Exploring the function of water molecules in drug discovery

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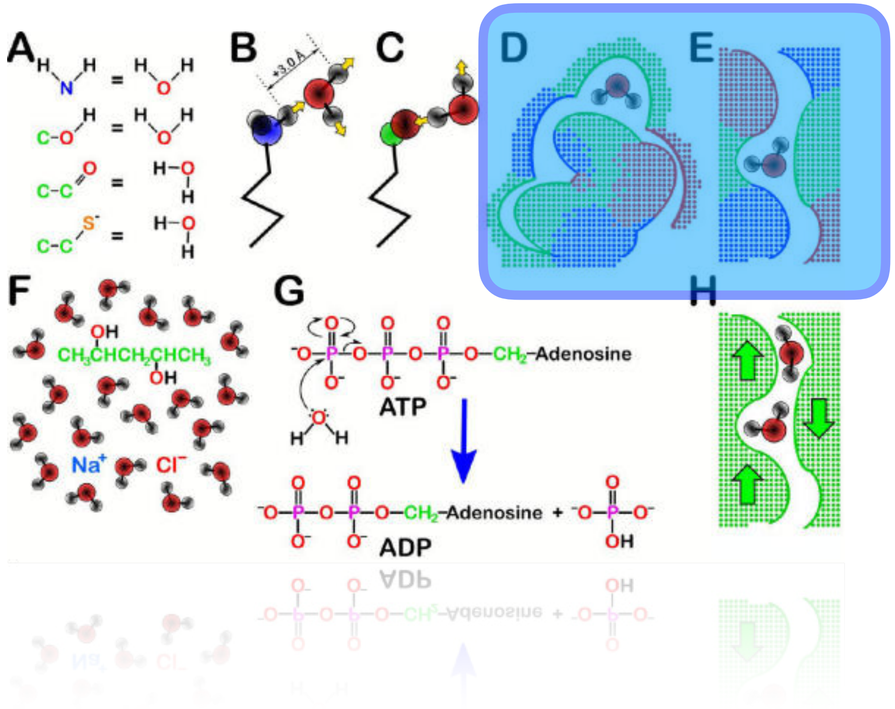
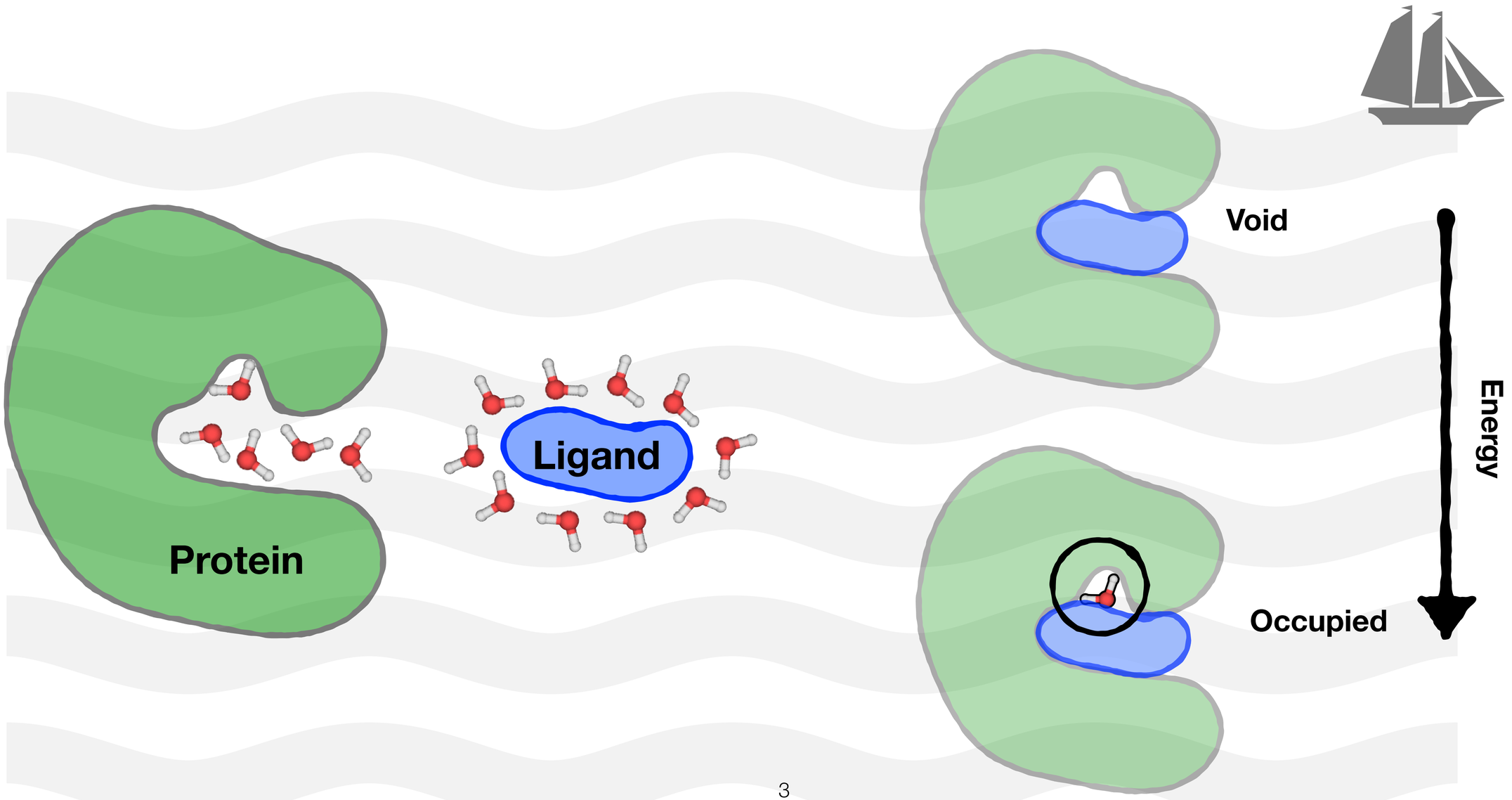
The versatile of water

- **Mimic** of the organic molecules) (A)
- Hydrogen bond (B-C)
- **occupy void** (D-E)
- Accommodate organic molecules (F)
- Proton transfer, Mediate interactions, work as lubricant…

