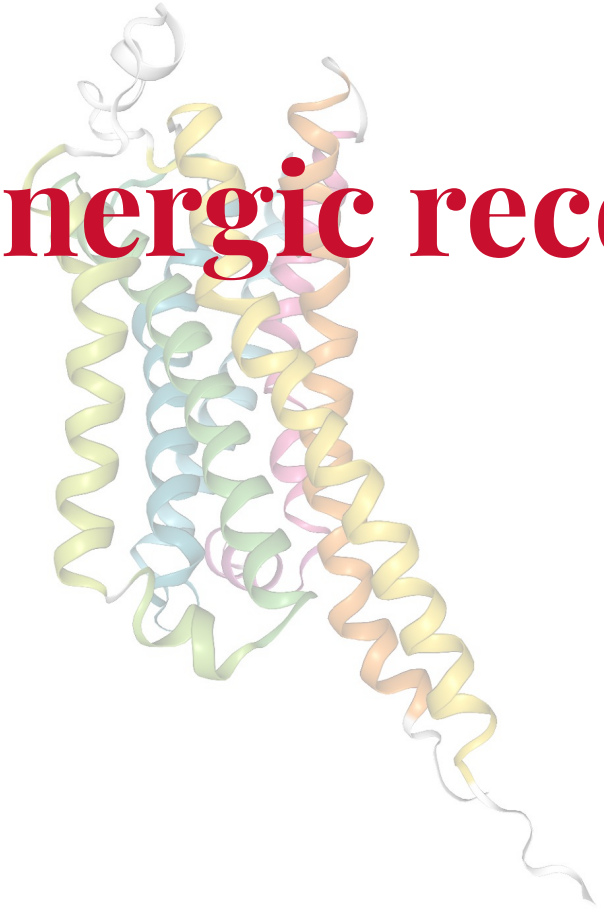
# β2 adrenergic receptor



03.03.2020

Structural Biology, 4th course

Degree in Human Biology

Èric Bautista

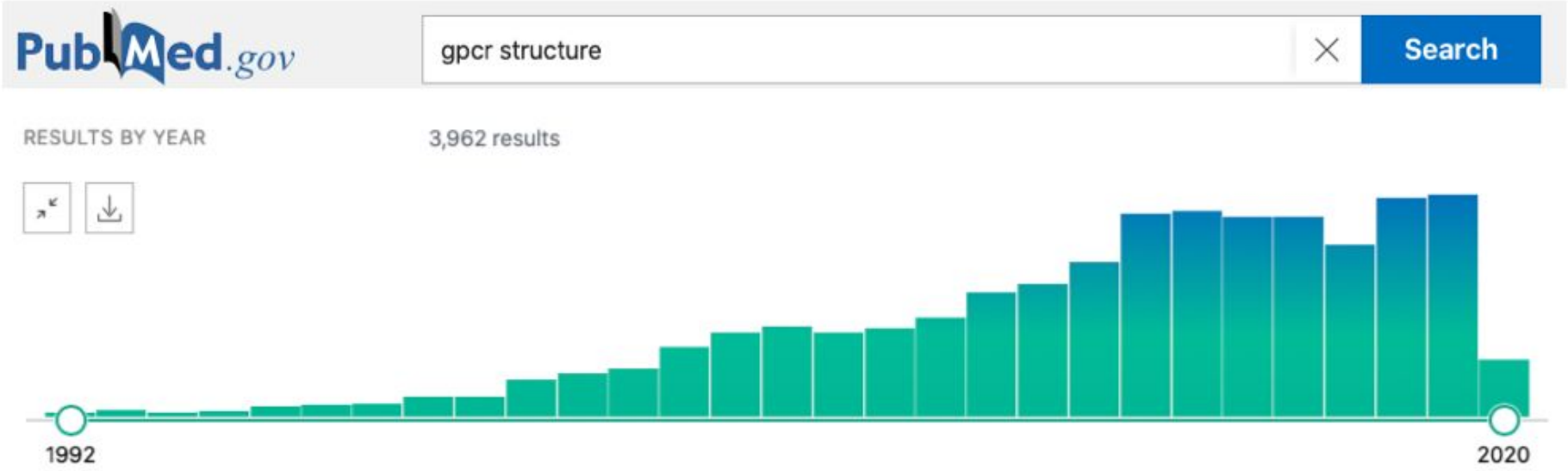
Maria Estarellas

Pol Jiménez

Núria Sánchez

# Outline

# 1. Introduction



# 1.1. Introduction: GPCRs

- Member of the **class A G protein-coupled receptors** superfamily (GPCRs)
  - Integral membrane proteins; variety of signals
  - First characterized in the **1970s**
  - Formed by almost **1000** different **proteins**
- Target for **asthma and cardiac drugs**
  - **≃50%** of all the current **drug targets**
  - Ongoing research for new drugs with **higher efficacy and specificity**

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**High resolution structures** needed in order to **develop new and** more specific drugs through **chemical screening methods.**

# 1.1. Introduction: GPCRs

- As rhodopsin-like rc., its structure includes **7 transmembrane domains**
- They **couple G proteins**, which in turn activate downstream enzymes

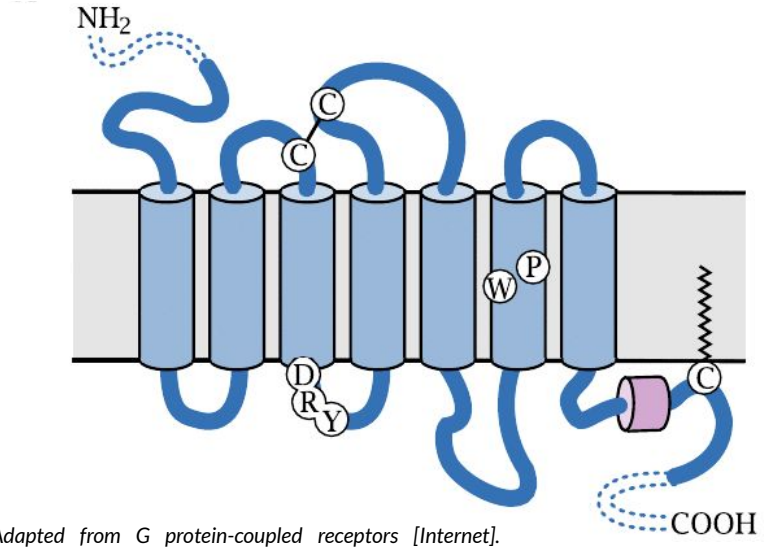



***Fig. 1.*** *Adapted from G protein-coupled receptors [Internet]. Watcut.uwaterloo.ca. 2020 [cited 24 February 2020]. Available from: http://watcut.uwaterloo.ca/webnotes/Pharmacology/GPCRs.html*

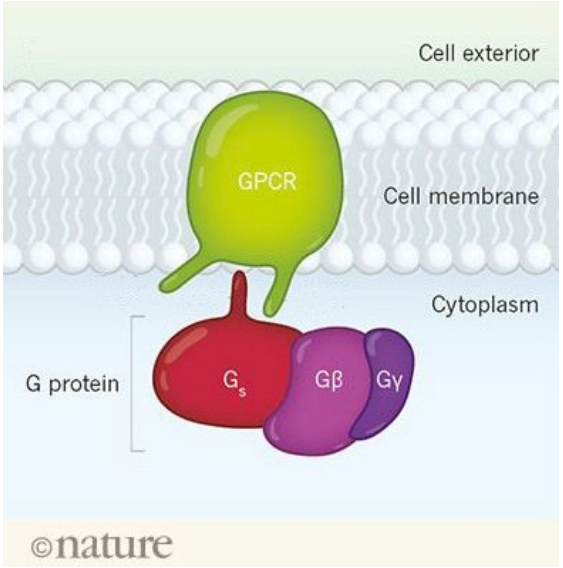



***Fig. 2.*** *Adapted from Capper M, Wacker D. How the ubiquitous GPCR receptor family selectively activates signalling pathways. Nature. 2018;558(7711):529-530.*

# 1.2. Introduction: β2-AR

- Intronless gene (ADRB2) of approximately **1200bp**; encoded in the long arm of **chr. 5**

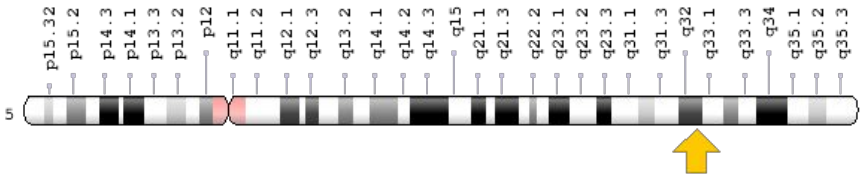



***Fig. 3.*** *ADRB2 gene [Internet]. Genetics Home Reference. 2020 [cited 24 February 2020]. Available from: https://ghr.nlm.nih.gov/gene/ADRB2*

- Gene product of **413 residues**, with several ligands and implied in different pathologies
- Mainly expressed by **airway smooth muscle, epithelial** and **endothelial cells of the lung**

# 1.2. Introduction: β2-AR

## Adrenergic receptors

| Rc. | Subtype | Mechanism |
|---|---|---|
| α-AR | α**1**-AR | Gq *(PLC)* |
| | α**2**-AR | Gi *(↓cAMP)* |
| β-AR | β**1**-AR | Gs *(↑cAMP)* |
| | **β2-AR** | **Gs & Gi** |
| | β**3**-AR | Gs & Gi |

