Supplementary Materials

In Silico Prediction of O^6-Methylguanine-DNA Methyltransferase Inhibitory Potency of Base analogs with QSAR and Machine Learning Methods

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Figure S1

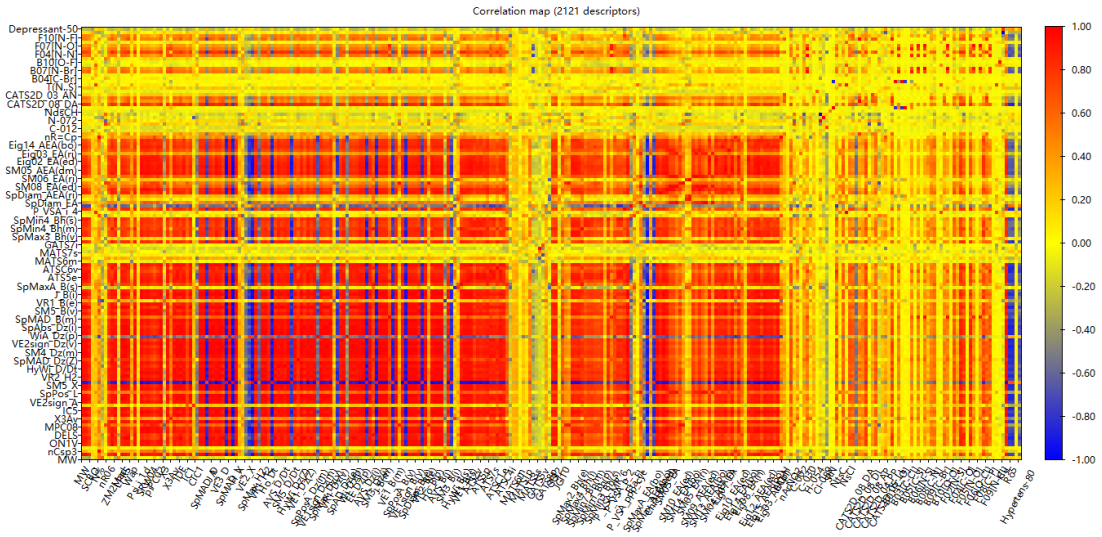


Figure S1. Description of correlated descriptors for all compounds in this study.

Table S2. Fitting and internal validation parameters of initial QSAR models selected by MCDM.

Fitting and internal validation parameters

No.	Model No.	Number of descriptors	Descriptors	R^2	R^2_{adj}	$RMSE_{tr}$	CCC_{tr}	F	Q^2_{loo}	$RMSE_{cv}$	CCC_{cv}	R^2_{Yscr}	Q^2_{Yscr}
1	**54**	**5**	**J_Dz(p), VE1sign_B(i), GATS1p, JGI4, CATS2D_05_AA**	**0.68**	**0.66**	**0.87**	**0.81**	**32.9383**	**0.6367**	**0.9338**	**0.7850**	**0.0591**	**-0.0978**
2	56	5	J_Dz(p), VE3sign_B(s), GATS2m, GATS1p, CATS2D_07_PL	0.68	0.66	0.88	0.81	32.60	0.64	0.93	0.79	0.06	-0.10
3	58	5	J_Dz(p), VE3sign_B(s), GATS1p, GATS2p, CATS2D_07_PL	0.67	0.64	0.89	0.80	31.33	0.62	0.94	0.78	0.06	-0.10
4	59	5	J_Dz(p), SpMAD_B(m), JGI4, CATS2D_05_AA, CATS2D_07_PL	0.67	0.65	0.89	0.80	31.28	0.63	0.94	0.78	0.06	-0.10

External validation parameters

No.	Model No.	Number of descriptors	R^2_{ext}	$RMSE_{ext}$	Q^2_{F1}	Q^2_{F2}	Q^2_{F3}	CCC_{ext}	MAE_{ext}	r^2_m	Δr^2_m	k	k′	$(R^2_{ext} - R_0^2)/R^2_{ext}$	$(R^2_{ext} – R'^2_0)/R^2_{ext}$
1	**54**	**5**	**0.78**	**0.75**	**0.76**	**0.76**	**0.77**	**0.88**	**0.58**	**0.69**	**0.02**	**0.97**	**1.01**	**0.01**	**0.02**
2	56	5	0.77	0.82	0.71	0.71	0.72	0.87	0.71	0.68	0.19	0.98	0.99	0	0.08
3	58	5	0.75	0.79	0.73	0.73	0.74	0.87	0.66	0.65	0.01	0.99	0.98	0.03	0.02
4	59	5	0.73	0.90	0.65	0.65	0.66	0.85	0.75	0.63	0.10	1.02	0.95	0.01	0.06

Table S3. Fitting and internal validation parameters of further QSAR models selected by MCDM.

