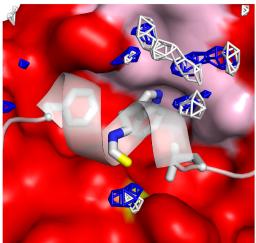


Slippery Peptide Inhibitors of Mdm2/MdmX



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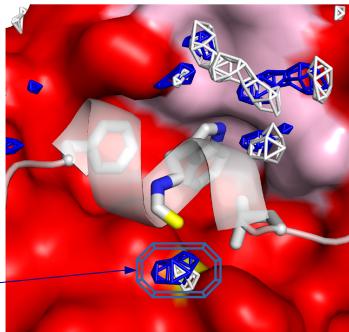


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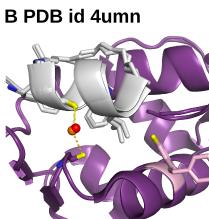
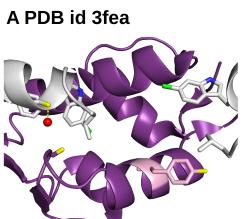
High water density grids from
experiments (blue) and
simulations (white)

Waters around Mdm2/MdmX

- Water densities of 95 experimental x-ray structures (Blue)
- Water densities of simulations (white)
- Waters around Mdm-V93/92 and p53-L22 O atoms were stable lasting >1ns.



Strategies to mitigate closed state of Y100/99



- Inhibitor forces Y99 to an open state. Water with B factors of 17.15, lower than ~60% of protein atoms
- Water is unaffected by Y100 state. B factors are 24, lower than ~90% of protein atoms

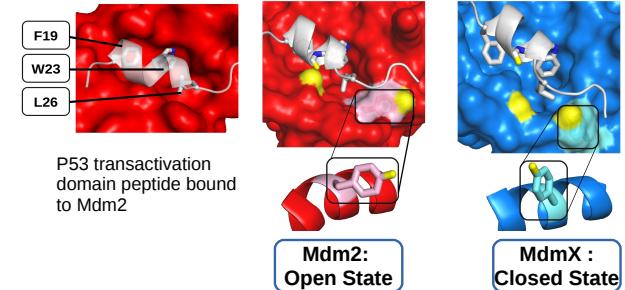
How would our observations hold for a dual inhibitor?

POTENT dual inhibitor : ATSP7041

Abstract/Summary

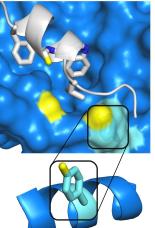
- Mdm inhibitors bind Mdm2/MdmX to release p53, allowing for apoptosis.
- Dual Mdm inhibitors are hard to design due to amino-acid level substitutions and the closed state of the gatekeeper residue: Y100/99.
- Studying water molecule(s) from experimental and simulation structures, we proposed strategies to mitigate the closed state of the gatekeeper and proposed that the potent dual inhibitor (Atsp7041) is unaffected by the closed state.

Open vs closed conformation of Y100/99



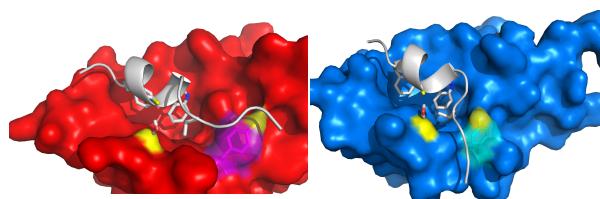
P53 transactivation
domain peptide bound
to Mdm2

Mdm2:
Open State



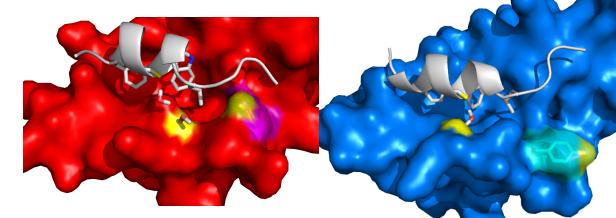
MdmX :
Closed State

Water(s) around Mdm-V93/92 and p53-L22



MDM2	MDMX, closed state
One long-lived water. (plots at appendix)	Mostly zero waters, sometimes one or two waters. (plots at appendix)

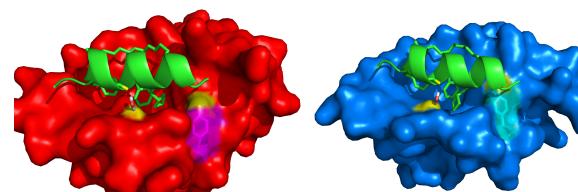
Restraining Y100/99 from open to closed and vice-versa



MDM2, Y100_restrained_to_closed	MDMX, Y99_restrained_to_open
Mostly zero waters, sometimes one or two waters. (plots at appendix)	One long-lived water. (plots at appendix)

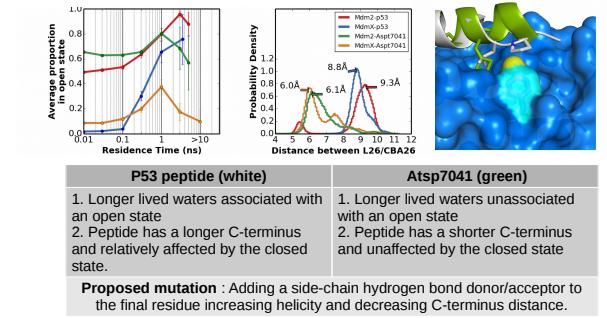
Conclusion : The open (closed) conformation causes a one long-lived water network (zero or two waters).

Water(s) around Mdm-V93/92 and Atsp7041-F22 O atoms

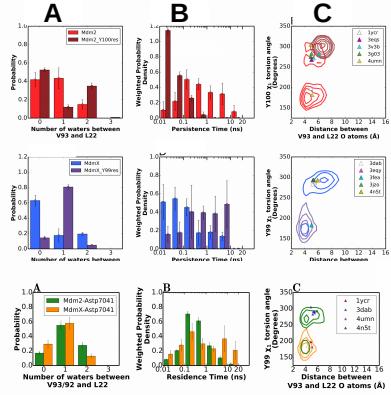


MDM2, Y100_open	MDMX, Y99_closed
One long-lived water (plots at appendix)	One long-lived water (plots at appendix)

Atsp7041 vs p53 peptide



Appendix : Quantification of waters



Legend :

(A) Number of bridging waters, with error bars denoting standard error between simulation repeats.

(B) Persistence times of the water network. Error bars denote the standard error between simulation repeats.

(C) Clustering of Y100/99 v 1 dihedral angle and distance between O atoms of V93/92 and L22.

Dihedral angles from PDB crystal structures are shown in colored triangles.