Acknowledgements

Shoichet Lab @ UCSF


Chase Webb


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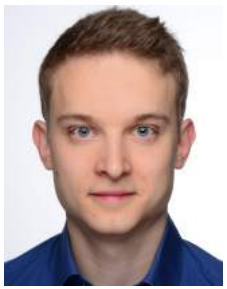
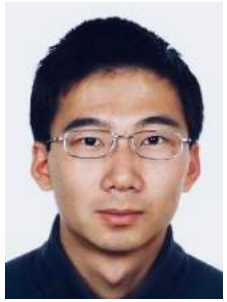

Stefan Gahbauer


Anat Levit

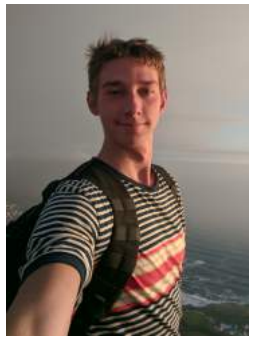

Moira Rachman


Tia Tummino


Isha Singh


Shuo Gu


Shiming Peng


Henry O'Donnell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Jiankun Lyu


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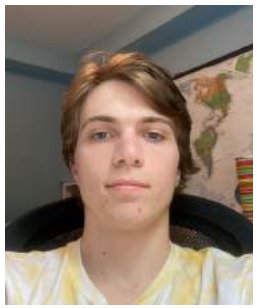
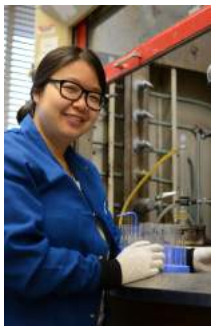
Munkzhul Khurelbaatar


John Gutierrez


Benjamin Tingle

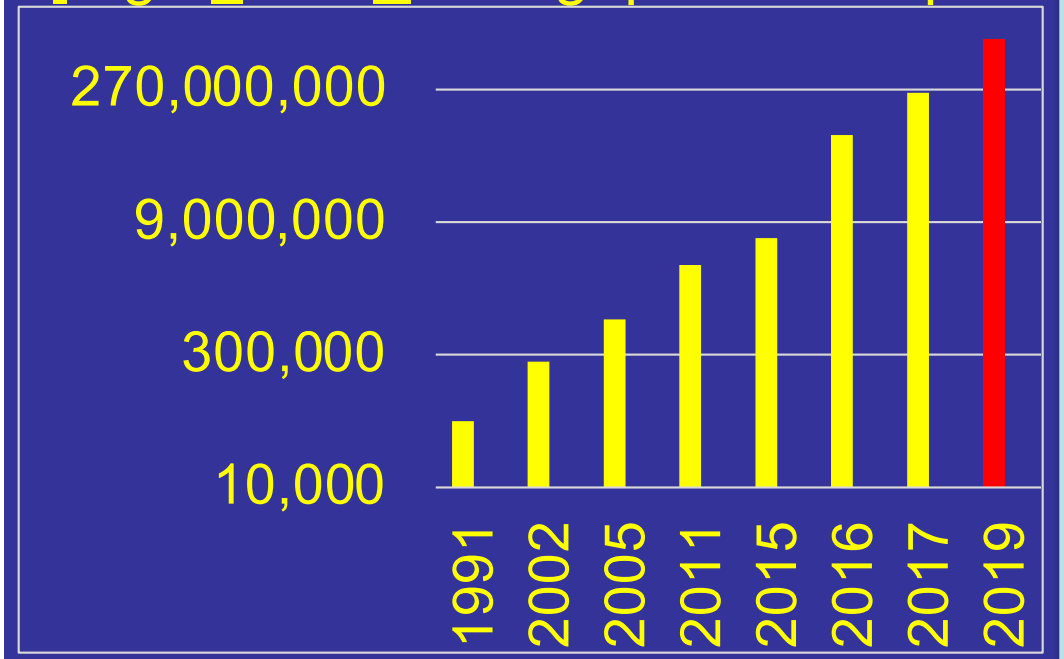

Khanh Tang

Thanks to software vendors
OpenEye Scientific Software
Molinspiration. ChemAxon
NextMove Software
Molecular Networks
Schrodinger

