Electronic Supplementary Material (ESI) for New Journal of Chemistry.

A quantum mechanics and molecular mechanics study of bis-thiosemicarbazones with strong antiplasmodial properties as Fe(III)-selective chelators and inhibitors of hemozoin formation

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1. Samples of the ORCA ONIOM input files used in this work

1.1 Input file for geometry optimization

```
! QM/XTB r2SCAN-3c opt Numfreq DEFGRID2 TightSCF PAL4 ALPB(water)
%maxcore 2000

%scf
  maxiter 5000
  AutoTRAH False
end

%qmmm
   QMAtoms {0:45} end
   ActiveAtoms {0:312} end
   Charge_Total 0 # total charge = 0 and 1 for F(II) and F(III), respectively
end

%geom
   MaxIter 1000
end

*pdbfile 0 1 L4Fe2_microsolvated.xtbopt_oniomopt.pdb
```

1.2 Input file for single-point calculations

```
! QM/XTB RIJK def2/JK def2-TZVPD/C DSD-BLYP D3BJ def2-TZVPD GCP(DFT/TZ)
DEFGRID2 TightSCF PAL4 ALPB(water)

%maxcore 2000

%scf
  maxiter 5000
  AutoTRAH False
end

%qmmm
   QMAtoms {0:45} end
   ActiveAtoms {0:312} end
   Charge_Total 0 # total charge = 0 and 1 for F(II) and F(III), respectively
end

*pdbfile 0 1 L4Fe2_microsolvated_DSD-BLYP_SP.pdb
```

2. Sample ONIOM-optimized coordinates using microsolvation

F(II)–L4

C	20.899	15.653	15.372
C	20.177	16.737	14.887
C	18.78	16.654	14.901
N	18.19	15.561	15.425
C	18.861	14.593	16.069
C	20.253	14.569	15.983
C	18	13.804	16.926
C	17.807	17.538	14.313
N	16.757	14.235	16.919
N	16.584	17.078	14.495
N	15.592	17.393	13.615
N	15.886	13.769	17.862
C	18.193	18.716	13.492
C	18.569	12.772	17.842
C	14.932	16.297	13.275
C	14.817	14.546	17.993
S	15.216	14.773	14.063
S	14.38	15.731	16.83
N	13.921	16.465	12.297
C	12.676	17.041	12.845
C	13.649	15.282	11.471
N	14.069	14.465	19.194
C	14.644	13.724	20.333
C	12.602	14.264	19.145
C	12.645	15.632	10.394
C	12.272	12.787	19.115
O	12.825	12.084	20.254
C	14.27	12.259	20.316
C	11.696	17.326	11.728
O	11.415	16.115	10.984
Fe	16.42	15.712	15.758
H	20.836	13.772	16.431
H	21.984	15.665	15.324

F(III)–L4

C	20.91	15.684	15.348
C	20.19	16.771	14.873
C	18.793	16.675	14.888
N	18.226	15.573	15.402
C	18.887	14.599	16.04
C	20.275	14.585	15.952
C	18.033	13.796	16.903
C	17.805	17.557	14.328
N	16.796	14.225	16.938
N	16.588	17.084	14.517
N	15.576	17.418	13.665
N	15.925	13.764	17.877
C	18.16	18.763	13.527
C	18.624	12.749	17.793
C	14.951	16.308	13.289
C	14.859	14.552	18.002
S	15.27	14.772	14.054
S	14.426	15.736	16.829
N	13.956	16.456	12.309
C	12.714	17.083	12.829
C	13.668	15.245	11.521
N	14.11	14.489	19.193
C	14.661	13.725	20.335
C	12.632	14.322	19.141
C	12.672	15.578	10.432
C	12.274	12.853	19.101
O	12.804	12.127	20.237
C	14.253	12.271	20.301
C	11.739	17.326	11.7
O	11.446	16.088	11.007
Fe	16.451	15.708	15.769
H	20.867	13.789	16.386
H	21.996	15.701	15.302

H	20.681	17.618	14.51	H	20.692	17.655	14.503
H	19.525	13.113	18.252	H	19.566	13.107	18.222
H	18.788	11.83	17.322	H	18.87	11.834	17.238
H	17.913	12.55	18.685	H	17.968	12.484	18.623
H	18.469	18.433	12.472	H	18.398	18.503	12.492
H	19.091	19.189	13.907	H	19.066	19.229	13.931
H	17.409	19.468	13.414	H	17.365	19.508	13.499
H	14.565	14.986	10.95	H	14.585	14.929	11.013
H	13.276	14.43	12.064	H	13.287	14.42	12.146
H	13.053	16.404	9.729	H	13.089	16.328	9.749
H	12.407	14.759	9.78	H	12.427	14.69	9.844
H	12.179	14.717	18.248	H	12.225	14.79	18.243
H	12.142	14.728	20.029	H	12.187	14.798	20.025
H	12.671	12.35	18.195	H	12.669	12.418	18.179
H	11.19	12.628	19.135	H	11.189	12.718	19.113
H	14.271	14.181	21.262	H	14.292	14.193	21.26
H	15.735	13.815	20.329	H	15.753	13.795	20.336
H	14.602	11.775	21.238	H	14.574	11.769	21.217
H	14.717	11.746	19.46	H	14.689	11.76	19.439
H	12.098	18.076	11.035	H	12.147	18.044	10.977
H	10.747	17.686	12.137	H	10.795	17.711	12.099
H	12.883	17.987	13.344	H	12.94	18.048	13.281
H	12.212	16.353	13.575	H	12.248	16.433	13.591
O	17.555	22.781	14.366	O	17.528	22.82	14.367
H	17.064	22.076	13.87	H	17.03	22.115	13.879
H	17.17	22.696	15.261	H	17.161	22.733	15.269
O	11.978	18.941	19.055	O	11.996	18.911	19
H	12.582	18.285	19.476	H	12.605	18.277	19.446
H	11.179	18.955	19.602	H	11.189	18.932	19.536
O	10.513	9.957	22.541	O	10.439	10.01	22.459
H	11.361	9.497	22.38	H	11.275	9.527	22.296
H	10.058	9.997	21.693	H	9.998	10.092	21.606
O	16.15	17.814	19.437	O	16.213	17.817	19.481
H	16.09	18.703	19.063	H	16.164	18.716	19.131
H	15.214	17.572	19.63	H	15.272	17.583	19.665
O	19.153	11.114	11.831	O	19.117	11.143	11.793
H	18.285	10.712	12.011	H	18.274	10.69	11.966
H	19.522	11.315	12.712	H	19.501	11.302	12.675
O	8.253	19.763	11.983	O	8.212	19.797	11.953
H	9.146	20.162	12.005	H	9.112	20.18	11.985
H	8.204	19.284	11.14	H	8.177	19.294	11.124
O	16.861	23.792	11.787	O	16.818	23.816	11.782
H	17.254	23.029	11.315	H	17.218	23.058	11.31
H	17.197	23.706	12.695	H	17.161	23.74	12.687
O	21.711	10.141	18.691	O	21.635	10.135	18.679
H	21.627	10.948	19.222	H	21.565	10.938	19.217
H	20.849	9.688	18.751	H	20.781	9.673	18.77
O	10.303	14.906	16.71	O	10.322	14.894	16.672
H	10.717	15.784	16.897	H	10.742	15.772	16.844
H	9.744	15.078	15.934	H	9.754	15.061	15.901
O	14.291	23.278	12.582	O	14.25	23.289	12.588
H	15.109	23.637	12.183	H	15.064	23.648	12.183
H	13.652	23.132	11.864	H	13.609	23.134	11.874
O	7.778	18.392	14.364	O	7.772	18.403	14.328

