Conformations and three-dimensional structures of selected SARS-CoV-2 drug candidates.

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Abstract

Quantum mechanical theories are used to search and optimize the conformations of proposed small molecule candidates for treatment of SARS-CoV-2. These candidate compounds are taken from what is reported in the news and in other pre-peer-reviewed literature (e.g. ChemRxiv, bioRxiv). The goal herein is to provide predicted structures and relative conformational stabilities for selected drugs and ligands, in the hopes that other research groups can make use of them for developing a treatment. The following six compounds are investigated: **chloroquine**, **hydroxychloroquine**, **remdesivir**, **eriodictyol**, **silmitasertib** and **valproic acid**.

Initial exploration for conformations are performed at the HF/6-31G(d)//HF/6-31G(d) theory level, which are then further optimized at more rigorous theory levels (e.g. B97-D3(BJ)/cc-pVTZ//B97-D3(BJ)/cc-pVTZ). The resulting structures are made available via GitHub.

Please note that we are not advocating that the compounds focused herein should be used as medical treatments for the SARS-CoV-2. Instead we are simply providing predicted conformations and relative energies of compounds that can be used for further research purposes.

1 Introduction

Across the world researchers are focused upon finding a drug treatment for the Coronavirus Disease-2019 (SARS-CoV-2). Logically, much of the focus is repurposing approved drugs, followed by those that are in drug development pipeline. Repurposing drugs is a much quicker endeavor than discovering new ones since their chemical optimization, toxicology profiling, clinical trials and bulk manufacturing are already in place [1]. Several research groups have already proposed possible candidates for testing [2–7]. The results of this testing could provide a spectrum of outcomes - ranging from a compound that show high promise for use in patient treatment to very little activity. However, hindering some our understanding will be the lack of three-dimensional (3D) knowledge of the drugs' structures and their conformations.

Promiscuity underlies the concept of drug repurposing [8–13]. A promiscuous drug (i.e. ligand) implies that it is structurally and chemically complementary to several receptor, while a promiscuous receptor implies that several ligands possess high similarity. Limiting our ability to exploit ligand similarity for repurposing are the difficulties to experimentally elucidate or theoretically predict 3D conformations and their electrostatic profiles. This difficulty arises from the dynamic nature of molecules and their complex multidimensional potential energy surface [14]. Affirming this is the fact that only a fraction of the 1634 approved small-molecule drugs [15] have *a single* 3D conformation resolved.

Herein, the 3D structures of the top candidates for SARS-CoV-2 treatment are computed using quantum mechanical (QM) theories, starting with chloroquine since it is already being tested in hospitals and proceeding to other approved drugs according to Table 1 in reference [4]. An semi-extensive conformational search is performed for each molecule in hopes that the low energy conformations are well represented. Since this work is ongoing, we provide the coordinates of the conformations via GitHub (https://github.com/karlkirschner/SARS-CoV-2-3D-Structures) to allow other researchers immediate access to the data.

Partial Atomic Charges While not the current focus, partial atomic charges for these structures can also be determined relatively quickly using the AM1-BCC or RESP methodologies. If you would like to have partial atomic charges computed for a certain compound (e.g. for use in MD simulation, docking, similarity calculations) please contact the corresponding author (KNK).

2 Methodology

Initial structures were obtained from the Protein Data Bank [16] when and experimentally determined geometry is available, or from ChemPub [17]. Full geometry optimizations were performed at the HF/6-31G(d)//HF/6-31G(d) theory level. Optimizations at more rigorous theory levels will be performed (e.g. B97-D3(BJ)/cc-pVTZ and MP2/cc-pVTZ) as time allows. The B97-D3(BJ) [18–20] is believed to be a fairly reliable density functional approximation (i.e. GGA+dispersion) for computing geometries [21] and energetics [22]. Frequencies calculations were performed on selected minima using finite-differences of gradients at the same theory level reported for the relative energies.

Initial 3D structure generation:

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- chloroquine [23] (model building): 2 configurational stereoisomer
- hydroxychloroquine (model building using chloroquine's results): 2 configurational stereoisomer
- remdesivir [24] (model building): single topology
- eriodictyol [**?**] (initial structure: ERD X-ray): 2 envelope conformations
- silmitasertib [25] (initial structure: 3NGA X-ray): single topology
- valproic acid [26]: (initial structure: 1DIT X-ray): single topology

All QM calculations were done using Psi4 (v. 1.1a2.dev170) [27]. Figures were created using PyMol [28], Python3, Matplotlib [29] and Inkscape.

