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Review article

Therapeutic strategies for COVID-19: progress and lessons learned

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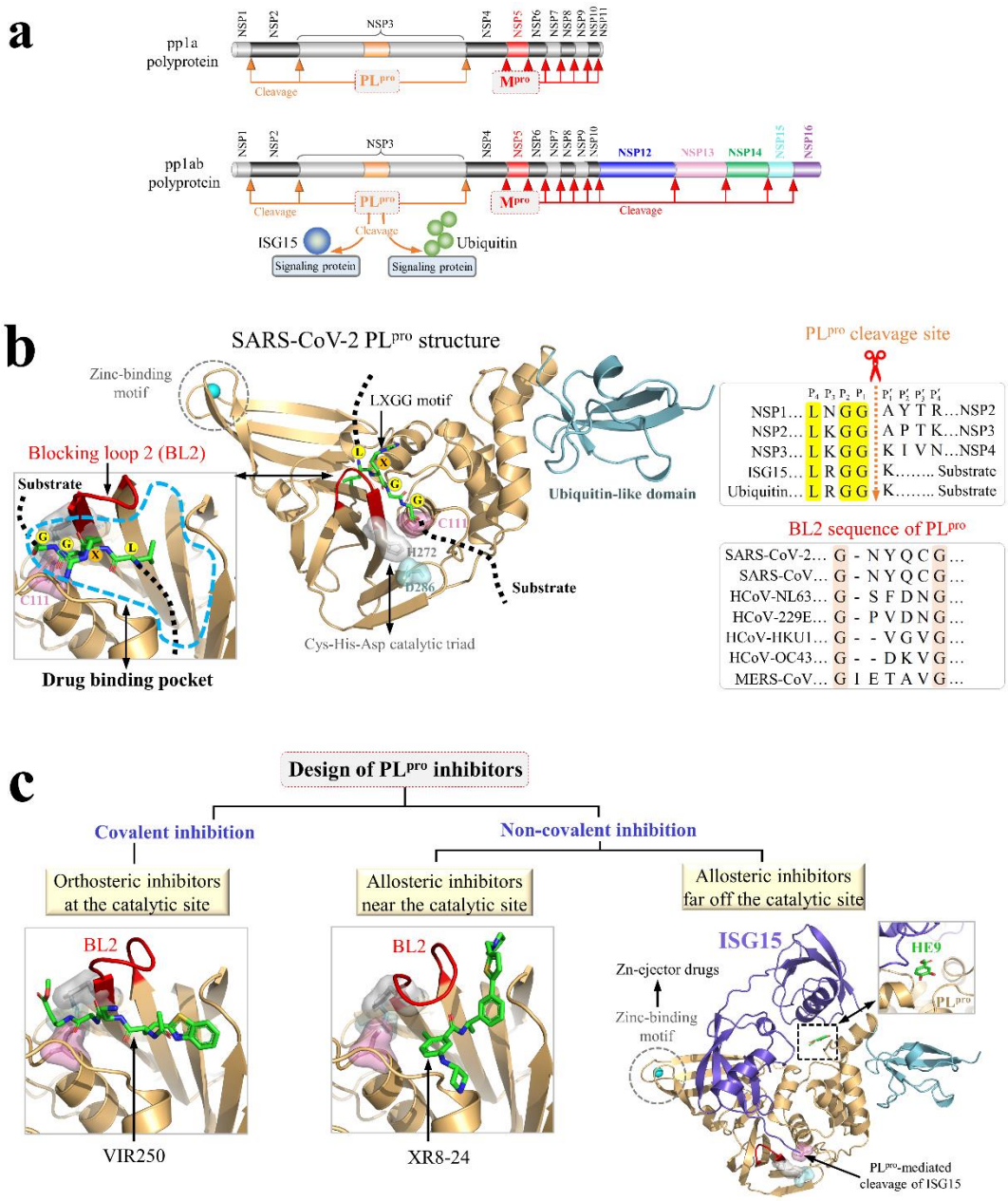

Fig. S1 | SARS-CoV-2 papain-like protease and its drug-binding pocket

a, Cleavage sites of papain-like protease (PL^{pro}) and main protease (M^{pro}) in the pp1a and pp1ab polyproteins. PL^{pro} also cleaves the C-terminal tails of ISG15 and ubiquitin to remove them from signaling proteins, thus suppressing innate immune responses [1].

b, Protein structure of SARS-CoV-2 PL^{pro} (PDB: 7RBS). The substrate motif LRGG is located at the active site with the catalytic triad (Cys111−His272−Asp286). The structure of blocking loop 2 (BL2) is visualized in red. PL^{pro} cleavage site sequences and BL2 sequences from reference genomes are shown in boxes on the right.

c, Three classes of PL^{pro} inhibitors and drug-binding pockets of VIR250 (PDB: 6WUU), XR8-24 (PDB: 7LBS), HE9 (PDB: 7OFU). HE9 targets an allosteric pocket to block

binding of PL^{pro} with ISG15 [2].

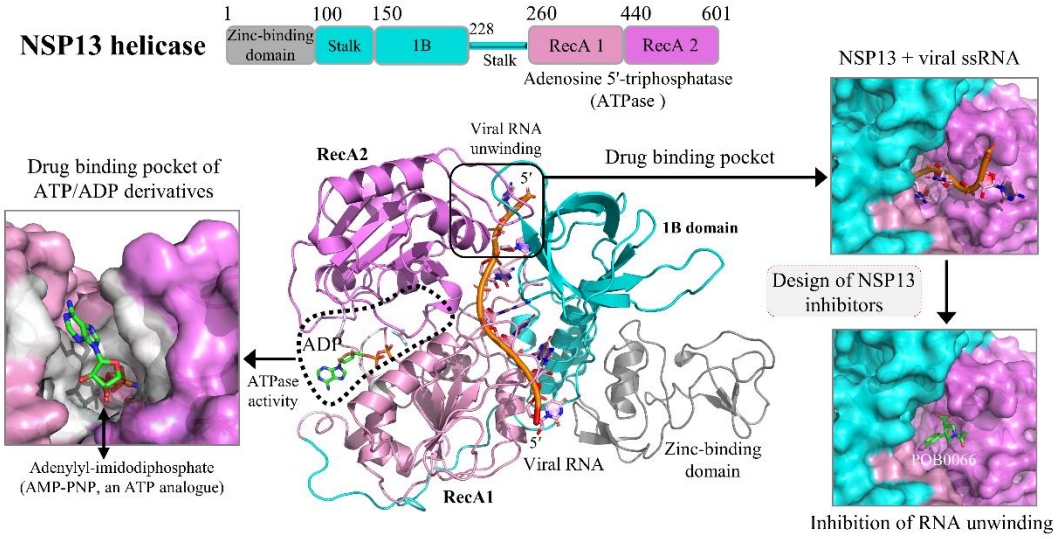

Fig. S2 | Structures of NSP13 and its drug-binding pockets

Functional domains of NSP13 helicase (PDB: 7RDY). One drug-binding pocket is located within the ATP/ADP−binding site where adenylyl-imidodiphosphate, a nonhydrolyzable ATP analogue, blocks the ATP/ADP−binding site (PDB: 7NN0). The other is located within the RNA-binding site, where the experimental inhibitor POB0066 blocks the entry of viral ssRNA (PDB: 5RMM).

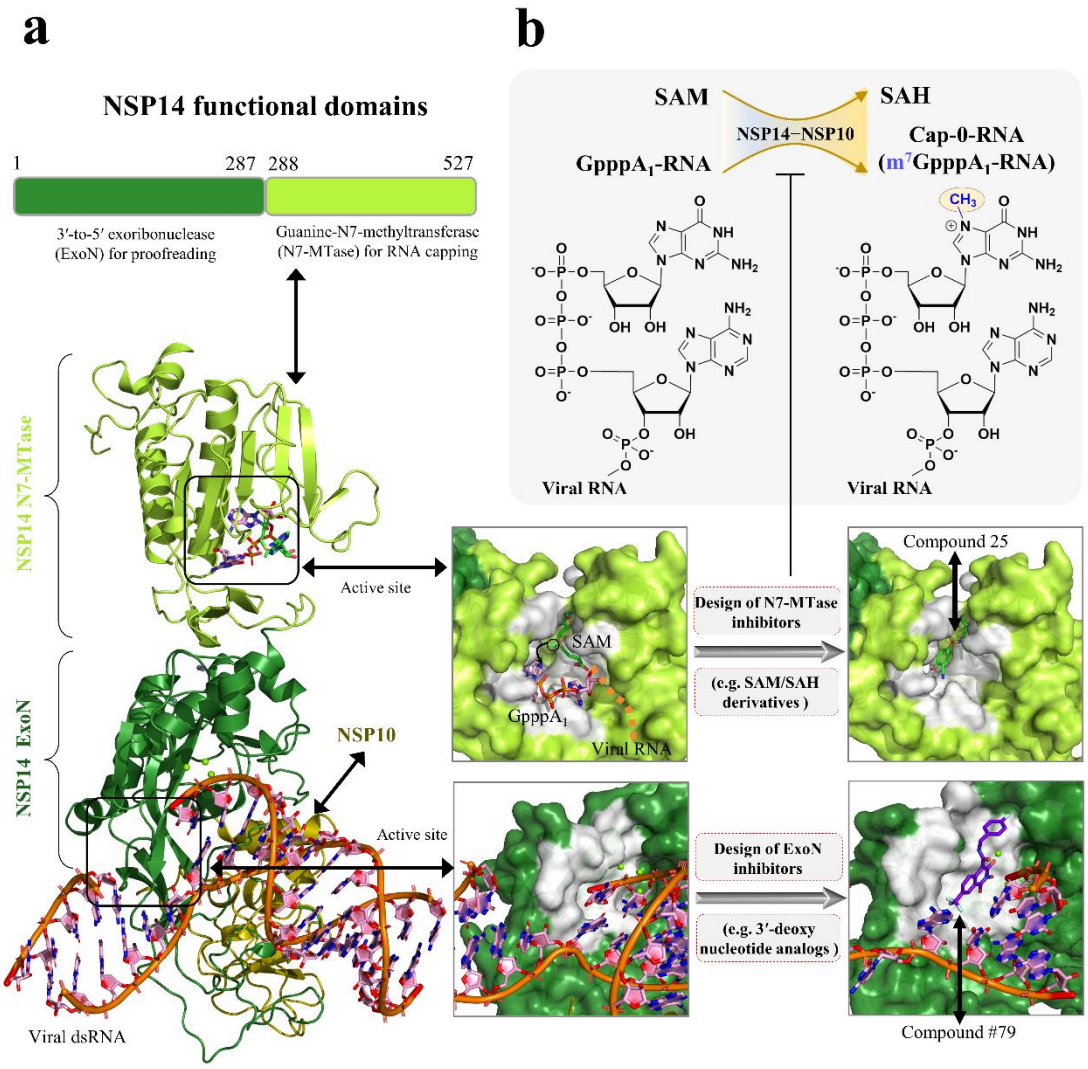

Fig. S3 | Structures of NSP14 and its drug-binding pockets

a, NSP14 functional domains. NSP14/NSP10 is visualized in complex with viral dsRNA (PDB: 7N0D), $GpppA_1$ and SAM (modified from PDB: 5C8S). Two drug-binding pockets are located within the catalytic sites of exoribonuclease and guanine-N7-methyltransferase domains. The N7-MTase inhibitor compound 25 [3] and the ExoN inhibitor compound #79 [4] are highlighted. We thank Dr. Andras Zeke from the New York University for his creation on the subfigure of NSP14 plus compound #79; Dr. Rostom Ahmed-Belkacem from the University of Montpellier for sharing the PDB file of NSP14 in complex with compound 25.

b, NSP14 methyltransferase transfers the methyl group from S-adenosyl methionine (SAM) to its substrate viral $GpppA_1$-RNA, producing m^7GpppA_1-RNA during viral RNA capping (see all processes in **Figure 5b**).

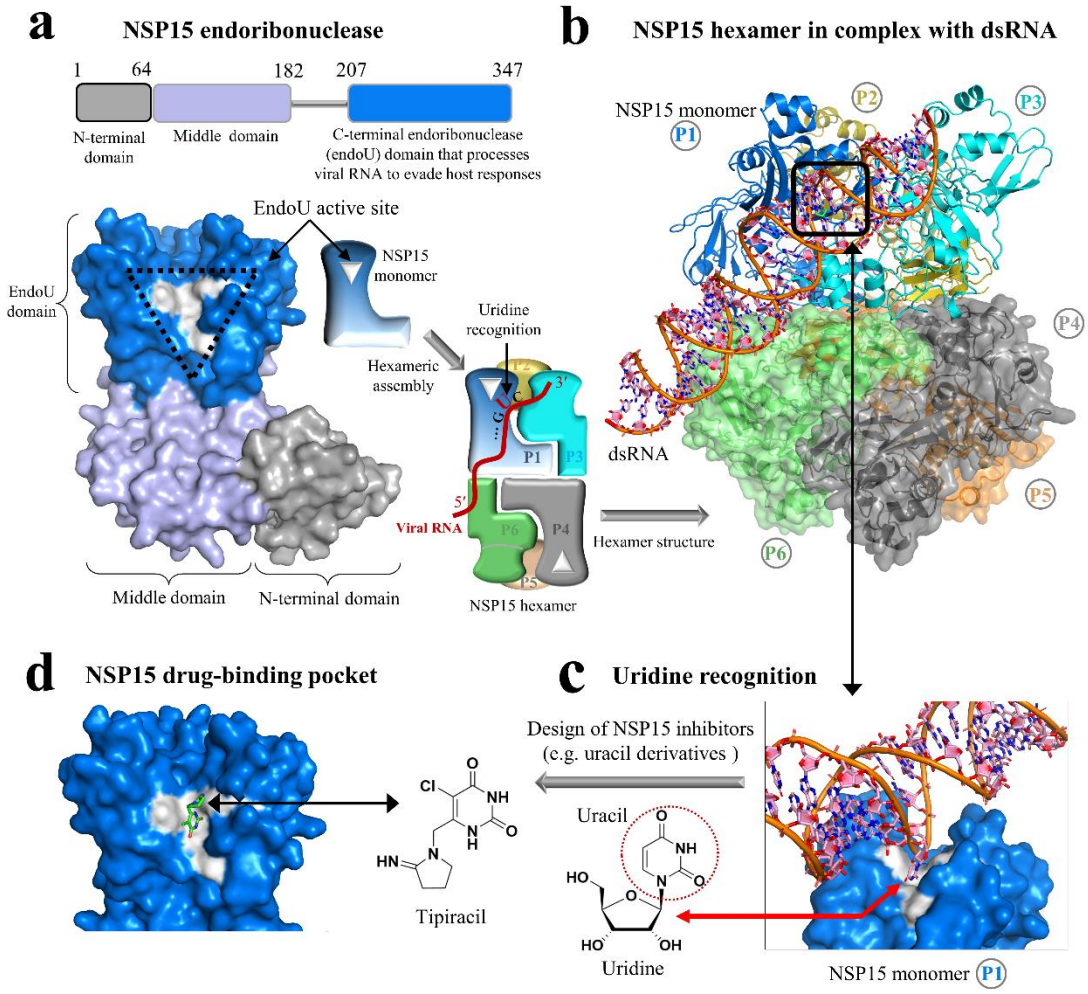

Fig. S4 | Structures of NSP15 and its drug-binding pockets

a, Functional domains of the NSP15 monomer consist of the N-terminal domain, the middle domain, and the C-terminal endoribonuclease (endoU) domain. The NSP15 catalytic site is located within the endoU domain.

b, Six NSP15 monomers form a hexamer (PDB: 7TQV) that recognizes uridine and cleaves the polyuridine tail from double-stranded or single-stranded viral RNA.

c, One subunit of the NSP15 hexamer targets the uridine of double-stranded RNA (PDB: 7TQV).

d, NSP15 drug-binding pocket blocked by a uracil derivative called tipiracil (PDB: 6WXC).

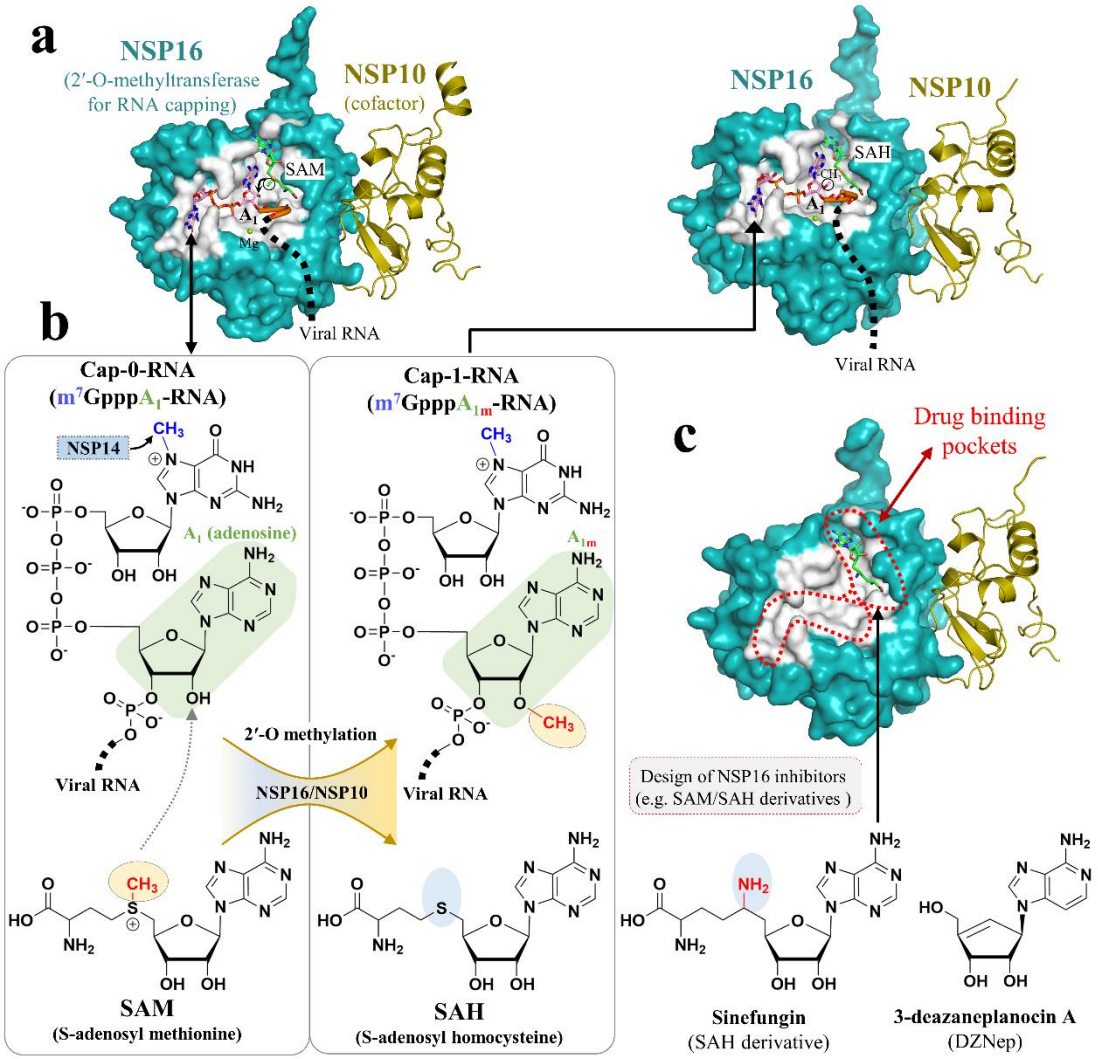

Fig. S5 | Structures of NSP16/NSP10 and its drug-binding pockets

a, NSP16 2′-O-methyltransferase and its activator NSP10 form a heterodimer complex to efficiently convert viral RNA from the Cap-0-RNA to the Cap-1-RNA configuration. SAM (PDB: 7JYY) and SAH (PDB: 7L6T) within the catalytic site are shown.

b, Catalytic site of NSP16 methylates the ribose 2′-O of the first nucleotide (usually adenosine) in nascent SARS-CoV-2 RNA by transferring the methyl group from S-adenosyl methionine (SAM) to the substrate Cap-0-RNA [5].

c, Drug-binding pockets within the catalytic site of NSP16. Sinefungin mimics the SAM structure to competitively block 2′-O methylation of viral RNA capping (PDB: 6YZ1).

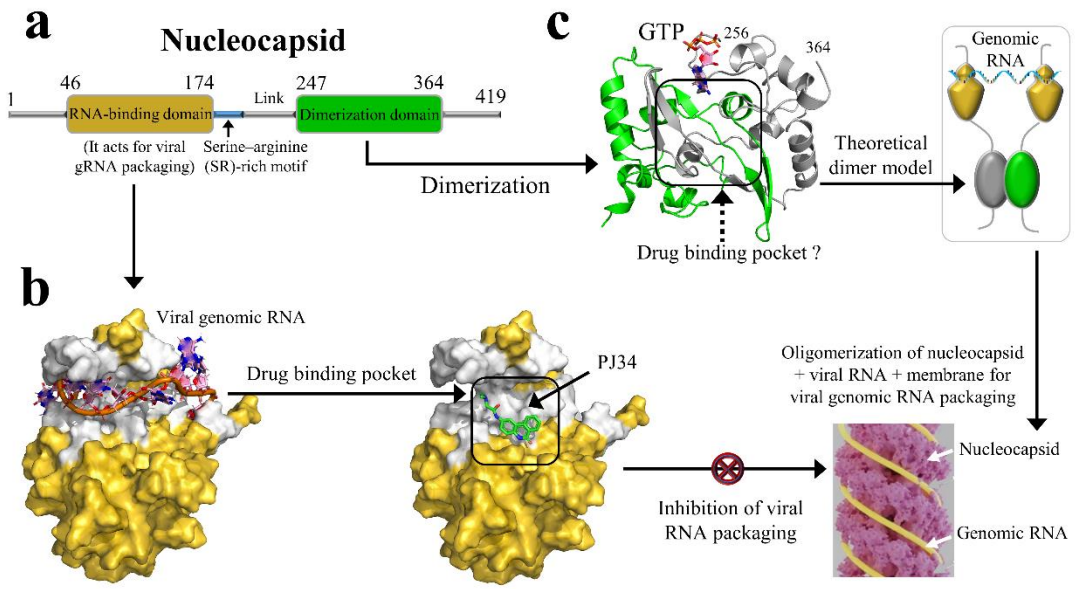

Fig. S6 | Structures of nucleocapsid and its drug-binding pockets

a, Functional domains of SARS-CoV-2 nucleocapsid.

b, RNA-binding domain in complex with the viral single-stranded RNA (PDB: 7ACT). The drug-binding pocket of the experimental inhibitor PJ34 (PDB: 4KXJ) is located within the interaction interface between the RNA-binding domain and viral ssRNA.

c, Dimerization domains of the SARS-CoV-2 nucleocapsid dimer in complex with GTP (PDB: 7O35). A hypothetical drug-binding pocket is located between two subunits. Viral RNA packaging is mediated via oligomerization of nucleocapsid dimers, viral genomic RNA, and viral membrane protein [6].

Our data collection procedure

Literature collection

(i) We used the keywords “coronavirus”, “COVID”, and “SARS” to collect relevant publications from the PubMed database and Google Scholar. The publication date was set from 2020/01/01 to 2023/02/01.

(ii) We used protein sequences from the SARS-CoV-2 reference genome to collect publications from the Protein Data Bank (RCSB PDB: Homepage). Publications that reported the PDB data of SARS-CoV-2 proteins were collected.

(iii) We also searched references from any relevant publication that has reported anti-SARS-CoV-2 inhibitors.

Data collection

(i) We screened publications and selected those publications that only reported anti-SARS-CoV-2 activities of inhibitors in cell culture or animal models.

(ii) We removed all prediction results of anti-SARS-CoV-2 inhibitors unless *in vitro* or *in vivo* results were also provided to prove the anti-SARS-CoV-2 activity.

(iii) We collected IC_{50}, EC_{50}, and CC_{50} results if any of them were reported in certain cell lines and SARS-CoV-2 strains. If results were evaluated by purified proteins without using live viruses in cell culture, we used “biochemical assays” to indicate such results.

(iv) We obtained the clinical status of inhibitors by searching the database of clinical trials (http://clinicaltrials.gov). The status of inhibitors was classified as either preclinical or clinical stage (only the highest phase was indicated with the clinical trial ID).

(v) We only selected the most potent inhibitors from each individual publication.

(vi) For the summary of clinical results in Table S5, we focused on the randomized clinical trials with the sample size > 100 and excluded observational studies.

Data website:

We created www.virusface.com to update results of anti-SARS-CoV-2 inhibitors.

