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Supporting Information

Identification of SARS-CoV-2 Papain-like Protease (PLpro) Inhibitors Using Combined Computational Approach**

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Supporting Information

Table S1. Ranking of the candidate compounds based on similarity distance from the centroid

Ergometrine	1.0983
Methylergometrine	1.2657
Clidinium	1.6500
Phentolamine	1.7025
Oxamniquine	1.8842
Metergoline	2.0399
Clonidine	2.0595
Indacaterol	2.1215
Methscopolamine bromide	2.1833
Quinine	2.2219
Stiripentol	2.2338
Tubocurarine	2.3355
Dichlorobenzyl alcohol	2.4
Osimertinib	2.4437
Eugenol	2.4456
Undecoylium chloride iodine complex	2.5165
Dihydro-alpha-ergocryptine	2.5484
Lacosamide	2.559
Epicriptine	2.5965
Phenoxyethanol	2.6076
Mephenesin	2.631
Vandetanib	2.7469
Benzyl alcohol	2.7908
Bosutinib	2.8336
Medifoxamine	3.0265
Orciprenaline	3.0323
Cisatracurium	3.037
Methdilazine	3.0404
Almitrine	3.1207
Dimercaprol	3.3001
Fidaxomicin	3.3195
Sacubitril	3.3286
Guanidine	3.5501
Nabumetone	3.6113
Bepotastine	3.7253

Diacetyl benzoyl lathyrol	3.746
Ivabradine	3.9308
Terconazole	4.0701
Digoxin	4.1656
Cinoxate	4.3016
Citalopram	4.3764
Escitalopram	4.3764
Meglumine	4.6809
Troleandomycin	4.9497

Table S2. Statistics of the Plpro compounds PCA model

Component	SSX	SSXacc	VarX	VarXacc
1	34.61	34.61	33.13	33.13
2	13.03	47.64	12.09	45.23
3	10.86	58.5	10.34	55.57
4	7.77	66.28	7.45	63.03
5	4.41	70.69	4.05	67.08

Figure S1. PCA plot of the first two components, with marked Plpro cocrystalized compounds and candidates Ergometrine, Metergoline and Epicriptine

