

Table S1. Effects of MGL50 on PTMs of H1 histone variant in Hs27 and HT-29 cells. Cells were seeded (2.5x10⁵ cells/well) into 12-well plates, were treated with 0.03 mg/mL MGL (MGL50) for 48 h and then were collected. Histones were extracted and peptides were analyzed by mass spectrometry. Data are represented as mean and standard error. NT, non-treated; MGL50, concentration of MGL able to reduce cell viability to 50%. Heteroscedastic two-tails t-test are applied and statistical analysis was carried out comparing Hs27 treated vs not treated, HT-29 treated vs not treated, HT-29 non treated vs Hs27 non treated. p-value are reported as -log2. Statistically significant differences are highlighted in green.

	mean				standard error									
	Hs27 cells		HT-29 cells		Hs27 cells		HT-29 cells		Hs27 MGL50/NT	p-value	HT-29 MGL50/NT	p-value	HT29/Hs27 NT	p-value
	NT	MGL50	NT	MGL50	NT	MGL50	NT	MGL50						
H14_25_32 unmod	65.51%	76.43%	62.88%	61.05%	13.62%	7.39%	5.28%	13.86%	0.22	1.19	-0.03	0.12	-0.07	0.31
H14_25_32 K25me1	25.55%	18.21%	11.73%	27.08%	13.95%	7.10%	5.97%	14.57%	-0.49	0.74	-0.23	0.44	0.31	0.63
H14_25_32 K25me2	0.00%	0.00%	0.00%	0.01%	0.00%	0.00%	0.00%	0.01%	0.00	0.00	0.00	0.00	0.00	0.00
H14_25_32 K25me3	0.50%	0.41%	1.62%	1.51%	0.24%	0.14%	0.12%	1.15%	-0.27	0.46	-0.10	0.12	1.69	7.15
H14_25_32 K25ac	2.75%	0.22%	1.89%	1.63%	1.36%	0.12%	0.73%	1.22%	-3.67	2.74	-0.21	0.26	-0.54	0.90
H14_25_32 K31ac	4.94%	3.42%	2.38%	8.04%	1.09%	0.45%	0.71%	3.96%	-0.53	2.39	1.75	2.64	-1.05	3.75
H14_25_32 S26ac	0.74%	1.31%	0.00%	0.68%	0.65%	1.60%	0.00%	0.84%	0.82	0.50	0.00	0.00	0.00	0.00
H14_25_32 S26ph	0.01%	0.00%	0.00%	0.00%	0.02%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00
H12_33_53 unmod	59.22%	67.97%	60.12%	70.05%	1.19%	2.82%	4.58%	0.44%	0.19	5.11	0.22	3.11	0.02	0.27
H12_33_53 K33me1	40.60%	32.43%	39.72%	29.91%	1.16%	2.82%	4.60%	0.46%	-0.32	5.03	-0.41	3.07	-0.03	0.27
H12_33_53 K33me2	0.02%	0.00%	0.09%	0.04%	0.03%	0.00%	0.05%	0.02%	0.00	0.00	-1.31	1.94	1.89	2.27
H12_33_53 K33me3	0.15%	0.00%	0.05%	0.00%	0.06%	0.00%	0.05%	0.00%	0.00	0.00	0.00	0.00	-1.72	2.69
H12_33_53 K33ac	0.00%	0.00%	0.02%	0.00%	0.00%	0.00%	0.03%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00
H15_36_56 unmod	22.33%	16.11%	22.57%	16.88%	0.29%	4.84%	3.52%	0.55%	-0.47	1.97	-0.42	2.45	0.02	0.09
H15_36_56 K36me2	0.01%	0.00%	0.01%	0.00%	0.01%	0.00%	0.02%	0.00%	0.00	0.00	0.00	0.00	0.24	0.13
H15_36_56 K36me3	38.75%	42.50%	38.63%	41.48%	0.14%	2.17%	1.77%	0.26%	0.13	2.58	0.10	2.43	0.00	0.08
H15_36_56 K36ac	38.38%	41.39%	38.59%	41.44%	0.46%	2.72%	1.82%	0.24%	0.11	1.99	0.10	2.37	0.01	0.16
H15_36_56 S43ac	0.53%	0.00%	0.19%	0.20%	0.50%	0.00%	0.05%	0.05%	0.00	0.00	0.10	0.26	-1.51	1.03
H1_1_35 H12.SETAPAAPAAPAEKAPVKKAAKAGGTPR	0.90%	0.30%	0.06%	0.26%	0.99%	0.37%	0.07%	0.31%	-1.57	0.92	2.07	1.00	-3.88	1.29
H1_1_35 H14.SETAPAAPAAPAEKTPVKKKAR	66.91%	71.50%	74.49%	49.38%	2.46%	11.84%	3.25%	20.63%	0.10	0.59	-0.59	1.87	0.15	3.56
H1_1_35 H15.SETAPAEATAPAPVEKSPAKKATKKAAGAGAAKR	32.19%	28.19%	25.45%	50.37%	1.62%	11.84%	3.18%	20.32%	-0.19	0.47	0.98	1.89	-0.34	3.61
H1_54_81 H11.GGVSLAALKKALAAAGYDVEKNNSR	0.00%	33.87%	0.06%	1.02%	0.00%	20.91%	0.07%	0.68%	0.00	0.00	3.98	2.14	0.00	0.00
H1_54_81 H1v234.SGVSLAALKKALAAAGYDVEKNNSR	78.16%	62.15%	79.64%	68.16%	13.54%	23.41%	6.28%	3.56%	-0.33	0.98	-0.22	3.02	0.03	0.14
H1_54_81 H15.NGLSLAALKKALAAAGYDVEKNNSR	21.84%	3.98%	20.29%	30.82%	13.54%	2.52%	6.27%	2.88%	-2.46	2.41	0.60	2.89	-0.11	0.14

Table S2. Effects of MGL50 on PTMs of H2A histone variant in Hs27 and HT-29 cells. Cells were seeded (2.5×10^5 cells/well) into 12-well plates, were treated with 0.03 mg/mL MGL (MGL50) for 48 h and then were collected. Histones were extracted and peptides were analyzed by mass spectrometry. Data are represented as mean and standard error. NT, non-treated; MGL50, concentration of MGL able to reduce cell viability to 50%. Heteroscedastic two-tails t-test are applied and statistical analysis was carried out comparing Hs27 treated vs not treated, HT-29 treated vs not treated, HT-29 non treated vs Hs27 non treated. p-value are reported as -log2. Statistically significant differences are highlighted in green.

