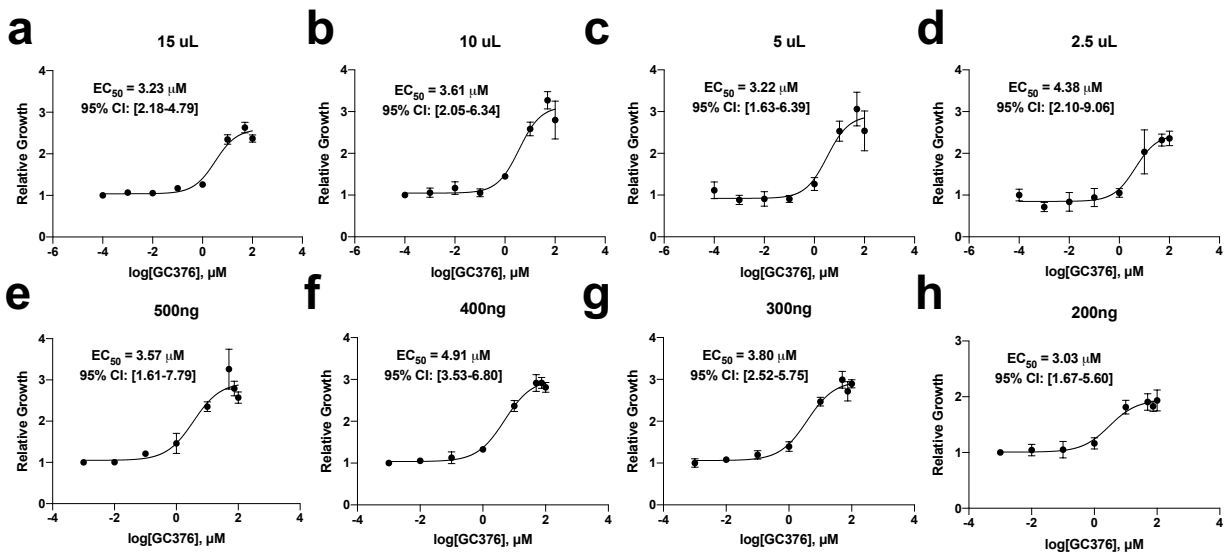
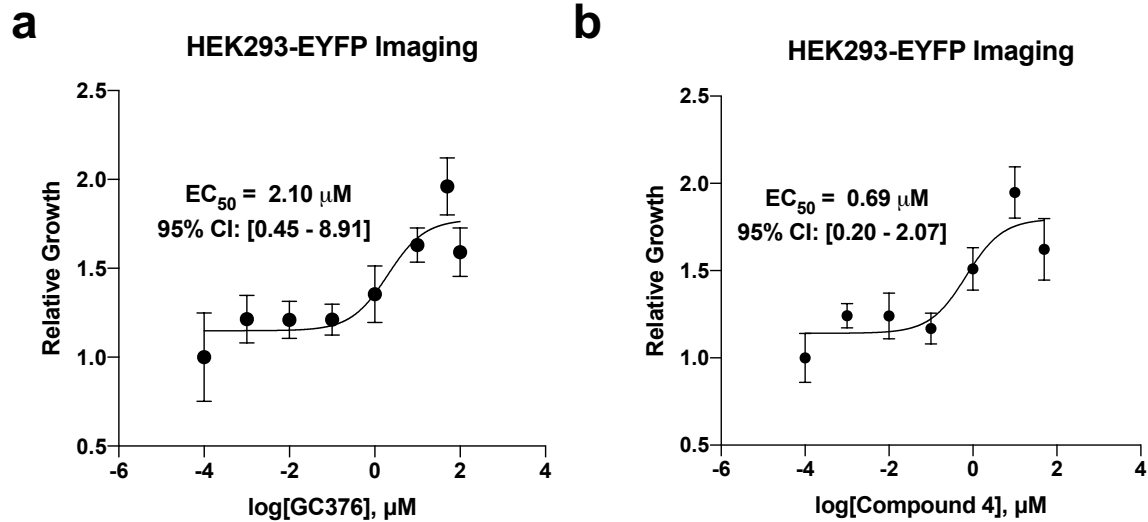


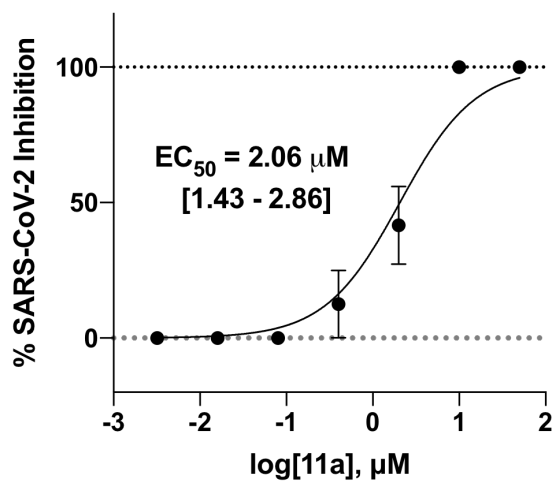
Supplementary Fig. 1. Dose response experiments with SARS-CoV-2 3CLpro and GC376 are robust to variable assay parameters. a-d. Repetition of assay with variable levels of cell seeding into drug conditions result in similar EC_{50} value predictions. **e-h.** Repetition of assay with variable levels of plasmid transfection results in similar EC_{50} value predictions. EC_{50} values are displayed as best-fit value alongside 95% confidence interval. Data are shown as mean \pm s.d. for four technical replicates.



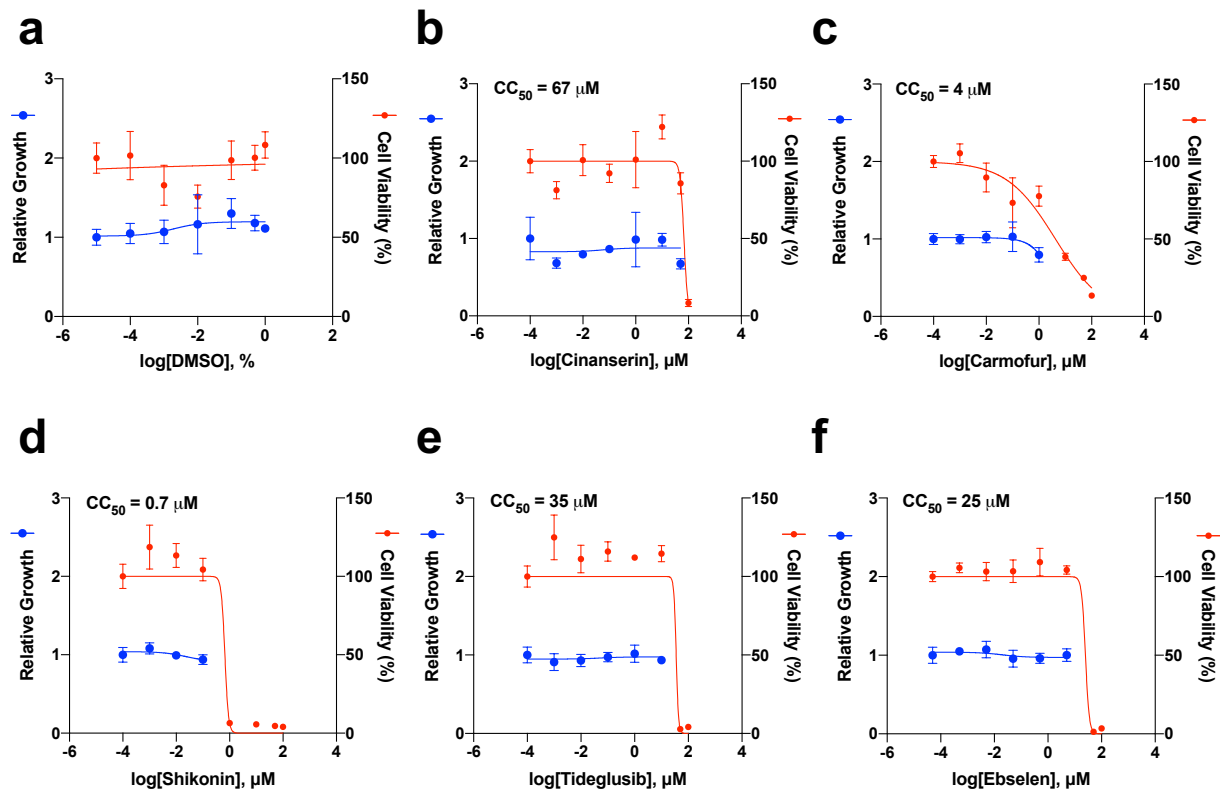
Supplementary Fig. 2. Dose response experiments with SARS-CoV-2 3CLpro can be determined with imaging of EYFP labeled HEK293 cells. a-b. The activity of GC376 and compound 4 can be detected using imaging rather than crystal violet staining. EC_{50} values are displayed as best-fit value alongside 95% confidence interval. Data are shown as mean \pm s.d. for four technical replicates.



