Supplementary material.

A

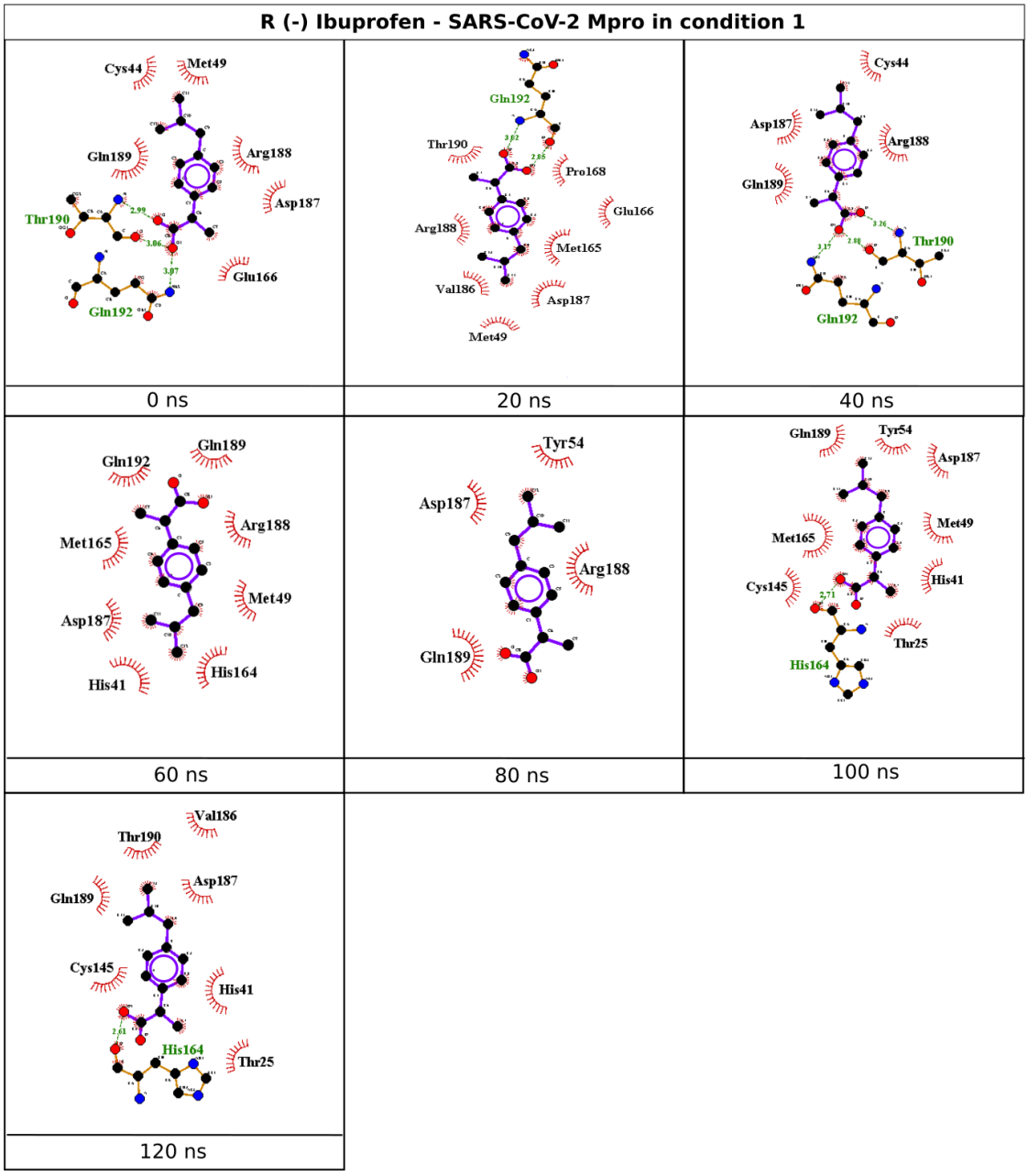

Figure S1. A. 2D interactions showing hydrogen bonds (green) and hydrophobic interactions (red) every 20 ns of MD-simulations in the binding pocket of the SARS-CoV-2 Mpro with R(-)Ibuprofen in condition 1, visualized by LigPlot+.

B

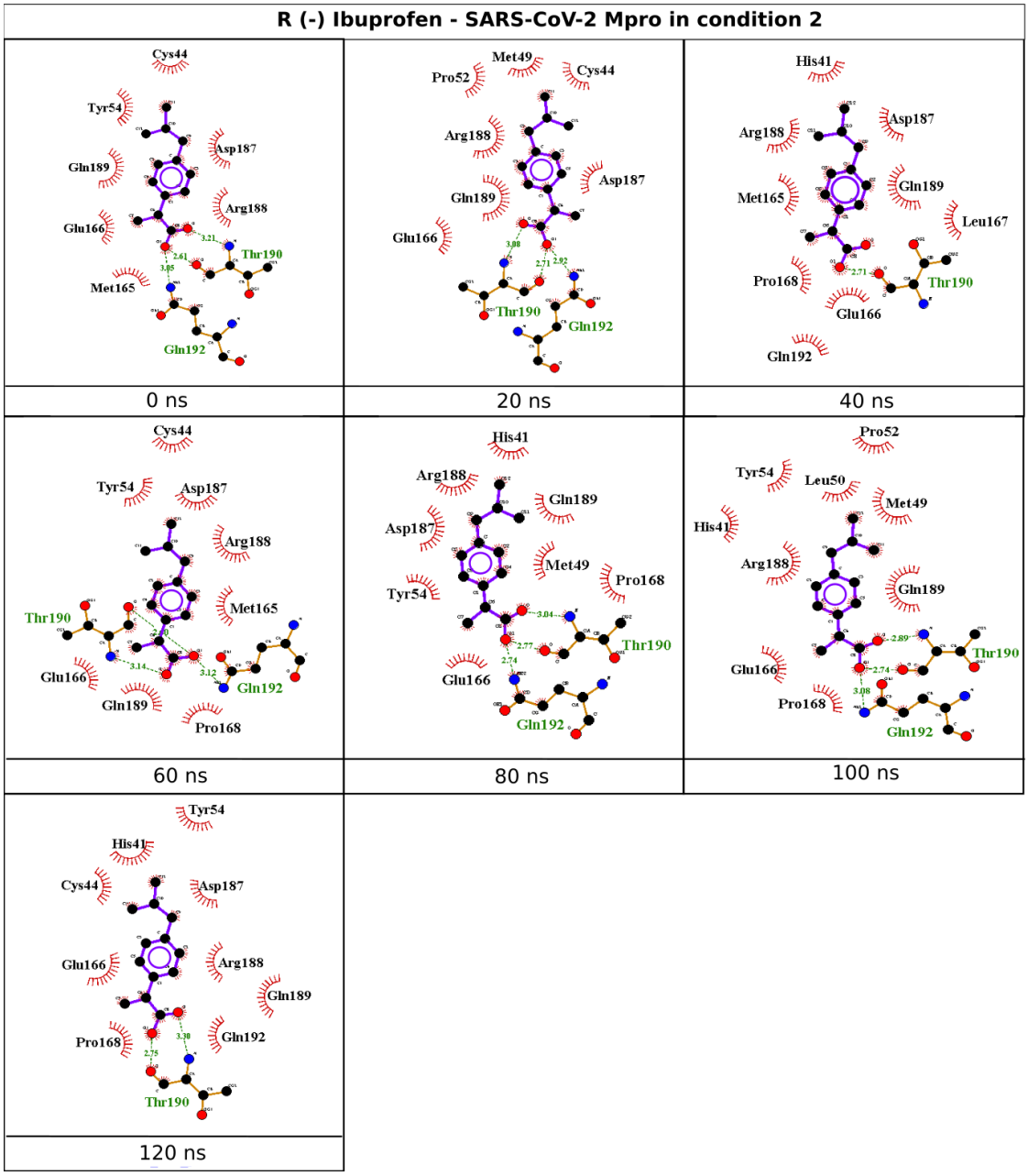

Figure S1. B. 2D interactions showing hydrogen bonds (green) and hydrophobic interactions (red) every 20 ns of MD-simulations in the binding pocket of the SARS-CoV-2 Mpro with R(-)Ibuprofen in condition 2, visualized by LigPlot+.

C

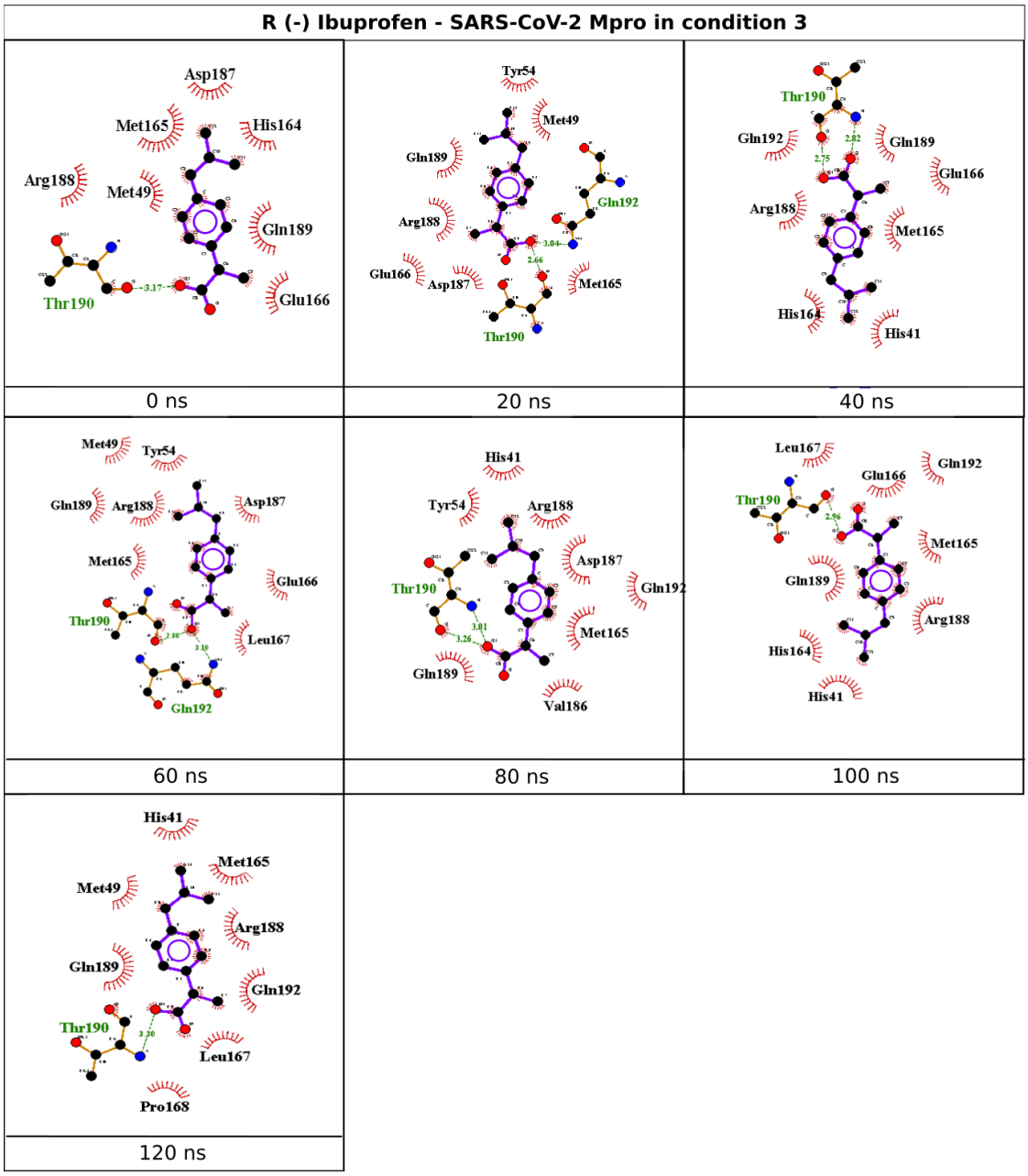

Figure S1. C. 2D interactions showing hydrogen bonds (green) and hydrophobic interactions (red) every 20 ns of MD-simulations in the binding pocket of the SARS-CoV-2 Mpro with R(-)Ibuprofen in condition 3, visualized by LigPlot+.

