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Electronic Supplementary Information

A ratiometric fluorescence sensor for caffeine

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1. Selectivity screening

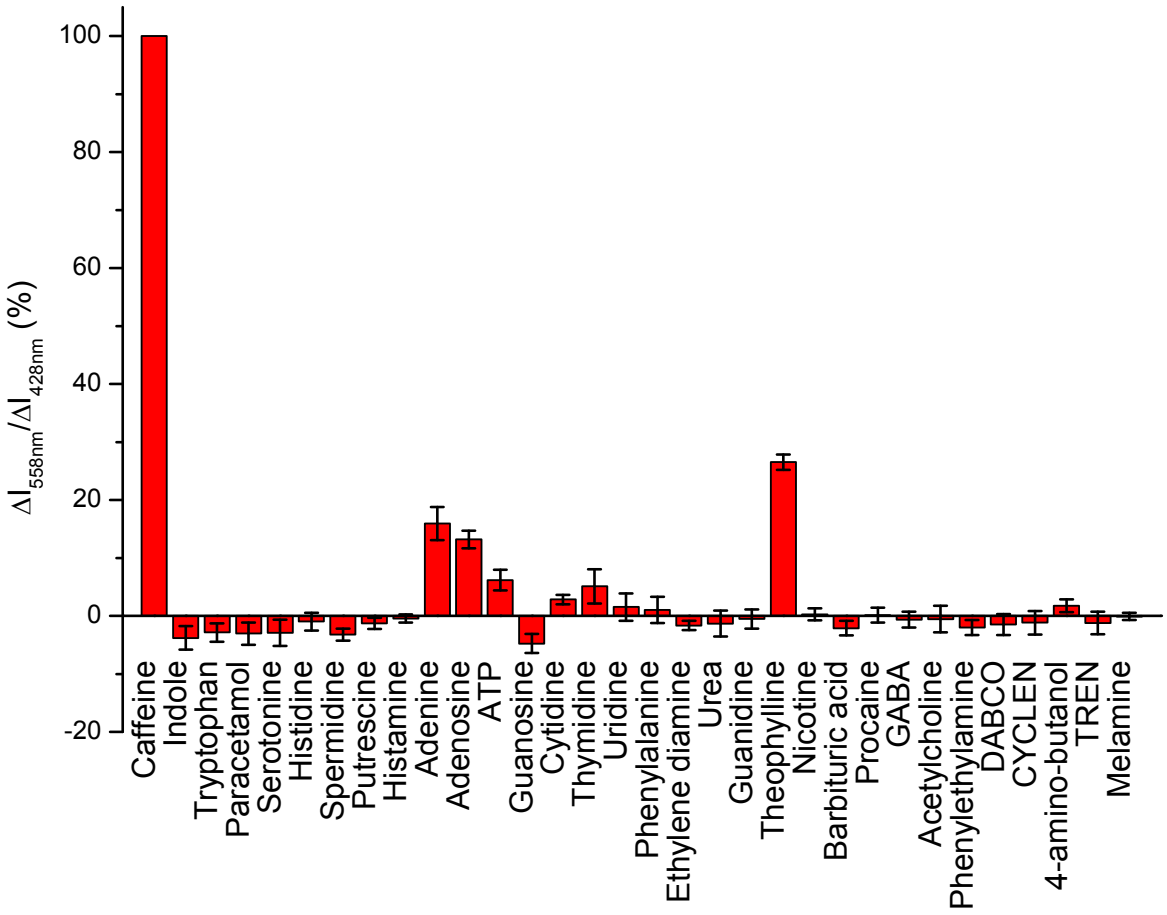

Figure S1. Normalized ratiometric change of the emission of **1** in the presence of different analytes ([**1**]= 150 μM, [analyte] = 750 μM, λ_{ex} = 350 nm, 100 mM phosphate buffer, pH 7.0, average value of three independent measurements).

