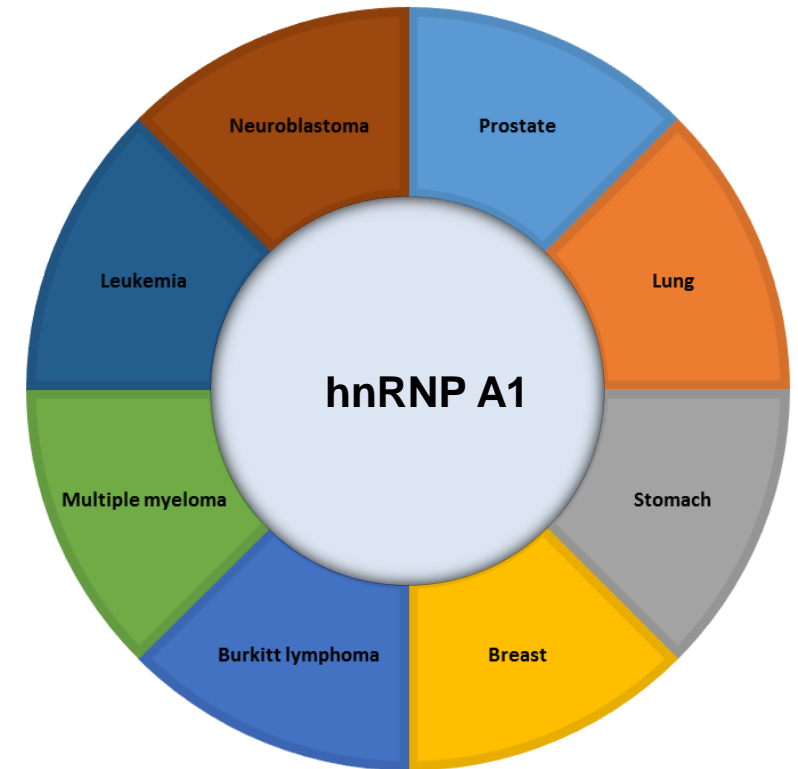
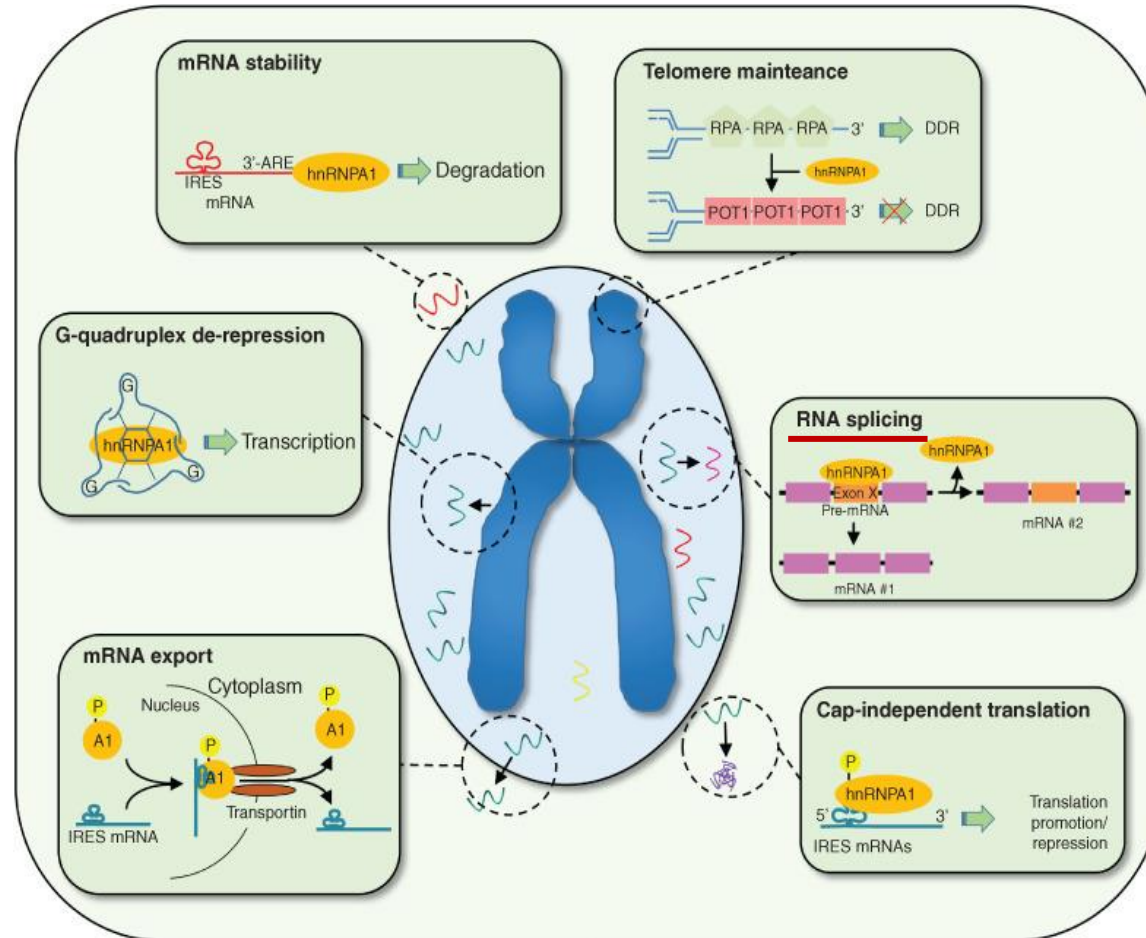