	mean				standard error				Hs27 MGL50/NT	p-value	HT-29 MGL50/NT	p-value	HT29/Hs27 NT	p-value
	Hs27 cells		HT-29 cells		Hs27 cells		HT-29 cells							
	NT	MGL50	NT	MGL50	NT	MGL50	NT	MGL50						
H2A1_36_42 unmod	98.62%	99.65%	99.73%	99.90%	0.91%	0.43%	0.14%	0.12%	0.02	1.84	0.00	1.74	0.02	1.87
H2A1_36_42 K36ac	0.05%	0.00%	0.27%	0.10%	0.06%	0.00%	0.14%	0.12%	0.00	0.00	-1.49	1.74	2.42	2.80
H2A1_36_42 Y39ac	1.33%	0.35%	0.00%	0.00%	0.87%	0.43%	0.00%	0.00%	-1.93	1.83	0.00	0.00	0.00	0.00
H2A3_36_42 unmod	66.67%	0.00%	100.00%	95.91%	40.82%	0.00%	0.00%	5.00%	0.00	0.00	-0.06	0.00	0.58	0.00
H2A3_36_42 Y39ac	0.00%	0.00%	0.00%	4.09%	0.00%	0.00%	0.00%	5.00%	0.00	0.00	0.00	0.00	0.00	0.00
H2AX_36_42 unmod	100.00%	66.67%	98.99%	98.86%	0.00%	40.82%	1.24%	1.40%	-0.58	0.00	0.00	0.10	-0.01	0.00
H2AX_36_42 Y39ac	0.00%	0.00%	1.01%	1.14%	0.00%	0.00%	1.24%	1.40%	0.00	0.00	0.18	0.10	0.00	0.00
H2A1_4_11 unmod	73.43%	85.29%	93.18%	87.47%	2.46%	8.14%	1.37%	5.15%	0.22	2.62	-0.09	1.95	0.34	9.95
H2A1_4_11 K5ac	0.61%	0.23%	1.76%	1.15%	0.74%	0.23%	1.07%	0.72%	-1.40	0.78	-0.62	0.75	1.53	1.55
H2A1_4_11 K9ac	1.66%	1.48%	1.26%	0.86%	0.77%	0.86%	0.79%	0.54%	-0.17	0.23	-0.56	0.66	-0.39	0.55
H2A1_4_11 K5acK9ac	0.01%	0.00%	0.22%	0.26%	0.01%	0.00%	0.05%	0.11%	0.00	0.00	0.22	0.46	4.96	7.29
H2A1_4_11 K9me1	13.59%	6.33%	0.98%	2.30%	4.18%	6.30%	0.80%	2.74%	-1.10	1.71	1.23	0.74	-3.80	5.49
H2A1_4_11 K5me1	10.70%	6.68%	2.60%	7.97%	1.74%	4.14%	0.39%	3.84%	-0.68	1.58	1.62	2.13	-2.04	7.61
H2A1_4_11 unmod	6.33%	0.90%	19.01%	8.84%	4.15%	0.59%	0.51%	7.12%	-2.81	2.01	-1.10	2.17	1.59	4.00
H2A1_4_11 K5ac	0.07%	0.21%	0.05%	3.14%	0.03%	0.25%	0.04%	0.72%	1.64	0.86	6.10	4.89	-0.58	0.68
H2A1_4_11 K9ac	28.53%	22.10%	9.13%	7.59%	20.80%	9.90%	6.53%	8.37%	-0.37	0.42	-0.27	0.21	-1.64	1.57
H2A1_4_11 K5acK9ac	0.02%	0.00%	0.00%	10.44%	0.03%	0.00%	0.00%	12.68%	0.00	0.00	11.85	1.25	-3.09	1.09
H2A1_4_11 K9me1	16.46%	0.22%	13.86%	1.13%	6.89%	0.18%	8.43%	0.95%	-6.24	3.29	-3.61	2.29	-0.25	0.35
H2A1_4_11 K5me1	48.59%	76.57%	57.95%	68.86%	23.72%	9.54%	1.79%	18.41%	0.66	1.99	0.25	0.88	0.25	0.56
H2AX_4_11 unmod	5.90%	3.88%	6.30%	9.17%	0.69%	0.19%	1.39%	4.79%	-0.60	5.29	0.54	0.94	0.09	0.37
H2AX_4_11 K5ac	0.27%	0.00%	0.17%	0.10%	0.16%	0.00%	0.03%	0.10%	0.00	0.00	-0.83	1.19	-0.66	1.01
H2AX_4_11 K9ac	0.12%	0.02%	0.08%	0.05%	0.08%	0.03%	0.02%	0.04%	-2.41	1.95	-0.58	1.02	-0.62	0.76
H2AX_4_11 K5acK9ac	0.63%	8.80%	0.93%	1.80%	0.39%	10.28%	0.19%	1.59%	3.81	1.21	0.95	0.80	0.56	1.15
H2AX_4_11 K9me1	69.02%	40.24%	70.86%	54.09%	1.23%	26.76%	1.13%	16.06%	-0.78	1.65	-0.39	1.60	0.04	2.01
H2AX_4_11 K5me1	24.06%	47.05%	21.66%	34.80%	1.21%	17.80%	1.51%	15.15%	0.97	1.98	0.68	1.32	-0.15	2.30
H2A1_1_11 unmod	50.90%	40.55%	3.13%	9.26%	9.77%	34.81%	0.39%	3.87%	-0.33	0.43	1.56	2.39	-4.02	5.23
H2A1_1_11 S1ac	1.46%	0.33%	0.00%	0.50%	0.49%	0.40%	0.00%	0.52%	-2.15	3.39	0.00	0.00	0.00	0.00
H2A1_1_11 K5ac	47.64%	59.12%	96.87%	90.24%	9.83%	35.20%	0.39%	3.53%	0.31	0.47	-0.10	2.77	1.02	5.30
H2AZ_1_19 unmod	91.49%	90.96%	91.19%	90.54%	1.57%	10.99%	1.08%	2.29%	-0.01	0.06	-0.01	0.38	0.00	0.22
H2AZ_1_19 K4ac	2.59%	4.58%	3.81%	2.79%	0.59%	5.61%	0.15%	0.89%	0.82	0.50	-0.45	2.08	0.55	3.83
H2AZ_1_19 K7ac	4.95%	0.00%	2.68%	3.95%	0.80%	0.00%	0.44%	0.76%	0.00	0.00	0.56	2.71	-0.88	4.72
H2AZ_1_19 K11ac	0.31%	0.04%	1.08%	1.43%	0.37%	0.05%	0.19%	0.36%	-2.79	1.05	0.41	1.53	1.82	3.51
H2AZ_1_19 K15ac	0.01%	4.37%	0.12%	0.34%	0.01%	5.36%	0.05%	0.29%	8.84	1.24	1.45	1.22	3.70	4.17
H2AZ_1_19 K4acK7ac	0.26%	0.00%	0.58%	0.28%	0.17%	0.00%	0.27%	0.18%	0.00	0.00	-1.04	1.61	1.17	1.81
H2AZ_1_19 K4acK11ac	0.24%	0.00%	0.01%	0.11%	0.19%	0.00%	0.01%	0.07%	0.00	0.00	4.38	2.34	-5.45	1.81
H2AZ_1_19 K4acK15ac	0.02%	0.00%	0.00%	0.00%	0.03%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	-2.85	1.06
H2AZ_1_19 K7acK11ac	0.00%	0.00%	0.39%	0.32%	0.00%	0.00%	0.25%	0.17%	0.00	0.00	-0.30	0.37	0.00	0.00
H2AZ_1_19 K7acK15ac	0.00%	0.00%	0.00%	0.05%	0.00%	0.00%	0.00%	0.07%	0.00	0.00	0.00	0.00	0.00	0.00
H2AZ_1_19 K11acK15ac	0.07%	0.00%	0.08%	0.09%	0.06%	0.00%	0.03%	0.09%	0.00	0.00	0.14	0.12	0.26	0.30
H2AZ_1_19 K4acK7acK15ac	0.02%	0.00%	0.04%	0.05%	0.03%	0.00%	0.03%	0.06%	0.00	0.00	0.14	0.09	1.08	0.88
H2AZ_1_19 K4acK7acK11ac	0.03%	0.00%	0.02%	0.05%	0.03%	0.00%	0.01%	0.06%	0.00	0.00	1.66	0.89	-0.62	0.40
H2AZ_1_19 K4acK7acK11acK15ac	0.03%	0.04%	0.00%	0.00%	0.04%	0.05%	0.00%	0.00%	0.52	0.29	0.00	0.00	0.00	0.00
H2A1_12_17 unmod	56.29%	62.62%	48.09%	45.61%	0.44%	0.95%	2.58%	11.96%	0.16	9.38	-0.08	0.29	-0.23	5.75
H2A1_12_17 K13ac	0.00%	0.00%	0.02%	0.02%	0.00%	0.00%	0.01%	0.01%	0.00	0.00	0.15	0.21	2.62	4.88
H2A1_12_17 K15ac	4.10%	0.87%	18.99%	23.61%	1.29%	0.67%	6.49%	13.29%	-2.24	4.24	0.31	0.47	2.21	4.29
H2A1_12_17 K15me1	38.96%	36.18%	30.02%	26.38%	0.91%	0.31%	4.74%	4.84%	-0.11	5.39	-0.19	0.87	-0.38	3.54
H2A1_12_17 K13me1	0.40%	0.00%	2.50%	3.55%	0.21%	0.00%	0.72%	1.20%	0.00	0.00	0.50	1.28	2.65	5.24
H2A1_12_17 T16ac	0.25%	0.03%	0.37%	0.84%	0.16%	0.04%	0.14%	0.51%	-2.86	2.53	1.16	1.53	0.56	0.94
H2A3_12_17 unmod	5.73%	1.27%	19.49%	23.98%	1.62%	0.94%	4.88%	12.82%	-2.17	4.51	0.30	0.50	1.77	5.03
H2A3_12_17 K13ac	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00
H2A3_12_17 K15ac	0.00%	0.01%	0.00%	0.00%	0.00%	0.02%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00
H2A3_12_17 K15me1	14.10%	67.20%	80.20%	44.43%	2.36%	38.23%	4.96%	24.00%	2.25	2.12	-0.85	2.75	2.51	12.98
H2A3_12_17 K13me1	80.18%	31.51%	0.31%	31.59%	3.97%	37.27%	0.18%	36.82%	-1.35	2.00	6.65	1.30	-7.99	9.27
H2A1_72_77 unmod	100.00%	100.00%	99.86%	99.99%	0.00%	0.00%	0.17%	0.01%	0.00	0.00	0.00	1.16	0.00	0.00
H2A1_72_77 K74ac	0.00%	0.00%	0.14%	0.01%	0.00%	0.00%	0.17%	0.01%	0.00	0.00	-3.98	1.16	0.00	0.00
H2A_1_88 H2A14s.HLQLAIR	44.43%	43.52%	63.99%	57.59%	8.29%	12.91%	2.25%	22.37%	-0.03	0.08	-0.15	0.40	0.53	4.34
H2A_1_88 H2AZ.AGGKAGKDSGKAKTAVSR	53.41%	42.63%	34.15%	40.40%	7.96%	11.92%	2.02%	21.74%	-0.33	1.29	0.24	0.40	-0.65	4.46
H2A_1_88 H2AZ.SAKAGVFPVGR	0.91%	12.70%	0.80%	1.19%	0.26%	4.79%	0.22%	0.45%	3.80	3.40	0.58	1.35	-0.19	0.51
H2A_1_88 H2AX.GKTGGKAR	1.24%	1.15%	1.05%	0.82%	0.28%	0.35%	0.12%	0.33%	-0.12	0.31	-0.35	1.09	-0.24	1.06

