

Targeting of the Mitochondrial TET1 Protein by Pyrrolo[3,2-*b*]pyrrole Chelators

Veronika Antonyová ^{1,2}, Ameneh Tatar ^{1,3}, Tereza Brogyányi ^{1,4}, Zdeněk Kejík ^{1,2,3}, Robert Kaplánek ^{1,2,3}, Frédéric Vellieux ², Nikita Abramenko ^{1,2}, Alla Sinica ^{2,3}, Jan Hajduch ^{2,3}, Petr Novotný ^{1,2}, Bettie Sue Masters ⁵, Pavel Martásek ^{1,*} and Milan Jakubek ^{1,2,3,*}

¹ Department of Paediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital in Prague, Ke Karlovu 455/2, 128 08 Prague, Czech Republic

² BIOCEV, First Faculty of Medicine, Charles University, 252 20 Vestec, Czech Republic

³ Department of Analytical Chemistry, Faculty of Chemical Engineering, University of Chemistry and Technology, 166 28 Prague, Czech Republic

⁴ Institute of Pathological Physiology, First Faculty of Medicine, Charles University, 128 53 Prague, Czech Republic

⁵ Duke University Medical Center, Department of Biochemistry, Durham, NC 27707, USA

* Correspondence: pavel.martasek@lf1.cuni.cz (P.M.); milan.jakubek@lf1.cuni.cz (M.J.)

Supplementary Materials

Contents

Figure S1. NMR spectra of Compound 1 in DMSO-*d*₆.

Figure S2. NMR spectra of Compound 2 in DMSO-*d*₆.

Figure S3. NMR spectra of Compound 3 in DMSO-*d*₆.

Figure S4. NMR spectra of Compound 4 in DMSO-*d*₆.

Figure S5. NMR spectra of Compound 5 in DMSO-*d*₆.

Figure S6. NMR spectra of Compound 6 in DMSO-*d*₆.

Figure S7. NMR spectra of Compound 7 in DMSO-*d*₆.

Figure S8. HRMS spectra of Compound 1.

Figure S9. HRMS spectra of Compound 2.

Figure S10. HRMS spectra of Compound 3.

Figure S11. HRMS spectra of Compound 4.

Figure S12. HRMS spectra of Compound 5.

Figure S13. HRMS spectra of Compound 6.

Figure S14. HRMS spectra of Compound 7.

Figure S15. Close up view of the TET1 active site showing docked compound 2 in a sphere representation.

Figure S16. Close up view of the TET1 active site showing docked compound 3 in a sphere representation.

Figure S17. Close up view of the TET1 active site showing docked compound 4 in a sphere representation.

Figure S18. Close up view of the TET1 active site showing docked compound 5 in a sphere representation.

Figure S19. Close up view of the TET1 active site showing docked compound 6 in a sphere representation.

Figure S20. Close up view of the TET1 active site showing docked compound 7 in a sphere representation.

Table S1. Residual TET1 protein activity on the concentration of compound 1.

Table S2. Viability of Caov-3 cells in the presence of compound 1.

Table S3. Viability of Caov-3 cells in the presence of compound 2.

Table S4. Viability of Caov-3 cells in the presence of compound 3.

Table S5. Viability of Caov-3 cells in the presence of compound 4.
Table S6. Viability of Caov-3 cells in the presence of compound 5.
Table S7. Viability of Caov-3 cells in the presence of compound 6.
Table S8. Viability of H-1299 cells in the presence of compound 1.
Table S9. Viability of H-1299 cells in the presence of compound 2.
Table S10. Viability of H-1299 cells in the presence of compound 3.
Table S11. Viability of H-1299 cells in the presence of compound 4.
Table S12. Viability of H-1299 cells in the presence of compound 5.
Table S13. Viability of H-1299 cells in the presence of compound 6.
Table S14. Viability of BT-20 cells in the presence of compound 1.
Table S15. Viability of BT-20 cells in the presence of compound 2.
Table S16. Viability of BT-20 cells in the presence of compound 3.
Table S17. Viability of BT-20 cells in the presence of compound 4.
Table S18. Viability of BT-20 cells in the presence of compound 5.
Table S19. Viability of BT-20 cells in the presence of compound 6.
Table S20. Viability of U-118 MG cells in the presence of compound 1.
Table S21. Viability of U-118 MG cells in the presence of compound 2.
Table S22. Viability of U-118 MG cells in the presence of compound 3.
Table S23. Viability of U-118 MG cells in the presence of compound 4.
Table S24. Viability of U-118 MG cells in the presence of compound 5.
Table S25. Viability of U-118 MG cells in the presence of compound 6.
Table S26. Viability of HF-P4 cells in the presence of compound 1.
Table S27. Viability of HF-P4 cells in the presence of compound 2.
Table S28. Viability of HF-P4 cells in the presence of compound 3.
Table S29. Viability of HF-P4 cells in the presence of compound 4.
Table S30. Viability of HF-P4 cells in the presence of compound 5.
Table S31. Viability of HF-P4 cells in the presence of compound 6.

NMR spectra of Compound 1-7 in DMSO-d₆

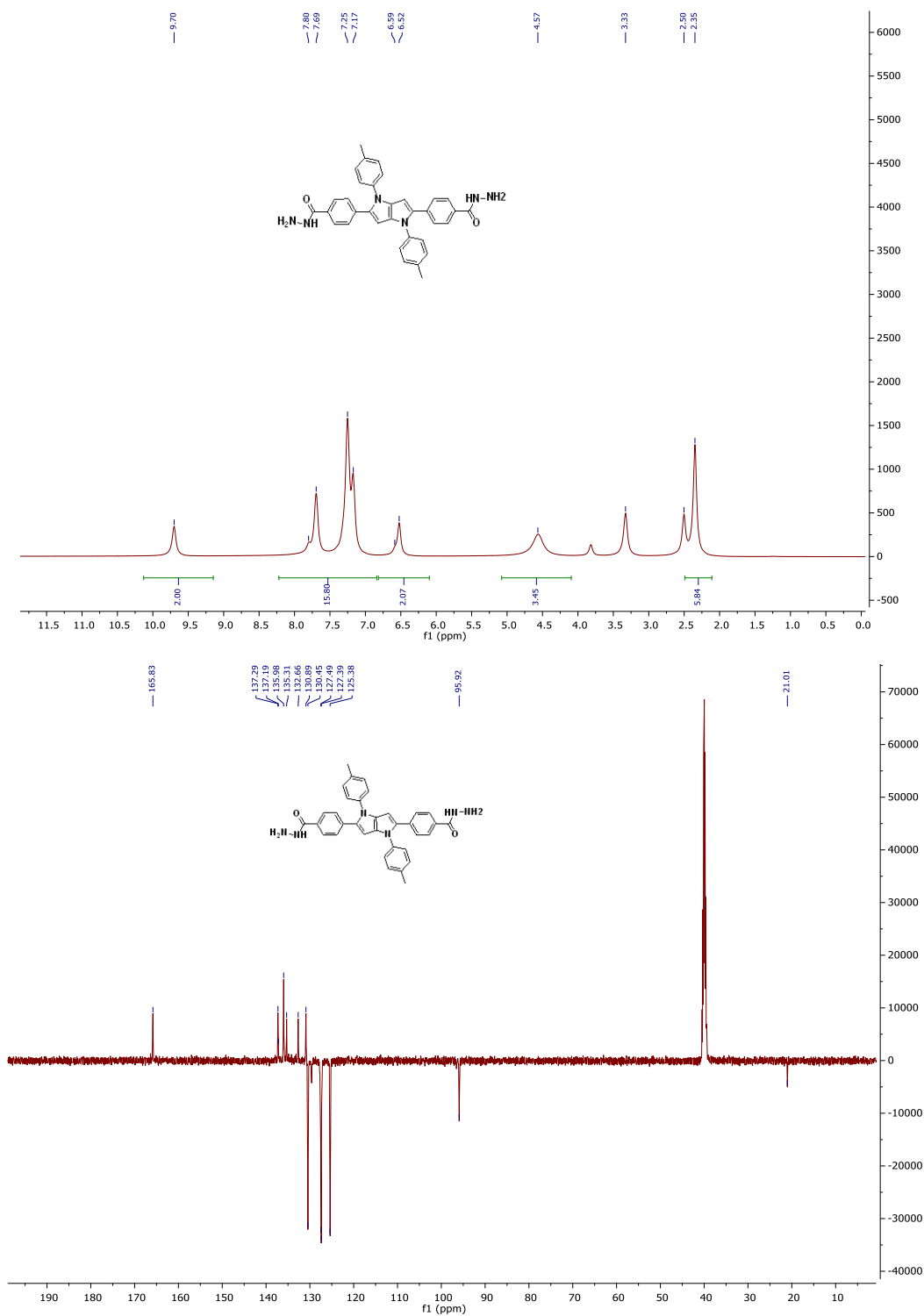


Figure S1. ¹H NMR and ¹³C NMR spectra of Compound 1 in DMSO-d₆.