Fitting and internal validation parameters

No.	Model No.	Number of descriptors	Descriptors	R^2	R^2_{adj}	$RMSE_{tr}$	CCC_{tr}	F	Q^2_{loo}	$RMSE_{cv}$	CCC_{cv}	R^2_{Yscr}	Q^2_{Yscr}
1	**4**	**9**	**VE3sign_X, J_Dz(p), SpPosA_B(p), VE3sign_B(s), MATS1i, JGI4, nArNH2, CATS2D_07_DA, B09[C-C]**	**0.87**	**0.85**	**0.53**	**0.93**	**44.06**	**0.82**	**0.62**	**0.91**	**0.13**	**-0.22**
2	13	9	VE3sign_X, J_Dz(p), SpPosA_B(p), VE3sign_B(s), MATS1i, GATS6e, JGI4, B05[N-O], B09[C-C]	0.87	0.85	0.54	0.93	41.59	0.82	0.62	0.90	0.13	-0.21
3	22	8	VE3sign_X, J_Dz(p), SpPosA_B(p), VE3sign_B(s), MATS1i, JGI4, B09[C-C], F05[N-O]	0.85	0.83	0.57	0.92	43.01	0.81	0.64	0.90	0.12	-0.19
4	23	8	VE3sign_X, J_Dz(p), SpPosA_B(p), MATS1i, GATS1p, JGI4, CATS2D_07_DA, B09[C-C]	0.85	0.83	0.57	0.92	42.89	0.81	0.64	0.90	0.12	-0.18
5	25	8	VE3sign_X, J_Dz(p), SpPosA_B(p), VE3sign_B(s), MATS1i, JGI4, B05[N-O], B09[C-C]	0.85	0.83	0.57	0.92	42.49	0.81	0.65	0.90	0.12	-0.19

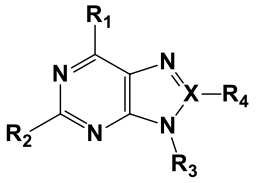
External validation parameters

No.	Model No.	Number of descriptors	R^2_{ext}	$RMSE_{ext}$	Q^2_{F1}	Q^2_{F2}	Q^2_{F3}	CCC_{ext}	MAE_{ext}	r^2_m	Δr^2_m	k	k′	$(R^2_{ext} - R_0^2)/R^2_{ext}$	$(R^2_{ext} – R'^2_0)/R^2_{ext}$
1	**4**	**9**	**0.69**	**0.79**	**0.67**	**0.67**	**0.71**	**0.83**	**0.70**	**0.58**	**0.01**	**0.99**	**0.99**	**0.04**	**0.03**
2	13	9	0.69	0.77	0.6900	0.69	0.73	0.83	0.71	0.57	0.16	0.98	1.00	0.12	0.004
3	22	8	0.62	0.85	0.62	0.62	0.67	0.78	0.75	0.49	0.17	0.99	0.99	0.19	0.01
4	23	8	0.55	0.97	0.50	0.50	0.57	0.74	0.84	0.41	0.05	0.98	0.98	0.16	0.08
5	25	8	0.59	0.9048	0.57	0.57	0.63	0.77	0.81	0.46	0.10	0.98	0.99	0.16	0.04

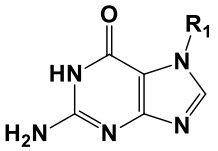
Table S4. Statistical description of compounds used in the training and test sets

Data sets	Inhibitors	Non-inhibitors	Total
Training set	50	54	104
External test set	12	13	25
Total	62	67	129

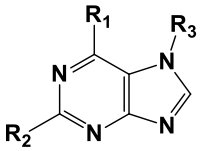
Table S6. Chemical structures and experimental activity values (pIC_{50}) of base analogs as MGMT inhibitors.



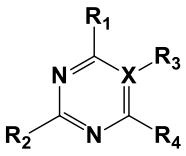
1~3, 5~17, 23~40, 42~117



4



18~22, 41



118~134

General molecular structures of all compounds used in this study.

