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Novel 3,5-Bis(bromohydroxybenzylidene)piperidin-4-ones as Coactivator-associated Arginine Methyltransferase 1 Inhibitors: Enzyme Selectivity and Cellular Activity

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Chart S1. Known CARM1 inhibitors.

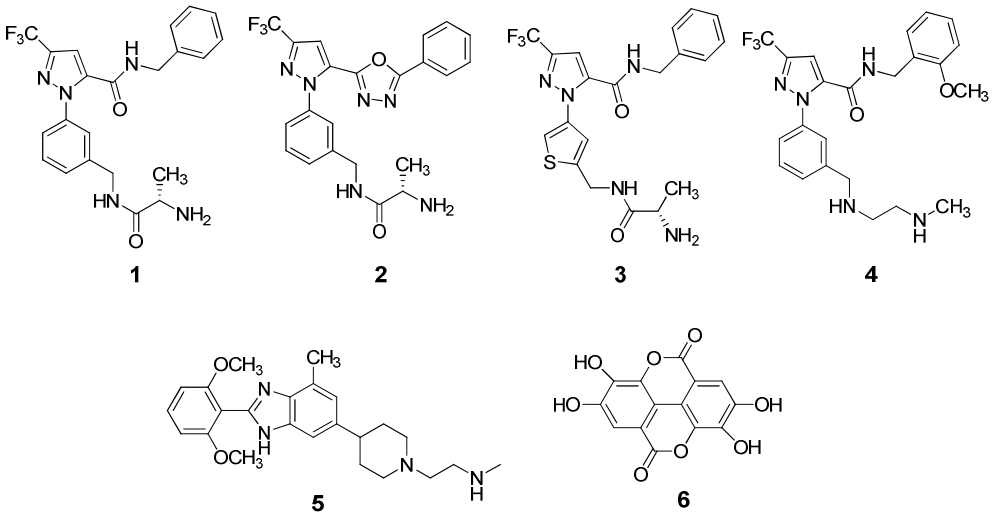


Figure S1. Bis(bromo- and dibromophenol)-containing compounds **7a-m** lacking the epi-ML behavior and showing some selectivity against CARM1 by fluorograph data.[1]

