

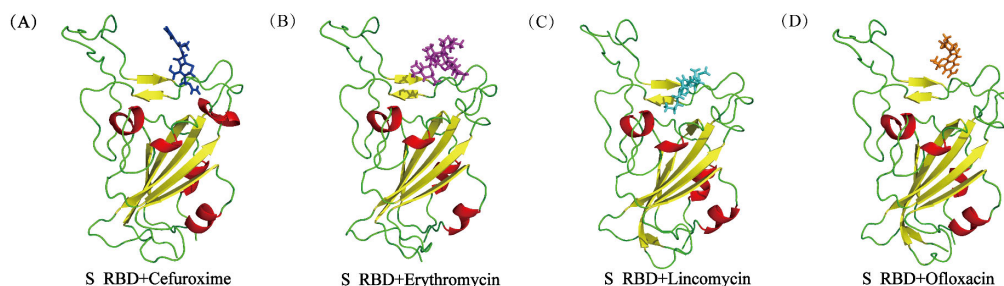
# Interactive Mechanism of Potential Inhibitors with Glycosyl for SARS-COV-2 by Molecular Dynamics Simulation

Yuqi Zhang <sup>1</sup>, Li Chen <sup>1</sup>, Xiaoyu Wang <sup>1</sup>, Yanyan Zhu <sup>1</sup>, Yongsheng Liu <sup>1</sup>, Huiyu Li <sup>1\*</sup> and Qingjie Zhao <sup>2\*</sup>

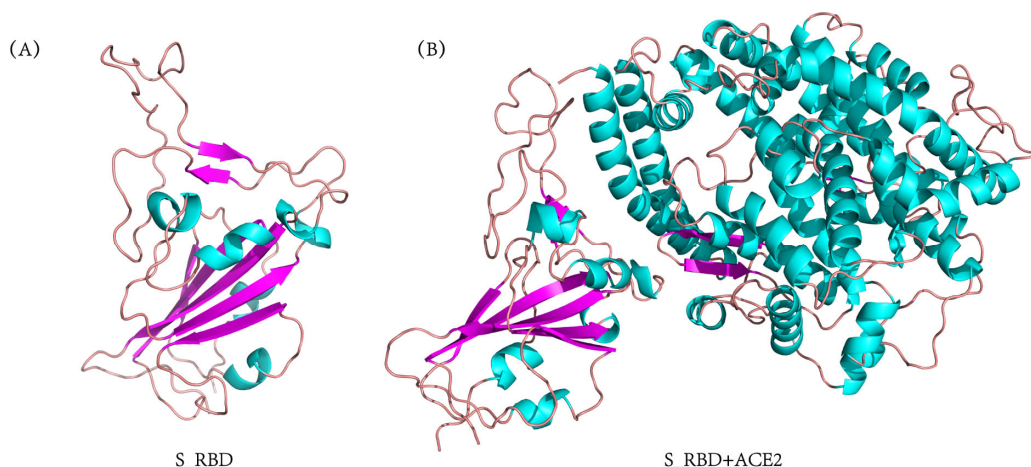
<sup>1</sup> College of Mathematics and Physics, Shanghai University of Electric Power, Shanghai 200090, China 1; 980300933@qq.com (Y.Z.); lichen@mail.shiep.edu.cn (L.C.); wxy94929@163.com (X.W.); yyzhu@shiep.edu.cn (Y.Z.); ys-liu@shiep.edu.cn (Y.L.); huiyuli@shiep.edu.cn (H.L.)

<sup>2</sup> Shanghai Institute of Material Medical, Chinese Academy of Sciences, Shanghai 201203, China 2; zhaoqingjie@simm.ac.cn

