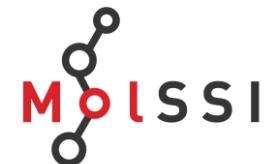


# Discovery and Characterization of Y4R Allosteric Modulators using Computer-Aided Drug Design (CADD)



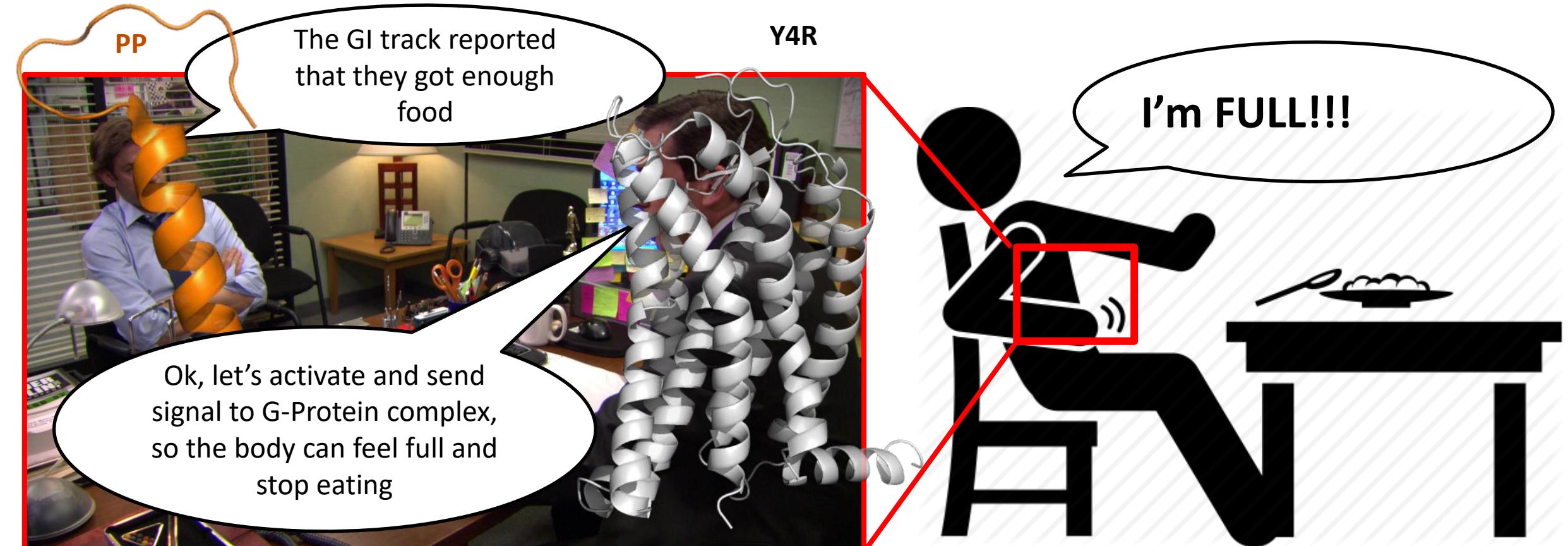
Oanh Vu

Advisor: Jens Meiler  
Vanderbilt University



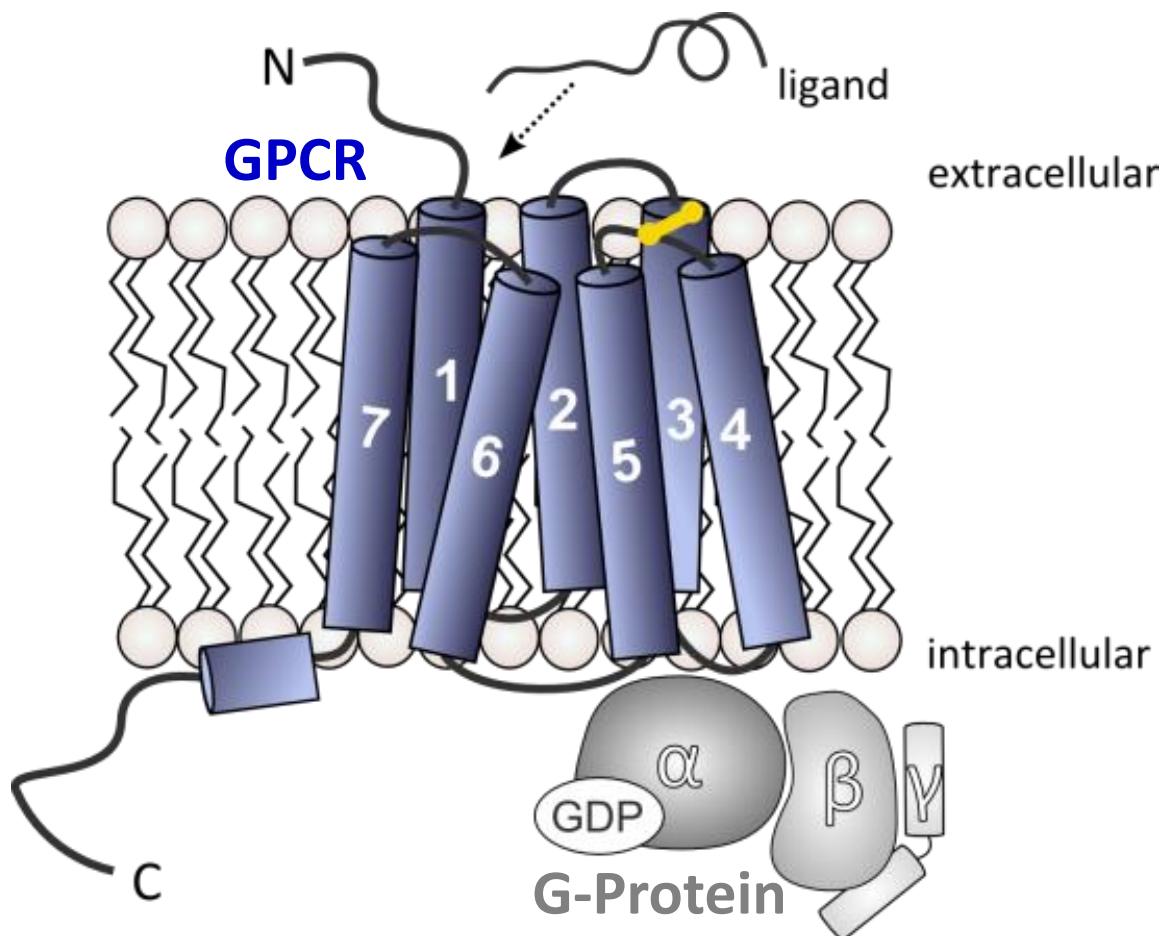


# Pancreatic Polypeptide Suppressed Appetite and Food Intake



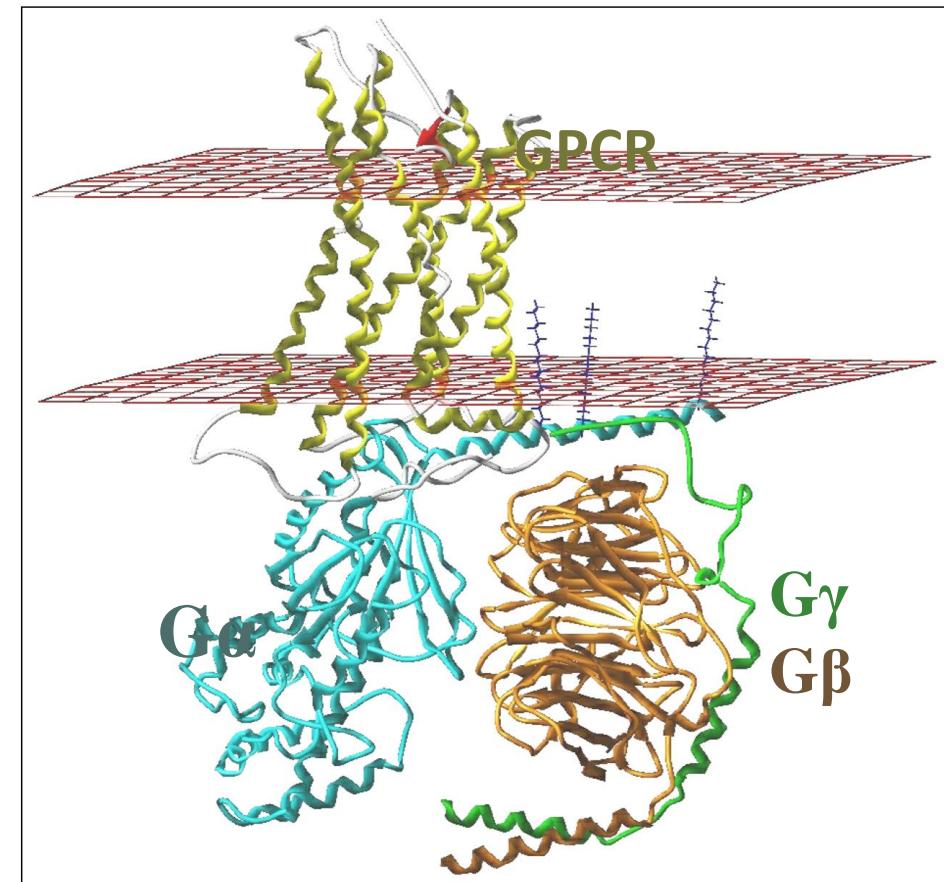
# Y4R is a peptide bound G protein coupled receptors

Schematic structure of a GPCR



<https://biophysik.medizin.uni-leipzig.de/>

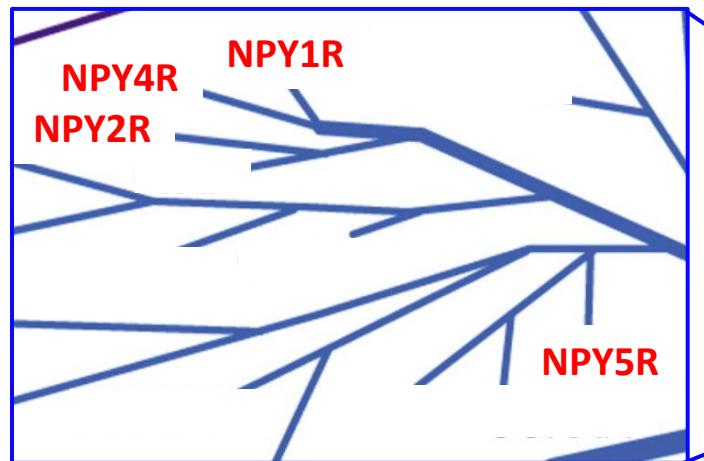
Atomic structure of a GPCR



Heng et al. (2013). *Biotechnology advances*, 31 8, 1676-94.

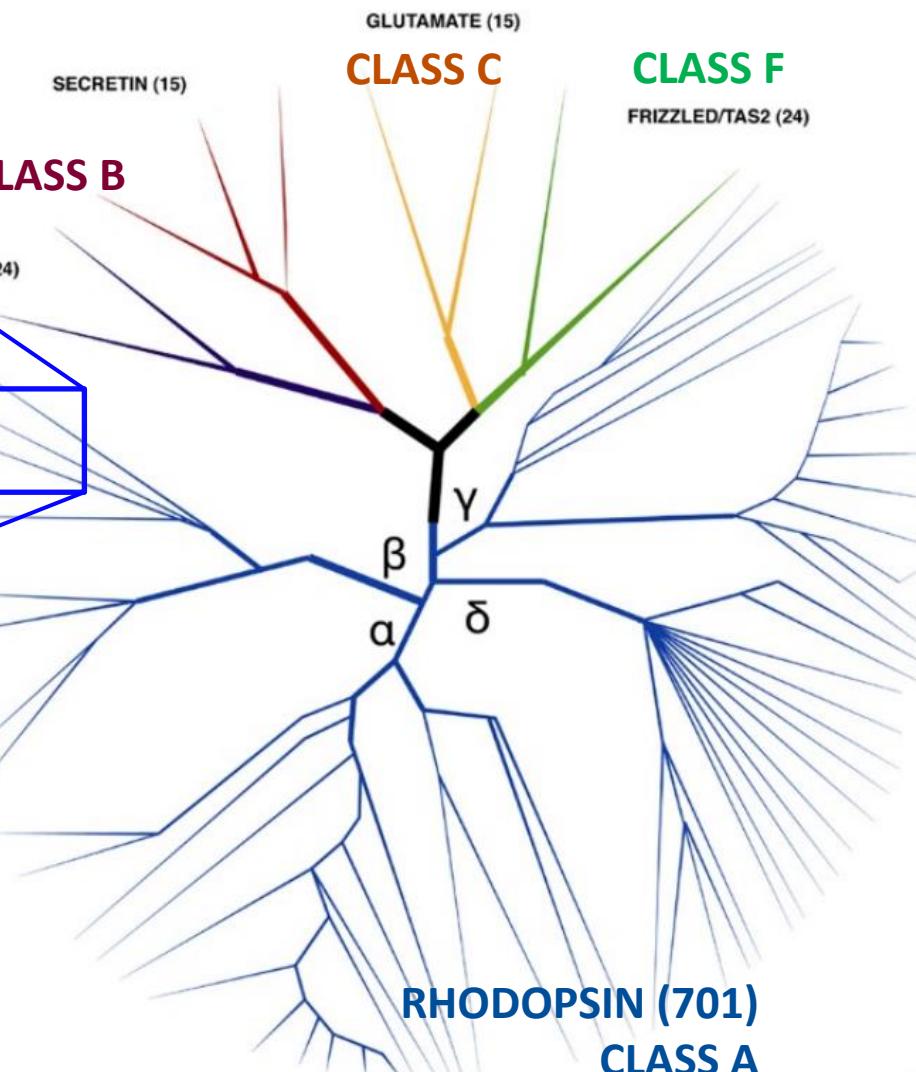
# NPY Receptors: Multi-peptide/Multi-Receptor System

## NPY receptors in GPCR Phylogenetic Tree



## Ligand preference of NPY receptors

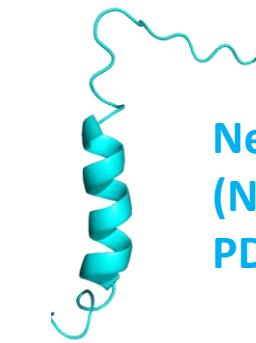
Receptor	hY <sub>1</sub>	hY <sub>2</sub>	hY <sub>4</sub>	hY <sub>5</sub>
Amino acids number	384	381	375	445–455
Native ligand	NPY	NPY	PP	NPY
	PYY	PYY		PYY



Kufareva et al. Structure 19, 1108–1126

Pedragosa-Badia X, Stichel J, Beck-Sickinger AG. Front Endocrinol (Lausanne). 2013 Feb 4;4:5

## Peptide Ligands



Neuropeptide Y  
(NPY)  
PDB ID: 1FVN



Peptide YY  
(PYY)  
PDB ID: 2DEZ

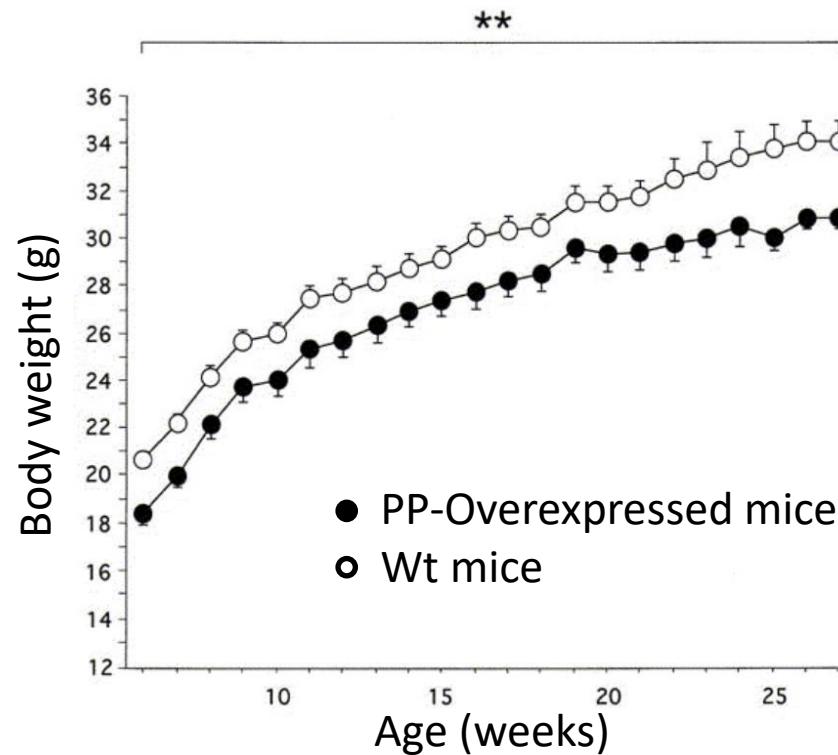


Pancreatic  
Polypeptide (PP)  
PDB ID: 1LJV



# Y4-PP as a Drug Target for Obesity and Eating Disorder

## Mice studies



PP transgenic mice gained less weight than control mice

## Human studies

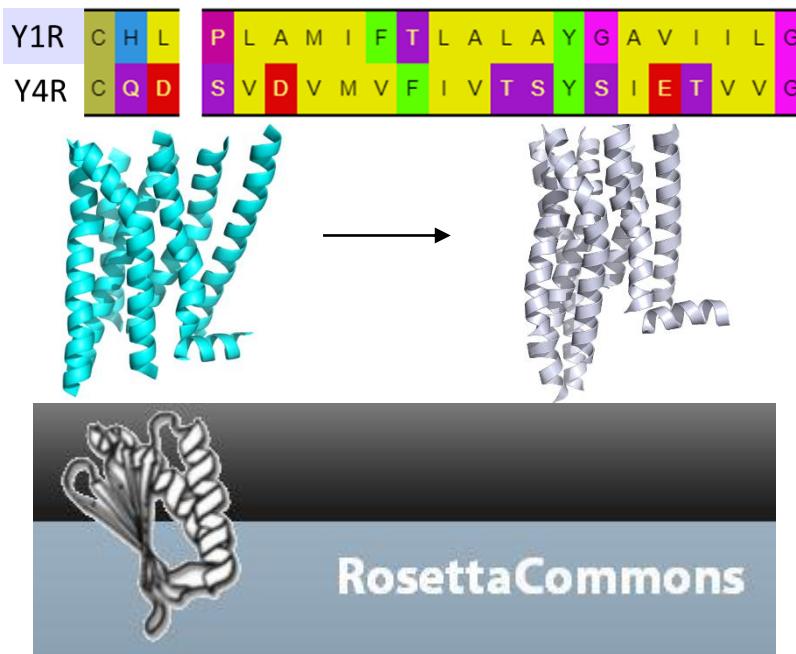
- PP infusion reduced cumulative 24-hour energy intake by ~25%.
- Phase I study of a PP analog (PP 1420) reported well tolerated in healthy human subjects with no nausea  
=> targeting PP-Y4R is safe

Ueno et al. Gastroenterology. 1999 Dec;117(6):1427-32.  
Batterham et al. J Clin Endocrinol Metab. 2003 Aug;88(8):3989-92.  
Tan et al. Pharmacokinetics. Br J Clin Pharmacol. 2012;73(2):232–239.

# Challenge #1: How do we understand the structure of Y4R without an experimentally determined structure?

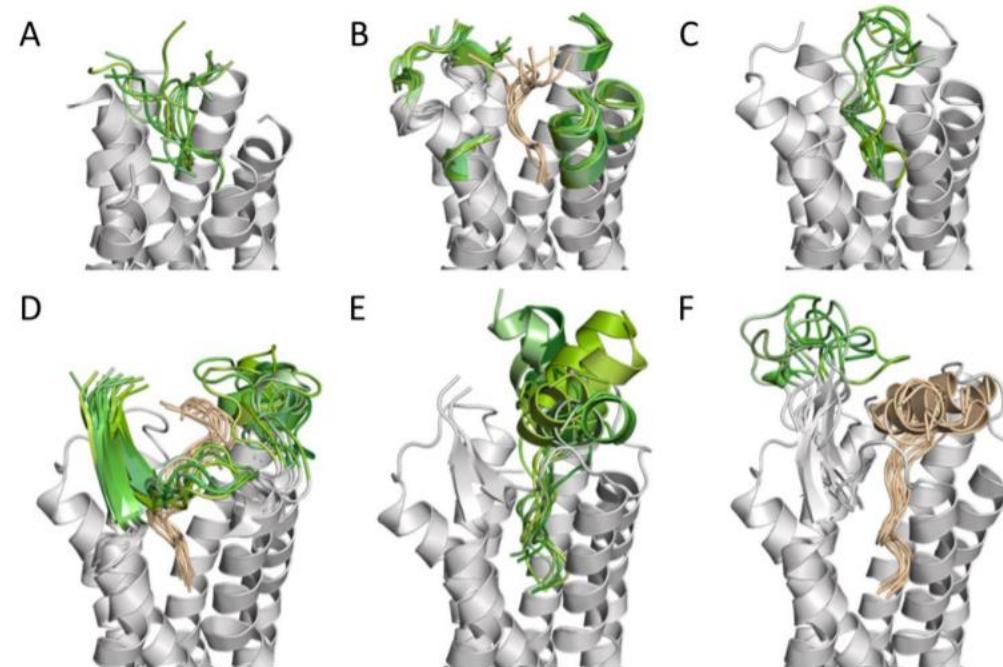
A computational model helps us understand the structure of Y4R

## Building homology models of Y4R from available GPCR structures



Song et al. 2013 Oct 8;21(10):1735-42.

