

Supplementary Material

Targeting the SARS-CoV-2 spike glycoprotein prefusion conformation: virtual screening and molecular dynamics simulations applied to the identification of potential fusion inhibitors

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Tables

Compound name	CID	Binding energy (kcal/mol)
31h-phthalocyanine	5282330	-16.3
hypericin	3663	-15.1
ergotamine	8223	-13.2
2-[3-({Methyl[1-(2-Naphthoyl)Piperidin-4-Yl]Amino}Carbonyl)-2-Naphthyl]-1-(1-Naphthyl)-2-Oxoethylphosphonic Acid (also known as JNJ-10311795)	656932	-13.1
laniquidar	6450806	-12.8
3,8-Diamino-6-Phenyl-5-[6-[1-[2-[(1,2,3,4-Tetrahydro-9-Acridinyl)Amino]Ethyl]-1h-1,2,3-Triazol-4-Yl]Hexyl]-Phenanthridinium (also known as TZ2PA6)	5289507	-12.7
quarfloxin	11635763	-12.6
TMC-647055	44556044	-12.5
tadalafil	110635	-12.4
tepotinib	25171648	-12.0

Table S1. Virtual Screening (VS) procedure results. Binding energies for each compound are calculated as an average of 3 repeated molecular docking simulations. CID column identifies the PubChem Compound ID.

Compound	Residue	VdW (kcal/mol)	Electrostatic (kcal/mol)	Binding energy (kcal/mol)
phthalocyanine #1	T912.A	-2.3	-0.1	-1.6
	N914.A	-2.0	0.0	-1.9
	R1091.A	-1.6	+0.3	-0.1
	E1092.A	-3.1	+0.3	-2.7
	V1104.A	-1.2	+0.1	-0.9
	T1105.A	-1.1	0.0	-0.7
	Q1106.A	-3.2	-2.5	-2.7
	E1111.A	-2.2	0.0	-1.7
	Q1113.A	-3.4	-0.5	-2.5
	N1119.A	-1.7	-0.1	-1.3
	F1089.C	-1.0	+0.1	-1.0
	R1091.C	-4.6	-0.9	-2.6
	E1092.C	-1.6	+0.1	-1.5
	F1121.C	-4.8	0.0	-5.1
phthalocyanine #2	F1089.A	-1.9	0.0	-2.0
	R1091.A	-3.3	-1.0	-2.1
	E1092.A	-1.9	+0.1	-1.3
	R1107.A	-1.0	+0.3	-0.6
	F1121.A	-3.1	+0.2	-2.9
	Y904.B	-0.6	0.0	-0.6
	N907.B	-2.5	-0.2	-1.2
	V911.B	-1.2	0.0	-1.1
	T912.B	-4.2	0.0	-3.8
	Q913.B	-2.8	-1.1	-2.9
	N914.B	-1.3	0.0	-1.2
	R1091.B	-1.7	-1.3	-1.1
	E1092.B	-2.8	+1.6	-1.4
	Q1106.B	-1.3	-0.1	-0.7
N1119.B	-0.9	0.0	-0.8	
phthalocyanine #3	Y904.B	-0.7	-0.1	-0.6
	N907.B	-1.4	0.0	-0.8
	G910.B	-1.1	-0.2	-0.9
	E1092.B	-3.0	+0.7	-2.6
	Y904.C	-1.1	-0.1	-1.3
	N907.C	-3.6	+0.4	-2.1
	G908.C	-1.0	-0.1	-0.6
	I909.C	-0.8	-0.0	-0.6
	G910.C	-1.5	-0.2	-1.2
	V911.C	-1.1	0.0	-1.1
	T912.C	-1.1	+0.1	-0.8

Compound	Residue	VdW (kcal/mol)	Electrostatic (kcal/mol)	Binding energy (kcal/mol)
hypericin #1	T912.A	-2.5	-1.8	-3.2
	Q913.A	-1.4	-1.7	-1.3
	N914.A	-0.7	+0.6	-0.5
	R1091.A	-1.6	+1.4	-1.3
	E1092.A	-3.0	-0.9	-2.5
	P1090.C	-0.5	-0.6	-0.5
	R1091.C	-6.5	-1.8	-4.6
	E1092.C	-2.5	+2.7	-0.9
	F1121.C	-2.2	+0.1	-2.0
hypericin #2	P1090.A	-0.6	-3.0	-1.7
	R1091.A	-3.0	+0.4	-1.1
	E1092.A	-2.4	-1.6	-0.5
	F1121.A	-2.0	+0.1	-1.7
	N907.B	-2.1	-0.3	-1.2
	T912.B	-3.0	-0.8	-3.4
	Q913.B	-2.3	-0.5	-2.3
	N914.B	-1.4	+0.1	-1.4
	E1092.B	-1.5	-0.9	-1.7
	Q1106.B	-1.0	-0.5	-0.5
	Q1113.B	-0.8	-0.5	-0.5
	hypericin #3	Y904.A	-1.1	0.0
N907.A		-1.4	-1.3	-1.3
G908.A		-0.6	-0.4	-0.5
R1091.B		-0.6	-1.0	-0.5
E1092.B		-1.0	-2.3	-0.8
N907.C		-2.4	+0.3	-2.2
G910.C		-1.2	-1.2	-1.1
T912.C		-1.1	-0.6	-1.4
E1092.C		-2.6	+1.9	-2.0

Table S2. Results of the MM/GBSA per-residue decomposition analysis (Genheden and Ryde, 2015) performed on spike glycoprotein residues surrounding the three phthalocyanine and three hypericin molecules. The spike monomer to which each residue belongs is indicated by the letter after the dot.