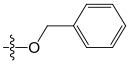
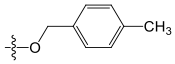
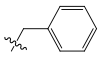
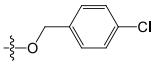
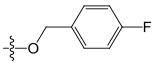
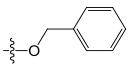
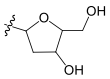
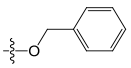
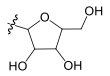
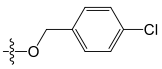
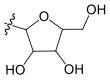
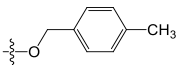
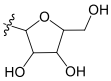
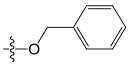
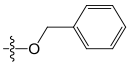
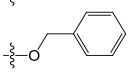
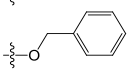
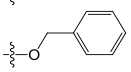
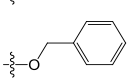
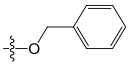
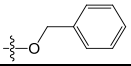
Comp.	R_1	R_2	R_3	R_4	X	pED_{50}
1[a]	-OCH_3	-NH_2	H	H	C	3.46(N^1)
2		-NH_2	H	H	C	6.70(P^2)
3		-NH_2	H	H	C	6.70(P)
4[b]		/	/	/	/	3.40(N)
5		-NH_2	H	H	C	6.70(P)
6[b,c]		-NH_2	H	H	C	6.70(P)
7[a]		-NH_2		H	C	5.70(P)
8		-NH_2		H	C	4.96(N)
9		-NH_2		H	C	5.00(P)
10[c]		-NH_2		H	C	5.05(P)
11[a,c]	-$OCH_2CH{=}CH_2$	-NH_2	H	H	C	4.70(N)
12[c]		-NH_2	-$CH_2COOCH_2CH_3$	H	C	4.52(N)
13		-NH_2	-CH_2COOH	H	C	3.80(N)
14[b]		-NH_2	-$CH_2C{\equiv}CH$	H	C	4.89(N)
15[a]		-NH_2	-CH_2CONH_2	H	C	4.33(N)
16[a]		-NH_2	-$CH_2CH(OH)CH_2$-CH_3	H	C	4.89(N)
17[a,c]		H	H	H	C	4.07(N)
18		-NH_2	-$CH_2COOCH_2CH_3$	/	/	3.40(N)
19		-NH_2	-CH_2COOH	/	/	3.40(N)

Table S3. *Cont.*

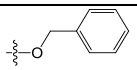
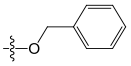
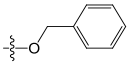
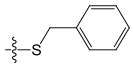
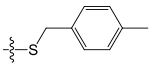
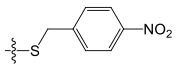
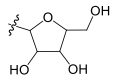
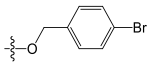
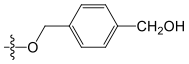
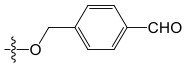
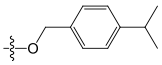
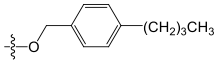
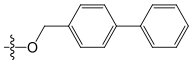
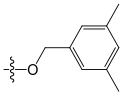
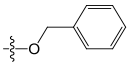
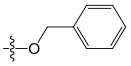
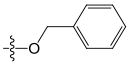
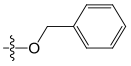
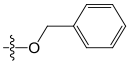
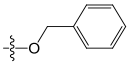
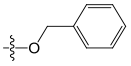
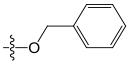
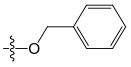
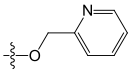
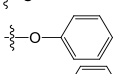
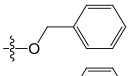
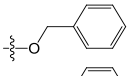
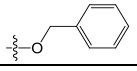
Comp.	R_1	R_2	R_3	R_4	X	pED_{50}
20[c]		$-NH_2$	$-CH_2C{\equiv}CH$	/	/	3.40(N)
21[a]		$-NH_2$	$-CH_2CONH_2$	/	/	3.40(N)
22[b]		$-NH_2$	$-CH_2CH(OH)CH_2CH_3$	/	/	3.40(N)
23		$-NH_2$	H	H	C	3.40(N)
24[c]		$-NH_2$	H	H	C	3.40(N)
25		$-NH_2$		H	C	3.40(N)
26[a]		$-NH_2$	H	H	C	6.52(P)
27		$-NH_2$	H	H	C	6.52(P)
28[a]		$-NH_2$	H	H	C	6.30(P)
29		$-NH_2$	H	H	C	6.30(P)
30		$-NH_2$	H	H	C	5.40(P)
31[c]		$-NH_2$	H	H	C	6.52(P)
32		$-NH_2$	H	H	C	6.00(P)
33		$-NH_2$	$-COCH_3$	H	C	6.40(P)
34		$-NH_2$	$-CH_3$	H	C	5.59(P)
35		$-NH_2$	$-CH_2OCOC(CH_3)_3$	H	C	5.51(P)
36		$-NH_2$	$-CH_2CH(OH)CH_2Cl$	H	C	4.74(N)
37		$-NH_2$	$-CH_2CH(OH)CH_2NH-CH(CH_3)_2$	H	C	3.97(N)
38		$-NH_2$	$-CH_2CH(OH)CH_2NH-C(CH_3)_3$	H	C	3.97(N)
39[a]		$-NH_2$	$-CH_2CH(OH)CH_2O-CH(CH_3)_2$	H	C	5.15(P)
40[b]		$-NHCOCH_3$	H	H	C	4.62(N)
41[a]		$-NH_2$	$-CH_3$	/	/	4.28(N)
42		$-NH_2$	H	H	C	4.24(N)
43		$-NH_2$	H	H	C	3.52(N)
44		$-NH_2$	H	$-NH_2$	C	6.15(P)
45		$-NH_2$	H	$-CH_3$	C	6.52(P)
46[b]		$-NH_2$	H	-OH	C	6.52(P)