Table S3. Effects of MGL50 on PTMs of H2B histone variant in Hs27 and HT-29 cells. Cells were seeded (2.5x10⁵ cells/well) into 12-well plates, were treated with 0.03 mg/mL MGL (MGL50) for 48 h and then were collected. Histones were extracted and peptides were analyzed by mass spectrometry. Data are represented as mean and standard error. NT, non-treated; MGL50, concentration of MGL able to reduce cell viability to 50%. Heteroscedastic two-tails t-test are applied and statistical analysis was carried out comparing Hs27 treated vs not treated, HT-29 treated vs not treated, HT-29 non treated vs Hs27 non treated. p-value are reported as -log2. Statistically significant differences are highlighted in green.

	mean				standard error								p-value	HT-29 MGL50/NT	p-value	HT29/Hs27 NT	p-value
	Hs27 cells		HT-29 cells		Hs27 cells		HT-29 cells		Hs27 MGL50/NT	p-value	HT-29 MGL50/NT	p-value					
	NT	MGL50	NT	MGL50	NT	MGL50	NT	MGL50									
H2B1B_80_86 unmod	99.87%	100.00%	99.33%	98.54%	0.16%	0.00%	0.82%	1.59%	0.00	0.00	-0.01	0.69	-0.01	1.07			
H2B1B_80_86 Y83ac	0.13%	0.00%	0.67%	1.46%	0.16%	0.00%	0.82%	1.59%	0.00	0.00	1.12	0.69	2.33	1.07			
H2B1A_81_87 unmod	26.09%	8.13%	3.32%	2.42%	16.10%	9.96%	4.06%	2.96%	-1.68	1.69	-0.46	0.26	-2.98	2.57			
H2B1A_81_87 K86ac	73.91%	25.20%	96.68%	97.58%	16.10%	30.87%	4.06%	2.96%	-1.55	2.63	0.01	0.26	0.39	2.57			
H2B_1_29 1C.PEPAKSAPAPKKGSKKAVTKAQKKDGKKR	62.08%	75.39%	46.65%	42.48%	1.31%	5.89%	5.79%	7.06%	0.28	4.21	-0.14	0.72	-0.41	4.91			
H2B_1_29 1H.PDPAKSAPAPKKGSKKAVTKAQKKDGKKR	11.11%	8.18%	5.20%	16.68%	0.84%	2.83%	1.20%	10.04%	-0.44	1.78	1.68	1.76	-1.10	7.01			
H2B_1_29 2F.PDPAKSAPAPKKGSKKAVTKVQKKDGKKR	2.05%	0.00%	1.12%	3.62%	2.30%	0.00%	1.08%	3.60%	0.00	0.00	1.70	1.12	-0.88	0.57			
H2B_1_29 1B.PEPSKSAPAPKKGSKKAITKAQKKDGKKR	2.25%	0.00%	0.08%	0.00%	2.76%	0.00%	0.09%	0.00%	0.00	0.00	0.00	0.00	-4.86	1.20			
H2B_1_29 1N.PEPSKSAPAPKKGSKKAVTKAQKKDGKKR	16.96%	1.68%	40.77%	23.37%	7.80%	1.06%	8.77%	17.52%	-3.34	2.88	-0.80	1.56	1.27	3.88			
H2B_1_29 1D.PEPTKSAPAPKKGSKKAVTKAQKKDGKKR	5.54%	3.95%	4.04%	6.89%	0.88%	2.62%	4.95%	4.79%	-0.49	0.95	0.77	0.65	-0.46	0.45			
H2B_1_29 1M.PEPVKSAPVPKKGSKKAINKAQKKDGKKR	0.00%	0.00%	1.46%	0.68%	0.00%	0.00%	1.79%	0.52%	0.00	0.00	-1.11	0.66	0.00	0.00			
H2B_1_29 1L.PELAKSAPAPKKGSKKAVTKAQKKDGKKR	0.00%	10.81%	0.68%	6.27%	0.00%	4.12%	0.84%	7.69%	0.00	0.00	3.20	1.10	0.00	0.00			

Table S4. Effects of MGL50 on PTMs of H3.3 histone variant in Hs27 and HT-29 cells. Cells were seeded (2.5×10^5 cells/well) into 12-well plates, were treated with 0.03 mg/mL MGL (MGL50) for 48 h and then were collected. Histones were extracted and peptides were analyzed by mass spectrometry. Data are represented as mean and standard error. NT, non-treated; MGL50, concentration of MGL able to reduce cell viability to 50%. Heteroscedastic two-tails t-test are applied and statistical analysis was carried out comparing Hs27 treated vs not treated, HT-29 treated vs not treat,; HT-29 non treated vs Hs27 non treated. p-value are reported as $-\log_2$. Statistically significant differences are highlighted in green.