hnRNP A1 splicing factor

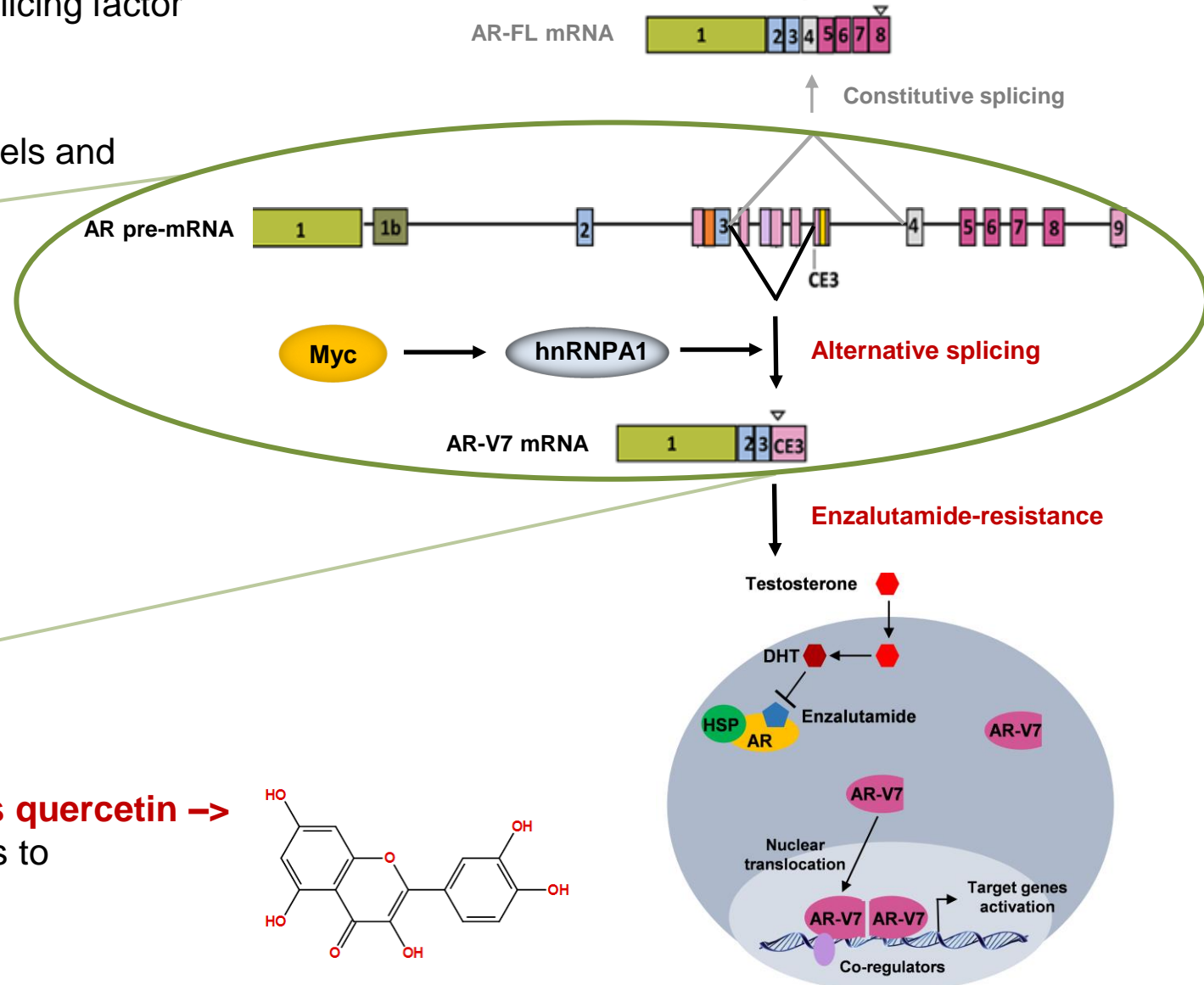
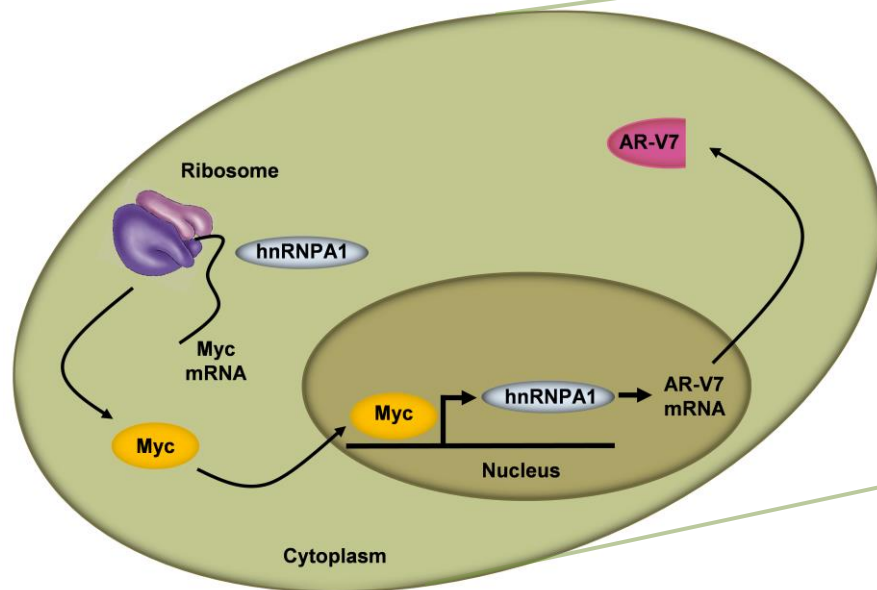
Multifunctional RNA-binding protein with critical role in alternative splicing regulation in cancer

