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SUPPLEMENTARY MATERIAL TO

Curcumin as a potential multiple-target inhibitor against SARS-CoV-2 infection: A detailed interaction study using quantum chemical calculations

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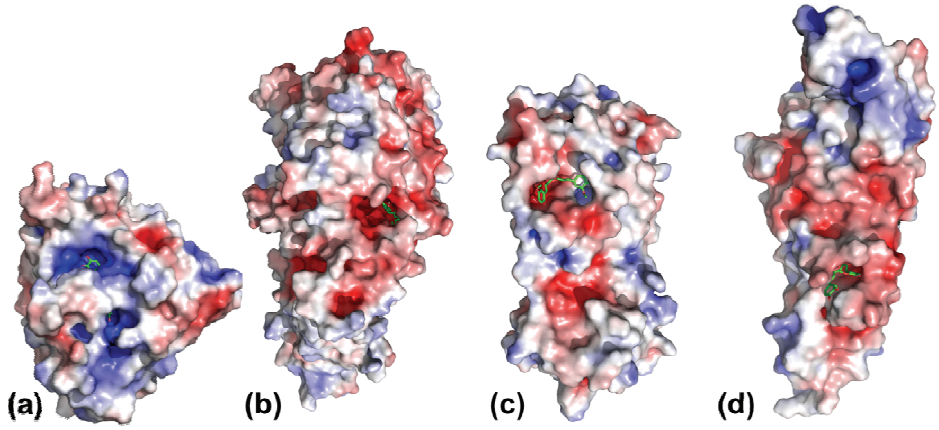

Figure S-1. Adaptive Poisson-Boltzmann Solver (ABPS) plots of the lowest binding energy docking site for the electrostatic interaction of curcumin with (a) TMPRSS2, (b) ACE2, (c) 3CLpro and (d) PLpro.

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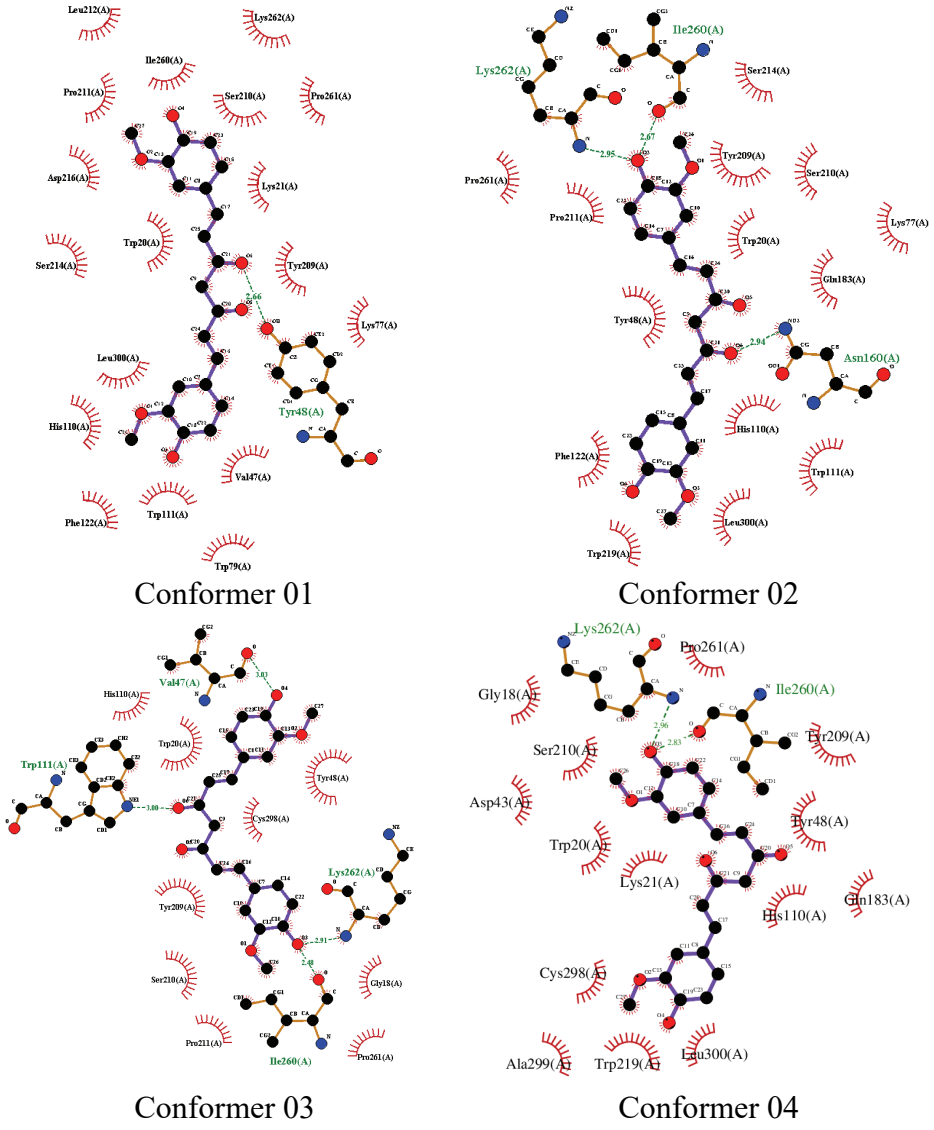

Figure S-2. The four most preferred docking poses of curcumin in the transmembrane serine protease 2 (TMPRSS2) PDB ID: 1Z8A.