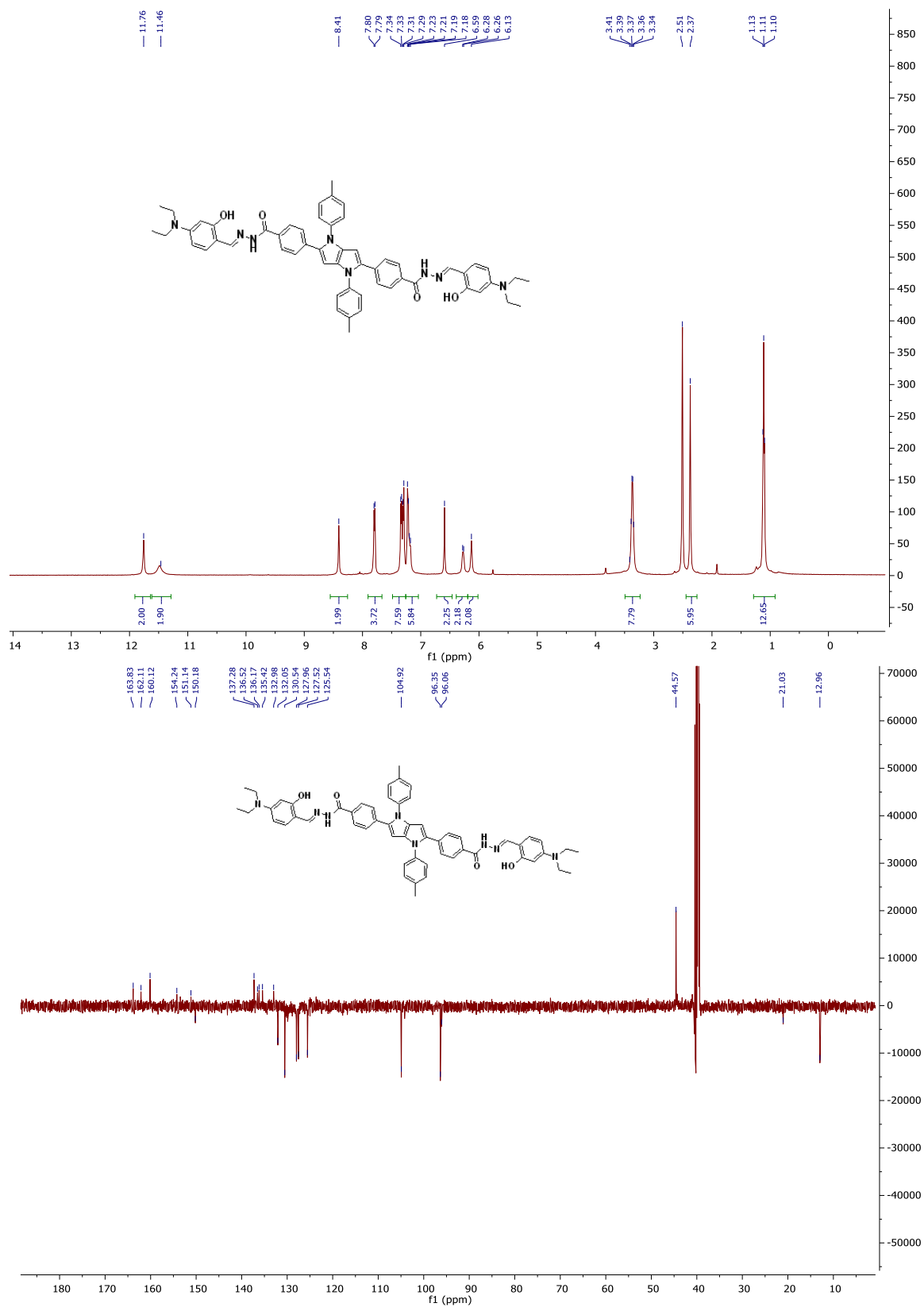


Figure S2. ¹H NMR and ¹³C NMR spectra of Compound 2 in DMSO-d₆.

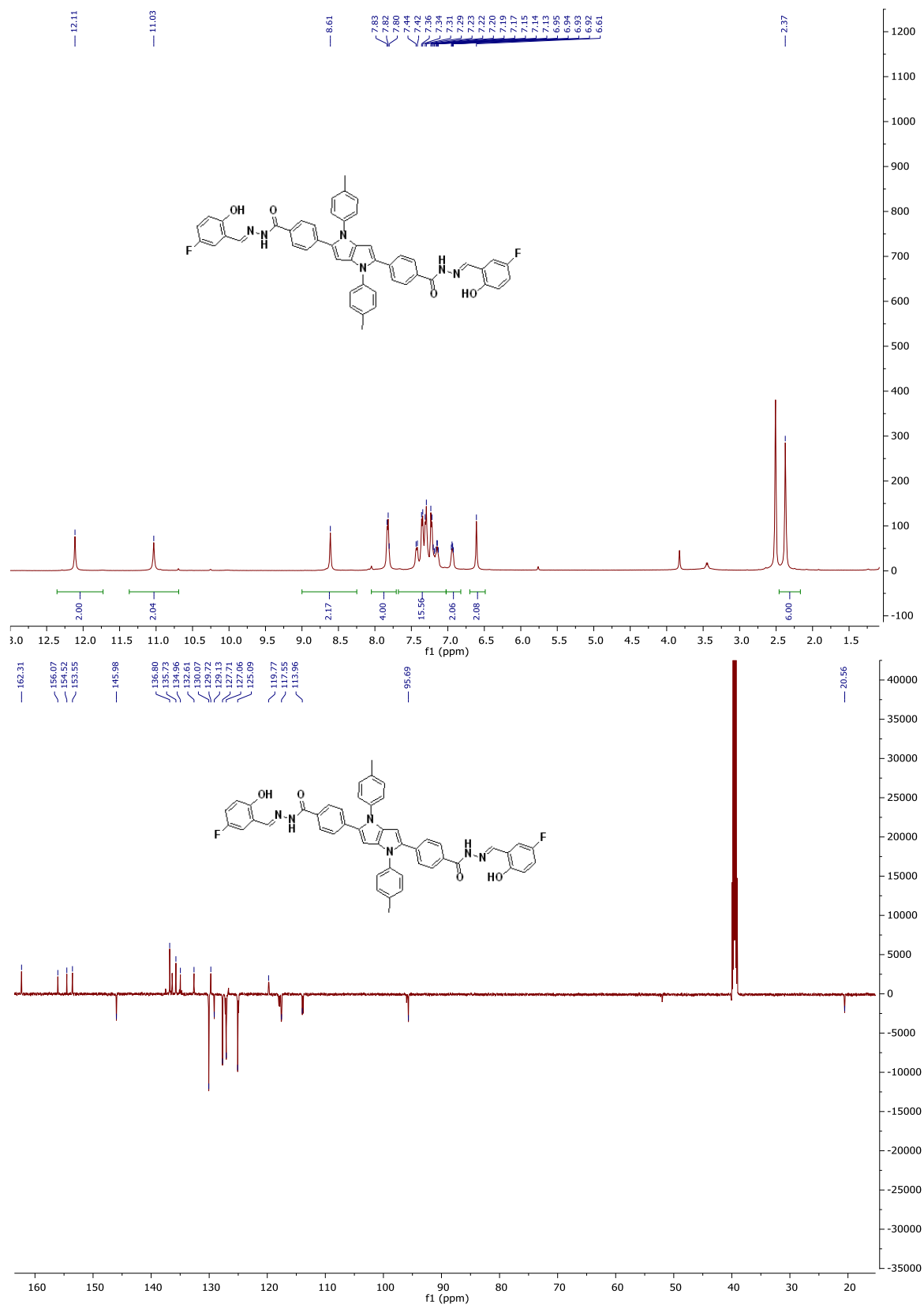


Figure S3. ¹H NMR and ¹³C NMR spectra of Compound 3 in DMSO-d₆.

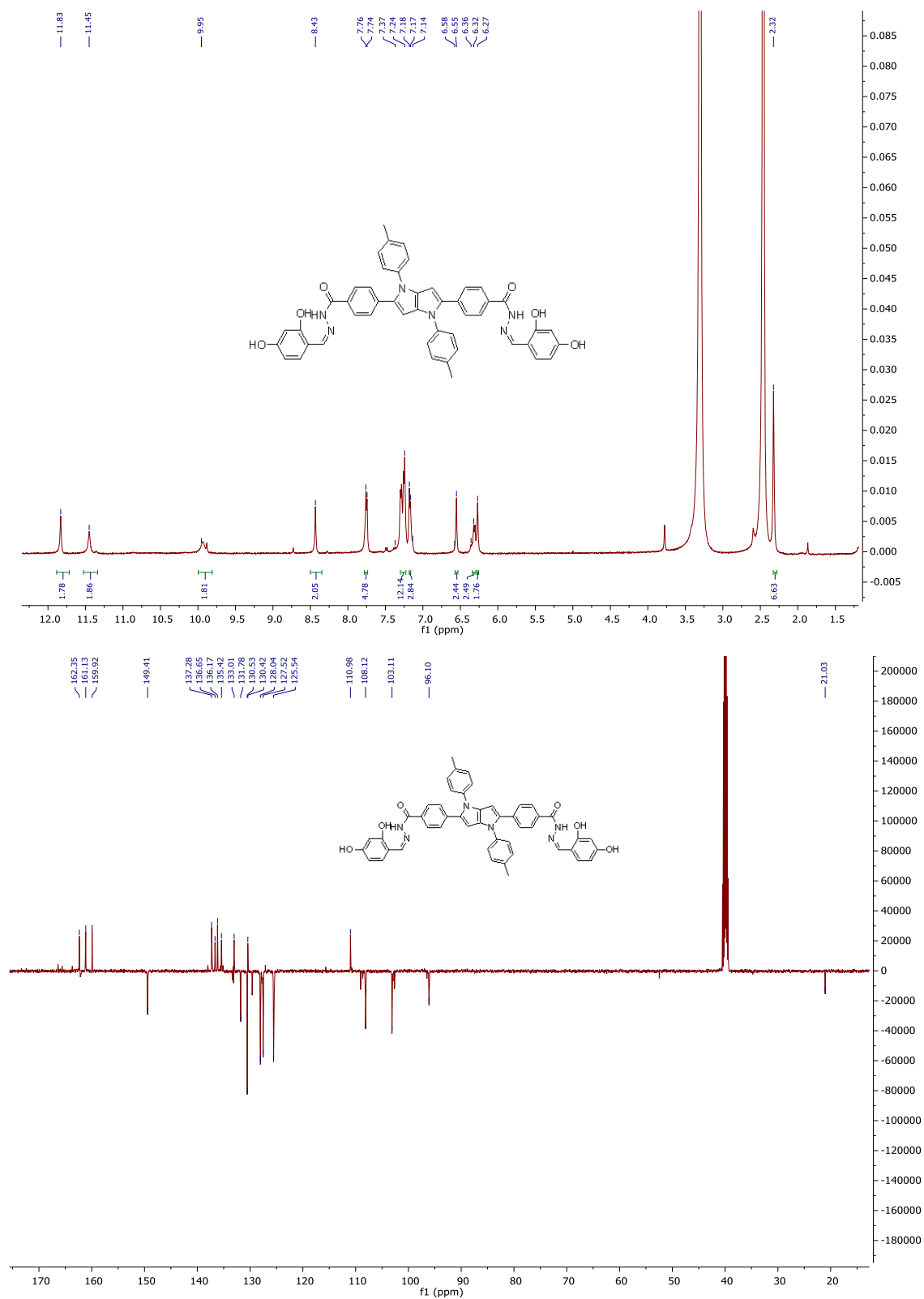


Figure S4. ¹H NMR and ¹³C NMR spectra of Compound **4** in DMSO-d₆.