Supplementary Figure 3. Live virus testing of compound 11a. The EC_{50} value is displayed as best-fit value alongside 95% confidence interval. Data are shown as mean \pm s.d. for three technical replicates.

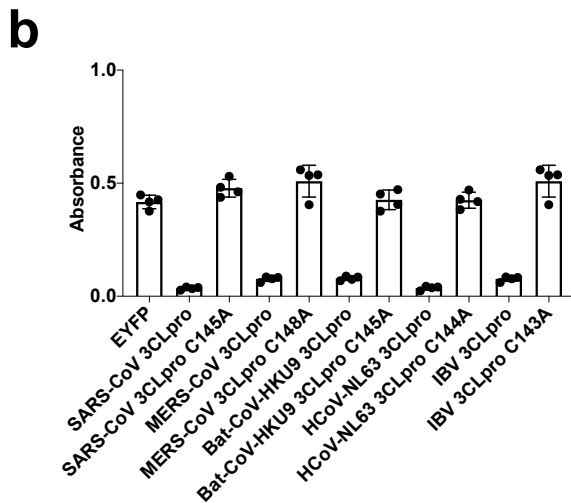
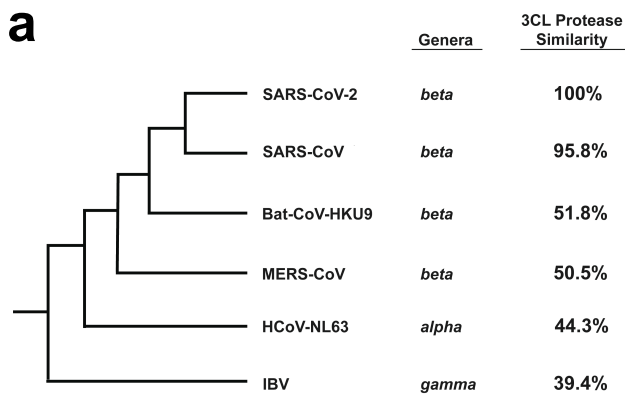


Supplementary Fig. 4. Compounds with activity against the SARS-CoV-2 3CLpro *in vitro* that are not efficacious against the SARS-CoV-2 live virus do not show activity in the transfection-based assay. a. DMSO was tested at concentrations up to 1%, the maximal concentration used to deliver compounds in this study, and does not show toxicity to HEK293T cells or protease inhibitory activity against the 3CLpro. **b-e.** Other compounds with reported activity against purified SARS-CoV-2 3CLpro but not against live virus. **f.** Ebselen, a compound with efficacy against the SARS-CoV-2 live virus does not rescue 3CLpro induced cytotoxicity within the transfection-based assay. EC₅₀ values are displayed as best-fit value alongside 95% confidence interval. CC₅₀ values are displayed as best-fit value. Data are shown as mean ± s.d. for three or four technical replicates.

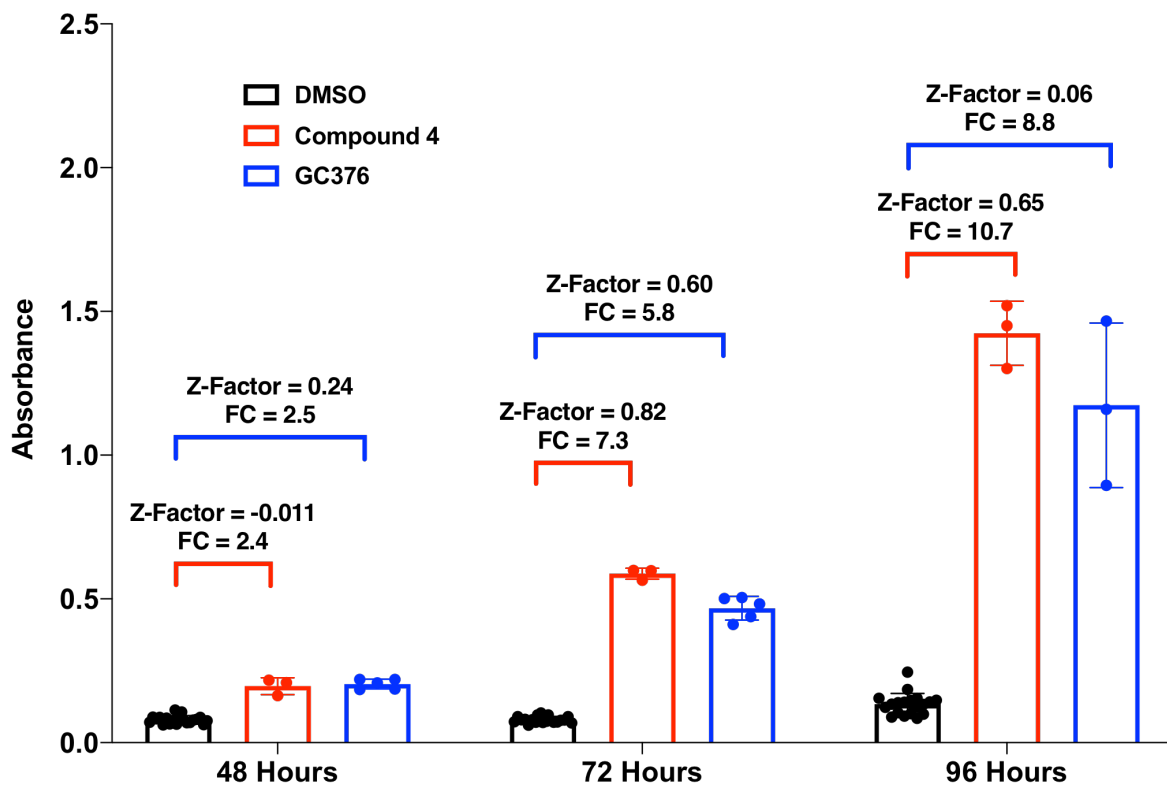


Supplementary Fig. 5. A number of other 3CLpro enzymes from different coronavirus species also show activity-dependent cytotoxicity. **a.** A phylogenetic tree of the six coronaviruses tested in this study, generated using NCBI Virus with the sequences of the ORF1ab polyprotein. The

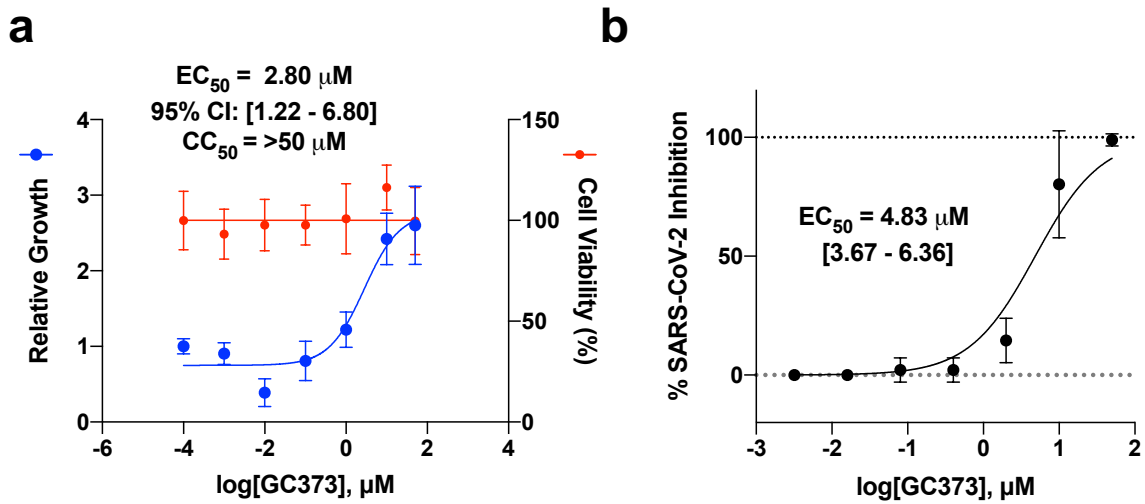
genera of each virus are shown along with the amino acid sequence similarity to the SARS-CoV-2 3CLpro calculated using the Protein BLAST tool from NCBI. **b.** Quantification of cytotoxicity upon expression of active or inactivated 3CLpro enzymes from SARS-CoV, MERS-CoV, Bat-CoV-HKU9, HCoV-NL63, and IBV in 293T cells. Data are shown as mean \pm s.d. for four technical replicates.