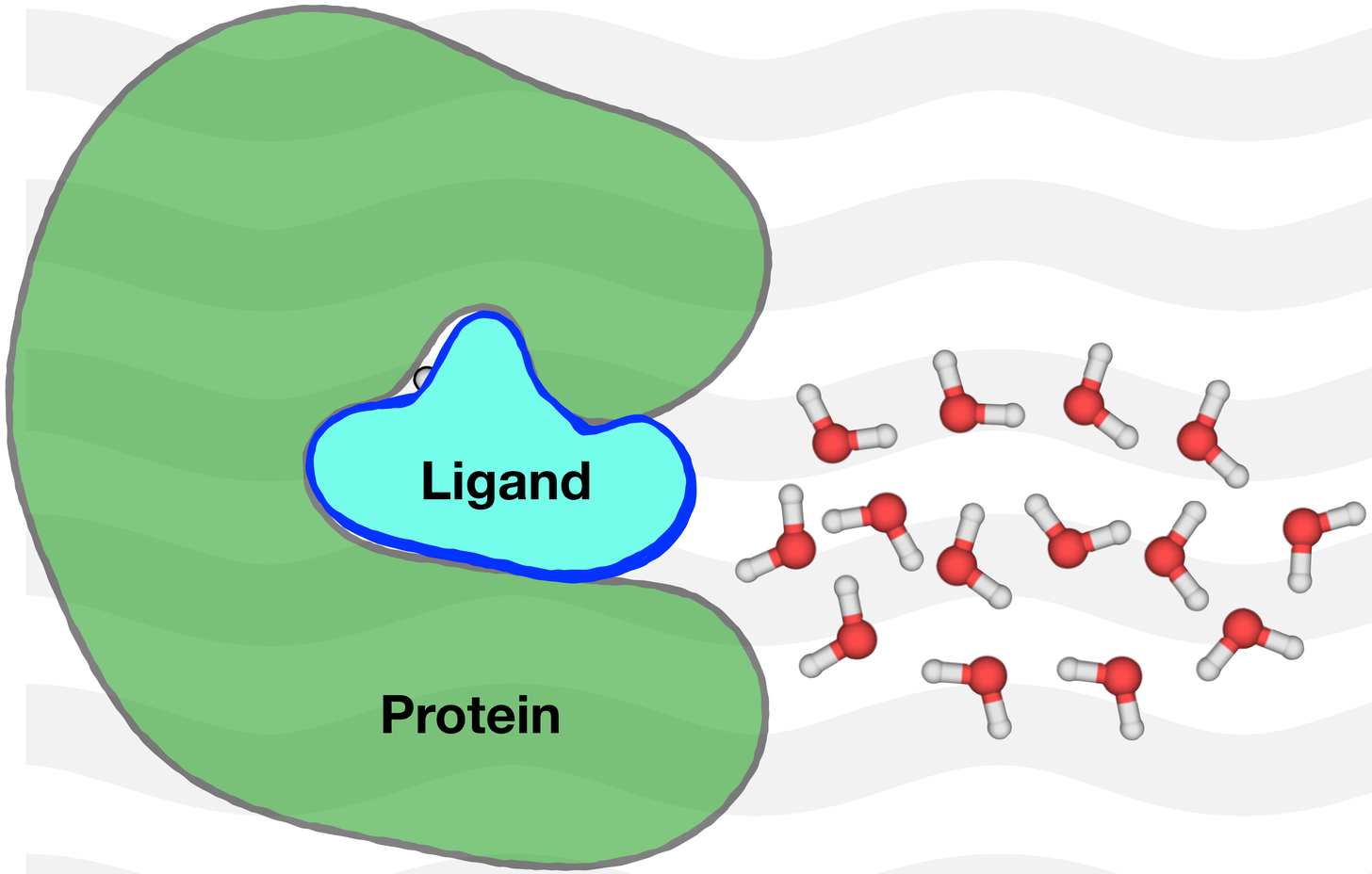


F. Spyrakis, et al., *J. Med. Chem.* **2017**.

Incomplete desolvation

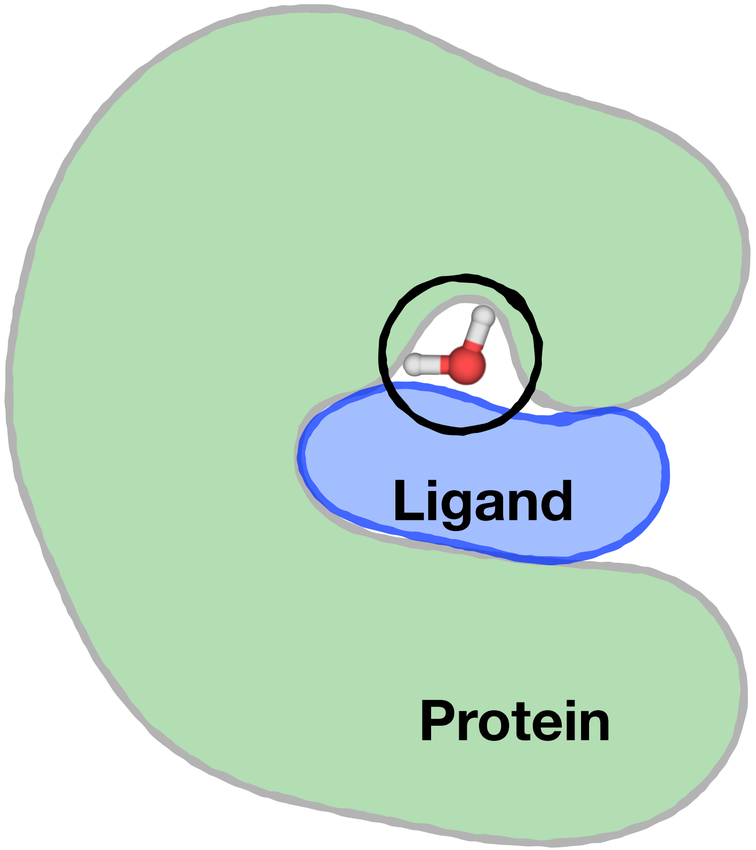


what we want to do



Repelling the water
Increase ligand binding **affinity**

Is such water common?

