Supplemental Information for

Novel Homodimer Metabolites of GDC-0994 via Cytochrome P450-Catalyzed Radical Coupling

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Supplemental Methods

In Vivo Study. Male and female nonsurgicalized and bile duct–cannulated (BDC) Sprague-Dawley rats (n = 3 per group) were orally administered a single dose of [^{14}C]GDC-0994 at 50 mg/kg (100 µCi/kg) in 1% carboxymethylcellulose, 0.5% Tween, and 5 mM citrate solution. BDC rats were supplemented with an infusion of taurocholic acid (2.3 mg/ml in 0.9% saline) via the distal (duodenal) cannula. Urine and bile were collected on dry ice at approximately 0-8 h, 8-24 h, and then at 24-h intervals. Feces were collected on dry ice at intervals of 24 h up to 168 and 96 hours postdose from intact and BDC rats, respectively, and homogenized with 3–5 volumes of 50% (by volume) aqueous isopropyl alcohol. Plasma samples at 0 hour (predose) and at 1, 2, 4, 8, and 24 hours post-dose were also collected from another group of male and female rats for metabolite profiling.

Radioactivity Analysis. Total radioactivity in each matrix was measured by LSC analyses using a Model 2800TR analyzer (Perkin Elmer) with counting for 5 min. Plasma (~0.1 mL), urine (~0.3 ml) or bile (~0.1 ml) were mixed with Ultima Gold scintillation cocktail (5 mL) for radio counting. Fecal homogenates (~0.5 g) were dried and combusted in a Model 307 sample oxidizer (Perkin Elmer) and the resulting $^{14}CO_2$ was trapped in CarboSorb and Perma-Fluor scintillation cocktail was added for LSC counting.

Sample Preparation for Metabolite Profiling. Urine, bile, and feces were pooled with an equal percentage of the weight or volume collected to give a single sample that represented >95% of the radioactivity eliminated by each excretion route. Pooled urine and bile samples (~0.4 ml) were centrifuged, and the supernatants were injected directly for metabolite profiling. Plasma samples (1 mL) were extracted twice with three volumes of acetonitrile. Fecal samples (~1 g) were extracted three times with CAN. The extracts were combined, evaporated to dryness by an N-

Evaporator (Caliper Life Sciences, Hopkinton, MA), and reconstituted in 500 µL of ACN/H_2O (v/v, 1:3).

LC-MS/MS and Radioprofiling of Metabolites. Chromatography was performed on a Kinetex XB C18 column (150 x 4.6 mm, 2.6 µm particle size, Phenomenex, Torrance, CA) with mobile phases A (0.1% formic acid in water), and B (acetonitrile), at a constant flow rate of 1 ml/min. The gradient was as follows: initial holding at 10% B for 5 min, increased to 25% B at 20 min, 35% B at 40 min, 40% at 41 min, 45% at 50 min, and 95% B at 54 min, holding until 57 min and then column re-equilibration. The flow was split 10:1 post-column for radio-measurements and mass spectrometry, respectively. Radio-measurements were completed via fractionation to Deepwell LumaPlate 96 microplates (PerkinElmer) (10s per fraction), evaporation of solvents under vacuum, then counting radioactivity on the plates using a TopCount NXT scintillation and luminescence counter (PerkinElmer) for 5 min at 20 ^oC. Radioprofiles were reconstructed and integrated using the LSC import function in Laura software (LabLogic Systems; Brandon, FL). Mass spectrometric measurements were made with high resolution accurate mass full scan and tandem mass spectrometry (MS) experiments with an LTQ-Orbitrap with a heated electrospray ionization source (Thermo Scientific, San Jose, CA). The electrospray voltage was set at 4.0 kV and capillary temperature was 270^oC. The full-scan mass spectra were obtained at resolving power of 30,000 and corresponding data dependent MS^n scans following collision induced dissociation were acquired at a resolving power of 7,500.

Molecular Modeling Details

A survey of structures in the protein databank revealed that the structure with PDB code 6BD5 had the largest binding pocket volume of all CYP 3A4 structures (Michael Drummond, personal communication). A protein structure with a larger binding site volume was created by mutating residues bordering the binding site (Hayes et al., 2014). Residues that had a heavy atom within 4.5 Å of the native ligand in the 6BD5 structure were mutated to alanine (residues affected: R105 F107 S119 I120 R212 F213 F215 F241 I301 F304 A305 T309 A370 R372 L373 E374).

Following the creation of the bound ligand protein complexes through iterative growth and structure relaxation as described in the main text, the final protein structures did not deviate significantly from the original structure. For protein Cα atoms that were within 10 Å of either modeled dimer (i.e, the α-carbons near the binding site), the root mean square deviation between their positions in the original CYP3A4 structure and those of the current models were 1.1 Å (CYP3A4-**M13**) and 0.48 Å (CYP3A4-**M14**). The difference between the two is presumably due to a more globular shape to **M13**, which requires greater protein motion to fit in the CYP3A4 pocket compared to **M14**.

References

Hayes C, Ansbro D, and Kontoyianni M (2014) Elucidating substrate promiscuity in the human cytochrome 3A4. *J Chem Inf Model* **54:**857-869.

Coordinates, Energies and Correction Factors from DFT Calculations

The 3D coordinates for each atom of each step of the reaction coordinate in Figure 4 are listed. The corresponding energies and correction factors for calculation of zero-point energy (ZPE), enthalpy, and entropy are listed below each of the coordinates.

cpdI (doublet)

Fe	0.08985	0.04161	-0.36327
N	1.84727	-0.93077	-0.14071
N	-0.87452	-1.73699	-0.26205
N	1.03648	1.80272	-0.13577
N	-1.68541	0.99525	-0.29118
C	3.09280	-0.36101	-0.04918
C	-2.23303	-1.94178	-0.33421
C	2.05554	-2.28389	-0.20173
C	-0.30141	-2.99012	-0.30345
C	2.38733	2.00299	-0.03687
C	-2.92911	0.42685	-0.37388
C	0.47161	3.05016	-0.16895
C	-1.88852	2.35346	-0.31607
C	4.11144	-1.38345	-0.03976
C	-2.52233	-3.35437	-0.38666
C	3.46749	-2.57748	-0.14054
C	-1.32597	-4.00228	-0.37250
C	2.68449	3.41484	0.00229
C	-3.94560	1.44915	-0.43826
C	1.49276	4.06639	-0.08286
C	-3.29878	2.64628	-0.40306
H	5.17465	-1.19305	0.03266
H	-3.51771	-3.77697	-0.43862
H	3.89073	-3.57352	-0.16558
H	-1.13589	-5.06744	-0.40702
H	3.67959	3.83335	0.08304
H	-5.00922	1.25777	-0.50248
H	1.30380	5.13233	-0.08541
H	-3.72052	3.64291	-0.43229
C	3.34901	1.00054	0.01346
C	-3.19138	-0.93969	-0.38033
C	-0.88974	3.31419	-0.25637
C	1.05876	-3.24847	-0.28863
H	4.38694	1.30975	0.09043
H	-4.23076	-1.24686	-0.44691
H	-1.19619	4.35561	-0.27751
H	1.37117	-4.28724	-0.33207
O	0.16227	0.04880	-1.98261
S	-0.02198	-0.39125	2.22824
C	-1.70731	-0.05746	2.81579
H	-2.40012	-0.74549	2.31539
H	-1.75928	-0.23968	3.89321
H	-2.01484	0.96587	2.58566

SCF energy: -1625.578559 hartree
zero-point correction: +0.317644 hartree
enthalpy correction: +0.341313 hartree
free energy correction: +0.266301 hartree
quasiharmonic free energy correction: +0.268727 hartree

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cpdI (quartet)

Fe	0.08878	0.03912	-0.36679
N	1.85127	-0.92254	-0.14551
N	-0.86400	-1.74016	-0.26736
N	1.02636	1.80770	-0.12872
N	-1.69164	0.98498	-0.29346
C	3.09355	-0.34529	-0.05010
C	-2.22246	-1.95248	-0.33403
C	2.06808	-2.27408	-0.20704
C	-0.28478	-2.99142	-0.30414
C	2.37579	2.01492	-0.03106
C	-2.93238	0.41123	-0.37789
C	0.45474	3.05174	-0.16140
C	-1.90127	2.34249	-0.31490
C	4.11809	-1.36179	-0.04083
C	-2.50412	-3.36645	-0.38038
C	3.48153	-2.55952	-0.14444
C	-1.30448	-4.00833	-0.36682
C	2.66572	3.42842	0.00867
C	-3.95391	1.42853	-0.44200
C	1.47049	4.07361	-0.07526
C	-3.31286	2.62861	-0.40350
H	5.18000	-1.16517	0.03408
H	-3.49749	-3.79419	-0.42845
H	3.91065	-3.55301	-0.16989
H	-1.10919	-5.07264	-0.39792
H	3.65871	3.85208	0.08850
H	-5.01651	1.23212	-0.50773
H	1.27581	5.13851	-0.07766
H	-3.73931	3.62328	-0.43099
C	3.34256	1.01716	0.01710
C	-3.18686	-0.95674	-0.38306
C	-0.90797	3.30833	-0.24982
C	1.07624	-3.24383	-0.29285
H	4.37887	1.33137	0.09552
H	-4.22431	-1.27049	-0.44851