Supplementary Fig. 6 Optimization of screening parameters and resulting Z-factors between positive and negative control wells. Z-factor, a measure of assay quality was determined for two positive control compounds, GC376 at 50 μ M and compound 4 at 20 μ M, at different time points to identify optimal screening conditions for compounds against the SARS-CoV-2-3CLpro. The DMSO condition was conducted with 21 technical replicates randomly positioned across a 96-well plate while positive control compounds were tested at three or five technical replicates. FC = Fold Change. Data are shown as mean \pm s.d. for specified technical replicates.

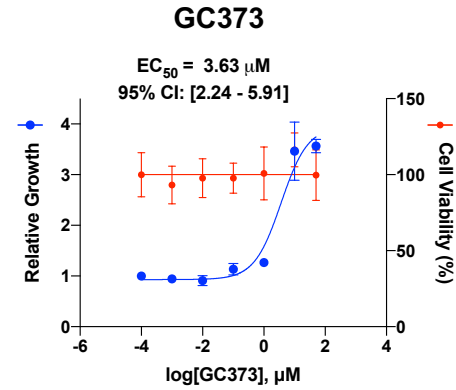
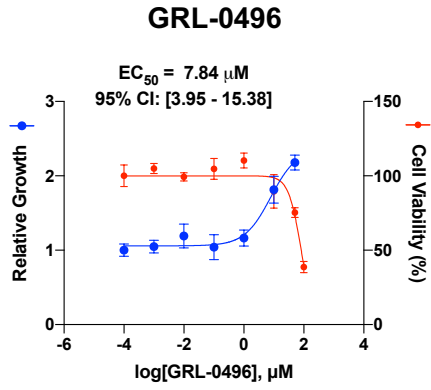


Supplementary Fig. 7. GC373 demonstrates activity against the SARS-CoV-2 3CLpro and against the SARS-CoV-2 live virus. a. Dose-response profiling and cytotoxicity determination using the transfection-based assay of GC373 against the SARS-CoV-2 3CLpro. **b.** Live virus testing of GC373 against SARS-CoV-2. EC₅₀ values are displayed as best-fit value alongside 95% confidence interval. The live virus assay was conducted with two biological replicates, each with three technical replicates and the EC₅₀ value was derived from all replicates. CC₅₀ values are displayed as best-fit value. Data are shown as mean ± s.d. for three or four technical replicates.

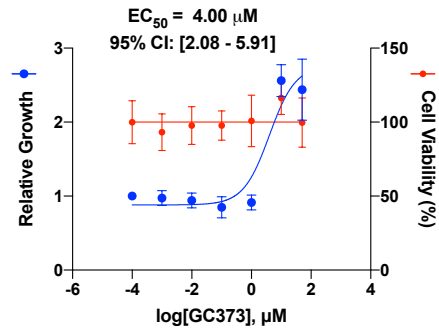
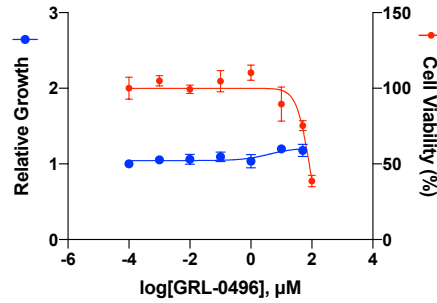


Supplementary Fig. 8. The activity of GRL-0496 and GC373 show variable efficacy and potency against the coronavirus 3CL proteases from SARS-CoV, MERS-CoV, Bat-CoV-HKU9, HCoV-NL63, and IBV. EC₅₀ values are displayed as best-fit value alongside 95% confidence interval. CC₅₀ values are displayed as best-fit value. Data are shown as mean ± s.d. for four technical replicates.

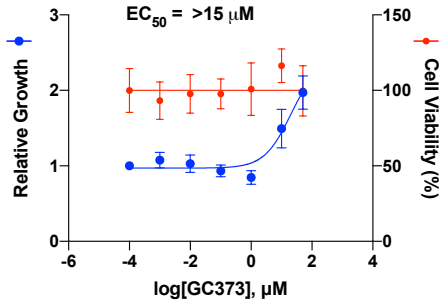
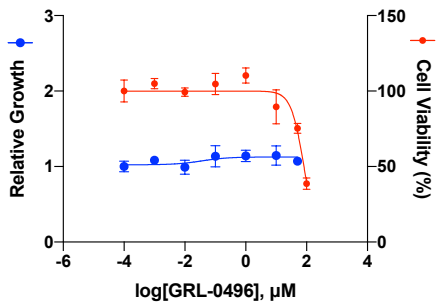
SARS-CoV 3CLpro



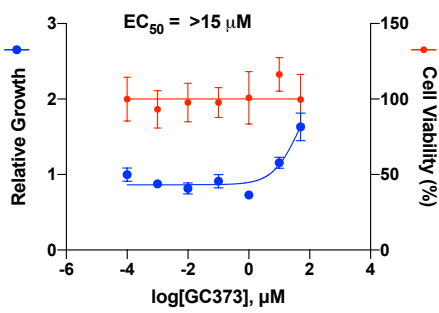
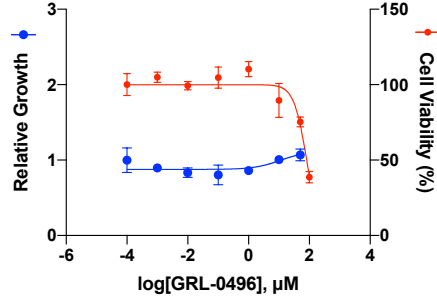
MERS-CoV 3CLpro



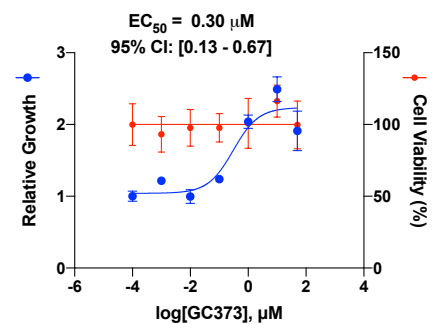
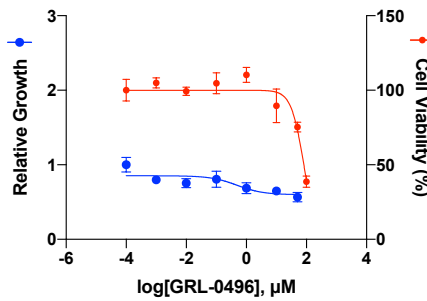
Bat-CoV-HKU9 3CLpro



HCoV-NL63 3CLpro



IBV 3CLpro



Supplementary Table 1. Selectivity Index (SI) for compounds tested with the transfection-based assay in this study.

Protease	Drug	EC₅₀ (μM)	CC₅₀ (μM)	SI (CC₅₀ /EC₅₀)
SARS-CoV-2 3CLpro	GC376	3.3	>100	>30.3
	compound 4	0.98	81	82.7
	11a	6.89	48	7
	GRL-0496	5.05	81	16
	GC373	2.8	>50	>17.9
SARS-CoV 3CLpro	GC376	5.83	>100	>17.2
	compound 4	3.17	81	25.6
	11a	5.38	48	8.9
	GRL-0496	7.84	81	10.3
	GC373	3.63	>50	>13.8
MERS-CoV 3CLpro	GC376	7.44	>100	>13.4
	compound 4	1.4	81	57.9
	GC373	4	>50	>12.5
Bat-CoV-HKU9 3CLpro	GC376	11.07	>100	>9.0
	compound 4	4.11	81	19.7
HCoV-NL63 3CLpro	compound 4	4.92	81	16.5
IBV 3CLpro	GC376	0.58	>100	>172
	compound 4	0.058	81	1396.5
	GC373	0.3	>50	>166.6

Supplementary Table 2. Compounds screened for activity against the SARS-CoV-2 3CLpro.