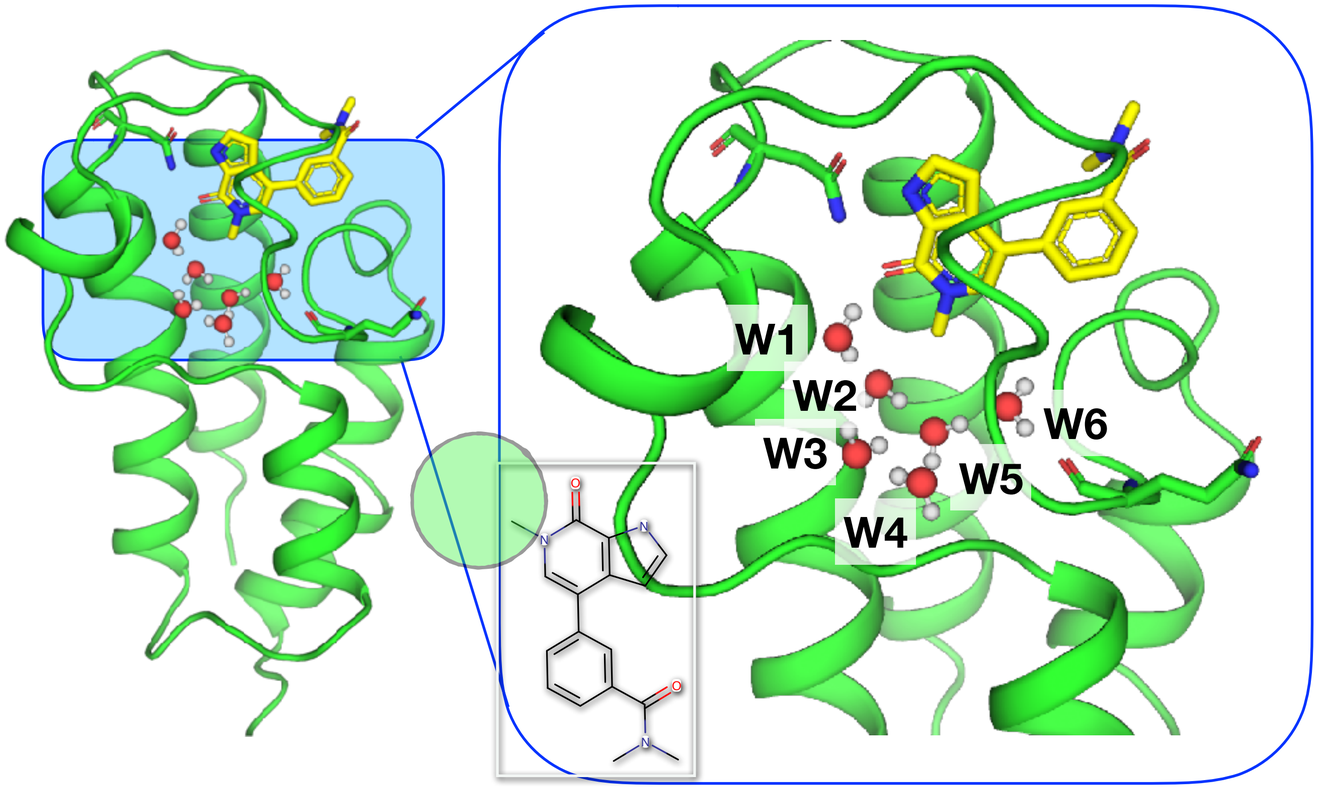


76%

in 392 high resolution (<=2Å) PDB structures

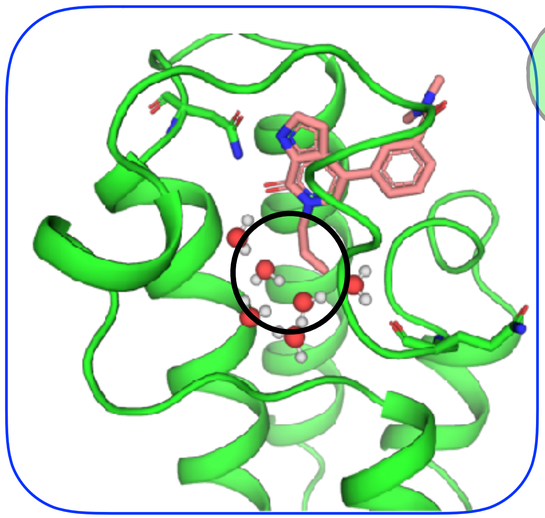
Y. Lu, et al., *Journal of Chemical Information and Modeling* **2007**, *47*, 668.

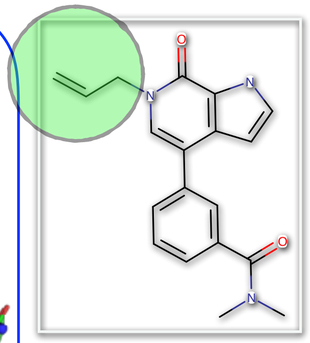
Can we repelling the water?



compound 2
92 nM

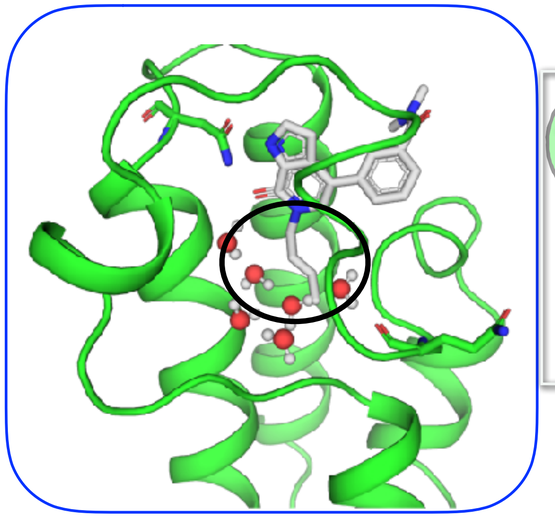
bromodomain (BRD4 BD1 domain)

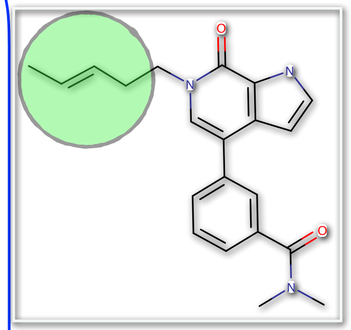




compound 3
6300 nM

NO!





