SUPPORTING INFORMATION

Discovery of First-in-class Protein Arginine Methyltransferase 5 (PRMT5) Degraders

Yudao Shen,[†,#] Guozhen Gao,[§,#] Xufen Yu,[†] Huensuk Kim,[†] Li Wang,[⊥] Ling Xie,[⊥] Megan Schwarz,[†] Xian Chen,[⊥] Ernesto Guccione,[†] Jing Liu,[†,*] Mark T. Bedford,[§,*] and Jian Jin[†,*]

[†]Mount Sinai Center for Therapeutics Discovery, Departments of Pharmacological Sciences and Oncological Sciences, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States

[§]Department of Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, Smithville, TX 78957, United States

[⊥]Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, United States

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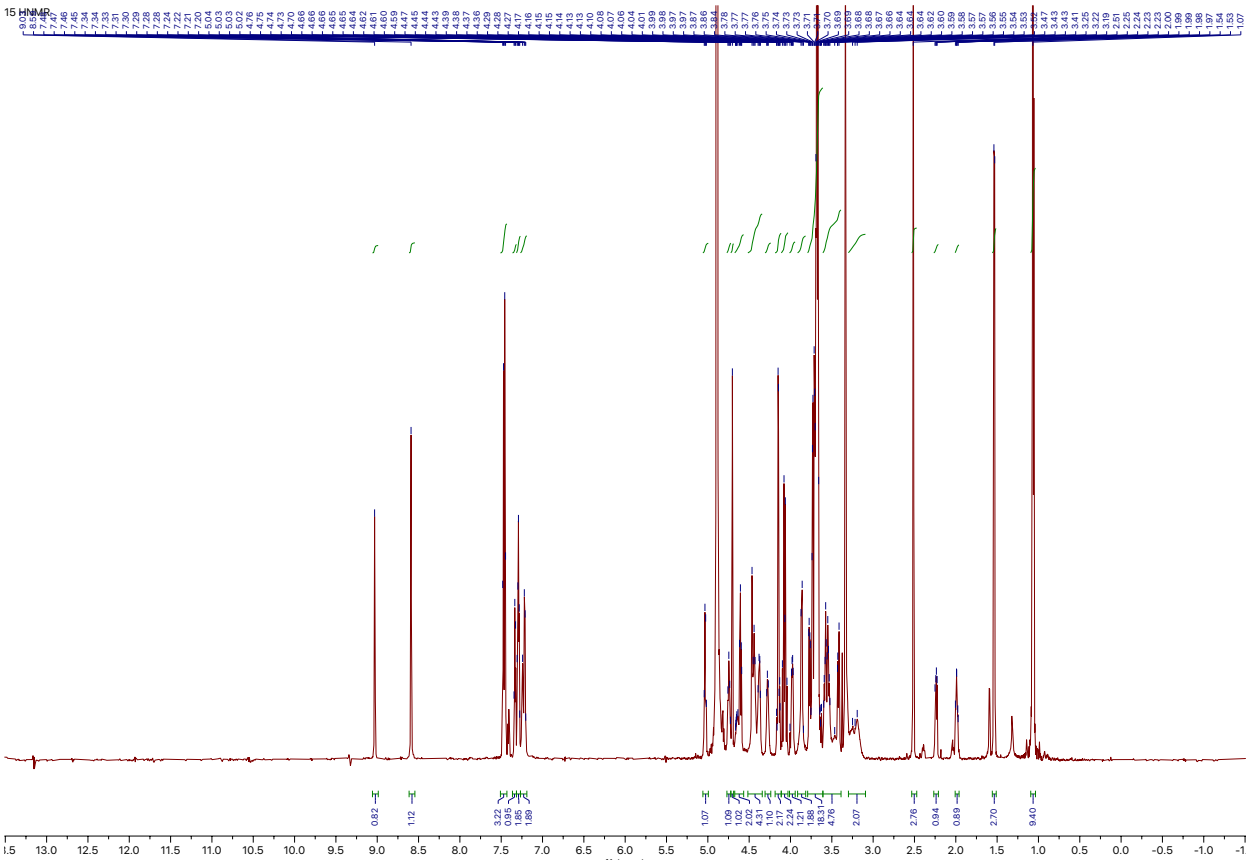

Figure S1. ^{1}H NMR spectrum of compound **15**, CD_3OD.