Absorbance	Well	Drug	Plate	Model	z-score
0.07156	A02	Omarigliptin	Plate1	SARS-CoV-2 3CLpro	0.07462451
0.03996	A03	Apoptosis Activator 2	Plate1	SARS-CoV-2 3CLpro	-3.5532747
0.06801	A04	Picolamine	Plate1	SARS-CoV-2 3CLpro	-0.3329401
0.07551	A05	Muscone	Plate1	SARS-CoV-2 3CLpro	0.52811191
0.08101	A06	2-Aminoethanethiol	Plate1	SARS-CoV-2 3CLpro	1.15955007
0.07101	A07	Dexibuprofen	Plate1	SARS-CoV-2 3CLpro	0.01148069
0.07496	A08	Glucosamine	Plate1	SARS-CoV-2 3CLpro	0.4649681
0.07141	A09	Gabexate mesylate	Plate1	SARS-CoV-2 3CLpro	0.05740347
0.09891	A10	Zalcitabine	Plate1	SARS-CoV-2 3CLpro	3.21459426
0.09016	A11	Amiloride hydrochloride	Plate1	SARS-CoV-2 3CLpro	2.21003355
0.06776	B02	Saxagliptin hydrate	Plate1	SARS-CoV-2 3CLpro	-0.3616419
0.07901	B03	Linagliptin	Plate1	SARS-CoV-2 3CLpro	0.9299362
0.07831	B04	Sitagliptin	Plate1	SARS-CoV-2 3CLpro	0.84957134
0.08006	B05	Hexylresorcinol	Plate1	SARS-CoV-2 3CLpro	1.05048348
0.06906	B06	Arbutin	Plate1	SARS-CoV-2 3CLpro	-0.2123928
0.03171	B07	Diminazene Aceturate	Plate1	SARS-CoV-2 3CLpro	-4.500432
0.06266	B08	3-Pyridylacetic acid hydrochloride	Plate1	SARS-CoV-2 3CLpro	-0.9471572
0.05386	B09	Racecadotril	Plate1	SARS-CoV-2 3CLpro	-1.9574583
0.06456	B10	Mizoribine	Plate1	SARS-CoV-2 3CLpro	-0.7290241
0.08056	B11	Sodium etidronate	Plate1	SARS-CoV-2 3CLpro	1.10788695
0.07191	C02	MAC-5576	Plate1	SARS-CoV-2 3CLpro	0.11480694
0.07666	C03	DMSO	Plate1	SARS-CoV-2 3CLpro	0.66013989
0.07206	C04	DMSO	Plate1	SARS-CoV-2 3CLpro	0.13202798
0.07451	C05	DMSO	Plate1	SARS-CoV-2 3CLpro	0.41330498
0.07591	C06	BTB07404	Plate1	SARS-CoV-2 3CLpro	0.57403469
0.06836	C07	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.2927577
0.06826	C08	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.3042384
0.07401	C09	Myrecetin	Plate1	SARS-CoV-2 3CLpro	0.35590151
0.06881	C10	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.2410946
0.08486	C11	Tipranavir	Plate1	SARS-CoV-2 3CLpro	1.60155678
0.06106	D02	DMSO	Plate1	SARS-CoV-2 3CLpro	-1.1308483
0.06566	D03	BTB07408	Plate1	SARS-CoV-2 3CLpro	-0.6027364
0.36221	D04	GC376	Plate1	SARS-CoV-2 3CLpro	33.443261
0.06851	D05	MAC-8120	Plate1	SARS-CoV-2 3CLpro	-0.2755367
0.06866	D06	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.2583156
0.07186	D07	MWP00332	Plate1	SARS-CoV-2 3CLpro	0.10906659

0.07301	D08	DMSO	Plate1	SARS-CoV-2 3CLpro	0.24109457
0.07556	D09	DMSO	Plate1	SARS-CoV-2 3CLpro	0.53385226
0.07011	D10	Rupintrivir	Plate1	SARS-CoV-2 3CLpro	-0.0918456
0.06876	D11	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.2468349
0.06221	E02	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.9988204
0.06836	E03	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.2927577
0.06486	E04	BTB07417	Plate1	SARS-CoV-2 3CLpro	-0.694582
0.07096	E05	DMSO	Plate1	SARS-CoV-2 3CLpro	0.00574035
0.06971	E06	AZV8-49F	Plate1	SARS-CoV-2 3CLpro	-0.1377683
0.06231	E07	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.9873397
0.07276	E08	MWP00508	Plate1	SARS-CoV-2 3CLpro	0.21239284
0.06846	E09	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.281277
0.06741	E10	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.4018243
0.07371	E11	MWP00333	Plate1	SARS-CoV-2 3CLpro	0.32145943
0.04971	F02	Grazoprevir	Plate1	SARS-CoV-2 3CLpro	-2.4339071
0.06991	F03	AZV8-57D	Plate1	SARS-CoV-2 3CLpro	-0.1148069
0.06831	F04	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.298498
0.06911	F05	BTB07407	Plate1	SARS-CoV-2 3CLpro	-0.2066525
0.07516	F06	DMSO	Plate1	SARS-CoV-2 3CLpro	0.48792949
0.47481	F07	CPD18-20	Plate1	SARS-CoV-2 3CLpro	46.3705222
0.07086	F08	DMSO	Plate1	SARS-CoV-2 3CLpro	-0.0057403
0.18266	F09	GRL-0496	Plate1	SARS-CoV-2 3CLpro	12.8296753
0.05571	F10	Saquinavir	Plate1	SARS-CoV-2 3CLpro	-1.7450655
0.06161	F11	DMSO	Plate1	SARS-CoV-2 3CLpro	-1.0677045
0.04941	G02	Monobenzene	Plate1	SARS-CoV-2 3CLpro	-2.4683492
0.08226	G03	Limonin	Plate1	SARS-CoV-2 3CLpro	1.30305874
0.02596	G04	Betulinic acid	Plate1	SARS-CoV-2 3CLpro	-5.1605719
0.07796	G05	PMSF	Plate1	SARS-CoV-2 3CLpro	0.80938891
0.08286	G06	Fenofibric acid	Plate1	SARS-CoV-2 3CLpro	1.37194291
0.07241	G07	Ramelteon	Plate1	SARS-CoV-2 3CLpro	0.17221041
0.05871	G08	Ritonavir	Plate1	SARS-CoV-2 3CLpro	-1.4006446
0.08216	G09	Alogliptin Benzoate	Plate1	SARS-CoV-2 3CLpro	1.29157805
0.00986	G10	Bortezomib	Plate1	SARS-CoV-2 3CLpro	-7.0089636
0.08641	G11	Acetohydroxamic acid	Plate1	SARS-CoV-2 3CLpro	1.77950754
0.07081	H02	8	Plate1	SARS-CoV-2 3CLpro	-0.0114807
0.05576	H03	Lopinavir	Plate1	SARS-CoV-2 3CLpro	-1.7393251
0.07581	H04	Penciclovir	Plate1	SARS-CoV-2 3CLpro	0.562554
0.01181	H05	AOB2796	Plate1	SARS-CoV-2 3CLpro	-6.78509
0.08421	H06	Maribavir	Plate1	SARS-CoV-2 3CLpro	1.52693227

0.08156	H07	Trelagliptin succinate	Plate1	SARS-CoV-2 3CLpro	1.22269389
0.01741	H08	MLN9708	Plate1	SARS-CoV-2 3CLpro	-6.1421712
0.07691	H09	SC514	Plate1	SARS-CoV-2 3CLpro	0.68884163
0.01011	H10	Ixazomib	Plate1	SARS-CoV-2 3CLpro	-6.9802618
0.08826	H11	Raltegravir potassium	Plate1	SARS-CoV-2 3CLpro	1.99190037
0.082225	A02	PSI6206	Plate2	SARS-CoV-2 3CLpro	0.48063475
0.069275	A03	Cilastatin	Plate2	SARS-CoV-2 3CLpro	-0.3492612
0.068975	A04	Taxifolin	Plate2	SARS-CoV-2 3CLpro	-0.3684866
0.084325	A05	Nafamostat mesylate	Plate2	SARS-CoV-2 3CLpro	0.61521247
0.047775	A06	Daclatasvir dihydrochloride	Plate2	SARS-CoV-2 3CLpro	-1.7270809
0.094525	A07	Darunavir†Ethanolate	Plate2	SARS-CoV-2 3CLpro	1.26887573
0.106675	A08	Ilomastat	Plate2	SARS-CoV-2 3CLpro	2.04750402
0.049625	A09	Elvitegravir	Plate2	SARS-CoV-2 3CLpro	-1.6085243
0.076575	A10	Dolutegravir sodium	Plate2	SARS-CoV-2 3CLpro	0.11855657
0.108725	A11	Astragaloside IV	Plate2	SARS-CoV-2 3CLpro	2.17887751
0.064175	B02	Arctigenin	Plate2	SARS-CoV-2 3CLpro	-0.6760929
0.086575	B03	Stigmasterol	Plate2	SARS-CoV-2 3CLpro	0.7594029
0.054075	B04	Nobiletin	Plate2	SARS-CoV-2 3CLpro	-1.3233477
0.005175	B05	Celastrol	Plate2	SARS-CoV-2 3CLpro	-4.4570862
0.093275	B06	Glucosamine sulfate	Plate2	SARS-CoV-2 3CLpro	1.18876994
0.068025	B07	Picoside I	Plate2	SARS-CoV-2 3CLpro	-0.429367
0.078775	B08	Alvelestat	Plate2	SARS-CoV-2 3CLpro	0.25954276
0.079225	B09	N-Ethylmaleimide	Plate2	SARS-CoV-2 3CLpro	0.28838085
0.068525	B10	DAPT	Plate2	SARS-CoV-2 3CLpro	-0.3973247
0.103975	B11	Trelagliptin	Plate2	SARS-CoV-2 3CLpro	1.87447551
0.085725	C02	Fosamprenavir	Plate2	SARS-CoV-2 3CLpro	0.70493096
0.057525	C03	DMSO	Plate2	SARS-CoV-2 3CLpro	-1.1022557
0.056875	C04	DMSO	Plate2	SARS-CoV-2 3CLpro	-1.1439107
0.060275	C05	Indinavir	Plate2	SARS-CoV-2 3CLpro	-0.9260229
0.081325	C06	DMSO	Plate2	SARS-CoV-2 3CLpro	0.42295858
0.085675	C07	DMSO	Plate2	SARS-CoV-2 3CLpro	0.70172673
0.726225	C08	CMPD18-20	Plate2	SARS-CoV-2 3CLpro	41.7511382
0.067575	C09	DMSO	Plate2	SARS-CoV-2 3CLpro	-0.4582051
0.117025	C10	SPB08384	Plate2	SARS-CoV-2 3CLpro	2.71077996
0.123825	C11	DMSO	Plate2	SARS-CoV-2 3CLpro	3.14655547
0.085025	D02	DMSO	Plate2	SARS-CoV-2 3CLpro	0.66007172
0.486725	D03	CMPD18-10	Plate2	SARS-CoV-2 3CLpro	26.4028686 8
0.074775	D04	DMSO	Plate2	SARS-CoV-2 3CLpro	0.00320423

