Supporting Information

Profiling SARS-CoV-2 Main Protease (M^{PRO}) Binding to Repurposed Drugs Using Molecular Dynamics Simulations in Classical and Neural Network-Trained Force Fields

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Table S1; Random set of 62 compounds that were filtered due to docking scores (> -8.5 kcal/mol). Entries are ordered according to docking score; any available experimental information on efficacy is also listed.

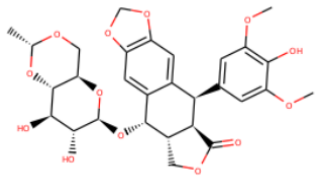
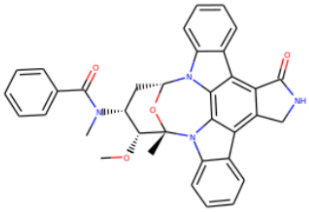
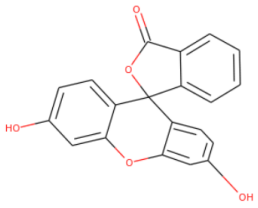
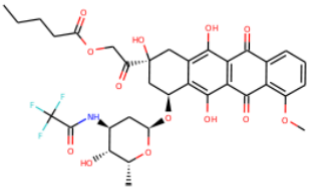
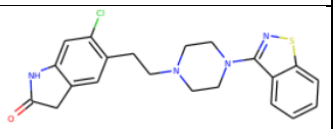
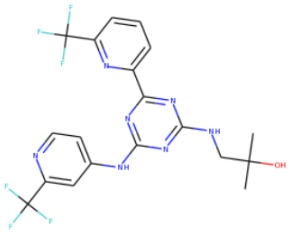
ZINCID	name	docking score (kcal/mol)	experimental information
ZINC000001530427	Fosfomycin	-3.8	
ZINC000004658290	Mercaptopurine	-4.4	
ZINC000100009383	D-glucose	-4.4	
ZINC000003831551	Tiopronin	-4.5	
ZINC000245204924	Lindane	-4.5	
ZINC000014881137	Didecyl-Dimethyl-Ammonium	-4.8	
ZINC000000008492	8-Hydroxyquinoline	-4.9	
ZINC000000896546	Flucytosine	-4.9	
ZINC000001690604	Norpholedrine	-5.0	
ZINC000008466459	Levmetamfetamine	-5.0	
ZINC000000896666	Tranylcypromine	-5.0	
ZINC000000967520	Camphor	-5.2	
ZINC000001530737	Nizatidine	-5.2	
ZINC000001633887	Octinoxate	-5.5	
ZINC000003830635	Deferoxamine	-5.5	
ZINC000003830960	Lopromide	-5.5	
ZINC000085205448	Nifedipine	-5.6	
ZINC000001633889	Octinoxate	-5.7	
ZINC000000001673	Melphalan	-5.8	
ZINC000000006016	Venlafaxine	-5.8	
ZINC000256433952	Norelgestromin	-6.0	
ZINC000000005895	Rizatriptan	-6.1	
ZINC000002548959	Methoxsalen	-6.2	
ZINC000003956788	Nitazoxanide	-6.2	
ZINC000001554010	Gabapentin	-6.3	
ZINC000000018635	Frovatriptan	-6.4	
ZINC000000607939	Isradipin	-6.4	
ZINC000003991624	Vilanterol	-6.4	
ZINC000003831405	Quinidine	-6.6	antiviral activity but target unknown[a]
ZINC000000005823	Torsemide	-6.6	
ZINC000003807804	Clotrimazole	-6.7	
ZINC000000120286	Triamteril	-6.7	
ZINC000003831404	Quinine	-6.7	
ZINC000000005560	Ketoprofen	-6.7	
ZINC000002570817	Bromfenac	-6.7	