## Flexible peptide docking with experimental restraints to model PP-Y4R interactions



Bender, B. et al., Structure, Volume 27, Issue 3, 2019



# Modeling membrane protein structure using Rosetta

## Physics-based energy terms

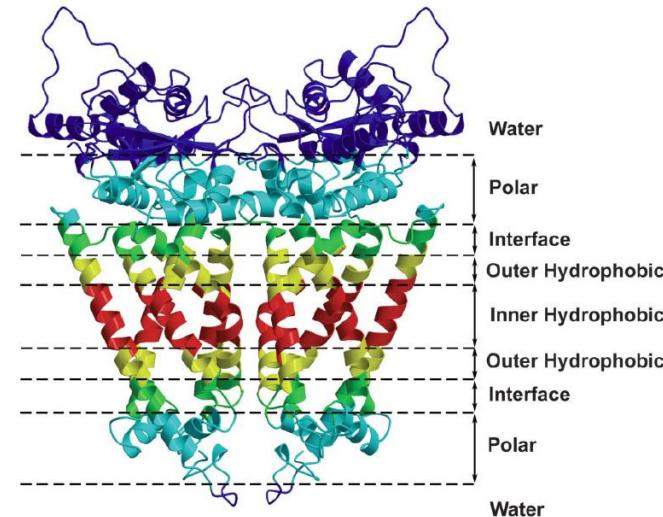
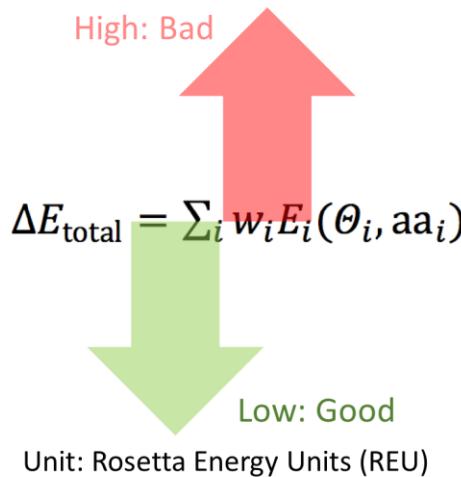
- Van der Waals energy
- Solvation
- Electrostatics
- Hydrogen bond energy

## Knowledge-based energy terms

- Ramachandran phi-psi angles

## Rosetta Membrane

- Secondary structure packing
- Implicitly considers polar, hydrophobic and transition environments

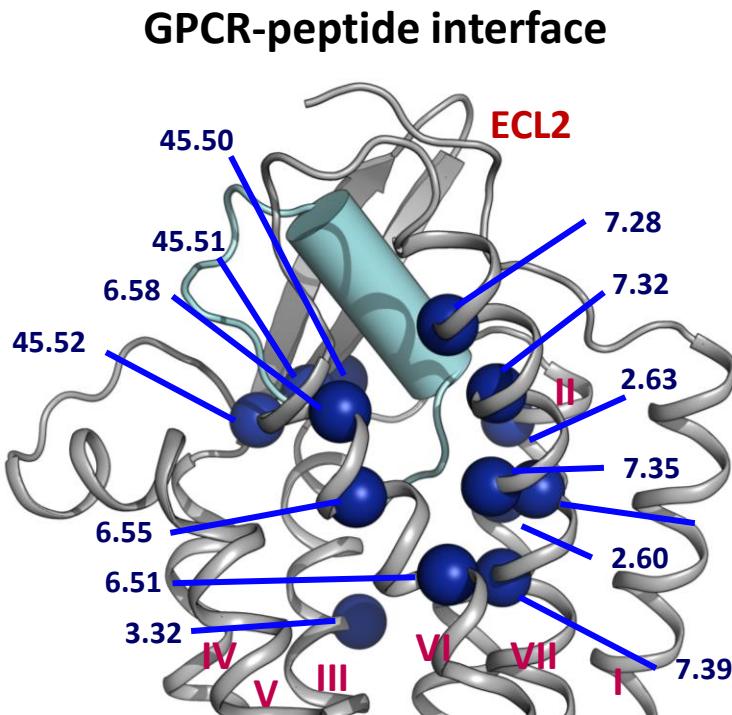


Alford et al. J Chem Theory Comput. 2017;13(6):3031-3048.

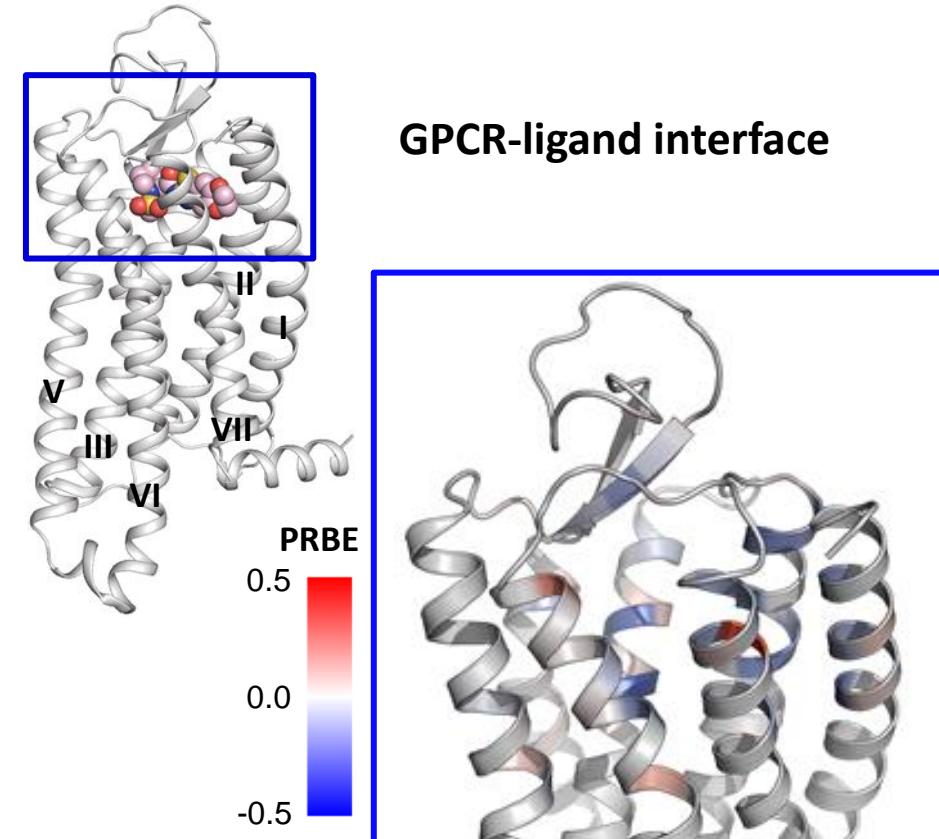
Yarov-Yarovoy, V., Schonbrun, J., & Baker, D (2006) Proteins, 62(4), 1010-25.



# Mapping Rosetta Binding Energy on Individual Residues Identifies Interface Hot Spots



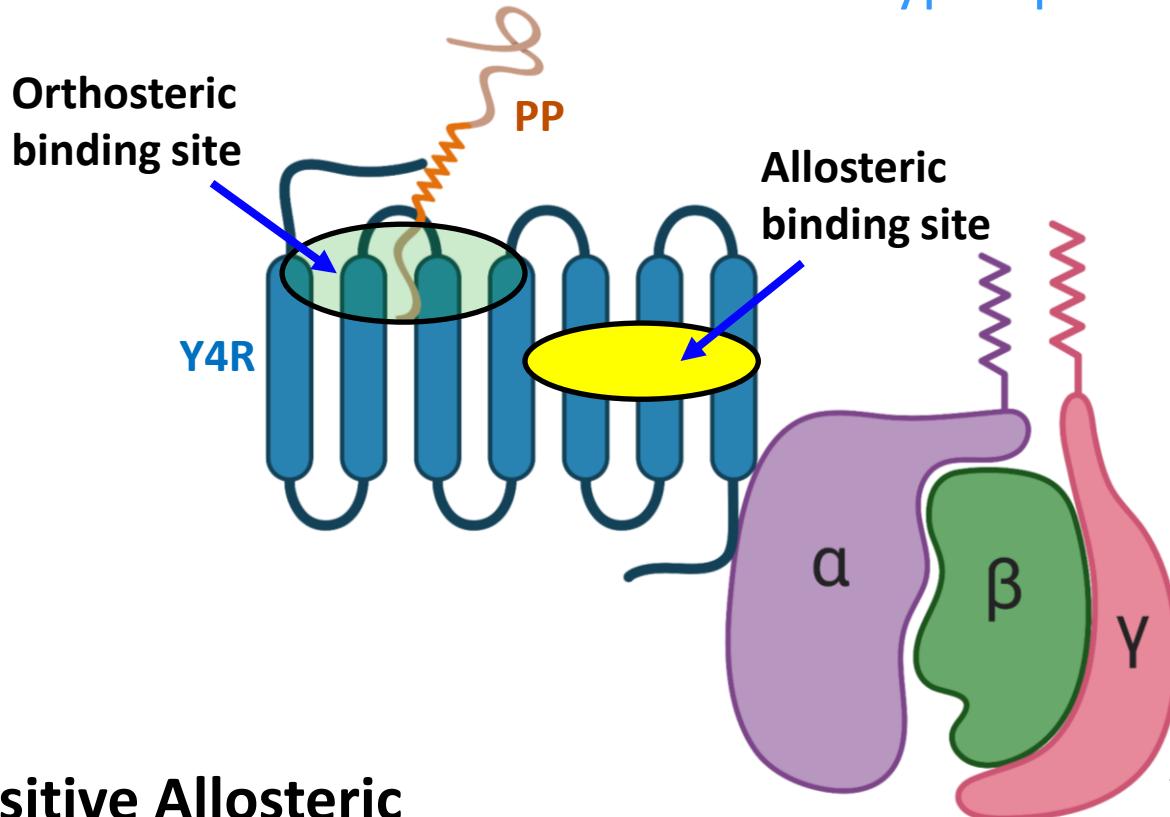
Receptor	apelinR
Residue #	PRBE
7.39	-1.3
2.60	-0.2
45.51	-0.2
7.35	-5.6
7.32	-0.8
45.52	-0.3
6.58	-5.0
6.51	-5.9
2.63	-0.2
3.32	-1.4
7.36	0.0
45.50	-0.1
7.28	-3.1
6.55	-4.3



\*PRBE: Per-residue binding energy

# Challenge #2: How do we specifically target Y4-PP interactions?

Allosteric modulators are subtype-specific for Y4R



**Y4R Positive Allosteric  
Modulators (PAMs)**

Weight gain, appetite  
enhancement

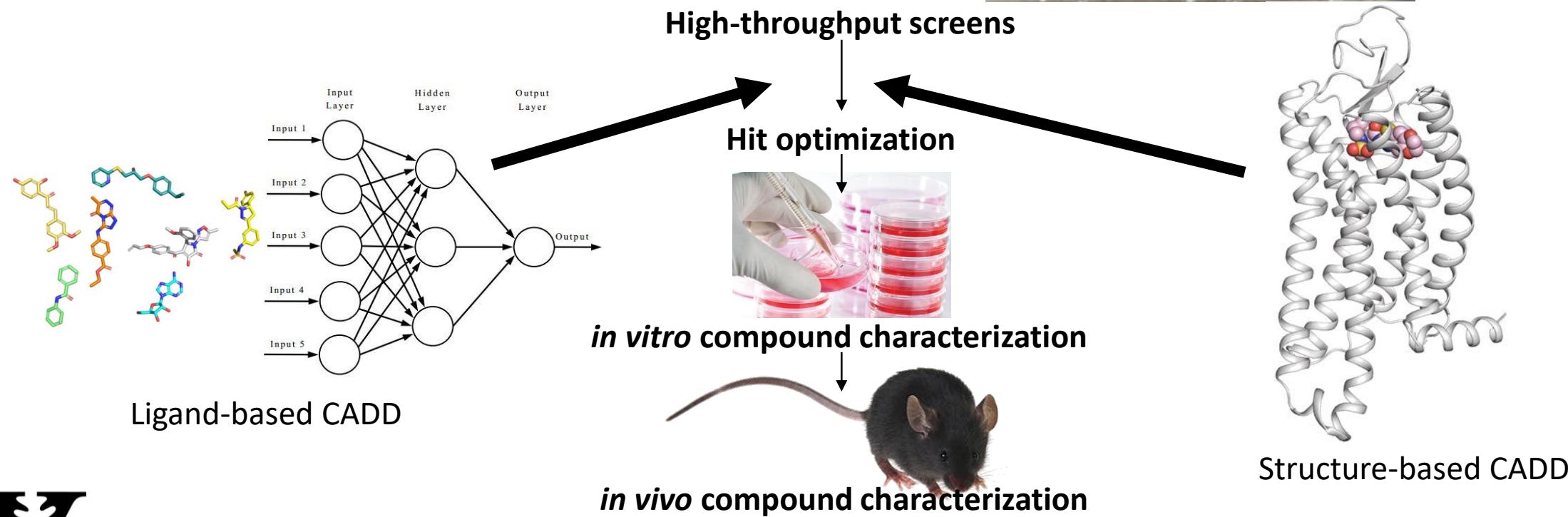
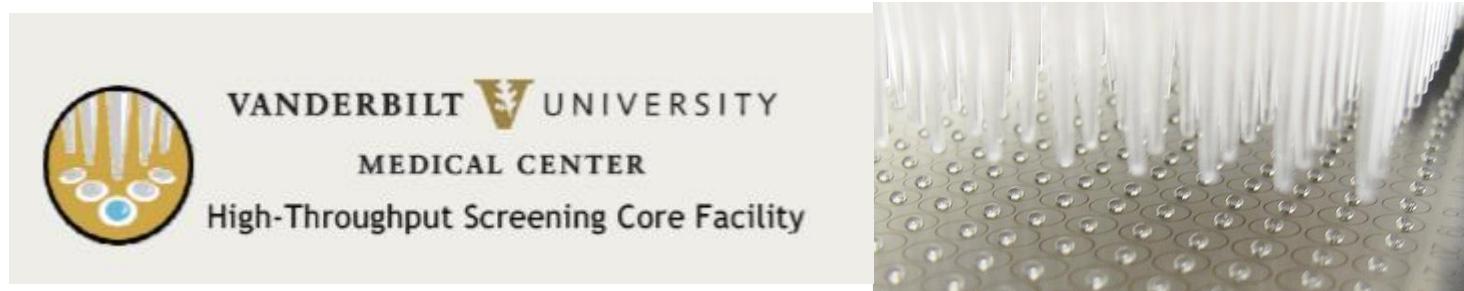
**Y4R Negative Allosteric  
Modulators (NAMs)**

Weight loss, Obesity  
treatment



# Challenge #3: How do we develop allosteric modulators for Y4R?

CADD can help optimize small molecules for Y4R



# Outline

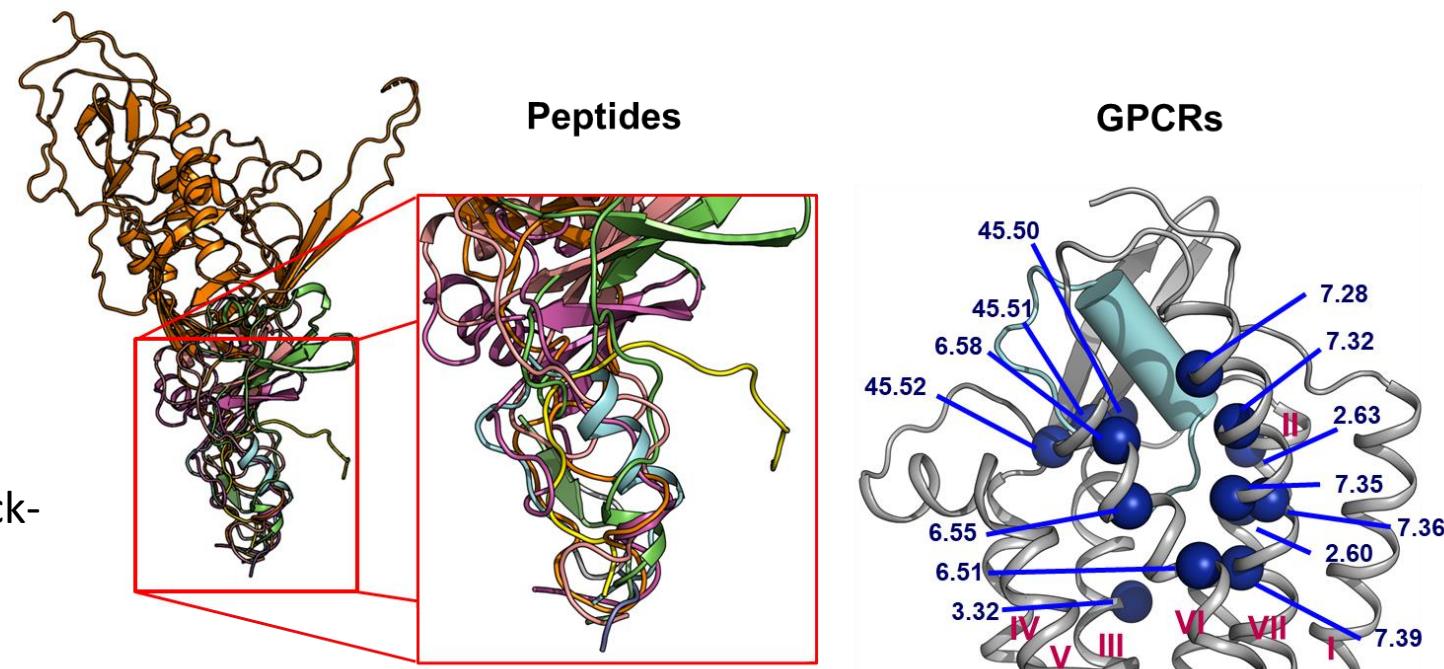
- Structural basis of peptide binding class A GPCRs
- Docking study and characterizing peptide-protein interaction between PP and Y4R
- Computer-aided drug discovery in finding allosteric modulators for PP-Y4R
  - Docking study of an antagonist with negative allosteric property to Y4R
  - Virtual screening for Y4R positive allosteric modulator (PAMs)



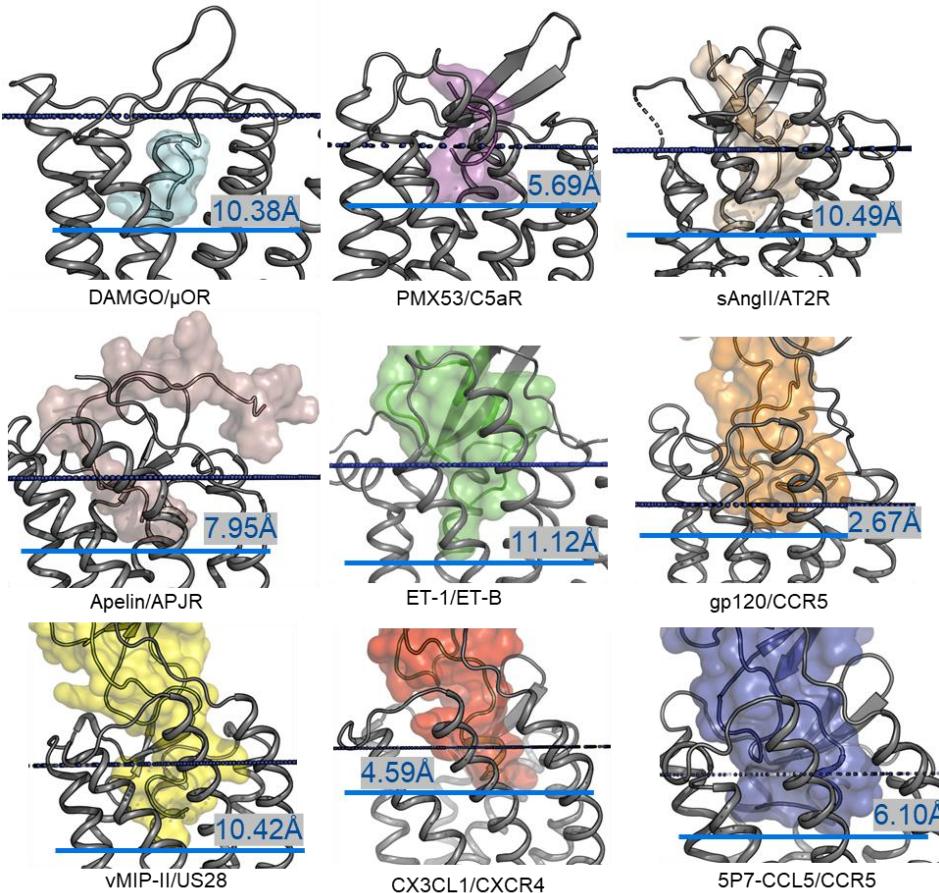
# Outline

- **Structural basis of peptide binding class A GPCRs**
- Docking study and characterizing peptide-protein interaction between PP and Y4R
- Computer-aided drug discovery in finding allosteric modulators for PP-Y4R

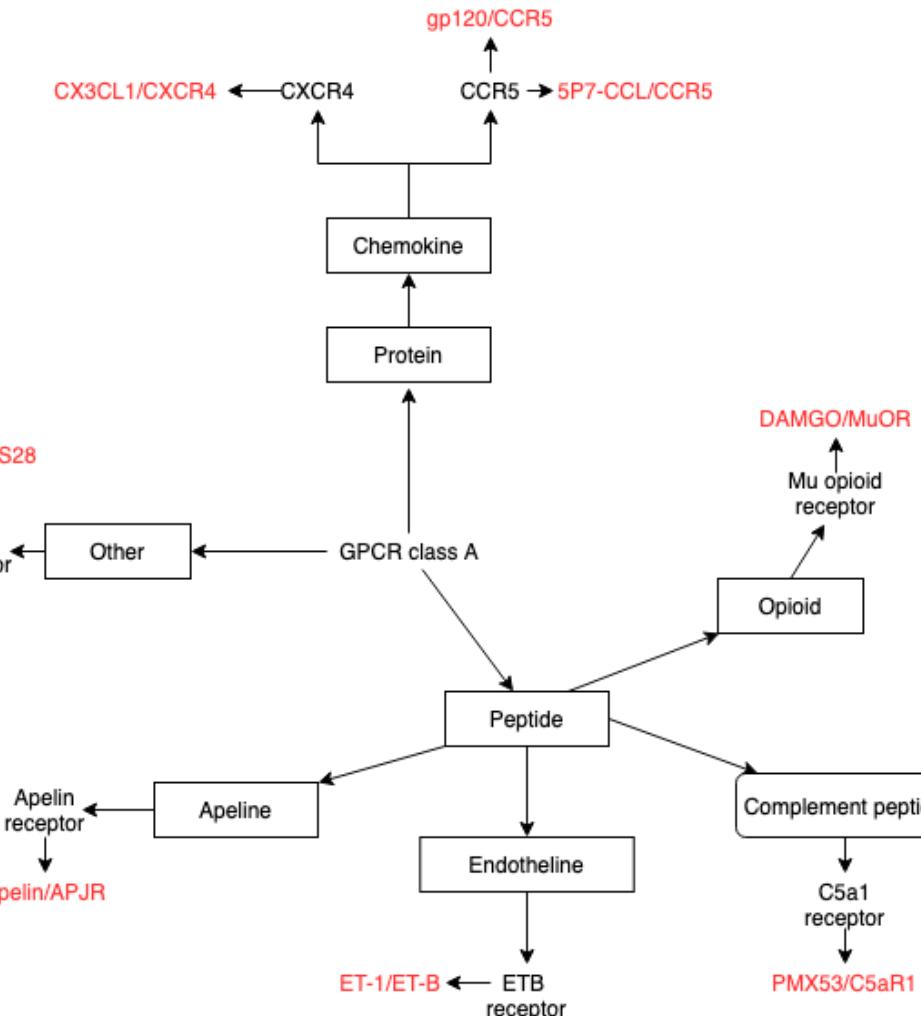
Oanh Vu\*, Brian Joseph Bender\*, Lisa Pankewitz, Daniel Huster, Annette G. Beck-Sickinger, and Jens Meiler.  
[Molecules. Under Review].



# Diversity of Binding Modes among Peptide Binding Class A GPCRs



Diversity in shape, size, and penetration depth of peptide ligands



Classification of 9 crystal structures based on receptor and ligand types

# Central Question

What are the common characteristics in the peptide ligand binding pockets of class A peptide GPCRs ?