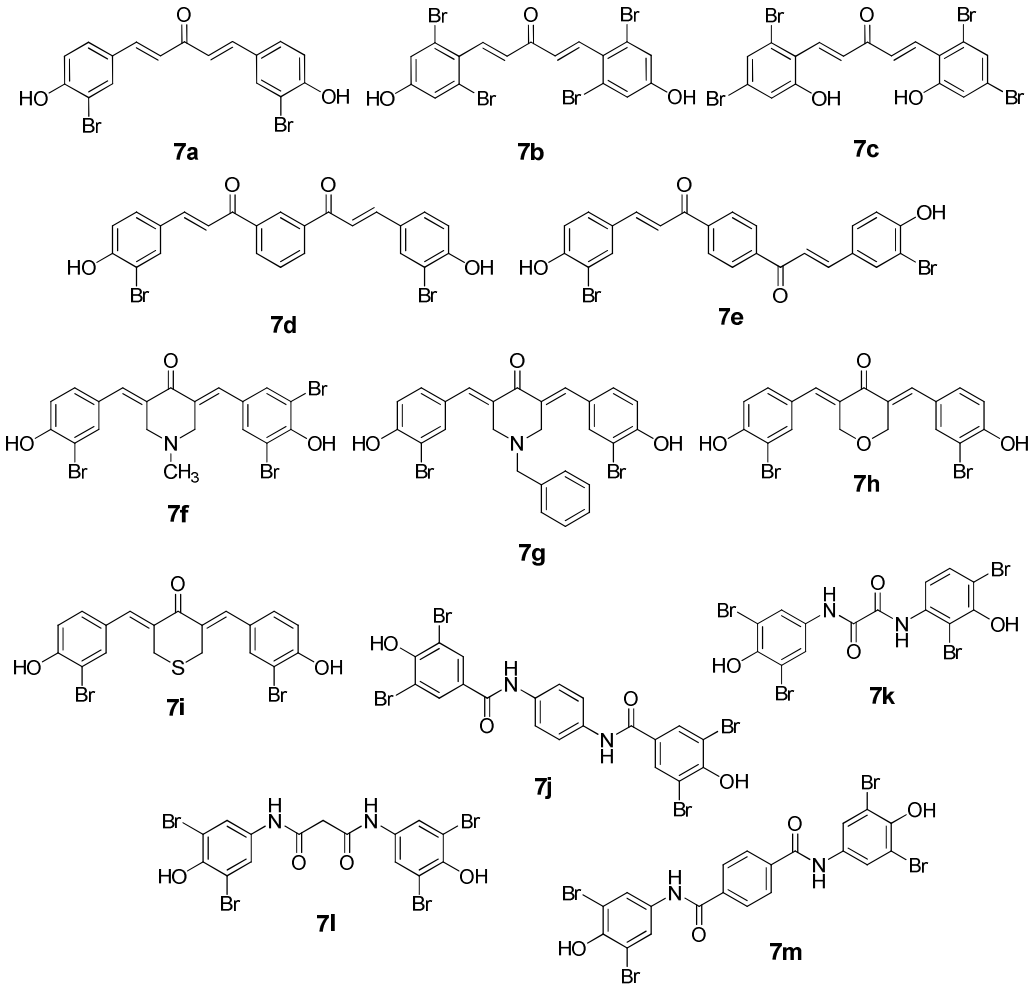


Figure S2. 7g is a reversible inhibitor of CARM1. A dilution experiment was performed, where 100 μM CARM1 enzyme with 500 μM **7g** were preincubated for 90 min and then diluted 1000-fold into reaction mix at final 100 nM CARM1 and 0.5 μM of compound with substrate 0.5 μM PABP1 and 0.5 μM [^{3}H] AdoMet for 1 h reaction. DMSO and 0.5 μM of **7g** were mixed with 100 nM CARM1 directly to react for 1 h as the controls. The dpm count is depicted.

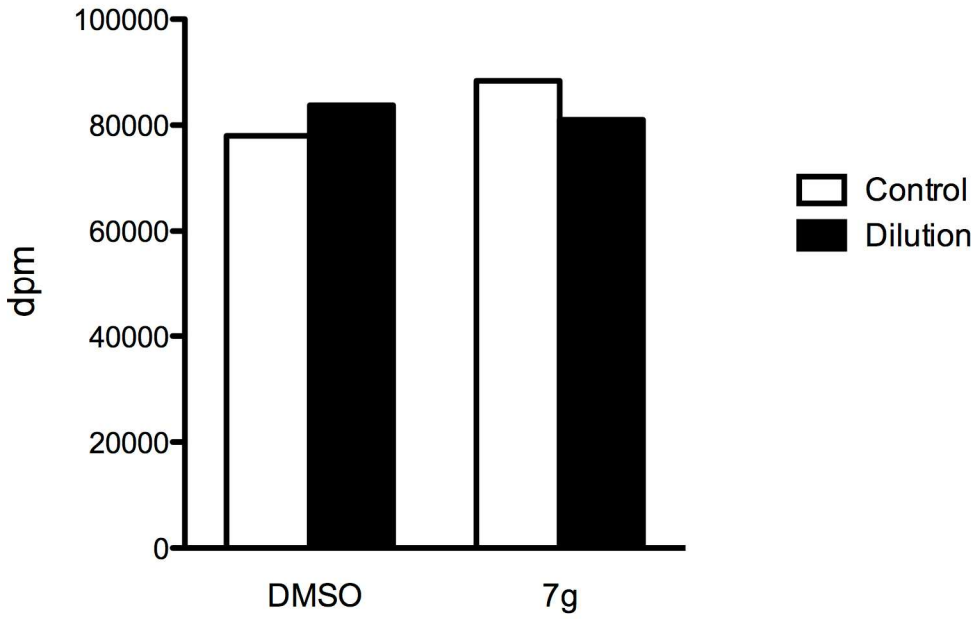
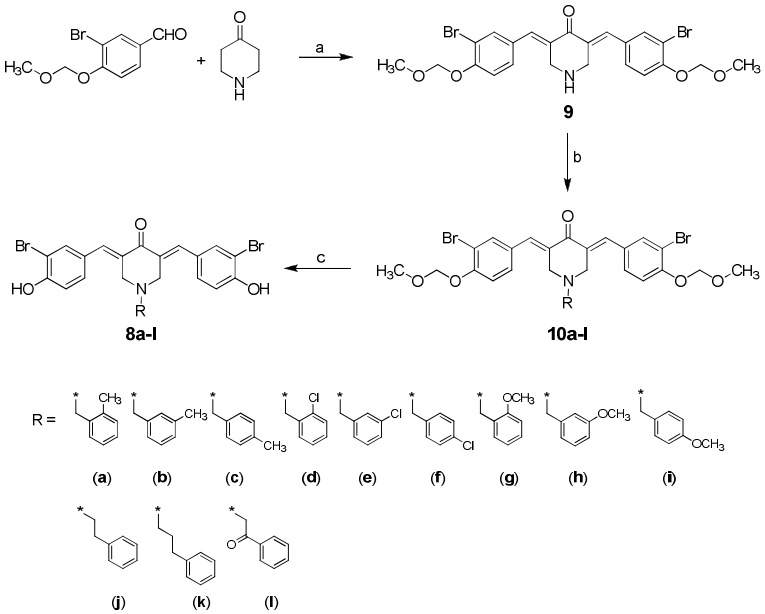


