Table S1: shows the calculated Accessible Surface Area (ASA) for the residues forming the deep groove between the two monomers (DGBM) of ORF8. This criterion was computed using the Accessible Surface Area and Accessibility Calculation for Protein (ver. 1.2) server. The letters i, o, and i-o correspond to the ASA positions of the respective residues inside, outside, and in-between these two states in DGBM.

AMINO ACID	CHAIN	Area(Å2)	Relative (0.0 - 1.0)	IN/OUT
Q27	A	51.395	0.275	i-o
	B	35.704	0.191	i-o
H28	A	113.382	0.567	i-o
	B	104.953	0.524	i-o
G50	A	38.077	0.426	i-o
	B	33.742	0.377	i-o
A51	A	7.49	0.062	i
	B	17.25	0.143	i
Q91	A	30.536	0.163	i-o
	B	39.66	0.212	i-o
E92	A	42.778	0.227	i
	B	46.285	0.246	i
P93	A	9.276	0.06	i
	B	13.627	0.088	i
K94	A	119.708	0.56	i-o
	B	92.338	0.432	i-o
L95	A	31.634	0.153	i-o
	B	30.612	0.148	i-o
G96	A	18.455	0.206	i
	B	6.772	0.076	i
S97	A	0.113	0.001	i
	B	**2.951**	**0.023**	i
R115	A	3.519	0.015	i
	B	**5.387**	**0.023**	i
F120	A	7.674	0.034	i
	B	**8.503**	**0.037**	i

Table S2: TOP RESULTS OF I-TASSER SERVER PREDICTIONS FOR ORF8 BINDING SITES RESIDUES AND ITS NATIVE LIGANDS. These two were selected among five predicted templates in the I-TASSER server. The I-TASSER has achieved it by using COACH and CO-FACTOR servers. C-score is refer to the confidence score of the prediction and its ranges [0-1], where a higher score indicates a more reliable prediction. S.S refers to the secondary structure in which binding residues are located there on the SARS-CoV-2 ORF8 3D crystallography structure (FIG 1).

NO	TEMPLATE PDB ID/CHAIN	INTRODUCTION	LIGAND	C-score	BINDING SITE/S.S					
1	4y1x/A 	Complex of human Galectin-1 (Gal-1) and Galbeta1-4(6OSO3)GlcNAc	6S2	0.07	R48/β3	–	R101/ β7	Y111/ β8	D113/ β8	R115/ β8
2	1y0l/H 	Catalytic elimination antibody 34E4 in complex with hapten	HAN	0.07	–	E59/β4	R101/ β7	Y111/ β8	–	–

Table S3. The residues inhibited in NPs predicted solo and co-functionalities. The numbers after the NPs' name refer to optimal binding poses that each NP inhibits predicted binding sites. The letters A and B in cells refer to the ORF8 chain

INHIBITED RESIDUES		PREDICTED BINDING SITE RESIDUES																	OTHER RESIDUES															
		DGBM													Gal1-like																				
		Q27	H28	G50	A51	Q91	E92	P93	K94	L95	G96	S97	F120	R115 †	R48	E59	R101	Y111	D113	Q18	F41	K44	K53	A55	L57	V62	S67	P70	Q72	F104	D107	F108	Y109	E110	H112	I121
NPs Solo-Functionality	Remdesivir 1				● B		● AB		● B				● A	● A																					
	Artemisinin 1,2					● A	● AB										● B					● B			● B			● B			● B				
	Ivermectin 1,5,9				● A	● A	● AB	● B					● B				● B	● AB	● B	● B	● A		● AB		● B		● B			● A	● B		● B	● A	● A	● A
	DEG-168 1,2,4	● B	● B		● A	● A	● A						● A		● A		● AB	● AB				● B		● AB	● AB	● A			● A			● B				
NPs Co-Functionality	Remdesivir 1-Artemisinin 2				● B		● AB		● B				● A	● A			● B					● B			● B			● B			● B				
	Remdesivir 1-DEG168 1, 4				● B		● AB		● B				● A	● A	● A		● AB	● AB				● B		● AB	● AB	● A			● A			● B				
	Ivermectin 1,5,9-DEG168 1				● A	● A	● AB	● B					● B		● A		● AB	● AB	● B	● B	● A		● AB		● B	● A	● B		● A	● A	● B		● B	● A	● A	● A

† Residue R115 is predicted for both binding sites, but in the minimized structure it was accessible and exposed only at the DGBM binding site, so it was considered for this binding site.