Table S1: Summary of virus-targeted inhibitors with anti-SARS-CoV-2 activity

Viral protein	Drug name	Type	IC_{50}	EC_{50}	CC_{50}	Cell line	SARS-CoV-2 strain	Status	Ref.
NSP1	Montelukast	Small	Kd:10.8± 0.2 μM			Vero E6	Hong Kong/VM20001061/2020	Preclinical	[7]
Papain-like protease	F0213	Small	7.4 μmol/L	4.549 μmol/L		Vero E6-TMPRSS2 cells	SARS-CoV-2 HKU-001a	Preclinical	[8]
	F0326	Small	8.2 μmol/L	7.62 μmol/L		Vero E6-TMPRSS2 cells	SARS-CoV-2 HKU-001a	Preclinical	[8]
	GRL-0617	Small	1.50 ± 0.08μM 0.74 ± 0.07μM				Strain FFM1 (accession no. MT358638)	Preclinical	[1]
			2.4 ± 0.2 μM	27.6 ± 1.2 μM		Vero E6	USA-WA1 / 2020		[9]
			1.61 μM	27.6 μM		A549-hACE2	USA-WA1 / 2020		[10]
				35.43 μM	48.28±20.74 μM	Vero E6	USA-WA1 / 2020		[11]
			FRET:2.05±0.12μM	23.64±4.72 μM, 19.96±8.82μM	>60 μM	Vero E6, Caco2-hACE2	USA-WA1/2020		[12]
	Compound 6	Small	5 ± 1.9 μM	21 ± 1.9 μM		Vero E6	USA-WA1 / 2020	Preclinical	[9]
	ZN-2-184	Small	1.01 ± 0.15 mM			A549-hACE2	USA-WA1 / 2020	Preclinical	[10]
	ZN-3-80	Small	0.59 ± 0.04 mM			A549-hACE2	USA-WA1 / 2020	Preclinical	[10]
	XR8-24	Small	0.56 ± 0.03 mM	1.2 μM	> 50 μM	A549-hACE2	USA-WA1 / 2020	Preclinical	[10]
	XR8-23	Small	0.39 ± 0.05 mM	1.4 μM	21.6 ± 1.1 μM	A549-hACE2	USA-WA1 / 2020	Preclinical	[10]
	6-TG	Small		2.13 ± 1.16 μM	35.5 μM	Vero E6	USA-WA1 / 2020	Preclinical	[11]
	Jun9-72-2	Small	FRET:0.67±0.08μM	6.62±1.31μM, 7.9±2.4μM	>60 μM, >60 μM	Vero E6, Caco2-hACE2	USA-WA1/2020	Preclinical	[12]
	Jun9-75-4	Small	FRET:0.62±0.06μM	7.88±1.44μM, 12.48±3.43μM	47.48±14.63μM, >60 μM	Vero E6, Caco2-hACE2	USA-WA1/2020	Preclinical	[12]
	VIR250	Small				HEK293T	BL21(DE3)	Preclinical	[13]
	VIR251	Small				HEK293T	BL21(DE3)	Preclinical	[13]
	Acriflavine	Small	86 nM 64 nM		3.1 μM 3.4 μM	A549ACE+ Vero	BavPat1/2020026V-03883	Preclinical	[14]
	EM-C	Small	7.4 ± 0.37 μM			HEK293T		Preclinical	[15]
	EC-M	Small	8.63 ± 0.55 μM			HEK293T		Preclinical	[15]
	Inhibitor19	Small	0.18 ± 0.1 μM		> 10 μM	hACE2-HeLa	SARS-CoV2 (SZ02)	Preclinical	[16]
	Cryptotanshinone	Small	5.63 ± 1.45 μmol/L	0.70 ± 0.09 μmol/L	> 300 μmol/L	Vero E6	nCoV-2019BetaCoV/Wuhan/WIV04/2019	Preclinical	[17]
	Tanshinone I	Small	2.21 ± 0.1 μmol/L	2.26 ± 0.11 μmol/L	> 300 μmol/L	Vero E6	nCoV-2019BetaCoV/Wuhan/WIV04/2019	Preclinical	[17]
	YM155	Small	2.47±0.46 μmol/L	0.17 ± 0.22 μmol/L	~ 400 μmol/L	Vero E6	nCoV-2019BetaCoV/Wuhan/WIV04/2019	Preclinical	[17]
	RI173	Small	0.2±0.1 μM	0.1 μM	0.3±0.1μM	Huh-7.5.1		Preclinical	[18]
	Rac5c Rac3j Rac3k	Small	0.81 μM 1.4 μM 1.15 μM			Vero (CCL-81)	From a COVID-19 patient	Preclinical Preclinical Preclinical	[19]

	Tropifexor	Small	5.11 μM	4.03 μM		Calu-3 cells		Preclinical	[20]
	Ebselen derivative 1d	Small	236±107nM				Biochemical assay	Preclinical	[21]
	Methyl 3,4-dihydroxybenzoate (HE9)	Small	0.2 μM	10 μM	>100 μM	Vero	SARS.CoV2/SP02.2020.HIAE.Br	Preclinical	[2]
	4-hydroxybenzaldehyde (HBA)	Small	1 μM	0.13 μM		Vero	SARS.CoV2/SP02.2020.HIAE.Br	Preclinical	[2]
	4-(2-hydroxyethyl) phenol (YRL)	Small	1.3 μM	1 μM	>100 μM	Vero	SARS.CoV2/SP02.2020.HIAE.Br	Preclinical	[2]
	3-amino-N-(naphthalene-1-yl)-5-trifluoromethyl)benzamide	Small	Biochemical assay: 43.2±9.4 μM	1.7 ± 4.4 μM		Vero E6	nCoV/Washington/1/2020	Preclinical	[22]
	Disulfiram	Small	17.45 μM		41.34 μM	Vero E6	SARS-CoV-2 (TCDC#4)	Preclinical	[23]
	Bis[2-(N,N-dimethylamino) ethyl] disulfide (DMGA)	Small	9.4 ±2.5 μM				Biochemical assay	Preclinical	[24]
	Compound 7	Small	6.0 μM	4.59±1.22 μM 2.70±0.99 μM 2.98±0.80 μM	>800 μM	Vero E6	WT, Delta, Omicron	Preclinical	[25]
	Proanthocyanidin	Small	2.4±0.3 μM	6.6±1.5 μM	>100 μM	Vero E6		Preclinical	[26]
	LY1	Small	3.9 μM			Vero E6		Preclinical	[27]
	Schaftoside	Small	3.91 ± 0.19 μmol/L	11.83 ± 3.23 μmol/L		Vero E6	nCoV-2019BetaCoV/Wuhan/WIV04/2019	Preclinical	[28]
	UbV.CV2.1	Peptide	11.8 nM				Biochemical assays	Preclinical	[29]
Mac1 (ADP-ribosylhydrolase)	50779772/F5941001	Small	8.5±0.1 to 68 μM in three assays				Biochemical assays	Preclinical	[30]
	Dasatinib	Small	37.5 to 57.5 μM				AMP-Glo assay	Preclinical	[31]
	LRH-0021	Small	1.7 μM					Preclinical	[32]
Main protease (NSP5)	Nirmatrelvir (PF-07321332)	Small		74.5 nM 77.9 nM		Vero E6 A549+ACE2	USA-WA1 / 2020	Approved or authorized in many countries	[33]
	Nirmatrelvir-derivative 5	Small	0.008±0.001 μM	0.193±0.118 μM			Biochemical assay	Preclinical	[34]
	Nirmatrelvir-derivative 10	Small	0.027±0.001 μM	0.242±0.132 μM			Biochemical assay	Preclinical	[34]
	Nirmatrelvir alkyne derivative 13	Small	0.41±0.03 μM	25.7±4.1μM		Vero E6	Victoria strain−100 FFU	Preclinical	[35]
	Ensitrelvir (S-217622)	Small		26 ± 6.65 nM 407 ± 21.3 nM 69 ± 11.2 nM		293 T hACE2-TMPRSS2, Vero-TMPRSS2, Vero-TMPRSS2 with CP-100356	Delta	Phase 3 (NCT05305547)	[36]
	SIM0417	Small					Omicron	Phase 2/3	

								(NCT05506176)	
	Lufotrelvir (PF-07304814)	Small		39.8 μM; 88.9 μM	> 100 μM; > 100 μM	Vero E6-enACE2	USA-WA1 / 2020; BetaCov GHB-03021/2020	Withdrawn from the ACTIV-3, phase 3 (NCT04501978)	[37]
	FB2001	Small		0.39 ± 0.01 μM 0.28 ± 0.11 μM 0.27 ± 0.05 μM 0.26 ± 0.06 μM	274.4 μM, 274.4 μM, 274.4 μM, 242.7 μM	Vero E6	B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), B.1.1.529 (Omicron)	Phase 2/3 (NCT05445934)	[38]
	Masitinib	Small	2.5 μM	3.2 μM	> 10 μM	A549	USA-WA1 / 2020	Phase 2 (NCT04622865, NCT05047783)	[39]
	Ebselen	Small	0.67 ± 0.09 μM	4.67 ± 0.8 μM		Vero E6	BetaCoV/ Wuhan/WIV04/2019	Phase 2 (NCT04484025, NCT04483973)	[40]
		Small	Vero E6: 0.33 μM	Calu-3: 5.0 ± 4.0 μM		Vero E6 Calu-3	USA-WA1 / 2020		[41]
	All-trans retinoic acid	Small	VeroE6/TMPRSS2: 2.69±0.09 μM Calu-3:0.82±0.01 μM		> 100 μM	VeroE6/TMPRSS2, Calu-3	JPN/TY-WK-521/2020P1/2021	Phase 2 (NCT04396067, NCT04568096)	[42]
	PF-00835231	Small	0.27 ± 0.1 nM	0.27 μM			Vero E6	Phase 1 (NCT04535167)	[43]
		Small		0.422 μM (24h) 0.344 μM (48h)	>10μM	A549+ACE2	USA-WA1 / 2020		[44]
		Small		0.326 μM (24h)	>10μM	A549+ACE2	USA/NYU-VC-003/2020		[44]
	MR6-31-2	Small	WT:0.824 μM	5.4 μM		Vero E6	nCoV-2019BetaCoV/ Wuhan/WIV04/2019	Preclinical	[45]
	GC373	Small	0.40±0.05μM	1.5μM	>200 μM	Vero E6	SARS-CoV-2/CANADA/ VIDO 01/2020	Preclinical	[46]
	GC376	Small	0.03 μM	0.49~3.37 μM	> 100μM	Vero 76	USA-WA1 / 2020	Preclinical	[47]
		Small	FRET Assay: 0.052 ± 0.007 μM SAMDI-MS Assay: 0.060 ± 0.019 μM	10 ± 4.2 μM	> 100 μM	Vero E6	SARS2_Belgium_20200414		[48]
		Small		0.48 ± 0.29 μM			USA-WA1 / 2020		[49]
		Small	160 ± 34 nM	2.189±0.092μM		Vero E6	USA-WA1 / 2020		[50]
		Small	0.19±0.04μM	0.92μM	>200 μM	Vero E6	SARS-CoV-2/CANADA/ VIDO 01/2020	Preclinical	[46]
	GRL-1720	Small	0.32 ± 0.02	15 ± 4 μM	> 100 μM	Vero E6	JPN/TY/WK-	Preclinical	[51]

			μM				521		
	Compound 5h	Small		VeroE6: 4.2 ± 0.7μM	VeroE6: > 100μM Calu-3: > 200μM	Vero E6, Calu-3	JPN/TY/WK-521	Preclinical	[51]
	YH-53	Small			> 100 μM	Vero	JPN/TY/WK-521	Preclinical	[52]
		Small	0.124 μM					Preclinical	[53]
	11r	Small	0.18 ± 0.02 μM			Calu-3		Preclinical	[54]
		Small	0.71 ± 0.36μM	1.8± 2.1μM		Vero E6	BetaCoV/Wuhan/2019	Preclinical	[55]
	11u	Small	1.27 ± 0.34 μM	4.9± 1.2μM 3.6±0.1μM		Vero E6	BetaCoV/Wuhan/2019	Preclinical	[55]
	13b	Small	0.67± 0.18 μM			Calu-3		Preclinical	[54]
	13b-K	Small	0.12±0.03 μM	2.4±0.7 μM 3.4 μM 1.3 μM 0.84 μM	>100 μM	Calu 3 Huh 7 Vero E6 A549-ACE2-TMPRSS2		Preclinical	[56]
	Rupintrivir (AG-7088, Rupinavir)	Small	68 ± 7 μM	3~183 nM		A549+ACE2		Preclinical	[57]
	6e	Small	0.17± 0.06 μM	0.15 ± 0.14 μM	63.3 ± 2.3 μM	Vero E6		Preclinical	[58]
	23R	Small	0.66 ±0.07 μM	3.03 μM	> 100 μM	Vero E6	USA-WA1 / 2020	Preclinical	[59]
	ALG-097111	Small	7 nM	200 ± 18.4 nM	> 100 μM	A549	GHB-03021/2020	Preclinical	[60]
	N3	Small		16.77±1.7 μM		Vero E6	BetaCoV/ Wuhan/WIV04/2019	Preclinical	[40]
	E24	Small	2.77 ± 0.51μM	0.84 ± 0.3 μM 1.3 ± 0.8 μM		Vero E6 Calu-3	USA-WA1 / 2020	Preclinical	[41]
	Compound 4	Small	151 ± 15 nM	2.883 ± 0.227 μM		Vero E6	USA-WA1 / 2020	Preclinical	[50]
	MAC-5576	Small	81 ± 12 nM	N/A		Vero E6	USA-WA1 / 2020	Preclinical	[50]
	CBS	Small	0.93 ±0.04 μM	177.3 ± 32 μM	>2000 μM	Vero E6		Preclinical	[61]
	2j	Small	0.75±0.2 μM			HEK293T	Wuhan-Hu-1	Preclinical	[62]
	14a	Small	0.42± 0.11 μM					Preclinical	[63]
	16a	Small	0.41±0.13 μM					Preclinical	[63]
	C1	Small	1.55± 0.21 μM					Preclinical	[64]
	C2	Small	1.81± 0.17 μM					Preclinical	[64]
	Chebulagic acid	Small	9.09±0.87 μM	9.76 ± 0.42 μM	> 100 μM	Vero E6	USA-WA1 / 2020	Preclinical	[65]
	p12 p13 p15 p16	Small	5.36±2.17 μM 3.11±1.80 μM 5.31±1.08 μM 3.76±0.51 μM					Preclinical Preclinical Preclinical Preclinical	[66]
	CDD-1976	Small	2.50 μM			Vero E6	USA-WA1 / 2020	Preclinical	[67]
	Ethacridine	Small	3.54±0.66μM	0.08 ± 0.01 μ M	> 40 μM	Vero E6	USA-WA1 / 2020	Preclinical	[68]
	Glycyrrhizin	Small		0.44 mg / mL		Vero E6	From a COVID-19 patient	Preclinical	[69]
	Entrectinib	Small	10.6 μM	198 ± 116 nM		Vero E6		Preclinical	[70]
	Calpeptin	Small		0.072 μM	> 100 μM	Vero E6	human/DEU/HH-1/2020	Preclinical	[71]
	Pelitinib	Small		1.25 μM	13.96 μM	Vero E6	human/DEU/HH-1/2020	Preclinical	[71]
	Boceprevir	Small	3.1 μM					Preclinical	[72]

		Small	4.13±0.61 μM	1.95±1.62 μM		Vero 76	USA-WA1 / 2020		[47]
	Narlaprevir	Small	5.1 μM					Preclinical	[72]
			23.8 ± 6.5 μmol/L				FlipGFP-M_{pro} assay	Preclinical	[73]
	Telaprevir	Small	19.9 ± 3.0 μmol/L				FlipGFP-M_{pro} assay	Preclinical	[73]
	Manidipine Boceprevir Lercanidipine Bedaquiline Efonidipine	Small	4.8 μM 5.4 μM 16.2 μM 18.7 μM 38.5 μM					Preclinical Preclinical Preclinical Preclinical Preclinical	[74]
	Carmofur	Small	1.82 μM	24.3 μM	133.4 μM	Vero E6	Wuhan/WIV04/2019	Preclinical	[75]
	Myricetin	Small	0.63 μM	8.00 μM	> 200 μM	Vero E6	A clinical isolate SARS-CoV-2	Preclinical	[76]
	Compound 7d	Small	73 nM	15 μM		Vero E6	JPN/TY/WK-521 (SARS-CoV-2WK-521)	Preclinical	[77]
	Jun9-62-2R	Small	0.43 μM	2.05 μM 0.90 μM	> 60 μM 33.11 μM	Caco2-hACE2 Vero E6	USA-WA1 / 2020	Preclinical	[78]
	Jun9-88-6R	Small	0.08 μM	2.15 μM 0.58 μM	10.15 μM 2.95 μM	Caco2-hACE2 Vero E6	USA-WA1 / 2020	Preclinical	[78]
	ML188	Small	2.5 ± 0.3 μM					Preclinical	[79]
	ML300	Small	4.99 ±0.62 μM	19.90 μM		Vero E6	USA-WA1/ 2020	Preclinical	[80]
	CCF0058981	Small	68±23 nM	0.497 μM	> 50 μM	Vero E6	USA-WA1 / 2020	Preclinical	[80]
	Compound19	Small	44 ± 9 nM	0.175 ± 0.005 μM	> 32.5μM	Vero E6	USA-WA1 / 2020	Preclinical	[81]
	Compound21	Small	61 ± 11nM	1.08 μM	> 100μM	Vero E6	USA-WA1 / 2020	Preclinical	[81]
	Cyanophenyl analogue 5	Small	140 ± 20 μM	MTT: 2.5 ± 0.7 μM Plaque: 1.5 μM	22 ± 7.2 μM 20 ± 2 μM	Vero E6 NHBE	USA-WA1 / 2020	Preclinical	[82]
	Cyanophenyl analogue 26	Small	170 ± 22 nM	MTT:2.0 μM Plaque:0.98 μM	> 100 μM > 100 μM	Vero E6 NHBE	USA-WA1 / 2020	Preclinical	[82]
	Ac-Abu-dTyr-Leu-Gln-VS (15)	Small		3.7 μM	> 100 μM	Huh7	BetaCov/Belgium/GHB-03021/2020	Preclinical	[83]
	MI-23	Small	7.6 nM	5.63 μM	> 500 μM	Vero E6	Strain 107	Preclinical	[84]
	MI-09	Small	15.2 nM	Vero E6: 0.86 ±0.07μM HPAEpiC: 1.2 ±0.1μM Huh 7: 35.3 μM	> 500 μM	Vero E6, HPAEpiC, Huh 7	Strain 107	Preclinical	[84]
	MI-30	Small	17.2 nM	Vero E6: 0.54±0.13 μM HPAEpiC: 1.1 ±0.2μM Huh 7: 31 μM	> 500 μM	Vero E6, HPAEpiC, Huh 7	Strain 107	Preclinical	[84]
	HL-3-68	Small	0.29 μM			Vero E6 TMPRSSS	USA-WA1 / 2020	Preclinical	[85]
	Mcule-CSR-494190-S1	Small	0.29 μM			Vero E6 TMPRSSS	USA-WA1 / 2020	Preclinical	[85]
	11a	Small	53 ± 5 nM	0.53 ± 0.01 μM	> 100 μM	Vero E6	BetaCoV/Wuhan/WIV04/2019	Preclinical	[86]
	11b	Small	40 ± 2 nM	0.72 ± 0.09 μM	> 100 μM	Vero E6	BetaCoV/Wuhan/WIV04/2019)	Preclinical	[86]
	Shikonin	Small	1.57 ± 0.32 μM					Preclinical	[87]

		Small	15.75±8.22μM			Vero E6		Preclinical	[88]
	Compound 21	Small	0.018 μM					Preclinical	[88]
	Compound 19	Small	0.077 μM	0.11 ±0.03 μM 77±8 nM	> 5 μM > 20 μM	Huh7 Vero E6	BetaCov/Belgium/GHB-03021/2020	Preclinical	[89]
	Compound 6	Small	4.8 ± 3.4μM					Preclinical	[90]
	Compound 12	Small	1.8 ± 0.8μM					Preclinical	[90]
	Compound 17	Small	2.5 ± 2.1μM					Preclinical	[90]
	Compound 18p	Small	34 ± 4 nM	290 ± 60 nM	808.7 ± 20.4	Vero E6	Wuhan/WIV04	Preclinical	[91]
	NK01-63	Small	16 nM	6 nM		Huh-7ACE2	USA_WA1/2020	Preclinical	[92]
	Y180	Small	8.1 nM	11.4 to 34.4 nM	>81 μM	Vero E6, Calu3	HKU-001a, Alpha Kappa, Theta	Preclinical	[93]
	3w	Small	11.4 ±2.8 μM	111 nM		Calu-3, Vero 76	SARS-CoV-2 isolate NK, Pango lineage B.1.513	Preclinical	[94]
	F8–B6	Small	1.57±0.08 μM		>100 μM	Vero		Preclinical	[95]
	x1187	Small						Preclinical	[96]
	MPI3	Small	8.5 ±1.5nM			Vero E6		Preclinical	[97]
	MPI5	Small	33 ±2nM			Vero E6		Preclinical	[97]
	MPI8	Small	105±22 nM			Vero E6		Preclinical	[97]
	MG-132	Small	0.4μM	0.1μM	>2.9 μM	Vero E6	MN908947.3	Preclinical	[98]
	Z-VAD(OMe)-FMK	Small	0.59±0.44uM	1.88±0.52 μM	>300μM	Vero		Preclinical	[99]
	2a	Small	0.18 ± 0.03 μM	Vero E6:0.035±0.001 μM	>100μM	Vero E6	MN908947.3	Preclinical	[100]
	3a	Small	0.17 ± 0.02 μM	0.032±0.001μM	>100μM	Vero E6	MN908947.3	Preclinical	[100]
	15h	Small	1 ± 0.17 nM	0.16±0.03 μM	>200μM	Vero E6	SARS-CoV-2/Canada/VIDO 01/2020	Preclinical	[101]
	15l	Small	19 ± 0.5 nM	0.30 ±0.02 μM	>200μM	Vero E6	SARS-CoV-2/Canada/VIDO 01/2020	Preclinical	[101]
	F01	Small	54 μM	150 μM	>400μM	Vero-81		Preclinical	[102]
	Leupeptin	Small	127.2μM	42.34 μM		Vero	Wuhan seafood market by the China CDC	Preclinical	[103]
	Cyclic peptide 1	Small	70 ± 18 nM	>50μM		HEK293-ACE2-TMPRSS2		Preclinical	[104]
	Peptide2	Small		11.8±0.6μM		HEK293-ACE2-TMPRSS2		Preclinical	[104]
	Peptide 5	Small		13.0 ±0.6μM		HEK293-ACE2-TMPRSS2		Preclinical	[104]
	BBH-1	Small		16.1μM	> 10 μM	Vero E6 TMPRSS	USA-WA1/2020	Preclinical	[105]
	BBH-2	Small		15.4μM	> 10 μM	Vero E6 TMPRSS	USA-WA1/2020	Preclinical	[105]
	NBH-2	Small		13.9μM	> 10 μM	Vero E6 TMPRSS	USA-WA1/2020	Preclinical	[105]
	Penicillin V derivative,10	Small	6.6 ±2.7 μM					Preclinical	[106]
	C6 dibromo-penicillin sulfones 28	Small	0.7 ±0.1 μM					Preclinical	[106]
	C6 dibromo-penicillin sulfones31	Small	0.6 ±0.1 μM					Preclinical	[106]