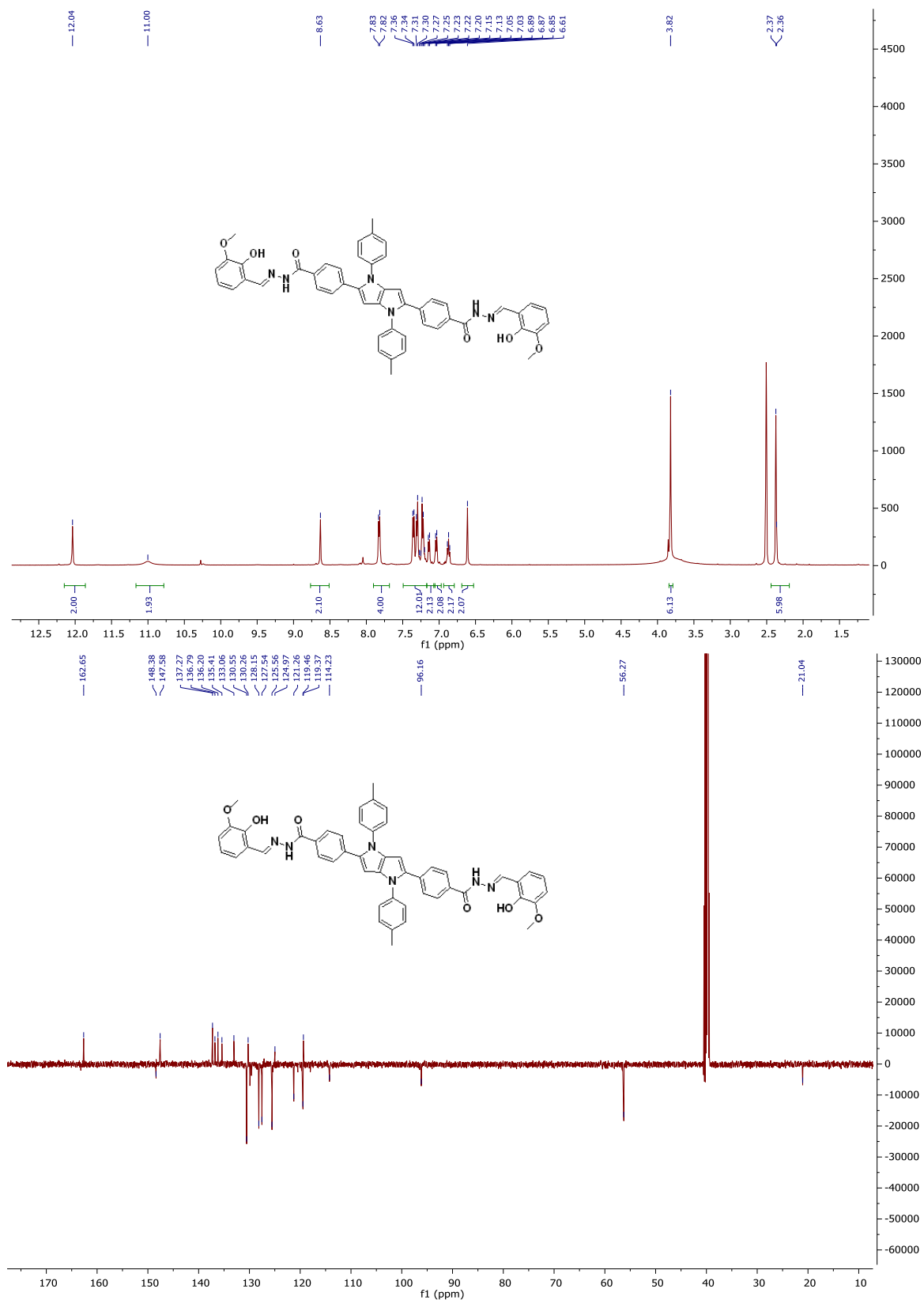


Figure S5. ¹H NMR and ¹³C NMR spectra of Compound 5 in DMSO-d₆.

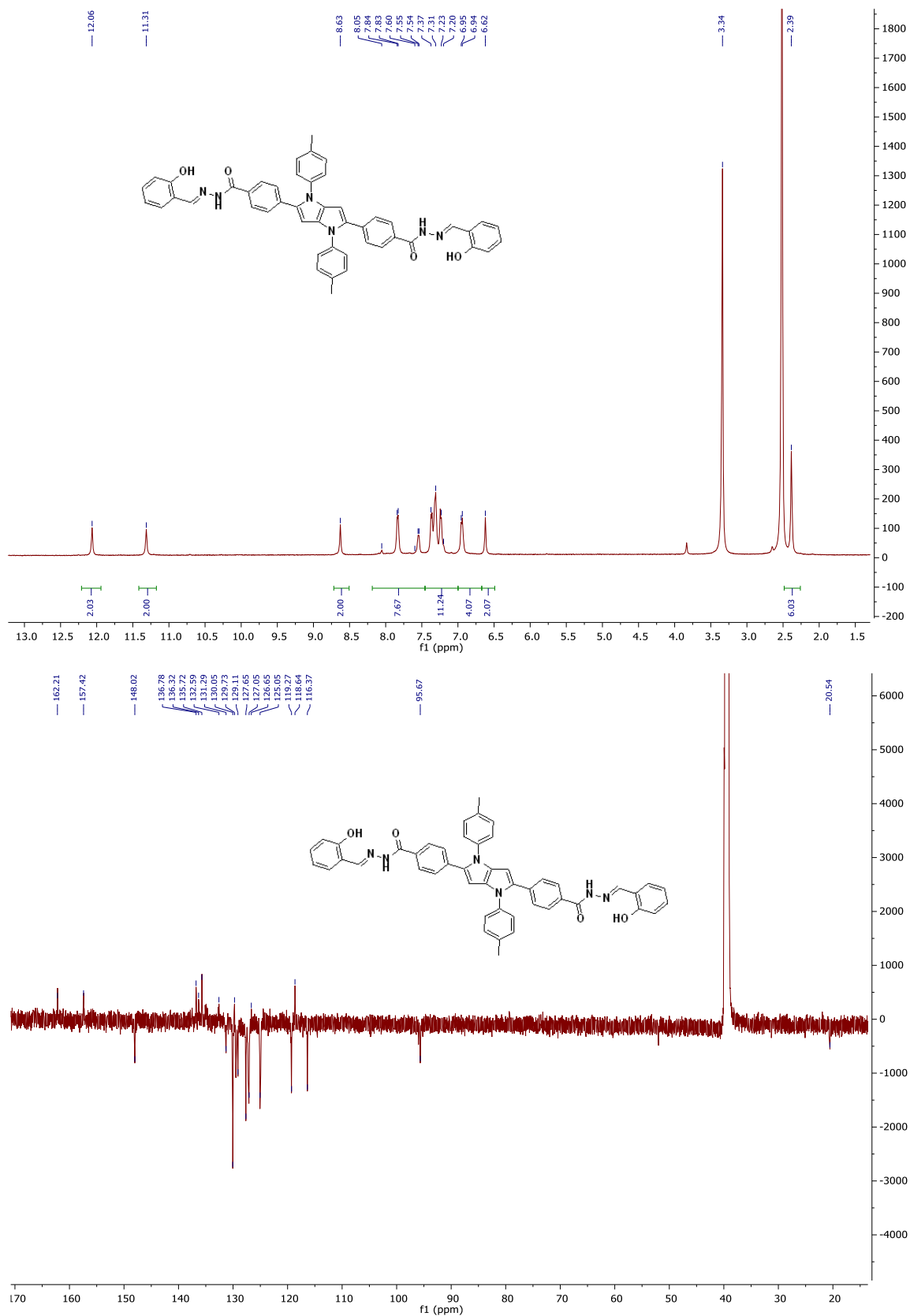


Figure S6. ¹H NMR and ¹³C NMR spectra of Compound **6** in DMSO-d₆.

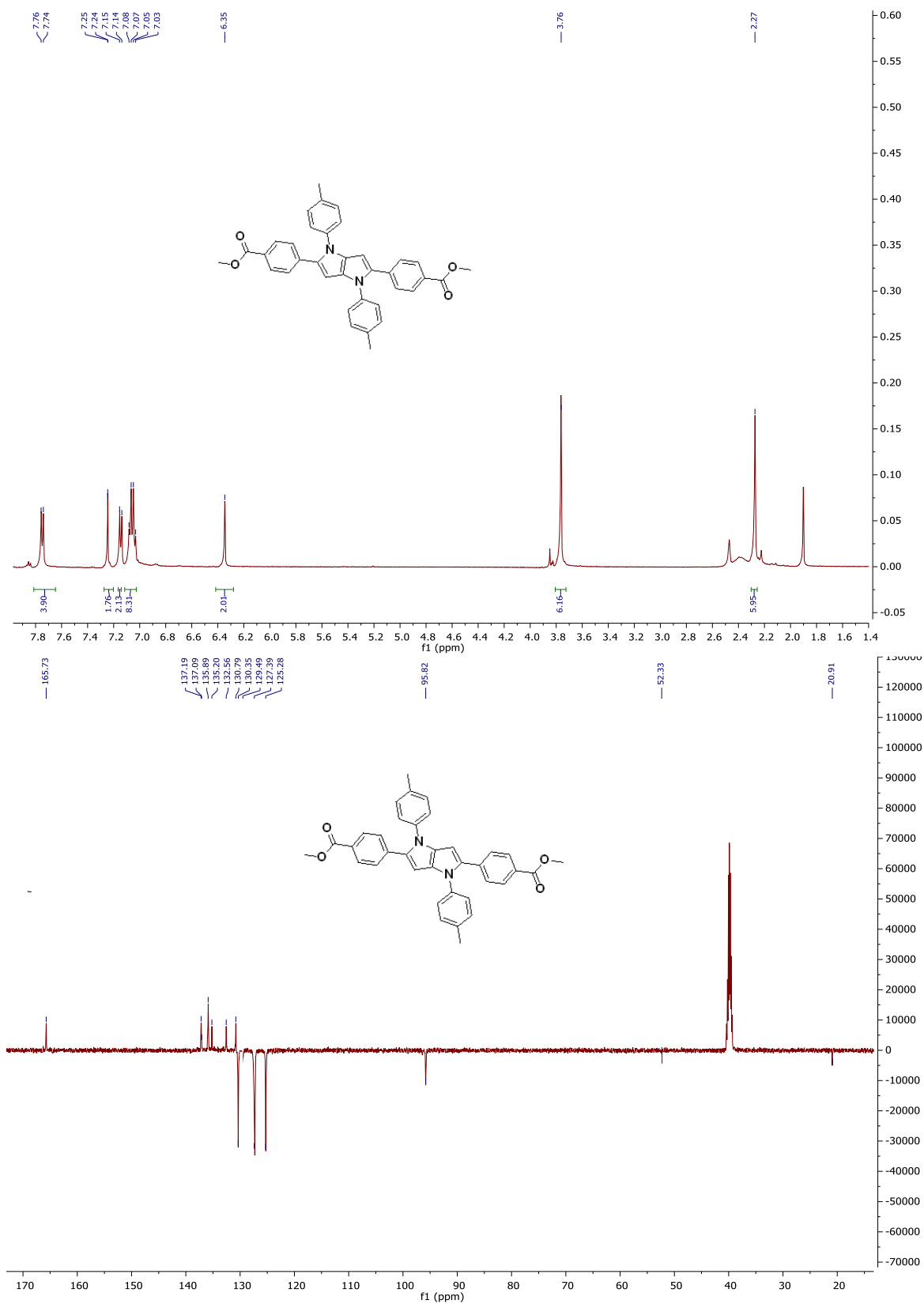


Figure S7. ¹H NMR and ¹³C NMR spectra of Compound 7 in DMSO-d₆.