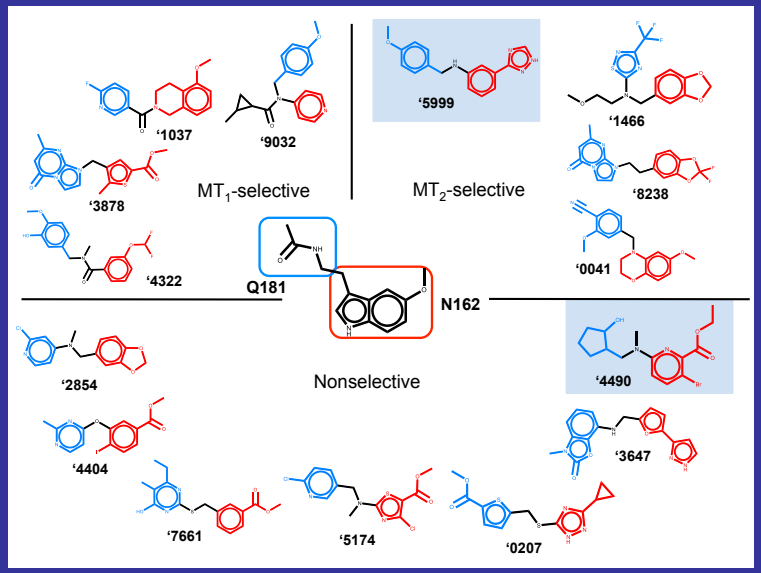
Support: NIH, DARPA

Large Library Docking for Receptor Deorphanization

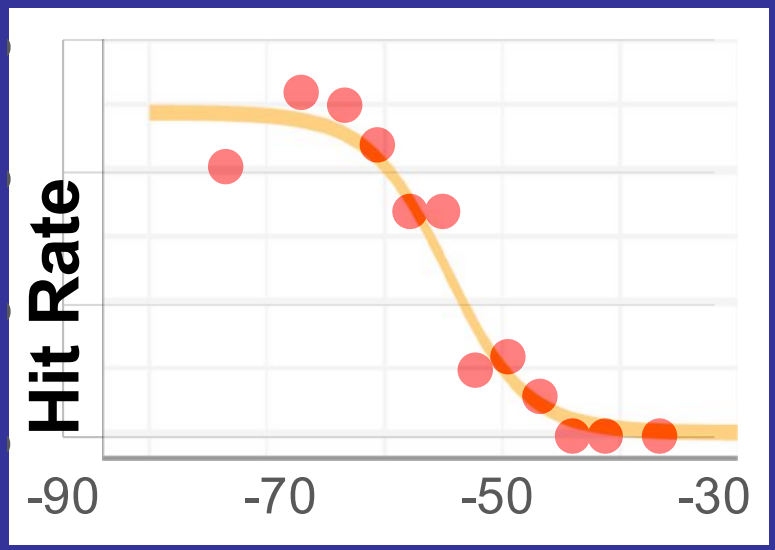
large scale docking: promise & peril



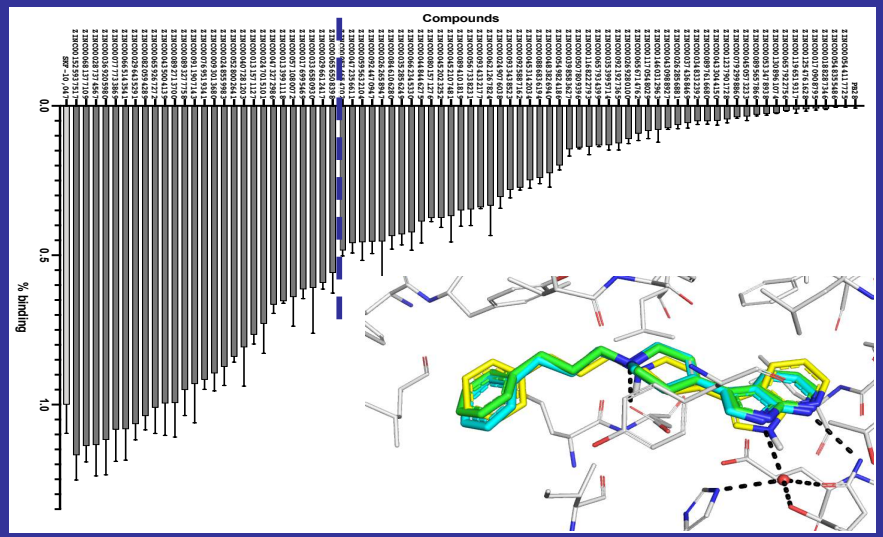
new melatonin receptor ligands



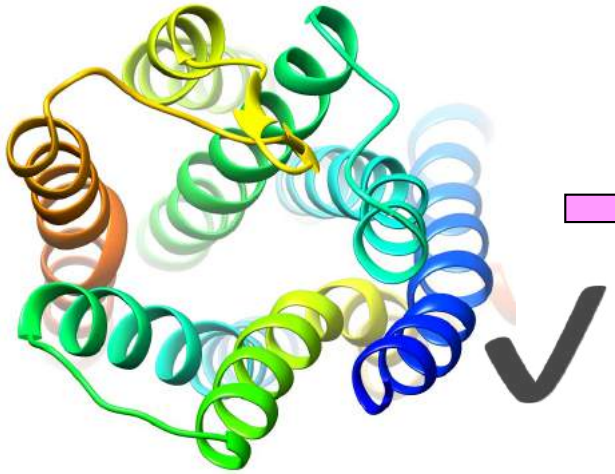
hit-rate by dock score (549 cmpds)

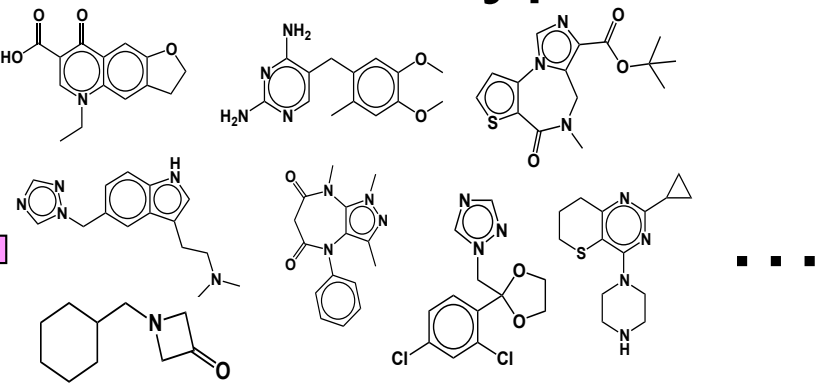


new sigma2 receptor ligands

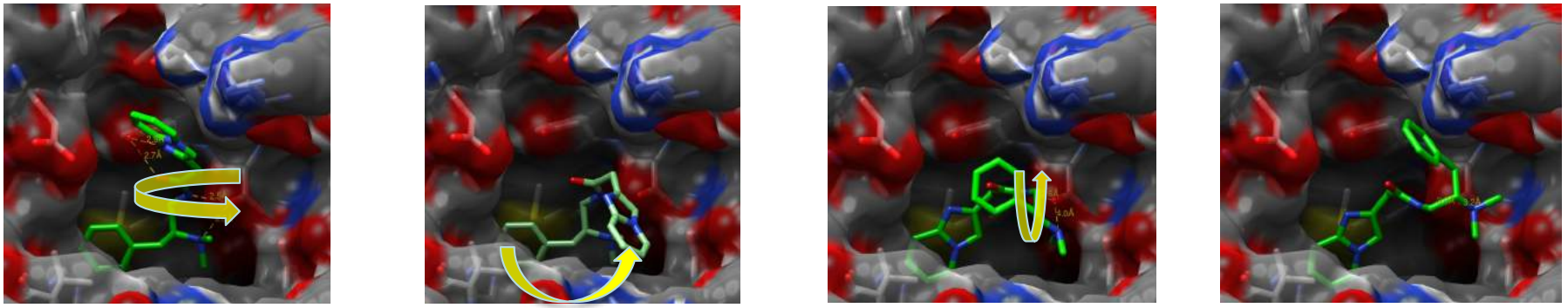


docking large libraries for new chemotypes





library of ***available*** molecules



each in ~10^6 orientations & conformations

Carlsson, *NCB* 2011
Kruse, *Mol Pharm* 2013
Huang, *Nature* 2015
Manglik, *Nature* 2016
Lansu, *NCB* 2017
Wang, *Science* 2017

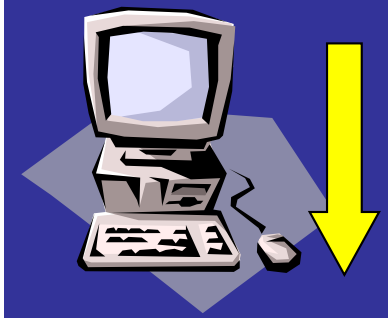
Score for fit

test high-ranking molecules

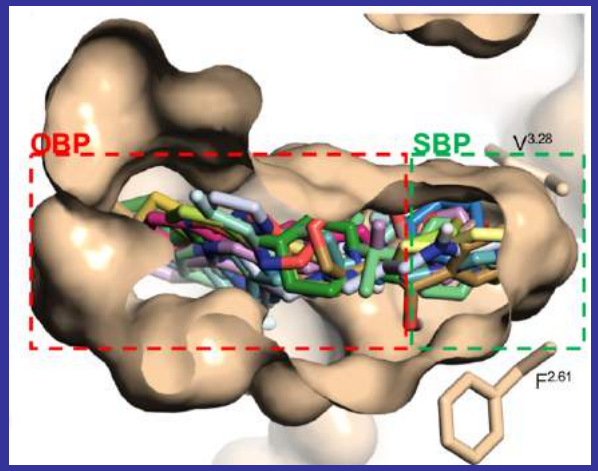
An explosion in readily-accessible molecules