Table S4: PREDICTED BINDING SITE RESIDUES AND THEIR CONSERVATION. Conservation has been calculated in Jalview software (101) by the AMAS method of multiple sequence alignment analysis (102) for 22947 aligned SARS-CoV-2 ORF8 sequences. AMSA scores the level of conservation of amino acid residues from 0-11 (from low to high). A score of 11 indicates grouping with default amino acid property, and a score of 10 indicates mutations that all default amino acid properties are conserved. SARS-CoV-2 ORF8 sequences had been aligned by MEGA7 (99) software using the MUSCLE algorithm (100)

NO	BINDING SITE SPECIFY METHOD		BINDING SITE RESIDUE NAME & NUMBER	MUTATION/MUT. FREQUENTLY%	CONSERVATION (0-11)	~CONSENSUS%
	I-TASSER Prediction	**Structural Analyses**				
1		●	**Q27**	**R/0.004, K/0.004, Gap**	**10**	**99**
2		●	**H28**	**L/0.004, Y/0.004, Gap**	**10**	**99**
3		●	**G50**	**Gap**	**11**	**99**
4		●	**A51**	**S/1.32, V/0.109, F/0.013,T/0.013, Gap**	**10**	**98**
5		●	**Q91**	**K/0.009, I/0.004, L/0.004, P/0.004, R/0.004, Gap**	**10**	**99**
6		●	**E92**	**K/1.286, S/0.004, Gap**	**10**	**98**
7		●	**P93**	**S/2.244, L/0.01, Gap**	**10**	**97**
8		●	**K94**	**E/0.009, R/0.004, Gap**	**10**	**99**
9		●	**L95**	**F/0.253, M/0.004, S/0.004, V/0.004, Gap**	**10**	**99**
10		●	**G96**	**D/0.004, Gap**	**10**	**99**
11		●	**S97**	**I/0.009, G/0.004, Gap**	**10**	**99**
12		●	**F120**	**L/0.689, K/0.022, V/0.017, I/0.004, Gap/14.2**	**2**	**85**
13	●	●	**R115**	**C/0.065, L/0.026, P/0.017, H/0.013, Gap**	**10**	**99**
14	●		**R48**	**I/0.004, Gap**	**10**	**99**
15	●		**E59**	**V/0.013, G/0.004, K/0.004, Gap**	**10**	**99**
16	●		**R101**	**L/0.022, Gap**	**10**	**99**
17	●		**Y111**	**C/0.004, Gap**	**10**	**99**
18	●		**D113**	**Y/0.004, Gap**	**10**	**99**

previously. R115 was predicted by both methods, but in our minimized ORF8 model, it was only exposed in the DGBM binding site.

Table S5: MOLECULAR DOCKING RESULTS FOR ORF8-REMDESIVIR COMPLEXES. The results are sorted from highest to lowest based on the binding affinity score (Kcal.mol^{-1}) from AutoDock Vina's output. Interacting residues of the predicted DGBM and Gal1-like binding sites are highlighted in green color and solid blue triangles, respectively. The letters A and B after the residue number refer to the chain where the residue is located. The R.46-83 is a structurally unique region of ORF8 located between residues 46-83.

BINDING POSE	SCORE Kcal.mol^{-1}	Lower Bond RMSD	INVOLVED RESIDUES IN H.bond	DISTANCE D-Å	INVOLVED RESIDUES IN HYDROPHOBIC INTERACTION	INVOLVED RESIDUES IN SALT BRIDGE INTERACTION	LOCATION ON ORF8
1	-7.4	0	92A 92B 94B 115A	3.94 3.09 4.06 3.44	51B 92A 92B 120A 120A	-	DGBM
2	-7.2	3.318	27A 93A 93B 96A	3.24 3.12 2.7 3.83	51A 91A 92A 94A 120B	-	DGBM
3	-7.0	2.706	27B 92A 92B 93A 115A 115A	4.02 3 3.92 3.81 3.25 4	51B 91A 92B 94A	-	DGBM
4	-6.9	2.521	27B 50A 93B 94B	3.74 3.37 2.97 3.66	51A 51B 92A	-	DGBM
5	-6.9	3.259	92B 115A 115A	3.65 3.84 3.32	51B 91B 92A 92A 92B 120B	-	DGBM
6	-6.8	1.936	92A 92B 94B 115A	3.78 2.92 3.98 3.46	92A 92A 120A	-	DGBM
7	-6.8	2.235	91B 94B	3.81 3.24	51A 51B 91A 92A 92B 92B 120A 120A	-	DGBM

					120B		
8	-6.7	3.192	27A 92A 92A 96B 115A	3.43 3.74 3.44 3.11 3.46	51B 92B 94A 120A	28A	DGBM
9	-6.7	2.949	27A 91A 92A 96B	3.01 3.92 3.07 2.8	51B 91B 92B	-	DGBM

Table S6: MOLECULAR DOCKING RESULTS FOR ORF8-ARTEMISININ COMPLEXES. The results are sorted from highest to lowest based on the binding affinity score (Kcal.mol-1) from AutoDock Vina's output. Interacting residues of the predicted DGBM and Gal1-like binding sites are highlighted in green color and solid blue triangles, respectively. The letters A and B after the residue number refer to the chain where the residue is located. The R.46-83 is a structurally unique region of ORF8 located between residues 46-83.