Table S1. IC_{50} values of selected bis(bromo- and dibromophenol) derivatives **7a-m** against PRMT1, CARM1, and SET7.[a]

compd	IC_{50}, μM		
	PRMT1/ NPL3	CARM1/ PABP1	SET7/ H3
7a[b]	11.8	53	64
7b[b]	3.4	36	37
7c	80	20	>333
7d	65	26	143
7e	34	22	701
7f	24	59	206
7g	63	7.1	943
7h	116	33	949
7i	16	68	206
7j	206	95	162
7k	17.7	21	>100
7l	80	26	232
7m	166	24	>667

[a]Values are means determined from at least two separate experiments; SDs are within ±10% of the values. [b]Ref. 2.

Scheme S1[a]



[a](a) $Ba(OH)_2 \times 8\ H_2O$, MeOH, rt, 2 h; (b) dry K_2CO_3, R-Br, CH_3CN, 60 °C, 1 h; (c) 3N HCl, MeOH, 60 °C, 3 h.

Chemistry. Melting points were determined on a Buchi 530 melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker AC 400 spectrometer; chemical shifts are reported in δ (ppm) units relative to the internal reference tetramethylsilane (Me_4Si). EIMS spectra were recorded with a Fisons Trio 1000 spectrometer; only molecular ions (M^+) and base peaks are given. All compounds were routinely checked by TLC and

^{1}H NMR. TLC was performed on aluminum-backed silica gel plates (Merck DC, Alufolien Kieselgel 60 F_{254}) with spots visualized by UV light. All solvents were reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at reduced pressure of ca. 20 Torr. Organic solutions were dried over anhydrous sodium sulfate. Analytical results are within ± 0.40% of the theoretical values. All chemicals were purchased from Aldrich Chimica, Milan (Italy), or from Alfa Aesar, Milan (Italy), and were of the highest purity.

Procedure for the Synthesis of 3,5-bis(3-bromo-4-(methoxymethoxy)benzylidene) piperidin-4-one (9).

The 3-bromo-4-(methoxymethoxy)benzaldehyde[1] (2.04 mmol, 0.5 g) was added to a suspension of 4-piperidone (1.02 mmol, 0.1 g) and barium hydroxide octahydrate (4.08 mmol, 1.3 g) in methanol (10 mL), and the mixture was kept in stirring for a period of 2 h. After this time, water (30 mL) was added and the solid precipitated was filtered, washed with water (3 × 10 mL) and dried to be purified by chromatographic column eluting with ethyl acetate/*n*-hexane 1/1, to afford pure **9** as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ; ppm) δ 1.90 (bs, 1H, N*H*), 3.50 (s, 6H, OCH_3), 4.11 (s, 4H, CH_2 piperidone), 5.27 (s, 4H, CH_2OCH_3), 7.17-7.65 (m, 8H, PhC*H* and benzene protons) ppm; ^{13}C NMR ($CDCl_3$, 400 MHz, δ; ppm) δ 46.6 (2C), 55.6 (2C), 94.2 (2C), 112.1 (2C), 112.2 (2C), 128.4 (2C), 129.2 (2C), 130.9 (2C), 140.6 (2C), 145.9 (2C), 156.2 (2C), 186.0 ppm; MS (EI): *m*/*z*: 552.99 $(M)^+$.

General Procedure for the Synthesis of *N*-substituted-3,5-bis(3-bromo-4-(methoxymethoxy)benzylidene)piperidin-4-ones (10a-l). Example: 3,5-Bis[3-bromo-4-(methoxymethoxy)benzylidene]-1-(2-oxo-2-phenylethyl)piperidin-4-one (10l).

2-Bromo-1-phenylethanone (1.51 mmol, 0.3 g) was added to a suspension of **9** and dry potassium carbonate (1.81 mmol, 0.3 g) in acetonitrile (15 mL), and the resulting mixture was stirred at 60 °C for 1 h. Then water (50 mL) was added to the reaction, and the precipitate was filtered, washed with water (3 × 10 mL), dried and purified by chromatography eluting with ethyl acetate/*n*-hexane 1/3 to obtain the pure **10l**. ^{1}H NMR (DMSO-d_6, 400 MHz, δ; ppm) δ 3.38 (s, 6H, OCH_3), 3.96 (s, 4H, CH_2 piperidone), 4.22 (s, 2H, PhCOCH_2), 5.31 (s, 4H, CH_2OCH_3), 7.23-7.90 (m, 13H, PhC*H* and benzene protons) ppm; ^{13}C NMR (DMSO-d_6, 400 MHz, δ; ppm) δ 53.3 (2C), 55.6 (2C), 70.9, 94.2 (2C), 112.1 (2C), 112.2 (2C), 128.4 (2C), 128.6 (2C), 128.8 (2C), 129.2 (2C), 130.9 (2C), 133.1, 135.1, 140.6 (2C), 145.9 (2C), 156.2 (2C), 186.0, 195.3 ppm; MS (EI): *m*/*z*: 671.03 $(M)^+$.