D

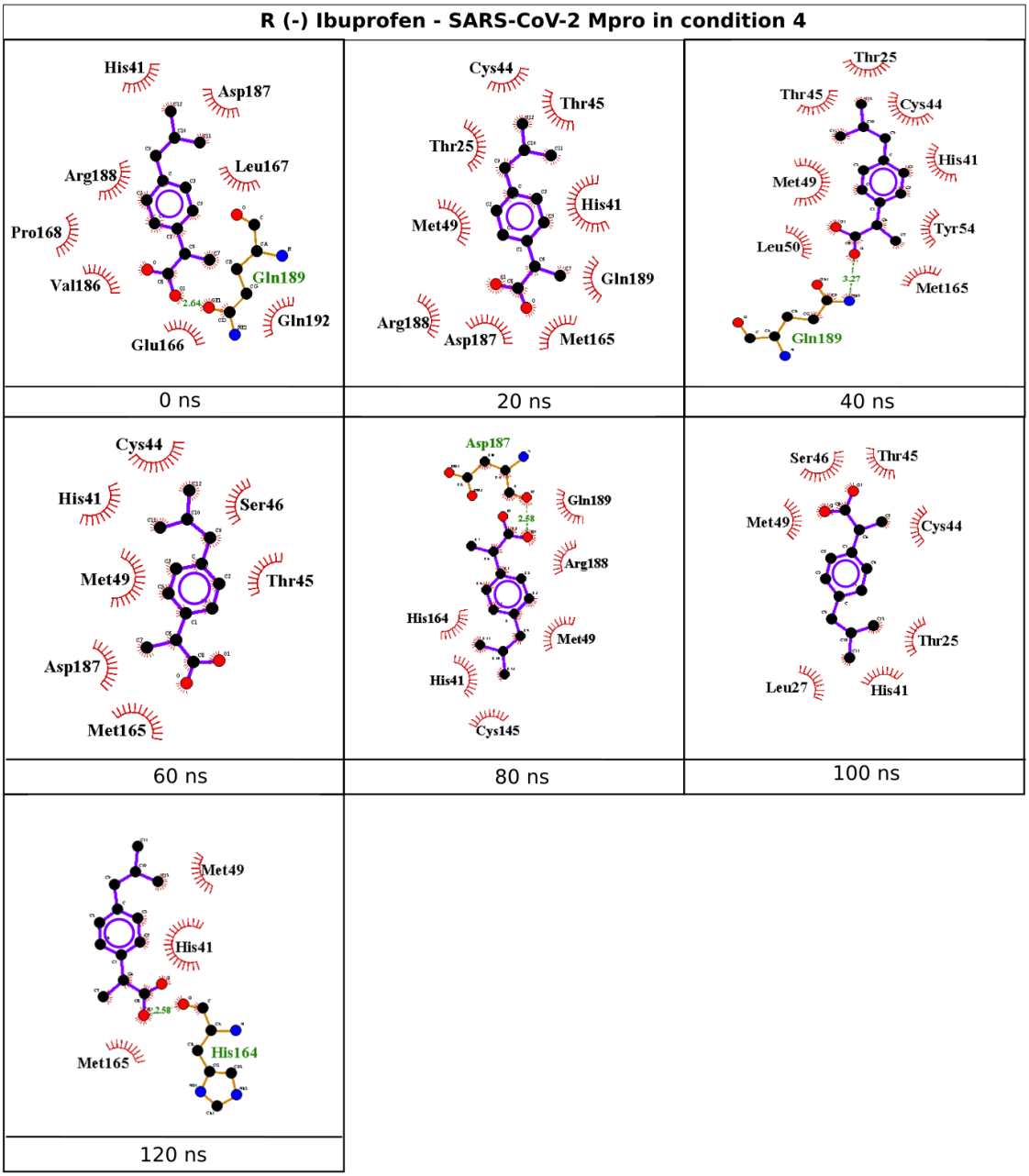

Figure S1. D. 2D interactions showing hydrogen bonds (green) and hydrophobic interactions (red) every 20 ns of MD-simulations in the binding pocket of the SARS-CoV-2 Mpro with R(-)Ibuprofen in condition 4, visualized by LigPlot+.

E

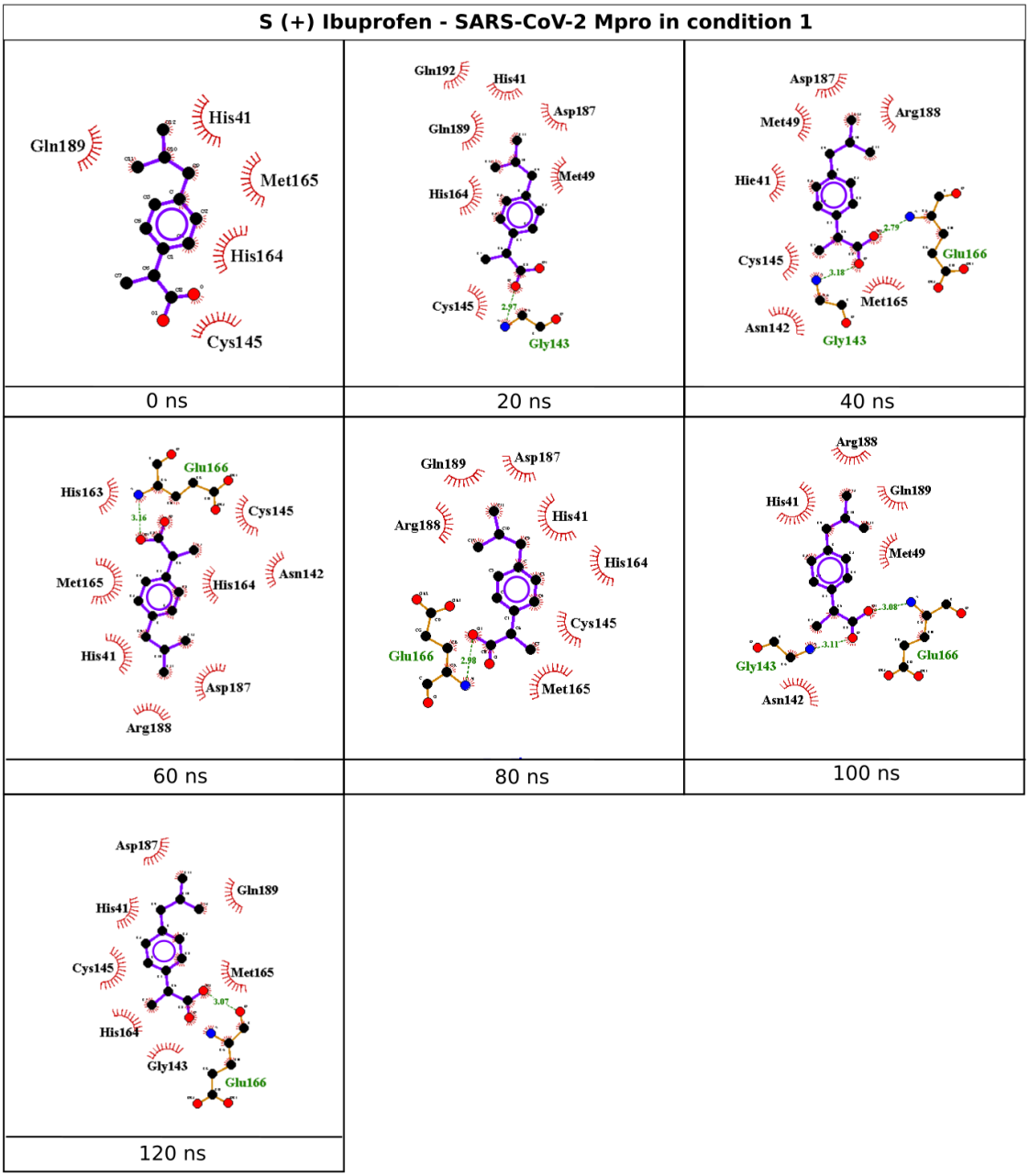

Figure S1. E. 2D interactions showing hydrogen bonds (green) and hydrophobic interactions (red) every 20 ns of MD-simulations in the binding pocket of the SARS-CoV-2 Mpro with S(+)Ibuprofen in condition 1, visualized by LigPlot+.

F

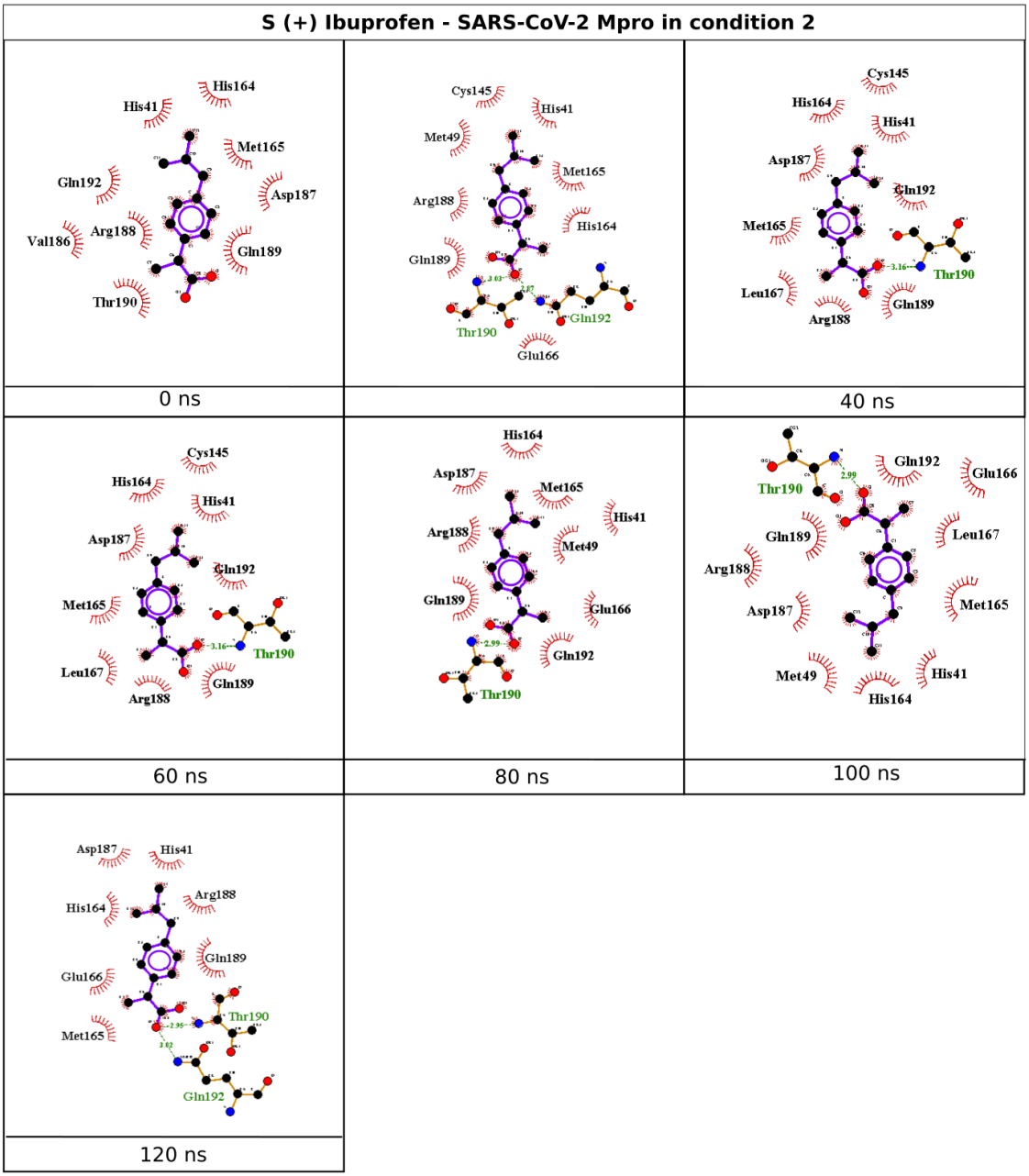

Figure S1. F. 2D interactions showing hydrogen bonds (green) and hydrophobic interactions (red) every 20 ns of MD-simulations in the binding pocket of the SARS-CoV-2 Mpro with S(+)Ibuprofen in condition 2, visualized by LigPlot+.

