Supplementary Materials

Identification of a Papain-Like Protease Inhibitor with Potential for Repurposing in Combination with an M^{pro} Protease Inhibitor for Treatment of SARS-CoV-2

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Supplementary Table

Compound name	CAS	MW	Well#	Pharmacological Class/Activity	Source	Cat #
Abemaciclib	1231929-97-7	540.68	1	CDK inhibitor	1 Plus Chem	1P000KLY
Aclidinium bromide	320345-99-1	564.6	2	Muscarinic antagonist	Cayman	20699
Alcaftadine	147084-10-4	307.4	3	H1 receptor antagonist	Cayman	21290
Avanafil	330784-47-9	483.96	4	PDE5 inhibitor	AK Scientific	Z5510
Axitinib	319460-85-0	386.5	5	Tyrosine kinase inhibitor	Cayman	13813
AZD-5423	1034148-04-3	430.53	6	Non-steroidal glucocorticoid	MCE	HY-108243
Bazedoxifene	198481-32-2	469.66	7	Selective estrogen receptor modulator (SERM)	MCE	HY-A0031
Berbamine	478-61-5	392.49	8	Calcium channel blocker.	AK Scientific	J98904
Betrixaban	330942-05-7	451.91	9	Factor Xa inhibitor	Sigma	SML2845
Bortezomib	179324-69-7	475.57	10	Proteosome inhibitor	1 Plus Chem	1P0027E4
Brigatinib	1197953-54-0	584.09	11	ALK inhibitor	MCE	HY-12857
Budesonide	51333-22-3	470.6	12	Corticosteroid	1 Plus Chem	1P00DEL8
Canagliflozin	842133-18-0	444.52	13	sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor	AKScientific	J53622
Capmatinib	1029712-80-8	412.42	14	c-Met kinase inhibitor	MCE	HY-13404
Cisclesonide	126544-47-6	506.59	15	Glucocorticoid	1 Plus Chem	1P007307
Cobicistat	1004316-88-4	776.04	16	CYP3A inhibitor	Sigma	ADV465750862
Dasatinib	302962-49-8	488.01	17	Tyrosine kinase inhibitor	Tocris	6793
Dithiobis(benzothiazole)	120-78-5	332.49	18	Food additive	Sigma	D218154
Diosmin	520-27-4	345.42	19	Glycosylated flavonoid	1 Plus Chem	1P00IKXD
Disulfiram	97-77-8	296.54	20	Acetaldehyde dehydrogenase inhibitor	Tocris	3807

E-64	66701-25-5	513.5	21	Cysteine protease inhibitor	1 Plus Chem	1P0037A9
Ebastine	90729-43-4	610.52	22	H1 receptor antagonist	1 Plus Chem	1P003QDK
Eltrombopag	496775-61-2	442.5	23	Thrombopoietin receptor agonist	Cayman	13247
Encorafenib	1269440-17-6	540.01	24	BRAF inhibitor	MCE	HY-15605
Entrectinib	1108743-60-7	560.6	25	Tyrosine kinase inhibitor	Cayman	19476
Ertuglifozin	1210344-57-2	436.88	26	Sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor	MCE	HY-15461
Esomeprarzole	119141-88-7	357.41	27	Proton pump inhibitor	1 Plus Chem	1P0078EN
Ezetimibe	163222-33-1	522.57	28	Cholesterol lowering	1 Plus Chem	1P001UD4
Fluspirilene	1841-19-6	441.54	29	Antipsychotic	AK Scientific	SYN5406
Fluticasone	90566-53-3	409.43	30	Corticosteroid	MCE	HY-15234
Fursultiamine	804-30-8	398.54	31	Vitamin B1 derrivative	AKScientific	M514
Gluiquidone	33342-05-1	487.45	32	Pottasium channel antagonist	1 Plus Chem	1P0035FH
GRL0617	1093070-16-6	304.39	33	PLpro inhibitor	Tocris	7280
Indoprofen	31842-01-0	281.31	34	Nonsteroidal anti-inflammatory	1 Plus Chem	1P003FB4
Ipratropium	22254-24-6	412.37	35	Anticholinergic	Tocris	O692
Ivacaftor	873054-44-5	527.63	36	CFTR activator	1 Plus Chem	1P0039Q3
Ivermectin	70288-86-7	608.54	37	Antiparisitic	1 Plus Chem	1P00ICI6
Lansoprazole	103577-45-3	369.36	38	Proton-pump inhibitor	Sigma	L8533
Lapatinib	231277-92-2	581.06	39	Tyrosine kinase inhibitor	Tocris	6811
Loperamide	53179-11-6	477.05	40	Antidiarrheal	AK Scientific	C598
Lumacaftor	936727-05-8	452.41	41	Protein chaperone	1 Plus Chem	1P00379M
Lusutrombopag	1110766-97-6	516.6	42	Thrombopoietin receptor agonist	1 Plus Chem	1P0090BL