General Procedure for the Synthesis of *N*-substituted-3,5-bis(3-bromo-4-hydroxybenzylidene)piperidin-4-ones (8a-l). Example: 3,5-Bis(3-bromo-4-(hydroxybenzylidene)-1-(3-chlorobenzyl)piperidin-4-one (8e).

A solution of **10e** (0.42 mmol, 0.3 g) in methanol (5 mL) and 3 N hydrochloric acid (5 mL) was stirred at 60 °C for 3 h, then the suspension was neutralized with 1 N sodium hydrogen carbonate, the precipitated solid was filtered and washed with water (3 × 10 mL) and diethyl ether (3 × 10 mL) to give the pure compound **8e** as a yellow powder. ^{1}H NMR (DMSO-d_6, 400 MHz, δ; ppm) δ 4.43-4.48 (s, 6H, PhCH_2 and CH_2 piperidone), 7.05-7.74 (m, 12H, PhC*H* and benzene protons), 11.13 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-d_6, 400 MHz, δ; ppm) δ 53.4 (2C), 63.9, 113.7 (2C), 118.0 (2C), 126.0, 126.9, 127.3, 128.7 (2C), 129.6 (2C), 131.3 (2C), 132.2, 134.0, 136.9, 140.6 (2C), 145.9 (2C), 155.8 (2C), 186.0 ppm; MS (EI): *m*/*z*: 588.95 $(M)^+$.

Table S2. Physical and Chemical Data for Compounds **8-10**[a]

compd	mp (°C)	recryst solvent[b]	% yield
8a	220-222	A	75
8b	225-227	A	84
8c	235-237	B	89
8d	253-255	B	79
8e	236-238	B	82

8f	>250	B	86
8g	>250	B	72
8h	210-212	A	75
8i	235-237	B	80
8j	206-208	A	81
8k	>250	B	83
8l	>250	B	74
9	158-160	C	77
10a	172-174	D	72
10b	175-177	D	75
10c	184-186	D	83
10d	202-204	D	69
10e	193-195	D	71
10f	205-207	D	76
10g	215-217	D	65
10h	173-175	D	68
10i	191-193	D	74
10j	168-170	D	83
10k	220-222	D	77
10l	183-185	D	85

[a]Analytic results were within ±0.40% of the theoretical values. [b]A, acetonitrile/methanol; B, methanol; C, benzene/acetonitrile; D, acetonitrile.

Table S3. Analytical results of compounds **7g** and **8a-l**.

cpd	MW	% calcd					% found				
		C	H	N	Br	Cl	C	H	N	Br	Cl
7g	555.26	56.24	3.81	2.52	28.78		56.45	3.99	2.37	28.64	
8a	569.28	56.96	4.07	2.46	28.07		57.11	4.18	2.29	27.97	
8b	569.28	56.96	4.07	2.46	28.07		56.79	3.84	2.68	28.18	
8c	569.28	56.96	4.07	2.46	28.07		57.18	4.19	2.21	27.81	
8d	589.70	52.96	3.42	2.38	27.10	6.01	53.17	3.51	2.12	27.28	5.83
8e	589.70	52.96	3.42	2.38	27.10	6.01	53.12	3.56	2.44	27.21	5.76
8f	589.70	52.96	3.42	2.38	27.10	6.01	52.77	3.36	2.51	26.89	6.19
8g	585.28	55.41	3.96	2.39	27.3		55.67	4.12	2.14	27.15	
8h	585.28	55.41	3.96	2.39	27.3		55.60	4.17	2.12	27.19	
8i	585.28	55.41	3.96	2.39	27.3		55.21	3.77	2.51	27.57	
8j	569.28	56.96	4.07	2.46	28.07		57.12	4.14	2.21	27.93	
8k	583.31	57.65	4.32	2.40	27.40		57.88	4.42	2.11	27.29	
8l	583.27	55.60	3.63	2.40	27.40		55.31	3.48	2.57	27.52	

Table S4. ^{1}H NMR, ^{13}C NMR and Mass Spectrum data for compounds **7g** and **8a-d,f-l**.

