Supporting Information

NOVEL APPROACH TO ACCURATELY PREDICT BOND STRENGTH AND LIGAND LABILITY IN PLATINUM-BASED ANTICANCER DRUGS

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Table S1. Selected bond lengths (Å) obtained at M06-2X/LANL2TZ(f)/6-311++G** level of theory for the native square-planar complexes (**I-R** and **II-R**) and the corresponding transition states (**I-TS** and **II-TS**).

Table S2. IBSI values and activation energies (kcal mol^{-1}) at M06-2X/LANL2TZ(f)/6-311++G** level of theory for the pre-reactive complexes (**I-PR** and **II-PR**) and the corresponding transition states (**I-TS** and **II-TS**).

Table S3. IBSI values of the Pt-L bonds in the constrained reactant geometries with a fixed Pt–L distance of 2.085 Å for **I-R** and 2.057 Å for **II-R**.

Table S4. IBSI values of the Pt-L and T-Pt bonds in the constrained reactant geometries with fixed Pt–L/T-Pt bond distances of 2.085 Å/2.616 Å for **I-R**, and 2.057 Å/2.697 Å for **II-R**.

Figure S1. 0.3 a.u. δg^{pair} isosurfaces in $[Pt(NH_3)_2(H_2O)_2T]^{n+}$ (**I-PR**) pre-reactive complexes and the integrated IBSI values for the T-Pt and Pt-H_2O coordinate bonds. BGR color code in the range $-0.1 < \rho \times sign\,(\lambda_2) < 0.1$ a.u.

Table S5. Optimized geometries of the platinum-based anticancer drugs obtained at the M06-2X/LANL2TZ(f)/6-311++G** level of theory.

Table S1. Selected bond lengths (Å) obtained at M06-2X/LANL2TZ(f)/6-311++G** level of theory for the native square-planar complexes (**I-R** and **II-R**) and the corresponding transition states (**I-TS** and **II-TS**).

Series I		**T = H_2O**	**T = F^-**	**T = NH_3**	**T = Cl^-**	**T = Br^-**	**T = I^-**	**T = SO_3^{2-}**	**T = CH_3^-**	**T = CN^-**	**T = CO**	**T = H^-**
I-R	**Pt−H_2O**	2.085	2.112	2.128	2.148	2.161	2.186	2.275	2.327	2.205	2.145	2.328
	T−Pt	2.085	1.966	2.024	2.297	2.417	2.616	2.202	1.989	1.888	1.820	1.507
	Pt−NH_3	2.057	2.051	2.060	2.051	2.063	2.062	2.074	2.062	2.068	2.069	2.061
		2.057	2.058	2.066	2.061	2.052	2.050	2.064	2.072	2.057	2.059	2.068
I-TS	**Pt−H_2O**	2.422	2.521	2.490	2.517	2.532	2.586	2.804	3.127	2.513	2.367	2.688
		2.474	2.509	2.493	2.523	2.513	2.528	2.799	2.923	2.519	2.425	2.696
	T−Pt	2.132	1.987	2.027	2.304	2.418	2.615	2.197	1.984	1.877	1.807	1.499
	Pt−NH_3	2.057	2.053	2.059	2.049	2.053	2.060	2.080	2.057	2.059	2.057	2.068
		2.048	2.049	2.058	2.054	2.053	2.048	2.064	2.078	2.058	2.057	2.068
Series II		**T = H_2O**	**T = F^-**	**T = NH_3**	**T = Cl^-**	**T = Br^-**	**T = I^-**	**T = SO_3^{2-}**	**T = CH_3^-**	**T = CN^-**	**T = CO**	**T = H^-**
II-R	**Pt−NH_3**	2.004	2.032	2.057	2.042	2.052	2.061	2.170	2.251	2.147	2.114	2.266
	T−Pt	2.130	2.018	2.056	2.379	2.499	2.697	2.246	2.003	1.914	1.835	1.523
	Pt−Cl	2.349	2.361	2.356	2.363	2.366	2.363	2.370	2.378	2.363	2.350	2.372
		2.350	2.362	2.356	2.363	2.365	2.362	2.381	2.383	2.362	2.351	2.371
II-TS	**Pt−NH_3**	2.413	2.501	2.488	2.481	2.483	2.476	2.605	2.783	2.517	2.369	2.680
		2.410	2.501	2.487	2.481	2.483	2.476	2.611	2.809	2.517	2.369	2.680
	T−Pt	2.196	2.024	2.030	2.366	2.471	2.666	2.209	1.986	1.874	1.795	1.504
	Pt−Cl	2.350	2.365	2.357	2.361	2.364	2.363	2.389	2.380	2.365	2.351	2.379
		2.350	2.365	2.357	2.361	2.364	2.363	2.380	2.385	2.365	2.351	2.379