BINDING POSE	SCORE Kcal.mol^{-1}	Lower Bond RMSD	INVOLVED RESIDUES IN H.bond	DISTANCE D-Å	INVOLVED RESIDUES IN HYDROPHOBIC INTERACTION	INVOLVED RESIDUES IN SALT BRIDGE INTERACTION	LOCATION ON ORF8
1	-6.9	0	92A	3.63	91A 92B 92B	-	DGBM
2	-6.9	21.372	44B 107B	3.45 4.08	57B 70B	101B▲	R.46-83
3	-6.8	1.577	92B	3.9	51B 91A 92A 92B	-	DGBM
4	-6.8	19.066	-	-	56B 57B 57B 57B 108B	101B▲ 101B▲	R.46-83
5	-6.7	6.176	-	-	91B 120B	-	DGBM
6	-6.7	20.846	-	-	57B 57B	44B	R.46-83
7	-6.7	2.874	93A	2.85	51B 91A	-	DGBM
8	-6.6	2.524	93B	2.85	51B 91A 92A 120A	-	DGBM
9	-6.5	5.237	92B	3.23	92A 92B 94B 120B	115A	DGBM

Table S7: MOLECULAR DOCKING RESULTS FOR ORF8-IVERMECTINE COMPLEXES. The results are sorted from highest to lowest based on the binding affinity score (Kcal.mol-1) from AutoDock Vina's output. Interacting residues of the predicted DGBM and Gal1-like binding sites are highlighted in green color and solid blue triangles, respectively. The letters A and B after the residue number refer to the chain where the residue is located. The R.46-83 is a structurally unique region of ORF8 located between residues 46-83.

BINDING POSE	SCORE Kcal.mol^{-1}	Lower Bond RMSD	INVOLVED RESIDUES IN H.bond	DISTANCE D-Å	INVOLVED RESIDUES IN HYDROPHOBIC INTERACTION	INVOLVED RESIDUES IN SALT BRIDGE INTERACTION	LOCATION ON ORF8
1	-8.4	0	93B	2.74	51A 91A 92A 92B 92B 120B 120B	-	DGBM
2	-8.3	4.3	27A 28A	3.01 3.84	51A 51B 91A 92A	94B	DGBM
3	-8.2	25.582	67B 73B	3.85 2.81	57B 73B 109B 109B	44B	R.46-83
4	-8.0	2.904	92B 96A	2.92 3.78	51A 51B 76B 91A 91B 92A 92A 92B 94A 94B 120A 120A	-	DGBM
5	-7.9	22.379	110A 111A▲ 111A▲	3.44 3.96 3.96	41A 41A 53A 104A 110A 110A 111A▲ 111A▲ 112A	112A	R.46-83
6	-7.8	3.045	92B 94B	2.86 3.9	51A 51B 76B 92B 92B 94A 120A 120B	-	DGBM
7	-7.7	2.729	27A	2.94	51A 91B	94B	DGBM
8	-7.7	26.831	43B 61B 64B	3.04 3.73 4.06	45B 86B 108B	-	R.46-83
9	-7.7	23.858	57B 101B▲ 111B▲ 113B▲ 113B▲	4.03 3.45 3.77 2.9 3.95	18B 53B 53B 111B▲ 121A	101B▲	R.46-83

Table S8: MOLECULAR DOCKING RESULTS FOR ORF8-DEG-168 COMPLEXES. The results are sorted from highest to lowest based on the binding affinity score (Kcal.mol-1) from AutoDock Vina's output. Interacting residues of the predicted DGBM and Gal1-like binding sites are highlighted in green color and solid blue triangles, respectively. The letters A and B after the residue number refer to the chain where the residue is located. The R.46-83 is a structurally unique region of ORF8 located between residues 46

BINDING POSE	SCORE Kcal.mol^{-1}	Lower Bond RMSD	INVOLVED RESIDUES IN H.bond	DISTANCE D-Å	INVOLVED RESIDUES IN HYDROPHOBIC INTERACTION	INVOLVED RESIDUES IN SALT BRIDGE INTERACTION	INVOLVED RESIDUES π-CATION INTERACTIONS	LOCATION ON ORF8
1	-7.6	0	48A 55A 57A 57A 101A 101A	3.78 3.02 3.3 2.86 2.92 3.3	62A 72A	101A	-	R.47-83
2	-7.3	19.258	27B 27B 28B	3.18 3.65 3.31	51B 91A 92A 92A 120A	-	-	DGBM
3	-7.3	23.747	27A 50B 96B	3.52 3.69 3.46	91B 92B 92B 120B	-	-	DGBM
4	-7-2	40.495	55B 57B 57B 101B 101B 108B	3.11 3.24 2.85 3 3.94 3.89	108B	101B	44B	R.47-83
5	-7.2	18.651	27B 27B 28B 50A 93A 95A	3.08 3.68 3.01 4.08 3.72 4.09	91A 120A	-	-	DGBM
6	-7.2	16.323	43A 45A 45A 45A 60A 83A 83A 86A	2.99 2.7 3.71 3.09 3.28 3.1 2.83 3.06	32A 85A	-	-	R.47-83
7	-7.0	18.103	28B 50A	3.68 3.73	51B 92B 92B	-	-	DGBM
8	-7.0	22.834	50A 92A 92B 95A	3.39 3.77 3.18 3.95	-	-	-	DGBM
9	-7.0	18.801	27B 28B 92B 93A 95A 96A 96A	3.45 3.94 3.43 3.82 3.69 3.37 2.79	51B 91A 92A 92A	-	-	DGBM