Supporting Information

Small Molecule Inhibitors of Histone Arginine Methyltransferases: Homology Modeling, Molecular Docking, Binding Mode Analysis and Biological Evaluations.

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Elemental analysis of compounds 6e, 6f, 9, 10b, 10c and 17.

Table A. Elemental Analysis of Compounds 6e,f, 9, 10b,c, and 17.

compd	Formula	calcd, %						found, %					
		C	H	Br	Cl	N	S	C	H	Br	Cl	N	S
6e	$C_{20}H_7Br_6NO_5$	29.27	0.86	58.42	-	1.71	-	29.21	0.86	58.27	-	1.72	-
6f	$C_{23}H_{12}Cl_2N_4O_5$	55.78	2.44	-	14.32	11.31	-	55.89	2.44	-	14.29	11.28	-
9	$C_{21}H_{16}N_2O_9S_2$	50.00	3.20	-	-	5.55	12.71	50.12	3.19	-	-	5.54	12.68
10b	$C_{17}H_{14}N_2O_5S$	56.98	3.94	-	-	7.82	8.95	57.12	3.89	-	-	7.80	8.93
10c	$C_{17}H_{14}N_2O_4S_2$	54.53	3.77	-	-	7.48	17.13	53.97	3.76	-	-	7.50	16.88
17	$C_{10}H_6Cl_2N_4O_2$	42.13	2.12	-	24.87	19.65	-	42.21	2.11	-	24.81	19.69	-

Figure A.
Plot of the hPRMT1/RmtA pIC_{50}correlation

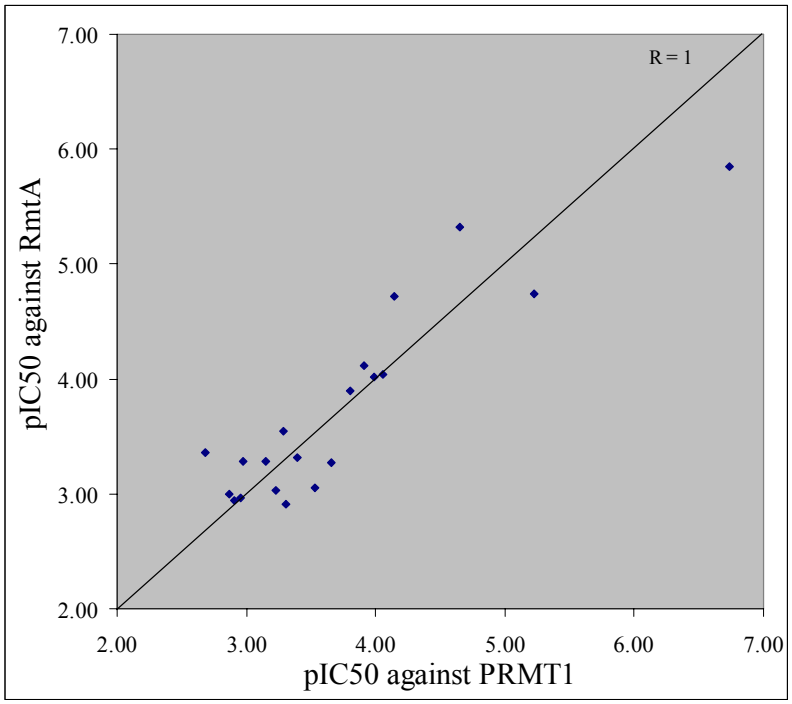
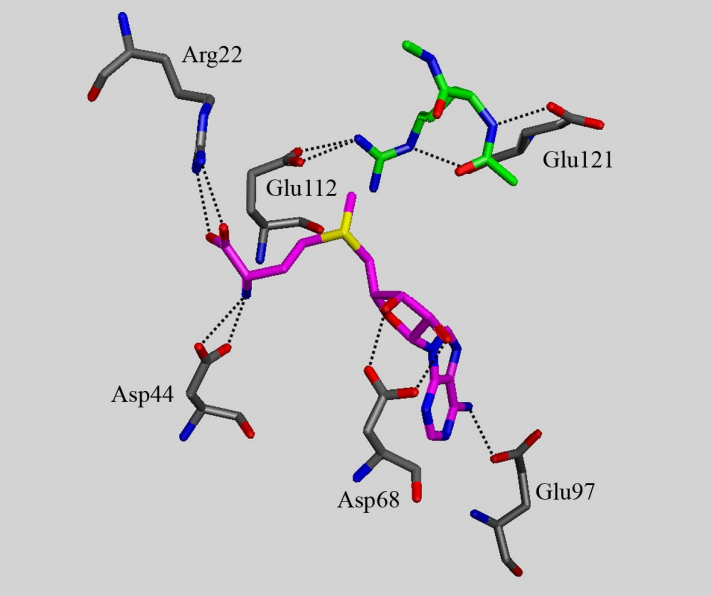


Figure B.

Construction of the RmtA-SAM-H4 ternary complex.

By homology modeling we built the 3-D structure of RmtA. The RmtA/SAM/H4 ternary complex was then built and refined by molecular mechanics calculations. Similarly as reported,[1] SAM and Arg pockets lie close each other to allow the monomethylation or the dimethylation of the arginine side chain guanidino nitrogen atoms (main text, Figure 2). A deeper inspection let us to distinguish different interactions of SAM with RmtA aminoacids. The amino group of adenine makes a hydrogen bond with the acid residue of Glu97 (2.7 Å), while the ribose hydroxyl oxygens form bifurcated hydrogen bonds with the carboxyl group of Asp68 (2.5 and 2.7 Å). Other important interactions concern the SAM methioninic moiety: the amino-terminal group can make an hydrogen bond with Asp44 carboxyl group (2.9 Å) and the carboxyl portion with Arg22 guanidine nitrogen atom (2.8 Å). Moreover, van der Waals contacts with the Gly46 and Gly48 backbone are also made.