2. ^{1}H and ^{13}C-NMR of disodium 3,4:3',4'-bibenzo[b]thiophene-2,2'-disulfonate

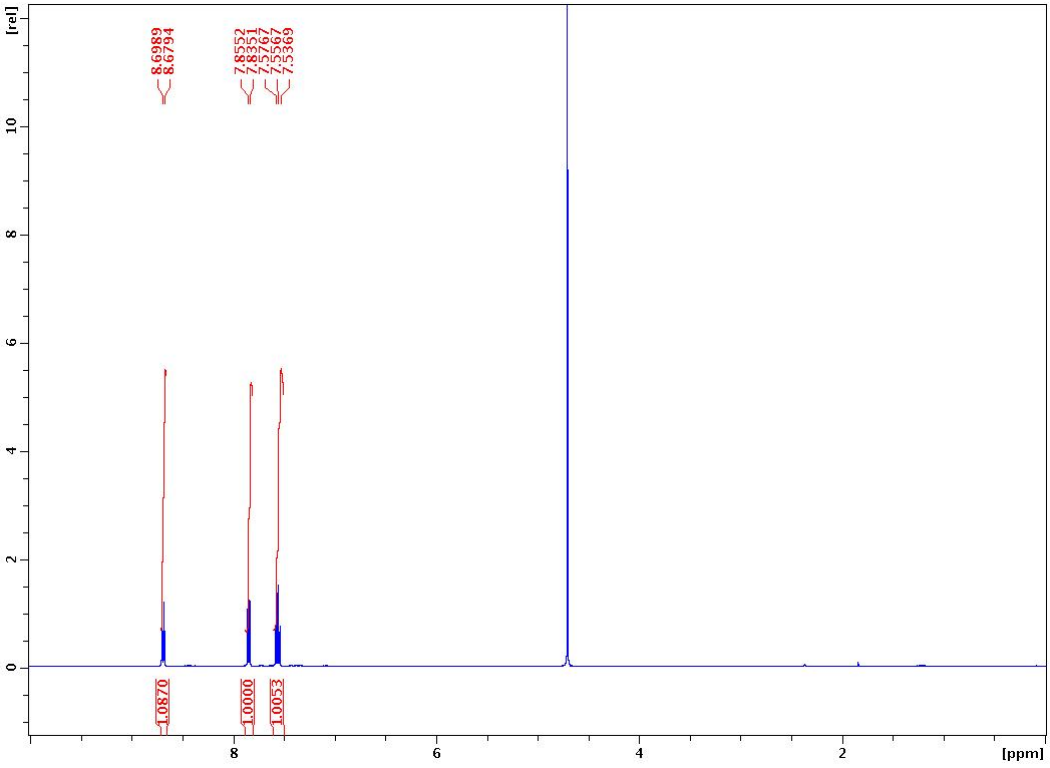

Figure S2. ^{1}H-NMR (400 MHz, D_2O) of disodium 3,4:3',4'-bibenzo[b]thiophene-2,2'-disulfonate.