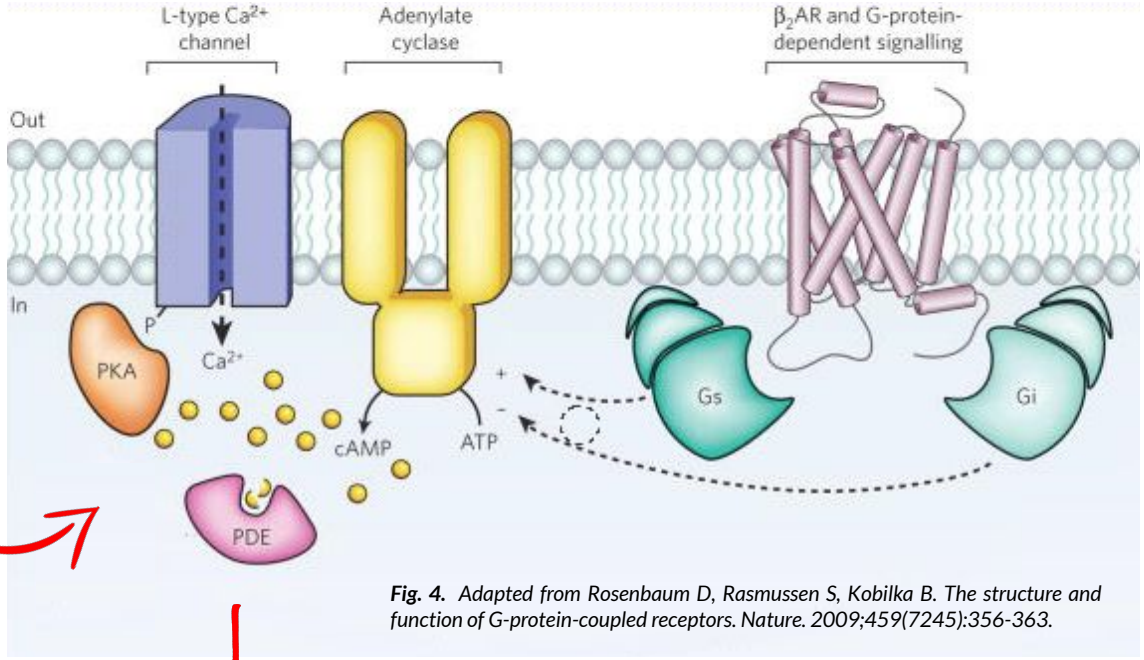



***Fig. 4.*** *Adapted from Rosenbaum D, Rasmussen S, Kobilka B. The structure and function of G-protein-coupled receptors. Nature. 2009;459(7245):356-363.*

**Smooth muscle relaxation**: GI tract, bronchi, blood vessels and arteries (vasodilatation)

# 1.2. Introduction: β2-AR

## Adrenergic receptors

| Rc. | Subtype | Mechanism |
|---|---|---|
| α-AR | α**1**-AR | Gq *(PLC)* |
| | α**2**-AR | Gi *(↓cAMP)* |
| β-AR | β**1**-AR | Gs *(↑cAMP)* |
| | **β2-AR** | **Gs & Gi** |
| | β**3**-AR | Gs & Gi |

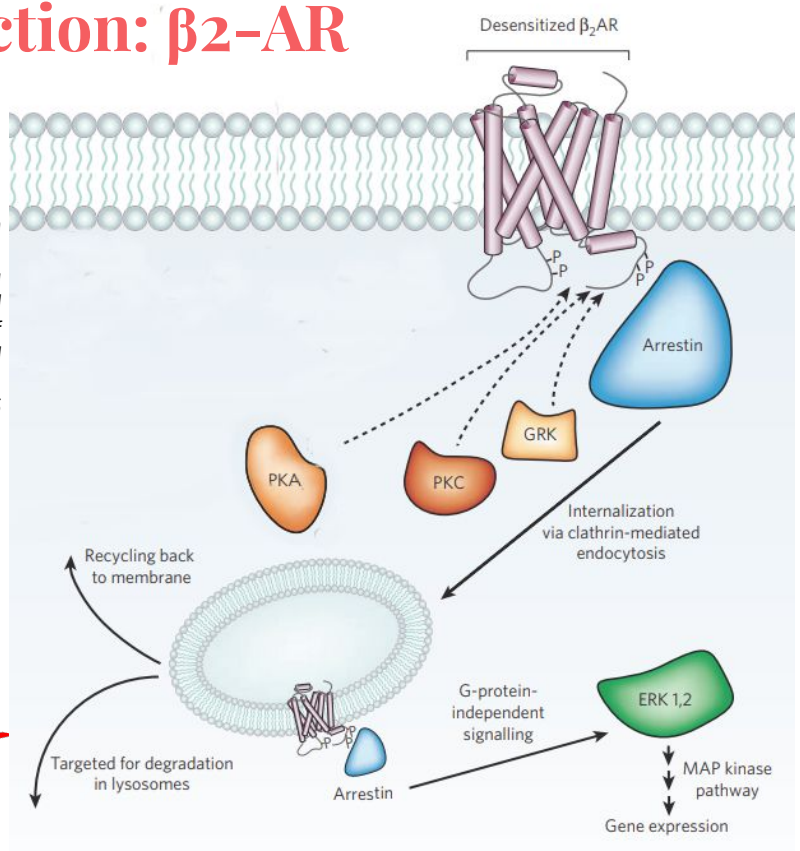


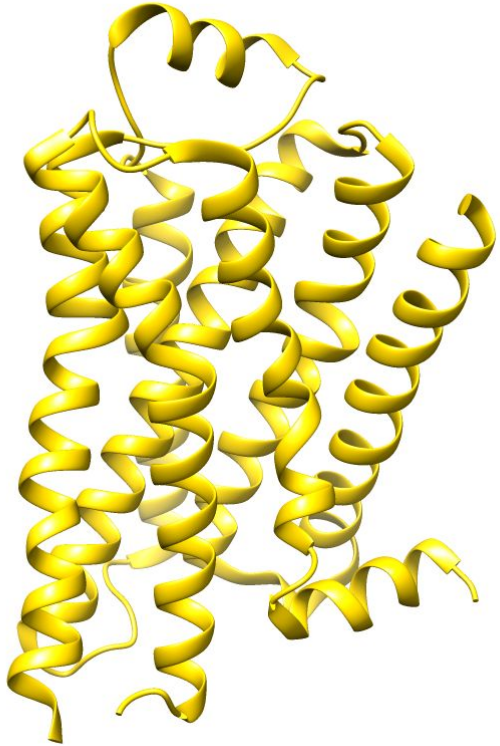

***Fig. 5.*** *Adapted from Rosenbaum D, Rasmussen S, Kobilka B. The structure and function of G-protein-coupled receptors. Nature. 2009;459(7245):356-363.*

**β2-AR phosphorylation** leads to its **coupling to arrestin** and **subsequent internalization**. ERK pathway is also activated

# 1.2. Introduction: β2-AR

## Structure

**7 transmembrane domains**



## Subcellular localization

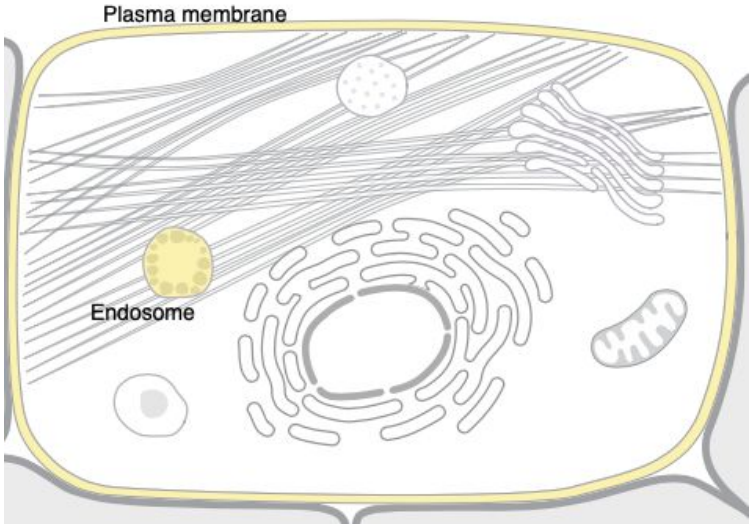
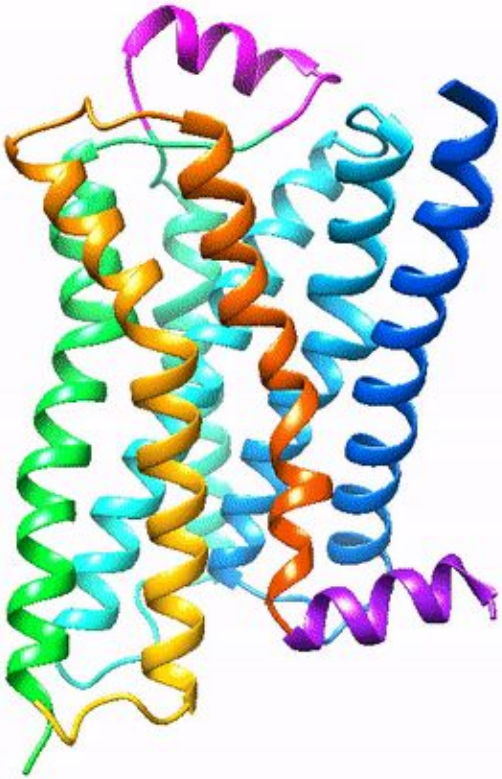
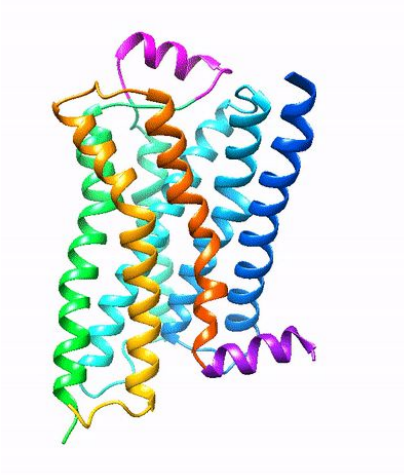



***Fig. 6.*** *Binder J, Frankild S, Tsafou K, Stolte C, O'Donoghue S, Schneider R et al. COMPARTMENTS - Search [Internet]. Compartments.jensenlab.org. 2020 [cited 24 February 2020]. Available from: https://compartments.jensenlab.org/Search*