3 Results and Discussion

The HF/6-31G(d)//HF/6-31G(d) theory level performs fairly well for generating optimized geometries and is relatively inexpensive with regards to computational cost. The use of this theory allows for a quick survey of the possible conformations that a given molecule might have. However, past experience has shown that it often over predicts the number of minima in comparison to an electron-correlated theory level using a larger basis set (e.g. B97-D3(BJ)/cc-pVTZ, MP2/cc-pVTZ). Due to the quick need of structural data, a majority of the initial calculations were done at HF/6-31G(d)//HF/6-31G(d) theory level.However, optimizations are continually being completed at more rigorous theory levels. Once completed and made available, these geometries should preferentially be considered.

All currently optimized geometries can be obtained following the GitHub link mentioned in the Introduction. Each xyz-formatted file contains all of the optimized conformations, ordered from most- to least-stable conformation.

The relative energies for a given molecule (and isomer when relevant) are provided in Tables 1–4. Concerning relative stability of the conformations, HF/6-31G(d)//HF/6-31G(d) is able to provide a very general ordering of the predicted relative energies. However, including electron correlation into the calculations with at least a triple-zeta basis set is required for more reliable predictions of relative energies. As time allows, more refined optimizations will be performed using more rigorous theory levels (e.g. B97-D3(BJ)/cc-pVTZ). The tables within the body of the manuscript represent the most rigorous theory levels currently computed, while the SI material will contain data computed at lower theory levels.

It should be noted that these geometries and relative energies are computed in the gas-phase at a temperature that is considered to be 0 K. Consequently, these results cannot be directly transferred to how the compounds behave at body temperature and under physiological conditions. There are other theoretical methods that are better for considering what conformations ligand adopt upon interacting with binding sites, for example molecular dynamics (MD) calculations. Never-the-less, the results herein provide a starting point for understanding their possible conformational space, incorporating these compounds into MD models and correlating their 3D structures to other observables (e.g. similarity calculations).

Chloroquine Chloroquine and its close analogue hydroxychloroquine has been mentioned in the news frequently as a possible drug to repurpose for treating coronavirus patients. However, several studies have shown that these drugs can cause dangerous heart rhythm, resulting in the U.S Food and Drug Administration issuing a warning [30, 31].

Chloroquine and hydroxychloroquine have an stereogenic sp^3 carbon atom in a central location of the molecules (Figure 1). It is unclear in our survey of the literature if it is known which stereoisomer is the preferentially active one, or if both are. Consequently, both stereoisomers were investigated, with B97-D3(BJ)/cc-pVTZ identifying over 100 unique stationary points for each isomer whose relative energies range up to 16.5 kcal·mol^{-1} (Tables 1 and 2). Only three and two conformations of chloroquine isomers 1 and 2 possessed relative energies below 2.0 kcal·mol^{-1}.

Hydroxychloroquine Isomer1 This drug is highly flexible and it is likely that a near complete identification of possible conformations was not made. Never-the-less, 265 unique conformations were optimized at the B97-D3(BJ)/cc-pVTZ theory level. In addition to the intramolecular hydrogen bond that is formed between the acyclic nitrogens (as found in chloroquine, see Figure 1a and b), this theory level predicts that the unique terminal hydroxyl group forms an intramolecular interaction with the conjugated rings system (e.g. conformer 1).

Eriodictyol Eriodictyol wsa suggested by Smith and Smith as an interfatial inhibitor between the virus S-protein and human ACE2 receptor [6]. Eriodictyol's conformations are predominately determined by a rotatable bond that connects the two ring systems, and by the envelope conformations adopted by the 4-chromanone residue. These envelope conformations result in either an overall bent structure (e.g. conformer 1, ΔE=0.000 kcal·mol^{-1}) or a more linear structure (e.g. conformer 2, ΔE=0.035 kcal·mol^{-1}; Figure 1f). The final factor that determines the conformations are the hydroxyl orientiations. A total of 49 stationary points were identified at the B97-D3(BJ)/cc-pVTZ theory level, with 16 minima being below a relative energy of 1.2 kcal·mol^{-1} (Tables 4). This likely implies that this conformation is highly flexible under physiological conditions and could easily adopt its conformation to the topology of the binding sites that it interacts with.