G

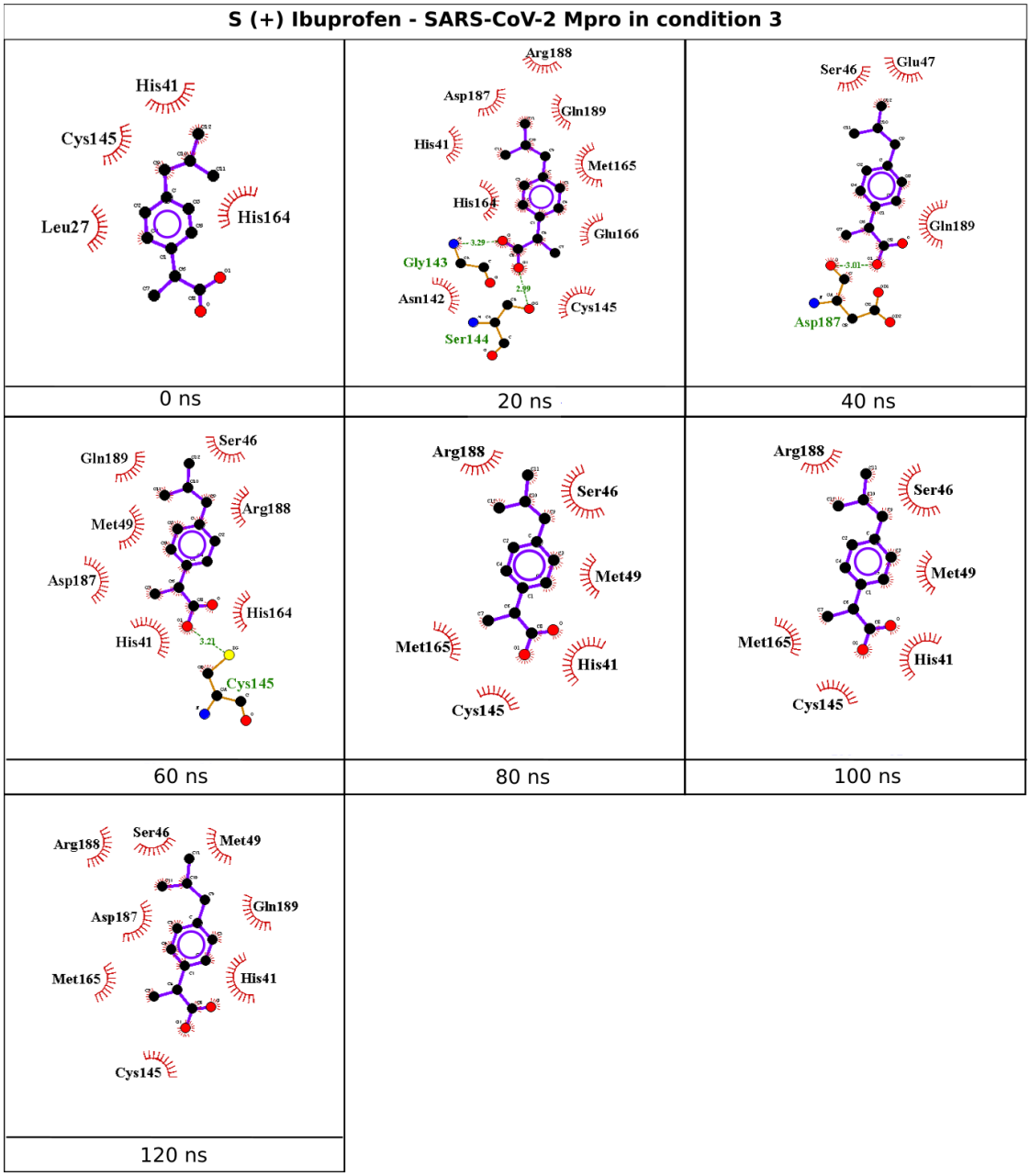

Figure S1. G. 2D interactions showing hydrogen bonds (green) and hydrophobic interactions (red) every 20 ns of MD-simulations in the binding pocket of the SARS-CoV-2 Mpro with S(+)Ibuprofen in condition 3, visualized by LigPlot+.

H

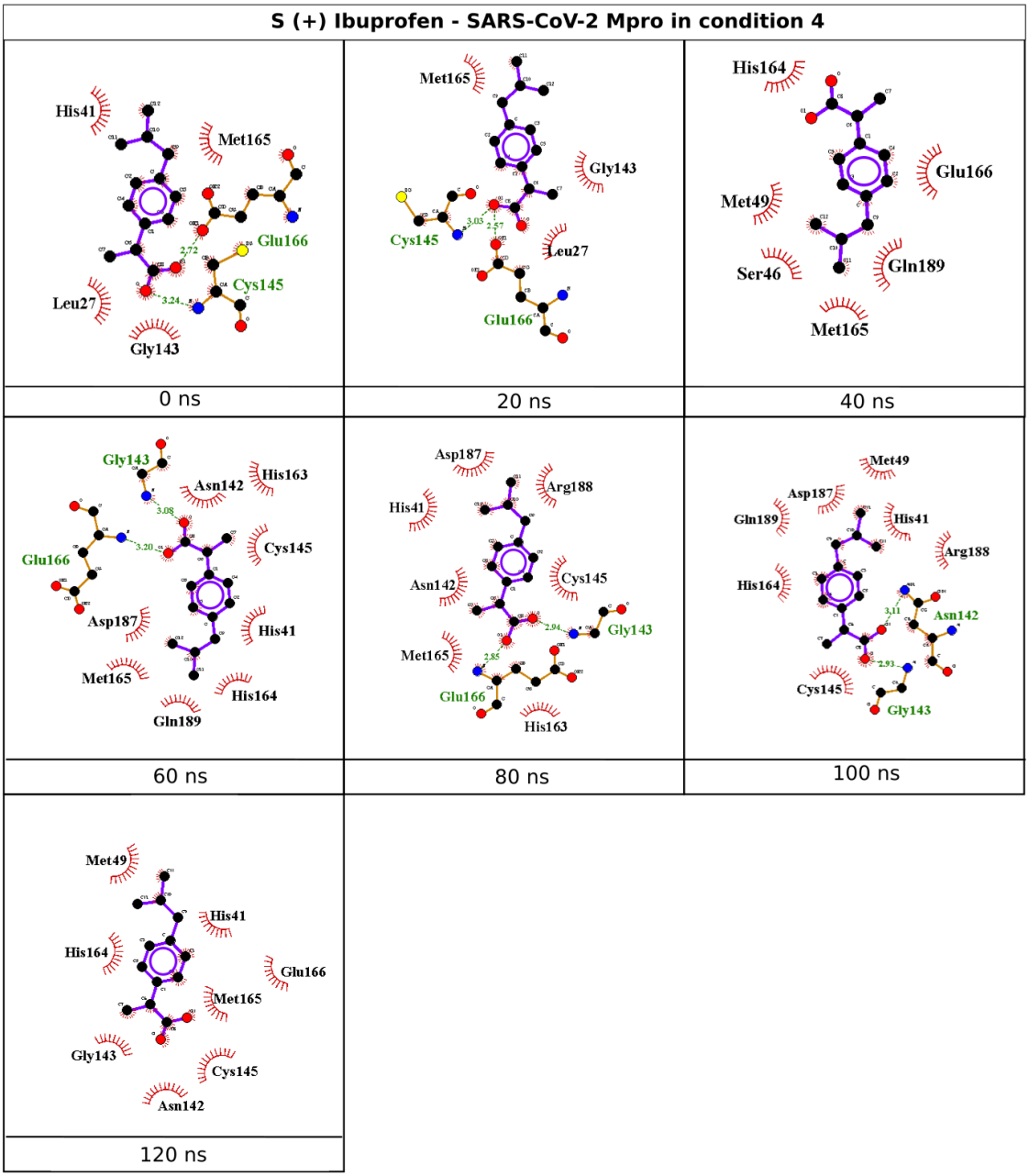

Figure S1. H. 2D interactions showing hydrogen bonds (green) and hydrophobic interactions (red) every 20 ns of MD-simulations in the binding pocket of the SARS-CoV-2 Mpro with S(+)Ibuprofen in condition 4, visualized by LigPlot+.

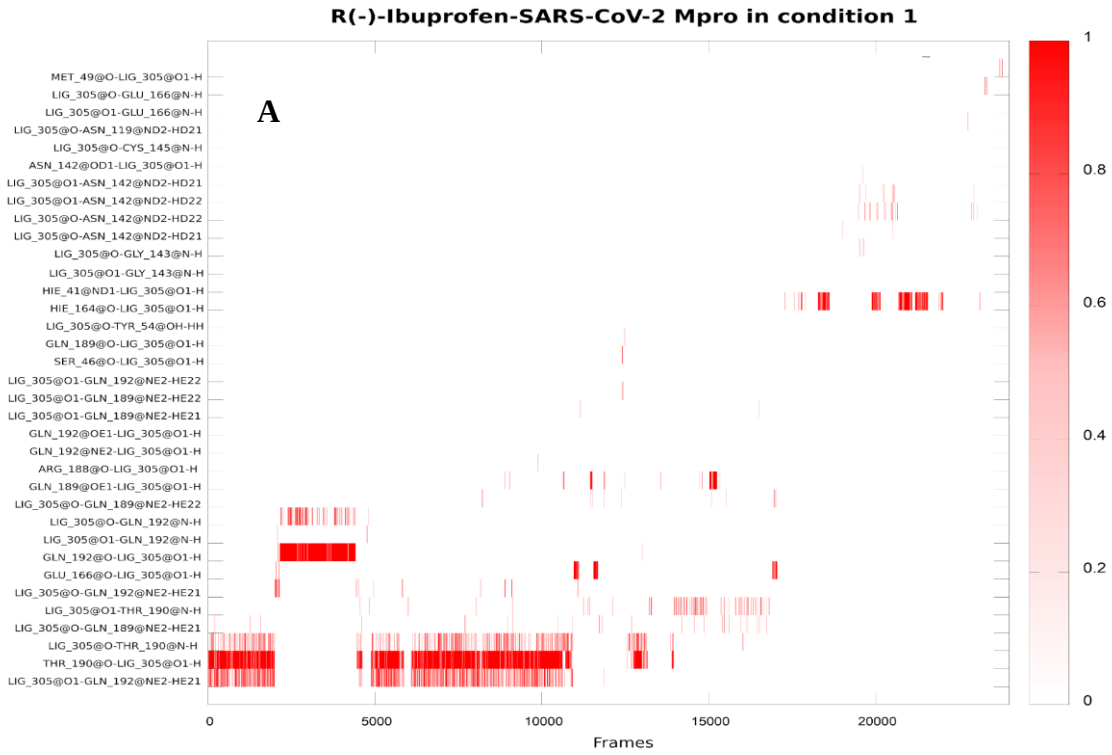

Figure S2. A. Hydrogen bonds analysis of complex R(-)Ibuprofen-SARS-CoV-2 Mpro (red) in condition 1.