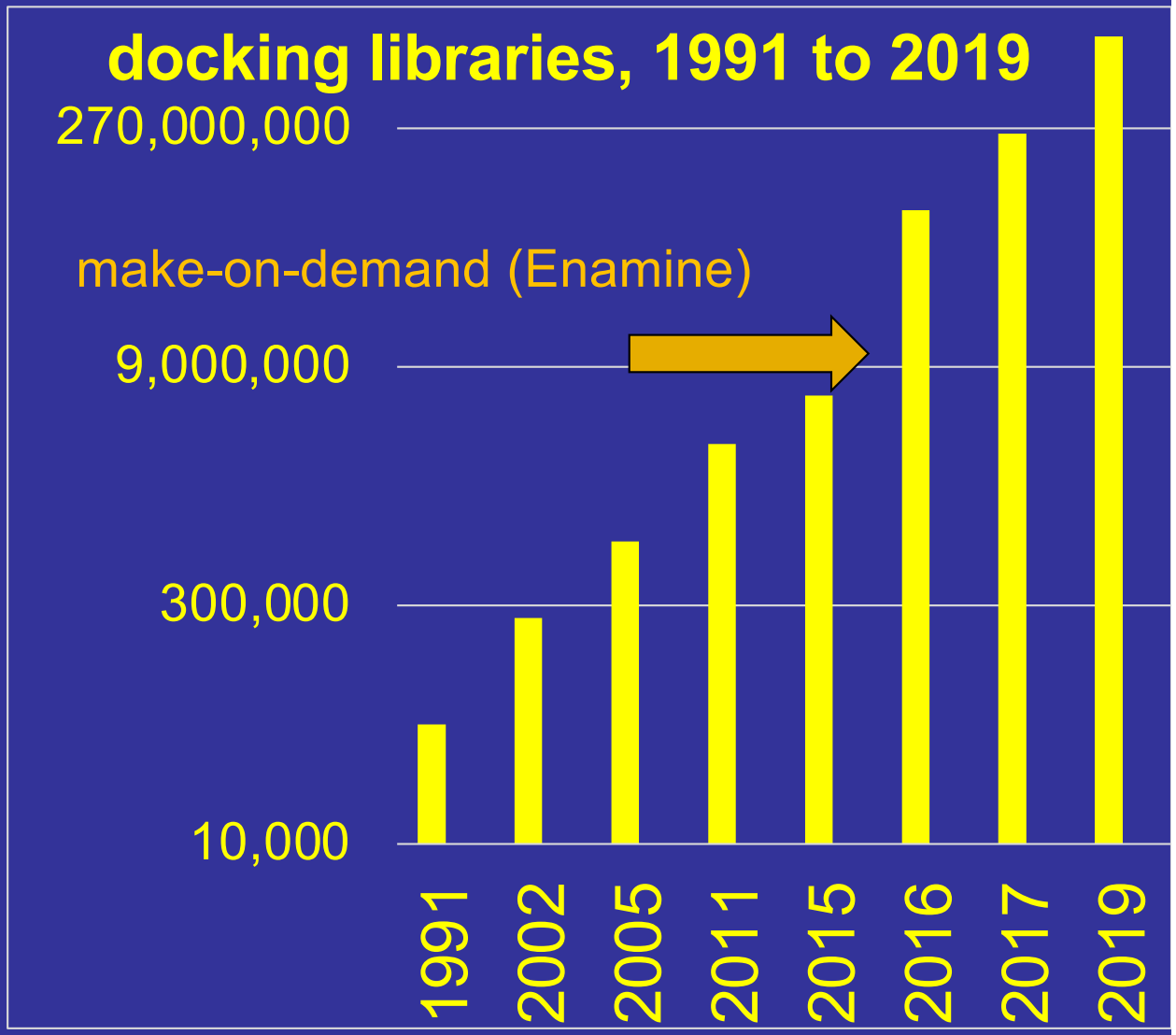
Yurii Moroz

3.5→500 million compounds



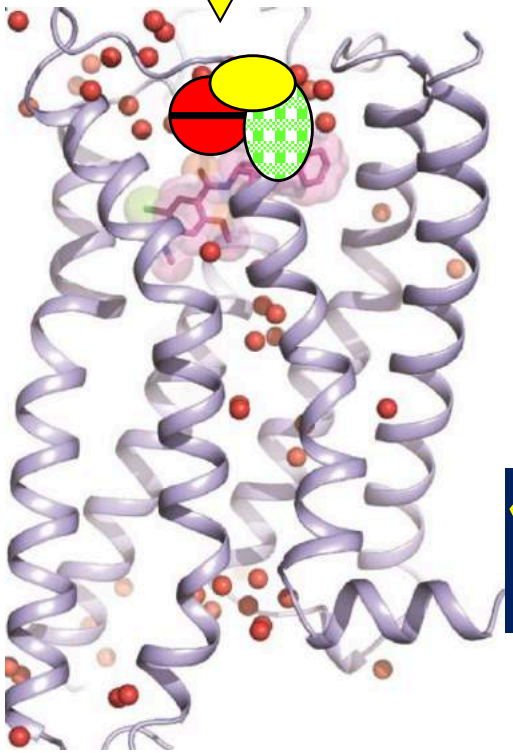
300 trillion complexes





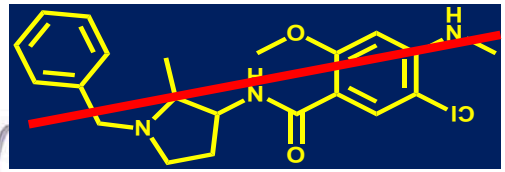
How does docking rank predict hit rate success? 138 million vs. dopamine D4