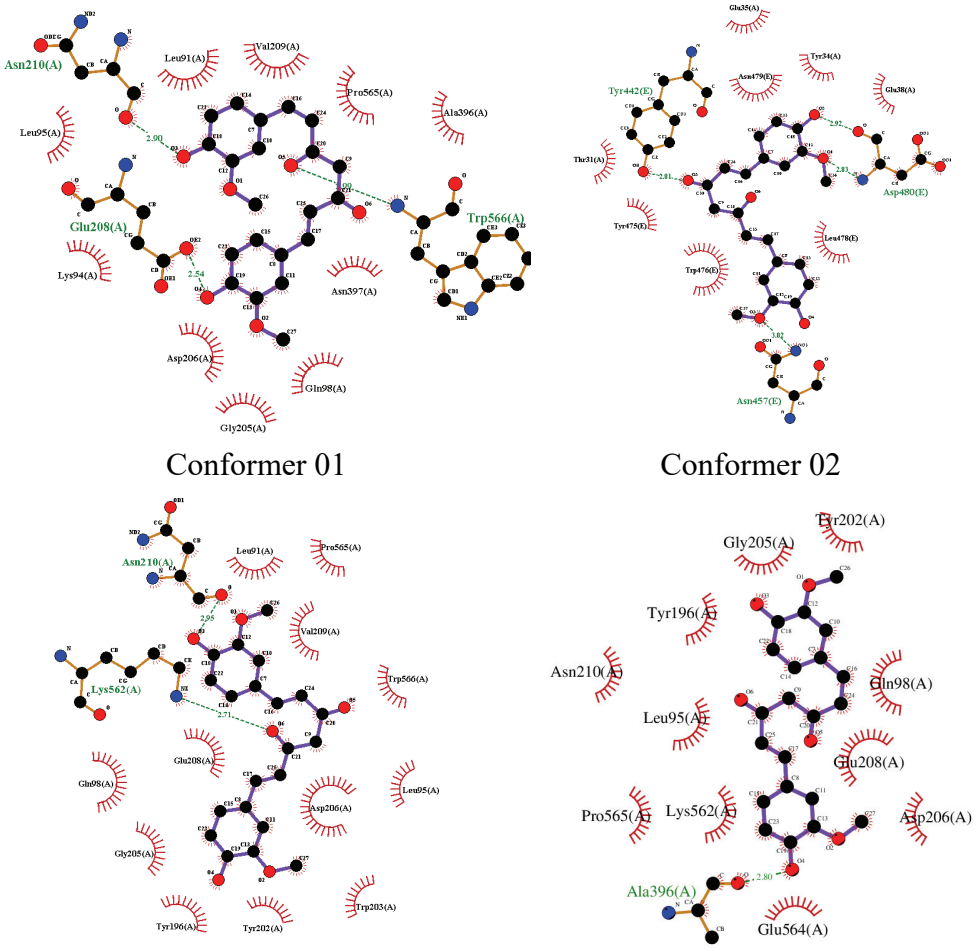

Figure S-3. The four most preferred docking poses of curcumin in the angiotensin-converting enzyme 2 (ACE2) PDB ID: 3D0G.

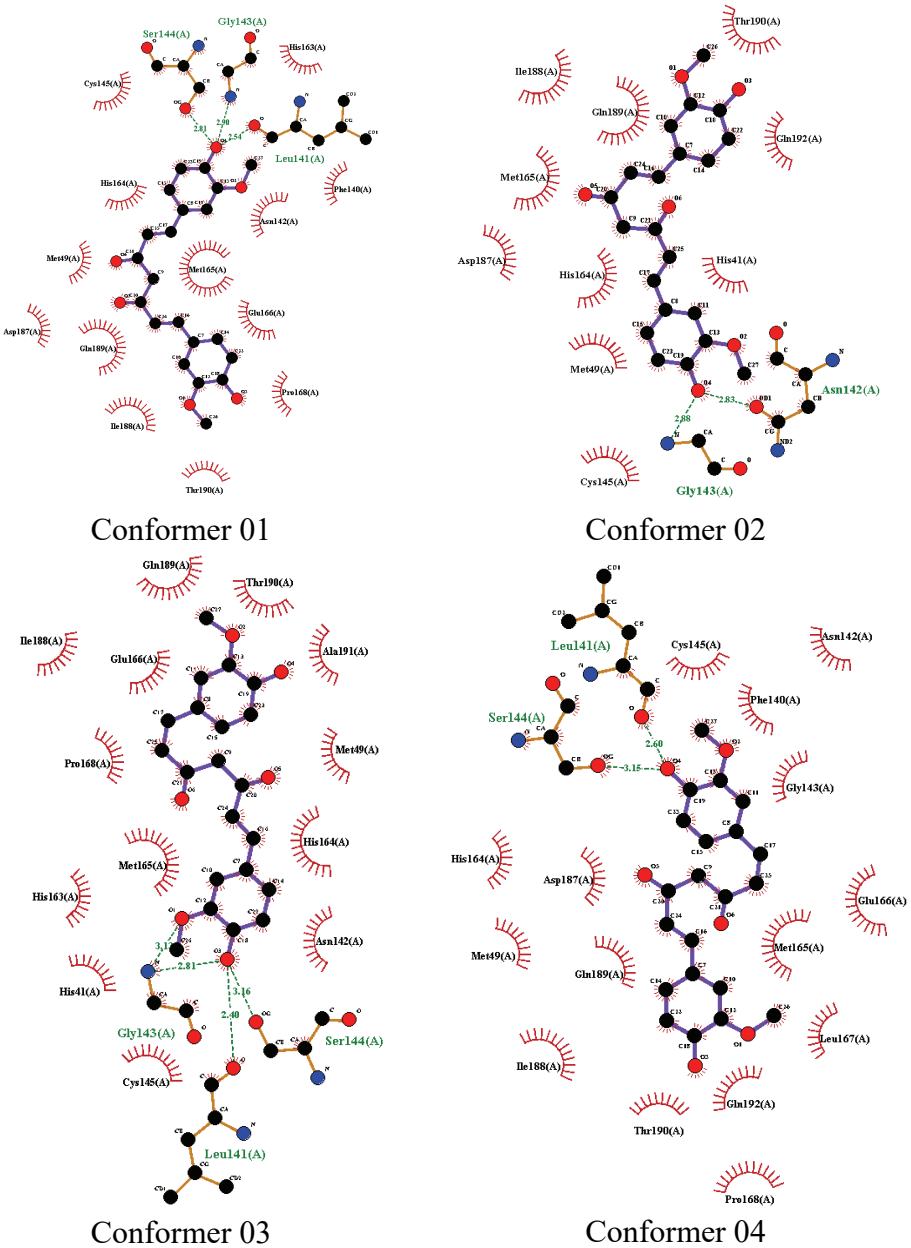

Figure S-4. The four most preferred docking poses of curcumin in the 3-chymotrypsin-like protease (3CLpro) PDB ID: 3AW0.