H	7.78	18.909	13.539	H	7.763	18.924	13.506
H	8.693	18.484	14.699	H	8.692	18.492	14.65
O	23.455	17.929	16.951	O	23.48	17.926	16.937
H	22.908	18.73	17.073	H	22.943	18.732	17.066
H	23.478	17.779	15.99	H	23.501	17.786	15.974
O	17.389	7.155	19.578	O	17.309	7.144	19.686
H	17.384	6.913	20.507	H	17.295	6.937	20.623
H	16.666	7.81	19.464	H	16.601	7.81	19.544
O	10.419	14.173	12.599	O	10.481	14.157	12.655
H	9.836	14.659	13.206	H	9.875	14.634	13.247
H	10.778	14.868	11.995	H	10.834	14.856	12.053
O	10.717	19.732	9.386	O	10.706	19.707	9.396
H	10.885	19.952	10.327	H	10.874	19.927	10.337
H	9.842	19.307	9.364	H	9.834	19.276	9.375
O	15.104	21.566	8.108	O	15.077	21.6	8.074
H	14.427	21.379	7.415	H	14.395	21.382	7.394
H	14.968	22.479	8.371	H	14.939	22.523	8.3
O	13.508	20.248	10.014	O	13.517	20.266	9.999
H	14.081	19.791	10.669	H	14.084	19.813	10.66
H	14.119	20.542	9.32	H	14.13	20.571	9.312
O	18.106	13.582	13.525	O	18.144	13.602	13.49
H	17.728	13.053	12.815	H	17.809	13.031	12.791
H	17.385	14.148	13.859	H	17.391	14.153	13.78
O	12.485	10.004	14.191	O	12.486	9.96	14.212
H	12.848	10.166	15.095	H	12.857	10.128	15.112
H	11.655	9.541	14.315	H	11.646	9.518	14.346
O	20.873	20.005	14.654	O	20.851	20.068	14.676
H	21.33	20.036	15.512	H	21.328	20.078	15.523
H	21.546	19.893	13.958	H	21.507	19.946	13.965
O	11.471	12.488	22.574	O	11.469	12.508	22.572
H	11.097	11.591	22.701	H	11.071	11.617	22.669
H	11.994	12.426	21.74	H	11.985	12.463	21.732
O	9.687	13.379	8.595	O	9.702	13.351	8.639
H	9.43	14.301	8.79	H	9.442	14.273	8.828
H	9.968	12.994	9.455	H	9.984	12.972	9.502
O	11.61	17.201	17.085	O	11.632	17.195	17.016
H	11.632	17.881	17.797	H	11.655	17.866	17.737
H	12.532	16.872	17.05	H	12.556	16.879	16.96
O	17.428	10.803	15.158	O	17.425	10.695	15.136
H	18.271	11.27	14.959	H	18.265	11.161	14.919
H	17.09	10.54	14.276	H	17.073	10.43	14.259
O	12.187	13.909	7.653	O	12.194	13.887	7.679
H	12.661	13.065	7.63	H	12.666	13.042	7.651
H	11.265	13.677	7.896	H	11.275	13.656	7.934
O	13.288	10.734	16.647	O	13.316	10.717	16.651
H	14.247	10.815	16.867	H	14.275	10.807	16.869
H	13.028	11.649	16.4	H	13.046	11.633	16.415
O	12.794	9.54	19.279	O	12.763	9.59	19.229
H	12.704	10.422	19.71	H	12.671	10.467	19.665
H	12.782	9.734	18.329	H	12.795	9.799	18.279
O	21.748	16.914	12.064	O	21.772	16.94	12.043
H	20.95	16.348	12.201	H	20.971	16.377	12.166
H	22.256	16.47	11.382	H	22.276	16.515	11.346
O	12.144	20.302	14.281	O	12.137	20.331	14.285

H	12.158	21.179	14.681	H	12.139	21.205	14.691
H	13.074	19.972	14.464	H	13.061	19.998	14.486
O	10.516	10.612	8.383	O	10.506	10.593	8.421
H	10.461	10.772	9.337	H	10.458	10.737	9.378
H	10.02	11.342	7.99	H	10.016	11.336	8.045
O	10.635	12.11	10.824	O	10.647	12.099	10.871
H	11.608	12	10.858	H	11.619	11.977	10.892
H	10.426	12.779	11.501	H	10.456	12.772	11.551
O	17.292	16.316	11.566	O	17.297	16.348	11.57
H	16.998	15.629	10.941	H	16.993	15.659	10.952
H	17.359	17.138	11.065	H	17.358	17.168	11.064
O	11.14	16.456	6.971	O	11.132	16.421	6.983
H	11.687	15.662	7.075	H	11.68	15.628	7.086
H	11.719	17.222	7.186	H	11.709	17.189	7.196
O	19.567	16.114	20.859	O	19.59	16.117	20.867
H	19.422	16.316	19.9	H	19.442	16.316	19.91
H	18.958	15.391	21.067	H	18.983	15.395	21.081
O	9.505	16.106	9.061	O	9.522	16.075	9.092
H	10.17	16.138	9.79	H	10.193	16.107	9.814
H	10.038	16.276	8.245	H	10.046	16.244	8.271
O	9.596	18.515	20.449	O	9.614	18.517	20.396
H	9.82	17.601	20.731	H	9.84	17.607	20.69
H	8.745	18.462	20.009	H	8.765	18.455	19.953
O	14.675	17.635	9.198	O	14.66	17.636	9.227
H	14.891	17.921	10.103	H	14.874	17.9	10.138
H	15.437	17.146	8.855	H	15.417	17.143	8.879
O	23.135	13.598	17.408	O	23.146	13.572	17.391
H	24.082	13.699	17.525	H	24.096	13.663	17.495
H	22.736	14.491	17.585	H	22.759	14.469	17.569
O	16.629	16.663	21.92	O	16.663	16.656	21.971
H	16.536	17.145	21.075	H	16.579	17.135	21.123
H	17.051	15.822	21.683	H	17.08	15.81	21.743
O	20.195	22.48	13.885	O	20.166	22.537	13.882
H	20.382	21.584	14.256	H	20.36	21.649	14.267
H	19.242	22.63	14.071	H	19.212	22.682	14.066
O	9.237	12.287	20.692	O	9.22	12.326	20.672
H	9.149	13.064	20.097	H	9.139	13.096	20.067
H	9.948	12.523	21.313	H	9.934	12.565	21.288
O	12.579	17.109	22.547	O	12.595	17.129	22.532
H	13.25	16.449	22.858	H	13.255	16.465	22.852
H	12.513	17.782	23.226	H	12.515	17.797	23.214
O	7.306	13.082	22.403	O	7.301	13.134	22.391
H	7.902	12.657	21.742	H	7.891	12.703	21.728
H	6.645	13.559	21.893	H	6.645	13.618	21.884
O	19.227	13.341	10.185	O	19.238	13.38	10.154
H	19.495	14.034	10.838	H	19.513	14.069	10.807
H	19.239	12.506	10.69	H	19.233	12.544	10.656
O	15.239	12.521	15.158	O	15.294	12.494	15.127
H	14.727	12.042	14.501	H	14.735	12.037	14.493
H	16.111	12.091	15.182	H	16.13	12.001	15.156
O	10.454	16.028	21.199	O	10.478	16.047	21.174
H	11.249	16.414	21.616	H	11.27	16.434	21.598
H	10.027	15.536	21.929	H	10.046	15.555	21.902
O	17.66	14.067	21.53	O	17.7	14.064	21.592