Table S3. *Cont.*

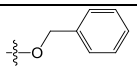
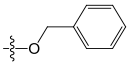
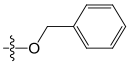
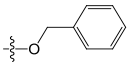
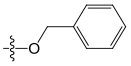
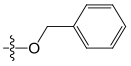
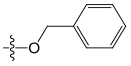
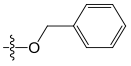
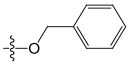
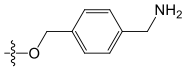
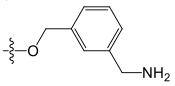
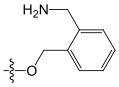
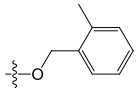
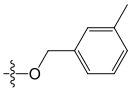
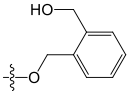
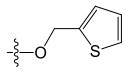
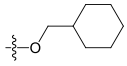
Comp.	R_1	R_2	R_3	R_4	X	pED_{50}
47[a,c]		$-NH_2$	H	-Br	C	7.10(P)
48		$-NH_2$	H	/	N	7.15(P)
49		$-NH_2$	H	-F	C	6.40(P)
50[c]		-OH	H	H	C	4.22(N)
51		-OH	H	-OH	C	4.60(N)
52[b]		-F	H	H	C	4.32(N)
53[b,c]		$-NHCOCH_3$	H	-OH	C	4.19(N)
54[a]		$-NHCH_3$	H	H	C	3.80(N)
55[b]		$-N(CH_3)_2$	H	H	C	3.70(N)
56		$-NH_2$	H	H	C	6.82(P)
57[b]		$-NH_2$	H	H	C	6.96(P)
58		$-NH_2$	H	H	C	4.28(N)
59[b]		$-NH_2$	H	H	C	3.91(N)
60[a,c]		$-NH_2$	H	H	C	6.77(P)
61		$-NH_2$	H	H	C	3.18(N)
62		$-NH_2$	H	H	C	8.52(N)
63	$-OCH_2CH_3$	$-NH_2$	H	H	C	<3.00(N)
64	$-O(CH_2)_2CH_3$	$-NH_2$	H	H	C	<3.00(N)
65[a,c]	$-O(CH_2)_3CH_3$	$-NH_2$	H	H	C	3.31(N)
66	$-O(CH_2)_2CH-(CH_3)_2$	$-NH_2$	H	H	C	<3.00(N)
67	$-O(CH_2)_4CH_3$	$-NH_2$	H	H	C	<3.00(N)
68	$-O(CH_2)_5CH_3$	$-NH_2$	H	H	C	3.26(N)
69[c]	$-O(CH_2)_6CH_3$	$-NH_2$	H	H	C	3.30(N)
70		$-NH_2$	H	H	C	<3.00(N)
71	$-OCH_2CH(=CH_2)-CH_3$	$-NH_2$	H	H	C	4.60(N)
72	$-O(CH_2)_4CH=CH_2$	$-NH_2$	H	H	C	/
73	(*Z*)-$O(CH_2)_2CH=CHCH_2CH_3$	$-NH_2$	H	H	C	/
74[a]	(*E*)-$O(CH_2)_2CH=CHCH_2CH_3$	$-NH_2$	H	H	C	<3.00(N)
75	$-O(CH_2)_2C\equiv CCH_2-CH_3$	$-NH_2$	H	H	C	/