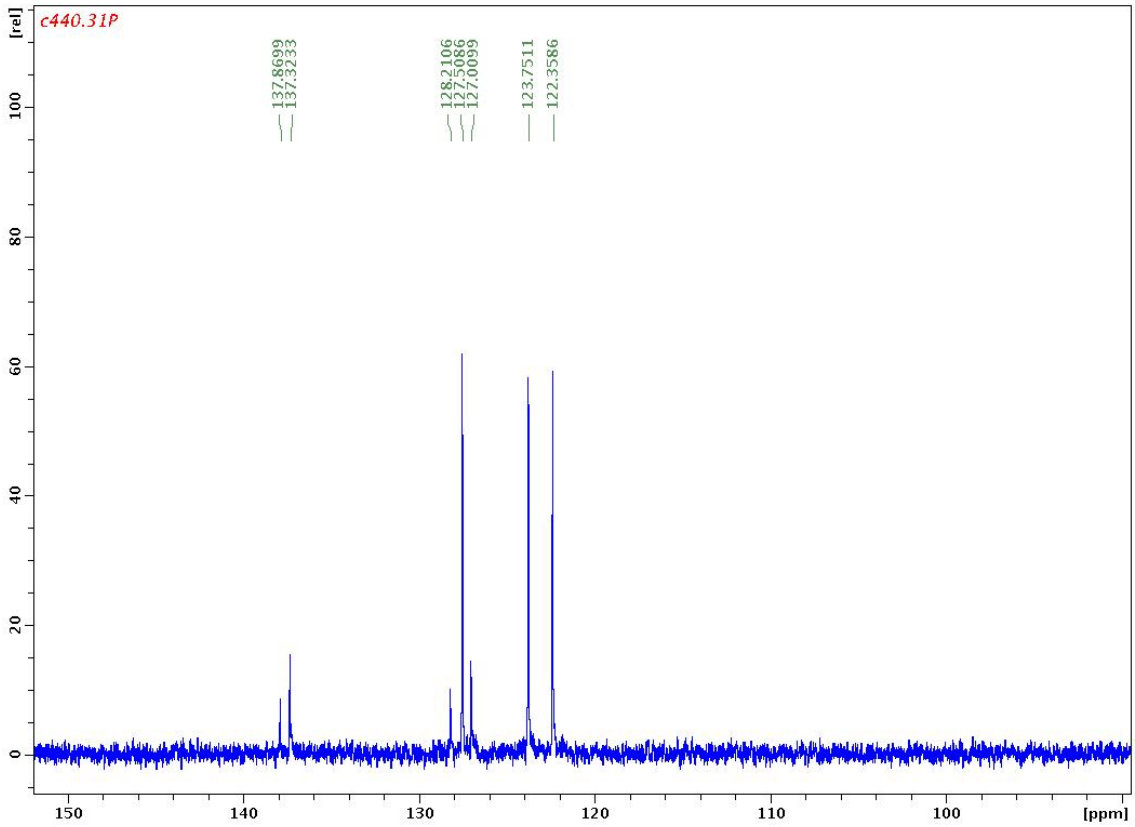

Figure S3. ^{13}C-NMR (100 MHz, D_2O) of disodium 3,4:3',4'-bibenzo[b]thiophene-2,2'-disulfonate.

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3. Computational study

DFT computations

All (TD)-DFT computations were performed in Gaussian 09[1] using the ωB97X-D[2] functional and def2-SVP[3] basis set in combination with the SMD implicit solvent model[4] with default parameters corresponding to water.

The interaction and, if applicable, the excitation/fluorescence energies are given in Table S1.

Note that the interaction energies are not corrected for basis set superposition, which is ill defined for an excimer.

Table S1. Interaction energies (ΔE) and excitation energies for the relevant species at the ωB97X-D/def2-SVP level of theory, supplemented by the SMD solvation model. An asterix is used to indicate geometries optimized in the first excited state

	Interaction energy/ (kcal mol^{-1})	Excitation/Fluorescence energy/eV (nm)
1 / 1*		3.5 (351) / 2.8 (436)
1···Caffeine	-26.1	
1···Caffeine*	-24.7	2.8 (438)
1_2	-24.4	
1_2*		2.4 (507)
1_2···Caffeine*	-23.6	2.5 (500)

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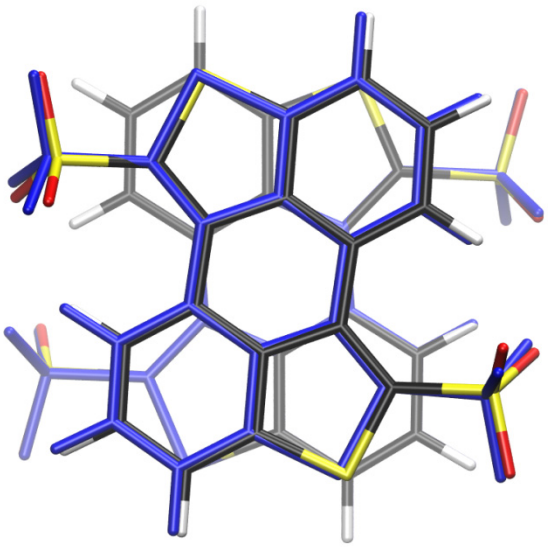

Figure S4 Excimer of $\mathbf{1}_2$···caffeine (in blue) superimposed on the excimer of $\mathbf{1}_2$. Three atoms of the central ring of the monomer on the opposite side of caffeine are taken for the superposition. The TD-ωB97X-D/def2-SVP transition energies are 506.7 and 500.0 nm for the freely optimized excimer of $\mathbf{1}_2$ and the geometry taken from $\mathbf{1}_2$···caffeine. The blue-shift in the presence of caffeine is due to the slight reorientation of the excimer and not to a direct implication of caffeine in the excited state.

MD simulations

The MD simulations were performed with the AMBER 11 suite of program.[5, 6]

Standard GAFF[7] parameters in combination with AM1-BCC[8, 9] atomic charges are used for organic molecules. The solvent was treated using by the TIP3P[10] water model. All bonds towards hydrogens are fixed with the SHAKE[11] algorithm and an integration step of 2 fs is used. Constant temperature (300 K) is maintained with a Langevin thermostat (collision frequency of 2 ps^{-1}).[12] Generalized-Born implicit solvent computations used the default settings and atomic radii.[13]

Explicit solvent computations:

The truncated octahedral solvation box has (initially) a minimal distance of 15 Å from the solute and the pressure (1 bar) is regulated with a Berendsen barostat (relaxation time of 1 ps and the default compressibility).[14] The electrostatic interactions are evaluated with a particle mesh-Ewald[15] summation (real space of 8 Å).