compound 3
470 nM

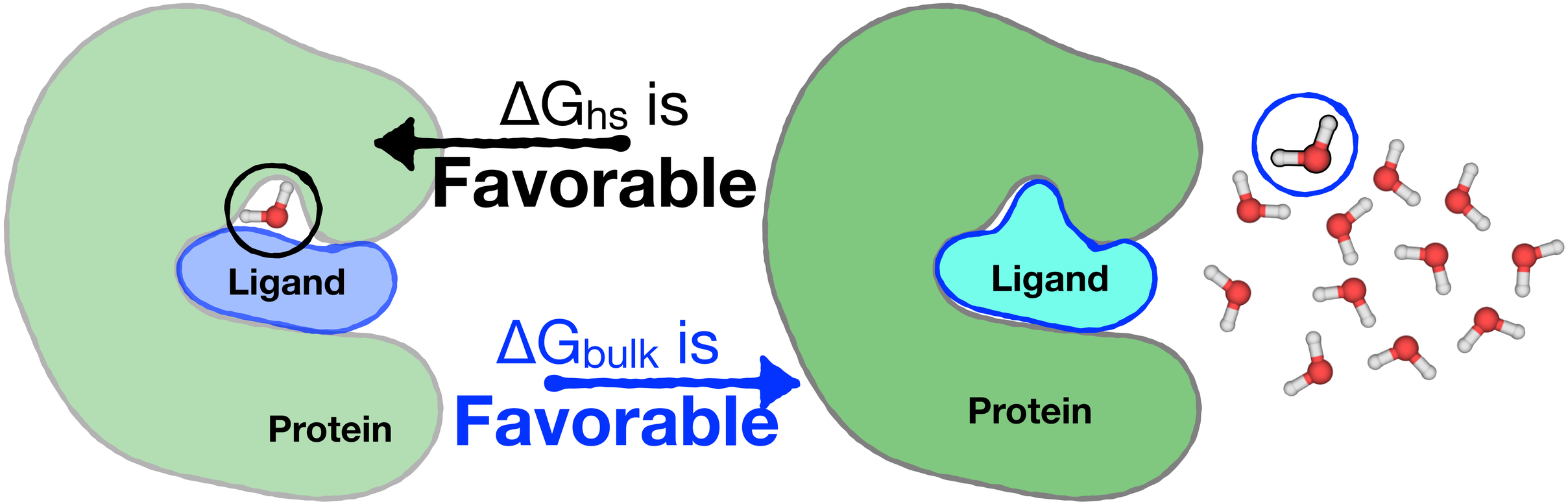
YES

T. D. Crawford, et al., *J. Med. Chem.* **2016**, *59*, 5391

Fundamentals

$\Delta G_{PL}+\Delta G_{hs}+\Delta G_{other}$

$\Delta G_{PL}+\Delta G_{bulk}+\Delta G_{other}$



Development of the methods

- Double decoupling (McCammon, et. al J Am Chem Soc. 2004 Jun 23;126(24):7683-9.)
- JAWS (Jorgensen group. J. Am. Chem. Soc. 2009, 131, 15403−15411.)
- 3d-reference interaction site model (Roux group, J. Phys. Chem. B 1997, 101, 7821−7826.)
- SZMAP (Openeye)
- WaterMap (Friesner group, J. Am. Chem. Soc., 2008, 130, 2817-2831)
- STOW (Lazaridis, Kaplus, Michael E. J. Phys. Chem. 1992, 96, 3841-3855)

Mathematical formula

$$\Delta\Delta G = \Delta G_{hs} - \Delta G_{bulk}$$

$$||$$

$$\Delta E - T\Delta S - \Delta G_{bulk}$$

Mathematical formula

$$\Delta E = \Delta E_{vdw} + \Delta E_{ee}$$

Force field +MD simulations

$$\Delta G_{bulk}$$

Experimental value

$$T\Delta S$$

Inhomogeneous fluid theory

Inhomogeneous fluid theory

$$\Delta S = S_{wp} + \Delta S_{ww}$$

Water-Protein correlation term

$$S_{wp} = -\kappa \frac{\rho}{\Omega} \int g_{wp}(\boldsymbol{r}, \omega) ln g_{wp}(\boldsymbol{r}, \omega) d\boldsymbol{r} d\omega$$

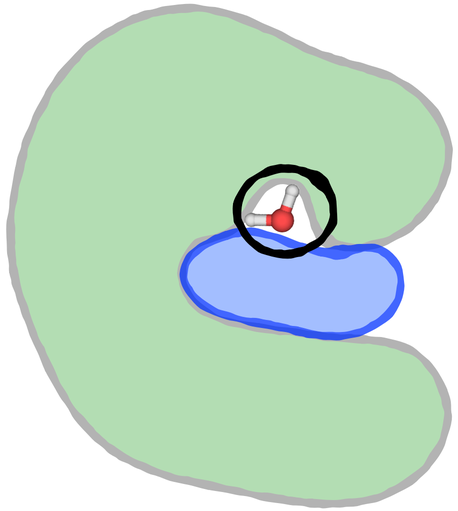
Water-water correlation term

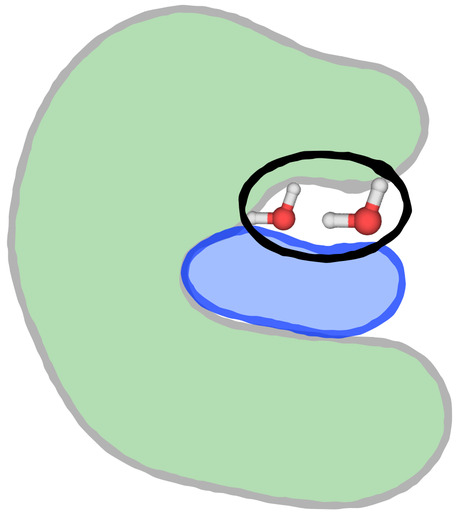
$$S_{ww} = S_{ww}^{trans} + S_{ww}^{orient}$$

$$S_{ww}^{trans} = -\frac{1}{2}\kappa\rho^2 \int g_{wp}^{trans}(\boldsymbol{r})\, g'^{trans}_{wp}(\boldsymbol{r}')\{g_{ww}^{bulk}(R) \ln g_{ww}^{bulk}(R) - g_{ww}^{bulk}(R) + 1\} d\boldsymbol{r} d\boldsymbol{r}',$$

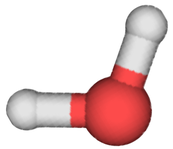
$$S_{ww}^{orient} = -\frac{1}{2}\kappa\rho^2 \int g_{wp}^{trans}(\boldsymbol{r})\, g'^{trans}_{wp}(\boldsymbol{r}') g_{ww}^{bulk}(R) \int g_{ww}^{orient}(\omega) g'^{orient}_{ww}(\omega') \{g_{ww}^{bulk}(\omega^{rel}|R) \ln g_{ww}^{bulk}(\omega^{rel}|R)\} d\boldsymbol{r} d\boldsymbol{r}' d\omega d\omega'$$