HRMS spectra of compound 1–7

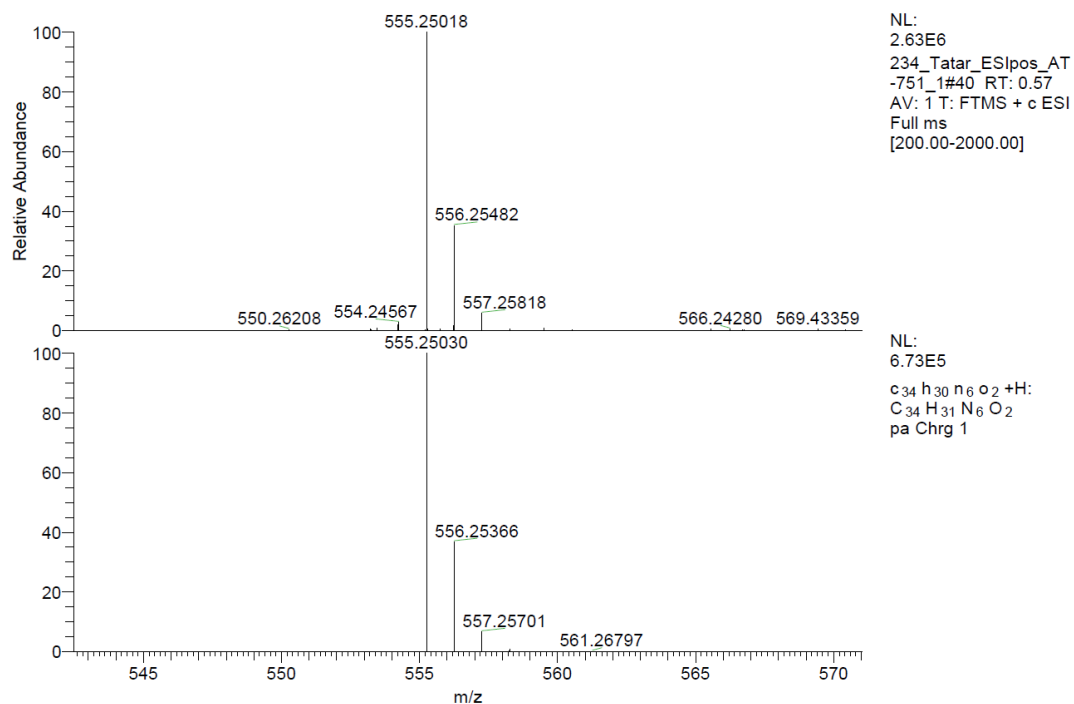


Figure S8. MS spectra of compound 1

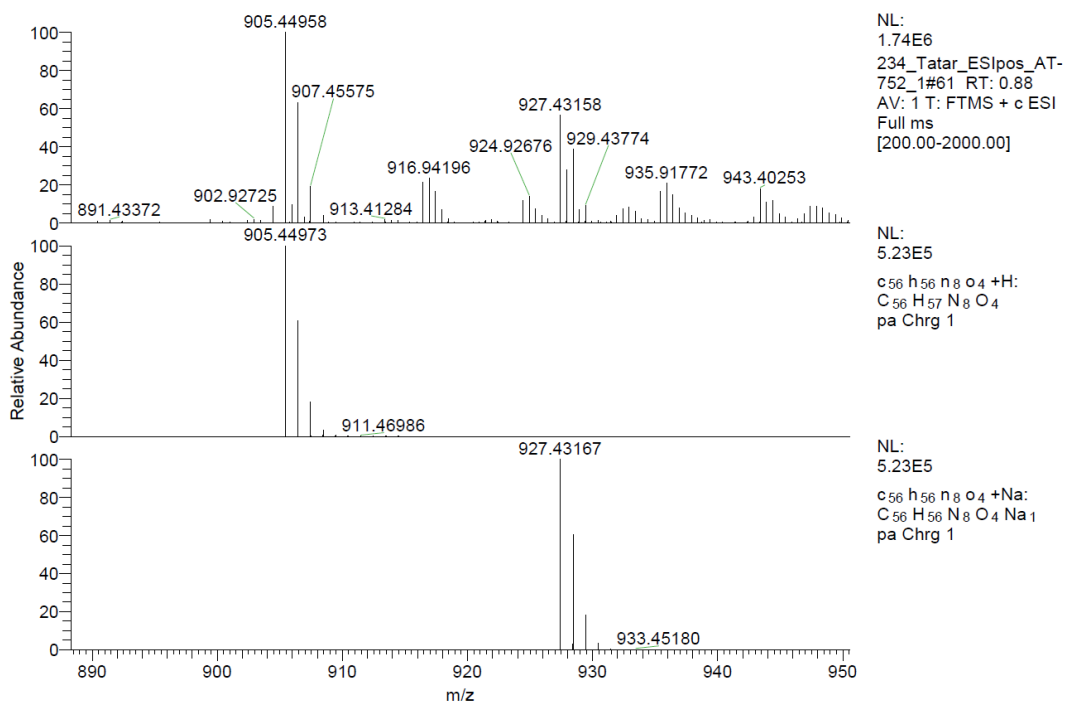


Figure S9. MS spectra of compound 2.

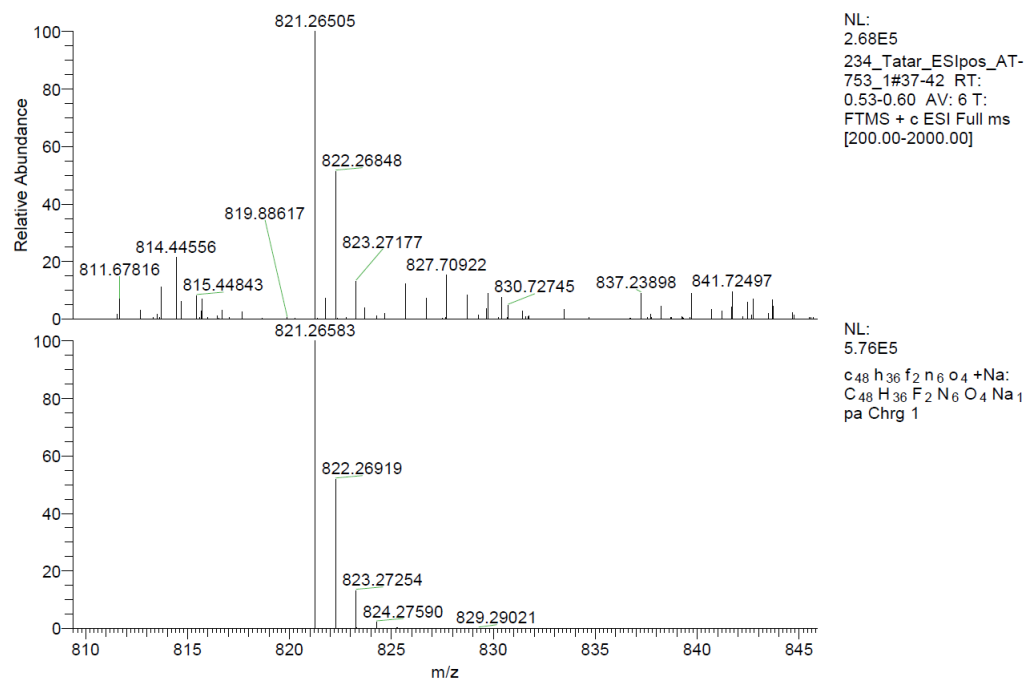


Figure S10. MS spectra of compound 3.

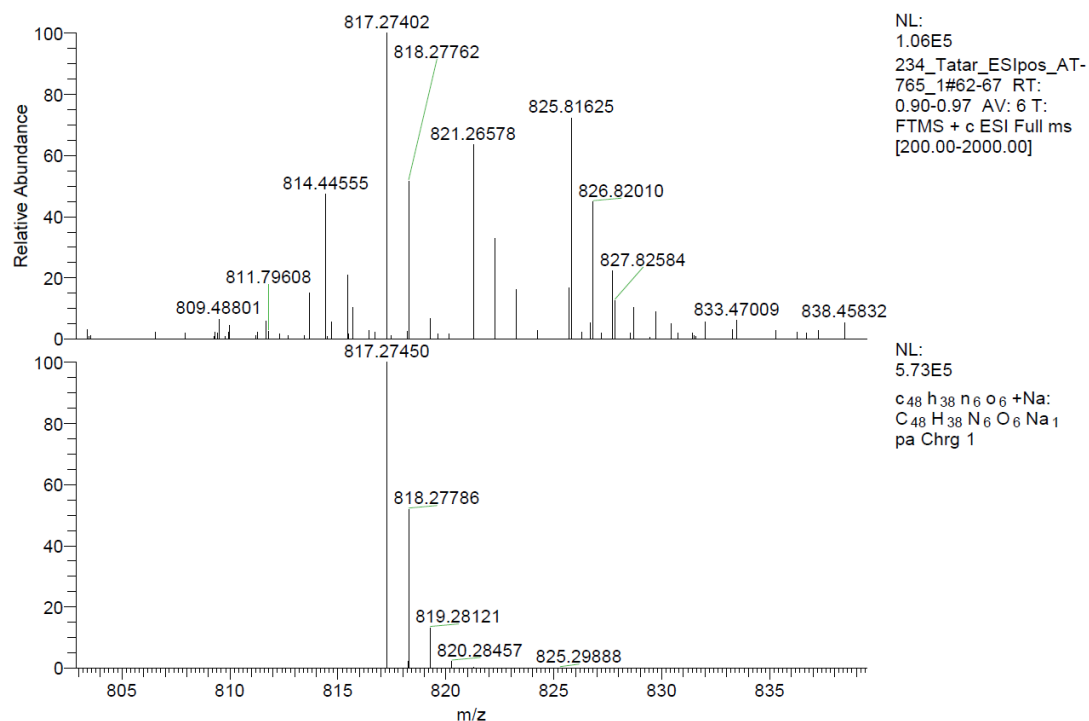


Figure S11. MS spectra of compound 4.