Fig. S1 Supplementary Material

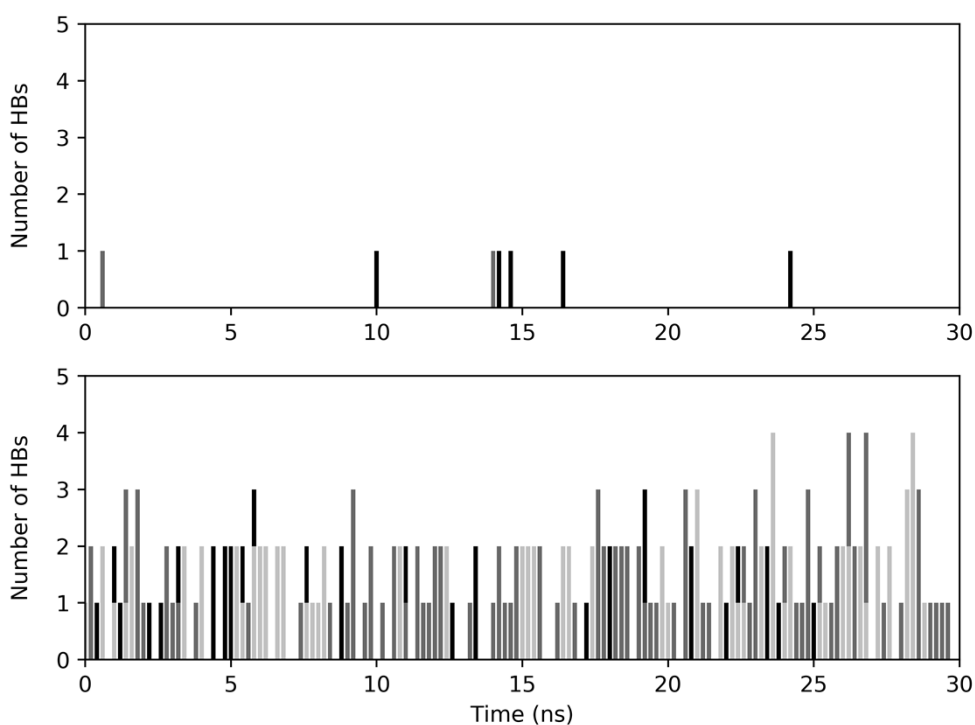
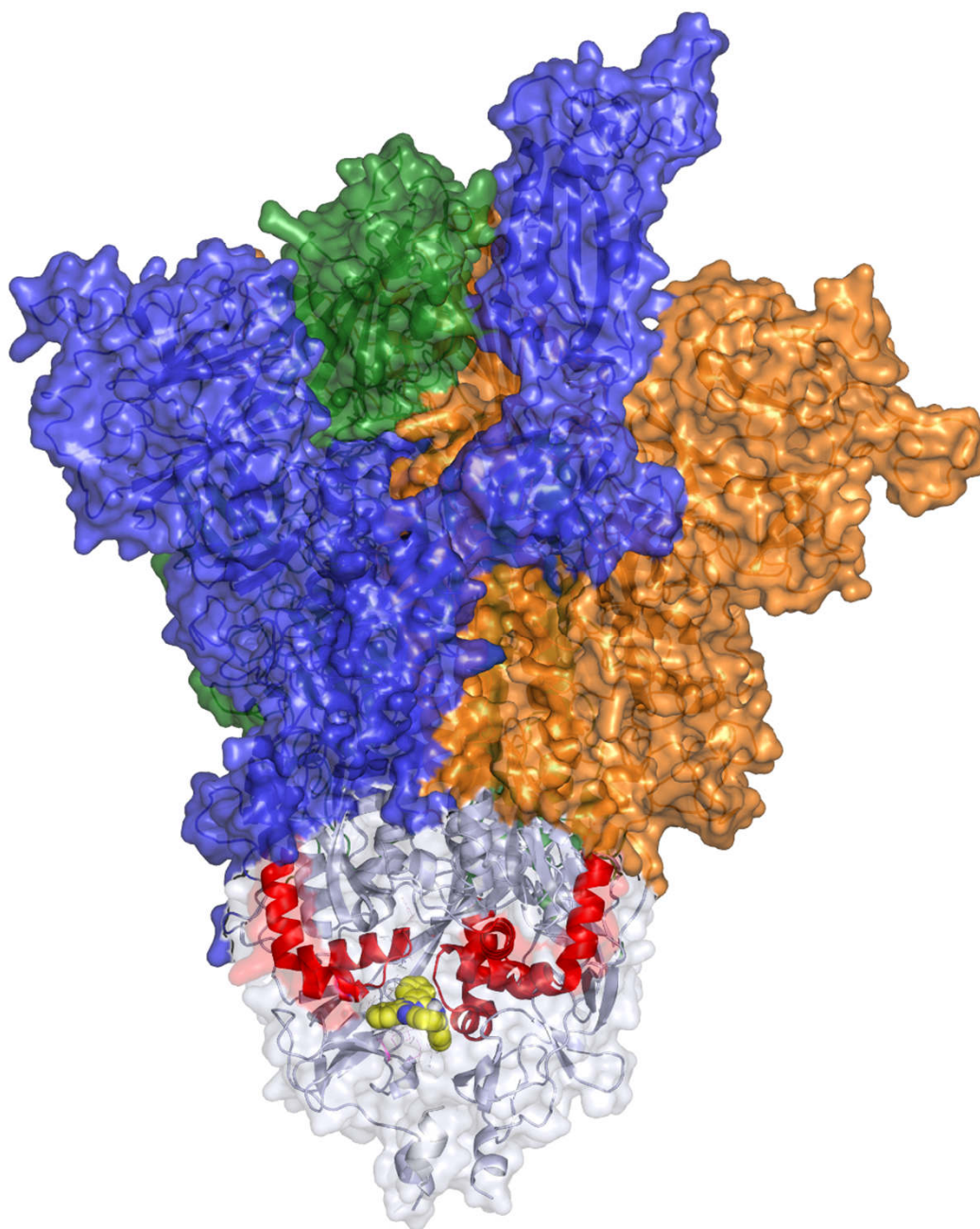


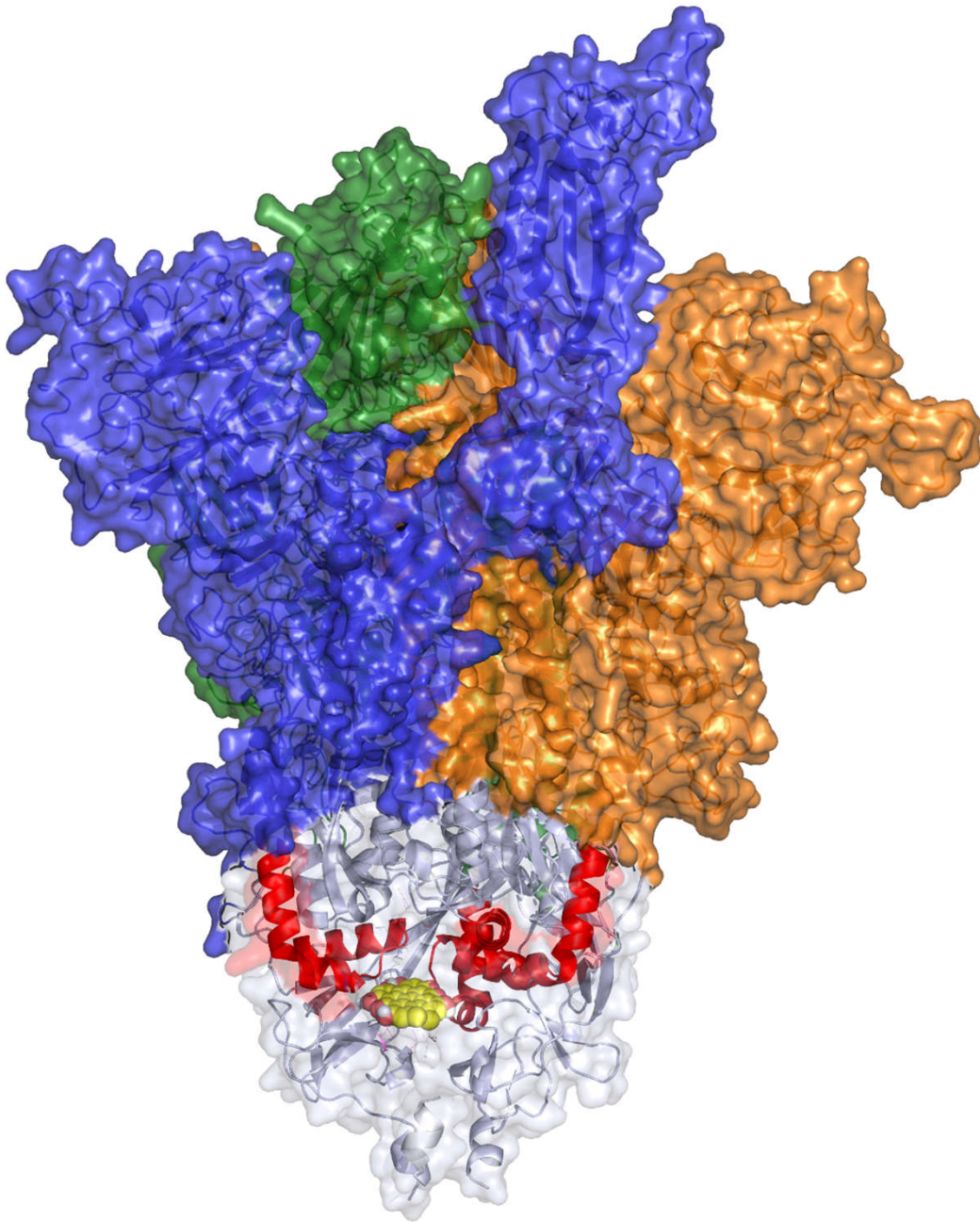
Figure S1. Hydrogen bond analyses performed for the three phthalocyanines (upper panel) and the three hypericines (lower panel). Black, dark grey and light grey lines indicate the first, second and third docked molecule, respectively, for both compounds. Hydrogen bonds (HBs) were computed every 100 ps. Plots have been realized using the *Matplotlib* library of Python3.