	mean				standard error				Hs27 MGL50/NT	p-value	HT-29 MGL50/NT	p-value	HT29/Hs27 NT	p-value
	Hs27 cells		HT-29 cells		Hs27 cells		HT-29 cells							
	NT	MGL50	NT	MGL50	NT	MGL50	NT	MGL50						
H33_27_40 unmod	0.55%	4.12%	0.22%	6.04%	0.67%	5.05%	0.23%	3.96%	2.91	1.06	4.80	2.23	-1.34	0.75
H33_27_40 K36me1	0.20%	0.00%	0.00%	0.36%	0.25%	0.00%	0.00%	0.44%	0.00	0.00	0.00	0.00	0.00	0.00
H33_27_40 K27me1	0.18%	0.00%	0.00%	1.08%	0.22%	0.00%	0.00%	1.17%	0.00	0.00	0.00	0.00	0.00	0.00
H33_27_40 K27me2	4.87%	1.19%	13.33%	13.36%	3.20%	1.46%	2.12%	5.22%	-2.03	1.89	0.00	0.01	1.45	4.21
H33_27_40 K36me2	7.76%	4.22%	3.98%	3.63%	3.05%	5.17%	1.22%	2.23%	-0.88	0.97	-0.13	0.19	-0.96	2.12
H33_27_40 K27me3	0.74%	0.00%	5.17%	5.67%	0.91%	0.00%	0.88%	2.47%	0.00	0.00	0.13	0.27	2.80	6.28
H33_27_40 K36me3	4.09%	2.15%	1.08%	0.80%	0.92%	2.63%	0.23%	0.17%	-0.93	1.18	-0.44	1.74	-1.92	5.83
H33_27_40 K27me2K36me1	9.19%	4.03%	9.55%	8.98%	3.12%	4.93%	1.62%	4.05%	-1.19	1.56	-0.09	0.18	0.06	0.14
H33_27_40 K27me1K36me2	13.23%	10.60%	5.41%	5.85%	2.30%	9.26%	0.92%	1.69%	-0.32	0.41	0.11	0.33	-1.29	5.79
H33_27_40 K27me1K36me1	2.16%	0.33%	0.02%	0.44%	1.98%	0.40%	0.02%	0.23%	-2.74	1.61	4.56	2.77	-6.85	1.66
H33_27_40 K27me3K36me1	0.00%	0.00%	1.10%	1.67%	0.00%	0.00%	0.68%	1.03%	0.00	0.00	0.60	0.73	0.00	0.00
H33_27_40 K27me1K36me3	4.62%	1.36%	1.57%	2.93%	0.90%	1.66%	1.07%	2.37%	-1.77	3.29	0.90	0.84	-1.56	4.17
H33_27_40 K27me2K36me3	11.72%	7.53%	12.45%	14.86%	2.24%	9.22%	1.47%	6.88%	-0.64	0.70	0.26	0.52	0.09	0.41
H33_27_40 K27me3K36me2	2.19%	0.00%	2.80%	2.85%	0.98%	0.00%	0.65%	1.77%	0.00	0.00	0.02	0.03	0.35	0.84

Table S5. Effects of MGL50 on PTMs of H1 histone variant in HT-29 cells. Cells were seeded (2.5×10^5 cells/well) into 12-well plates, were treated with 0.03 mg/mL MGL (MGL50) for 24, 48 and 72 h and then were collected. Histones were extracted and peptides were analyzed by mass spectrometry. Data are represented as mean and standard deviation. NT, non-treated; PLP, control vehicle, cells treated with 0.5 mM PLP in PBS; MGL50, concentration of MGL able to reduce cell viability to 50%. Heteroscedastic two-tails t-test are applied and statistical analysis was carried out comparing, at each incubation time, NT vs PLP and PLP vs MGL. *= $p \leq 0.05$; **= $p \leq 0.01$ and ***= $p \leq 0.001$. Statistically significant differences are highlighted in green.