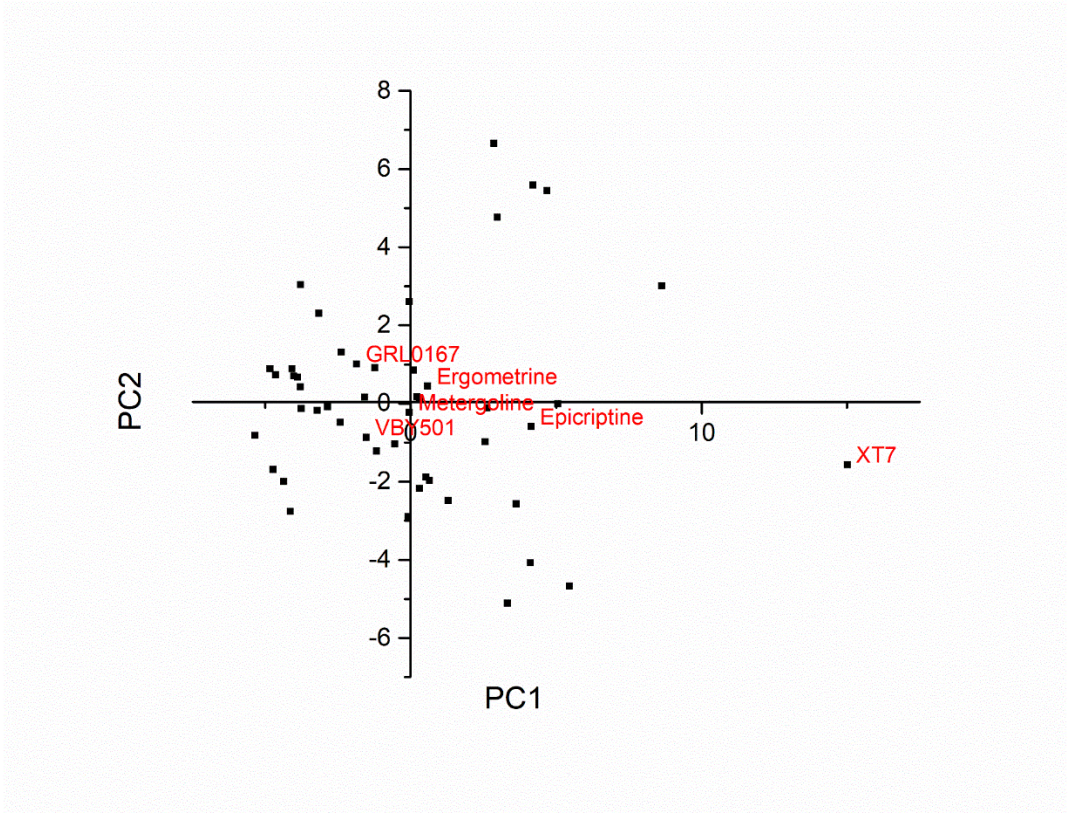

Table S3. Ranking of the PLpro candidate compounds, based on their docking score

Compound name]	Drugbank ID	Frequency	VINA binding energy (kcal/mol)
GRL 0617	-	0.382	-10.4
Epicriptine	DB11275	0.382	-10.3
XR8-89	-	0.279	-10.2
VBY501	-	0.382	-10.2
Metergoline	DB13520	0.382	-9.4
Dihydro-alpha-ergocryptine	DB11274	0.382	-8.9
Digoxin	DB00390	0.279	-8.8
Phentolamine	DB00692	0.279	-8.3
Fidaxomicin	DB08874	0.382	-8.1
Ergometrine	DB01253	0.382	-8.0
Sacubitril	DB09292	0.279	-7.8
Almitrine	DB01430	0.382	-7.7
Osimertinib	DB09330	0.279	-7.6
Indacaterol	DB05039	0.279	-7.6
Methylergometrine	DB00353	0.382	-7.6
Diacetyl benzoyl lathyrol	DB11260	0.279	-7.5
Bosutinib	DB06616	0.279	-7.4
Tubocurarine	DB01199	0.279	-7.4
Terconazole	DB00251	0.382	-7.3
Ivabradine	DB09083	0.382	-7.0
Vandetanib	DB05294	0.382	-7.0
Citalopram	DB00215	0.382	-7.0
Quinine	DB00468	0.382	-7.0
Clidinium	DB00771	0.279	-7.0
Nabumetone	DB00461	0.382	-7.0
Medifoxamine	DB13219	0.382	-6.9
Methdilazine	DB00902	0.382	-6.9
Stiripentol	DB09118	0.382	-6.8
Bepotastine	DB04890	0.382	-6.7
Oxamniquine	DB01096	0.279	-6.7
Orciprenaline	DB00816	0.279	-6.6
Methscopolamine	DB00462	0.382	-6.6

bromide			
Lacosamide	DB06218	0.382	-6.4
Escitalopram	DB01175	0.382	-6.3
Troleandomycin	DB13179	0.279	-6.3
Mephenesin	DB13583	0.382	-6.2
Cisatracurium	DB00565	0.382	-5.9
Clonidine	DB00575	0.382	-5.9
Eugenol	DB09086	0.382	-5.9
Cinoxate	DB15467	0.382	-5.7
Phenoxyethanol	DB11304	0.382	-5.4
Dichlorobenzyl alcohol	DB13269	0.279	-5.1
Benzyl alcohol	DB06770	0.382	-5.1
Undecoylium chloride iodine complex	DB09377	0.279	-4.9
Meglumine	DB09415	0.382	-4.4
Guanidine	DB00536	0.382	-4.0
Dimercaprol	DB06782	0.382	-2.9

Figure S2. RMSD plot of the PLpro backbone atoms during the production phase of MD simulation in complex with Metergoline