Overexpressed in several cancer types
Associated with progression and drug-resistance

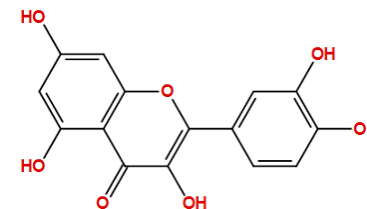


Myc/hnRNP A1/AR-V7 axis – resistance to enzalutamide

- Upregulated by c-Myc, overexpressed hnRNP A1 splicing factor selectively stimulates alternative splicing of AR-V7.
- hnRNP A1 siRNA knockdown suppresses AR-V7 levels and growth of CRPC cells.

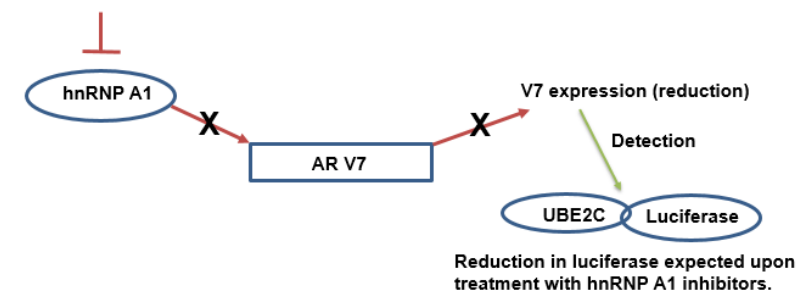
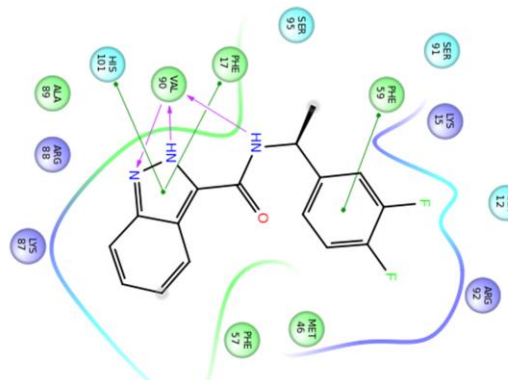
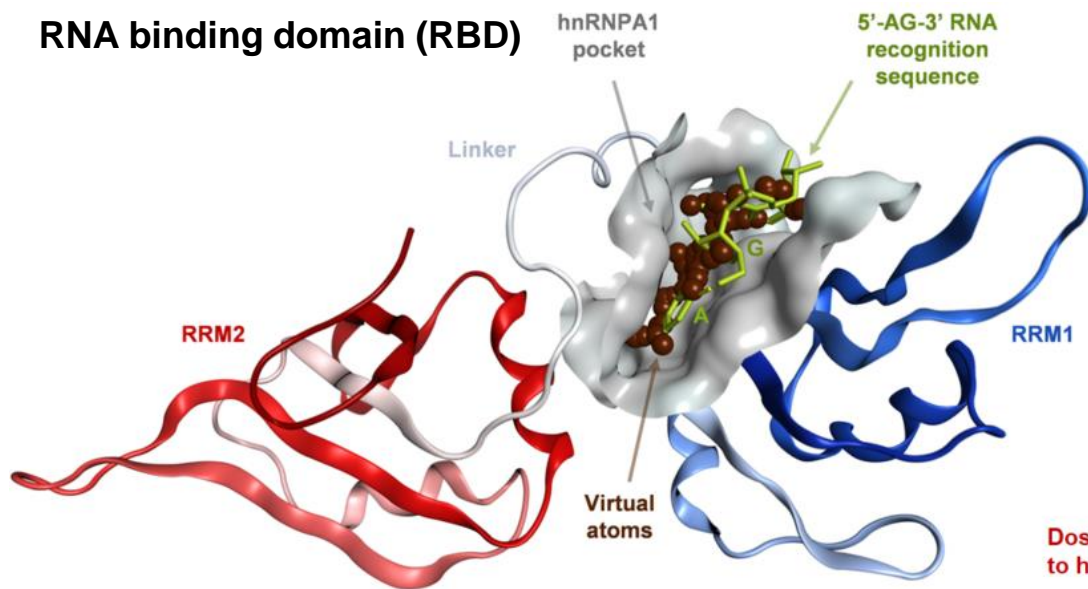


- hnRNP A1 inhibition demonstrated with **promiscuous quercetin** → re-sensitizes resistant cell lines and mouse xenografts to enzalutamide *in vivo*.

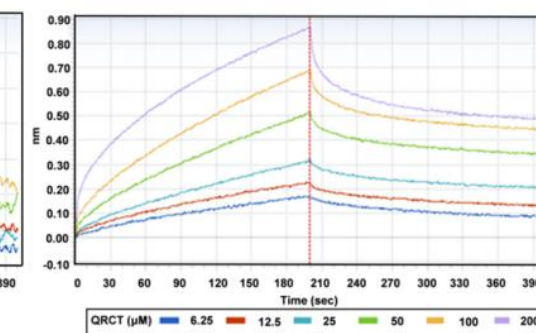
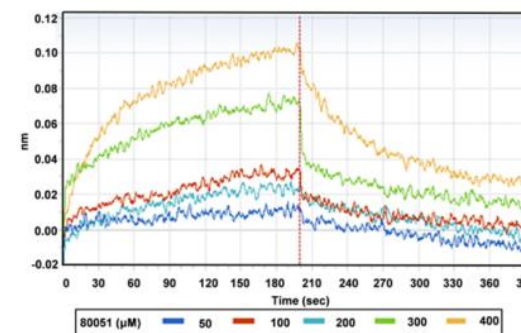


VPC-80051: hnRNP A1 RNA Binding Inhibitor

RNA binding domain (RBD)