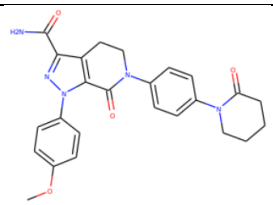
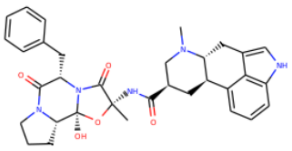
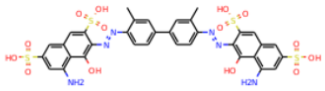
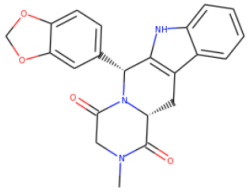
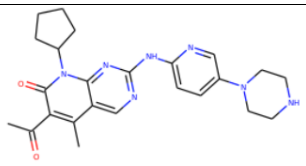
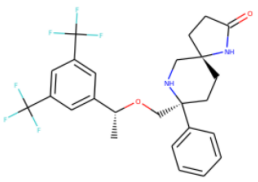
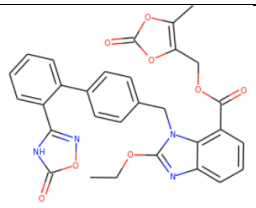
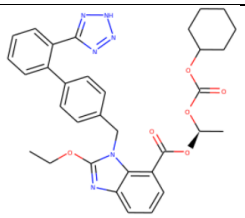
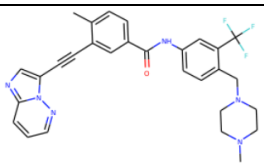
ZINC000053084692	Safinamide	-6.7	
ZINC000026011099	Omacetaxine Mepesuccinate	-6.8	
ZINC000256433955	Norelgestromin	-6.9	
ZINC000004216238	Fludarabine	-6.9	
ZINC000169677008	Everolimus	-6.9	
ZINC000002599970	Formoterol	-7.0	
ZINC000100014475	Nitisinone	-7.0	
ZINC000051133897	Piroxicam	-7.1	
ZINC000014961096	Alogliptin	-7.2	
ZINC000003861806	Podophyllotoxin	-7.3	
ZINC000000389747	Naloxone	-7.3	
ZINC000000602128	Bepotastine	-7.3	
ZINC000009574770	Telithromycin	-7.3	
ZINC000095616601	Prazosin	-7.5	
ZINC000002568036	Dantrolene	-7.5	
ZINC000003607120	Gatifloxacin	-7.6	
ZINC000004212809	Deflazacort	-7.6	
ZINC000000002299	Asenapine	-7.7	
ZINC000001529323	Methotrexate	-7.8	
ZINC000000608382	Flavoxate	-7.8	
ZINC000000025958	Rucaparib	-7.8	
ZINC000002005305	Levomefolic acid	-8.0	
ZINC000150588351	Elbasvir	-8.0	Negative[b]
ZINC000003918087	Doxorubicin	-8.2	
ZINC000000607986	Nebivolol	-8.2	
ZINC000034089131	Ulipristal	-8.3	
ZINC000003816287	Axitinib	-8.4	