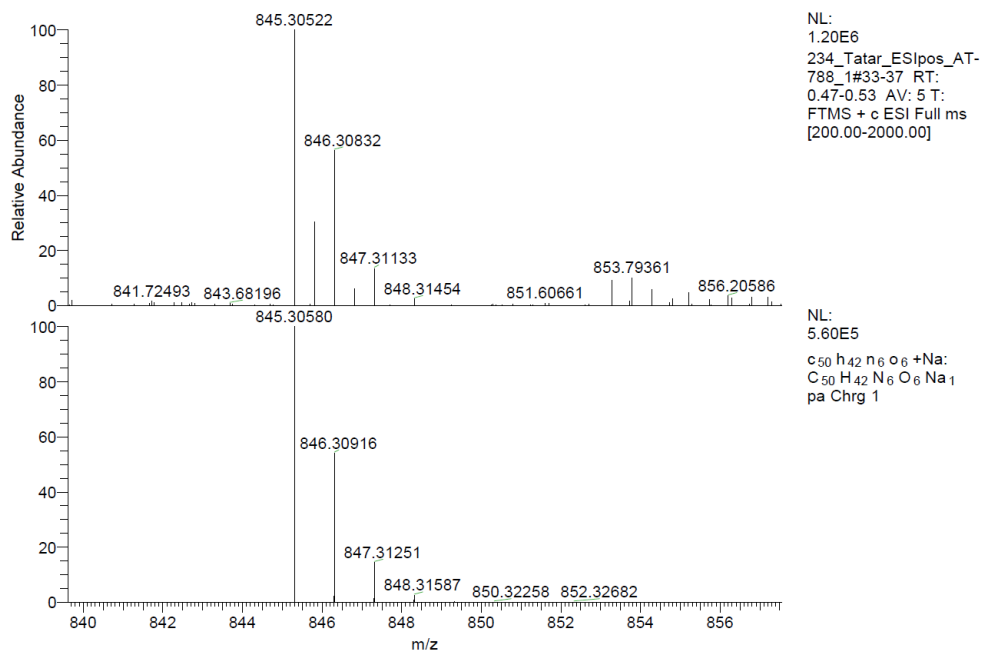


Figure S12. MS spectra of compound 5.

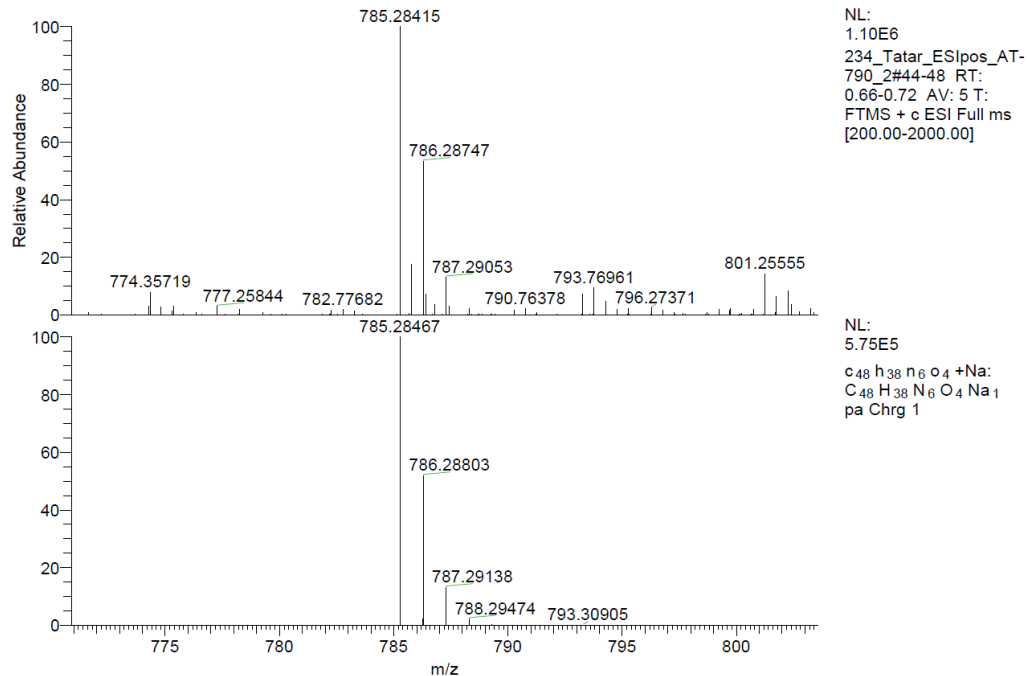


Figure S13. MS spectra of compound 6.

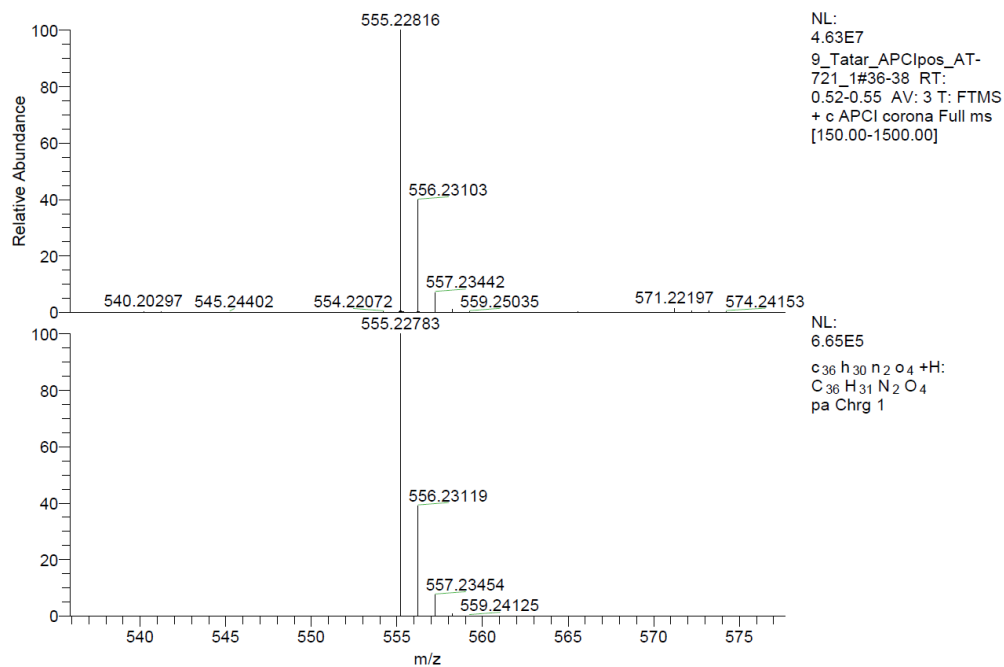


Figure S14. MS spectra of compound 7.

Docking compounds 2–6 to the TET1 protein

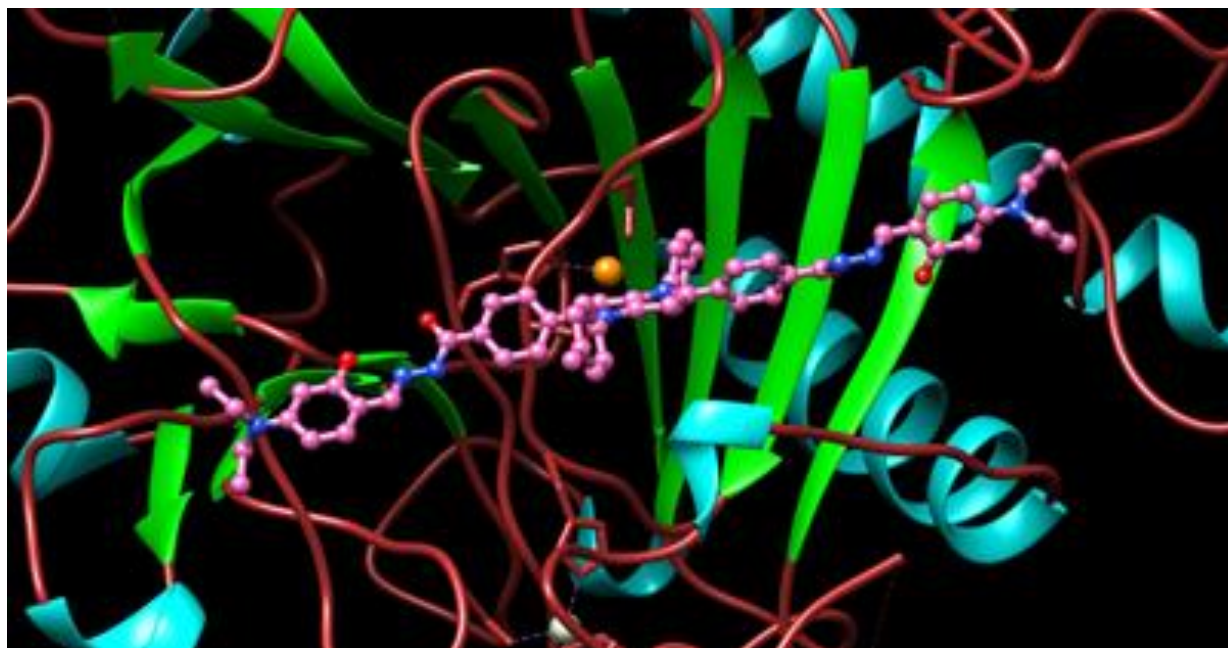


Figure S15. Close up view of the TET1 active site showing docked compound **2** in a sphere representation. The Fe(II) ion is displayed as a crossed orange sphere, the protein residues involved in contacts with compound **2** (pink sticks) are shown as sticks. The hydrogen bonds and carbon hydrogen bond are indicated by purple and yellow dotted lines, respectively.

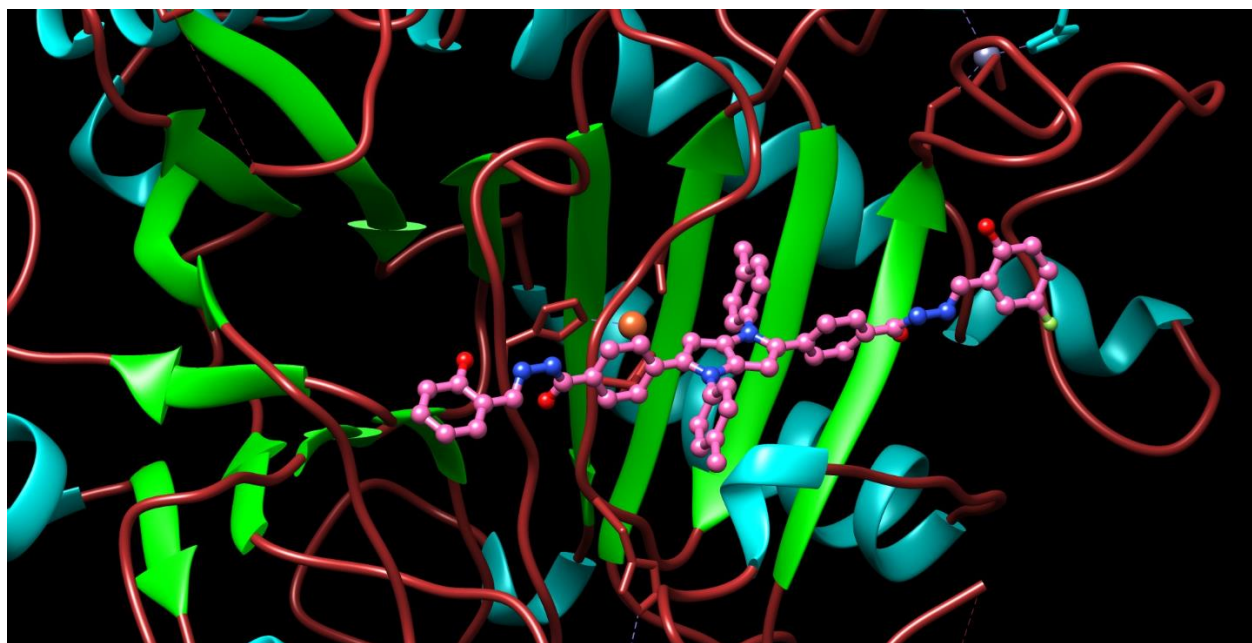


Figure S16. Close up view of the TET1 active site showing docked compound **3** in a sphere representation. The Fe(II) ion is displayed as a crossed orange sphere, the protein residues involved in contacts with compound **3** (pink sticks) are shown as sticks. The hydrogen bonds and carbon hydrogen bond are indicated by purple and yellow dotted lines, respectively.

