XXVIII Symposium on Bioinformatics and Computer-Aided Drug Discovery

A Flash Presentation

Multi-target approach on *Leishmania donovani* and finding out potent inhibitors for essential enzymes

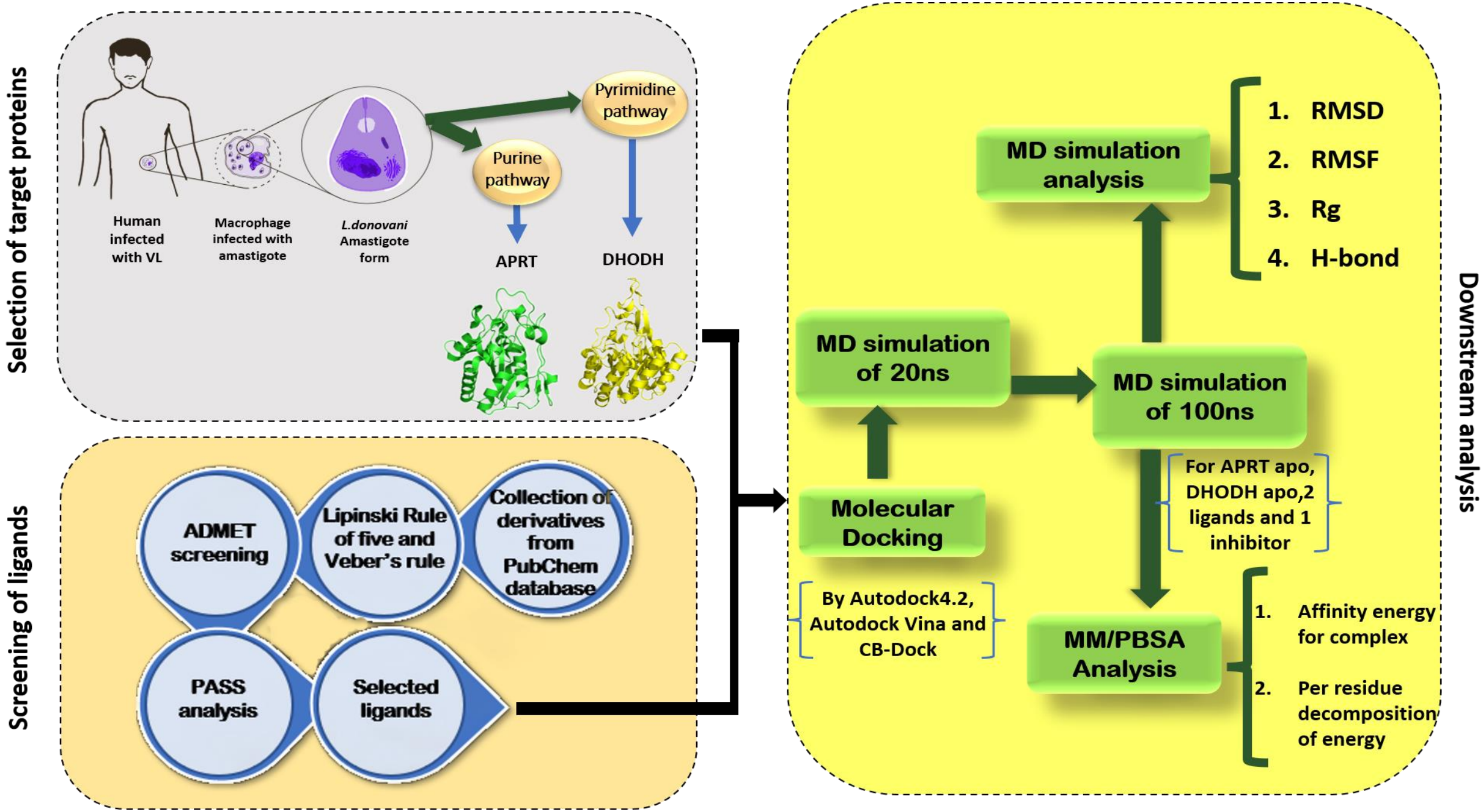
Debanjan Saha and Anupam Nath Jha

Computational Biophysics Laboratory, Department of Molecular Biology and Biotechnology, Tezpur University, Tezpur, India

Email: dsaha@tezu.ernet.in

Introduction

- **Visceral Leishmaniasis** (VL) also known as kala-azar is the most severe form caused by the sp. *Leishmania donovani* [1] having symptoms like irregular bouts of fever, weight loss, enlargement of the spleen and liver and anemia [2].
- VL has impacted Asian countries like Nepal, Bangladesh and some states of India such as Bihar, West Bengal and Uttar Pradesh.
- **Adenine Phosphoribosyl-transferase(APRT)** having PDB ID-1QB7 and **dihydroorotate dehydrogenase(DHODH)** having PDB ID-3C61 were selected as drug target from purine and pyrimidine pathways of *L. donovani* respectively [3].
- Different established inhibitors on the selected proteins of closely related species like *L. major* and *L. tarentolae* were collected.



