Dual Inhibitors of SARS-CoV-2 proteases: Pharmacophore and molecular dynamics based drug repositioning and phytochemical leads.

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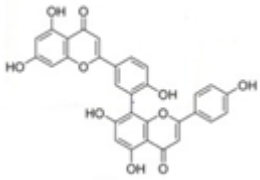
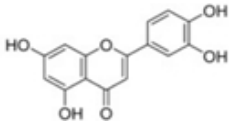
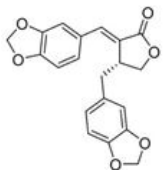
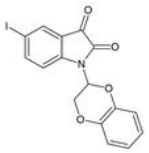
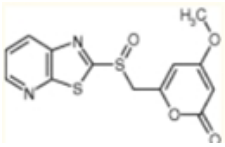
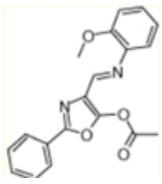
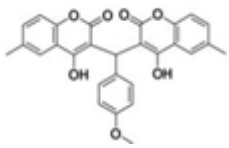
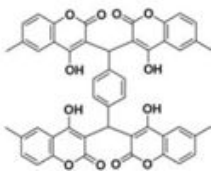
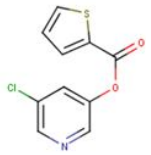
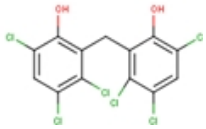
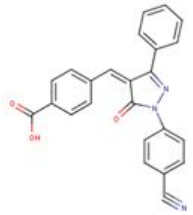
Supplementary files.

Table.1: Set-1 = reported SARs-CoV 3CL-proteases inhibitors with their binding scores and pharmacophoric similarity with respect to pharmacophore model -1 (Ph-1).

Name	Structure	IC_{50}	$-\Delta G_b$ (Kcal /mol)	Similarity / Ph-1
Amentoflavone		8.3±0.5	-9.4	0.690
luteolin		20.2	-7.4	0.517
savinin		25	-7.7	0.422

Isatin derivative		13.5	-7.3	0.433
Synthetic		7.3±0.7	-6.9	0.387
48511		3.3±0.3	-7.4	0.404
DC060251		9.56±1.8	-8.4	0.535
DC060170		6.86±0.91	-8.8	0.561
MAC-5576		0.5	-6.8	0.343
Hexachlorophene		5	-6.1	0.283
Compound- 2N		5.5	-8.0	0.156

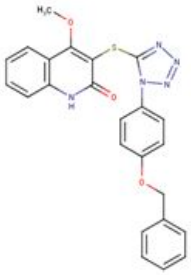
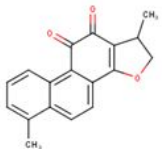
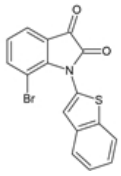
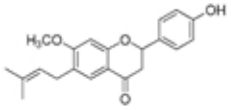
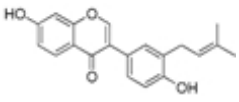
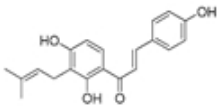
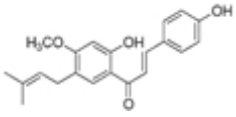
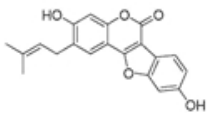
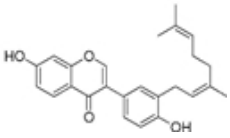
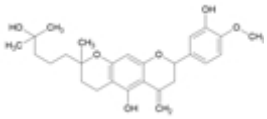
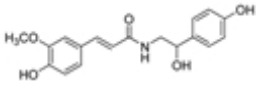
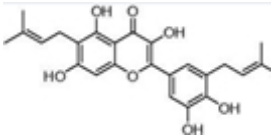
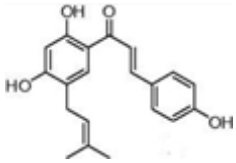
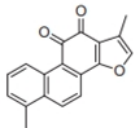
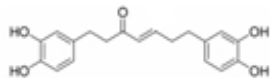
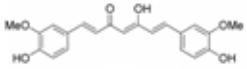
Compund -4		2.0	-8.7	0.628
Di - hydrotanshinone I		14.4	-8.1	0.637
Isatin derivative		0.98	-6.8	0.213

Table:2. Reported PLp inhibitors used for developing pharmacophore model -2 (Ph-2), along with their binding score and molecular similarity with Ph-2 model.