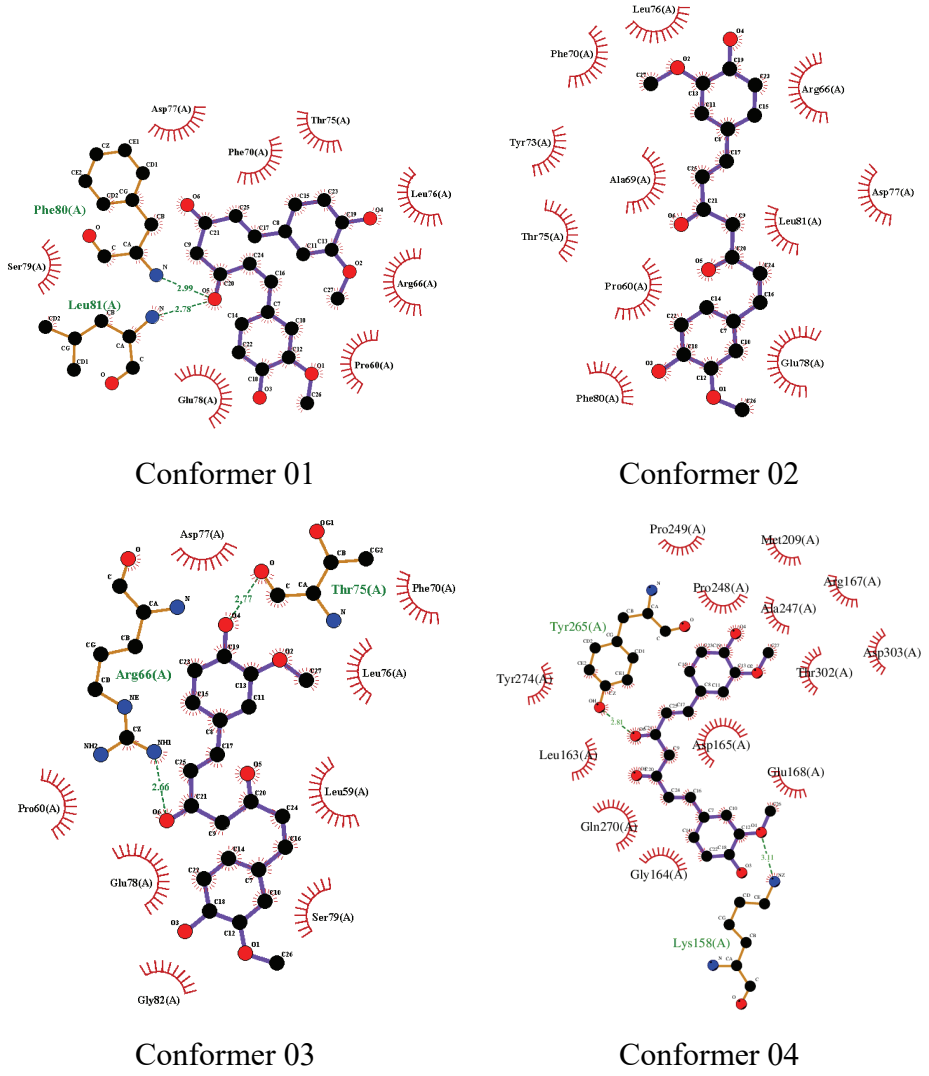

Figure S-5. The four most preferred docking poses of curcumin in the papain-like protease (PLpro) PDB ID: 3E9S.

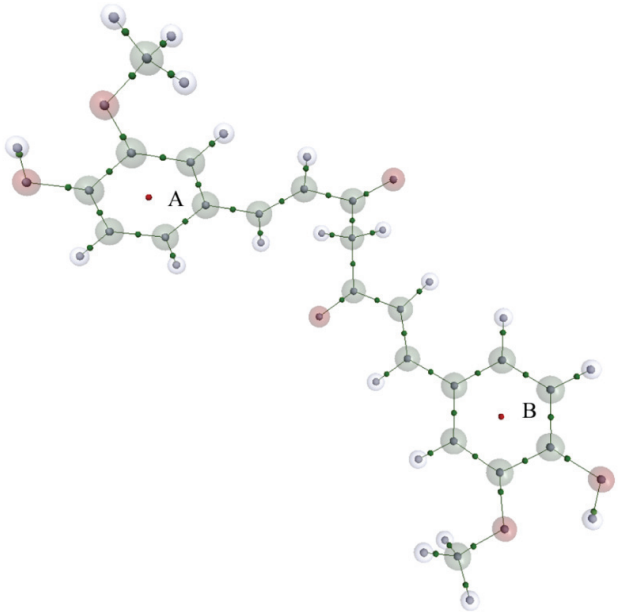

Figure S-6. Bond critical points (BCP) and ring critical points (RCPs) for curcumin in the gas phase obtained from AIM analysis at B3LYP/def2-TZVP level of theory.

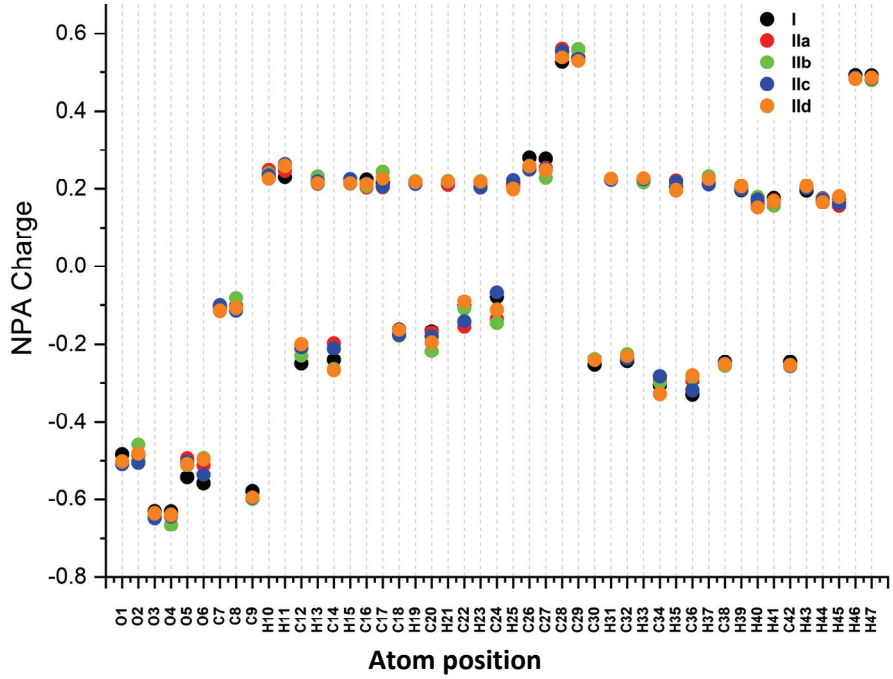

Figure S-7. Natural population analysis (NPA) charges of curcumin in the gas phase and that lifted from the active site of TMPRSS2 (IIb), ACE2 (IIb), 3CLpro (IIc) and PLpro (IId).

Table S-I. Estimated free energy of binding along with its subsidiary components and estimated inhibition constants for the four most preferred docking sites of curcumin in the transmembrane serine protease 2 (TMPRSS2) PDB ID: 1Z8A.

Receptor	Conformer 01	Conformer 02	Conformer 03	Conformer 04
Binding energy, kJ/mol	-42.34	-42.09	-41.97	-41.92
Inhibition constant, nM	38.37	42.32	44.57	45.47
Total intermolecular energy, kJ/mol	-54.43	-54.56	-54.43	-54.39
Total internal energy, kJ/mol	-8.74	-6.40	-5.52	-6.32
Torsional free energy, kJ/mol	12.47	12.47	12.47	12.47
Unbound system's energy, kJ/mol	-8.74	-6.40	-5.52	-6.32
Cluster RMSD, Å	0.00	1.29	0.00	0.79
Reference RMSD, Å	24.81	23.14	23.80	23.34

Table S-II. Estimated free energy of binding along with its subsidiary components and estimated inhibition constants for the four most preferred docking sites of curcumin in the angiotensin-converting enzyme 2 (ACE2) PDB ID: 3D0G.

Receptor	Conformer 01	Conformer 02	Conformer 03	Conformer 04
Binding energy, kJ/mol	-28.53	-27.24	-26.65	-25.65
Inhibition constant, μM	10.00	16.87	21.43	32.23
Total intermolecular energy, kJ/mol	-41.00	-39.71	-39.12	-38.12
Total internal energy, kJ/mol	-10.08	-10.88	-8.37	-9.00
Torsional free energy, kJ/mol	12.47	12.47	12.47	12.47
Unbound system's energy, kJ/mol	-10.08	-10.88	-8.37	-9.00
Cluster RMSD, Å	0.00	0.00	0.00	0.00
Reference RMSD, Å	102.60	127.25	104.15	104.66

Table S-III. Estimated free energy of binding along with its subsidiary components and estimated inhibition constants for the four most preferred docking sites of curcumin in the 3-chymotrypsin-like protease (3CLpro) PDB ID: 3AW0

Receptor	Conformer 01	Conformer 02	Conformer 03	Conformer 04
Binding energy, kJ/mol	-33.85	-32.05	-30.12	-29.71
Inhibition constant, μM	1.18	2.41	5.27	6.21
Total intermolecular energy, kJ/mol	-46.32	-44.56	-42.59	-42.22
Total internal energy, kJ/mol	-9.16	-9.50	-6.53	-9.62
Torsional free energy, kJ/mol	12.47	12.47	12.47	12.47
Unbound system's energy, kJ/mol	-9.16	-9.50	-6.53	-9.62
Cluster RMSD, Å	0.00	1.73	1.65	1.95
Reference RMSD, Å	42.05	42.92	42.20	41.44

Table S-IV. Estimated free energy of binding along with its subsidiary components and estimated inhibition constants for the four most preferred docking sites of curcumin in the papain-like protease (PLpro) PDB ID: 3E9S.