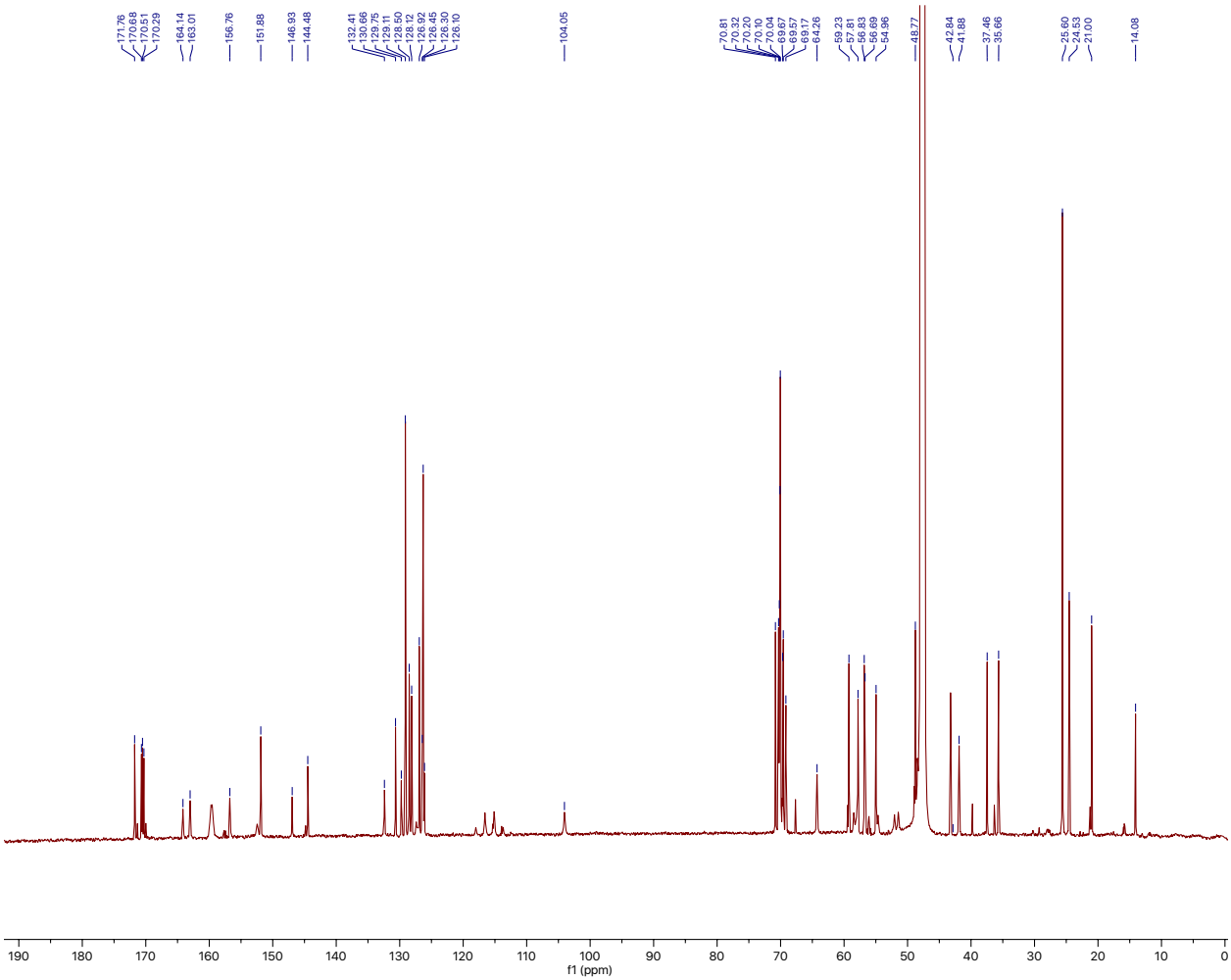

Figure S2. ^{13}C NMR spectrum of compound **15**, CD_3OD.