# 2. Structure



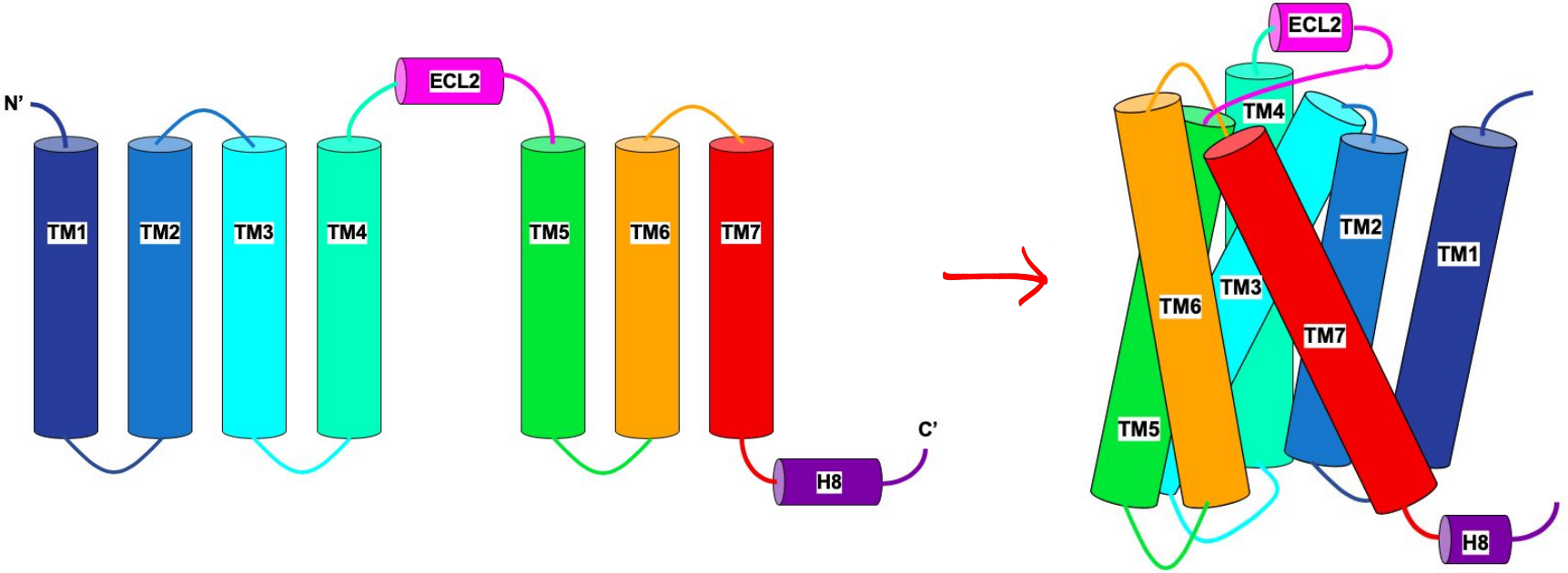
# 2.1. Structure: SCOP classification



1. **Root**: SCOP
2. **Class**: Membrane and cell surface proteins and peptides
   *Does not include proteins in the immune system*
3. **Fold**: Family A G protein-coupled receptor like
   *core: up-and-down bundle of seven transmembrane helices tilted 20 degrees with respect to the plane of the membrane*
4. **Superfamily**: Family A G protein-coupled receptor like
5. **Family**: Rhodopsin-like
   *Individual TM segments have a number of kinks and distortions*

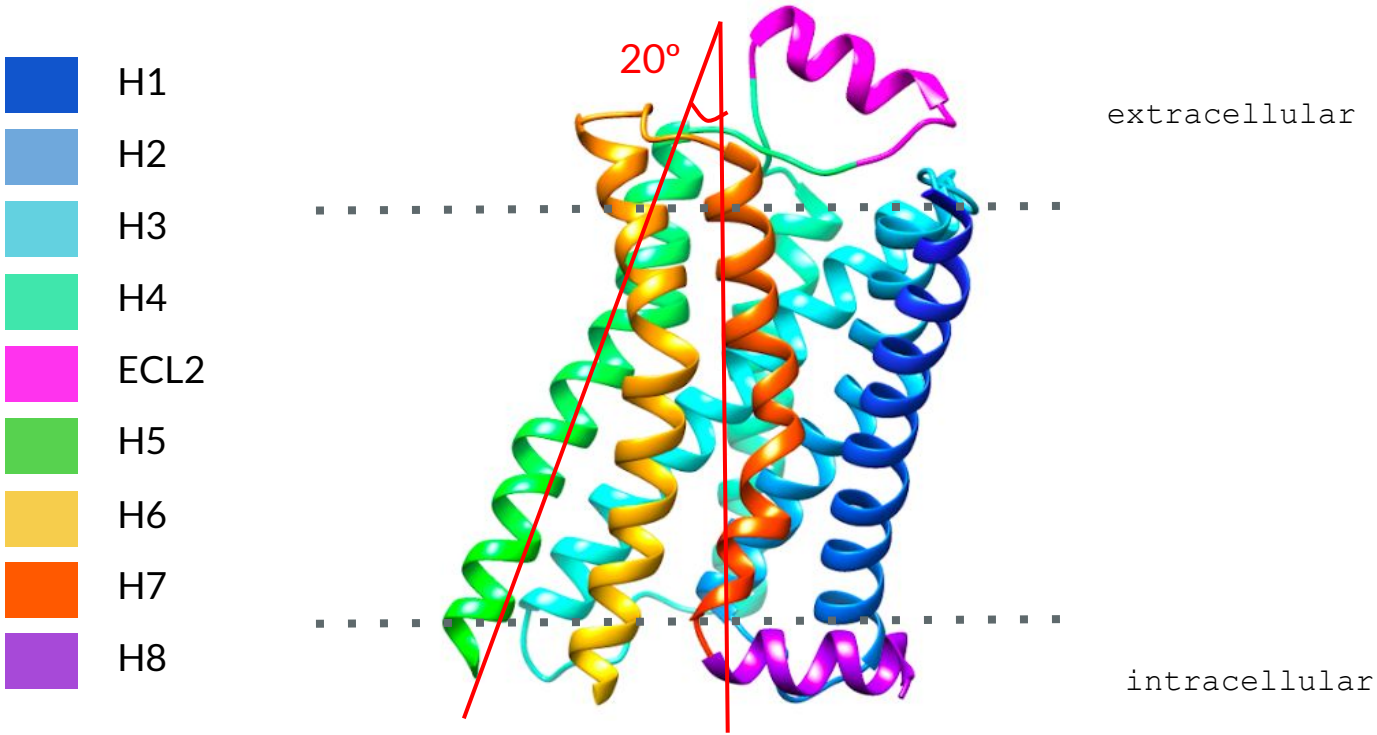
# 2.2. Structure: Fold explanation

"**all alpha, up-and-down helical bundle** formed by **7 transmembrane helices**, tilted 20 degrees with respect to the plane of the membrane"

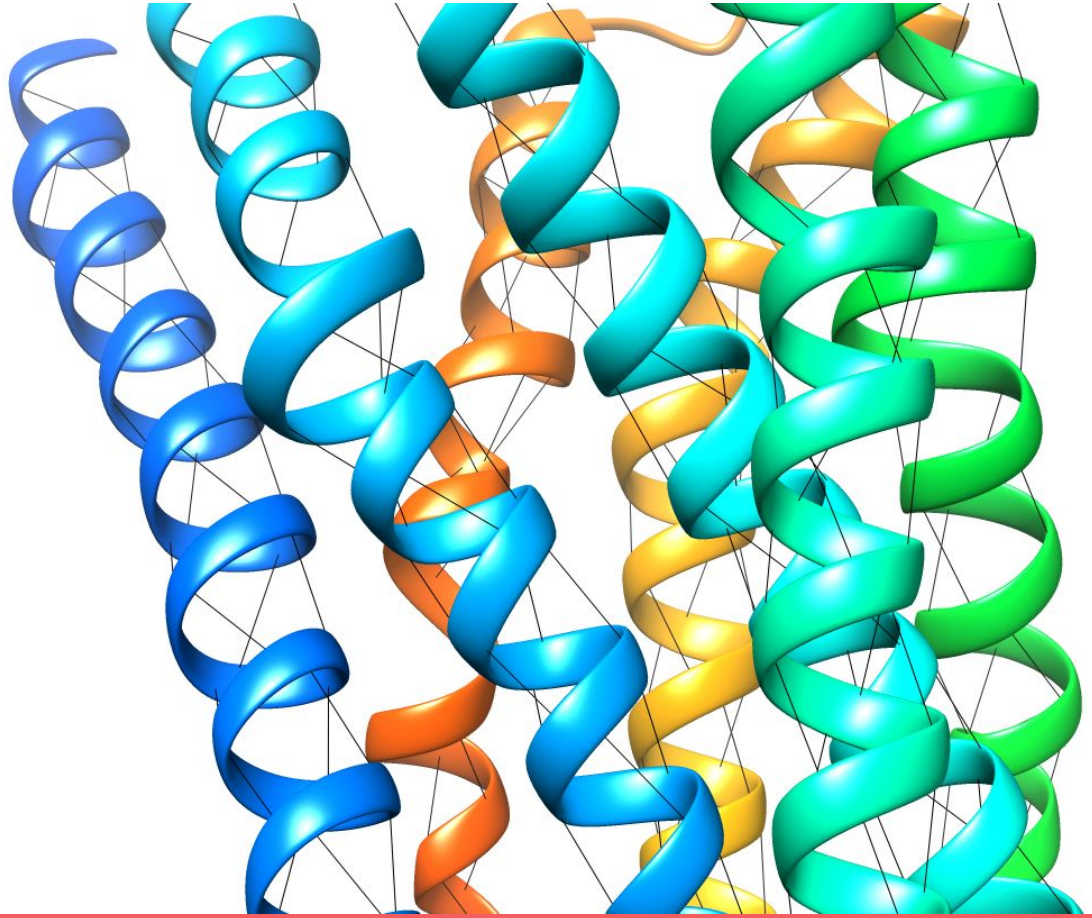


# 2.2. Structure: Fold explanation

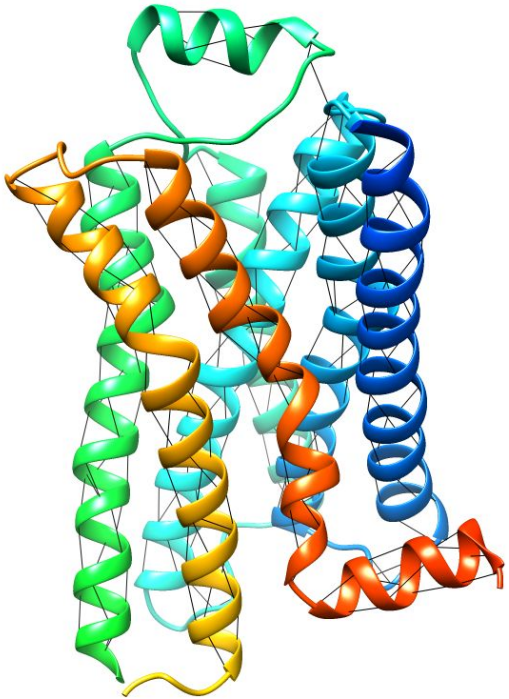
"all alpha, up-and-down helical bundle formed by 7 transmembrane helices, **tilted 20 degrees with respect to the plane of the membrane**"