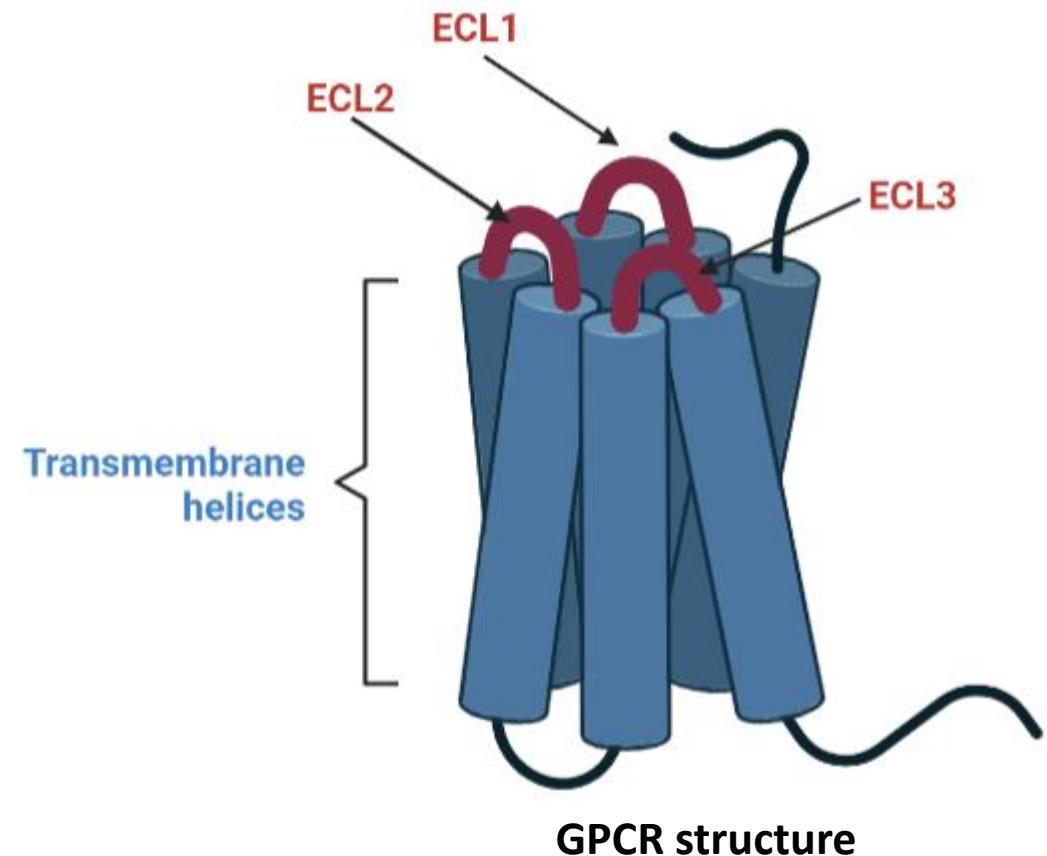
- Extracellular loops
- Transmembrane domains

## Computational tools

Structure-based sequence alignment ([gpcrdb.org](http://gpcrdb.org))

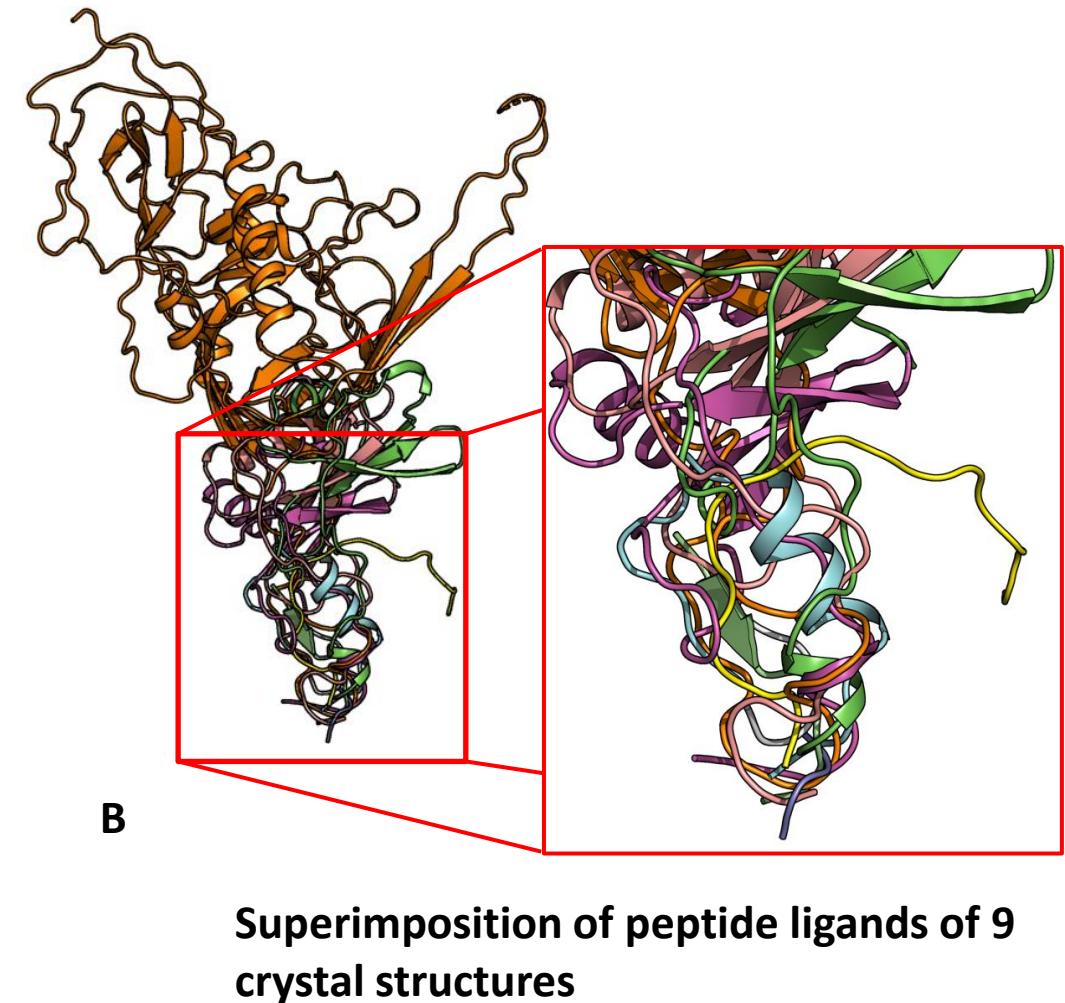
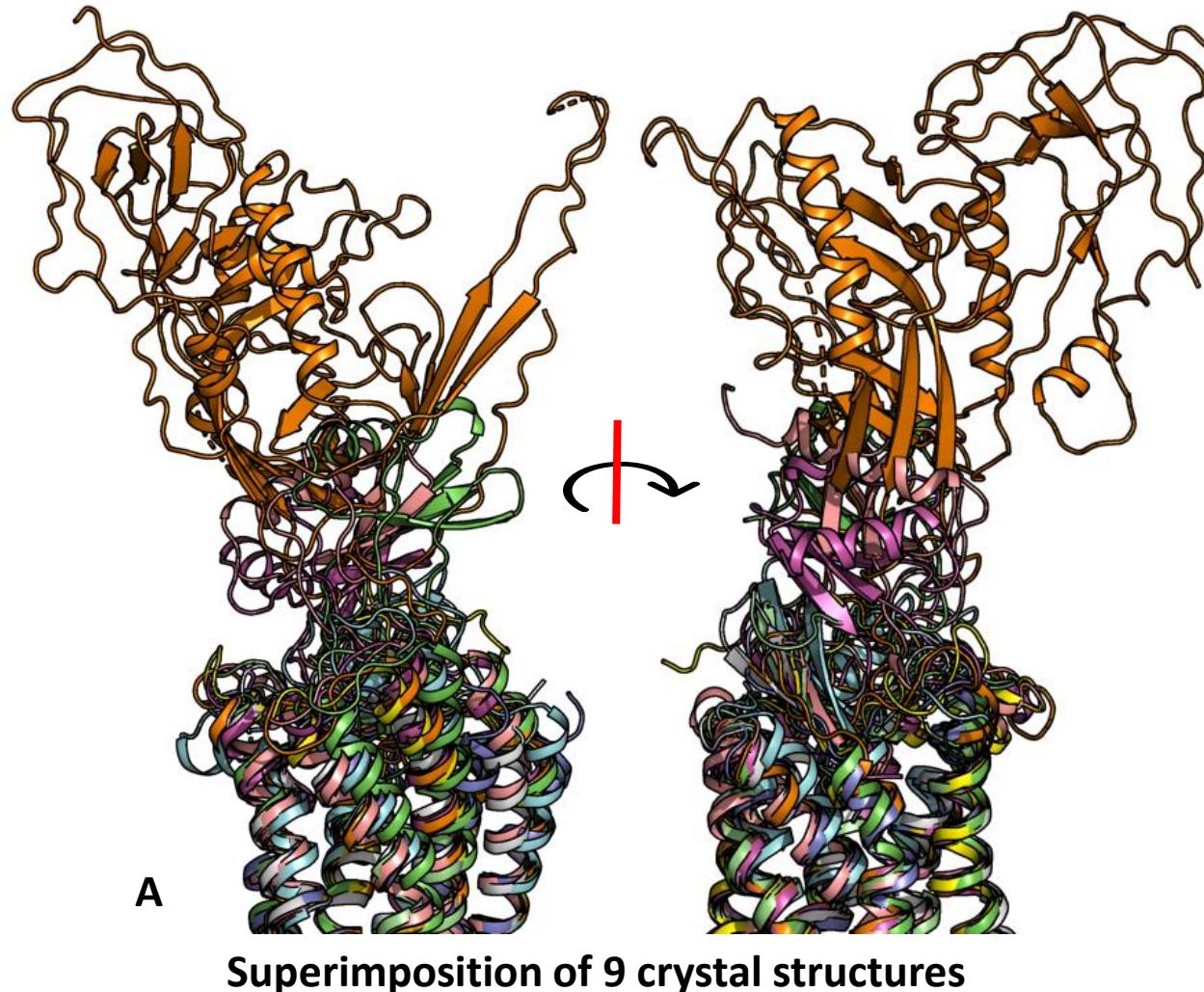
Structure minimization

Per-Residue Interface Energy analysis

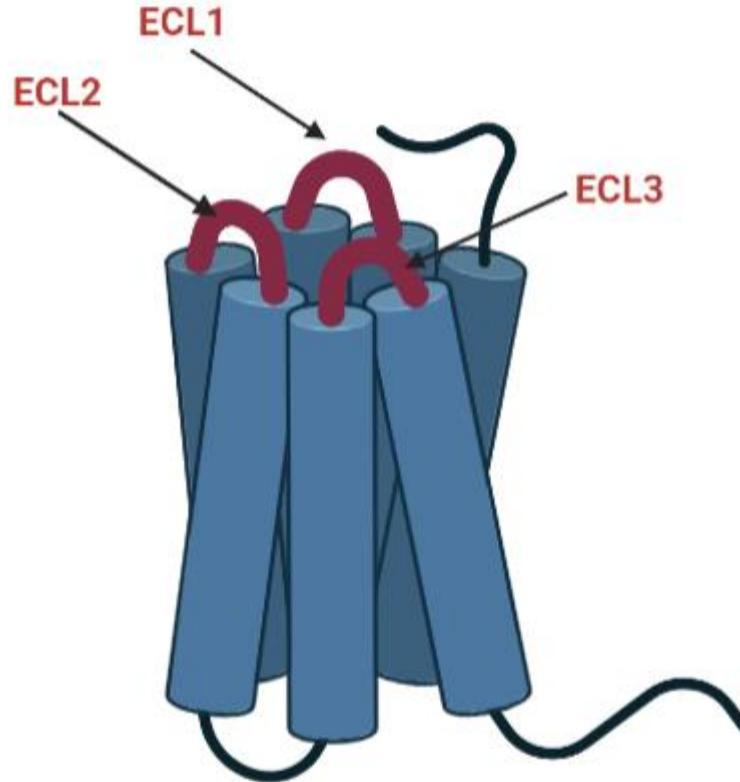


Conway et al. Protein Sci. 2014 Jan;23(1):47-55.

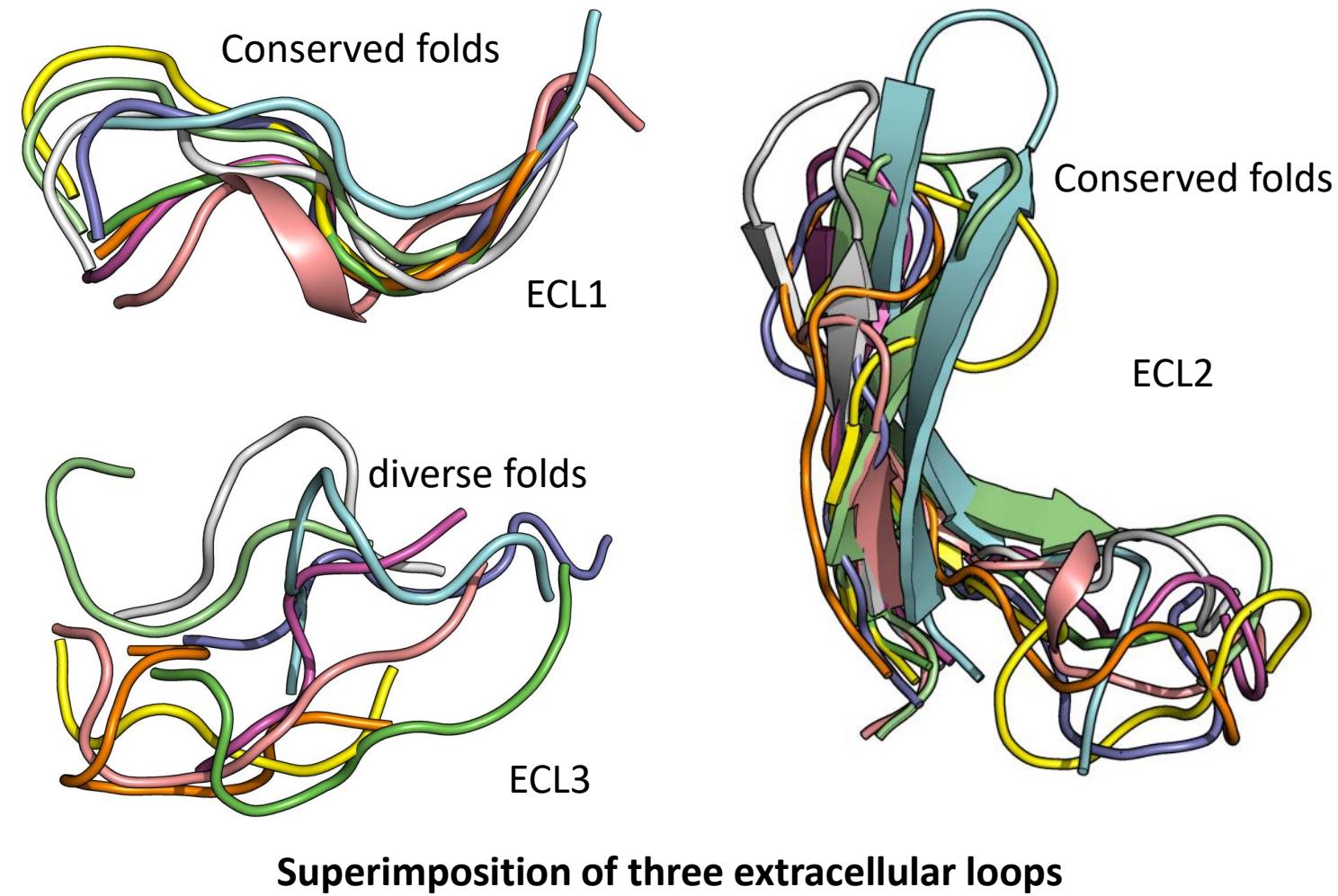
# Overlapping Region at the Core of Peptide Binding Pockets Suggest Common Binding Pattern Among Class A GPCRs



# ECL1 and ECL2 have conserved bound conformation

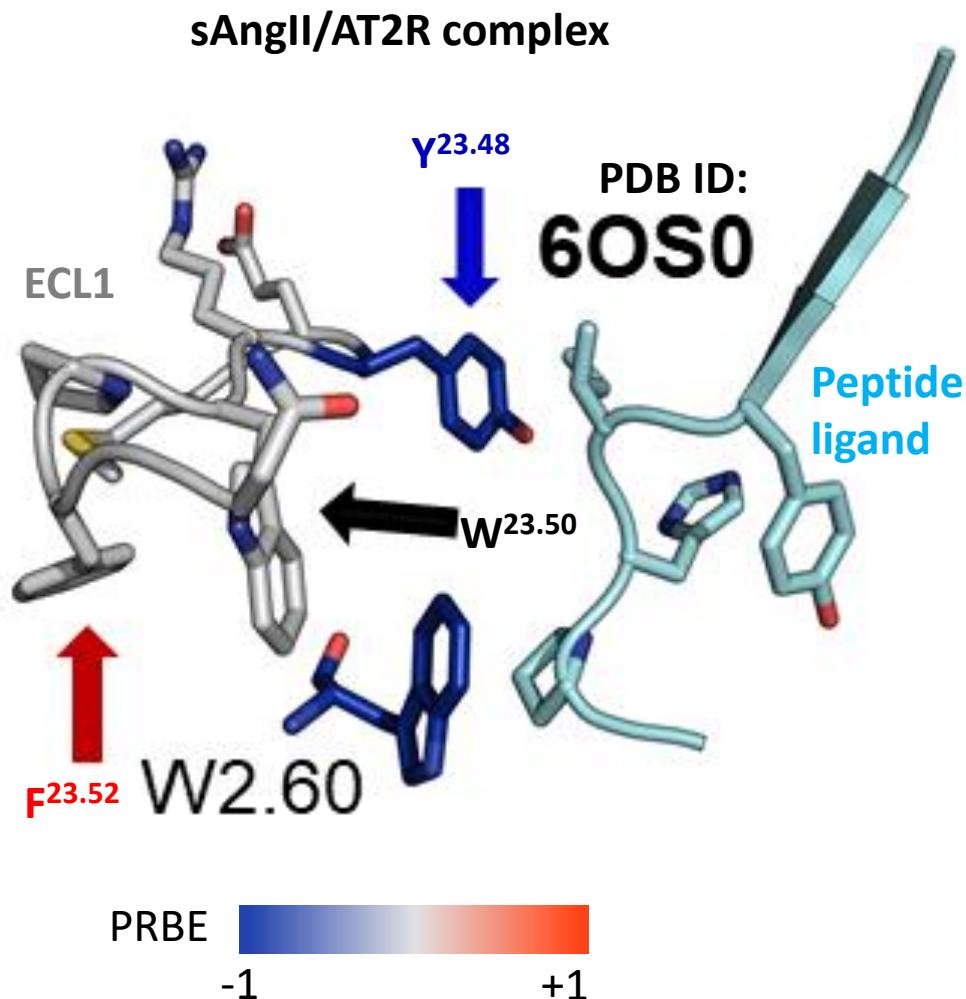


Location of three extracellular loops



Superimposition of three extracellular loops

# ECL1 and the role of motif Y/HxWxF in peptide binding



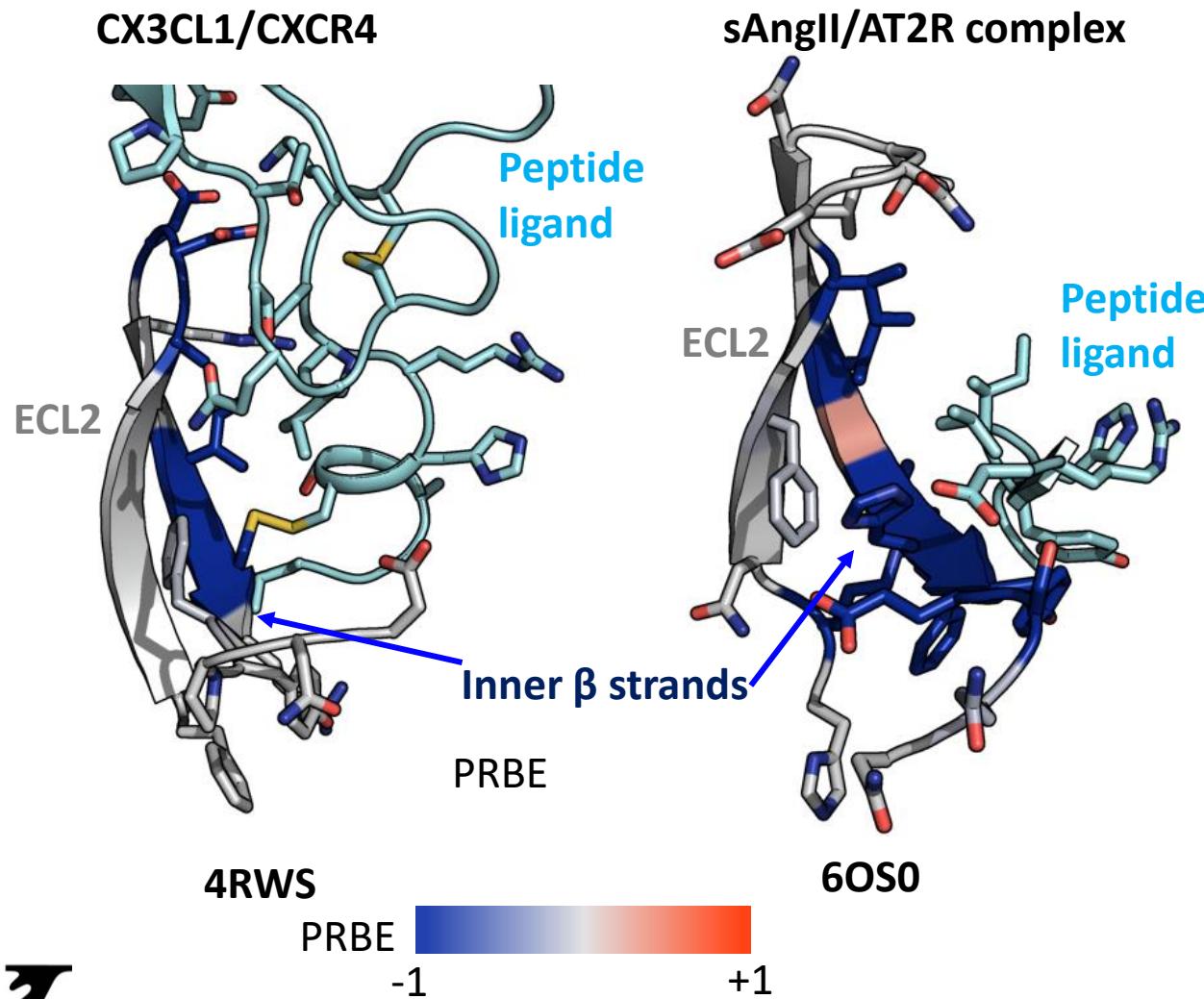
Motif Y/HxWxF

PDB IDs	Receptor	23.47	23.48	23.49	23.50	23.51	23.52
4RWS	CXCR4	—	—	N	W	Y	F
5GLH	ETBR	—	E	D	W	P	F
5UIW, 6MEO	CCR5	—	—	Q	W	D	F
5VBL	apelinR	D	Y	D	W	P	F
5WB2	US28	D	H	N	S	L	A
6C1Q	C5a1R	H	H	H	W	P	F
6DDF	MuOR	G	—	T	W	P	F
6OS0	AT1R	R	Y	D	W	L	F

**ECL1 sequence alignment**

- Y/H<sup>23.48</sup> form favorable interaction with the peptide
- F<sup>23.52</sup> stabilizes W<sup>23.50</sup> with pi-pi interactions
- W<sup>23.50</sup> interact directly or indirectly to the peptide through the residue 2.60