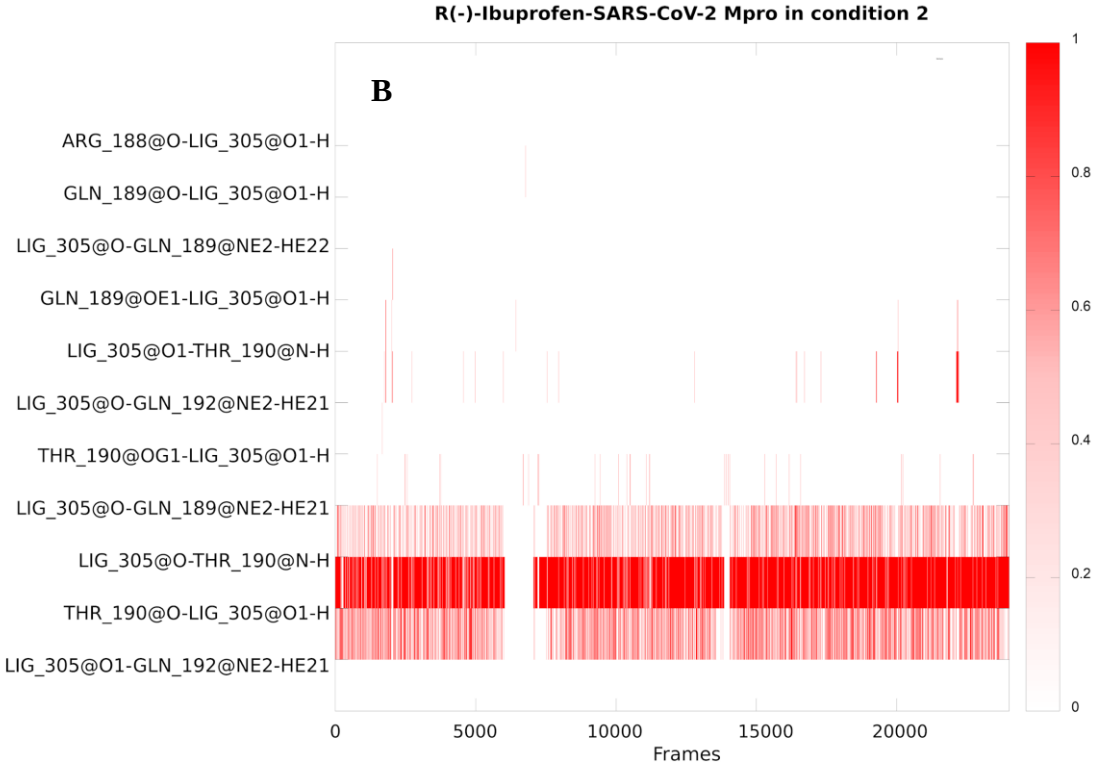

Figure S2. B. Hydrogen bonds analysis of complex R(-)Ibuprofen-SARS-CoV-2 Mpro (red) in condition 2.

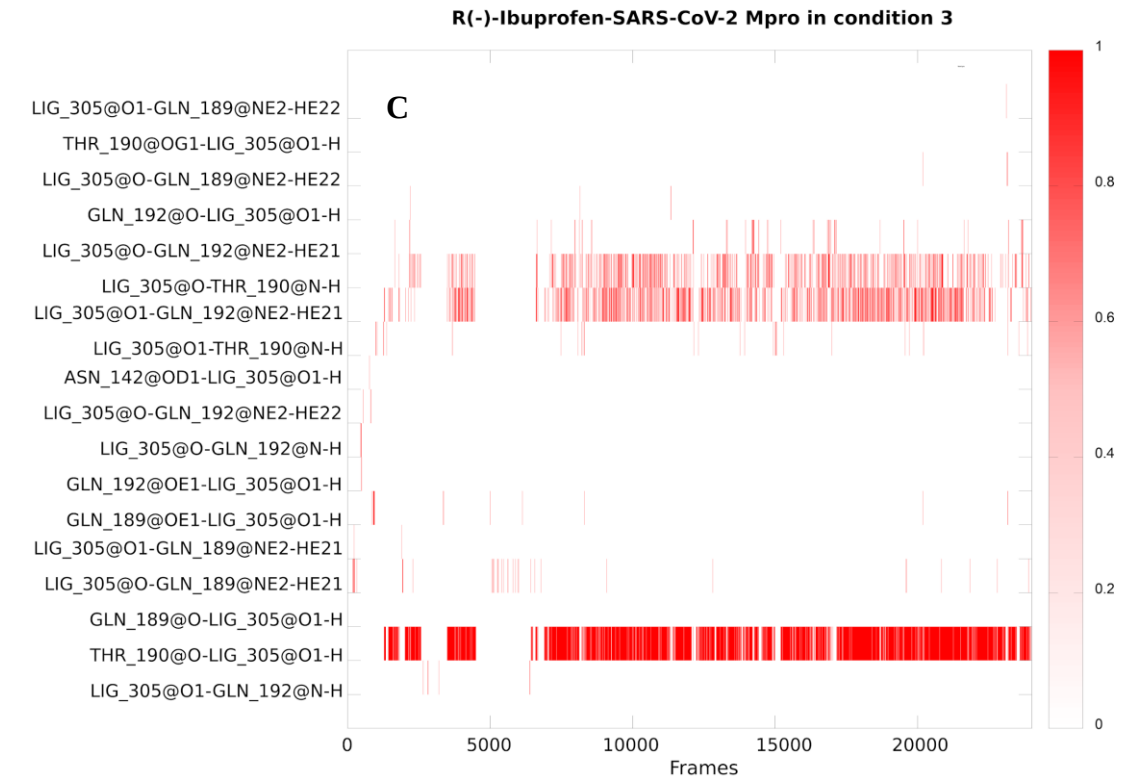

Figure S2. C. Hydrogen bonds analysis of complex R(-)Ibuprofen-SARS-CoV-2 Mpro (red) in condition 3.

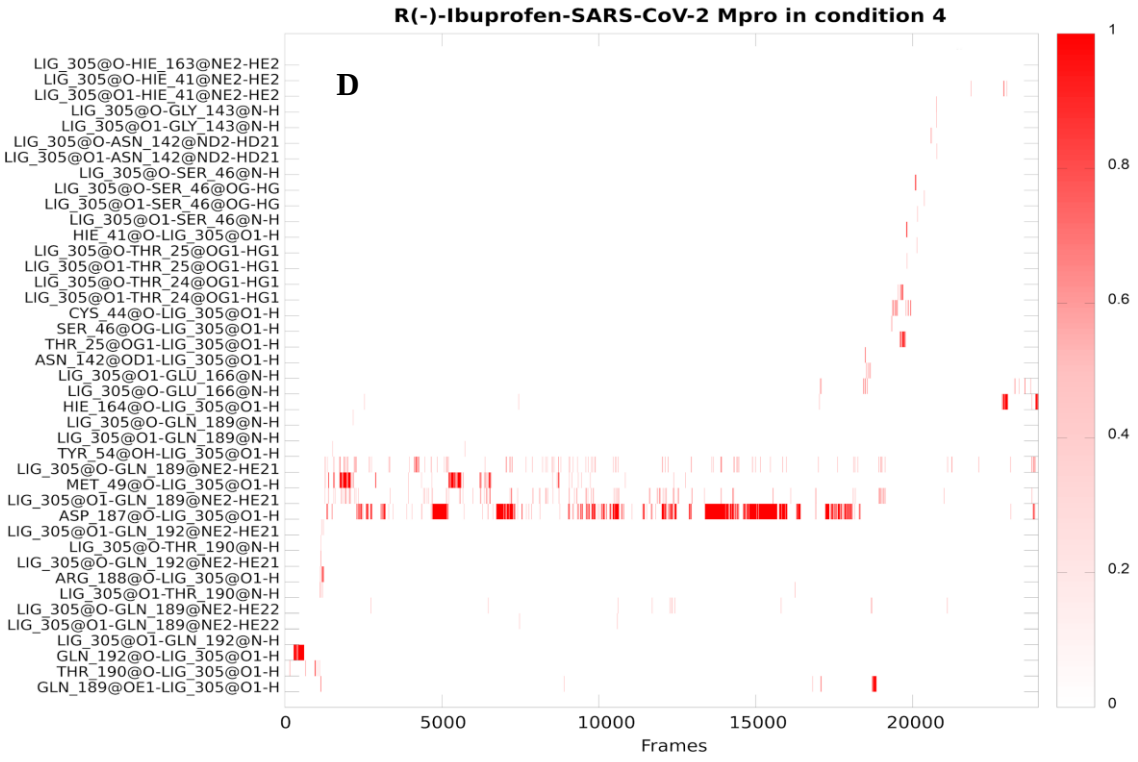

Figure S2. D. Hydrogen bonds analysis of complex R(-)Ibuprofen-SARS-CoV-2 Mpro (red) in condition 4.

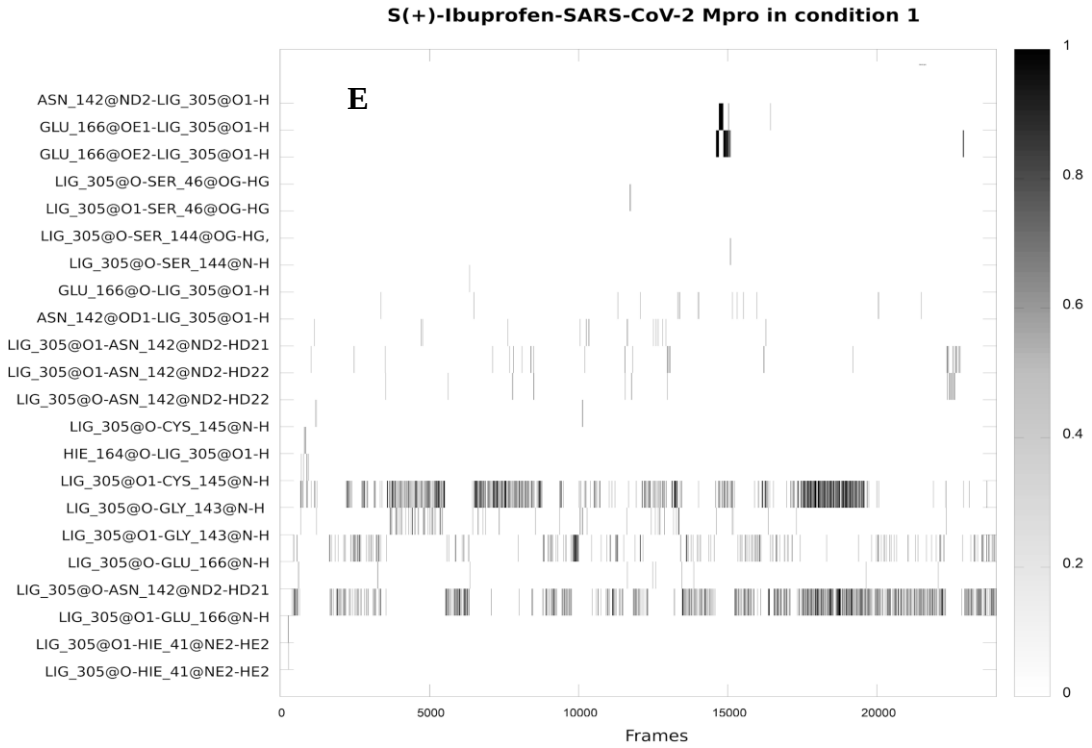

Figure S2. E. Hydrogen bonds analysis of complex S(+)Ibuprofen-SARS-CoV-2 Mpro (red) in condition 1.