Scheme . Integrative methodology used for the multi-target approach on *Leishmania donovani* enzymes

PASS analysis

The inhibitors that have shown antileishmanial activity with predicted Pa value were obtained from **PASS online server**

Table 1: PASS analysis for inhibitors

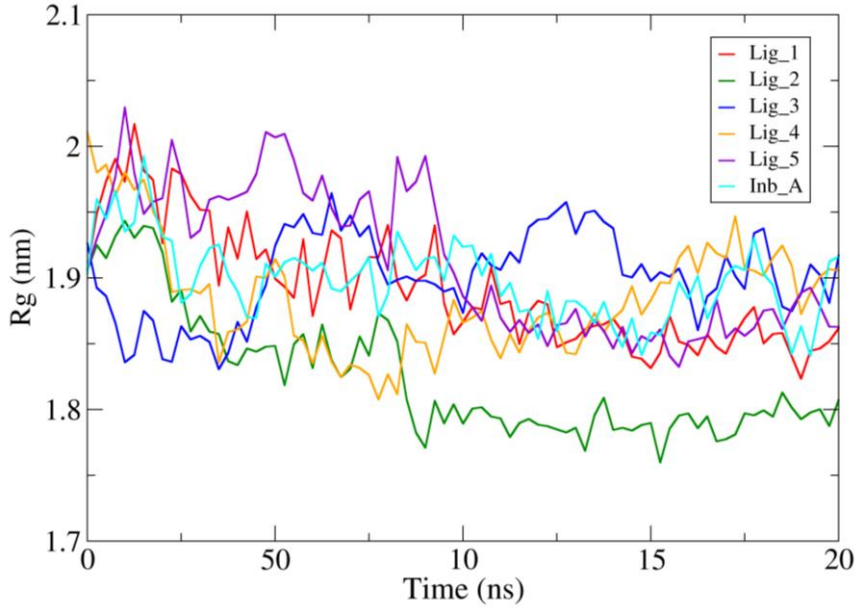
Sl.No.	Inhibitors	PubChem CID	Pa value	Pi value
1	Sophoraflavanone G	72936	0.231	0.161
2	Mammea BBA	5489487	0.248	0.152
3	Mammea AAA	5281419	0.253	0.139
4	Grandifotane	102171884	0.332	0.081
5	Kaurenoic acid	73062	0.348	0.072
6	Isoskimmianine	621199	0.439	0.035
7	Centratherin	44409502	0.483	0.027
8	Myricetin	5281672	0.521	0.022
9	4-nitrophenylisocyanate	66012	0.529	0.008
10	Elephantopin	442206	0.555	0.018
11	Vernolide-D	101412352	0.634	0.012
12	4-acetoxy-2-geranyl-5-hydroxy-3-n-pintyl phenol	44139611	0.690	0.009
13	Crotaorixin	11428177	0.775	0.006
14	Neurolenin-B	49799795	0.812	0.004

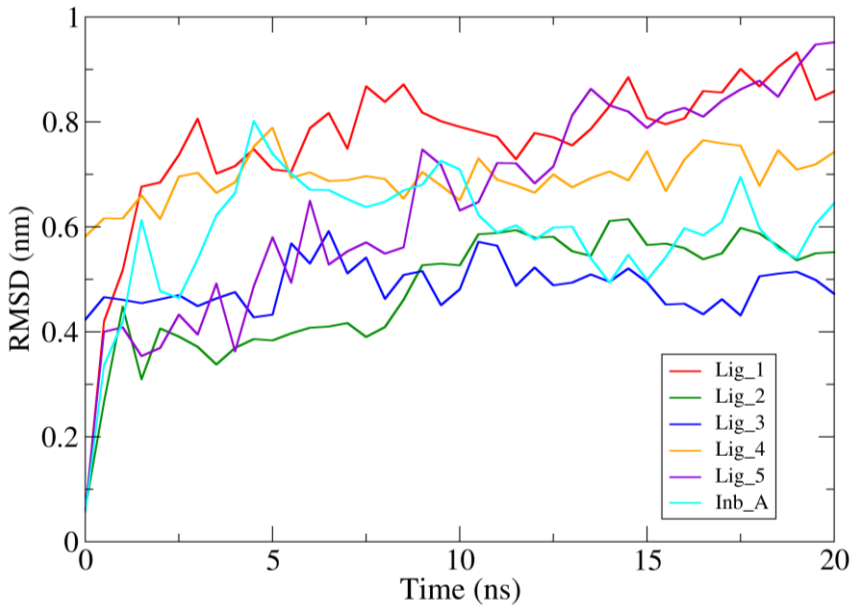
Docking result

Table 2: Docking result of APRT and DHODH proteins with five ligands by using three different docking software

Ligand No.	AutoDock 4.2.6 score (kcal/mol)		AutoDock Vina score (kcal/mol)		CB-Dock score (kcal/mol)	
	APRT	DHODH	APRT	DHODH	APRT	DHODH
1	-8.25	-6.93	-8.6	-10.0	-8.6	-9.2
2	-9.66	-8.24	-7.4	-5.9	-8.4	-8.1
3	-8.11	-8.42	-9.0	-10.9	-9.0	-9.4
4	-8.75	-7.89	-8.4	-8.0	-8.7	-9.9
5	-8.62	-8.25	-7.8	-7.9	-7.8	-9.1