Umbrella sampling:

The reaction coordinate is defined as the centre of mass (COM) distance between the central ring of **1** and the fused ring system of the analytes (see Figure S5). A force constant of 4 kcal mol^{-1} $Å^{-1}$ has been applied to simulations in the gas-phase and in the implicit solvent. With the explicit solvent, the force constant was increased to 10 kcal mol-1 $Å^{-1}$. After a 5 ns equilibration at 300 K, biased

simulations were performed for 18 windows between 3.2 and 15 Å, each with a length of 500 ps, giving a total sampling time of 9 ns for each free energy profile.

The biased simulations were analysed by the weighted histogram analysis method (WHAM)[16, 17] and the binding free energy (ΔG) was evaluated as the free energy difference between the minimum and the energy at 10 Å (see Table S2).

Interaction energies (ΔE) were computed for fully optimized geometries.

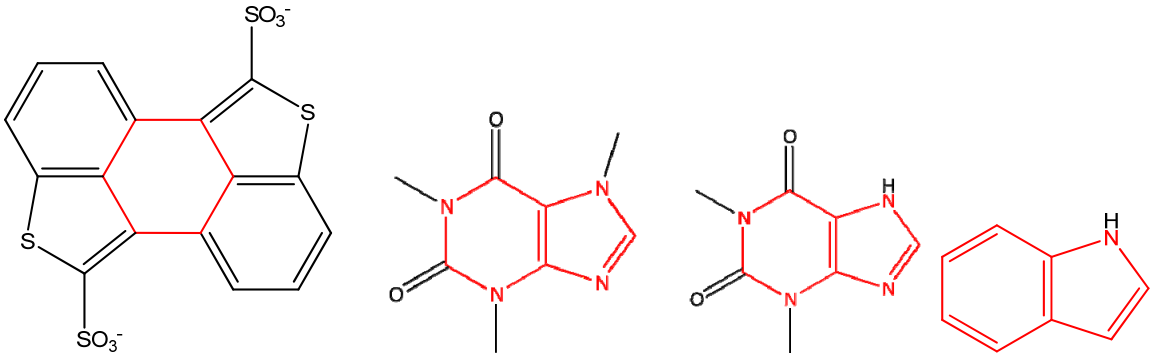

Figure S5: Representation of dye **1**, caffeine, theophylline, and indole with the atoms considered to calculate the center of mass (COM) given in red.

Table S2 Interaction energies (ΔE) and binding free energies (ΔG) in the gas-phase (GP), a generalized Born implicit solvation model (GB) and explicit water (H_2O). All values are in kcal mol^{-1}.

	ΔE/GP	ΔE/GB	ΔG/GP	ΔG/GB[1]	ΔG/H_2O[1]
Caffeine	-26.8	-12.2	-15.2	-3.9	-6.3
Theopylline	-26.8	-11.8	-16.8	-3.6	-5.0
Indole	-16.1	-9.1	-8.2	-2.3	-1.8

[1]ΔG at 10.0 Å.

ωB97X-D/def2-SVP geometries with SMD implicit solvation:

Caffeine

N	-1.09511	1.25433	5.97052
C	0.17336	1.83996	5.98419
N	1.26608	1.00826	6.04493
C	-1.37694	-0.12265	5.97681
C	-0.18222	-0.90633	6.01706
C	1.08075	-0.35346	6.04476

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N	0.02100	-2.27302	6.03414
C	1.35297	-2.44352	6.06680
N	2.03801	-1.30456	6.07376
C	2.59317	1.60508	6.03893
O	0.29988	3.05603	5.94522
O	-2.52470	-0.55124	5.94799
C	-0.99069	-3.31283	6.01033
C	-2.21070	2.19168	5.91362
H	1.79902	-3.43693	6.08538
H	2.66595	2.36686	6.82509
H	3.32662	0.81612	6.23119
H	2.80545	2.06990	5.06598
H	-1.69509	-3.17184	6.83892
H	-1.53864	-3.29100	5.05964
H	-0.49229	-4.28267	6.11970
H	-2.16619	2.88848	6.76015
H	-2.18146	2.76604	4.97779
H	-3.14114	1.62006	5.95864

1

S	-3.36334	1.63554	0.20372
C	-1.73170	2.24532	0.24251
C	-0.77475	1.26386	0.16172
C	-1.38872	-0.04580	0.06437
C	-2.79247	-0.00115	0.07449
C	0.69555	1.33283	0.15883
C	1.37301	0.09168	0.06202
C	0.75905	-1.21807	-0.03419
C	-0.71126	-1.28684	-0.03389
C	1.71601	-2.19979	-0.11165