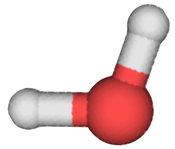
Inhomogeneous fluid theory



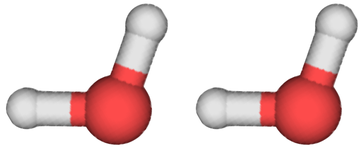


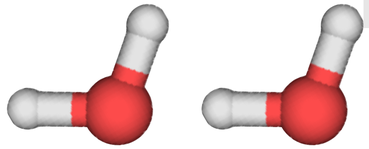
Water-Protein correlation term





Water-water correlation term

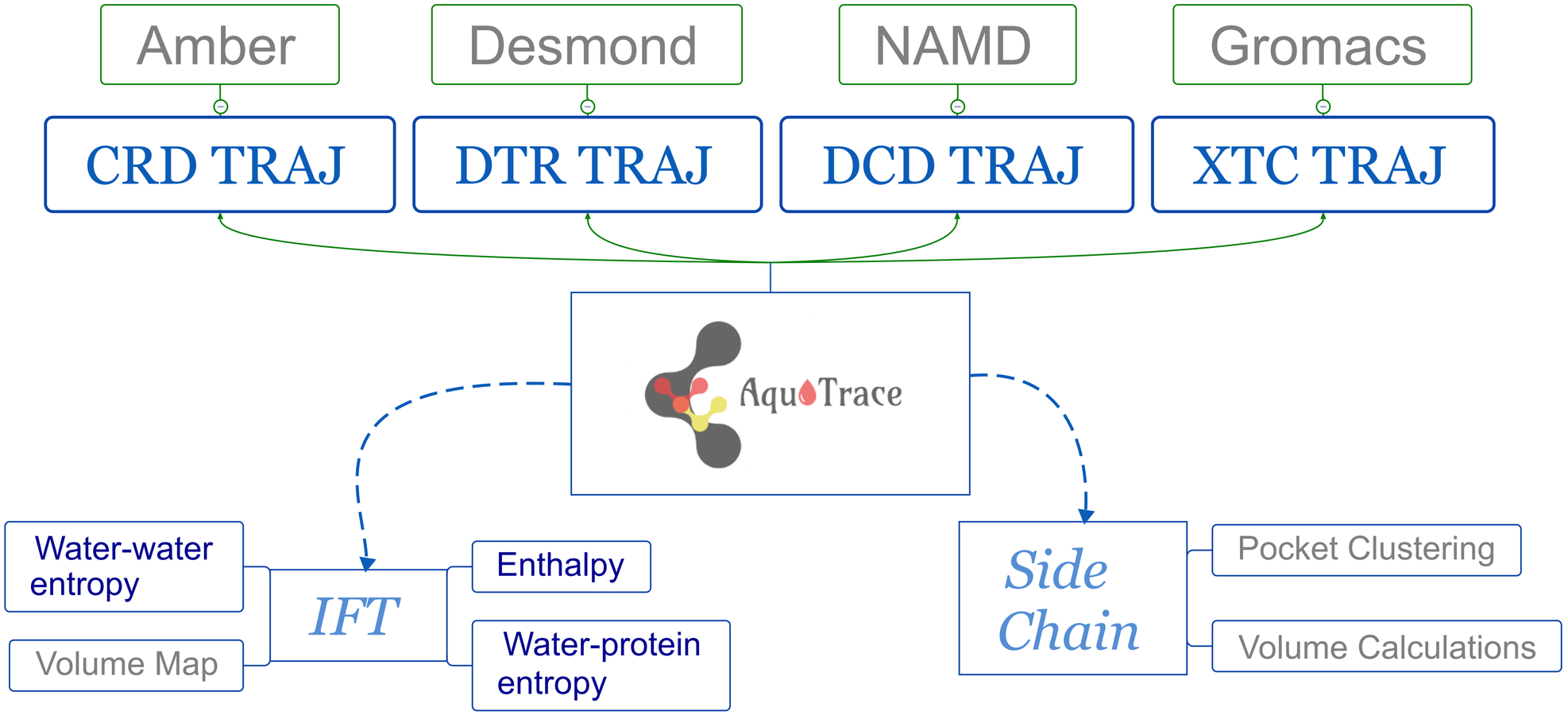




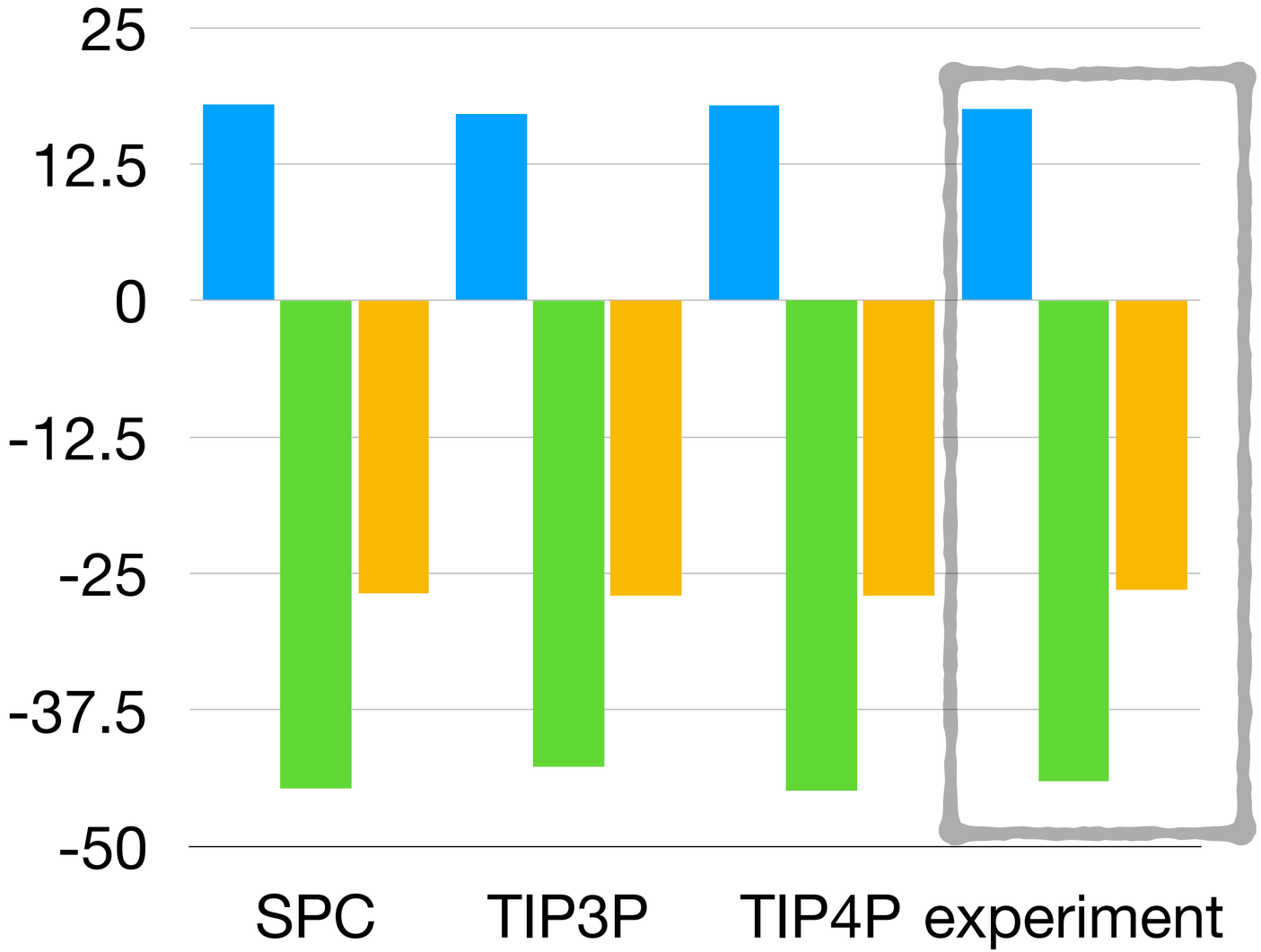
Separate the relative angle and distance into **states *i***

$$S = -k \int p_i ln p_i$$

Sampling the states and AquaTrace



Validation (bulk water)



entropy kJ/mol

excess energy kJ/mol with maximum divergency (6 kJ/mol)

enthalpy kJ/mol

Validation (Acetyl-CoA carboxylase)

