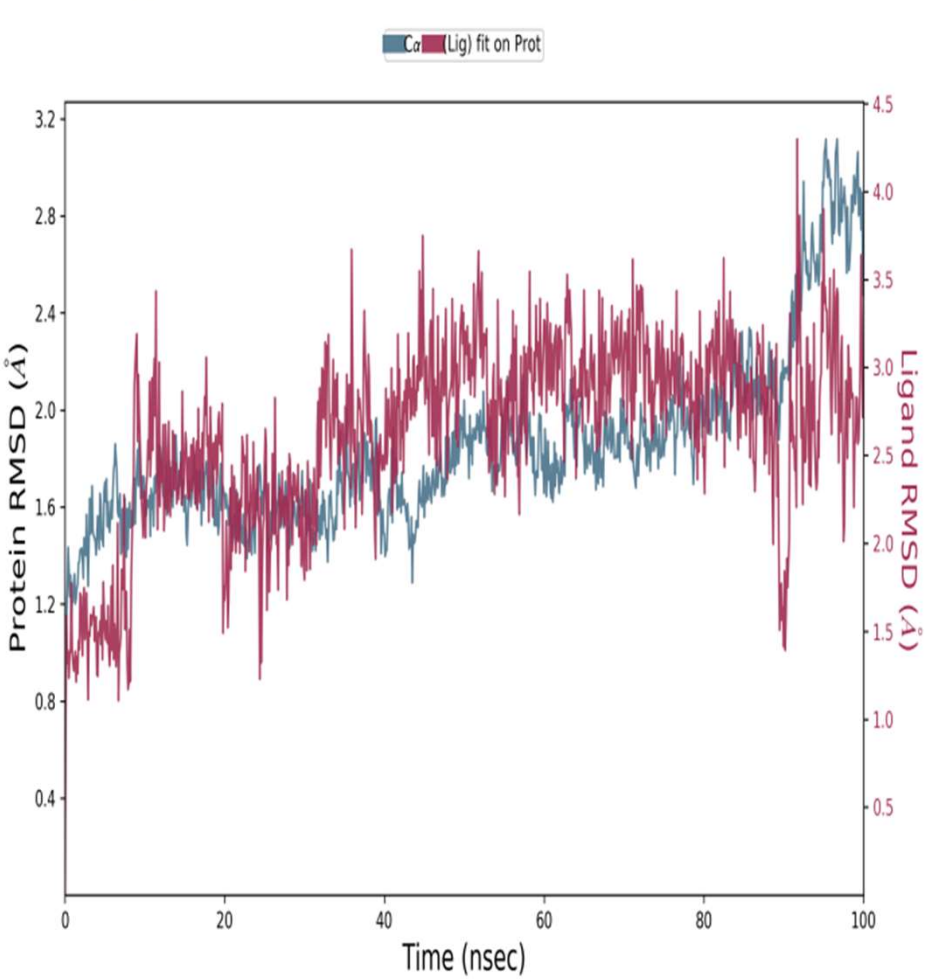


Fig. 7: Scatter plot from AutoQSAR modeling

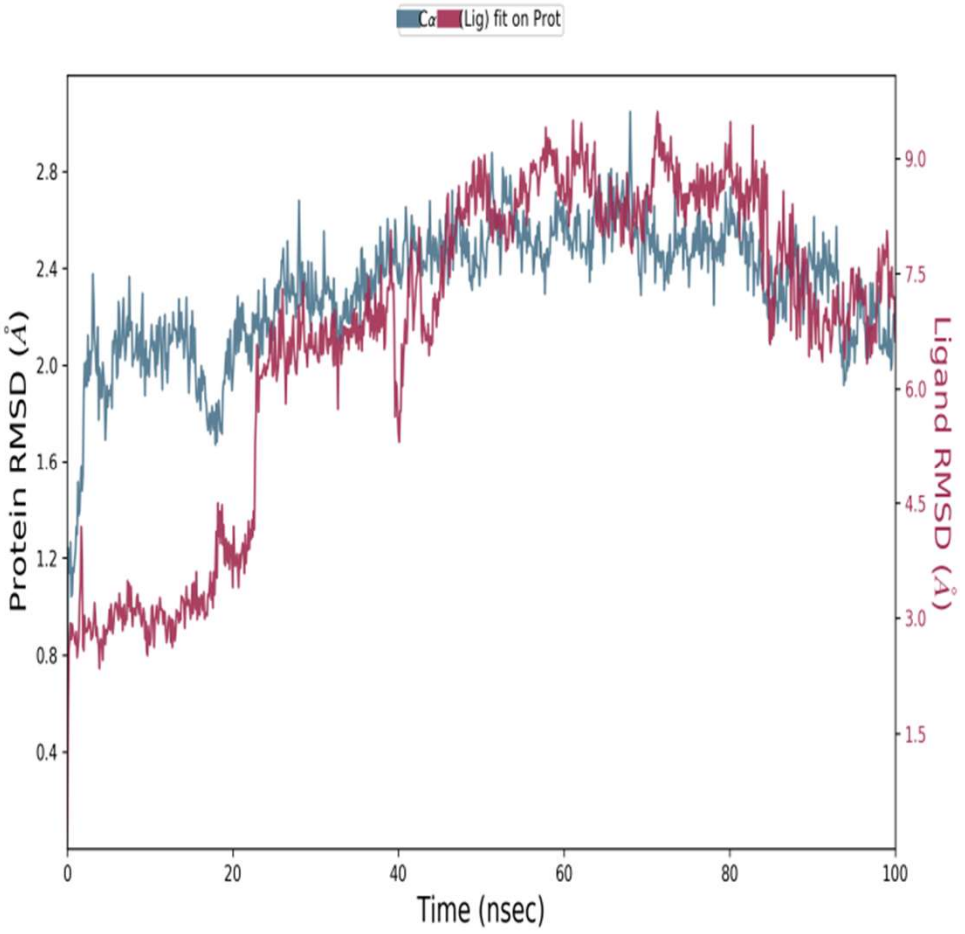
Compound Name	Fitness Score	Predicted pIC50 (μM)
Sildenafil	2.605	7.976
1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate	1.187	5.592
1-(3,4-dihydroxy-5-methoxyphenyl)-7-(3,4-dihdroxyphenyl)heptane-3,5-diyldiacetate	0.754	3.835
Apigenin	1.908	4.765
quercetin-3,7,3,4-tetramethylether	1.904	6.536
letestuianin A	1.483	6.167
kaempferol-3,7,4-trimethylether	1.355	5.742
Buplerol	1.247	5.706
Letestuianin C	1.312	5.727
5-hydroxy-7-methoxyflavone	1.986	5.459

Compound Name	MW	HBD	HBA	TPSA	RO5
Sildenafil	474.58	1.00	11.75	119.09	0
1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate	492.52	4.00	8.50	169.85	0
1-(3,4-dihydroxy-5-methoxyphenyl)-7-(3,4-dihdroxyphenyl)heptane-3,5-diyldiacetate	462.50	6.00	7.75	190.70	1
Apigenin	270.24	2.00	3.75	100.03	0
quercetin-3,7,3,4-tetramethylether	296.28	0.00	4.75	89.04	0
letestuianin A	324.38	2.00	3.25	87.36	0
kaempferol-3,7,4-trimethylether	324.38	0.00	2.75	28.35	0
Buplerol	372.42	1.00	6.00	85.35	0
Letestuianin C	312.37	2.00	5.50	95.15	0
5-hydroxy-7-methoxyflavone	268.27	0.00	3.00	63.25	0

Molecular weight (MW), Hydrogen bond donor (HBD), Hydrogen bond acceptor (HBA), topological surface area (TPSA), Rule of five (RO5)