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S	3.34766	-1.59001	-0.07283
C	2.77677	0.04700	0.05230
C	3.54704	1.21298	0.13598
C	2.87445	2.42209	0.22934
C	1.47162	2.48824	0.24113
C	-3.56275	-1.16692	-0.01202
C	-2.89018	-2.37578	-0.10879
C	-1.48735	-2.44196	-0.12007
H	3.44629	3.34987	0.29573
H	-3.46203	-3.30333	-0.17818
H	4.63770	1.17360	0.12798
H	-4.65341	-1.12756	-0.00390
H	0.99880	3.46429	0.31581
H	-1.01454	-3.41775	-0.19817
S	1.57909	-3.98554	-0.24419
O	2.98199	-4.44070	-0.28240
O	0.84095	-4.23927	-1.49840
O	0.84845	-4.42238	0.96310
S	-1.59475	4.03066	0.38044
O	-0.85268	4.28030	1.63313
O	-2.99763	4.48538	0.42450
O	-0.86805	4.47177	-0.82770

1*

S	-3.00965	-2.18125	-0.00064
C	-2.81657	-0.46727	-0.00076
C	-1.44876	-0.07886	-0.00147
C	-0.59304	-1.22860	-0.00165
C	-1.29113	-2.45572	-0.00153
C	-0.82914	1.21214	-0.00210

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C	0.59304	1.22860	-0.00165
C	1.44876	0.07886	-0.00145
C	0.82914	-1.21214	-0.00208
C	2.81657	0.46727	-0.00074
S	3.00965	2.18125	-0.00063
C	1.29113	2.45572	-0.00153
C	0.62837	3.67713	-0.00226
C	-0.78318	3.65756	-0.00326
C	-1.49726	2.47553	-0.00322
C	-0.62837	-3.67713	-0.00224
C	0.78318	-3.65756	-0.00323
C	1.49727	-2.47553	-0.00318
H	-1.32322	4.60649	-0.00418
H	1.32322	-4.60649	-0.00413
H	1.17319	4.62278	-0.00223
H	-1.17319	-4.62278	-0.00222
H	-2.58403	2.51203	-0.00444
H	2.58404	-2.51203	-0.00438
S	4.31247	-0.48814	0.00106
O	5.37970	0.53361	0.00244
O	4.28528	-1.31102	-1.22943
O	4.28207	-1.31122	1.23132
S	-4.31246	0.48814	0.00105
O	-4.28207	1.31122	1.23131
O	-5.37970	-0.53360	0.00243
O	-4.28529	1.31103	-1.22944

1...Caffeine

S	2.992395	0.921021	-1.829564

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C	2.627865	-0.601965	-1.063095
C	1.284456	-0.819511	-0.883024
C	0.513273	0.311944	-1.360896
C	1.308204	1.338693	-1.891236
C	0.546880	-1.954199	-0.306499
C	-0.863760	-1.829342	-0.287235
C	-1.634768	-0.701583	-0.770733
C	-0.896244	0.445022	-1.321262
C	-2.979551	-0.929792	-0.615010
S	-3.350829	-2.472407	0.105180
C	-1.661440	-2.859999	0.235974
C	-1.096935	-4.024358	0.768167
C	0.285782	-4.133851	0.750327
C	1.099488	-3.122424	0.216053
C	0.745571	2.522814	-2.380467
C	-0.633457	2.651395	-2.319310
C	-1.447475	1.633340	-1.798573
H	0.757650	-5.029814	1.158552
H	-1.102525	3.569114	-2.679152
H	-1.720969	-4.819797	1.179633
H	1.369573	3.321418	-2.785273
H	2.177223	-3.262109	0.232024
H	-2.522333	1.791596	-1.768982
S	-4.407779	0.080998	-1.009178
O	-5.553897	-0.759733	-0.616043
O	-4.334564	0.340975	-2.460640
O	-4.269215	1.306323	-0.189858
S	4.060343	-1.624678	-0.711732
O	4.017708	-1.938614	0.733298