H	-1.22015	4.34809	-0.26883
H	1.39328	-4.28120	-0.33539
O	0.17298	0.08304	-1.98569
S	-0.02032	-0.39498	2.22663
C	-1.70802	-0.07500	2.81567
H	-2.39713	-0.76358	2.31097
H	-1.75851	-0.26585	3.89174
H	-2.02172	0.94833	2.59416

SCF energy: -1625.578152 hartree
zero-point correction: +0.317687 hartree
enthalpy correction: +0.341320 hartree
free energy correction: +0.265742 hartree
quasiharmonic free energy correction: +0.268181 hartree

FeIII-heme (sextet)

Fe	0.06497	-0.00127	0.10880
N	1.67358	-1.28586	-0.27675
N	-1.20941	-1.58021	-0.42516
N	1.38616	1.58040	-0.30082
N	-1.49610	1.28655	-0.43079
C	3.00639	-0.95425	-0.27008
C	-2.57447	-1.52131	-0.57025
C	1.60773	-2.65882	-0.29822
C	-0.86726	-2.91121	-0.43575
C	2.75761	1.52097	-0.29329
C	-2.82273	0.95507	-0.57546
C	1.04882	2.91151	-0.33893
C	-1.42696	2.66011	-0.45597
C	3.80766	-2.15587	-0.28064
C	-3.11217	-2.85870	-0.66717
C	2.94249	-3.21022	-0.29584
C	-2.05636	-3.71813	-0.58157
C	3.30473	2.85843	-0.32442
C	-3.61576	2.15661	-0.68200
C	2.24751	3.71875	-0.35041
C	-2.75283	3.21101	-0.60498
H	4.89019	-2.17859	-0.28300
H	-4.16077	-3.09748	-0.79357
H	3.17600	-4.26732	-0.31527
H	-2.06931	-4.79995	-0.62521
H	4.36124	3.09545	-0.33145
H	-4.69083	2.18033	-0.80935
H	2.26557	4.80082	-0.38469
H	-2.98183	4.26796	-0.65870
C	3.50916	0.34675	-0.26850
C	-3.32373	-0.34574	-0.62801
C	-0.25211	3.40979	-0.39299
C	0.43328	-3.40851	-0.35622
H	4.58981	0.45513	-0.26238
H	-4.39810	-0.45343	-0.74614
H	-0.36068	4.49008	-0.42498
H	0.54463	-4.48880	-0.37536
S	0.02331	-0.03785	2.43647
C	-1.75623	0.05950	2.88333
H	-2.33612	-0.69413	2.34443
H	-1.84498	-0.12319	3.95761
H	-2.15534	1.05116	2.65466

SCF energy: -1550.410452 hartree
zero-point correction: +0.313197 hartree
enthalpy correction: +0.336183 hartree
free energy correction: +0.260862 hartree
quasiharmonic free energy correction: +0.263772 hartree

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3 (doublet)

C	-3.41679	-0.02312	3.04581
H	-4.33162	-0.23197	3.60793
H	-2.55633	-0.49259	3.52945
S	-3.61890	-0.61570	1.33990
O	-0.14368	0.24850	-0.97904
Fe	-1.49188	-0.24493	0.08833
N	-2.30218	1.61909	0.02703
N	-0.48216	0.22593	1.76977
N	-0.84810	-2.13841	0.26260
N	-2.61741	-0.73368	-1.52222
C	-3.14330	2.13885	-0.93120
C	-3.40394	3.53207	-0.65958
C	-2.70311	3.85392	0.46194
C	-2.00572	2.65864	0.87631
C	-0.42323	1.45881	2.36266
C	0.45736	1.42422	3.50680
C	0.92968	0.15042	3.59934
C	0.33831	-0.58995	2.51153
C	0.00545	-2.65362	1.20223
C	0.25585	-4.04999	0.94109
C	-0.45806	-4.37170	-0.17315
C	-1.14174	-3.16991	-0.58870
C	-2.65222	-1.95840	-2.13481
C	-3.49028	-1.90758	-3.31157
C	-3.95318	-0.63175	-3.40463
C	-3.40195	0.09099	-2.28090
C	-3.64875	1.43431	-2.01257
H	-4.29356	1.97116	-2.70186
C	-1.13624	2.58640	1.95730
H	-0.99036	3.49476	2.53481
C	0.56131	-1.93573	2.25635
H	1.23729	-2.46495	2.92020

C	-1.97911	-3.09216	-1.69839
H	-2.10989	-3.99968	-2.28061
H	-4.04029	4.16828	-1.26170
H	-2.64312	4.80949	0.96768
H	0.67252	2.27152	4.14575
H	1.61624	-0.26414	4.32644
H	0.89604	-4.68520	1.54003
H	-0.52597	-5.32648	-0.67916
H	-3.68413	-2.74591	-3.96873
H	-4.60868	-0.20384	-4.15252
H	-3.25560	1.06201	3.03400
H	0.70569	-0.00865	-0.56817
N	2.94369	0.39775	-0.48140
C	3.07888	1.64990	-0.87558
C	3.93948	-0.54658	-0.40723
C	2.00467	2.47443	-1.34386
N	4.20313	2.48423	-0.88656
C	2.57712	3.70347	-1.60915
H	0.98758	2.11989	-1.45553
C	5.53848	2.24650	-0.36136
N	3.89805	3.72084	-1.30825
C	4.64210	-2.49796	0.54202
C	5.78946	-1.55408	-1.29585
H	2.11846	4.60429	-1.99408
H	5.47588	1.71883	0.59488
H	6.12792	1.64871	-1.05861
H	5.99596	3.22447	-0.20888
H	4.50003	-3.25798	1.30998
H	6.57976	-1.53923	-2.04584
N	4.94235	-0.52380	-1.31726
N	3.75666	-1.50521	0.53082
C	5.69260	-2.59438	-0.37374
H	6.38987	-3.42477	-0.36638

SCF energy: -2209.812551 hartree
zero-point correction: +0.489856 hartree
enthalpy correction: +0.526463 hartree
free energy correction: +0.416984 hartree
quasiharmonic free energy correction: +0.429549 hartree

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1 (doublet)

C	3.30517	-1.94566	2.36126
H	4.05026	-2.07193	3.15220
H	2.33790	-2.30007	2.73823
S	3.16991	-0.18305	1.94527
O	0.15588	0.41213	-0.94060
Fe	1.40591	0.12272	0.05966
N	2.81721	0.39479	-1.34658
N	1.43325	-1.85950	-0.30456
N	0.23946	-0.20550	1.68187
N	1.59393	2.05450	0.62105
C	3.40856	1.57849	-1.69932
C	4.28666	1.38441	-2.82724
C	4.21229	0.06587	-3.15696
C	3.29196	-0.54121	-2.22675
C	2.08341	-2.49512	-1.33481
C	1.73574	-3.89522	-1.35637
C	0.85891	-4.09679	-0.33536
C	0.67465	-2.82027	0.31065
C	-0.34314	-1.39759	2.04954
C	-1.21886	-1.19632	3.17743
C	-1.18287	0.13220	3.47321
C	-0.28146	0.74776	2.53254
C	0.88727	2.70308	1.60023
C	1.20528	4.11039	1.59962
C	2.11502	4.30580	0.60738
C	2.34547	3.01901	-0.00315
C	3.20036	2.80160	-1.07289
H	3.73891	3.65948	-1.46359
C	2.95377	-1.88899	-2.22803
H	3.40473	-2.51635	-2.99078
C	-0.14511	-2.61495	1.41525
H	-0.69859	-3.46950	1.79080
C	0.00572	2.10119	2.48947
H	-0.48645	2.74047	3.21556
H	4.87316	2.16588	-3.29319
H	4.72563	-0.46279	-3.94995
H	2.11912	-4.61387	-2.06944
H	0.36875	-5.01374	-0.03497
H	-1.78599	-1.98118	3.66122
H	-1.71188	0.66380	4.25389
H	0.78165	4.83690	2.28105
H	2.59409	5.22700	0.30131
H	3.57268	-2.54286	1.48586
H	-1.77726	0.47030	-0.77468
N	-2.75972	0.18936	-0.72655
C	-3.01612	-1.18528	-0.81263
C	-3.67628	1.18112	-0.97200
C	-2.50190	-2.13312	-1.68472
N	-3.78540	-1.85963	0.09325
C	-3.03448	-3.35267	-1.22643
H	-1.84047	-1.94688	-2.51775
C	-4.55408	-1.31094	1.19287
N	-3.81944	-3.18886	-0.15908
C	-4.05545	3.40372	-1.26195
C	-5.81738	1.83638	-1.36661
H	-2.88909	-4.34654	-1.63092
H	-3.93241	-0.62025	1.77059
H	-5.43139	-0.77763	0.81686
H	-4.85930	-2.14929	1.81999

H	-3.65038	4.41453	-1.30471
H	-6.86208	1.55378	-1.49444
C	-5.41897	3.16808	-1.45412
H	-6.12111	3.96943	-1.65402
N	-3.17594	2.43544	-1.01956
N	-4.96972	0.83401	-1.12562