	C6 dibromo-penicillin sulfones32	Small	0.5 ±0.1 μM					Preclinical	[106]
	SAA	Small	2.49±0.57μM			VeroE6	MN908947.3	Preclinical	[107]
	EGCG	Small	11.58±1.62μM			VeroE6	MN908947.3	Preclinical	[107]
	Oridonin	Small	2.16±0.22μM	4.95μm	24.94μm	VeroE6	MN908947.3	Preclinical	[107]
	10a	Small	3889±51 nM			Vero E6	SARS-CoV-2 (WIV04)	Preclinical	[108]
	10b	Small	374±6 nM	1.06μM		Vero E6	SARS-CoV-2 (WIV04)	Preclinical	[108]
	10c	Small	373±11nM			Vero E6	SARS-CoV-2 (WIV04)	Preclinical	[108]
	14b	Small	0.41±0.04μM	0.38μM	> 100 μM	Vero E6		Preclinical	[109]
	MPI16	Small	Enzymatic IC_{50}: 150nM	1.2μM 1.2μM, 0.58μM,	>200μM	Vero E6	USA-WA1/2020, Beta and Delta	Preclinical	[110]
	MPI17	Small	Enzymatic IC_{50}: 60 nM	1.2 μM, 1.8 μM, 1.1 μM	>200μM	Vero E6	USA-WA1/2020, Beta, Delta	Preclinical	[110]
	MPI25	Small	Enzymatic IC_{50}: 650 nM	2.2 μM, 1.6 μM, 0.87 μM	130.0μM	Vero E6	USA-WA1/2020, Beta, Delta	Preclinical	[110]
	MPI26	Small	Enzymatic IC_{50}: 530 nM	1.9 μM, 0.65 μM, 1.6 μM	182.9μM	Vero E6	USA-WA1/2020, Beta, Delta	Preclinical	[110]
	MPI43	Small	Enzymatic IC_{50}: 45±5 nM	0.61 μM, 0.36 μM, 1 μM	34.2 μM	Vero E6	USA-WA1/2020, Beta, Delta	Preclinical	[111]
	MPI44	Small	Enzymatic IC_{50}: 59±7 nM	2.94 μM 0.86 μM 1.04 μM	143.7 μM	Vero E6	USA-WA1/2020, Beta, Delta	Preclinical	[111]
	MPI46	Small	Enzymatic IC_{50}: 120±10 nM	1.08 μM 2.28 μM 0.75 μM	163.4 μM	Vero E6	USA-WA1/2020, Beta, Delta	Preclinical	[111]
	JMX0286	Small	4.8 μM	2.3 μM	53.1 μM	A549-hACE2	USA-WA1/2020	Preclinical	[112]
	JMX0301	Small	4.5 μM		342.4 μM	A549-hACE2	USA-WA1/2020	Preclinical	[112]
	JMX0941	Small	3.9 μM	1.7 μM	30 μM	A549-hACE2	USA-WA1/2020	Preclinical	[112]
	Compound 18	Small	6.1±0.5 μM		55.2±8.5 μM		Biochemical assay	Preclinical	[113]
	YH-6	Small	3.8 ± 0.3 nM	21.2 ± 2.7 nM; 13.8 ± 1.3 nM; 7.57 ± 2.59 nM; 9.01 ± 2.45 nM; 17.1 ± 2.5 nM;	>50000nM	293TAT	Fluorescence 3CLpro Inhibition Assay	Preclinical	[114]
	GC-14	Small	0.40 μM	1.1±0.2 μM	>100 μM	Vero E6		Preclinical	[115]
	Tollovir (NLC-V)	Small						Phase 2 (NCT05226767)	
	PBI-0451	Small						Phase 2 (NCT05543707)	
	EDP-235	Small						Phase 2 (NCT05616728)	
	AG7404	Small	47 ± 1.05 μM	6.8 μM	250 μM	A549-ACE2	Biochemical FRET assays	Preclinical	[116]

	SM141	Small	8.2 nM	8.2 ± 0.9 nM		A549	USA-WA1/2020/NR-52281	Preclinical	[117]
	SM142	Small	14.7 nM	14.7 ± 2.2 nM		A549	USA-WA1/2020/NR-52281	Preclinical	[117]
	9a	Small	1.66 ± 0.02 μM	15.7 ± 8.3 μM		Vero E6-GFP		Preclinical	[118]
	9e	Small	2.63 ± 0.11 μM	>100 μM		Vero E6-GFP		Preclinical	[118]
	Compound 13	Small	4.9 μM				Fluorescence 3CLpro Inhibition Assay	Preclinical	[119]
	Bardoxolone	Small	27.99±2.34 μM	0.43 μM 0.42 μM	24.36 μM 11.86 μM	Vero, Calu-3		Preclinical	[120]
	Bardoxolone methyl	Small	5.81±0.79 μM	0.29 μM 0.20 μM	6.94 μM 1.16 μM	Vero, Calu-3		Phase 2 (NCT04494646)	[120]
	Bepridil	Small	72±3 μM	0.86 μM 0.46 μM		Vero E6, A549/ACE2		Preclinical	[121]
	GD-9	Small	0.18±0.01 μM	2.64±0.62 μM	12.5±2.1 μM	Vero E6		Preclinical	[122]
	Azanitrile 8							Preclinical	[123]
	Pyridyl ester 17							Preclinical	[123]
	Compound 17a	Small	40±8 nM	>5 μM	>200 μM	Vero E6		Preclinical	[124]
	Peptidomimetic compound 15	Small	15 ± 6 μM						[125]
	LY1	Small	3.9 μM			Vero E6		Preclinical	[27]
	Schaftoside	Small	1.73 ± 0.22 μmol/L	11.83 ± 3.23 μmol/L		Vero E6	nCoV-2019BetaCoV/Wuhan/WIV04/2019	Preclinical	[28]
	Acrylamide compound 2	Small	10 μmol/L				Biochemical assay	Preclinical	[126]
	Acrylamide compound 5	Small	17 μmol/L				Biochemical assay	Preclinical	[126]
	Compound 1	Small	0.021 μM			Vero-81 cells	hCoV-19_IPL_France strain	Preclinical	[127]
	SPR39	Small		1.5±0.3 μM	100 μM	Huh-7-ACE2 cells	Munich 929	Preclinical	[128]
	3CVL-4	Peptide	2.44±0.6 μM				nCoV-2019BetaCoV/Wuhan/WIV04/2019	Preclinical	[129]
	NB1A2	Nanobody	186.6±23.1nM	pEC_{50}:15.76 nM			MN908947.3	Preclinical	[130]
	NB2B4	Nanobody	122 ± 7.7 nM				MN908947.3	Preclinical	[130]
NSP6	1 ,25-dihydroxyvitamin D3	Small					It abrogates NSP6-induced pyroptosis	Preclinical	[131]
	Metformin	Small					It abrogates NSP6-induced pyroptosis	Preclinical	[131]
	Polydatin	Small					It abrogates NSP6-induced pyroptosis	Preclinical	[131]
NSP7	Licorice-saponin A3	Small		0.075 μM	>100 μM	Caco-2	nCoV-2019BetaCoV/Wuhan/WIV0	Preclinical	[132]

							4/2019		
NSP9	Oridonin	Small	37 ± 10 μM				UMPylation assay	Preclinical	[133]
	2NSP23	Nanobody						Preclinical	[134]
	2NSP90	Nanobody						Preclinical	[134]
RNA-dependent RNA polymerase (NSP12)	Remdesivir (GS-5734)	Small		0.74–1.34 μM, <0.001 μM	0.3-2.2μM, >100 μM	Vero E6, Huh7	BetaCov/Belgium/GHB-03021/2020, BetaCoV/Germany/BavPat1/2020	Phase 4 (NCT04738045,NCT04944082,NCT04978259, NCT04779047)	[135]
		Small	1.031 μM		>100 μM	LLC-MK2 cells	CGMH-CGU-01		[136]
	VV116 (JT001)	Small	0.67 ± 0.24 μM	0.35 ± 0.09 μM	280.19 ± 15.39 μM	Vero E6	2019-nCoV-WIV04	Approved, Phase 3 (NCT05279235,NCT05341609, NCT05582629)	[137]
	Molnupiravir (MK-4482, EIDD-2801)	Small	48h: 0.30 μM 72h: 0.08 μM		>10 μM	Vero E6, Calu-3	USA-WA1 / 2020	Approved, Phase 3 (NCT05459532 , NCT05595824 , NCT04939428)	[138]
				0.22 μM		HEK293T			[139]
	Bemnifosbuvir (AT-527, RO7496998)	Small		> 100 μM, > 100 μM, > 10 μM	> 100 μM > 100 μM > 10 μM	VeroE6-GFP Huh7 HAEC	BetaCov/Belgium/GHB-03021/2020	Phase 3 (NCT05629962)	[135]
				1.8 ± 0.3 μM	> 100 μM	BHK-21	USA-WA1/2020		[140]
	GS-5245	Small						Phase 3 (NCT05603143)	
	GS-441524	Small		2454 ± 63 nM	>10 μM	Human bronchial epithelial cells	USA-WA1	Phase 1 (NCT04859244)	[141]
	GS-621763	Small		125 ± 22 nM	>10 μM	Human bronchial epithelial cells	USA-WA1	Preclinical	[141]
	ODBG-P-RVn	Small		420 ± 90 nM, 100 ± 5 nM	>100 μM	Vero E6, Huh7/NCI-H358	USA-WA1	Preclinical	[142]
	ATV006	Small		B.1: 1.36 μM, Beta: 1.127 μM, Delta: 0.349 μM, Omicron: 0.106 μM	128 μM	Vero E6	B.1, Beta, Delta, Omicron	Preclinical	[143]
	MMT5-14	Small		2.5 μM 15.9 μM 1.7 μM 5.6 μM		Vero E6	Alpha(B.1.1.7) Beta(B.1.351), Gamma(P.1), Delta(B.1.617.2)	Preclinical	[144]
	4′-fluorouridine (EIDD-2749)	Small		2.47 μM	467.9 μM	HAEC	USA-WA1 / 2020	Preclinical	[145]

	Favipiravir (T-705)	Small		Replication: 207.1 μM CPE:118.3 μM		Vero E6	BetaCoV/Germany/BavPat1/2020	Phase 4 (NCT04359615	[146]
	Galidesivir (BCX4430)	Small		48 μM, 58 μM, 24 μM		Huh7.5 Calu-1 A549	human/Denmark/DK-AHH1/2020	Phase 1 (NCT03891420)	[147]
	5-Hydroxymethyl tubercidin	Small			> 50 μM > 50 μM > 20 μM > 20 μM > 20 μM	Caco-2 MRC5 Huh7 A549 Vero E6	JP/TY/WK-521	Preclinical	[148]
	5-Iodotubercidin	Small		0.75 μM	59.46 μM	HEK293T		Preclinical	[149]
	HeE1-2Tyr (compound 16)	Small	27.6 ± 2.1 μM	653.5 nM 949.3 nM 1.062 μM	> 50 μM > 50 μM > 50 μM	Vero CaCo-2 CRFK	human/Czech Republic/951/2020	Preclinical	[150]
	6d5	Small	1.11 ± 0.05 μM		> 100 μM	HEK293T		Preclinical	[151]
	GSK-650394	Small	29 to 31 μM	7.6 μM		Vero E6	England/2/2020	Preclinical	[152]
	C646	Small	6.1 to 7.8 μM	19 μM		Vero E6	England/2/2020	Preclinical	[152]
	BH3I-1	Small	13 to 14 μM	77 μM		Vero E6	England/2/2020	Preclinical	[152]
	6-72-2a	Small		1.41 μM 1.18 μM	> 100 μM > 100 μM	HEK293T A549		Preclinical	[153]
	4-46b	Small		1.70 μM 1.58 μM	75.52 μM 76.23 μM	HEK293T A549		Preclinical	[153]
	Sangivamycin	Small	34 ± 1 nM 14 ± 2 nM 61 ± 8 nM		491 nM 285 nM 322 nM	Vero E6 Caco-2 Calu-3	USA-WA1 / 2020	Preclinical	[154]
	Corilagin (RAI-S-37)	Small		0.13 μmol/L		Vero E6 cells	A strain isolated from a COVID-19 patient	Preclinical	[155]
	Gossypol	Small	14.15 μM	0.31 μM, 0.76 μM	39.57 μM	Vero E6, Calu-3	delta variant SARS-CoV-2/SZTH12	Preclinical	[156]
	ATV041	Small		1.15 μM		L929 cells	MHV-A59	Preclinical	[157]
	CM12.1	Antibody				Vero E6	2019n-CoV/USA-WA1/2019	Preclinical	[158]
	Suramin	Large	0.26 ±0.03 μM	2.93 ± 0.28 μM	>1000 μM	Vero E6	Wuhan/ WIV04/2019	Preclinical	[159]
				20±2.7 μM		Vero E6	SARS-CoV-2/Leiden-0002	Preclinical	[160]
Helicase (NSP13)	6g	Small	0.42±0.23μM	8.8±5.6 μM	>100 μM	Vero E6		Preclinical	[161]
	C2 (5645-0263)	Small	42 ± 3 μM				Biochemical assay using purified NSP13	Preclinical	[162]
	FPA-124	Small	9 μM	14 μM		Vero E6	England/2/2020	Preclinical	[163]
	SSYA10-001	Small	14 to 21 μM	81 μM		Vero E6	England/2/2020	Preclinical	[163]
	Ranitidine bismuth citrate	Small	~0.7 μM	2.3±0.5 μM	2243±43 μM	Vero E6	HKU-001a	Preclinical	[164]
	Punicalagin	Small	0.43 μM	347 nM 196 nM	46.77 μM 32.92 μM	A549-ACE2 Vero	BetaCov/Shenzhen/SZTH-003/2020	Preclinical	[165]
	Licoflavone C	Small	1.34 ± 0.31 μM	>100 μM	>100 μM	Vero-E6-GFP		Preclinical	[166]

Exoribonuclease (NSP14)	Sinefungin	Small	18.2 ± 2 nM				Methyltransferase assay	Preclinical	[167]
	Compound 16	Small	3 ± 0.5 nM				Methyltransferase assay	Preclinical	[167]
	Compound #79	Small	19.43±8.37 μM				FRET exonuclease activity assay	Preclinical	[4]
	Compound #96 (Isobavachalcone)	Small	17.43±1.39 μM				FRET exonuclease activity assay	Preclinical	[4]
	Compound#102 (Sofalcone)	Small	21.99 ± 6.02 μM				FRET exonuclease activity assay	Preclinical	[4]
	Patulin	Small	1.8 (1.6 to 2.1) μM			Vero E6	BetaCoV/England/02/2020 (EPI_ISL_407073)	Preclinical	[168]
	Pyridostatin	Small	3.1 to 3.19 μM	3.58±0.16 μM	59.3±21.6 μM	Huh 7	Belgium/GHB-03021/2020	Preclinical	[169]
	Reactive Blue 2	Small	1.5±0.28 to 4.12±0.74 μM	16.3±0.3 μM	52.6±10.2 μM	Huh 7	Belgium/GHB-03021/2020	Preclinical	[169]
	A-2	Small	20.7 ± 0.5 μM					Preclinical	[170]
	B-1	Small	32.2 ± 4.5 μM					Preclinical	[170]
	Compound 25	Small	0.019±0.02 μM				Filter-binding assay using SARS-CoV-2 NSP14	Preclinical	[3]
	ZINC33037945	Small	125 ± 6 μM		>100 μM	Biochemical assays	Biochemical assays	Preclinical	[171]
	SS148	Small	70 ± 6 nM			Radiometric assays	Radiometric assays	Preclinical	[172]
	DS0464	Small	1.1 ± 0.2 μM			Radiometric assays	Radiometric assays	Preclinical	[172]
	Inhibitor 10	Small	0.093 μM	0.72 μM	>100 μM	A549	SARS-CoV-2	Preclinical	[173]
Endoribonuclease (NSP15)	NSC95397	Small	43 μM					Preclinical	[174]
	Tipiracil	Small				A549	USA-WA1 / 2020	Preclinical	[175]
	Exebryl-1	Small	9.27 μM	65.6 μM 10 μM	>100 μM 52 μM 61 μM	Calu-3 Vero 76 Calu-2	USA WA1 / 2020	Preclinical	[176]
2′-O-methyltransferase (NSP16)	3-deazaneplanocin A (DZNep)	Small	586 nM, 579 nM			A549-ACE2, A549-RFP-ACE2	SARS-CoV-2-MUC-IMB-1	Preclinical	[177]
	Sinefungin	Small	138 ± 30 nM			Biochemical tests	Biochemical tests	Preclinical	[178]
	2a	Small	4.0 ± 0.5 nM		>100 μM	Biochemical assay	Biochemical assay	Preclinical	[179]
	Aurintricarboxylic acid	Small	SARS-CoV nsp14: 6.4 μM SARS-CoV nsp14/nsp16: 2.1 μM					Preclinical	[180]
Spike	Clofazimine	Small	>100 μM	0.31 μM		Vero-E6	USA-WA1 / 2020	Phase 2 (NCT04465695)	[181]
	ALD-R491	Small	13.5 nM (MOI=0.5), 34.7 nM	0.036 μM	>10 μM	HEK-GFP		Preclinical	[182]

			(MOI=5), 64.9 nM (MOI=50)						
	Sertraline	Small	Pseudotyped: 0.649 ± 0.128 μM 0.295 ± 0.062 μM 1.344 ± 0.721 μM Authentic (Vero E6), 1.638 ± 0.622 μM(WT) 4.137 ± 0.930 μM(Delta)			ACE2/293T, Vero E6, Caco-2,	WT, Delta	Preclinical	[183]
	DRI-C23041	Small	SARS-CoV-2-S-RBD-hACE2 Binding: 0.52 μM					Preclinical	[184]
			PSV: 5.6 μM			HEK293T-ACE2		Preclinical	[184]
			PSV: 7.4 μM			Vero-E6		Preclinical	[184]
	AB-00011778	Small	1 μM, 0.25 μM, 1 μM	250 nM	>50 μM >30 μM >30 μM	293T-ACE2, A549-ACE2, Calu3	Wuhan-HU-1	Preclinical	[185]
	Aminobenztropine	Small	0.21 μM		>200 μM	293T	D614G	Preclinical	[186]
	15f	Small		1.45 μM	323 μM	Huh-7	Wuhan-Hu-1 pseudovirus	Preclinical	[187]
	MU-UNMC-2	Small	1.72 μM		>100 μM	UNCN1T	USA-WA1 / 2020	Preclinical	[188]
			1.63 μM		7.13 μM	Vero-STAT1 knockout cells	USA-WA1 / 2020	Preclinical	[188]
			3.0 μM			Calu-3	South African variant B.1.351	Preclinical	[188]
			1.39 μM			Calu-3	Scotland variant B.1.222	Preclinical	[188]
	H69C2	Small	85.75 μM		> 250 μM	Vero E6	nCoV-2019BetaCoV / Wuhan / WIV04 / 2019	Preclinical	[189]
	P2119	Small		22 ± 5.6 ng/mL				Preclinical	[190]
	P2165	Small		37 ± 4.7 ng/mL				Preclinical	[190]
	6-Thioguanine	Small		0.55 μM	>40 μM	Calu-3		Preclinical	[191]
	Glycyrrhetinic acid	Small		3.17 μM	>100 μM	Vero E6	nCoV-2019BetaCoV/ Wuhan/WIV04/2019	Preclinical	[132]
	Raloxifene	Small						Phase 2/3 (NCT05172050)	[192]
	Amiodarone	Small						Phase 2/3 (NCT04351763)	[192]
	UA-30	Saponin macromolecular		9.84±0.65 μM, 2.05±0.27 μM	>100 μM, >100 μM	293T-ACE2, Vero-E6	Wuhan-HU-1	Preclinical	[193]
	Polystyrene sulfonate	Macromolecular	<1 g/L			Caco-2	France/IDF0372/2020	Preclinical	[194]
	FBP	Peptide	2.9 μg/mL 3.0 μg/mL 3.9 μg/mL			Vero E6	SARS-CoV-2 (HKU001a), SARS-CoV-2	Preclinical	[195]

							(B.1.1.63), SARS-CoV-2 (B.1.617.2)		
	R7-02	Peptide	138.9 nM			hACE2-293T cells	Pseudotyped SARS-CoV-2	Preclinical	[196]
	TGCGTNCMG KLKCNRC	Peptide				Vero E6	SARS-CoV-2 (NCCP No. 43326)	Preclinical	[197]
	AMK-1057	Peptide						Preclinical	[198]
	HR1MFd	Peptide	1.23±0.18 μM, 1.61±0.29 μM,			Caco-2, Huh-7	Pseudotyped virus encoding SARS-CoV-2 spike /variants	Preclinical	[199]
	5-Helix	Peptide	293 nM		19.89 nM	Calu-3	nCoV-SH01	Preclinical	[200]
	5HB-H2	Peptide	0.59 μM; 1.63 μM; 3.08 μM; 3.25 μM; 2.66 μM			293T-hACE2	Wuhan-Hu-1, B.1.1.529, B.1.351, B.1.617.1, B.1.617.2,	Preclinical	[201]
	S-20-1	Peptide	Huh-7: 0.54 μM 3.92 μM 1.50 μM 9.63 μM 4.41 μM 10.23 μM 2.48 μM Caco-2: 4.44 μM(B.1.1.7) 6.37 μM(B.1.351) 5.35 μM(B.1.617.2) 4.69 μM(B.1.1.529)		692.7 μM	Huh-7, Caco-2	B.1.1.7, B.1.351, P.1, C.37, B.1.617.2, B.1.1.529, SARS-CoV-2(N501Y, K417N, E484K)	Preclinical	[202]
	4H30	Peptide	44 nM, 67 nM			VeroE6 VeroE6-T	Omicron, Delta	Preclinical	[203]
	SIH-5	Helix-hairpin peptide	326 pM			HEK293T-hACE2	SARS-CoV-2	Preclinical	[204]
	Frogdefensin-derived basic peptide	Peptide				Calu3 293T/ACE2	SARS-CoV-2(HKU001a), Delta, Omicron	Preclinical	[205]
	EK1	Peptide	B.1.1.7:1.24 μM B.1.1.248:1.25 μM			Calu-3 and Caco2	B.1.1.7 (Alpha), B.1.1.248 (Gamma)	Phase Ib/IIa (CTR20220003)	[206]
	EK1C4	Peptide	B.1.1.7:5.45 nM B.1.1.248:6.55 nM			Calu-3 and Caco2	B.1.1.7 (Alpha), B.1.1.248 (Gamma)	Preclinical	[206]
		Peptide	36.5 nM		>5 μM			Preclinical	[207]
	longHR2_42	Peptide	Caco-2+hACE2: 1.5 nM(Wuhan), 0.6 nM(Alpha), 5.0 nM(Delta), 15.6 nM(Omicron)			Caco-2+hACE2 Vero E6+TMPRSS2	Wuhan Alpha, D6124G, Delta, Omicron	Preclinical	[208]

			Vero E6+TMPRSS: 0.9 nM(D614G), 0.9 nM(Delta), 4.1 nM(Omicron)						
	P29S1	Peptide	0.3±0.1 μM	3.1±0.4 μM		Vero E6	2019-nCoV/USA-IL1/2020	Preclinical	[209]
	EKL1C	Lipopeptide	45±6 nmol/L, 40±5 nmol/L, 37±9 nmol/L		10 μmol/L, 13.81μmol/L, 8.49μmol/L	Huh-7, Caco-2, 293T/ACE2	Pseudotyped virus	Preclinical	[210]
	IPB02V3	Lipopeptide	293T/ACE2: 18.53±1.70nM 17.00±2.15nM 19.10±3.69nM 16.64±0.04nM 17.54±1.75nM 12.81±1.63nM 16.72±0.70nM 6.35±0.75nM Huh-7: 16.29±1.26nM 18.57±1.61nM 14.03±1.81nM 18.02±3.88nM 24.52±7.02nM 15.37±3.73nM 19.50±7.29nM 11.52±3.20nM Vero: 23.17±0.97nM (WT) 2.56±0.14nM (Omicron)			293T/ACE2 Huh-7 Vero	WT, D614G, Alpha, Beta, Gamma, Delta, Lambda, Omicron	Preclinical	[211]
		Lipopeptide	15.3±0.76 nM 4.69±0.37 nM 8.21±3.11 nM 5.64±0.05 nM 3.9±1.61 nM 3.91±0.95 nM			293T/ACE2	Wuhan-Hu-1 BA.1 BA.2 BA.2.12.1 BA.3 BA.4/5	Preclinical	[212]
	IPB24	Lipopeptide	293T/ACE2: 5.51±0.54nM 6.17±0.05nM 5.94±0.19nM 5.65±0.01nM 6.41±0.17nM 4.94±0.05nM 6.57±0.02nM 4.51±0.30nM Huh-7: 2.43±0.07nM 3.15±0.06nM 5.42±0.30nM 3.29±0.76nM 3.95±0.71nM 3.46±0.13nM 4.10±0.69nM 2.56±0.47nM Vero: 10.69±1.18nM (WT) 0.44±0.01nM			293T/ACE2 Huh-7 vero	WT, D614G, Alpha, Beta, Gamma, Delta, Lambda, Omicron	Preclinical	[211]