MD simulation analysis of APRT with ligands and inhibitors for 20ns





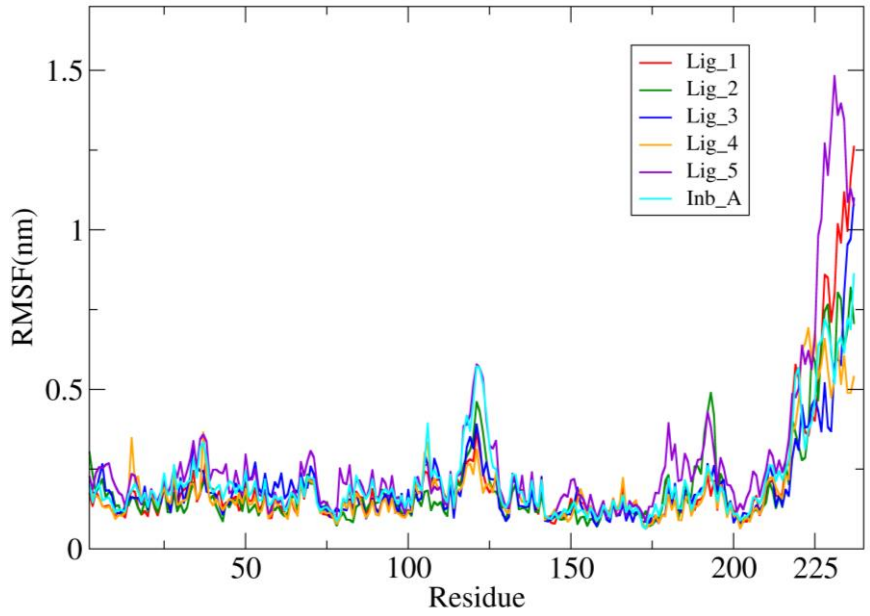
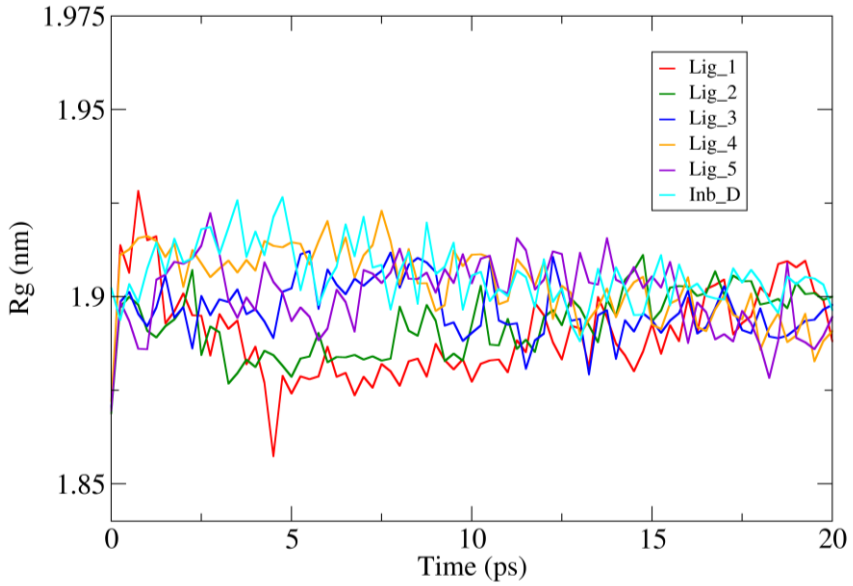
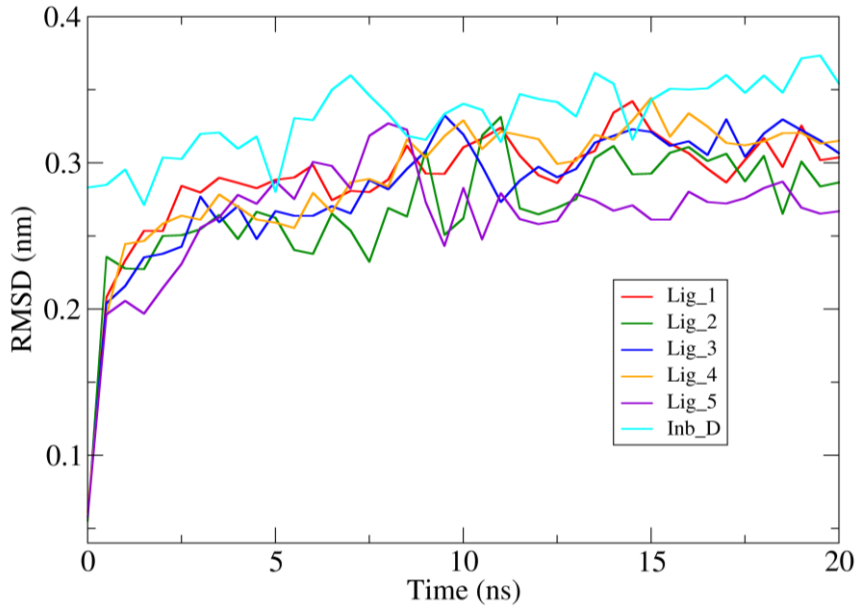


Fig 1: Rg, RMSD and RMSF plot of APRT protein with five ligands and with one inhibitor (Isoskimmianine) having cyan colour