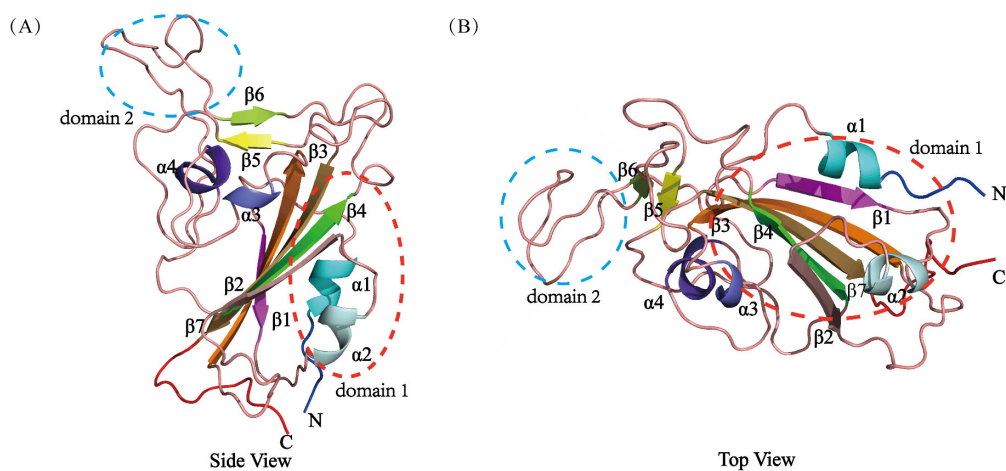
\* Correspondence: huiyuli@shiep.edu.cn (H.L.); zhaoqingjie@simm.ac.cn (Q.Z.)



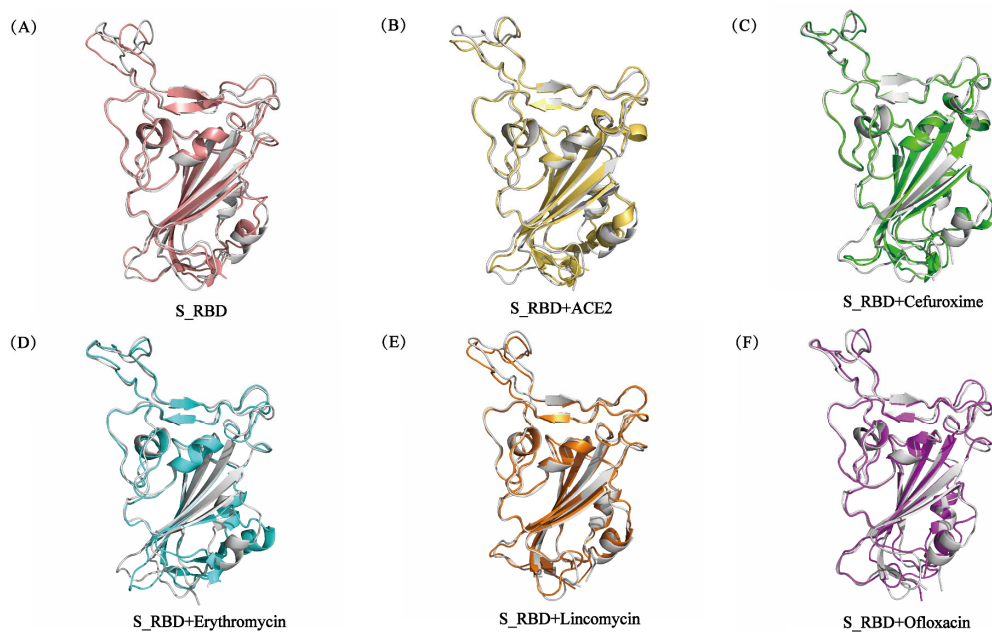
**Figure S1.** The initial structures of complex. (A) S\_RBD in the presence Cefuroxime (blue), (B) S\_RBD in the presence of Erythromycin (purple), (C) S\_RBD in the presence of Lincomycin (cyan) and (D) S\_RBD in the presence of Ofloxacin (orange).



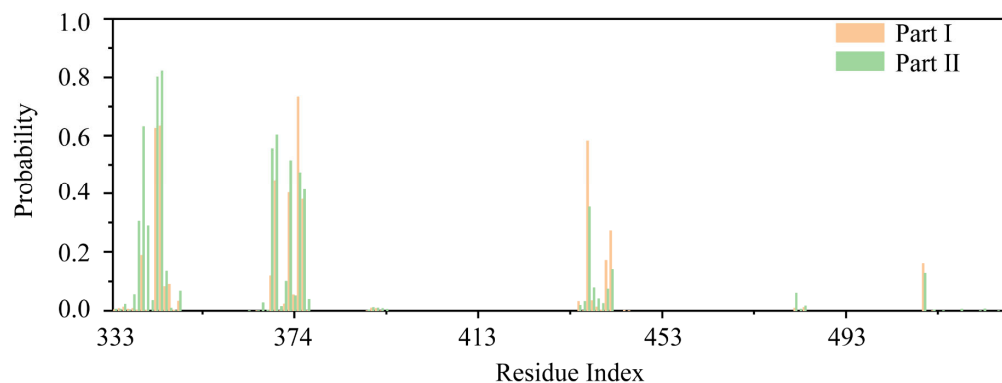
**Figure S2.** The initial structure in the S\_RBD with ACE2 system and the S\_RBD system by cartoon representation.