3,5-bis(3-bromo-4-hydroxybenzylidene)-1-benzylpiperidin-4-one (7g): ^{1}H NMR (DMSO-d_6, 400 MHz, δ; ppm) δ 4.45 (s, 6H, PhCH_2 and CH_2 piperidone), 7.05-7.40 (m, 9H, benzene protons), 7.62 (s, 2H, PhC*H*), 7.74 (s, 2H, benzene protons), 11.14 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-d_6, 400 MHz, δ; ppm) δ 53.40 (2C), 64.40, 113.70 (2C), 118.0 (2C), 127.20, 128.40 (2C), 128.70 (2C), 128.80 (2C), 129.60 (2C), 131.30 (2C), 132.60, 140.60 (2C), 145.90 (2C), 155.80 (2C), 186.0 ppm; MS (EI): *m*/*z*: 554.99 $(M)^+$

3,5-bis(3-bromo-4-hydroxybenzylidene)-1-(2-methylbenzyl)piperidin-4-one (8a): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 2.41 (s, 3H, C*H*$_3$), 4.54 (s, 6H, PhC*H*$_2$ and C*H*$_2$ piperidone), 7.06-7.34 (m, 7H, benzene protons), 7.48-7.51 (t, 1H, benzene proton), 7.61 (s, 2H, PhC*H*), 7.73 (s, 2H, benzene protons), 11.17 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 18.80, 53.40 (2C), 60.70, 113.70 (2C), 118.0 (2C), 125.40, 127.10, 128.70 (2C), 129.60 (2C), 129.90, 131.30 (2C), 136.60, 137.70, 140.60 (2C), 145.90 (2C), 155.80 (2C), 186.0 ppm; MS (EI): *m*/*z*: 569.00 $(M)^+$.

3,5-bis(3-bromo-4-hydroxybenzylidene)-1-(3-methylbenzyl)piperidin-4-one (8b): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 2.17 (s, 3H, C*H*$_3$), 4.50 (s, 6H, PhC*H*$_2$ and C*H*$_2$ piperidone), 7.00-7.40 (m, 8H, benzene protons), 7.50 (s, 2H, PhC*H*), 7.66 (s, 2H, benzene protons), 11.15 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 21.60, 53.40 (2C), 64.70, 113.70 (2C), 118.0 (2C), 125.80, 127.50, 128.30, 128.70 (2C), 129.60 (2C), 130.70, 131.30 (2C), 138.10, 138.50, 140.60 (2C), 145.90 (2C), 155.80 (2C), 186.0 ppm; MS (EI): *m*/*z*: 569.00 $(M)^+$.

3,5-bis(3-bromo-4-hydroxybenzylidene)-1-(4-methylbenzyl)piperidin-4-one (8c): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 2.23 (s, 3H, C*H*$_3$), 4.42 (s, 4H, C*H*$_2$ piperidone), 4.49 (s, 2H, PhC*H*$_2$), 7.05-7.40 (m, 8H, benzene protons), 7.62 (s, 2H, PhC*H*), 7.74 (s, 2H, benzene protons), 11.14 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 21.30, 53.40 (2C), 64.40, 113.70 (2C), 118.0 (2C), 128.70 (4C), 129.60 (2C), 130.0 (2C), 131.30 (2C), 135.60, 136.90, 140.60 (2C), 145.90 (2C), 155.80 (2C), 186.0 ppm; MS (EI): *m*/*z*: 569.00 $(M)^+$.

3,5-bis(3-bromo-4-hydroxybenzylidene)-1-(2-chlorobenzyl)piperidin-4-one (8d): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 4.52 (s, 6H, PhC*H*$_2$ and C*H*$_2$ piperidone), 7.04-7.07 (d, 2H, benzene protons), 7.32-7.37 (m, 4H, benzene protons), 7.50-7.53 (d, 1H, benzene proton), 7.62 (s, 2H, PhC*H*), 7.69 (s, 2H, benzene protons), 11.17 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 53.40 (2C), 58.10, 113.70 (2C), 118.0 (2C), 126.50, 128.50, 128.60, 128.70 (2C), 129.60 (2C), 131.30 (2C), 134.10, 136.30, 140.60 (2C), 145.90 (2C), 155.80 (2C), 186.0 ppm; MS (EI): *m*/*z*: 588.95 $(M)^+$.

3,5-bis(3-bromo-4-hydroxybenzylidene)-1-(4-chlorobenzyl)piperidin-4-one (8f): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 4.45 (s, 6H, PhC*H*$_2$ and C*H*$_2$ piperidone), 7.05-7.07 (d, 2H, benzene protons), 7.31-7.33 (d, 2H, benzene protons), 7.39-7.41 (d, 2H, benzene protons), 7.54-7.56 (d, 2H, benzene protons), 7.61 (s, 2H, PhC*H*), 7.73 (s, 2H, benzene protons), 11.14 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 53.40 (2C), 64.40, 113.70 (2C), 118.0 (2C), 128.50 (2C), 128.70 (2C), 129.60 (2C), 131.20 (2C), 131.30 (2C), 132.80, 136.70, 140.60 (2C), 145.90 (2C), 155.80 (2C), 186.0 ppm; MS (EI): *m*/*z*: 588.95 $(M)^+$.

