

## SUPPORTING INFORMATION

### 7-Aminoalkoxy-Quinazolines from Epigenetic Focused Libraries are Potent and Selective Inhibitors of DNA Methyltransferase 1

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#### Contents

		Page
<b>Table S1</b>	Number of quinazolines and 7-aminoalkoxy-quinazolines present in various epigenetic focused libraries.	S2
<b>Table S2</b>	Results of the relative enzymatic activity of DNMT1 as percentages <sup>a</sup> .	S3
<b>Table S3</b>	Results of dose-response evaluations for selected quinazolines (IC <sub>50</sub> ) with DNMT1, DNMT3A and DNMT3B <sup>a</sup> .	S3
<b>Figure S1</b>	Analysis of 150 ns production of the molecular dynamics of production S-Adenil-Metione (SAM) against DNMT1.	S4
<b>Figure S2</b>	Final conformational changes on DNMT1 from molecular dynamics calculations.	S5
<b>Figure S3</b>	<i>In silico</i> profiling of the three compounds with the free online and validate server Epigenetic Target Profiler.	S6

**Table S1.** Number of quinazolines and 7-aminoalkoxy-quinazolines present in various epigenetic focused libraries.

DATABASE	QUINAZOLINES	7-AMINOALKOXY- QUINAZOLINES
ASINEX	4	
AXON	8	7
CHEMDIV	559	
ENAMINE	61	
TARGETMOL	16	12
SELLECK	19	10
OTAVA_DNMT1	5	
OTAVA_DNMT3B	17	1
ENZO	1	1
LIFECHEM	18	
TOTAL	708	31

**Table S2.** Results of the relative enzymatic activity of DNMT1 as percentages <sup>a</sup>.

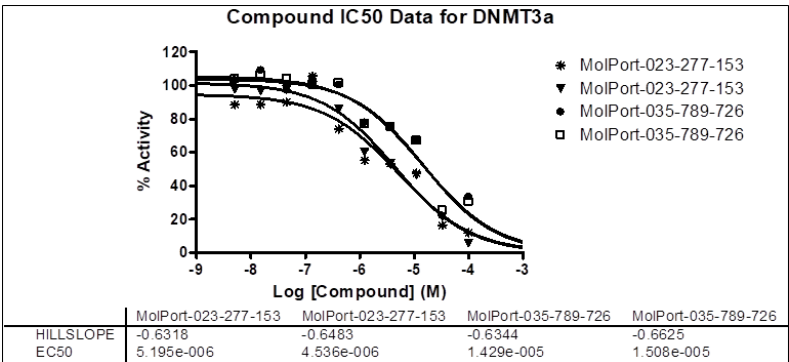
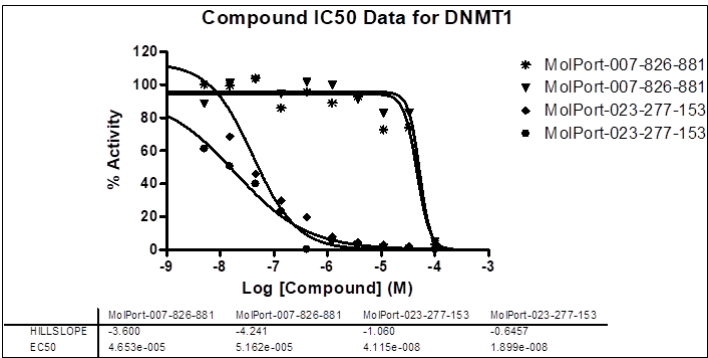
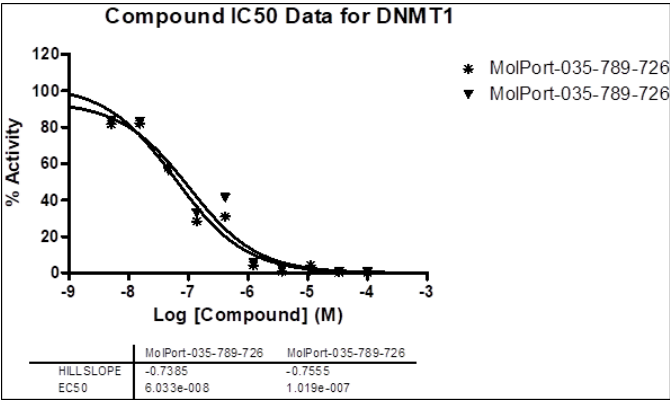
COMPOUND	DNMT1
MOLPORT-023-277-153	0.3 ± 0.10
MOLPORT-035-789-726	0.7 ± 0.02
MOLPORT-006-396-396	92.6 ± 2.40

