SUPPORTING INFORMATION

Assessing hERG1 Blockade from Bayesian Machine Learning Optimized Site-Identification by Ligand Competitive Saturation (SILCS) Simulations

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Table S1. Fifty-five blockers from the MICE model to perform a proof-of-principle assessment of the ability of SILCS-Method are listed as below. The |LGFE| score for neutral, charged, and HH-Weighted compounds in S1 and S2 are provided. Glide |Gscore| of compounds for neutral, charged, and HH-Weighted states are listed.

			SILCS |LGFE|-S1 (kcal/mol)-Original ACS 2018			SILCS |LGFE|-S2 (kcal/mol)-Original ACS 2018			SILCS |LGFE|-S1 (kcal/mol)-BML Optimized ACS			SILCS |LGFE|-S2 (kcal/mol)-BML Optimized ACS			Glide |Gscore| (kcal/mol)		
#	Drug	pIC50	Neutral	Charged	HH-Weighted	Neutral	Charged	HH-Weighted	Neutral	Charged	HH-Weighted	Neutral	Charged	HH-Weighted	Neutral	Charged	HH-Weighted
1	amiodarone	**6.07**	6.76	7.94	7.85	6.5	6.11	6.14	5.94	7.05	6.96	5.40	5.40	5.40	6.18	6.18	6.18
2	astemizole	**8.40**	7.52	9.12	9.05	6.54	7.43	7.39	6.84	8.74	8.66	6.22	7.34	7.29	6.22	6.22	6.22
3	bepridil	**6.80**	6.11	7.22	7.2	5.84	6.57	6.55	5.74	6.97	6.95	5.28	5.97	5.96	5.37	5.37	5.37
4	ceftriaxone	**3.35**	8.77	9.91	8.77	8.36	8.84	8.36	6.78	7.70	6.78	3.75	4.25	3.75	6.03		6.03
5	chlorpromazine	**5.82**	4.65	5.1	5.09	4.21	4.59	4.59	4.42	5.24	5.22	3.75	4.25	4.24	5.79	5.79	5.79
6	cilostazol	**4.86**	8.12		8.12	7.04		7.04	6.76		6.76	5.91		5.91	5.73		5.73
7	cisapride	**7.70**	7.32	7.7	7.65	7.17	7.44	7.4	6.70	6.14	6.21	6.33	6.45	6.44	7.63	7.63	7.63
8	Clozapine	**5.64**	5.3	5.17	5.24	4.76	4.68	4.72	4.80	4.97	4.88	4.00	4.32	4.15	5.97	5.97	5.97
9	Dasatinib	**4.61**	8.55	9.43	8.9	8.62	8.42	8.54	6.60	7.87	7.11	6.51	6.78	6.62	6.54	6.54	6.54