# 2.3. Structure: Description



**Hydrogen bonds** are essential for maintaining the conformation



# 2.3. Structure: Description

## Ligand binding site

- H3
- ECL2
- H5
- H6
- H7

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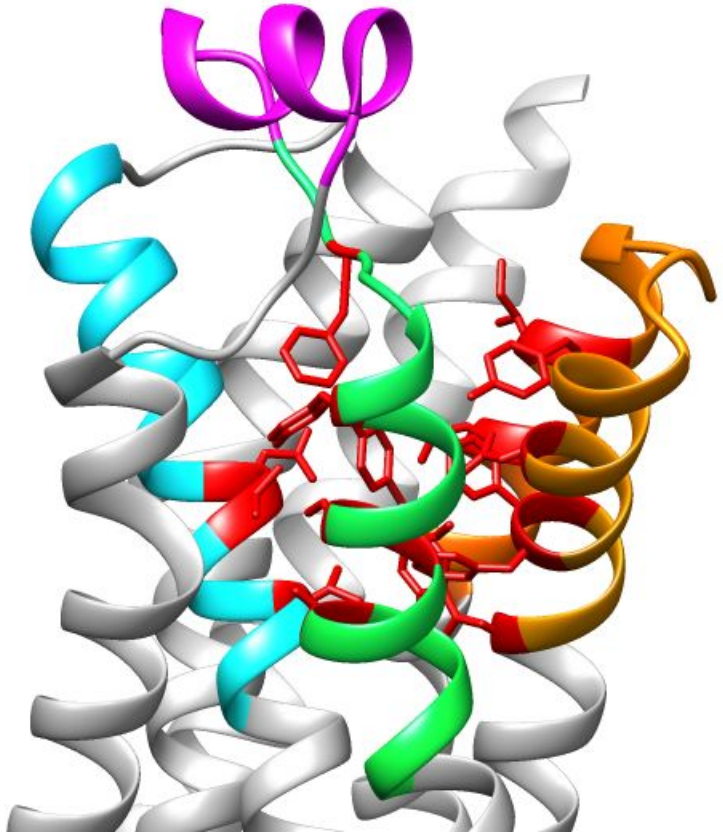
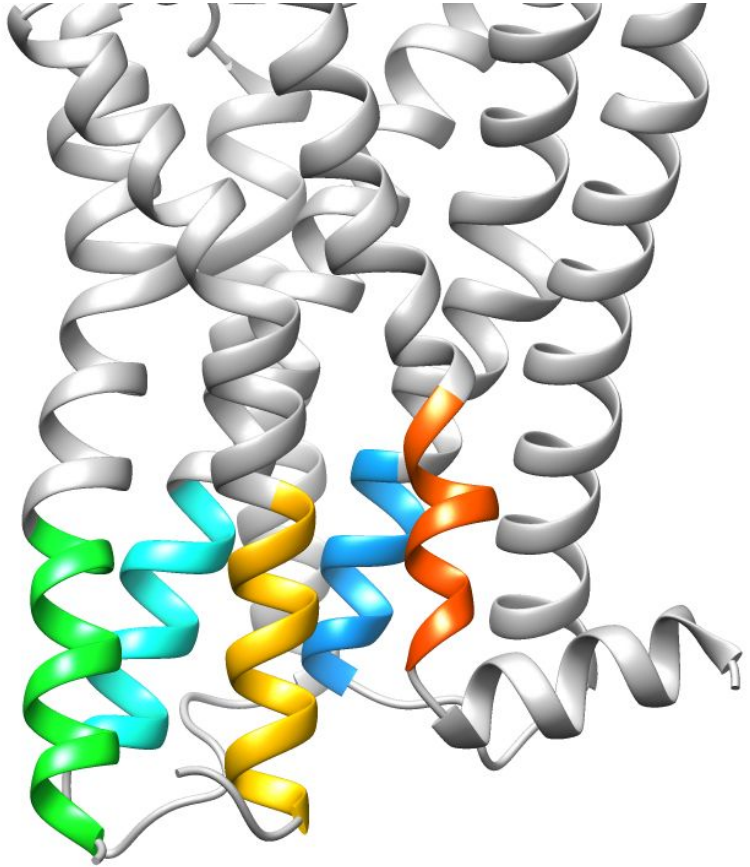
- Ligand binding residues