Name	Structure	IC 50	- ΔG_b (Kcal /mol)	Similarity / Ph-1	Ref
Bavachinin		38.4 ± 2.4	-7.9	0.591	(Kim et al., 2014)
Neobavaisoflavone		18.3 ± 1.1	-7.8	0.567	
Isobavachalcone		7.3 ± 0.8	-8.2	0.691	
Methylbavachalcone		10.1 ± 1.2	-8.6	0.658	

Psoralidin		4.2 ± 1.0	-8.3	0.601	
corylifol A		32.3 ± 3.2	-8.4	0.640	
Tormentin- B		6.1 ± 0.02	-8.7	0.684	(Cho et al., 2013)
N-trans-feruloyloctopamine		26.6±0.5	-7.1	0.503	
papyriflavonol A		3.7 ± 1.6	-8.3	0.642	(Song et al., 2014)
broussochalcone B		11.6 ± 0.7	-8.5	0.655	(Kim et al., 2014)
Tanshinone-I		11.5 ± 1.5	-8.3	0.651	(Park et al., 2012)
hirsutenone		4.1±0.3	-7.7	0.513	
Curcumin		5.7±0.3	-7.3	0.550	

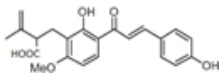
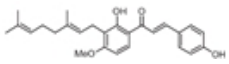
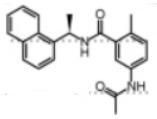
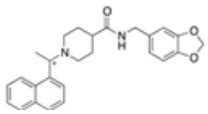
xanthoangelol E		1.2±0.5	-7.7	0.539	(Park et al., 2016)
xanthoangelol F		5.6±0.5	-8.0	0.634	
Compound -6		2.6±0.1	-8.7	0.713	(Báez-Santos et al., 2014)
Compound -5g		0.67±0.1	-9.3	0.763	

Figure : 1

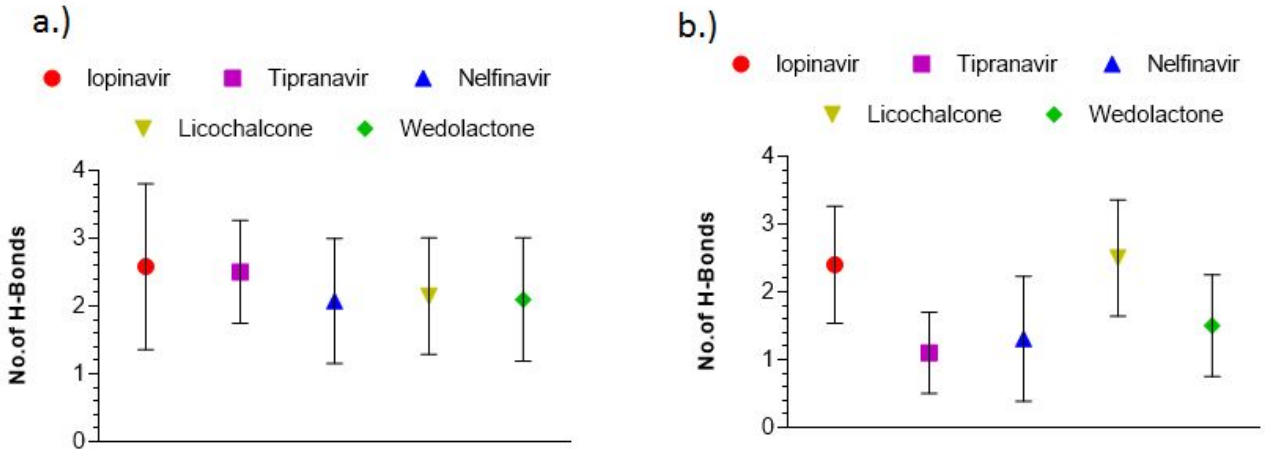


Fig.1:. H-bond analysis of complexes throughout the trajectory, a.) 3CLp complexex , b.) PLp complexes.In case of 3CLp Lopinavir was showing very high variation in H-bonds due to its unstable binding.