Receptor	Conformer 01	Conformer 02	Conformer 03	Conformer 04
Binding energy, kJ/mol	-31.33	-30.33	-29.71	-27.36
Inhibition constant, μM	3.22	4.84	6.26	16.02
Total intermolecular energy, kJ/mol	-43.81	-42.84	-42.17	-39.87
Total internal energy, kJ/mol	-10.92	-10.71	-9.41	-8.62
Torsional free energy, kJ/mol	12.47	12.47	12.47	12.47
Unbound system's energy, kJ/mol	-10.92	-10.71	-9.41	-8.62
Cluster RMSD, Å	0.00	0.00	0.00	0.00
Reference RMSD, Å	31.12	30.86	29.67	43.00

Table S-V. List of interactions present in the lowest binding energy active site of curcumin with TMPRSS2 (PDB ID: 1Z8A), ACE2 (PDB ID: 3D0G), 3CLpro (PDB ID: 3AW0) and PLpro (PDB ID: 3E9S). These interactions are obtained from PLIP analysis

Receptor	Residues number	Residue	Curcumin	Distance, Å	Angle, °	Types
TMPRSS2P	21A	LYS	O2	4.01	133	H-bond
	48A	TYR	O5	3.15	109	H-bond
	111A	TRP	O1	3.72	112	H-bond
	212A	LEU	O4	3.86	126	H-bond
	20A	TRP	-	5.49	-	π-stack
ACE2	94A	LYS	O3	3.92	143	H-bond
	98A	GLN	O1	3.84	135	H-bond
	196A	TYR	O2	3.79	120	H-bond
	208A	GLU	O4	2.54	126	H-bond
	566A	TRP	O5	2.99	162	H-bond
PLpro	143A	GLY	O4	2.9	122	H-bond
	144A	SER	O4	2.58	122	H-bond
	144A	SER	O4	2.81	146	H-bond
	189A	GLN	O6	2.56	162	H-bond
3CLpro	66A	ARG	O1	3.43	116	H-bond
	80A	PHE	O5	2.99	115	H-bond
	81A	LEU	O5	2.78	168	H-bond

Table S-VI. Coordinate of the curcumin in the gas phase optimized at def2-TZVP level of theory

O	14.5117	-6.7691	16.0957
O	20.4987	-6.8693	28.2342
O	15.7944	-8.9503	15.3302
O	19.3112	-4.6659	29.1076
O	18.3812	-2.2935	20.5274
O	21.0747	-5.7176	20.9155
C	17.8078	-6.1900	17.7049
C	20.1320	-4.9955	25.0412
C	20.3892	-3.5407	20.1988
H	20.8293	-2.6088	20.5558
H	20.8837	-3.8494	19.2796
C	16.4706	-5.9625	17.3217
H	15.9673	-5.0634	17.6452
C	20.4781	-6.0331	25.9287
H	20.9616	-6.9160	25.5335
C	15.8034	-6.8770	16.5336
C	20.2089	-5.9300	27.2810
C	18.4350	-7.3600	17.2656
H	19.4610	-7.5502	17.5553
C	19.5054	-3.8566	25.5628
H	19.2215	-3.0457	24.9060
C	18.5578	-5.2635	18.5379
H	19.5838	-5.5629	18.7249
C	20.4412	-5.1645	23.6322
H	20.8962	-6.1125	23.3567
C	16.4525	-8.0535	16.1029
C	19.5803	-4.7777	27.7844
C	18.9021	-3.2475	19.9717
C	20.6134	-4.6378	21.2432
C	17.7663	-8.2846	16.4738
H	18.2508	-9.1912	16.1360
C	19.2332	-3.7501	26.9168
H	18.7475	-2.8728	27.3237
C	18.1124	-4.1254	19.1037
H	17.0884	-3.7908	18.9807
C	20.2382	-4.2962	22.6251
H	19.7949	-3.3212	22.7849
C	13.7576	-5.6251	16.4727
H	12.7751	-5.7499	16.0238
H	14.2176	-4.7084	16.0937
H	13.6566	-5.5615	17.5596
C	21.1405	-8.0712	27.8315
H	21.2731	-8.6603	28.7359
H	22.1172	-7.8654	27.3846
H	20.5237	-8.6284	27.1210

H	14.8986	-8.6158	15.1794
H	19.6223	-5.4710	29.5460

Table S-VII. Coordinate of the curcumin lifted from the active site of transmembrane serine protease 2 (TMPRSS2) PDB ID: 1Z8A

O	17.5840	-6.0610	14.7080
O	23.1110	-6.7400	26.5750
O	15.7480	-8.1100	14.3190
O	23.0290	-4.5390	28.2700
O	15.2930	-2.7810	21.1560
O	16.3560	-5.2890	23.0120
C	15.9100	-6.1260	17.9410
C	20.1520	-5.0140	25.3410
C	17.4680	-3.7490	21.5280
H	18.0140	-2.7930	21.7060
H	18.2130	-4.2860	20.8960
C	16.7810	-5.7550	16.9280
H	17.5070	-4.9400	17.0880
C	21.1520	-5.9640	25.4640
H	21.1790	-6.8350	24.7880
C	16.7290	-6.4230	15.7050
C	22.1250	-5.8080	26.4520
C	14.9890	-7.1450	17.7620
H	14.3030	-7.4260	18.5790
C	20.0970	-3.9110	26.1790
H	19.2930	-3.1650	26.0660
C	15.9640	-5.4210	19.2340
H	15.8380	-6.0210	20.1510
C	19.1240	-5.1780	24.2990
H	19.0380	-6.1660	23.8160
C	15.8070	-7.4510	15.5100
C	22.0840	-4.7040	27.3030
C	16.2050	-3.4860	20.7330
C	17.2700	-4.4870	22.8380
C	14.9370	-7.8130	16.5380
H	14.2080	-8.6270	16.3840
C	21.0700	-3.7550	27.1670
H	21.0380	-2.8820	27.8400
C	16.1550	-4.1020	19.3730
H	16.2760	-3.4680	18.4790
C	18.2860	-4.2130	23.8960
H	18.3480	-3.2090	24.3490
C	18.8180	-6.7710	14.6200
H	19.5180	-6.4750	13.8040
H	18.6130	-7.8650	14.5540
H	19.3470	-6.7180	15.6000
C	22.9350	-7.7430	27.5740
H	23.7420	-8.5060	27.6750
H	21.9570	-8.2550	27.4180

H	22.7580	-7.2570	28.5620
H	16.3880	-7.7030	13.7110
H	23.6110	-5.3180	28.2800

Table S-VIII. Coordinate of the curcumin lifted from the active site of angiotensin-converting enzyme 2 (ACE2) PDB ID: 3D0G.