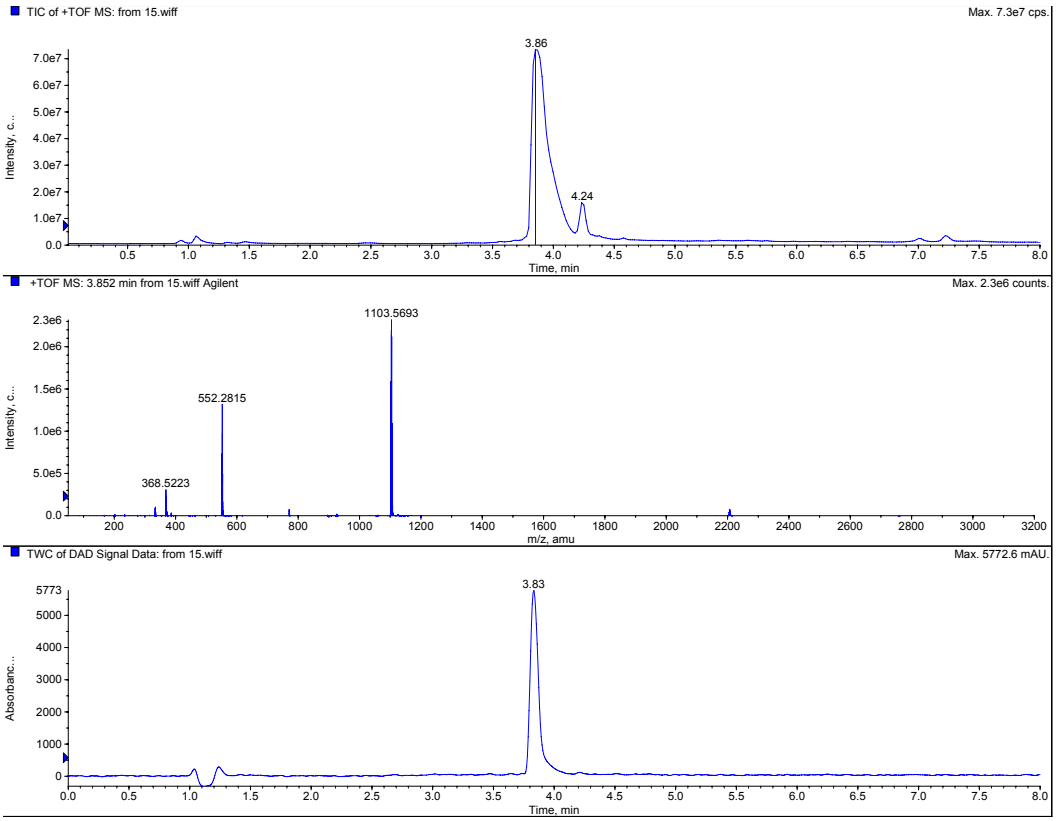

Figure S3. HPLC spectrum of compound **15.**

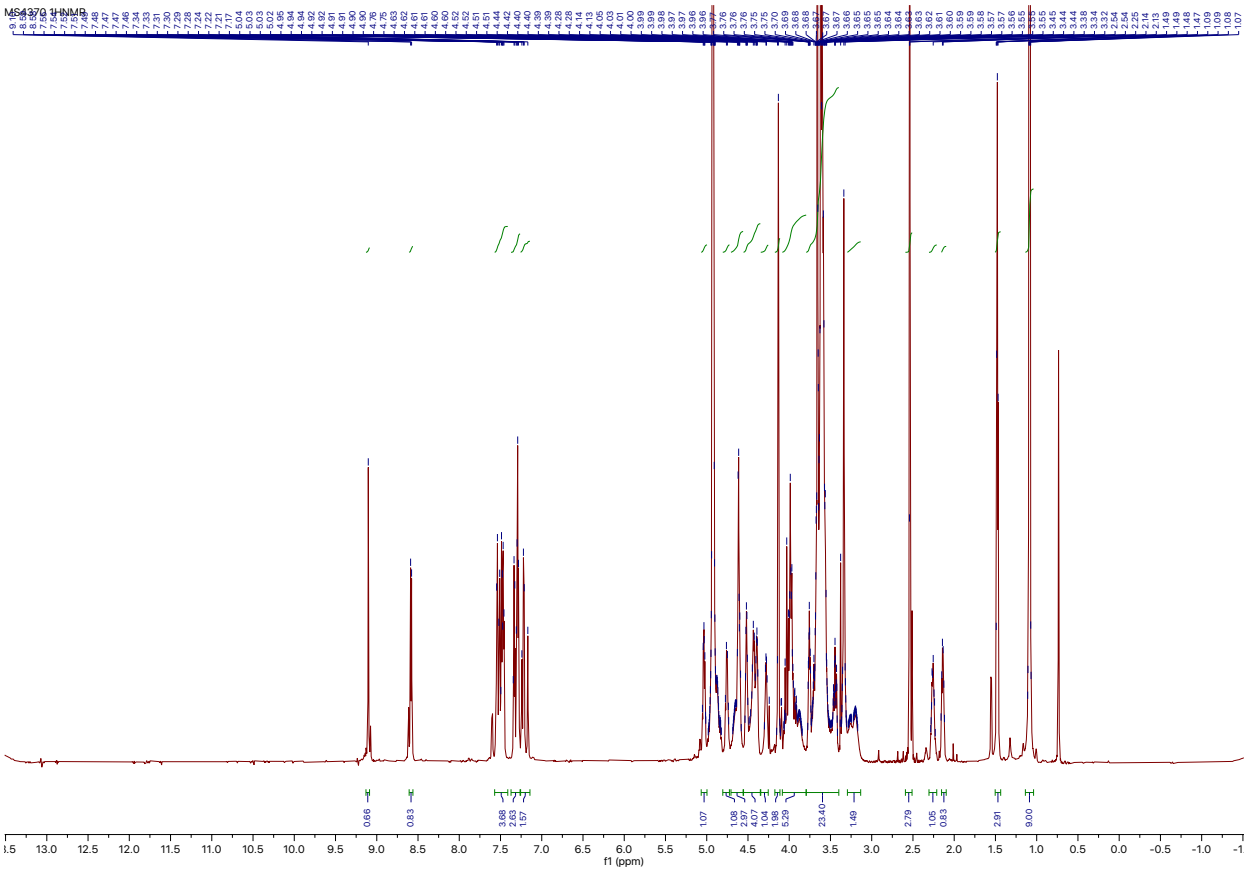

Figure S4. ^{1}H NMR spectrum of compound **17**, CD_3OD.