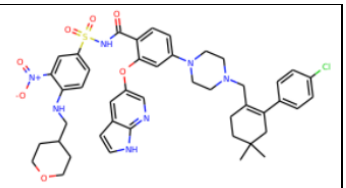
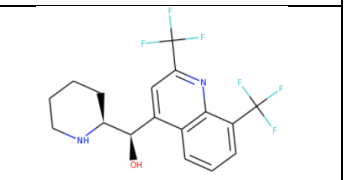
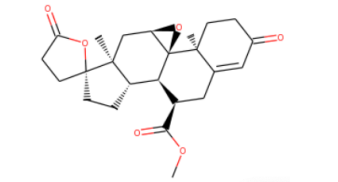
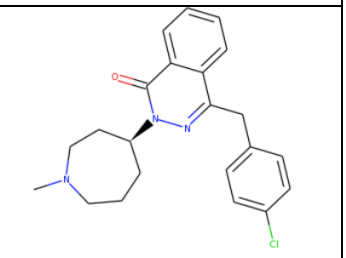
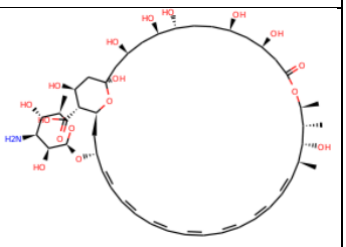
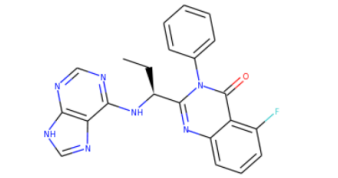
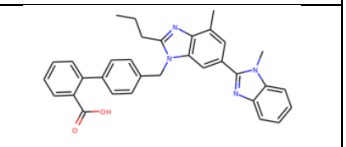
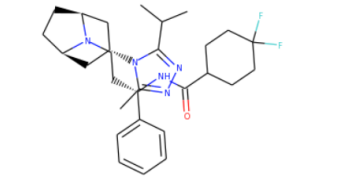
[a]Touret, Franck, Magali Gilles, Karine Barral, Antoine Nougairède, Jacques van Helden, Etienne Decroly, Xavier de Lamballerie, and Bruno Coutard. "In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication." *Scientific reports* 10, no. 1 (2020): 1-8.

[b]Drayman, N., Jones, K.A., Azizi, S.A., Froggatt, H.M., Tan, K., Maltseva, N.I., Chen, S., Nicolaescu, V., Dvorkin, S., Furlong, K. and Kathayat, R.S., 2020. Drug repurposing screen identifies masitinib as a 3CLpro inhibitor that blocks replication of SARS-CoV-2 in vitro. *bioRxiv*.

Table S2. List of 26 FDA-approved drugs, showing ZINC IDs, marketed names, docking scores, lig-RMSDs in ANI/MM MD simulations, and 2D structures. Entries are ordered according to ascending lig-RMSDs.

ZINC-ID	name	docking score (kcal/mol)	lig-RMSD (Å; ANI/MM)	2D structure
ZINC000003938684	Etoposide	-9.4	2.13	
ZINC000100013130	Midostaurin	-8.9	2.17	
ZINC000003860453	Fluorescein	-9.3	2.59	
ZINC000028232750	Valrubicin	-8.7	2.76	
ZINC000000538550	Ziprasidone	-8.5	3.27	
ZINC000222731806	Enasidenib	-9.0	3.64	

ZINC000011677837	Apixaban	-8.5	3.82	
ZINC000003978005	Dihydroergotamine	-9.5	3.85	
ZINC000169289767	Trypan Blue	-8.7	3.87	
ZINC000003993855	Tadalafil	-9.2	4.47	
ZINC000003938686	Palbociclib	-8.7	4.58	
ZINC000003816514	Rolapitant	-9.3	4.95	
ZINC000014210642	Azilsartan	-8.6	5.89	
ZINC000004074875	Candesartan	-8.6	5.96	
ZINC000036701290	Ponatinib	-8.5	6.18	

ZINC000150338755	Venetoclax	-9.5	6.20	
ZINC000000897089	Mefloquine	-8.5	6.36	
ZINC000003985982	Eplerenone	-8.8	7.26	
ZINC000000897240	Azelastine	-9.0	7.90	
ZINC000253387843	Amphotericin B	-8.7	8.85	
ZINC000013986658	Idelalisib	-8.5	8.91	
ZINC000100003902	Maraviroc	-8.7	9.03	
ZINC000001530886	Telmisartan	-8.8	9.98	