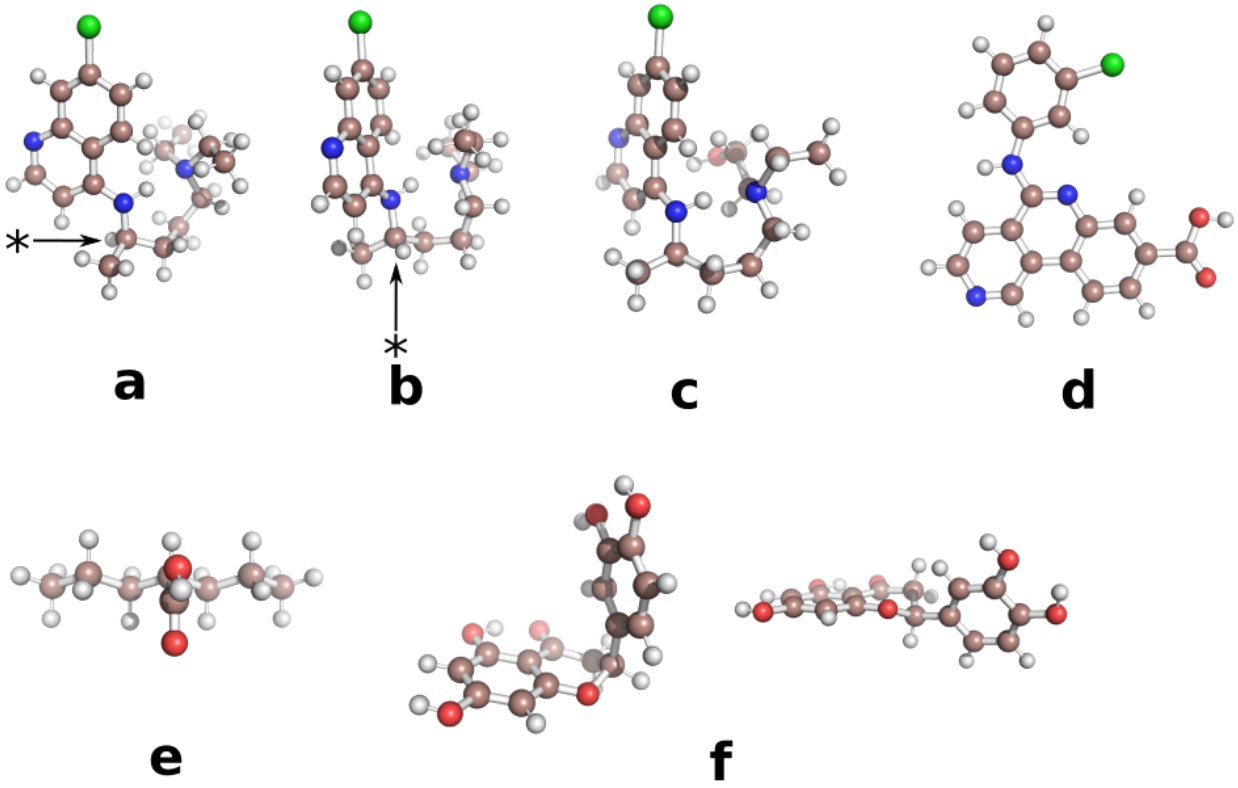

Figure 1: Geometries of the most stable minima identified using B97-D3(BJ)/cc-pVTZ//B97-D3(BJ)/cc-pVTZ for a) Chloroquine isomer 1 (*: stereocenter) b) Chloroquine isomer 2 (*: stereocenter), c) Silmitasertib, d) Valproic acid and e) the two lowest energy conformers of eriodictyol, each representing one of the possible envelope conformations.

Table 1: Chloroquine isomer 1's relative energies (kcal·mol^{-1}) computed at B97-D3(BJ)/cc-pVTZ//B97-D3(BJ)/cc-pVTZ theory level.