0.075325	D05	DMSO	Plate2	SARS-CoV-2 3CLpro	0.03845078
0.088475	D06	Apigenin	Plate2	SARS-CoV-2 3CLpro	0.8811637
0.080225	D07	AZVIII-57G	Plate2	SARS-CoV-2 3CLpro	0.35246548
0.060775	D08	DMSO	Plate2	SARS-CoV-2 3CLpro	-0.8939806
0.066125	D09	SPB06613	Plate2	SARS-CoV-2 3CLpro	-0.5511278
0.074225	D10	DMSO	Plate2	SARS-CoV-2 3CLpro	-0.0320423
0.113225	D11	SPB06636	Plate2	SARS-CoV-2 3CLpro	2.46725836
0.071675	E02	AZVIII-38	Plate2	SARS-CoV-2 3CLpro	-0.1954581
0.083175	E03	DMSO	Plate2	SARS-CoV-2 3CLpro	0.54151515
0.073475	E04	AZVIII-49C	Plate2	SARS-CoV-2 3CLpro	-0.0801058
0.085225	E05	DMSO	Plate2	SARS-CoV-2 3CLpro	0.67288864
0.070925	E06	Quercetin	Plate2	SARS-CoV-2 3CLpro	-0.2435216
0.078575	E07	DMSO	Plate2	SARS-CoV-2 3CLpro	0.24672584
0.073625	E08	SPB06591	Plate2	SARS-CoV-2 3CLpro	-0.0704931
0.076475	E09	DMSO	Plate2	SARS-CoV-2 3CLpro	0.11214811
0.077875	E10	SPB06593	Plate2	SARS-CoV-2 3CLpro	0.20186659
0.117725	E11	DMSO	Plate2	SARS-CoV-2 3CLpro	2.75563921
0.074675	F02	DMSO	Plate2	SARS-CoV-2 3CLpro	-0.0032042
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0.077325	F04	DMSO	Plate2	SARS-CoV-2 3CLpro	0.16662005
0.078525	F05	Famotidine	Plate2	SARS-CoV-2 3CLpro	0.2435216
0.071325	F06	DMSO	Plate2	SARS-CoV-2 3CLpro	-0.2178878
0.412325	F07	GC376	Plate2	SARS-CoV-2 3CLpro	21.634972
0.070025	F08	DMSO	Plate2	SARS-CoV-2 3CLpro	-0.3011978
0.068675	F09	DMSO	Plate2	SARS-CoV-2 3CLpro	-0.387712
0.076275	F10	DMSO	Plate2	SARS-CoV-2 3CLpro	0.09933118
0.096375	F11	DMSO	Plate2	SARS-CoV-2 3CLpro	1.3874323
0.071175	G02	Z-VAD(OMe)-FMK	Plate2	SARS-CoV-2 3CLpro	-0.2275004
0.076225	G03	Abietic Acid	Plate2	SARS-CoV-2 3CLpro	0.09612695
0.061225	G04	Atazanavir sulfate	Plate2	SARS-CoV-2 3CLpro	-0.8651425
0.089475	G05	Abacavir	Plate2	SARS-CoV-2 3CLpro	0.94524833
0.056675	G06	Balicatib	Plate2	SARS-CoV-2 3CLpro	-1.1567276
0.011625	G07	Carfilzomib	Plate2	SARS-CoV-2 3CLpro	-4.0437403
0.054975	G08	Atazanavir	Plate2	SARS-CoV-2 3CLpro	-1.2656715
0.068275	G09	Vildagliptin	Plate2	SARS-CoV-2 3CLpro	-0.4133459
0.025775	G10	Dapivirine	Plate2	SARS-CoV-2 3CLpro	-3.1369428
0.072375	G11	SB-3CT	Plate2	SARS-CoV-2 3CLpro	-0.1505989
0.060825	H02	PD 151746	Plate2	SARS-CoV-2 3CLpro	-0.8907764
0.018775	H03	PAC1	Plate2	SARS-CoV-2 3CLpro	-3.5855352