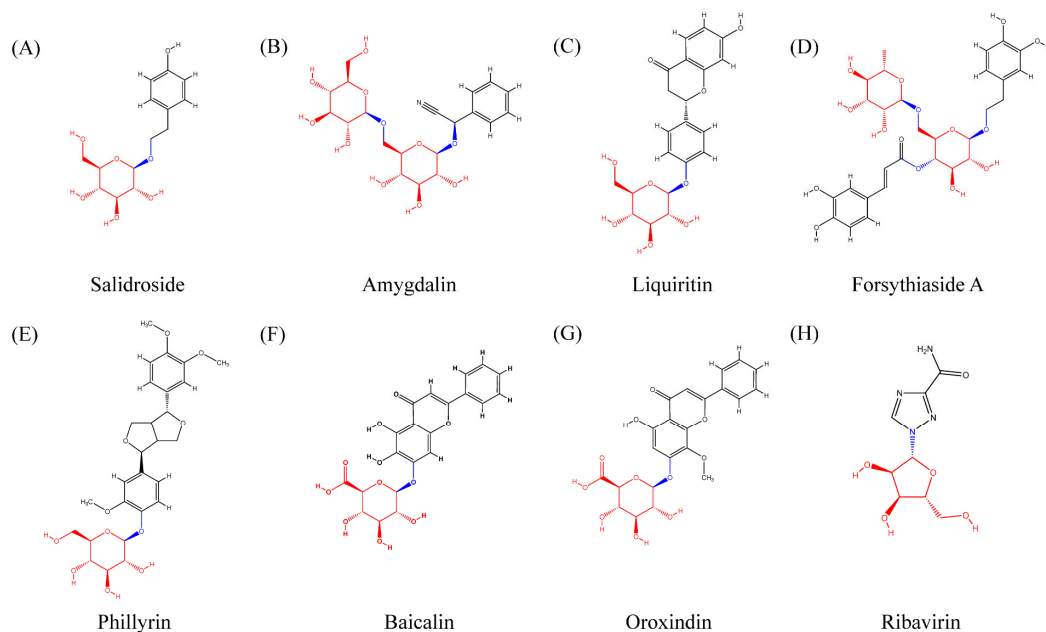
**Figure S3.** The side and top views of two binding regions.