138 million molecules
10^{14} complexes
1 mol/sec;10^3 cores
1.8 cluster days



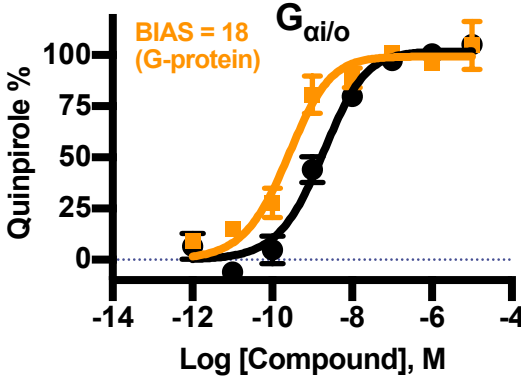
~~Test 30~~

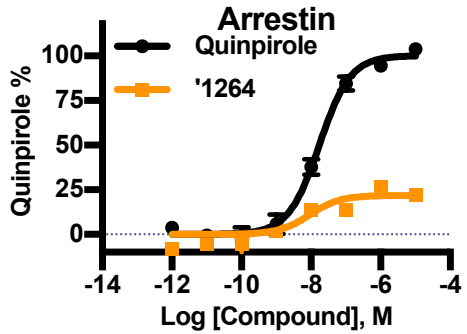
Test 549



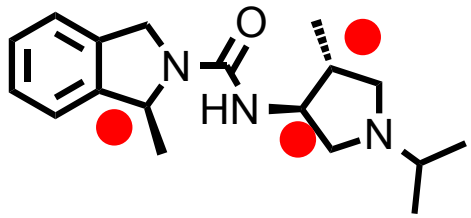
ZINC361131264, 18x bias

Rank: 1067



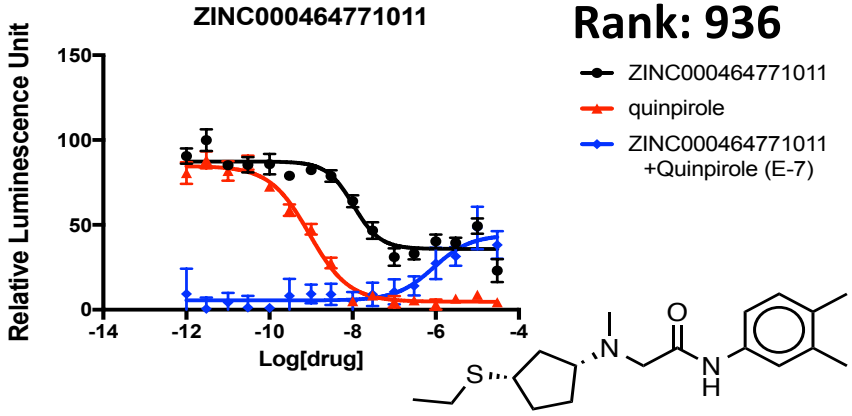


D4 = 0.18 nM
D2 > 10,000 nM
D3 > 10,000 nM



ZINC000464771011

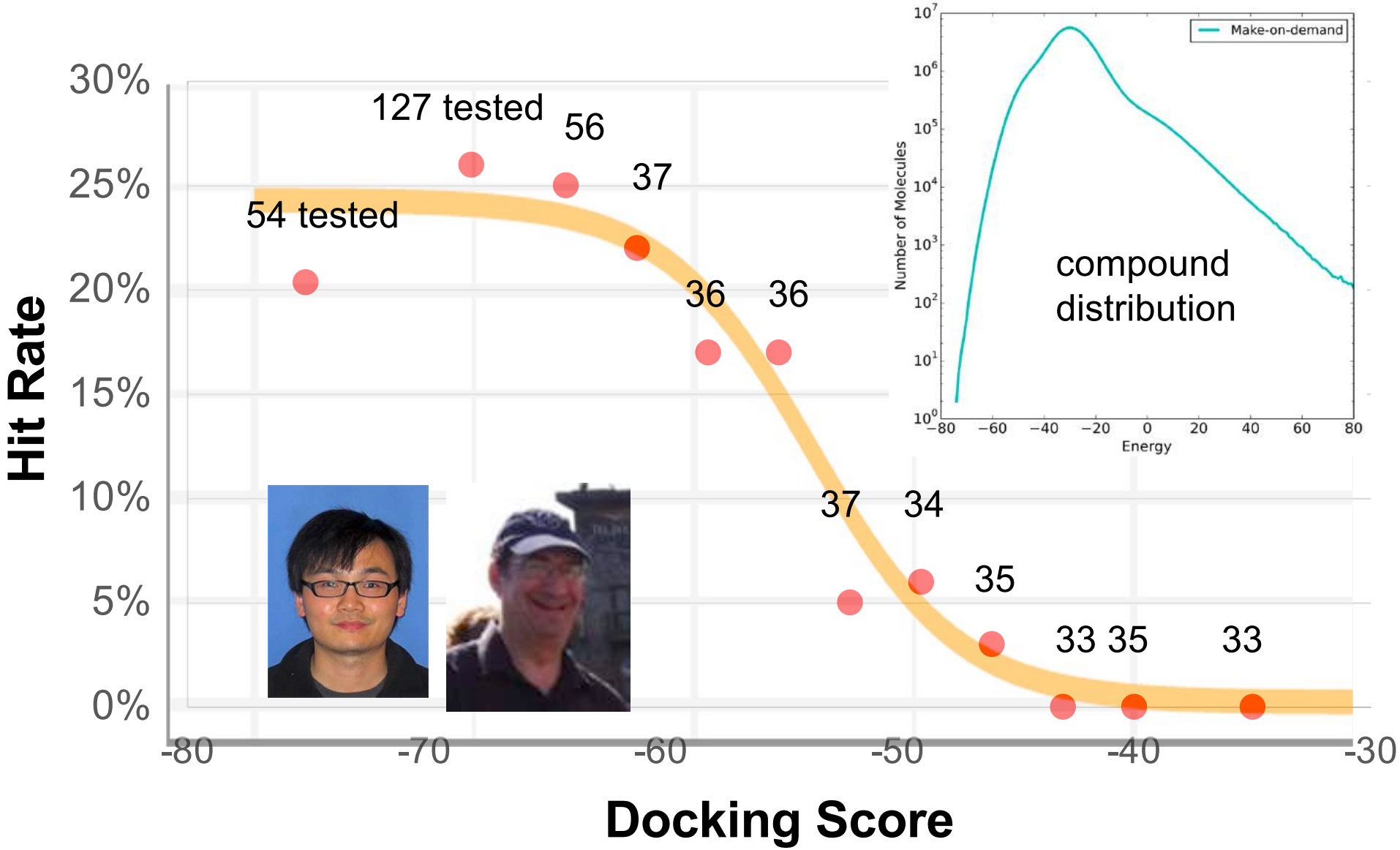
Rank: 936



D4 = 10 nM
D2 > 10,000 nM
D3 > 10,000 nM

JK Liu, T Balius, S. Wang, B. Roth, ***Nature*** 2019

AUC predicts 452,000 DRD4 actives in 72,600 scaffold families

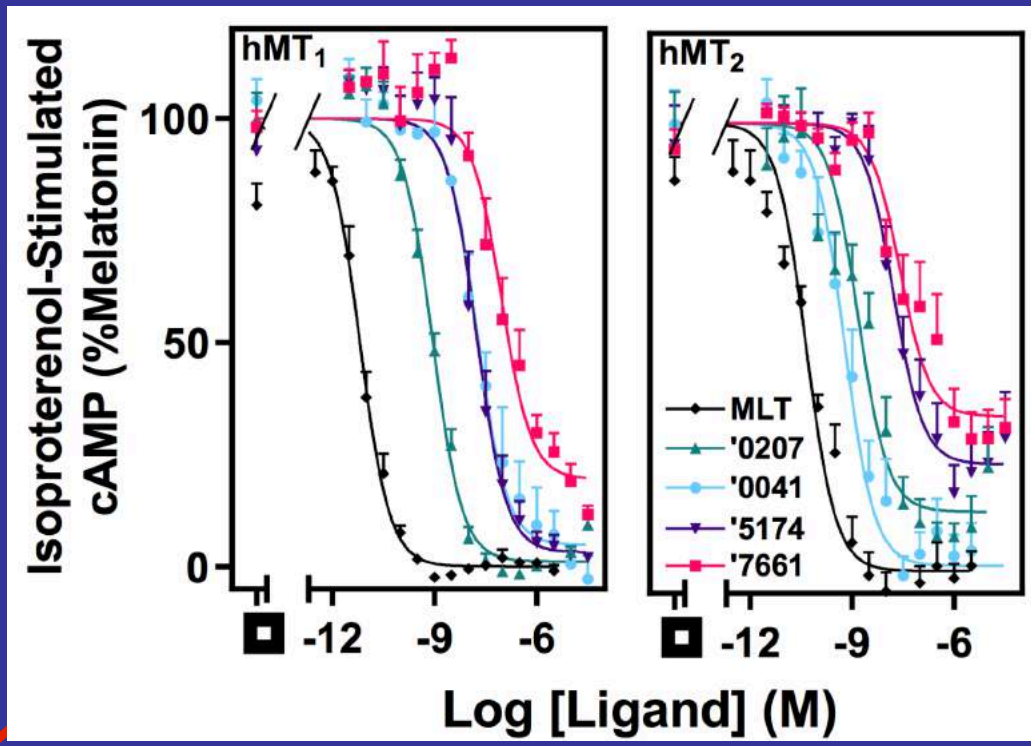


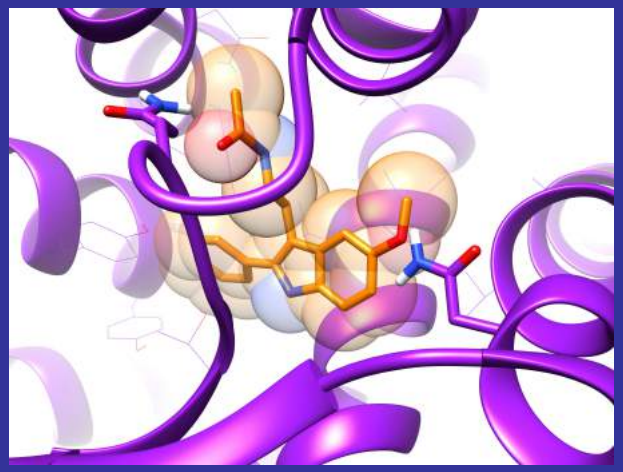
Sheng Wang & Bryan Roth; Lyu et al., ***Nature*** 2019

LSD vs melatonin GPCR: novel ligands with new pharmacology

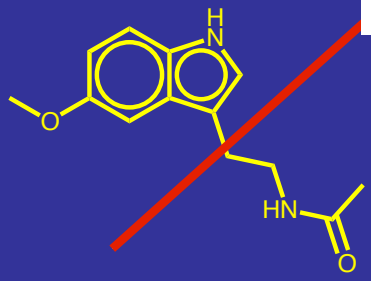
1.7×10^8 molecules
1.7×10^6 configs each
2.5×10^{14} complexes
2 cluster days