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O	5.199200	-0.765634	-1.086708
O	3.905080	-2.820522	-1.563799
N	0.279967	3.107927	1.057763
C	1.637982	2.789624	1.133165
N	1.983496	1.566415	1.657126
C	-0.787443	2.307037	1.489498
C	-0.335204	1.057369	2.014971
C	0.998307	0.718693	2.101553
N	-1.015390	-0.011410	2.562252
C	-0.074380	-0.902457	2.916256
N	1.165915	-0.492338	2.672872
C	3.390074	1.217594	1.775927
O	2.489278	3.585251	0.759461
O	-1.950083	2.687705	1.417197
C	-2.449047	-0.132892	2.747765
C	-0.031155	4.420945	0.504705
H	-0.335404	-1.858637	3.368705
H	3.856061	1.747257	2.618906
H	3.466180	0.138564	1.928680
H	3.919456	1.474750	0.853112
H	-2.776095	0.490600	3.590601
H	-2.971188	0.193578	1.841974
H	-2.687328	-1.181426	2.958729
H	0.170660	5.211237	1.242433
H	0.575500	4.601501	-0.387835
H	-1.090636	4.440482	0.237108

1...Caffeine*

S	2.98047	0.93886	-1.80115
C	2.66015	-0.57554	-1.03936

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C	1.26838	-0.79834	-0.85378
C	0.50404	0.31205	-1.33847
C	1.29292	1.35137	-1.87550
C	0.55328	-1.89815	-0.28258
C	-0.86369	-1.79570	-0.28156
C	-1.62924	-0.69143	-0.77950
C	-0.91245	0.42669	-1.31408
C	-3.02096	-0.93903	-0.63357
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C	-1.65166	-2.83912	0.24972
C	-1.08331	-3.97996	0.80324
C	0.32476	-4.07114	0.81515
C	1.12446	-3.07549	0.28963
C	0.72890	2.51701	-2.37846
C	-0.67650	2.63741	-2.33167
C	-1.47867	1.63683	-1.82006
H	0.79201	-4.95511	1.25356
H	-1.13948	3.55153	-2.70794
H	-1.69807	-4.78085	1.21792
H	1.34499	3.31903	-2.78863
H	2.20552	-3.18306	0.33671
H	-2.55639	1.77778	-1.80061
S	-4.43621	0.06011	-1.00702
O	-5.58046	-0.78819	-0.61723
O	-4.38206	0.34943	-2.45699
O	-4.30833	1.28729	-0.18297
S	4.06502	-1.62831	-0.78462
O	4.10727	-1.97239	0.65844
O	5.20761	-0.79593	-1.21286

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O	3.84091	-2.82170	-1.63034
N	0.29377	3.09515	1.06443
C	1.65353	2.78446	1.15035
N	1.99974	1.56570	1.68561
C	-0.77502	2.28672	1.48164
C	-0.32041	1.04723	2.02689
C	1.01433	0.71960	2.13177
N	-0.99953	-0.01888	2.57966
C	-0.05571	-0.89851	2.95525
N	1.18498	-0.48244	2.72050
C	3.40243	1.19875	1.80222
O	2.49718	3.58594	0.77147
O	-1.94033	2.65398	1.38411
C	-2.43540	-0.15243	2.73773
C	-0.01533	4.40573	0.50604
H	-0.31578	-1.85012	3.41769
H	3.80924	1.50502	2.77767
H	3.49871	0.11411	1.68510
H	3.97040	1.69142	1.00639
H	-2.78566	0.46421	3.57691
H	-2.94354	0.17088	1.82189
H	-2.66846	-1.20446	2.94004
H	0.24703	5.20070	1.21896
H	0.54480	4.56115	-0.42262
H	-1.08775	4.44620	0.29818

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S	0.97445	3.51359	1.93322
C	1.87861	2.02275	1.89420
C	1.08525	0.90611	1.79019

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C	-0.31667	1.26935	1.76533
C	-0.52999	2.65511	1.81949
C	1.41748	-0.52493	1.73236
C	0.31674	-1.41813	1.70169
C	-1.08553	-1.05621	1.72960
C	-1.41735	0.37609	1.73855
C	-1.87999	-2.17607	1.76951
S	-0.97547	-3.66760	1.73861
C	0.52989	-2.80470	1.68484
C	1.82073	-3.34717	1.66192
C	2.88848	-2.46521	1.67843
C	2.69645	-1.07410	1.72104
C	-1.82081	3.19808	1.81431
C	-2.88809	2.31665	1.77082
C	-2.69643	0.92506	1.73971
H	3.90695	-2.85619	1.64965
H	-3.90613	2.70889	1.75200
H	1.98090	-4.42621	1.63283
H	-1.98133	4.27699	1.84432
H	3.56889	-0.42484	1.71733
H	-3.56823	0.27645	1.69235
S	-3.63899	-2.37663	2.08302
O	-3.83325	-3.83934	2.04316
O	-4.38533	-1.66693	1.02250
O	-3.84234	-1.78280	3.42013
S	3.63833	2.20327	2.21225
O	3.85199	1.52993	3.50936
O	3.83446	3.66548	2.25839
O	4.37193	1.55721	1.10299