Fig. S2 Supplementary Material

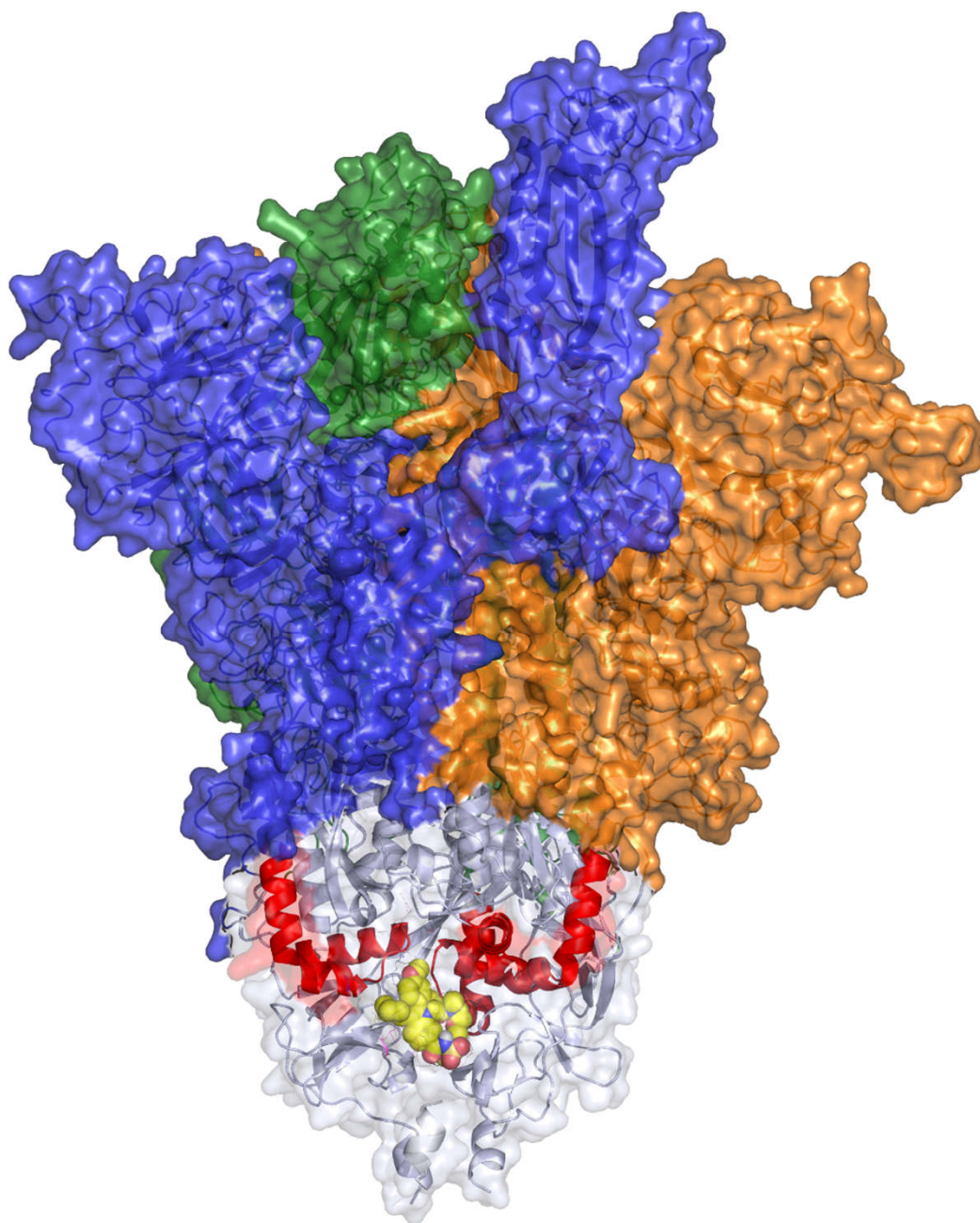
A) Phthalocyanine



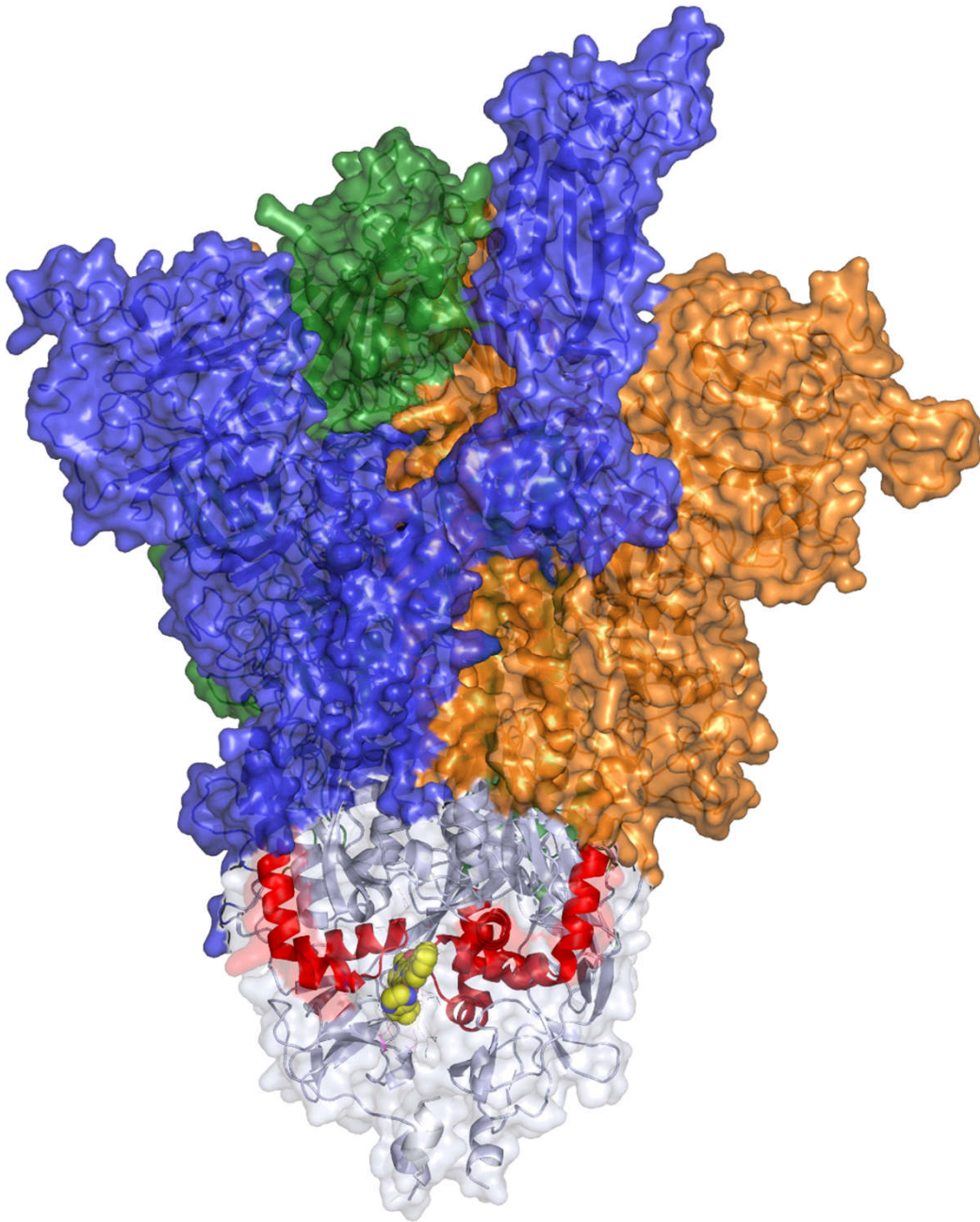
B) Hypericin



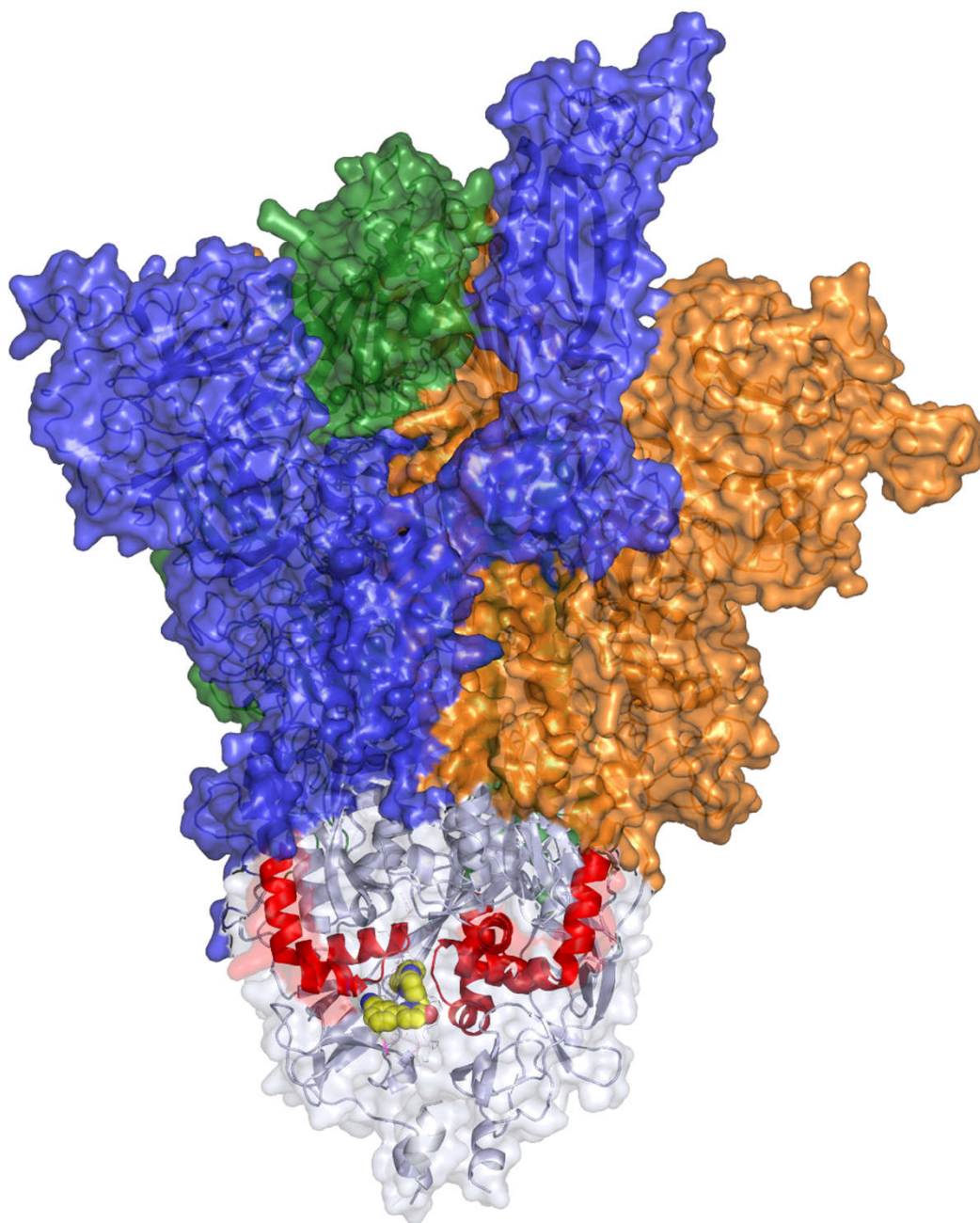
C) TMC-647055



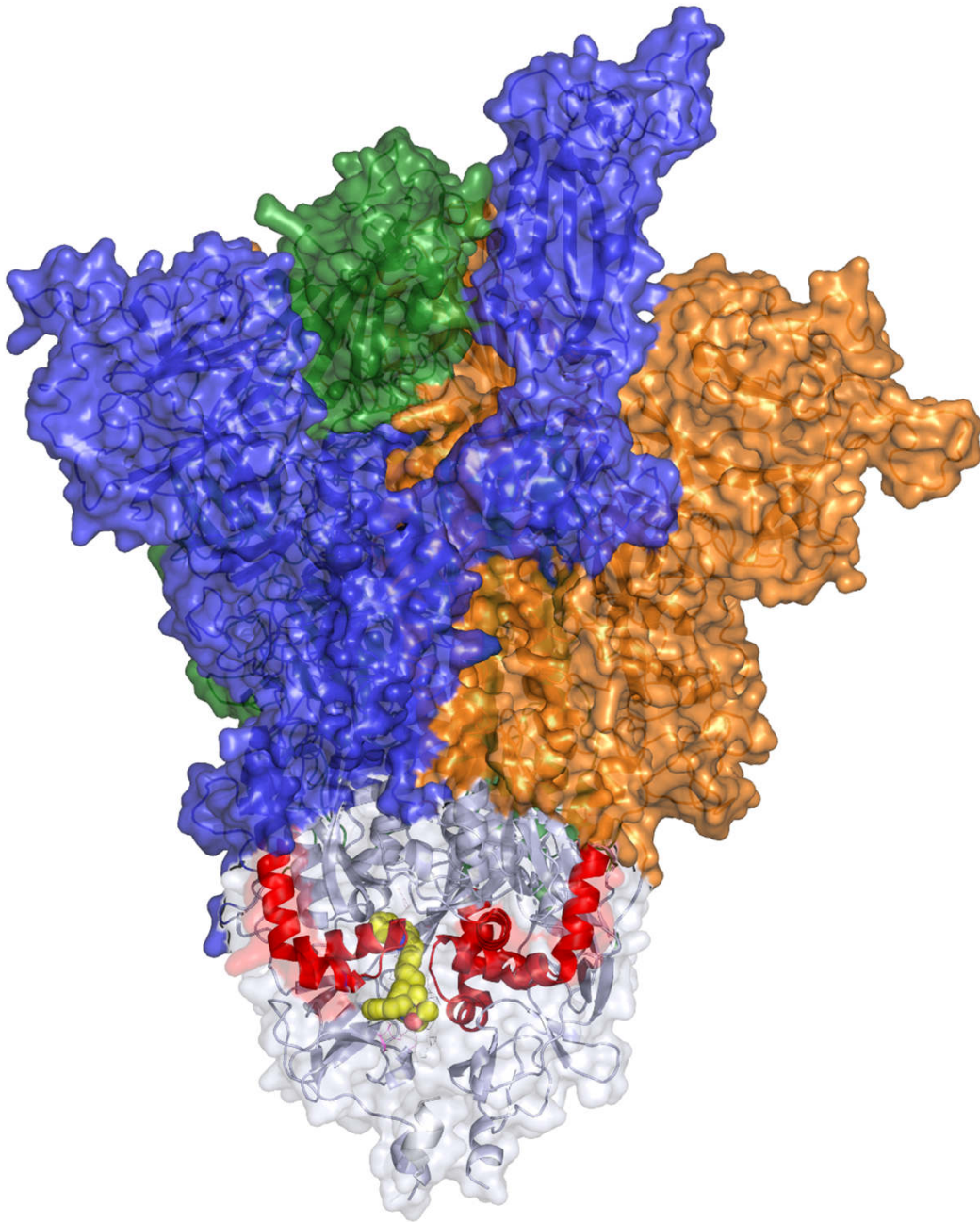