MD simulation analysis of DHODH with ligands and inhibitors for 20ns





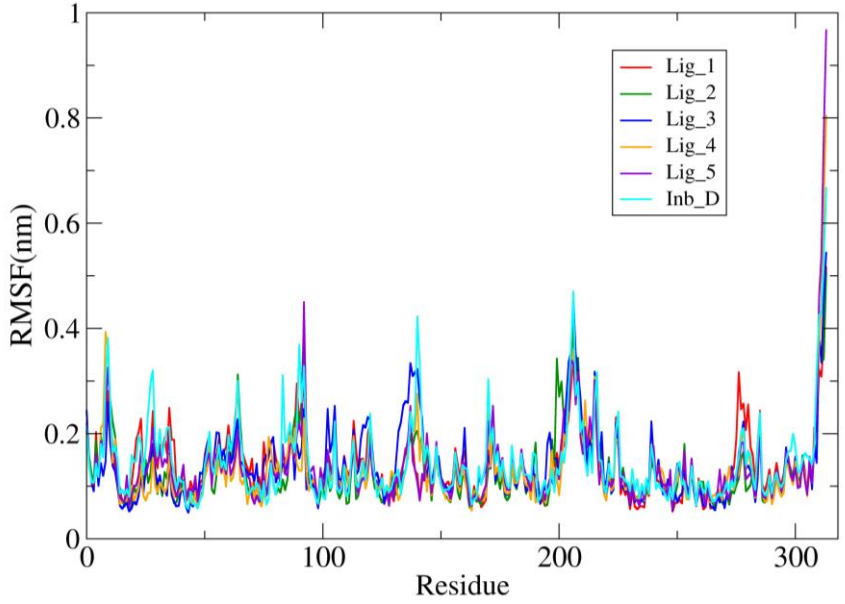
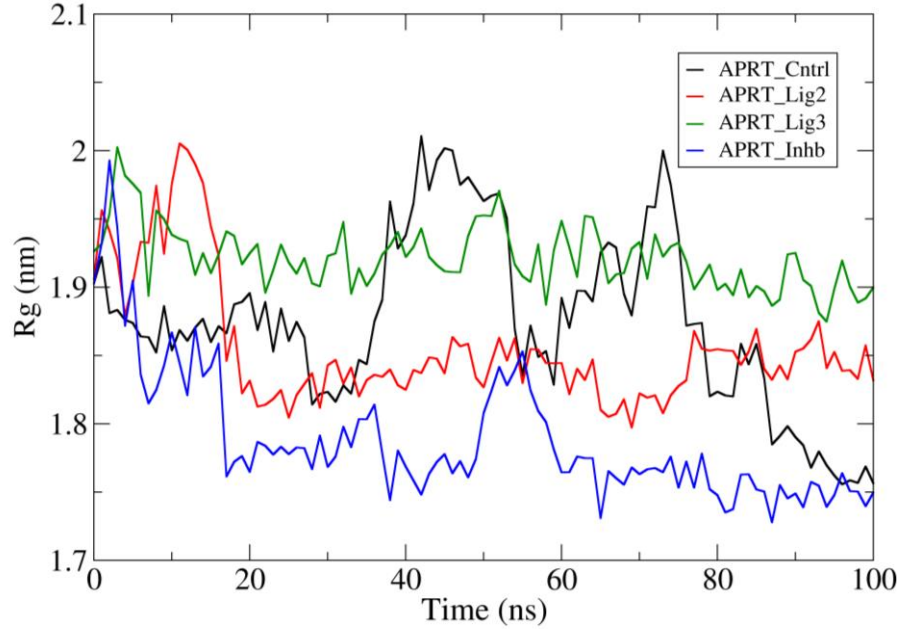


Fig 2: Rg, RMSD and RMSF plot of DHODH protein with five ligands and with one inhibitor (Neurolenin-B) having cyan colour

Rg and RMSD plot of APRT and DHODH (MD 100ns)



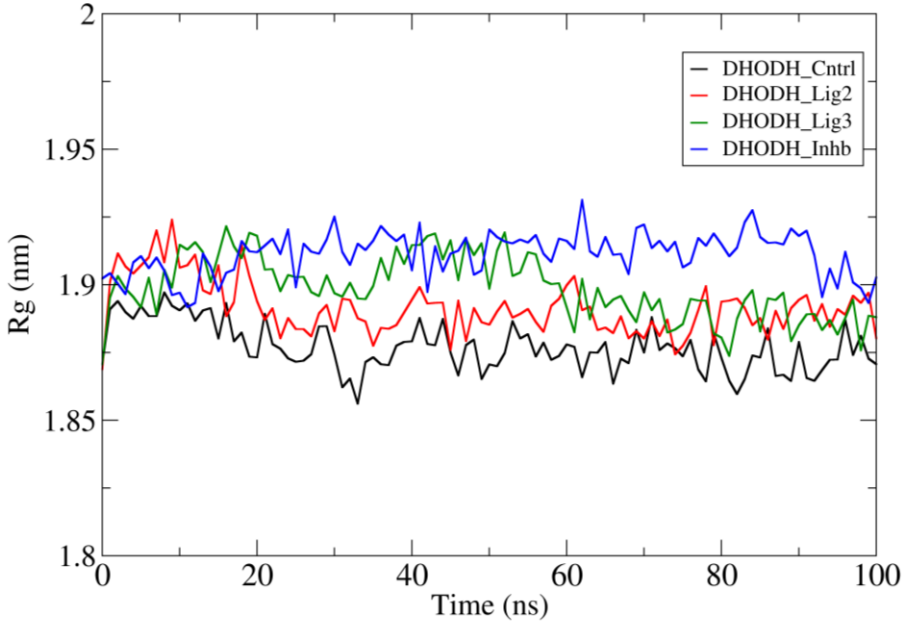
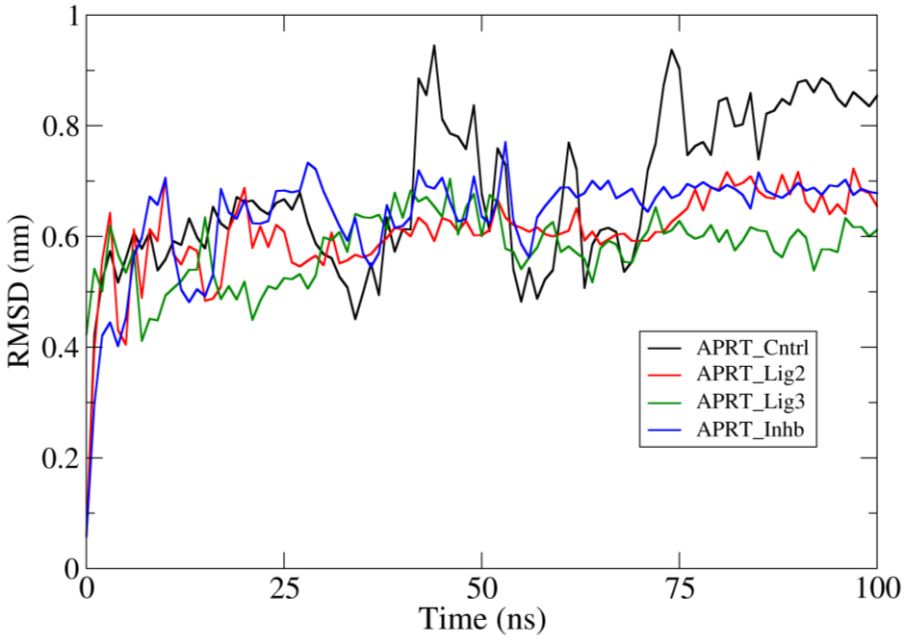