On the substrate side, the Arg residue presents significant interactions with two RmtA residues. In particular, the Arg guanidino nitrogen atoms makes two strong hydrogen bonds with the carboxylic and carbonylic group of Glu112 (2.8 and 2.9 Å) and one with Glu121 carboxylate (2.9 Å). One further interaction can be observed between the Arg amidic nitrogen and Glu121 amidic carbonyl group (2.8 Å).



SAM (carbon atoms in magenta) and Arg (carbon atoms in green) binding modes into RmtA (carbon atoms in dark gray). For sake of clarity hydrogen atoms are not displayed.

Figure C.
Binding mode of compound 6a.

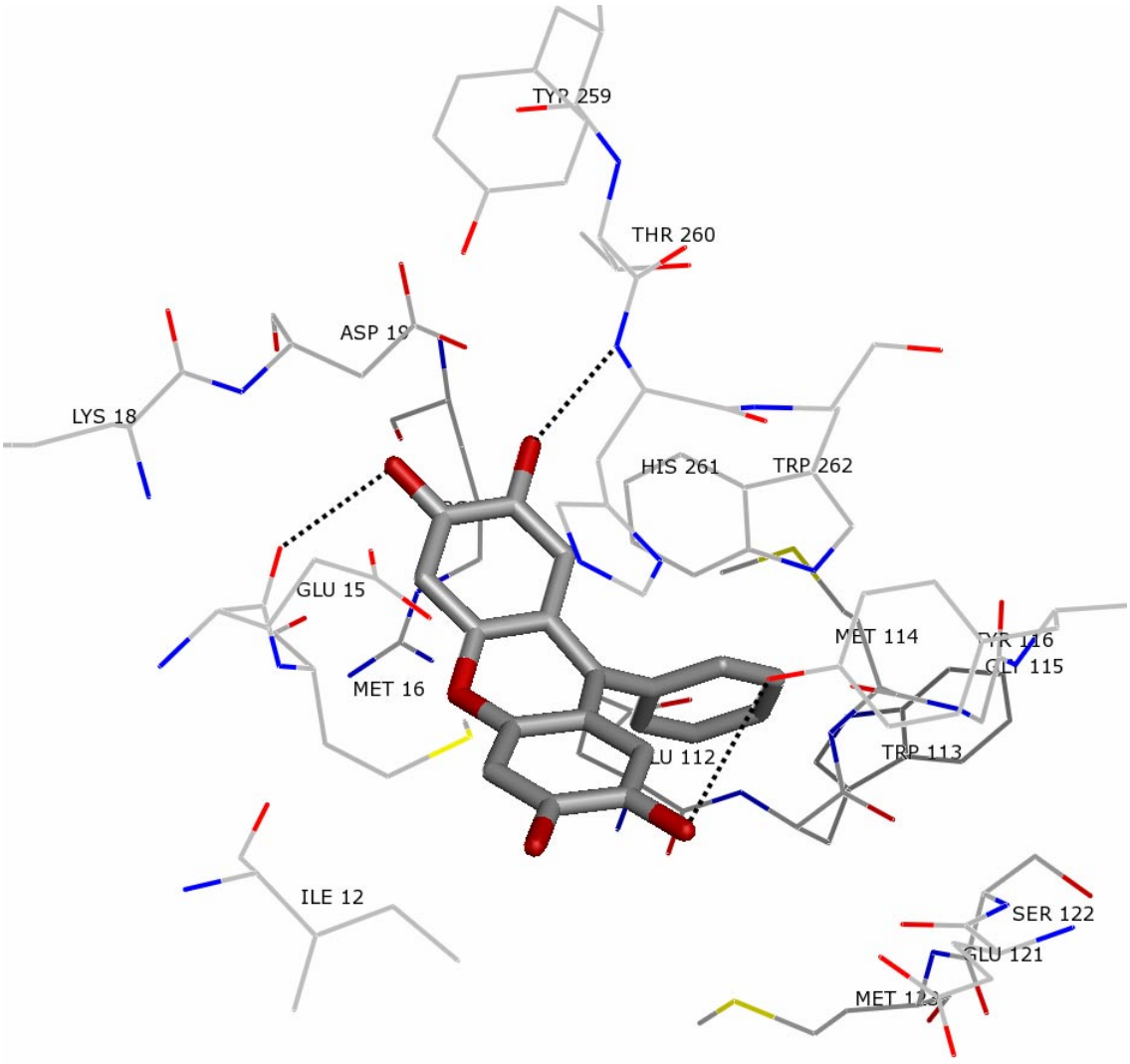


Figure D.
Binding mode of compound 12.