H	17.1	13.709	22.235	H	17.111	13.672	22.254
H	18.407	13.434	21.483	H	18.441	13.424	21.535
O	17.424	19.505	16.63	O	17.448	19.52	16.662
H	17.783	19.496	15.738	H	17.806	19.54	15.77
H	17.148	18.553	16.778	H	17.174	18.567	16.792
O	16.189	14.82	25.236	O	16.137	14.695	25.235
H	16.969	15.348	25.036	H	16.945	15.197	25.09
H	16.303	13.982	24.741	H	16.243	13.869	24.719
O	21.921	11.322	16.233	O	21.867	11.322	16.228
H	22.442	12.099	16.485	H	22.41	12.084	16.477
H	21.848	10.797	17.057	H	21.783	10.798	17.053
O	13.527	22.63	15.186	O	13.536	22.655	15.212
H	13.397	23.446	15.669	H	13.395	23.474	15.688
H	13.81	22.884	14.289	H	13.798	22.907	14.308
O	12.601	18.605	7.747	O	12.581	18.578	7.761
H	12.006	19.008	8.415	H	11.98	18.983	8.421
H	13.398	18.34	8.254	H	13.376	18.324	8.276
O	21.825	20.133	17.236	O	21.861	20.136	17.243
H	20.952	19.855	17.615	H	20.992	19.865	17.632
H	22.049	20.967	17.651	H	22.099	20.967	17.66
O	9.182	14.515	19.18	O	9.2	14.543	19.146
H	9.681	15.125	19.748	H	9.712	15.145	19.712
H	9.539	14.63	18.275	H	9.562	14.645	18.241
O	13.347	11.578	10.767	O	13.352	11.543	10.773
H	13.441	11.544	9.801	H	13.439	11.511	9.807
H	14.115	12.087	11.11	H	14.119	12.054	11.115
O	19.849	11.725	14.472	O	19.808	11.687	14.446
H	19.605	12.667	14.424	H	19.538	12.621	14.386
H	20.612	11.652	15.072	H	20.569	11.634	15.049
O	17.669	18.961	10.403	O	17.642	18.991	10.422
H	16.729	18.98	10.748	H	16.703	19.013	10.766
H	17.936	19.893	10.509	H	17.908	19.925	10.517
O	16.578	10.388	12.639	O	16.57	10.314	12.613
H	16.249	11.266	12.329	H	16.251	11.199	12.317
H	15.841	9.784	12.436	H	15.82	9.723	12.415
O	16.402	12.597	23.63	O	16.362	12.503	23.59
H	17.04	11.904	23.824	H	16.99	11.806	23.795
H	15.534	12.163	23.559	H	15.491	12.076	23.51
O	13.125	11.261	7.999	O	13.112	11.231	8.007
H	12.196	10.945	8.085	H	12.182	10.92	8.104
H	13.594	10.602	7.483	H	13.572	10.566	7.49
O	19.634	15.243	12.07	O	19.65	15.281	12.045
H	19.323	14.64	12.778	H	19.336	14.668	12.743
H	18.807	15.763	11.881	H	18.821	15.799	11.855
O	8.287	18.439	9.454	O	8.287	18.403	9.464
H	8.664	17.527	9.355	H	8.667	17.492	9.38
H	7.605	18.518	8.784	H	7.615	18.474	8.784
O	19.424	16.736	18.255	O	19.482	16.747	18.26
H	20.271	16.359	17.967	H	20.339	16.375	17.996
H	19.546	17.711	18.258	H	19.6	17.722	18.285
O	14.551	19.545	14.872	O	14.536	19.562	14.912
H	14.628	19.331	15.829	H	14.626	19.348	15.868
H	14.875	18.757	14.369	H	14.858	18.77	14.412
O	9.577	14.468	23.238	O	9.588	14.499	23.217