Table S2. IBSI values and activation energies (kcal mol^{-1}) at M06-2X/LANL2TZ(f)/ 6-311++G** level of theory for the pre-reactive complexes (**I-PR** and **II-PR**).

Series I		**T = H_2O**	**T = F^-**	**T = NH_3**	**T = Cl^-**	**T = Br^-**	**T = I^-**	**T = SO_3^{2-}**	**T = CH_3^-**	**T = CN^-**	**T = CO**	**T = H^-**
Pt$^{\underline{\text{IBSI}}}$$H_2O$	**I-PR**	0.306	0.277	0.253	0.243	0.232	0.212	0.164	0.141	0.204	0.242	0.141
	IBSI$^{\sigma}$	-0.207	-0.191	-0.166	-0.159	-0.150	-0.138	-0.120	-0.117	-0.122	-0.130	-0.090
T$^{\underline{\text{IBSI}}}$Pt	**I-PR**	0.274	0.356	0.384	0.296	0.275	0.211	0.464	0.474	0.540	0.679	0,533
	IBSI$^{\pi}$	-0.032	-0.009	0.004	0.005	0.001	-0.001	-0.002	0.006	0.023	0.037	0.001
IBSI$^{\text{trans}}$		**-0.239**	**-0.200**	**-0.162**	**-0.154**	**-0.149**	**-0.139**	**-0.122**	**-0.111**	**-0.099**	**-0.093**	**-0.089**
Activation energy ($\Delta G^{\neq}$)		16.6	17.4	15.9	13.6	12.1	11.8	9.5	6.7	12.4	11.6	7.8
Series II		**T = H_2O**	**T = F^-**	**T = NH_3**	**T = Cl^-**	**T = Br^-**	**T = I^-**	**T = SO_3^{2-}**	**T = CH_3^-**	**T = CN^-**	**T = CO**	**T = H^-**
Pt$^{\underline{\text{IBSI}}}$$NH_3$	**II-PR**	0.423	0.390	0.359	0.372	0.365	0.348	0.256	0.200	0.284	0.319	0,197
	IBSI$^{\sigma}$	-0.297	-0.290	-0.257	-0.267	-0.260	-0.245	-0.183	-0.151	-0.188	-0.177	-0,135
T$^{\underline{\text{IBSI}}}$Pt	**II-PR**	0.228	0.300	0.334	0.238	0.220	0.186	0.416	0.451	0.492	0.635	0,513
	IBSI$^{\pi}$	-0.028	0.010	0.046	0.017	0.021	0.012	0.062	0.031	0.073	0.104	0,030
IBSI$^{\text{trans}}$		**-0.325**	**-0.280**	**-0.211**	**-0.250**	**-0.239**	**-0.233**	**-0.121**	**-0.120**	**-0.115**	**-0.073**	**-0.105**
Activation energy ($\Delta G^{\neq}$)		13.2	27.0	23.9	24.1	22.2	20.7	14.6	13.2	15.0	11.8	13.1

To clearly establish the electronic effects captured by IBSI without considering the influence of the bond distance we followed the methodology proposed by De Proft and coworkers[34]. Thus, to eliminate the distance effects we take the frozen $Pt(NH_3)_2H_2O$ part of the $[Pt(NH_3)_2(H_2O)_2]^{2+}$ complex and we complete it with the *trans* ligands T keeping the Pt-T bond distances of their corresponding structures. Results demonstrate that electronic effects exerted by the T ligand are well recovered by IBSI, as the *trans*-effect trend is preserved.