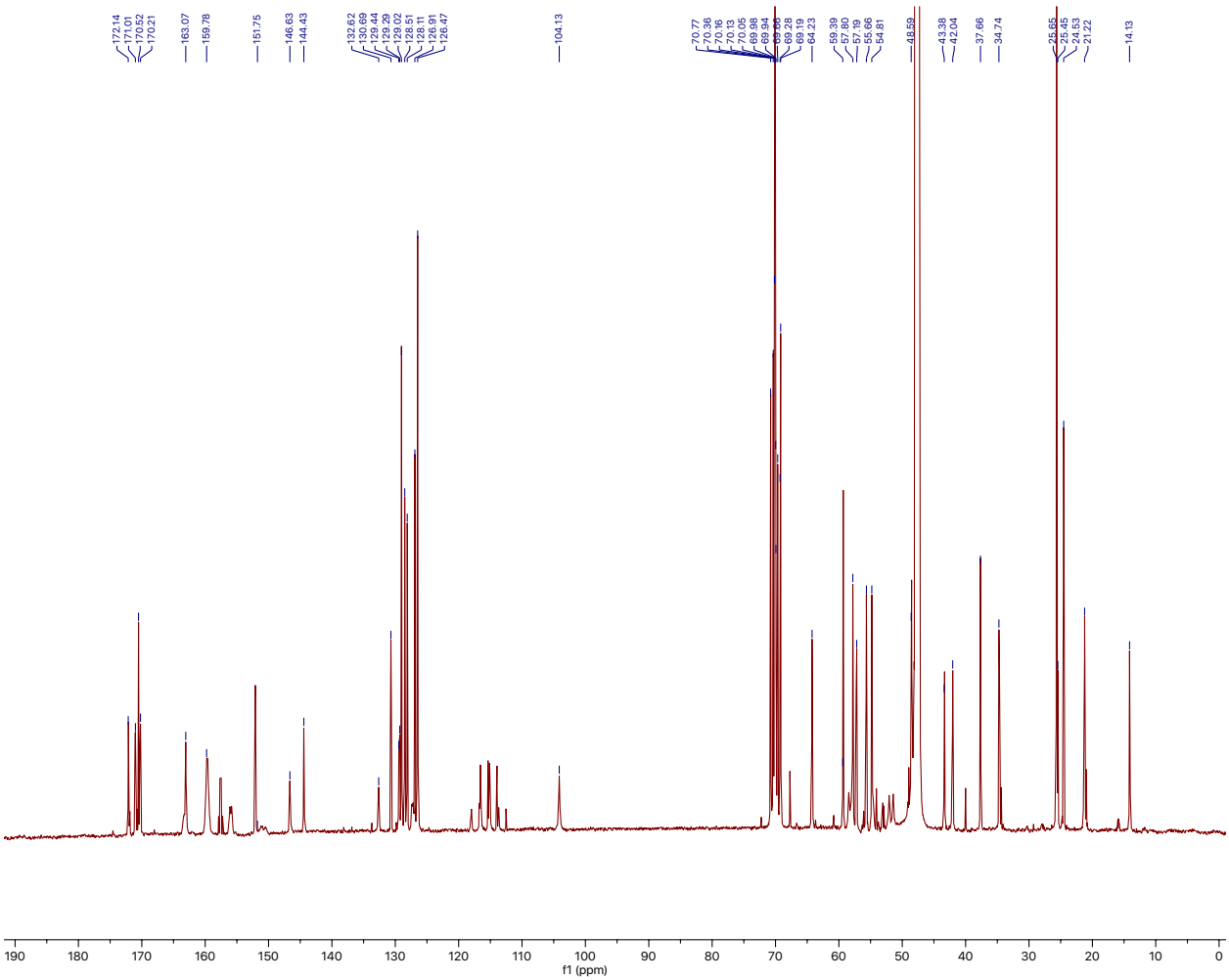

Figure S5. ^{13}C NMR spectrum of compound **17**, CD_3OD.