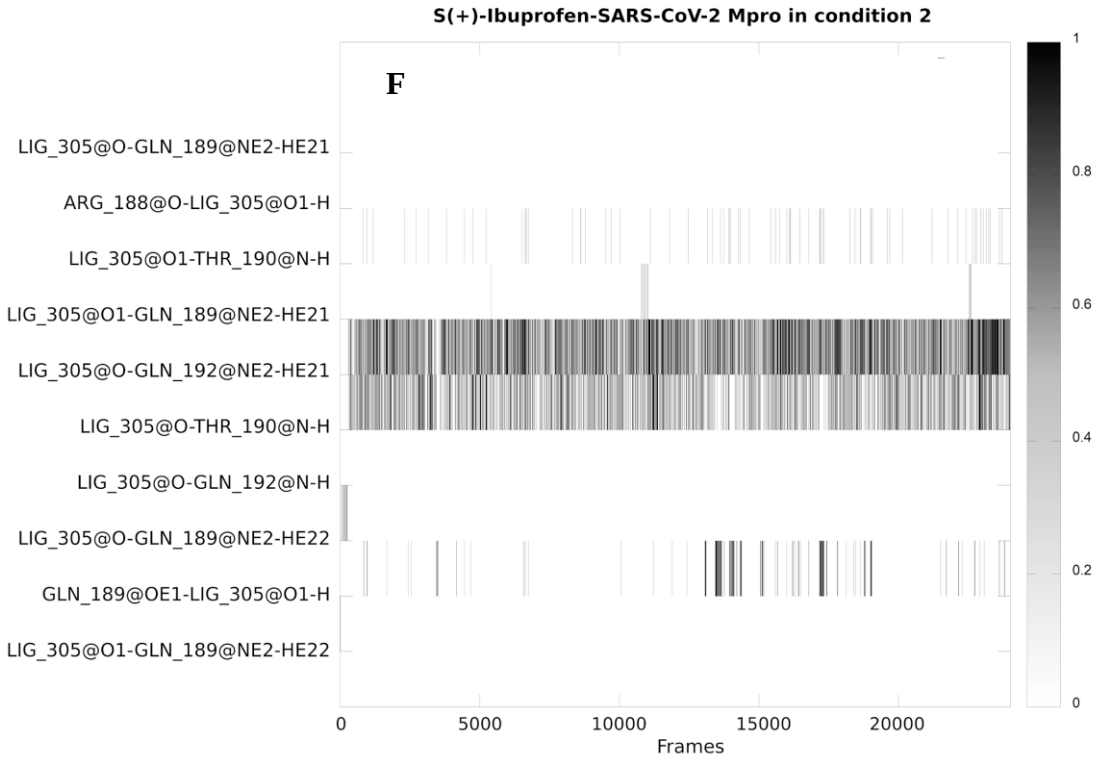

Figure S2. F. Hydrogen bonds analysis of complex S(+)Ibuprofen-SARS-CoV-2 Mpro (red) in condition 2.

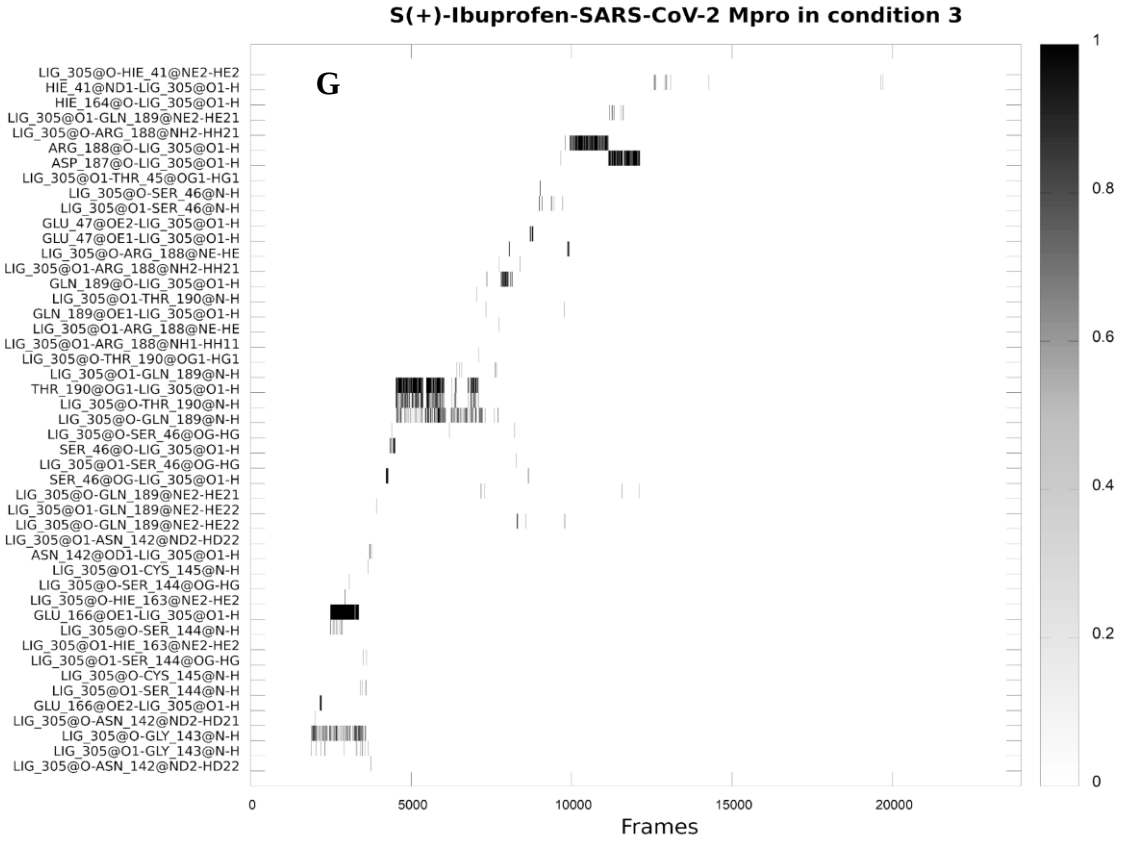

Figure S2. G. Hydrogen bonds analysis of complex S(+)Ibuprofen-SARS-CoV-2 Mpro (red) in condition 3.

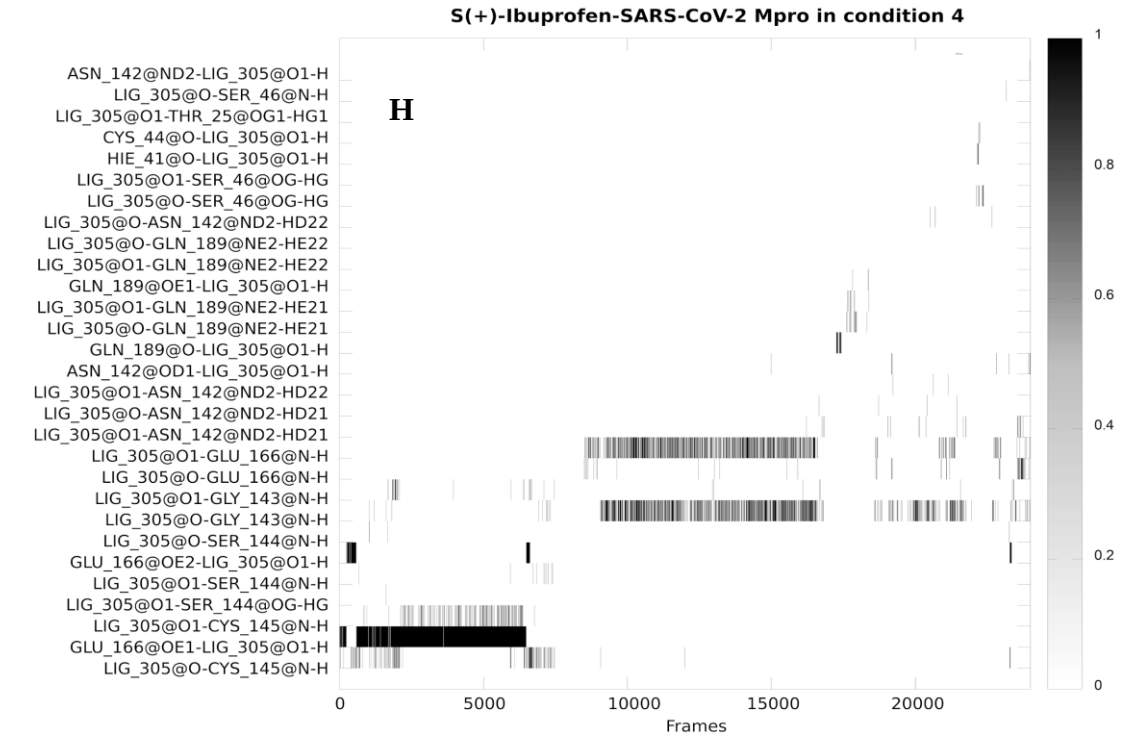

Figure S2. H. Hydrogen bonds analysis of complex S(+)Ibuprofen-SARS-CoV-2 Mpro (red) in condition 4.