For the halogenated series (T = F^-, Cl^-, Br^- and I^-) we also fix the T-Pt bond, and we calculate the IBSI value for the Pt-L and T-Pt bonds. We can observe the decrease of the IBSI associated to Pt-L in line with the increase of the T-Pt IBSI values as expected, revealing a too affluence role played by the bond distance in the halogenated series.

Table S3. IBSI values of the Pt-L bonds in the constrained reactant geometries with a fixed Pt–L distance of 2.085 Å for **I-R** and 2.057 Å for **II-R**.

		T = H_2O	**T = F^-**	**T = NH_3**	**T = Cl^-**	**T = Br^-**	**T = I^-**	**T = SO_3^{2-}**	**T = CH_3^-**	**T = CN^-**	**T = CO**	**T = H^-**
I-R	**Pt-H_2O**	0.279	0.274	0.265	0.259	0.258	0.248	0.237	0.211	0.252	0.262	0.232
II-R	**Pt-NH_3**	0.362	0.355	0.344	0.344	0.343	0.332	0.314	0.305	0.330	0.337	0.306

Table S4. IBSI values of the Pt-L and T-Pt bonds in the constrained reactant geometries with fixed Pt–L/T-Pt bond distances of 2.085 Å/2.616 Å for **I-R**, and 2.057 Å/2.697 Å for **II-R**.

		T = F^-	**T = Cl^-**	**T = Br^-**	**T = I^-**
I-R	**Pt-H_2O**	0.280	0.268	0.264	0.248
	T-Pt	0.092	0.160	0.190	0.214
II-R	**Pt-NH_3**	0.371	0.357	0.352	0.332
	T-Pt	0.077	0.135	0.159	0.192