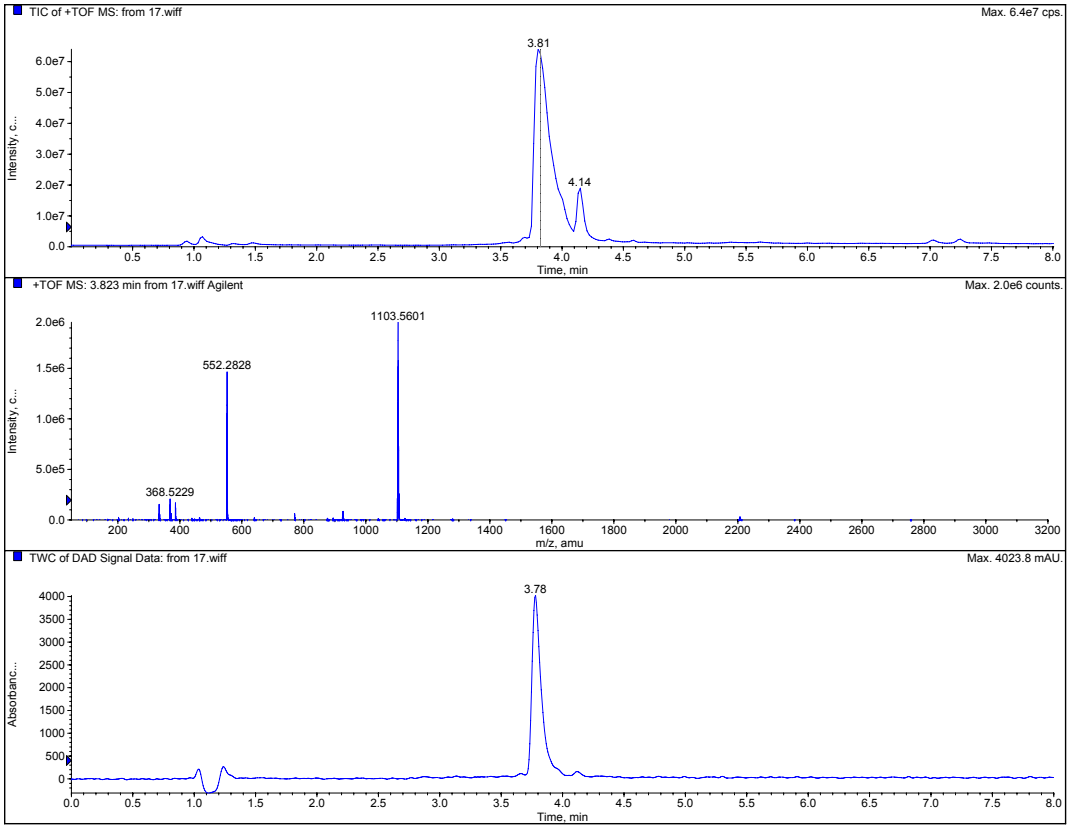

Figure S6. HPLC spectrum of compound **17.**

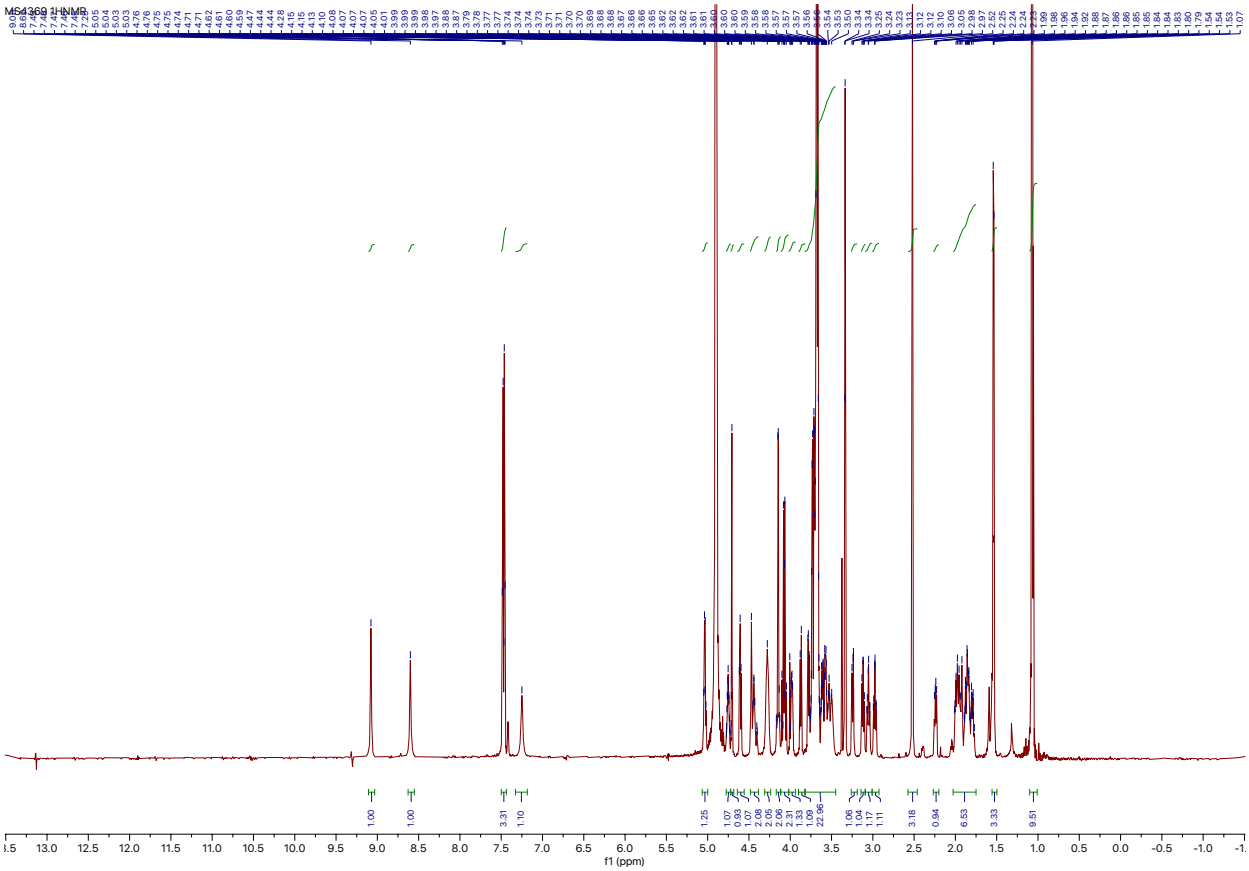