# ECL2 Inner Beta Strands and Conserved Residues Interact with Peptides



Peptides generally engage with the inner  $\beta$  strands of ECL2

Especially at the tip where the three conserved residues (45.50, 45.51, and 45.52) are located

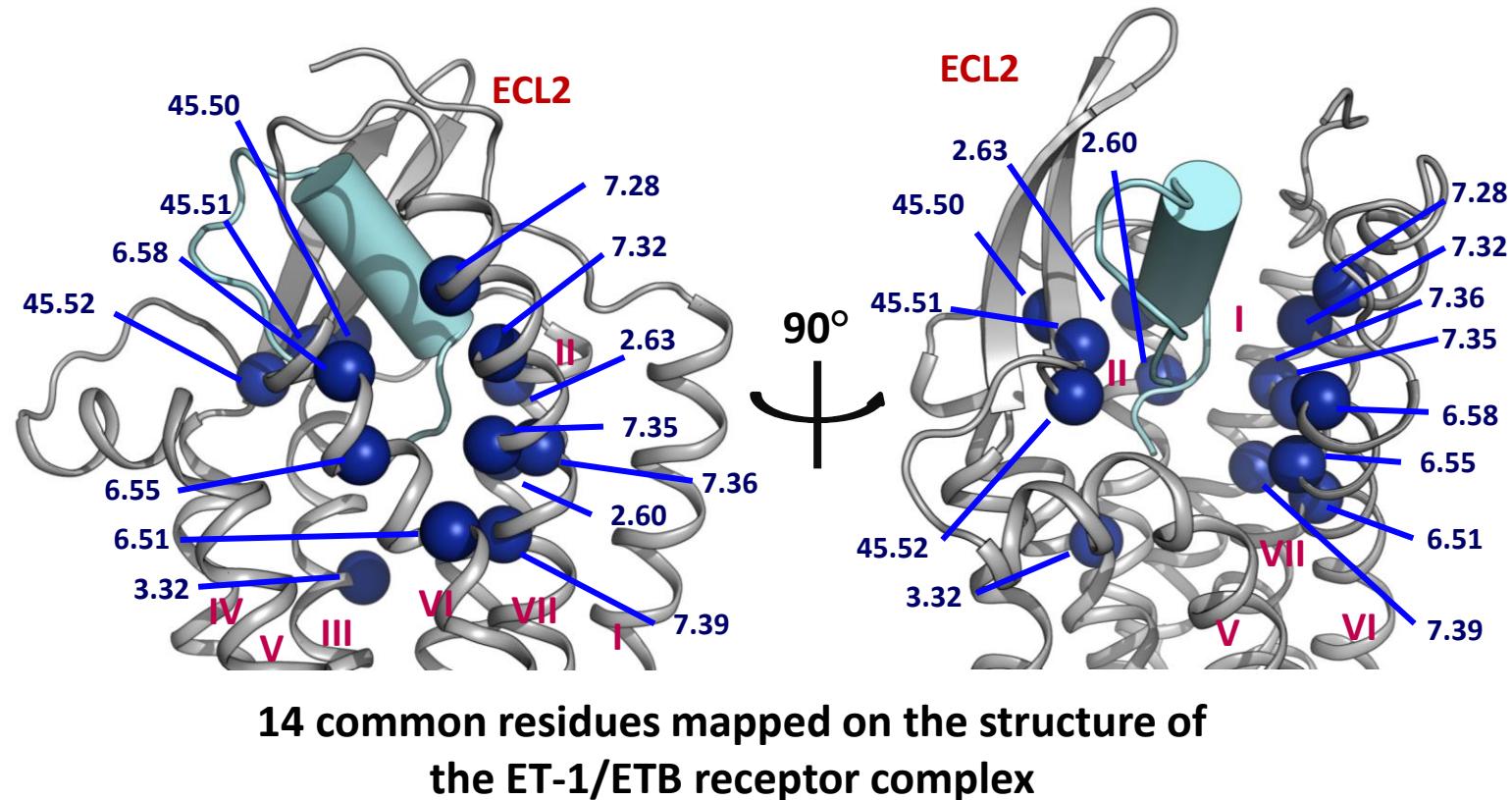
# Identified 14 Residues Forming a Common Binding Pocket of Peptide Ligands among Class A GPCRs

**14 residues were selected:**

- PRBE of less than -1
- Contact peptide ligands in at least seven out of nine GPCR-peptide complexes.

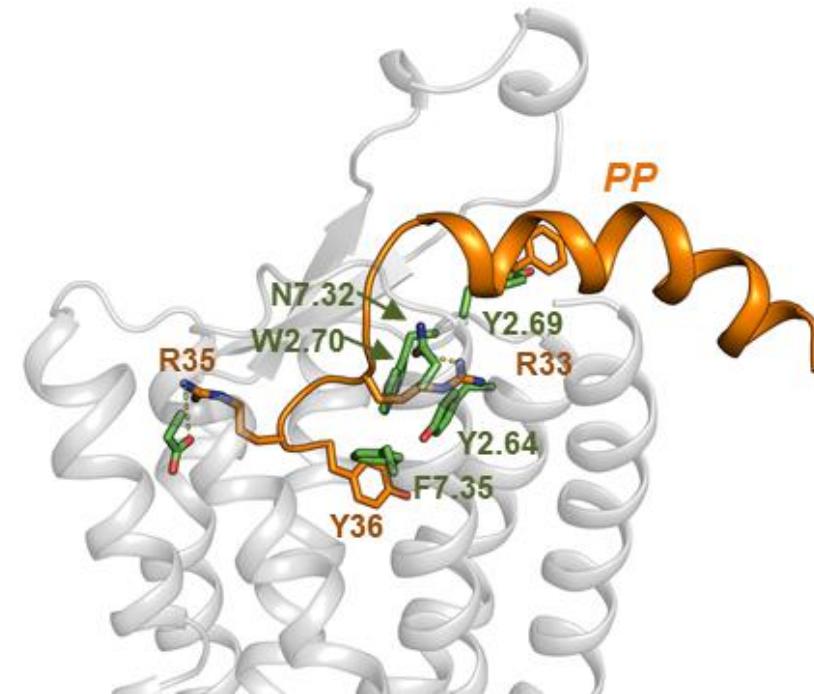
**Common peptide binding pocket:**

- Starts from the end of the  $\beta$ -hairpin of ECL2
- Extends to the tip of TM2
- Touches the extracellular half of TM7 and TM6
- Ends at the core of TM3

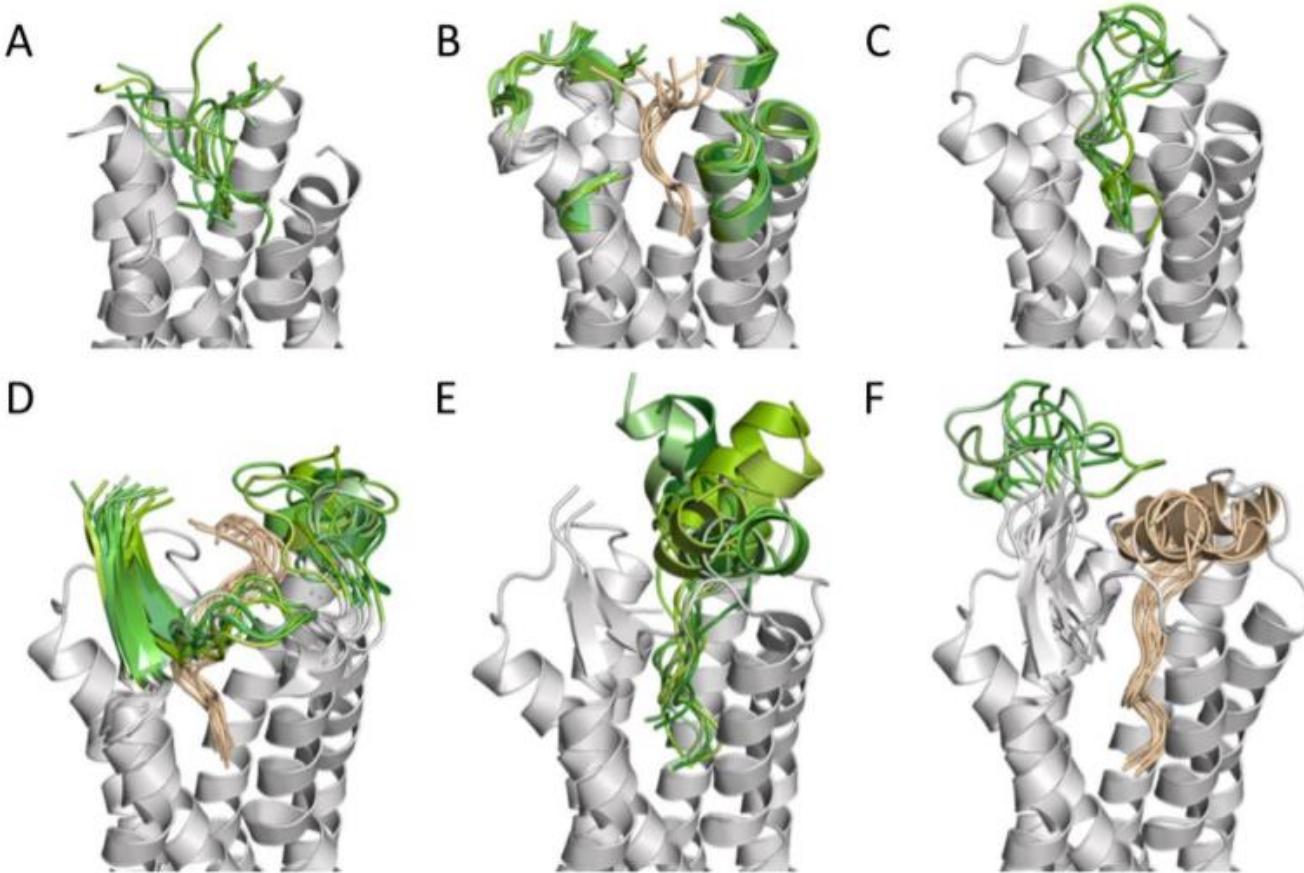


# Outline

- Structural basis of peptide binding class A GPCRs
- **Docking study and characterizing peptide-protein interaction between PP and Y4R**
- Computer-aided drug discovery in finding allosteric modulators for PP-Y4R



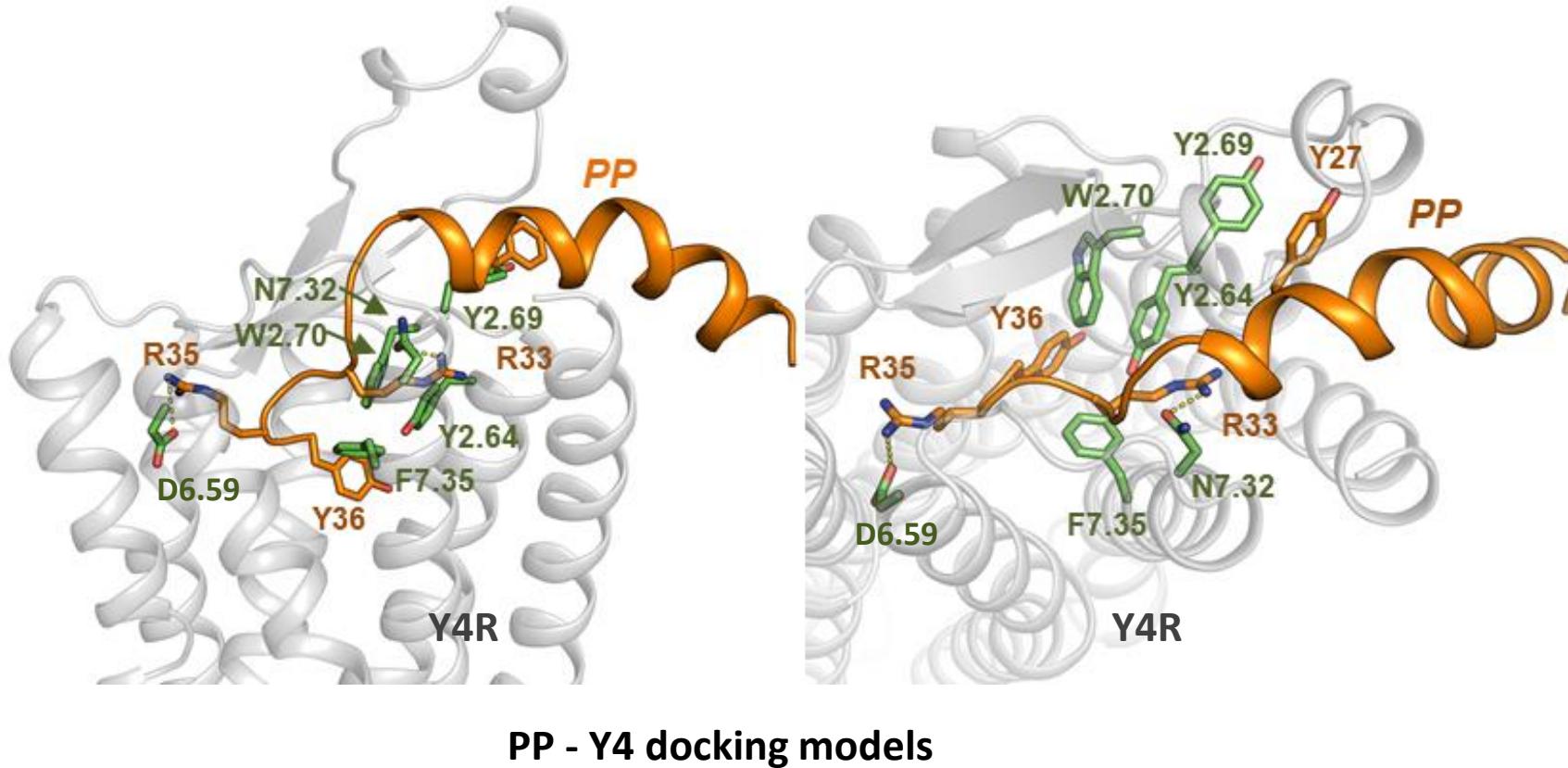
# Iterative flexible peptide docking and loop building of PP-Y4 Complex with experimental restraints



Bender, B. et al., Structure, Volume 27, Issue 3, 2019

Raveh et al.(2011). PLOS ONE 6(4): e18934

# Proposed binding mode of PP to Y4 agrees with mutagenesis data



Interactions suggested  
by mutagenesis data

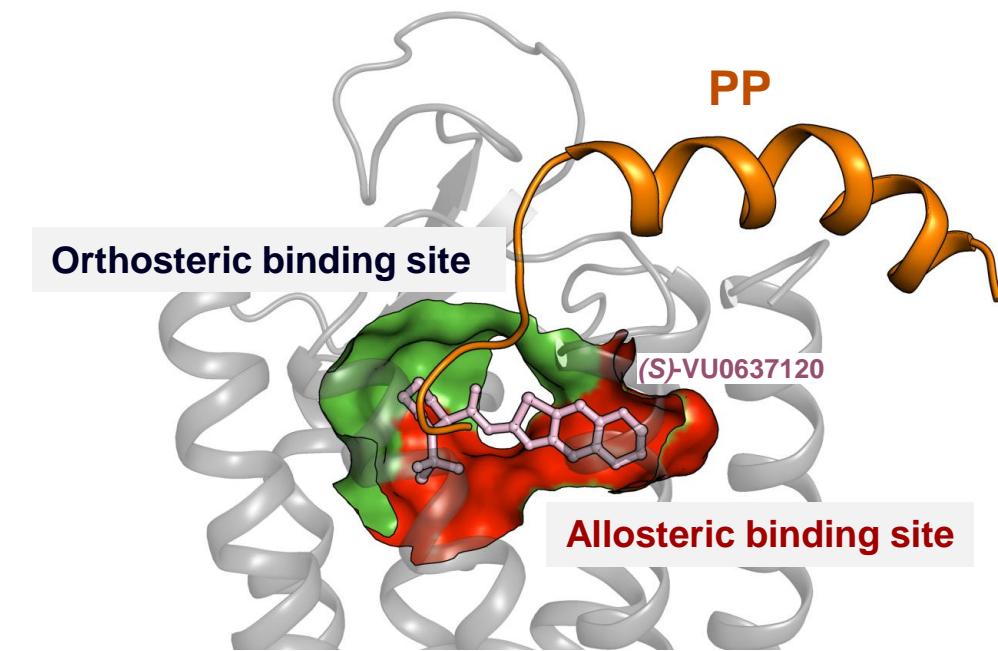
Y4R residues	PP residues
Y2.64 or/and Y2.69	Y27
D6.59	R35
D7.32	R33
F7.35	R33
F7.35	Y36
D2.68	??
W2.70	??

The Beck-Sickinger lab

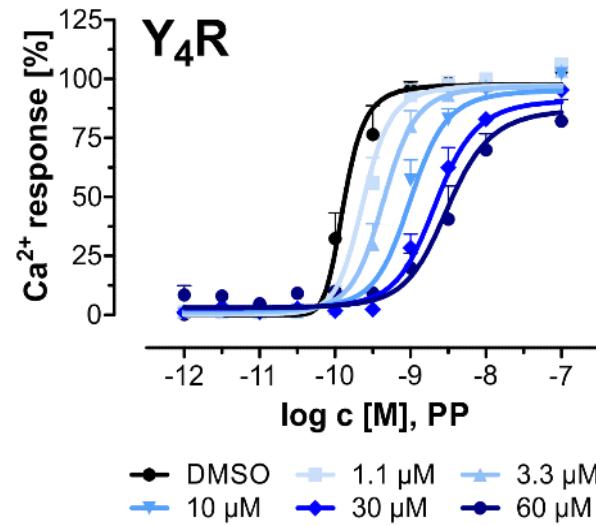
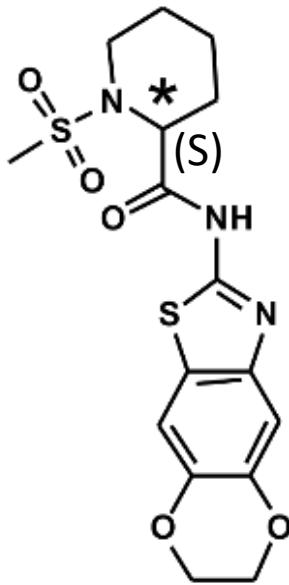
# Outline

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  - Virtual screening for Y4R PAMs

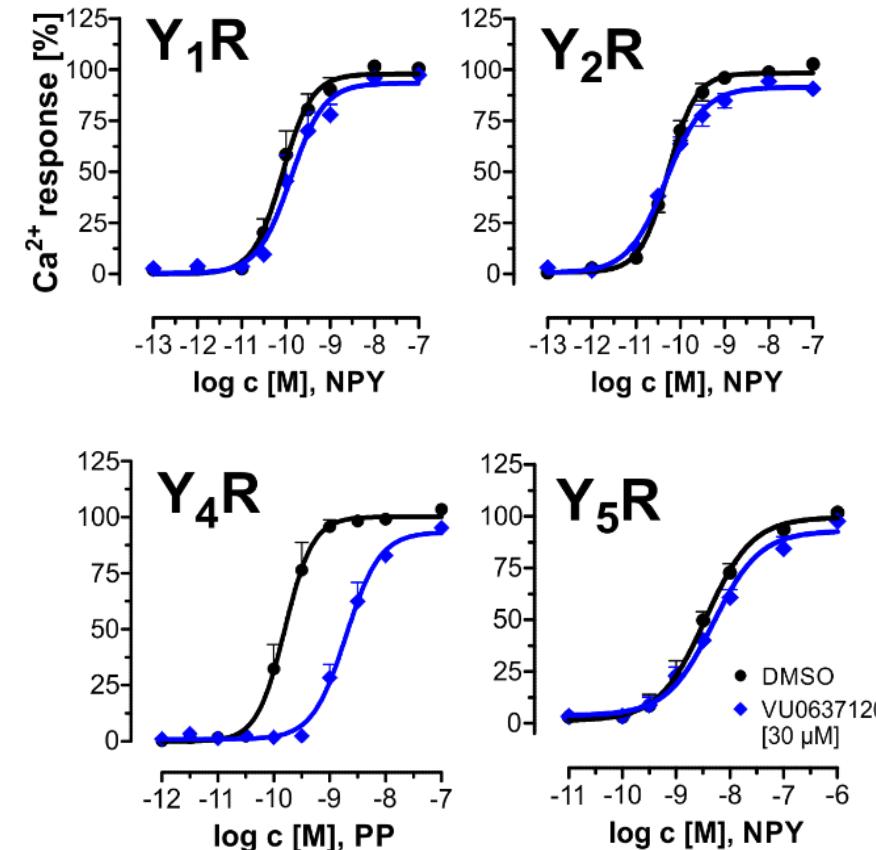
Corinna Schub\*, Oanh Vu\*, Mario Schubert\*, Yu Du, Nigam M. Mishra, Iain R. Tough, Jan Stichel, C. David Weaver, Kyle A. Emmitt, Helen M. Cox, Jens Meiler, and Annette G. Beck-Sickinger. **The Highly Selective Y4 Receptor Antagonist Binds in a Deep, Allosteric Binding Pocket.** *Journal of Medicinal Chemistry.* 2021 Mar 11;64(5):2801-2814.