D) Quarfloxin



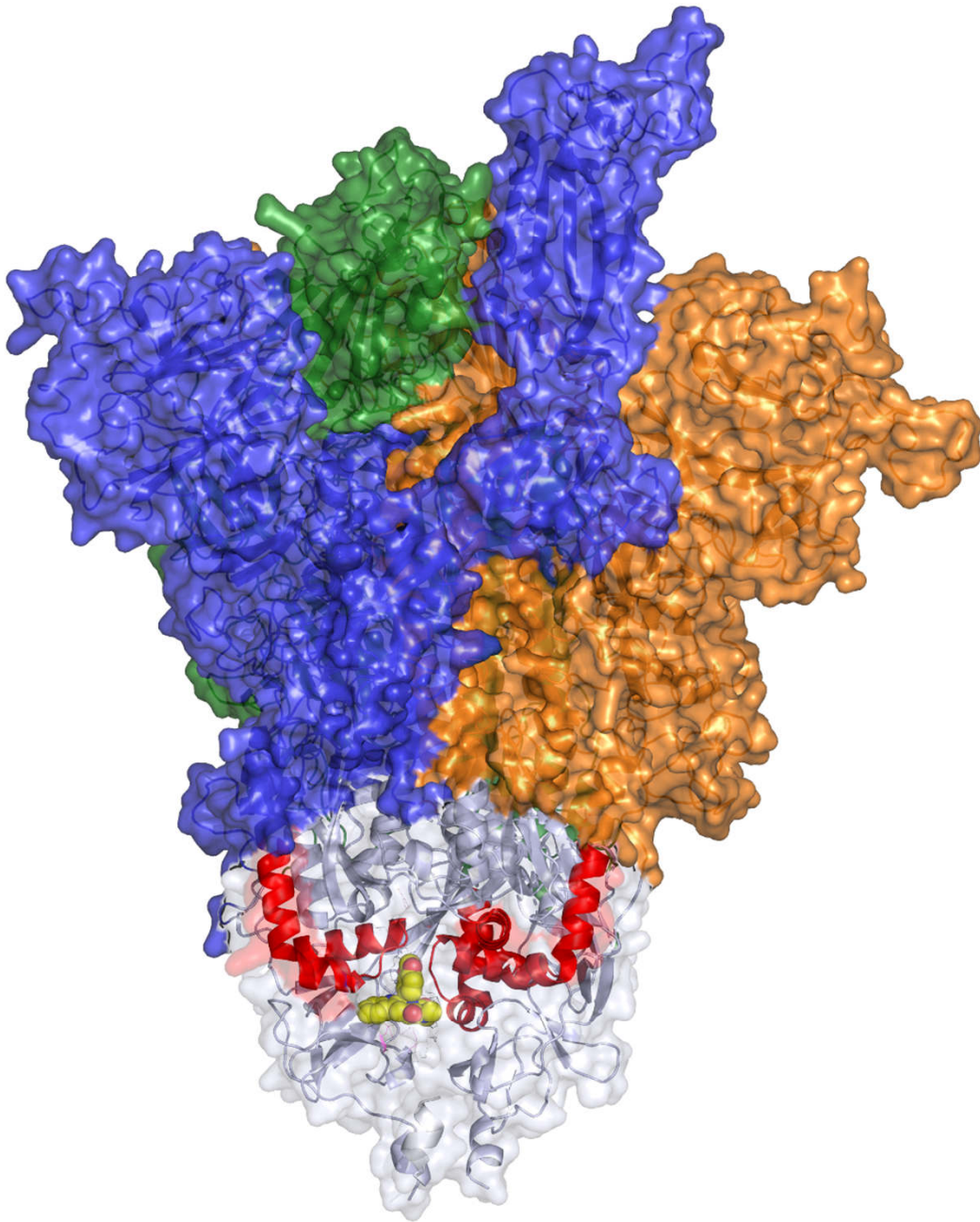
E) Tepotinib



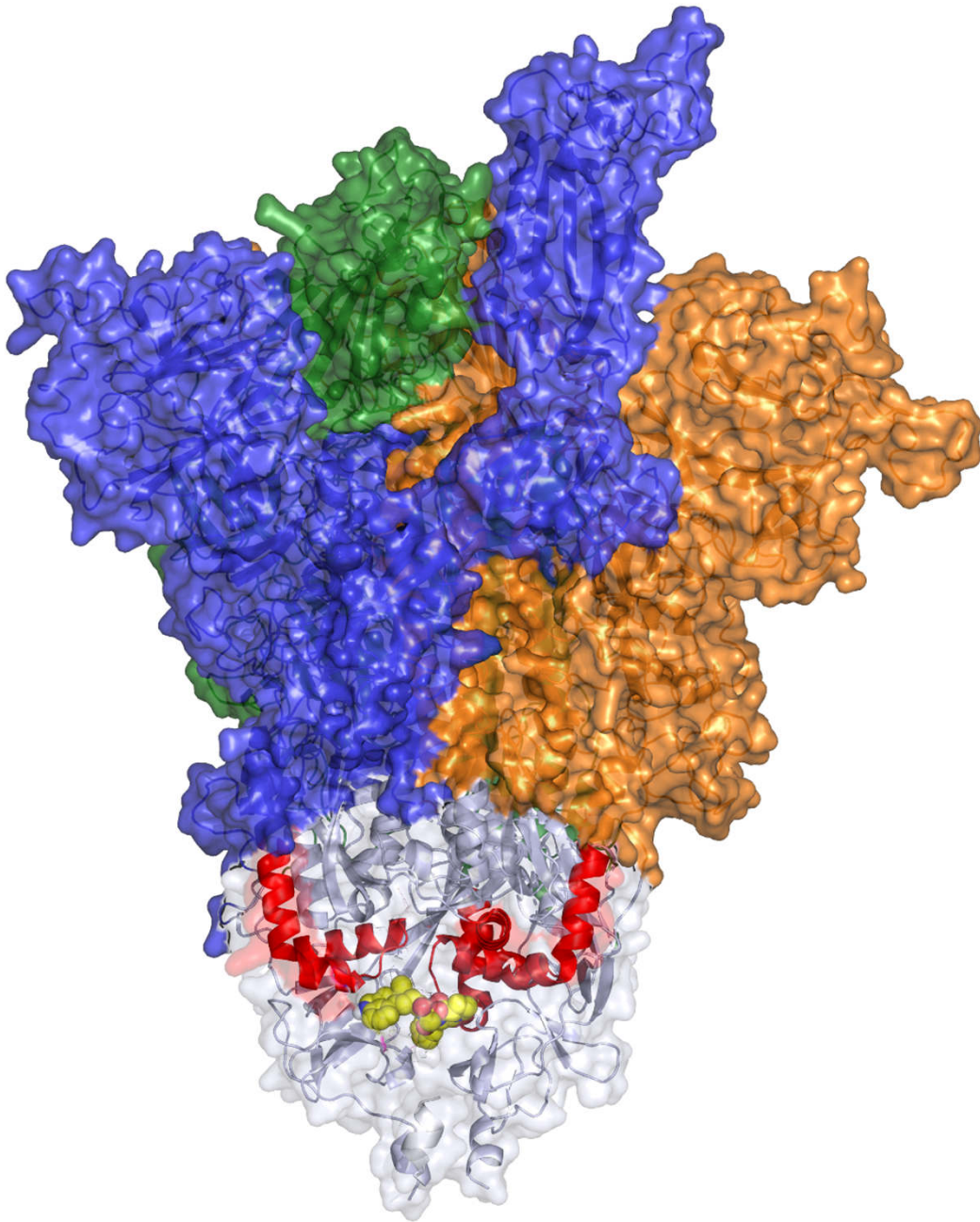
F) Laniquidar



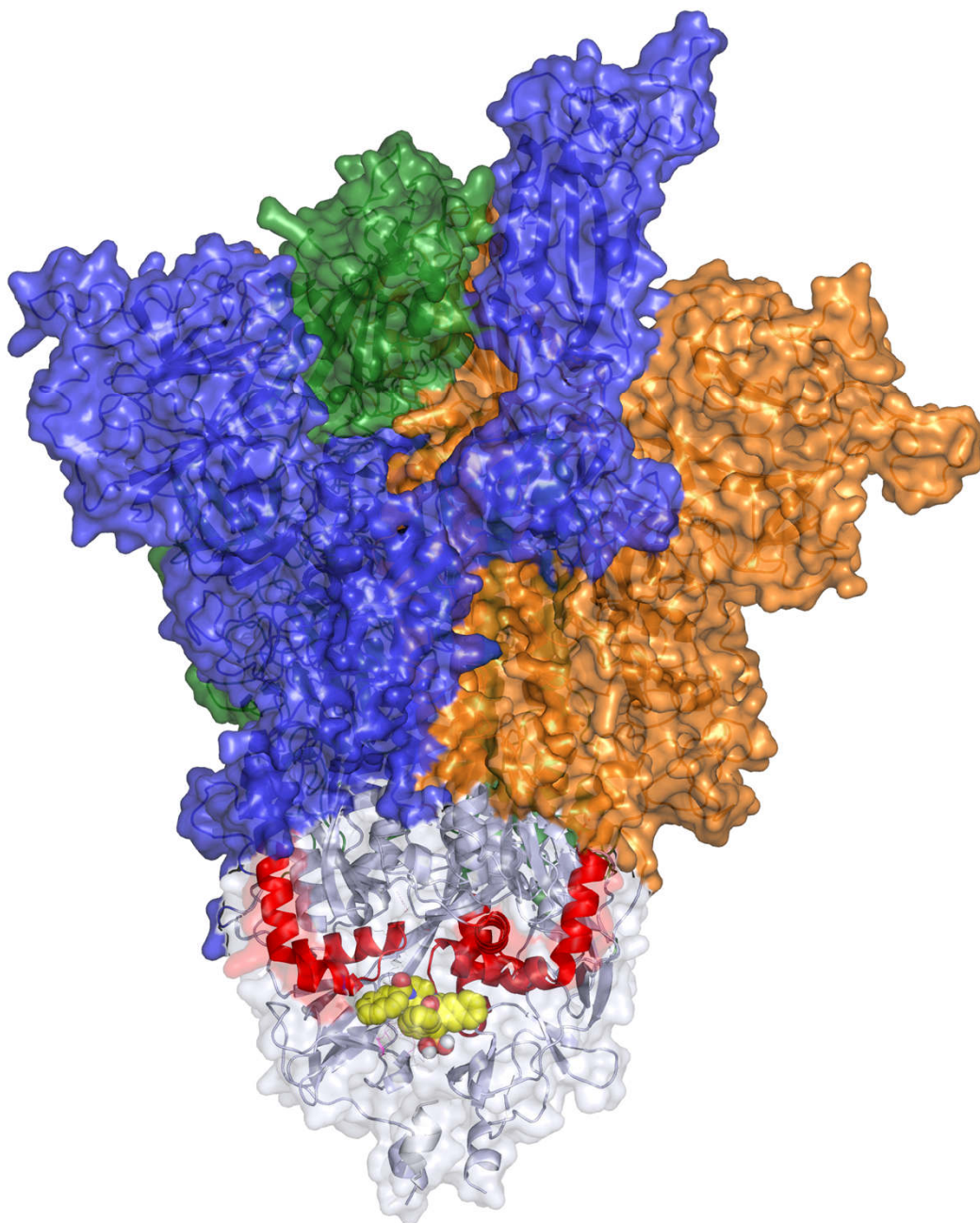
G) Tadalafil



H) Ergotamine



I) JNJ-10311795



J) TZ2PA6

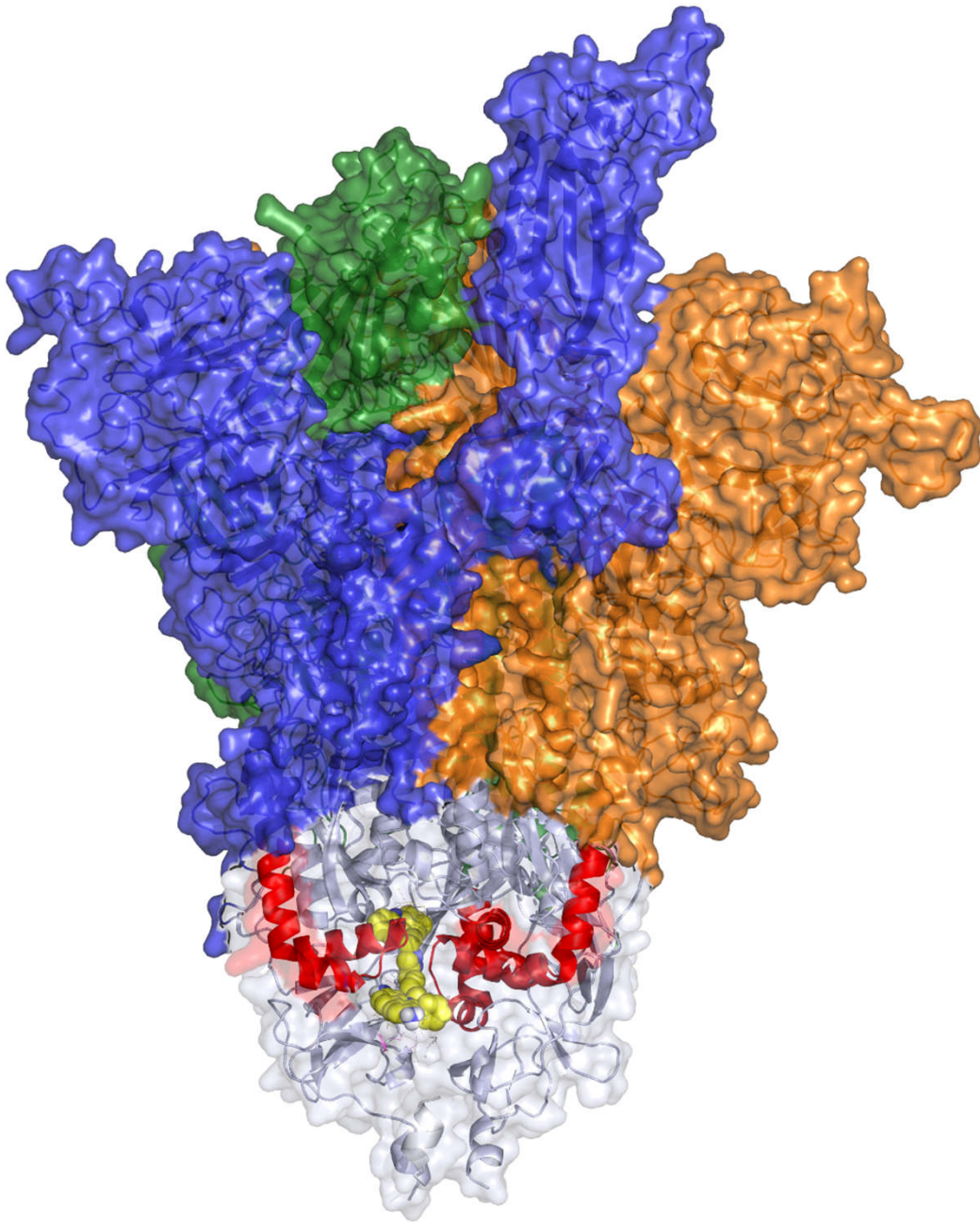