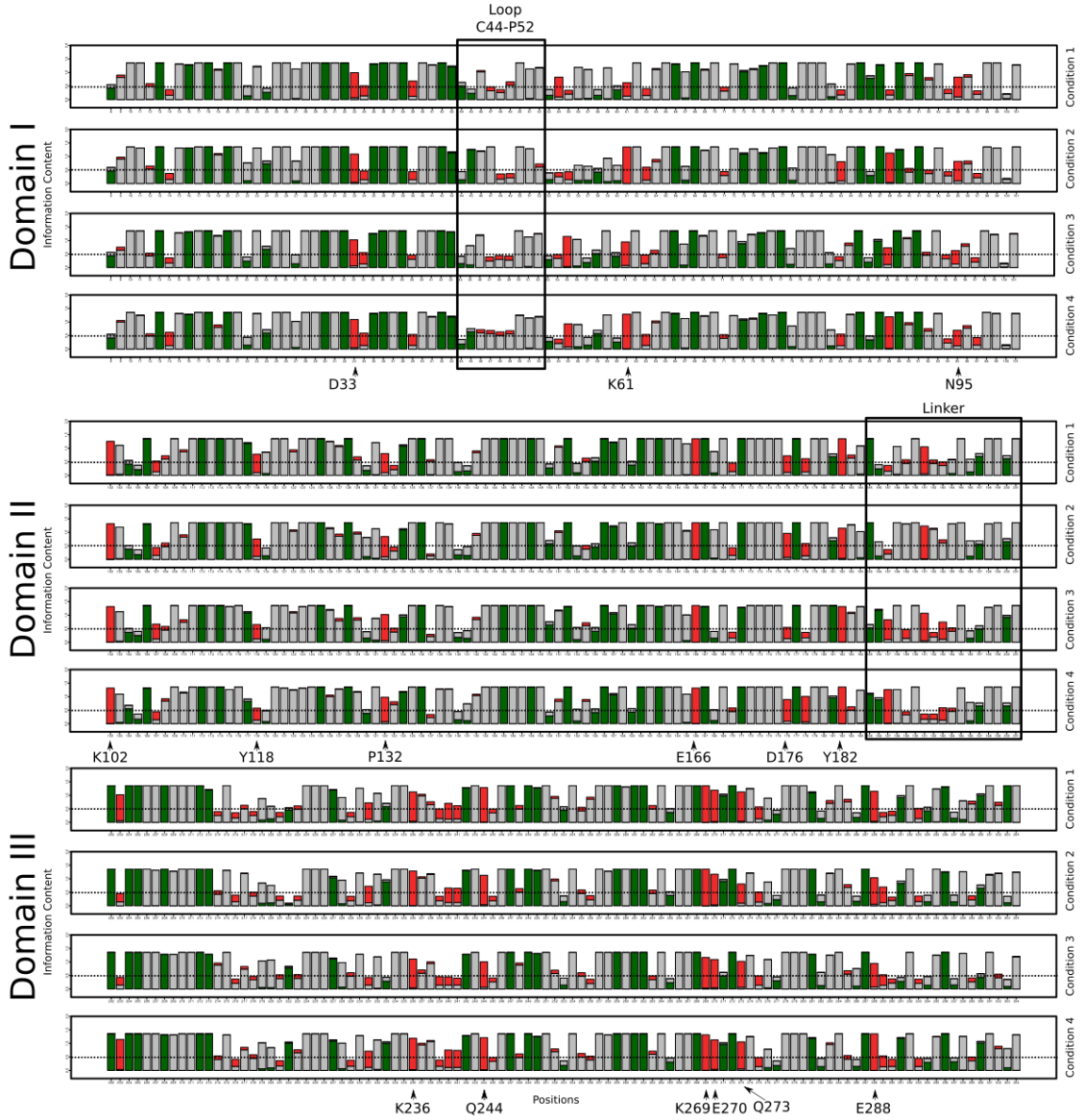

Figure S3. Conservation of local frustration for S(+)Ibuprofen-SARS-CoV-2 Complex for all conditions. For Domain I (in black square the loop C44-P5), Domain II (in black square Linker Loop) and for Domain III. Marked with narrow residues that are highly frustrated and conserved (Information Content (IC) > 0.5) in all conditions. In green minimally frustrated, in red highly frustrated and in grey neutral residues.

Table S1. Binding free energies calculated for the complex R(-)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 1 by MM-GBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2401.3061	23.1143	3.2366
EEL	-21360.1179	55.7635	7.8085
EGB	-2944.3908	37.5106	5.2525
ESURF	103.2904	1.2083	0.1692
G gas	-3599.0244	66.6270	9.3297
G solv	-2841.1004	37.1690	5.2047
TOTAL	-6440.1248	48.4155	6.7795
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2376.0433	23.1540	3.2422
EEL	-21345.7716	55.7312	7.8039
EGB	-2954.1779	37.9157	5.3093
ESURF	103.7456	1.2696	0.1778
G gas	-3561.4529	67.5640	9.4609
G solv	2850.4323	37.5444	5.2573
TOTAL	-6411.8852	48.9448	6.8536
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-1.6778	0.7957	0.1114
EEL	0.9678	0.6609	0.0925
EGB	-10.7312	0.5784	0.0810
ESURF	2.7462	0.0193	0.0027
G gas	1.3280	3.6724	0.5142
G solv	-7.9850	0.5728	0.0802
TOTAL	-6.6570	3.7177	0.5206
Differences (Complex-Receptor-Ligand)			

VDWAALS	-23.5850	2.8254	0.3956
EEL	-15.3141	2.4270	0.3398
EGB	20.5182	1.2301	0.1723
ESURF	-3.2014	0.1840	0.0258
ΔG gas	-38.8994	2.4028	0.3365
ΔG solv	17.3169	1.2057	0.1688
ΔTOTAL	-21.5825	1.8585	0.2602

Table S2. Binding free energies calculated for the complex R(-)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 1 by MM-PBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2401.3061	23.1143	3.2366
EEL	-21360.1179	55.7635	7.8085
EPB	-2833.8425	37.4701	5.2469
ENPOLAR	73.1556	0.5735	0.0803
G gas	-3599.0244	66.6270	9.3297
G solv	-2760.6869	37.2166	5.2114
TOTAL	-6359.7113	47.5589	6.6596
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2376.0433	23.1540	3.2422
EEL	-21345.7716	55.7312	7.8039
EPB	-2842.5031	37.6369	5.2702
ENPOLAR	73.5228	0.5812	0.0814
G gas	-3561.4529	67.5640	9.4609
G solv	-2768.9803	37.3743	5.2335
TOTAL	-6330.4331	48.1462	6.7418
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***

VDWAALS	-1.6778	0.7957	0.1114
EEL	0.9678	0.6609	0.0925
EPB	-11.0840	0.5701	0.0798
ENPOLAR	2.2714	0.0195	0.0027
G gas	1.3280	3.6724	0.5142
G solv	-8.8127	0.5624	0.0788
TOTAL	-7.4847	3.6908	0.5168
Differences (Complex-Receptor-Ligand)			
VDWAALS	-23.5850	2.8254	0.3956
EEL	-15.3141	2.4270	0.3398
EPB	19.7446	1.3211	0.1850
ENPOLAR	-2.6385	0.0914	0.0128
ΔG gas	-38.8994	2.4028	0.3365
ΔG solv	17.1060	1.2972	0.1816
ΔTOTAL	-21.7934	2.1582	0.3022

Table S3. Binding free energies calculated for the complex R(-)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 2 by MM-GBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2381.1332	19.8575	2.7806
EEL	-21314.8883	42.1245	5.8986
EGB	-3029.9515	34.2878	4.8013
ESURF	103.9653	1.4620	0.2047
G gas	-3500.7110	54.4519	7.6248
G solv	-2925.9862	33.5476	4.6976
TOTAL	-6426.6972	45.2404	6.3349
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***

VDWAALS	-2349.9444	19.3285	2.7065
EEL	-21299.2816	42.0293	5.8853
EGB	-3041.9099	34.3082	4.8041
ESURF	104.9811	1.4289	0.2001
G gas	-3454.5414	54.0110	7.5631
G solv	-2936.9289	33.6416	4.7108
TOTAL	-6391.4703	45.1472	6.3219
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-1.9889	0.5331	0.0747
EEL	0.9958	0.4898	0.0686
EGB	-10.5626	0.4749	0.0665
ESURF	2.7417	0.0173	0.0024
G gas	-0.3672	3.9447	0.5524
G solv	-7.8208	0.4764	0.0667
TOTAL	-8.1880	3.8824	0.5436
Differences (Complex-Receptor-Ligand)			
VDWAALS	-29.1999	2.3350	0.3270
EEL	-16.6026	2.4385	0.3415
EGB	22.5210	1.3405	0.1877
ESURF	-3.7575	0.1633	0.0229
ΔG gas	-45.8023	2.4673	0.3455
ΔG solv	18.7635	1.3401	0.1877
ΔTOTAL	-27.0388	1.9960	0.2795

Table S4. Binding free energies calculated for the complex R(-)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 2 by MM-PBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2381.1332	19.8575	2.7806

EEL	-21314.8883	42.1245	5.8986
EPB	-2914.6439	33.4723	4.6871
ENPOLAR	73.7691	0.6080	0.0851
G gas	-3500.7110	54.4519	7.6248
G solv	-2840.8748	33.2083	4.6501
TOTAL	-6341.5858	48.2244	6.7528
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2349.9444	19.3285	2.7065
EEL	-21299.2816	42.0293	5.8853
EPB	-2925.9303	33.5313	4.6953
ENPOLAR	74.2385	0.5885	0.0824
G gas	-3454.5414	54.0110	7.5631
G solv	-2851.6918	33.2863	4.6610
TOTAL	-6306.2333	48.3500	6.7703
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-1.9889	0.5331	0.0747
EEL	0.9958	0.4898	0.0686
EPB	-10.7464	0.4485	0.0628
ENPOLAR	2.2806	0.0157	0.0022
G gas	-0.3672	3.9447	0.5524
G solv	-8.4659	0.4440	0.0622
TOTAL	-8.8331	3.8671	0.5415
Differences (Complex-Receptor-Ligand)			
VDWAALS	-29.1999	2.3350	0.3270
EEL	-16.6026	2.4385	0.3415
EPB	22.0329	1.2894	0.1805
ENPOLAR	-2.7499	0.0839	0.0117

ΔG gas	-45.8023	2.4673	0.3455
ΔG solv	19.2829	1.2770	0.1788
ΔTOTAL	-26.5194	2.0926	0.2930

Table S5. Binding free energies calculated for the complex R(-)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 3 by MM-GBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2403.0240	19.6297	2.7487
EEL	-21115.9582	52.3429	7.3295
EGB	-3270.0650	36.3508	5.0901
ESURF	105.3021	0.9352	0.1309
G gas	-3262.6962	56.0906	7.8543
G solv	-3164.7629	36.0843	5.0528
TOTAL	-6427.4591	39.5787	5.5421
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2370.2984	19.6732	2.7548
EEL	-21107.0080	52.0591	7.2897
EGB	-3279.6502	36.3013	5.0832
ESURF	106.3524	0.9134	0.1279
G gas	-3222.8685	56.6908	7.9383
G solv	-3173.2978	36.0556	5.0488
TOTAL	-6396.1663	39.9966	5.6006
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-1.9388	0.5936	0.0831
EEL	1.5659	0.5458	0.0764
EGB	-11.1893	0.5300	0.0742
ESURF	2.7427	0.0215	0.0030

G gas	1.4788	4.0013	0.5603
G solv	-8.4466	0.5288	0.0740
TOTAL	-6.9678	3.8919	0.5450
Differences (Complex-Receptor-Ligand)			
VDWAALS	-30.7868	2.7071	0.3791
EEL	-10.5161	4.5740	0.6405
EGB	20.7745	2.8537	0.3996
ESURF	-3.7930	0.1763	0.0247
ΔG gas	-41.3064	3.8482	0.5389
ΔG solv	16.9815	2.8347	0.3969
ΔTOTAL	-24.3249	1.7928	0.2510

Table S6. Binding free energies calculated for the complex R(-)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 3 by MM-PBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2403.0240	19.6297	2.7487
EEL	-21115.9582	52.3429	7.3295
EPB	-3152.6152	36.1080	5.0561
ENPOLAR	74.3742	0.4507	0.0631
G gas	-3262.6962	56.0906	7.8543
G solv	-3078.2410	35.9396	5.0326
TOTAL	-6340.9372	41.4907	5.8099
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2370.2984	19.6732	2.7548
EEL	-21107.0080	52.0591	7.2897
EPB	-3162.8371	36.3370	5.0882
ENPOLAR	75.0052	0.4400	0.0616
G gas	-3222.8685	56.6908	7.9383

G solv	-3087.8319	36.1635	5.0639
TOTAL	-6310.7005	41.6778	5.8361
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-1.9388	0.5936	0.0831
EEL	1.5659	0.5458	0.0764
EPB	-11.7394	0.5678	0.0795
ENPOLAR	2.2671	0.0153	0.0021
G gas	1.4788	4.0013	0.5603
G solv	-9.4722	0.5663	0.0793
TOTAL	-7.9935	3.8390	0.5376
Differences (Complex-Receptor-Ligand)			
VDWAALS	-30.7868	2.7071	0.3791
EEL	-10.5161	4.5740	0.6405
EPB	21.9613	2.8924	0.4050
ENPOLAR	-2.8981	0.0836	0.0117
ΔG gas	-41.3064	3.8482	0.5389
ΔG solv	19.0631	2.8884	0.4045
ΔTOTAL	-22.2433	2.4110	0.3376