10	diazepam	**4.27**	4.19		4.19	3.42		3.42	4.29		4.28	3.32		3.32	5.28		5.28
11	diltiazem	**4.88**	5.66	6.64	6.5	5.35	5.29	5.3	4.94	6.20	6.02	4.81	4.99	4.97	4.74	4.74	4.74
12	disopyramide	**4.84**	6.21	6.26	6.26	5.17	5.44	5.44	5.67	5.95	5.95	4.80	5.10	5.10	3.35	3.35	3.35
13	dofetilide	**7.52**	6.18	6.77	6.76	5.54	5.67	5.67	5.66	6.04	6.03	4.96	5.28	5.27	5.30	5.30	5.30
14	donepezil	**6.15**	5.62	5.83	5.82	5.89	5.74	5.75	5.84	5.43	5.45	5.13	5.46	5.44	6.58	6.58	6.58
15	droperidol	**7.22**	6.55	11.3	7.42	6.29	7.18	6.46	6.23	10.65	7.04	5.47	6.41	5.64	6.61	6.63	6.61
16	duloxetine	**5.42**	5.05	6.16	6.15	4.95	4.92	4.92	5.08	6.15	6.15	4.84	4.97	4.97	5.01	4.96	4.96
17	flecainide	**5.82**	6.56	6.74	6.73	6.1	6.39	6.39	5.63	6.07	6.06	5.19	5.36	5.36	5.82	5.85	5.85
18	halofantrine	**6.42**	8.1	8.07	8.07	7.79	7.74	7.74	6.88	7.32	7.32	6.32	6.58	6.58	2.74	2.74	2.74
19	Haloperidol	**7.40**	6.68	6.94	6.9	6.63	7.01	6.94	5.99	6.25	6.20	5.44	5.87	5.79	6.33	6.33	6.33
20	Ibutilide	**7.74**	7.74	7.9	7.89	6.99	7.3	7.3	6.26	7.43	7.42	5.55	5.94	5.94	5.14	5.14	5.14
21	Lamivudine	**2.69**	6.45		6.45	5.26		5.26	4.51		4.51	3.83		3.83	5.61		5.61
22	Linezolid	**2.94**	6.67		6.67	5.63		5.63	5.23		5.23	4.40		4.40	5.04		5.04
23	Loratadine	**5.21**	5.96		5.95	6.05		6.04	5.57		5.57	5.65		5.64	5.65		5.65
24	Methadone	**5.46**	4.35	5.02	5.01	4.17	4	4	4.52	4.77	4.76	3.68	3.88	3.88	2.86	2.86	2.86
25	Metronidazole	**2.87**	4.98		4.98	4.25		4.25	3.35		3.35	2.78		2.78	3.42		3.42
26	Mibefradil	**5.77**	8.92	7.13	7.14	7.2	6.92	6.92	7.50	7.20	7.20	5.86	6.73	6.72	5.92	6.05	6.05
27	Mitoxantrone	**3.27**	10.83	11.3	11.29	9.42	9.33	9.33	6.74	7.63	7.62	6.50	6.50	6.50	6.12	6.13	6.13
28	Moxifloxacin	**4.06**	6.89	8.45	8.44	6.66	8.08	8.07	5.82	6.39	6.38	5.26	6.23	6.22	5.42	6.37	6.36