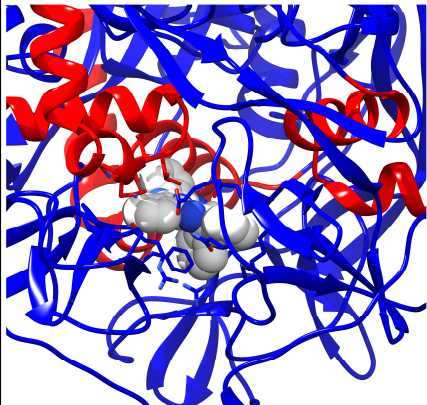
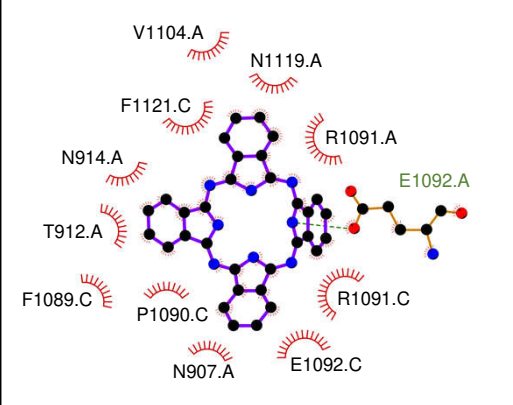
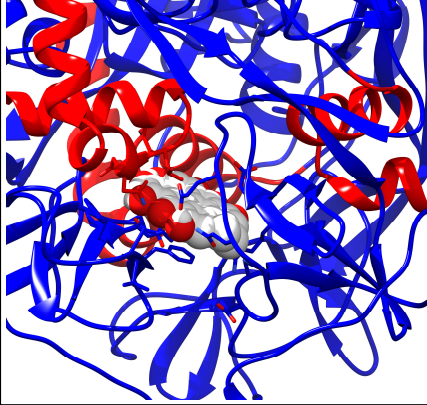
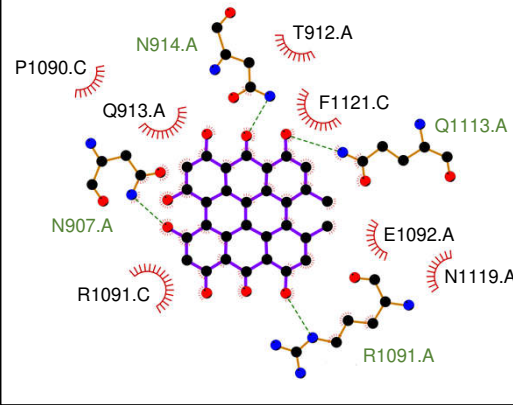
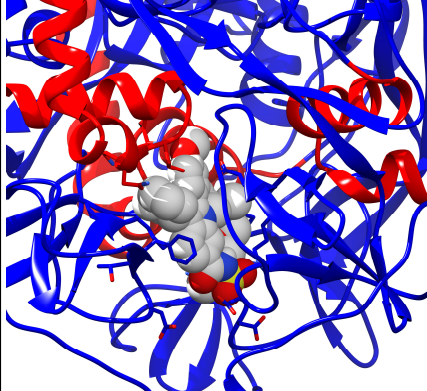
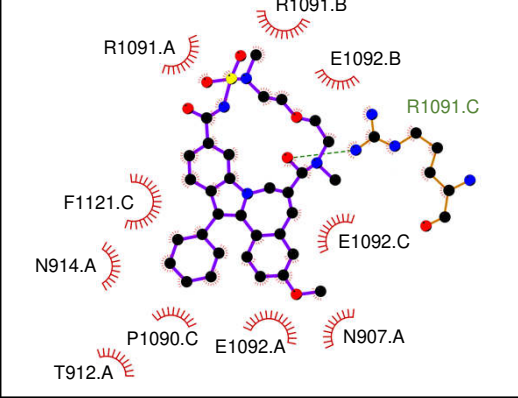