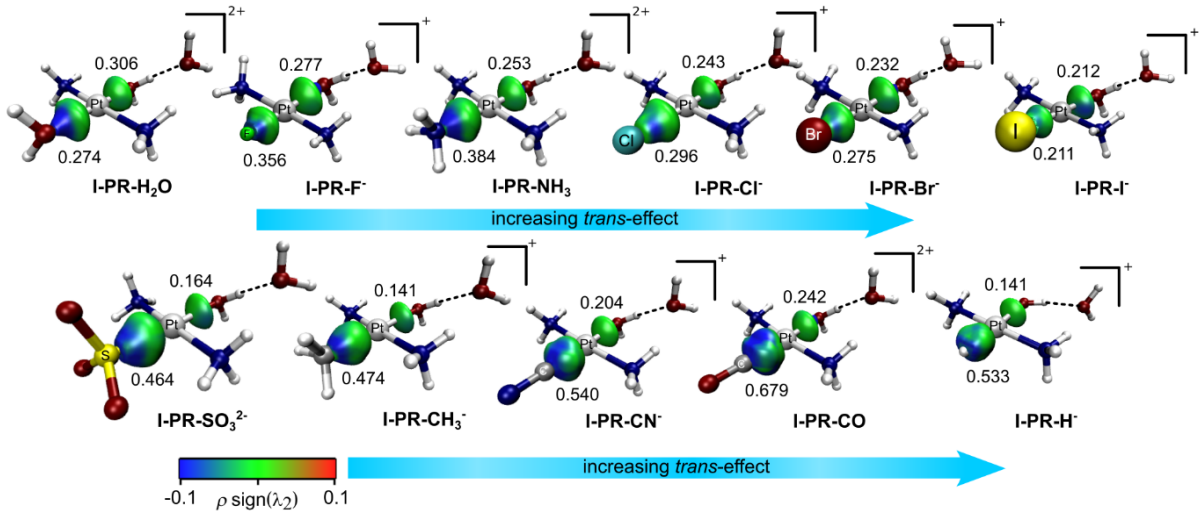

Figure S1. 0.3 a.u. δg^{pair} isosurfaces in $[Pt(NH_3)_2(H_2O)_2T]^{n+}$ (**I-PR**) pre-reactive complexes and the integrated IBSI values for the T-Pt and Pt-H_2O coordinate bonds. BGR color code in the range $-0.1 < \rho \times sign\,(\lambda_2) < 0.1$ a.u.

Table S5. Optimized geometries of the platinum-based anticancer drugs obtained at the M06-2X/LANL2TZ(f)/6-311++G** level of theory.

1. Cisplatin

Pt	0.048548	0.068813	-0.169693
N	0.417089	1.539848	1.220271
H	-0.019708	2.429026	0.984782
H	1.411409	1.714944	1.352788
H	0.039621	1.249185	2.121697
N	0.908781	1.183948	-1.669043
H	0.443396	2.076554	-1.821088
H	0.855779	0.663681	-2.544313
H	1.893081	1.379243	-1.495773
Cl	-0.935470	-1.185708	1.579249
Cl	-0.358594	-1.605116	-1.793930

2. *cis*-$[PtCl(H_2O)(NH_3)_2]^+$

Pt	-0.001273	0.000333	-0.005948
N	0.419836	1.396138	1.385859
H	0.042234	2.312761	1.148373
H	1.421023	1.507715	1.540180
H	0.006632	1.123929	2.278456
N	0.913907	1.080366	-1.502209
H	0.429586	1.952307	-1.708107
H	0.915340	0.534206	-2.363120
H	1.884087	1.312384	-1.297749
Cl	-1.059321	-1.278816	1.657723
O	-0.455838	-1.445262	-1.508908
H	-1.396223	-1.665758	-1.540744
H	0.017371	-2.286503	-1.374146

3. *cis*-[Pt $(H_2O)_2(NH_3)_2]^{2+}$

Pt	0.039338	0.096029	-0.006363
N	0.442530	1.490822	1.391030
H	-0.005168	2.384032	1.186545
H	1.439143	1.667934	1.510530
H	0.083247	1.179909	2.294495
N	0.937695	1.133783	-1.479849
H	0.483118	2.028010	-1.662196
H	0.892901	0.597107	-2.347278
H	1.922744	1.320810	-1.296605
O	-0.900638	-0.996018	1.561730
H	-1.843377	-1.177399	1.453565
H	-0.471440	-1.826021	1.807552
O	-0.400966	-1.357938	-1.495037
H	-1.336870	-1.547109	-1.641477
H	0.051681	-2.205194	-1.388583

4. *cis*-$[PtI_2(NH_3)_2]$

Pt	0.087052	-0.031356	-0.014607
N	0.599290	1.468181	1.334357
H	0.276553	2.389600	1.045253
H	1.608834	1.522085	1.457618
H	0.196312	1.280593	2.250958
N	0.811671	1.152510	-1.564422
H	0.125309	1.856766	-1.830123
H	0.995721	0.589503	-2.392968
H	1.673872	1.641144	-1.330973
I	-0.853659	-1.472166	2.046203
I	-0.506940	-1.920612	-1.833370