H	10.271	13.788	23.178	H	10.278	13.813	23.162
H	8.733	13.998	23.108	H	8.741	14.035	23.088
O	13.006	21.016	6.555	O	12.975	20.986	6.557
H	12.875	20.082	6.838	H	12.855	20.053	6.849
H	12.323	21.508	7.048	H	12.29	21.475	7.05
O	19.204	8.994	18.564	O	19.146	8.932	18.633
H	18.738	8.213	18.908	H	18.668	8.166	18.995
H	19.143	8.913	17.586	H	19.085	8.832	17.657
O	19.596	12.187	21.512	O	19.617	12.16	21.514
H	18.983	11.554	21.089	H	18.984	11.559	21.07
H	20.284	12.357	20.852	H	20.301	12.345	20.854
O	17.831	21.213	7.813	O	17.802	21.217	7.816
H	17.979	20.256	7.7	H	17.941	20.259	7.706
H	16.859	21.314	7.831	H	16.831	21.326	7.825
O	16.668	16.247	7.78	O	16.647	16.252	7.807
H	16.324	16.161	6.891	H	16.304	16.16	6.917
H	17.277	17.021	7.771	H	17.256	17.025	7.794
O	13.685	17.09	20.006	O	13.733	17.119	20.01
H	13.845	16.167	19.693	H	13.889	16.195	19.705
H	13.41	17.035	20.93	H	13.445	17.072	20.931
O	11.04	22.115	8.216	O	11.012	22.09	8.217
H	10.927	21.223	8.635	H	10.906	21.2	8.642
H	10.172	22.366	7.895	H	10.144	22.332	7.891
O	15.631	12.721	11.747	O	15.65	12.673	11.744
H	15.481	13.369	12.473	H	15.509	13.312	12.476
H	16.041	13.222	11.023	H	16.052	13.183	11.022
O	12.613	12.759	13.455	O	12.67	12.698	13.467
H	12.488	11.799	13.466	H	12.529	11.74	13.495
H	11.767	13.153	13.172	H	11.824	13.101	13.202
O	12.448	22.532	10.666	O	12.413	22.524	10.671
H	12.889	21.651	10.459	H	12.868	21.654	10.454
H	11.989	22.751	9.846	H	11.951	22.745	9.852
O	20.78	21.874	11.392	O	20.752	21.904	11.394
H	21.279	22.614	11.042	H	21.255	22.639	11.038
H	20.535	22.134	12.326	H	20.505	22.174	12.325
O	15.345	19.109	11.557	O	15.325	19.128	11.593
H	15.554	19.917	12.078	H	15.531	19.941	12.107
H	15.385	18.401	12.261	H	15.374	18.426	12.298
O	14.54	15.461	23.082	O	14.541	15.468	23.089
H	14.892	15.27	23.964	H	14.882	15.238	23.966
H	15.274	15.944	22.622	H	15.288	15.946	22.648
O	14.143	9.295	12.079	O	14.119	9.249	12.075
H	13.835	10.031	11.507	H	13.82	9.999	11.515
H	13.609	9.398	12.886	H	13.59	9.347	12.885
O	10.867	20.678	11.929	O	10.843	20.668	11.931
H	11.291	21.496	11.605	H	11.267	21.482	11.596
H	11.369	20.447	12.738	H	11.346	20.447	12.741
O	22.058	15.331	20.872	O	22.084	15.335	20.856
H	22.44	15.521	21.729	H	22.472	15.517	21.713
H	21.102	15.633	20.917	H	21.13	15.636	20.912
O	10.494	18.219	14.878	O	10.489	18.228	14.828
H	11.016	19.011	14.643	H	11.005	19.027	14.607
H	10.896	17.902	15.717	H	10.901	17.9	15.66
O	9.168	15.875	14.36	O	9.151	15.875	14.344

H	9.767	16.647	14.425	H	9.751	16.647	14.394
H	8.295	16.282	14.297	H	8.278	16.28	14.276
O	14.495	18.923	17.465	O	14.548	18.914	17.492
H	14.525	17.947	17.413	H	14.591	17.94	17.42
H	13.663	19.143	17.888	H	13.699	19.115	17.893
O	19.459	19.439	18.247	O	19.494	19.451	18.273
H	19.145	19.825	19.065	H	19.191	19.844	19.093
H	18.689	19.508	17.597	H	18.72	19.524	17.63
O	21.644	12.865	19.659	O	21.666	12.861	19.664
H	22.129	13.001	18.825	H	22.148	12.983	18.827
H	21.826	13.677	20.168	H	21.85	13.679	20.162
O	23.45	17.663	14.145	O	23.461	17.707	14.131
H	22.803	17.265	13.53	H	22.829	17.298	13.508
H	23.68	18.503	13.734	H	23.661	18.562	13.736
O	18.168	21.662	10.507	O	18.141	21.69	10.503
H	19.106	21.741	10.763	H	19.079	21.77	10.759
H	18.133	21.668	9.531	H	18.107	21.689	9.527
O	16.759	14.304	9.811	O	16.753	14.314	9.84
H	17.667	13.915	9.827	H	17.665	13.934	9.84
H	16.697	14.822	8.997	H	16.677	14.832	9.026
O	15.797	11.113	17.575	O	15.825	11.102	17.577
H	16.462	10.947	16.894	H	16.497	10.93	16.906
H	15.884	12.098	17.791	H	15.916	12.084	17.796
O	12.553	13.309	16.087	O	12.583	13.29	16.089
H	12.654	13.215	15.116	H	12.704	13.194	15.12
H	11.685	13.723	16.225	H	11.717	13.712	16.211
O	18.274	18.416	7.957	O	18.252	18.423	7.978
H	17.995	18.612	8.909	H	17.974	18.626	8.928
H	19.208	18.199	8.008	H	19.187	18.213	8.027
O	17.781	10.664	20.211	O	17.764	10.727	20.17
H	16.937	10.195	20.248	H	16.911	10.282	20.255
H	18.315	10.166	19.564	H	18.283	10.164	19.564
O	16.067	21.921	16.495	O	16.074	21.947	16.517
H	15.187	21.84	16.097	H	15.19	21.877	16.127
H	16.399	21.002	16.588	H	16.397	21.026	16.606
O	17.045	16.931	17.185	O	17.091	16.931	17.221
H	17.964	16.768	17.496	H	18.016	16.773	17.508
H	16.541	17.095	18.021	H	16.597	17.09	18.065
O	13.952	11.261	23.377	O	13.905	11.19	23.331
H	13.678	10.396	23.037	H	13.611	10.337	22.976
H	13.152	11.812	23.353	H	13.118	11.761	23.314
O	19.071	8.808	15.885	O	19.054	8.723	15.953
H	19.881	9.137	15.485	H	19.879	9.046	15.578
H	18.37	9.455	15.626	H	18.363	9.367	15.66
O	12.987	8.858	22.037	O	12.876	8.835	21.956
H	13.192	7.938	22.223	H	13.03	7.902	22.117
H	12.97	8.953	21.071	H	12.874	8.959	20.992
O	15.856	21.104	13.217	O	15.82	21.132	13.248
H	15.393	20.623	13.951	H	15.361	20.653	13.985
H	15.246	21.817	12.961	H	15.207	21.839	12.985
O	22.307	19.696	12.337	O	22.268	19.73	12.358
H	21.779	20.374	11.879	H	21.744	20.405	11.89
H	21.944	18.835	12.066	H	21.921	18.867	12.077
O	15.536	9.154	19.398	O	15.501	9.171	19.427

H	14.563	9.12	19.404	H	14.527	9.153	19.412
H	15.744	9.798	18.683	H	15.733	9.8	18.706
O	22.095	15.929	18.134	O	22.132	15.921	18.119
H	22.612	16.679	17.77	H	22.652	16.671	17.758
H	22.225	15.91	19.095	H	22.267	15.896	19.08