0.073725	H04	Camostat mesilate	Plate2	SARS-CoV-2 3CLpro	-0.0640846
0.073525	H05	Efavirenz	Plate2	SARS-CoV-2 3CLpro	-0.0769016
0.088325	H06	Des(benzylpyridyl) Atazanavir	Plate2	SARS-CoV-2 3CLpro	0.87155101
0.073375	H07	LY2811376	Plate2	SARS-CoV-2 3CLpro	-0.0865143
0.013175	H08	FLI06	Plate2	SARS-CoV-2 3CLpro	-3.9444091
0.056425	H09	SRPIN340	Plate2	SARS-CoV-2 3CLpro	-1.1727488
0.096125	H10	NSC 405020	Plate2	SARS-CoV-2 3CLpro	1.37141114
0.088525	H11	Leupeptin Hemisulfate	Plate2	SARS-CoV-2 3CLpro	0.88436793
0.01024	A02	Epoxomicin	Plate3	SARS-CoV-2 3CLpro	-4.8596643
0.02879	A03	MG101	Plate3	SARS-CoV-2 3CLpro	-3.6239306
0.06649	A04	lavendustin C	Plate3	SARS-CoV-2 3CLpro	-1.1124934
0.08099	A05	BMS707035	Plate3	SARS-CoV-2 3CLpro	-0.146556
0.05509	A06	Asunaprevir	Plate3	SARS-CoV-2 3CLpro	-1.87192
0.07839	A07	Loxistatin Acid	Plate3	SARS-CoV-2 3CLpro	-0.3197586
0.00484	A08	GK921	Plate3	SARS-CoV-2 3CLpro	-5.2193927
0.06729	A09	L-685,458	Plate3	SARS-CoV-2 3CLpro	-1.0592003
0.07469	A10	Tenofovir Disoproxil Fumarate	Plate3	SARS-CoV-2 3CLpro	-0.5662392
0.02539	A11	GSK690693	Plate3	SARS-CoV-2 3CLpro	-3.8504263
0.03379	B02	Ledipasvir	Plate3	SARS-CoV-2 3CLpro	-3.2908487
0.01554	B03	ONX0914	Plate3	SARS-CoV-2 3CLpro	-4.5065975
0.06614	B04	PI1840	Plate3	SARS-CoV-2 3CLpro	-1.1358091
0.08239	B05	(+)-Isocorydine hydrochloride	Plate3	SARS-CoV-2 3CLpro	-0.0532931
0.09179	B06	UAMC 00039 dihydrochloride	Plate3	SARS-CoV-2 3CLpro	0.57290079
0.01119	B07	PE859	Plate3	SARS-CoV-2 3CLpro	-4.7963787
0.08269	B08	RO4929097	Plate3	SARS-CoV-2 3CLpro	-0.0333082
0.09519	B09	Emricasan	Plate3	SARS-CoV-2 3CLpro	0.79939646
0.07204	B10	CGS 27023A	Plate3	SARS-CoV-2 3CLpro	-0.7427725
0.08719	B11	Talabostat mesylate	Plate3	SARS-CoV-2 3CLpro	0.26646549
0.09014	C02	AZVIII-33B	Plate3	SARS-CoV-2 3CLpro	0.46298378
0.07829	C03	DMSO	Plate3	SARS-CoV-2 3CLpro	-0.3264202
0.07454	C04	MDL28170	Plate3	SARS-CoV-2 3CLpro	-0.5762316
0.08274	C05	DMSO	Plate3	SARS-CoV-2 3CLpro	-0.0299774
0.08389	C06	DMSO	Plate3	SARS-CoV-2 3CLpro	0.04663146
0.09039	C07	AZVIII-44H	Plate3	SARS-CoV-2 3CLpro	0.47963787
0.08804	C08	DMSO	Plate3	SARS-CoV-2 3CLpro	0.3230894
0.08794	C09	DMSO	Plate3	SARS-CoV-2 3CLpro	0.31642776
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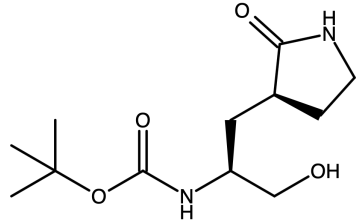
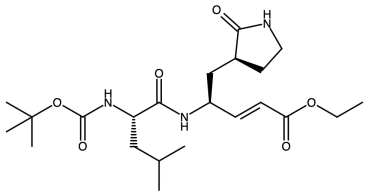
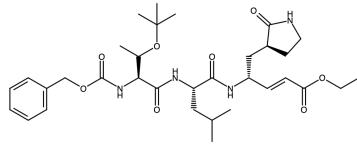
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0.08329	D02	DMSO	Plate3	SARS-CoV-2 3CLpro	0.00666164
0.07209	D03	Bicailein	Plate3	SARS-CoV-2 3CLpro	-0.7394417
0.50684	D04	CMPD18-20	Plate3	SARS-CoV-2 3CLpro	28.2220257
0.23874	D05	GC373	Plate3	SARS-CoV-2 3CLpro	10.3621766
0.07824	D06	DMSO	Plate3	SARS-CoV-2 3CLpro	-0.329751
0.08409	D07	DMSO	Plate3	SARS-CoV-2 3CLpro	0.05995473
0.10644	D08	AZVIII-41A	Plate3	SARS-CoV-2 3CLpro	1.54883063
0.44099	D09	GC376	Plate3	SARS-CoV-2 3CLpro	23.8353377
0.09614	D10	DMSO	Plate3	SARS-CoV-2 3CLpro	0.86268201
0.04954	D11	MWP00709	Plate3	SARS-CoV-2 3CLpro	-2.2416409
0.02289	E02	NT 1-32	Plate3	SARS-CoV-2 3CLpro	-4.0169672
0.09329	E03	DMSO	Plate3	SARS-CoV-2 3CLpro	0.67282535
0.08949	E04	GRL0617	Plate3	SARS-CoV-2 3CLpro	0.41968314
0.09009	E05	DMSO	Plate3	SARS-CoV-2 3CLpro	0.45965296
0.13364	E06	AZVIII-34D	Plate3	SARS-CoV-2 3CLpro	3.36079593
0.07969	E07	DMSO	Plate3	SARS-CoV-2 3CLpro	-0.2331573
0.08989	E08	DMSO	Plate3	SARS-CoV-2 3CLpro	0.44632969
0.09419	E09	DMSO	Plate3	SARS-CoV-2 3CLpro	0.73278008
0.10229	E10	AZVIII-30	Plate3	SARS-CoV-2 3CLpro	1.27237269
0.08209	E11	DMSO	Plate3	SARS-CoV-2 3CLpro	-0.073278
0.08309	F02	DMSO	Plate3	SARS-CoV-2 3CLpro	-0.0066616
0.08234	F03	AZVIII-37A	Plate3	SARS-CoV-2 3CLpro	-0.0566239
0.09354	F04	DMSO	Plate3	SARS-CoV-2 3CLpro	0.68947944
0.07304	F05	Betrixaban	Plate3	SARS-CoV-2 3CLpro	-0.6761562
0.08944	F06	DMSO	Plate3	SARS-CoV-2 3CLpro	0.41635232
0.08344	F07	AZVIII-43A	Plate3	SARS-CoV-2 3CLpro	0.01665409
0.00659	F08	MAC22272	Plate3	SARS-CoV-2 3CLpro	-5.102814
0.10049	F09	Amentoflavone	Plate3	SARS-CoV-2 3CLpro	1.15246322
0.09359	F10	DMSO	Plate3	SARS-CoV-2 3CLpro	0.69281026
0.09164	F11	DMSO	Plate3	SARS-CoV-2 3CLpro	0.56290834
0.02859	G02	Ledipasvir acetone	Plate3	SARS-CoV-2 3CLpro	-3.6372539
0.08679	G03	Batimastat	Plate3	SARS-CoV-2 3CLpro	0.23981894
0.03034	G04	TOFA	Plate3	SARS-CoV-2 3CLpro	-3.5206752
0.03934	G05	HZ1157	Plate3	SARS-CoV-2 3CLpro	-2.9211279
0.09814	G06	Abacavir sulfate	Plate3	SARS-CoV-2 3CLpro	0.99591475
0.09834	G07	Sivelestat	Plate3	SARS-CoV-2 3CLpro	1.00923803
0.05434	G08	Dasabuvir	Plate3	SARS-CoV-2 3CLpro	-1.9218823
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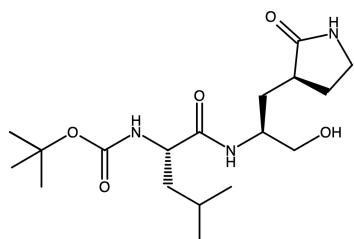
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0.07394	H02	Deoxyarbutin	Plate3	SARS-CoV-2 3CLpro	-0.6162014
0.10384	H03	2-5-dihydroxyacetophenone	Plate3	SARS-CoV-2 3CLpro	1.37562807
0.09194	H04	Oxyresveratrol	Plate3	SARS-CoV-2 3CLpro	0.58289325
0.09649	H05	Aloxistatin	Plate3	SARS-CoV-2 3CLpro	0.88599774
0.11434	H06	Fostemsavir	Plate3	SARS-CoV-2 3CLpro	2.07509997
0.07149	H07	Tasisulam	Plate3	SARS-CoV-2 3CLpro	-0.7794115
0.09304	H08	Semagacestat	Plate3	SARS-CoV-2 3CLpro	0.65617126
0.07974	H09	Triciribine	Plate3	SARS-CoV-2 3CLpro	-0.2298265
0.09534	H10	IMR-1A	Plate3	SARS-CoV-2 3CLpro	0.80938891
0.09124	H11	IMR1	Plate3	SARS-CoV-2 3CLpro	0.53626179
0.12075	A02	Z-IETD-FMK	Plate4	SARS-CoV-2 3CLpro	3.10166071
0.1	A03	VR23	Plate4	SARS-CoV-2 3CLpro	1.72277566
0.08645	A04	Amprenavir	Plate4	SARS-CoV-2 3CLpro	0.82234711
0.10545	A05	AA26-9	Plate4	SARS-CoV-2 3CLpro	2.08494065
0.04395	A06	Dolutegravir	Plate4	SARS-CoV-2 3CLpro	-2.0018753
0.0624	A07	Lomibuvir	Plate4	SARS-CoV-2 3CLpro	-0.7758305
0.05675	A08	Ginsenoside Rh2	Plate4	SARS-CoV-2 3CLpro	-1.151286
0.08095	A09	UK371804	Plate4	SARS-CoV-2 3CLpro	0.45685951
0.02685	A10	CA-074 methyl ester	Plate4	SARS-CoV-2 3CLpro	-3.1382095
0.0603	A11	ML281	Plate4	SARS-CoV-2 3CLpro	-0.9153803
0.1165	B02	CP 640186	Plate4	SARS-CoV-2 3CLpro	2.81923847
0.10795	B03	Hydroumbellic acid	Plate4	SARS-CoV-2 3CLpro	2.25107138
0.084	B04	Ethyl gallate	Plate4	SARS-CoV-2 3CLpro	0.65953899
0.0811	B05	Senegenin	Plate4	SARS-CoV-2 3CLpro	0.46682735
0.0767	B06	lithospermic acid	Plate4	SARS-CoV-2 3CLpro	0.17443727
0.0637	B07	Dibenzazepine	Plate4	SARS-CoV-2 3CLpro	-0.6894425
0.0658	B08	LY411575	Plate4	SARS-CoV-2 3CLpro	-0.5498927
0.0668	B09	Paritaprevir	Plate4	SARS-CoV-2 3CLpro	-0.4834404
0.06765	B10	Sofosbuvir	Plate4	SARS-CoV-2 3CLpro	-0.426956
0.0935	B11	Crenigacestat	Plate4	SARS-CoV-2 3CLpro	1.29083576
0.11605	C02	Avagacestat	Plate4	SARS-CoV-2 3CLpro	2.78933494
0.1044	C03	Stearic acid	Plate4	SARS-CoV-2 3CLpro	2.01516574
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0.5042	C05	CMPD18-20	Plate4	SARS-CoV-2 3CLpro	28.5827919
0.0761	C06	DMSO	Plate4	SARS-CoV-2 3CLpro	0.13456589