O	42.8250	-16.3020	95.6150
O	50.0770	-15.7900	95.8640
O	40.8640	-16.5800	93.6670
O	48.2690	-17.2730	94.3620
O	44.9740	-9.1740	93.7350
O	47.6670	-8.9640	96.8100
C	43.1640	-13.1510	93.8230
C	47.2450	-13.5070	95.7220
C	45.4010	-9.3750	96.0980
H	44.8310	-9.8140	96.9500
H	45.2330	-8.2890	96.2880
C	43.3860	-14.1540	94.7530
H	44.1660	-14.0370	95.5240
C	48.4970	-14.0160	96.0240
H	49.2100	-13.4230	96.6200
C	42.6110	-15.3130	94.7030
C	48.8470	-15.2860	95.5670
C	42.1910	-13.2740	92.8450
H	42.0300	-12.4650	92.1130
C	46.3320	-14.2340	94.9740
H	45.3390	-13.8120	94.7430
C	43.9830	-11.9260	93.8750
H	44.7220	-11.7690	93.0710
C	46.8750	-12.1650	96.2040
H	46.1990	-12.1010	97.0740
C	41.6270	-15.4530	93.7240
C	47.9400	-16.0300	94.8130
C	44.7630	-9.7780	94.7830
C	46.8750	-9.7050	96.2330
C	41.4160	-14.4340	92.7960
H	40.6370	-14.5440	92.0230
C	46.6820	-15.5040	94.5160
H	45.9650	-16.0920	93.9190
C	43.8930	-10.9900	94.8300
H	43.1720	-11.1160	95.6550
C	47.3010	-11.0160	95.6610
H	47.9710	-11.0400	94.7850
C	43.7440	-17.3310	95.2530
H	43.9190	-18.1410	95.9990
H	44.7190	-16.8740	94.9650
H	43.4330	-17.7820	94.2820
C	50.8690	-15.0590	96.7990
H	51.8760	-15.4720	97.0420

H	50.2910	-14.9110	97.7410
H	50.9730	-14.0040	96.4530
H	41.1590	-17.1860	94.3670
H	49.0740	-17.2110	93.8210

Table S-IX. Coordinate of the curcumin lifted from the active site of 3-chymotrypsin-like protease (3CLpro) PDB ID: 3AW0

O	-28.1110	-35.0320	5.3490
O	-18.9650	-41.3030	2.1840
O	-26.3900	-32.8820	5.7220
O	-19.2640	-43.4760	0.4770
O	-24.5710	-40.5870	8.9140
O	-25.7900	-40.3060	4.7770
C	-25.2220	-36.6910	6.8200
C	-22.5060	-42.0400	2.5990
C	-25.2360	-41.5120	6.7900
H	-24.5480	-42.3530	7.0400
H	-26.2200	-42.0250	6.8970
C	-26.4790	-36.5040	6.2660
H	-27.1580	-37.3610	6.1210
C	-21.2750	-41.4240	2.7510
H	-21.1630	-40.5620	3.4300
C	-26.8760	-35.2200	5.8940
C	-20.1780	-41.9050	2.0360
C	-24.3530	-35.6300	7.0120
H	-23.3570	-35.7990	7.4540
C	-22.6720	-43.1240	1.7520
H	-23.6600	-43.6020	1.6440
C	-24.8010	-38.0480	7.2130
H	-23.7220	-38.2310	7.3500
C	-23.6650	-41.5320	3.3540
H	-24.4750	-41.0460	2.7840
C	-26.0120	-34.1410	6.0810
C	-20.3280	-42.9950	1.1790
C	-25.1080	-40.4100	7.8240
C	-25.0280	-41.0800	5.3520
C	-24.7510	-34.3450	6.6400
H	-24.0680	-33.4910	6.7880
C	-21.5750	-43.6040	1.0370
H	-21.6930	-44.4660	0.3590
C	-25.6380	-39.0750	7.4160
H	-26.7240	-38.9330	7.2810
C	-23.8060	-41.6180	4.6840
H	-23.0140	-42.0900	5.2890
C	-28.3040	-35.4820	4.0100
H	-29.3140	-35.3280	3.5640
H	-28.0250	-36.5590	3.9360
H	-27.5320	-35.0230	3.3490
C	-18.6590	-40.2320	1.2930

H	-17.6660	-39.7390	1.4140
H	-19.4640	-39.4630	1.3460
H	-18.7750	-40.5800	0.2400
H	-27.3610	-32.8560	5.6720
H	-18.4710	-42.9660	0.7150

Table S-X. Coordinate of the curcumin lifted from the active site of papain-like protease (PLpro) PDB ID: 3E9S

O	-1.0210	30.1960	14.9090
O	-4.1630	32.2480	14.0690
O	1.2650	29.3220	16.2260
O	-4.0660	32.8400	11.3550
O	-5.8730	24.7800	16.2730
O	-8.5190	25.6350	13.7490
C	-2.0800	26.9030	16.0450
C	-5.2980	29.1040	12.6250
C	-6.1760	25.0910	13.9020
H	-5.4210	25.1480	13.0830
H	-6.4780	24.0210	13.8170
C	-2.1170	28.1500	15.4420
H	-3.0280	28.4910	14.9210
C	-4.9360	30.0520	13.5680
H	-4.9750	29.8110	14.6440
C	-0.9890	28.9690	15.5010
C	-4.5210	31.3150	13.1440
C	-0.9490	26.4530	16.7040
H	-0.9390	25.4570	17.1780
C	-5.2550	29.3840	11.2680
H	-5.5460	28.6160	10.5310
C	-3.2710	26.0360	15.9830
H	-3.2750	25.1250	16.6050
C	-5.7370	27.7720	13.0720
H	-4.9620	27.0620	13.4050
C	0.1580	28.5300	16.1610
C	-4.4720	31.6110	11.7820
C	-5.5100	25.3390	15.2420
C	-7.3550	25.9900	13.5860
C	0.1790	27.2730	16.7630
H	1.0860	26.9270	17.2860
C	-4.8400	30.6470	10.8440
H	-4.8030	30.8830	9.7670
C	-4.3490	26.2770	15.2240
H	-4.3780	27.1740	14.5820
C	-7.0130	27.3610	13.1030
H	-7.8150	28.0400	12.7690
C	-1.4140	31.2990	15.7230
H	-1.4400	32.3030	15.2390
H	-0.7670	31.3410	16.6300
H	-2.4050	31.0840	16.1860

C	-4.4920	31.9720	15.4300
H	-4.1990	32.7360	16.1870
H	-4.0720	30.9810	15.7200
H	-5.5850	31.7660	15.5140
H	1.0130	30.2220	15.9550
H	-3.8470	33.3870	12.1280

Table S-XI. Geometrical parameters of curcumin in the gas phase and the same lifted from the active sites of TMPRSS2 (IIa), ACE2 (IIb), 3CLpro (IIc) and PLpro (IId).