Table S3. *Cont.*

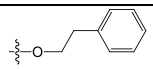
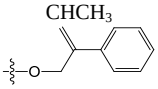
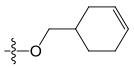
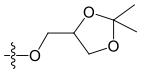
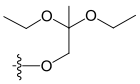
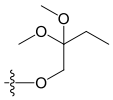
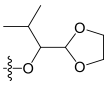
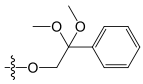
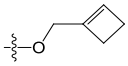
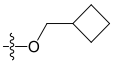
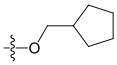
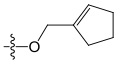
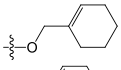
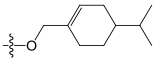
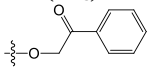
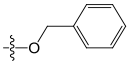
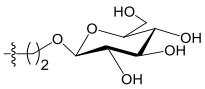
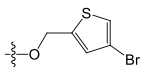
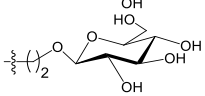
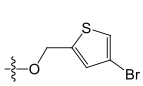
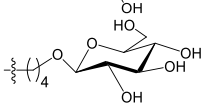
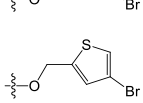
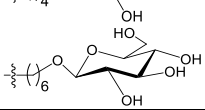
Comp.	R_1	R_2	R_3	R_4	X	pED_{50}
76		$-NH_2$	H	H	C	3.26(N)
77[c]	$-OCH_2CH(=CH_2)-CH_2CH_3$	$-NH_2$	H	H	C	4.80(N)
78	$-OCH_2CH(=CH_2)-CH_2(CH_3)_2$	$-NH_2$	H	H	C	<3.00(N)
79	$-OCH_2C(CH_3)=CHCH_3$	$-NH_2$	H	H	C	/
80		$-NH_2$	H	H	C	4.11(N)
81	$-OCH_2C\equiv CH$	$-NH_2$	H	H	C	4.70(N)
82		$-NH_2$	H	H	C	<3.00(N)
83		$-NH_2$	H	H	C	<3.00(N)
84		$-NH_2$	H	H	C	<3.00(N)
85[a]		$-NH_2$	H	H	C	<3.00(N)
86		$-NH_2$	H	H	C	/
87		$-NH_2$	H	H	C	<3.00(N)
88[b]		$-NH_2$	H	H	C	6.26(P)
89		$-NH_2$	H	H	C	<3.00(N)
90		$-NH_2$	H	H	C	<3.00(N)
91[b,c]		$-NH_2$	H	H	C	6.41(P)
92		$-NH_2$	H	H	C	5.80(P)
93[b]		$-NH_2$	H	H	C	5.59(P)
94	$-OCH_2COCH_3$	$-NH_2$	H	H	C	3.72(N)
95	$-OCH_2COCH_2-CH_3$	$-NH_2$	H	H	C	3.82(N)
96	$-OCH_2COCH-(CH_3)_2$	$-NH_2$	H	H	C	<3.00(N)
97[a,c]		$-NH_2$	H	H	C	<3.00(N)
98[b]		$-NH_2$		H	C	5.10(P)
99[a]		$-NH_2$		H	C	6.66(P)
100		$-NH_2$		H	C	6.82(P)
101		$-NH_2$		H	C	6.82(P)