H1 variant	mean									standard deviation									NT vs PLP				PLP vs MGL			
	NT 24h	NT 48h	NT 72h	PLP 24h	PLP 48h	PLP 72h	MGL50 24h	MGL50 48h	MGL50 72h	NT 24h	NT 48h	NT 72h	PLP 24h	PLP 48h	PLP 72h	MGL50 24h	MGL50 48h	MGL50 72h	24h	48h	72h	24h	48h	72h		
H14_25_32 unmod	82.64%	77.81%	81.52%	77.77%	76.57%	84.73%	71.90%	84.71%	83.37%	0.05	0.06	0.02	0.14	0.19	0.02	0.11	0.01	0.02	0.00	0.92	0.42	0.613	0.525	0.440		
H14_25_32 K25me1	4.83%	9.69%	1.75%	8.78%	12.17%	1.70%	14.75%	2.31%	5.31%	0.06	0.08	0.01	0.13	0.18	0.00	0.12	0.00	0.03	0.65	0.84	0.87	0.579	0.444	0.143		
H14_25_32 K25me2	0.60%	0.80%	0.15%	0.65%	0.63%	0.31%	0.43%	0.20%	0.05%	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.88	0.54	0.23	0.521	0.015	0.069		
H14_25_32 K25me3	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.000	1.000	1.000		
H14_25_32 K25ac	0.75%	0.92%	1.05%	0.45%	0.84%	0.83%	0.89%	0.02%	0.66%	0.00	0.01	0.01	0.01	0.01	0.01	0.00	0.01	0.52	0.91	0.77	0.458	0.203	0.787			
H14_25_33 K33ac	8.46%	7.58%	7.70%	6.21%	6.34%	10.49%	7.91%	10.52%	8.74%	0.01	0.03	0.02	0.02	0.02	0.00	0.01	0.01	0.16	0.59	0.04	0.305	0.030	0.038			
H14_25_33 S26ac	1.83%	1.07%	2.26%	3.55%	1.87%	0.82%	1.46%	0.78%	0.53%	0.01	0.00	0.01	0.01	0.00	0.00	0.00	0.00	0.20	0.05	0.10	0.127	0.024	0.369			
H14_25_33 S26ph	0.90%	2.12%	3.57%	2.69%	1.59%	1.12%	2.66%	1.41%	1.48%	0.00	0.00	0.01	0.01	0.00	0.01	0.01	0.01	0.01	0.06	0.23	0.05	0.965	0.591	0.576		
H12_33_53 unmod	68.60%	72.96%	70.05%	69.05%	67.57%	67.78%	71.37%	58.49%	58.42%	0.04	0.06	0.03	0.03	0.11	0.02	0.03	0.50	0.10	0.31	0.21	0.31	0.050	0.847	0.170		
H12_33_53 K33me1	29.49%	25.66%	29.32%	30.20%	34.43%	31.56%	25.66%	8.90%	19.49%	0.02	0.04	0.02	0.04	0.08	0.01	0.05	0.13	0.14	0.78	0.16	0.24	0.286	0.940	0.282		
H12_33_53 K33me2	0.03%	0.28%	0.35%	0.48%	1.19%	0.40%	2.21%	0.52%	0.66%	0.00	0.00	0.00	0.01	0.00	0.01	0.04	0.00	0.01	0.25	0.21	0.92	0.494	0.330	0.744		
H12_33_53 K33me3	1.06%	0.22%	0.15%	2.59%	0.13%	0.01%	0.05%	15.87%	16.20%	0.01	0.00	0.00	0.03	0.00	0.00	0.00	0.27	0.14	0.50	0.65	0.19	0.314	0.426	0.183		
H12_33_53 K33ac	0.45%	0.87%	0.12%	0.00%	0.84%	0.25%	0.36%	18.22%	2.72%	0.01	0.01	0.00	0.00	0.01	0.00	0.00	0.30	0.05	1.00	0.98	0.41	1.000	0.416	0.459		
H12_33_53 S46ac	0.38%	0.02%	0.01%	1.69%	0.83%	0.00%	0.36%	0.00%	2.52%	0.01	0.00	0.00	0.02	0.01	0.00	0.00	0.04	0.24	0.43	0.68	0.218	1.000	0.423			
H15_36_56 unmod	27.07%	25.46%	28.98%	27.76%	26.49%	31.59%	23.26%	7.67%	19.29%	0.02	0.05	0.02	0.01	0.03	0.02	0.04	0.11	0.13	0.66	0.78	0.19	0.141	0.044	0.232		
H15_36_56 K36me1	0.02%	0.00%	0.14%	0.00%	1.46%	0.03%	0.00%	1.21%	0.00%	0.00	0.00	0.00	0.00	0.02	0.00	0.00	0.02	0.00	1.00	1.00	0.45	1.000	0.888	1.000		
H15_36_56 K36me2	0.21%	0.22%	0.15%	1.97%	0.18%	0.01%	0.42%	33.33%	17.39%	0.00	0.00	0.00	0.03	0.00	0.00	0.01	0.58	0.15	0.47	0.86	0.24	0.485	0.425	0.175		
H15_36_56 K36me3	0.92%	1.52%	0.70%	1.92%	0.89%	0.06%	6.25%	0.96%	0.00%	0.01	0.02	0.01	0.02	0.02	0.00	0.05	0.02	0.00	0.42	0.71	0.19	0.222	0.960	1.000		
H15_36_56 K36ac	67.16%	72.33%	69.34%	67.94%	67.47%	67.32%	70.17%	58.41%	59.02%	0.03	0.03	0.03	0.02	0.05	0.02	0.03	0.49	0.05	0.72	0.47	0.48	0.366	0.697	0.046		
H15_36_56 S43ac	4.61%	0.44%	0.78%	0.41%	1.51%	0.48%	0.00%	0.20%	4.30%	0.04	0.01	0.01	0.00	0.02	0.00	0.00	0.00	0.07	0.20	0.43	0.65	1.000	0.326	0.468		
H1_1_35 H12.SETAPAAPAAPPAEKAPVKKKKAAKKAA	0.72%	10.96%	0.17%	1.10%	1.39%	0.00%	11.98%	0.00%	1.81%	0.00	0.14	0.00	0.02	0.02	0.00	0.11	0.00	0.03	0.76	0.31	1.00	0.163	1.000	1.000		
H1_1_35 H13.SETAPLAPTIPAPAEKTPVKKKKAKAGAT	29.11%	29.08%	5.37%	20.55%	1.42%	1.75%	11.93%	30.57%	34.79%	0.39	0.48	0.07	0.28	0.01	0.03	0.21	0.34	0.22	0.77	0.43	0.46	0.691	0.276	0.115		
H1_1_35 H14.SETAPAAPAAPAPAEKTPVKKKKAR	55.20%	19.08%	21.21%	38.22%	58.80%	14.77%	22.79%	34.98%	29.11%	0.48	0.33	0.22	0.50	0.48	0.26	0.39	0.48	0.50	0.94	0.23	0.76	0.392	0.777	0.683		
H1_1_35 H15.SETAPATATATAPAEKTPAAKKATTKAAJ	14.98%	40.88%	73.25%	20.12%	30.40%	83.58%	31.30%	14.50%	34.30%	0.12	0.44	0.34	0.24	0.51	0.24	0.45	0.16	0.31	0.75	0.80	0.63	0.320	0.633	0.084		
H1_54_81 H11.GVSLAALKKALAAAGDYVEKNNSR	3.64%	25.27%	10.36%	0.00%	4.46%	0.22%	17.61%	33.82%	69.96%	0.06	0.43	0.18	0.00	0.07	0.00	0.31	0.48	0.33	1.00	0.49	0.43	1.000	0.215	0.084		
H1_54_81 H1234.SGVSLAALKKALAAAGDYVEKNNSR	58.46%	44.85%	60.62%	61.80%	69.33%	60.83%	59.05%	38.49%	29.02%	0.04	0.28	0.20	0.18	0.16	0.10	0.13	0.53	0.17	0.77	0.25	0.99	0.842	0.382	0.049		
H1_54_81 H15.NGLSLAALKKALAAAGDYVEKNNSR	37.83%	29.64%	28.97%	37.99%	24.56%	38.54%	22.80%	7.69%	10.02%	0.04	0.16	0.02	0.18	0.13	0.11	0.17	0.13	0.17	0.99	0.69	0.20	0.343	0.196	0.072		
H1_54_81 H17.VGMSLVALKKALAAAGDYVEKNNSR	0.07%	0.23%	0.04%	0.22%	1.05%	0.41%	0.54%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.02	0.01	0.01	0.00	0.00	0.35	0.44	0.34	0.592	1.000	1.000		

Table S6. Effects of MGL50 on PTMs of H2A histone variant in HT-29 cells. Cells were seeded (2.5×10^5 cells/well) into 12-well plates, were treated with 0.03 mg/mL MGL (MGL50) for 24, 48 and 72 h and then were collected. Histones were extracted and peptides were analyzed by mass spectrometry. Data are represented as mean and standard deviation. NT, non-treated; PLP, control vehicle, cells treated with 0.5 mM PLP in PBS; MGL50, concentration of MGL able to reduce cell viability to 50%. Heteroscedastic two-tails t-test are applied and statistical analysis was carried out comparing, at each incubation time, NT vs PLP and PLP vs MGL. * = $p \leq 0.05$; ** = $p \leq 0.01$ and *** = $p \leq 0.001$. Statistically significant differences are highlighted in green.