15 hits, 6 μM to 250 pM

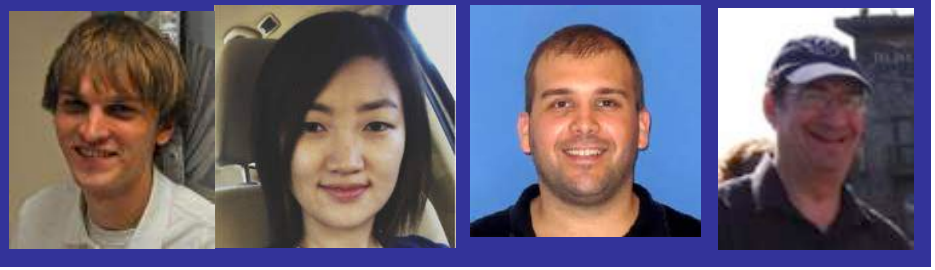




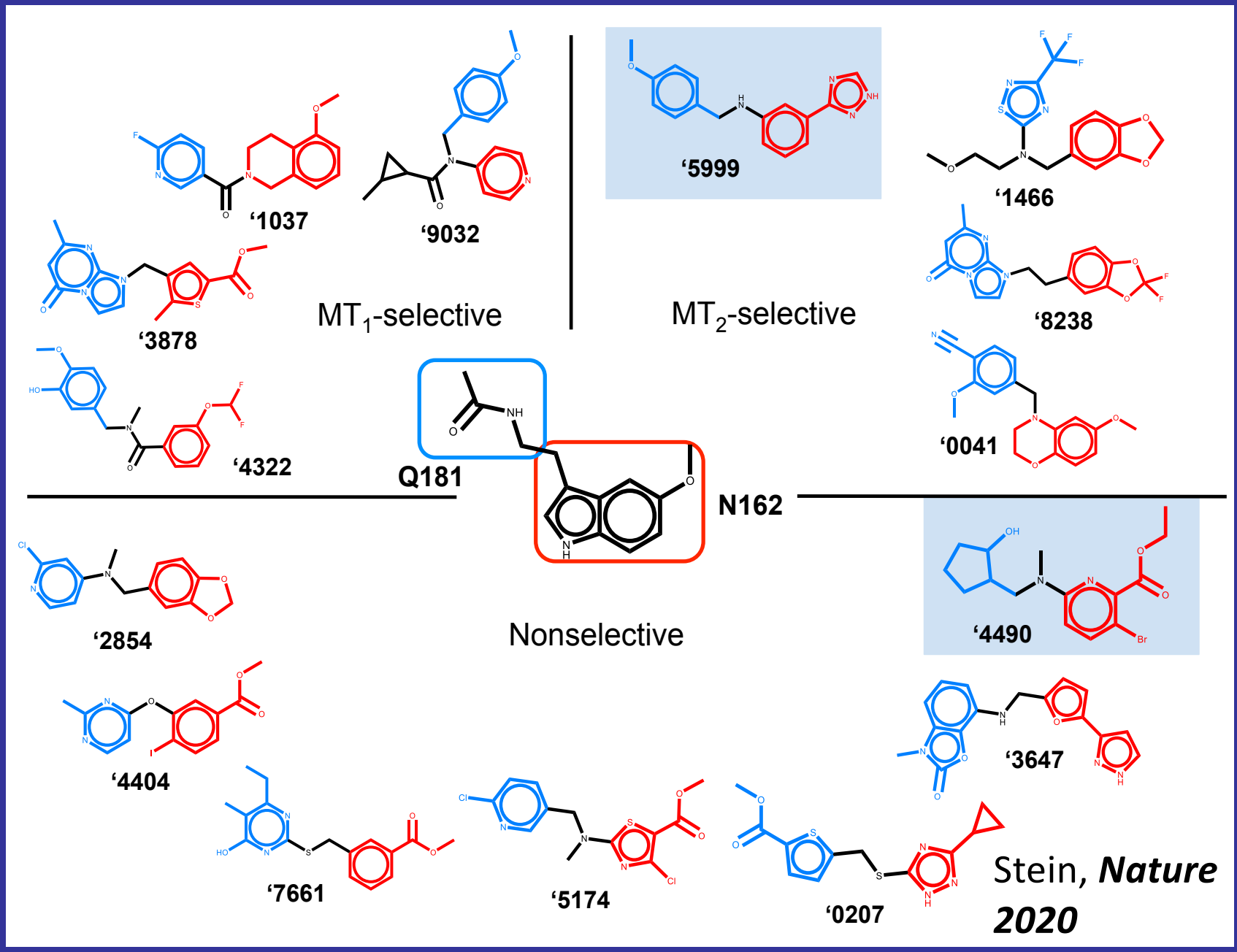
synthesize & test 38



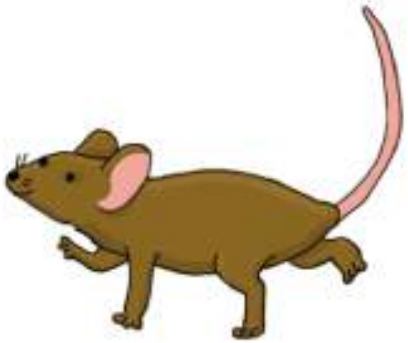
Reed Stein, Hye Jin Kang, John McCorvy, Bryan Roth, ***Nature*** *2020*

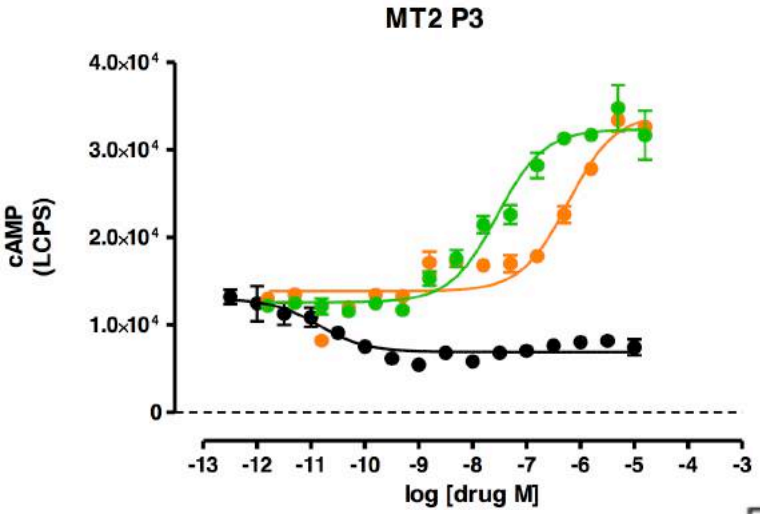


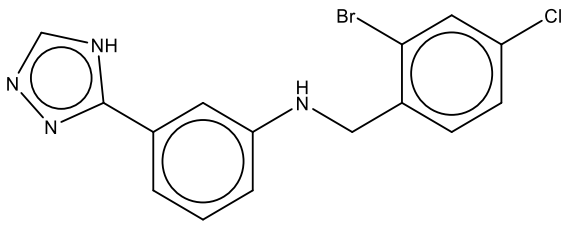
15 novel chemotypes, with a range of functions