Figure : 2

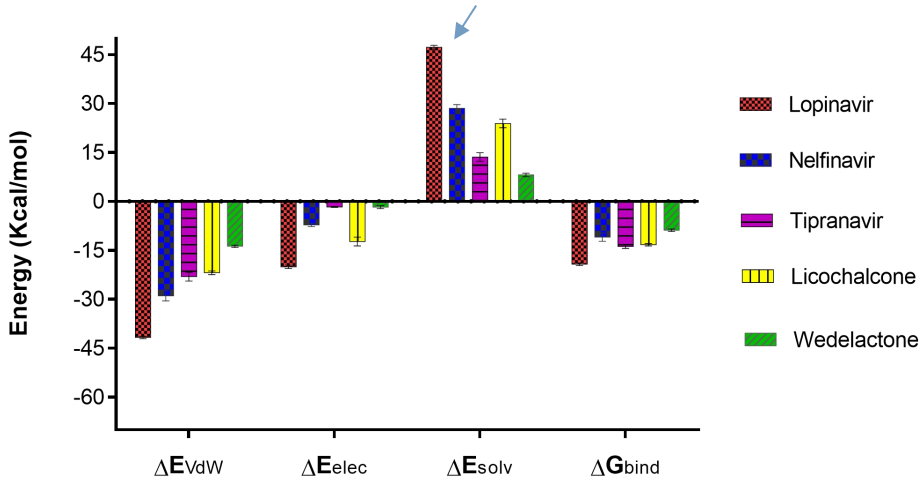


Fig:2. MM/PBSA - Energy Decomposition analysis of PLp complexes.

Figure : 3

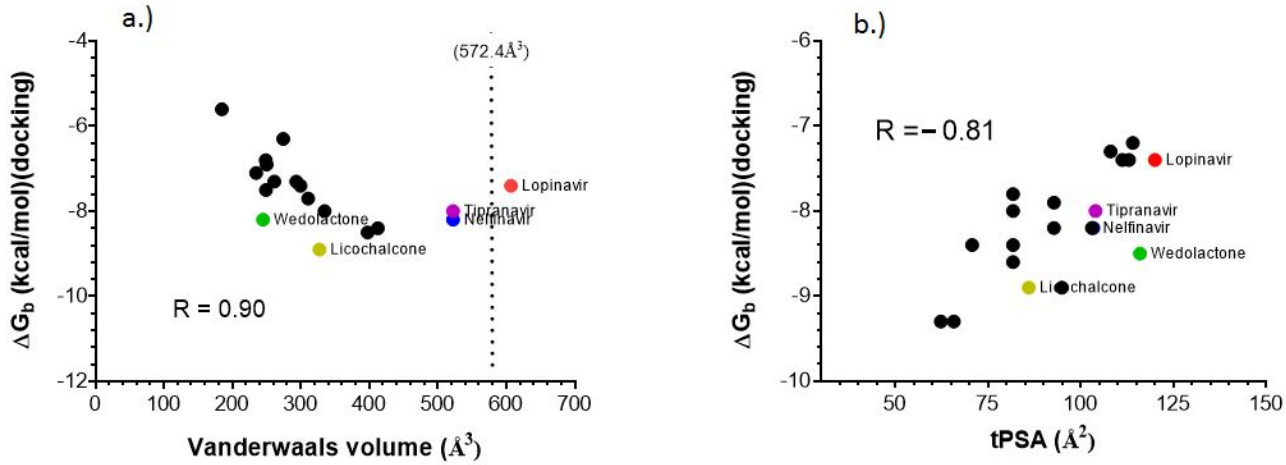


Fig:3.a.) The plot indicates the relationship between vanderwaal volume of reported 3CLp inhibitors and their binding energy (R=0.90).The dotted line indicates the active site pocket volume of 3CLp = 572.4 A^3 as cut-off; **b.)** The plot indicates the relationship between total polar surface of reported PLp inhibitors and their binding energy (R=0.81). Coloured points indicate binding energies estimated from MD simulation and black points indicate binding energies estimated form docking.