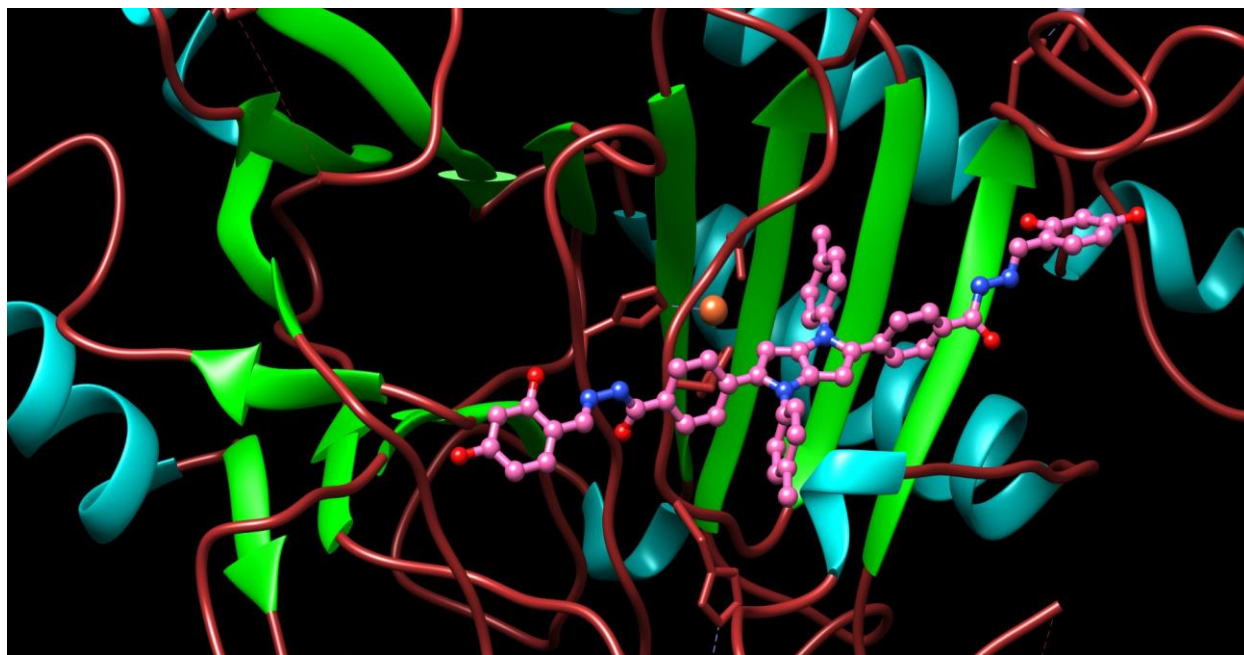


Figure S17. Close up view of the TET1 active site showing docked compound **4** in a sphere representation. The Fe(II) ion is displayed as a crossed orange sphere, the protein residues involved in contacts with compound **4** (pink sticks) are shown as sticks. The hydrogen bonds and carbon hydrogen bond are indicated by purple and yellow dotted lines, respectively.

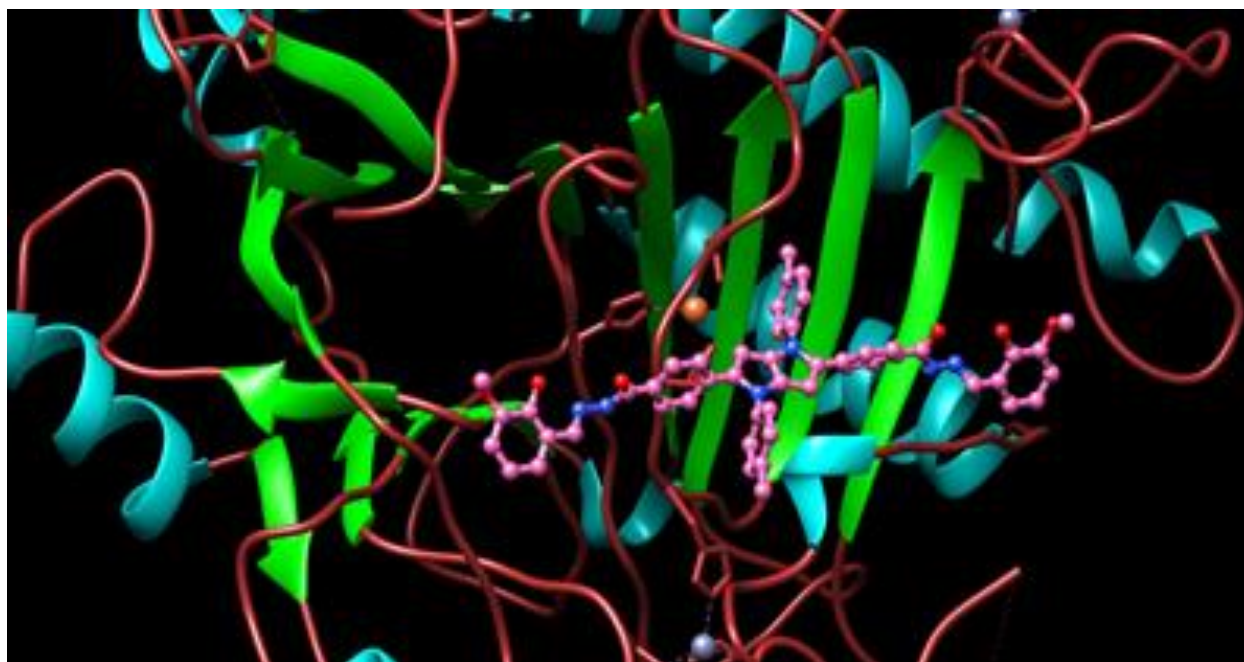


Figure S18. Close up view of the TET1 active site showing docked compound **5** in a sphere representation. The Fe(II) ion is displayed as a crossed orange sphere, the protein residues involved in contacts with compound **5** (pink sticks) are shown as sticks. The hydrogen bonds and carbon hydrogen bond are indicated by purple and yellow dotted lines, respectively.

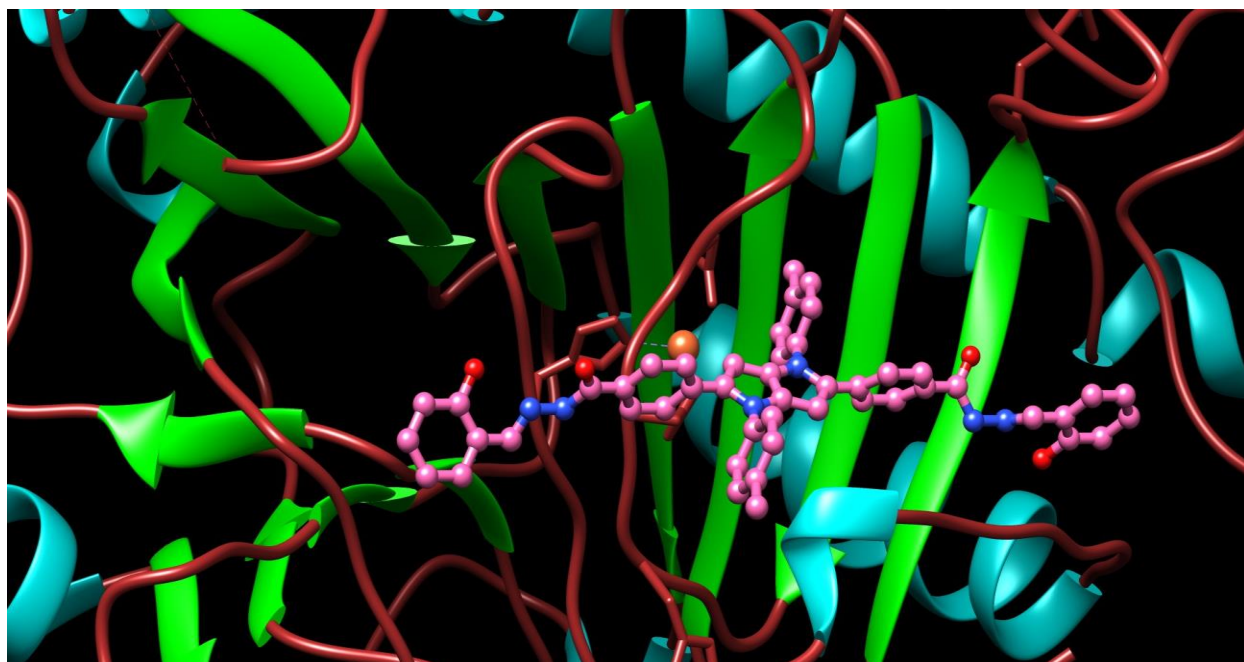


Figure S19. Close up view of the TET1 active site showing docked compound **6** in a sphere representation. The Fe(II) ion is displayed as a crossed orange sphere, the protein residues involved in contacts with compound **6** (pink sticks) are shown as sticks. The hydrogen bonds and carbon hydrogen bond are indicated by purple and yellow dotted lines, respectively.