29	Nifedipine	**4.36**	4.94		4.89	4.91		4.87	4.35		4.31	3.99		3.95	5.24		5.19
30	Nilotinib	**6.00**	6.54		6.33	6.41		6.2	6.43		6.22	6.00		5.81	7.54		7.30
31	Nitrendipine	**4.61**	5.35		5.29	4.97		4.91	4.73		4.67	3.83		3.79	5.46		5.40
32	Paliperidone	**6.11**	8.22	8.33	8.32	6.97	8.04	8	6.66	6.48	6.49	5.41	6.66	6.61	7.91	7.91	7.91
33	Paroxetine	**5.72**	6.4	6.54	6.54	5.85	5.91	5.91	5.87	6.04	6.03	5.48	5.57	5.57	5.77	5.77	5.77
34	Pentobarbital	**2.84**	5.15	5.09	5.12	4.06	4.06	4.06	4.27	4.27	4.27	3.31	3.22	3.26	5.43	5.43	5.43
35	Phenytoin	**3.83**	4.59		4.59	3.82		3.82	4.63		4.63	3.74		3.74	5.29		5.29
36	Pimozide	**7.40**	6.94	10.89	10.51	5.9	7.52	7.37	6.71	10.23	9.90	5.93	6.85	6.76	6.80	6.79	6.79
37	Piperacillin	**2.47**	7.93	8.01	7.93	7.61	7.6	7.6	6.77	6.73	6.77	6.27	6.12	6.27	6.62	6.62	6.62
38	Procainamide	**3.56**	5.14	5.42	5.41	4.46	4.67	4.67	4.77	4.95	4.94	4.04	4.39	4.38	4.78	4.78	4.78
39	Quinidine	**6.14**	6.92	7.55	7.53	6.55	7.32	7.3	5.78	6.46	6.45	5.29	6.03	6.01	6.76	6.76	6.76
40	Raltegravir	**3.11**	7.99	7.86	7.99	7.75	7.33	7.75	6.29	6.35	6.29	5.75	5.78	5.75	6.19	6.19	6.19
41	Ribavirin	**3.01**	7.73		7.72	7.02		7.02	4.74		4.74	4.02		4.02	7.75		7.75
42	Risperidone	**6.59**	7.49	8.74	8.68	6.42	7.43	7.38	6.24	7.52	7.46	5.49	6.57	6.53	4.26	4.26	4.26
43	Saquinavir	**4.77**	10.29	10.74	10.7	9.94	10.79	10.72	9.13	9.48	9.45	9.34	9.42	9.41	8.87	8.87	8.87
44	sertindole	**7.48**	6.76	9.1	8.96	6.52	8.55	8.43	6.05	7.79	7.68	6.11	7.27	7.20	4.05	4.94	4.89
45	Sitagliptin	**3.76**	6.84	6.99	6.98	5.39	5.42	5.42	5.37	6.12	6.09	4.91	4.91	4.91	6.12	6.12	6.12
46	Solifenacin	**6.55**	6.75	7.02	7.01	5.78	5.47	5.48	6.54	6.52	6.52	5.44	5.26	5.26	6.30	6.30	6.30
47	Sotalol	**3.95**	5.85	6.79	6.78	5.41	5.55	5.55	4.78	5.57	5.56	4.17	4.13	4.13	5.45	5.45	5.45
48	Sparfloxacin	**4.66**	6.61	8.76	8.68	6.28	7.62	7.57	5.41	7.22	7.15	5.15	5.84	5.81	4.44	5.84	5.78
49	Sunitinib	**5.92**	6.84	7.39	7.38	6.93	7.16	7.16	5.94	6.39	6.38	5.76	5.94	5.94	4.31	4.31	4.31
50	Telbivudine	**3.37**	6.69		6.69	6.08		6.08	4.75		4.75	3.96		3.96	7.15		7.15
51	Terfenadine	**7.30**	9.15	9.29	9.28	8.05	8.29	8.29	7.35	8.28	8.26	6.94	7.06	7.06	7.17	7.15	7.15
52	terodiline	**6.19**	5.06	5.49	5.49	4.18	4.49	4.49	4.91	5.35	5.35	4.22	4.42	4.42	2.51	2.51	2.51
53	Thioridazine	**6.30**	5.79	6.04	6.03	5.38	5.34	5.34	5.53	6.13	6.11	4.82	5.00	4.99	4.75	4.75	4.75
54	Verapamil	**6.60**	7.27	7.9	7.89	7.06	6.78	6.79	6.03	7.13	7.12	5.86	6.12	6.12	5.87	5.87	5.87
55	Voriconazole	**3.31**	6.26		6.26	5.24		5.24	4.95		4.95	4.39		4.39	6.11		6.11