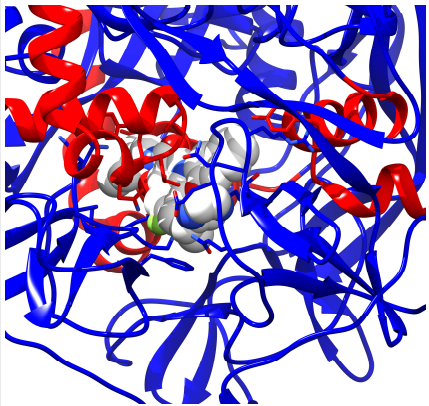
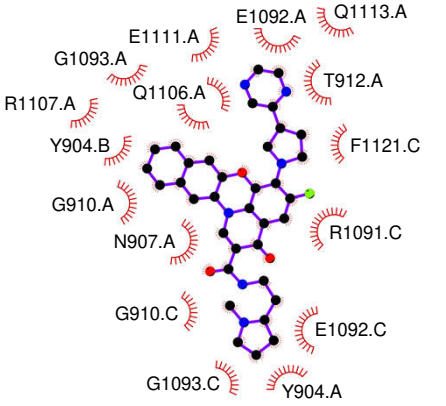
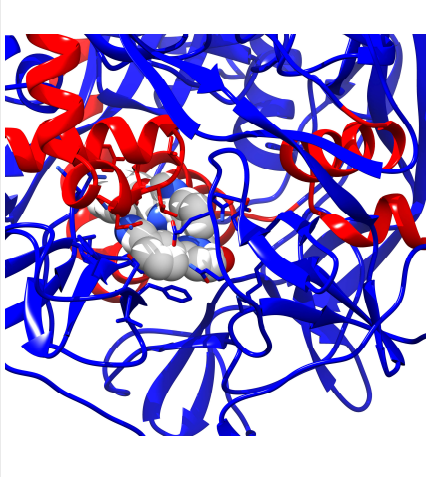
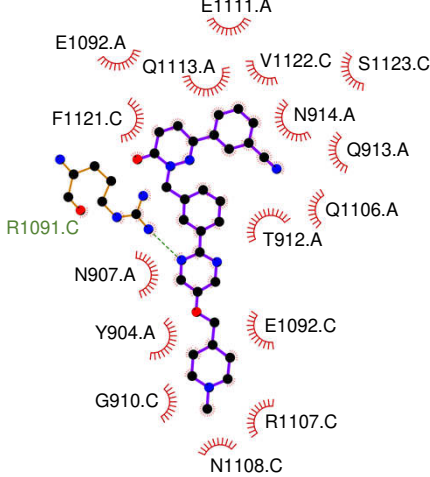
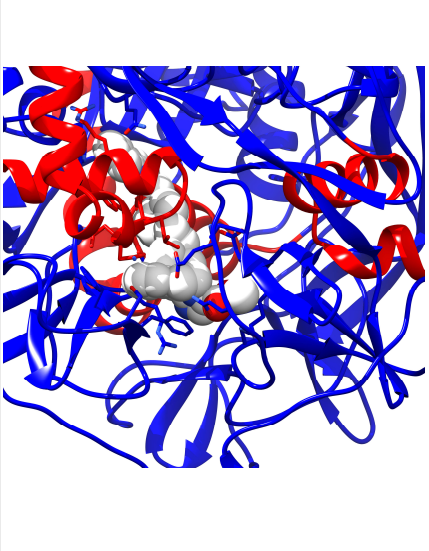
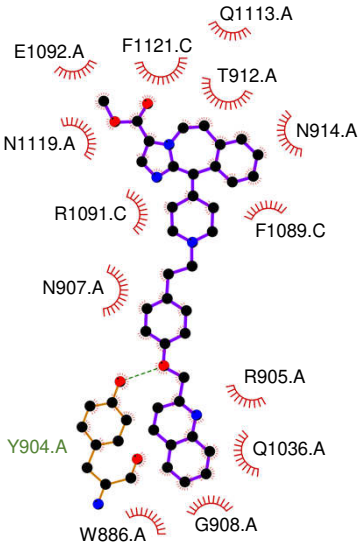