			(Omicron)						
		Lipopeptide	4.09±0.44 nM 3.83±0.56 nM 0.91±0.47 nM 1.19±0.23 nM 0.98±0.12 nM 1.00±0.18 nM			293T/ACE2	Wuhan-Hu-1 BA.1 BA.2 BA.2.12.1 BA.3 BA.4/5	Preclinical	[212]
	F9-C2	Engineered protein	12 nM	33 nM 15 nM >184 nM 18 nM		Vero E6	Beta, Gamma, Delta, Omicron	Preclinical	[213]
	FSR16m	Engineered protein	3.4 ng/mL, 2.2 ng/mL, 3.3 ng/mL, 44.7 ng/mL, 7.4 ng/mL, 33.3 ng/mL			Vero-hACE2-TMPRSS2	B.1.351, B.1.617.2 , B.1.617.2/ AY1 , B.1.1.519/ BA.1, B.1.1.519/ BA.1.1, B.1.1.519/ BA.2	Preclinical	[214]
	FSR22	Engineered protein	57.2 ng/mL, 41.7 ng/mL, 44.2 ng/mL, 169.2 ng/mL, 41.2 ng/mL, 216.2 ng/mL			Vero-hACE2-TMPRSS2	B.1.351, B.1.617.2 , B.1.617.2/ AY1 , B.1.1.519/ BA.1, B.1.1.519/ BA.1.1, B.1.1.519/ BA.2	Preclinical	[214]
	Mosaic-8	Nanoparticle				Vero E6	Beta, Delta	Preclinical	[215]
	H84T-BanLec	Engineered protein	5.2±1.1 nM 3.9±0.8 nM 2.6±0.5 nM			Vero E6	Wild-type Delta, Omicron	Preclinical	[216]
	Berbamine hydrochloride	Small		1.732 μM 1.887 μM	66.88 μM 31.86 μM	Vero E6, Caco2	SARS-CoV-2 (WIV-04)	Preclinical	[217]
	Ceftazidime	Small	40±1 μM 113±1 μM 28±1 μM			HPAEpiC, 293T, Vero E6		Preclinical	[218]
	Diltiazem	Small	RNA copies: 11.99 μM Virus titers: 9.511 μM		279.2 μM	Vero-E6	SARS-CoV-2/HRB25/human/2020/CHN	Phase 2 (NCT05563168)	[219]
	N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride(HTCC)	Polymeric	12.5 μM/mL		158.0 μM/mL	Vero-E6	SARS-CoV-2 (026V-03883)	Preclinical	[220]
	nCoV-S1-Apt1	Aptamer	80.12 nM					Preclinical	[221]
	[SARSHRC-PEG4]2-chol	Peptide	~300 nM ~5 nM			VeroE6, VeroE6-TMPRSS2		Preclinical	[222]
	33-7^{HR1}	Peptide	49 ng/mL 7.2 ng/mL 7.6 ng/mL 6.5 ng/mL 12 ng/mL 45 ng/mL 260 ng/mL			Vero E6	B.1, B.1.1, B.1.1.7, B.1.351, B.1.525, B.1.128, B.1.1.529	Preclinical	[223]

	hACE221-55A36K-F40E	Peptide	3.6 μM					Preclinical	[224]
	Mannose-binding lectin (MBL)	Protein	1.7nM	0.27nM		293T	MN908947	Preclinical	[225]
	HCC1	Small		125.6 μM	391.5 μM	293T		Preclinical	[226]
	Dichlorcyclizine	Small		MA104: 4.53 μM 293ACE2: 2.34 μM Huh7: 3.05 μM Vero E6: 2.9±1.6 μM (WT), 4.52±2.4 μM (Alpha), 3.38±1.0 μM (Beta), 2.57±1.0 μM (Delta)	>100 μM >100 μM 69.15 μM	MA104, 293ACE2, Huh7, Vero E6	WT, Alpha, Beta, Delta	Preclinical	[227]
	Fluoxazolevir	Small		MA104: 3.86 μM 293ACE2: 6.62 μM Huh7: 2.64 μM Vero E6: 3.96±1.0 μM (WT), 2.63±0.85 μM (Alpha), 2.29±0.79 μM (Beta), 3.02±096 μM (Delta)	>100 μM >100 μM 32.64 μM	MA104, 293ACE2, Huh7, Vero E6	WT, Alpha, Beta, Delta	Preclinical	[227]
	(–)-hopeaphenol	Small	0.11 μM	13.5 μM 11.4 μM 8.8 μM	>100 μM	Vero-E6	WA1/2020, B.1.1.7, B.1.351	Preclinical	[228]
Nucleocapsid	nCoV396	Monoclonal antibody	K_D=1.02 nM	0.0032 μg/mL		293 cells		Preclinical	[229]
	(-)-gallocatechin gallate	Polyphenol	44.4 μM	-	-	A549-hACE2	SARS-CoV-2 nCoV-SH01 strain	Preclinical	[230]
	CVL218 (mefuparib)	Small		5.194 μM	90.64 μM	Vero E6	BetaCoV/JS03 /human/2020	Preclinical	[231]
	PJ-34	Small						Preclinical	[231]
	Compound12	Small		3.69±0.23 μM	> 200μM	Vero E6	SARS-CoV-2 strain 107	Preclinical	[232]
	Compound16	Small		2.18 ±0.43 μM	> 200μM	Vero E6	SARS-CoV-2 strain 107	Preclinical	[232]
	Ceftriaxone sodium	Small					Structure analysis	Preclinical	[233]
ORF6	Selinexor	Small					Selinexor reduced ORF6-induced cellular toxicity	Preclinical	[234]

Viral RNA	Azacitidine (5-azacytidine)	Small	6.99 μmol/L, 2.63 μmol/L		142.7 μmol/L, 25.4 μmol/L	Vero E6, Calu-3	Wuhan/WIV04/2019	Preclinical	[235]
	5'-ASO#26	Small					WA1, B.1.351, B.1.427, B.1.1.529	Preclinical	[236]
	XNAzyme	Enzyme				HEK293T		Preclinical	[237]
	C6G25S	siRNA	0.46 nM 0.50 nM 0.091 nM 0.73 nM			Vero E6	B.1.1.7, P.1, B.1.617.2, B.1.429		[238]
	DMA-155	RNA binding scaffold	16 μM		90 μM	Vero E6			[239]
	Cas13d	RNA ribonuclease				Vero E6	D614G, Alpha, Zeta, Epsilon (B.1.427), Epsilon (B.1.429)		[240]
	AS_1-75	circRNA		20-50 nM		Vero E6		Preclinical	[241]
	ASO4 (locked nucleic acid antisense oligonucleotide	Oligonucleotide				Hela, Vero E6	USA-WA1/2020	Preclinical	[242]
	O3	siRNA	1.52 nM			Vero E6	hCoV-19/Germany/BAV-Lvirotum-nacq/2020	Preclinical	[243]
	RBM24	RNA binding protein				H1299-ACE2 cells		Preclinical	[244]

Table S2: Summary of anti-spike antibodies against SARS-CoV-2

Antibody name	Resource	Target	Format	Fc	IC_{50}	EC_{50}	SARS-CoV-2 strain	Cell line	PDB	Status	Ref.
Bebtelovimab (LY-CoV1404, LY3853113)	Convalescent COVID-19 patients	RBD	Human IgG1λ monoclonal antibody	WT	9.034 ng/mL		SARS-CoV-2/MT020880.1	Vero E6	7MMO	Phase 2 (NCT04634409)	[245]
Imdevimab (REGN10987)	COVID-19 patient	RBD	Human IgG1λ monoclonal antibody	WT	42.1 pM		USA-WA1 / 2020	Vero E6	6XDG	Phase 4 (NCT05502081)	[246]
Casirivimab (REGN10933)	Humanized mice	RBM	Human IgG1κ monoclonal antibody	WT	37.4 pM		USA-WA1 / 2020	Vero E6	6XDG	Phase 4 (NCT04748588)	[246]
Romlusevimab (BRII-198)	COVID-19 patients		Human IgG1λ monoclonal antibody	YTE						Phase 3 (NCT04501978)	[247]
Amubarvimab (BRII-196, P2C-1F11)	COVID-19 patients	RBD	Human IgG1κ monoclonal antibody	YTE	0.03 μg/mL		Beta / Shenzhen / SZTH-003 / 2020	Vero E6	7E8M	Phase 3 (NCT04501978)	[248, 249]
	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody		WT D614:0.020 μg/mL WT D614G:0.016 μg/mL		WT, beta, delta	Vero E6	7CDI		[250]
Bamlanivimab (LY-CoV555)	COVID-19 patient	RBD	Human IgG1κ monoclonal antibody	WT	0.012 to 0.103 μg/mL		USA-WA1 /2020 Italy-INMI1	Vero E6	7KMG 7L3N	Phase 4 (NCT04656691, NCT04796402,NCT04748588)	[251]
Etesevimab (CB6,JS016, LY-CoV016)	COVID-19 patient	RBM	Human IgG1κ monoclonal antibody	LALA	0.32 nM				7C01	Phase 3 (NCT05205759, NCT04790786,NCT04497987)	[252, 253]
Sotrovimab (VIR-7831, GSK4182136)	SARS-CoV-1 survivor	RBD	Human IgG1κ monoclonal antibody	LS	100.1 ng/mL		USA-WA1 / 2020	Vero E6		Phase 4 (NCT04748588)	[254]
S309	SARS-CoV-1 survivor	RBD	Human IgG1 monoclonal antibody	LS	79 ng/mL		USA-WA1 / 2020	Vero E6	6WPT	Preclinical	[255]
					0.13 μg/mL, 0.094 μg/mL, 0.138 μg/mL, 0.638 μg/mL, 0.228 μg/mL, 1.041 μg/mL,		Victoria BA.1, BA.1.1 BA.2 BA.3 BA.4/5	HEK293T/17	7YQY	Preclinical	[256]
VIR-7832 (GSK4182137)	SARS-CoV-1 survivor	RBD	Human IgG1κ monoclonal antibody	LS/GAALIE	78.3 ng/mL		USA-WA1 / 2020	Vero E6		Phase 1/2 (NCT04746183)	[254]
Cilgavimab (AZD1061)	COVID-19 patients	RBD	Human IgG1κ monoclonal antibody	TM/YTE	0.53 nM		USA-WA1 / 2020	HEK293T-human ACE2 cells	7L7E	Phase 3 (NCT04625972, NCT04625725,NCT0472	[257]

										3394)	
Tixagevimab (AZD8895)	COVID-19 patients	RBD	Human IgG1κ monoclonal antibody	TM/YTE	0.32 nM		USA-WA1 / 2020	HEK293T-human ACE2 cells	7L7E	Phase 3 (NCT04625972, NCT04625725,NCT04723394)	[257]
Regdanvimab (CT-P59)	COVID-19 patient	RBM	Human IgG1λ rAb	WT	8.4 ng/mL, 5.7 ng/mL		wide-type: hCoV-19/Korea/KUMC17/2020, D614G: SARS-CoV-2 (B.1.617.2)	Vero E6	7CM4	Phase 3 (NCT05271929)	[258]
Adintrevimab (ADG20)	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody	LALA	19.6 ng/mL 403 ng/mL		Delta: SARS-CoV-2 (B.1.617.2) Omicron: SARS-CoV-2 (B.1.1.529)	Vero cells	7U2D	Phase 2/3(NCT04859517,NCT04805671)	[259]
					9ng/mL 15ng/mL 13ng/mL 14ng/mL 15ng/mL 1203ng/mL		Alpha Beta Gamma Delta Mu Omicron	HEK293T		Phase 2/3 (NCT04859517, NCT04805671)	[260]
P2B-2F6	COVID-19 patients	RBD	Human IgG1 monoclonal antibody		0.41μg/mL		Beta / Shenzhen / SZTH-003 / 2020	Vero E6	8DCC	Phase 3 (NCT04501978)	[248, 249]
MAD0004J08	convalescent COVID-19 patient	RBD	Human IgG1 monoclonal antibody			4.8 to 5.8 ng/mL	MT066156, MT527178	Vero E6		Phase 2/3 (NCT04952805)	[261]
DZIF-10c	Convalescent COVID-19 patients	RBM	Human IgG1 monoclonal antibody		0.007 μg/mL	0.046 μg/mL	D614G	Vero E6	6XDG	Phase 1/2 (NCT04631666, NCT04631705)	[262]
COV44-62	Convalescent COVID-19 patients	RBD	Human IgG1λmonoclonal antibody				Wuhan Hu-1	Vero E6	8D36	Preclinical	[263]
COV44-79	Convalescent COVID-19 patients	RBD	Human IgG1κ monoclonal antibody				Wuhan Hu-1	Vero E6	8DAO	Preclinical	[263]
1212C2	Convalescent COVID-19 patient	RBD	Human IgG1 monoclonal antibody	LALA			USA-WA1 / 2020	Vero E6		Preclinical	[264]
B38	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody		0.177 μg/mL		BetaCoV/Shenzhen/SZTH-003/2020	Vero E6	7bZ5	Preclinical	[265]
H4	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody		0.896 μg/mL		BetaCoV/Shenzhen/SZTH-003/2020	HEK293T-human ACE2 cells	7UNK	Preclinical	[265]
BD-368-2	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody		15 ng/mL		2019-nCoV BetaCoV/Wuhan/AMMS01/2020	Vero E6	7CHH	Preclinical	[266]

BD23	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody				2019-nCoV BetaCoV/Wuhan/AMMS01/2020	Vero E6	7BYR	Preclinical	[266]
H014	Mice immunized with recombinant SARS-CoV RBD	RBD	Human IgG1 monoclonal antibody		38 nM		BetaCoV/Beijing/AMMS01/2020	Vero	7CAH	Preclinical	[267, 268]
P17	Mice immunized with recombinant SARS-CoV RBD	RBM	Human IgG1 monoclonal antibody		0.195 nM	29 pM		Vero E6	7CWM	Preclinical	[267]
S2H97	COVID-19 patients	RBD	Human IgG1 monoclonal antibody	LS	749 ng/mL		USA-WA1 / 2020	Vero E6		Preclinical	[269]
S2K146	Convalescent COVID-19 patients	RBM	Human IgG1 monoclonal antibody	LS	10 ng/mL 9 ng/mL, 9 ng/mL, 8 ng/mL		USA-WA1 / 2020 Alpha, Beta, Delta	Vero E6	7TAT	Preclinical	[270]
S5D2	Mice immunized with the recombinant trimeric S protein	RBD	Human IgG1 monoclonal antibody		Live virus: 0.056 μg/mL		CoV-SH01	Vero E6	7WD7	Preclinical	[271]
S5G2	Mice immunized with the recombinant trimeric S protein	RBD	Human IgG1 monoclonal antibody		Live virus: 0.205 μg/mL		nCoV-SH01	Vero E6	7WCZ	Preclinical	[271]
S3H3	Mice immunized with the recombinant trimeric S protein	non-RBD	Human IgG1 monoclonal antibody		Live virus: 0.457 μg/mL		nCoV-SH01	Vero E6	7WK8	Preclinical	[271]
STI-9167	Harbour H2L2® mice	RBD	Human IgG1 monoclonal antibody	LALA	6.041 ng/mL 13.7 ng/mL 54.29ng/mL	0.025 μg/mL 0.011 μg/mL 0.024 μg/mL	USA-WA1 / 2020 Delta: SARS-CoV-2 (B.1.617.2) Omicron: SARS-CoV-2 (B.1.1.529)	Vero E6		Preclinical	[272]
Clone2	Mice immunized with purified SARS-CoV-2 RBD	RBD	Human IgG1 monoclonal antibody		108.3 ng/mL		USA-WA1 / 2020	Vero E6		Preclinical	[273]
Clone6	Mice immunized with purified SARS-CoV-2	RBD	Human IgG1 monoclonal antibody		35.73 ng/mL		USA-WA1 / 2020	Vero E6		Preclinical	[273]

	RBD										
35B5	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody		1.55 ng/mL (WT) 7.29 ng/mL (D614G) 13.04 ng/mL (B.1.351) 5.63 ng/mL (B.1.617.2)	0.0183 μg/mL (RBD)	WT (EPI_ISL403934) D614G, B.1.351, B.1.617.2	Vero E6	7WLZ	Preclinical	[274]
87G7	Mice	RBD	Human IgG1 monoclonal antibody		5.4 ng/mL, 5.7 ng/mL, 3.7 ng/mL, 4.2 ng/mL, 6.7 ng/mL, 10.2 ng/mL		Wuhan-Hu-1; D614G; Alpha; Delta; Omicron BA.1; Omicron BA.2	Calu-3	7R40	Preclinical	[275]
J08	Convalescent COVID-19 patient	RBD	Human IgG1 monoclonal antibody		22 ng/mL, 77 ng/mL, 499 ng/mL, 147 ng/mL, 226 ng/mL		D614G; Alpha; Beta; Gamma Delta	HEK293TN-hACE2	7SBU	Preclinical	[276]
G9	Convalescent COVID-19 patient	RBD	Human IgG1 monoclonal antibody		23.9 to 405 ng/mL		WT, B.1.1.7, B.1.351, B.1.617.2, B.1.525	Huh-7		Preclinical	[277]
NT-193	humanized mice	RBD	Human IgG1 monoclonal antibody		< 100 ng/mL			VeroE6/TMPRSS2	7E5O	Preclinical	[278]
76E1	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody		Vero-E6: 0.373 μg/mL HeLa-hACE2 :0.727μg/mL Calu-3:0.433 μg/mL	Vero-E6: 0.072 μg/mL	B.1.1.7、P.1、B.1.351、B.1.617.1、A.1.616.2 B.1.1.529 Omicron BA.1	Vero-E6 HeLa-hACE2 Calu-3	7X9E	Preclinical	[279]
N-612-017	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody		0.09–0.25 μg/mL		wild-type (D614G), B.1.1.7	Vero E6	7S0C	Preclinical	[280]
CV07-287	Convalescent COVID-19	RBD	Human IgG1 monoclonal antibody		< 200 ng/mL		Wildtype Munich isolate 984, Beta, Delta	Vero E6	7S5P 7S5Q 7S5R	Preclinical	[281]
IMM20184	Convalescent COVID-19 patients	RBD	Human IgG1monoclonal antibody		BavPat(D614G)33.8 nM Alpha 43.3 nM Beta 81 nM Gamma 18.4 nM		WA1/2020 D614G, BA.1, BA.1.1.	VeroE6		Preclinical	[282]
IMM20190	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody		BavPat(D614G)0.4 nM Alpha 2.7 nM Beta >393 nM Gamma>393 nM		WA1/2020 D614G, BA.1, BA.1.1.	VeroE6		Preclinical	[282]
IMM20253	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody		BavPat(D614G)39.4 nM Alpha 1.4 nM Beta 155.4 nM Gamma 13.4 nM		WA1/2020 D614G, BA.1, BA.1.1.	VeroE6		Preclinical	[282]
DXP-604	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.287 μg/mL		Omicron: SARS-CoV-2 (B.1.1.529)	HEK293F		Phase 2 (NCT05381519)	[283]
ADG-2	SARS-CoV-1 survivor	RBM	Human IgG monoclonal antibody		~ 1 ng/mL		USA-WA1 / 2020	HeLa-hACE2		Preclinical	[284]
2-43	COVID-19	Non-	Human		0.003 μg/mL		USA-WA1 /	Vero E6	7L56	Preclinic	[285]

	patients	RBD, non-NTD	IgG monoclonal antibody				2020			al	
2-51	COVID-19 patients	Non-RBD, non-NTD	Human IgG monoclonal antibody		0.007 μg/mL		USA-WA1 / 2020	Vero E6	7L2C	Preclinical	[285]
Ab2-4	COVID-19 patients	Non-RBD, non-NTD	Human IgG monoclonal antibody		0.394μg /mL		USA-WA1 / 2020	Vero E6	6XEY	Preclinical	[285]
A23-58.1	COVID-19 patients	RBD	Human IgG monoclonal antibody		2.1 ng/mL	81 ng/mL	USA-WA1 / 2020	Vero E6	7LRT 7LRS	Preclinical	[286]
B1-182.1	COVID-19 patients	RBD	Human IgG monoclonal antibody		2.4 ng/mL	122 ng/mL	USA-WA1 / 2020	Vero E6	7MLZ 7MM0	Preclinical	[286]
4A8	Convalescent COVID-19 patients	Non-RBD	Human IgG monoclonal antibody		0.39 μg/mL	0.61μg/mL		Vero E6	7C2L	Preclinical	[287]
ADI-55689	SARS-CoV-1 survivor	RBD	Human IgG monoclonal antibody				SARS-CoV-2/MT020880.1	Vero E6		Preclinical	[288]
ADI-56046	SARS-CoV-1 survivor	RBD	Human IgG monoclonal antibody				SARS-CoV-2/MT020880.1	Vero E6		Preclinical	[288]
C121	COVID-19 patients	RBM	Human IgG monoclonal antibody		1.64 ng/mL		USA-WA1 / 2020	Vero E6	7K8Y	Preclinical	[289]
C144-LS (BMS-986413)	COVID-19 patients	RBD	Human IgG monoclonal antibody		2.55 ng/mL		USA-WA1 / 2020	Vero E6		Phase 2/3 (NCT04518410)	[289]
C135-LS (BMS-986414)	COVID-19 patients	RBD	Human IgG monoclonal antibody		2.98 ng/mL		USA-WA1 / 2020	Vero E6		Phase 2/3 (NCT04518410)	[289]
COVA1-16	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody	WT	0.02 μg/mL		German isolate; GISAID ID EPI-ISL 406862	Vero E6	7JMW	Preclinical	[290]
COVA1-18	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.007 μg/mL		German isolate; GISAID ID EPI-ISL 406862	Vero E6		Preclinical	[291]
COVA2-15	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.009 μg/mL		German isolate; GISAID ID EPI-ISL 406862	Vero E6		Preclinical	[291]
COVA2-04	a convalescent donor from Amsterdam	RBD	Human IgG monoclonal antibody		2.5μg/mL		GenBank:QHD43416.1		7JMO	Preclinical	[292]
COVA2-39	a convalescent donor from Amsterdam	RBD	Human IgG monoclonal antibody		0.054 μg/mL		GenBank:QHD43416.1		7JMP	Preclinical	[292]
EY6A	Convalescent COVID-19 patient	RBD	Human IgG monoclonal antibody		ND_{50}: 0.39 μg/mL		Australia/VIC01/2020(PRNT)(PHE, Porton	Vero E6	6ZER 6ZDG 6ZDH	Preclinical	[293]

							Down)				
S2H13	COVID-19 patients	RBM	Human IgG monoclonal antibody		PSV: 500 ng/mL		Wu-hu-1	Vero E6	7JV4 7VJ2	Preclinical	[294]
S2H14	COVID-19 patients	RBM	Human IgG monoclonal antibody		PSV: 900 ng/mL		Wu-hu-1	Vero E6	7JXC	Preclinical	[294]
S2A4	COVID-19 patients	RBM	Human IgG monoclonal antibody		PSV: 3.5 μg/mL		Wu-hu-1	Vero E6	7JVA	Preclinical	[294]
S304	COVID-19 patients	RBM	Human IgG monoclonal antibody		PSV: 500 ng/mL		Wu-hu-1	Vero E6	7JW0	Preclinical	[294]
R40-1G8	Convalescent COVID-19 individuals	RBD	Human IgG monoclonal antibody		< 0.02 μg/mL		SARS-2-S Wu01, SARS-2-S SARS-1,SARS-2-S WiV-1, SARS-2-S B.1	HEK293T cells	7SC1	Preclinical	[295]
JMB2002	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		1.8 nM		Omicron: SARS-CoV-2 (B.1.1.529)			Preclinical	[296]
CC40.8	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		CC40.8-treated animals exhibited less weight loss and reduced lung viral titers		SARS-CoV-2 (WT-Wuhan)	HEK293T	7SJS	Preclinical	[297]
1-57	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.008 μg/mL		USA-WA1 / 2020	Vero E6	7LS9	Preclinical	[298]
2-7	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.003 μg/mL		USA-WA1 / 2020	Vero E6	7LSS	Preclinical	[298]
DH1047	Convalescent patient with SARS-CoV	RBD	Human IgG monoclonal antibody		0.397 μg/mL 0.059 μg/mL		Q498Y/P499T, D614G	Vero E6	7SG4 7LD1	Preclinical	[299]
hMab5.17	Mice	RBD	Human IgG monoclonal antibody		12.2 μg/mL		hCoV-19/Taiwan/4/2020 and variants	Vero		Preclinical	[300]
1Ba-3H	Mouse	RBM	Human IgG monoclonal antibody		PSV: 16.8μg/ mL			ACE2-293T		Preclinical	[301]
2-36	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.029 μg/mL		USA-WA1 / 2020	Vero E6	7N5H	Preclinical	[302]
G32R7	Convalescent COVID-19 patients	RBD-1	Human IgG monoclonal antibody		0.109 μg/mL, 0.08 μg/mL, 0.375 μg/mL, 1.851 μg/mL, 0.162 μg/mL		Wuhan-Hu-1, Alpha, Gamma, Delta, Omicron BA.1	293FT co-expressing human ACE2 and TMPRSS2	7N64	Preclinical	[303]
G32Q4	Convalescent COVID-19 patients	RBD-3	Human IgG monoclonal antibody		0.578 μg/mL, 1.476 μg/mL, 0.089 μg/mL, 0.316 μg/mL, 6.666 μg/mL		Wuhan-Hu-1, Alpha, Gamma, Delta, Omicron BA.1	293FT co-expressing human ACE2 and TMPRSS2	7SWP	Preclinical	[303]
C549	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		15 ng/mL		SARS-CoV-2 pseudotyped HIV-1	HT1080/ACE2.cl14 cells		Preclinical	[304]
C099	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		15 - 48 ng/mL, L455R (123 ng/mL)		SARS-CoV-2 pseudotyped HIV-1	HT1080/ACE2.cl14 cells	7N3H	Preclinical	[304]
C080	Convalescent COVID-	RBD	Human IgG monoclonal		71 ng/mL		SARS-CoV-2 pseudotyped	HT1080/A	7N3F	Preclinical	[304]