3. Unit cell of the β-hematin crystal

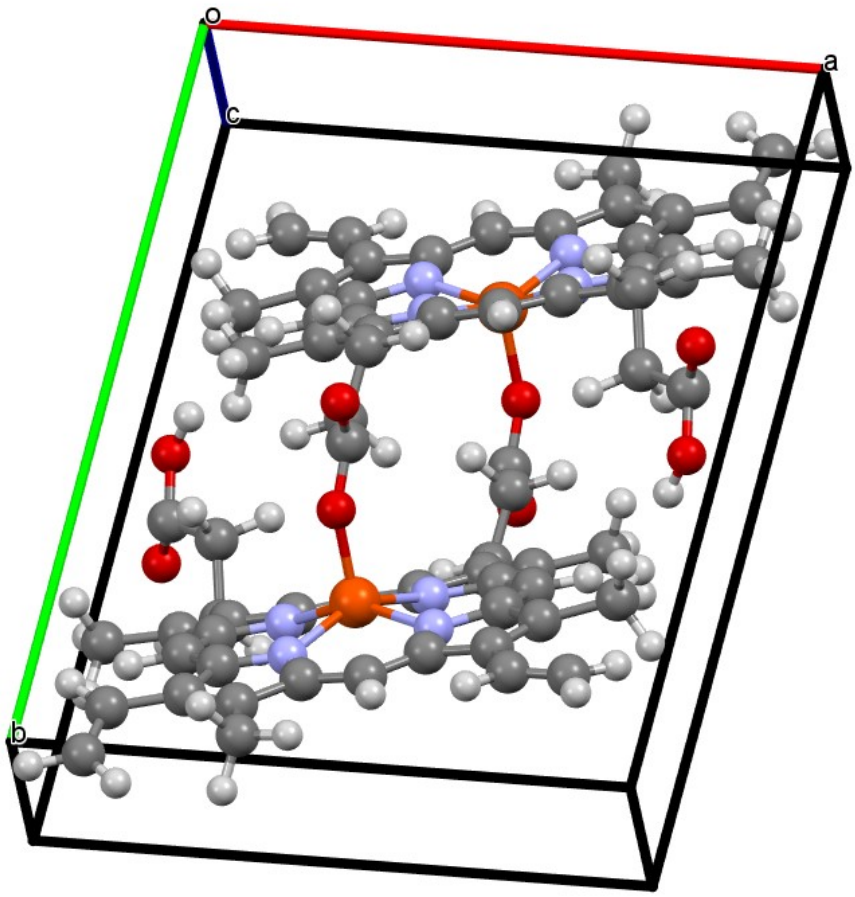


Figure S1: The optimized β-hematin bulk unit cell using the pGFNFF forcefield implementation in GULP-6.1

4. Forcefield settings used for molecular dynamics simulations with LAMMPS

4.1 Styles (pair, atom, bond, angle, dihedral and improper) and special bonds

```
pair_style      lj/cut/coul/long 10.0
pair_modify     mix arithmetic
atom_style      full
bond_style      harmonic
angle_style     harmonic
dihedral_style  harmonic
improper_style  harmonic
special_bonds   amber
kspace_style    pppm 1e-6
```

4.2 Masses and coefficients (pair, atom, bond, angle, dihedral and improper)

BHM–L1

Masses

1	55
2	14.01
3	12.01
4	12.01
5	16
6	16
7	16
8	1.008
9	1.008
10	1.008
11	12.01
12	14.01
13	14.01
14	12.01
15	32.06
16	1.008
17	1.008
18	1.008
19	1.008
20	16

Pair	***Coeffs***	
1	0.05	2.138157
2	0.17	3.249999
3	0.086	3.39967
4	0.1094	3.39967
5	0.2104	3.066473
6	0.21	2.959922
7	0.17	3.000012
8	0.015	2.599642
9	0.0157	2.649533
10	0	0
11	0.0988	3.315212
12	0.0941	3.384168
13	0.1174	3.269955
14	0.1078	3.39771
15	0.2824	3.532413
16	0.01	1.106496
17	0.0161	2.625479
18	0.0208	2.600177
19	0.0208	2.421997
20	0.152	3.150752

Bond	***Coeffs***	
1	365	1.08
2	655	1.25
3	340	1.09
4	315	1.522
5	555	0.96
6	450	1.364
7	570	1.229
8	550	1.35
9	310	1.526
10	365	1.08
11	470	1.39
12	425	1.433
13	470	1.45

BHM–L2

Masses

1	55
2	14.01
3	12.01
4	12.01
5	16
6	16
7	16
8	1.008
9	1.008
10	1.008
11	12.01
12	14.01
13	14.01
14	12.01
15	32.06
16	14.01
17	1.008
18	1.008
19	1.008
20	1.008
21	16

Pair	***Coeffs***	
1	0.05	2.138157
2	0.17	3.249999
3	0.086	3.39967
4	0.1094	3.39967
5	0.2104	3.066473
6	0.21	2.959922
7	0.17	3.000012
8	0.015	2.599642
9	0.0157	2.649533
10	0	0
11	0.0988	3.315212
12	0.0941	3.384168
13	0.1174	3.269955
14	0.1078	3.39771
15	0.2824	3.532413
16	0.1636	3.180865
17	0.01	1.106496
18	0.0161	2.625479
19	0.0208	2.600177
20	0.0208	2.421997
21	0.152	3.150752

Bond	***Coeffs***	
1	365	1.08
2	655	1.25
3	340	1.09
4	315	1.522
5	555	0.96
6	450	1.364
7	570	1.229
8	550	1.35
9	310	1.526
10	365	1.08
11	470	1.39
12	425	1.433
13	470	1.45

14	470	1.4
15	315	1.51
16	422	1.385
17	422	1.385
18	55	2.09
19	55	2.09
20	155	1.85
21	450	1.323
22	410	1.394
23	55	2.09
24	155	1.85
25	345.25	1.0962
26	228.89	1.5354
27	344.22	1.0969
28	261.66	1.4556
29	473.59	1.0132
30	290.99	1.6704
31	347.12	1.3703
32	287.72	1.3597
33	464.18	1.2878
34	246.79	1.5109
35	360.69	1.086
36	354.25	1.3986
37	271.85	1.48
38	386.49	1.3392
39	553	1.5136
40	553	0.9572

Angle	***Coeffs***	
1	35	120.0001
2	35	109.5
3	50	119.7001
4	80	126.0001
5	50	109.5
6	50	109.5
7	70	117.0001
8	80	120.0001
9	50	113
10	80	110
11	80	120.4001
12	65	111.1
13	65	124.0001
14	50	116.8001
15	70	120.0001
16	50	116.2
17	65	126.1001
18	70	125.0001
19	65	129.5001
20	65	106.4
21	50	109.5
22	70	106.2
23	70	125.0001
24	70	110.4
25	70	125.0001
26	70	126.2001
27	65	114
28	70	106.2
29	45	87.00004
30	70	110.4
31	70	125.0001
32	65	152.0001