# (S)-VU0637120 is a selective antagonist with allosteric properties to Y4R



IC<sub>50</sub> value of 2.8 μM ( $\text{pIC}_{50} 5.5 \pm 0.03$ )  
Negative allosteric effect on the affinity of PP  
Slightly reduces PP signaling efficacy



VU0637120 is selective to the Y<sub>4</sub>R subtype

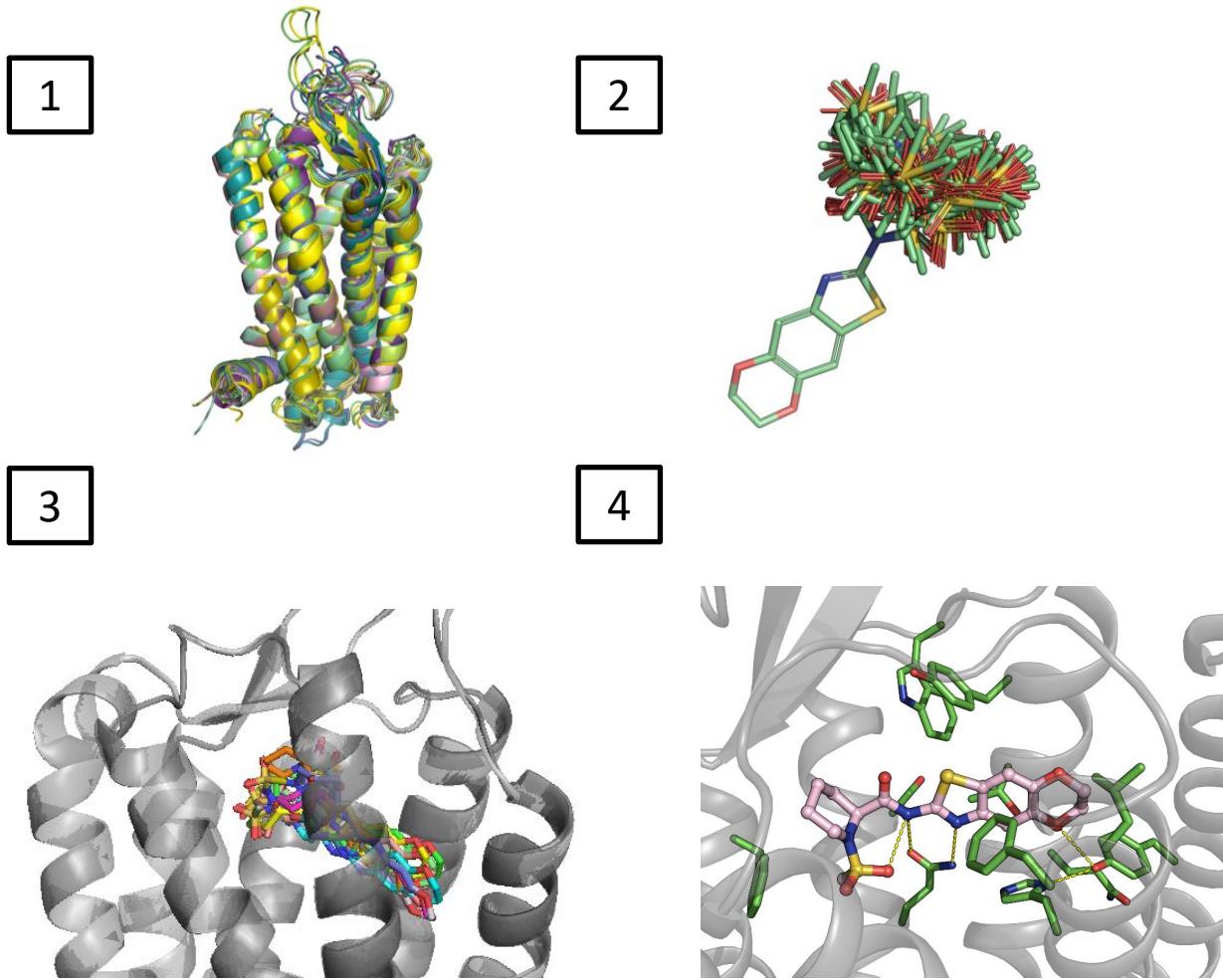
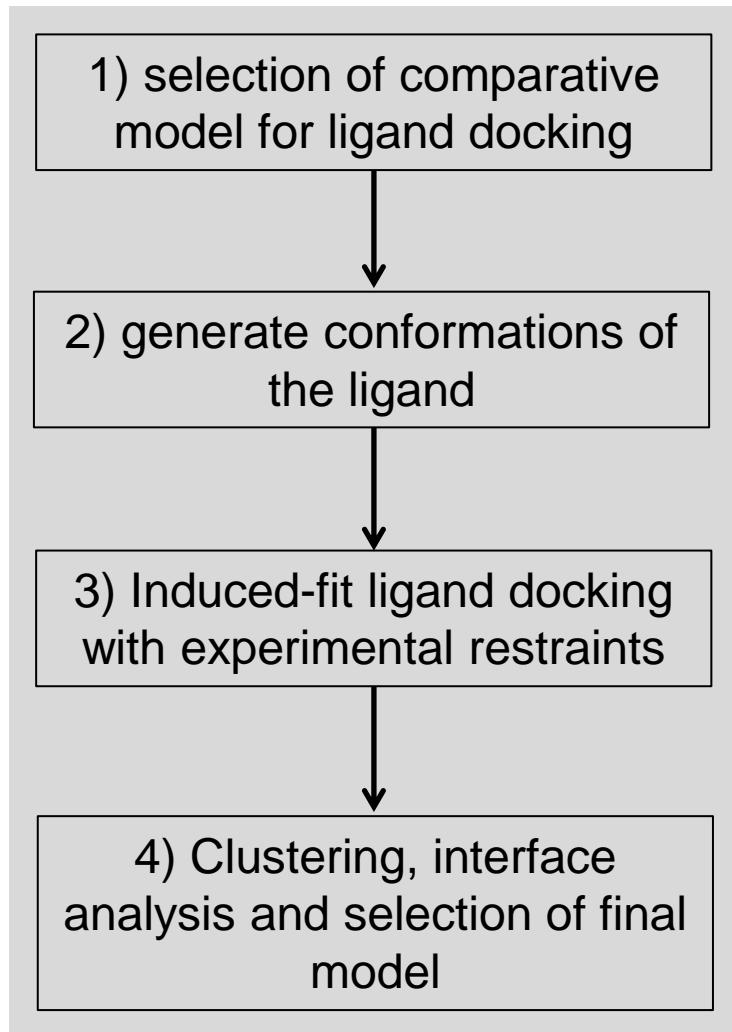
The Emmitt lab

The Weaver lab

The Beck-Sickinger lab

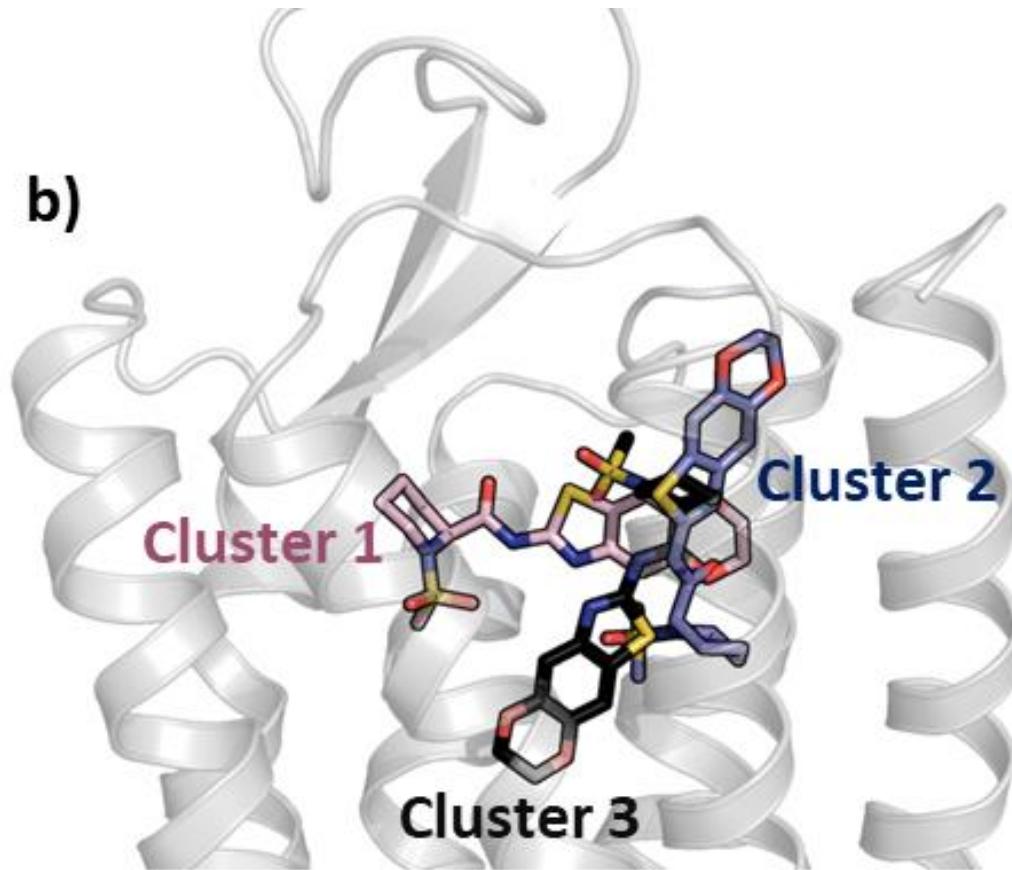
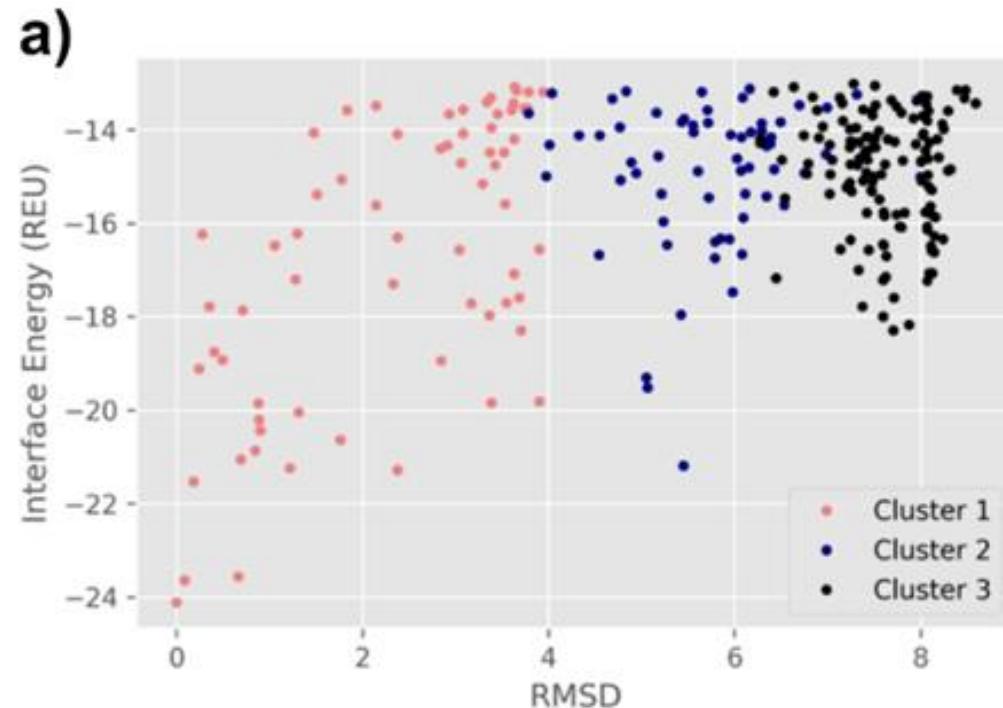


# Docking (S)-VU0637120 to Y4R homology models



Combs, S.A., et al (2013) Nat Protoc, 1(7), 1277-98.  
Lemmon G, Meiler J. Methods Mol Biol. 2012;819:143-155

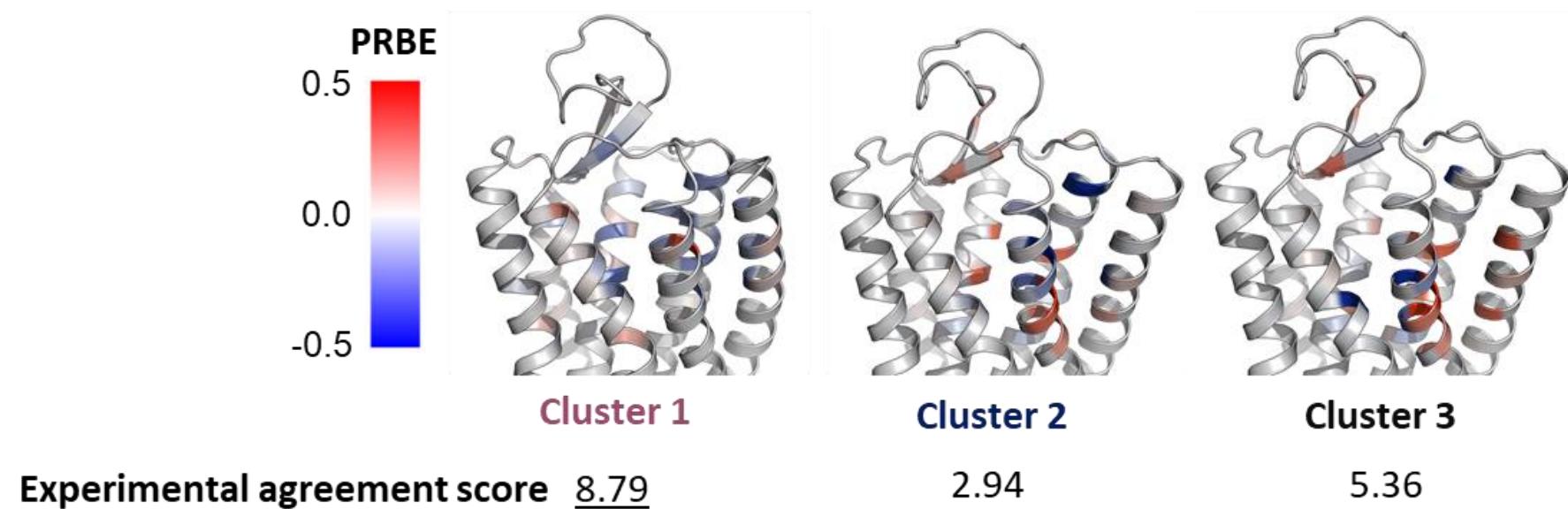
# Docking results – 3 clusters



# Experimental Agreement Scores Rank Clusters by Per-Residue Binding Energy (PRBE)

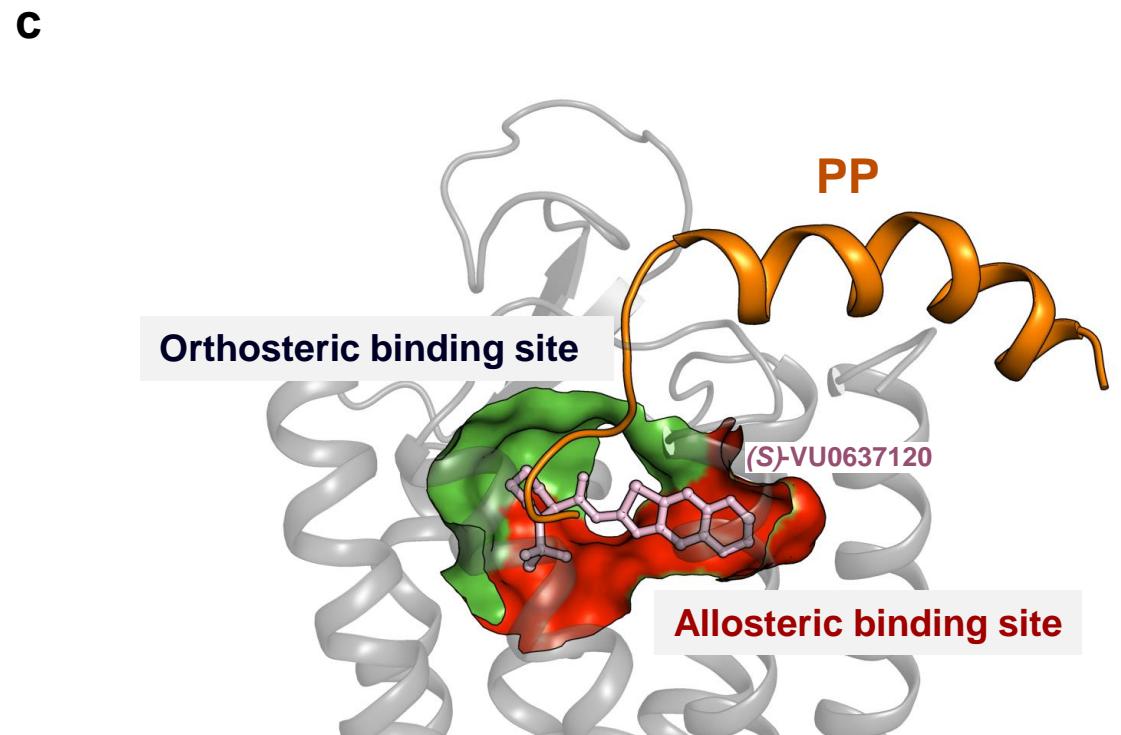
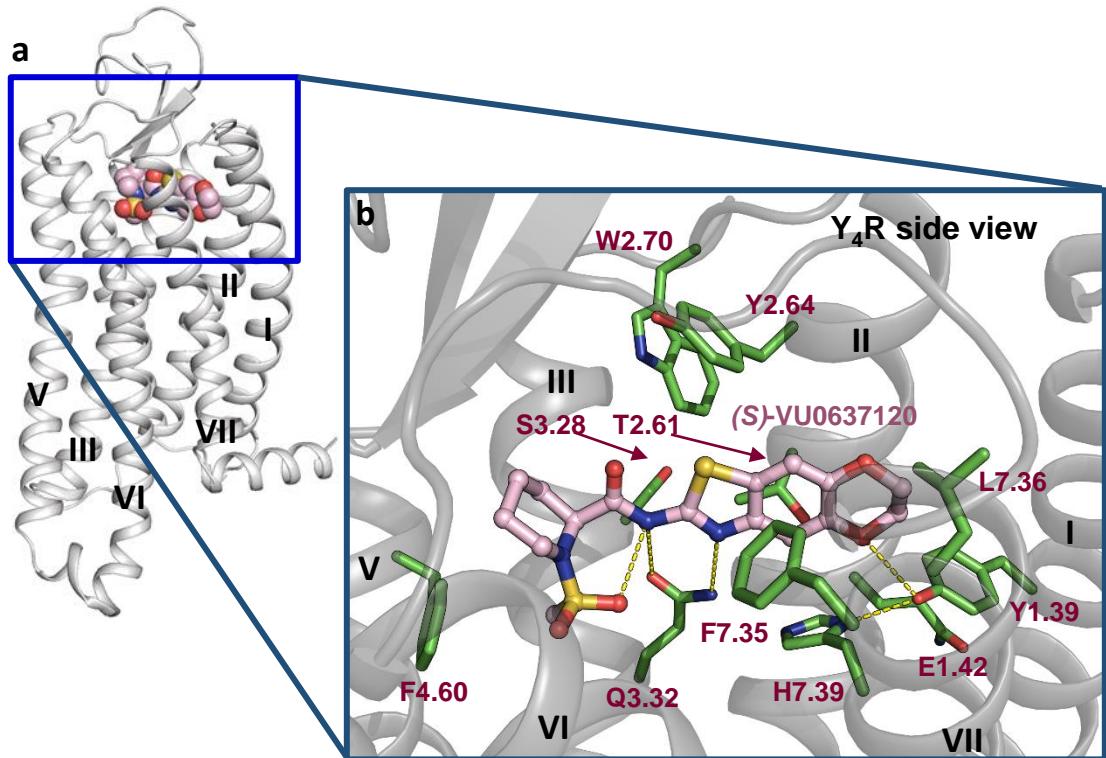
Res#	cluster1	cluster 2	cluster 3
Y1.39	-0.27	-0.38	0.02
E1.42	0.00	0.15	0.33
T1.43	0.01	-0.01	-0.03
Q2.58	-0.33	0.40	0.46
T2.61	-0.36	-0.05	0.00
Y2.64	-0.42	-0.95	-0.62
W2.70	0.01	-0.09	-0.43
S3.28	0.12	0.94	0.18
Q3.32	-0.94	1.10	-0.09
F4.60	-0.17	-0.02	0.00
F7.35	-0.16	-0.09	-0.07
L7.36	0.37	-1.08	0.24
H7.39	-0.03	-0.30	-0.49

PRBE of residues that are important to VU0637120 potency

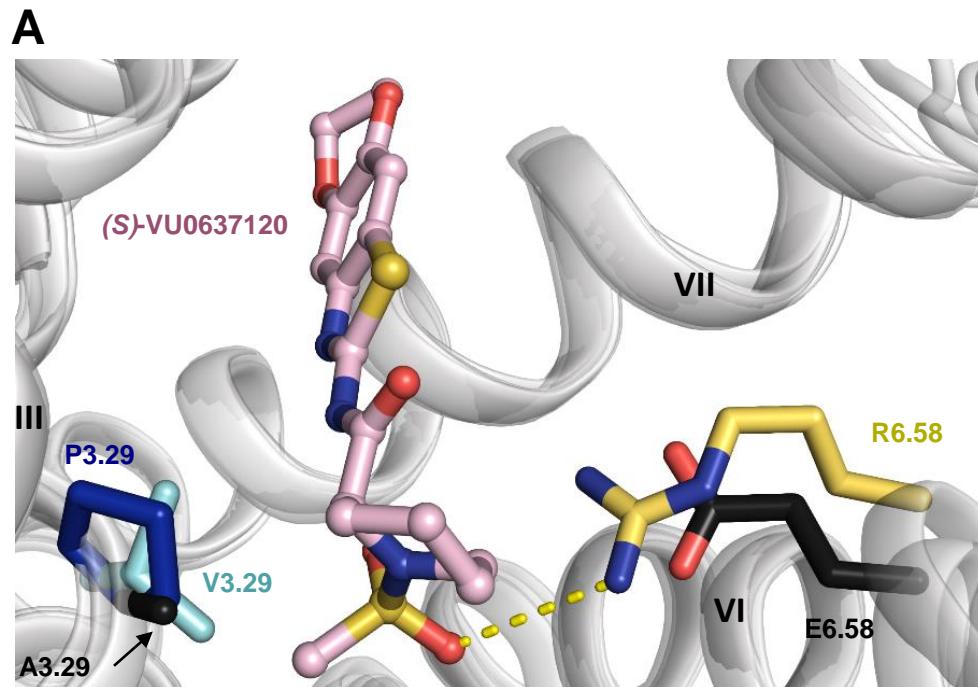


\*Experimental agreement scores evaluate the agreement between the calculated PRBE values and the mutagenesis data

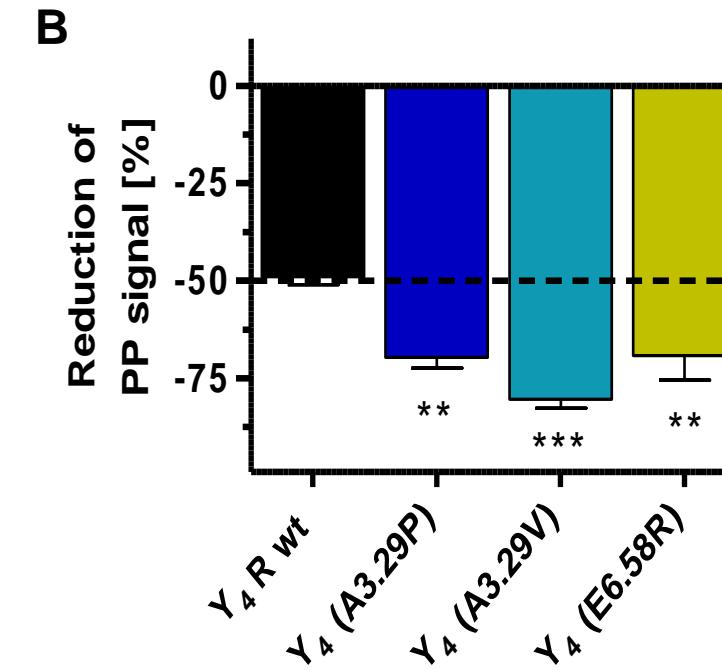
# Predicted binding mode of (S)-VU0637120 suggests a new allosteric binding pocket