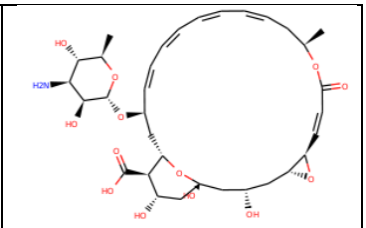
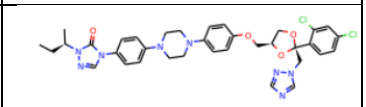
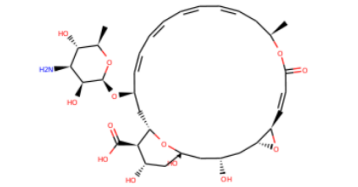
ZINC000169621220	Natamycin I	-9.5	10.85	
ZINC000004097343	Itraconazole	-8.7	11.09	
ZINC000008220909	Natamycin II	-8.8	16.15	

Table S3. MM/PBSA binding free energies for 26 drug molecules, from ANI/MM MD simulations.[a]

Drug	Coul	LJ	PB	SA	gas	sol	pol	npol	total
Etoposide	-24.56	-47.42	67.27	-5.24	-71.98	62.03	42.70	-52.66	-9.96
Midostaurin	-16.86	-43.40	49.11	-5.05	-60.26	44.06	32.25	-48.45	-16.20
Fluorescein	-18.69	-17.48	32.39	-3.22	-36.17	29.17	13.70	-20.70	-7.00
Valrubicin	-18.57	-43.99	68.42	-5.61	-62.56	62.81	49.85	-49.60	0.25
Ziprasidone	-12.08	-35.68	40.92	-4.29	-47.76	36.63	28.84	-39.97	-11.13
Enasidenib	-12.78	-12.42	30.66	-2.58	-25.20	28.08	17.88	-14.99	2.89
Apixaban	-13.63	-33.47	43.96	-4.29	-47.10	39.67	30.33	-37.76	-7.43
Dihydroergotamine	-17.40	-37.71	41.51	-4.26	-55.12	37.26	24.11	-41.97	-17.86
Trypan Blue	-43.81	-49.72	101.58	-5.89	-93.52	95.69	57.77	-55.60	2.17
Tadalafil	-6.73	-21.99	26.15	-3.09	-28.71	23.07	19.43	-25.07	-5.65
Palbociclib	-10.90	-37.02	49.51	-5.24	-47.91	44.27	38.61	-42.25	-3.64
Rolapitant	-7.15	-27.23	32.97	-3.77	-34.38	29.20	25.81	-31.00	-5.19
Azilsartan	-7.78	-25.69	33.90	-3.39	-33.47	30.51	26.13	-29.08	-2.95
Candesartan	1.44	-29.19	24.63	-4.22	-27.74	20.41	26.07	-33.41	-7.33
Ponatinib	-4.03	-18.95	20.49	-2.99	-22.98	17.50	16.46	-21.94	-5.48
Venetoclax	-1.24	-13.50	16.37	-2.73	-14.73	13.64	15.13	-16.23	-1.10
Mefloquine	-4.92	-16.84	18.71	-2.78	-21.75	15.93	13.80	-19.62	-5.82
Eplerenone	-8.20	-18.03	22.96	-3.21	-26.23	19.75	14.76	-21.23	-6.48
Azelastine	-0.09	-29.58	22.74	-4.06	-29.67	18.68	22.65	-33.64	-10.99
Amphotericin B	-24.32	-34.90	62.63	-5.03	-59.22	57.60	38.31	-39.93	-1.62
Idelalisib	-4.37	-13.19	17.68	-2.58	-17.56	15.10	13.31	-15.77	-2.46
Maraviroc	-17.96	-38.74	45.35	-4.98	-56.69	40.37	27.39	-43.72	-16.32
Telmisartan	-7.36	-28.50	36.99	-4.53	-35.86	32.46	29.63	-33.03	-3.40
Natamycin I	-23.45	-51.59	72.39	-5.88	-75.04	66.50	48.93	-57.47	-8.54
Itraconazole	-8.34	-30.30	34.56	-4.11	-38.64	30.45	26.22	-34.41	-8.19
Natamycin II	-10.95	-22.77	31.92	-3.58	-33.71	28.33	20.97	-26.35	-5.38