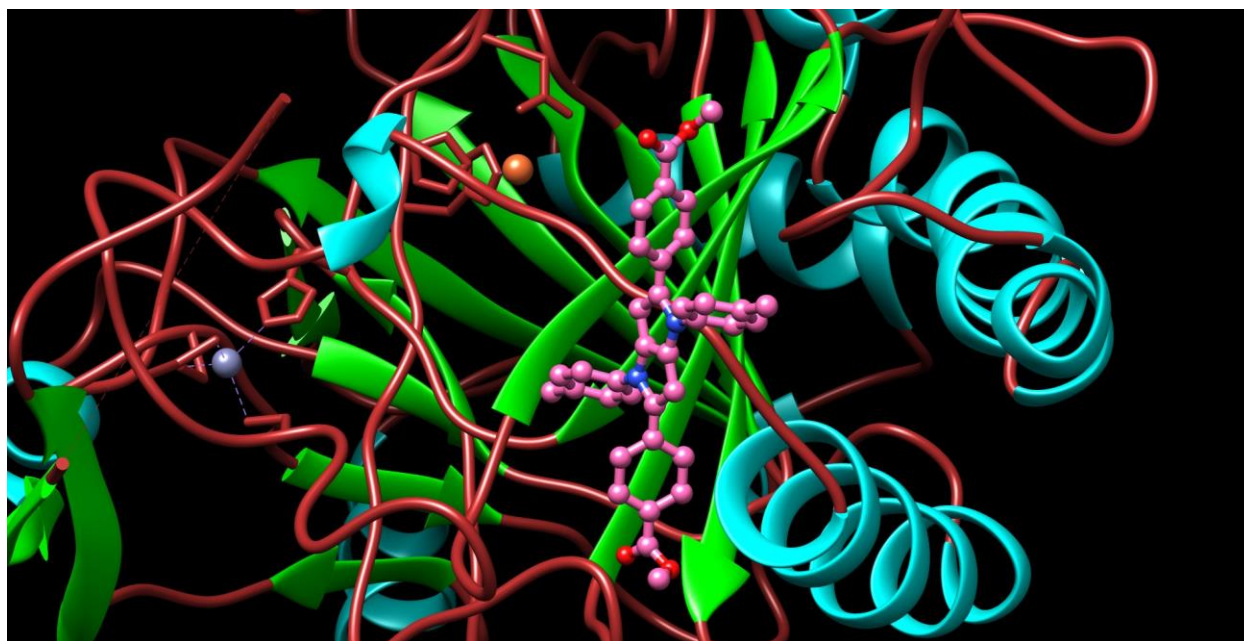


Figure S20. Close up view of the TET1 active site showing docked compound **7** in a sphere representation. The Fe(II) ion is displayed as a crossed orange sphere, the protein residues involved in contacts with compound **7** (pink sticks) are shown as sticks. The hydrogen bonds and carbon hydrogen bond are indicated by purple and yellow dotted lines, respectively.

Inhibition of TET1 protein

Table S1. Residual TET1 protein activity on the concentration of compound 1.

Log c (751/compound 1)	average residual TET activity (%)
4	5.107745
5	19.97357
6	56.08355
7	82.58792

Toxicity (MTT assay)

Caov-3

Table S2. Viability of Caov-3 cells in the presence of compound 1.

Cell viability %			
20 uM	28.51596	35.73407	39.69061
15 uM	35.10045	41.90383	45.92074
10 uM	45.06162	53.56232	43.67450
7.5 uM	56.44099	51.67812	65.52312
5 uM	50.93702	48.77331	58.08483
2.5 uM	55.86696	71.78777	55.75334
1 uM	81.16343	71.06968	89.65883
750 nM	78.45686	95.40726	77.66887
500 nM	91.35573	100.9421	76.34775
100 nM	97.8727	80.60844	94.80077
Control	100	100	100

Table S3. Viability of Caov-3 cells in the presence of compound 2.

Cell viability %			
20 uM	28.42292	25.29919	23.24628
15 uM	42.75603	50.9752	42.32679
10 uM	52.13448	51.36046	52.94626
7.5 uM	73.28024	79.19576	67.96892
5 uM	59.21257	86.03419	70.4727
2.5 uM	64.6096	82.47049	61.81465
1 uM	78.50034	67.15627	48.54306
750 nM	73.36872	52.90151	76.28723
500 nM	76.19996	78.8105	77.84582
100 nM	95.32425	105.779	93.87006
Control	100	100	100

Table S4. Viability of Caov-3 cells in the presence of compound 3.

Cell viability %			
20 μ M	35.49563	34.97841	37.90087
15 μ M	58.99942	57.50729	62.97376
10 μ M	65.43991	67.36582	81.12244
7.5 μ M	83.03623	61.93708	104.0087
5 μ M	70.6153	67.61258	86.51603
2.5 μ M	85.27889	89.38926	98.68805
1 μ M	89.3617	86.92165	97.81341
750 nM	86.6015	81.49291	112.9009
500 nM	93.50201	75.38556	98.76093
100 nM	84.41633	80.39359	71.13703
Control	100	100	100

Table S5. Viability of Caov-3 cells in the presence of compound 4.

Cell viability %			
20 μ M	14.32384	14.90858	14.49109
15 μ M	19.49414	17.58087	17.59632
10 μ M	42.88256	41.06892	42.6107
7.5 μ M	53.11536	53.65682	54.16907
5 μ M	50.70943	80.94234	55.26165
2.5 μ M	74.64528	110.1266	69.69523
1 μ M	100.802	98.73418	92.86946
750 nM	92.84392	102.8833	94.07706
500 nM	104.1332	102.391	108.5681
100 nM	68.5943	84.94756	82.17366
Control	100	100	100

Table S6. Viability of Caov-3 cells in the presence of compound 5.

Cell viability %			
20 μ M	17.9126	16.1941	14.82686
15 μ M	31.48711	34.22252	36.44149
10 μ M	29.50216	41.31352	47.32635
7.5 μ M	62.47383	49.34999	63.65028
5 μ M	83.63463	81.63093	70.92022
2.5 μ M	106.339	69.33987	79.185
1 μ M	115.5595	95.47527	128.3145
750 nM	97.71646	117.0859	120.9681
500 nM	90.56137	116.6807	137.4211
100 nM	124.7159	131.0561	82.39908
Control	100	100	100

Table S7. Viability of Caov-3 cells in the presence of compound 6.

Cell viability %			
20 μ M	17.40035	17.33918	16.87916
15 μ M	36.28942	42.46159	49.26344
10 μ M	52.61726	73.89153	61.73714
7.5 μ M	57.99583	65.62553	91.09419
5 μ M	62.99023	65.69306	100.7653
2.5 μ M	67.85657	93.922	75.10942
1 μ M	64.71906	111.7508	115.9087
750 nM	66.96014	65.96319	78.49627
500 nM	89.11477	125.1899	99.08169
100 nM	90.2569	126.2705	118.7488
Control	100	100	100

H-1299

Table S8. Viability of H-1299 cells in the presence of compound 1.

Cell viability %			
20 μ M	19.24406	17.01043	14.67647
15 μ M	23.87986	23.04042	23.96276
10 μ M	35.21357	36.64265	31.8986
7.5 μ M	38.35093	36.84003	36.66628
5 μ M	57.68489	61.73559	69.22959
2.5 μ M	68.0251	76.07293	72.38632
1 μ M	69.85522	81.23464	63.29924
750 nM	97.30258	84.13106	122.0664
500 nM	114.5756	80.35216	108.7959
100 nM	86.71852	74.42021	77.19802
Control	100	100	100

Table S9. Viability of H-1299 cells in the presence of compound 2.

Cell viability %			
20 μ M	28.59897	32.03724	28.81821
15 μ M	39.77581	39.64275	37.79295
10 μ M	45.51456	38.48482	47.34705
7.5 μ M	42.29877	36.16895	50.74895
5 μ M	53.16155	53.26162	57.69069
2.5 μ M	73.18867	66.9068	60.81677
1 μ M	72.40433	69.86743	82.46944
750 nM	74.14295	70.73588	81.48872
500 nM	71.47733	66.22258	72.35567
100 nM	77.6381	61.36715	71.29831
Control	100	100	100

Table S10. Viability of H-1299 cells in the presence of compound 3.

Cell viability %			
20 μ M	31.42255	35.73111	34.4596
15 μ M	58.89207	44.57329	46.49157
10 μ M	47.85276	61.93151	65.75698
7.5 μ M	56.61426	68.90741	84.49209
5 μ M	85.7362	93.25965	99.67511
2.5 μ M	123.9575	110.6978	112.6272
1 μ M	70.17579	93.78511	104.6587
750 nM	90.73998	102.5498	126.8789
500 nM	146.8316	115.9449	119.3443
100 nM	132.2567	108.7232	102.9023
Control	100	100	100

Table S11. Viability of H-1299 cells in the presence of compound 4.

Cell viability %			
20 μ M	7.35088	7.889723	6.314614
15 μ M	11.0926	10.45612	11.77551
10 μ M	14.81916	21.63938	18.83578
7.5 μ M	35.84548	38.28207	33.07157
5 μ M	66.67298	68.73663	52.75386
2.5 μ M	77.6406	77.91344	68.92042
1 μ M	88.01973	73.99385	66.83116
750 nM	86.06311	86.19959	81.88825
500 nM	110.8313	69.07882	86.71517
100 nM	109.7831	109.0835	92.98296
Control	100	100	100

Table S12. Viability of H-1299 cells in the presence of compound 5.

Cell viability %			
20 μ M	31.42255	35.73111	28.72878
15 μ M	46.49157	44.57329	49.80137
10 μ M	47.85276	61.93151	54.82123
7.5 μ M	56.61426	68.90741	70.44059
5 μ M	85.7362	93.25965	83.0986
2.5 μ M	105.6814	110.6978	93.89671
1 μ M	59.82921	93.78511	88.11845
750 nM	77.36145	98.71354	102.5498
500 nM	125.183	115.9449	119.3443
100 nM	112.7571	101.9931	108.7232
Control	100	100	100

Table S13. Viability of H-1299 cells in the presence of compound 6.

Cell viability %			
20 μ M	34.39408	33.42316	31.59845
15 μ M	38.6779	36.41601	29.23822
10 μ M	54.81208	52.11373	46.78871
7.5 μ M	63.73957	53.98429	50.35933
5 μ M	69.39882	77.63368	53.79378
2.5 μ M	77.44904	63.25052	56.68356
1 μ M	86.37654	69.89151	61.19579
750 nM	90.21244	83.61392	74.74846
500 nM	82.0418	69.87655	74.97541
100 nM	74.56842	77.16424	73.26575
Control	100	100	100

BT-20

Table S14. Viability of BT-20 cells in the presence of compound 1.

Cell viability %			
20 μ M	19.84508	18.85411	15.23017
15 μ M	33.46688	32.99136	30.01959
10 μ M	41.4797	44.0939	37.78159
7.5 μ M	41.17171	50.1262	42.238
5 μ M	56.78419	56.30994	56.39079
2.5 μ M	69.15064	55.65371	54.6523
1 μ M	102.5641	98.92008	100.049
750 nM	91.1859	98.59611	95.51909
500 nM	87.76709	106.1555	91.84623
100 nM	101.7094	100.0252	99.53477
Control	100	100	100

Table S15. Viability of BT-20 cells in the presence of compound 2.