# Rational Design of Gain of Function Mutants From the Proposed Docking Models



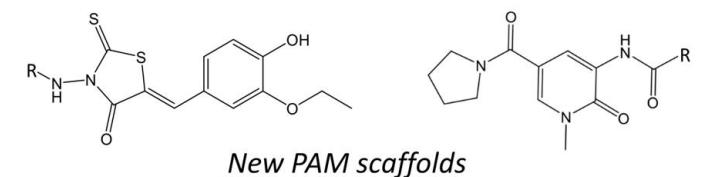
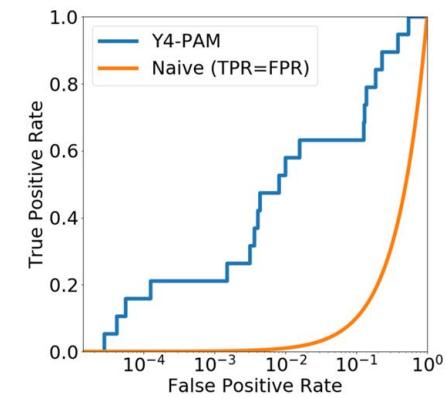
A3.29P and A3.29V mutants form more favorable hydrophobic interactions  
E6.58R forms additional Hbond to the ligand



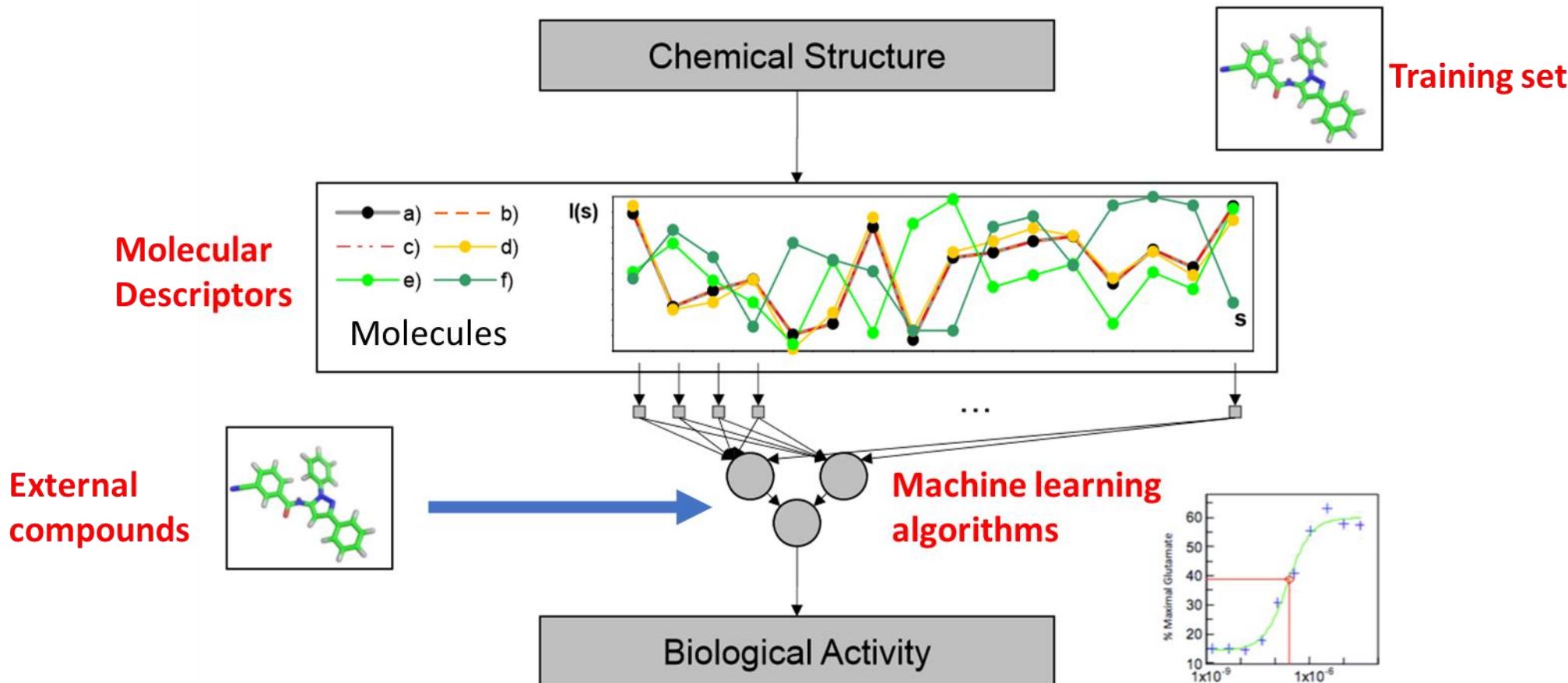
Three mutants were confirmed GOF in cell assays

# Outline

- Structural basis of peptide binding class A GPCRs
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  - Docking study of an antagonist with negative allosteric property to Y4R
  - **Virtual screening for Y4R PAMs**

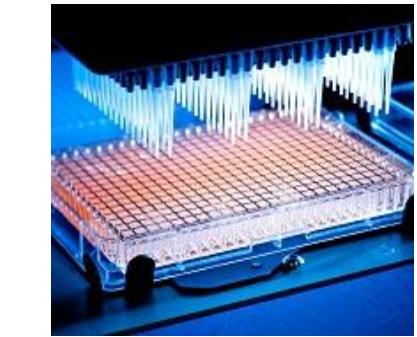


# Quantitative structure-activity relationship (QSAR) calculates activity from numerical descriptors



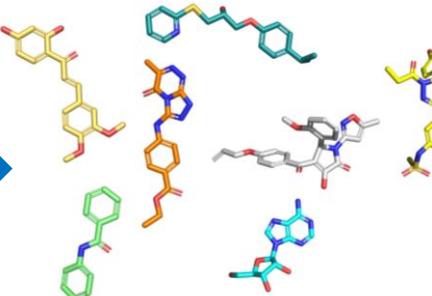
Cherkasov et al. Journal of Medicinal Chemistry. 2014;57(12):4977-5010.  
Artwork by Jens Meiler

# QSAR for Virtual screening of Y4 positive allosteric modulators

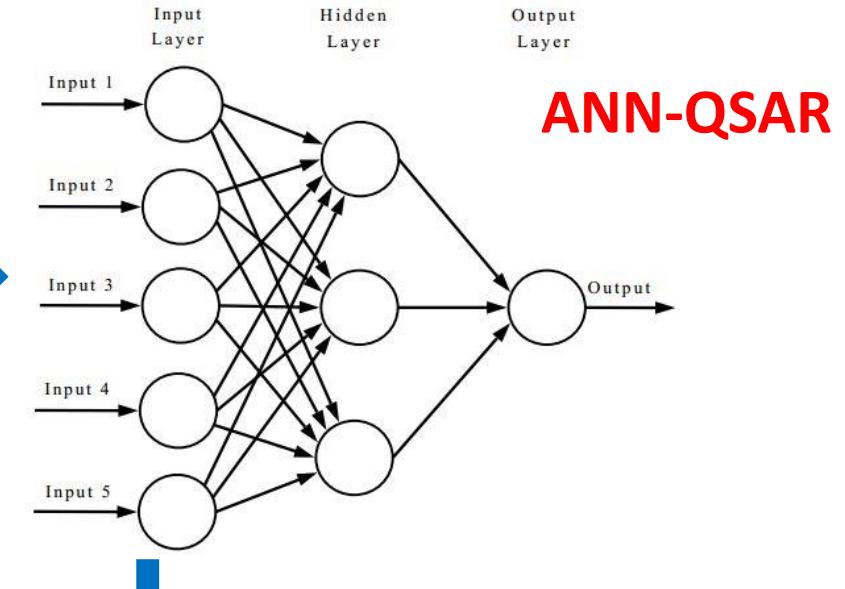


Previous PAM HTS

19 active  
80K inactive



Train



Predict



Small molecule  
database  
**150K**

Experimental validation

Molecules with highest predicted activity

**600**

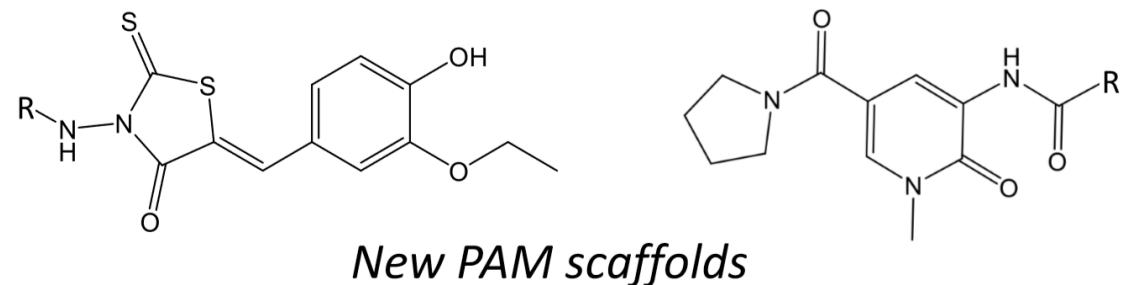
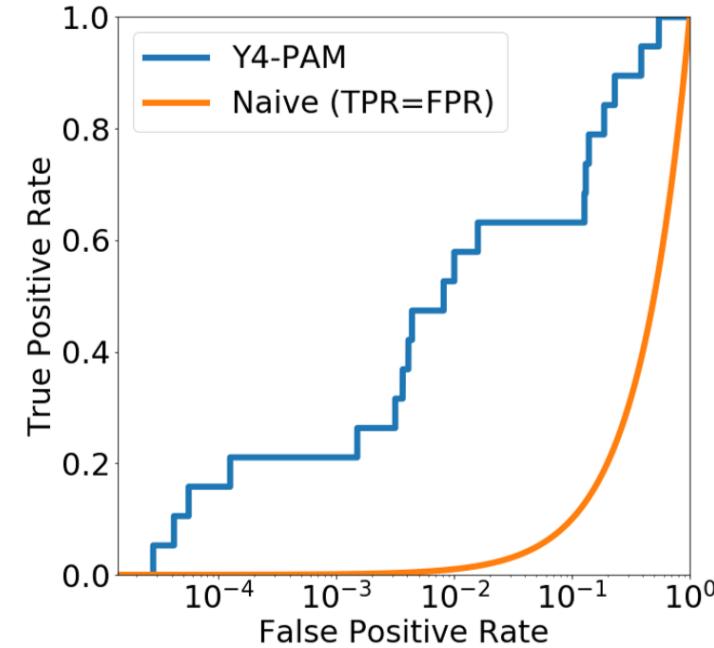
Sliwski et al., *PLOS ONE* 2016, 11

Schubert et al., *J. Med. Chem.* 2017, 60, 7605–7612



# Virtual Screening for Positive Allosteric Modulators (PAM) of a GPCR receptor

- Previous HTS: ( hit rate : 0.02%)
- QSAR: 20/600 selected compounds were confirmed active (hit rate : 3.33%)



The Weaver lab  
The Beck-Sickinger lab

# Summary

- Modeling for the (*S*)-VU0637120/Y<sub>4</sub>R complex that not only agrees with known mutagenesis data but also predicted three 'gain-of-function' mutations.
- We identified an allosteric binding pocket in the core of the Y<sub>4</sub>R transmembrane domains below the endogenous ligand binding site, that ultimately strengthening our understanding of allosteric modulation of the Y<sub>4</sub>R.
- ANN-QSAR models improved Y4 PAM hit rates and discovery new Y4 PAM scaffolds



# Acknowledgement

The Meiler lab:

**Jens Meiler, PhD**

**Gregory R. Sliwoski, PhD**

**Brian Bender, PhD**

**Rocco Moretti, PhD**

**Jeffrey Mendenhall**

**Benjamin Muller, PhD**

**Benjamin Brown**

Ellie Okwei

Nina Bozhanova, PhD

Shannon Smith

Hope Wood

Cristina Elisa Martina, PhD

Eli McDonald

Lance (Yunchao) Liu

Fabian Liessmann

And everyone else



My Dissertation Committee:

Jens Meiler, PhD

Lauren Elizabeth Buchanan, PhD

David Weaver, PhD

Zhongyue (John) Yang, PhD



Doaa Altarawy, PhD



The Weaver lab:  
David Weaver, PhD  
Sunny Du, PhD

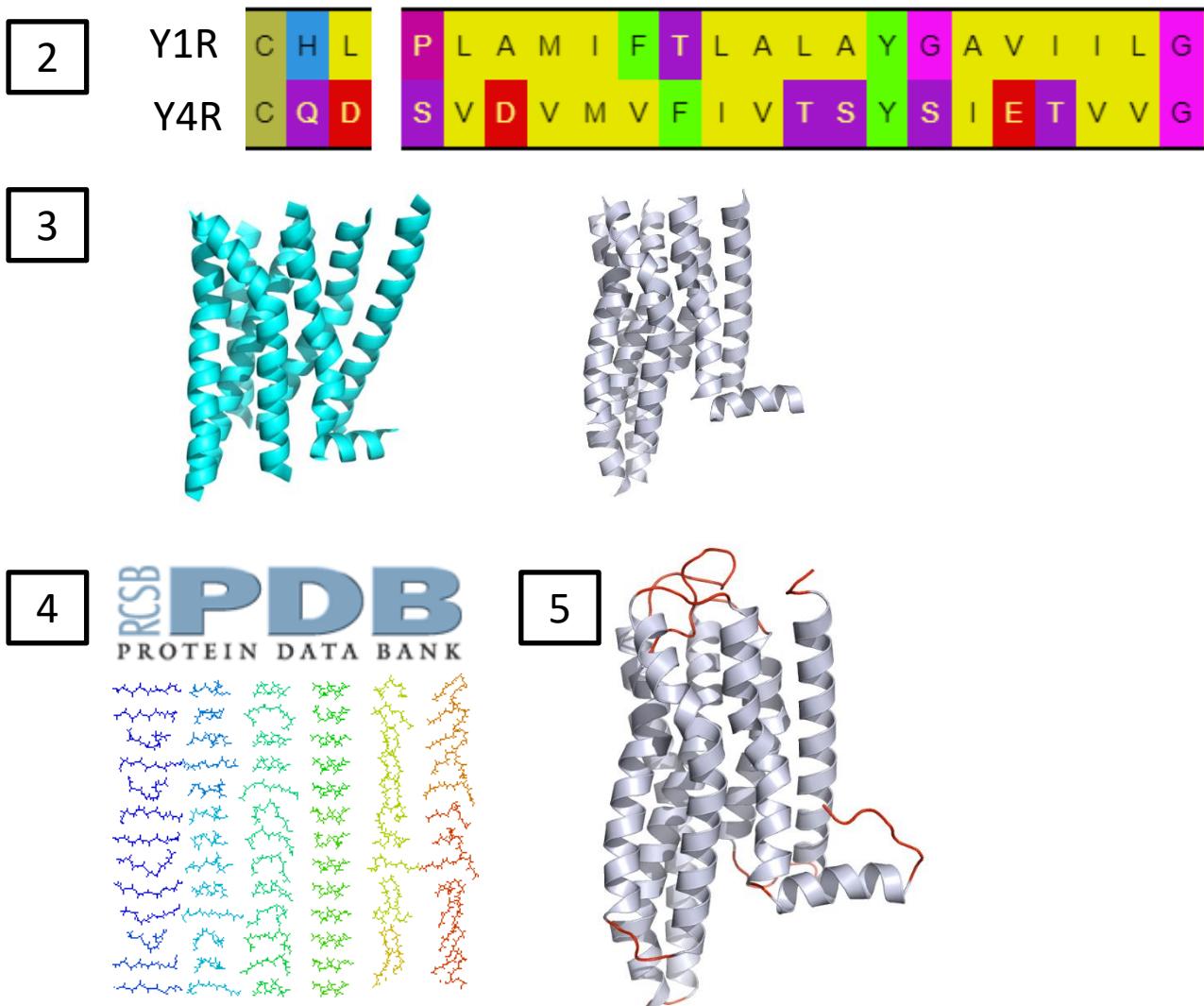
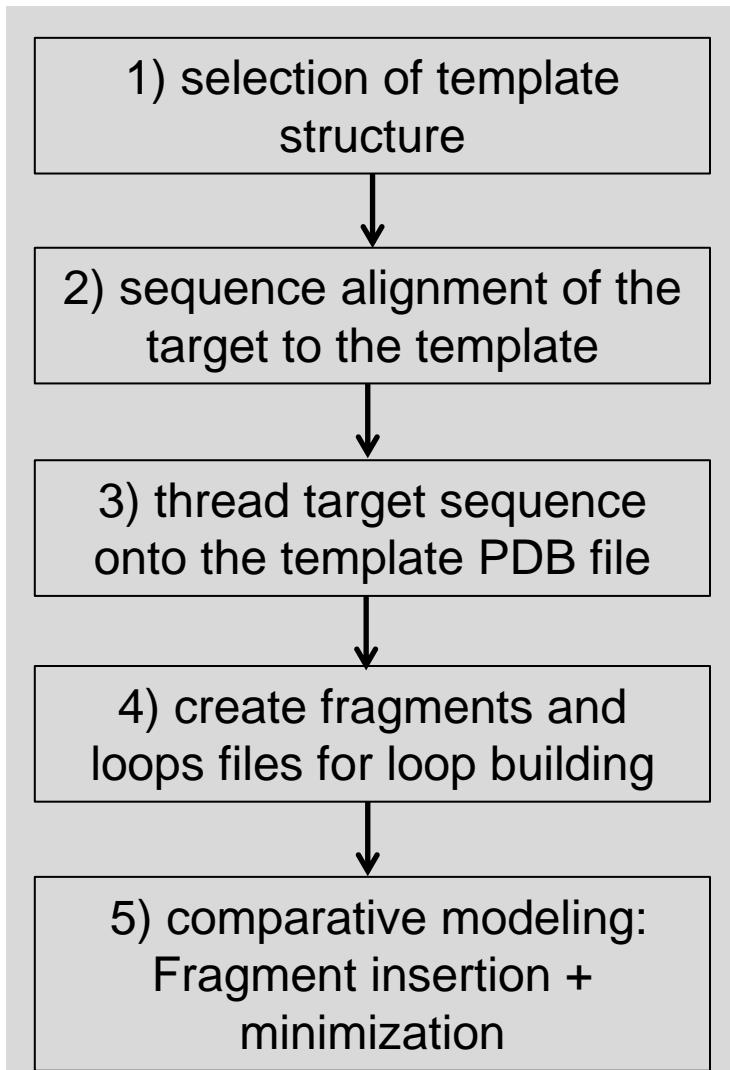
The Emmitte lab:  
Kyle Emmitte, PhD

The Beck-Sickinger lab:  
Annette Beck-Sickinger, PhD  
Corinna Schüß  
Mario Schubert, PhD  
Jan Stichel, PhD  
Nikolas Kühn



4/19/2024

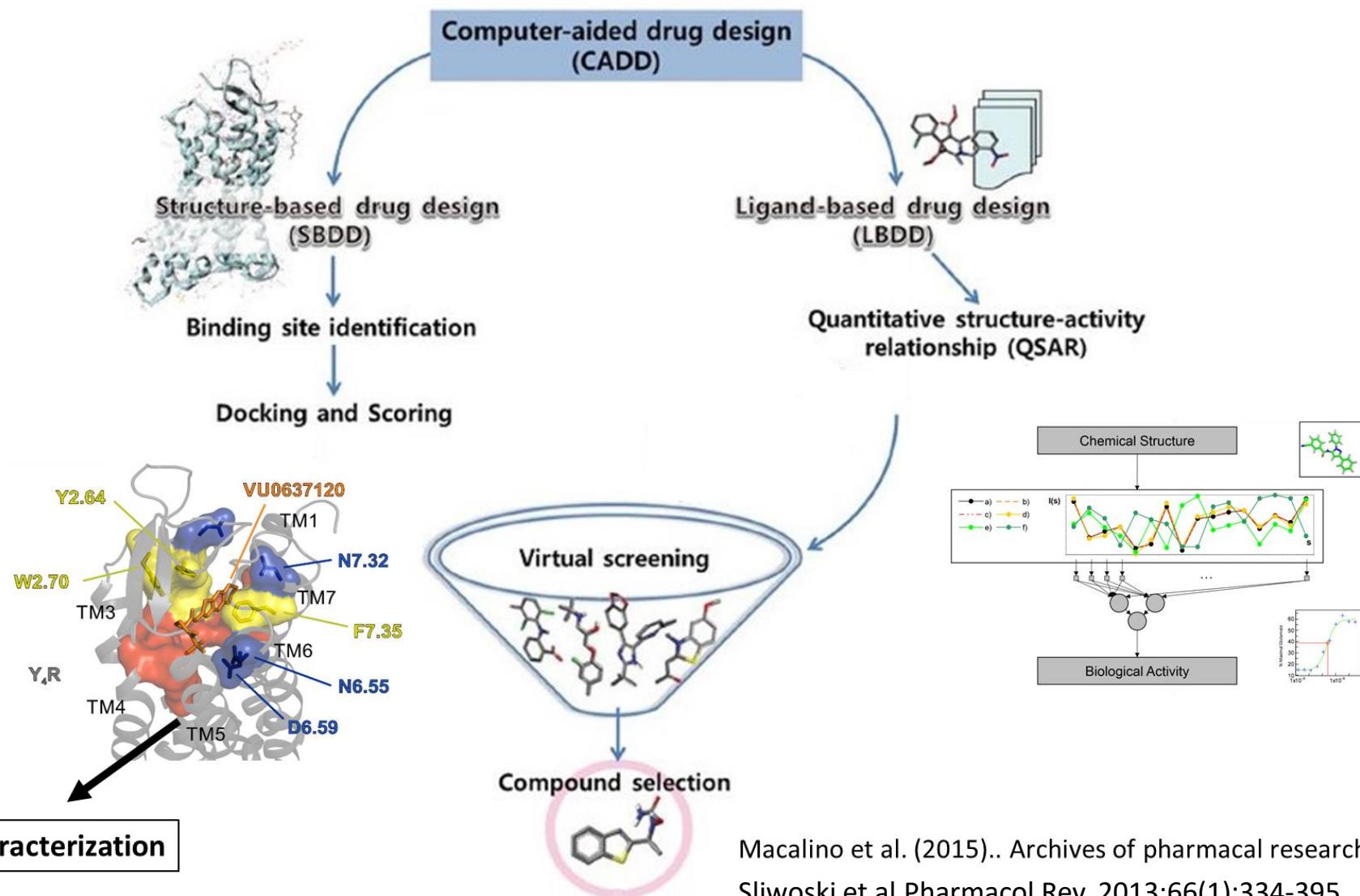
# Generating Y4R homology modeling with RosettaCM



Combs, S.A., et al (2013) Nat Protoc, 1(7), 1277-98.