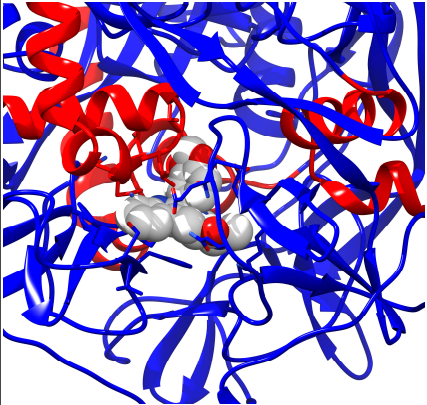
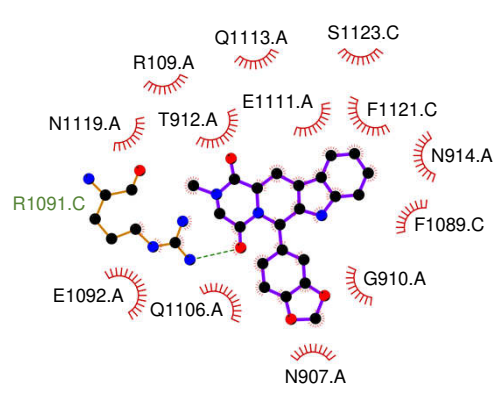
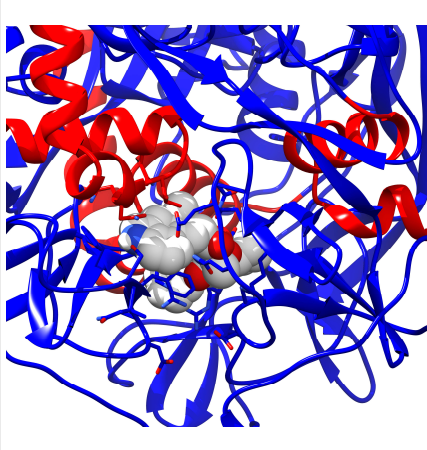
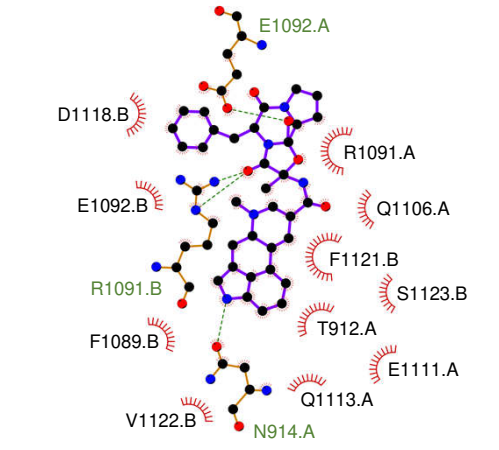
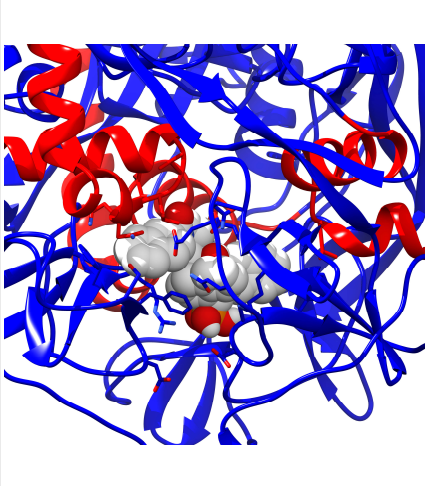
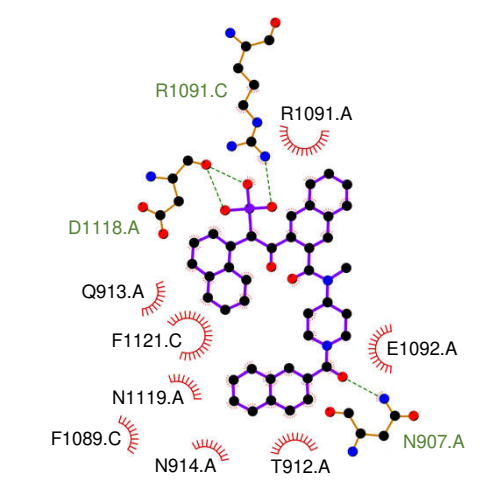