5. Carboplatin

Pt	0.577647	-0.009717	0.066232
N	0.550612	1.667788	1.242678
H	-0.277093	2.244898	1.107440
H	1.361924	2.268502	1.109827
H	0.553689	1.373225	2.219139
N	0.584619	1.022428	-1.703443
H	-0.238262	1.606060	-1.840429
H	0.599890	0.343567	-2.464578
H	1.400765	1.619977	-1.820815
O	0.640960	-1.083603	1.787284
O	0.661263	-1.701337	-1.055349
C	0.184065	-2.836560	-0.645194
O	0.323069	-3.868657	-1.285453
C	0.200134	-2.303197	1.851385
O	0.383835	-3.009692	2.832679
C	-0.617578	-2.828094	0.667658
C	-1.394915	-4.136827	0.899967
H	-0.963992	-5.036656	0.466313
H	-1.569596	-4.278349	1.965898
C	-1.994432	-2.114501	0.434898
H	-2.349434	-1.654917	1.359436
H	-2.038731	-1.382481	-0.371625
C	-2.618442	-3.507582	0.197021
H	-3.598949	-3.693065	0.633609
H	-2.642711	-3.754039	-0.865173

6. *cis*-diammine(pyridine)-chloroplatinum

Pt	-0.060285	-0.034570	-0.075812
N	-0.774134	-1.277403	-1.563628
H	-1.778022	-1.439032	-1.504928
H	-0.321472	-2.189958	-1.566183
H	-0.592710	-0.854615	-2.473481
N	-0.774823	-1.315034	1.381003
H	-1.789971	-1.276029	1.459405
H	-0.397859	-1.098088	2.302517
H	-0.527821	-2.285472	1.194555
Cl	0.769318	1.392160	-1.755929
C	1.605494	2.958052	3.291048
C	0.252999	2.646765	3.232297
C	-0.191165	1.772971	2.254802
N	0.646779	1.215758	1.363889
C	1.955291	1.517099	1.415549
C	2.468147	2.382851	2.366358
H	1.980622	3.639664	4.044094
H	-0.458518	3.071759	3.926833
H	-1.237156	1.508957	2.163957
H	2.581287	1.050238	0.667311
H	3.528017	2.597212	2.371082

7. $[(NHC)Cl_2Pt]^{2-}$

Pt	-1.995242	-0.791610	-1.685027
Cl	-3.534962	-0.816619	0.282378
Cl	-3.582038	-2.252551	-2.949922
N	0.198925	2.053340	0.418373
C	1.166736	1.448607	-0.264065
C	-1.014961	1.441372	0.136099
C	-0.797336	0.423133	-0.748881
N	0.583064	0.465822	-0.971196
N	0.242432	-0.706262	-5.200214
C	1.198119	-0.538968	-4.290870
C	-0.982173	-0.843713	-4.560774
C	-0.785049	-0.761056	-3.210987
N	0.596262	-0.567219	-3.089500
H	-1.888692	-0.994575	-5.120087
H	-1.928779	1.781417	0.590710
C	1.262510	-0.506996	-1.802927
H	2.304367	-0.225142	-1.932010
H	1.200279	-1.485172	-1.325819
C	2.651332	-0.371310	-4.547237
H	3.216887	-1.200337	-4.117825
H	2.842181	-0.345182	-5.617795
H	3.011717	0.563204	-4.113101
C	2.614051	1.779679	-0.238101
H	2.781004	2.679368	0.350142
H	3.188134	0.965120	0.207395
H	2.983734	1.958666	-1.249263
C	0.375882	3.191917	1.319038
H	-0.595329	3.433647	1.741738
H	1.063070	2.929591	2.121293
H	0.752088	4.050612	0.765485
C	0.441781	-0.742023	-6.648653
H	1.100837	-1.566822	-6.914143
H	-0.528783	-0.893233	-7.112844
H	0.861566	0.202118	-6.991345