0.0685	C07	AZVIII-42	Plate4	SARS-CoV-2 3CLpro	-0.3704715
0.0781	C08	DMSO	Plate4	SARS-CoV-2 3CLpro	0.26747047
0.07245	C09	DMSO	Plate4	SARS-CoV-2 3CLpro	-0.107985
0.07745	C10	CC42746	Plate4	SARS-CoV-2 3CLpro	0.22427648
0.07475	C11	DMSO	Plate4	SARS-CoV-2 3CLpro	0.0448553
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0.07965	D03	BTB07789	Plate4	SARS-CoV-2 3CLpro	0.37047153
0.41755	D04	GC376	Plate4	SARS-CoV-2 3CLpro	22.8247009
0.0346	D05	AZVIII-40A	Plate4	SARS-CoV-2 3CLpro	-2.6232042
0.04545	D06	BTB07420	Plate4	SARS-CoV-2 3CLpro	-1.9021968
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0.07115	D08	DMSO	Plate4	SARS-CoV-2 3CLpro	-0.194373
0.0744	D09	AZVIII-44E	Plate4	SARS-CoV-2 3CLpro	0.021597
0.0888	D10	DMSO	Plate4	SARS-CoV-2 3CLpro	0.97850999
0.0955	D11	MWP00710	Plate4	SARS-CoV-2 3CLpro	1.42374035
0.1017	E02	BTB07421	Plate4	SARS-CoV-2 3CLpro	1.83574456
0.09715	E03	DMSO	Plate4	SARS-CoV-2 3CLpro	1.53338663
0.0795	E04	MAC-30731	Plate4	SARS-CoV-2 3CLpro	0.36050368
0.08255	E05	DMSO	Plate4	SARS-CoV-2 3CLpro	0.56318317
0.1028	E06	NT 1-24	Plate4	SARS-CoV-2 3CLpro	1.90884208
0.0716	E07	DMSO	Plate4	SARS-CoV-2 3CLpro	-0.1644694
0.07325	E08	AZVIII-44D	Plate4	SARS-CoV-2 3CLpro	-0.0548231
0.0693	E09	DMSO	Plate4	SARS-CoV-2 3CLpro	-0.3173097
0.07195	E10	DMSO	Plate4	SARS-CoV-2 3CLpro	-0.1412111
0.0803	E11	DMSO	Plate4	SARS-CoV-2 3CLpro	0.41366552
0.0946	F02	DMSO	Plate4	SARS-CoV-2 3CLpro	1.36393329
0.09095	F03	AZVIII-44B	Plate4	SARS-CoV-2 3CLpro	1.12138242
0.07375	F04	DMSO	Plate4	SARS-CoV-2 3CLpro	-0.021597
0.0791	F05	NT 1-21	Plate4	SARS-CoV-2 3CLpro	0.33392277
0.0642	F06	DMSO	Plate4	SARS-CoV-2 3CLpro	-0.6562164
0.076	F07	SCR00533	Plate4	SARS-CoV-2 3CLpro	0.12792066
0.07345	F08	DMSO	Plate4	SARS-CoV-2 3CLpro	-0.0415327
0.05335	F09	Glecaprevir	Plate4	SARS-CoV-2 3CLpro	-1.3772237
0.0681	F10	SEW03089	Plate4	SARS-CoV-2 3CLpro	-0.3970524
0.07905	F11	DMSO	Plate4	SARS-CoV-2 3CLpro	0.33060015
0.0656	G02	Doravirine	Plate4	SARS-CoV-2 3CLpro	-0.5631832
0.0011	G03	Delanzomib	Plate4	SARS-CoV-2 3CLpro	-4.849356
0.0675	G04	Morrisoniside	Plate4	SARS-CoV-2 3CLpro	-0.4369238
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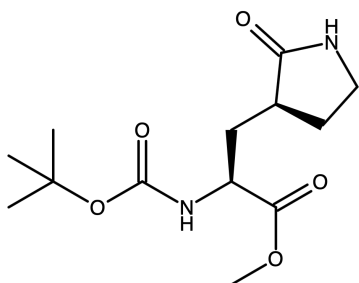
		glucoside			
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0.0358	G07	Licochalcone A	Plate4	SARS-CoV-2 3CLpro	-2.5434615
0.01645	G08	Velpatasvir	Plate4	SARS-CoV-2 3CLpro	-3.8293133
0.0393	G09	Telaprevir	Plate4	SARS-CoV-2 3CLpro	-2.3108784
0.0612	G10	Odanacatib	Plate4	SARS-CoV-2 3CLpro	-0.8555733
0.08295	G11	Darunavir	Plate4	SARS-CoV-2 3CLpro	0.58976409
0.0721	H02	Danoprevir	Plate4	SARS-CoV-2 3CLpro	-0.1312433
0.03045	H03	Nelfinavir Mesylate	Plate4	SARS-CoV-2 3CLpro	-2.8989812
0.00735	H04	Oprozomib	Plate4	SARS-CoV-2 3CLpro	-4.4340292
0.0658	H05	AEBSF hydrochloride	Plate4	SARS-CoV-2 3CLpro	-0.5498927
0.075	H06	Belnacasan	Plate4	SARS-CoV-2 3CLpro	0.06146837
0.0761	H07	Z-DEVD-FMK	Plate4	SARS-CoV-2 3CLpro	0.13456589
0.1242	H08	Z-FA-FMK	Plate4	SARS-CoV-2 3CLpro	3.33092112
0.0698	H09	Trovirdine	Plate4	SARS-CoV-2 3CLpro	-0.2840835
0.0076	H10	MG132	Plate4	SARS-CoV-2 3CLpro	-4.4174161
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Supplementary Table 3. Structures of synthesized and structurally similar compounds for this study.

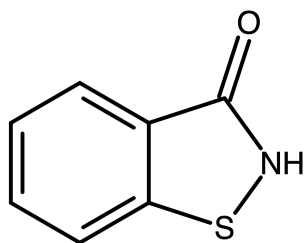
Compound	Structure
AZVIII-30	 <p>The chemical structure of AZVIII-30 consists of a central chiral carbon atom bonded to four groups: a tert-butyl ester group (-O-C(=O)-C(CH₃)₃), a hydrogen atom (H), a 2-hydroxyethyl group (-CH₂-CH₂-OH), and a 2-imidazolidinonepropyl group (-CH₂-CH₂-CH₂-N₂H₂-C=O).</p>
AZVIII-33B	 <p>The chemical structure of AZVIII-33B is a complex molecule featuring a central chiral carbon atom bonded to a tert-butyl ester group, a hydrogen atom, a 2-imidazolidinonepropyl group, and a side chain containing a secondary amide, a methyl group, and an ethyl ester group.</p>
AZVIII-34D	 <p>The chemical structure of AZVIII-34D is a highly complex molecule with multiple chiral centers. It features a tert-butyl ester group, a benzyl ester group, a secondary amide, a methyl group, and a 2-imidazolidinonepropyl group, all connected to a central chiral carbon atom.</p>



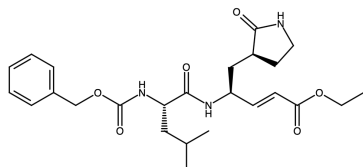
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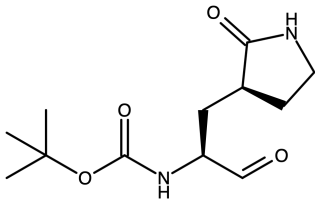
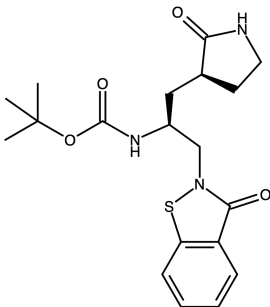
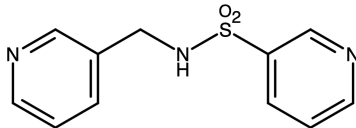
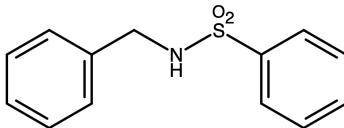
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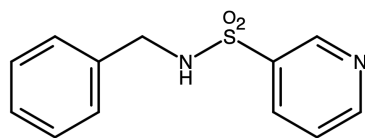