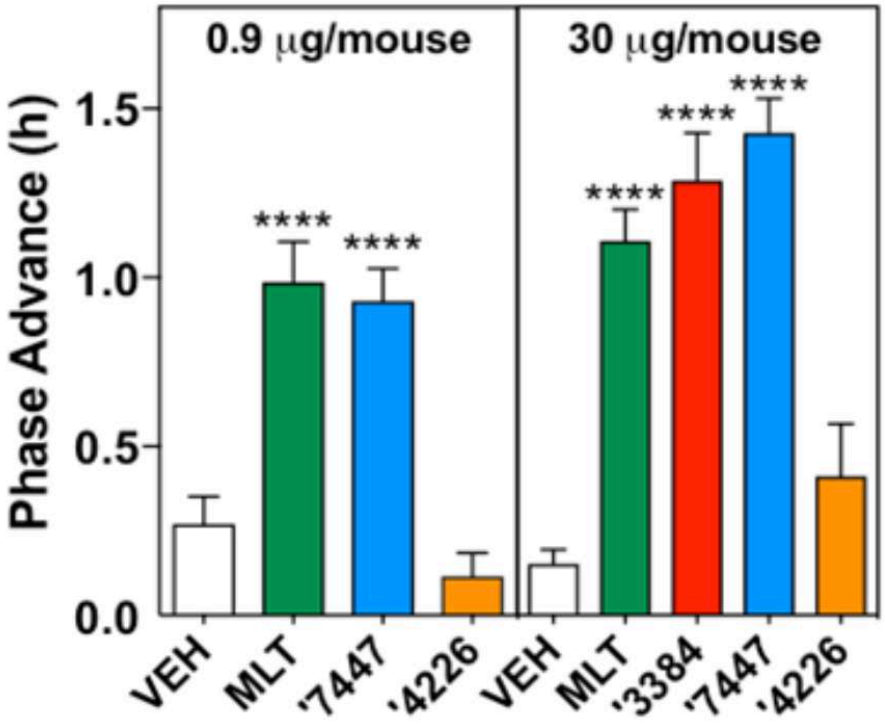


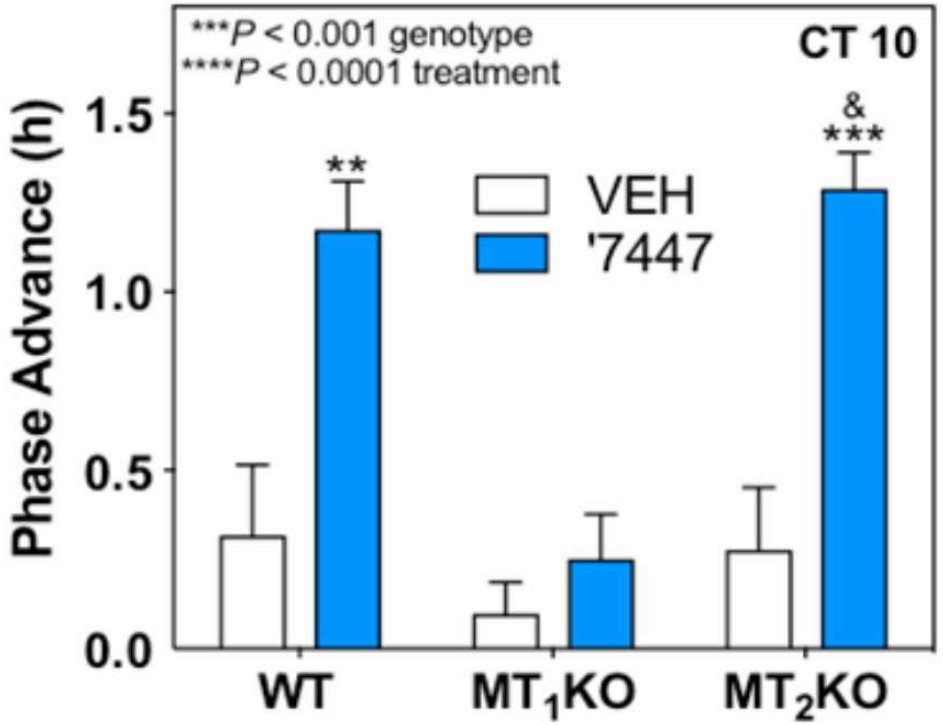
unexpected in vivo behavior of MT_1-selective inverse agonists in circadian rhythm









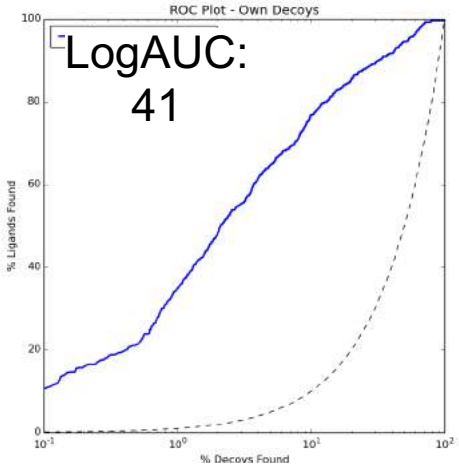


Margarita Dubocovich, Stein ***Nature*** 2020

Docking 103 million cations *vs* sigma2 receptor predicts new chemotypes

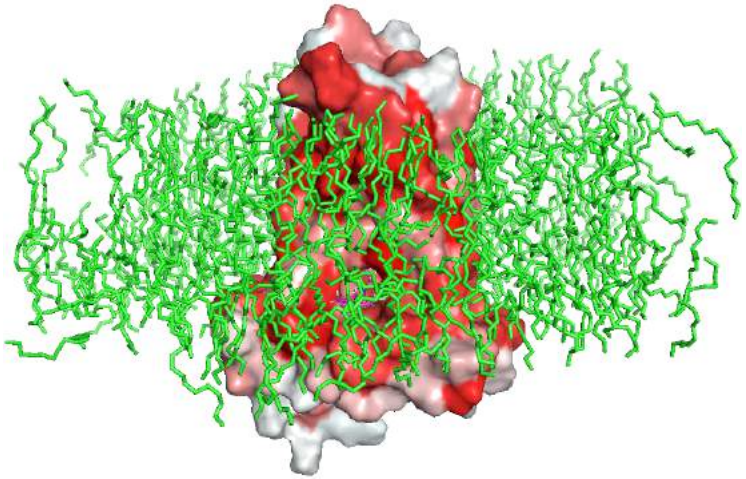
Sigma2 structures from Kruse lab Aug/7th/2019

- Little is known about sigma2
- Sigma2-selective probes



86 ordered Jan/3rd/2020
79 received
93% success rate Feb/25th/2020

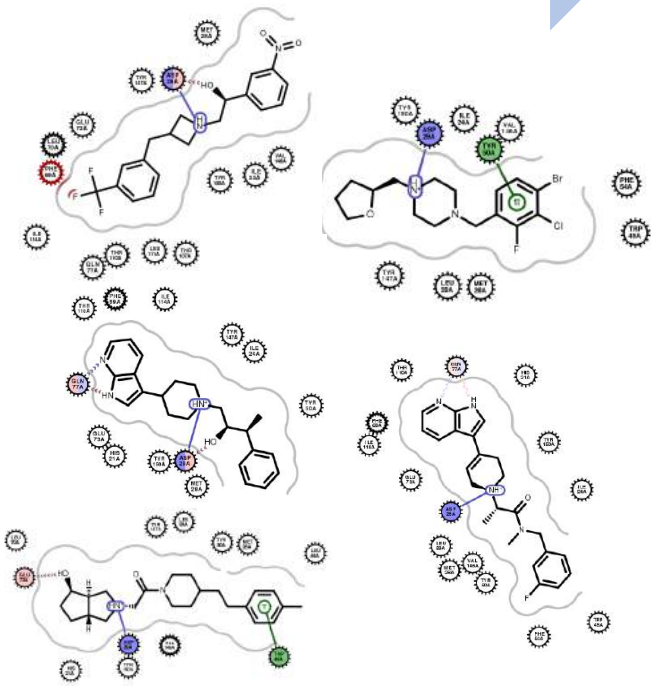
Model optimization → Hit picking



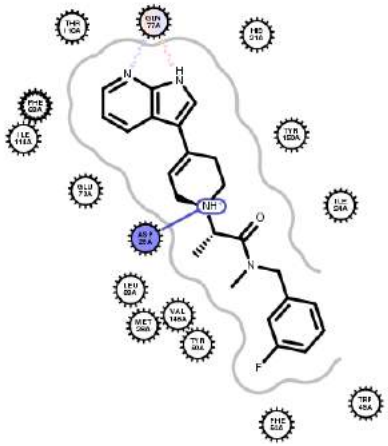
Unpublished

Large-scale docking of **103M cations** from ZINC15 Oct/10th - Oct/12th/2019

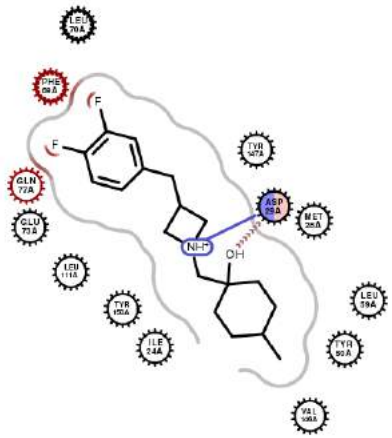
5.3×10^{13} complexes
4.5×10^{4} core hours
1.9 cluster days (1000 cores)



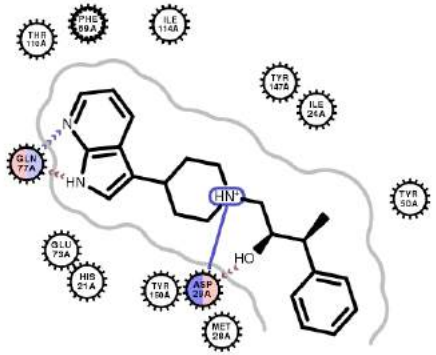
13 best sigma2 molecules from the primary screen have a K_i value against sigma2 from 2.4 nM to 67.8 nM



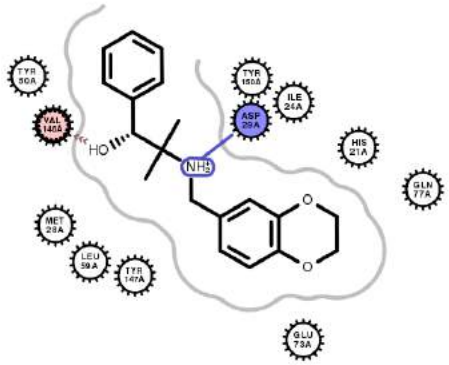
ZINC000533478938 (**43x**):
S1R Ki = 1470 nM
S2R Ki = 34 nM