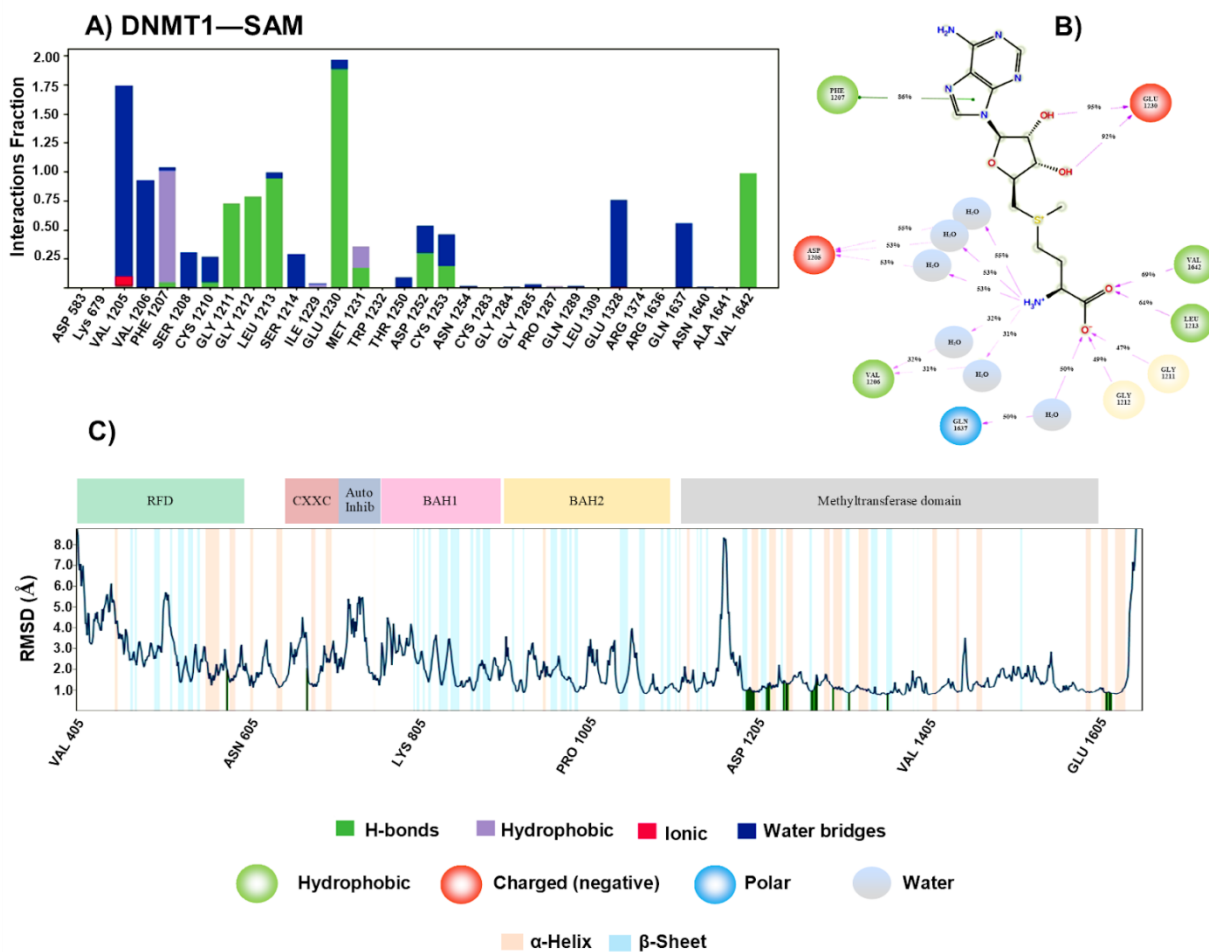
<sup>a</sup> Mean value of two measurements ± standard deviation.