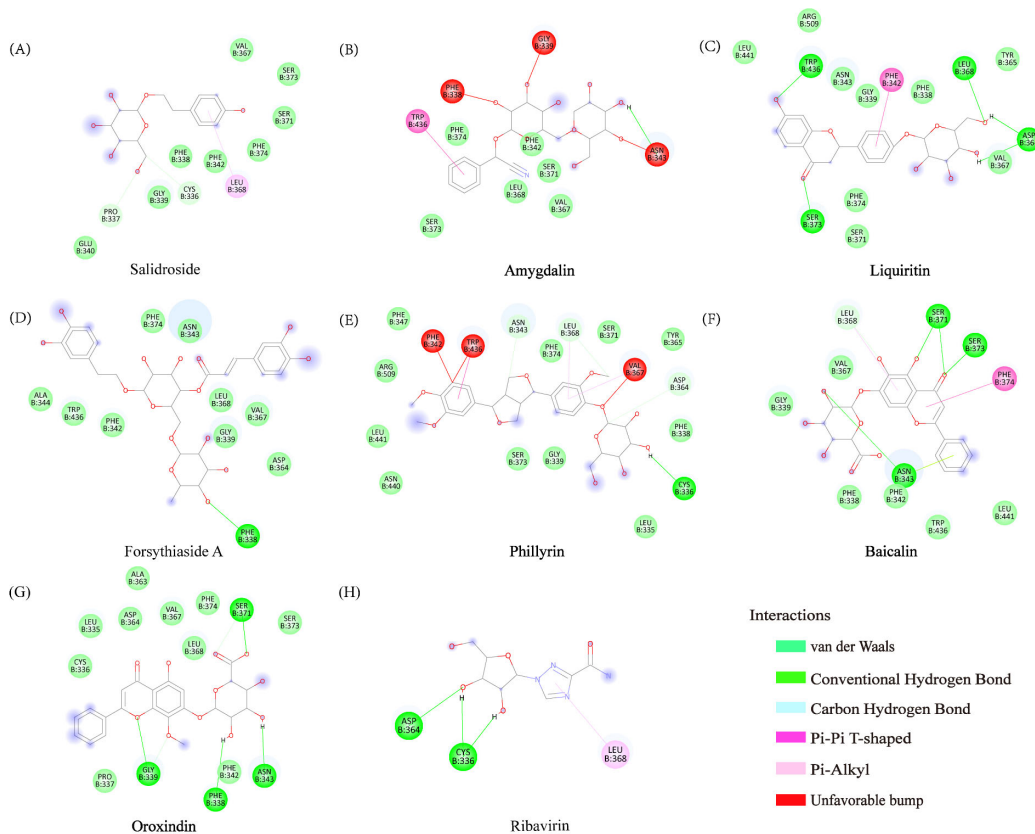
**Figure S4.** The alignment of the initial conformation (grey) and the representative snapshot at 400 ns in each simulation with the cartoon representation. **(A)** for the S\_RBD system, **(B-F)** for the S\_RBD in the presence of ACE2, Cefuroxime, Erythromycin, Lincomycin and Ofloxacin system, respectively.



**Figure S5.** The residue-based contact probability between S\_RBD and part I/part II of the inhibitor Lincomycin.



**Figure S6.** The chemical structures of potential inhibitors with the glycosyl group. (A) Salidroside, (B) Amygdalin, (C) Liquiritin, (D) Forsythiaside A, (E) Phillyrin, (F) Baicalin, (G) Oroxindin and (H) Ribavirin.



**Figure S7.** The binding models between the inhibitors and S\_RBD in binding domain 1 with Discovery Studio method. **(A)** Salidroside, **(B)** Amygdalin, **(C)** Liquiritin, **(D)** Forsythiaside A, **(E)** Phillyrin, **(F)** Baicalin, **(G)** Oroxindin and **(H)** Ribavirin.

**Table S1.** The detail of each simulation system.

Research system	Number of MD	Simulation Time	Total Time
S_RBD	2	400ns	0.8μs
S_RBD + ACE2	2	400ns	0.8μs
S_RBD + Cefuroxime	2	400ns	0.8μs
S_RBD + Erythromycin	2	400ns	0.8μs
S_RBD + Lincomycin	2	400ns	0.8μs
S_RBD + Ofloxacin	2	400ns	0.8μs

**Table S2.** The lowest free binding energy of potential effective inhibitors and the in different domains using Autodock.

Drug name		Main ingredients	Binding energy (KJ/mol)
			Domain 1
Lianhuaqingwen capsules	Rhodiola	Salidroside	-13.305
	Bitter almonds	Amygdalin	-16.150
	Licorice	Liquiritin	-25.606
	Forsythia	Forsythiaside A	-5.648
Double Coptis		Phillyrin	-25.397
	Scutellaria	Baicalin	-13.430
		Oroxindin	-16.820
Ribavirin	Ribavirin	Ribavirin	-14.016

**Table S3.** The lowest free binding energy of Lincomycin, Phillyrin and Liquiritin with the mutated Spike RBD of the genetic variants of SARS-CoV-2 (m\_S\_RBD) using Autodock.

Variants Name	Mutated Spike RBD of the genetic variants of SARS-CoV-2	Binding energy (KJ/mol)		
		Lincomycin	Phillyrin	Liquiritin
B.1.525	E484K	-9.037	-20.585	-19.456
B.1.526.1	L452R	-13.598	-18.786	-19.832
B.1.617	L452R, E484Q	-8.577	-19.246	-19.079
B.1.617.2	L452R, T478K	-11.673	-16.318	-22.635