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S	0.97503	-3.51350	-1.93169
C	1.87916	-2.02261	-1.89361
C	1.08570	-0.90596	-1.79034
C	-0.31622	-1.26920	-1.76562
C	-0.52946	-2.65499	-1.81913
C	1.41791	0.52505	-1.73252
C	0.31716	1.41821	-1.70174
C	-1.08513	1.05631	-1.72981
C	-1.41697	-0.37599	-1.73901
C	-1.87952	2.17623	-1.76992
S	-0.97499	3.66772	-1.73879
C	0.53036	2.80477	-1.68492
C	1.82119	3.34724	-1.66219
C	2.88897	2.46528	-1.67882
C	2.69690	1.07417	-1.72127
C	-1.82025	-3.19803	-1.81389
C	-2.88758	-2.31667	-1.77070
C	-2.69603	-0.92504	-1.73984
H	3.90744	2.85625	-1.65023
H	-3.90558	-2.70903	-1.75193
H	1.98133	4.42630	-1.63365
H	-1.98073	-4.27696	-1.84375
H	3.56932	0.42489	-1.71751
H	-3.56783	-0.27644	-1.69247
S	-3.63847	2.37655	-2.08377
O	-3.83291	3.83925	-2.04478
O	-3.84180	1.78190	-3.42052
O	-4.38459	1.66730	-1.02278
S	3.63887	-2.20335	-2.21175

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O	4.37294	-1.55678	-1.10310
O	3.83490	-3.66561	-2.25708
O	3.85217	-1.53079	-3.50931

12*

S	-1.37248	-3.44411	1.76096
C	-2.11197	-1.87794	1.78353
C	-1.17633	-0.84175	1.72738
C	0.16645	-1.36163	1.69554
C	0.22321	-2.76695	1.67910
C	-1.33512	0.59614	1.68007
C	-0.14129	1.36153	1.69737
C	1.20166	0.84166	1.72086
C	1.36023	-0.59616	1.67114
C	2.13737	1.87789	1.77404
S	1.39790	3.44400	1.75614
C	-0.19827	2.76690	1.68261
C	-1.41234	3.45088	1.60052
C	-2.58465	2.68885	1.55863
C	-2.55581	1.29874	1.60093
C	1.43675	-3.45084	1.58809
C	2.60865	-2.68882	1.53786
C	2.58013	-1.29865	1.58158
H	-3.54712	3.19549	1.46663
H	3.57040	-3.19533	1.43796
H	-1.45046	4.54124	1.57605
H	1.47465	-4.54117	1.56232
H	-3.49232	0.74869	1.54245
H	3.51619	-0.74891	1.51599
S	3.89197	1.86486	2.11089

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O	4.23851	3.29796	2.21576
O	4.57848	1.19447	0.98435
O	4.03407	1.12078	3.38132
S	-3.86422	-1.86666	2.13353
O	-3.99458	-1.13946	3.41488
O	-4.21162	-3.30072	2.22221
O	-4.55977	-1.18063	1.02222
S	-1.39867	3.44455	-1.75494
C	-2.13781	1.87830	-1.77353
C	-1.20183	0.84226	-1.72077
C	0.14098	1.36240	-1.69708
C	0.19767	2.76778	-1.68178
C	-1.36007	-0.59559	-1.67165
C	-0.16615	-1.36081	-1.69627
C	1.17652	-0.84064	-1.72788
C	1.33496	0.59724	-1.68016
C	2.11238	-1.87668	-1.78428
S	1.37318	-3.44298	-1.76190
C	-0.22267	-2.76615	-1.68022
C	-1.43608	-3.45029	-1.58962
C	-2.60814	-2.68849	-1.53903
C	-2.57986	-1.29832	-1.58219
C	1.41159	3.45198	-1.59966
C	2.58408	2.69017	-1.55805
C	2.55552	1.30009	-1.60088
H	-3.56980	-3.19524	-1.43947
H	3.54644	3.19703	-1.46602
H	-1.47379	-4.54063	-1.56441
H	1.44951	4.54234	-1.57487