Top ten ranked Hotspots.

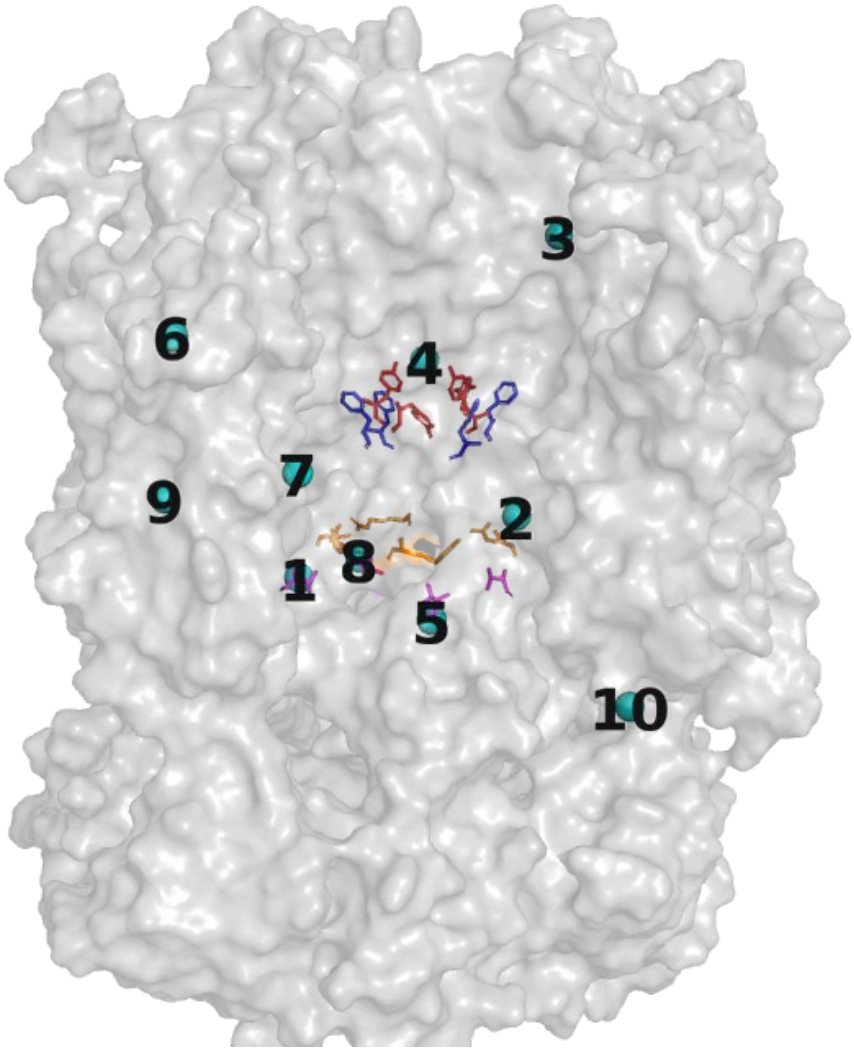

Figure S1. The top ten ranked hotspots are shown as cyan spheres with labels corresponding to their ranking. The protein is shown as a grey transparent surface with 656 and 675 residues shown as red and green sticks, respectively. The Y652, F656, R665, and T675 are shown as red, blue, orange, and magenta sticks, respectively

Protonated vs neutral state of Dofetilide.

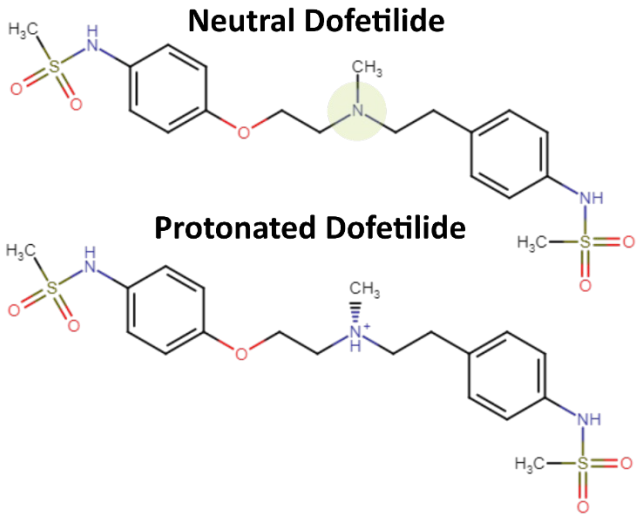

Figure S2. The neutral and protonated structures of dofetilide is shown as 2D stick representations. The ionizable nitrogen is highlighted in green in the neutral dofetilide representation.