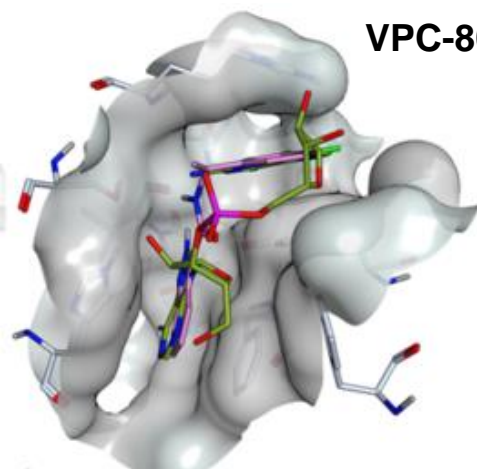
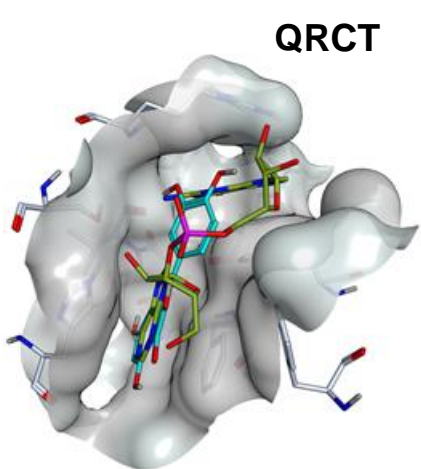


Dose-dependent direct binding to hnRNP A1 RBD

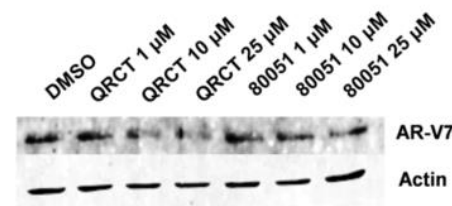


QRCT

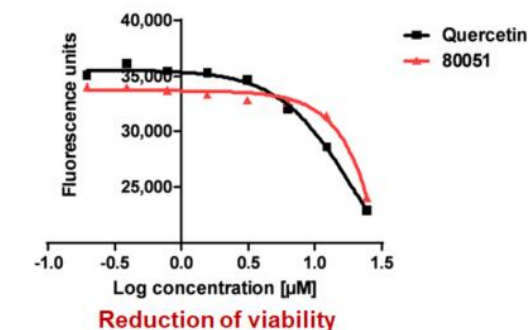
VPC-80051



Compound ID	$\frac{\Delta\text{CT}_{\text{AR-V7}}}{\Delta\text{CT}_{\text{Actin}}}$ (10 μM)	$\frac{\Delta\text{CT}_{\text{AR-V7}}}{\Delta\text{CT}_{\text{Actin}}}$ (25 μM)
VPC-80051	79.55%	66.20%
QRCT	71.15%	62.25%



Reduction of AR-V7 mRNA and protein levels
22Rv1 cells androgen-deprived conditions