Table S7. Binding free energies calculated for the complex R(-)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 4 by MM-GBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2386.8998	20.8697	2.9223
EEL	-21243.7226	52.1246	7.2989
EGB	-3098.1953	35.6429	4.9910
ESURF	103.8716	1.2289	0.1721
G gas	-3449.5145	62.2510	8.7169
G solv	-2994.3237	35.4253	4.9605

TOTAL	-6443.8382	48.7299	6.8236
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2356.6114	20.4300	2.8608
EEL	-21235.6785	51.5943	7.2247
EGB	-3104.7177	35.4189	4.9596
ESURF	104.7370	1.2473	0.1747
G gas	-3415.4207	62.4258	8.7414
G solv	-2999.9807	35.1972	4.9286
TOTAL	-6415.4013	48.8811	6.8447
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2.1073	0.5935	0.0831
EEL	1.6284	0.8884	0.1244
EGB	-16.3677	0.6151	0.0861
ESURF	2.7303	0.0242	0.0034
G gas	3.7594	3.1690	0.4437
G solv	-13.6374	0.6065	0.0849
TOTAL	-9.8781	3.1600	0.4425
Differences (Complex-Receptor-Ligand)			
VDWAALS	-28.1812	1.9857	0.2781
EEL	-9.6724	5.1068	0.7151
EGB	22.8901	4.1242	0.5775
ESURF	-3.5957	0.1037	0.0145
ΔG gas	-37.8532	4.8168	0.6745
ΔG solv	19.2944	4.1341	0.5789
ΔTOTAL	-18.5589	2.0213	0.2830

Table S8. Binding free energies calculated for the complex R(-)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 4 by MM-PBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2386.8998	20.8697	2.9223
EEL	-21243.7226	52.1246	7.2989
EPB	-2971.1614	30.7084	4.3000
ENPOLAR	73.3307	0.5765	0.0807
G gas	-3449.5145	62.2510	8.7169
G solv	-2897.8307	30.4695	4.2666
TOTAL	-6347.3453	49.7766	6.9701
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2356.6114	20.4300	2.8608
EEL	-21235.6785	51.5943	7.2247
EPB	-2977.4978	30.5592	4.2791
ENPOLAR	73.8774	0.5708	0.0799
G gas	-3415.4207	62.4258	8.7414
G solv	-2903.6203	30.3229	4.2461
TOTAL	-6319.0410	49.9289	6.9914
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2.1073	0.5935	0.0831
EEL	1.6284	0.8884	0.1244
EPB	-16.9258	0.6599	0.0924
ENPOLAR	2.2620	0.0172	0.0024
G gas	3.7594	3.1690	0.4437
G solv	-14.6638	0.6582	0.0922
TOTAL	-10.9044	3.1081	0.4352
Differences (Complex-Receptor-Ligand)			

VDWAALS	-28.1812	1.9857	0.2781
EEL	-9.6724	5.1068	0.7151
EPB	23.2621	3.7915	0.5309
ENPOLAR	-2.8087	0.0491	0.0069
ΔG gas	-37.8532	4.8168	0.6745
ΔG solv	20.4534	3.7857	0.5301
ΔTOTAL	-17.3998	2.5163	0.3523

Table S9. Binding free energies calculated for the complex S(+)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 1 by MM-GBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2407.3698	20.3433	2.8486
EEL	-21348.7208	45.3135	6.3452
EGB	-3044.4981	34.9853	4.8989
ESURF	103.1701	1.2257	0.1716
G gas	-3511.8581	66.3808	9.2952
G solv	-2941.3281	34.4764	4.8277
TOTAL	-6453.1862	52.7564	7.3874
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2381.5010	20.3595	2.8509
EEL	-21340.4548	44.9162	6.2895
EGB	-3047.9555	34.9745	4.8974
ESURF	103.8100	1.2186	0.1706
G gas	-3482.1059	64.7230	9.0630
G solv	-2944.1455	34.4822	4.8285
TOTAL	-6426.2514	51.0088	7.142
Ligand			

Energy Component	*Average*	*Std. Dev.*	*Std. Err. of Mean*
VDWAALS	-1.9343	0.6565	0.0919
EEL	1.9962	1.2541	0.1756
EGB	16.9413	0.9593	0.1343
ESURF	2.7358	0.0169	0.0024
G gas	4.4422	3.6755	0.5147
G solv	-14.2055	0.9538	0.1336
TOTAL	-9.7633	3.6608	0.5126
Differences (Complex-Receptor-Ligand)			
VDWAALS	-23.9345	1.5096	0.2114
EEL	-10.2622	2.2649	0.3171
EGB	20.3986	1.8411	0.2578
ESURF	-3.3757	0.1478	0.0207
ΔG gas	-34.1944	2.6647	0.3731
ΔG solv	17.0229	1.8260	0.2557
ΔTOTAL	-17.1715	1.6315	0.2284

Table S10. Binding free energies calculated for the complex S(+)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 1 by MM-PBSA method.

Complex			
Energy Component	*Average*	*Std. Dev.*	*Std. Err. of Mean*
VDWAALS	-2407.3698	20.3433	2.8486
EEL	-21348.7208	45.3135	6.3452
EPB	-2904.2903	36.8351	5.1580
ENPOLAR	73.3022	0.5592	0.0783
G gas	-3511.8581	66.3808	9.2952
G solv	-2830.9880	36.5560	5.1189
TOTAL	-6342.8461	50.7277	7.1033
Receptor			
Energy Component	*Average*	*Std. Dev.*	*Std. Err. of Mean*

VDWAALS	-2381.5010	20.3595	2.8509
EEL	-21340.4548	44.9162	6.2895
EPB	-2906.7086	36.8009	5.1532
ENPOLAR	73.7711	0.5449	0.0763
G gas	-3482.1059	64.7230	9.0630
G solv	-2832.9375	36.5187	5.1136
TOTAL	-6315.0434	49.3468	6.9099
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-1.9343	0.6565	0.0919
EEL	1.9962	1.2541	0.1756
EPB	-17.5291	0.9939	0.1392
ENPOLAR	2.2555	0.0142	0.0020
G gas	4.4422	3.6755	0.5147
G solv	-15.2736	0.9918	0.1389
TOTAL	-10.8314	3.6545	0.5117
Differences (Complex-Receptor-Ligand)			
VDWAALS	-23.9345	1.5096	0.2114
EEL	-10.2622	2.2649	0.3171
EPB	19.9474	2.2080	0.3092
ENPOLAR	-2.7243	0.0659	0.0092
ΔG gas	-34.1944	2.6647	0.3731
ΔG solv	17.2230	2.2127	0.3098
ΔTOTAL	-16.9713	1.8023	0.2524

Table S11. Binding free energies calculated for the complex S(+)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 2 by MM-GBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2432.0188	20.6643	2.8936

EEL	-21376.1770	89.7023	12.5608
EGB	-2882.2061	52.9053	7.4082
ESURF	101.6505	1.2601	0.1764
G gas	-3680.8533	80.6695	11.2960
G solv	-2780.5556	52.3109	7.3250
TOTAL	-6461.4089	53.9353	7.5525
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2396.5576	21.0033	2.9410
EEL	-21358.4507	90.6579	12.6946
EGB	-2895.4347	53.7095	7.5208
ESURF	103.1093	1.2867	0.1802
G gas	-3633.3619	82.4560	11.5462
G solv	-2792.3254	53.0841	7.4333
TOTAL	-6425.6873	54.2354	7.5945
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-1.7634	0.6269	0.0878
EEL	1.4342	0.6703	0.0939
EGB	-16.6506	0.5618	0.0787
ESURF	2.7346	0.0208	0.0029
G gas	5.3654	4.0837	0.5718
G solv	-13.9160	0.5583	0.0782
TOTAL	-8.5506	4.1055	0.5749
Differences (Complex-Receptor-Ligand)			
VDWAALS	-33.6977	2.1136	0.2960
EEL	-19.1605	3.3188	0.4647
EGB	29.8792	2.3841	0.3338
ESURF	-4.1934	0.1062	0.0149

ΔG gas	-52.8569	3.6918	0.5170
ΔG solv	25.6858	2.3262	0.3257
ΔTOTAL	-27.1710	2.2541	0.3156

Table S12. Binding free energies calculated for the complex S(+)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 2 by MM-PBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2432.0188	20.6643	2.8936
EEL	-21376.1770	89.7023	12.5608
EPB	-2761.5640	53.2599	7.4579
ENPOLAR	71.8246	0.5285	0.0740
G gas	-3680.8533	80.6695	11.2960
G solv	-2689.7394	53.0295	7.4256
TOTAL	-6370.5927	53.8224	7.5366
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2396.5576	21.0033	2.9410
EEL	-21358.4507	90.6579	12.6946
EPB	-2775.1878	53.8027	7.5339
ENPOLAR	72.4920	0.5339	0.0748
G gas	-3633.3619	82.4560	11.5462
G solv	-2702.6958	53.5577	7.4996
TOTAL	-6336.0577	54.3086	7.6047
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-1.7634	0.6269	0.0878
EEL	1.4342	0.6703	0.0939
EPB	-17.5271	0.6285	0.0880
ENPOLAR	2.2517	0.0162	0.0023

G gas	5.3654	4.0837	0.5718
G solv	-15.2754	0.6260	0.0877
TOTAL	-9.9100	4.1130	0.5759
Differences (Complex-Receptor-Ligand)			
VDWAALS	-33.6977	2.1136	0.2960
EEL	-19.1605	3.3188	0.4647
EPB	31.1509	2.2017	0.3083
ENPOLAR	-2.9191	0.0639	0.0090
ΔG gas	-52.8569	3.6918	0.5170
ΔG solv	28.2319	2.1707	0.3040
ΔTOTAL	-24.6250	2.5289	0.3541

Table S13. Binding free energies calculated for the complex S(+)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 3 by MM-GBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2424.5913	17.4897	2.4491
EEL	-21218.4158	69.0588	9.6702
EGB	-3029.2366	45.4814	6.3687
ESURF	102.5913	1.3185	0.1846
G gas	-3489.3506	72.2005	10.1101
G solv	-2926.6453	44.9969	6.3008
TOTAL	-6415.9959	45.3471	6.3499
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2397.1656	17.8039	2.4930
EEL	-21214.4935	69.3896	9.7165
EGB	-3032.1771	46.1027	6.4557
ESURF	103.1307	1.2707	0.1779
G gas	-3464.0718	72.5195	10.1548

G solv	-2929.0464	45.6061	6.3861
TOTAL	-6393.1182	45.2121	6.3310
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-1.5724	0.6024	0.0844
EEL	3.4487	0.6895	0.0966
EGB	-18.5678	0.4656	0.0652
ESURF	2.7532	0.0189	0.0027
G gas	7.9463	3.2073	0.4491
G solv	-15.8145	0.4636	0.0649
TOTAL	-7.8682	3.3253	0.4656
Differences (Complex-Receptor-Ligand)			
VDWAALS	-25.8532	1.5725	0.2202
EEL	-7.3710	2.3878	0.3344
EGB	21.5082	2.3608	0.3306
ESURF	-3.2926	0.1444	0.0202
ΔG gas	-33.2251	2.6684	0.3737
ΔG solv	18.2156	2.3231	0.3253
ΔTOTAL	-15.0095	1.7316	0.2425