Figure : 4

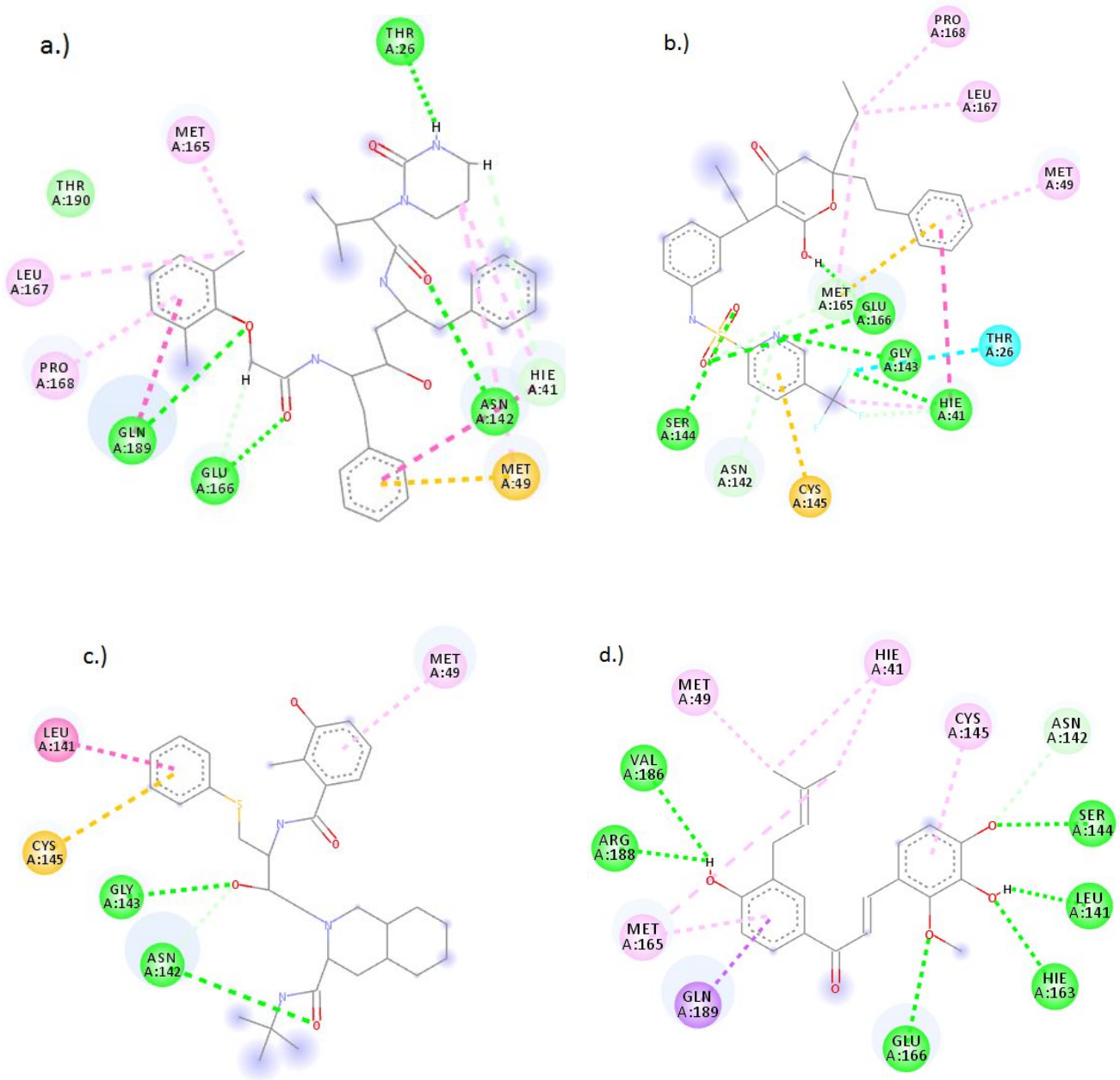


Fig:4. Interaction plot of 3CLp complexes after 30ns simulation a.)Lopinavir , b.)Tipranavir , c.)Nelfinavir, d.)Licochalcone-D and e.) Wedelolactone.