Figure S7. ^{1}H NMR spectrum of compound **21**, CD_3OD

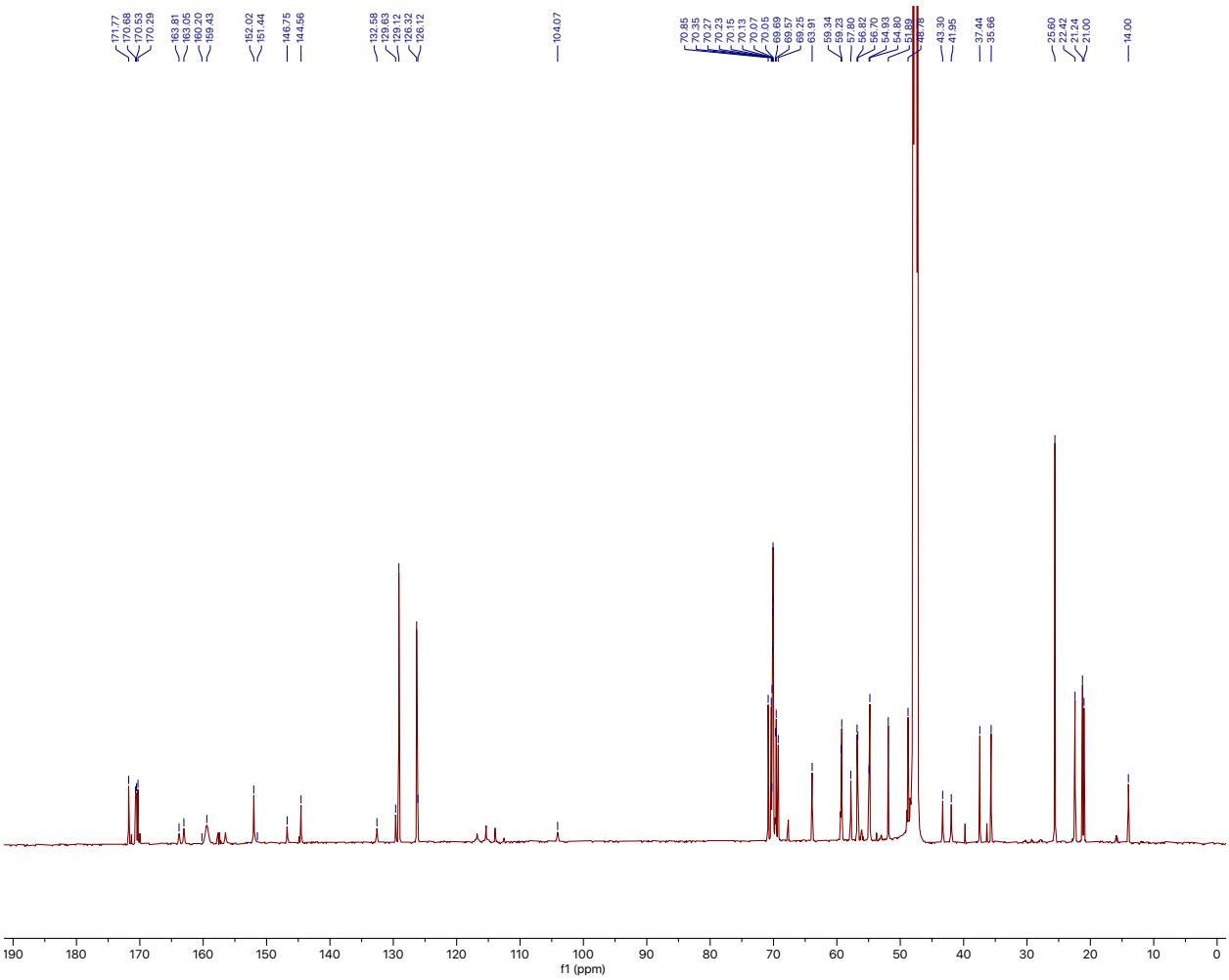

Figure S8. ^{13}C NMR spectrum of compound **21**, CD_3OD.