Correlation analysis of SILCS |LGFE| for 163 compounds

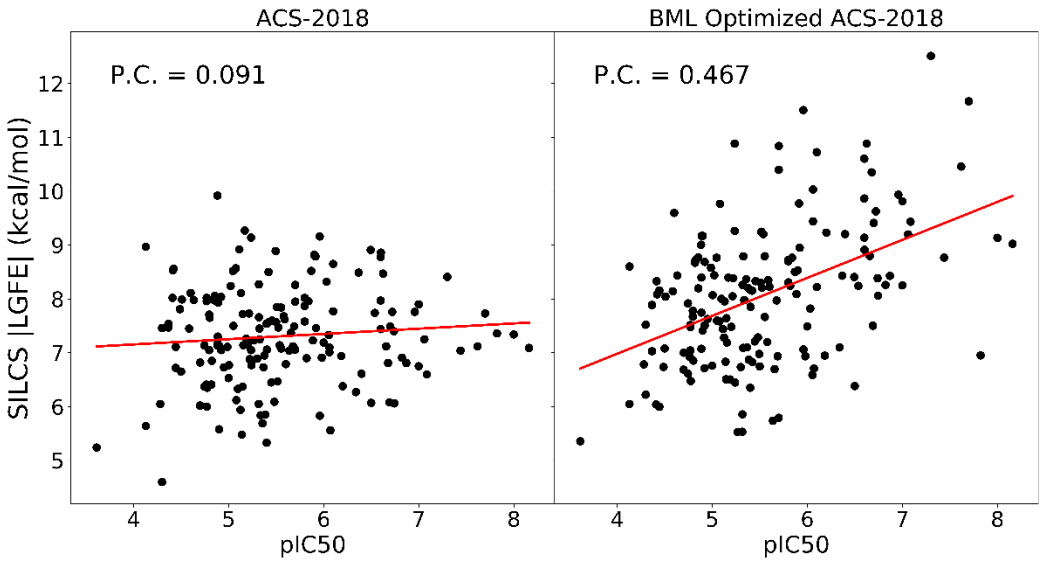

Figure S3. The SILCS-MC methodology by using the reweighted parameters from Bayesian Machine Learning shows a Pearson Correlation (P.C.) improvement from 0.091 to 0.467 for 163 compounds with diverse scaffolds that are used for BML training.

Electrostatic potential map for the cryo-EM structure of the hERG1 channel and MD refined structure.

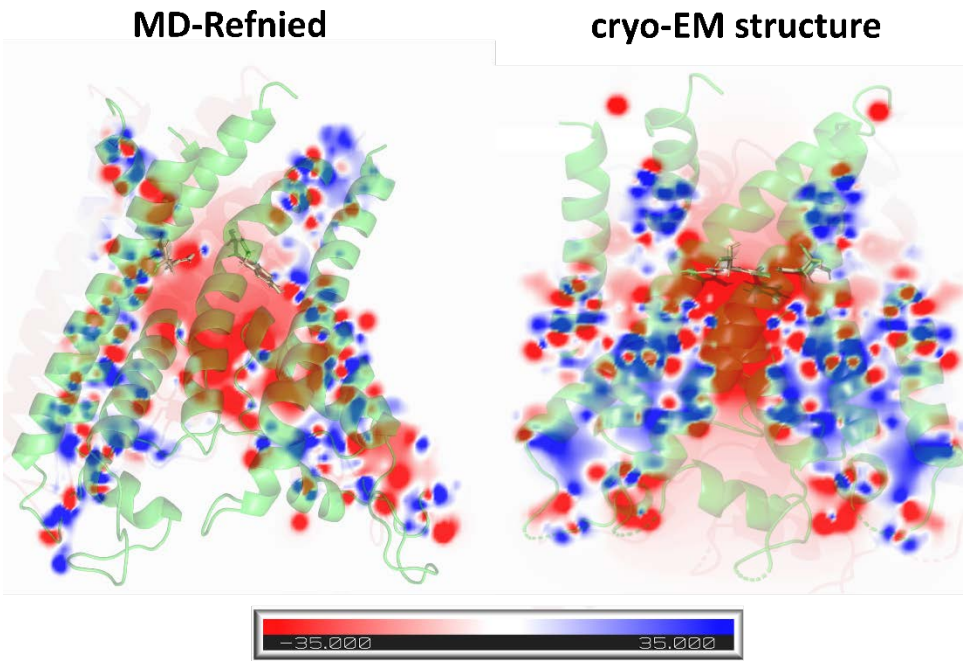

Figure S4. The electrostatic potential map of the hERG1 channel from the cryo-EM structure and MD refined structure is shown. The cryo-EM structure reveals a negative electrostatic potential below the selectivity filter which aids positively charged blockers to dock. MD refined structure shows relatively weaker negative electrostatic potential in the central cavity while it is extended. The Y652 is shown as sticks to have a better view of the IC pocket location.