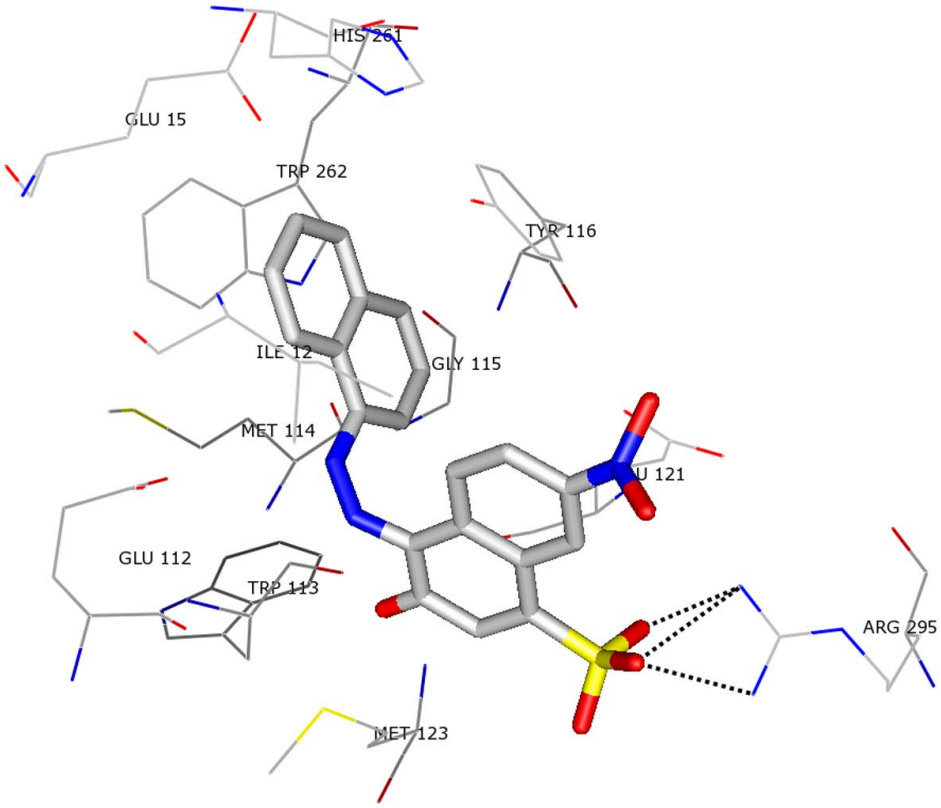


Figure E.
Binding mode of compound 13, 16b and 17.

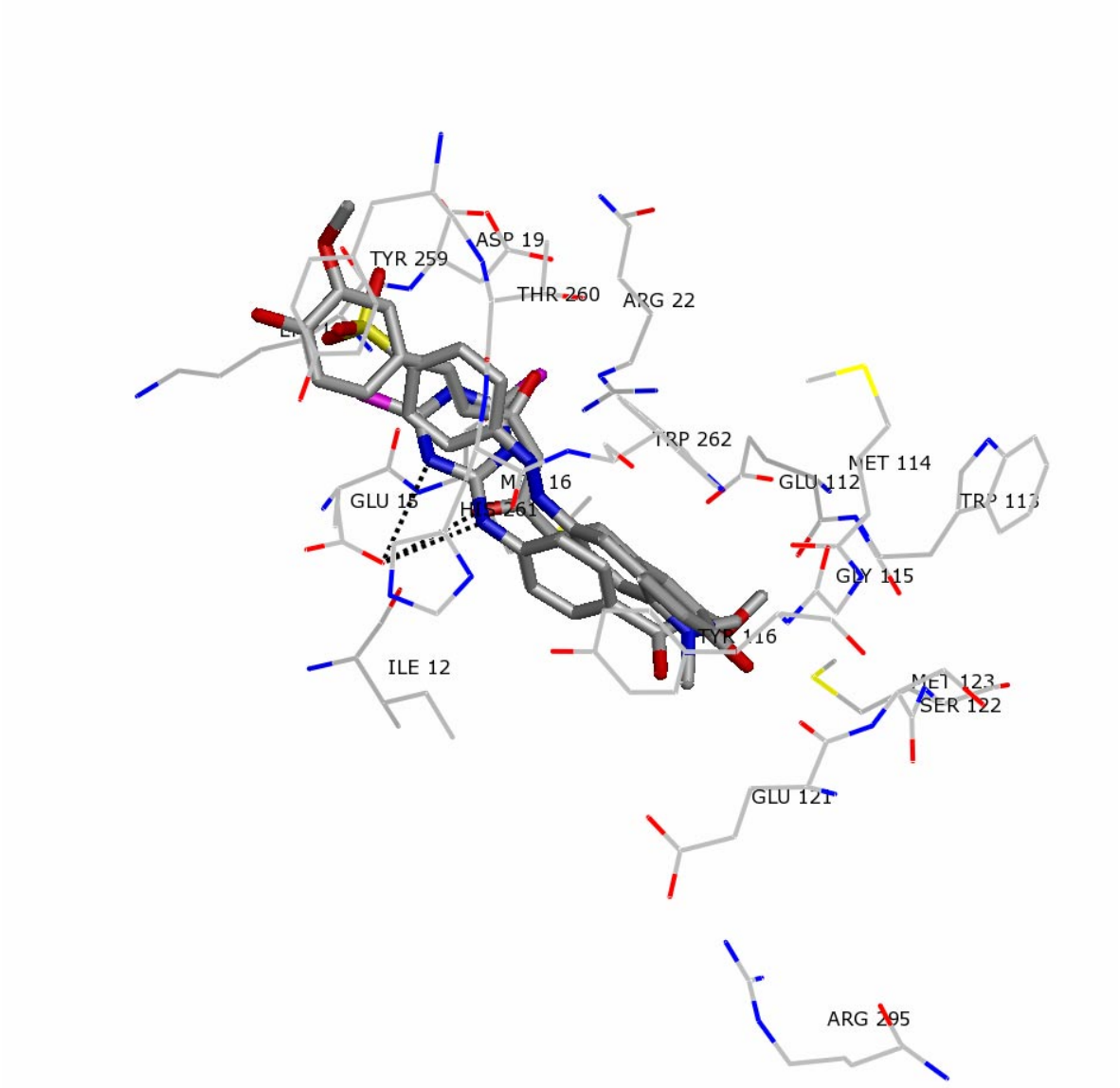
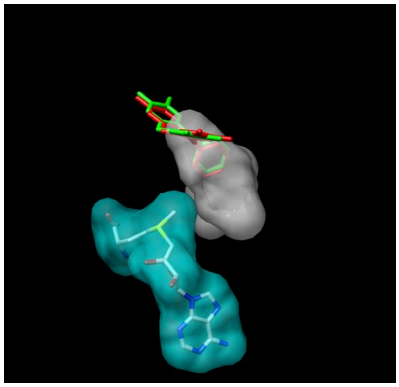
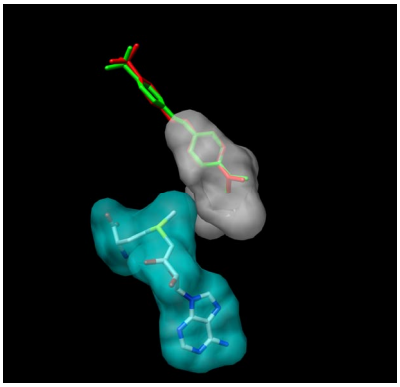