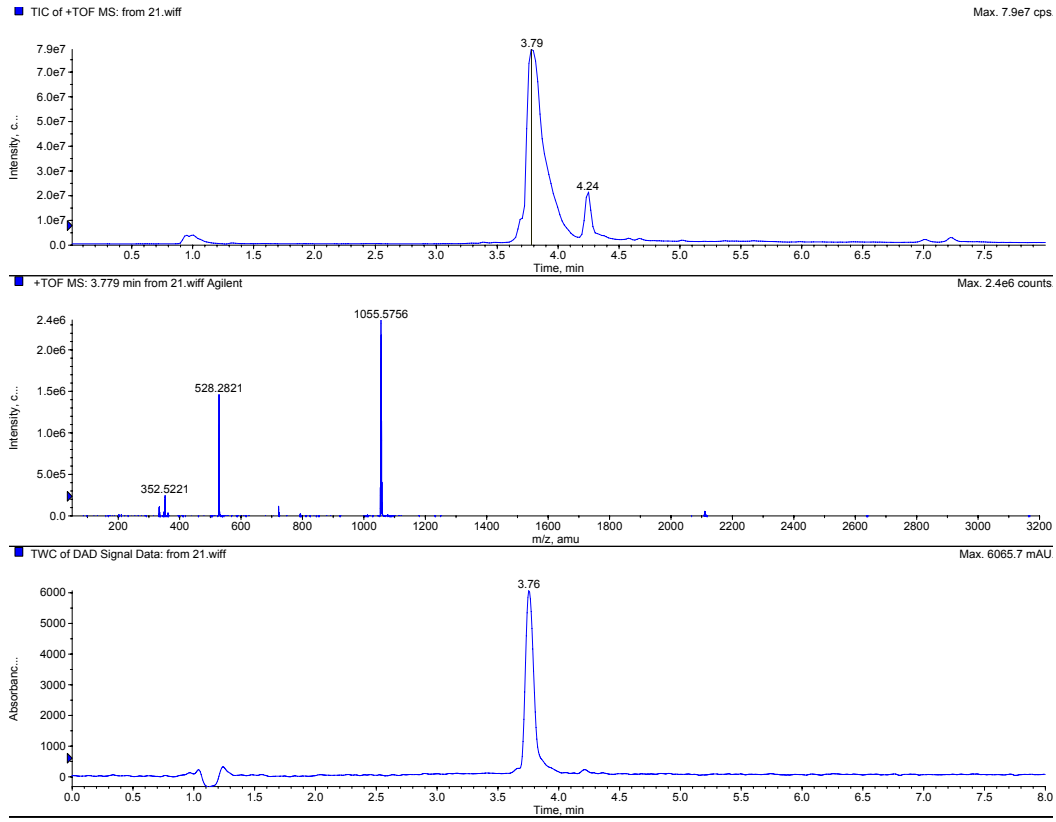

Figure S9. HPLC spectrum of compound **21.**

Table S1. Raw data of compounds **15**, **21**, **17** and EPZ015666 inhibiting the PRMT5 methyltransferase activity in the PRMT5 biochemical assay.

FlashPlate Methyltransferase Profiling I	PRMT5/MEP50 Complex								
Raw data									
	Conc.(M)	**15**	**15**	**17**	**17**	**21**	**21**	**EPZ015666**	**EPZ015666**
	5.00E-06	116	144	121	122	1950	1891	124	152
	1.67E-06	168	112	206	95	3113	2942	220	244
	5.56E-07	225	271	231	271	3594	3576	337	495
	1.85E-07	383	467	448	421	4301	4218	904	833
	6.17E-08	1105	943	865	903	4719	4132	1469	1616
	2.06E-08	2033	1883	1486	1608	4829	4665	2756	2915
	6.86E-09	3163	3061	2960	2749	4591	4785	3532	3140
	2.29E-09	3992	3925	3777	3937	4624	4888	4545	4517
	7.62E-10	4329	4462	4426	4504	5091	4640	4554	4600
	2.54E-10	4355	4332	4350	4470	4897	4792	4143	4419
	DMSO	4256	3923	4462	4498	4479	4626	4623	4776
%Activity									
	Conc.(M)	**15**	**15**	**17**	**17**	**21**	**21**	**EPZ015666**	**EPZ015666**
	5.00E-06	2.55	3.16	2.66	2.68	42.90	41.60	2.72	3.34
	1.67E-06	3.69	2.46	4.53	2.08	68.48	64.72	4.83	5.36
	5.56E-07	4.94	5.96	5.08	5.96	79.07	78.67	7.41	10.88
	1.85E-07	8.42	10.27	9.85	9.26	94.62	92.80	19.88	18.32
	6.17E-08	24.31	20.74	19.03	19.86	103.82	90.90	32.31	35.55
	2.06E-08	44.72	41.42	32.69	35.37	106.24	102.63	60.63	64.13
	6.86E-09	69.58	67.34	65.12	60.48	101.00	105.27	77.70	69.08
	2.29E-09	87.82	86.35	83.09	86.61	101.73	107.54	99.99	99.37
	7.62E-10	95.24	98.16	97.37	99.09	112.00	102.08	100.19	101.20
	2.54E-10	95.81	95.30	95.70	98.34	107.74	105.43	91.15	97.22
	DMSO	93.63	86.31	98.16	98.96	98.54	101.77	101.71	105.07
	HILLSLOPE	**-0.99**	**-1.04**	**-0.96**	**-0.93**	**-0.77**	**-0.68**	**-0.91**	**-0.77**
	IC50 (M)	**1.88E-08**	**1.76E-08**	**1.21E-08**	**1.16E-08**	**3.18E-06**	**2.98E-06**	**3.18E-08**	**2.83E-08**