Conf.	ΔE	Conf.	ΔE	Conf.	ΔE
1	0.000[a]	35	8.627	69	10.719
2	1.560[a]	36	8.627	70	10.785
3	1.958[a]	37	8.638	71	10.901
4	2.085[a]	38	8.646	72	10.990
5	3.697	39	8.797	73	11.031
6	4.339	40	8.868	74	11.094
7	4.358	41	9.059	75	11.126
8	4.918	42	9.115	76	11.158
9	5.566	43	9.150	77	11.177
10	5.911	44	9.168	78	11.240
11	6.339	45	9.168	79	11.286
12	6.863	46	9.172	80	11.460
13	7.142	47	9.201	81	11.527
14	7.253	48	9.245	82	11.594
15	7.303	49	9.274	83	11.905
16	7.370	50	9.303	84	11.927
17	7.448	51	9.309	85	11.964
18	7.534	52	9.429	86	11.964
19	7.557	53	9.531	87	11.991
20	7.603	54	9.583	88	12.043
21	7.639	55	9.594	89	12.075
22	7.752	56	9.611	90	12.079
23	7.779	57	9.655	91	12.084
24	7.866	58	10.003	92	12.138
25	7.961	59	10.068	93	12.381
26	8.049	60	10.153	94	12.656
27	8.147	61	10.156	95	13.011
28	8.217	62	10.200	96	13.162
29	8.279	63	10.226	97	13.308
30	8.347	64	10.231	98	13.417
31	8.348	65	10.301	99	13.590
32	8.408	66	10.403	100	13.957
33	8.421	67	10.411	101	14.119
34	8.536	68	10.423	102	14.490

[a] Frequency analysis confirms that this conformer is a minimum on the potential energy surface.

Table 2: Chloroquine isomer 2's relative energies (kcal·mol^{-1}) computed at B97-D3(BJ)/cc-pVTZ//B97-D3(BJ)/cc-pVTZ theory level.

Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE
1	0.000[a]	20	6.489	39	7.740	58	9.072	76	9.913	94	11.440
2	1.048[a]	21	6.606	40	8.117	59	9.072	77	9.929	95	11.560
3	2.759	22	6.630	41	8.166	60	9.088	78	9.939	96	11.576
4	2.906	23	6.693	42	8.220	61	9.093	79	9.978	97	11.710
5	4.508	24	6.844	43	8.265	62	9.102	80	10.050	98	11.805
6	5.069	25	6.913	44	8.318	63	9.176	81	10.061	99	12.021
7	5.241	26	6.922	45	8.320	64	9.229	82	10.190	100	12.041
8	5.283	27	6.927	46	8.383	65	9.266	83	10.233	101	12.097
9	5.670	28	7.026	47	8.460	66	9.296	84	10.506	102	12.298
10	5.797	29	7.035	48	8.476	67	9.365	85	10.553	103	12.402
11	5.820	30	7.042	49	8.498	68	9.368	86	10.614	104	12.538
12	5.823	31	7.250	50	8.560	69	9.459	87	10.870	105	12.618
13	5.875	32	7.250	51	8.570	70	9.535	88	10.873	106	12.637
14	5.891	33	7.262	52	8.626	71	9.549	89	10.909	107	13.027
15	5.897	34	7.446	53	8.719	72	9.561	90	10.929	108	13.449
16	5.975	35	7.498	54	8.797	73	9.578	91	11.021	109	13.523
17	6.456	36	7.540	55	9.011	74	9.718	92	11.133	110	15.352
18	6.461	37	7.599	56	9.025	75	9.795	93	11.191	111	16.435
19	6.462	38	7.692	57	9.072						

[a] Frequency analysis confirms that this conformer is a minimum on the potential energy surface.

Table 3: Hydrochloroquine isomer 1's relative energies (kcal·mol^{-1}) computed at B97-D3(BJ)/cc-pVTZ//B97-D3(BJ)/cc-pVTZ theory level.

Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE
1	0.000	46	6.271	90	8.027	134	9.353	178	10.535	222	11.849
2	0.400	47	6.315	91	8.043	135	9.373	179	10.544	223	11.863
3	0.988	48	6.325	92	8.052	136	9.394	180	10.595	224	11.900
4	1.440	49	6.381	93	8.063	137	9.395	181	10.618	225	12.072
5	1.603	50	6.426	94	8.083	138	9.401	182	10.740	226	12.134
6	2.162	51	6.477	95	8.105	139	9.413	183	10.770	227	12.166
7	2.165	52	6.571	96	8.118	140	9.517	184	10.779	228	12.192
8	2.213	53	6.610	97	8.136	141	9.525	185	10.810	229	12.222
9	2.320	54	6.634	98	8.170	142	9.548	186	10.872	230	12.236
10	2.431	55	6.644	99	8.196	143	9.591	187	10.878	231	12.261
11	2.448	56	6.665	100	8.264	144	9.622	188	10.901	232	12.276
12	2.615	57	6.733	101	8.334	145	9.655	189	10.938	233	12.353
13	2.681	58	6.748	102	8.372	146	9.740	190	10.954	234	12.367
14	2.707	59	6.853	103	8.398	147	9.745	191	10.958	235	12.371
15	2.858	60	6.856	104	8.416	148	9.786	192	10.963	236	12.376
16	3.105	61	6.986	105	8.422	149	9.791	193	10.969	237	12.413
17	3.357	62	7.151	106	8.447	150	9.792	194	11.006	238	12.465
18	3.499	63	7.191	107	8.596	151	9.820	195	11.040	239	12.533
19	3.508	64	7.250	108	8.609	152	9.833	196	11.072	240	12.580
20	3.768	65	7.284	109	8.641	153	9.836	197	11.118	241	12.607
21	3.844	66	7.296	110	8.680	154	9.874	198	11.176	242	12.785
22	3.845	67	7.297	111	8.680	155	9.884	199	11.176	243	12.868
23	3.848	68	7.418	112	8.710	156	9.891	200	11.209	244	12.904
24	3.888	69	7.419	113	8.725	157	9.907	201	11.221	245	12.911
25	3.952	70	7.473	114	8.806	158	10.005	202	11.249	246	12.975
26	4.057	71	7.473	115	8.822	159	10.021	203	11.253	247	13.129
27	4.263	72	7.505	116	8.839	160	10.033	204	11.255	248	13.169
28	4.334	73	7.507	117	8.863	161	10.051	205	11.274	249	13.199
29	4.356	74	7.542	118	8.873	162	10.052	206	11.282	250	13.283
30	4.411	75	7.590	119	8.877	163	10.075	207	11.330	251	13.322
31	4.453	76	7.592	120	8.907	164	10.085	208	11.338	252	13.414
32	4.794	77	7.593	121	8.973	165	10.107	209	11.352	253	13.428
33	5.024	78	7.675	122	8.980	166	10.142	210	11.372	254	13.482
34	5.228	79	7.736	123	9.010	167	10.149	211	11.390	255	13.537
35	5.298	80	7.749	124	9.046	168	10.294	212	11.414	256	13.721
36	5.337	81	7.752	125	9.067	169	10.297	213	11.440	257	13.771
37	5.475	82	7.763	126	9.105	170	10.320	214	11.523	258	13.802
38	5.743	83	7.775	127	9.136	171	10.331	215	11.534	259	13.907
39	5.771	84	7.819	128	9.172	172	10.335	216	11.541	260	13.956
40	5.862	85	7.859	129	9.273	173	10.463	217	11.630	261	14.359
41	5.887	86	7.868	130	9.277	174	10.468	218	11.641	262	14.416
42	5.938	87	7.880	131	9.299	175	10.494	219	11.688	263	14.629
43	6.034	88	7.962	132	9.308	176	10.505	220	11.696	264	14.660
44	6.114	89	7.994	133	9.353	177	10.529	221	11.826	265	14.826
45	6.183										

[a] Frequency analysis confirms that this conformer is a minimum on the potential energy surface.

Table 4: Eriodictyol relative energies (kcal·mol^{-1}) computed at B97-D3(BJ)/cc-pVTZ//B97-D3(BJ)/cc-pVTZ theory level.