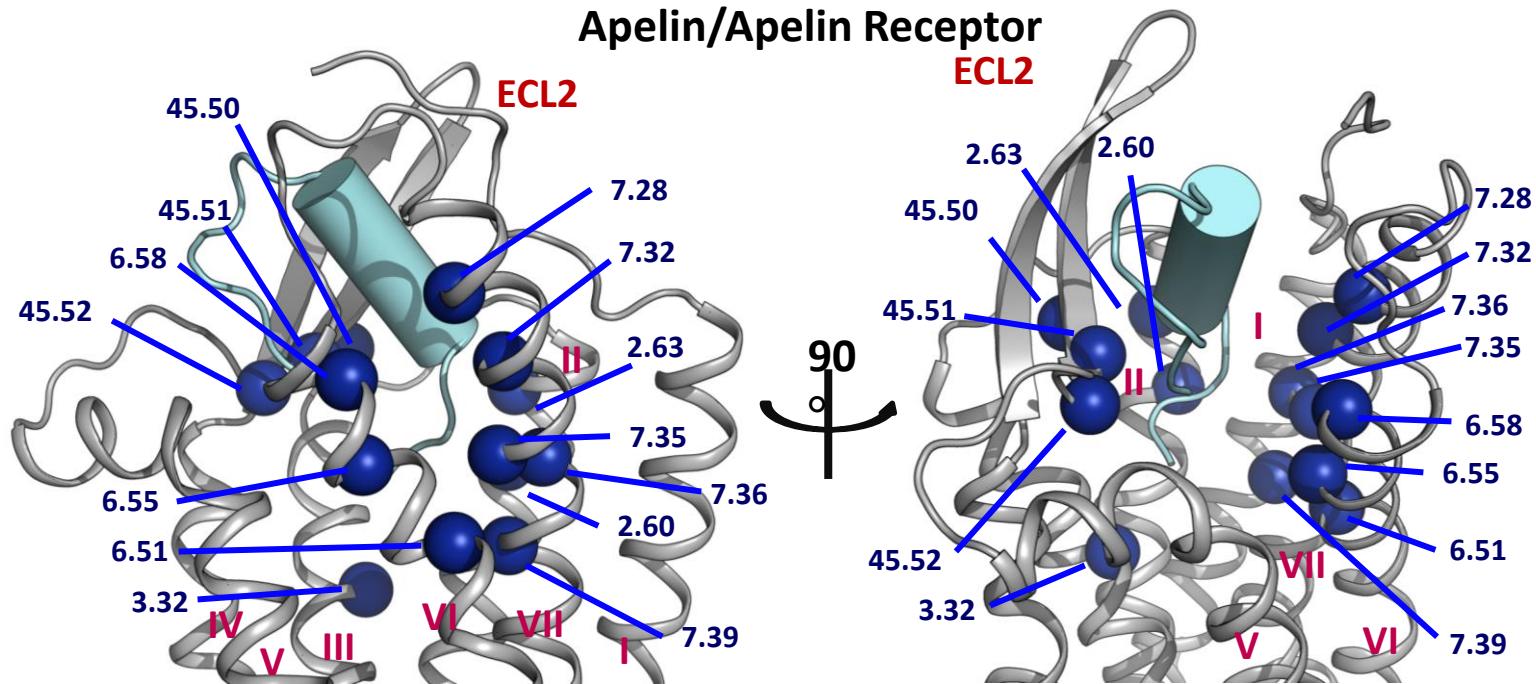


# Computer-aided drug discovery



# Top scored residues suggest common binding pocket of peptide ligands

Receptor	CXCR4	ETBR	CCR5	apelinR	US28	C5a1R	MuOR	CCR5	AT1R	Sum ΔΔG	Average ΔΔG
Residue #	4RWS	5GLH	5UIW	5VBL*	5WB2	6C1Q*	6DDF	6MEO	6OS0		
7.39	-4.0	-3.7	-5.1	-1.3	-5.0	-3.3	-1.4	-0.6	-2.7	-27.1	-3.0
2.60	-5.4	-4.5	-3.8	-0.2	-2.4	-2.3	-1.7	-2.8	-3.1	-26.1	-2.9
45.51	-2.2	-4.9	-3.0	-0.2	-2.4	-3.0	-2.7	-1.9	-3.4	-23.8	-2.6
7.35	-2.2	0.0	-1.1	-5.6	-3.1	-5.4	-1.0	-1.9	-1.8	-22.2	-2.5
7.32	-2.8	-6.2	-3.3	-0.8	-2.5	0.1		-0.6	-6.0	-22.0	-2.4
45.52	0.0	-2.2	-4.1	-0.3	0.1	-5.4	-0.4	-4.1	-5.3	-21.6	-2.4
6.58	-4.7	-2.8	-0.9	-5.0	0.1	-1.6	-0.6	-1.7	-3.4	-20.6	-2.3
6.51	0.1	-2.8	0.0	-5.9	-3.8	-0.8	-3.1	-0.2	-0.1	-16.6	-1.8
2.63	-6.5	-3.6	-2.7	-0.2	-0.4	-0.2	0.1	-1.9	-0.6	-15.9	-1.8
3.32	0.0	-1.2	-2.0	-1.4	-1.2	-0.5	-5.7	-1.8	-1.9	-15.6	-1.7
7.36	-0.8	-4.8	-2.8	0.0	-3.4	-0.7	0.0	-2.6	-0.2	-15.3	-1.7
45.50	-3.5	-0.3	-0.6	-0.1	-1.2	-4.2	-1.6	-0.7	0.4	-11.8	-1.3
7.28	-1.7	-4.3	-0.6	-3.1	-0.6	-0.1			-0.6	-10.9	-1.2
6.55	0.0	-2.1	-0.4	-4.3	-1.2	0.1	-1.9	-0.9	0.0	-10.5	-1.2



# Mutagenesis Constraints for Docking

<b>Y<sub>4</sub>R residues</b>	<b>PP residues</b>	<b>Centroid restraints</b>	<b>Full atom restraints</b>	<b>Proposed interaction</b>
Y2.64 or/and Y2.69	Y27	CB within 7A	CB within 7A	Unknown
D6.59	R35	CB within 7A	OD1-NH1 within 4A OD2-NH2 within 4A	Salt bridge/Hbond
D7.32	R33	CB within 7A	Distance: combination of OD1 Hbond and1(2)HH1(2)/HE within 4A Angle: combination of possible acceptor and H-donor > 90°	
F7.35	R33	CB within 7A	CZ-NH1 within 7A CG-NH1 within 7A	Pi-cation
F7.35	Y36	CB within 7A	CZ-CZ within 7A	Unknown
D2.68	??	None	None	Unknown
W2.70	??	None	None	Unknown

The Beck-Sickinger lab



## Monte Carlo (MC)

Metropolis algorithm:

Given N particles interacting with a potential energy function  $U(\mathbf{r}_1, \dots, \mathbf{r}_N)$

Probability:  $P \propto e^{-U/kT}$

- Assume some initial configuration with energy  $U_0$
- Move the particles by small increments to new positions with energy  $U_1$
- If  $U_1 < U_0$ , accept the new configuration
- If  $U_1 > U_0$ , select a random number  $r$  between 0 and 1, and accept the new configuration if

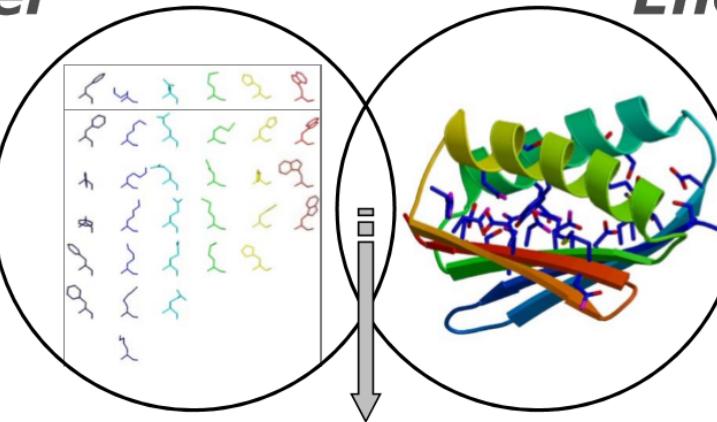
$$\exp[-(U_1 - U_0)/kT] > r$$

- Keep iterating until the minimum energy is found

# Sampling and Scoring for Side Chain Repacking and Design

## *Local Rotamer Bias*

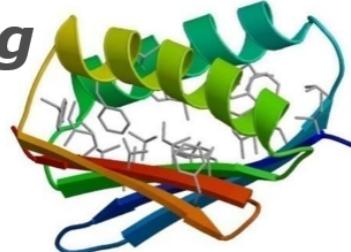
Approximate interactions within sidechain using the distribution of sidechain conformations (rotamers) seen in known protein structures



## *Energy function*

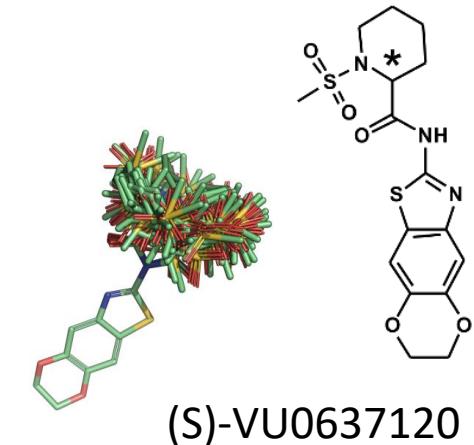
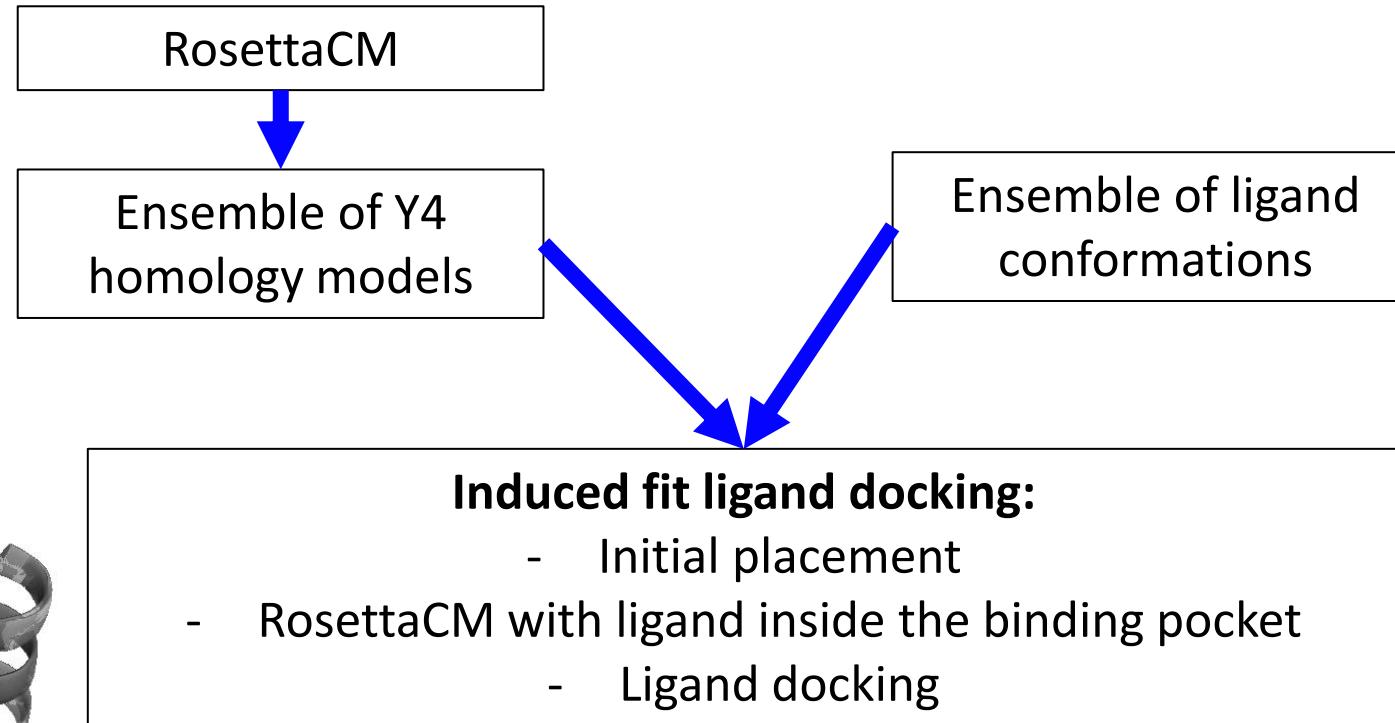
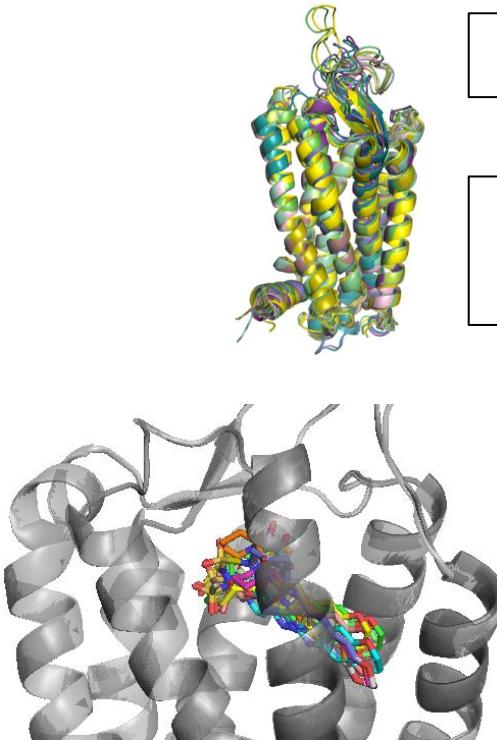
Statistically derived potential function  
• VDW interaction  
• solvation  
• hydrogen bonding potential  
• pair wise interactions  
• rotamer probability

## *Simulated Annealing Monte Carlo energy minimization*



Dahiyat, B. I. and Mayo, S. L. (1997) *Science*, 278, 82-7.  
Dunbrack, R. L., Jr. and Karplus, M. (1993) *J Mol Biol*, 230, 543-74.  
Kuhlman, B., et. al. (2003) *Science*, 302, 1364-1368.

# Ligand docking protocol



Combs, S.A., et al (2013) Nat Protoc, 1(7), 1277-98.  
Nguyen, E.D., et al (2013) PLOS ONE 8(7):e67302

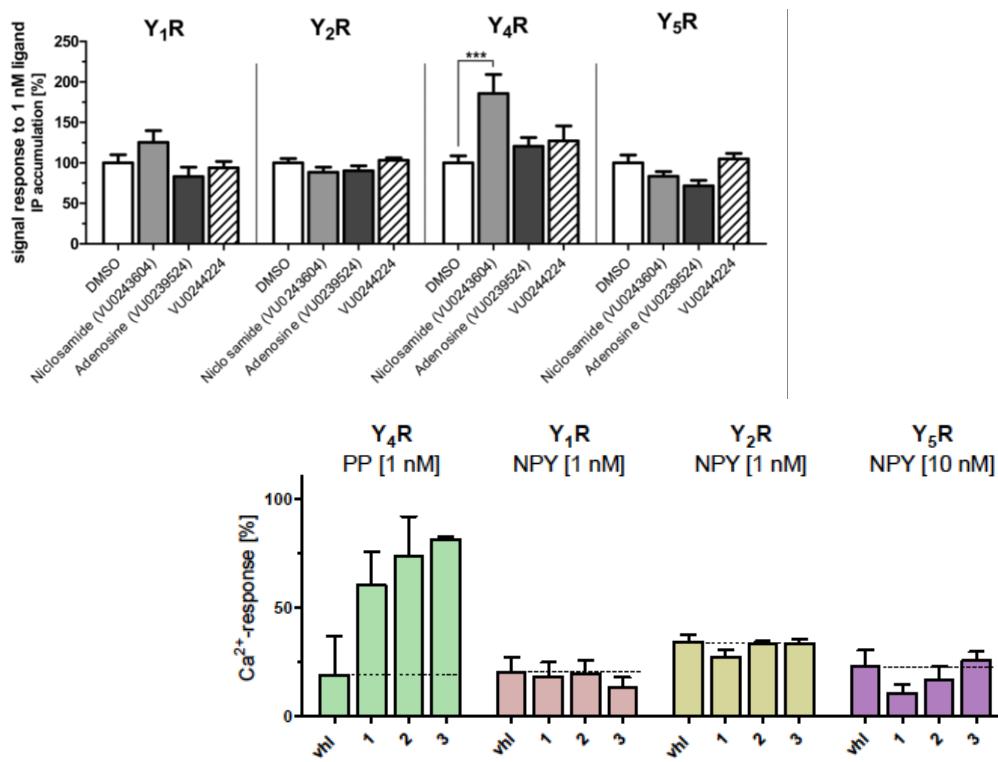
# Datasets

Protein class—target	PubChem SAID	# Active molecules (%)	# Inactive molecules
GPCR—Orexin1 Receptor Antagonists	435008	233 (0.11)	217925
GPCR—M1 Muscarinic Receptor Agonists	1798	187 (0.30)	61646
GPCR—M1 Muscarinic Receptor Antagonists	435034	362 (0.59)	61394
Ion channel—Kir <sub>2.1</sub> K <sup>+</sup> channel inhibitors	1843	172 (0.06)	301321
Ion channel—KCNQ2 K <sup>+</sup> channel potentiators	2258	213 (0.07)	302192
Ion channel—Cav3 T-type Ca <sup>2+</sup> inhibitors	463087	703 (0.70)	100172
Transporter—choline transporter inhibitors	488997	252 (0.08)	302054
Kinase inhibitor—serine/threonine Kinase 33 Inhib.	2689	172 (0.05)	319620
Enzyme—Tyrosyl-DNA Phosphodiesterase Inhib.	485290	281 (0.08)	341084



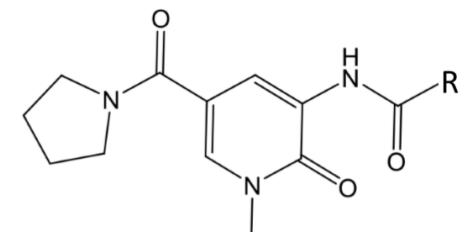
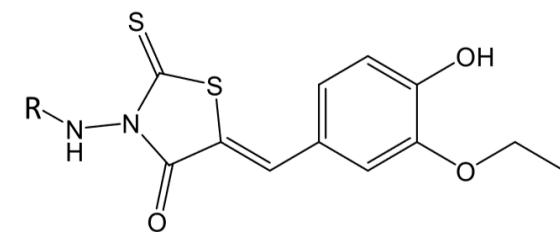
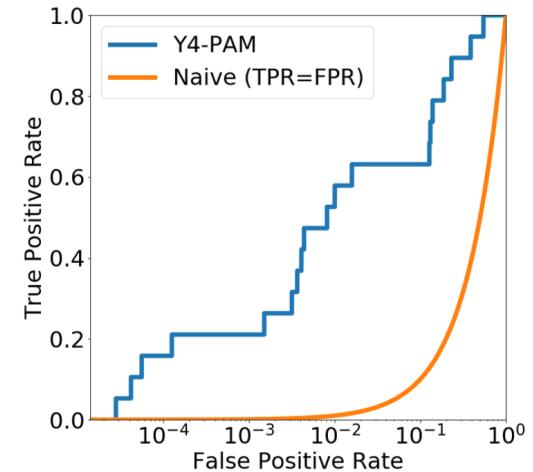
# Experimental validation results

Bioassay : potency + selectivity



Weaver group, Vanderbilt University  
Beck-sickinger group, University of Leipzig

- Previous HTS: ( hit rate : 0.02%)
- QSAR: 20/600 selected compounds were confirmed active (hit rate : 3.33%)



New PAM scaffolds

## Monte Carlo (MC)

Metropolis algorithm:

Given  $N$  particles interacting with a potential energy function  $U(\mathbf{r}_1, \dots, \mathbf{r}_N)$

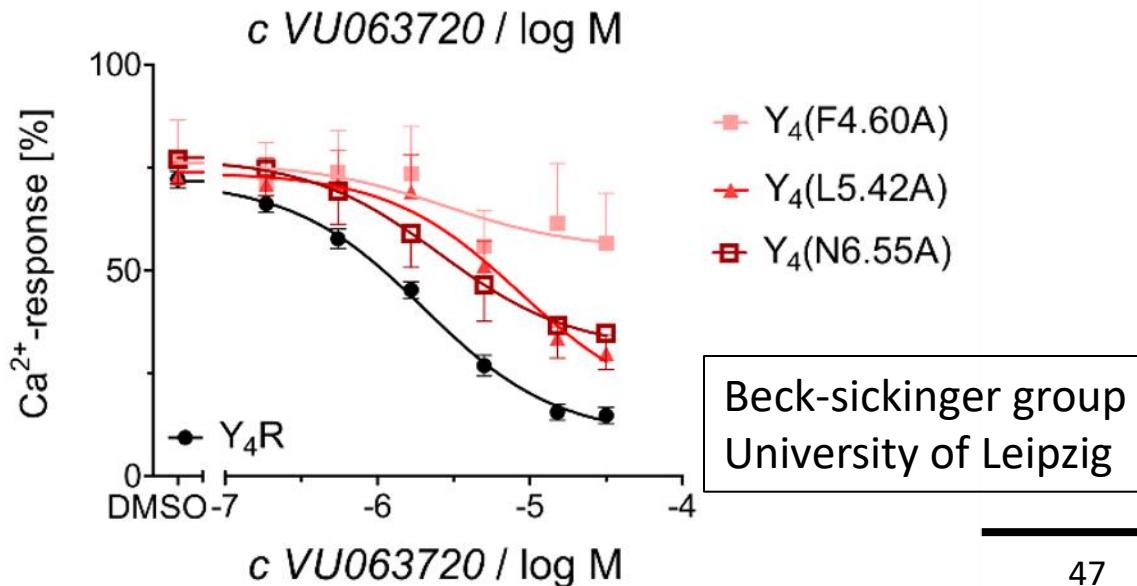
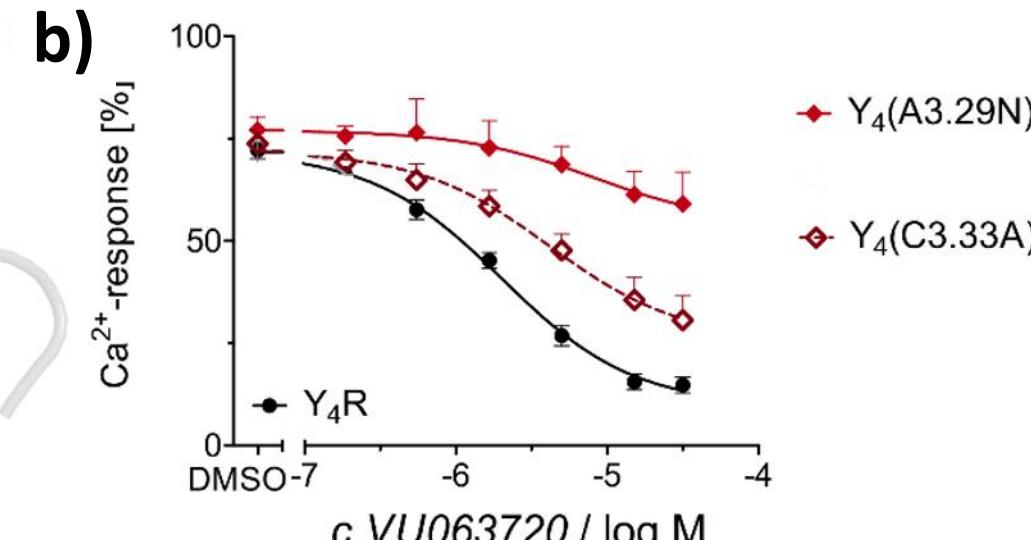
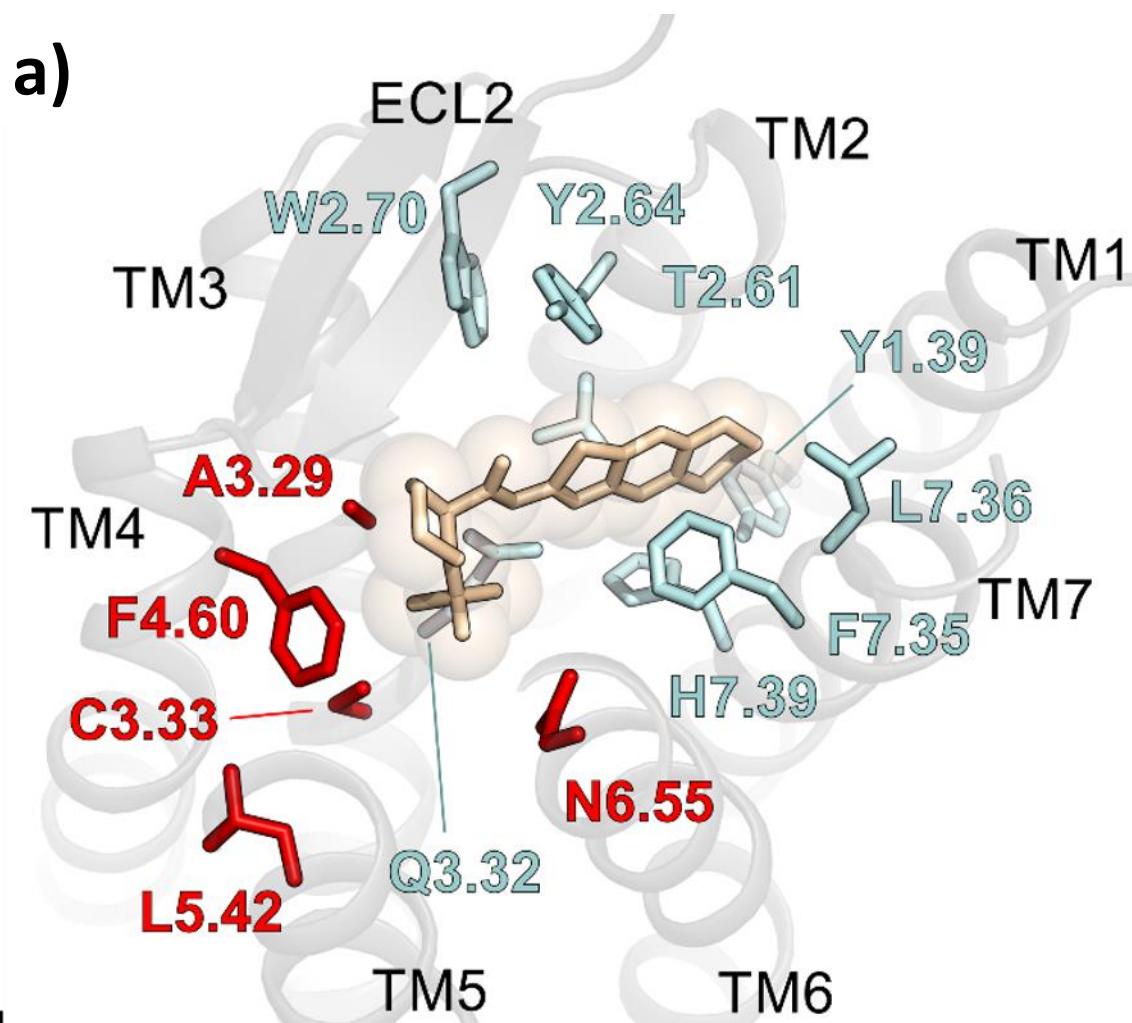
Probability:  $P \propto e^{-U/kT}$