Table S2. Raw data of compounds **15**, **21**, **17** and EPZ015666 in cell viability assays.

MCF-7 cells treated with 15, 21, 17 or EPZ015666							
Viability							
15				**21**			
0.1	105.3077	102.5247	105.3358	0.1	99.81698	94.54928	98.16948
0.3	101.6677	106.2998	106.4838	0.3	89.39629	98.89076	97.29685
1	85.34882	88.73061	84.29195	1	95.61483	90.29079	100.6339
3	56.84664	56.60026	51.08575	3	87.3941	84.40584	90.06798
10	58.18388	57.54127	53.61291	10	91.98856	88.77088	98.9971
17				**EPZ015666**			
0.1	97.97854	94.24979	97.7071	0.1	103.8627	98.19344	100.0024
0.3	120.1471	117.759	118.7336	0.3	96.15282	93.91667	96.44916
1	107.2821	102.9658	104.964	1	94.18891	95.47858	94.44257
3	100.6041	99.2952	102.034	3	61.49821	61.87478	60.87047
10	76.52726	74.18326	77.28988	10	54.81862	50.49923	52.3403
HeLa cells treated with 15 or EPZ015666							
Viability							
EPZ015666				**15**			
0.1	96.816214	93.0627502	92.8846653	0.1	94.6964077	94.2944438	94.1496581
0.3	95.0155297	94.6469275	93.8997271	0.3	86.3629676	89.0964654	91.7373441
1	100.396497	102.711569	105.225155	1	97.30633	94.421143	96.8578848
3	72.5700914	68.3261055	67.4301835	3	76.2240952	79.4630465	76.1345061
10	58.4619042	59.2699552	59.1871759	10	61.5377335	61.5555388	58.6177167
A549 cells treated with 15 or EPZ015666							
Viability							
EPZ015666				**15**			
0.1	103.62602	96.2622638	98.1237621	0.1	96.3164154	105.372071	100.632464
0.3	92.1401016	90.2927454	99.5908353	0.3	88.3634049	93.7588869	96.1283189
1	92.3172031	92.8489194	90.9699991	1	89.4851719	88.7338083	87.1566657
3	76.4004128	73.9695657	75.3071557	3	76.2267372	77.9163393	77.1286976
10	64.8761976	63.1769948	63.8969935	10	66.5349925	67.5400241	69.7962396
A172 cells treated with 15 or EPZ015666							
Viability							
EPZ015666				**15**			
0.1	96.2826641	98.7078705	112.622898	0.1	96.5712757	104.550821	104.301089
0.3	95.1304114	104.347687	88.5882668	0.3	80.1068795	73.5889905	78.7630812
1	89.1714242	79.0851651	84.4504481	1	79.9647062	83.4034113	88.5711313
3	82.6013681	88.8621611	79.2044812	3	71.6700219	60.0499253	60.7686492
10	64.9747572	66.3505145	52.660909	10	52.718707	54.8407956	54.0105839
Jurkat cells treated with 15 or EPZ015666							
Viability							
EPZ015666				**15**			
0.1	100.032582	106.529389	93.4706112	0.1	95.2583287	101.49024	101.607242
0.3	99.9348364	93.6986837	94.0831487	0.3	83.3979925	87.2221196	95.7509699
1	80.9331422	74.4037534	81.6303923	1	83.4842047	70.8294846	65.1702691
3	61.6121465	55.1544376	55.1088231	3	58.402611	53.0697703	48.7653181
10	37.6124071	44.1743777	45.2560928	10	40.5012624	31.929306	40.1317815