SCF energy: -2209.820209 hartree
zero-point correction: +0.492867 hartree
enthalpy correction: +0.529296 hartree
free energy correction: +0.421668 hartree
quasiharmonic free energy correction: +0.432320 hartree

2-TS (doublet)

C	2.91891	-1.53561	2.74569
H	3.56661	-1.46676	3.62591
H	1.93452	-1.88779	3.07031
S	2.81759	0.13686	2.01577
O	0.16469	0.14638	-1.12439
Fe	1.28430	0.10035	0.15259
N	2.81391	0.56265	-1.08211
N	1.64410	-1.86393	-0.13436
N	-0.14854	-0.36317	1.49461
N	1.06809	2.05545	0.60141
C	3.21794	1.81387	-1.45408
C	4.30190	1.72825	-2.40434
C	4.55246	0.40402	-2.59098
C	3.61264	-0.31503	-1.76327
C	2.59811	-2.41256	-0.95148
C	2.46574	-3.84944	-0.97374
C	1.40275	-4.15757	-0.18020
C	0.89765	-2.90936	0.33729
C	-0.64007	-1.61147	1.77137
C	-1.69080	-1.52546	2.75689
C	-1.81964	-0.20803	3.07852
C	-0.85819	0.51351	2.28120
C	0.19382	2.59991	1.49981
C	0.29301	4.04009	1.48363
C	1.22836	4.35717	0.54787
C	1.70929	3.10942	0.00378
C	2.69864	3.00620	-0.96275
H	3.12050	3.92999	-1.34641
C	3.53083	-1.69943	-1.69363
H	4.23163	-2.27128	-2.29417
C	-0.18127	-2.79778	1.20869
H	-0.68257	-3.71463	1.50166
C	-0.69614	1.88875	2.29646
H	-1.33082	2.45929	2.96725
H	4.79818	2.58010	-2.85144
H	5.29460	-0.06081	-3.22738
H	3.10435	-4.51795	-1.53698
H	0.98889	-5.13167	0.04724
H	-2.23694	-2.37389	3.14911
H	-2.49400	0.24964	3.79128
H	-0.28679	4.70378	2.11247
H	1.58104	5.33570	0.24777
H	3.34526	-2.26135	2.04784
H	-1.02394	0.09220	-0.99412
N	-2.30777	-0.07202	-0.95819
C	-2.73677	-1.35471	-1.04867
C	-3.07812	1.05746	-0.99500
C	-2.03785	-2.41137	-1.67767
N	-3.86572	-1.92721	-0.50213
N	-4.37634	0.97578	-1.37313
N	-2.41759	2.20436	-0.70292
C	-2.83892	-3.53672	-1.48443
H	-1.10505	-2.30993	-2.21135
C	-4.84927	-1.35016	0.39906
N	-3.93138	-3.25418	-0.76109
C	-5.03329	2.12997	-1.48246
C	-3.10930	3.33269	-0.81986
H	-2.67935	-4.55067	-1.82710
H	-5.57950	-0.75643	-0.15254
H	-5.33360	-2.18337	0.90931
H	-4.34598	-0.71265	1.13153
C	-4.44753	3.36846	-1.22087
H	-6.07417	2.05808	-1.79718
H	-2.56786	4.24789	-0.58214
H	-4.99632	4.29807	-1.32103

SCF energy: -2209.803080 hartree
zero-point correction: +0.485930 hartree
enthalpy correction: +0.521590 hartree
free energy correction: +0.418128 hartree
quasiharmonic free energy correction: +0.426252 hartree

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3 (quartet)

C	-3.86662	0.52585	2.41582
H	-4.78154	0.22210	2.93266
H	-3.09697	0.76914	3.15308
S	-3.33895	-0.86024	1.35272
O	-0.12230	0.23224	-0.91002
Fe	-1.47612	-0.22535	0.15097
N	-2.51478	1.31617	-0.64773
N	-0.82893	0.97082	1.62712
N	-0.44305	-1.76330	0.94713
N	-2.20388	-1.45785	-1.27528
C	-3.34368	1.26831	-1.73638

C	-3.85147	2.58870	-2.02648
C	-3.30409	3.43173	-1.10818
C	-2.47121	2.62493	-0.24698
C	-1.01427	2.33014	1.71844
C	-0.34271	2.83744	2.88879
C	0.24433	1.77205	3.50249
C	-0.05103	0.61172	2.69974
C	0.25383	-1.76140	2.12913
C	0.79878	-3.07335	2.38289
C	0.42645	-3.86290	1.33965
C	-0.36166	-3.04045	0.45221
C	-1.86015	-2.76603	-1.48174
C	-2.55224	-3.28042	-2.63992
C	-3.31511	-2.26374	-3.12603
C	-3.08165	-1.12195	-2.27389
C	-3.63293	0.13388	-2.48347
H	-4.31154	0.24747	-3.32305
C	-1.76161	3.10896	0.84560
H	-1.81950	4.17357	1.05002
C	0.42950	-0.66551	2.95938
H	1.02337	-0.80498	3.85693
C	-0.99406	-3.50915	-0.68987
H	-0.83024	-4.54654	-0.96397
H	-4.53029	2.82226	-2.83693
H	-3.44407	4.50042	-1.00451
H	-0.33403	3.87765	3.18921
H	0.83885	1.75778	4.40722
H	1.38853	-3.33424	3.25253
H	0.63958	-4.91168	1.17504
H	-2.45458	-4.29106	-3.01574
H	-3.97093	-2.26349	-3.98742
H	-4.07258	1.41329	1.81071
H	0.74998	-0.00233	-0.52280
N	2.83180	0.40045	-0.52762
C	3.03680	1.65759	-0.87677
C	3.76910	-0.60263	-0.46418
C	2.01143	2.54089	-1.34510
N	4.19509	2.44137	-0.83632
C	2.64170	3.75081	-1.56230
H	0.98341	2.23900	-1.49118
C	5.50302	2.13647	-0.27566
N	3.95345	3.70139	-1.22827
C	4.27724	-2.66075	0.37827
C	5.61937	-1.65732	-1.29096
H	2.23230	4.68097	-1.93253
H	5.38757	1.57933	0.65837
H	6.09317	1.54051	-0.97328
H	5.98911	3.09141	-0.07395
H	4.02303	-3.46476	1.06780
H	6.46499	-1.63900	-1.97774
N	4.83723	-0.57622	-1.29543
N	3.45863	-1.61315	0.37945
C	5.38960	-2.75440	-0.46268
H	6.03417	-3.62636	-0.47124

SCF energy: -2209.813230 hartree
zero-point correction: +0.490060 hartree
enthalpy correction: +0.526591 hartree
free energy correction: +0.416940 hartree
quasiharmonic free energy correction: +0.429276 hartree

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1 (quartet)

C	3.30508	-1.94135	2.36340
H	4.04929	-2.06605	3.15546
H	2.33789	-2.29637	2.73998
S	3.16874	-0.17913	1.94538
O	0.16706	0.40787	-0.96672
Fe	1.39503	0.12336	0.06220
N	2.81477	0.39239	-1.34315
N	1.42610	-1.86037	-0.29932
N	0.23616	-0.20194	1.68156
N	1.58266	2.05643	0.61689
C	3.40070	1.57637	-1.70185
C	4.27712	1.38120	-2.83101
C	4.20657	0.06108	-3.15532
C	3.28979	-0.54513	-2.22085
C	2.07959	-2.49728	-1.32717
C	1.73172	-3.89746	-1.34794
C	0.85233	-4.09793	-0.32899
C	0.66745	-2.82067	0.31538
C	-0.34238	-1.39544	2.05539
C	-1.21013	-1.19362	3.18873
C	-1.17348	0.13513	3.48352
C	-0.27977	0.75148	2.53683
C	0.87940	2.70721	1.59657
C	1.19665	4.11456	1.59218
C	2.10384	4.30791	0.59725
C	2.33372	3.01986	-0.01081
C	3.18906	2.80116	-1.07952
H	3.72530	3.65922	-1.47297
C	2.95293	-1.89340	-2.21858
H	3.40555	-2.52247	-2.97894
C	-0.14975	-2.61339	1.42152
H	-0.70258	-3.46676	1.80064
C	0.00278	2.10532	2.49070
H	-0.48706	2.74410	3.21875
H	4.85952	2.16300	-3.30152
H	4.71943	-0.46894	-3.94772
H	2.11704	-4.61692	-2.05916
H	0.36162	-5.01454	-0.02848

H	-1.77332	-1.97869	3.67678
H	-1.69789	0.66664	4.26735
H	0.77482	4.84232	2.27339
H	2.58241	5.22841	0.28832
H	3.57445	-2.53940	1.48917
H	-1.76603	0.46382	-0.78791
N	-2.74869	0.18491	-0.73364
C	-3.00868	-1.18900	-0.81981
C	-3.66386	1.17950	-0.97359
C	-2.49870	-2.13738	-1.69385
N	-3.77757	-1.86221	0.08727
C	-3.03334	-3.35598	-1.23547
H	-1.83870	-1.95203	-2.52823
C	-4.54212	-1.31302	1.18951
N	-3.81551	-3.19114	-0.16627
C	-4.03821	3.40350	-1.25870
C	-5.80490	1.84112	-1.35742
H	-2.89134	-4.34984	-1.64117
H	-3.91787	-0.62332	1.76563
H	-5.41995	-0.77845	0.81655
H	-4.84638	-2.15127	1.81725
H	-3.63054	4.41324	-1.30196
H	-6.85093	1.56153	-1.48085
C	-5.40325	3.17184	-1.44479
H	-6.10414	3.97540	-1.64017
N	-3.16029	2.43244	-1.02176
N	-4.95884	0.83607	-1.12184