# 2.3. Structure: Description

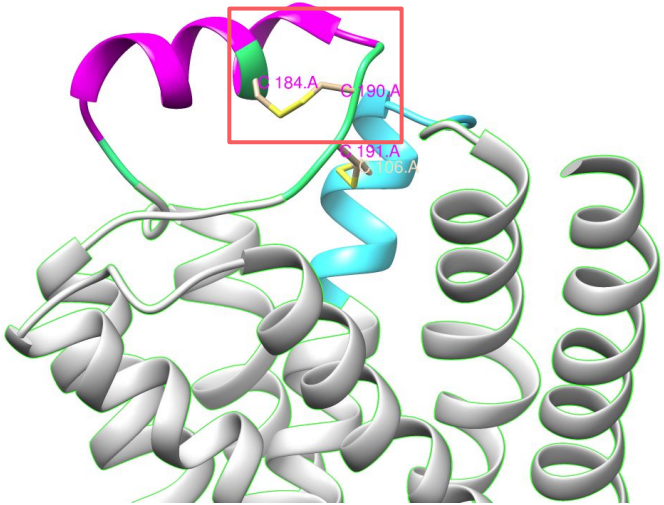
## Intracellular pocket

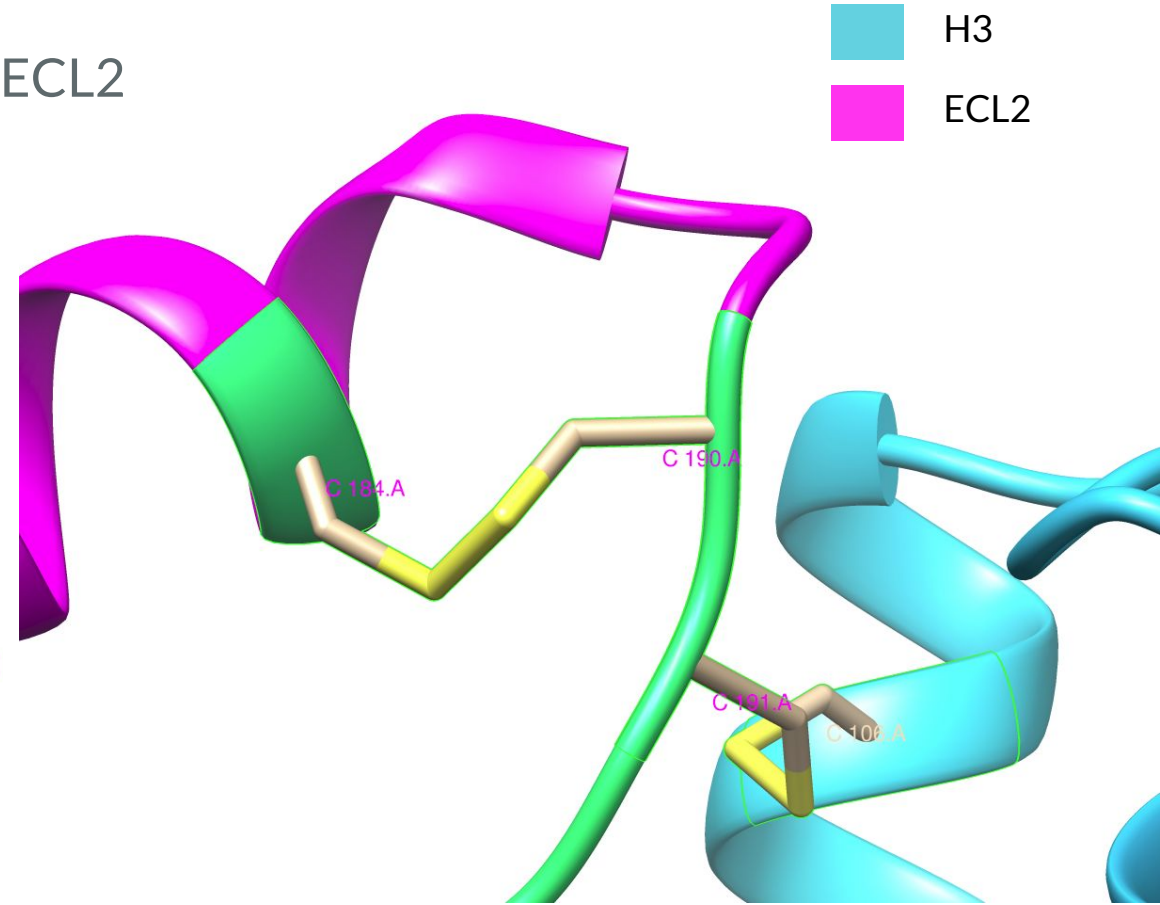
- H2
- H3
- H5
- H6
- H7



# 2.3. Structure: Description

- **2 disulfide bridges** stabilize ECL2
  - **C184-C190**
  - C191-C106



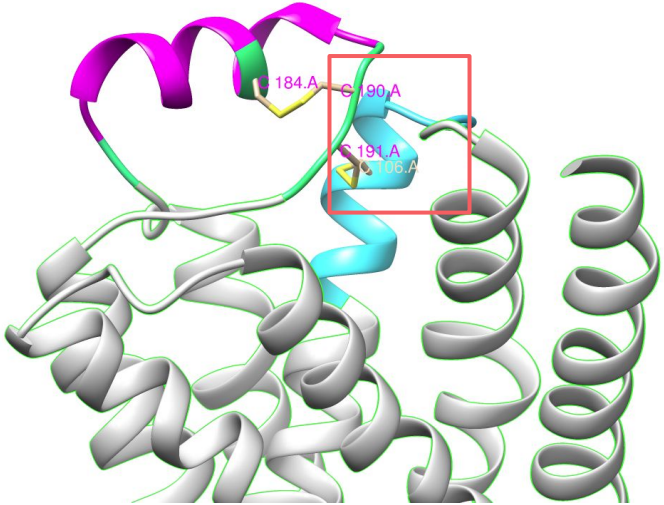



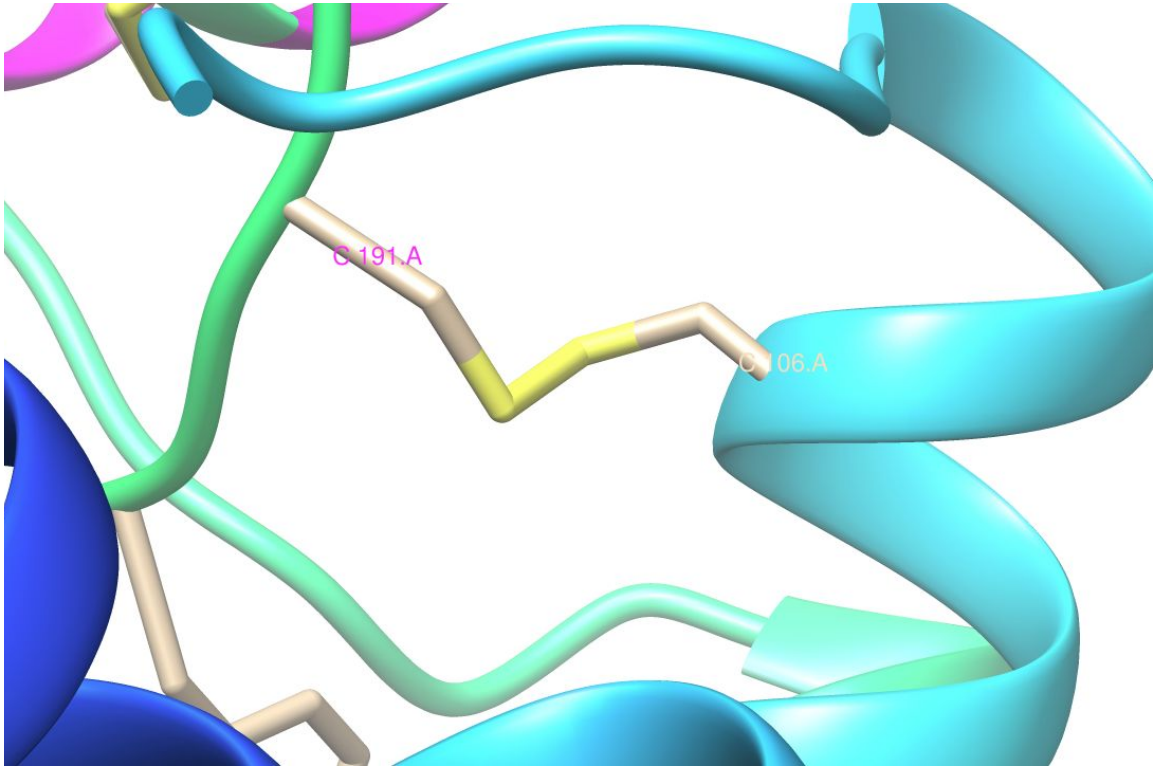
# 2.3. Structure: Description

H3

ECL2

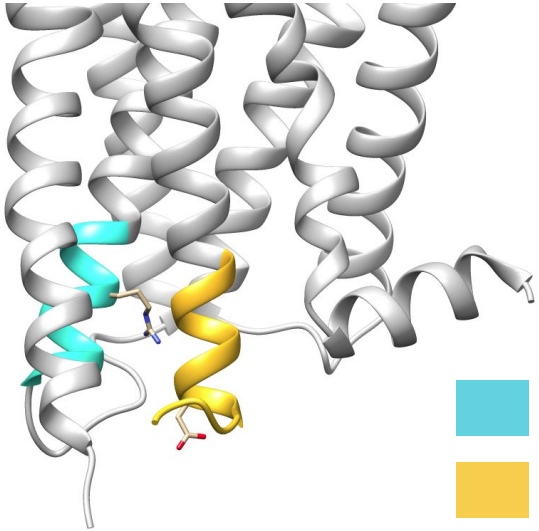
- **2 disulfide bridges** stabilize ECL2
  - C184-C190
  - **C191-C106**

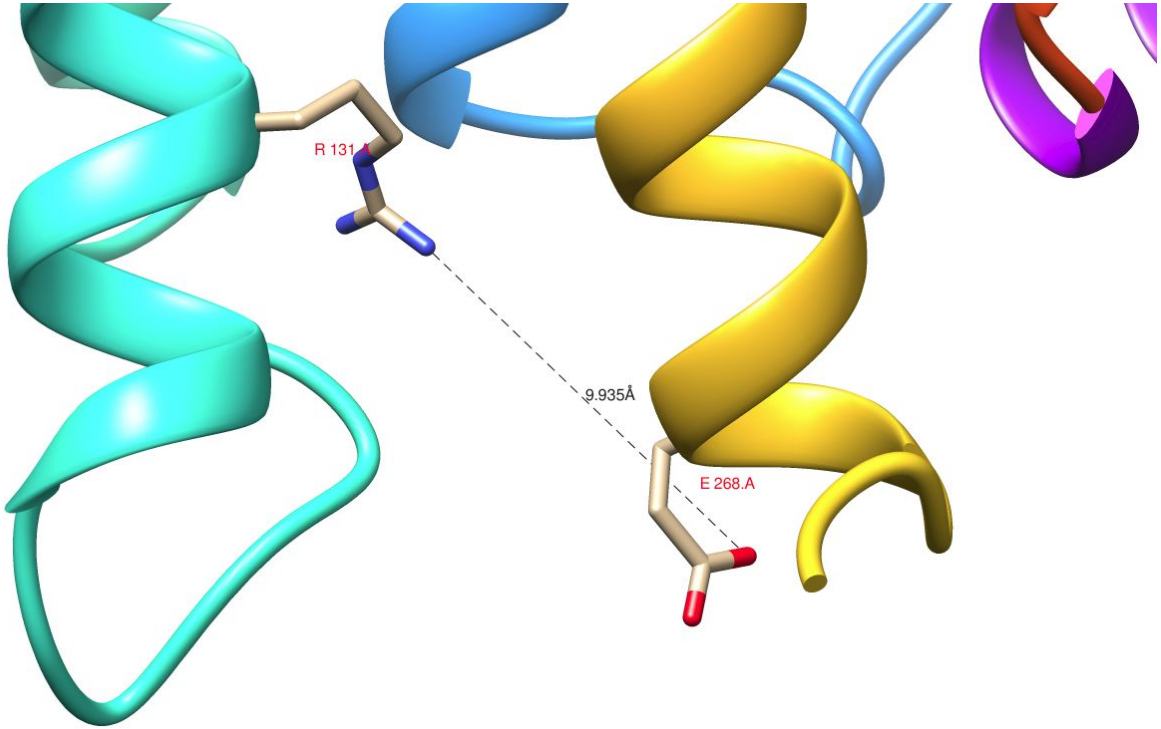


# 2.3. Structure: Description

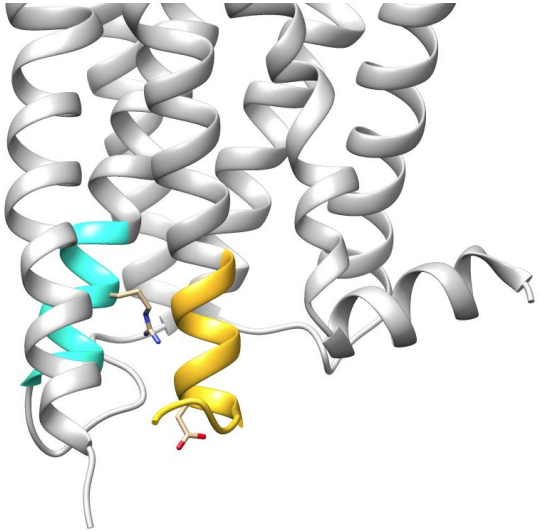
- 2 disulfide bridges stabilize ECL2
- Lack of **ionic lock** (***DRY***)
  - **R131-E268**



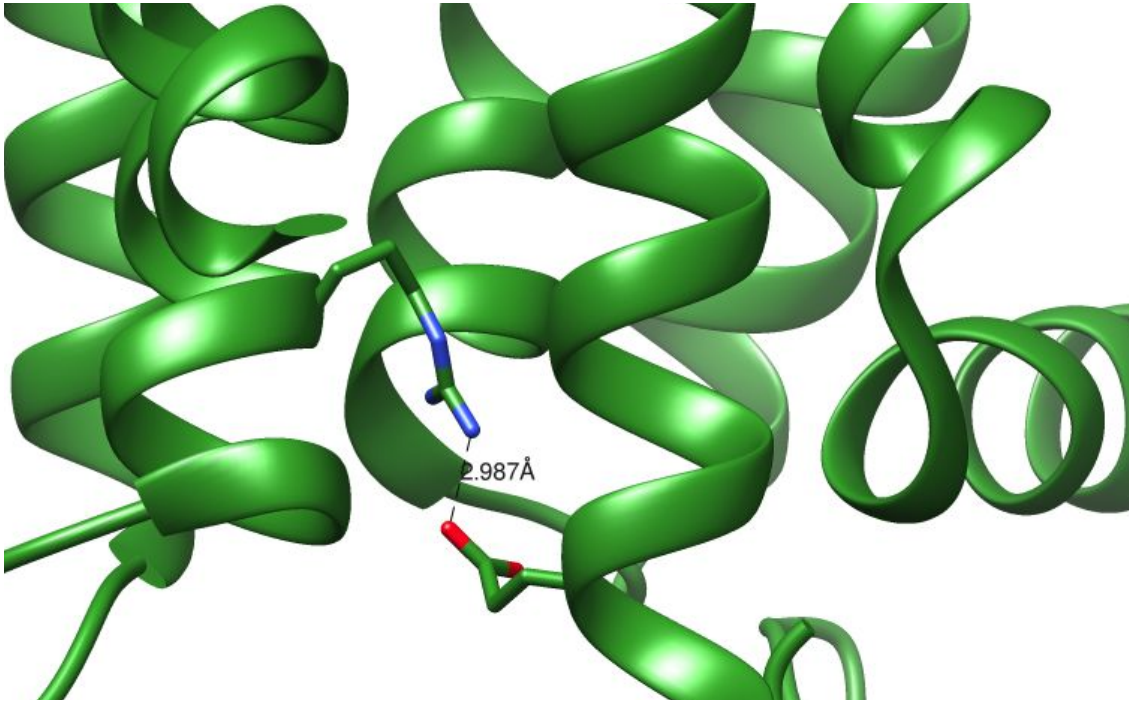



# 2.3. Structure: Description

- 2 disulfide bridges stabilize ECL2
- Lack of ionic lock (*DRY*)