8. $[(NHC)Br_2Pt]^{2-}$

Pt	-2.455625	-0.803465	-1.581403
Br	-4.127930	-2.364421	-2.889170
Br	-4.079214	-0.767859	0.496484
N	-0.198545	2.032713	0.482677
C	0.755724	1.389193	-0.183163
C	-1.427050	1.449329	0.204945
C	-1.233855	0.409166	-0.660006
N	0.148601	0.410251	-0.875456
N	-0.212499	-0.718946	-5.099393
C	0.745932	-0.590647	-4.186559
C	-1.440090	-0.842148	-4.463462
C	-1.242686	-0.790384	-3.112281
N	0.142256	-0.630081	-2.986520
H	-2.348394	-0.961906	-5.027184
H	-2.332253	1.822427	0.650714
C	0.803303	-0.588159	-1.696954
H	1.854555	-0.340853	-1.820600
H	0.705244	-1.561600	-1.216541
C	2.202110	-0.445296	-4.439794
H	2.754508	-1.280202	-4.005147
H	2.395626	-0.427421	-5.510044
H	2.574956	0.486241	-4.009662
C	2.211538	1.680410	-0.154172
H	2.402189	2.572902	0.437801
H	2.762183	0.848980	0.289471
H	2.587769	1.853117	-1.163942
C	0.005100	3.178469	1.368556
H	-0.962430	3.457264	1.776685
H	0.674585	2.905848	2.182316
H	0.414478	4.016523	0.807097
C	-0.013779	-0.728046	-6.548389
H	0.636391	-1.554306	-6.830368
H	-0.985955	-0.860175	-7.015066
H	0.415759	0.218371	-6.872324

9. Lobaplatin

Pt	-0.139399	0.059211	-0.177369
N	0.053489	1.486154	1.347243
H	-0.915235	1.756549	1.516625
N	1.618884	0.330479	-1.206198
H	1.635457	-0.489828	-1.815147
O	-1.948660	-0.446791	0.608231
O	-0.572159	-1.344946	-1.525185
C	-1.593221	-2.176155	-1.035572
C	-2.470970	-1.486605	0.023966
H	2.442693	0.249426	-0.610790
H	0.338367	0.997848	2.194569
O	-3.573675	-1.932524	0.316090
C	-1.020425	-3.451770	-0.408205
H	-0.380623	-3.188755	0.439389
H	-1.815377	-4.115975	-0.062989
H	-0.415011	-3.977851	-1.148295
H	-2.260202	-2.455528	-1.860642
C	1.747514	1.556960	-2.041592
H	2.576379	1.426555	-2.742913
C	0.864418	2.731054	1.219983
H	1.882014	2.503733	1.544364
H	0.458191	3.482833	1.901797
C	0.882120	3.254167	-0.200220
C	1.393778	4.689007	-0.458723
C	2.013769	4.171015	-1.778741
C	1.988224	2.757406	-1.161237
H	-0.101478	3.122989	-0.665411
H	2.172359	4.959083	0.259295
H	0.654521	5.487320	-0.510612
H	1.299812	4.247560	-2.602280
H	2.976965	4.571814	-2.091484
H	2.908209	2.607335	-0.582308
H	0.822775	1.667559	-2.610805

9a. Protonated Lobaplatin

Pt	0.020230	-0.002173	0.029282
N	0.269661	1.377509	1.583594
H	-0.686847	1.592561	1.863790
N	1.797579	0.243260	-0.899667
H	1.885164	-0.606673	-1.460396
O	-1.908018	-0.551223	0.723545
O	-0.429014	-1.356540	-1.380746
C	-1.445261	-2.211275	-0.959382
C	-2.304359	-1.534340	0.088309
H	2.586291	0.232484	-0.252513
H	0.668799	0.884960	2.381076
O	-3.472337	-2.069807	0.323800
C	-0.902188	-3.506478	-0.336308
H	-0.279007	-3.265470	0.528243
H	-1.707020	-4.177320	-0.030995
H	-0.286209	-4.006352	-1.083598
H	-2.103514	-2.465478	-1.799379
C	1.917462	1.431821	-1.797784
H	2.770607	1.279211	-2.463409
C	0.993409	2.677430	1.412808
H	2.023182	2.534335	1.745583
H	0.531460	3.415410	2.072389
C	0.979166	3.157849	-0.021737
C	1.429152	4.603611	-0.329774
C	2.059742	4.067983	-1.638078
C	2.103339	2.678146	-0.970064
H	-0.000485	2.973130	-0.476376
H	2.201750	4.928947	0.371391
H	0.656290	5.367578	-0.400744
H	1.335160	4.083484	-2.455522
H	3.001206	4.499514	-1.974338
H	3.031539	2.594185	-0.391247
H	1.007815	1.483423	-2.397914
H	-3.919652	-1.599582	1.046600