Fig 3: Rg plot of APRT and DHODH with Lig2, Lig3 and one inhibitor, respectively



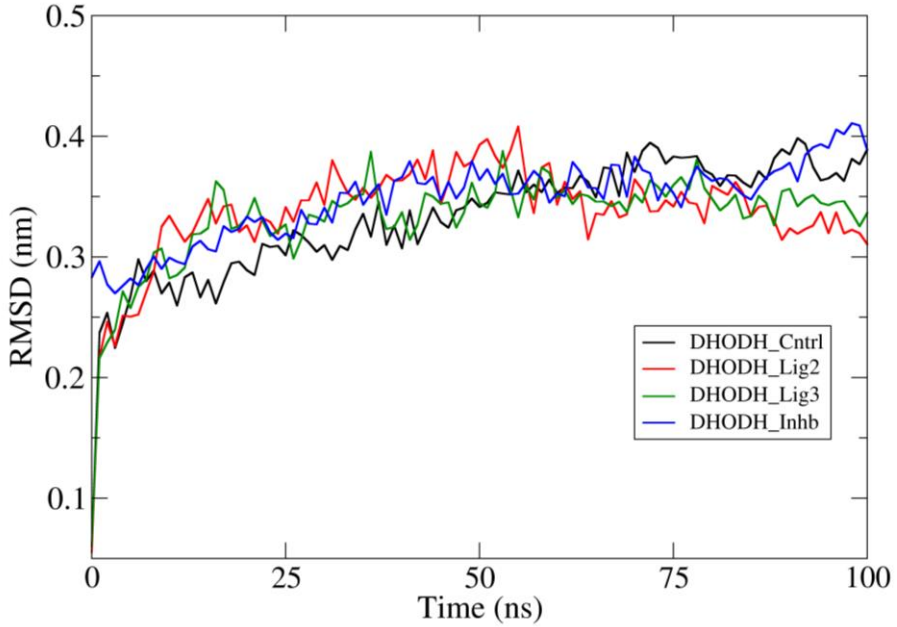


Fig 4: RMSD plot of APRT and DHODH with Lig2, Lig3 and one inhibitor, respectively

RMSF and H-bond plot of APRT and DHODH (MD 100ns)

