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.

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-D3BJ/cc-pVTZ//B97-D3BJ/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.

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.

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-D3BJ/cc-pVTZ and MP2/cc-pVTZ) as time allows.

Molecules studied:

- chloroquine [18] (model building): 2 configurational stereoisomer
- silmitasertib [19] (initial structure: 3NGA X-ray): single topology
- valproic acid [20]: (initial structure: 1DIT X-ray): single topology

All QM calculations were done using Psi4 (v. 1.1a2.dev170) [21]. Figures were created using PyMol [22], Python3, Matplotlib [23] and Inkscape.

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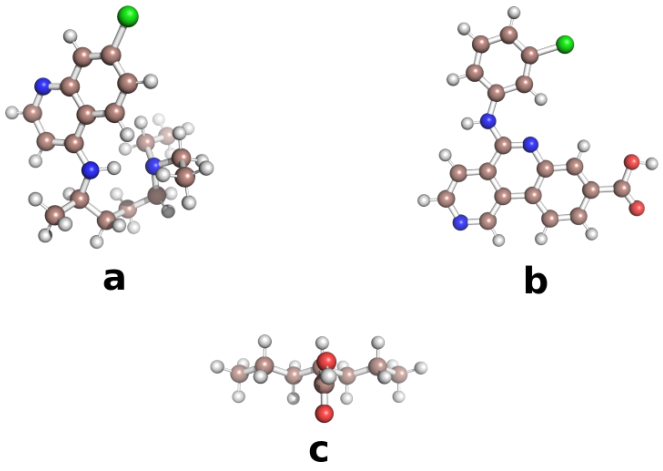

Figure 1: Geometries of the most stable minima identified using B97-D3BJ/cc-pVTZ//B97-D3BJ/cc-pVTZ for a) Chloroquine isomer 1 b) Silmitasertib and c) Valproic acid.

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 preview 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 and larger basis set (e.g. B97-D3BJ/cc-pVTZ, MP2/cc-pVTZ). Due to the quick need of structural data, a majority of the initial calculations will be done at HF/6-31G(d)//HF/6-31G(d) theory level. The resulting structures should be an adequate starting point for our initial understanding of how structure might influence the activity observed experimentally. Alternatively, these structures can also be used for computational docking studies and for building molecular dynamics models if desired. However, optimizations are continually being completed at higher theory levels. When these are completed, 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-D3BJ/cc-pVTZ, MP2/cc-pVTZ). The tables within the body of the manuscript represent the most rigorous theory levels currently computed.

Upon request, partial atomic charges for these structures can also be determined relatively quickly using the AM1-BCC or RESP methodologies.

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Table 1: Chloroquine isomer 1's relative energies (kcal·mol^{-1}) computed at B97-D3BJ/cc-pVTZ//B97-D3BJ/cc-pVTZ theory level.

Conf.	ΔE	Conf.	ΔE	Conf.	ΔE
1	0.000	35	8.627	69	10.719
2	1.560	36	8.627	70	10.785
3	1.958	37	8.638	71	10.901
4	2.085	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

Table 2: 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						

Table 3: Silmitasertib relative energies (kcal·mol^{-1}) computed at B97-D3BJ/cc-pVTZ//B97-D3BJ/cc-pVTZ theory level.

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

Table 4: Valproic acid relative energies (kcal·mol^{-1}) computed at B97-D3BJ/cc-pVTZ//B97-D3BJ/cc-pVTZ theory level.

Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE	Conf.	ΔE
1	0.000	30	1.534	59	2.289	88	3.061	117	3.537	146	4.597
2	0.206	31	1.534	60	2.328	89	3.082	118	3.573	147	4.597
3	0.206	32	1.561	61	2.328	90	3.102	119	3.573	148	4.710
4	0.427	33	1.561	62	2.328	91	3.102	120	3.582	149	4.710
5	0.587	34	1.571	63	2.328	92	3.138	121	3.582	150	4.956
6	0.643	35	1.571	64	2.388	93	3.138	122	3.583	151	4.956
7	0.643	36	1.604	65	2.450	94	3.149	123	3.608	152	5.021
8	0.680	37	1.604	66	2.450	95	3.149	124	3.608	153	5.021
9	0.680	38	1.622	67	2.498	96	3.198	125	3.618	154	5.095
10	0.729	39	1.622	68	2.498	97	3.198	126	3.762	155	5.095
11	0.789	40	1.679	69	2.527	98	3.202	127	3.762	156	5.144
12	0.789	41	1.679	70	2.527	99	3.202	128	3.925	157	5.144
13	0.934	42	1.681	71	2.532	100	3.205	129	3.925	158	5.187
14	0.934	43	1.681	72	2.532	101	3.205	130	4.079	159	5.187
15	1.010	44	1.724	73	2.574	102	3.208	131	4.079	160	5.225
16	1.010	45	1.724	74	2.601	103	3.233	132	4.131	161	5.225
17	1.113	46	1.777	75	2.601	104	3.238	133	4.131	162	5.435
18	1.113	47	1.777	76	2.603	105	3.256	134	4.194	163	5.435
19	1.166	48	1.835	77	2.780	106	3.256	135	4.194	164	5.594
20	1.166	49	1.835	78	2.780	107	3.328	136	4.198	165	5.594
21	1.197	50	1.857	79	2.806	108	3.328	137	4.198	166	6.072
22	1.197	51	1.857	80	2.806	109	3.340	138	4.382	167	6.072
23	1.197	52	1.884	81	2.826	110	3.340	139	4.382	168	6.732
24	1.315	53	1.884	82	2.826	111	3.341	140	4.416	169	6.934
25	1.315	54	2.012	83	2.840	112	3.341	141	4.416	170	6.934
26	1.344	55	2.012	84	2.907	113	3.353	142	4.449		
27	1.344	56	2.138	85	2.958	114	3.353	143	4.449		
28	1.404	57	2.138	86	2.958	115	3.353	144	4.450		
29	1.404	58	2.289	87	3.000	116	3.398	145	4.450		

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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		