**Table S3.** Results of concentration-response assays for selected quinazolines (IC<sub>50</sub>) with DNMT1, DNMT3A and DNMT3B <sup>a</sup>.

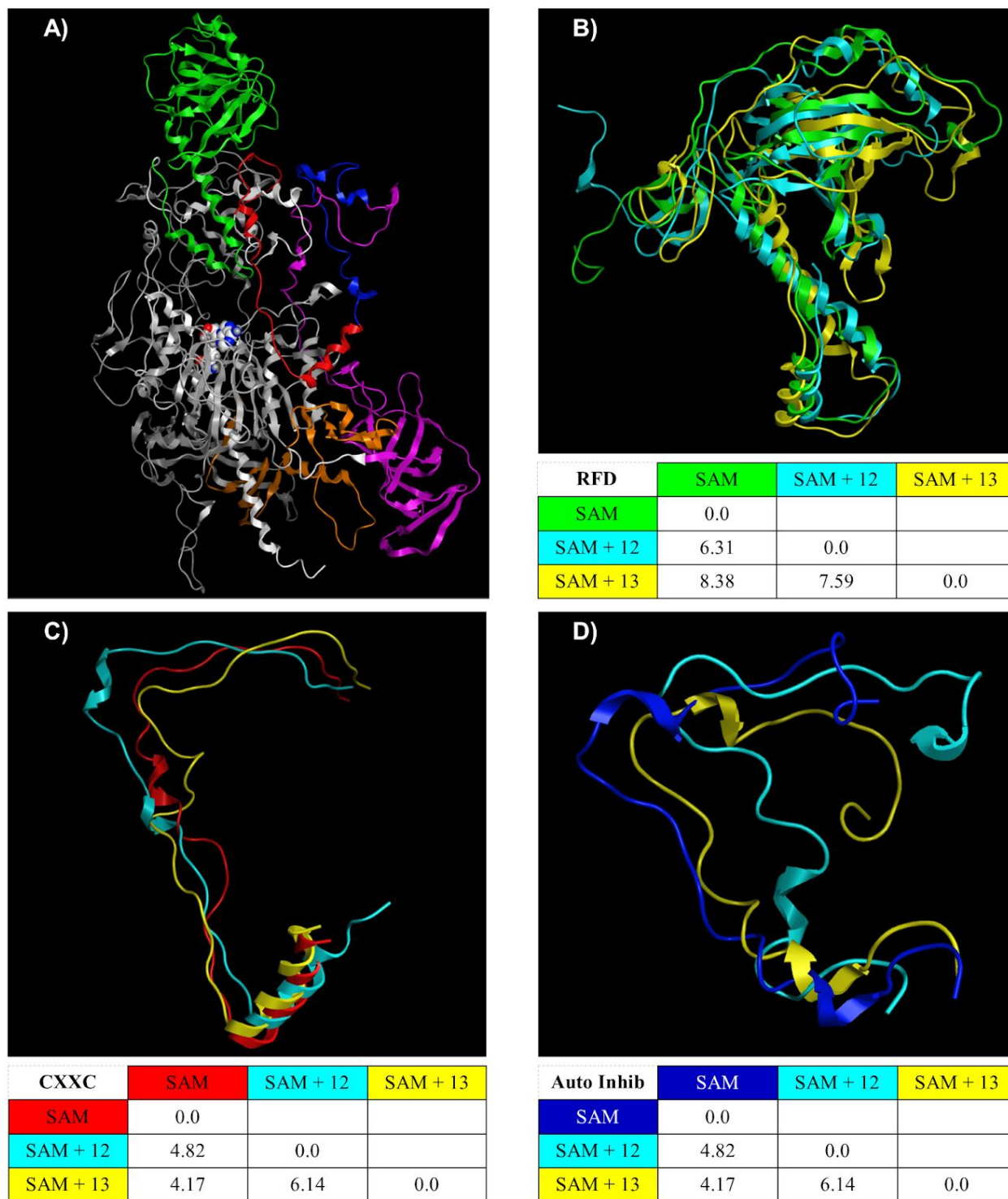
COMPOUND	DNMT1 (IC <sub>50</sub> MM)	DNMT3A (IC <sub>50</sub> MM)	DNMT3B (IC <sub>50</sub> MM)
MOLPORT-023-277-153	0.030 (± 0.016)	4.87 (± 0.47)	> 100 µM
MOLPORT-035-789-726	0.081 (± 0.029)	14.69 (± 0.56)	> 100 µM