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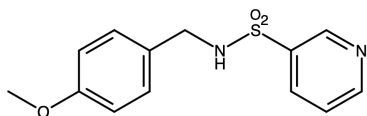


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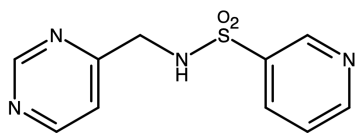
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AZVIII-43A	
AZVIII-44B	
AZVIII-44D	



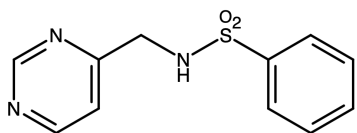
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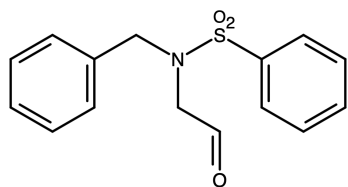
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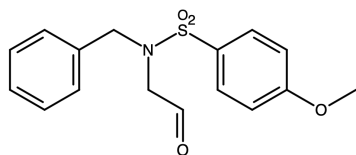
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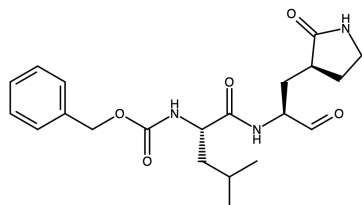
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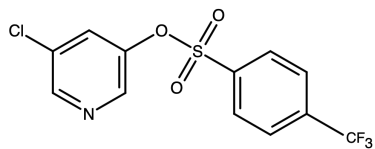
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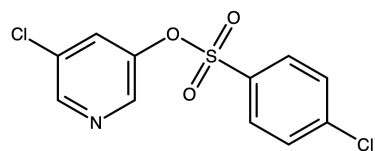
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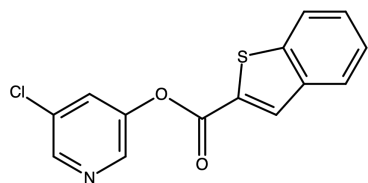
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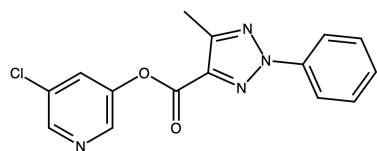
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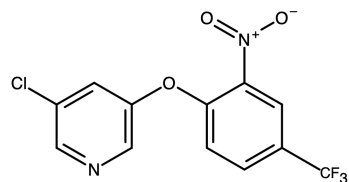
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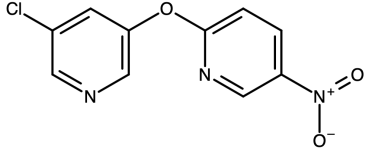
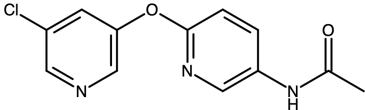
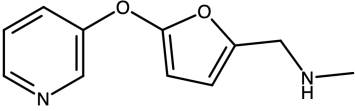
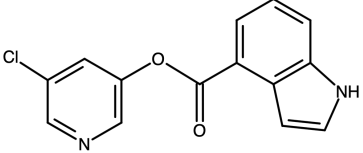
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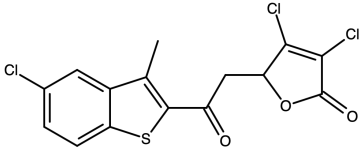
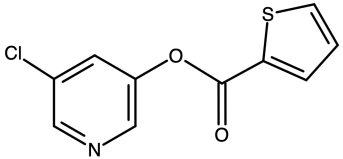
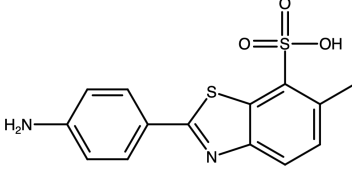
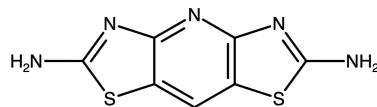


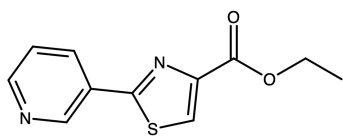
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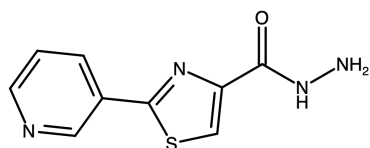
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BTB07421	 <p>Chemical structure of BTB07421: 4-(3-chloropyridin-2-yloxy)pyridin-2-yl nitro. It consists of a pyridine ring with a chlorine atom at the 3-position and an oxygen atom at the 2-position, which is linked to the 4-position of another pyridine ring. This second pyridine ring has a nitro group (-NO₂) at the 2-position.</p>
BTB07789	 <p>Chemical structure of BTB07789: 4-(3-chloropyridin-2-yloxy)pyridin-2-yl acetamide. It features a pyridine ring with a chlorine atom at the 3-position and an oxygen atom at the 2-position, which is linked to the 4-position of another pyridine ring. This second pyridine ring has an acetamide group (-NHCOCH₃) at the 2-position.</p>
CC42746	 <p>Chemical structure of CC42746: 4-(3-pyridin-2-yloxy)furan-2-yl N,N-dimethylmethanamine. It consists of a pyridine ring with an oxygen atom at the 2-position, which is linked to the 4-position of a furan ring. The furan ring has an N,N-dimethylmethanamine group (-CH₂N(CH₃)₂) at the 2-position.</p>
GRL-0496	 <p>Chemical structure of GRL-0496: 4-(3-chloropyridin-2-yloxy)indole-3-carboxamide. It features a pyridine ring with a chlorine atom at the 3-position and an oxygen atom at the 2-position, which is linked to the 4-position of an indole ring. The indole ring has a carboxamide group (-CONH₂) at the 3-position.</p>

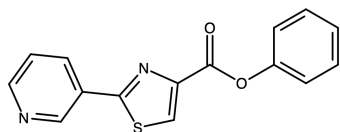
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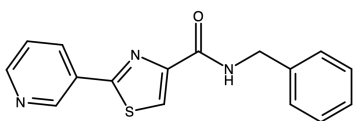
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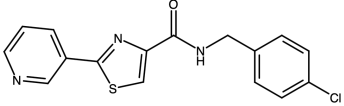
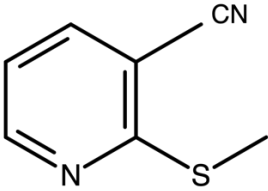
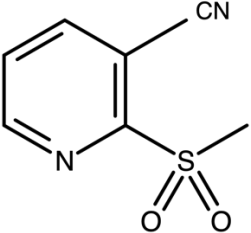
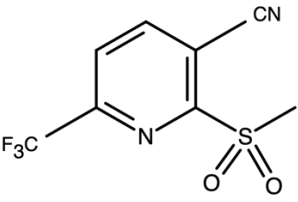
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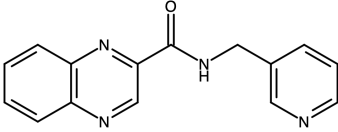
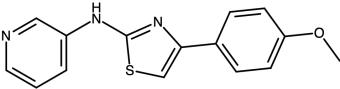
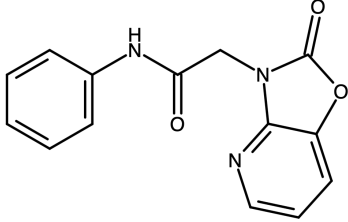
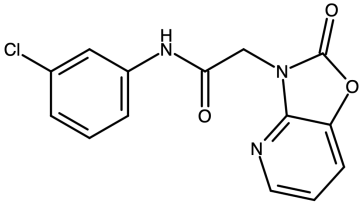


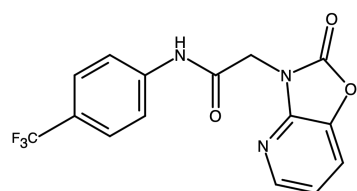
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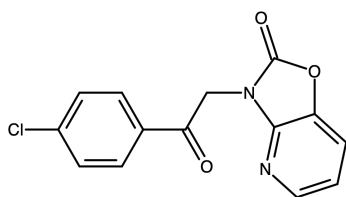
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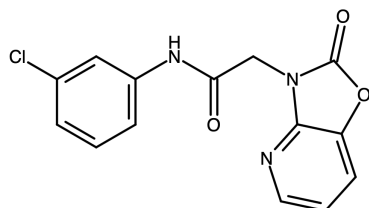
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SPB06613



SPB06636



SPB08384

Supplementary Table 4. DNA sequences of proteases used in this study

Protease	Sequence
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