1	0.000[a]	10	0.522[a]	18	3.565	26	13.786	34	14.555	42	17.254
2	0.035[a]	11	0.557[a]	19	3.626	27	13.904	35	14.631	43	17.337
3	0.175[a]	12	0.692[a]	20	3.828	28	13.968	36	14.669	44	17.626
4	0.213[a]	13	0.739[a]	21	3.900	29	13.998	37	14.698	45	17.665
5	0.284[a]	14	0.777[a]	22	3.966	30	14.128	38	14.820	46	17.864
6	0.340[a]	15	0.805[a]	23	3.975	31	14.147	39	14.897	47	17.915
7	0.355[a]	16	1.116[a]	24	4.233	32	14.185	40	15.238	48	18.192
8	0.407[a]	17	3.536	25	13.245	33	14.419	41	16.999	49	18.312
9	0.514[a]										

[a] Frequency analysis confirms that this conformer is a minimum on the potential energy surface.

Table 5: Silmitasertib relative energies (kcal·mol^{-1}) computed at B97-D3(BJ)/cc-pVTZ//B97-D3(BJ)/cc-pVTZ theory level.

Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE
1	0.000[a]	8	1.749[a]	15	5.942	21	6.749
2	0.247[a]	9	1.749[a]	16	6.588	22	7.324
3	0.431[a]	10	1.904[a]	17	6.588	23	7.324
4	1.521[a]	11	1.904[a]	18	6.712	24	7.489
5	1.521[a]	12	5.384	19	6.712	25	7.489
6	1.657[a]	13	5.384	20	6.749	26	7.520
7	1.657	14	5.942				

[a] Frequency analysis confirms that this conformer is a minimum on the potential energy surface.

Table 6: Valproic acid relative energies (kcal·mol^{-1}) computed at B97-D3(BJ)/cc-pVTZ//B97-D3(BJ)/cc-pVTZ theory level.

Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE
1	0.000[a]	29	1.534[a]	57	2.289	85	3.061	113	3.398	141	4.450
2	0.206[a]	30	1.534[a]	58	2.289	86	3.082	114	3.537	142	4.450
3	0.206[a]	31	1.561[a]	59	2.328	87	3.102	115	3.573	143	4.597
4	0.427[a]	32	1.561[a]	60	2.328	88	3.102	116	3.573	144	4.597
5	0.587[a]	33	1.571[a]	61	2.388	89	3.138	117	3.582	145	4.710
6	0.643[a]	34	1.571[a]	62	2.450	90	3.138	118	3.582	146	4.710
7	0.643[a]	35	1.604[a]	63	2.450	91	3.149	119	3.583	147	4.956
8	0.680[a]	36	1.604[a]	64	2.498	92	3.149	120	3.608	148	4.956
9	0.680[a]	37	1.622[a]	65	2.498	93	3.198	121	3.608	149	5.021
10	0.729[a]	38	1.622[a]	66	2.527	94	3.198	122	3.618	150	5.021
11	0.789[a]	39	1.679[a]	67	2.527	95	3.202	123	3.762	151	5.095
12	0.789[a]	40	1.679[a]	68	2.532	96	3.202	124	3.762	152	5.095
13	0.934[a]	41	1.681[a]	69	2.532	97	3.205	125	3.925	153	5.144
14	0.934[a]	42	1.681[a]	70	2.574	98	3.205	126	3.925	154	5.144
15	1.010[a]	43	1.724[a]	71	2.601	99	3.208	127	4.079	155	5.187
16	1.010[a]	44	1.724[a]	72	2.601	100	3.233	128	4.079	156	5.187
17	1.113[a]	45	1.777[a]	73	2.603	101	3.238	129	4.131	157	5.225
18	1.113[a]	46	1.777[a]	74	2.780	102	3.256	130	4.131	158	5.225
19	1.166[a]	47	1.835[a]	75	2.780	103	3.256	131	4.194	159	5.435
20	1.166[a]	48	1.835[a]	76	2.806	104	3.328	132	4.194	160	5.435
21	1.197[a]	49	1.857[a]	77	2.806	105	3.328	133	4.198	161	5.594
22	1.197[a]	50	1.857[a]	78	2.826	106	3.340	134	4.198	162	5.594
23	1.315[a]	51	1.884[a]	79	2.826	107	3.340	135	4.382	163	6.072
24	1.315[a]	52	1.884[a]	80	2.840	108	3.341	136	4.382	164	6.072
25	1.344[a]	53	2.012	81	2.907	109	3.341	137	4.416	165	6.732
26	1.344[a]	54	2.012	82	2.958	110	3.353	138	4.416	166	6.934
27	1.404[a]	55	2.138	83	2.958	111	3.353	139	4.449	167	6.934
28	1.404[a]	56	2.138	84	3.000	112	3.353	140	4.449		

[a] Frequency analysis confirms that this conformer is a minimum on the potential energy surface.