Montelukast	158966-92-8	575.68	43	leukotriene receptor antagonists (LTRAs)	AvaChem Scientific.	2041A
Omeprazole	73590-58-6	875.09	44	Proton-pump inhibitor	1 Plus Chem	1P003TY2
Oxitropium bromide	30286-75-0	412.32	45	Anticholinergic	Sigma	Y0000709
Pantoprazole	718635-09-7	405.35	46	Proton pump inhibitor	Sigma	P0021
Rabeprazole	117976-90-6	381.42	47	Proton-pump inhibitor	Sigma	SML0476
Roflumilast	162401-32-3	403.21	48	PDE4 inhibitor	Tocris	6641
Rutin	153-18-4	472.42	49	Bioflavonoid	1 Plus Chem	1P00HYK6
Salbutamol	18559-94-9	239.31	50	β2 adrenergic receptor agonist	Sigma	S8260
Siponimod	1230487-00-9	442.5	51	Sphingosine-1-phosphate receptor modulator	1 Plus Chem	1P009D0W
Ticagrelor	274693-27-5	591.55	52	P2Y12 receptor antagonist	1 Plus Chem	1P00I5O1
Tiotropium bromide	136310-93-5	472.42	53	Muscarinic antagonist	AKScientific	A626
TPO agonist 1	1033040-23-1	438	54	Thrombopoietin (TPO) agonist	MCE	HY-100380
Troglitazone	97322-87-7	386.44	55	Antihyperglycemic agent	1 Plus Chem	1P00JO1Y
Umeclidinium Bromide	869113-09-7	508.5	56	Muscarinic antagonist	AKScientific	4140AH
Voxelotor	1446321-46-5	337.4	57	Hemoglobin polymerization inhibitor	Cayman	23933
Zafirlukast	107753-78-6	598.66	58	Leukotriene receptor antagonists (LTRAs)	1 Plus Chem	1P007EAT

Table S1: The 58-compound custom library screened for PL^{pro} inhibition activity.

Supplementary Figures

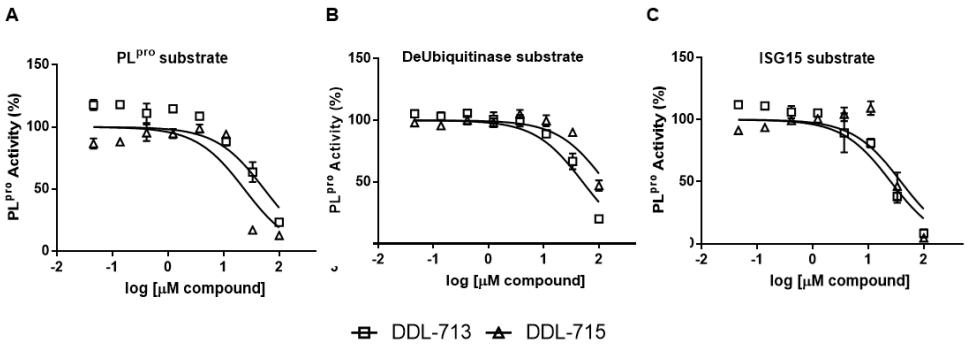

Figure S1: DDL-713 and DDL-715 dose-response in PL^{pro}, deubiquitinase, and ISG15 assays. The IC_{50} (μM) for the (A) PL^{pro}, (B) deubiquitinase, and (C) ISG15 assays for DDL-713 and DDL-715 are 54, 51, and 26; and 24, >100, and 39, respectively. The legend in (C) applies to all panels.

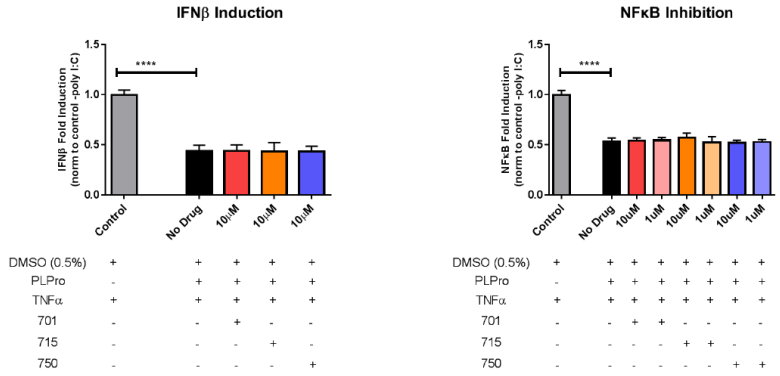

Figure S2: A) The IFN- β induction assay B) The NFkB assay. Compounds were tested at the concentrations listed above (y-axis) and as described in Methods.