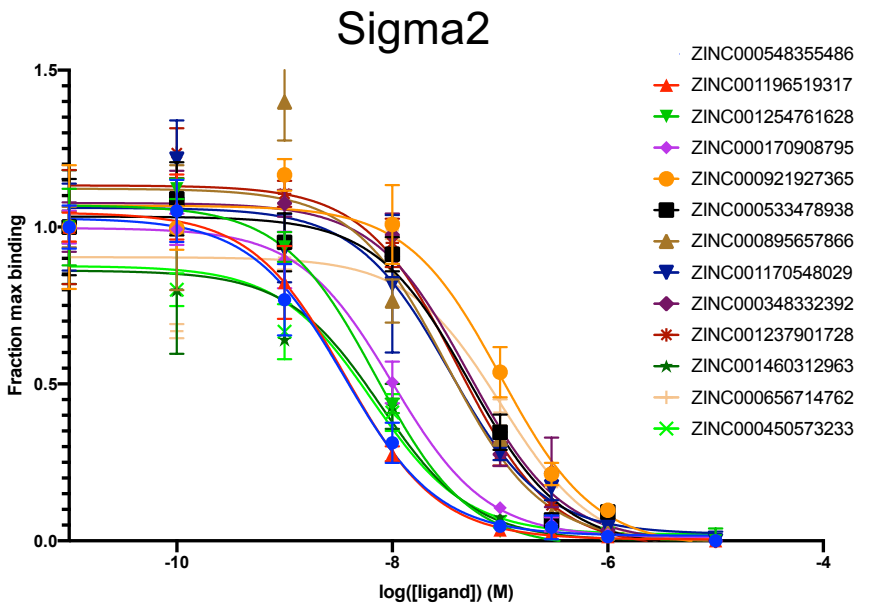
ZINC000548355486 (**2x**)
S1R Ki = 4.9 nM
S2R Ki = 2.4 nM

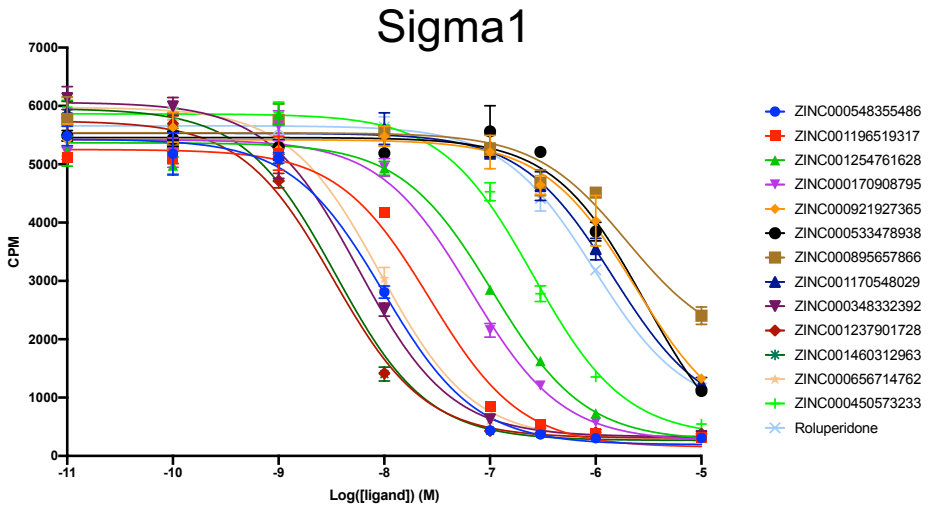


ZINC000450573233 (**30x**):
S1R Ki = 128 nM
S2R Ki = 4.3 nM



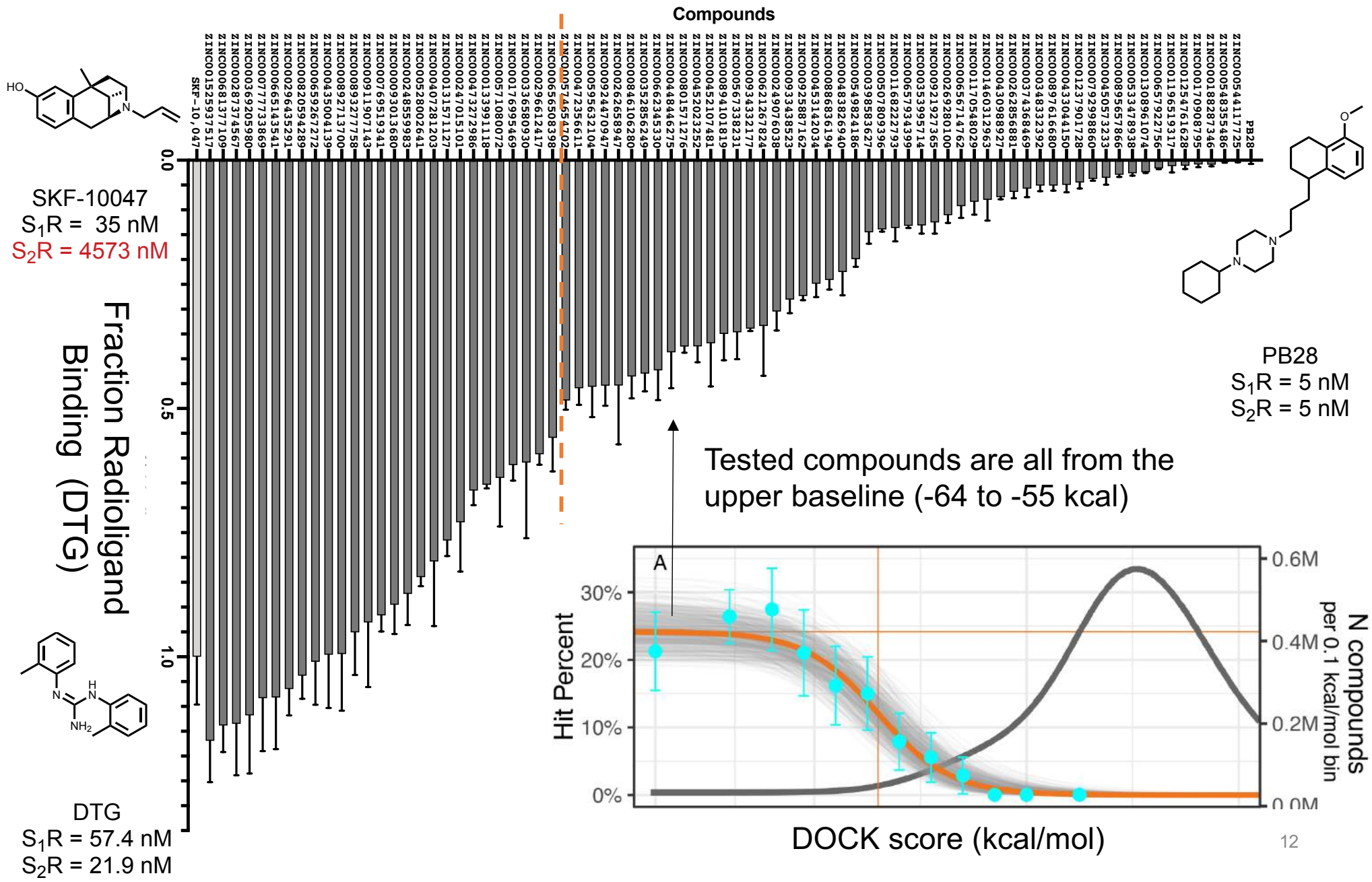
ZINC000895657866 (**46x**):
S1R Ki = 990 nM
S2R Ki = 21 nM