SCF energy: -2209.819777 hartree
zero-point correction: +0.492904 hartree
enthalpy correction: +0.529304 hartree
free energy correction: +0.421082 hartree
quasiharmonic free energy correction: +0.431762 hartree

2-TS (quartet)

C	2.95421	-1.51792	2.73143
H	3.61516	-1.45814	3.60145
H	1.97982	-1.89574	3.05861
S	2.79172	0.16009	2.03290
O	0.16626	0.15972	-1.10844
Fe	1.28678	0.10101	0.16131
N	2.80676	0.54299	-1.09445
N	1.62757	-1.86578	-0.11735
N	-0.14179	-0.34002	1.51626
N	1.08300	2.06344	0.59681
C	3.22354	1.79023	-1.46808
C	4.29127	1.69060	-2.43542
C	4.51754	0.36323	-2.63138
C	3.58108	-0.34453	-1.78998
C	2.55874	-2.42685	-0.95422
C	2.41536	-3.86277	-0.96206
C	1.37154	-4.15813	-0.13887
C	0.88597	-2.90346	0.38148
C	-0.62289	-1.58673	1.82495
C	-1.66573	-1.48445	2.81734
C	-1.80443	-0.16067	3.10705
C	-0.85374	0.54996	2.28743
C	0.19860	2.62313	1.47775
C	0.30571	4.06224	1.44398
C	1.25601	4.36265	0.51769
C	1.73595	3.10640	-0.00744
C	2.72601	2.98915	-0.97199
H	3.15727	3.90709	-1.35908
C	3.48441	-1.72813	-1.71736
H	4.16662	-2.30969	-2.32976
C	-0.16832	-2.78159	1.28016
H	-0.66229	-3.69451	1.59699
C	-0.69781	1.92603	2.27797
H	-1.33726	2.50663	2.93537
H	4.79281	2.53622	-2.88856
H	5.24147	-0.11062	-3.28204
H	3.03487	-4.53972	-1.53655
H	0.95720	-5.12784	0.10596
H	-2.20290	-2.32744	3.23315
H	-2.47828	0.30847	3.81288
H	-0.27899	4.73692	2.05644
H	1.61707	5.33571	0.20974
H	3.37484	-2.21570	2.00248
H	-1.00650	0.09713	-1.01157
N	-2.30343	-0.07605	-1.01528
C	-2.72693	-1.36152	-1.08260
C	-3.08204	1.04852	-1.02332
C	-2.05159	-2.41438	-1.74122
N	-3.82541	-1.94159	-0.48173
N	-4.38874	0.95640	-1.36843
N	-2.42363	2.19979	-0.74632
C	-2.83123	-3.54515	-1.50549
H	-1.14301	-2.30852	-2.31459
C	-4.78201	-1.36333	0.44743
N	-3.89388	-3.26718	-0.73441
C	-5.05646	2.10601	-1.46314
C	-3.12633	3.32273	-0.84594
H	-2.67995	-4.55945	-1.85067
H	-5.24656	-2.19564	0.97712
H	-4.25864	-0.71995	1.16023
H	-5.53163	-0.77608	-0.08498
C	-4.47399	3.34865	-1.21568
H	-6.10407	2.02607	-1.75252
H	-2.58654	4.24184	-0.61983
H	-5.03201	4.27414	-1.30201

SCF energy: -2209.803206 hartree
zero-point correction: +0.486147 hartree
enthalpy correction: +0.521675 hartree
free energy correction: +0.417926 hartree
quasiharmonic free energy correction: +0.425915 hartree

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6 (triplet)

C	3.83181	-1.80762	1.79700
H	4.47928	-1.90521	2.67448
H	3.23379	-2.71737	1.69661
S	2.77781	-0.33818	2.07126
O	0.24021	0.32114	-1.39190
Fe	1.46371	-0.04946	0.29002
N	2.98393	-0.20688	-1.01303
N	1.06306	-2.01028	0.02492
N	-0.15949	0.13298	1.49463
N	1.73602	1.94753	0.42396
C	3.82186	0.80630	-1.39927
C	4.80580	0.30948	-2.33548
C	4.54002	-1.01188	-2.51989
C	3.39810	-1.32439	-1.69025
C	1.73213	-2.89863	-0.78380
C	1.16529	-4.21918	-0.64861
C	0.15487	-4.12158	0.25997
C	0.09708	-2.73920	0.67420
C	-0.94061	-0.89689	1.95491
C	-1.93009	-0.39572	2.88157
C	-1.73550	0.95009	2.97345
C	-0.62281	1.26789	2.10916
C	1.01544	2.84963	1.16453
C	1.58706	4.17091	1.03626
C	2.66943	4.05058	0.21975
C	2.75598	2.65725	-0.15495
C	3.72988	2.13280	-0.99644
H	4.47217	2.82253	-1.38716
C	2.81387	-2.58229	-1.59618
H	3.24804	-3.38273	-2.18777
C	-0.82783	-2.23005	1.57980
H	-1.52877	-2.93206	2.02135
C	-0.09080	2.54192	1.94749
H	-0.55720	3.35379	2.49783
H	5.58332	0.91117	-2.78932
H	5.05475	-1.72235	-3.15455
H	1.51148	-5.09660	-1.18060
H	-0.50033	-4.90216	0.62616
H	-2.66018	-1.00932	3.39497
H	-2.27196	1.66992	3.57943
H	1.20528	5.05911	1.52442
H	3.35740	4.82047	-0.10674
H	4.45775	-1.68922	0.90851
H	-0.39174	1.06352	-1.22465
N	-2.75034	-0.17206	-1.31824
C	-3.51251	-1.18441	-0.94620
C	-3.08292	1.15830	-1.30882
C	-3.30197	-2.54257	-1.34617
N	-4.61013	-1.23670	-0.08071
C	-4.28997	-3.27367	-0.71681
H	-2.52650	-2.87072	-2.02201
C	-5.15507	-0.19965	0.78633
N	-5.06259	-2.48900	0.07119
C	-2.27825	3.30947	-1.29328
C	-4.57890	2.85944	-1.61278
H	-4.49803	-4.33383	-0.76565
H	-4.34033	0.32012	1.29929
H	-5.73888	0.51491	0.20557
H	-5.78244	-0.70754	1.51907
H	-1.41891	3.96868	-1.18944
H	-5.61093	3.16027	-1.78849
H	-0.36154	-0.43900	-1.48315
C	-3.56316	3.80931	-1.50821
H	-3.75873	4.87205	-1.59337
N	-4.36341	1.54756	-1.50158
N	-2.02694	2.00479	-1.21317

SCF energy: -2210.482540 hartree
zero-point correction: +0.502921 hartree
enthalpy correction: +0.539543 hartree
free energy correction: +0.433131 hartree
quasiharmonic free energy correction: +0.442285 hartree

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4 (triplet)

C	2.63916	-1.43751	3.13875
H	3.47913	-1.77094	3.75402
H	2.05648	-0.67812	3.66681
S	3.27991	-0.78609	1.56800
O	0.13284	0.18012	-1.03689
Fe	1.43496	-0.07035	0.17513
N	2.85017	-0.16975	-1.25971
N	1.13051	-2.08242	-0.02754
N	0.16560	-0.02368	1.72613
N	1.76871	1.90088	0.39520
C	3.57402	0.88110	-1.76219
C	4.41456	0.43396	-2.84624
C	4.17077	-0.89570	-3.00789
C	3.18687	-1.26307	-2.01878
C	1.69630	-2.91774	-0.95590
C	1.15192	-4.25132	-0.82502