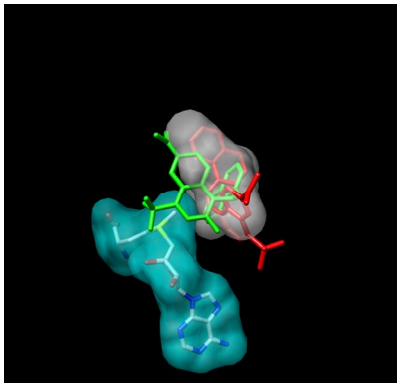
Figure F.
Binding modes of DAP group compounds in the presence of SAM.



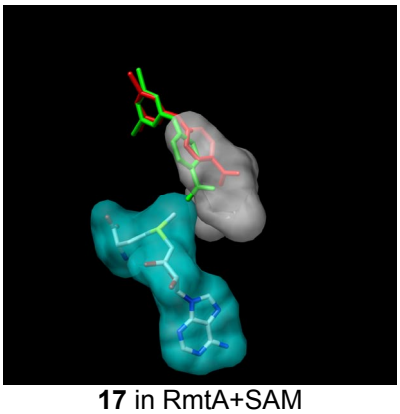
6a in RmtA+SAM



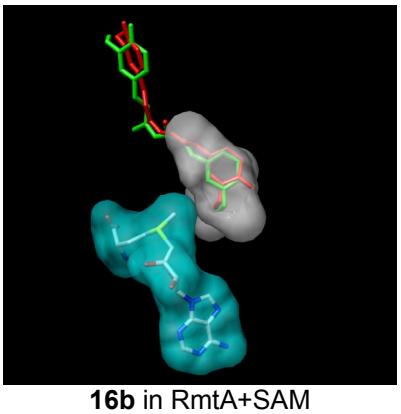
13 in RmtA+SAM



12 in RmtA+SAM



17 in RmtA+SAM



16b in RmtA+SAM

Figure G.
Binding mode of compound 6b and 6d.

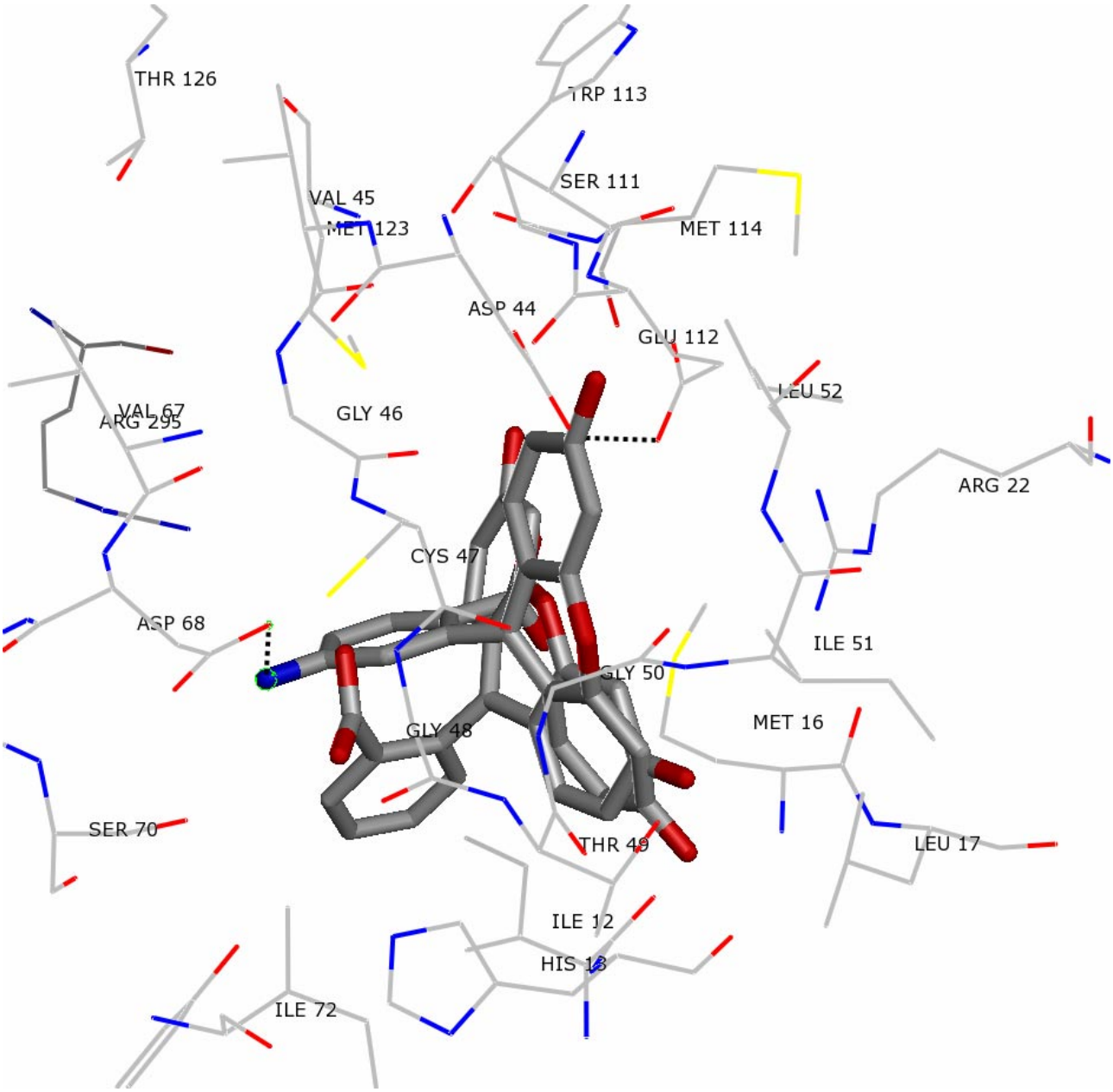


Figure H.
Binding mode of compound 10a and 18.