H2A variant	mean										standard deviation										NT vs PUP				PUP vs MZL			
	NT 24h	NT 48h	NT 72h	PUP 24h	PUP 48h	PUP 72h	MG150 24h	MG150 48h	MG150 72h	NT 24h	NT 48h	NT 72h	PUP 24h	PUP 48h	PUP 72h	MG150 24h	MG150 48h	MG150 72h	24h	48h	72h	24h	48h	72h	24h	48h	72h	
H2A1_36_42 unmod	99.87%	99.81%	99.91%	99.91%	99.94%	99.92%	99.88%	99.83%	99.84%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.15	0.65	0.76	0.246	0.880	0.053	0.00	0.00	0.00	
H2A1_36_42 K36ac	0.12%	0.16%	0.05%	0.09%	0.14%	0.07%	0.10%	0.13%	0.16%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.16	0.76	0.21	0.579	0.853	0.038	0.00	0.00	0.00	
H2A1_36_42 Y93ac	0.00%	0.00%	0.03%	0.05%	0.00%	0.02%	0.01%	0.02%	0.03%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.71	0.10	0.500	0.100	0.251	1.000	0.00	0.00	
H2A1_36_42 K36ac	99.97%	99.28%	99.69%	99.69%	99.69%	99.86%	99.86%	99.82%	99.82%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.30	0.71	0.334	0.788	0.020	0.222	0.00	0.00	
H2A1_36_42 K36ac	0.02%	0.00%	0.00%	0.00%	0.01%	0.00%	0.00%	0.00%	0.01%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.52	0.83	1.00	0.482	0.100	0.000	0.000	0.00	0.00	
H2A1_36_42 Y93ac	0.02%	0.06%	0.31%	0.41%	0.89%	0.14%	0.50%	0.80%	0.67%	0.00	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.01	0.14	0.68	0.34	0.779	0.868	0.034	0.191	0.00	0.00	
H2A1_36_42 unmod	99.92%	99.26%	99.97%	99.81%	99.63%	99.91%	99.81%	99.72%	99.52%	0.00	0.00	0.00	0.02	0.00	0.00	0.01	0.01	0.00	0.37	0.15	0.50	0.872	0.864	0.505	0.00	0.00	0.00	
H2A1_36_42 K36ac	0.02%	0.11%	0.00%	0.02%	0.11%	0.00%	0.00%	0.13%	0.48%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.80	0.98	0.47	0.847	0.885	1.000	0.00	0.00	0.00	
H2A1_36_42 Y93ac	0.00%	0.63%	0.03%	1.17%	0.26%	0.09%	1.39%	0.15%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.37	0.07	0.47	0.884	0.588	1.000	0.00	0.00	0.00	
H2A1_11 unmod	99.94%	80.65%	87.24%	86.64%	87.24%	99.83%	99.83%	99.83%	99.83%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
H2A1_4_11 K5ac	2.41%	1.00%	1.99%	0.98%	2.00%	3.29%	2.47%	1.74%	2.06%	0.02	0.02	0.02	0.02	0.02	0.00	0.00	0.00	0.02	0.02	0.41	0.52	0.34	0.210	0.853	0.360	0.00	0.00	
H2A1_4_11 K9ac	1.60%	2.61%	1.34%	2.99%	1.56%	0.48%	1.83%	1.23%	1.20%	0.02	0.02	0.02	0.02	0.02	0.00	0.00	0.02	0.01	0.63	0.51	0.43	0.223	0.813	0.491	0.00	0.00	0.00	
H2A1_4_11 K5acK9ac	0.09%	0.17%	0.06%	0.10%	0.14%	0.13%	0.15%	0.26%	0.05%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.89	0.68	0.39	0.443	0.154	0.343	0.00	0.00	0.00	
H2A1_4_11 K9me1	0.04%	2.71%	3.73%	2.08%	2.25%	1.17%	1.80%	0.44%	0.49%	0.00	0.01	0.04	0.01	0.02	0.01	0.02	0.00	0.00	0.05	0.76	0.33	0.842	0.195	0.252	0.00	0.00	0.00	
H2A1_4_11 K5me1	2.44%	4.47%	5.63%	5.02%	4.17%	1.97%	2.87%	0.91%	0.98%	0.00	0.02	0.02	0.02	0.01	0.01	0.02	0.01	0.00	0.84	0.08	0.287	0.023	0.157	0.00	0.00	0.00		
H2A1_11 unmod	11.62%	16.07%	12.27%	14.65%	11.61%	14.65%	11.61%	14.65%	11.61%	0.00	0.04	0.11	0.08	0.13	0.00	0.00	0.00	0.00	0.30	0.81	0.40	0.565	0.177	0.00	0.00	0.00	0.00	
H2A1_4_11 K5ac	0.00%	0.01%	0.00%	0.00%	0.04%	0.01%	0.01%	0.01%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.42	1.00	1.000	1.000	1.000	0.00	0.00	0.00	
H2A1_4_11 K9ac	1.81%	4.16%	3.30%	3.71%	2.54%	1.83%	2.32%	1.02%	0.21%	0.00	0.01	0.01	0.01	0.01	0.00	0.00	0.00	0.00	0.03	0.27	0.17	0.890	0.294	0.068	0.00	0.00	0.00	
H2A1_4_11 K5acK9ac	0.15%	53.72%	37.13%	59.24%	47.93%	57.24%	47.57%	56.63%	57.81%	0.03	0.09	0.16	0.13	0.13	0.11	0.06	0.07	0.50	0.32	0.56	0.14	0.772	0.036	0.986	0.00	0.00	0.00	
H2A1_4_11 K9me1	4.74%	9.72%	5.44%	6.47%	1.63%	5.89%	1.42%	0.03%	0.04%	0.08	0.08	0.07	0.03	0.03	0.02	0.00	0.00	0.00	0.74	0.16	0.92	0.070	0.423	0.031	0.00	0.00	0.00	
H2A1_4_11 K5me1	22.47%	36.32%	33.43%	24.93%	30.67%	21.26%	28.15%	33.46%	33.46%	0.00	0.04	0.11	0.08	0.13	0.00	0.00	0.00	0.00	0.46	0.75	0.05	0.275	0.086	0.617	0.00	0.00	0.00	
H2A1_11 unmod	9.97%	9.60%	40.93%	8.49%	40.93%	11.32%	10.79%	10.93%	10.11%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.20	0.79	0.00	0.051	0.000	0.179	0.00	0.00	0.00	
H2A1_4_11 K5ac	0.16%	0.41%	1.82%	0.34%	0.24%	0.43%	0.24%	0.32%	0.17%	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.05	0.22	0.193	0.271	0.169	0.00	0.00	0.00	
H2A1_4_11 K9ac	0.47%	0.75%	2.35%	0.53%	0.50%	0.56%	0.75%	0.75%	0.29%	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.84	0.52	0.03937	0.412	0.542	0.247	0.00	0.00	0.00	
H2A1_4_11 K5acK9ac	0.00%	0.25%	0.58%	0.07%	0.09%	0.05%	0.08%	0.05%	0.01%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.63	0.21	0.03890	0.868	0.206	0.070	0.00	0.00	0.00	
H2A1_4_11 K9me1	42.37%	43.93%	37.99%	63.37%	63.82%	68.41%	0.09%	39.40%	40.06%	0.37	0.36	0.14	0.02	0.02	0.10	0.00	0.37	0.40	0.43	0.41	0.037896	0.000	0.421	0.396	0.00	0.00	0.00	
H2A1_4_11 K5me1	46.47%	47.67%	46.33%	39.19%	46.33%	46.33%	46.33%	46.33%	46.33%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.17	0.00	0.00	0.465	0.177	0.00	0.00	0.00	0.00	
H2A1_11 unmod	20.16%	35.49%	30.80%	30.60%	35.57%	39.87%	17.92%	13.91%	18.99%	0.02	0.02	0.05	0.09	0.03	0.06	0.04	0.09	0.06	0.11	0.11	0.09	0.066	0.214	0.011	0.00	0.00	0.00	
H2A1_11 K5ac	6.91%	19.53%	25.08%	25.33%	28.87%	10.64%	11.81%	14.80%	13.43%	0.05	0.07	0.09	0.15	0.10	0.02	0.04	0.06	0.02	0.11	0.26	0.06	0.234	0.104	0.162	0.00	0.00	0.00	
H2A1_11 K5acK9ac	72.93%	44.98%	44.06%	40.07%	31.57%	44.49%	67.73%	53.81%	67.34%	0.07	0.08	0.09	0.23	0.13	0.08	0.07	0.15	0.05	0.14	0.20	0.55	0.144	0.121	0.024	0.00	0.00	0.00	
H2A1_11 unmod	85.85%	86.79%	89.48%	83.56%	80.93%	87.46%	82.13%	79.53%	85.35%	0.00	0.01	0.08	0.07	0.07	0.01	0.09	0.06	0.13	0.64	0.33	0.03	0.888	0.816	0.808	0.00	0.00	0.00	
H2A1_19 K4ac	0.00%	1.51%	1.79%	1.08%	0.56%	1.05%	1.21%	0.00%	0.00%	0.00	0.02	0.01	0.00	0.00	0.01	0.01	0.00	0.00	0.01	0.38	0.42	0.875	1.000	1.000	1.000	0.00	0.00	0.00
H2A1_19 K9ac	0.00%	0.17%	0.79%	0.00%	0.32%	0.18%	0.42%	0.32%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.81	0.49	0.10	0.007	0.000	0.000	0.00	0.00	0.00	
H2A1_19 K11ac	1.77%	0.04%	2.86%	1.87%	0.54%	1.22%	2.21%	0.05%	0.01%	0.00	0.01	0.02	0.01	0.00	0.00	0.00	0.00	0.00	0.96	0.26	0.10	0.855	0.266	0.076	0.00	0.00	0.00	
H2A1_19 K15ac	2.46%	4.29%	1.58%	3.17%	6.93%	2.80%	5.17%	4.52%	0.87%	0.01	0.02	0.01	0.01	0.05	0.01	0.00	0.00	0.00	0.38	0.45	0.10	0.557	0.644	0.119	0.00	0.00	0.00	
H2A1_19 K4acK7ac	0.12%	0.00%	0.04%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.000	1.000	1.000	0.00	0.00	0.00	
H2A1_19 K4acK11ac	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.000	1.000	1.000	0.00	0.00	0.00	
H2A1_19 K4acK15ac	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.000	1.000	1.000	0.00	0.00	0.00	
H2A1_19 K7acK11ac	1.13%	0.18%	1.30%	0.95%	0.26%	0.69%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.79	0.70	0.10	0.167	0.000	0.247	0.00	0.00	0.00		
H2A1_19 K7acK15ac	0.01%	0.00%	0.05%	0.01%	0.01%	0.01%	0.01%	0.01%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.000	1.000	1.000	0.00	0.00	0.00	
H2A1_19 K11acK15ac	1.60%	0.40%	0.98%	1.23%	1.34%	0.76%	0.77%	0.45%	0.00%	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.01	0.00	0.73	0.04	0.61	0.358	0.095	1.000	0.00	0.00	0.00	
H2A1_19 K7acK11acK15ac	0.02%	0.66%	0.29%	0.14%	0.01%	0.04%	0.25%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.53	0.14	0.32	0.583	1.000	1.000	0.00	0.00	0.00	
H2A1_19 K4acK11acK15ac	0.00%	0.02%	0.00%	0.00%	0.00%	0.00%	0.02%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	1.00	1.000	1.000	1.000	0.00	0.00	0.00	
H2A1_19 K4acK15acK11ac	0.00%	0.23%	0.42%	0.00%	0.75%	0.00%	0.02%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.35	0.14	0.10	0.100	0.000	0.000	0.00	0.00	0.00	
H2A1_19 K4acK7acK11ac	0.09%	0.08%	0.05%	0.53%	0.63%	0.08%	0.04%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00</										