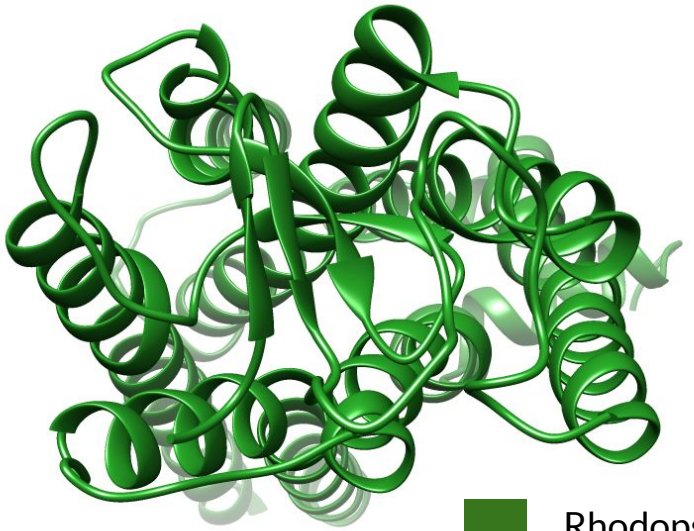
Rhodopsin



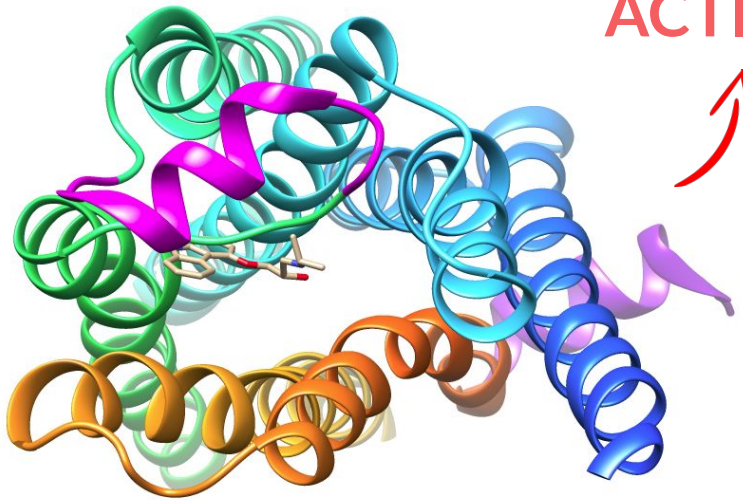
# 2.3. Structure: Description

- **2 disulfide bridges** stabilize ECL2
- Lack of **ionic lock** (***DRY***)
  - \+ **Lack of interaction** between **N-terminus and ECL2**
  - \+ **Short helical conformation of ECL2**

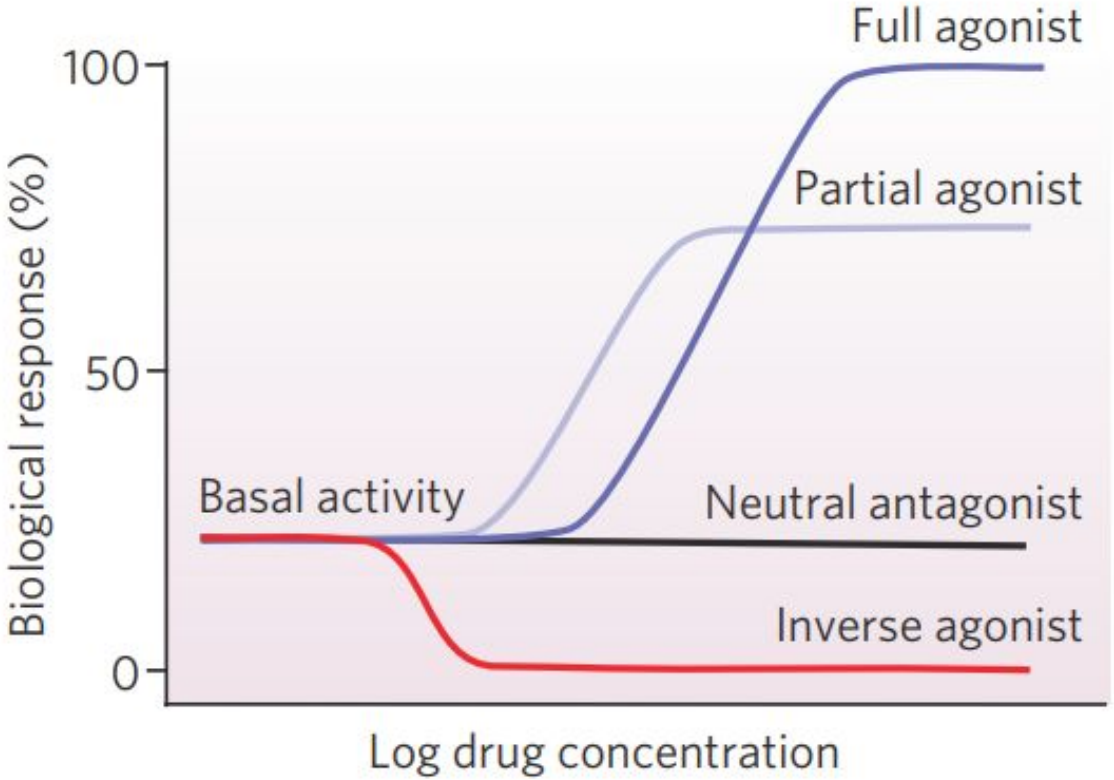
**BASAL ACTIVITY**



Rhodopsin



# 2.3. Structure: Description



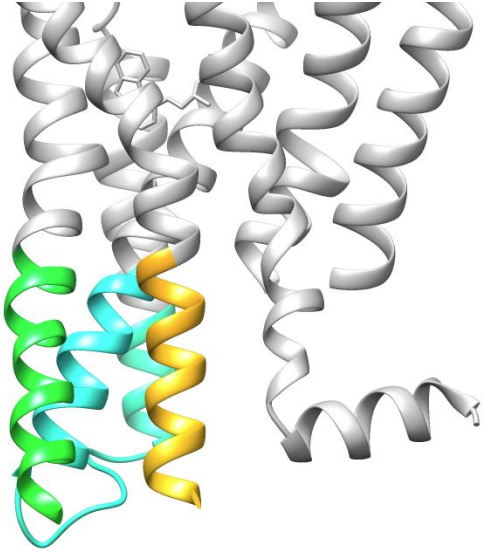

BASAL ACTIVITY

***Fig. 7.*** *Rosenbaum D, Rasmussen S, Kobilka B. The structure and function of G-protein-coupled receptors. Nature. 2009;459(7245):356-363.*