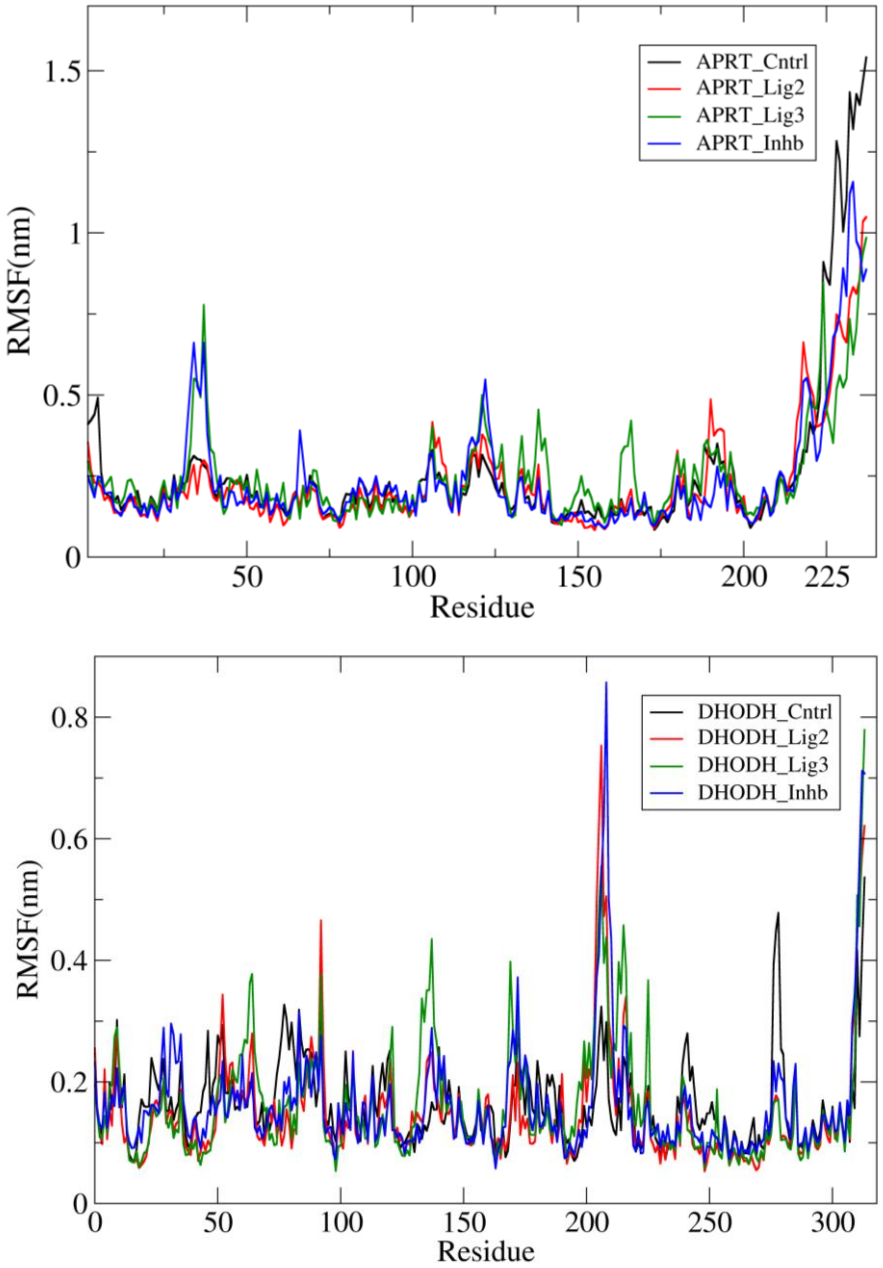


Fig 5: RMSF plot of APRT and DHODH with Lig2, Lig3 and one inhibitor, respectively