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H	-3.51596	-0.74869	-1.51619
H	3.49209	0.75011	-1.54267
S	3.86473	-1.86523	-2.13375
O	4.21231	-3.29926	-2.22225
O	3.99538	-1.13808	-3.41511
O	4.56000	-1.17906	-1.02235
S	-3.89244	1.86520	-2.11022
O	-4.57882	1.19367	-0.98427
O	-4.23920	3.29834	-2.21376
O	-4.03449	1.12226	-3.38131

12...Caffeine*

S	1.79057	-0.24682	3.22114
C	2.17596	0.48590	1.69908
C	1.33211	0.06170	0.67082
C	0.37404	-0.89871	1.15287
C	0.48422	-1.15485	2.53079
C	1.26717	0.41325	-0.73232
C	0.31013	-0.28345	-1.51291
C	-0.63293	-1.26431	-1.03646
C	-0.62452	-1.54894	0.38074
C	-1.40098	-1.77082	-2.09343
S	-0.98575	-1.05420	-3.61793
C	0.22143	-0.04435	-2.89517
C	1.01837	0.90623	-3.53237
C	1.93650	1.61277	-2.75029
C	2.06444	1.37431	-1.38541
C	-0.39394	-2.01858	3.19014
C	-1.39156	-2.63519	2.42797
C	-1.51014	-2.41202	1.06101

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H	2.56027	2.37792	-3.21626
H	-2.11019	-3.29336	2.92014
H	0.93286	1.09065	-4.60442
H	-0.30624	-2.20747	4.26121
H	2.78626	1.95408	-0.81629
H	-2.30801	-2.89989	0.50465
S	-2.50079	-3.16911	-2.26416
O	-3.03849	-3.01221	-3.63289
O	-3.54860	-3.09854	-1.22471
O	-1.65238	-4.37948	-2.11750
S	3.58503	1.58337	1.72484
O	4.49005	1.12533	0.64767
O	4.14264	1.39067	3.08243
O	3.10419	2.96039	1.49172
S	-1.40651	3.22157	-2.97402
C	-0.71461	3.51482	-1.41266
C	-1.25970	2.69535	-0.42337
C	-2.28006	1.83695	-0.96807
C	-2.46141	1.99262	-2.35337
C	-0.97347	2.57197	0.99225
C	-1.77969	1.66213	1.72065
C	-2.83077	0.83749	1.18247
C	-3.06064	0.89830	-0.24342
C	-3.44791	0.09559	2.19453
S	-2.73591	0.36287	3.74887
C	-1.58562	1.49141	3.10332
C	-0.57860	2.16832	3.79099
C	0.22208	3.05320	3.06230
C	0.03235	3.25910	1.69943

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C	-3.37501	1.21157	-3.06642
C	-4.11733	0.26643	-2.35216
C	-3.96985	0.10700	-0.97714
H	1.03343	3.57876	3.56883
H	-4.81461	-0.37948	-2.88848
H	-0.42207	2.01979	4.86070
H	-3.50998	1.33505	-4.14208
H	0.69879	3.93482	1.16937
H	-4.55413	-0.65511	-0.46659
S	-4.95764	-0.85913	2.20727
O	-5.15620	-1.17330	3.63761
O	-5.98735	0.04245	1.64620
O	-4.75083	-2.06964	1.38194
S	0.35227	4.94794	-1.31695
O	1.67523	4.51797	-0.81310
O	0.40485	5.43284	-2.71234
O	-0.33259	5.87368	-0.38819
N	4.66341	-2.14482	0.83474
C	5.18059	-1.56176	-0.32604
N	4.41757	-1.62360	-1.46938
C	3.47204	-2.87779	0.93310
C	2.81844	-3.00107	-0.33166
C	3.26975	-2.37833	-1.47557
N	1.69103	-3.69539	-0.71983
C	1.53423	-3.44051	-2.02954
N	2.48106	-2.65505	-2.53520
C	4.86500	-0.89841	-2.64647
O	6.27971	-1.02616	-0.32401
O	3.09006	-3.35725	1.99629

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C	0.86609	-4.55762	0.10547
C	5.41757	-1.88110	2.05409
H	0.69470	-3.85568	-2.58579
H	5.72588	-1.39493	-3.11727
H	4.03771	-0.85847	-3.36241
H	5.14988	0.12298	-2.36374
H	1.35359	-5.53341	0.24225
H	0.71378	-4.09420	1.08564
H	-0.10076	-4.68905	-0.39356
H	6.45885	-2.20625	1.93724
H	5.39129	-0.80715	2.28206
H	4.95185	-2.43715	2.87185

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