	19 patients		antibody				HIV-1	CE2.cl14 cells			
mAb222	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.019μg/mL, 0.018±0.001μg/mL		Victoria, B.1.617.2	Vero	7NX6, 7NX7, 7NX8, 7NX9, 7NXB, 7NXA, 7NXC	Preclinical	[305]
mAb298	Mice	RBD	Human IgG monoclonal antibody		57 ng/mL		D614GB.1.351	293T-ACE2		Preclinical	[306]
S-E6	Healthy donors before the COVID-19 pandemic	RBD	Human IgG monoclonal antibody		12.2±0.7 nm		B.1.351and P.1	Vero	7KN4	Preclinical	[307]
P5A-3C8	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.0112 μg/mL		Beta/Shenzhen/SZTH-003/2020, EPI_ISL_406594	Vero-E6	7CHP	Preclinical	[308]
Omi-3	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.007±0.000μg/mL, 0.012±0.007μg/mL, 0.009±0.001 μg/mL, 0.004±0.000 μg/mL, 0.004±0.000 μg/mL, 0.009±0.002 μg/mL, 0.015±0.000 μg/mL, 0.028±0.002 μg/mL		Victoria Alpha, Beta, Gamma, Delta, BA.1 BA.1.1 BA.2	Vero cells		Preclinical	[309]
C1C-A3	Convalescent COVID-19	RBD	Human IgG monoclonal antibody		0.141 μg/mL, 0.139 μg/mL, 0.185 μg/mL, 1.4 μg/mL, 0.234 μg/mL, 0.158 μg/mL, 0.06 μg/mL	0.087μg/mL	WT (D614G), Alpha, Beta, Epsilon Kappa, Lambda, Gamma	HEK293T	7SN2	Preclinical	[310]
510A5	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		WT:17.10 ng/mL Delta:22.26 ng/mL	WT:16.78ng/mL Delta:14.14 ng/mL	Omicron, Delta, and WT	Lenti-X293T		Preclinical	[311]
Beta-53	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody				Alpha Beta Gamma	HEK-293T	7Q9M	Preclinical	[312]
COV2-2196	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody				OmicronBA.1; OmicronBA.1.1 D614G	VeroE6/TMPRSS2	8D8R	Preclinical	[313]
COV2-2130	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody				OmicronBA.1; OmicronBA.1.1 D614G	VeroE6/TMPRSS2		Preclinical	[313]
COV2-3434	Convalescent COVID-19 patients	Non-RBD(NTD)	Human trimer-interface monoclonal antibody		32 μg/mL, 5.5 μg/mL	0.025μg/ML (SARS-CoV-2 S6Pect)	D614G; Wash-B 1.351	Vero		Preclinical	[314]
P2G3	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		Omicron BA.1 0.021μg /mL BA .2 0.0O08μg /mL		2019-nCoV (D614G) strain, Alpha, Beta, Gamma, Delta and Omicron	Vero E6	7QTK	Preclinical	[315]
P5C3	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		Omicron BA.1 0.351μg /mL BA .2 0.158μg /mL		2019-nCoV (D614G) strain, Alpha, Beta, Gamma, Delta and Omicron	Vero E6	7P40 or 7PHG	Preclinical	[315]
VH01H1	Convalescent COVID-	RBD	Human IgG monoclonal		IgG:43μg /mL 12.5μg /mL		WA-1 (USA-WA1/2020) ,	Vero-TMPRSS2		Preclinical	[316]

	19 patients		antibody		19.7μg /mL scFv:7.3μg /mL 0.9μg /mL 2.6μg /mL		BA.1 (hCoV-19/USA/MD-HP20874/2021) BA.2 (hCoV-19/USA/MD-HP24556/2022)				
C77G12	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		IgG:26.9μg /mL 2.9μg /mL 5.4μg /mL scFv:2μg /mL 0.6μg /mL 0.8μg /mL		WA-1 (USA-WA1/2020) , BA.1 (hCoV-19/USA/MD-HP20874/2021) BA.2 (hCoV-19/USA/MD-HP24556/2022)	Vero-TMPRSS2		Preclinical	[316]
C102	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		34ng/mL			Expi293F	7K8M	Preclinical	[317]
C104	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		23.3ng/mL			Expi293F	7K8U	Preclinical	[317]
C119	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		9.1ng/mL			Expi293F	7K8W	Preclinical	[317]
C144	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		6.9ng/mL			Expi293F	7K90	Preclinical	[317]
CV30	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.118 μg/mL		USA-WA1/2020	VeroE6	6XE1	Preclinical	[318]
CV07-250	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		3.5 ng/mL		Munich isolate 984	HEK293T	6XKQ	Preclinical	[319]
CV07-270	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		82.3 ng/mL		Munich isolate 984	HEK293T	6XKP	Preclinical	[319]
5A6	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		IgG:140.7 ng/mL Fab:3.3ng/m		isolated from a nasopharyngeal swab of an individual in Singapore	Vero E6 C1008	7M71	Preclinical	[320]
47D11	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		WT: 0.063μg /mL E484K: 0.078 μg /mL N501Y: 0.054μg /mL K417N: 0.059 μg /mLl		WT, E484K, N501Y, K417N	VeroE6	7AKJ	Preclinical	[321]
BG10-19	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.002μg /mL 0.001μg /mL 0.004μg /mL		WT B.1.1.7, B.1.351	Vero E6-TMPRSS2	7M6E	Preclinical	[322]
CC12.1	Convalescent COVID-19 patients	RBD	Human IgG1 monoclonal antibody		0.019 μg/mL		USA-WA1/2020	HeLa-ACE2 cells	6XC2	Preclinical	[323]
CC12.3	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		20 ng/mL				6XC4	Preclinical	[324]
553-49	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		11.44 ng/mL		Omicron	293T	7WOG	Preclinical	[325]
58G6	A COVID-19 patients	RBD	Human IgG monoclonal antibody		Pseudovirus: 4.75 ng/mL 1.35 ng/mL 183.6 ng/mL Authentic Virus: 1.32 ng/mL		WT, Delta(B.1.617.2) , Omicron BA.1	Vero E6	7E3L	Preclinical	[326]

					1.69 ng/mL 54.31 ng/mL						
F61	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		HEK293T(Pseudovirus): 7 ng/mL 11 ng/mL 2 ng/mL 10 ng/mL 9 ng/mL 10 ng/mL 16 ng/mL 19 ng/mL 12 ng/mL Vero E6(Athuentic virus): 10 ng/mL 160 ng/mL 200 ng/mL 130 ng/mL	2.638 ng/mL (Delta), 4.399 ng/mL (Omicron)	Pseudoviruses: Alpha(B.1.1.7), Beta(B.1.351) Delta(B.1.617.2), Delta(B.1.617.3) Omicron(BA.1), Omicron(BA.1.1), Omicron(BA.2), Omicron(BA.3), Omicron(BA.4) Athuentic viruses: Omicron(BA.1), Omicron(BA.1.1), Omicron(BA.2)	HEK293T, Vero E6	7XST	Preclinical	[327]
D2	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		HEK293T(Pseudovirus): 1 ng/mL 22 ng/mL 8 ng/mL 43 ng/mL 18 ng/mL 249 ng/mL 11 ng/mL 32 ng/mL 318 ng/mL Vero E6(Athuentic virus): 390 ng/mL 350 ng/mL >800 ng/mL 162 ng/mL	3.303 ng/mL (Delta), 4.150 ng/mL (Omicron)	Pseudoviruses: Alpha(B.1.1.7), Beta(B.1.351) Delta(B.1.617.2), Delta(B.1.617.3) Omicron(BA.1), Omicron(BA.1.1), Omicron(BA.2) Omicron(BA.3), Omicron(BA.4) Athuentic viruses: Omicron(BA.1), Omicron(BA.1.1), Omicron(BA.2)	HEK293T, Vero E6	7XMZ	Preclinical	[327]
CV10-2449–ACE2	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody				WT, Alpha, Beta, Gamma, Delta, Omicron			Preclinical	[328]
002-S21F2	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.05 μg /mL, 0.05 μg /mL, 0.02 μg /mL, 0.03 μg /mL, 0.03 μg /mL, 0.05 μg /mL, 0.04 μg /mL, 0.12 μg /mL, 0.13 μg /mL, 0.13 μg /mL		WA.1, Alpha, Beta, Gamma, Delta, BA.1, BA.2, BA.2.12.1, BA.4, BA.5	Vero-TMPRSS2	7UPL	Preclinical	[329]
5317-10	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		0.1311 μg /mL, 0.0108 μg /mL, 0.1172 μg /mL, 0.1857 μg /mL, 0.2733 μg /mL,		WA1, Alpha, Beta, Gamma, Delta	Vero E6		Preclinical	[330]
JS026	A Convalescent COVID-19 patient	RBD	Human IgG monoclonal antibody		3.2 μg /mL, 0.6 μg /mL, 2.0 μg /mL, 3.2 μg /mL, 1.4 μg /mL,		WT, Alpha, Beta, Gamma, Delta	HEK293T-hACE2		Preclinical	[331]
scFv76	Mice	RBD	Human IgG		Caco-2:		Omicron BA.1,	Caco-2	7ZCF	Preclinic	[332]

			monoclonal antibody		2.84 nM(Omicron BA.1) 2.47 nM(Omicron BA.2) Vero E6: 1.99 nM(Delta), 6.38 nM(Omicron BA.1) Calu-3: 13.5 nM(Delta)		Omicron BA.2, Delta	Vero E6 Calu-3		al	
CT-P63	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		Live viruses: 50.50 ng/mL 96.48 ng/mL 88.67 ng/mL 46.95 ng/mL 18.88 ng/mL 7.21 ng/mL 20.58 ng/mL 25.84 ng/mL 22.46 ng/mL 58.48 ng/mL 34.28 ng/mL 14.53 ng/mL 44.44 ng/mL 31.79 ng/mL Pseudoviruses: 4.81 ng/mL 22.29 ng/mL 9.45 ng/mL 5.46 ng/mL 12.0 ng/mL 5.32 ng/mL 1.71 ng/mL 3.27 ng/mL 18.69 ng/mL 12.18 ng/mL 8.26 ng/mL 4.85 ng/mL 14.10 ng/mL 5.86 ng/mL 5.57 ng/mL 3.53 ng/mL 2.16 ng/mL		Live viruses: WT, B.1.1.529/BA.1, B1.1.529/BA.2, BA.2.12.1, Delta(B.1.617.2), Gamma(P.1), Beta(B.1.351), Kappa(B.1.617.1), Alpha(B.1.1.7), Epsilon(B.1.427), Epsilon(B.1.429), Eta(B.1.525), Iota(B.1.526), Zeta(P.2) Pseudoviruses: D614G, B.1.1.529/BA.1, B1.1.529/BA.2, BA.2.12.1, Omicron BA.3, Delta(L452R/T478K/P681R), Gamma(P.1), Beta(B.1.351), Lambda(C.37), Mu(B.1.621), Kappa(L452R/E484Q/P681R), Alpha(B.1.1.7), Epsilon(B.1.427), Epsilon(B.1.429),Eta(B.1.525), Iota(B.1.526), Zeta(P.2)	HEK293T		Phase 3 (NCT05224856)	[333]
6M6	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		16.8 ng/mL 15.6 ng/mL 69.0 ng/mL 48.0 ng/mL 653 ng/mL 19.9 ng/mL		WT, Alpha, Beta, Gamma, Delta, Omicron		7WK0	Preclinical	[334]
S2X324	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		2.72 ng/mL 3.68 ng/mL 2.78 ng/mL 3.86 ng/mL 2.46 ng/mL		WA1/2020 BA.1 BA.2 BA.4-V3G BA.5	VeroE6-TMPRSS2 cells	8ERQ	Preclinical	[335]
R1-32	Convalescent COVID-19 patients	RBD	Human IgG monoclonal antibody		4.03 nM 9.03 nM 33.7 nM		Wildtype Beta Delta	293T-ACE2 cells	7YDI	Preclinical	[336]

CR3022	SARS-CoV-1 patient	RBD	Human IgG1kappa monoclonal antibody				Australia/VIC01/2020	Vero E6	7JN5	Preclinical	[337]
S2M11	Convalescent COVID-19 patients	RBM	Human IgG1m3 monoclonal antibody	LS	0.02 nM		USA-WA1/2020	Vero E6	7K43	Preclinical	[338]
S2E12	Convalescent COVID-19 patients	RBD	Human IgG1m3 monoclonal antibody	LS	0.04 nM		USA-WA1/2020	Vero E6	7K4N, 7R6X	Preclinical	[338]
SARS2-38	Splenocytes of BALB/c mice	RBD	IgG1 monoclonal antibody			1 to 7 ng/mL	B.1.1.7, B.1.429, B.1.1.298, B.1.222, B.1.617.1, B.1.617.2, B.1.526+S477N	Vero E6	7MKL, 7MKM	Preclinical	[339]
3E8	BALB/c mice were immunized with Fc-tagged human ACE2	RBD	Human IgG4 monoclonal antibody		0.04 nM		SARS-CoV2 (IVCAS 6.7512）	Vero E6	7V61	Preclinical	[340]
bsAb15	Convalescent COVID-19 patients	RBD	Human IgG-ScFv monoclonal antibody		3.34 nM		hCoV-19/China/CAS-B001/2020	Vero E6		Preclinical	[341]
STE90-C11	Convalescent COVID-19 patients	RBD	Human IgG1		2.56a: 50nM Spike 0.99a: 10nM RBD		B.1.617,B.1.525, B.1.526, B.1.1.33, B.1.258, and B.1.429/B.1.427	VeroE6	7B3O	Phase Ib/II tria (ID: NCT04674566).	[342]
ZCB11	Convalescent COVID-19 patients	RBD	Human IgG1		51 ng/mL, 85.1 ng/mL, 39.9 ng/mL, 56.9 ng/mL, 11.2 ng/mL, 36.8 ng/mL, 11.7 ng/mL, 27.7 ng/mL,		D614G, Alpha, Beta, Gamma, Delta, Omicron BA.1, Omicron BA.1.1, Omicron BA.2	Vero E6	7XH8	Preclinical	[343]
HP6017	Convalescent COVID-19 patients	RBD	Human IgG					HEK293F		Preclinical	[344]
10-40	Convalescent COVID-19 patients	RBD	IgG monoclonal antibody		0.029 μg/mL, 0.045 μg/mL, 0.104 μg/mL, 0.079 μg/mL, 0.298 μg/mL, 0.139 μg/mL, 0.225 μg/mL,		USA-WA1/2020 B.1.1.7 B.1.351 P.1 B.1.617.2 C.37 B.1.621	Vero E6	7SD5	Preclinical	[345]
C022	Convalescent COVID-19 patients	RBD	IgG		173ng/mL, 255ng/mL, 455ng/mL, 250ng/mL, 377ng/mL		D614G B.1.1.7, B.1.351, B.1.429, B.1.536,	$293T_{ACE2}$	7RKU	Preclinical	[346]
C118	Convalescent COVID-19 patients	RBD	IgG		440ng/mL, 316ng/mL, 709ng/mL, 359ng/mL, 464ng/mL,		D614G B.1.1.7, B.1.351, B.1.429, B.1.536,	$293T_{ACE2}$	7RKS	Preclinical	[346]
MW01	Convalescent	RBD	Human monoclonal					Huh7 Vero	7DJZ	Preclinical	[347]

	COVID-19 patients		antibody								
MW05	Convalescent COVID-19 patients	RBD	Human monoclonal antibody					Huh7 Vero	7DK0	Preclinical	[347]
2H2	Mice	RBD	IgG1 monoclonal antibody		0.007μg/mL		nCoV-SH01 (GenBank: MT121215.1)	VeroE6	7DK5	Preclinical	[348]
3C1	Mice	RBD	IgG1 monoclonal antibody		3.127 μg/mL	31.4ng/mL	nCoV-SH01 (GenBank: MT121215.1)	VeroE6	7DD8	Preclinical	[348]
UT28K	Convalescent COVID-19 patients	RBD	Human IgG CH1 monoclonal antibody		Omicron variant：200 pM)		WT, Alpha, Beta, Gamma, Delta	VeroE6/TMPRSS2	7X7O	Preclinical	[349]
$CA521^{FALA}$	Mice	RBD	IgG monoclonal antibody		CA521 FALA:0.343 nM hACE2protein:8.887 nM pseudoviruses transduction into Huh-7: 0.121 nM hACE2:0.104 nM	CA521FALA:0.014 nM CA13f SARS-CoV-2: 0.015nM CA13f SARS-CoV: 0.019 nM		Vero	7E23	Preclinical	[350]
NAb 15033-7	Convalescent COVID-19 patients	RBD	Human IgG		IgG 15033-7:550 pM tetravalent Fab-IgG and IgG-Fab Versions:60 and 37 pM		2019 nCoV/USA_WA1/2020	Vero E6	7KXK	Preclinical	[351]
10D12	RenMab mice	RBD	IgG monoclonal antibody			0.02μg/mL	E406W	Huh-7 cells		Preclinical	[352]
7B8	RenMab mice	RBD	IgG monoclonal antibody			0.05μg/mL, a	B1.1.7	Huh-7 cells		Preclinical	[352]
9G11	RenMab mice	RBD	IgG monoclonal antibody			0.05 μg/mL	E406W	Huh-7 cells		Preclinical	[352]
FBR002	Convalescent COVID-19 patients	RBM	Monoclonal antibody		81.9 ng/mL 234.9 ng/mL 2950 ng/mL 688.5 ng/mL		D614G BA.1 BA.4 BA.4/5			Phase 2 (NCT05279352)	[353]
mAb253	Convalescent COVID-19	RBD	Monoclonal antibody		55±8 ng/mL, 5±1 ng/mL		Victoria, B.1.617.2	HEK293T/17 cells		Preclinical	[354]
COV89-22	Convalescent COVID-19 patients	RBD	Monoclonal antibody		NT_{50}: 1.83 μg /mL 5.16 μg /mL 6.28 μg /mL 5.94 μg /mL 9.87 μg /mL 5.30 μg /mL 3.00 μg /mL 9.20 μg /mL 7.30 μg /mL 25.0 μg /mL 7.42 μg /mL		WT, Alpha, Beta, Gamma, Delta, Mu, Omicron BA.1, Omicron BA.2, BA.2.12.1, Omicron BA.2.75, Omicron BA.4/5	Hela	8DTX	Preclinical	[355]
COV72-37	Convalescent COVID-19 patients	RBD	Monoclonal antibody		NT_{50}: 8.25 μg /mL 10.63 μg /mL 9.36 μg /mL 6.09 μg /mL 14.08 μg /mL 10.52 μg /mL 9.72 μg /mL		WT, Alpha, Beta, Gamma, Delta, Mu, Omicron BA.1, Omicron BA.2,	Hela		Preclinical	[355]

					10.35 μg /mL 10.59 μg /mL 24.2 μg /mL 7.85 μg /mL		BA.2.12.1, Omicron BA.2.75, Omicron BA.4/5				
NA8	Convalescent COVID-19 patients	RBD	Monoclonal antibody		0.008 μg /mL 0.002 μg /mL 0.004 μg /mL 0.450 μg /mL 0.005 μg /mL 0.008 μg /mL 5.701 μg /mL 0.512 μg /mL		WA-1, Alpha, Beta, Delta, Omicron BA.1, Omicron BA.2, Omicron BA.4, BA.2.12.1	Vero-E6	7U9P	Preclinical	[356]
NE12	Convalescent COVID-19 patients	RBD	Monoclonal antibody		0.003 μg /mL 0.004 μg /mL >10 μg /mL 0.001 μg /mL 2.819 μg /mL 0.498 μg /mL 0.412 μg /mL 1.742 μg /mL		WA-1, Alpha, Beta, Delta, Omicron BA.1, Omicron BA.2, Omicron BA.4, BA.2.12.1	Vero-E6	7U9O	Preclinical	[356]
P4A2	K18-hACE2-transgenic mice against SARS-CoV-2 VOCs	RBD	Monoclonal antibody		230 ng/mL(WA1/2020) 45 ng/mL(BA.1)	0.0093 μg /mL, 0.0099 μg /mL, 0.6002 μg /mL, 0.1158 μg /mL, 0.0131 μg /mL, 0.0121 μg /mL, 0.2616 μg /mL	WA1/2020, Alpha, Beta, Gamma, Kappa, Delta, BA.1	Vero E6	7WVL	Preclinical	[357]
CV3-1	Convalescent COVID-19	RBD	SARS-CoV-2 spike (S)-neutralizing monoclonal		0.004-0.014 μg/mL		b .1.1.7 (SARS-CoV2 a), b .1.351 (b), P.1, b .1.617.2，b .1.429, b .1.525 ,b .1.526, b .1.617.1	293T-ACE2	7NAB	Preclinical	[358]
CV3-25	Convalescent COVID-19	RBD	SARS-CoV-2 spike-neutralizing monoclonal		0.05-0.2 μg/mL		b .1.1.7 (SARS-CoV2), b .1.351, P.1, b .1.617.2，b .1.429, b .1.525, b .1.526, b.1.617.1 (k)	V293T-ACE2	7NAB, 7RAQ	Preclinical	[358]
SW186	Mice	RBD	SARS-CoV-2 spike-neutralizing monoclonal		64 ng/mL 78 ng/mL 15 ng/mL 36 ng/mL 42 ng/mL 38 ng/mL <1 ng/mL		Wuhan-Hu-1, B.1.1.7(Alpha), B.1.351(Beta), P.1(Gamma), B.1.617.2(Delta), C.37(Lambda), B.1.621(Mu)	Huh-7	8DT3	Preclinical	[359]
sACE22.v2.4-IgG1	Mice	RBD	SARS-CoV-2 spike(S)-neutralizing monoclonal		BA.1 omicron: 18±7 pM(Hela-hACE2-11,Engineered) 580±70 pM(Hela-hACE2-11,WT) 0.14±0.22 nM(Calu-3,Engineered) 7.5±9.2 nM(Calu-3,WT) BA.2 omicron: 130±40 pM(Hela-hACE2-11,Engineered) 350±90 pM(Hela-		BA.1 omicron, BA.2 omicron,	Hela-hACE2-11 Calu-3		Preclinical	[360]

					hACE2-11,WT)						
14-H-06		RBD	Bi-specific antibody		21.2 nM		WA		7WPV	Preclinical	[361]
VHH-E	Llama	RBD	Multivalent nanobody		60 nM		SARS-CoV-2/human/Germany/Heinsberg-01/2020	Vero E6	7KN5	Preclinical	[362]
VHH-U	Alpaca	RBD	Multivalent nanobody		286 nM		SARS-CoV-2/human/Germany/Heinsberg-01/2020	Vero E6		Preclinical	[362]
VHH-W	Alpaca	RBD	Multivalent nanobody		257 nM		SARS-CoV-2/human/Germany/Heinsberg-01/2020	Vero E6	7KN7	Preclinical	[362]
mNb6	Yeast	RBD	Nanobody		54 pM		France/IDF0372/2020	Vero E6	7KKJ	Preclinical	[363]
mNb6-tri	Yeast	RBD	Ttrivalent nanobody		PSV: 120 pM		France/IDF0372/2020	Vero E6		Preclinical	[363]
Sb23		RBD	Synthetic nanobody		0.6 μg/mL			HEK293T-ACE2	7A25, 7A29	Preclinical	[364]
H11-H4	Llama	RBD	Synthetic nanobody		34 nM		Australia/VIC01/2020	Vero E6	6ZBP	Preclinical	[365]
H11-D4	Llama	RBD	Synthetic nanobody		28 nM		Australia/VIC01/2020	Vero E6	6Z43	Preclinical	[365]
Sb#15	convalescent COVID-19 patients	RBD	Synthetic nanobody		Sb#15:2.3μg/mL (147 nM)		B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta)	Vero E6	3K1K	Preclinical	[366]
Sb#68	convalescent COVID-19 patients	RBD	Synthetic nanobody		2.3μg/mL (138 nM)		B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta)	Vero E6	7KLW	Preclinical	[366]
Ty1	Alpaca	RBD	Alpaca nanobody		54 nM			HEK293T Vero E6		Preclinical	[367]
Nb20	Llama	RBD	Nanobody		0.048 nM		SARS-CoV-2 (Munich strain)	Vero E6	7JVB	Preclinical	[368]
Nb21	Llama	RBD	Nanobody		0.022 nM		SARS-CoV-2 (Munich strain)	Vero E6	7N9A, 7N9B	Preclinical	[368]
Nb34	Llama	RBD	Nanobody		1.125 nM		SARS-CoV-2 (Munich strain)	Vero E6	7N9E	Preclinical	[368]
Nb95	Llama	RBD	Nanobody		5.105 nM		SARS-CoV-2 (Munich strain)	Vero E6	7N9C	Preclinical	[368]
NB1A7	A camel immunized with recombinant RBD	RBD	Nanobody		808.1 ± 1.02 nM (against RDB) 59.3 ± 1.40 nM (PRNT: ND_{50})		P.1, B.1.526, B.1.617.1, B.1.617.2	Vero E6 (PRNT)	7FAT	Preclinical	[369]
NB1B11	A camel immunized with recombinant RBD	RBD	Nanobody		709.4 ± 1.03 nM (against RDB) 36.5 ± 1.52 nM (PRNT: ND_{50})		P.1, B.1.526, B.1.617.1, B.1.617.2	Vero E6 (PRNT)	7FAU	Preclinical	[369]
7A3+8A2	Camels	RBD	Nanobodies		20 nM (WT) 6 nM (D614G) 2 nM (B.1.1.7) 0.87 nM (B.1.351) 0.14 nM (P.1) 27 nM (B.1.617.2)		Wuhan-Hu-1 D614G B.1.1.7 B.1.351 P.1 B.1.617.2	Vero E6	7TPR	Preclinical	[370]
C5-trimer	Camelid	RBD	Nanobody		Victoria - B; 18 pM Alpha - B1.1.7: 25 pM		Victoria, Alpha, Beta	Vero E6	7OAO	Preclinical	[371]
Nb-0	Mice	RBD	Nanobody					HEK293	7R9D	Preclinic	[372]