# 2.3. Structure: Description

**Stabilization** of **TM6**

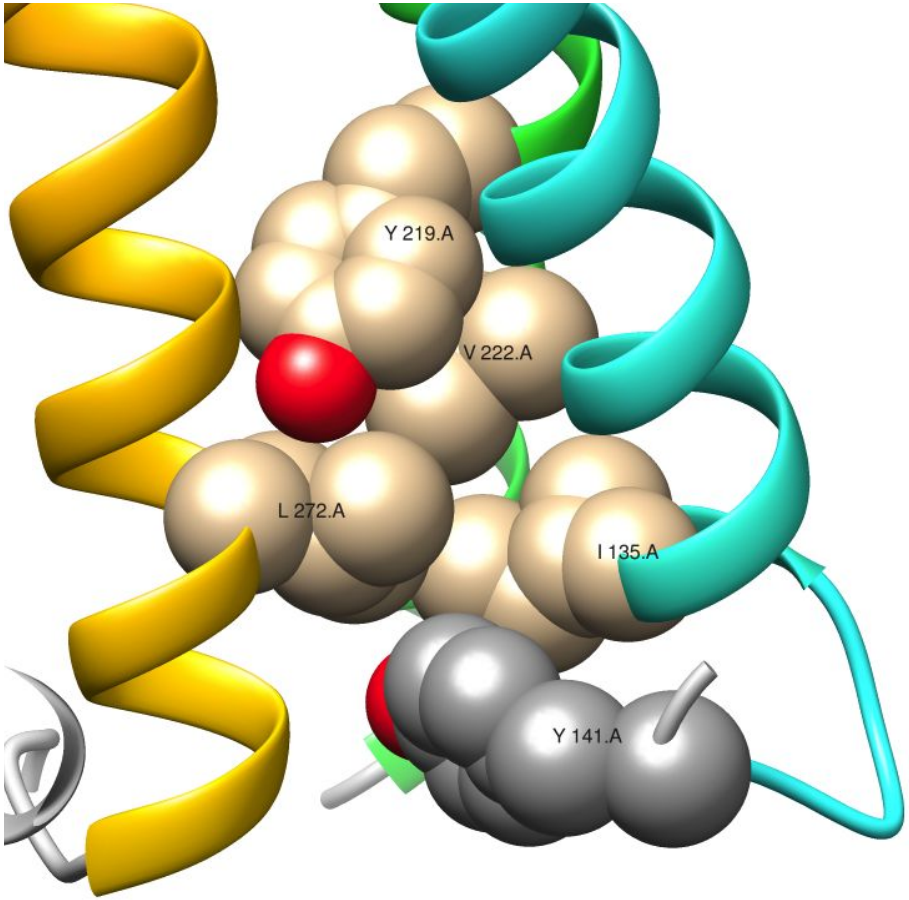
- VDW L272



H3

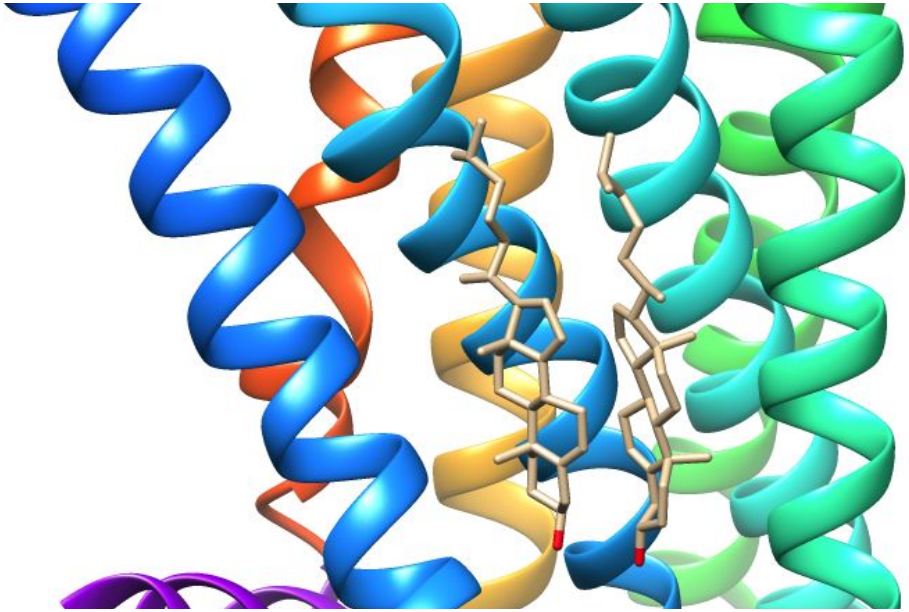
H5

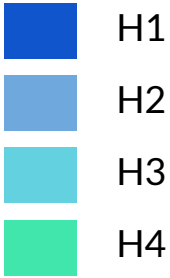
H6



# 2.3. Structure: Description

## Cholesterol Consensus Motif (*CCM*)





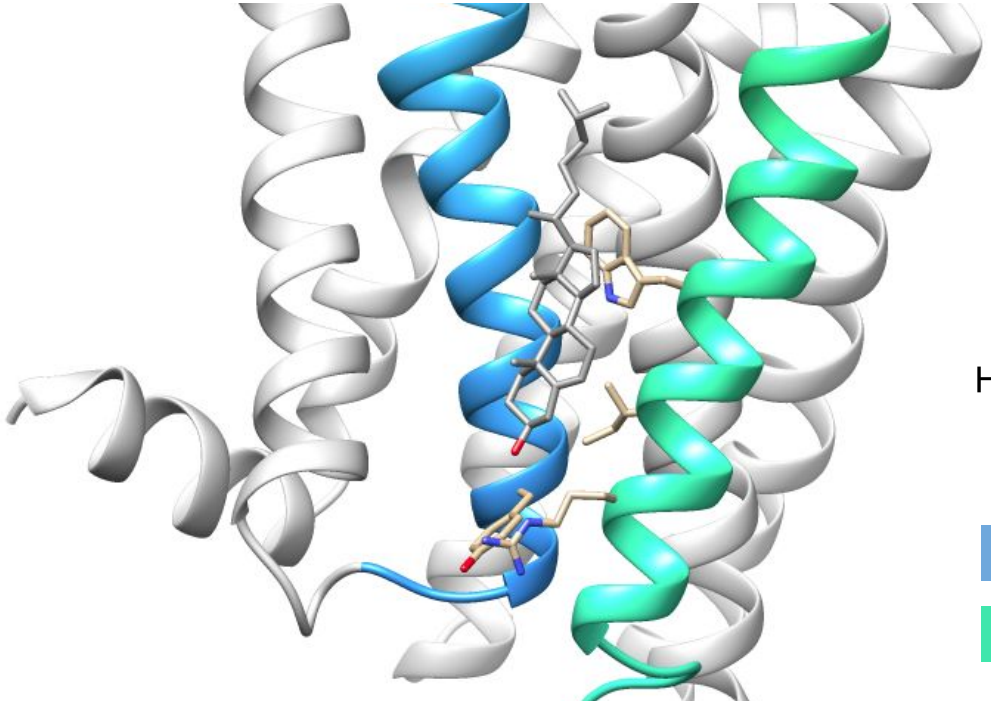

2 cholesterol molecules per rc

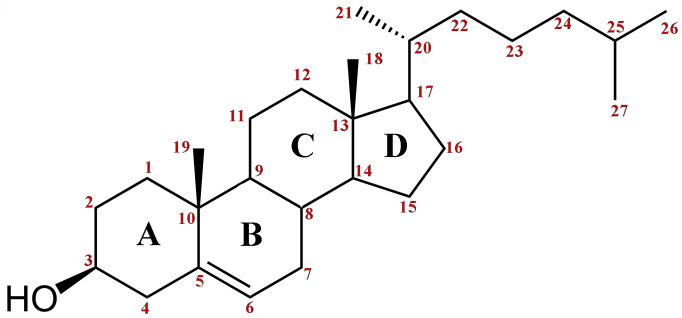
**Varying concentrations of cholesterol between cell types' membranes explain differences in β2-AR activities**

# 2.3. Structure: Description

## Cholesterol Consensus Motif (*CCM*)

**[4.39-4.43(R,K)]-[4.50(W,Y)]-[4.46(I,V,L)]-[2.41(F,Y)]**



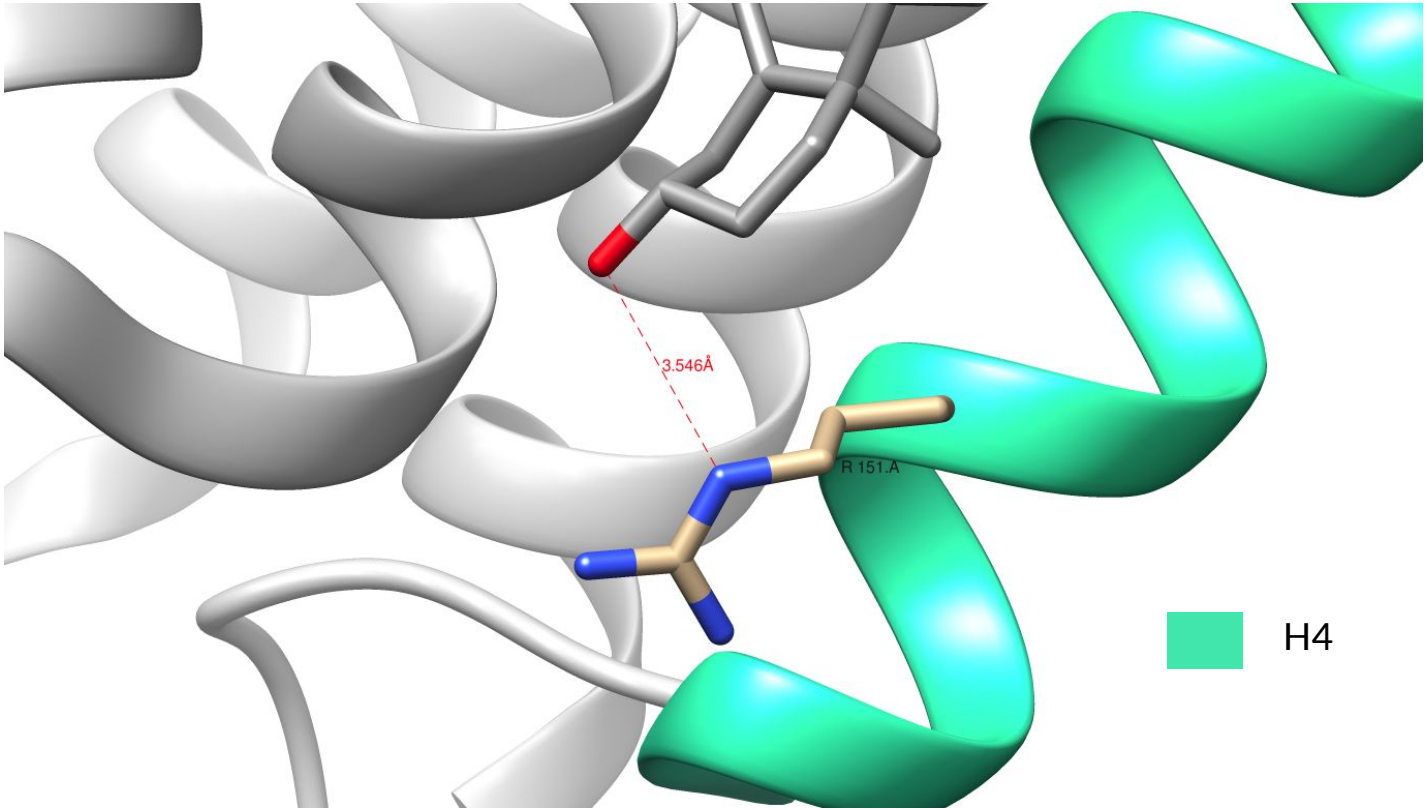



H2

H4

# 2.3. Structure: Description

## Cholesterol Consensus Motif (*CCM*)



# 2.3. Structure: Description

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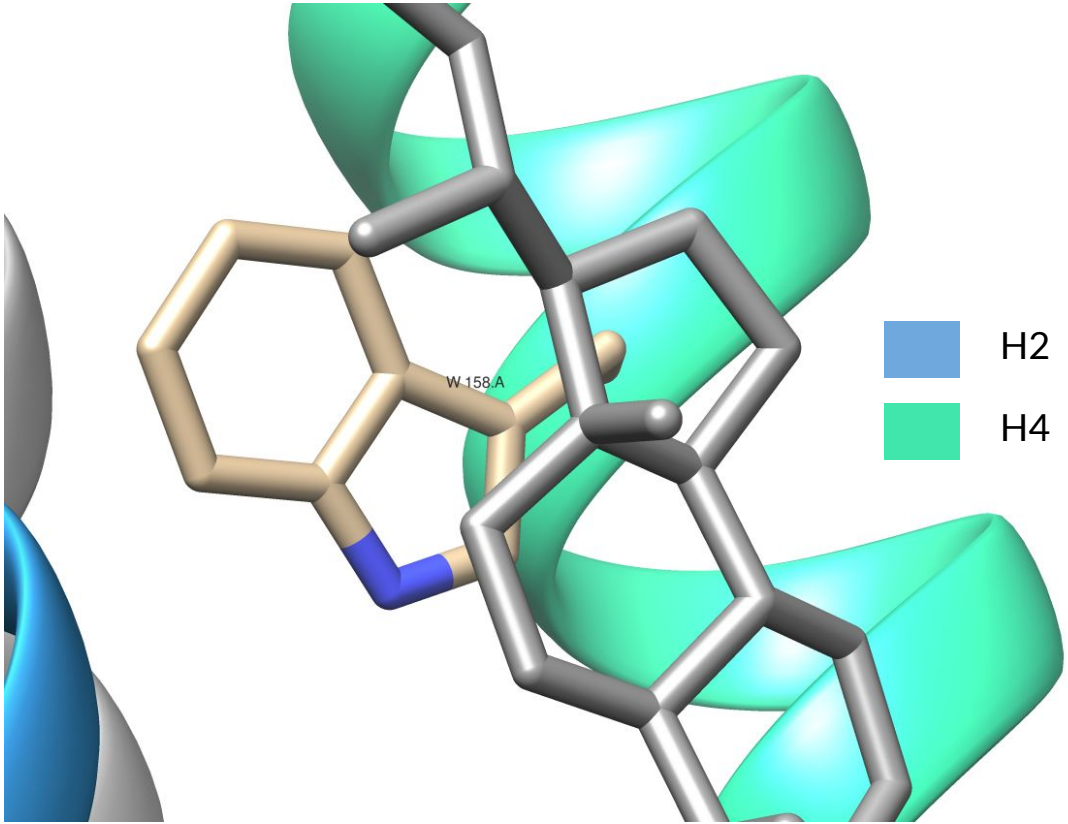