C	0.24949	-4.20795	0.19109
C	0.24110	-2.84578	0.67945
C	-0.59331	-1.07006	2.19080
C	-1.44942	-0.62401	3.26170
C	-1.21028	0.70791	3.42992
C	-0.21158	1.07652	2.45887
C	1.18980	2.74709	1.30628
C	1.69332	4.09001	1.13581
C	2.59795	4.04099	0.12024
C	2.64534	2.66823	-0.32769
C	3.49049	2.19810	-1.32638
H	4.13361	2.92366	-1.81533
C	2.65298	-2.53984	-1.88698
H	3.01526	-3.30221	-2.56986
C	-0.55880	-2.37886	1.71599
H	-1.22826	-3.09188	2.18755
C	0.27060	2.36680	2.27598
H	-0.11267	3.14064	2.93417
H	5.08733	1.06982	-3.40757
H	4.60361	-1.57798	-3.72837
H	1.43411	-5.09575	-1.44090
H	-0.36738	-5.00734	0.58135
H	-2.13908	-1.25892	3.80344
H	-1.66625	1.39083	4.13553
H	1.39148	4.94263	1.73094
H	3.19333	4.84532	-0.29298
H	1.98511	-2.29370	2.93707
H	-1.66616	-0.14348	-0.91382
N	-2.67809	0.05213	-0.87822
C	-3.56053	-1.02978	-0.98987
C	-3.01486	1.36776	-1.04704
C	-3.56611	-2.07873	-1.89714
N	-4.55380	-1.28554	-0.08625
C	-4.61598	-2.90959	-1.46219
H	-2.90687	-2.19995	-2.74423
C	-4.96123	-0.47988	1.04773
N	-5.22123	-2.42621	-0.37601
C	-2.28898	3.52626	-1.21523
C	-4.58424	2.98990	-1.33724
H	-4.96445	-3.83887	-1.89495
H	-4.07674	-0.12316	1.58393
H	-5.54998	0.38090	0.71816
H	-5.55809	-1.11941	1.69903
H	-1.44996	4.22082	-1.22006
H	-5.63772	3.24652	-1.44605
H	-0.13324	1.12323	-1.01269
N	-1.97757	2.24172	-1.05515
N	-4.31693	1.69363	-1.17589
C	-3.60040	3.97715	-1.36816
H	-3.83808	5.02618	-1.50112

SCF energy: -2210.472727 hartree
zero-point correction: +0.504262 hartree
enthalpy correction: +0.540744 hartree
free energy correction: +0.432626 hartree
quasiharmonic free energy correction: +0.443510 hartree

5-TS (triplet)

C	4.41169	-0.54881	1.53432
H	5.09880	-0.47011	2.38224
H	4.30097	-1.60031	1.25524
S	2.81587	0.17599	2.04414
O	0.04609	0.12922	-1.17873
Fe	1.33502	0.07060	0.26923
N	2.61463	1.16000	-0.83456
N	2.14533	-1.61567	-0.51504
N	0.05389	-1.03595	1.37552
N	0.51403	1.74401	1.03427
C	2.68099	2.53409	-0.87128
C	3.71057	2.95647	-1.79225
C	4.25700	1.82696	-2.31739
C	3.56131	0.71120	-1.71783
C	3.15464	-1.70971	-1.44340
C	3.45170	-3.09362	-1.71979
C	2.61674	-3.83565	-0.93816
C	1.80712	-2.90293	-0.19190
C	-0.00022	-2.40667	1.42563
C	-1.04317	-2.82915	2.33317
C	-1.61118	-1.69586	2.82983
C	-0.91208	-0.58661	2.22424
C	-0.51528	1.83507	1.94253
C	-0.80446	3.22167	2.23253
C	0.05354	3.96204	1.48318
C	0.86837	3.02621	0.73708
C	1.87356	3.40055	-0.15215
H	2.04215	4.46433	-0.29033
C	3.81359	-0.62638	-2.01253
H	4.59368	-0.83919	-2.73738
C	0.81586	-3.27451	0.71718
H	0.65678	-4.33813	0.86696
C	-1.18444	0.75879	2.49514
H	-1.97893	0.97217	3.20397
H	3.96472	3.98813	-2.00001
H	5.05209	1.73789	-3.04690
H	4.20453	-3.43742	-2.41784
H	2.54352	-4.91338	-0.86469
H	-1.29727	-3.85991	2.54442
H	-2.42098	-1.60314	3.54235
H	-1.56754	3.56137	2.92121
H	0.14612	5.03943	1.42793

H	4.83635	-0.00220	0.68623
H	-1.15471	0.04428	-1.01454
H	0.33766	-0.49118	-1.86486
N	-2.42088	-0.09760	-0.90886
C	-2.87660	-1.38422	-1.00233
C	-3.20513	1.01839	-1.00794
C	-2.25836	-2.44590	-1.68515
N	-3.97156	-1.93380	-0.37260
N	-4.51675	0.89513	-1.32733
N	-2.55484	2.19285	-0.81187
C	-3.06006	-3.55902	-1.42482
H	-1.37358	-2.37749	-2.30001
C	-4.86154	-1.32867	0.60140
N	-4.08516	-3.25800	-0.61616
C	-5.20252	2.02910	-1.46368
C	-3.27475	3.29914	-0.95382
H	-2.94813	-4.57436	-1.78251
H	-5.22953	-2.13159	1.24132
H	-4.30487	-0.60422	1.20153
H	-5.69149	-0.81886	0.10841
C	-4.63218	3.28984	-1.29092
H	-6.25465	1.92184	-1.72727
H	-2.74375	4.23617	-0.78943
H	-5.20399	4.20308	-1.41136

SCF energy: -2210.458244 hartree
zero-point correction: +0.497199 hartree
enthalpy correction: +0.533434 hartree
free energy correction: +0.427794 hartree
quasiharmonic free energy correction: +0.436809 hartree

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6 (open-shell singlet)

C	3.83424	-1.80739	1.79304
H	4.48244	-1.90572	2.66990
H	3.23678	-2.71741	1.69183
S	2.77943	-0.33905	2.07005
O	0.23909	0.32296	-1.39028
Fe	1.46302	-0.04963	0.29037
N	2.98364	-0.20063	-1.01320
N	1.06656	-2.01044	0.02080
N	-0.16046	0.12663	1.49525
N	1.73161	1.94776	0.42927
C	3.81971	0.81513	-1.39674
C	4.80451	0.32258	-2.33431
C	4.54107	-0.99876	-2.52227
C	3.39977	-1.31553	-1.69339
C	1.73712	-2.89535	-0.79051
C	1.17313	-4.21744	-0.65837
C	0.16298	-4.12426	0.25095
C	0.10242	-2.74302	0.66862
C	-0.93933	-0.90586	1.95340
C	-1.93018	-0.40875	2.88076
C	-1.73871	0.93734	2.97521
C	-0.62650	1.25934	2.11186
C	1.00886	2.84668	1.17151
C	1.57782	4.16940	1.04654
C	2.66079	4.05315	0.23019
C	2.75029	2.66089	-0.14771
C	3.72526	2.14039	-0.99045
H	4.46626	2.83252	-1.37938
C	2.81791	-2.57479	-1.60245
H	3.25345	-3.37286	-2.19623
C	-0.82346	-2.23800	1.57558
H	-1.52274	-2.94257	2.01568
C	-0.09716	2.53483	1.95318
H	-0.56559	3.34448	2.50507
H	5.58094	0.92687	-2.78657
H	5.05706	-1.70660	-3.15884
H	1.52091	-5.09277	-1.19274
H	-0.49037	-4.90714	0.61554
H	-2.65909	-1.02496	3.39267
H	-2.27694	1.65477	3.58246
H	1.19401	5.05571	1.53655
H	3.34730	4.82520	-0.09426
H	4.45947	-1.68737	0.90425
H	-0.39134	1.06656	-1.22288
N	-2.74866	-0.17153	-1.31767
C	-3.50989	-1.18437	-0.94498
C	-3.08267	1.15847	-1.30938
C	-3.29789	-2.54271	-1.34360
N	-4.60774	-1.23692	-0.07985
C	-4.28550	-3.27416	-0.71396
H	-2.52186	-2.87078	-2.01883
C	-5.15422	-0.19949	0.78575
N	-5.05921	-2.48950	0.07292
C	-2.28068	3.31066	-1.29444
C	-4.58034	2.85757	-1.61650
H	-4.49253	-4.33456	-0.76191
H	-4.34030	0.32135	1.29892
H	-5.73811	0.51406	0.20383
H	-5.78179	-0.70718	1.51846
H	-1.42230	3.97103	-1.19002
H	-5.61253	3.15699	-1.79371
H	-0.36460	-0.43575	-1.48123
C	-3.56590	3.80878	-1.51145
H	-3.76265	4.87121	-1.59771
N	-4.36340	1.54605	-1.50404
N	-2.02785	2.00634	-1.21284

SCF energy: -2210.482551 hartree

zero-point correction: +0.502918 hartree
enthalpy correction: +0.539540 hartree
free energy correction: +0.434161 hartree
quasiharmonic free energy correction: +0.443320 hartree

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4 (open-shell singlet)