- Assume some initial configuration with energy  $U_0$
- Move the particles by small increments to new positions with energy  $U_1$
- If  $U_1 < U_0$ , accept the new configuration
- If  $U_1 > U_0$ , select a random number  $r$  between 0 and 1, and accept the new configuration if

$$\exp[-(U_1 - U_0)/kT] > r$$

- Keep iterating until the minimum energy is found

# Mutagenesis data support cluster 1's pose

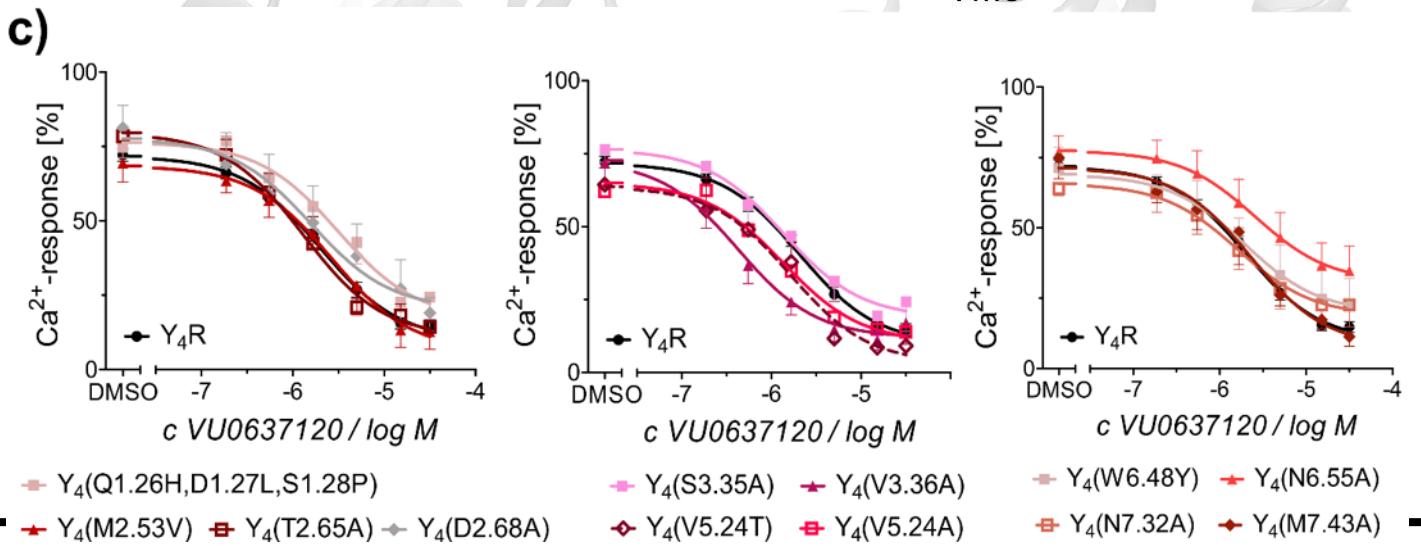
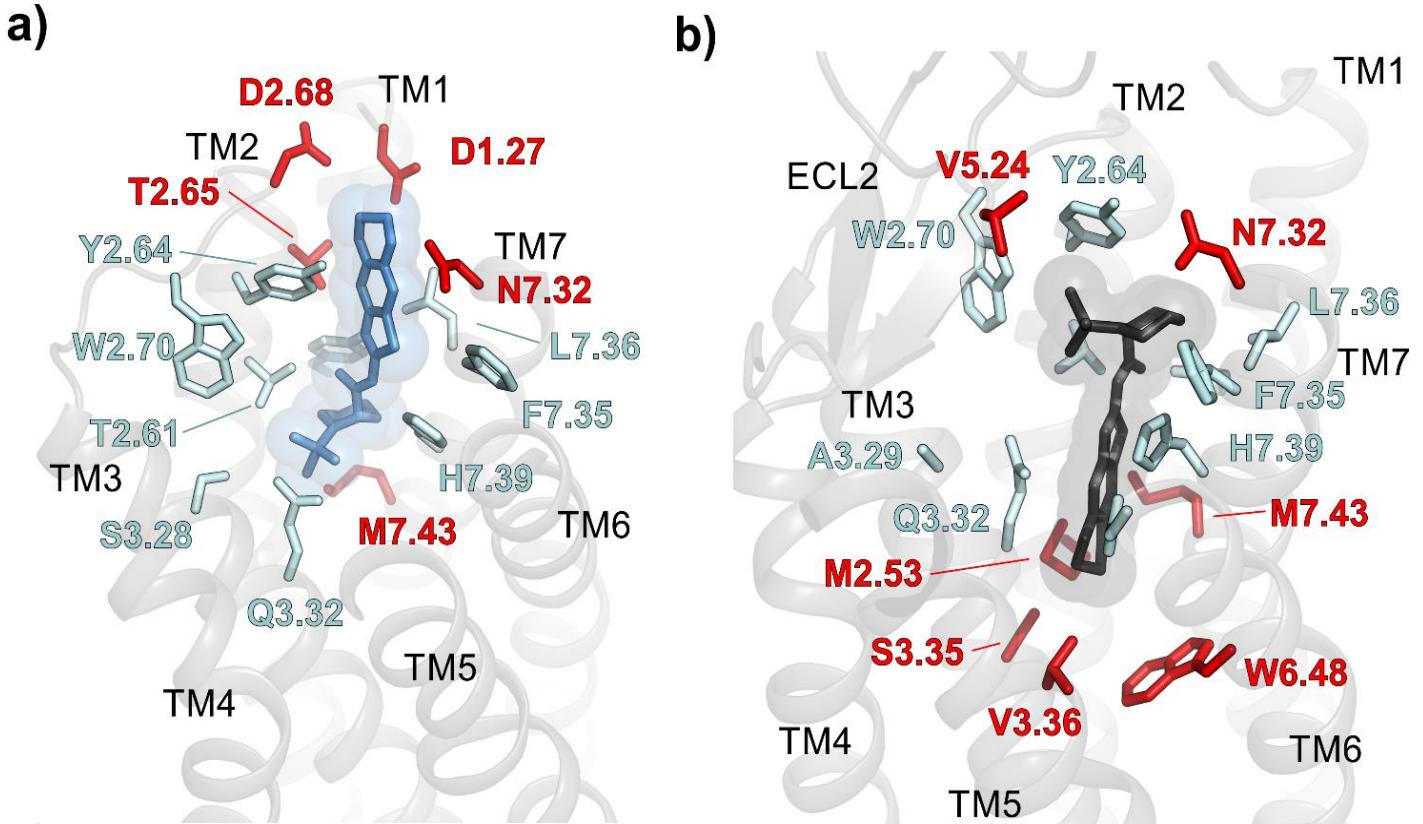


Beck-sickinger group  
University of Leipzig



# Mutagenesis data do not support poses of cluster 2&3

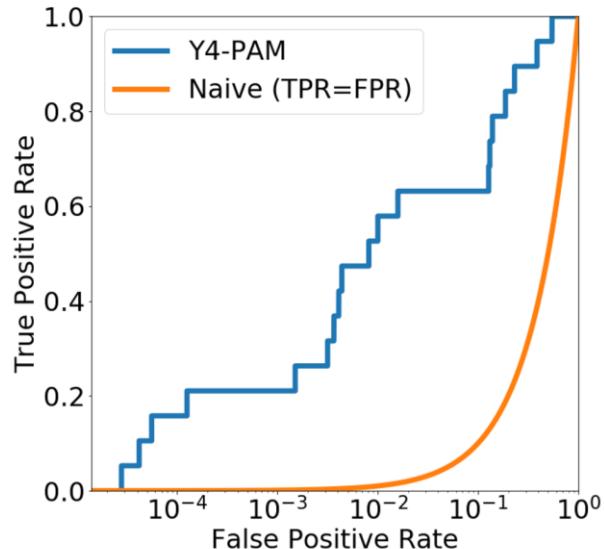
Beck-sickinger group  
University of Leipzig



# Datasets

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# Measuring Prediction performance



LogAUC score  
Early enrichment

Lopes et al. J Cheminform (2017) 9:7

Matthews correlation coefficient (MCC)

$$\frac{TP * TN - FP * FN}{\sqrt{(TP + FP)(TP + FN)(TN + FP)(TN + FN)}}$$

correlation coefficient between the measured and predicted classifications

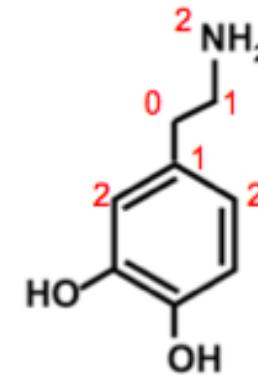
$$EF(x) = \frac{TP / (TP + FP)}{(TP + FN) / (TP + TN + FP + FN)}$$

Proportion of true active compounds in the selection set in relation to the proportion of true active compounds in the entire dataset



# Atom environment-based descriptors are shown to be most robust among 2D descriptors

fingerprint	average of all settings EF(1%)	best single setting EF(1%)
dendritic	16.2	34.7
linear	14.5	33.5
MACCS	7.3	21.6
<b>MOLPRINT2D</b>	<b>22.2</b>	<b>35.1</b>
pairwise	13.2	29.5
radial	13.3	33.8
torsion	15.3	34.0
triplet	15.3	34.9



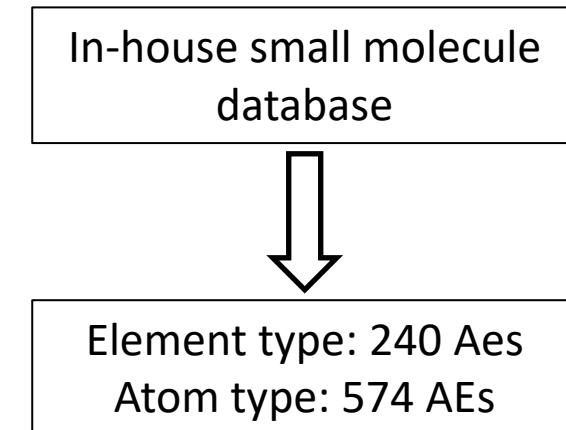
Layers	0	1	2
	C	-C	-N
		-C	~C
			~C

Sastray., M et al. *J. Chem. Inf. Model.* 2010 50 (5), 771-784

Bender et al. *J Chem Inf Comput Sci.* 2004;44(5):1708-18.

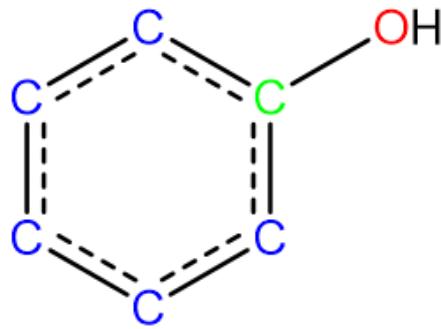
# BCL::Mol2D – an improved version of Molprint2D

Characteristics	Molprint2D	BCL::Mol2D
AE Layer #	2	1
Atomic encoding	Element Bond order	Element Bond order Hybridization (Atom type)
AE Value type	Presence	Count

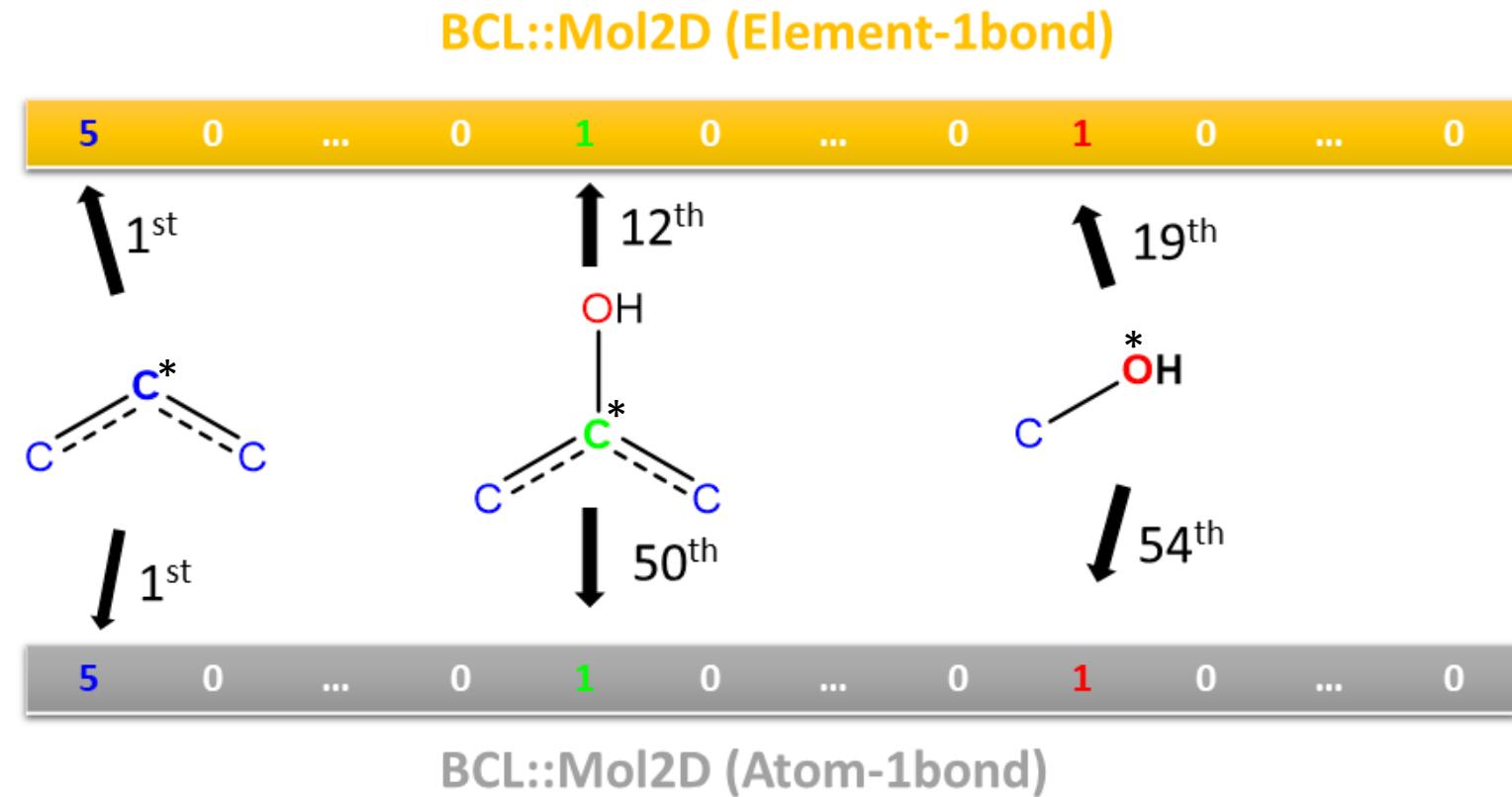


# Illustration of BCL::Mol2D fingerprints of Phenol

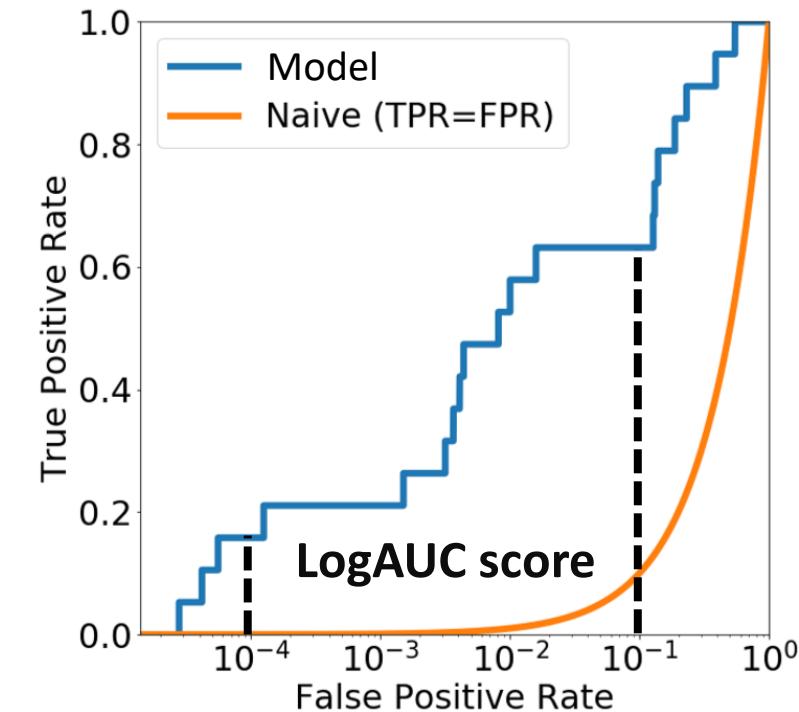
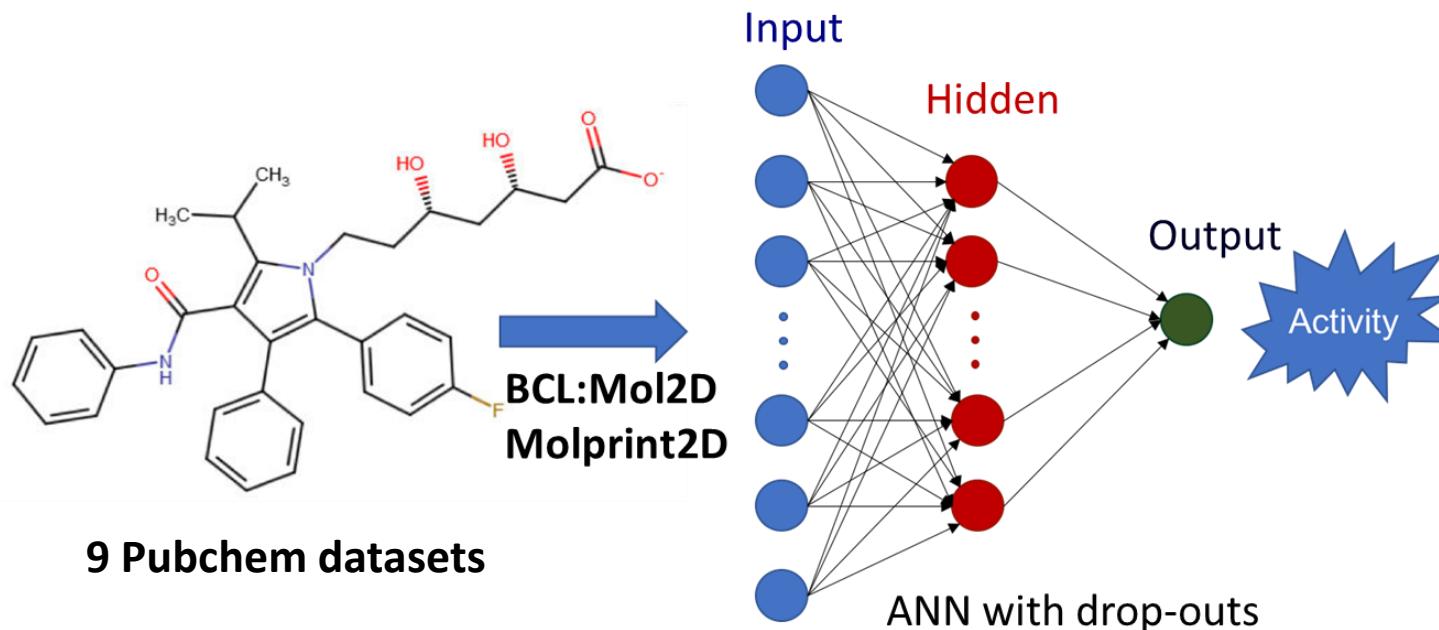
A



B



# Benchmarking BCL::Mol2D against Molprint 2D



**Classifiers:**

- Shallow ANNs with drop-outs

**Descriptor:**

- BCL::Mol2D
- Molprint2D

**Performance metrics:**  
Log AUC

# BCL::Mol2D outperform Molprint2D in QSAR across 9 Pubchem Datasets