14	470	1.4
15	315	1.51
16	422	1.385
17	422	1.385
18	55	2.09
19	55	2.09
20	155	1.85
21	450	1.323
22	410	1.394
23	55	2.09
24	155	1.85
25	344.22	1.0969
26	254.46	1.4643
27	290.99	1.6704
28	347.12	1.3703
29	345.25	1.0962
30	347.12	1.3703
31	473.59	1.0132
32	287.72	1.3597
33	464.18	1.2878
34	246.79	1.5109
35	360.69	1.086
36	354.25	1.3986
37	271.85	1.48
38	386.49	1.3392
39	553	1.5136
40	553	0.9572

Angle	***Coeffs***	
1	35	120.0001
2	35	109.5
3	50	119.7001
4	80	126.0001
5	50	109.5
6	50	109.5
7	70	117.0001
8	80	120.0001
9	50	113
10	80	110
11	80	120.4001
12	65	111.1
13	65	124.0001
14	50	116.8001
15	70	120.0001
16	50	116.2
17	65	126.1001
18	70	125.0001
19	65	129.5001
20	65	106.4
21	50	109.5
22	70	106.2
23	70	125.0001
24	70	110.4
25	70	125.0001
26	70	126.2001
27	65	114
28	70	106.2
29	45	87.00004
30	70	110.4
31	70	125.0001
32	65	152.0001

33	65	152.0001
34	80	126.0001
35	80	126.0001
36	35	104
37	35	104
38	80	125.0001
39	50	146.0001
40	80	115
41	70	106.2
42	35	104
43	70	110.4
44	70	125.0001
45	65	152.0001
46	80	126.0001
47	50	146.0001
48	35.8	107.73
49	35.64	108.55
50	43.28	109.59
51	54.62	117.4201
52	43.27	109.68
53	65.43	111.69
54	48.39	108.49
55	69.72	123.8701
56	57.7	117.3601
57	76.37	124.4001
58	75.64	112.5
59	65.69	123.7601
60	85.01	121.6701
61	61.2	119.1101
62	88.93	117.8601
63	43.66	110.88
64	44.9	119.8801
65	61.58	120.7901
66	67.49	120.6001
67	59.77	119.1001
68	67.45	117.4601
69	68.17	122.9401
70	83.15	117.2401
71	63.67	120.0201

Dihedral	Coeffs		
1	6.65	-1	2
2	0.15	1	3
3	0	1	2
4	0.155556	1	3
5	0.8	1	1
6	0.08	-1	3
7	1.9	1	1
8	2.3	-1	2
9	3.625	-1	2
10	2.55	-1	2
11	4.8	-1	2
12	0	1	1
13	0.155556	1	3
14	2.4	-1	2
15	0.155556	1	3
16	2.5	-1	2
17	1.15	-1	1
18	0.8	-1	2
19	0	1	3
20	0.4	1	2

33	65	152.0001
34	80	126.0001
35	80	126.0001
36	35	104
37	35	104
38	80	125.0001
39	50	146.0001
40	80	115
41	70	106.2
42	35	104
43	70	110.4
44	70	125.0001
45	65	152.0001
46	80	126.0001
47	50	146.0001
48	35.64	108.55
49	35.8	107.73
50	76.21	116.7501
51	48.09	108.76
52	69.23	125.6401
53	57.7	117.3601
54	76.77	122.2501
55	69.72	123.8701
56	76.43	110.18
57	65.69	123.7601
58	85.01	121.6701
59	61.2	119.1101
60	88.93	117.8601
61	43.66	110.88
62	44.9	119.8801
63	61.58	120.7901
64	67.49	120.6001
65	59.77	119.1001
66	67.45	117.4601
67	68.17	122.9401
68	83.15	117.2401
69	63.67	120.0201

Dihedral	Coeffs		
1	6.65	-1	2
2	0.15	1	3
3	0	1	2
4	0.155556	1	3
5	0.8	1	1
6	0.08	-1	3
7	1.9	1	1
8	2.3	-1	2
9	3.625	-1	2
10	2.55	-1	2
11	4.8	-1	2
12	0	1	1
13	0.155556	1	3
14	2.4	-1	2
15	2.5	-1	2
16	0	-1	2
17	0.8	-1	2
18	0	1	3
19	0.4	1	2
20	0.82	-1	1

21	0.82	-1	1
22	1	-1	2
23	0.75	-1	3
24	0.6	-1	2
25	0.26	-1	3
26	0.7	-1	2
27	1.1	-1	2
28	10.5	-1	2

21	1	-1	2
22	0.75	-1	3
23	0.6	-1	2
24	0.26	-1	3
25	0.7	-1	2
26	1.1	-1	2
27	10.5	-1	2

BHM–L3

Masses

1	55
2	14.01
3	12.01
4	12.01
5	16
6	16
7	16
8	1.008
9	1.008
10	1.008
11	12.01
12	14.01
13	12.01
14	14.01
15	1.008
16	32.06
17	14.01
18	14.01
19	1.008
20	1.008
21	1.008
22	16

Pair	***Coeffs***	
1	0.05	2.138157
2	0.17	3.249999
3	0.086	3.39967
4	0.1094	3.39967
5	0.2104	3.066473
6	0.21	2.959922
7	0.17	3.000012
8	0.015	2.599642
9	0.0157	2.649533
10	0	0
11	0.0988	3.315212
12	0.0941	3.384168
13	0.1078	3.39771
14	0.1174	3.269955
15	0.01	1.106496
16	0.2824	3.532413
17	0.1636	3.180865
18	0.0858	3.365103
19	0.0161	2.625479
20	0.0208	2.600177
21	0.0208	2.421997
22	0.152	3.150752

Bond	***Coeffs***	
1	365	1.08
2	655	1.25

BHM–L4

Masses

1	55
2	14.01
3	12.01
4	12.01
5	16
6	16
7	16
8	1.008
9	1.008
10	1.008
11	12.01
12	14.01
13	12.01
14	14.01
15	1.008
16	32.06
17	14.01
18	16
19	1.008
20	1.008
21	1.008
22	16

Pair	***Coeffs***	
1	0.05	2.138157
2	0.17	3.249999
3	0.086	3.39967
4	0.1094	3.39967
5	0.2104	3.066473
6	0.21	2.959922
7	0.17	3.000012
8	0.015	2.599642
9	0.0157	2.649533
10	0	0
11	0.0988	3.315212
12	0.0941	3.384168
13	0.1078	3.39771
14	0.1174	3.269955
15	0.01	1.106496
16	0.2824	3.532413
17	0.1636	3.180865
18	0.0726	3.156098
19	0.0161	2.625479
20	0.0208	2.600177
21	0.0208	2.421997
22	0.152	3.150752