Group		I	IIa	IIb	IIc	IId
Aromatic ring 1		Bond distance, Å				
	C7-C18	1.39830	1.3852	1.3850	1.3848	1.3842
	C18-C30	1.38888	1.3954	1.3959	1.3957	1.3958
	C30-C26	1.38457	1.3945	1.3943	1.3944	1.3939
	C26-C16	1.41102	1.3946	1.3951	1.3949	1.3942
	C16-C12	1.37934	1.3945	1.3951	1.3945	1.3952
	C12-C7	1.40950	1.3865	1.3857	1.3863	1.3856
Aromatic ring 2		Bond distance, Å				
	C8-C20	1.40064	1.3863	1.3862	1.3856	1.3863
	C20-C32	1.38519	1.3954	1.3947	1.3946	1.3954
	C32-C27	1.38895	1.3955	1.3955	1.395	1.3945
	C27-C17	1.40583	1.3945	1.3945	1.3947	1.3947
	C17-C14	1.38268	1.3954	1.3944	1.395	1.3954
	C14-C8	1.40856	1.3848	1.3848	1.3849	1.3853
Aromatic ring 1		Bond angles, °				
	C7-C18-C30	121.3	119.4	119.3	119.3	119.3
	C18-C30-C26	119.9	119.9	120.0	120.0	120.0
	C30-C26-C16	119.6	120.1	120.0	120.1	120.1
	C26-C16-C12	120.3	120.0	120.0	120.0	120.0
	C16-C12-C7	120.5	119.3	119.2	119.3	119.2
	C12-C7-C18	118.4	121.3	121.5	121.4	121.4
Aromatic ring 2	Angles	Bond angles, °				
	C8-C20-C32	121.0	119.3	119.3	119.2	119.3
	C20-C32-C27	120.3	120.0	120.0	120.1	120.0
	C32-C27-C17	119.6	120.0	120.0	120.0	120.1
	C27-C17-C14	119.9	120.0	120.0	120.0	120.0
	C17-C14-C8	120.9	119.3	119.4	119.3	119.4
	C14-C8-C20	118.3	121.4	121.4	121.4	121.3
Chain		Dihedral angles, °				
	C7-C22-C34-C28	178.0	-179.5	-179.5	-179.5	-179.5
	C22-C34-C28-C9	5.2	73.8	-135.7	-111.7	-141.1
	C34-C28-C9-C29	-80.3	-119.1	104.3	36.9	-93.1
	C28-C9-C29-C36	-67.5	-152.4	-39.1	112.5	79.3
	C9-C29-C36-C24	-177.3	-113.4	-66.7	166.2	-5.4
	C29-C36-C24-C8	-179.9	-179.5	-179.5	-179.5	-179.5
Chain		Bond distance, Å				
	C8-C24	1.45239	1.47290	1.47316	1.47356	1.47199
	C24-C36	1.34514	1.34010	1.34035	1.34022	1.34092
	C36-C29	1.47211	1.49221	1.49244	1.49297	1.49328
	C29-C9	1.53123	1.51656	1.51651	1.51583	1.51595
	C9-C28	1.53265	1.51538	1.51614	1.51656	1.51679
	C28-C34	1.46552	1.49384	1.49267	1.49318	1.49268
	C34-C22	1.34677	1.33999	1.34023	1.34034	1.34024
	C22-C7	1.45423	1.47370	1.47448	1.47416	1.47445

	C29-O6	1.21908	1.22836	1.22853	1.22896	1.22780
	C28-O5	1.22076	1.22788	1.22786	1.22792	1.22769
	C27-O4	1.35491	1.36211	1.36260	1.36245	1.36294
	C17-O2	1.36925	1.36233	1.36260	1.36223	1.36172
	C26-O3	1.35440	1.36244	1.36218	1.36266	1.36270
	C16-O1	1.36817	1.36238	1.36223	1.36294	1.36272

Table S-XII. Detailed summary of Mulliken population analysis (MPA) and natural population analysis (NPA) charges of curcumin in gas phase (I) and curcumin lifted from the active site of (b) transmembrane serine protease 2 (TMPRSS2) PDB ID: 1Z8A (IIa), (c) angiotensin-converting enzyme 2 (ACE2) PDB ID: 3D0G (IIb), (d) 3-chymotrypsin-like protease (3CLpro) PDB ID: 3AW0 (IIc) and (e) papain-like protease (PLpro) PDB ID: 3E9S (IId). The calculation is performed at B3LYP/def2-TZVP level of theory.