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4 Supplementary Information

Note that the conformation numbers reported in the following supplementary tables do not correspond to the same numbered conformations reported in the Results and Discussion sections. This is do to a) the fact that the conformations can change when optimized at different theory level, and b) the lowest energy conformation can also change.

Table S1: Chloroquine isomer 1's relative energies (kcal·mol^{-1}) computed at HF/6-31G(d)//HF/6-31G(d) theory level.

Conf.	ΔE	Conf.	ΔE	Conf.	ΔE
1	0.000	40	5.293	79	8.023
2	0.585	41	5.413	80	8.113
3	0.643	42	5.726	81	8.115
4	0.837	43	5.730	82	8.303
5	1.261	44	5.735	83	8.403
6	1.324	45	5.781	84	8.459
7	1.436	46	5.810	85	8.501
8	1.790	47	5.923	86	8.691
9	1.961	48	5.936	87	8.725
10	2.256	49	5.947	88	8.794
11	2.613	50	6.009	89	8.845
12	2.707	51	6.016	90	8.900
13	2.764	52	6.111	91	8.921
14	3.238	53	6.155	92	8.923
15	3.416	54	6.201	93	9.028
16	3.481	55	6.268	94	9.065
17	3.518	56	6.483	95	9.097
18	3.906	57	6.568	96	9.198
19	4.006	58	6.648	97	9.221
20	4.114	59	6.650	98	9.364
21	4.167	60	6.678	99	9.703
22	4.393	61	6.692	100	10.016
23	4.429	62	6.754	101	10.020
24	4.466	63	6.881	102	10.307
25	4.589	64	6.922	103	10.633
26	4.622	65	7.075	104	10.634
27	4.643	66	7.093	105	10.765
28	4.652	67	7.164	106	10.817
29	4.656	68	7.205	107	11.006
30	4.858	69	7.208	108	11.069
31	4.870	70	7.308	109	11.359
32	4.909	71	7.358	110	11.497
33	4.935	72	7.472	111	11.529
34	5.077	73	7.494	112	11.870
35	5.146	74	7.498	113	11.901
36	5.156	75	7.505	114	13.385
37	5.244	76	7.793	115	13.643
38	5.262	77	7.942	116	13.989
39	5.277	78	8.002		

Table S2: Chloroquine isomer 2's relative energies (kcal·mol^{-1}) computed at HF/6-31G(d)//HF/6-31G(d) theory level.

Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE
1	0.000	20	2.398	39	3.966	58	4.882	76	5.973	94	8.504
2	0.529	21	2.570	40	3.975	59	4.917	77	6.222	95	8.610
3	0.653	22	2.647	41	3.995	60	4.977	78	6.237	96	8.630
4	0.911	23	2.668	42	3.998	61	5.013	79	6.377	97	8.711
5	0.970	24	2.682	43	4.031	62	5.184	80	6.468	98	8.838
6	1.197	25	2.809	44	4.075	63	5.195	81	6.589	99	8.862
7	1.260	26	2.919	45	4.092	64	5.237	82	6.679	100	8.897
8	1.263	27	2.973	46	4.203	65	5.248	83	6.947	101	8.944
9	1.282	28	3.100	47	4.317	66	5.333	84	7.064	102	8.993
10	1.337	29	3.105	48	4.365	67	5.431	85	7.065	103	9.032
11	1.415	30	3.113	49	4.373	68	5.560	86	7.354	104	9.280
12	1.468	31	3.279	50	4.469	69	5.593	87	7.387	105	9.327
13	1.549	32	3.338	51	4.470	70	5.642	88	7.432	106	10.234
14	1.670	33	3.371	52	4.492	71	5.697	89	7.486	107	10.297
15	1.841	34	3.461	53	4.507	72	5.816	90	7.782	108	10.582
16	2.057	35	3.570	54	4.512	73	5.841	91	7.824	109	10.868
17	2.163	36	3.664	55	4.735	74	5.930	92	8.042	110	11.805
18	2.294	37	3.857	56	4.798	75	5.961	93	8.415	111	12.530
19	2.309	38	3.861	57	4.808						