Figure. 5:

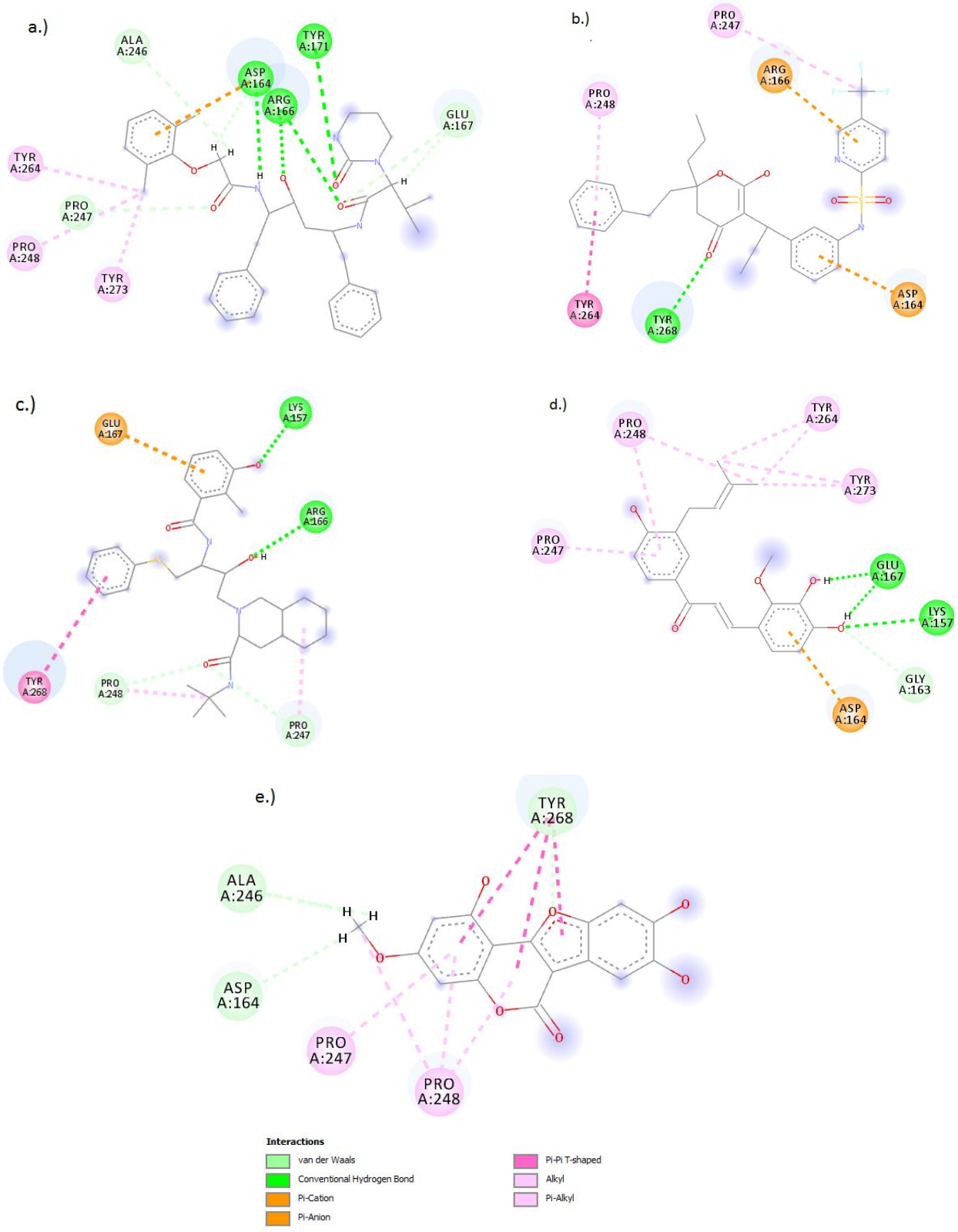


Fig:5. Interaction plot of PLp complexes after 30ns simulation a.)Lopinavir , b.)Tipranavir , c.)Nelfinavir, d.)Licochalcone-D and e.) Wedelolactone.