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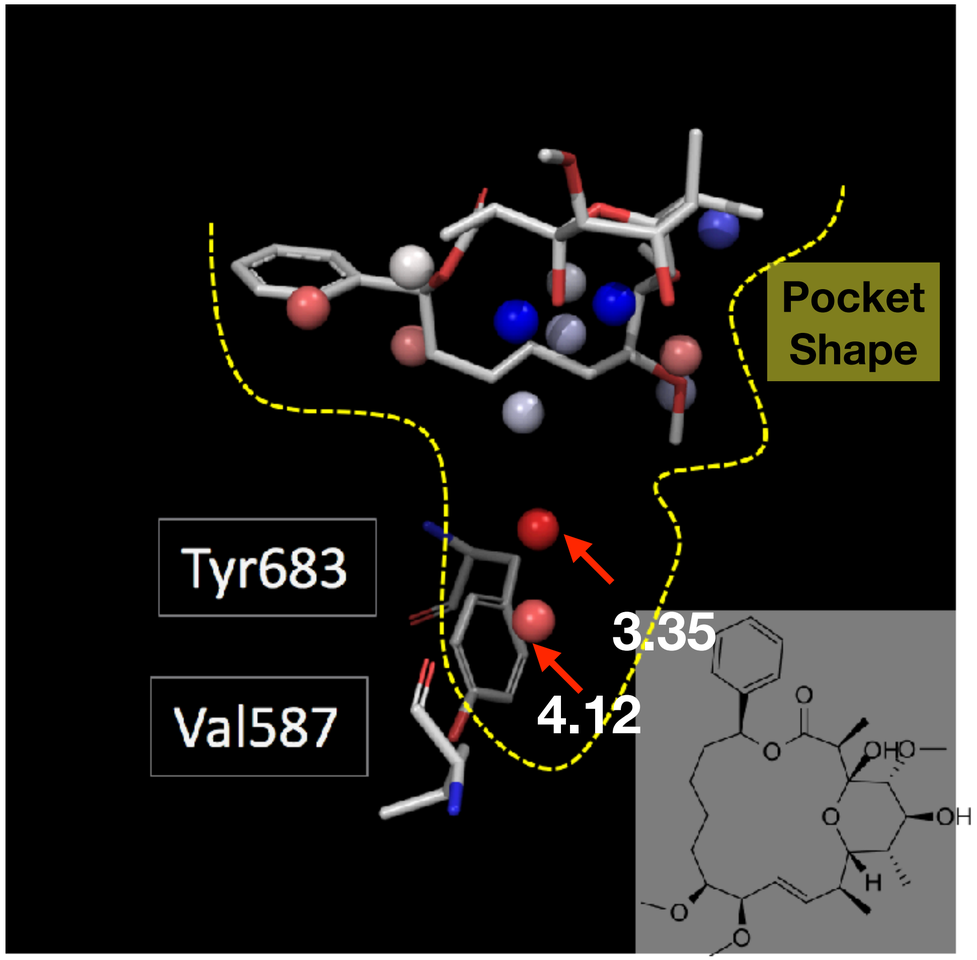
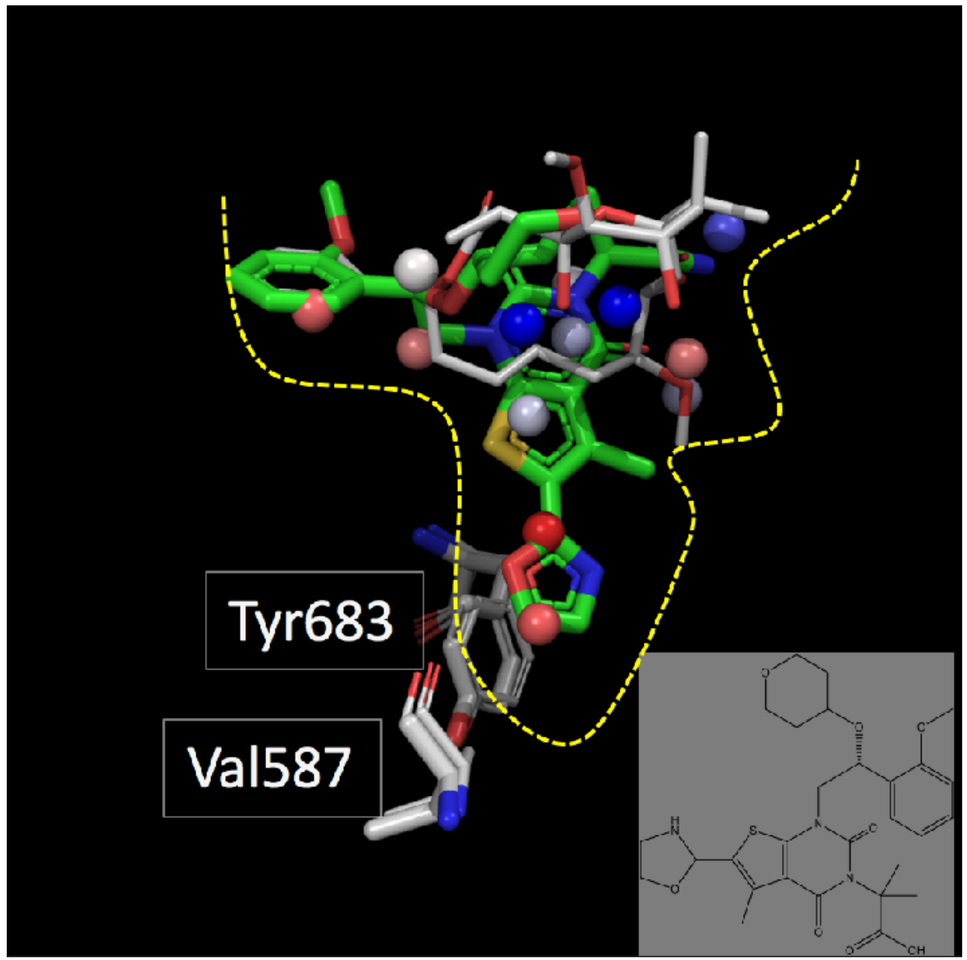
Fast track for NASH