Table S7. Effects of MGL50 on PTMs of H2B histone variant in HT-29 cells. Cells were seeded (2.5×10^5 cells/well) into 12-well plates, were treated with 0.03 mg/mL MGL (MGL50) for 24, 48 and 72 h and then were collected. Histones were extracted and peptides were analyzed by mass spectrometry. Data are represented as mean and standard deviation. NT, non-treated; PLP, control vehicle, cells treated with 0.5 mM PLP in PBS; MGL50, concentration of MGL able to reduce cell viability to 50%. Heteroscedastic two-tails t-test are applied and statistical analysis was carried out comparing, at each incubation time, NT vs PLP and PLP vs MGL. * = $p \leq 0.05$; ** = $p \leq 0.01$ and *** = $p \leq 0.001$. Statistically significant differences are highlighted in green.

H2B variant	mean									standard deviation									NT vs PLP			PLP vs MGL		
	NT 24h	NT 48h	NT 72h	PLP 24h	PLP 48h	PLP 72h	MGL50 24h	MGL50 48h	MGL50 72h	NT 24h	NT 48h	NT 72h	PLP 24h	PLP 48h	PLP 72h	MGL50 24h	MGL50 48h	MGL50 72h	24h	48h	72h	24h	48h	72h
H2B18_80_86 unmod	99.94%	99.79%	99.88%	99.92%	99.73%	99.91%	99.67%	98.36%	96.15%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.03	0.18	0.73	0.42	0.120	0.001	0.126
H2B18_80_86 Y83ac	0.06%	0.21%	0.12%	0.08%	0.27%	0.09%	0.33%	1.64%	3.85%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.03	0.18	0.73	0.42	0.120	0.001	0.126
H2B1A_81_87 unmod	6.86%	10.93%	21.22%	8.03%	5.86%	11.65%	20.11%	2.68%	19.54%	0.04	0.05	0.16	0.01	0.05	0.10	0.06	0.03	0.18	0.62	0.32	0.43	0.028	0.421	0.545
H2B1A_81_87 K86ac	93.14%	89.07%	78.78%	91.97%	94.14%	88.33%	79.89%	97.32%	80.46%	0.04	0.05	0.16	0.01	0.05	0.10	0.06	0.03	0.18	0.62	0.32	0.43	0.028	0.421	0.545
H2B_1_29 1C.PEPKSAAPAPKKGSKKAVTKAQK	44.39%	35.37%	56.40%	50.48%	57.04%	58.15%	54.73%	44.74%	48.22%	0.09	0.26	0.09	0.14	0.12	0.04	0.10	0.31	0.32	0.57	0.26	0.73	0.692	0.559	0.636
H2B_1_29 1H.PDPKSAAPAPKKGSKKAVTKVQK	9.41%	6.67%	11.96%	6.33%	5.18%	13.68%	9.05%	5.40%	5.32%	0.03	0.06	0.03	0.06	0.08	0.02	0.12	0.09	0.09	0.47	0.81	0.45	0.751	0.976	0.201
H2B_1_29 2F.PDPKSAAPAPKKGSKKAVTKVQK	2.22%	1.40%	5.59%	11.50%	0.80%	6.00%	3.32%	0.45%	10.38%	0.02	0.01	0.00	0.12	0.01	0.02	0.06	0.01	0.12	0.30	0.63	0.73	0.335	0.727	0.579
H2B_1_29 1B.PEPKSAAPAPKKGSKKAVTKAQK	6.78%	32.65%	4.74%	6.79%	3.64%	0.02%	6.11%	32.62%	10.73%	0.06	0.47	0.08	0.06	0.05	0.00	0.05	0.40	0.19	1.00	0.40	0.42	0.894	0.334	0.423
H2B_1_29 1N.PEPKSAAPAPKKGSKKAVTKAQK	10.41%	8.69%	6.60%	4.27%	6.85%	5.23%	0.19%	0.00%	0.00%	0.07	0.08	0.11	0.06	0.06	0.09	0.00	0.00	0.00	0.30	0.76	0.88	0.360	1.000	1.000
H2B_1_29 1D.PEPTKSAAPAPKKGSKKAVTKAQK	10.63%	6.95%	13.61%	7.81%	12.74%	14.25%	9.74%	4.85%	13.77%	0.00	0.06	0.01	0.05	0.07	0.01	0.01	0.08	0.17	0.44	0.35	0.53	0.560	0.282	0.965
H2B_1_29 1M.PEPTKSAAPAPKKGSKKAVTKAQK	3.80%	0.58%	1.10%	6.61%	10.70%	2.38%	16.64%	1.56%	11.58%	0.03	0.01	0.01	0.02	0.11	0.01	0.17	0.03	0.14	0.20	0.26	0.29	0.407	0.241	0.383
H2B_1_29 1L.PELAKSAAPAPKKGSKKAVTKAQK	12.37%	7.68%	0.00%	6.21%	3.05%	0.00%	0.22%	10.36%	0.00%	0.04	0.08	0.00	0.03	0.04	0.00	0.00	0.11	0.00	0.10	0.42	1.00	0.079	0.349	1.000

Table S8. Effects of MGL50 on PTMs of H3.3 histone variant in HT-29 cells. Cells were seeded (2.5×10^5 cells/well) into 12-well plates, were treated with 0.03 mg/mL MGL (MGL50) for 24, 48 and 72 h and then were collected. Histones were extracted and peptides were analyzed by mass spectrometry. Data are represented as mean and standard deviation. NT, non-treated; PLP, control vehicle, cells treated with 0.5 mM PLP in PBS; MGL50, concentration of MGL able to reduce cell viability to 50%. Heteroscedastic two-tails t-test are applied and statistical analysis was carried out comparing, at each incubation time, NT vs PLP and PLP vs MGL. * = $p \leq 0.05$; ** = $p \leq 0.01$ and *** = $p \leq 0.001$. Statistically significant differences are highlighted in green.