<sup>a</sup> Mean value of two measurements ± standard deviation. SAH was included as a positive control: IC<sub>50</sub> (DNMT1) of 0.34 µM; IC<sub>50</sub> (DNMT3A) of 0.10 µM; (DNMT3B) of 0.03 µM.





**Figure S1.** Analysis of 150 ns production of the molecular dynamics of production S-Adenil-Metione (SAM) against DNMT1. **A)** Molecular dynamic interactions of SAM against DNMT1. **B)** Molecular dynamic interactions of SAM against DNMT1 during the last 30ns of production. **C)** Conformational changes observed during the molecular dynamics of SAM against DNMT1.



**Figure S2.** Final conformational changes on DNMT1 from molecular dynamics calculations. **A)** DNMT1-SAM model. The RFD (green), CXXC (red), autoinhibition (navy blue), BAH1 (pink), BAH2 (orange), and DNA-methyl transferase (gray) domains were shown. Panels **B)**, **C)**, and **D)** illustrate the conformational changes (with RMSD values) on the RFD, CXXC, and autoinhibition domains of DNMT1 in presence of SAM, SAM + 12, and SAM + 13, respectively.

# Epigenetic Target Profiler

MolPort-023-277-153

Name	ChEMBL ID	Gene	Status	Quartile
Histone-lysine N-methyltransferase, H3 lysine-9 specific 3	<a href="#">CHEMBL6032</a>	<a href="#">EHMT2</a>	Known	
Serine-protein kinase ATM	<a href="#">CHEMBL3797</a>	<a href="#">ATM</a>	Predicted	Q4
Serine/threonine-protein kinase Aurora-A	<a href="#">CHEMBL4722</a>	<a href="#">AURKA</a>	Predicted	Q4
Serine/threonine-protein kinase Aurora-B	<a href="#">CHEMBL2185</a>	<a href="#">AURKB</a>	Predicted	Q4
Bromodomain-containing protein 2	<a href="#">CHEMBL1293289</a>	<a href="#">BRD2</a>	Predicted	Q4
Histone-arginine methyltransferase CARM1	<a href="#">CHEMBL5406</a>	<a href="#">CARM1</a>	Predicted	Q4
Cyclin-dependent kinase 7	<a href="#">CHEMBL3055</a>	<a href="#">CDK7</a>	Predicted	Q4
CREB-binding protein	<a href="#">CHEMBL5747</a>	<a href="#">CREBBP</a>	Predicted	Q4
Histone deacetylase 1	<a href="#">CHEMBL325</a>	<a href="#">HDAC1</a>	Predicted	Q4
Histone deacetylase 6	<a href="#">CHEMBL1865</a>	<a href="#">HDAC6</a>	Predicted	Q4
Histone deacetylase 8	<a href="#">CHEMBL3192</a>	<a href="#">HDAC8</a>	Predicted	Q4
Lysine-specific demethylase 4C	<a href="#">CHEMBL6175</a>	<a href="#">KDM4C</a>	Predicted	Q4
Lysine-specific demethylase 5A	<a href="#">CHEMBL2424504</a>	<a href="#">KDM5A</a>	Predicted	Q4
Poly [ADP-ribose] polymerase-1	<a href="#">CHEMBL3105</a>	<a href="#">PARP1</a>	Predicted	Q4