Cell viability %			
20 μ M	28.29374	24.60878	32.37022
15 μ M	46.67927	49.89904	44.53966
10 μ M	45.0324	57.49622	51.12635
7.5 μ M	60.23218	62.61989	57.00293
5 μ M	73.8391	79.32862	68.97649
2.5 μ M	98.61111	100.513	96.3761
1 μ M	123.7041	111.0298	97.08619
750 nM	88.88888	105.3004	102.8159
500 nM	89.79482	89.90409	93.14397
100 nM	89.52991	96.38229	111.3369
Control	100	100	100

Table S16. Viability of BT-20 cells in the presence of compound 3.

Cell viability %			
20 μ M	40.96308	33.39072	29.51477
15 μ M	48.94036	53.93698	48.1349
10 μ M	62.90925	60.85546	57.18601
7.5 μ M	73.13243	71.92611	72.15611
5 μ M	85.1299	91.78971	101.4304
2.5 μ M	99.35225	99.33788	98.89039
1 μ M	103.802	95.2857	94.69757
750 nM	99.71837	90.49196	101.3318
500 nM	95.26861	90.62438	106.8284
100 nM	83.41196	73.85949	70.55268
Control	100	100	100

Table S17. Viability of BT-20 cells in the presence of compound 4.

Cell viability %			
20 μ M	8.369255	9.863568	12.91981
15 μ M	8.055758	8.453554	10.83292
10 μ M	20.10301	18.92421	21.27463
7.5 μ M	37.492	44.30446	44.18081
5 μ M	73.46471	77.51811	61.61889
2.5 μ M	82.73526	106.2024	110.5893
1 μ M	96.26043	100.5483	88.50558
750 nM	103.1798	88.69378	109.7163
500 nM	77.83127	90.8088	82.56707
100 nM	89.04617	76.96978	98.11308
Control	100	100	100

Table S18. Viability of BT-20 cells in the presence of compound 5.

Cell viability %			
20 μ M	20.91107	18.3694	26.24032
15 μ M	28.47104	28.44734	34.27277
10 μ M	41.28907	52.47014	37.54404
7.5 μ M	45.69905	52.633	55.7373
5 μ M	60.98861	87.48642	89.10418
2.5 μ M	80.30046	100.57	104.0262
1 μ M	98.95808	92.10098	100.302
750 nM	86.63815	80.99891	102.8391
500 nM	97.43155	90.47231	107.0261
100 nM	85.99467	94.73398	89.5899
Control	100	100	100

Table S19. Viability of BT-20 cells in the presence of compound 6.

Cell viability %			
20 μ M	18.802	24.04454	23.03115
15 μ M	37.77038	26.72284	42.10711
10 μ M	36.17304	29.6118	40.91705
7.5 μ M	50.48253	49.86458	58.52293
5 μ M	85.79034	70.29792	79.41897
2.5 μ M	89.15141	84.17092	92.78626
1 μ M	91.21464	79.29582	90.75954
750 nM	85.05824	84.44176	98.05343
500 nM	79.86689	79.34897	86.48855
100 nM	103.6273	95.0647	99.23664
Control	100	100	100

U-118 MG

Table S20. Viability of U-118 MG cells in the presence of compound 1.

Cell viability %			
20 μ M	32.43007	38.37077	42.77049
15 μ M	52.86713	49.75257	52.18157
10 μ M	49.80769	65.4465	62.16216
7.5 μ M	65.89161	73.35363	73.21463
5 μ M	64.50323	72.2848	61.20133
2.5 μ M	59.82518	71.64119	61.0448
1 μ M	61.64336	65.24553	66.50362
750 nM	75.25695	75.76429	76.03209
500 nM	81.23335	77.57442	78.28213
100 nM	74.91259	89.41759	92.95637
Control	100	100	100

Table S21. Viability of U-118 MG cells in the presence of compound 2.

Cell viability %			
20 μ M	39.14967	44.6621	48.65798
15 μ M	51.07196	55.67384	56.44768
10 μ M	57.92607	65.41163	61.06994
7.5 μ M	66.32476	62.32276	65.79428
5 μ M	62.14151	65.49889	62.22748
2.5 μ M	70.66434	64.2773	70.34197
1 μ M	84.08913	82.07757	80.29337
750 nM	69.99316	77.01671	67.38152
500 nM	63.95961	68.29109	66.75732
100 nM	82.47858	87.05401	87.05401
Control	100	100	100

Table S22. Viability of U-118 MG cells in the presence of compound 3.

Cell viability %			
20 μ M	35.11642	30.46595	32.81925
15 μ M	42.59714	46.07461	47.08923
10 μ M	45.5567	53.28832	53.00398
7.5 μ M	48.34217	52.95491	55.16316
5 μ M	57.14173	68.44211	68.47725
2.5 μ M	64.67516	61.47371	71.57868
1 μ M	75.91201	71.03783	66.44352
750 nM	70.23028	72.44006	70.84993
500 nM	87.97183	59.47373	56.29184
100 nM	90.89415	99.64991	109.711
Control	100	100	100

Table S23. Viability of U-118 MG cells in the presence of compound 4.

Cell viability %			
20 μ M	15.17047	15.6756	12.30857
15 μ M	21.16659	21.17125	19.81549
10 μ M	29.97722	29.03249	31.25504
7.5 μ M	24.82409	24.18593	24.16683
5 μ M	73.68801	72.70924	76.45973
2.5 μ M	78.81056	87.60953	83.16356
1 μ M	88.82355	94.85053	87.09975
750 nM	88.64679	93.98062	97.44762
500 nM	81.50854	94.34568	91.80472
100 nM	89.69409	88.01342	106.1964
Control	100	100	100

Table S24. Viability of U-118 MG cells in the presence of compound 5.

Cell viability %			
20 μ M	21.02625	24.2419	18.84402
15 μ M	28.8956	30.29581	23.7185
10 μ M	45.49669	44.7379	34.30884
7.5 μ M	47.16612	44.60394	36.57689
5 μ M	65.29145	61.9341	54.54753
2.5 μ M	58.217	62.66636	72.48403
1 μ M	87.35514	91.36398	94.34816
750 nM	101.0241	97.48939	72.15236
500 nM	91.72102	83.56483	99.83889
100 nM	97.80089	97.50102	97.94004
Control	100	100	100

Table S25. Viability of **U-118 MG** cells in the presence of compound **6**.

Cell viability %			
20 μM	22.54731	18.63575	22.51363
15 μM	28.04868	29.05686	32.77937
10 μM	49.60407	51.17363	52.18558
7.5 μM	45.91981	45.39844	56.877
5 μM	59.03976	63.22346	58.23376
2.5 μM	63.02409	69.74832	76.68138
1 μM	68.44211	80.40844	81.53043
750 nM	67.1918	73.07008	81.92678
500 nM	73.47671	83.7778	86.54896
100 nM	98.13287	91.37361	92.91959
Control	100	100	100

HF-P4

Table S26. Viability of **HF-P4** cells in the presence of compound **1**.

Cell viability %			
20 μM	63.95658	64.64763	61.04274
15 μM	67.05804	59.85663	63.15062
10 μM	70.53611	75.93788	65.94317
7.5 μM	77.31501	87.02509	78.04878
5 μM	80.70447	90.58038	81.47236
2.5 μM	94.32875	106.4486	88.2524
1 μM	105.1617	114.0028	114.925
750 nM	93.95214	108.0378	98.14276
500 nM	106.2251	109.6499	91.29559
100 nM	101.152	110.5137	108.5444
Control	100	100	100

Table S27. Viability of **HF-P4** cells in the presence of compound **2**.

Cell viability %			
20 μM	60.27913	51.8655	56.81361
15 μM	69.42844	82.12665	69.57623
10 μM	83.07232	82.91517	77.13135
7.5 μM	84.40811	87.78973	98.14276
5 μM	103.5928	91.30227	88.76707
2.5 μM	91.9392	112.4492	91.40747
1 μM	107.1396	107.7419	92.48154
750 nM	100.1551	106.3799	108.6149
500 nM	120.4253	121.1654	117.1851
100 nM	112.667	100.0956	124.6811
Control	100	100	100

Table S28. Viability of **HF-P4** cells in the presence of compound **3**.

Cell viability %			
20 uM	59.02883	62.77504	65.696
15 uM	65.59934	66.39747	65.2
10 uM	82.57799	74.36797	72.544
7.5 uM	78.68825	83.18117	77.088
5 uM	85.84565	90.27387	73.392
2.5 uM	87.06795	92.78441	93.77668
1 uM	100.1686	97.12644	98.88
750 nM	106.525	98.1566	91.216
500 nM	99.88198	100.1756	103.312
100 nM	95.80172	96.12008	98.08001
Control	100	100	100

Table S29. Viability of **HF-P4** cells in the presence of compound **4**.

Cell viability %			
20 uM	36.4007	38.67986	44.62788
15 uM	45.12022	53.93521	54.86213
10 uM	59.88019	62.49443	65.68416
7.5 uM	66.93568	70.27355	58.23608
5 uM	74.85648	73.33582	61.31848
2.5 uM	74.54031	86.63056	76.23162
1 uM	85.95557	81.66592	86.70585
750 nM	84.8196	85.09943	92.37617
500 nM	94.85814	87.47438	94.86558
100 nM	102.3796	100.6236	114.7117
Control	100	100	100

Table S30. Viability of **HF-P4** cells in the presence of compound **5**.

Cell viability %			
20 uM	52.22591	55.03193	53.23501
15 uM	62.99003	60.11892	45.66372
10 uM	76.65559	58.3808	56.93216
7.5 uM	74.4629	71.79035	64.34612
5 uM	83.96829	65.29699	72.64504
2.5 uM	96.80687	91.7616	90.46214
1 uM	105.1971	86.79821	100.59
750 nM	84.18605	95.78926	102.0649
500 nM	105.4928	98.20993	101.0423
100 nM	104.2968	105.3072	105.0738
Control	100	100	100

Table S31. Viability of **HF-P4** cells in the presence of compound **6**.

Cell viability %			
20 uM	48.01772	42.61595	43.53982
15 uM	62.45847	54.90236	58.15143
10 uM	66.11296	61.41172	64.7001
7.5 uM	62.32558	61.49309	69.34596
5 uM	84.31894	73.0472	65.60473
2.5 uM	94.52935	75.57806	74.70994
1 uM	84.38669	84.11311	85.78171
750 nM	97.81986	92.16844	90.67847
500 nM	102.5471	95.78926	101.8289
100 nM	114.4851	90.23597	95.39749
Control	100	100	100