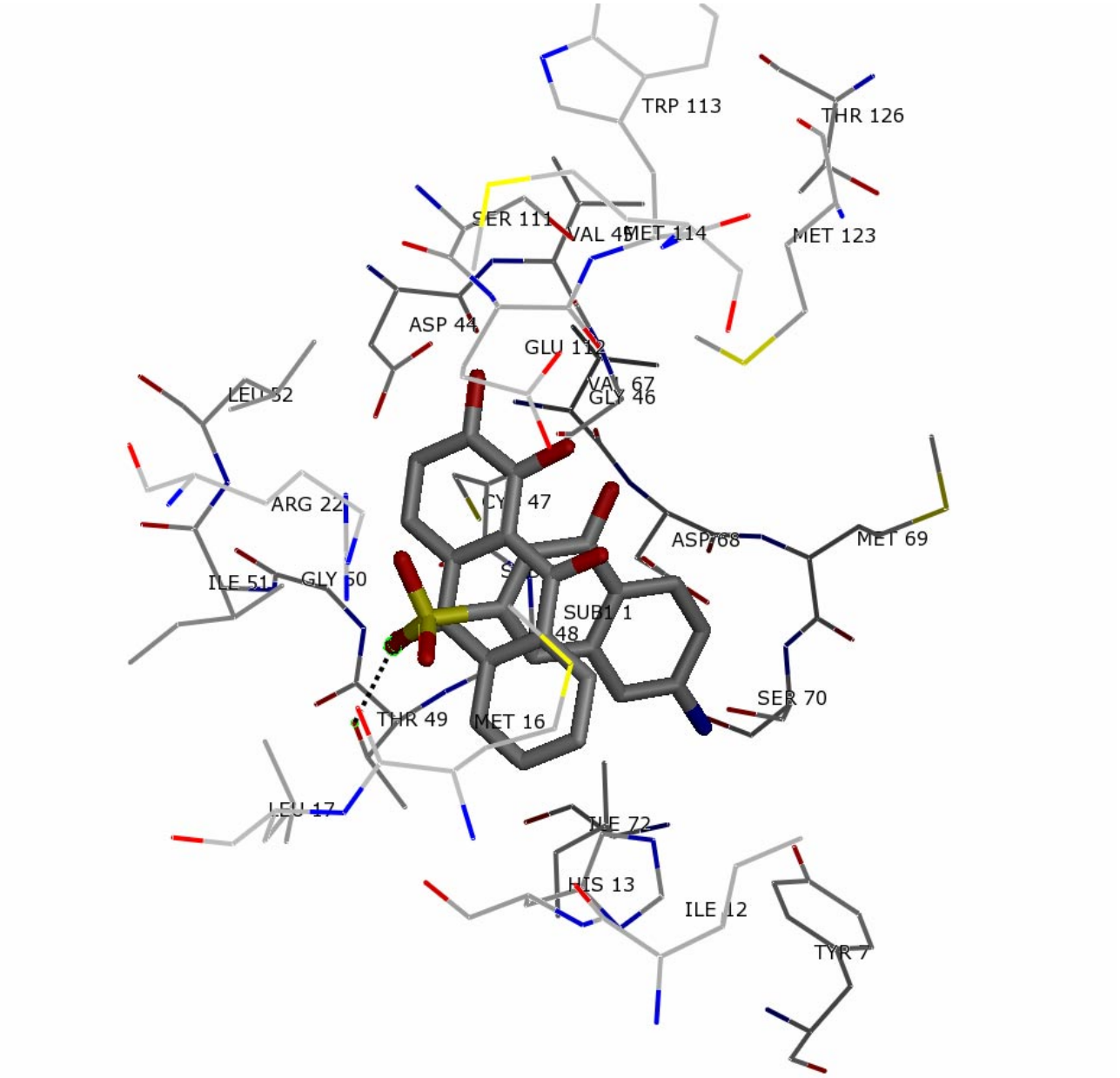


Figure I.
Binding mode of DBP group compounds.