C	4.35181	-1.40134	1.33740
H	5.22946	-1.39603	1.98996
H	3.76085	-2.30569	1.50510
S	3.37132	0.09271	1.66621
O	0.04815	0.36624	-0.95388
Fe	1.40413	0.09593	0.21974
N	2.79581	0.50098	-1.20033
N	1.55480	-1.85789	-0.24396
N	0.12812	-0.32040	1.71125
N	1.35512	2.04601	0.74525
C	3.21549	1.75509	-1.58600
C	4.16187	1.64760	-2.66990
C	4.31147	0.32102	-2.93730
C	3.44326	-0.38671	-2.02770
C	2.34083	-2.44183	-1.20562
C	2.09070	-3.86072	-1.26480
C	1.13114	-4.12714	-0.33475
C	0.80500	-2.87291	0.29798
C	-0.41464	-1.54513	1.99288
C	-1.32045	-1.44639	3.11364
C	-1.30782	-0.14359	3.51064
C	-0.40601	0.54943	2.62095
C	0.64985	2.61492	1.77407
C	0.82378	4.04879	1.76920
C	1.62743	4.33894	0.71094
C	1.95892	3.07993	0.08263
C	2.80684	2.95054	-1.01311
H	3.21516	3.86484	-1.43318
C	3.24295	-1.76249	-2.02256
H	3.80588	-2.35167	-2.74044
C	-0.11783	-2.72996	1.32789
H	-0.64763	-3.62230	1.64567
C	-0.14797	1.91729	2.67017
H	-0.64636	2.49031	3.44620
H	4.64310	2.48919	-3.15174
H	4.93593	-0.14913	-3.68638
H	2.58579	-4.54780	-1.93927
H	0.67655	-5.07795	-0.08795
H	-1.87814	-2.27529	3.53014
H	-1.85432	0.32108	4.32145
H	0.37314	4.72804	2.48143
H	1.97931	5.30645	0.37623
H	4.69181	-1.40013	0.29465
H	-1.78285	0.37595	-0.77737
N	-2.77847	0.10607	-0.75561
C	-3.04959	-1.26714	-0.79683
C	-3.69257	1.08887	-1.03433
C	-2.54556	-2.24965	-1.63720
N	-3.82740	-1.90619	0.12722
C	-3.09150	-3.44895	-1.14265
H	-1.89047	-2.10005	-2.48287
C	-4.59834	-1.31434	1.20274
N	-3.87557	-3.24253	-0.08253
C	-4.08036	3.30346	-1.37696
C	-5.83122	1.72480	-1.48258
H	-2.95740	-4.45660	-1.51595
H	-3.97600	-0.60573	1.75691
H	-5.47227	-0.79283	0.80290
H	-4.90900	-2.12756	1.85955
H	-3.68027	4.31581	-1.43249
H	-6.87193	1.43345	-1.62399
H	0.27878	-0.10522	-1.77226
N	-3.19967	2.34623	-1.09896
N	-4.98298	0.73273	-1.20599
C	-5.43901	3.05700	-1.58956
H	-6.14173	3.85022	-1.81797

SCF energy: -2210.477210 hartree
zero-point correction: +0.503507 hartree
enthalpy correction: +0.540221 hartree
free energy correction: +0.433641 hartree
quasiharmonic free energy correction: +0.443541 hartree

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4 (open-shell singlet)

C	4.18797	-1.03260	1.70420
H	4.86278	-0.98118	2.56464
H	3.86315	-2.06903	1.57511
S	2.77788	0.07708	2.05833
O	0.07430	0.21924	-1.20104
Fe	1.33668	0.08780	0.27214
N	2.84384	0.38190	-1.04413
N	1.51373	-1.90215	-0.04029
N	-0.21013	-0.20346	1.54207
N	1.14166	2.07835	0.56053
C	3.35049	1.59584	-1.42267
C	4.41879	1.41859	-2.37782
C	4.55088	0.07710	-2.57370
C	3.56123	-0.55942	-1.73800
C	2.39922	-2.55800	-0.86156
C	2.18390	-3.98325	-0.79374
C	1.15171	-4.17976	0.07367
C	0.74238	-2.87372	0.53335

C	-0.72979	-1.41485	1.90730
C	-1.79185	-1.23664	2.87217
C	-1.89935	0.10327	3.08877
C	-0.90688	0.73806	2.25208
C	0.26608	2.72879	1.37890
C	0.46293	4.15922	1.29886
C	1.47071	4.36167	0.40881
C	1.88867	3.05324	-0.04574
C	2.90593	2.83454	-0.96502
H	3.40770	3.71227	-1.36212
C	3.35632	-1.93451	-1.65488
H	3.99434	-2.57144	-2.26063
C	-0.30664	-2.65003	1.42677
H	-0.83216	-3.52626	1.79398
C	-0.68831	2.10767	2.18087
H	-1.31531	2.74652	2.79551
H	4.98283	2.22450	-2.83000
H	5.24457	-0.44586	-3.21978
H	2.75317	-4.72200	-1.34362
H	0.69813	-5.11313	0.38189
H	-2.36119	-2.04174	3.31896
H	-2.57410	0.62771	3.75363
H	-0.10420	4.89353	1.85683
H	1.90570	5.29725	0.08088
H	4.73700	-0.71671	0.81245
H	-1.15646	0.07460	-1.06295
H	0.39094	-0.32133	-1.94179
N	-2.39067	-0.09643	-0.97138
C	-2.82592	-1.38591	-0.94544
C	-3.17327	1.02285	-1.06908
C	-2.16370	-2.49612	-1.51266
N	-3.93382	-1.90073	-0.31011
N	-4.47764	0.90143	-1.41347
N	-2.52290	2.19371	-0.86214
C	-2.96503	-3.59572	-1.19780
H	-1.25386	-2.46074	-2.09219
C	-4.88186	-1.24220	0.57279
N	-4.02452	-3.24452	-0.46042
C	-5.15353	2.03803	-1.57765
C	-3.23323	3.30345	-1.03552
H	-2.82452	-4.63536	-1.46345
H	-5.33364	-2.02296	1.18570
H	-4.35320	-0.53171	1.21408
H	-5.64374	-0.71242	-0.00097
C	-4.58017	3.29780	-1.40722
H	-6.20022	1.93309	-1.86269
H	-2.70058	4.23912	-0.86739
H	-5.14422	4.21239	-1.55141

SCF energy: -2210.469885 hartree
zero-point correction: +0.497252 hartree
enthalpy correction: +0.533452 hartree
free energy correction: +0.429312 hartree
quasiharmonic free energy correction: +0.437940 hartree

C-N X1• X2 radical addition (conformer 1)

C	0.66303	-2.13674	1.21407
C	0.25532	-0.74662	1.01927
H	0.28078	-0.02262	1.82877
C	-1.00033	-0.93308	0.31098
N	-1.10162	-2.24842	-0.01215
H	1.53135	-2.49225	1.75199
C	-2.02978	-2.92030	-0.90272
H	-1.52787	-3.81682	-1.26893
H	-2.95476	-3.18219	-0.38484
H	-2.27079	-2.26180	-1.74119
N	-0.10108	-2.98856	0.57196
N	-1.82168	0.09875	-0.07701
H	-1.32238	1.00095	-0.07548
C	-3.19814	0.18169	-0.05060
N	-3.68485	1.40319	-0.35691
N	-3.91450	-0.90673	0.27688
C	-5.01006	1.52224	-0.32943
C	-5.24121	-0.74666	0.28906
C	-5.86325	0.46244	-0.01022
H	-6.94101	0.57564	0.00679
H	-5.40603	2.50765	-0.57202
H	-5.82384	-1.62751	0.55556
N	1.49108	0.09588	-0.02723
C	2.61992	-0.62733	-0.39440
C	1.45262	1.45552	-0.06465
C	2.80100	-1.49442	-1.46470
H	2.08776	-1.69732	-2.24986
N	3.76381	-0.71349	0.36389
N	0.26228	2.04903	0.22282
N	2.58213	2.13139	-0.39889
C	4.08809	-2.02864	-1.27977
H	4.61823	-2.74571	-1.89354
C	4.12093	0.06565	1.53269
N	4.67458	-1.54845	-0.18044
C	0.22012	3.38303	0.17115
C	2.48974	3.45597	-0.46033
H	4.92298	-0.46414	2.04798
H	4.45483	1.06655	1.24287
H	3.25662	0.16002	2.19625
C	1.31841	4.16265	-0.17353
H	1.26744	5.24395	-0.22229

H	-0.74403	3.83365	0.40222
H	3.40121	3.98135	-0.74591

SCF energy: -1167.770036 hartree
zero-point correction: +0.336050 hartree
enthalpy correction: +0.359093 hartree
free energy correction: +0.281479 hartree
quasiharmonic free energy correction: +0.286736 hartree

C-N X1• X2 radical addition (conformer 2)

C	-0.80488	-1.94108	-1.38179
C	-0.34797	-0.57348	-1.10184
H	-0.29253	0.16566	-1.89831
C	0.88145	-0.85833	-0.36941
N	0.90990	-2.19170	-0.10589
H	-1.67220	-2.22646	-1.96064
C	1.79909	-2.94879	0.75471
H	1.25867	-3.84328	1.06755
H	2.71841	-3.22026	0.23146
H	2.05842	-2.34662	1.62946
N	-0.10193	-2.85613	-0.75533
N	1.74825	0.10410	0.09399
H	1.29310	1.02813	0.13826
C	3.12706	0.12377	0.06709
N	3.67110	1.30073	0.44448
N	3.79193	-0.97593	-0.32592
C	5.00044	1.35888	0.42035
C	5.12464	-0.87745	-0.33272
C	5.80292	0.28123	0.03591
H	6.88481	0.34461	0.02230
H	5.44238	2.30840	0.72008
H	5.66534	-1.76721	-0.65270
N	-1.57466	0.26224	-0.10344
C	-2.83190	-0.34558	-0.10285
C	-1.46696	1.62872	-0.04899
C	-3.93013	-0.25728	-0.95252
H	-4.05418	0.43161	-1.77460
N	-3.13325	-1.32198	0.81090
N	-2.58152	2.36780	0.15761
N	-0.21802	2.14796	-0.17610
C	-4.83570	-1.21188	-0.45978
H	-5.82561	-1.45505	-0.82480
C	-2.29216	-1.83783	1.87335
N	-4.35152	-1.86288	0.60215
C	-2.42009	3.68414	0.24604
C	-0.09871	3.47657	-0.09929
H	-1.72145	-2.70784	1.53035
H	-1.60125	-1.05486	2.19160
H	-2.93713	-2.12955	2.70386
C	-1.18240	4.32005	0.11390
H	-1.07307	5.39614	0.18089
H	-3.32699	4.26122	0.42706
H	0.91307	3.86586	-0.20195