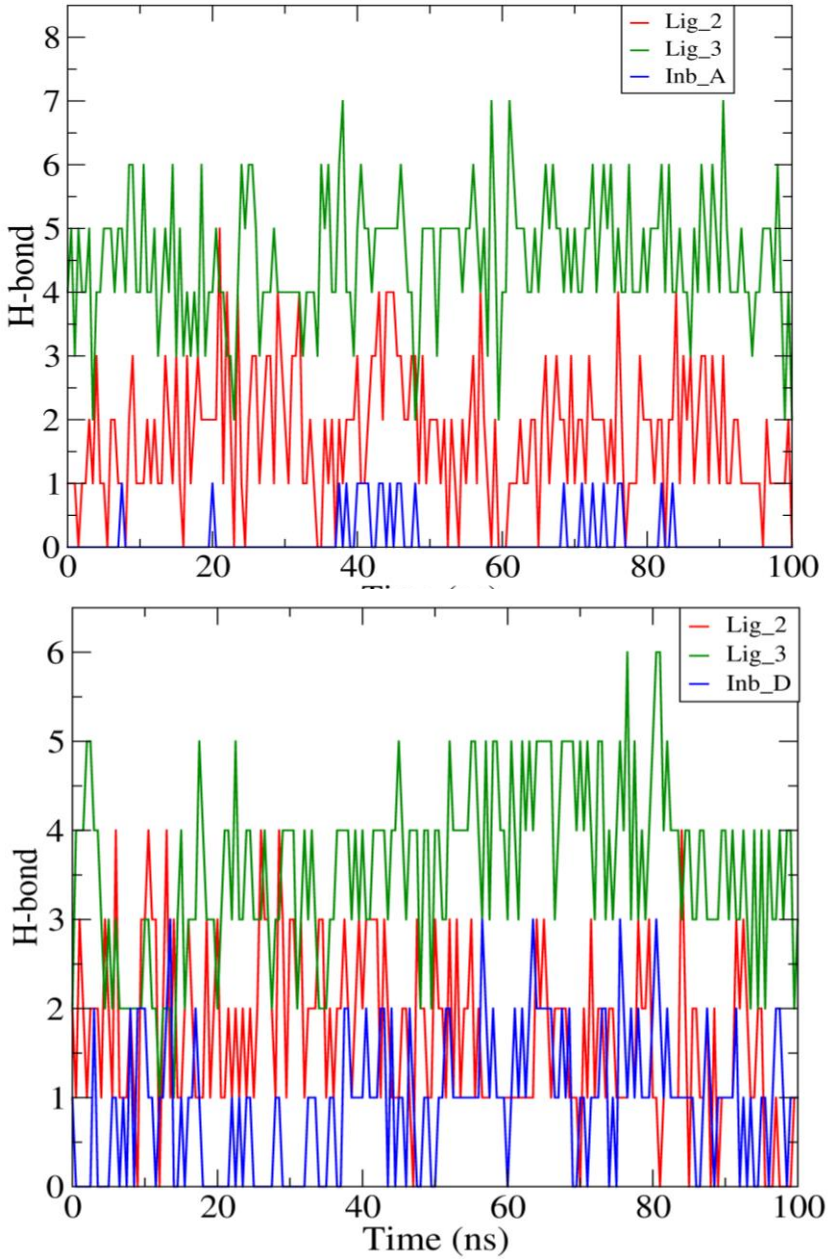


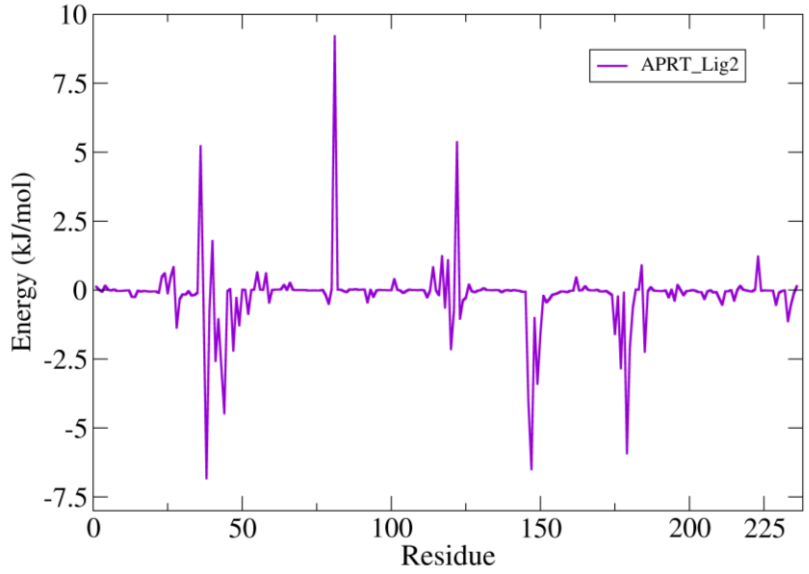
Fig 6: H-bond plot of APRT and DHODH with Lig2, Lig3 and one inhibitor, respectively

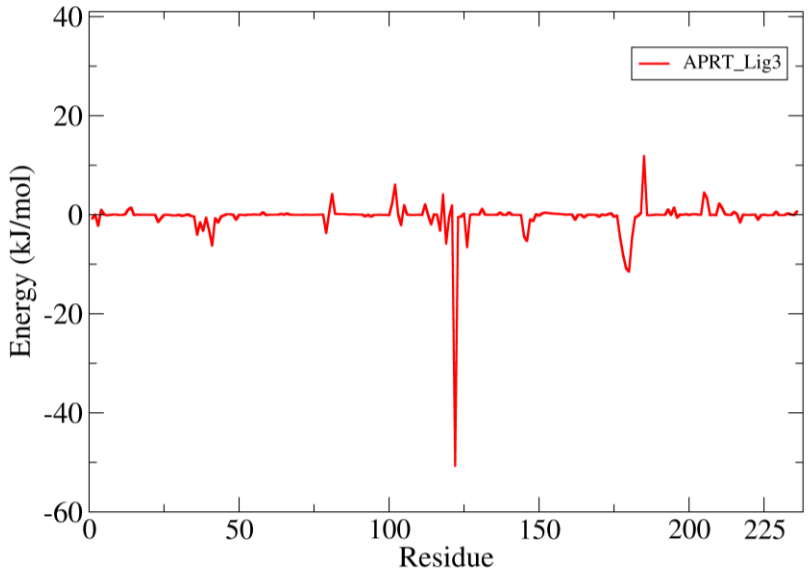
MM/PBSA analysis

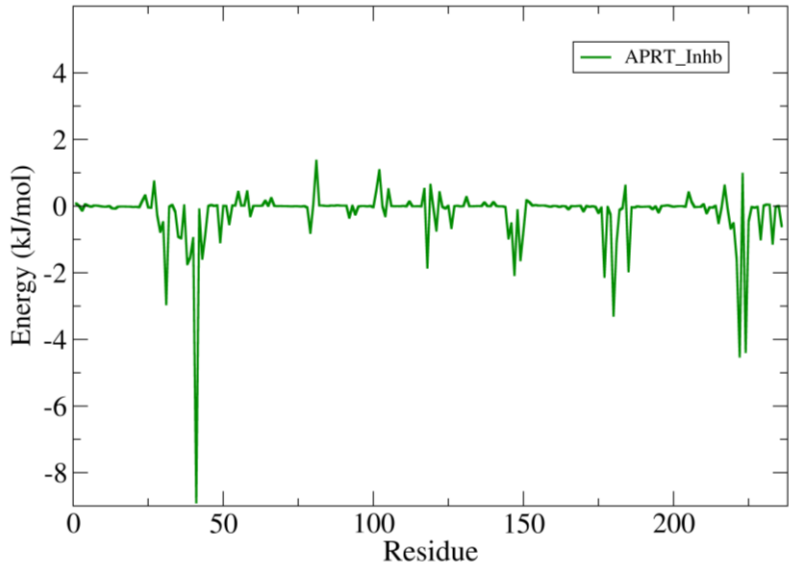
Sl. No.	System	Binding energy(kJ/mol)	van der Waal energy(kJ/mol)	Electrostatic energy(kJ/mol)	Polar solvation energy(kJ/mol)	SASA energy (kJ/mol)
1	APRT-Lig2	-154.063 ± 15.676	-188.701 ± 9.474	-115.414 ± 21.570	173.270 ± 18.037	-23.217 ± 0.994
2	APRT-Lig3	**-204.470 ± 22.193**	-69.304 ± 14.010	**-324.792 ± 43.249**	202.667 ± 28.433	-13.042 ± 0.984
3	APRT-Inb_A	-108.553 ± 14.238	-115.676 ± 10.480	-23.520 ± 15.749	43.023 ± 15.346	-12.380 ± 0.939
4	DHODH-Lig2	-132.959 ± 17.816	-226.586 ± 11.470	-51.384 ± 29.086	169.760 ± 27.069	-24.749 ± 1.067
5	DHODH-Lig3	**-232.950 ± 19.534**	-172.462 ± 13.210	**-248.339 ± 26.261**	207.491 ± 12.787	-19.639 ± 0.870
6	DHODH-Inb_D	-137.251 ± 16.784	-207.042 ± 9.742	-62.660 ± 10.090	154.550 ± 11.022	-22.099 ± 0.924