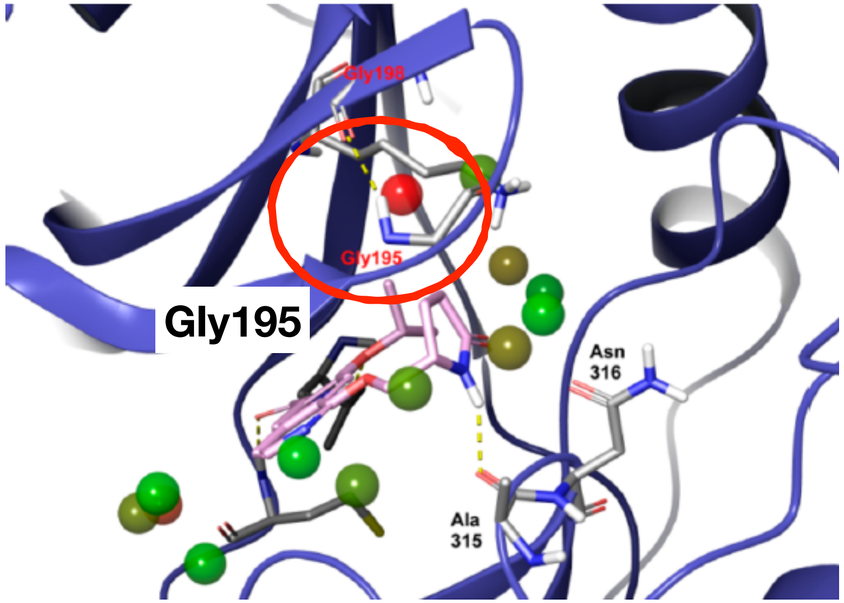


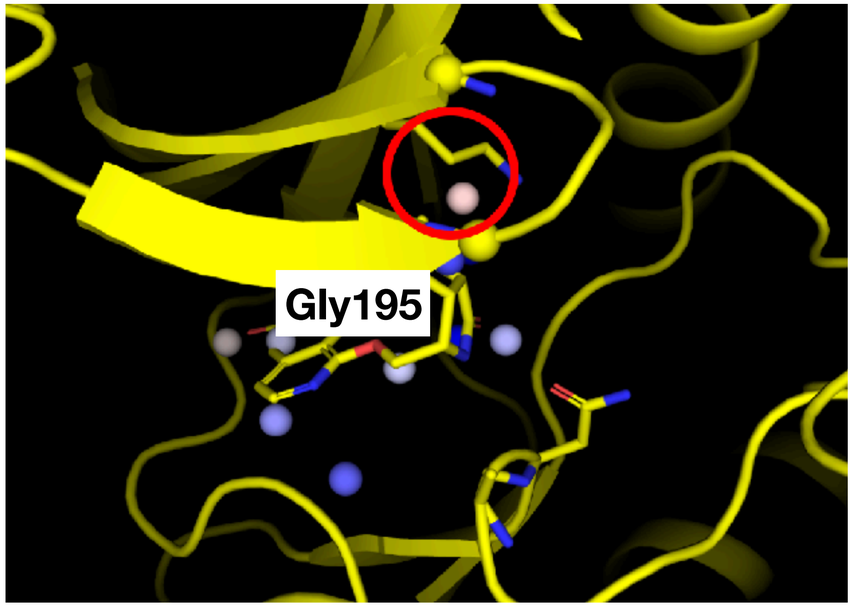
5 kcal/mol

-5 kcal/mol

(2016) Proc.Natl.Acad.Sci.USA **113**: E1796-E1805

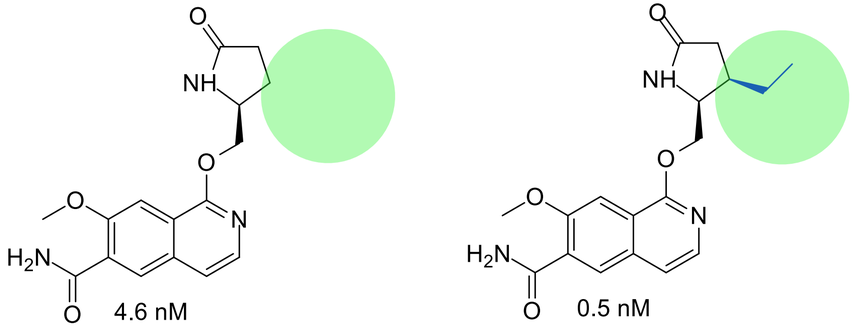
Validation (Interleukin-1 receptor-associated kinase 4)





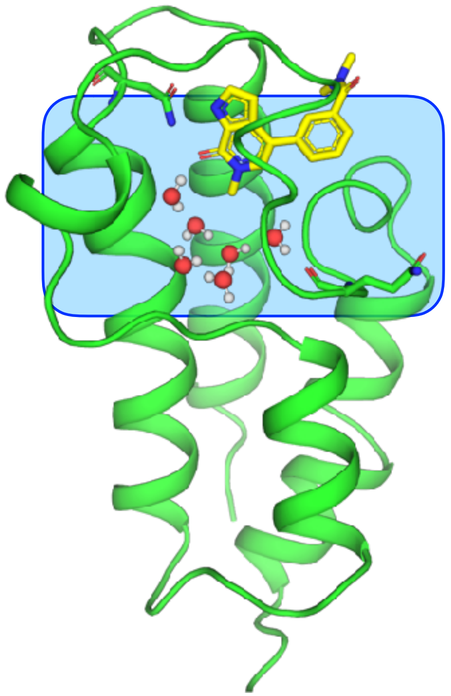
5 kcal/mol

-5 kcal/mol

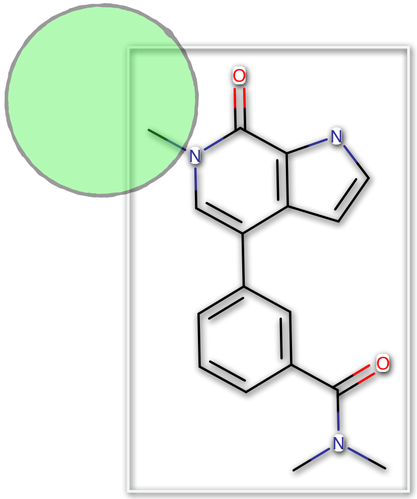


J. Med. Chem., **2017**, *60* (13), pp 5521–5542

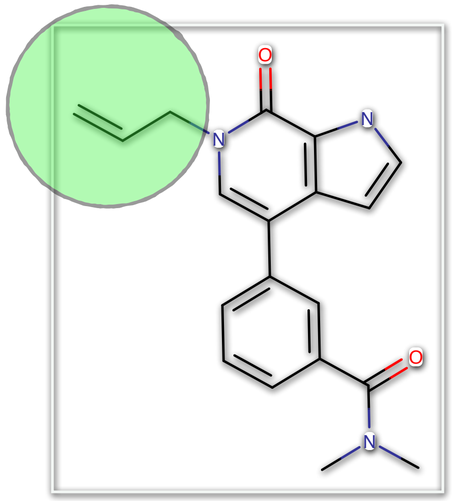
Can we repelling the water?