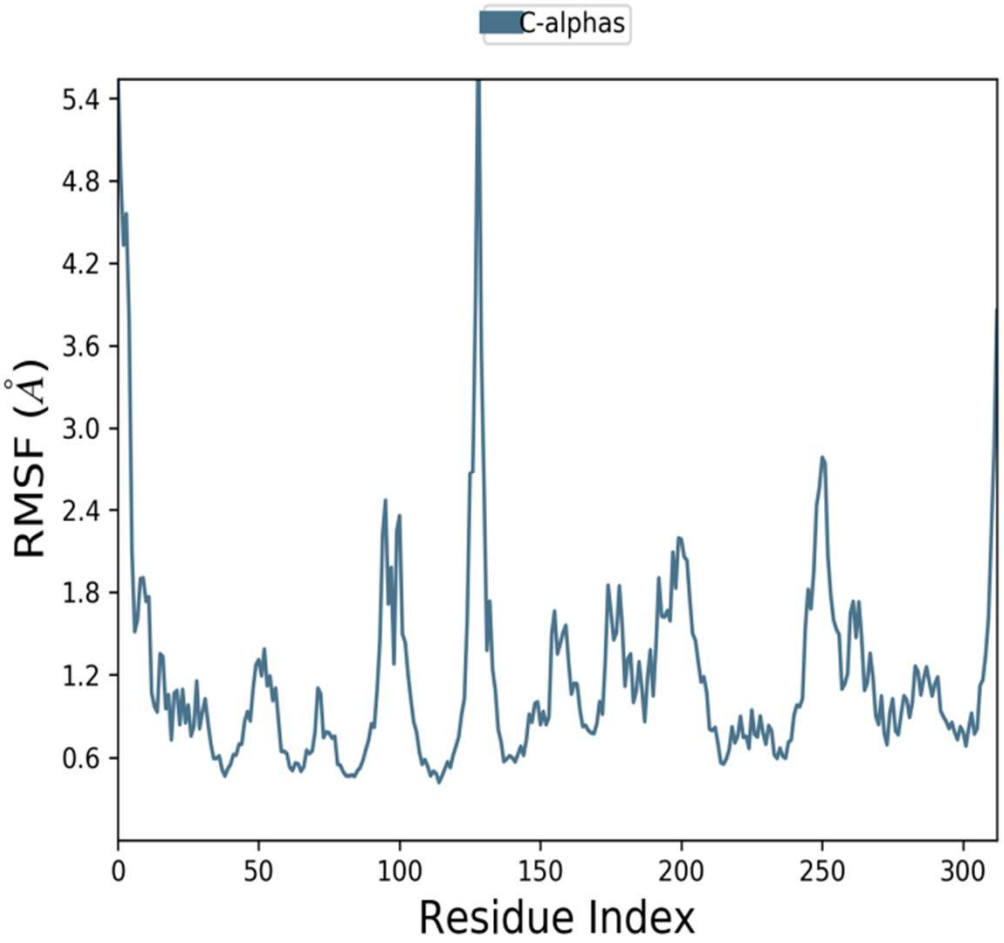


Sildenafil

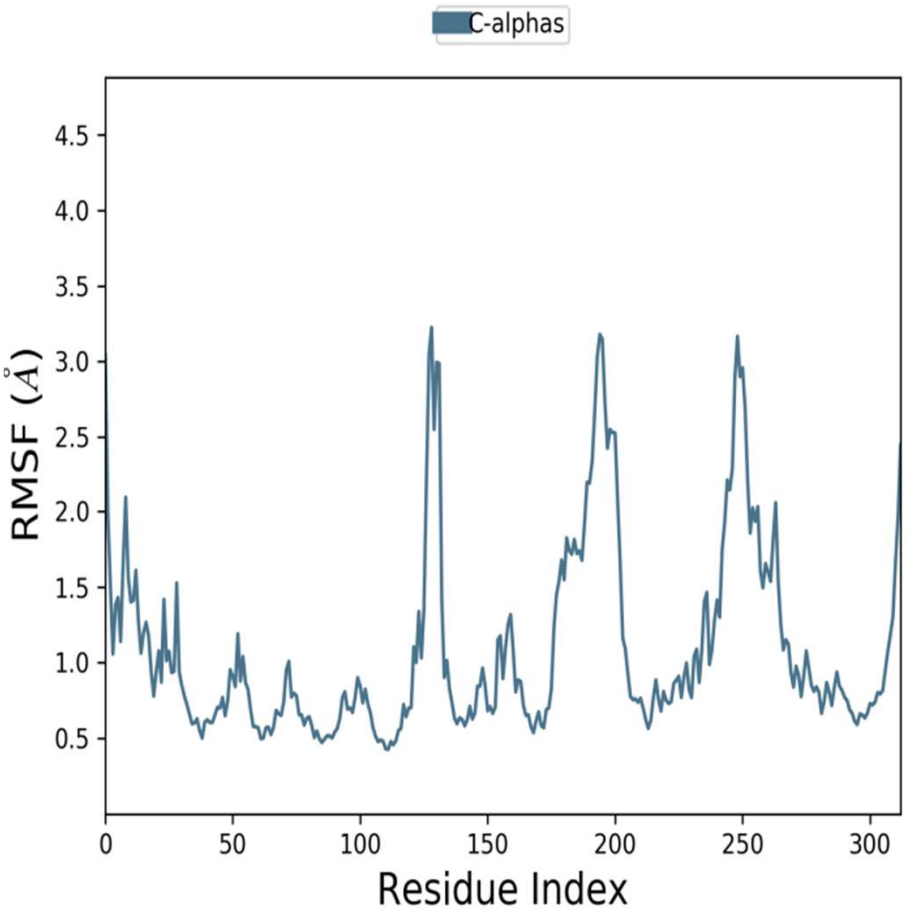


Compound 1

Fig. 8: Evaluation of RMSD of protein-ligand complex for 100 ns

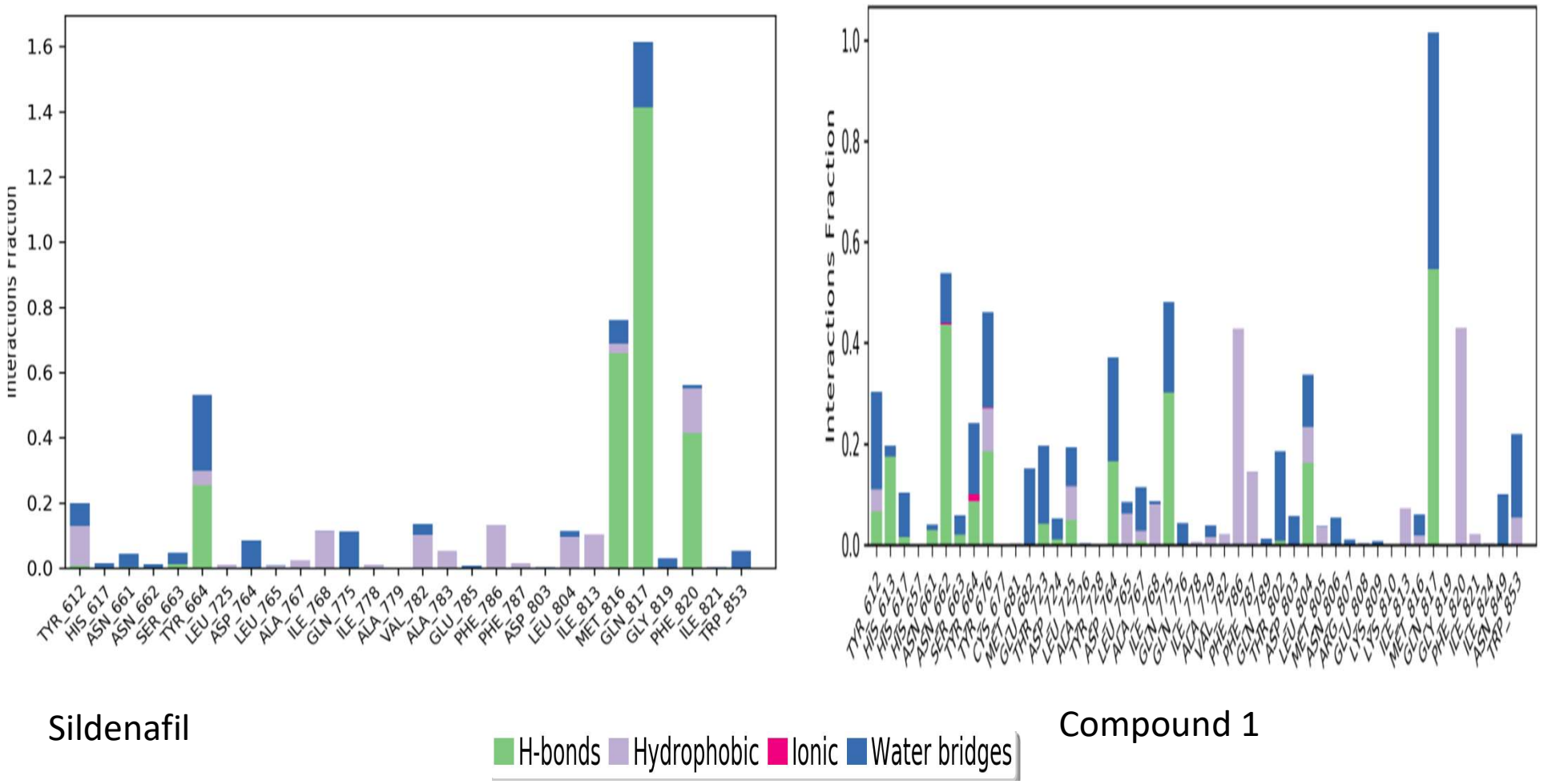


Sildenafil



Compound 1

Fig. 9: Representation of the Root mean square fluctuation (RMSF) of complex over 100 ns simulation



Sildenafil

Compound 1

Fig. 10: Complex protein-Ligand interaction mapping

Conclusions

Overall, this study predicted phytochemicals from *A. melegueta* as inhibitors of PDE-5 for further experimentally validation for erectile dysfunction management.

It doesn’t matter how many resources you have

THANK YOU

FOR

LISTENING

If you don’t know how to use them, it will never be enough