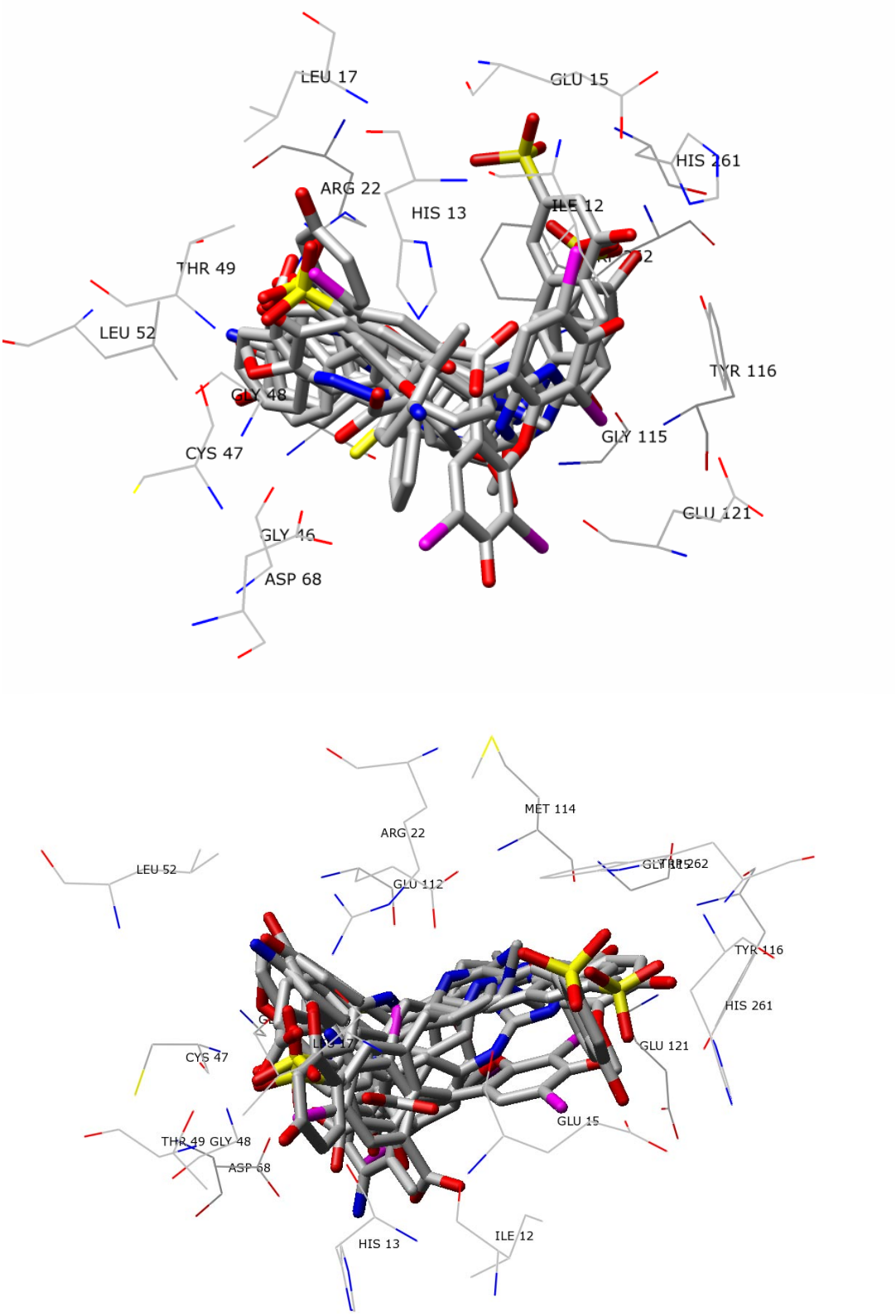


Figure J.
Binding mode of compound 6e.
The surface of the compound is displayed in green. For comparison purpose the Arg (yellow) and SAM (cyan) binding site areas are also displayed.