SCF energy: -1167.770553 hartree
zero-point correction: +0.336279 hartree
enthalpy correction: +0.359165 hartree
free energy correction: +0.282315 hartree
quasiharmonic free energy correction: +0.287167 hartree

C-C X1• X2 radical addition

C	0.12653	-1.72953	1.17031
C	-0.61613	-0.59448	0.58676
H	-0.40029	0.41450	0.93180
C	-1.97697	-1.09811	0.70438
N	-1.90165	-2.41396	1.06980
H	1.19587	-1.76078	1.33825
C	-2.98301	-3.35663	1.24326
H	-3.48061	-3.58254	0.29049
H	-2.54447	-4.27396	1.63560
H	-3.72744	-2.98145	1.95792
N	-0.61387	-2.78389	1.38616
N	-3.18694	-0.54980	0.33254
H	-3.99267	-1.15929	0.26528
C	-3.50819	0.77828	0.13241
N	-4.80373	0.99023	-0.17704
N	-2.54236	1.70149	0.25417
C	-5.14438	2.26185	-0.37769
C	-2.92302	2.96503	0.04272
C	-4.23213	3.31704	-0.28023
H	-4.52517	4.34671	-0.44800
H	-6.18901	2.44281	-0.62640
H	-2.14172	3.71704	0.13694
C	-0.12727	-0.30010	-1.14129
H	-0.76702	0.55002	-1.36241
C	-0.18823	-1.49779	-1.98081
C	1.33635	-0.04641	-1.06157
H	-1.07478	-2.00261	-2.34602
N	0.98468	-1.99722	-2.23281
N	1.91835	-1.14814	-1.65111
N	1.85844	1.00199	-0.49784
C	3.32024	-1.38100	-1.93748
C	3.09332	1.06462	0.08718
H	3.84979	-1.73459	-1.04892
H	3.36694	-2.12634	-2.73258
H	3.79119	-0.45304	-2.27937
N	3.72229	2.26460	0.03156
N	3.55212	-0.01978	0.77132

C	4.86630	2.36826	0.70162
C	4.69771	0.13362	1.43808
C	5.41945	1.32455	1.44765
H	6.34828	1.43344	1.99656
H	5.36672	3.33564	0.64321
H	5.04954	-0.73924	1.98876

SCF energy: -1167.765018 hartree
zero-point correction: +0.335008 hartree
enthalpy correction: +0.358282 hartree
free energy correction: +0.279746 hartree
quasiharmonic free energy correction: +0.285541 hartree

pyrimidine

C	-3.34268	-0.55724	-0.78331
C	-2.22126	-1.38928	-0.60348
H	-2.06150	-2.39831	-0.95518
C	-1.33621	-0.61354	0.12924
N	-1.95230	0.58405	0.35616
H	-4.26623	-0.77318	-1.30484
C	-1.42208	1.74475	1.04546
H	-2.26982	2.36509	1.33756
H	-0.87248	1.42196	1.93390
H	-0.74677	2.30599	0.39351
N	-3.17406	0.63860	-0.21667
N	-0.07969	-0.93242	0.66717
H	0.00582	-1.80326	1.17535
C	1.13056	-0.43357	0.23075
N	1.12079	0.62846	-0.59117
N	2.21501	-1.07584	0.70878
C	2.32112	1.07251	-0.97410
C	3.39269	-0.59916	0.30690
C	3.51632	0.49227	-0.55470
H	4.48168	0.86589	-0.87597
H	2.31813	1.93091	-1.64453
H	4.27215	-1.11556	0.68965

SCF energy: -584.222959 hartree
zero-point correction: +0.174300 hartree
enthalpy correction: +0.185962 hartree
free energy correction: +0.136754 hartree
quasiharmonic free energy correction: +0.137950 hartree

pyrimidine radical

C	-3.56553	-0.37618	-0.30747
C	-2.56152	-1.32020	-0.39831
H	-2.61345	-2.35882	-0.68852
C	-1.35370	-0.63860	-0.04557
N	-1.76415	0.66934	0.24808
H	-4.62436	-0.47688	-0.50417
C	-0.99856	1.77265	0.80899
H	-1.72121	2.49237	1.19414
H	-0.36760	1.41316	1.62718
H	-0.36593	2.22816	0.04562
N	-3.08809	0.82134	0.10789
N	-0.16681	-1.20377	0.02301
C	1.05224	-0.56974	-0.00486
N	1.21448	0.51740	-0.79587
N	2.03253	-1.18346	0.69686
C	2.45814	0.98949	-0.90700
C	3.25056	-0.65883	0.59188
C	3.54051	0.43730	-0.22517
H	4.54474	0.83507	-0.32086
H	2.58661	1.84925	-1.56389
H	4.03265	-1.14349	1.17575

SCF energy: -583.572063 hartree
zero-point correction: +0.160484 hartree
enthalpy correction: +0.171874 hartree
free energy correction: +0.122661 hartree
quasiharmonic free energy correction: +0.123865 hartree

water

O	0.00000	-0.00000	0.11943
H	-0.00000	0.76262	-0.47770
H	-0.00000	-0.76262	-0.47770

SCF energy: -76.472546 hartree
zero-point correction: +0.021140 hartree
enthalpy correction: +0.024919 hartree
free energy correction: +0.003474 hartree
quasiharmonic free energy correction: +0.003474 hartree

Supplemental Figures

Figure S1. Radiochromatogram of male $AUC_{0\text{-}8h}$ pooled plasma, 0 to 48 hour pooled urine, bile and 0 to 72 hour pooled feces samples