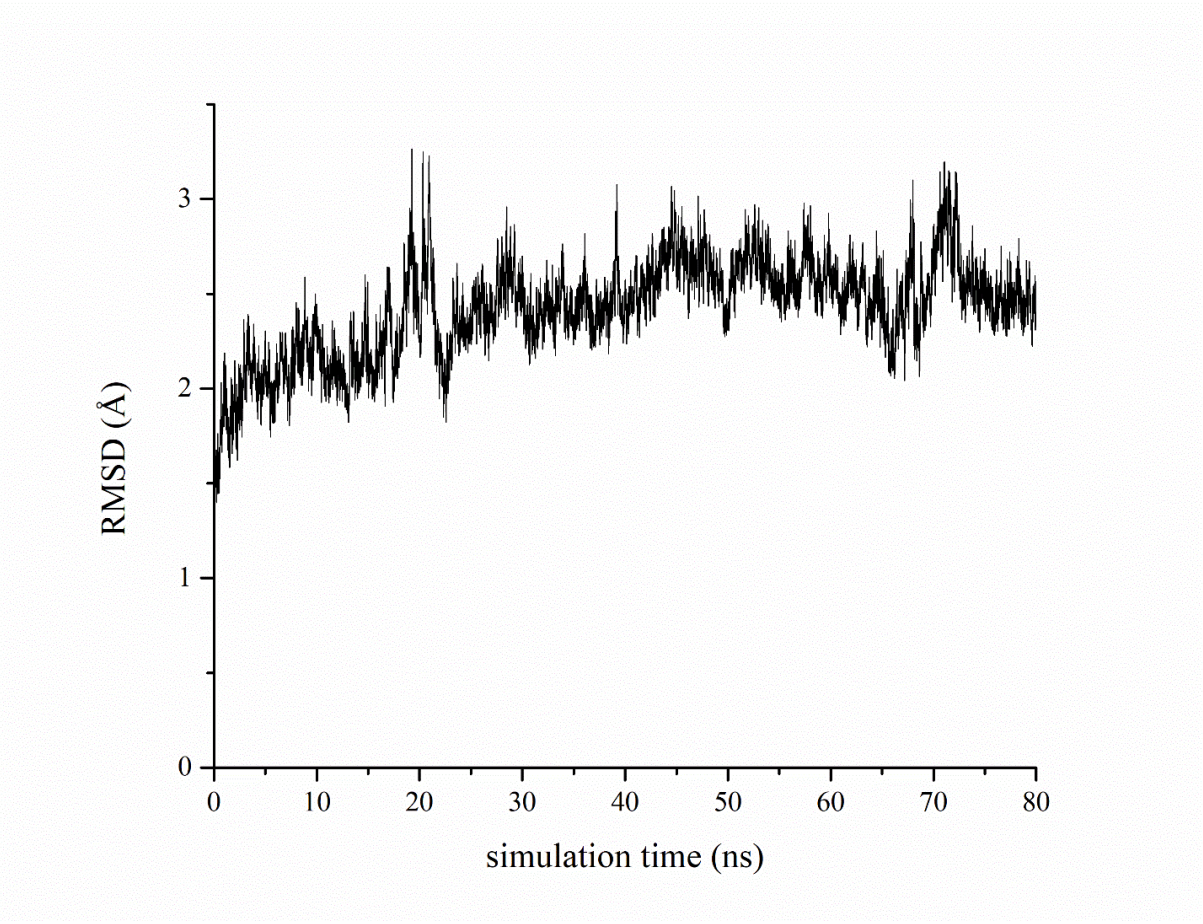

Figure S3. Metadynamics trajectory plot of the PLpro – Metergoline complex

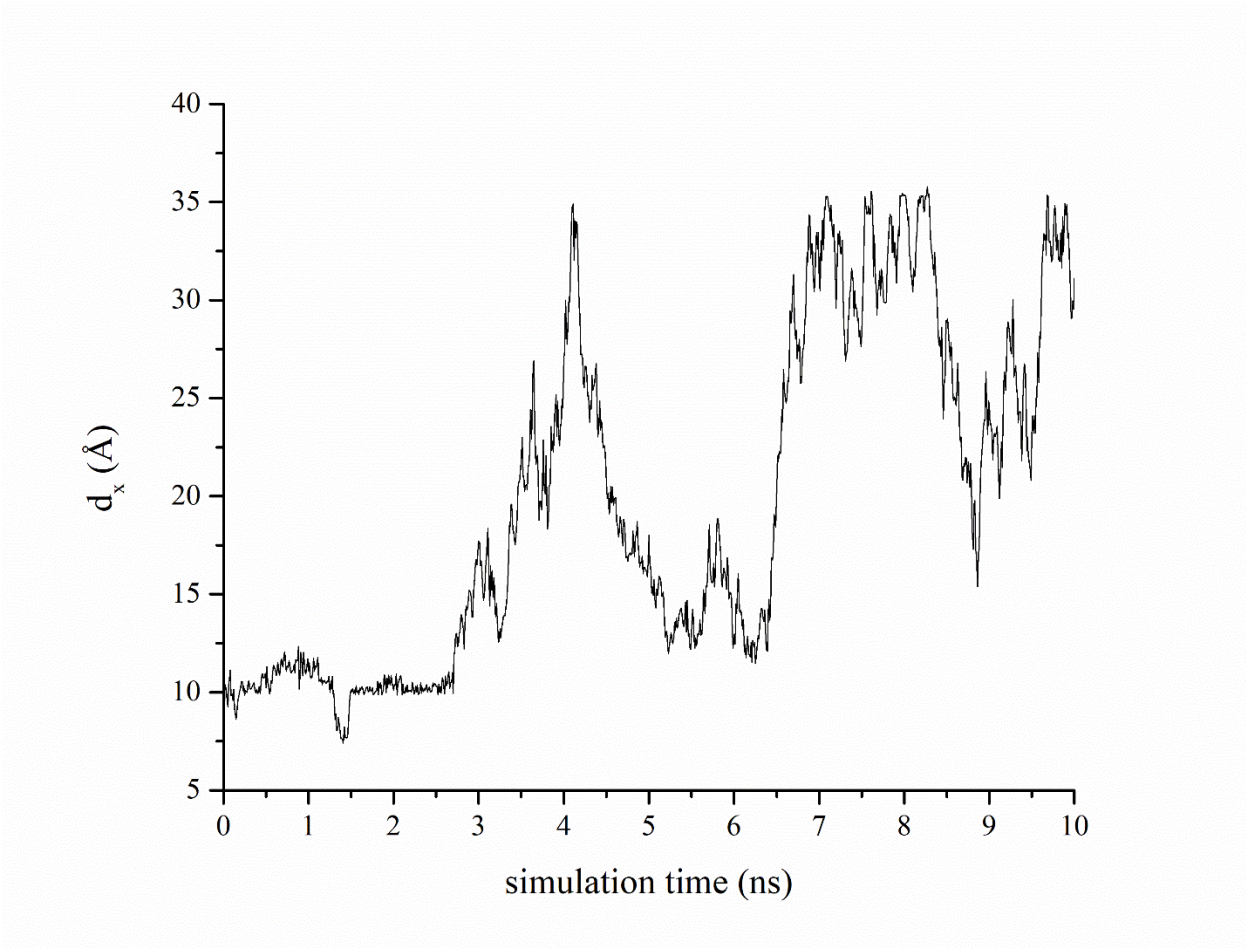

Table S4. RMSD and docking energy values between docked and co-crystalized conformations

Ligand	PDB structure	Binding energy (kcal/mol)	RMSD of the docked conformation from the co-crystalized (A)
GRL0167	7CJM	-10.4	0.3204
VBY501	7JIW	-10.2	0.0000
XR8-89	7LBR	-10.5	2.2253

Additional material:

1) Video of the metadynamics simulation of the PLpro – Metergoline complex (Metadynamics.mp4)
2) SDF file of 1490 Drugbank approved drugs