										al	
Fab_8D3	Mice	RBD	Nanobody					HEK293	7R9D	Preclinical	[372]
DL4	Immunized alpaca	RBD	Nanobody		0.101 μg/mL (6.23 nM) Fc-DL4：3.23 μg/mL		Alpha (B.1.1.17), Beta (B.1.351), Gamma (P.1)	HEK293T	7F5G	Preclinical	[373]
Nb12	Nanomouse	RBD	Nanobody		248pM 64pM 286pM 2755pM 1874pM		USA-WA1/2020 (WA1) B.1.1.7 B.1.351 P.1	Vero-E6	7MY3	Preclinical	[374]
Nb30	Nanomouse	RBD	Nanobody		9374pM 538pM 2755pM 1874pM		USA-WA1/2020 (WA1) B.1.1.7 B.1.351 P.1	Vero-E6	7MY2	Preclinical	[374]
WNbFc2	Alpacas	RBD	Nanobody		WT:0.33nM N501Y D614G:0.30nM	2.65nM	WT (hCoV-19/Australia/VIC01/2020)SARS-CoV-2 (hCoV19/Australia/VIC2089/2020)			Preclinical	[375]
WNbFc36	Alpacas	RBD	Nanobody		WT:0.10nM N501Y D614G:0.11nM	0.97nM	WT (hCoV-19/Australia/VIC01/2020)SARS-CoV-2 (hCoV19/Australia/VIC2089/2020)			Preclinical	[375]
nCoV617	Convalescent COVID-19	RBD	Nanobody					Vero cells (Corning; no. 3988)	7E3O	Preclinical	[376]
Nanosota-1C	Camelidae family	RBD	Nanobody				(US_WA-1 isolate) from CDC (Atlanta)	VeroE6	7KM5	Preclinical	[377]
Nanosota-1C-Fc	Camelidae family	RBD	Nanobody				(US_WA-1 isolate) from CDC (Atlanta)	VeroE6		Preclinical	[377]
2-3-Fc	Fusing aSA3-Fc to aRBD-2	RBD	Nanobody		Authentic: 10.3 ng/mL 4.6 ng/mL 2.6 ng/mL 5.3 ng/mL Pseudotyped: 4.0 ng/mL 6.6 ng/mL 8.1 ng/mL 138.3 ng/mL		Authentic: WT, Beta, Delta, BA.1 Pseudotyped: BA.1 BA.2, BA.5, BA.2.75	ACE2-293T	7X4I	Preclinical	[378]
aRBD-2-5-Fc	Mice	RBD	Nanobody		0.0830 nM 0.0511 nM 0.0438 nM 0.1087 nM 0.0271 nM 0.0769 nM 0.0293 nM		WT, Alpha, Beta Gamma, Delta, Kappa, BA.1		7VOA	Preclinical	[379]
X01	Mice	RBD	Nanobody		0.17 μg /mL 0.07 μg /mL 0.13 μg /mL 0.06 μg /mL 33.25 μg /mL	3.29 μg /mL	B.1.1.7, B.1.351, B.1.1.28, B.1.617.2, B.1.1.529	Vero E6	7X7T	Preclinical	[380]
X10	Mice	RBD	Nanobody		0.07 μg /mL 0.02 μg /mL 0.09 μg /mL 0.17 μg /mL	18.79 μg /mL	B.1.1.7, B.1.351, B.1.1.28, B.1.617.2,	Vero E6	7X7T	Preclinical	[380]

					12.22 μg /mL		B.1.1.529				
X17	Mice	RBD	Nanobody		0.28 μg /mL 0.29 μg /mL 1.02 μg /mL 0.54 μg /mL 1.67 μg /mL	0.005 μg /mL	B.1.1.7, B.1.351, B.1.1.28, B.1.617.2, B.1.1.529	Vero E6	7X7T	Preclinical	[380]
XG014	Convalescent COVID-19 patients	RBD	Nanobody		Huh-7: 0.014±0.002 μg /mL 0.021±0.002 μg /mL 0.032±0.004 μg /mL 0.017±0.002 μg /mL Caco-2: 0.023±0.003 μg /mL 0.018±0.001 μg /mL 0.031±0.002 μg /mL 0.016±0.002 μg /mL	0.014 to 0.032μg/mL	WT, B.1.1.7, B.1.351, P.1	Huh-7 Caco-2	7V2A	Preclinical	[381]
P3E6	Fully-vaccinated individuals after BA.1 natural infection	RBD	Monoclonal antibody		0.0105 μg /mL 0.0114 μg /mL 0.0153 μg /mL 0.0234 μg /mL 0.0183 μg /mL 0.0064 μg /mL 0.0204 μg /mL 0.11 μg /mL 0.0743 μg /mL		WT, Alpha, Beta, Gamma, Delta, BA.1, BA.2, BA.2.12.1, BA.4/5	Vero-E6-TMPRSS2	7YKJ	Preclinical	[382]
IMM-BCP-01	Convalescent COVID-19 patients	RBD	Three antibody cocktail		REF (WA1/2020) 1.0nM BavPat (D614G) 0.6 nM Alpha 3.0 nM Beta 13.5 nM Gamma 24.8 nM B.1.617(L452/E484Q) 1.0 nM Delta 0.4 nM Delta plus 3.0 nM Epsilon 0.6 nM Kappa (complete sequence) 2.7 nM Lambda 0.4 nM Mu 9.1 nM Zeta 1.53 nM		WA1/2020 D614G, BA.1, BA.1.1.	VeroE6	7JVB	Phase 1 (NCT05429021)	[282]
SAB-185	Ranschromosomic bovines	Ectodomain	Human IgG polyclonal antibody				USA-WA1 / 2020	293-ACE2-TMPRSS2		Phase 2/3 (NCT04518410)	[383]
XAV-19	Swine glyco-humanized IgG	RBD	Polyclonal antibody							Phase 2, Phase 3 (NCT04928430)	[384]
COV21	Convalescent COVID-19 patients	RBD	Human IgG polyclonal antibody		62.3 nM	20–50 μg/mL	Wu-Hu-1	HEK293T-human ACE2 cells		Preclinical	[385]
C105	Convalescent COVID-19 patients	RBD	Human IgG polyclonal antibody		26.1 ng/mL		Wu-Hu-1	HEK293T-human ACE2 cells	6XCA	Preclinical	[385]
bn03	Camels	RBD	A bispecific single-domain antibody		(Pseudovirus neutralization assay) 0.11-0.76 μg/mL		Wuhan-Hu-1; Alpha; Beta; Gamma; Delta; Omicron;	Huh-7	7WHK	Preclinical	[386]
7D6	Mice	RBD	Cross-neutralizing		2.23 μg/mL		B.1.1.7, B.1.351, P.1	BHK21-hACE2	7EAM	Preclinical	[387]

			antibody				variants, the B.1.351 authentic virus				
6D6	Mice	RBD	Cross-neutralizing antibody		1.77 μg/mL		B.1.1.7, B.1.351, P.1 variants, the B.1.351 authentic virus	BHK21-hACE2	7EAN	Preclinical	[387]
XGv347	Mice	RBD	Antibodies against Omicron		0.006 μg/mL		Omicron, Beta (B.1.351)	293T	7WED	Preclinical	[388]
SP1-77	Single human VH-rearranging mouse	RBD	Monoclonal antibody		Pseudotype viruses: 20 ng/mL 28 ng/mL 16 ng/mL 15 ng/mL 36 ng/mL 19 ng/mL 11 ng/mL 76 ng/mL 6.5 ng/mL 33 ng/mL 7 ng/mL 16 ng/mL 8 ng/mL Live Viruses: 1.1 ng/mL 1.1 ng/mL 0.8 ng/mL 0.8 ng/mL 9.7 ng/mL		Pseudotype viruses: G614, B.1.1.7, B.1.351, P.1, B.1.429, B.1.526.K484E, B.1.617, BA.1, BA.2, BA.3, BA.4/BA.5, BA.2.12.1 Live Viruses: WA1, B.1.1.7, B.1.351, P.1, B.1.617.2	ACE2-HEK293T cells	7UPX	Preclinical	[389]
AB-3467	RBD-immunized Ig-humanized mice	RBD	IgG1 antibody		0.328 μg/mL 0.314 μg/mL 0.274 μg/mL 0.322 μg/mL 0.27 μg/mL 0.145 μg/mL 0.296 μg/mL 0.576 μg/mL 0.473 μg/mL 0.271 μg/mL 0.226 μg/mL 0.352 μg/mL		WT(clade A early) D614G B.1.17 B.1.351 B.1.617 B.1.617.2 P1 P2 B.1.525 B.1.427 B.1.429 C36	ACE2-HEK293T cells	7MSQ	Preclinical	[390]
910-30	COVID-19 convalescent patient, Donor 910	RBD	IgG1 monoclonal antibody		0.142 μg/mL		USA-WA1/2020	Vero-E6 cells	7KS9	Preclinical	[391]
Bi-Nab35B5-47D10	Convalescent COVID-19 patient	RBD	bsAb		0.046 nM 0.038 nM 0.360 nM 0.065 nM 0.079 nM 0.150 nM 0.670 nM	WT S1 protein: 0.023 nM WT S2 protein: 628.3 nM	WT, Alpha, Beta, Kappa, Delta, Omicron BA.1, Omicron BA.2	HEK293		Preclinical	[392]
Fu2	Alpaca	RBD	Bispecific monomeric nanobody		106 ng/mL			HEK293T-hACE2	7NS6	Preclinical	[393]
CV38-142	A COVID-19 patient	RBD	Cross-neutralizing antibody		3.46 μg/mL(lgG) >100 μg/mL(Fab)	K_D=29.2 nM			7LM9	Preclinical	[394]
THSC20.HVTR04	Convalescent COVID-19 patient	RBD	Monoclonal antibody			SARS-CoV-2 (Wuhan)： K_D=0.196 nM	SARS-CoV-2 (Wuhan)	HEK 293T	7Z0Y	Preclinical	[395]

THSC20.HVTR26	Convalescent COVID-19 patient	RBD	Monoclonal antibody		Kappa：0.003-0.01 μg/mL Omicron：2.71 μg/mL	SARS-CoV-2 (Wuhan)：K_D=0.255 nM	SARS-CoV-2 (Wuhan), Kappa，Omicron	HEK 293T	7Z0X	Preclinical	[395]
CV3-13	Convalescent COVID-19 patient	RBD	Non-neutralizing antibody			K_D=55.2 nM(Fab)			7RQ6	Preclinical	[396]
SR31	Synthetic libraries by ribosome and phage display	RBD	Synthetic nanobody (sybody)			K_D=5.6 nM		HEK293T	7D2Z	Preclinical	[397]
hu33	Mice	RBD	Monoclonal antibody		ND_{50}: 12.5 ng/mL 4.7 ng/mL 154.3 ng/mL		Beta, Delta, Omicron	Vero E6	7WB5	Preclinical	[398]
Nb15-NbH-Nb15	Mice	RBD	Bispecific nanobody		0.4 ng/mL 0.26 ng/mL 88.95 ng/mL 5.16 ng/mL		WT, Alpha, Epsilon, Delta			Preclinical	[399]
P4A1	Convalescent COVID-19 patient	RBD	Neutralizing antibody		2.077 nM		WT	HEK293	7CJF	Preclinical	[400]
MR3	Synthetic nanobody	RBD	Synthetic nanobody (sybody)		0.42 μg/mL			VeroE6-hACE2	EMD-31328	Preclinical	[401]
XVR011(humVHH_S56A/LALA-Fc/Gen2)	Hamster	RBD	Neutralizing heavy chain–only antibody		$PRNT_{50}$=0.13 μg/mL	K_D>20 μM	BetaCov/Belgium/GHB-03021/2020	Vero E6 cells		Phase 1, Phase2 (NCT04884295)	[402]
S2P6	COVID-19 convalescent individuals	RBD	Monoclonal antibody		1.4 μg/mL	K_D=7 μM		Vero-E6	7RNJ	Preclinical	[403]
S1D7	Mice	RBD	Monoclonal antibody		405.2 ng/mL	42.7 ng/mL		VeroE6/TMPRSS2		Preclinical	[404]
S3D8	Mice	RBD	Monoclonal antibody		139 ng/mL	57.7 ng/mL				Preclinical	[404]
C98C7	Convalescent COVID-19 patient	RBD	Monoclonal antibody		0.013 μg/mL 0.015 μg/mL 0.012 μg/mL 0.023 μg/mL 1.067 μg/mL		Wuhan， Alpha, Gamma, Delta, Omicron BA.1		7SWO	Preclinical	[405]
G32Q4	Convalescent COVID-19 patient	RBD	Monoclonal antibody		0.578 μg/mL 1.476 μg/mL 0.089 μg/mL 0.316 μg/mL 6.666 μg/mL		Wuhan， Alpha, Gamma, Delta, Omicron BA.1		7SWP	Preclinical	[405]
3-2A2-4	Convalescent COVID-19 patients	RBD	Nanobody		0.102 μg/mL 0.115 μg/mL 0.098 μg/mL 0.130 μg/mL 0.106 μg/mL		WT, Alpha, Beta, Delta, Omicron BA.1		7X2L	Preclinical	[406]
ZWD12	Mice	RBD	Monoclonal antibody		258 ng/mL 169 ng/mL 54 ng/mL 915 ng/mL		Wuhan-Hu-1, B.1.351, B.1.617.2, B.1.1.529		7WWL	Preclinical	[407]
KC3.ep3	Synthetic nanobody	RBD	Nanobody		1.82±1.09 ng/mL 38.53±3.98 ng/mL	34±1 pM		HEK293T, VeroE6		Preclinical	[408]
nCoVmab1	Synthetic nanobody	RBD	Monoclonal antibody		0.010 μg/mL	16 nM		Vero E6		Preclinical	[409]
S1-27	Llama	RBD	Nanobody		19.5 nM			TMPRSS2 + Vero E6 cells		Preclinical	[410]

S1-23	Llama	RBD	Nanobody		5.7 nM			TMPRSS2 + Vero E6 cells		Preclinical	[410]
COV2-2676	Mice	RBD	Monoclonal antibody		501 ng/mL	896 ng/mL	WA1/2020	Vero E6		Preclinical	[411]
COV2-2489	Mice	RBD	Monoclonal antibody		199 ng/mL	1438 ng/mL	WA1/2020	Vero E6		Preclinical	[411]
2B04	Convalescent COVID-19 patients	RBD	Monoclonal antibody		0.04 μg/mL			Chimeric VSV expressing SARS-CoV-2 S protein	7K9I 7K9H	Phase 1 (NCT04644120)	[412]
2C03	Convalescent COVID-19 patients	RBD	Monoclonal antibody		5 μg/mL			Chimeric VSV expressing SARS-CoV-2 S protein		Preclinical	[412]
XMA01	Convalescent COVID-19 patients	RBD	Monoclonal antibody		23.6 ng/mL		Omicron	BHK21-hACE2 cells	7WHZ	Preclinical	[413]
XMA04	Convalescent COVID-19 patients	RBD	Monoclonal antibody		24.9 ng/mL		Omicron	BHK21-hACE2 cells	7WI0	Preclinical	[413]
5-7	Convalescent COVID-19 patients	NTD	Monoclonal antibody		0.050 μg/mL 0.595 μg/mL 0.905 μg/mL >20 μg/mL 0.760 μg/mL >20 μg/mL >20 μg/mL		WT, B.1.1.7, B.1.351, P.1, B.1.526, B.1.427/9, B.1.617.2	Vero E6 cells	7RW2	Preclinical	[414]
aRBD-2-5	Alpaca	RBD	Nanobody		ND_{50}:0.043 nM		USA-WA1/2020	Vero E6	7VOA	Preclinical	[415]
aRBD-2-7	Alpaca	RBD	Nanobody		ND_{50}:0.111 nM		USA-WA1/2020	Vero E6	7FH0	Preclinical	[415]
S2-4D	Mice	RBD	Monoclonal antibody			20.05±1.69 μg/mL 20.88±3.93 μg/mL 37.10±6.12 μg/mL 27.20±8.03 μg/mL 21.47±4.23 μg/mL	WT, Alpha, Epsilon, Delta, Gamma	Vero E6		Preclinical	[416]
S2-5D	Mice	RBD	Monoclonal antibody			25.80±4.72 μg/mL 21.84±2.23 μg/mL 21.18±3.51 μg/mL 15.00±3.27 μg/mL 16.43±3.03 μg/mL	WT, Alpha, Epsilon, Delta, Gamma	Vero E6		Preclinical	[416]
S2-8D	Mice	RBD	Monoclonal antibody			20.78±3.32 μg/mL 12.88±5.11 μg/mL 21.00±8.63 μg/mL 30.54±6.60 μg/mL 10.92±3.59 μg/mL	WT, Alpha, Epsilon, Delta, Gamma	Vero E6		Preclinical	[416]
PR1077	Mice	RBD	Monoclonal antibody		6.810 ng/mL 27.9 ng/mL	2.58 ng/mL	Wuhan/WIV04/2019	HEK293-ACE2, Vero E6	7DEO	Preclinical	[417]
RBD-chAb-25	Mice	RBD	Monoclonal antibody		25.44 ng/mL 4.32 ng/mL		WT (TCDC#4), D614G	Vero E6	7EJ4	Preclinical	[418]
RBD-chAb-45	Mice	RBD	Monoclonal antibody		2.30 ng/mL 1.57 ng/mL		WT (TCDC#4), D614G	Vero E6	7EJ5	Preclinical	[418]
Sb45	Synthetic nanobody	RBD	Nanobody		K_D=47.1 nM				7KGJ	Preclinical	[419]
54042-4	Convalescent COVID-19 patients	RBD	Monoclonal antibody		3.2 ng/mL 5.5 ng/mL 9.7 ng/mL 3.7 ng/mL 1.5 ng/mL		USA-WA1, Alpha, Beta, Gamma, Delta,	Vero E6	7T01	Preclinical	[420]

2H04	Mice	RBD	Monoclonal antibody		154 ng/mL	602 ng/mL 8596 ng/mL 2084 ng/mL 6287 ng/mL 274 ng/mL 1562 ng/mL 785 ng/mL 175 ng/mL 5363 ng/mL 3378 ng/mL	D614G, B.1.1.7, Wash-B.1.351, Wash-B.1.1.28, B.1.429, B.1.617.1, B.1.526, Denmark B.1.1.298, Scotland B.1.222	Vero-hACE2-TMPRSS2 cells	7K9K 7K9J	Preclinical	[421]
9-105	Convalescent COVID-19 patients	RBD	Monoclonal antibody		0.0035 μg/mL 0.0019 μg/mL 0.00092 μg/mL		Wuhan-Hu-1	293FT/ACE2/TMPRSS2, Calu-3, Caco-2		Preclinical	[422]
10-121	Convalescent COVID-19 patients	RBD	Monoclonal antibody		0.018 μg/mL 0.12 μg/mL 0.015 μg/mL		Wuhan-Hu-1	293FT/ACE2/TMPRSS2, Calu-3, Caco-2		Preclinical	[422]
Cv2.1169	Convalescent COVID-19 patients	RBD	Monoclonal antibody		331 ng/mL		BA.2	Vero E6	7QEZ	Preclinical	[423]
Cv2.3194	Convalescent COVID-19 patients	RBD	Monoclonal antibody		40.5 ng/mL		BA.2	Vero E6		Preclinical	[423]
XG014	Convalescent COVID-19 patients	RBD	Monoclonal antibody		0.004-0.018 μg/mL		B.1.1.7, B.1.351, P.1, B.1.617.2	Huh-7	7V2A	Preclinical	[424]
P5-22	Convalescent COVID-19 patients	RBD	Monoclonal antibody		~0.007214 μg/mL		BetaCoV/JS02/human/2020	HEK293/ACE2 cells		Preclinical	[425]
P14-44	Convalescent COVID-19 patients	RBD	Monoclonal antibody		0.7066 μg/mL		BetaCoV/JS02/human/2020	HEK293/ACE2 cells	7FCQ	Preclinical	[425]
Nb1–Nb2-Fc	Synthetic nanobody	RBD	Nanobody		0.0168 nM 0.0117 nM 0.0097 nM 0.0987 nM 0.0232 nM 1.46 nM		WT, Alpha, Beta, Gamma, Delta, Omicron	HEK293T		Preclinical	[426]
NM1267	Mice	RBD	Nanobody		0.33 nM 0.78 nM 52.55 nM		B.1, B.1.351, B.1.617.2	Caco-2		Preclinical	[427]
NM1268	Mice	RBD	Nanobody		2.37 nM 6.06 nM 0.67 nM		B.1, B.1.351, B.1.617.2	Caco-2		Preclinical	[427]
Re9F06	Alpaca	RBD	Nanobody		K_D=4 nM					Preclinical	[428]
Re9B09	Alpaca	RBD	Nanobody		K_D=20 pM K_D=20 pM K_D=100 pM K_D=100 pM K_D=200 pM		WT, B.1.1.7, B.1.351, P.1, B.1.427/B.1.429			Preclinical	[428]
FD20	Convalescent COVID-19 patients	RBD	Monoclonal antibody		12.0 nM 10.7 nM 22.4 nM 12.4 nM 12.6 nM		WT, B.1.1.7, B.1.35, P.1, B.1.617.2	VeroE6-hACE2	7CYV	Preclinical	[429]
1F	Convalescent COVID-19 patients	RBD	Monoclonal antibody		18 ng/mL	1.63 ng/mL	SARS-CoV-2/SH01/human/2020/CHN	Vero-E6 cells		Preclinical	[430]

Ab08	Convalescent COVID-19 patients	RBD	Monoclonal antibody		0.18 μg/mL, 0.19 μg/mL, 0.18 μg/mL, 0.26 μg/mL, 0.20 μg/mL, 1.65 μg/mL $PRNT_{50}$: 1.18μg/mL		Wuhan-Hu-1, Omicron BA.1, D614G, Omicron, BA.1.1, BA.2.12.1, Authentic Wuhan-Hu-1	VeroE2-hACE6, Vero E6		Preclinical	[431]
GAR05	Convalescent COVID-19 patients	RBD	Monoclonal antibody		28 ng/mL 50 ng/mL 82.45 ng/mL 71.31 ng/mL 198.9 ng/mL 337.6 ng/mL		Wuhan-Hu-1, Delta, Omicron A.2.2, Omicron BA1, Omicron BA2, Omicron BA5	Vero E6		Preclinical	[432]
GAR12	Convalescent COVID-19 patients	RBD	Monoclonal antibody		182 ng/mL 255 ng/mL 12.77 ng/mL 16.17 ng/mL 26.58 ng/mL 62.59 ng/mL		Wuhan-Hu-1, Delta, Omicron A.2.2, Omicron BA1, Omicron BA2, Omicron BA5	Vero E6		Preclinical	[432]
sd1.040	Convalescent COVID-19 patients	RBD	Monoclonal antibody		245 ng/mL		SARS-CoV-2/human/Czech Republic/951/2020	293T	8D48	Preclinical	[433]
rbd.042	Convalescent COVID-19 patients	RBD	Monoclonal antibody				SARS-CoV-2/human/Czech Republic/951/2020	293T		Preclinical	[433]
ShAb01	Shark	RBD	Nanobody		609 ng/mL, 420 ng/mL, 619 ng/mL, 188 ng/mL, >18000 ng/mL, >12000 ng/mL		WA-1, Alpha, Beta, Delta, Omicron BA.1, Omicron BA.4/5	HEK293T /17 cells		Preclinical	[434]
ShAb02	Shark	RBD	Nanobody		52 ng/mL, <23 ng/mL, <23 ng/mL, 15 ng/mL, 178 ng/mL, 1003 ng/mL		WA-1, Alpha, Beta, Delta, Omicron BA.1, Omicron BA.4/5	HEK293T /17 cells		Preclinical	[434]
P2D9	Convalescent COVID-19 patients	RBD	Monoclonal antibody		7.5 ng/mL, 3 ng/mL, 0.8 ng/mL, 3.2 ng/mL, 9.1 ng/mL, 11.7 ng/mL, 138.1 ng/mL, 125 ng/mL, 75.3 ng/mL	0.028 ug/ml	WA-1, Alpha, Beta, Gamma, Delta, BA.1, BA.2, BA.2.12.1, BA.4/5	HEK293T /17 cells		Preclinical	[435]