Figure S2. Complexes between the SARS-CoV-2 spike glycoprotein and each of the ten best compounds obtained from the VS procedure. The red ribbons represent the HR1 regions of the spike S glycoprotein while residues 703-717 and 1070-1138 of the monomer A have been hidden to highlight the ligands, represented by yellow spheres. The three glycoprotein monomers are identified by different coloured surfaces (blue: monomer A; orange: monomer B; green: monomer C). Compound order follows the reweighted ranking in Table 3. Pictures have been obtained using the PyMOL 2.1.0 program (The PyMOL Molecular Graphics System Version 2.1.0 Schrödinger, LLC).

Fig. S3 Supplementary Material

Name	Binding energy (kcal/mol)
Phthalocyanine	-16.3
	
Hypericin	-15.1
	
TMC-647055	-12.5
	

<p style="text-align: center;">Quarfloxin</p>	<p style="text-align: center;">-12.6</p>
	
<p style="text-align: center;">Tepotinib</p>	<p style="text-align: center;">-12.0</p>
	
<p style="text-align: center;">Laniquidar</p>	<p style="text-align: center;">-12.8</p>
	

Tadalafil	-12.4
	
Ergotamine	-13.2
	
JNJ-10311795	-13.1
	

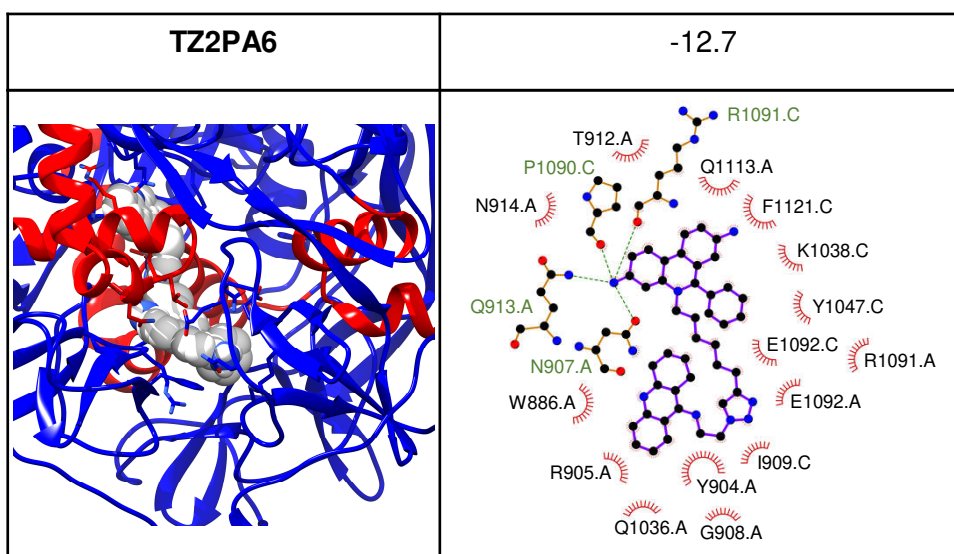


Figure S3. Representation of the best molecular docking complexes ranked after the literature-based reweighting. Binding energies are calculated as an average from 3 repeated molecular docking simulations. Left panels: best binding pose of each docked molecule within the inner cavity of the spike glycoprotein. Drugs are shown as spheres, colored by atom type with carbon atoms in grey. The spike glycoprotein is shown in blue cartoon representation with the HR1 regions highlighted in red. Right panels: 2D schematic view of the interactions established by each docked compound within the inner cavity of the spike glycoprotein. Drugs bonds and carbon atoms are represented as blue sticks and black filled circles, respectively. Hydrogen bonds are shown as green dashed lines between the interacting partners, represented as brown sticks. Hydrophobic interactions are shown as radial half-circles. Labels indicate the residue name in one-letter code, the residue number and the spike monomer to which the residue belongs. Pictures in the left panels have been generated using the UCSF Chimera 1.13 program (Pettersen et al., 2004), while schematic views in the right panels have been created using the LigPlot+ 1.4 software (Laskowski and Swindells, 2011).

Fig. S4 Supplementary Material

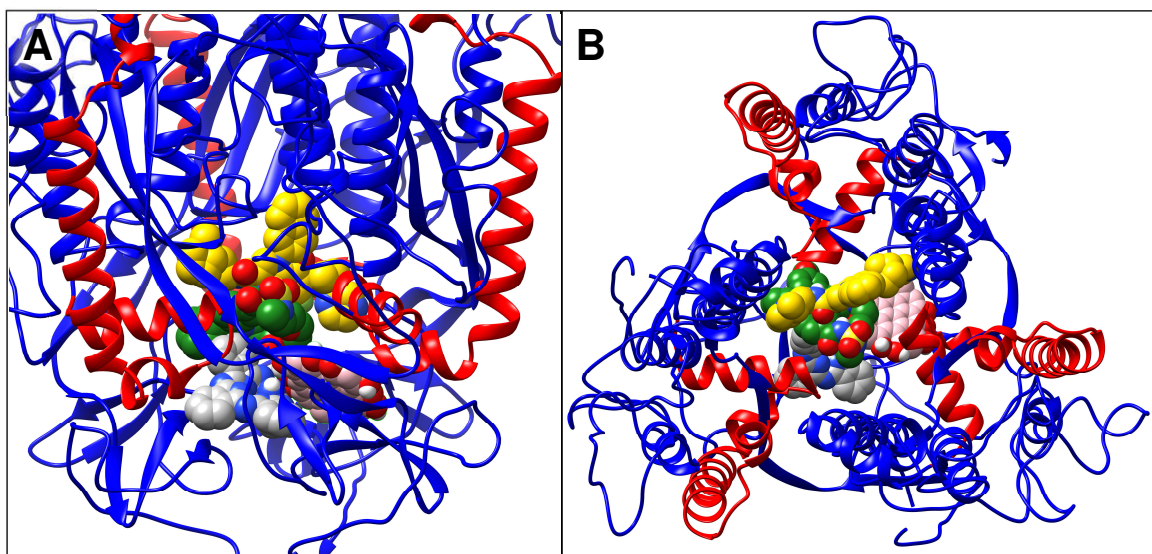


Figure S4. Frontal (A) and downward (B) representation of the complex obtained from the sequential molecular docking simulations of the top 4 drugs, selected after the VS results reweighting. Drugs are shown as spheres coloured by atom type. Carbon atoms are coloured according to the following scheme: phthalocyanine (grey), hypericin (pink), TMC-647055 (green), quarfloxin (yellow). The spike glycoprotein is shown in blue cartoon representation with the HR1 regions highlighted in red. Only residues 700 to 950 of the three monomers are shown in the figure B. Pictures have been generated using the UCSF Chimera 1.13 program (Pettersen et al., 2004).