3,5-bis(3-bromo-4-hydroxybenzylidene)-1-(2-methoxybenzyl)piperidin-4-one (8g): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 3.69 (s, 3H, OC*H*$_3$), 4.44 (s, 2H, PhC*H*$_2$), 4.51 (s, 4H, C*H*$_2$ piperidone), 6.90-7.33 (m, 8H, benzene protons), 7.63 (s, 2H, PhC*H*), 7.74 (s, 2H, benzene protons), 11.14 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 53.40 (2C), 56.10, 57.30, 112.0, 113.70 (2C), 118.0 (2C), 120.70, 126.50, 128.20, 128.70 (2C), 129.60 (2C), 129.80, 131.30 (2C), 140.60 (2C), 145.90 (2C), 155.80 (2C), 158.40, 186.0 ppm; MS (EI): *m*/*z*: 585.00 $(M)^+$.

3,5-bis(3-bromo-4-hydroxybenzylidene)-1-(3-methoxybenzyl)piperidin-4-one (8h): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 3.69 (s, 3H, OC*H*$_3$), 4.44 (s, 2H, PhC*H*$_2$), 4.51 (s, 4H, C*H*$_2$ piperidone), 7.00-7.33 (m, 8H, benzene protons), 7.63 (s, 2H, PhC*H*), 7.74 (s, 2H, benzene protons), 11.14 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 53.40 (2C), 55.80, 64.70, 112.80, 112.90, 113.70 (2C), 118.0 (2C), 128.70 (2C), 129.40, 129.60 (2C), 131.30 (2C), 140.60 (2C), 140.90, 145.90 (2C), 155.80 (2C), 160.30, 186.0 ppm; MS (EI): *m*/*z*: 585.00 $(M)^+$.

3,5-bis(3-bromo-4-hydroxybenzylidene)-1-(4-methoxybenzyl)piperidin-4-one (8i): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 3.70 (s, 3H, OC*H*$_3$), 4.44 (s, 2H, PhC*H*$_2$), 4.51 (s, 4H, C*H*$_2$ piperidone), 4.43 (s, 2H, PhC*H*$_2$), 4.50 (s, 4H, C*H*$_2$ piperidone), 7.05-7.33 (m, 8H, benzene protons), 7.63 (s, 2H, PhC*H*), 7.74 (s, 2H, benzene protons), 11.14 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 53.40 (2C), 55.80, 64.40, 113.70 (2C), 114.0 (2C), 118.0 (2C),

128.70 (2C), 129.60 (2C), 130.90, 131.30 (2C), 132.40, 140.60 (2C), 145.90 (2C), 155.80 (2C), 159.10, 186.0 ppm; MS (EI): *m*/*z*: 585.00 $(M)^+$.

3,5-bis(3-bromo-4-hydroxybenzylidene)-1-phenethylpiperidin-4-one (8j): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 2.70-2.73 (t, 2H, PhCH_2CH$_2$), 2.75-2.78 (t, 2H, PhCH$_2$CH_2), 4.55 (s, 4H, CH_2 piperidone), 7.10-7.45 (m, 9H, benzene protons), 7.48 (s, 2H, PhC*H*), 7.72 (s, 2H, benzene protons), 11.15 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 33.60, 53.80 (2C), 58.90, 113.70 (2C), 118.0 (2C), 125.90, 127.70 (2C), 128.60 (2C), 128.70 (2C), 129.60 (2C), 131.30 (2C), 139.40, 140.60 (2C), 145.90 (2C), 155.80 (2C), 186.0 ppm; MS (EI): *m*/*z*: 569.00 $(M)^+$.