IV: intravenous infusion, IM: intramuscular infusion
RBD: receptor binding domain, RBM: receptor binding motif
mAb: monoclonal antibody, rAb: recombinant antibody

Table S3: Summary of host-targeted agents against SARS-CoV-2

Host factor	Drug name	Type	IC_{50}	EC_{50}	CC_{50}	Cell line	SARS-CoV-2 strain	Status	Ref.
ACE2	APN01	Miniprotein	6.08 μM		6259 μg/mL	Vero E6	A clinical SARS-CoV-2 isolate	Phase 2 (NCT04335136)	[436]
	LCB1	Miniprotein	23.54 pM	<50 pM		Vero E6	USA_WA1/2020	Preclinical	[437]
	LCB3	Miniprotein	48.1 pM	<50 pM		Vero E6	USA_WA1/2020	Preclinical	[437]
	ACE2615-foldon-T27W	Miniprotein	0.08μg/mL			Vero E6	USA_WA1/2020	Preclinical	[438]
	ACE2615-foldon-T27Y	Miniprotein	0.14μg/mL			Vero E6	USA_WA1/2020	Preclinical	[438]
	CVD313	Miniprotein	0.073 ± 0.02μg/mL			Vero E6	USA-WA1/2020	Preclinical	[439]
	CVD310	Miniprotein	0.089 ± 0.01μg/mL			Vero E6	USA-WA1/2020	Preclinical	[439]
	sACE2(v1)	Miniprotein	0.37±0.06nM 0.27±0.12nM 0.21±0.05nM 0.23±0.03nM 0.21±0.06nM 0.34±0.08nM			Vero-CCL81	Wild-type, Alpha, Beta, Gamma, Delta, Omicron	Preclinical	[440]
	P10	Peptide	42 nM			Calu-3	#SARS-CoV-2 / PSL2020	Preclinical	[441]
	P8	Peptide	46 nM			Calu-3	#SARS-CoV-2 / PSL2020	Preclinical	[441]
	P9	Peptide	53 nM			Calu-3	#SARS-CoV-2 / PSL2020	Preclinical	[441]
	Dalbavancin	Peptide	HEK293/hACE2 cells: ~53 nM	12.07 nM (Vero E6), 173.06 nM (Caco-2)	> 3200 nM (Vero E6)	Vero E6, Caco-2, HEK293/hACE2	A clinical SARS-CoV-2 isolate	Preclinical	[442]
	SB27012	Small	7.7±0.5 μM			Vero monkey kidney epithelial cells	SARS-CoV-2 lineage A	Preclinical	[443]
	SB27041	Small	2.2 μM			Vero monkey kidney epithelial cells	SARS-CoV-2 lineage A	Preclinical	[443]
	SB27047	Small	2.6 μM			Vero monkey kidney epithelial cells	SARS-CoV-2 lineage A	Preclinical	[443]
	Bifonazole	Small	36.84 μM, 40.00 μM			VerohACE2-TMPRSS2cells, Vero E6	VSV (Indiana serotype) with SARS-CoV-2 spike from with the Wuhan-Hu-1 isolate MN908947.3	Preclinical	[444]
	Methazolamide	Small				Vero E6	hCoV-19/CHN/SYSU-IHV/2020	Preclinical	[445]
	NMT5	Small		5.28 μM	48.66μM	HeLa-ACE2	USA-WA1 / 2020	Preclinical	[446]
	Bruceine A	Small		54±5 nM	>40μM	Vero E6	USA-WA1/2020, BEI NR-52281	Preclinical	[447]
	Gamabufotalin	Small		2.7±0.2 nM	>40μM	Vero E6	USA-WA1/2020, BEI NR-52281	Preclinical	[447]
	h11B11	Antibody	0.95±0.12μg/mL 0.61±0.13μg/mL 0.56±0.19μg/mL			HEK293T-hACE2	Wuhan-1, D614G, B.1.1.7, B.1.351	Preclinical	[448]

			1.59±0.20μg/mL						
TMPRSS2	Camostat mesylate	Small	9.3±1.2 nM	1 μM		293T and Vero	hCoV-19/Germany/FI1103201/2020 SARS-CoV-2 isolate Munich 929	Phase 4 (NCT04338906)	[449]
	Nafamostat mesylate	Small	2.2 nM	5 nM		Calu-3	USA-WA1 / 2020	Phase 3 (NCT04390594,NCT04483960)	[450]
	Enzalutamide	Small				A549	SARS-CoV-2/England/IC19/202 (IC19)	Phase 2 (NCT04456049)	[451]
	Halofuginone	Small	30 nM, 0.069 μM		~5.54 μM	Caco-2 cells, TMPRSS2-HiBiT-BEAS-2B cells	USA-WA1/2020	Preclinical	[452]
	Homoharringtonine	Small	30 nM, 0.061 μM		>10 μM	Caco-2 cells, TMPRSS2-HiBiT-BEAS-2B cells	USA-WA1/2020	Preclinical	[452]
	N-0385	Small	1.9±1.4nM	2.6 to 26.5 nM	3.5 mM	Calu-3	VIDO-01, B.1.1.7, B.1.351, P.1 and B.1.617.2	Preclinical	[453]
	Avoralstat	Small	2.7±0.19 nM	2.8±0.7 μM		Calu-3 2B4 cells	2019n-CoV/USA-WA1/2019 strain of SARS-CoV-2	Preclinical	[454]
	Benzamidine	Small	120±20 μM			Biochemical assay	Biochemical assay	Preclinical	[455]
	6-amidino-2-napthol	Small	1.6±0.5 μM			Biochemical assay	Biochemical assay	Preclinical	[455]
	Sunflower trypsin inhibitor-1	Small	0.4±0.2 μM			Biochemical assay	Biochemical assay	Preclinical	[455]
	MM3122	Small	340 pM	430 pM		Calu-3	HCoV EMC/2012 strain	Preclinical	[456]
	Otamixaban	Small	18.7 μM			Calu-3	hCoV-19/Germany/FI1103201/2020	Preclinical	[457]
	Compound 7	Small		Vero E6-TMPRSS2: 14.33±0.23μM 13.82±0.79μM 15.96±1.30μM 9.815±0.33μM 13.67±0.29μM	Vero E6: 110.90μM Calu3: 94.87μM	Vero E6, Vero E6-TMPRSS2, Calu3	WT, B1.1.7, B1.351, B1.617, B1.618	Preclinical	[458]
	Tafenoquine	Small	31.8 μM	Vero E6-TMPRSS2: 11.30±1.14μM 11.61±1.67μM 24.22±6.31μM 23.61±1.06μM 23.45±4.93μM	Vero E6: 9.74±1.31μM Calu3:7.0±0.31 μM	Vero E6 HEK-293T Calu3	NTU02，GenBank：MT066176.1	Phase2 (NCT04533347)	[458]
Cathepsin B/L	Alpha-1 antitrypsin	Human protein	21.2 μM			Vero E6	BetaCoV/France/IDF0372/ 2020 (#014V-03890)	Early Phase 1(NCT04385836)	[459]
		Human protein	17.3 μM			Vero E6	BetaCoV/Netherlands/01/ NL/2020 (#010V-03903)		[459]

	E-64d	Small				293T and Vero	hCoV-19/Germany/FI1103201/2020	Preclinical	[449]
Cathepsin L	SM141	Small		8.2±0.9 nM		A549-hACE2		Preclinical	[117]
	SM142	Small		14.7±2.2 nM		A549-hACE2		Preclinical	[117]
	Obatoclax	Small	< 1 μM			HEK293T, Calu-3, Caco-2, A549	SARS-CoV-2 S - pseudovirus(Wuhan-Hu-1)	Preclinical	[460]
	E-64d	Small		0.27 μM		Vero E6	Wuhan-Hu-1	Preclinical	[461]
	Z-FY-CHO	Small	5 μM	0.62 μM		Vero E6	Wuhan-Hu-1	Preclinical	[461]
	K777	Small		4 nM (Hela/ACE2), 7 nM (Calu-3/2B4), ≥ 70 nM (Vero E6), < 80 nM (A549/ACE2 cells), > 10 μM (Calu-3 ATCC cells)	>10μM (Vero E6), >10μM (Caco-2), Calu-3 > 20μM	Vero E6, Calu-3, HeLa/ACE2	USA-WA1 / 2020	Preclinical	[462]
Furin	Naphthofluorescein	Small	9.025 μM		57.44 μM	Vero E6	hCoV-19/Taiwan/NTU03/2020	Preclinical	[463]
	Decanoyl-RVKR-CMK	Peptide	0.057 μM		318.2 μM	Vero E6	hCoV-19/Taiwan/NTU03/2020	Preclinical	[463]
PIKfyve kinase	Apilimod	Small		0.023 μM		Vero E6	USA-WA1 / 2020	Phase 2 (NCT04446037)	[464]
			< 0.08 μM			Vero E6	BetaCoV/France/IDF0372/2020		[465]
			0.007 μM			A549-ACE2	USA-WA1 / 2020		[465]
MAPK11/14 inhibitor	Ralimetinib	Small	0.873 μM			Vero E6	BetaCoV/France/IDF0372/2020	Preclinical	[465]
MAPK13 inhibitor	MAPK13-IN-1	Small	4.63 μM			Vero E6	BetaCoV/France/IDF0372/2020	Preclinical	[465]
MAPK14 inhibitor	ARRY-797	Small	0.913 μM			A549-ACE2	USA-WA1 / 2020	Preclinical	[465]
CDK	Dinaciclib	Small	0.127 μM 0.032 μM			Vero E6; A549-ACE2	BetaCoV/France/IDF0372/2020; USA-WA1 / 2020	Preclinical	[465]
Glycogen synthase kinase 3 (GSK-3)	CHIR99021	Small	~5 μM			Calu-3	SARS-CoV-2/human/USA/CA-CZB017/2020 (GenBank ID: MT385497.1)	Preclinical	[466]
	Tideglusib	Small	1.55± 0.30 μM					Preclinical	[40]
HSP90	17-AAG	Small			50 μM	Vero E6	SARS-CoV-2 (GenBank ID: MT230904)	Preclinical	[467]
Transmembrane protein 16F (TMEM16F), Anoctamin 6 (ANO6)	Niclosamide	Small	0.34 μM			Vero E6	SARS-CoV-2/England/IC19/2020 (IC19) SARS-CoV-2 strain England 02/2020/407073	Phase 4 (NCT05087381)	[468]
	A6-001	Small	0.97 μM		>100μM	Calu-3	SARS-CoV-2 (BetaCoV/korea/KUMC-2)	Preclinical	[469]

Cyclophilin	Alisporivir	Small	2.3 μM			Primary human nasal epithelial cells	SARS-CoV-2/Munchen-1.1/2020/929	Phase 2 (NCT04608214)	[470]
	Cyclosporine A	Small	7.9 μM			Primary human nasal epithelial cells	SARS-CoV-2/Munchen-1.1/2020/929	Phase 4 (NCT04392531),Phase 3(NCT04979884)	[470]
Dihydroorotate dehydrogenase	Leflunomide	Small		41.49 ± 8.84 μmol/L	879.00 ± 62.58 μmol/L	Vero E6 (MOI = 0.05)	BetaCoV/Wuhan/WIV04/2019	Phase 3 (NCT05007678)	[471]
	S312	Small	29.2 nmol/L	1.59 ± 0.01 μmol/L	158.20 ± 20.67 μmol/L	Vero E6 (MOI = 0.03)	BetaCoV/Wuhan/WIV04/2019	Preclinical	[471]
	S416	Small	7.5 nmol/L	0.014 ± 0.0001 μmol/L	178.60 ± 16.38 μmol/L	Vero E6 (MOI = 0.03)	BetaCoV/Wuhan/WIV04/2019	Preclinical	[471]
	Teriflunomide	Small	307.1 nmol/L	6.00 ± 0.77 μmol/L	850.50 ± 67.69 μmol/L	Vero E6 (MOI = 0.03)	BetaCoV/Wuhan/WIV04/2019	Preclinical	[471]
	Emvododstat (PTC299)	Small	1.96 nM	2.6 nM	>10 μM	Vero E6	USA-WA1 / 2020	Phase 2/3 (NCT04439071)	[472]
	IMU-838	Small	160 nM	7.6 ± 5.8 μM	>100 μM	Vero E6	SARS-CoV-2 (MUC-IMB-1/2020)	Phase 2 and Phase 3 (NCT04379271)	[473]
	BAY-2402234	Small		0.005 μM	> 20 μM	Calu-3	USA-WA1 / 2020	Preclinical	[474]
	Brequinar	Small		0.794 μM	> 50 μM	Calu-3	USA-WA1 / 2020	Phase 2 (NCT05166876, NCT04575038)	[474]
Uridine monophosphate synthetase	Pyrazofurin	Small		0.185 μM	> 50 μM	Calu-3	USA-WA1 / 2020	Preclinical	[474]
Equilibrative nucleoside transporters -1	Dipyridamole	Small		>50 μM		A549/ACE2	Beta(B.1.351)	Preclinical	[475]
Eukaryotic translation elongation factor 1A (eEF1A)	Plitidepsin	Small	0.7 nM 0.73 nM 1.62 nM		1.99 nM > 200 nM 65.43 nM	Vero E6 hACE2-293T Pneumocyte-like cells		Phase 3 (NCT04784559)	[476]
RAD51	B02	Small	27.4 μM	8.81 μM		Calu-3	USA-WA1 / 2020	Preclinical	[477]
	Fluoxetine	Small		＜1 μM ＜1 μM	41.97 μM 40.16 μM	Calu-3 Vero E6	hCoV-19/Germany/FI1103201/2020 (EPI-ISL_463008)	Phase 4 (NCT04377308)	[478]
AKT1	MK-2206	Small	0.11 μM			Vero FM	SARS-CoV-2 Munich/2020/984 (BetaCoV/Munich/BavPat1/2020)	Preclinical	[479]

CD147	Meplazumab	Monoclonal Antibody				Vero E6		Phase 2 and Phase 3 (NCT04586153,NCT05113784)	[480]
Bromodomain-containing protein 2	ABBV-744	Small	4 to 18nM			Vero E6	BetaCoV/France/IDF0372/2020	Phase 1 (NCT03360006, NCT04454658)	[481]
Histamine H2-receptor	Famotidine	Small	2.3 to 0.2 μM			Vero E6 Caco2	SARS-CoV-2 FFM1	Phase 4 (NCT04565392,NCT04836806)	[482]
Casein kinase 1α (CK1α)	Lenalidomide	Small	~168.1μM			UMRC2 cells		Phase 4 (NCT04361643)	[483]
Casein Kinase 2 (CSNK2)	SGC-CK2-1	Small	0.21 μM			Primary human airway epithelial cells	USA-WA1 / 2020	Preclinical	[484]
AXL inhibitor	Gilteritinib	Small	0.807 μM			Vero E6	BetaCoV/France/IDF0372/2020	Preclinical	[465]
			0.13±0.05 μM			Vero E6	BetaCoV/France/IDF0372/2020	Preclinical	[485]
GFR pathway	RO5126766	Small	0.6 μM			CaCo-2	A clinical SARS-CoV-2 isolate	Preclinical	[486]
	Omipalisib	Small	0.014 μM			CaCo-2	A clinical SARS-CoV-2 isolate	Preclinical	[486]
	Sorafenib	Small	4.85 μM			CaCo-2	A clinical SARS-CoV-2 isolate	Preclinical	[486]
	Pictilisib	Small	2.58 μM			CaCo-2	A clinical SARS-CoV-2 isolate	Preclinical	[486]
	Lorafenib	Small	4.99 μM			CaCo-2	A clinical SARS-CoV-2 isolate	Preclinical	[486]
Topical antitumor medication	Ingenol	Small		0.06 μM	> 20 μM	Vero E6	USA_WA1/2020	Preclinical	[487]
Antiinflammatory, antineoplastic	Cepharanthine	Small		1.41 μM	11.22 μM	Vero E6	USA_WA1/2020	Phase 2 NCT05398705)	[487]
CDK	Abemaciclib	Small		3.16 μM	7.08 μM	Vero E6	USA_WA1/2020	Preclinical	[487]
EGFR	Osimertinib	Small		3.98 μM	10.00 μM	Vero E6	USA_WA1/2020	Preclinical	[487]
Tricyclic antidepressant	Trimipramine	Small		20.52 μM	> 20 μM	Vero E6	USA_WA1/2020	Preclinical	[487]
ER stress response	Thapsigargin	Small		260 nM	MTT: 18.25 μM, ATPlite: 20.27 μM	Vero E6	SRX9907172	Preclinical	[488]
9-O-acetylated-sialic acids	9-AcSA-porphyrin tetramer 11	Macrocycle agent	1 μM			Vero E6	BavPat1 strain	Preclinical	[489]
Carnitine palmitoyl transferase 1-a (CPT1a)	ST1326	Small	0.86 μM, 0.541 μM			Caco-2, HEK293T-ACE2	CHN/Beijing_IME-BJ01/2020	Preclinical	[490]
Calmodulindependent protein kinase	STO-609	Small	0.346 μM, 50.43 μM			Caco-2, HEK293T-ACE2	CHN/Beijing_IME-BJ01/2020	Preclinical	[490]

kinase (CaM-KK)									
PGC1-α	Valproic acid	Small	0.347 μM, 3.035 μM			Caco-2, HEK293T-ACE2	CHN/Beijing_IME-BJ01/2020	Phase 4 NCT04513314)	[490]
Sec61	Apratoxin S4	Small	0.17 μM, 0.71 nM		>10 μM, >1 μM	Vero E6, HeLa-hACE2	USA_WA1/2020	Preclinical	[491]
Caspase-6	z-VEID-fmk	Small	3.3 μM			Calu3	HKU-001a	Preclinical	[492]
Vacuolar-ATPases	Bafilomycin A1	Macrolide	9.6 nM; 5.6nM; 3.4nM; 1.8nM			Vero-TMPRSS2 cells	WT; D614G; B.1.351; B.1.1.529	Preclinical	[493]
Proteasome machinery	MG-132	Small	0.32μM	2.90μM		Vero E6 EGFP	BetaCov/Belgium/GHB-03021/2020	Preclinical	[494]
Topoisomerase II	Amrubicin	Small	0.33μM	33.00μM		Vero E6 EGFP	BetaCov/Belgium/GHB-03021/2020	Preclinical	[494]
Dihydrofolate reductase	Trimetrexate	Small	0.33μM	1.99μM		Vero E6 EGFP	BetaCov/Belgium/GHB-03021/2020	Preclinical	[494]
Sulfatase inhibitor	Coumarin 7	Small	0.36μM	33.00μM		Vero E6 EGFP	BetaCov/Belgium/GHB-03021/2020	Preclinical	[494]
SecA ATPase	Fluorescein	Small	0.67μM	33.00μM		Vero E6 EGFP	BetaCov/Belgium/GHB-03021/2020	Preclinical	[494]
Vacuolar-ATPases	Rhodamine-123	Small	0.80μM	33.00μM		Vero E6 EGFP	BetaCov/Belgium/GHB-03021/2020	Preclinical	[494]
Class III phosphoinositide 3-kinase (PI3K) vacuolar protein sorting 34	VPS34-IN-1	Small	0.40μM	26.83μM		Vero E6 EGFP	BetaCov/Belgium/GHB-03021/2020	Preclinical	[494]
	PIK-III	Small	0.12 μM		>50 μM	Calu-3 cells	USA/WA/1/2020	Preclinical	[495]
	Copanlisib	Small		> 20 μM	5.74 μM	Vero E6	USA_WA1/2020	Preclinical	[487]
Eukaryotic Translation Initiation Factor 2 Alpha Kinase 2 (EIF2AK2)	C16	Small		48H direct virus Inhibition: 0.568 μM, 1.65 μM, 1.25 μM 72H CPE assays: 1.06 μM, 2.06 μM, 2.96 μM	11.1μM, 14.4μM, 26.2μM	VeroE6, VeroE6+TMPRSS2, A549+ACE2	?	Preclinical	[496]
Farnesoid X receptor	Ursodeoxycholic acid	Small						Preclinical	[497]
?	Cannabidiol	Small		0.63 μM 4.96 μM 1.75 μM		A549-ACE Vero E6 Calu-3	USA_WA1/2020	Phase 2/3 (NCT04467918,NCT04504877)	[498]
?	Clofoctol	Small		Vero-81: 9.3 μM, Vero-81-TMPRSS2: 11.59 μM		Vero-81, Vero-81-TMPRSS2	BetaCoV/France/IDF0372/2020	Preclinical	[499]
?	JIB-04	Small		695 nM	>1000μM	Vero E6	Wild-type	Preclinical	[500]
?	Lactoferrin	Small	308 nM 1170 nM			Huh-7, Caco-2	USA-WA1/2020	Phase 2/3 (NCT04421534)	[501]
Ataxia-telangectasia and Rad3	Berzosertib	Small	Calu-3: 0.48 μM, A549-ACE2:		HeLa-ACE2:	Calu-3, A549-ACE2, HeLa-ACE2	USA-WA1/2020	Preclinical	[502]

related (ATR) kinase			0.24 μM		3.89 μM				
Complement protein C3	AMY-101							Phase 2 (NCT04395456)	[503]
Glucosylceramide synthase	GZ-161	Small	2.5 μM		47.98μM	Vero E6	SARS-CoV-2 (GISAID accession EPI_ISL_406862)	Preclinical	[504]
	GZ-346	Small	2.7 μM		46.04 μM	Vero E6	SARS-CoV-2 (GISAID accession EPI_ISL_406862)	Preclinical	[504]
Heparanase enzyme	Roneparstat	Small	0.07μg/mL			Vero E6	SARS-CoV-2 (USA-WA1/2020)	Preclinical	[505]
	Lenalidomide							Phase 4 (NCT04421534)	[505]
Nucleotide-binding oligomerization domain-containing protein 2 (NOD2)	GSK717	Small	10.22 to 14.38 μM		75.30 μM	ACE2-SK-N-SH cells	SARS-CoV-2 (SARS-CoV-2/CANADA/VIDO01/2020)	Preclinical	[506]
Methylenetetrahydrofolate dehydrogenase 1 (MTHFD1)	Carolacton	Small	0.14 μM 0.05 μM		>16 μM	Vero E6, Calu3		Preclinical	[507]
Carbamoyl phosphate synthetase, aspartate transcarbamoylase, and dihydroorotase (CAD)	2-TCPA	Small	2.36 μM, 11.61 μM		>64 μM >64 μM	Caco-2, Calu-3	USA-WA1/2020	Preclinical	[508]
Cyclin-dependent kinase 2 (CDK2)	SNS-032	Small		0.073 μM, 87 μM		HEK293T, Vero		Preclinical	[509]
Poly(ADP-ribose) polymerase (PARP)	Stenoparib	Small		25.5 μM		LLC-MK2	USA-WA1/2020	Preclinical	[510]
Protein arginine methyltransferases	GSK3326595	Small				HEK-293T	WT, Omicron, Delta, Beta	Preclinical	[511]
Ubiquitin-specific peptidase 25 (USP25)	AZ1	Small		0.846 μM, 0.145 μM		HEK293, Vero E6	Wuhan-Hu-1	Preclinical	[512]
α-glucosidase	UV-4	Small	α -glucosidase I: 0.5371 μM α -glucosidase II: 0.0685 μM	3.32 μM	>100 μM	ACE2-A549 cells	USA-WA1/2020	Preclinical	[513]