Bond	***Coeffs***	
1	365	1.08
2	655	1.25

3	340	1.09
4	315	1.522
5	555	0.96
6	450	1.364
7	570	1.229
8	550	1.35
9	310	1.526
10	365	1.08
11	470	1.39
12	425	1.433
13	470	1.45
14	470	1.4
15	315	1.51
16	422	1.385
17	422	1.385
18	55	2.09
19	55	2.09
20	155	1.85
21	450	1.323
22	410	1.394
23	55	2.09
24	155	1.85
25	342.02	1.0984
26	226.81	1.5384
27	344.22	1.0969
28	255.85	1.4626
29	253.33	1.4657
30	252.36	1.4669
31	290.99	1.6704
32	347.12	1.3703
33	473.59	1.0132
34	347.12	1.3703
35	287.72	1.3597
36	345.25	1.0962
37	246.79	1.5109
38	464.18	1.2878
39	360.69	1.086
40	354.25	1.3986
41	271.85	1.48
42	386.49	1.3392
43	553	1.5136
44	553	0.9572

3	340	1.09
4	315	1.522
5	555	0.96
6	450	1.364
7	570	1.229
8	550	1.35
9	310	1.526
10	365	1.08
11	470	1.39
12	425	1.433
13	470	1.45
14	470	1.4
15	315	1.51
16	422	1.385
17	422	1.385
18	55	2.09
19	55	2.09
20	155	1.85
21	450	1.323
22	410	1.394
23	55	2.09
24	155	1.85
25	342.02	1.0984
26	279.78	1.43
27	226.81	1.5384
28	252.36	1.4669
29	347.12	1.3703
30	290.99	1.6704
31	473.59	1.0132
32	347.12	1.3703
33	345.25	1.0962
34	287.72	1.3597
35	464.18	1.2878
36	246.79	1.5109
37	360.69	1.086
38	354.25	1.3986
39	271.85	1.48
40	386.49	1.3392
41	553	1.5136
42	553	0.9572

Angle	***Coeffs***	
1	35	120.0001
2	35	109.5
3	50	119.7001
4	80	126.0001
5	50	109.5
6	50	109.5
7	70	117.0001
8	80	120.0001
9	50	113
10	80	110
11	80	120.4001
12	65	111.1
13	65	124.0001
14	50	116.8001
15	70	120.0001
16	50	116.2
17	65	126.1001

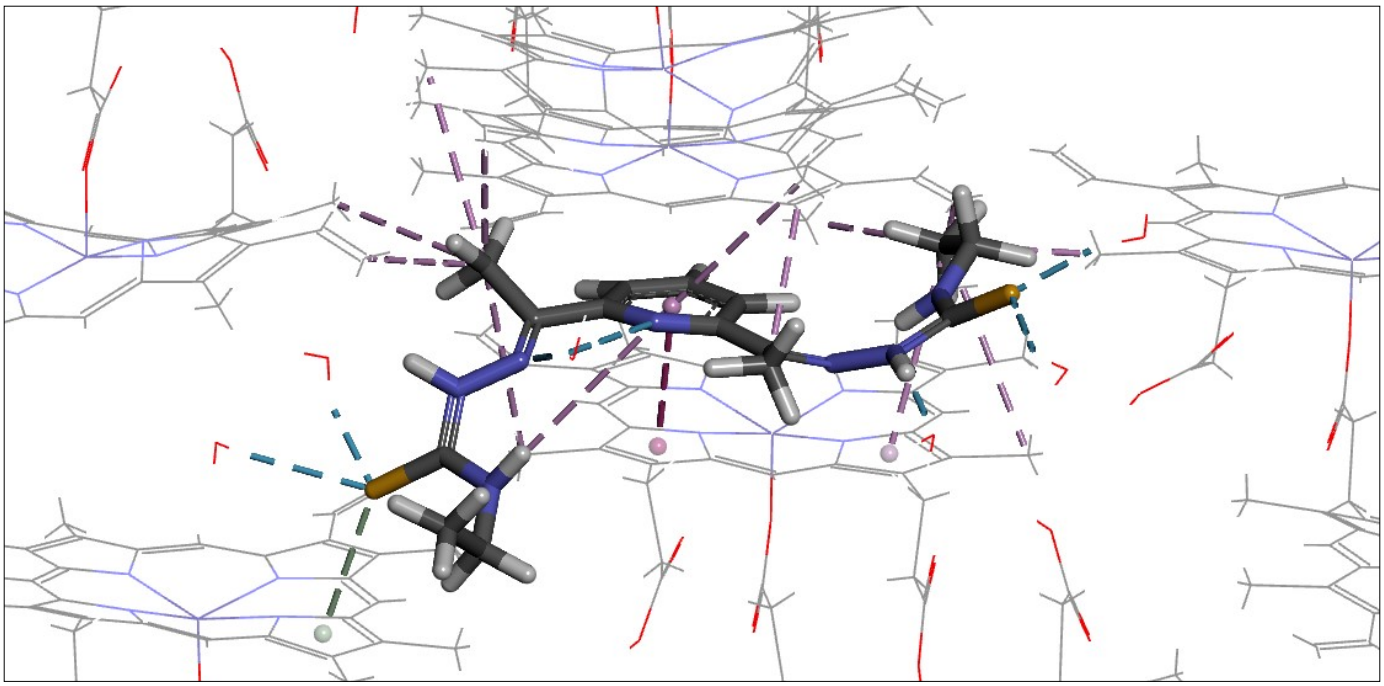
Angle	***Coeffs***	
1	35	120.0001
2	35	109.5
3	50	119.7001
4	80	126.0001
5	50	109.5
6	50	109.5
7	70	117.0001
8	80	120.0001
9	50	113
10	80	110
11	80	120.4001
12	65	111.1
13	65	124.0001
14	50	116.8001
15	70	120.0001
16	50	116.2
17	65	126.1001

18	70	125.0001
19	65	129.5001
20	65	106.4
21	50	109.5
22	70	106.2
23	70	125.0001
24	70	110.4
25	70	125.0001
26	70	126.2001
27	65	114
28	70	106.2
29	45	87.00004
30	70	110.4
31	70	125.0001
32	65	152.0001
33	65	152.0001
34	80	126.0001
35	80	126.0001
36	35	104
37	35	104
38	80	125.0001
39	50	146.0001
40	80	115
41	70	106.2
42	35	104
43	70	110.4
44	70	125.0001
45	65	152.0001
46	80	126.0001
47	50	146.0001
48	35.77	107.5
49	35.64	108.55
50	35.8	107.73
51	43.28	109.18
52	77.68	112.38
53	47.85	109.63
54	47.84	110.09
55	65.42	110.84
56	78.19	110.7
57	76.96	114.07
58	65.29	111.17
59	48.06	108.52
60	69.23	125.6401
61	76.49	122.9001
62	57.7	117.3601
63	69.72	123.8701
64	76.43	110.18
65	61.2	119.1101
66	85.01	121.6701
67	65.69	123.7601
68	43.66	110.88
69	88.93	117.8601
70	44.9	119.8801
71	61.58	120.7901
72	59.77	119.1001
73	67.49	120.6001
74	67.45	117.4601
75	68.17	122.9401
76	83.15	117.2401
77	63.67	120.0201