Table S2. The SILCS FragMaps and atoms types definitions. The weighting factors (weights) are shown for the default 2018 ACS and optimized BML-2018 ACS

SILCS type	Weigths Default 2018 ACS	Weights for BML-2018 ACS	First atom type	Second atom type	Third atom type
BENC	0.167	0.203	6 C on benzene		
PRPC	0.333	0.297	3 C on propane		
ACEO	0.500	0.500	2 O on acetat		
ACEC	1.000	0.378	C on acetate		
GENN	0.333	0.333	3 C on propane	6 C on Benzene	
GEND	0.500	0.409	N(H) on imidazole	N on formamide	
GENA	0.333	0.125	O on formamide	O on acetaldehyde	N on imidazole
GEHC	0.333	0.321	3 C on imidazole		
MEOO	1.000	0.375	O on methane		
FORN	1.000	1.000	N on formamide		
FORO	1.000	1.000	O on formamide		
MAMN	1.000	0.877	N on methylammonium		
MAMC	1.000	1.000	C on methylammonium		
AALO	1.000	1.000	O on acetaldehyde		
AALC	1.000	1.000	C(=O) on acetaldehyde		
IMIN	1.000	1.000	N on imidazole		
IMINH	1.000	1.000	N(H) on imidazole		

Docked conformation of neutral/charged drugs from the MICE protocol.

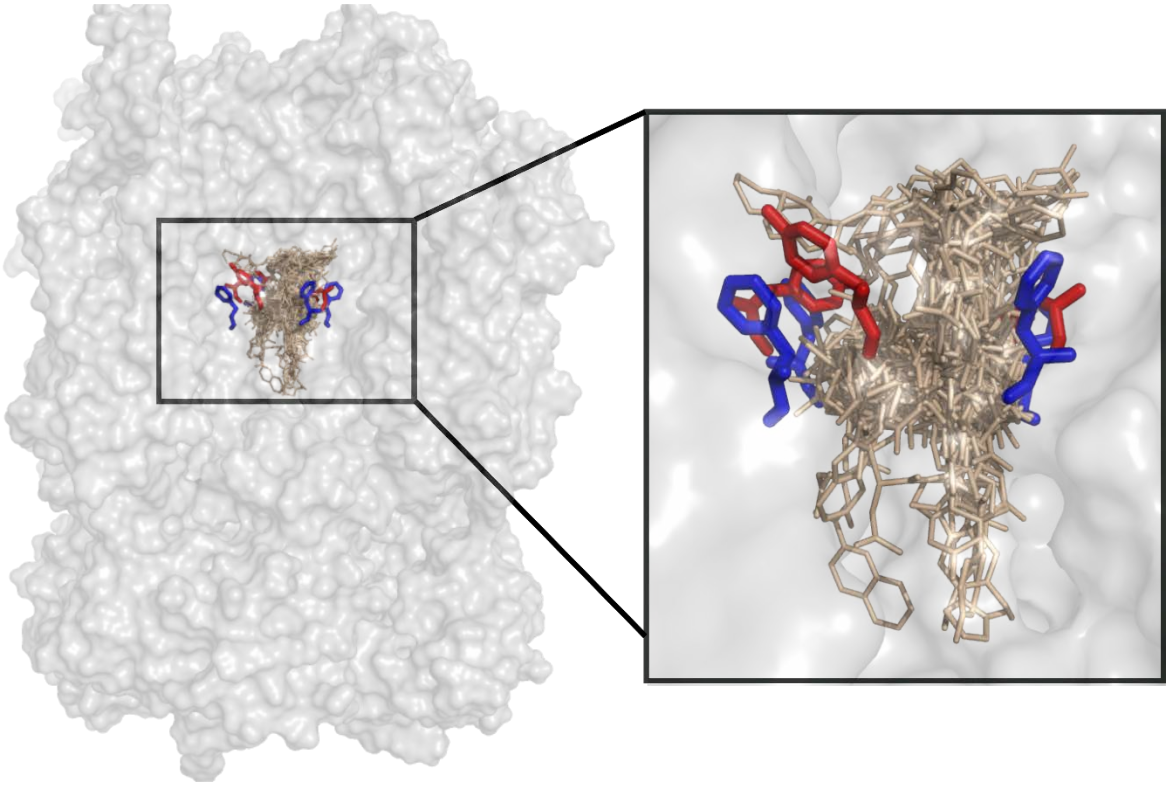

Figure S5. The conformational space sampled by the 55 blockers from the MICE protocol is shown. Blockers are shown in a stick model (wheat color) to illustrate the volume of the main drug-binding domain in IC. The Y652 and F656 are shown as red and blue sticks. The hERG1 channel is shown as transparent grey surface.