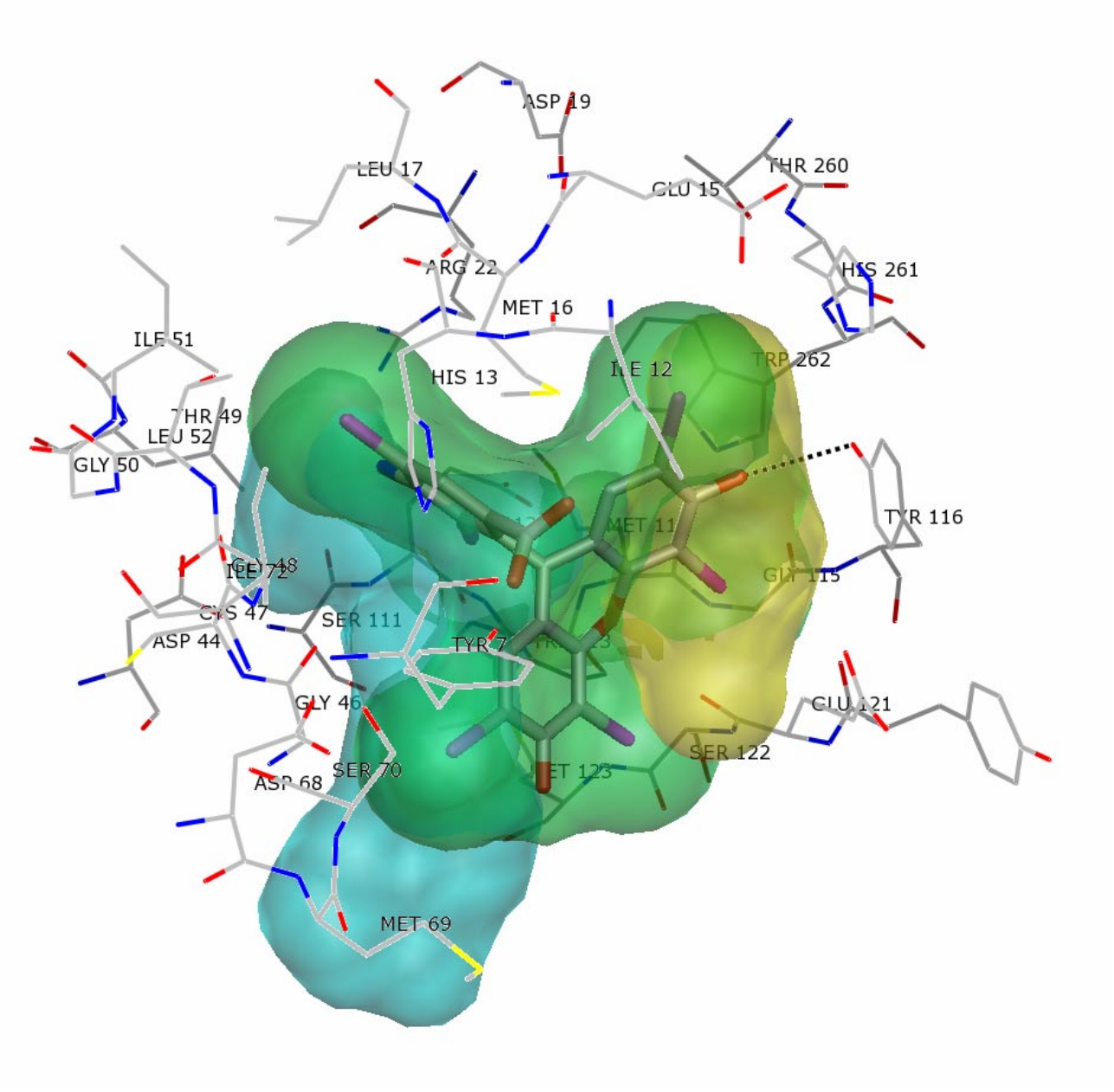


Figure K.

Superimposition of substrates binding sites in RmtA and *h*PRMT1.

Superimposed RmtA (yellow wire) and *h*PRMT1 (magenta wire) residues surrounding the bound SAM (in stick atom type coloured, surface area in cyan) and Arginine substrates (only surface area in white). In stick are represented the residue differences.

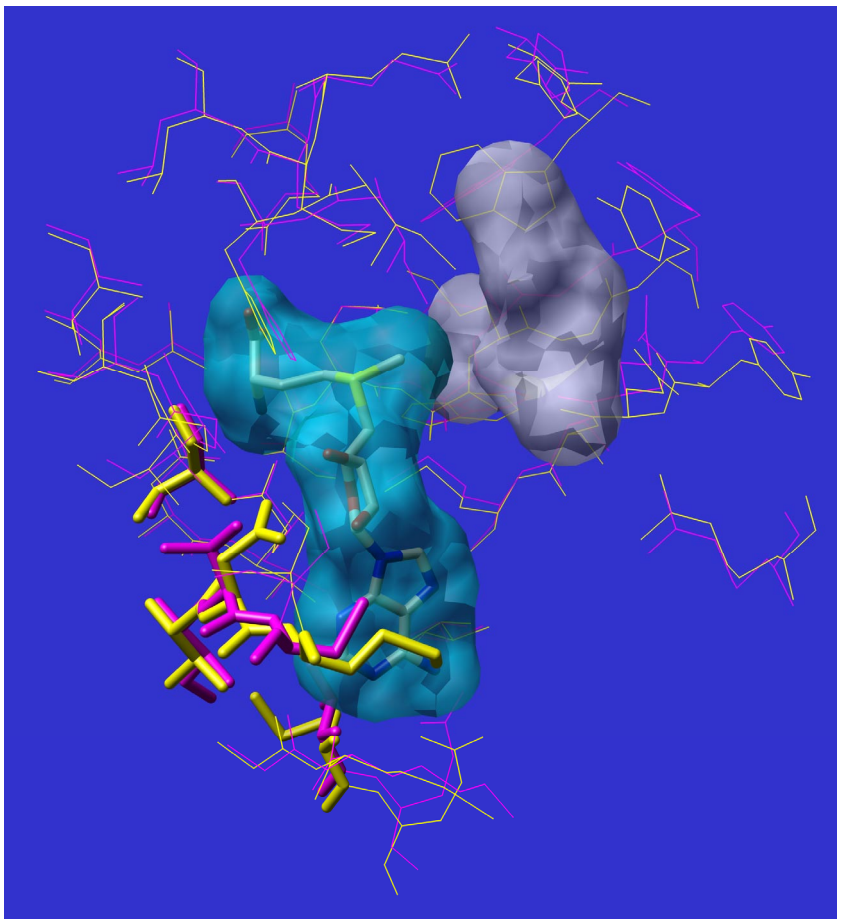


Figure L.
Grid plot for compound 12.
Grid plot of the present fields for the OH2 (a) and C3 (b) probes for the compound **12** (in magenta) The cyan contours represent negative field values while the yellow contours represent the positive field values.