Table S4: Repurposed drugs with limited clinical benefits for COVID-19 patients

Repurposed drugs	Original indications	COVID-19 severity	Country	Treatment vs control	Patients in treated vs control	Major findings	Conclusion	Study	Phase (trial ID)	Ref.
Aspirin	Antithrombotic therapy	Hospitalized patients with COVID-19	UK, Nepal, Indonesia	Usual standard of care plus aspirin 150 mg by mouth (or nasogastric tube) or by rectum every day until discharge vs usual standard of care alone	7351 vs 7541	Aspirin was not associated with reductions in 28-day mortality.	Not effective	A randomized controlled trial	2, 3	[514]
Atorvastatin	Statin medication to prevent cardiovascular disease	COVID-19 adults in ICU	Iran	Atorvastatin 20 mg orally once daily versus placebo	215 vs 229	Atorvastatin did not reduce all-cause mortality, venous/arterial thrombosis.	Not effective	A randomized controlled trial	3	[515]
Azithromycin	Infections caused by bacteria, (Antirheumatic drugs)	Patients with suspected COVID-19 within 14 days of symptom onset, and at an increased risk of complications	UK	Usual care plus azithromycin 500 mg daily for three days vs usual care alone vs other interventions	500 vs 823 vs 797	Azithromycin plus usual care did not shorten the time to first self-reported recovery or decrease the risk of hospitalization	Not effective	A randomized controlled trial	3 (ISRCTN86534580)	[516]
		In-patients with severe COVID-19	Brazil	Hydroxychloroquine [400 mg 2x/day, 12/12 h] + azithromycin [500 mg 1x/day]) for 10 days plus standard of care Vs hydroxychloroquine [400 mg 2x/day, 12/12 h] plus standard of care	214 vs 183	Adding azithromycin to standard of care treatment (which included hydroxychloroquine) did not improve clinical outcomes.	Not effective	A randomized controlled trial	3	[517]
		Outpatients with mild-to-moderate COVID-19	UK	Azithromycin 500 mg OD PO 14 days plus standard care vs standard care alone	145 vs 147	Azithromycin plus standard care did not reduce the risk of subsequent hospital admission or death.	Not effective	Prospective, open-label, randomized trial	3	[518]
		Symptomatic outpatients with COVID-19	USA	Single oral 1.2-g dose of azithromycin vs placebo	171 vs 92	Treatment with a single dose of azithromycin did not result in greater likelihood	Not effective	A randomized controlled trial	3	[519]

						of being symptom free at day 14.				
Allogeneic mesenchymal cells	An immunomodulatory agent	Mechanicallyventilated patients with moderate or severe COVID-induced respiratory failure	USA	Two infusions of 2 million cells/kg versus sham infusions	112 vs 110	Mesenchymal cells did not improve 30-day survival or 60-day ventilator-free days in patients with moderate/severe COVID-related acute respiratory distress syndrome	Not effective	Randomized, double blind, parallel design, placebo controlled trial	3	[520]
Canakinumab	Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Cold Auto-inflammatory Syndrome (FCAS), Moersch-Woltman Syndrome (MWS)	Hospitalized patients with severe COVID-19	USA, Europe	Canakinumab 450 mg for body weight of 40-60 kg, 600 mg for 60-80 kg, and 750 mg for >80 kg) vs placebo	227 vs 227	Treatment with canakinumab did not significantly increase the likelihood of survival without IMV at day 29	Not effective	A randomized controlled trial	3	[521]
Camostat mesylate	A TMPRSS2 inhibitor	Adult Patients with Mild to Moderate COVID-19	Japan	Camostat (600 mg qid) versus placebo	78 vs 77	Camostat mesilate did not substantially reduce the time to viral clearance	Not effective	Multicenter, double-blind, randomized, parallel-group, placebo-controlled trial	3	[522]
		Patients with mild-to-moderate COVID-19	South Korea	Camostat mesylate (orally at 200 mg three times a day for 14 days) versus placebo	172 vs 170	Camostat mesylate did not show clinical benefit in patients with mild to moderate COVID-19.	Not effective	A double-blind, randomized, placebo-controlled, clinical study	2	[523]
Ciclesonide	Asthma, allergic rhinitis	Outpatients with symptomatic COVID-19	USA	Ciclesonide metered-dose inhaler 160 µg per actuation, for a total of 2 actuations twice a day (total daily dose, 640 µg) or placebo for 30 days.	197 vs 203	ciclesonide did not reduce time to alleviation of all COVID-19–related symptoms.	Not effective	A phase 3, multicenter, double-blind, randomized clinical trial	3	[524]
		Symptomatic outpatients with COVID-19	Canada	Inhaled ciclesonide (600 µg twice daily), intranasal ciclesonide (200 µg daily)	105 vs 98	Inhaled and intranasal ciclesonide did not improve the resolution of COVID-19 symptoms among younger adults	Not effective	A randomized, double blind, placebo-controlled trial	2	[525]

Colchicine	Acute gout and pericarditis	Hospitalized patients with COVID-19	UK, Indonesia, Nepal	Usual standard of care plus colchicine: colchicine 1 mg followed by 500 µg 12 h later and then 500 µg twice a day by mouth or nasogastric tube for 10 days in total vs Usual standard of care alone	5610 vs 5730	In adults hospitalized with COVID-19, colchicine was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death.	Not effective	A randomized controlled trial	2, 3	[526]
Dapagliflozin	Type 2 diabetes, heart failure, chronic kidney disease	COVID-19 inpatients with at least one cardiometabolic risk factor	Argentina, Brazil, Canada, India, Mexico, UK, USA	Patients were treated with either dapagliflozin 10 mg once daily orally or matching placebo for 30 days	625 vs 625	Dapagliflozin did not result in a significant risk reduction in organ dysfunction, death, improvement in clinical recovery.	Not effective	Randomized, double-blind, placebo-controlled trial	3	[527]
Gimsilumab	Anti-Granulocyte-macrophage colony-stimulating factor (GM-CSF) monoclonal antibody	COVID-19 inpatients with elevated inflammatory markers and hypoxemia (BREATHE)	USA	Gimsilumab 400 mg on Day 1, Gimsilumab 200 mg on Day 8 versus normal saline on day 1, Normal saline on Day 8	114 vs 113	Gimsilumab did not improve mortality or other key clinical outcomes in patients with COVID-19 pneumonia and evidence of systemic inflammation.	Not effective	Multi-center, adaptive, double-blind, A randomized controlled trial	2	[528]
Otilimab	Anti–GM-CSF monoclonal antibody	Hospitalized adults with severe COVID-19	Many countries	Otilimab 90 mg versus standard care	175 vs 175	Otilimab showed no significant benefit in the proportion of patients alive and free of respiratory failure at Day 28.	Not effective	Randomised, sequential, multicentre, placebo controlled, double-blind study	2 (NCT04376684)	[529]
Fluticasone furoate	A corticosteroid for the treatment of non-allergic and allergic rhinitis	Outpatients with mild-to-moderate COVID-19	USA	Inhaled fluticasone furoate 200 µg once daily for 14 days versus placebo	656 vs 621	Inhaled fluticasone furoate for 14 days did not result in improved time to recovery among outpatients with COVID-19	Not effective	Decentralized, placebo-controlled, randomized, platform trial	3 (ACTIV-6)	[530]
Interferon beta-1a	Multiple Sclerosis	Hospitalized adult patients with COVID-19	Japan, Mexico, Singapore, South Korea, and the USA.	Interferon beta-1a, 44 mcg on Days 1, 3, 5, and 7; Remdesivir, 200 mg on Day 1, followed by a 100 mg maintenance dose daily for up to 9 days.	487 vs 482	Interferon beta-1a plus remdesivir was not superior to remdesivir alone in hospitalized patients with COVID-19 pneumonia.	Not effective	A randomized controlled trial	3	[531]

				vs Placebo						
Peginterferon lambda-1a	Chronic viral hepatitis	Outpatients with mild to moderate COVID-19	USA	Peginterferon Lambda-1a (180 ug subcutaneous injection) with Standard of Care vs Standard of Care	60 vs 60	A single dose of subcutaneous Peginterferon Lambda-1a didn't improve symptoms in outpatients with uncomplicated COVID-19.	Not effective	A randomized controlled trial	2	[532]
Imatinib	Chronic myelogenous leukemia and malignant gastrointestinal interstitial tumors	Hospitalised patientswith severe COVID-19	Netherlands	Oral imatinib given as a loading dose of 800 mg on day 0 followed by 400 mg daily on days 1–9 vs placebo	197 vs 188	Imatinib did not reduce the time to discontinuation of ventilation and supplemental O_2 for more than 2 successive days in patients with COVID-19 requiring O_2.	Not effective	A randomized, double-blind, placebo-controlled, clinical trial	EudraCT 2020–001236–10	[533]
Ivermectin	Parasitic diseases	Symptomatic patients with mild COVID-19	Colombia	Ivermectin, 300 µg/kg, once daily for 5 days vs placebo	200 vs 198	A 5-day course of Ivermectin did not significantly improve the time to resolution of symptoms.	Not effective	A randomized controlled trial	2, 3	[534]
		Nonhospitalized adults enrolled ≤3 days after a confirmed diagnosis ≤7 days	USA	Ivermectin versus control	663 vs 660	It did not prevent the occurrence of hypoxemia, an emergency department visit, hospitalization, or death associated with Covid-19.	Not effective	Double-blind, randomized, placebo-controlled trial	3 (COVID-OUT)	[535]
		Outpatients with early mild to moderate COVID-19	USA	Ivermectin versus control	817 vs 774	Among outpatients with mild to moderate COVID-19, treatment with ivermectin, compared with placebo, did not significantly improve time to recovery.	Not effective	Decentralized, double-blind, randomized, placebo controlled platform trial	3 (ACTIV-6, NCT04885530)	[536]
		Acutely symptomatic outpatients with COVID-19	Brazil	Ivermectin 400 µg/kg once daily for 3 days vs placebo	679 vs 679	Ivermectin did not result in a lower incidence of hospitalization.	Not effective	A double blind, adaptive,randomized controlled trial	3	[537]
Nicotine	Parkinson's disease	Critically ill COVID-19 inpatients on mechanical ventilation	France	Transdermal patches containing nicotine at a daily dose of 14 mg vs placebo	106 vs 102	Nicotine did not significantly reduce day-28 mortality.	Not effective	A randomized, double-blind, placebo-controlled, multicentre trial	3 (NCT04598594)	[538]

Nitazoxanide	Diarrhea caused by certain parasite infections	Symptomatic patients with mild COVID-19	Brazil	Nitazoxanide 500 mg vs Placebo TID for 5 days	194 vs 198	Symptom resolution was similar between nitazoxanide and placebo groups after 5-day therapy.	Not effective	A randomized controlled trial	2 (SARITA-2, NCT04552483)	[539]
N-acetylcysteine	Mucolytic therapy and acetaminophen overdose	Inpatients with severe COVID-19 (confirmed or suspected)	Brazil	Acetylcysteine 21 g (~300 mg/kg) for 20 hours vs Dextrose 5%	67 vs 68	N-acetylcysteine high doses did not affect the evolution of severe COVID-19.	Not effective	A randomized controlled trial	Not applicable	[540]
Pirfenidone	Interstitial fibrosis	Hospitalized adults with severe COVID-19	China	Pirfenidone treatment vs standard treatment alone	73 vs 73	Pirfenidone has not been found to improve the interstitial changes in severe COVID-19 patients.	Not effective	A randomized, open-label trial	3	[541]
Remdesivir, Hydroxychloroquine, Lopinavir, Interferon β-1a		Inpatients with COVID-19	405 hospitals in 30 WHO countries	Remdesivir, 200 mg (day 0), 100 mg/d (day 2 to 9), Hydroxychloroquine sulfate (200 mg, 4 tablets at hours 0 and 6, twice/d, starting at hour 12, for 10 days), Lopinavir 200mg/ritonavir 50mg, twice/d for 14 d, Interferon β-1a,44 mcg/d (day 0, 3, 6) or IV, 10 mcg/d for 6 d	Remdesivir: 2750 vs 2725 Hydroxychloroquine: 954 vs 909 Lopinavir: 1411 vs 1380 Interferon β-1a: 2063 vs 2064	No significant benefit of remdesivir, hydroxychloroquine, lopinavir, or interferon β-1a in patients hospitalized with COVID-19.	Not effective	The multinational randomized controlled trial	3	[542]
Ruxolitinib	JAK1/JAK2 inhibitor	Adults who were hospitalized but not on mechanical ventilation or in an intensive care unit	Many countries	Oral ruxolitinib 5 mg twice per day versus placebo for 14 days	287 vs 145	Ruxolitinib 5 mg twice per day showed no benefit in the overall study population	Not effective	A randomized, double-blind, placebo-controlled trial	3	[543]
Astegolimab, **Efmarodocokin alfa**	IL-33 antagonists	Hospitalized adults with severe COVID-19 pneumonia	United States, Brazil, Mexico, Spain	Astegolimab 700/350 mg IV + SOC; Efmarodocokin alfa 90 μg/kg IV + SOC; versus placebo	130 vs 132 vs 134	Treatment with astegolimab or efmarodocokin alfa did not improve time to recovery in patients with severe COVID-19 pneumonia.	Not effective	Double-blind, placebo controlled study(COVID-astegolimab-IL)	2	[544]

Siltuximab	IL6 antagonist for multicentric Castleman's disease	Hospitalised patients with COVID-19, hypoxia, and signs of a cytokine release syndrome	Belgium	Interleukin (IL)-1 blockade vs no IL-1 blockade; IL-6 blockade vs no IL-6 blockade	IL-1: 112 vs placebo 230 IL-6: 227 (114 for tocilizumab and 113 for siltuximab) vs 115	The benefits of siltuximab in a patient population with moderate 28-day mortality were not detected.	Not effective	A prospective, multicentre, open-label, randomised, controlled trial	3	[545]
Sofosbuvir (SOF)+ Velpatasvir (VEL)	Hepatitis C virus	Inpatients with moderate to severe COVID-19	Iran	Sofosbuvir 400 mg and velpatasvir 100 mg plus national standard of care (including hydroxychloroquine 400 mg and lopinavir/ritonavir 100 to 400 mg) vs standard care alone	40 vs 40	Adding SOF/VEL to the standard of care did not improve clinical status or reduce mortality in patients with moderate to severe COVID-19.	Not effective	A randomized controlled trial	3	[546]
Sofosbuvir+ daclatasvir	Hepatitis C virus	Hospitalized patients with COVID-19	Iran	hospitalized patients with COVID-19	541 vs 542	Sofosbuvir/daclatasvir versus placebo did not reduce hospital discharge or survival in hospitalized patients with COVID-19.	Not effective	A randomized double-blind clinical trial (DISCOVER)	3	[547]
		Outpatients with mild COVID-19	Iran	Sofosbuvir/daclatasvir plus hydroxychloroquine or a control arm receiving hydroxychloroquine alone.	27 vs 28	Sofosbuvir/daclatasvir did not significantly alleviate symptoms after 7 days of treatment compared with control.	Not effective	A double-blind, randomized controlled trial	NA	[548]
Tenofovir disoproxil fumarate/Emtricitabine (TDF/FTC)	Human immunodeficiency virus-reverse transcriptase (HIV-RT) inhibitor	COVID-19 adults with high risk for severe COVID-19	Spain	TDF/FTC versus no TDF/FTC	177 vs 178	TDF/FTC did not improve 28-day mortality relative risk.	Not effective	An open-label, double-randomized, phase 3 pragmatic trial	3 (PANCOVID, EudraCT: 2020-001156-18)	[549]
		Healthcare workers with negative SARS-CoV-2 IgM/IgG test	Spain	TDF/FTC (N=233), HCQ (N=231), TDF/FTC+HCQ(N=220), Placebo (N=223)	233 vs 231 vs 220 vs 223	TDF/FTC and HCQ, alone or in combination, compared with placebo, showed comparable effects for pre-exposure prophylaxis of	Not effective	A double-blind placebo-controlled randomized trial	3 (NCT04334928)	[550]

						COVID-19				
Ticagrelor, clopidogrel	P2Y12 inhibitors	Non-critically ill inpatients with COVID-19	Brazil, Italy, Spain, USA	Heparin plus a P2Y12 inhibitor (ticagrelor 63%, clopidogrel 37%) or standard heparin only (n = 269)	293 vs 269	Compared with heparin alone, P2Y12 inhibitor plus heparin did not result in an increased odds of improvement in organ support–free days within 21 days during hospitalization.	Not effecti ve	An open-label, Bayesia n, adaptive randomi zed clinical trial	4 (NCT0 450577 4)	[551]
Vitamin D3 (cholecalcifer ol)	Supplementat ion	Inpatients with moderate or severe COVID-19	Brazil	A single high dose of vitamin D3 versus placebo	120 vs 120	High dose vitamin D3 did not significantly reduce hospital length of stay.	Not effecti ve	Multice nter, double-blind, randomi zed, placebo controll ed trial	NCT04 449718	[552]
Zinc gluconate, ascorbic acid(vitamin C)	Supplementat ion	Outpatient with COVID-19	USA	Zinc, ascorbic acid, zinc plus ascorbic acid, control	58 vs 48 vs 58 vs 50	High-dose zinc gluconate, ascorbic acid, or their combination did not significantly decrease the duration of COVID-19 symptoms.	Not effecti ve	Random ized, open-label, trial	NCT04 342728	[553]
Vitamin C	Supplementat ion	Patients with mild-to-moderate COVID-19	USA	Placebo (n = 34), vitamin C 1000 mg (n = 32), or melatonin 10 mg (n = 32)	34 vs 32 vs 32	Vitamin C 1000 mg once daily has no effect on disease progression.	Not effecti ve	A randomi zed, double-blind, placebo-controll ed trial	NCT04 530539	[554]
Metformin	A first-line agent to treat type 2 diabetes	Nonhospital ized adults enrolled ≤3 days after a confirmed diagnosis ≤7 days	USA	Metformin versus control	663 vs 660	It did not prevent the occurrence of hypoxemia, an emergency department visit, hospitalization, or death associated with COVID-19.	Not effecti ve	Double-blind, randomi zed, placebo-controll ed trial	3 (COVI D-OUT)	[535]
Fluvoxamine	An antidepressan t	Nonhospital ized adults enrolled ≤3 days after a confirmed diagnosis ≤7 days	USA	Fluvoxamine versus control	334 vs 327	It did not prevent the occurrence of hypoxemia, an emergency department visit, hospitalization, or death associated with COVID-19.	Not effecti ve	Double-blind, randomi zed, placebo-controll ed trial	3 (COVI D-OUT)	[535]
Ensovibep (MP0420)	A designed ankyrin repeat protein	Hospitalize d adults with COVID-19	USA	Ensovibep versus placebo	247 vs 238	Ensovibep did not improve clinical outcomes for hospitalized participants receiving standard care	Not effecti ve	Double-blind, randomi zed, placebo-controll ed trial	3 (ACTI V-3/TICO)	[555]
Telmisartan	Angiotensin receptor blockers	Inpatients with wild COVID-19	India, Austral ia	Angiotensin receptor blockers	388 vs 394	No evidence of benefit was found	Not effecti ve	A pragmat ic,	3 (NCT0 439411	[556]

				(Telmisartan) versus control		for treatment with angiotensin receptor blockers, using predominantly 40 mg/day of telmisartan		adaptive, multicentre, phase 3, randomised controlled trial	7)	
Aviptadil acetate	A vasoactive intestinal polypeptide binds to alveolar type 2 cells in lungs to inhibit pro-inflammatory cytokines.	196 inpatients with COVID-19 respiratory failure.	USA	Three 12-hour IV infusions of Aviptadil at graduating doses of 50, 100, and 150 pmol/kg/hr or a normal saline placebo on 3 successive days	136 vs 67	The primary end point (alive and free from respiratory failure at day 60) did not reach statistical significance between Aviptadil versus placebo	Not effective	A multicenter, placebo controlled trial	2b/3 (NCT04311697)	[557]
Baloxavir marboxil	Anti-influenza drug	29 hospitalized adults with COVID-19	China	Baloxavir marboxil versus Favipiravir versus control	10 vs 9 vs 10	No benefit of addition of either baloxavir marboxil or favipiravir under the trial dosages to the existing standard treatment	Not effective	An exploratory randomized, controlled trial	ChiCTR 2000029544	[558]
Losartan	An angiotensin receptor blocker	117 outpatients with mild symptomatic COVID-19	USA	Losartan 25 mg orally twice daily for 10 days versus placebo	58 vs 59	Losartan did not reduce hospitalizations in outpatients with mild symptomatic COVID-19	Not effective	A placebo-controlled blinded randomized clinical trial	2	[559]
		Hospitalized patients with covid-19–induced lung injury	USA	Losartan 50mg orally twice daily vs equivalent placebo for 10 days or until hospital discharge.	101 vs 104	Losartan did not significantly affect PaO2:FiO2 ratio at 7 days	Not effective	Blinded, placebo-controlled randomized clinical trial	2 (the ALPS-IP trial)	[560]
Intravenous immunoglobulins (IVIG)	A therapy treatment for patients with antibody deficiencies.	COVID-19 inpatients with invasive mechanical ventilation for up to 72 h and moderate-to-severe ARDS	France	IVIG (2 g/kg over 4 days) or placebo	69 vs 77	Intravenous immunoglobulins did not improve clinical outcomes at day 28 and tended to be associated with an increased frequency of serious adverse events, although not significant.	Not effective	A multicenter, double-blind, placebo controlled, phase 3 trial	3	[561]
	IgM-enriched immunoglobulins	Critically ill COVID-19 patients in ICU	Germany	146 received IgM-enriched immunoglobulins, 170 cases did not.	146 vs 170	IgM-enriched immunoglobulins did not improve 30-day survival.	Not effective	A multicentre propensity-weighted cohort study		[562]

Almitrine	An agonist of peripheral chemoreceptors located on the carotid bodies.	COVID- 19 inpatients experiencing acute hypoxemic respiratory failure	France	5 days of intravenous low-dose (2 µg/kg/min) almitrine versus placebo.	89 vs 92	Low-dose almitrine failed in reducing the need for mechanical ventilation or death at day 7.	Not effective	A multicenter, randomized, double blind, placebo-controlled trial	3	[563]
Brensocatib	An investigational oral inhibitor of dipeptidyl peptidase-1	COVID-19 inpatients with at least one risk factor for severe disease	UK	Once-daily brensocatib 25 mg or placebo orally for 28 days	192 vs 214	Brensocatib failed to improve clinical status at day 29 in COVID-19 inpatients	Not effective	A multicenter, double-blind, randomized, parallel-group, placebo-controlled trial	3	[564]

Table S5: Summary of FDA-approved cytokine antagonists

Drug target	Drug name	FDA-approved indications	Approved year
Interleukin-1 (IL-1)	Canakinumab	Periodic fever syndromes; Active systemic juvenile idiopathic arthritis	2009
	Rilonacept	Cryopyrin-associated periodic syndromes	2008
IL-1 receptor	Anakinra	Rheumatoid arthritis; Cryopyrin-associated periodic syndromes	2001
IL-2	Basiliximab	Immunosuppression therapy of organ transplantation	1998
IL-2 receptor	Daclizumab	Relapsing forms of multiple sclerosis	2016
IL-4 receptor	Dupilumab	Moderate-to-severe atopic dermatitis	2017
IL-5	Mepolizumab	Severe eosinophilic asthma; Chronic rhinosinusitis with nasal polyps; Eosinophilic granulomatosis with polyangiitis; Hypereosinophilic syndrome	2015
	Reslizumab	Add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype	2016
IL-5 receptor	Benralizumab	Severe asthma with an eosinophilic phenotype	2017
IL-6	Siltuximab	Multicentric Castleman's disease	2014
IL-6 receptor	Tocilizumab	Rheumatoid arthritis; Giant cell arteritis; Polyarticular juvenile idiopathic arthritis; Systemic juvenile idiopathic arthritis; Cytokine release syndrome	2010
	Sarilumab	Moderately to severely active rheumatoid arthritis	2017
	Satralizumab	Neuromyelitis optica spectrum disorder	2020
IL-12, IL-23	Ustekinumab	Moderate to severe plaque psoriasis; Active psoriatic arthritis; Moderately to severely active crohn's disease	2009
IL-13	Tralokinumab	Moderate-to-severe atopic dermatitis	2021
IL-17	Ixekizumab	Moderate-to-severe plaque psoriasis; Active psoriatic arthritis	2016
	Secukinumab	Moderate to severe plaque psoriasis; Adults with active psoriatic arthritis; Adults with active ankylosing spondylitis	2015
IL-17 receptor	Brodalumab	Moderate to severe plaque psoriasis	2017
IL-23	Guselkumab	Moderate-to-severe plaque psoriasis	2017
	Risankizumab	Moderate-to-severe plaque psoriasis; Active psoriatic arthritis	2019
	Tildrakizumab	Moderate-to-severe plaque psoriasis	2018

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