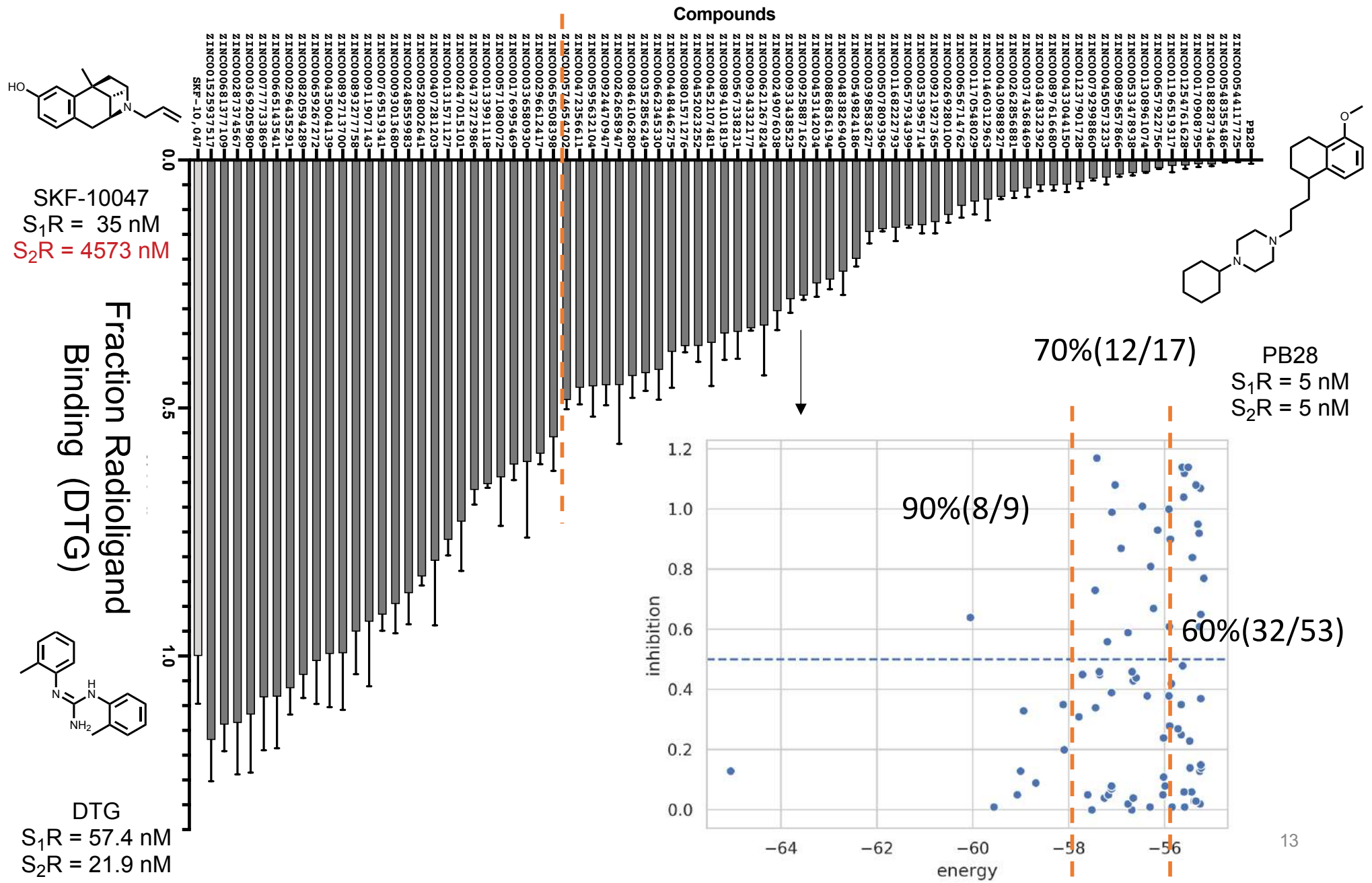


Assaf Alon, Andrew Kruse

At 1 μM concentration, 52 of the 79 molecules displaced more than 50% radioligand DTG, high hit rate 66%

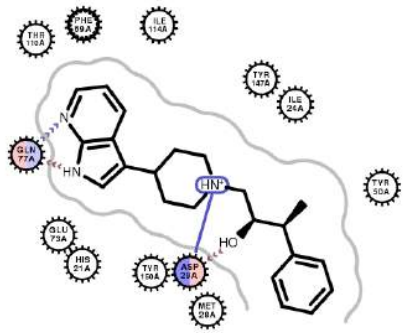


A full hit rate curve may reveal a slope to the upper plateau



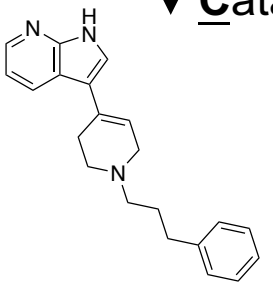
The ‘5220-bound crystal structure confirms the docking prediction and reveals a water-mediated interaction between the azaindole and Gln77

- The docked pose
- The crystal pose of chain a (RMSD: 0.88Å)
- The crystal pose of chain b (RMSD: 0.87Å)

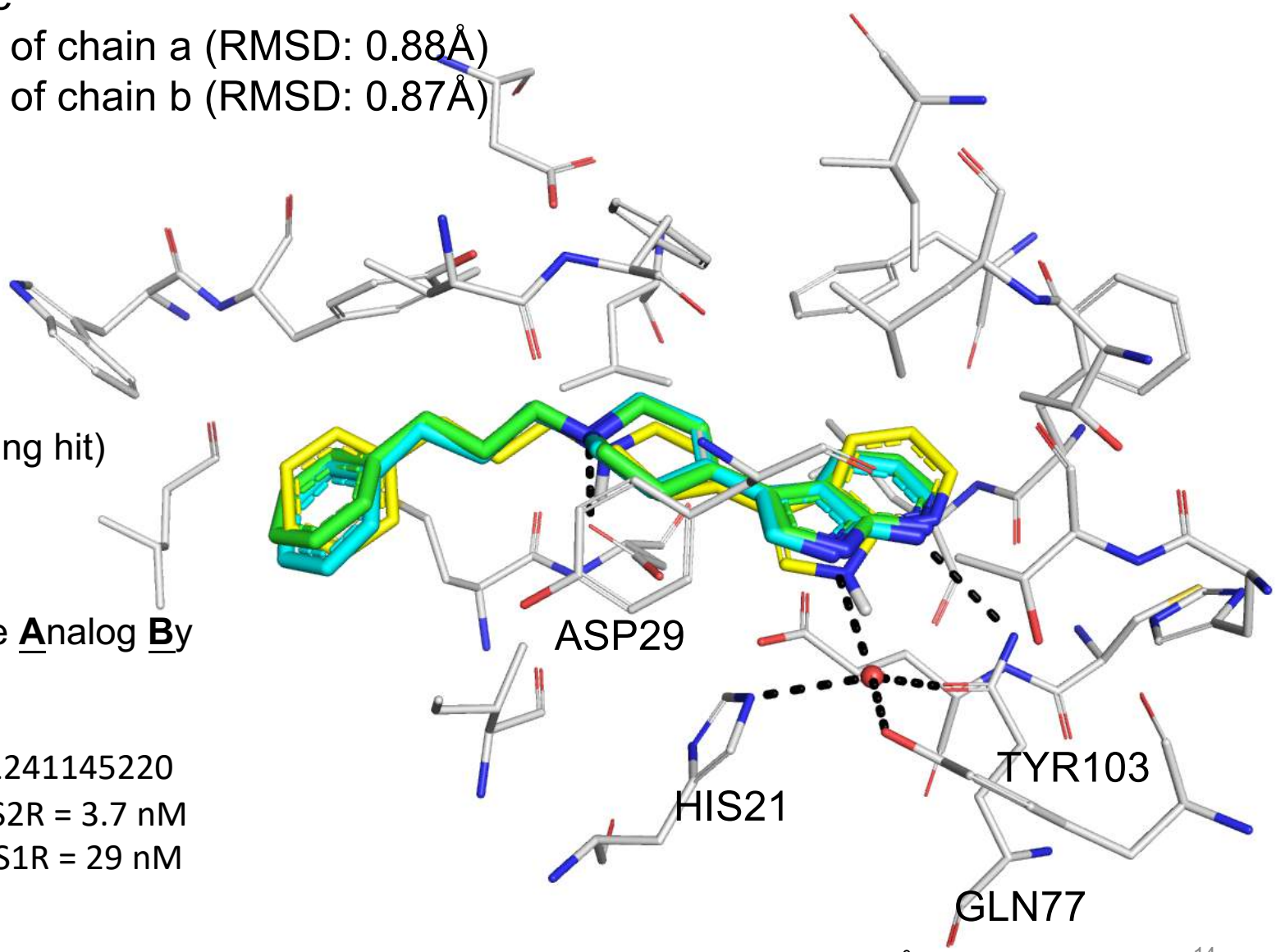


‘3233 (original docking hit)
S1R Ki = 128 nM
S2R Ki = 4.3 nM

↓ extensive **A**nalog **B**y **C**atalog



Z1241145220
Ki S2R = 3.7 nM
Ki S1R = 29 nM



Assaf Alon, Andrew Kruse

Resolution: 2.4Å

access to new chemotypes is exploding