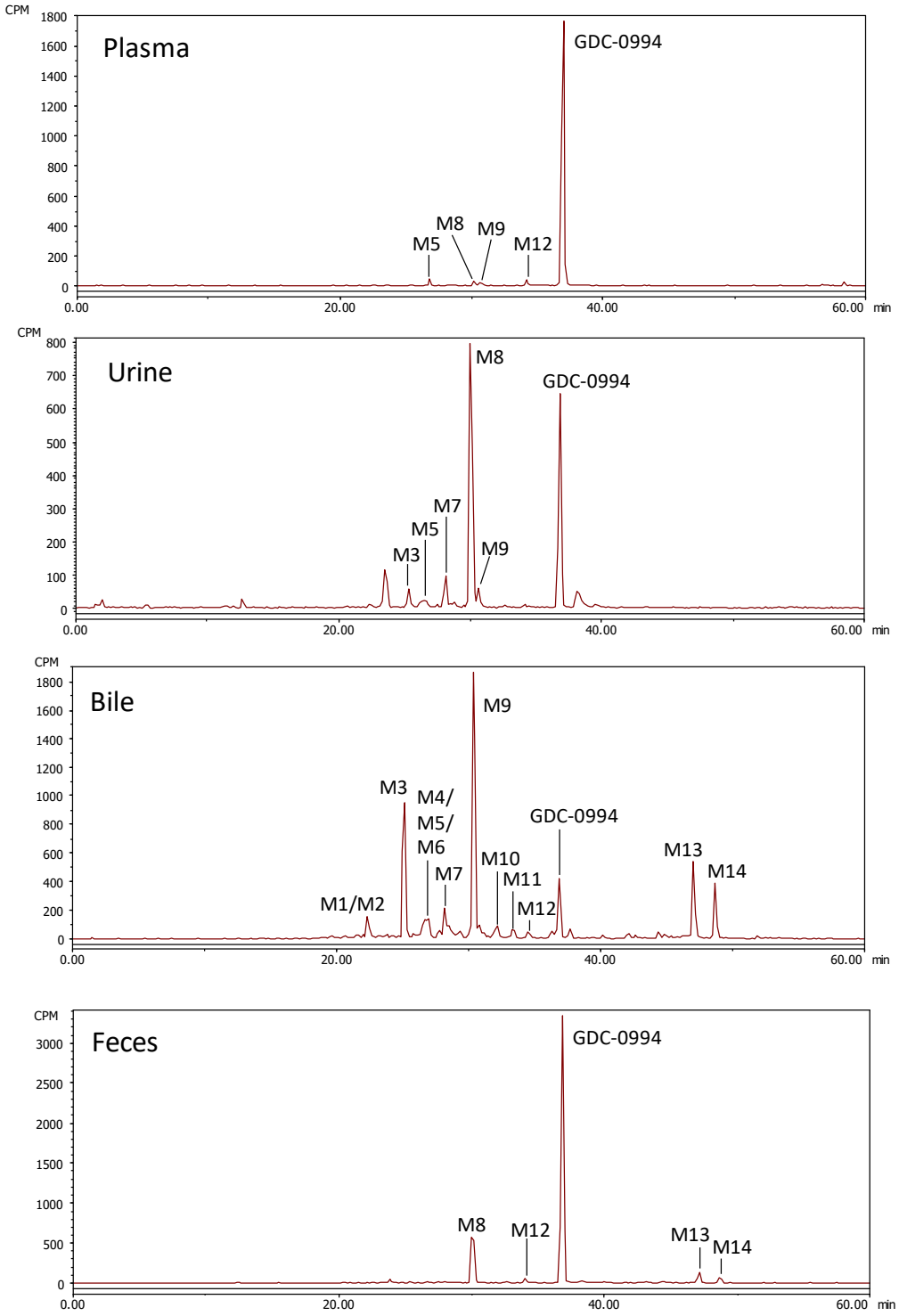

Figure S2. Proposed metabolic pathways of GDC-0994 in rats

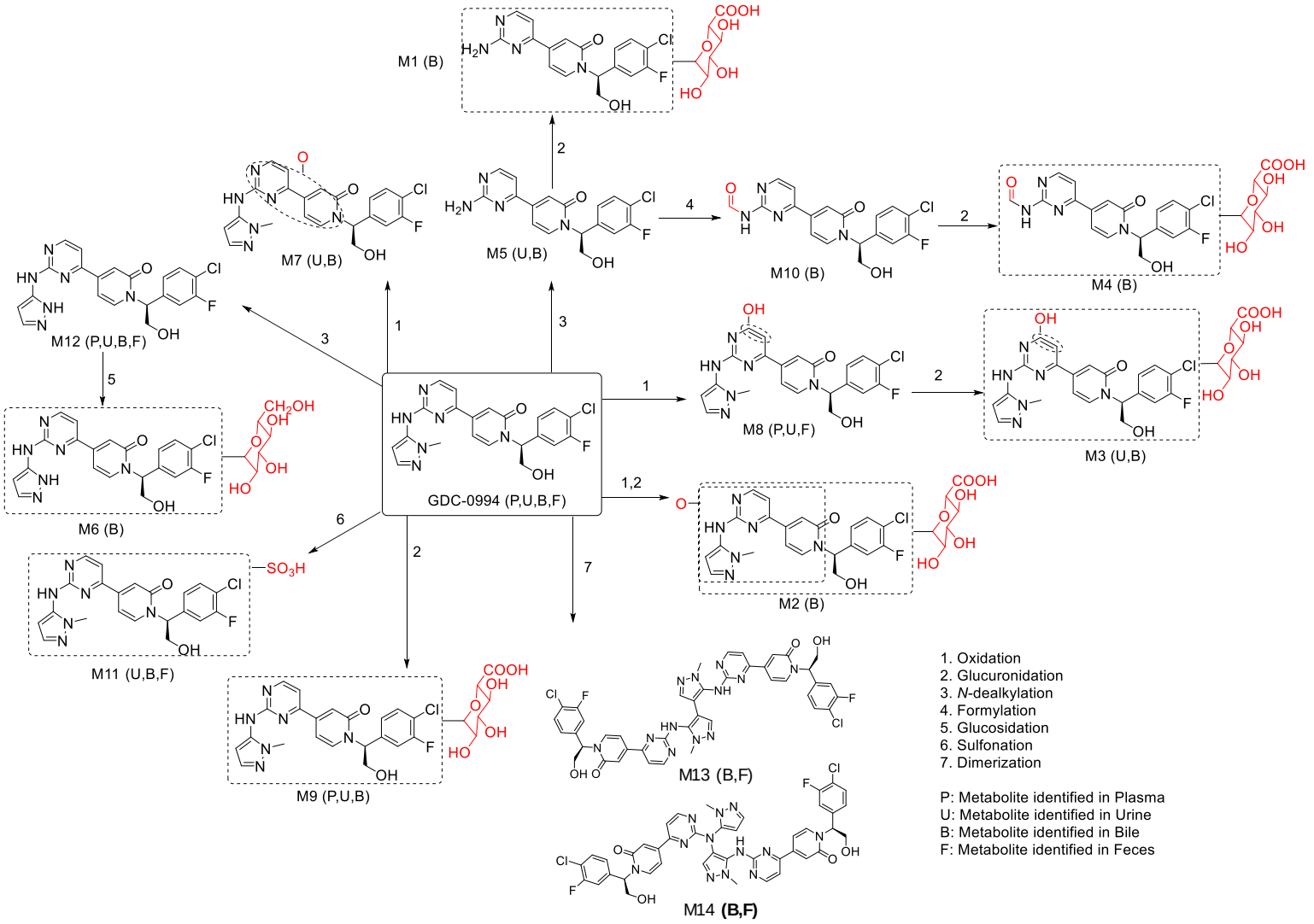

Figure S3. (a) Extracted ion chromatogram of GDC-0994, **M13** and **M14** from the incubation of (a) GDC-0994 with human liver microsomes and NADPH, (b) GDC-0994 with human liver microsomes and NADPH after a preincubation with ABT, a pan P450 inhibitor, and (c) GDC-0994 with human liver microsome and NADPH after a preincubation with ketoconazole, a selective CYP3A inhibitor.

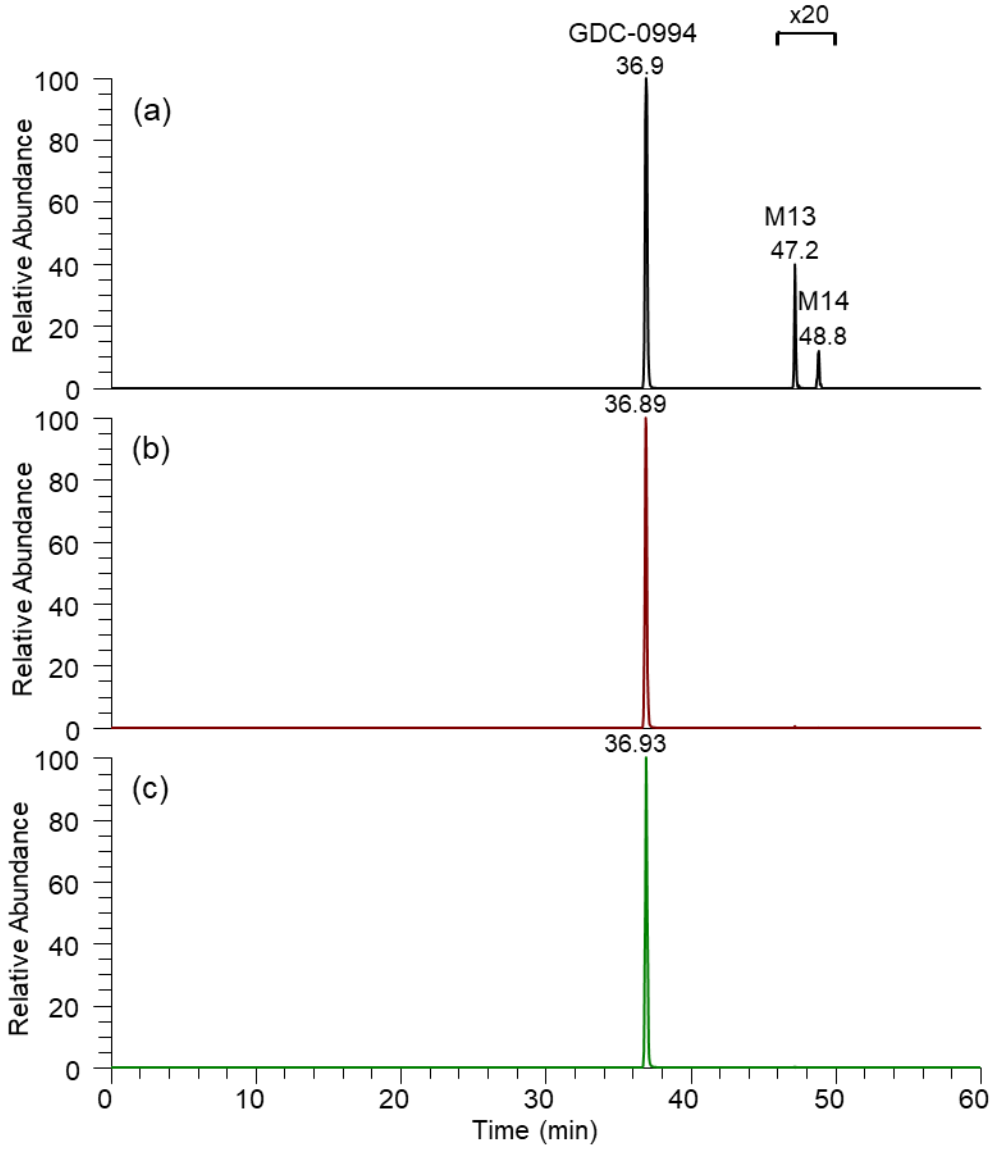

Figure S4. (a) Extracted ion chromatogram of GDC-0994, **M13** and **M14** from the incubation of GDC-0994 with horseradish peroxidase. (b) MS^2 and MS^3 product ion spectra of **M13**