Curcumin		I	I	IIa	IIa	IIb	IIb	IIc	IIc	IId	IId
Sequence Number	Atom Symbol	MPA, e	NPA, e	MPA, e	NPA, e	MPA, e	NPA, e	MPA, e	NPA, e	MPA, e	NPA, e
1	O	-0.34563	-0.48409	-0.35051	-0.50581	-0.34798	-0.50634	-0.35644	-0.50833	-0.33756	-0.50172
2	O	-0.34552	-0.48398	-0.34018	-0.50261	-0.2836	-0.45772	-0.35045	-0.50514	-0.34102	-0.48199
3	O	-0.38681	-0.63191	-0.39929	-0.64285	-0.39646	-0.64221	-0.40884	-0.64768	-0.38819	-0.63608
4	O	-0.38775	-0.63212	-0.38995	-0.64007	-0.42946	-0.66471	-0.39773	-0.6432	-0.39995	-0.64037
5	O	-0.31345	-0.54325	-0.28097	-0.49423	-0.29018	-0.51148	-0.27884	-0.50347	-0.28818	-0.50889
6	O	-0.33479	-0.559	-0.30249	-0.51179	-0.27549	-0.49379	-0.33061	-0.53663	-0.283	-0.49625
7	C	0.13326	-0.1051	0.24018	-0.10286	0.22315	-0.11405	0.23682	-0.10156	0.24939	-0.11455
8	C	0.23511	-0.10494	0.26268	-0.10899	0.06402	-0.08182	0.19978	-0.113	0.09404	-0.10695
9	C	-0.14137	-0.57914	-0.23387	-0.59987	-0.20352	-0.60048	-0.21577	-0.59736	-0.14111	-0.59554
10	H	0.1165	0.24062	0.13782	0.24843	0.12723	0.23957	0.12073	0.23431	0.13364	0.225
11	H	0.12212	0.22952	0.13569	0.24653	0.1383	0.25891	0.13711	0.26319	0.12805	0.25944
12	C	-0.33067	-0.24997	-0.28759	-0.20999	-0.28569	-0.23003	-0.25196	-0.20657	-0.19996	-0.19958
13	H	0.12873	0.21338	0.11896	0.21897	0.15095	0.23174	0.1225	0.21922	0.10724	0.21413
14	C	-0.3196	-0.24068	-0.30899	-0.19752	-0.29467	-0.26476	-0.28309	-0.21102	-0.33625	-0.26737
15	H	0.13047	0.21368	0.11406	0.21986	0.11399	0.22101	0.12789	0.22514	0.1555	0.21427
16	C	0.34123	0.22379	0.26257	0.20379	0.22971	0.20741	0.24608	0.21316	0.20376	0.21147
17	C	0.32459	0.21373	0.26533	0.2041	0.29276	0.24351	0.27688	0.20609	0.35394	0.22617
18	C	-0.17153	-0.16122	-0.19352	-0.17354	-0.19417	-0.17784	-0.20341	-0.17568	-0.17304	-0.16262
19	H	0.11884	0.21364	0.11744	0.21723	0.11913	0.21952	0.10688	0.2125	0.11549	0.21723
20	C	-0.18438	-0.16599	-0.14899	-0.16894	-0.15615	-0.21804	-0.16854	-0.18008	-0.1893	-0.19542
21	H	0.11428	0.21231	0.10164	0.20996	0.24189	0.22004	0.11612	0.21656	0.11467	0.21891
22	C	-0.06459	-0.1032	-0.18668	-0.15483	-0.16767	-0.10785	-0.17416	-0.14112	-0.20351	-0.0909
23	H	0.13719	0.21665	0.13677	0.21552	0.13531	0.2197	0.10102	0.20383	0.12365	0.21794
24	C	-0.11913	-0.07977	-0.16874	-0.13451	-0.22839	-0.14582	-0.12144	-0.06783	-0.08674	-0.11201
25	H	0.11747	0.21388	0.11177	0.20656	0.12025	0.19909	0.14488	0.22229	0.12859	0.19898
26	C	0.18269	0.27931	0.1669	0.24971	0.15455	0.25076	0.16694	0.25042	0.17703	0.25822
27	C	0.17419	0.27689	0.16268	0.25325	0.21694	0.22745	0.15689	0.2507	0.16409	0.24794
28	C	0.15692	0.52655	0.25821	0.56067	0.273	0.5418	0.14805	0.55414	0.19004	0.53778
29	C	0.20286	0.53703	0.20127	0.55782	0.18926	0.55985	0.30592	0.53452	0.19593	0.52913
30	C	-0.20365	-0.25309	-0.20859	-0.23992	-0.19409	-0.23775	-0.19799	-0.24143	-0.21829	-0.24124
31	H	0.11323	0.22326	0.11442	0.22325	0.11736	0.22427	0.11248	0.222	0.11899	0.22579
32	C	-0.18847	-0.24377	-0.22177	-0.23601	-0.25726	-0.22518	-0.19986	-0.23754	-0.19101	-0.23078
33	H	0.11533	0.22317	0.11721	0.22387	0.11222	0.21626	0.11599	0.22396	0.11858	0.22702
34	C	-0.14545	-0.30723	-0.14817	-0.29466	-0.17835	-0.3	-0.03469	-0.28283	-0.14413	-0.32849
35	H	0.08325	0.20485	0.12793	0.22155	0.1276	0.21434	0.1064	0.2181	0.09229	0.19591
36	C	-0.23364	-0.32978	-0.10318	-0.29563	-0.11374	-0.2844	-0.23287	-0.31913	-0.17246	-0.28048
37	H	0.13062	0.21134	0.11573	0.2124	0.13883	0.23168	0.12708	0.21135	0.12622	0.22473
38	C	-0.20067	-0.24674	-0.18784	-0.25576	-0.15926	-0.25625	-0.1702	-0.25155	-0.16392	-0.25306
39	H	0.13627	0.19673	0.13876	0.20143	0.13864	0.20353	0.13291	0.19903	0.1404	0.20649
40	H	0.12737	0.17574	0.11664	0.16248	0.07241	0.17893	0.12261	0.17241	0.11142	0.15256

41	H	0.12904	0.17617	0.11514	0.17056	0.11663	0.1567	0.11249	0.16767	0.08497	0.16837
42	C	-0.20035	-0.24622	-0.19482	-0.25703	-0.19847	-0.25598	-0.19225	-0.25542	-0.23597	-0.25451
43	H	0.13558	0.19621	0.14146	0.20359	0.14336	0.20698	0.14039	0.20256	0.15155	0.20683
44	H	0.12839	0.17516	0.12184	0.17401	0.12611	0.17248	0.12153	0.17156	0.12053	0.16569
45	H	0.12841	0.1752	0.10756	0.15653	0.12195	0.16789	0.1168	0.16266	0.14804	0.18028
46	H	0.3268	0.49129	0.32349	0.48239	0.3237	0.48365	0.32285	0.4853	0.32344	0.48294
47	H	0.32671	0.49106	0.32198	0.48298	0.32533	0.47945	0.32314	0.4839	0.32212	0.48556

Table S-XIII. Detailed summary of electron density, ρ_{bcp} (r) and Laplacian of electron density, $\nabla^2\rho_{bcp}$(r) of curcumin in gas phase (I) and curcumin lifted from the active site of (b) transmembrane serine protease 2 (TMPRSS2) PDB ID: 1Z8A (IIa), (c) angiotensin-converting enzyme 2 (ACE2) PDB ID: 3D0G (IIb), (d) 3-chymotrypsin-like protease (3CLpro) PDB ID: 3AW0 (IIc) and (e) papain-like protease (PLpro) PDB ID: 3E9S (IId). The calculation is performed at B3-LYP/def2-TZVP level of theory