10. Nedaplatin

Pt	0.022256	0.051048	-0.016260
N	0.240970	1.713585	1.166103
H	-0.141668	2.563036	0.755744
N	1.133976	0.863626	-1.577566
H	1.202428	0.184628	-2.333778
O	-1.059535	-0.817952	1.413489
O	-0.295074	-1.681145	-1.027008
C	-1.015836	-2.537118	-0.364456
O	-1.318133	-3.640464	-0.802095
C	-1.486081	-2.093336	1.024306
H	2.087481	1.104111	-1.314715
H	-0.264803	1.548787	2.035880
H	0.714541	1.701405	-1.975346
H	1.207920	1.910124	1.416470
H	-1.133911	-2.862473	1.725910
H	-2.583345	-2.159587	1.007924

10a. Protonated Nedaplatin

Pt	0.019633	-0.052268	0.001770
N	0.234964	1.607723	1.127054
H	-0.166210	2.442702	0.703373
N	1.068880	0.791405	-1.578340
H	1.141971	0.138198	-2.356490
O	-0.981929	-0.928673	1.498992
O	-0.346164	-1.911945	-0.934859
C	-1.062913	-2.613526	-0.213902
O	-1.443555	-3.806869	-0.584365
C	-1.563415	-2.132140	1.122291
H	2.022208	1.046442	-1.326762
H	-0.250686	1.456238	2.011594
H	0.622493	1.629388	-1.946475
H	1.207365	1.815151	1.349514
H	-1.368357	-2.931774	1.848671
H	-2.657693	-2.062850	1.012795
H	-1.098820	-4.011969	-1.468938

11. Heptaplatin

Pt	-0.072246	0.024150	-0.031848
N	-0.207982	1.666693	1.199072
H	-1.207597	1.875457	1.218305
N	1.734105	0.407401	-0.932235
H	1.955810	-0.485009	-1.378133
O	-1.906736	-0.414610	0.726391
O	-0.064087	-1.625254	-1.229090
C	-0.720721	-2.699253	-0.915758
C	-2.340884	-1.634333	0.804809
H	2.493437	0.573216	-0.271319
H	0.014492	1.356780	2.144618
C	-1.359934	-2.760453	0.472806
H	-1.871946	-3.711944	0.580265
H	-0.546599	-2.705360	1.204573
O	-3.477472	-1.904617	1.163476
C	1.741824	1.458639	-1.982790
H	2.632264	1.347888	-2.603932
C	0.541578	2.917543	0.925758
H	1.565027	2.789591	1.281130
H	0.088266	3.734977	1.487290
C	0.519252	3.267538	-0.557408
O	0.558004	4.682478	-0.698468
O	1.759567	3.793799	-2.402380
C	1.750641	2.837512	-1.360805
H	-0.393210	2.874441	-1.024691
H	2.647971	2.964309	-0.735471
H	0.855337	1.329697	-2.603946
O	-0.810369	-3.657396	-1.669034
C	1.409432	5.019353	-1.794973
H	2.311010	5.496922	-1.383700
C	0.711616	5.928933	-2.784944
H	-0.184291	5.393877	-3.119110
C	0.301898	7.228291	-2.093140
H	-0.220615	7.880094	-2.795785
H	-0.355709	7.037562	-1.243993
H	1.185480	7.763806	-1.732136
C	1.623729	6.201007	-3.980197
H	2.546070	6.690933	-3.652824
H	1.889769	5.279049	-4.498673
H	1.125623	6.865141	-4.689133