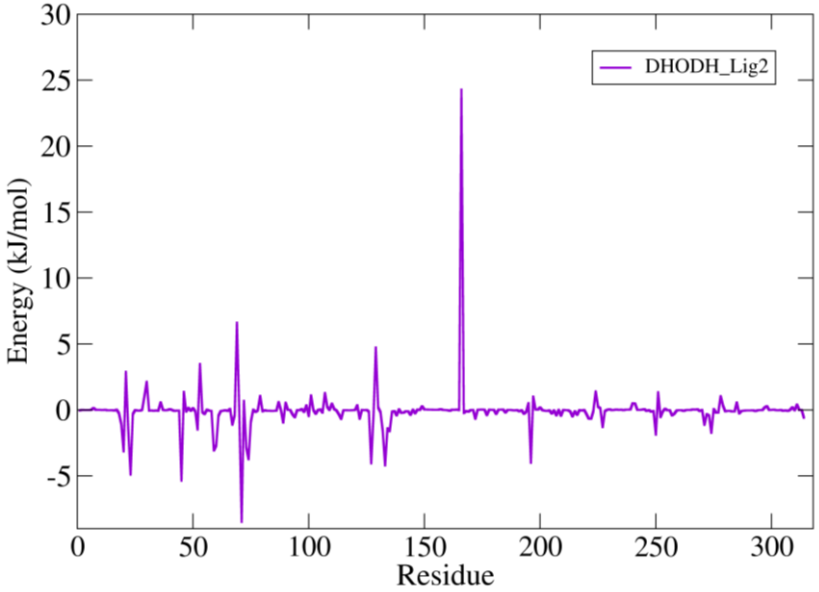
Table 3: MM/PBSA analysis of the bound complexes

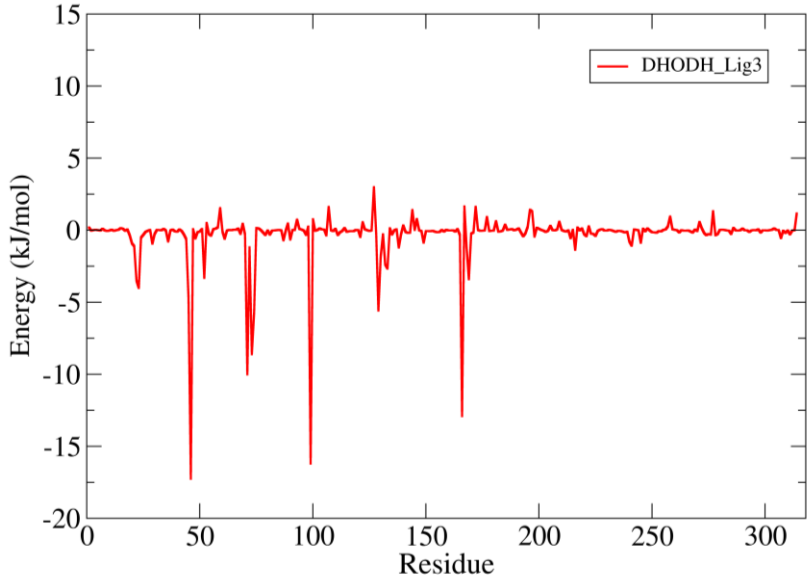
Per-residue decomposition of binding energy











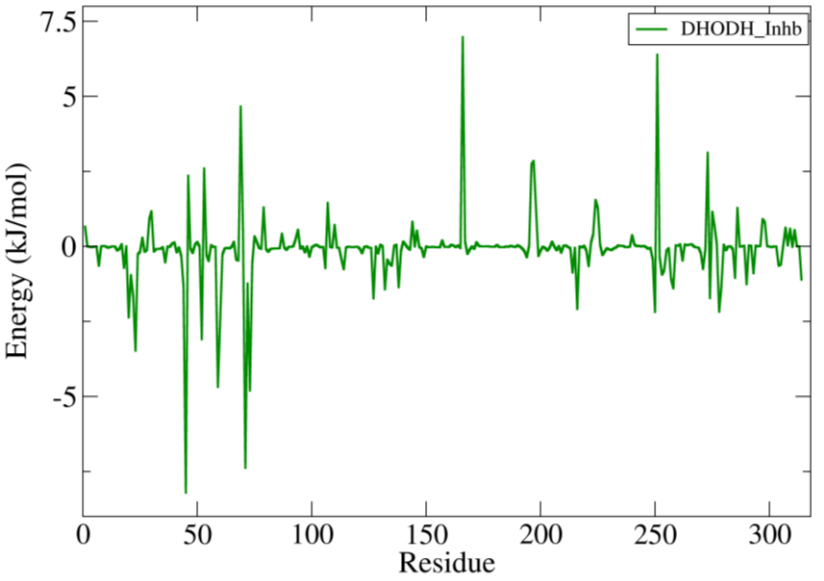


Fig 7: Per residue decomposition of binding energy of APRT and DHODH with Lig2, Lig3 and inhibitor complexes, respectively

Conclusion

- The present study screened ligands with different filter parameters against APRT and DHODH proteins of *L.donovani* and selected 5 ligands from it.
- After 20ns of MD simulation, it was observed that Ligand 2 and 3 showed good result compared to established inhibitors.
- From the inference of 100ns MD simulation and MM/PBSA analysis, Ligand 3 have the potential to inhibit both proteins and act as antileishmanial agent in treating VL.
- From above result, Ligand 3 showed better binding energy and stability with APRT and DHODH proteins which provide evidence that they could be used for further study.

References

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Thank You