**Table S4.** The respective RMSF value of residues belonging to domain 1 and domain 2.

Domain	Residue Name	RMSF (nm)					
		S_RBD	S_RBD + ACE2	S_RBD + Cefuroxime	S_RBD + Erythromycin	S_RBD + Lincomycin	S_RBD + Ofloxacin
Domain 1	GLU 340	0.19155	0.16505	0.15035	0.1299	0.09425	0.10615
	PHE 342	0.1862	0.1952	0.11565	0.1011	0.0688	0.07455
	ARG 346	0.2572	0.25625	0.11835	0.11415	0.10225	0.17835
	ASN 354	0.1119	0.1137	0.0556	0.06335	0.04665	0.06845
	LYS 356	0.15305	0.13355	0.0578	0.06225	0.05115	0.0576
	SER 371	0.34515	0.28775	0.22105	0.2153	0.0919	0.137
	ASN 440	0.1687	0.15965	0.07415	0.08385	0.06965	0.0747
	LEU 441	0.12365	0.10825	0.069	0.07625	0.06495	0.0697
Domain 2	SER 473	0.23515	0.06235	0.0713	0.08225	0.0648	0.07435
	PHE 474	0.17605	0.1173	0.1083	0.1056	0.0828	0.09685
	GLY 481	0.258	0.20795	0.2027	0.17045	0.1415	0.17275
	LEU 490	0.0978	0.0627	0.0627	0.062	0.0551	0.05605

**Table S5.** Free energy (KJ/mol) between S\_RBD and the small molecules Cefuroxime, Erythromycin, Lincomycin and Ofloxacin.

System name	Binding energy in gas phase: $\Delta E_{MM}$		Solvation energy			Total binding energy (KJ/mol)
	$\Delta E_{ele}$	$\Delta E_{vdW}$	$\Delta G_{PB}$	$\Delta G_{surf}$	$\Delta G_{solv}$	$\Delta G_{bind}$
S_RBD+ Cefuroxime	-33.047	-94.613	111.1985	-9.9515	101.247	-36.304
S_RBD+ Erythromycin	-11.2705	-103.896	77.903	-12.902	65.001	-63.1055
S_RBD+ Lincomycin	-21.0395	-104.958	88.425	-12.632	75.793	-62.862
S_RBD+ Ofloxacin	-11.3155	-118.7435	84.8675	-12.3875	72.48	-69.961

**Table S6** The residues of binding energy less than -1KJ/mol in four systems.

Residue name	Binding energy (KJ/mol)			
	Cefuroxime	Erythromycin	Lincomycin	Ofloxacin
GLY 339	> -1	> -1	> -1	-1.56318
GLU 340	> -1	> -1	> -1	-1.03874
PHE 342	> -1	> -1	-3.87812	-5.66395
ASN 343	> -1	> -1	> -1	-1.56551
VAL 367	> -1	> -1	-2.20858	-1.64858
LEU 368	> -1	> -1	-2.41782	> -1
PHE 374	> -1	> -1	-2.54069	-4.56719
TRP 436	> -1	> -1	-4.78005	-6.56706
LEU 441	> -1	> -1	-1.71205	> -1
ASP 442	> -1	> -1	> -1	-1.3078
LEU 455	> -1	-5.77209	> -1	> -1
PHE 456	> -1	-8.38275	> -1	> -1
TYR 473	-5.35686	-3.91764	> -1	> -1
GLN 474	-3.17544	> -1	> -1	> -1
ALA 475	-1.64618	-2.85914	> -1	> -1
GLY 476	-2.23624	> -1	> -1	> -1
SER 477	-2.07175	> -1	> -1	> -1
THR 478	-2.23841	> -1	> -1	> -1
PRO 479	-1.13987	> -1	> -1	> -1
TYR 489	-2.05506	-6.80675	> -1	> -1
PRO 491	> -1	-1.16799	> -1	> -1

**Table S7.** The specific value of residue-based contact probability more than 0.2 between S\_RBD and part I/part II of Lincomycin in domain 1.

Residue Name	Contact Probability	
	part I	part II
PHE 338	<0.2	0.30452
GLY 339	<0.2	0.63119
GLU 340	<0.2	0.28907
PHE 342	0.62519	0.80157
ASN 343	0.63374	0.82177
VAL 367	<0.2	0.55509
LEU 368	0.44531	0.60279
SER 371	0.40191	0.5138
SER 373	0.73278	0.4719
PHE 374	0.38021	0.41301
TRP 436	0.58194	0.35362
LEU 441	0.27187	<0.2