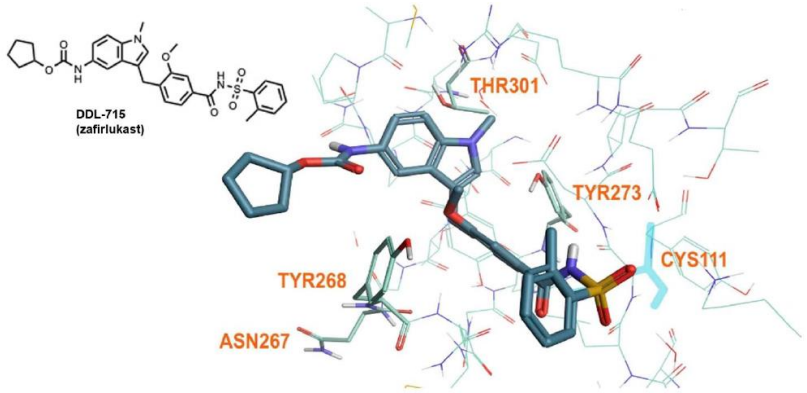

Figure S3: Docking of DDL-715 (zafirlukast) using the crystal structure of the PL^{pro} inhibitor GRL-0617 with the SARS-CoV-2 PL^{pro} (PDB ID: 7CMD).

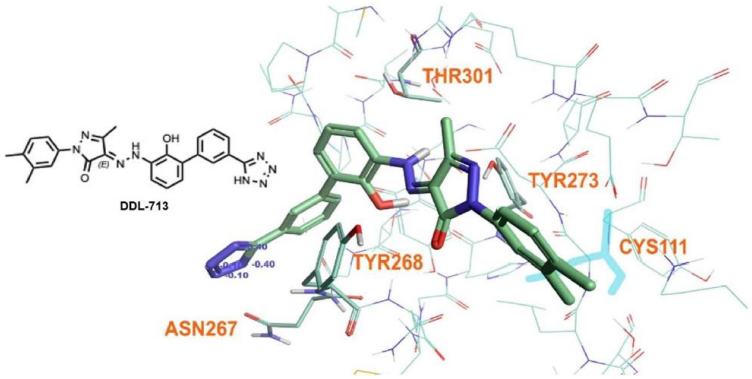

Figure S4: Docking of DDL-713 (TPO-agonist-1) using the crystal structure of the PL^{pro} inhibitor GRL-0617 with the SARS-CoV-2 PL^{pro} (PDB ID: 7CMD).

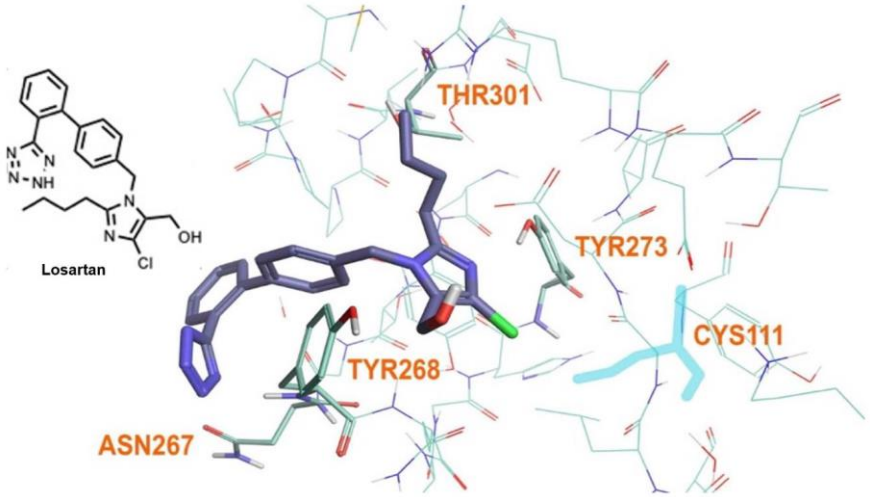

Figure S5: Docking of losartan using the crystal structure of the PL^{pro} inhibitor GRL-0617 with the SARS-CoV-2 PL^{pro} (PDB ID: 7CMD).

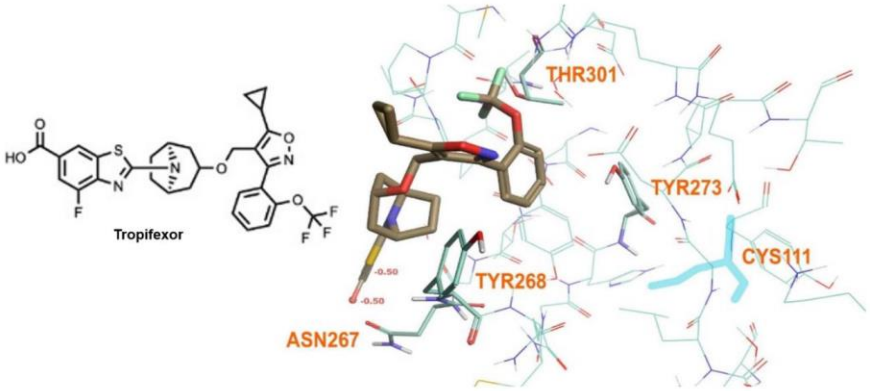

Figure S6: Docking of tropifexor using the crystal structure of the PL^{pro} inhibitor GRL-0617 with the SARS-CoV-2 PL^{pro} (PDB ID: 7CMD).