MolPort-035-789-726

Name	ChEMBL ID	Gene	Status	Quartile
Histone-lysine N-methyltransferase, H3 lysine-9 specific 3	<a href="#">CHEMBL6032</a>	<a href="#">EHMT2</a>	Known	
Serine-protein kinase ATM	<a href="#">CHEMBL3797</a>	<a href="#">ATM</a>	Predicted	Q4
Serine/threonine-protein kinase Aurora-A	<a href="#">CHEMBL4722</a>	<a href="#">AURKA</a>	Predicted	Q4
Serine/threonine-protein kinase Aurora-B	<a href="#">CHEMBL2185</a>	<a href="#">AURKB</a>	Predicted	Q4
Bromodomain-containing protein 2	<a href="#">CHEMBL1293289</a>	<a href="#">BRD2</a>	Predicted	Q4
Histone-arginine methyltransferase CARM1	<a href="#">CHEMBL5406</a>	<a href="#">CARM1</a>	Predicted	Q4
Cyclin-dependent kinase 7	<a href="#">CHEMBL3055</a>	<a href="#">CDK7</a>	Predicted	Q4
CREB-binding protein	<a href="#">CHEMBL5747</a>	<a href="#">CREBBP</a>	Predicted	Q4
Histone deacetylase 1	<a href="#">CHEMBL325</a>	<a href="#">HDAC1</a>	Predicted	Q4
Histone deacetylase 8	<a href="#">CHEMBL3192</a>	<a href="#">HDAC8</a>	Predicted	Q4
Lysine-specific demethylase 4C	<a href="#">CHEMBL6175</a>	<a href="#">KDM4C</a>	Predicted	Q4
Lysine-specific demethylase 5A	<a href="#">CHEMBL2424504</a>	<a href="#">KDM5A</a>	Predicted	Q4
Poly [ADP-ribose] polymerase-1	<a href="#">CHEMBL3105</a>	<a href="#">PARP1</a>	Predicted	Q4
Protein kinase N1	<a href="#">CHEMBL3384</a>	<a href="#">PKN1</a>	Predicted	Q4
DNA-dependent protein kinase	<a href="#">CHEMBL3142</a>	<a href="#">PRKDC</a>	Predicted	Q4

MolPort-006-396-396

Name	ChEMBL ID	Gene	Status	Quartile
Serine/threonine-protein kinase Aurora-A	<a href="#">CHEMBL4722</a>	<a href="#">AURKA</a>	Known	
Serine/threonine-protein kinase Aurora-B	<a href="#">CHEMBL2185</a>	<a href="#">AURKB</a>	Known	
Serine-protein kinase ATM	<a href="#">CHEMBL3797</a>	<a href="#">ATM</a>	Predicted	Q1
Histone-arginine methyltransferase CARM1	<a href="#">CHEMBL5406</a>	<a href="#">CARM1</a>	Predicted	Q2
Histone deacetylase 1	<a href="#">CHEMBL325</a>	<a href="#">HDAC1</a>	Predicted	Q2
Histone deacetylase 3	<a href="#">CHEMBL1829</a>	<a href="#">HDAC3</a>	Predicted	Q2
CREB-binding protein	<a href="#">CHEMBL5747</a>	<a href="#">CREBBP</a>	Predicted	Q3
Histone deacetylase 6	<a href="#">CHEMBL1865</a>	<a href="#">HDAC6</a>	Predicted	Q3
Histone deacetylase 8	<a href="#">CHEMBL3192</a>	<a href="#">HDAC8</a>	Predicted	Q3
Lysine-specific demethylase 4C	<a href="#">CHEMBL6175</a>	<a href="#">KDM4C</a>	Predicted	Q3
Lysine-specific demethylase 5A	<a href="#">CHEMBL2424504</a>	<a href="#">KDM5A</a>	Predicted	Q3
Bromodomain-containing protein 2	<a href="#">CHEMBL1293289</a>	<a href="#">BRD2</a>	Predicted	Q4

**Figure S3.** *In silico* profiling of the three compounds with the free online and validate server Epigenetic Target Profiler. EHMT2 = G9a. The Quartile column indicates the confidence in the prediction (higher values indicate higher confidence. See details in the reference: Sánchez-Cruz. N. et al. J. Med. Chem. 2021, 64:8208-8220.