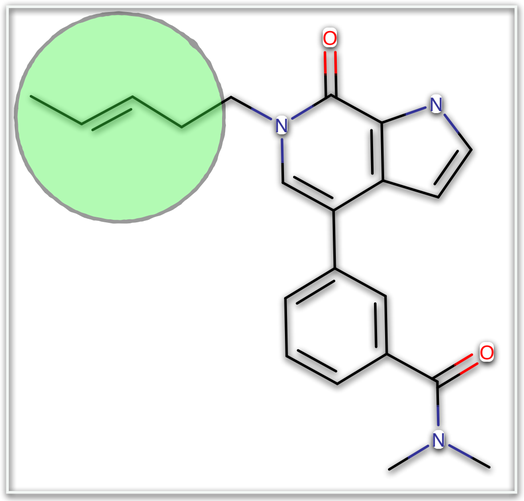
bromodomain
(BRD4 BD1 domain)



compound 2
92 nM



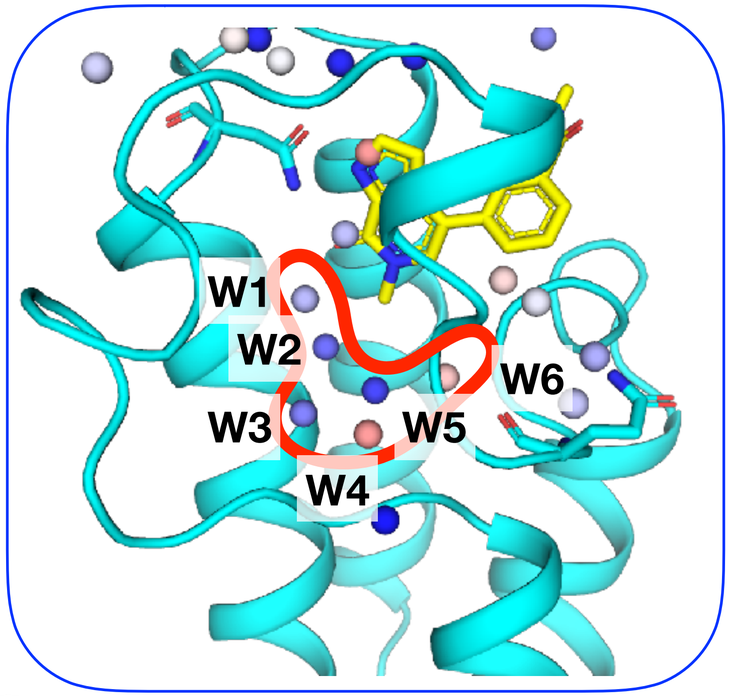
compound 3
6300 nM

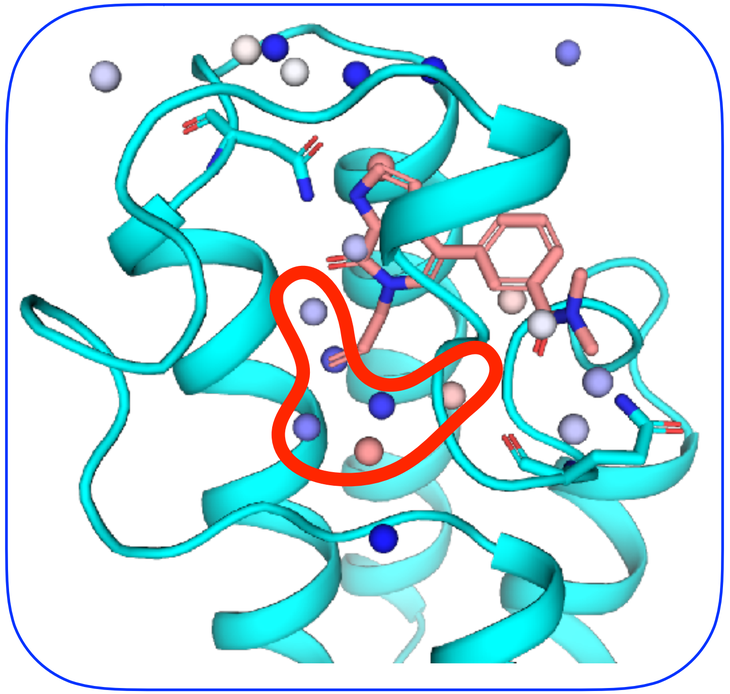


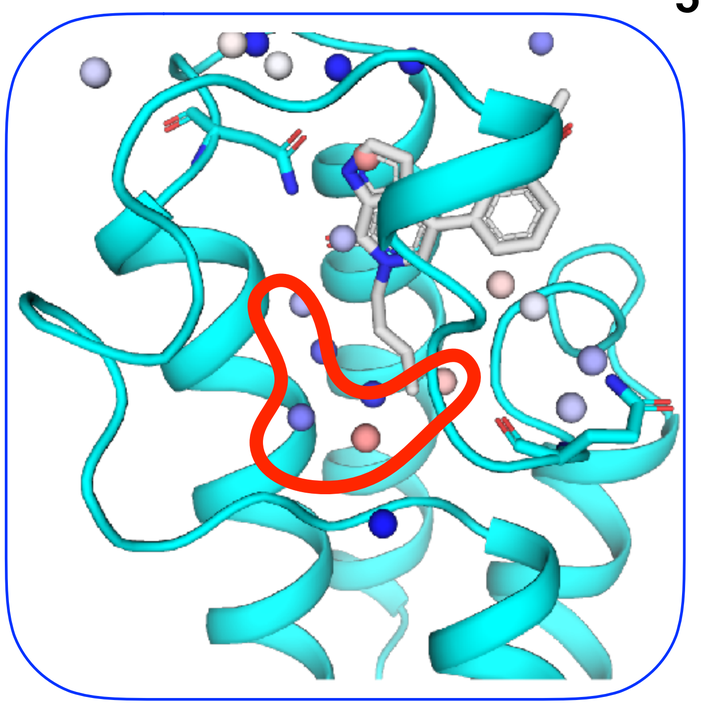
compound 3
470 nM

T. D. Crawford, et al., *J. Med. Chem.* **2016**, *59*, 5391

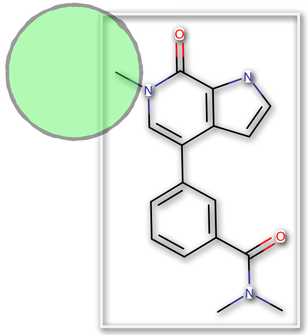
Validation (Bromodomain)





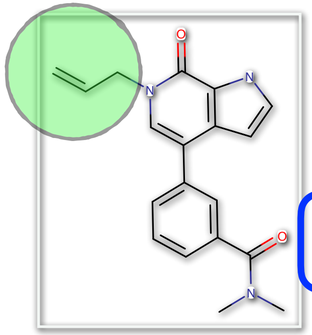


5 kcal/mol



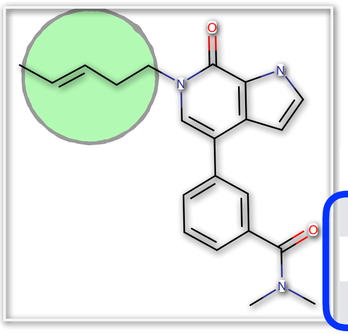
compound 2
92 nM

	Distance (Å)
W2	3.0
W5	3.4
W6	3.8



compound 3
6300 nm

	Distance (Å)
W2	0.7
W5	2.2
W6	3.8



compound 4
470nm

	Distance (Å)
W2	2.6
W5	2.0
W6	1.2

-5 kcal/mol

Conclusion

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Rationally Repelling Water
Gain **Higher** Affinity
(Higher probability)

I appreciated for your time
Q&A