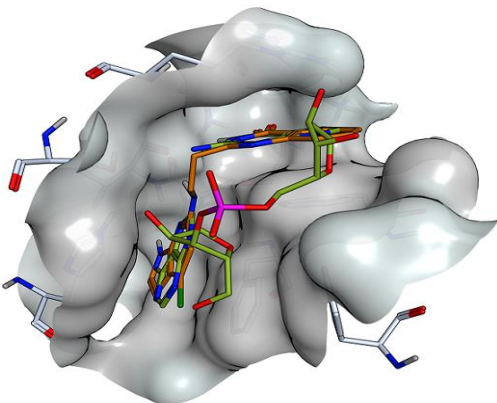


QED = 0.5 ✗

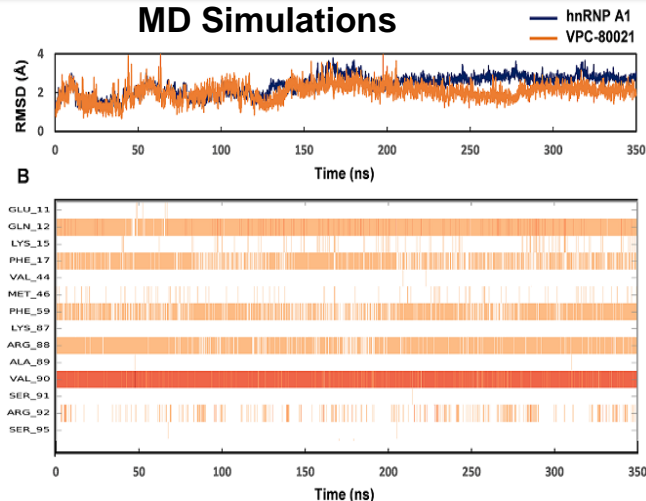
QED = 0.78 ✓

VPC-80021

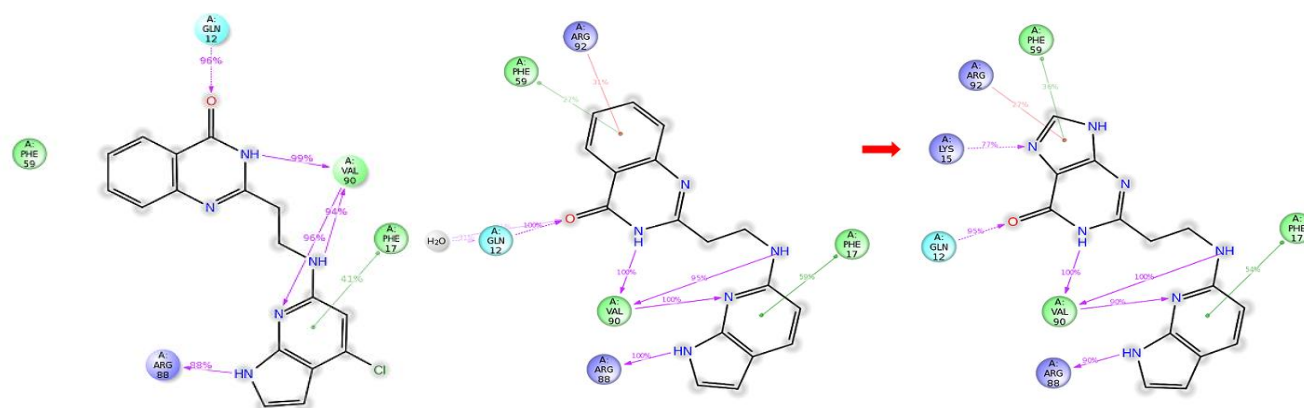
Docking



MD Simulations

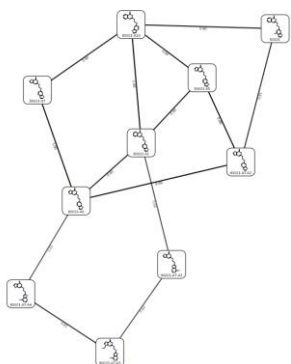


FEP+ $\Delta\Delta G = -2.21$ kcal/mol

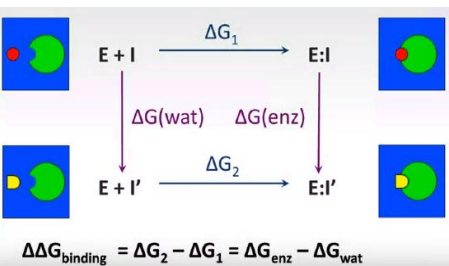


VPC-80021 Optimization - Synthesis Cost Roadblock

FEP+



VPC ID	Glide	pKi	LE	logP	tPSA	ADMET	RMSD	$\Delta\Delta G$ FEP+	\$\$\$
80021	-9.32	6.78	-0.39	2.66	86.5	2.1			\$900
80021-A5	-9.78	6.88	-0.44	1.58	94.5	1.1	1.17	-0.85	\$12,900
80021-A5-M4	-10.34	7.31	-0.44	0.55	114.8	2.9	1.13	-0.94	\$12,580
80021-A7	-10.32	7.16	-0.46	1.83	108.2	3.1	1.58	-1.42	\$13,080
80021-A5-M2	-10.20	6.70	-0.44	1.47	114.8	0.2	2.52	-2.04	\$12,580
80021-A6	-9.98	7.03	-0.45	1.56	110.9	1.6	1.04	-2.21	\$7,500
80021-A7-A2	-9.90	6.17	-0.45	0.62	133.9	4.5	2.07	-2.47	\$14,900



$$\Delta\Delta G = -RT \ln IC_{50,1}/IC_{50,2}$$