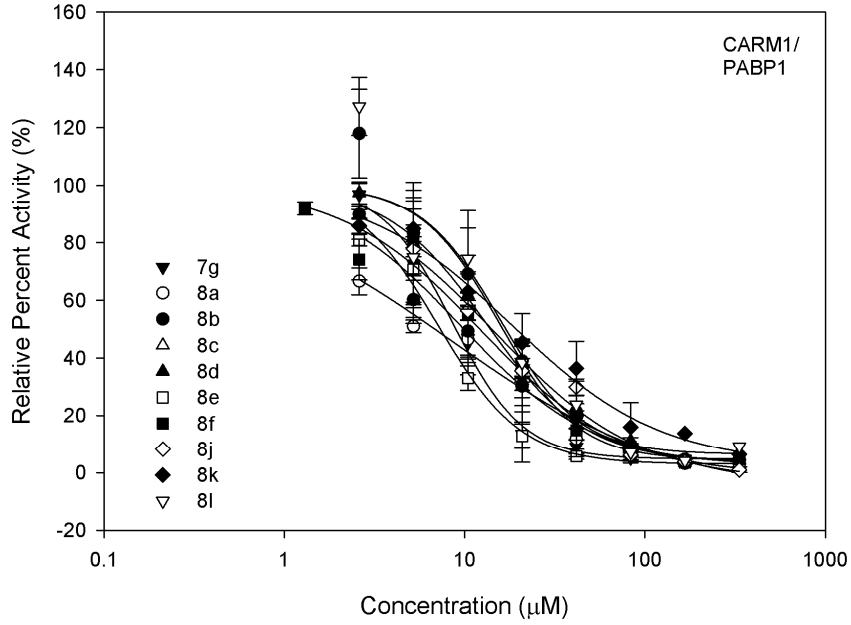
3,5-bis(3-bromo-4-hydroxybenzylidene)-1-(3-phenylpropyl)piperidin-4-one (8k): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 1.95-2.00 (m, 2H, PhCH$_2$CH_2CH$_2$), 2.50-2.53 (t, 2H, PhCH_2CH$_2$CH$_2$), 3.25-3.28 (t, 2H, PhCH$_2$CH$_2$CH_2), 4.55 (s, 4H, CH_2 piperidone), 7.09-7.37 (m, 9H, benzene protons), 7.71 (s, 2H, PhC*H*), 7.73 (s, 2H, benzene protons), 11.15 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 27.50, 31.0, 53.80 (2C), 57.0, 113.70 (2C), 118.0 (2C), 126.0, 128.10 (2C), 128.70 (2C), 128.80 (2C), 129.60 (2C), 131.30 (2C), 140.60 (2C), 142.0, 145.90 (2C), 155.80 (2C), 186.0 ppm; MS (EI): *m*/*z*: 583.02 $(M)^+$.

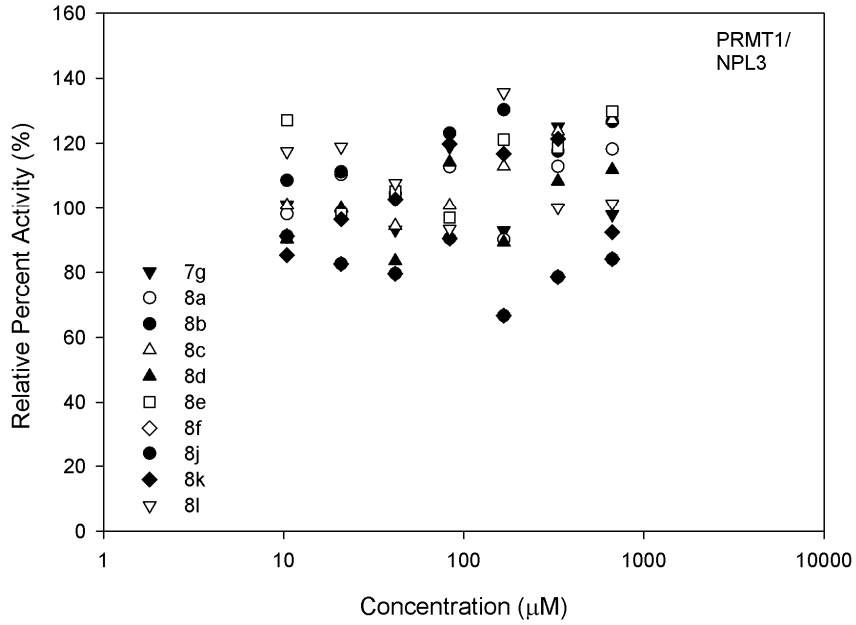
3,5-bis(3-bromo-4-hydroxybenzylidene)-1-(2-oxo-2-phenylethyl)piperidin-4-one (8l): ^{1}H NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 3.92 (s, 4H, CH_2 piperidone), 4.22 (s, 2H, PhCOCH_2), 6.97-7.00 (d, 2H, benzene protons), 7.27-7.30 (d, 2H, benzene protons), 7.44-7.60 (m, 7H, PhC*H* and benzene protons), 7.92-7.95 (d, 2H, benzene protons), 10.85 (bs, 2H, O*H*) ppm; ^{13}C NMR (DMSO-*d*6, 400 MHz, δ; ppm) δ 53.30 (2C), 70.90, 113.70 (2C), 118.0 (2C), 128.60 (2C), 128.70 (2C), 128.80 (2C), 129.60 (2C), 131.30 (2C), 133.10, 135.10, 140.60 (2C), 145.90 (2C), 155.80 (2C), 186.0, 195.30 ppm; MS (EI): *m*/*z*: 582.98 $(M)^+$.