Table S3. *Cont.*

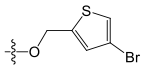
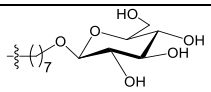
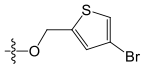
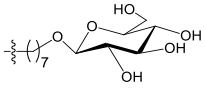
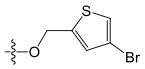
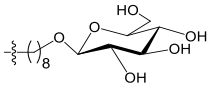
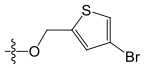
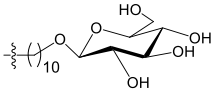
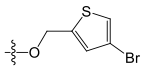
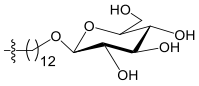
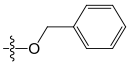
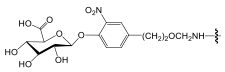
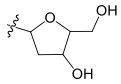
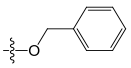
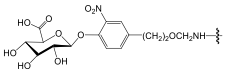
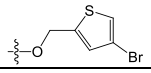
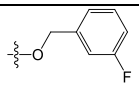
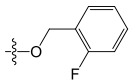
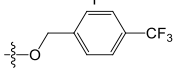
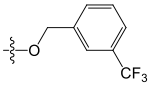
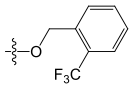
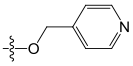
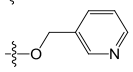
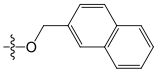
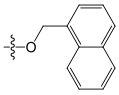
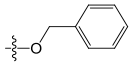
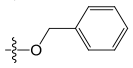
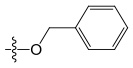
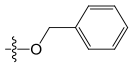
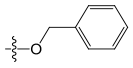
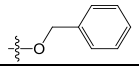
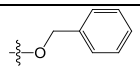
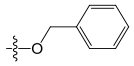
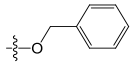
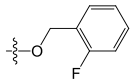
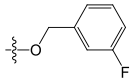
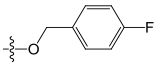
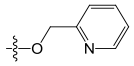
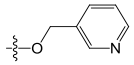
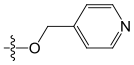
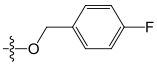
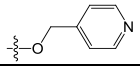
Comp.	R_1	R_2	R_3	R_4	X	pED_{50}
102		$-NH_2$		H	C	7.10(P)
102		$-NH_2$		H	C	7.10(P)
103		$-NH_2$		H	C	8.00(P)
104[b,c]		$-NH_2$		H	C	8.00(P)
105[a]		$-NH_2$		H	C	8.00(P)
106				H	C	4.30(N)
107[c]			H	H	C	4.30(N)
108		$-NH_2$	H	H	C	8.54(P)
ED_{50} values of 109~134 were determined on HeLa S3 cell extracts						
109		$-NH_2$	H	H	C	P
110		$-NH_2$	H	H	C	P
111		$-NH_2$	H	H	C	N
112		$-NH_2$	H	H	C	P
113		$-NH_2$	H	H	C	P
114		$-NH_2$	H	H	C	N
115[c]		$-NH_2$	H	H	C	P
116[c]		$-NH_2$	H	H	C	P
117[c]		$-NH_2$	H	H	C	N
118		H	$-NO_2$	$-NH_2$	C	N
119		$-NH_2$	H	$-NH_2$	C	N
120		$-NH_2$	$-NH_2$	$-NH_2$	C	P
121[c]		$-NH_2$	-NO	$-NH_2$	C	P
122		$-NH_2$	$-NO_2$	$-NH_2$	C	P
123[c]		$-NH_2$	-Br	$-NH_2$	C	P

Table S3. *Cont.*

Comp.	R_1	R_2	R_3	R_4	X	pED_{50}
124		$-NH_2$	$-NO_2$	H	C	P
125		$-NH_2$	$-NO_2$	$-CH_3$	C	P
126[c]		$-NH_2$	/	$-NH_2$	N	P
127		$-NH_2$	$-NO_2$	$-NH_2$	C	P
128		$-NH_2$	$-NO_2$	$-NH_2$	C	P
129		$-NH_2$	$-NO_2$	$-NH_2$	C	P
130		$-NH_2$	$-NO_2$	$-NH_2$	C	P
131		$-NH_2$	$-NO_2$	$-NH_2$	C	P
132		$-NH_2$	$-NO_2$	$-NH_2$	C	P
133		$-NH_2$	-NO	$-NH_2$	C	P
134		$-NH_2$	-NO	$-NH_2$	C	P

[1] "N" represents MGMT non-inhibitors;

[2] "P" represents MGMT inhibitors;

[a] Test set in initial QSAR study (Model I);

[b] Test set in further QSAR study (Model II);

[c] Test set in classification study.