Probing PRMT5 inhibitors with distinct binding modes using surface plasmon resonance

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Introduction

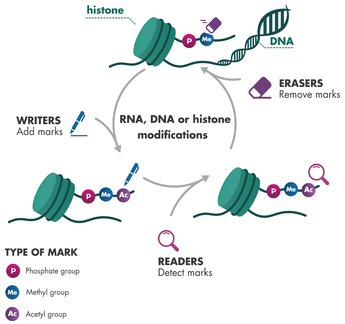
Epigenetic modifications are dynamic and reversible processes that regulate gene expression via chromatin modifications and do not alter the sequence of the DNA.

The proteins that participate in epigenetic modifications can be categorized as:

- **Writers :** covalently modify the chromatin
- **Readers :** recognize the modifications
- **Erasers :** remove the modifications

While essential for normal cellular function, abnormal expression or alterations can lead to disease, which make these epigenetic regulators an attractive target for drug discovery and development.

At Reaction Biology we offer a suite of services and products for drug discovery including the largest panel for epigenetic screening and profiling in the industry.

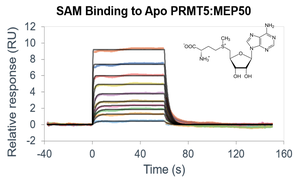


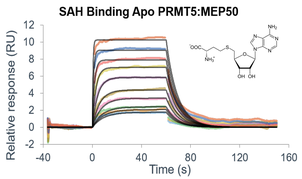
Writers: PRMT5

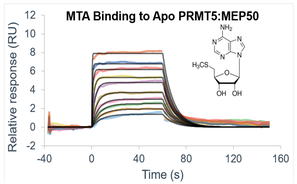
Protein arginine methyltransferase 5 (PRMT5) belongs to a group of enzymes that are responsible for arginine methylation of both histones and other cellular proteins using SAM as the methyl donor. PRMT5 is involved in cell death, cell growth proliferation, and cell cycle progression and has emerged as an attractive drug target due to its role in tumorigenesis.

Inhibitors of PRMT5 can be competitive, noncompetitive, uncompetitive with respect to the substrate and SAM (or SAM analogues). Here we show SPR binding data for SAM and SAM analogues, along with three known PRMT5 selective inhibitors:

- **EPZ015666 =** a substrate competitive inhibitor that binds only in the presence of SAM or SAM analogue (2).
- **LLY-283 =** an inhibitor that binds the SAM-binding pocket but appears to be noncompetitive for both SAM and substrate (3).
- **JNJ-64619178 =** a pseudo-irreversible inhibitor that binds the SAM-binding pocket and reaches into the substrate pocket (4).

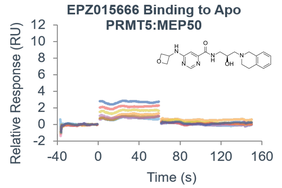


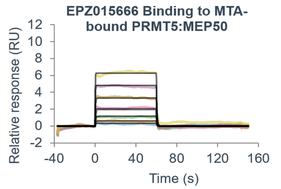


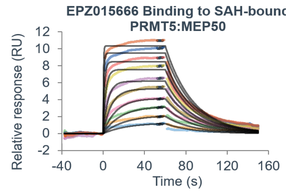


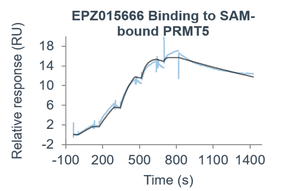
Target	Analyte	ka (1/Ms)	kd (1/s)	KD (M)
Apo PRMT5:MEP50	SAM	3.02E+05	3.31E-01	1.10E-06
Apo PRMT5:MEP50	SAH	3.92E+05	1.08E-01	2.76E-07
Apo PRMT5:MEP50	MTA	7.80E+05	1.14E-01	1.46E-07

PRMT5 Selective Inhibitors

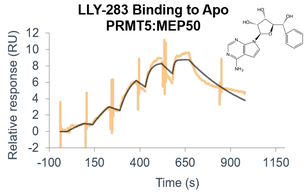


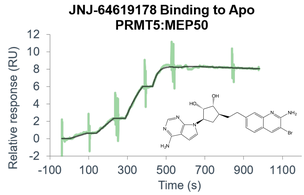






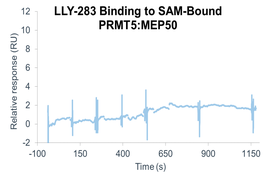
Target	Analyte	ka (1/Ms)	kd (1/s)	KD (M)
Apo PRMT5:MEP50	EPZ015666	Minimal signal changes/binding		
MTA+ PRMT5:MEP50	EPZ015666	6.64e+04	1.03E00	1.60E-05
SAH+ PRMT5:MEP50	EPZ015666	3.46E+04	3.64E-02	1.05E-06
SAM+ PRMT5:MEP50	EPZ015666	1.55E+05	4.76E-04	3.07E-09

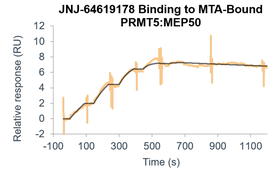


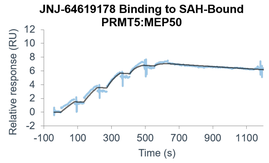


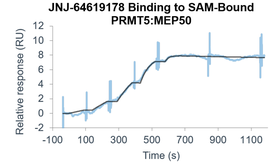
Target	Analyte	ka (1/Ms)	kd (1/s)	KD (M)
Apo PRMT5:MEP50	LLY-283	1.17E+06	2.70E-03	2.31E-09
Apo PRMT5:MEP50	JNJ-64619178	1.69E+06	1.49E-04	8.81E-11

In the Presence of Co-Factors









Target	Analyte	ka (1/Ms)	kd (1/s)	KD (M)
SAM+ PRMT5:MEP50	LLY-283	Minimal signal changes/binding		
MTA+ PRMT5:MEP50	JNJ-64619178	2.40E+05	1.70E-04	7.11E-10
SAH+ PRMT5:MEP50	JNJ-64619178	4.11E+05	2.78E-04	6.76E-10
SAM+ PRMT5:MEP50	JNJ-64619178	5.58E+05	5.66E-05	1.01E-10

References

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