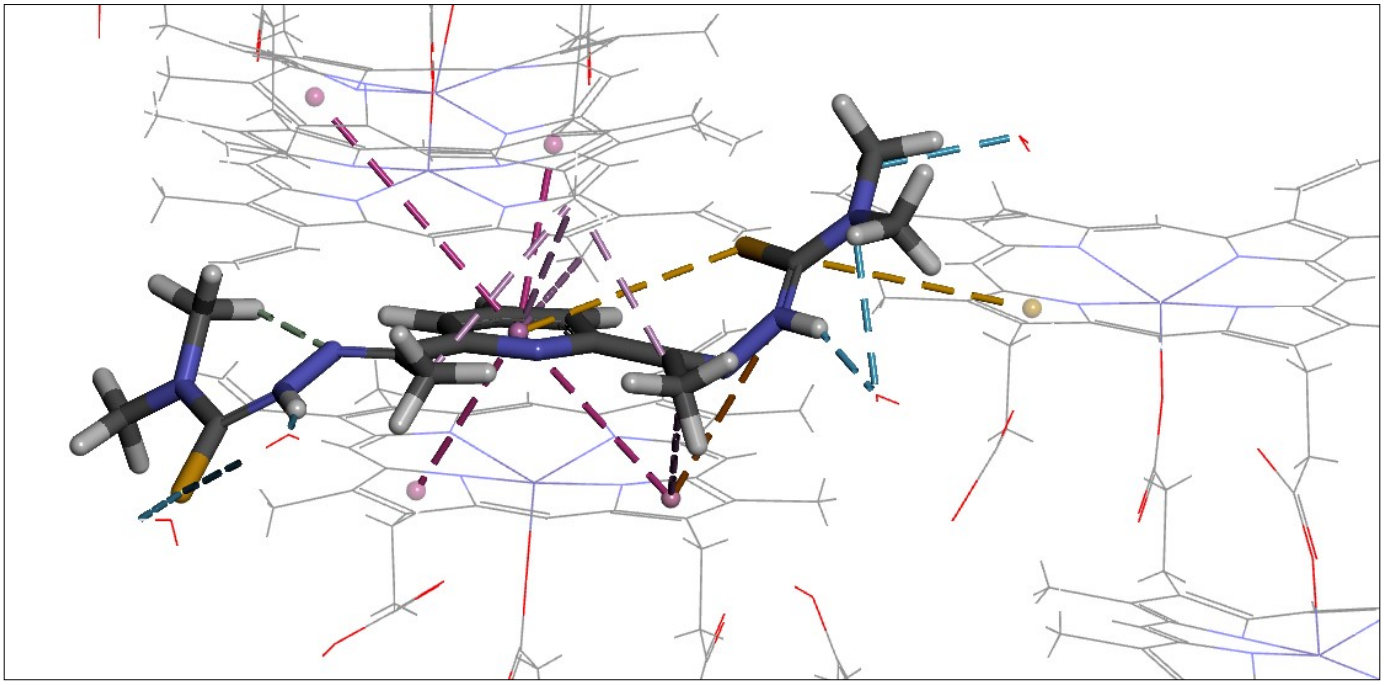
18	70	125.0001
19	65	129.5001
20	65	106.4
21	50	109.5
22	70	106.2
23	70	125.0001
24	70	110.4
25	70	125.0001
26	70	126.2001
27	65	114
28	70	106.2
29	45	87.00004
30	70	110.4
31	70	125.0001
32	65	152.0001
33	65	152.0001
34	80	126.0001
35	80	126.0001
36	35	104
37	35	104
38	80	125.0001
39	50	146.0001
40	80	115
41	70	106.2
42	35	104
43	70	110.4
44	70	125.0001
45	65	152.0001
46	80	126.0001
47	50	146.0001
48	35.77	107.5
49	35.8	107.73
50	43.28	109.18
51	56.68	108.08
52	88.28	113.3
53	76.42	110.09
54	76.96	114.07
55	69.23	125.6401
56	65.29	111.17
57	48.06	108.52
58	76.49	122.9001
59	57.7	117.3601
60	76.43	110.18
61	69.72	123.8701
62	65.69	123.7601
63	61.2	119.1101
64	85.01	121.6701
65	88.93	117.8601
66	43.66	110.88
67	44.9	119.8801
68	61.58	120.7901
69	67.49	120.6001
70	59.77	119.1001
71	67.45	117.4601
72	68.17	122.9401
73	83.15	117.2401
74	63.67	120.0201

Dihedral	*Coeffs*		
1	6.65	-1	2
2	0.15	1	3
3	0	1	2
4	0.155556	1	3
5	0.8	1	1
6	0.08	-1	3
7	1.9	1	1
8	2.3	-1	2
9	3.625	-1	2
10	2.55	-1	2
11	4.8	-1	2
12	0	1	1
13	0.155556	1	3
14	2.4	-1	2
15	0.155556	1	3
16	0.225	1	3
17	0.73	1	3
18	2.5	-1	2
19	2.26	1	1
20	0.03	-1	3
21	0.65	-1	4
22	0	-1	2
23	0	1	3
24	0.8	-1	2
25	0.4	1	2
26	0.6	-1	2
27	0.82	-1	1
28	1	-1	2
29	0.75	-1	3
30	0.26	-1	3
31	0.7	-1	2
32	1.1	-1	2
33	10.5	-1	2

Dihedral	*Coeffs*		
1	6.65	-1	2
2	0.15	1	3
3	0	1	2
4	0.155556	1	3
5	0.8	1	1
6	0.08	-1	3
7	1.9	1	1
8	2.3	-1	2
9	3.625	-1	2
10	2.55	-1	2
11	4.8	-1	2
12	0	1	1
13	0.155556	1	3
14	2.4	-1	2
15	0.155556	1	3
16	0.337	1	3
17	0.25	1	1
18	0	1	3
19	2.5	-1	2
20	0.35	-1	1
21	1.38	1	2
22	1.16	1	3
23	2.26	1	1
24	0.03	-1	3
25	0.65	-1	4
26	0	-1	2
27	0.8	-1	2
28	0.4	1	2
29	0.82	-1	1
30	1	-1	2
31	0.75	-1	3
32	0.6	-1	2
33	0.26	-1	3
34	0.7	-1	2
35	1.1	-1	2
36	10.5	-1	2



(a) βHM–L1 complex



(b) βHM–L2 complex

Figure S2: 3D representation of important non-covalent interactions in: (a) βHM–L1 and (b) βHM–L2 complexes. βHM molecular fragments are represented by lines and the ligand molecules are represented by sticks, with C, N, O, H and S atoms colored gray, blue, red, white and yellow respectively. The colored dashed-lines represent non-covalent interactions, which are purple for hydrophobic interactions, orange for electrostatic interactions, yellow for π-Sulfur interactions and blue/light-green for hydrogen bonds.