Curcumin	I		IIa		IIb		IIc		IId	
Bond	ρ_{bcp} (r), a.u.	$\nabla^2\rho_{bcp}$(r), a.u.	ρ_{bcp} (r), a.u.	$\nabla^2\rho_{bcp}$(r), a.u.	ρ_{bcp} (r), a.u.	$\nabla^2\rho_{bcp}$(r), a.u.	ρ_{bcp} (r), a.u.	$\nabla^2\rho_{bcp}$(r), a.u.	ρ_{bcp} (r), a.u.	$\nabla^2\rho_{bcp}$(r), a.u.
O1-C38	0.2511	-0.5045	0.2519	-0.5639	0.2509	-0.5516	0.2509	-0.5504	0.2519	-0.5608
O2-C17	0.2872	-0.5830	0.2914	-0.5827	0.2915	-0.5761	0.2915	-0.5833	0.2897	-0.5296
O2-C42	0.2515	-0.5078	0.2521	-0.5655	0.2510	-0.5435	0.2515	-0.5601	0.2497	-0.5301
O3-C26	0.3003	-0.6409	0.2947	-0.6446	0.2952	-0.6502	0.2950	-0.6562	0.2952	-0.6576
O3-H46	0.3555	-2.4420	0.3523	-2.3750	0.3525	-2.3810	0.3510	-2.3690	0.3514	-2.3630
O4-H47	0.3555	-2.4410	0.3520	-2.3710	0.3507	-2.3370	0.3516	-2.3720	0.3521	-2.3810
O6-C29	0.4150	-0.2481	0.4075	-0.3306	0.4076	-0.3334	0.4068	-0.3333	0.4087	-0.3393
C7-C12	0.3076	-0.8863	0.3220	-0.9593	0.3211	-0.9469	0.3227	-0.9647	0.3235	-0.9724
C7-C18	0.3169	-0.9326	0.3243	-0.9754	0.3227	-0.9619	0.3248	-0.9793	0.3257	-0.9864
C7-C22	0.2854	-0.8065	0.2755	-0.7637	0.2761	-0.7736	0.2749	-0.7571	0.2750	-0.7554
C8-C14	0.3090	-0.8925	0.3241	-0.9733	0.3223	-0.9571	0.3220	-0.9558	0.3212	-0.9497
C8-C20	0.3147	-0.9232	0.3239	-0.9745	0.3217	-0.9530	0.3226	-0.9628	0.3214	-0.9514
C8-C24	0.2865	-0.8135	0.2756	-0.7598	0.2769	-0.7812	0.2771	-0.7794	0.2775	-0.7815
C9-C28	0.2481	-0.6202	0.2597	-0.6867	0.2589	-0.6802	0.2556	-0.6600	0.2560	-0.6624
C9-C29	0.2497	-0.6283	0.2568	-0.6674	0.2562	-0.6641	0.2591	-0.6804	0.2559	-0.6619
C9-H10	0.2804	-0.9676	0.2637	-0.8617	0.2631	-0.8554	0.2676	-0.8849	0.2659	-0.8670
C9-H11	0.2829	-0.9839	0.2648	-0.8686	0.2658	-0.8792	0.2613	-0.8491	0.2669	-0.8860
C12-H13	0.2882	-1.0260	0.2743	-0.9451	0.2787	-0.9638	0.2750	-0.9485	0.2749	-0.9459
C14-C17	0.3249	-0.9672	0.3201	-0.9461	0.3204	-0.9498	0.3203	-0.9482	0.3189	-0.9362
C14-H15	0.2872	-1.0210	0.2744	-0.9471	0.2762	-0.9490	0.2748	-0.9497	0.2749	-0.9381
C16-C12	0.3266	-0.9719	0.3205	-0.9471	0.3198	-0.9438	0.3206	-0.9449	0.3198	-0.9400
C16-C26	0.3168	-0.9510	0.3246	-0.9791	0.3243	-0.9758	0.3246	-0.9816	0.3253	-0.9875
C16-O1	0.2879	-0.5817	0.2909	-0.5741	0.2918	-0.5893	0.2913	-0.5904	0.2917	-0.5967
C17-C27	0.3194	-0.9619	0.3247	-0.9787	0.3244	-0.9857	0.3246	-0.9779	0.3238	-0.9810
C18-C30	0.3201	-0.9487	0.3161	-0.9223	0.3155	-0.9191	0.3160	-0.9220	0.3161	-0.9233
C18-H19	0.2879	-1.0310	0.2754	-0.9532	0.2757	-0.9553	0.2752	-0.9509	0.2756	-0.9547
C20-C32	0.3220	-0.9551	0.3158	-0.9179	0.3158	-0.9224	0.3163	-0.9236	0.3159	-0.9242
C20-H21	0.2889	-1.0370	0.2761	-0.9544	0.2800	-0.9646	0.2755	-0.9533	0.2750	-0.9497

Curcumin	I		IIa		IIb		IIc		IId	
Bond	ρ_{bcp} (r), a.u.	$\nabla^2\rho_{bcp}$(r), a.u.	ρ_{bcp} (r), a.u.	$\nabla^2\rho_{bcp}$(r), a.u.	ρ_{bcp} (r), a.u.	$\nabla^2\rho_{bcp}$(r), a.u.	ρ_{bcp} (r), a.u.	$\nabla^2\rho_{bcp}$(r), a.u.	ρ_{bcp} (r), a.u.	$\nabla^2\rho_{bcp}$(r), a.u.
C22-C34	0.3463	-1.0660	0.3472	-1.0420	0.3489	-1.0600	0.3474	-1.0470	0.3501	-1.0770
C22-H23	0.2899	-1.0460	0.2762	-0.9562	0.2764	-0.9596	0.2758	-0.9524	0.2776	-0.9694
C24-C25	0.2883	-1.0360	0.2762	-0.9565	0.2742	-0.9388	0.2772	-0.9677	0.2818	-0.9713
C24-C36	0.3473	-1.0710	0.3482	-1.0560	0.3467	-1.0350	0.3507	-1.0810	0.3498	-1.0700
C26-C30	0.3267	-0.9919	0.3203	-0.9586	0.3206	-0.9601	0.3205	-0.9583	0.3209	-0.9619
C27-C32	0.3242	-0.9815	0.3200	-0.9594	0.3196	-0.9440	0.3201	-0.9576	0.3197	-0.9510
C27-O4	0.3000	-0.6394	0.2948	-0.6432	0.2953	-0.6663	0.2948	-0.6489	0.2948	-0.6559
C28-O5	0.4143	-0.2675	0.4078	-0.3170	0.4078	-0.3187	0.4077	-0.3235	0.4082	-0.3262
C29-C36	0.2806	-0.7786	0.2721	-0.7501	0.2731	-0.7611	0.2706	-0.7328	0.2708	-0.7366
C30-H31	0.2870	-1.0260	0.2742	-0.9451	0.2746	-0.9477	0.2741	-0.9441	0.2749	-0.9502
C32-H33	0.2872	-1.0280	0.2748	-0.9495	0.2751	-0.9472	0.2745	-0.9475	0.2745	-0.9483
C34-C28	0.2841	-0.7991	0.2723	-0.7556	0.2722	-0.7478	0.2717	-0.7469	0.2703	-0.7293
C34-H35	0.2859	-1.0120	0.2720	-0.9279	0.2733	-0.9361	0.2722	-0.9279	0.2772	-0.9367
C36-H37	0.2871	-1.0200	0.2721	-0.9254	0.2729	-0.9386	0.2748	-0.9445	0.2756	-0.9575
C38-H39	0.2899	-1.0470	0.2714	-0.9331	0.2714	-0.9326	0.2715	-0.9334	0.2719	-0.9362
C38-H40	0.2853	-1.0100	0.2721	-0.9180	0.2745	-0.9301	0.2728	-0.9238	0.2714	-0.9115
C38-H41	0.2853	-1.0100	0.2724	-0.9217	0.2717	-0.9135	0.2722	-0.9195	0.2745	-0.9279
C42-H43	0.2898	-1.0460	0.2715	-0.9338	0.2715	-0.9343	0.2714	-0.9332	0.2718	-0.9352
C42-H44	0.2851	-1.0090	0.2726	-0.9228	0.2723	-0.9195	0.2727	-0.9231	0.2745	-0.9259
C42-H45	0.2852	-1.0090	0.2718	-0.9148	0.2729	-0.9206	0.2721	-0.9179	0.2725	-0.9213

Table S-XIV. HUMO-LUMO band gap and dipole moments of curcumin in the gas phase and that lifted from the active site of TMPRSS2 (IIa), ACE2 (IIb), 3CLpro (IIc) and PLpro (IId)

Structure	I	IIa	IIb	IIc	IId
HOMO-LUMO band gap, eV	3.699	4.367	4.392	3.714	4.058
μ_x , D	-0.632	2.574	0.317	0.328	1.725
μ_y , D	-1.058	-1.003	-1.547	-0.036	2.033
μ_z, D	0.355	-0.044	0.412	-1.711	0.218
μ, D	3.26	7.022	4.147	4.429	6.8

μ_x, μ_y and μ_z are the dipole moments in x, y, and z-directions whereas μ represents the resultant dipole moment