H3.3 variant	mean										standard deviation										NT vs PLP		PLP vs MGL		
	NT 24h	NT 48h	NT 72h	PLP 24h	PLP 48h	PLP 72h	MGL50 24h	MGL50 48h	MGL50 72 24h	NT 24h	NT 48h	NT 72h	PLP 24h	PLP 48h	PLP 72h	MGL50 24h	MGL50 48h	MGL50 72 24h	NT vs PLP	48h	72h	24h	48h	72h	
H33_27_40 unmod	3.41%	3.67%	2.89%	2.52%	3.26%	3.12%	10.14%	11.59%	7.42%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.020	0.023	0.016	0.01	0.06	0.55	0.021	0.024	0.011
H33_27_40 K36me1	1.72%	2.34%	1.62%	1.45%	1.94%	1.59%	2.55%	1.34%	0.06%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.004	0.004	0.001	0.18	0.03	0.92	0.007	0.089	0.000
H33_27_40 K27me1	2.95%	3.69%	2.64%	2.51%	3.19%	2.57%	4.47%	2.76%	0.52%	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.005	0.010	0.002	0.28	0.04	0.82	0.006	0.508	0.000
H33_27_40 K27me2	25.04%	14.79%	24.49%	23.52%	22.00%	26.37%	15.13%	25.68%	23.55%	0.01	0.01	0.01	0.01	0.03	0.01	0.016	0.080	0.058	0.14	0.02	0.09	0.001	0.498	0.451	
H33_27_40 K36me2	23.46%	8.39%	21.82%	20.03%	9.00%	24.24%	8.34%	7.16%	2.57%	0.01	0.04	0.05	0.02	0.01	0.01	0.043	0.025	0.012	0.06	0.83	0.50	0.013	0.323	0.000	
H33_27_40 K27me3	5.40%	6.03%	4.97%	4.81%	6.67%	5.10%	6.73%	7.31%	10.60%	0.00	0.00	0.01	0.00	0.01	0.00	0.008	0.012	0.021	0.05	0.20	0.85	0.017	0.435	0.043	
H33_27_40 K36me3	0.10%	0.69%	0.06%	0.11%	0.10%	0.03%	0.08%	1.05%	0.81%	0.00	0.01	0.00	0.00	0.00	0.00	0.000	0.010	0.014	0.53	0.43	0.15	0.286	0.237	0.438	
H33_27_40 K27me2K36me1	10.51%	13.40%	12.57%	12.74%	12.71%	12.08%	12.78%	10.87%	5.63%	0.01	0.01	0.00	0.00	0.00	0.02	0.010	0.022	0.045	0.01	0.27	0.74	0.950	0.238	0.089	
H33_27_40 K27me1K36me2	5.30%	7.96%	6.56%	5.81%	6.95%	4.89%	7.24%	4.99%	1.05%	0.00	0.01	0.01	0.01	0.00	0.00	0.007	0.011	0.001	0.40	0.04	0.08	0.085	0.041	0.000	
H33_27_40 K27me1K36me1	1.63%	3.38%	2.09%	2.09%	2.09%	1.56%	2.96%	0.13%	0.00%	0.01	0.01	0.00	0.00	0.01	0.00	0.007	0.001	0.000	0.53	0.06	0.19	0.098	0.005	1.000	
H33_27_40 K27me3K36me1	2.23%	2.97%	1.95%	2.34%	2.84%	1.98%	3.25%	2.92%	1.43%	0.00	0.00	0.00	0.00	0.00	0.00	0.003	0.004	0.006	0.43	0.10	0.89	0.011	0.738	0.186	
H33_27_40 K27me1K36me3	2.39%	3.85%	2.78%	2.35%	3.36%	2.19%	2.81%	1.70%	0.23%	0.00	0.00	0.00	0.00	0.00	0.00	0.002	0.004	0.002	0.72	0.01	0.22	0.040	0.002	0.000	
H33_27_40 K27me2K36me2	10.64%	15.46%	10.77%	14.02%	15.32%	9.86%	15.03%	15.80%	17.02%	0.02	0.01	0.01	0.01	0.01	0.01	0.006	0.034	0.100	0.04	0.82	0.23	0.193	0.833	0.340	
H33_27_40 K27me3K36me2	3.09%	4.49%	2.68%	3.71%	4.31%	2.58%	3.92%	3.47%	2.26%	0.00	0.00	0.00	0.00	0.00	0.00	0.002	0.007	0.016	0.13	0.42	0.77	0.392	0.118	0.749	
H33_27_40 K27ac	0.53%	0.52%	0.50%	0.42%	0.50%	0.40%	0.81%	0.86%	0.75%	0.00	0.00	0.00	0.00	0.00	0.00	0.001	0.002	0.006	0.12	0.67	0.31	0.003	0.044	0.451	
H33_27_40 S28ph	0.07%	0.82%	0.40%	0.35%	0.38%	0.06%	0.72%	1.28%	25.77%	0.00	0.00	0.00	0.00	0.00	0.00	0.002	0.000	0.223	0.02	0.53	0.00	0.072	0.633	0.184	
H33_27_40 K27me1S28ph	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.000	0.000	0.000	1.00	1.00	1.00	1.000	1.000	1.000	
H33_27_40 K27me2S28ph	0.09%	0.01%	0.00%	0.05%	0.05%	0.03%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.000	0.000	0.000	0.43	0.19	1.00	0.265	1.000	1.000	
H33_27_40 K27me3S28ph	0.04%	0.01%	0.01%	0.05%	0.10%	0.02%	0.02%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.000	0.000	0.000	0.53	0.29	0.12	0.100	0.281	1.000	
H33_27_40 K27me2S28phK36me	0.04%	0.00%	0.01%	0.05%	0.01%	0.01%	0.01%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.000	0.000	0.000	0.71	0.56	0.52	0.050	1.000	1.000	
H33_27_40 K27me3S28phK36me	0.00%	0.13%	0.00%	0.00%	0.15%	0.00%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.000	0.000	0.000	0.52	0.89	1.00	1.000	1.000	1.000	
H33_27_40 S28ac	0.47%	5.90%	0.20%	0.17%	3.33%	0.02%	1.85%	0.42%	0.00%	0.01	0.03	0.00	0.00	0.00	0.02	0.00	0.007	0.007	0.000	0.54	0.26	0.31	0.015	0.051	1.000
H33_27_40 K27me2S28ac	0.16%	0.02%	0.08%	0.20%	0.12%	0.51%	0.04%	0.02%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.000	0.000	0.000	0.64	0.23	0.16	0.131	0.207	1.000	
H33_27_40 K27me3S28ac	0.42%	0.84%	0.55%	0.39%	0.62%	0.50%	0.63%	0.54%	0.34%	0.00	0.00	0.00	0.00	0.00	0.00	0.002	0.001	0.004	0.84	0.25	0.55	0.097	0.434	0.497	
H33_27_40 K27me2S28acK36me	0.31%	0.65%	0.37%	0.29%	0.39%	0.28%	0.48%	0.10%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00	0.001	0.001	0.000	0.83	0.09	0.17	0.053	0.011	1.000	