a **b**

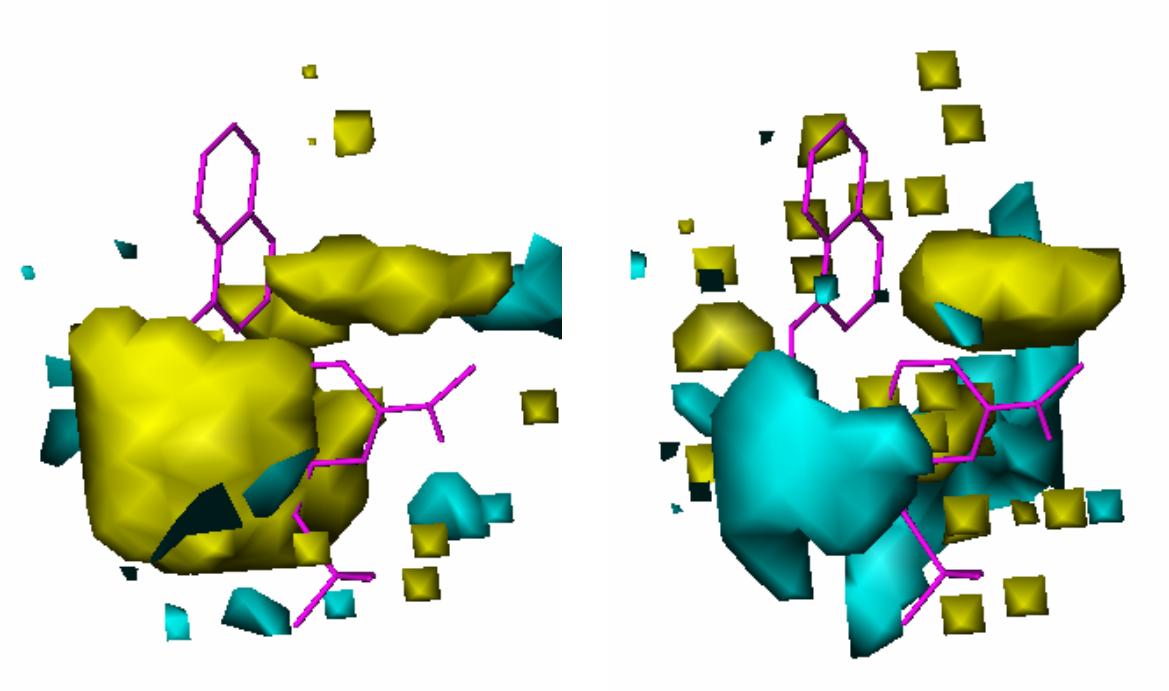
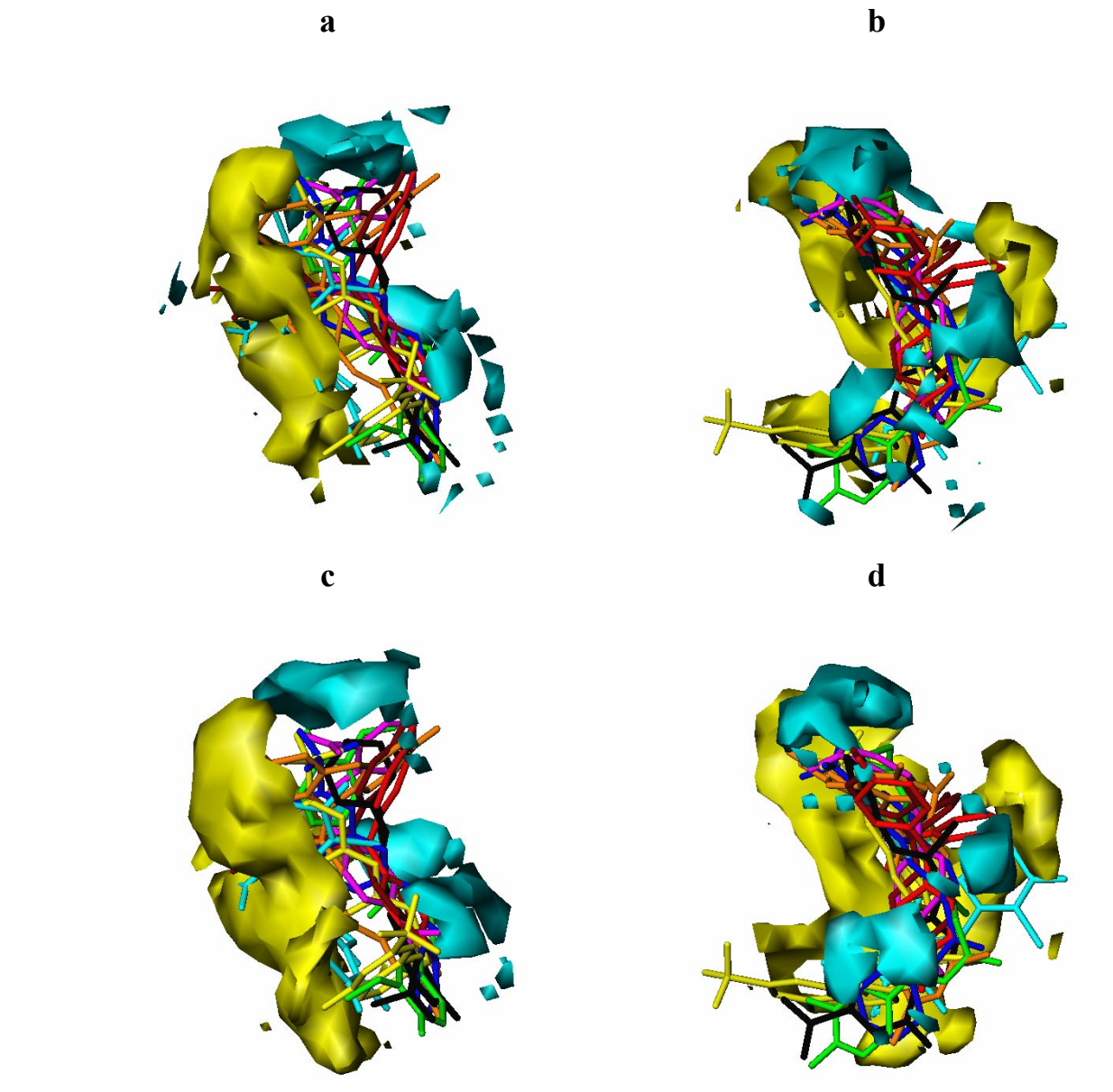


Figure M.
Grid plot for DBP group compounds.
DBP group grid plots of the PLS coefficients for the OH2 (two rotated views, a and b) and C3 (two rotated views, c and d) probes. The molecules of the DBP group are also displayed: **6e** in cyan, **6f** in orange, **7a** in red, **8** in brown, **9** in yellow, **10b** in blue, **10c** in black, **14** in magenta and **16a** in green. The cyan contours represent negative coefficients under -0.0003 energy value while the yellow contours represent the positive coefficients over 0.0003.



References

1. Zhang, X.; Cheng, X., Structure of the predominant protein arginine methyltransferase PRMT1 and analysis of its binding to substrate peptides. *Structure* **2003,** *11*, 509-520.