Table S14. Binding free energies calculated for the complex S(+)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 3 by MM-PBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2424.5913	17.4897	2.4491
EEL	-21218.4158	69.0588	9.6702
EPB	-2907.3492	42.1443	5.9014
ENPOLAR	72.5739	0.4846	0.0679
G gas	-3489.3506	72.2005	10.1101
G solv	-2834.7754	42.0195	5.8839

TOTAL	-6324.1259	47.1150	6.5974
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2397.1656	17.8039	2.4930
EEL	-21214.4935	69.3896	9.7165
EPB	-2910.0192	42.7211	5.9821
ENPOLAR	72.8820	0.4791	0.0671
G gas	-3464.0718	72.5195	10.1548
G solv	-2837.1372	42.5974	5.9648
TOTAL	-6301.2090	46.6471	6.5319
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-1.5724	0.6024	0.0844
EEL	3.4487	0.6895	0.0966
EPB	-19.3554	0.5098	0.0714
ENPOLAR	2.2597	0.0174	0.0024
G gas	7.9463	3.2073	0.4491
G solv	-17.0957	0.5049	0.0707
TOTAL	-9.1493	3.3263	0.4658
Differences (Complex-Receptor-Ligand)			
VDWAALS	-25.8532	1.5725	0.2202
EEL	-7.3710	2.3878	0.3344
EPB	22.0253	2.7939	0.3912
ENPOLAR	-2.5678	0.0543	0.0076
ΔG gas	-33.2251	2.6684	0.3737
ΔG solv	19.4575	2.7795	0.3892
ΔTOTAL	-13.7676	2.3249	0.3256

Table S15. Binding free energies calculated for the complex S(+)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 4 by MM-GBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2405.5243	21.3879	2.9949
EEL	-21326.2807	59.0912	8.2744
EGB	-3103.8243	33.2974	4.6626
ESURF	100.8803	1.0701	0.1498
G gas	-3448.9206	45.9224	6.4304
G solv	-3002.9440	33.1491	4.6418
TOTAL	-6451.8646	37.0687	5.1907
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2381.8500	21.1953	2.9679
EEL	-21303.2624	59.0269	8.2654
EGB	-3116.2327	33.0394	4.6264
ESURF	101.4237	1.0443	0.1462
G gas	-3407.4180	46.8125	6.5551
G solv	-3014.8089	32.9089	4.6082
TOTAL	-6422.2269	37.8897	5.3056
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2.0627	0.5401	0.0756
EEL	1.1780	0.7754	0.1086
EGB	-16.6507	0.6290	0.0881
ESURF	2.7322	0.0216	0.0030
G gas	4.3047	3.2440	0.4542
G solv	-13.9185	0.6217	0.0870
TOTAL	-9.6137	3.2010	0.4482
Differences (Complex-Receptor-Ligand)			

VDWAALS	-21.6116	2.2292	0.3121
EEL	-24.1963	3.3771	0.4729
EGB	29.0591	2.5435	0.3562
ESURF	-3.2757	0.1675	0.0234
ΔG gas	-45.8074	2.5524	0.3574
ΔG solv	25.7834	2.4789	0.3471
ΔTOTAL	-20.0240	1.7041	0.2386

Table S16. Binding free energies calculated for the complex S(+)Ibuprofen – SARS-CoV-2 Mpro simulated in condition 4 by MM-PBSA method.

Complex			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2405.5243	21.3879	2.9949
EEL	-21326.2807	59.0912	8.2744
EPB	-2980.5891	31.8794	4.4640
ENPOLAR	72.2114	0.4558	0.0638
G gas	-3448.9206	45.9224	6.4304
G solv	-2908.3777	31.8516	4.4601
TOTAL	-6357.2983	40.7549	5.7068
Receptor			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***
VDWAALS	-2381.8500	21.1953	2.9679
EEL	-21303.2624	59.0269	8.2654
EPB	-2990.3196	31.5150	4.4130
ENPOLAR	72.5069	0.4463	0.0625
G gas	-3407.4180	46.8125	6.5551
G solv	-2917.8128	31.4944	4.4101
TOTAL	-6325.2307	41.7461	5.8456
Ligand			
Energy Component	***Average***	***Std. Dev.***	***Std. Err. of Mean***

VDWAALS	-2.0627	0.5401	0.0756
EEL	1.1780	0.7754	0.1086
EPB	-17.4245	0.6748	0.0945
ENPOLAR	2.2665	0.0186	0.0026
G gas	4.3047	3.2440	0.4542
G solv	-15.1581	0.6740	0.0944
TOTAL	-10.8533	3.1729	0.4443
Differences (Complex-Receptor-Ligand)			
VDWAALS	-21.6116	2.2292	0.3121
EEL	-24.1963	3.3771	0.4729
EPB	27.1551	2.1529	0.3015
ENPOLAR	-2.5619	0.0472	0.0066
ΔG gas	-45.8074	2.5524	0.3574
ΔG solv	24.5932	2.1380	0.2994
ΔTOTAL	-21.2142	1.7204	0.2409

Table S17. Highly frustrated contact of the residues that are forming the **Loop Cys44-Pro52.** R(-)Ibuprofen-SARS-CoV-2 Complex in red and S(+)Ibuprofen-SARS-CoV-2 Complex in black**.**

Res1	**Res2**	**IC_Contact**	**IC_total**	**FrustrationState**
Condition 1				
44	47	0.9512	1.32117783941774	MAX
44	47	0.8902	1.31889015131908	MAX
44	48	0.9959	0.718899758212992	MAX
46	49	1	0.57998835911734	MAX
46	48	0.9959	0.615212122874075	MAX
46	49	0.9959	0.544869951910359	MAX
47	50	0.9471	0.544623860686514	MAX
47	50	0.9796	0.732242498348354	MAX
48	51	1	0.926396689059416	MAX

48	51	0.9959	0.872855899152643	MAX
48	54	0.9186	1.36096404744368	MAX
48	54	0.9430	1.36096404744368	MAX
48	57	1	0.665827948338456	MAX
48	57	0.9959	0.911682219947375	MAX
50	52	0.9959	0.390013452989012	MAX
51	53	1	0.750107400369383	MAX
51	53	0.9959	0.769291268861354	MAX
51	54	0.9918	1.21677100324897	MAX
51	54	0.9512	1.32117783941774	MAX
52	54	0.9959	0.898471274330148	MAX
Condition 2				
44	47	0.9674	1.36096404744368	MAX
44	47	1	1.36096404744368	MAX
44	48	1	0.95421786488322	MAX
46	48	1	1.19553701344741	MAX
46	48	1	1.15408623993896	MAX
46	49	1	0.837709974214813	MAX
46	49	1	0.81455339691634	MAX
48	52	1	0.781428700518709	MAX
48	54	0.8536	1.36096404744368	MAX
52	188	0.9918	0.707779264708386	MAX
52	188	1	0.760355472030494	MAX
Condition 3				
44	47	0.9878	1.36096404744368	MAX
44	47	0.5894	1.36096404744368	MAX
44	48	1	1.15408623993896	MAX
46	48	1	0.64066495183839	MAX
46	48	1	0.95421786488322	MAX

46	49	1	0.781428700518709	MAX
47	50	0.9959	1.15343692472228	MAX
48	51	1	1.29283942163836	MAX
48	54	0.9634	1.36096404744368	MAX
48	57	1	0.998386679403042	MAX
51	54	0.6869	1.16865365987039	MAX
51	54	1	1.36096404744368	MAX
52	54	0.9959	1.2172378775043	MAX
Condition 4				
44	47	1	1.36096404744368	MAX
44	47	0.9552	1.21241455701333	MAX
44	48	1	0.559494154310152	MAX
44	48	1	1.02965843438589	MAX
46	48	1	1.17437901999795	MAX
46	49	1	1.15408623993896	MAX
47	50	0.9959	0.690808165453571	MAX
48	51	1	0.710941625795327	MAX
48	51	1	0.968600474504709	MAX
48	54	0.9634	1.36096404744368	MAX
48	54	0.9536	1.36096404744368	MAX
48	57	1	0.546480319171419	MAX
48	57	0.9918	0.530774076025637	MAX
51	53	1	0.516136533531159	MAX
51	54	0.9796	1.13098307587172	MAX
51	54	0.9959	1.3225604737177	MAX
52	54	0.9959	1.09664893369632	MAX

Table S18. Highly frustrated contact of the residues that are forming the **Linker Loop.** R(-)Ibuprofen-SARS-CoV-2 Complex in red and S(+)Ibuprofen-SARS-CoV-2 Complex in black**.**

Res1	Res2	IC_Contacts	IC_total	FrustrationState
Condition 1				
182	184	0.9024	1.31937009832559	MAX
183	185	1	0.81455339691634	MAX
183	185	1	0.648899992553133	MAX
185	192	0.9390	0.893342219718786	MAX
185	192	1	0.983317726069981	MAX
184	186	1	1.15408623993896	MAX
184	186	1	0.781428700518709	MAX
186	188	1	0.521959986075983	MAX
186	190	1	1.32282472525741	MAX
186	192	0.9065	0.733999617068083	MAX
186	192	0.9837	0.573424368032343	MAX
190	192	1	0.510433379165587	MAX
185	192	1	0.983317726069981	MAX
183	195	0.5731	0.702772781630463	MAX
184	193	0.6951	0.576184848329131	MAX
Condition 2				
182	184	0.7601	1.36096404744368	MAX
185	190	0.6097	0.514756847547976	MAX
185	192	1	1.29283942163836	MAX
184	186	1	1.36096404744368	MAX
186	188	1	0.72046674696313	MAX
186	188	1	0.803302936778609	MAX
186	190	1	1.36096404744368	MAX
186	190	1	1.15408623993896	MAX
186	192	1	1.21770145472988	MAX
52	188	1	0.760355472030494	MAX

52	188	0.9918	0.707779264708386	MAX
183	195	0.6544	1.02519248974497	MAX
190	192	1	1.01382641900365	MAX
165	192	0.7439	0.539038102268355	MAX
Condition 3				
182	184	0.9065	1.1823349656614	MAX
183	185	1	0.792263180506606	MAX
185	189	0.6544	0.654195624706034	MAX
185	190	0.5487	0.535337521285786	MAX
185	190	0.6910	0.663198846808258	MAX
185	192	1	0.616847740184277	MAX
185	192	0.9512	0.567062688318587	MAX
184	186	1	1.2659468017726	MAX
186	188	1	0.64066495183839	MAX
186	189	0.7195	0.923175544685279	MAX
186	190	1	1.07977025101164	MAX
186	190	0.7764	0.708919459670825	MAX
186	192	0.7235	0.681378850165387	MAX
189	191	1	0.710941625795327	MAX
Condition 4				
184	186	1	1.21770145472988	MAX
182	185	1	0.434751834709015	MAX
183	185	1	0.594318202261694	MAX
183	185	1	0.648899992553133	MAX
185	190	0.6869	0.552038971970804	MAX
185	192	1	1.07977025101164	MAX
185	192	1	0.983317726069981	MAX
184	186	1	1.21770145472988	MAX
184	186	1	0.781428700518709	MAX
186	190	0.9959	1.2926095303848	MAX

186	192	1	0.781428700518709	MAX
190	192	1	0.683383325583724	MAX
185	190	0.6869	0.552038971970804	MAX
185	192	1	1.07977025101164	MAX
186	190	0.9959	1.2926095303848	MAX
186	192	1	0.781428700518709	MAX
186	192	0.9837	0.573424368032343	MAX
190	192	1	0.683383325583724	MAX
183	195	0.5731	0.702772781630463	MAX
184	193	0.6951	0.576184848329131	MAX
185	192	1	0.983317726069981	MAX
186	192	0.9837	0.573424368032343	MAX