[a]The MM/PBSA calculations were done on 500 snapshots sampled from 5 ns of ANI/MM simulations. The components are: Coul, Coulomb; LJ, Lennard-Jones; PB, Poisson-Boltzmann solvation; SA, surface area; gas = Coul + LJ, gas phase; sol = PB + SA, total solvation; pol = Coul + PB, polar component; npol = LJ + SA, nonpolar component; total = pol + npol, total binding energy.

Table S4. MD and ANI/MM based MM/PBSA binding free energies for the final selection of 9 drugs

Drug Name	MD (kcal/mol)	ANI/MM (kcal/mol)
Dihydroergotamine	-14.13	-17.86
Midostaurin	-9.41	-16.20
Ziprasidone	-9.42	-11.13
Etoposide	-4.93	-9.96
Apixaban	-4.84	-7.43
Fluorescein	-3.48	-7.00
Tadalafil	-4.97	-5.65
Rolapitant	-4.01	-5.19
Palbociclib	-1.56	-3.64

Supporting Text: NAMD input script for ANI/MM:

```
structure          ionized.psf
coordinates        ionized.pdb
set temp           303;
outputName         cov4;
set inputname      cov3;
binCoordinates     $inputname.coor;
binVelocities      $inputname.vel;
extendedSystem     $inputname.xsc;

proc get_first_ts { xscfile } {
  set fd [open $xscfile r]
  gets $fd
  gets $fd
  gets $fd line
  set ts [lindex $line 0]
  close $fd
  return $ts
```

```
}
set firsttime [get_first_ts $inputname.restart.xsc]
firsttimestep      $firsttime

restartfreq             1000;
dcdfreq                 1000;
xstFreq                         1000;
outputEnergies          1000;
outputTiming            1000;

# Force-Field Parameters
paraTypeCharmm          on;
parameters          ../charmm/toppar/par_all36_carb.prm
parameters          ../charmm/toppar/par_all36_cgenff.prm
parameters          ../charmm/toppar/par_all36_lipid.prm
parameters          ../charmm/toppar/par_all36m_prot.prm
parameters          ../charmm/toppar/par_all36_na.prm
parameters          ../charmm/toppar/par_interface.prm
parameters          ../charmm/toppar/toppar_all36_prot_na_combined.str
parameters          ligand.par

exclude                 scaled1-4
1-4scaling              1.0
Switching               on
vdwForceSwitching       yes;
cutoff                  12.0;
switchdist              10.0;
pairlistdist            14.0;
stepspercycle           20;
pairlistsPerCycle       2;

# Integrator Parameters
Timestep                 2.0;
rigidBonds              all;
nonbondedFreq           1;
fullElectFrequency      1;

wrapWater               on;
wrapAll                 on;
wrapNearest             off;

# PME (for full-system periodic electrostatics)
PME                     yes;
PMEInterpOrder          6;
PMEGridSpacing          1.0;
```

```
# Constant Pressure Control (variable volume)
useGroupPressure      yes;
useFlexibleCell       no;
useConstantRatio      no;

langevinPiston              on;
langevinPistonTarget        1.01325;
langevinPistonPeriod        50.0;
langevinPistonDecay         25.0;
langevinPistonTemp          $temp;

# Constant Temperature Control
langevin              on;
langevinDamping        1.0;
langevinTemp          $temp;
langevinHydrogen       off;

qmforces              on
qmParamPDB                  qmmm.pdb
qmSoftware            custom
qmexecpath            /home/agupt8/covid-dock/allfda/above8.5/36/client.py
qmBaseDir             /home/agupt8/covid-dock/allfda/above8.5/36/
QMColumn              occ
qmChargeMode          none
qmElecEmbed           off

# run
Run                   2500000;          # 5ns
```