Plasmids and antibodies. All amplified fragments were subcloned into a glutathione S-transferase (GST) bacterial expression vector pGEX-6p-1 (Amersham Biosciences). GST-PABP1,[3] GST-SMB,[4] GST-rPS2[5] and GST-CA150[6] have been described. GST-PRMT1, GST-PRMT3, GST-PRMT4, and GST-PRMT6 have been described.[7] GST-Npl3 was a gift from Pam Silver and has been described previously.[8] GST-Suv39H1 was a gift from Thomas Jenuwein.[9] GST-SET7 and GST-DOT1 were gifts from Yi Zhang.[10] GST-G9a was a gift from Yoichi Shinkai.[11] Myc-PRMT5 was a gift from Stéphane Richard. The PSA-LUC plasmid was kindly provided by Dr. Roland Schüle (Freiburg, Germany).[48] Histones H3 and H4 (calf thymus) were purchased from Roche Applied Science. The methyl-specific PABP1 antibody was raised in rabbits against peptides sequence (CGAIR*PAAPR*PPFS) of PABP1. The anti-FLAG antibody M2 and anti-β-actin antibodies were purchased from Sigma-Aldrich, and anti-c-Myc antibody from Covance.

Cell lines and cultures. A stable/inducible T-Rex-3XFlag-PABP1 cell line was established by transfection with pcDNA/FRT/TO-3XFlag-PABP1 and pOG44 plasmids into Flp-in T-Rex HEK293 cells (Invitrogen). Transfected cells were maintained in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum supplemented with 10 μg/mL blasticidin and 100 μg/mL hygromycin. The resistant single colony was picked up to propagate. The human prostate cancer cell lines LNCaP (American Type Tissue Collection) were grown in RPMI-1640 media with 10% fetal bovine serum (FBS) and antibiotics (penicillin 100 U/mL, streptomycin 100 μg/mL).

Figure S3. IC_{50} curves for **7g** and **8a-l** against CARM1/PABP1, PRMT1/NPL3, and SET7/H3.





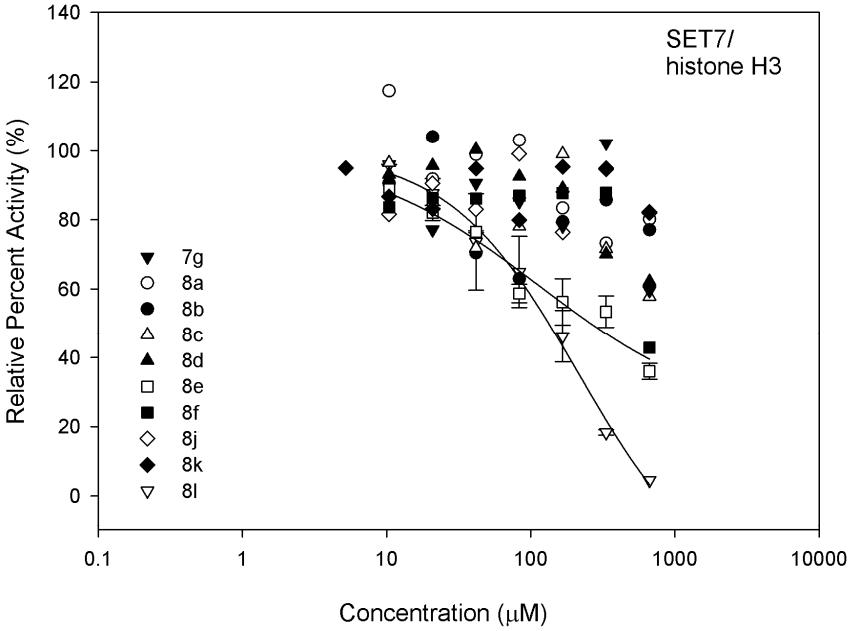
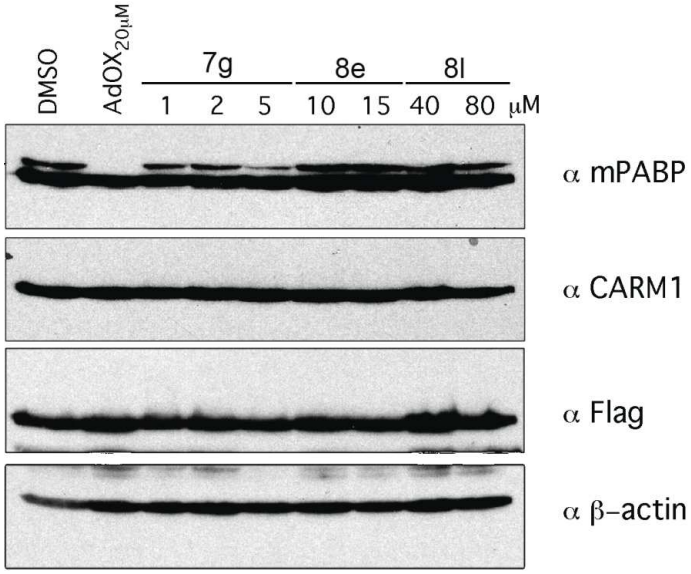


Figure S4. Effects of **7g**, **8e**, and **8l** on Flag-PABP1 methylation in stable Flag-tagged PABP1-inducible HEK293 cells.



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