An alaysis of atomic contributions to SICLS |LGFE| for Saquinavir

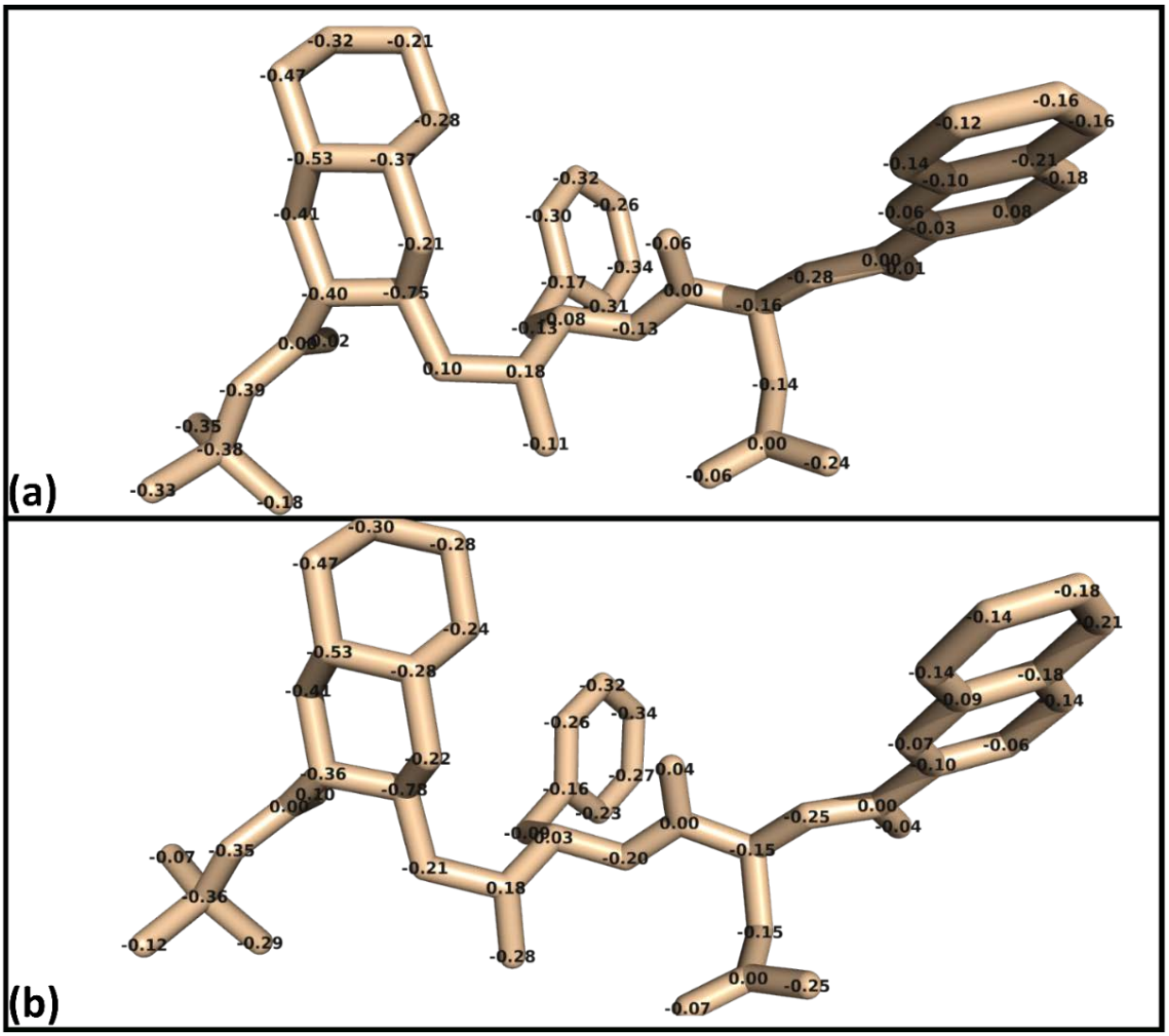

Figure S6. The atomic contributions to the SILCS |LGFE| for Saquinavir. The calculated LGFE score from SILCS simulations is overestimated due to the favourable contribution of non-polar and aromatic moieties as shown by atomic contribution to the total LGFE in both S1 (a) and S2 (b) regions.