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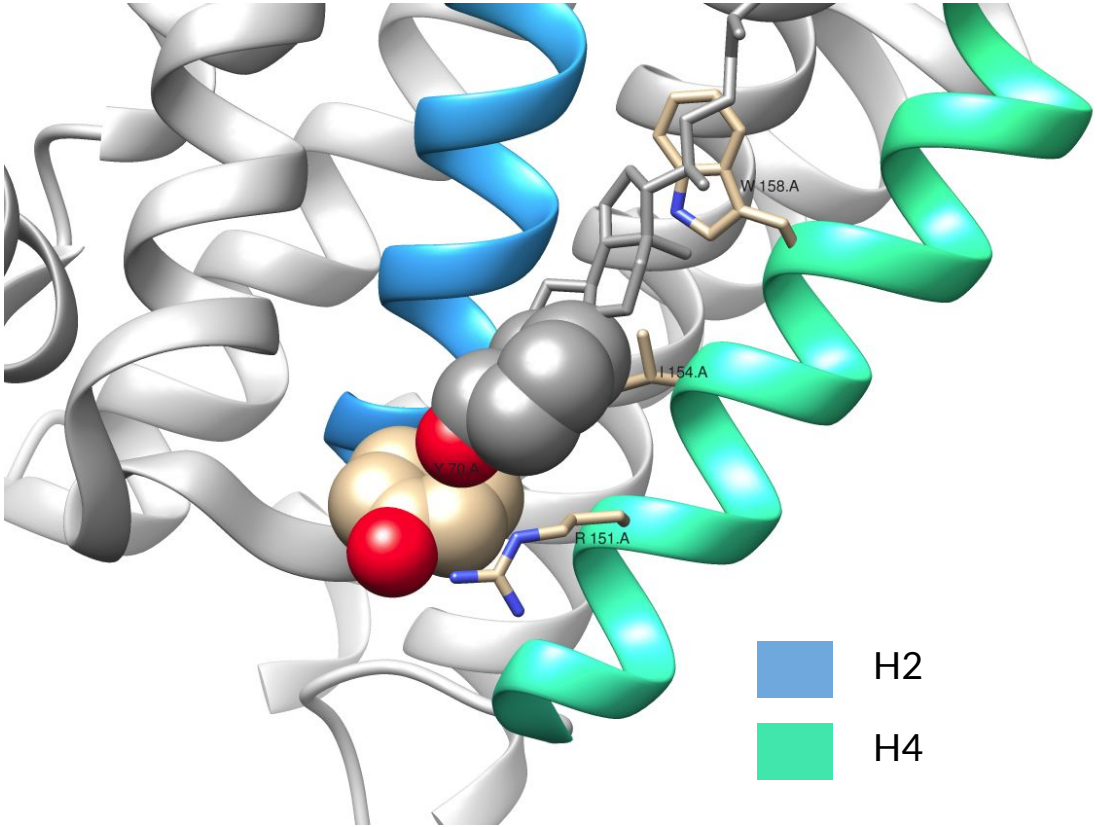
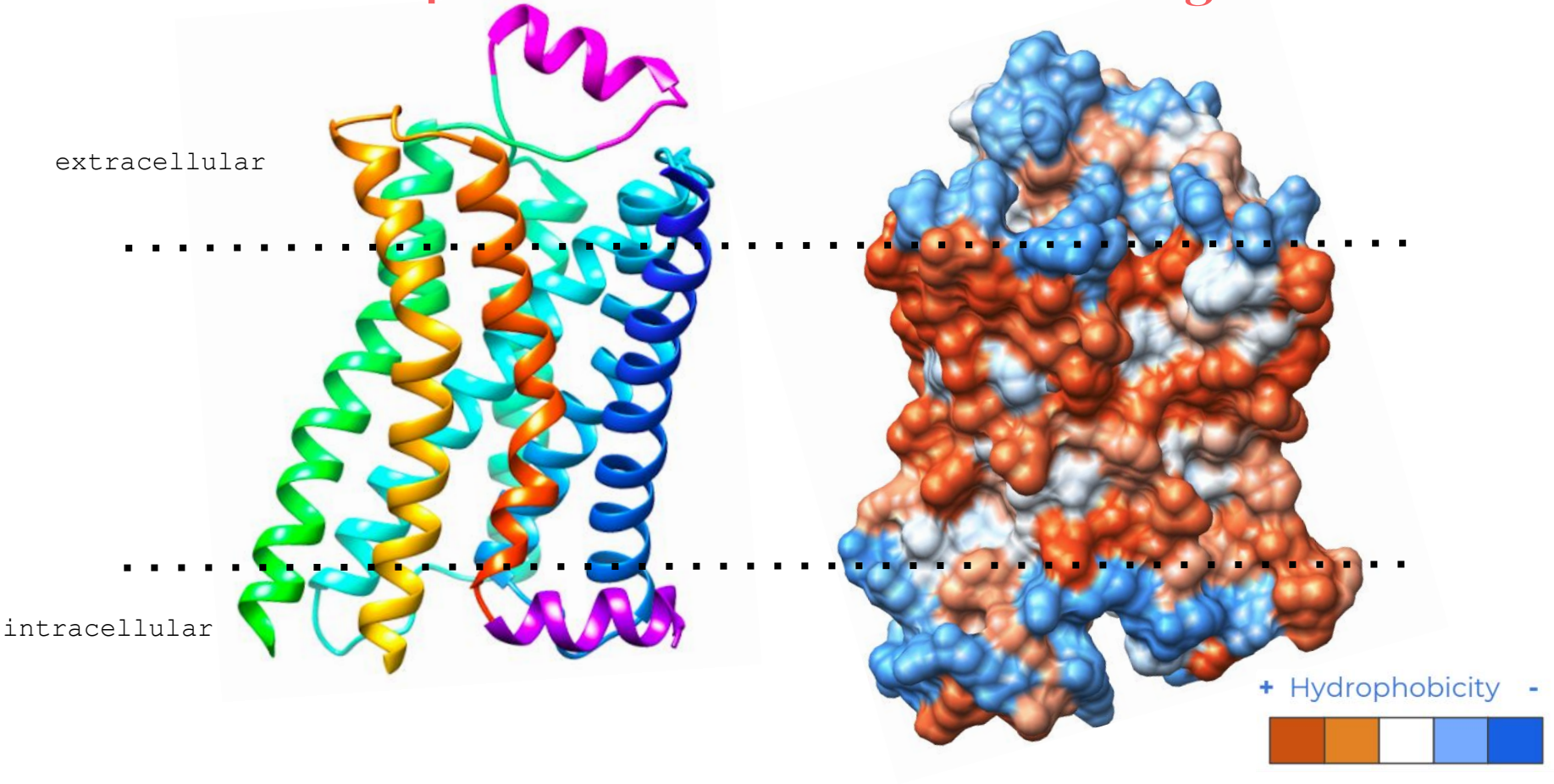
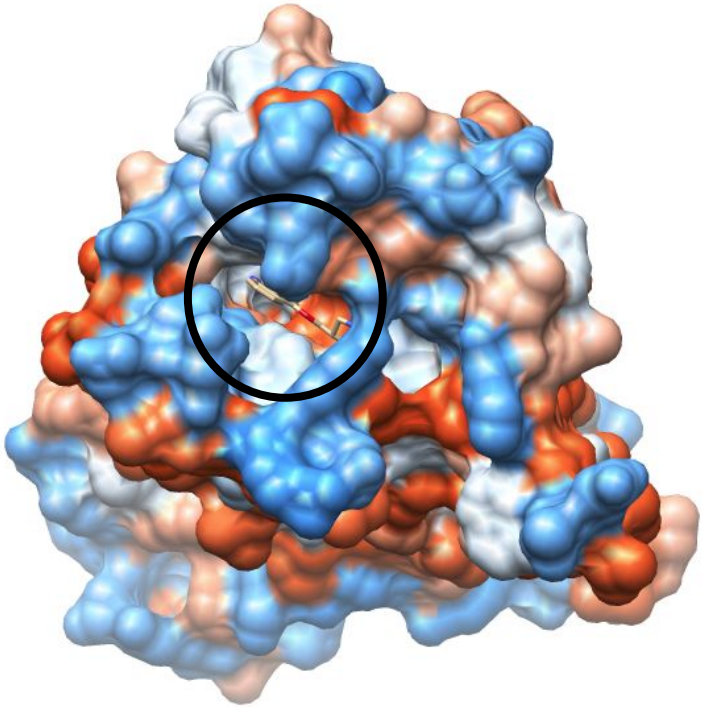
## Cholesterol Consensus Motif (*CCM*)



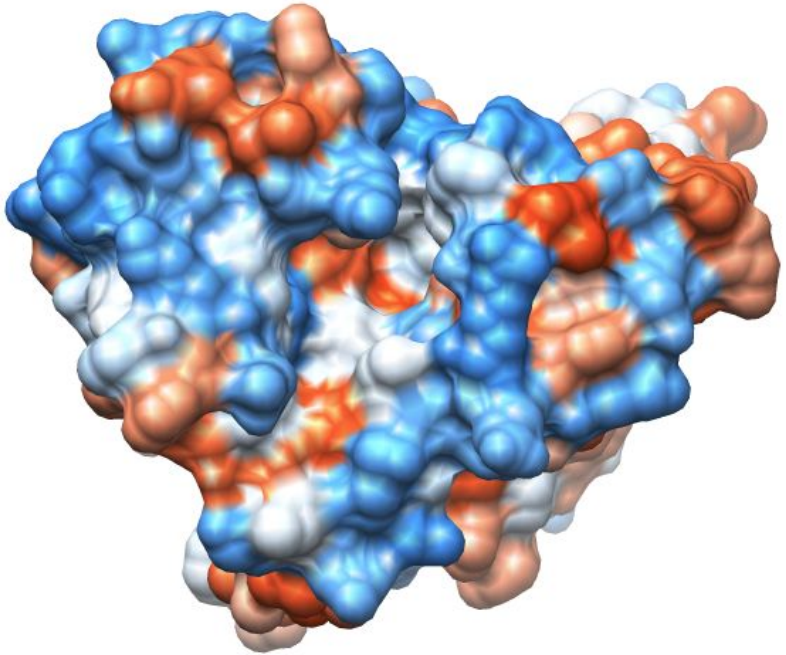
# 2.4. Structure: Membrane binding



# 2.4. Structure: Membrane binding

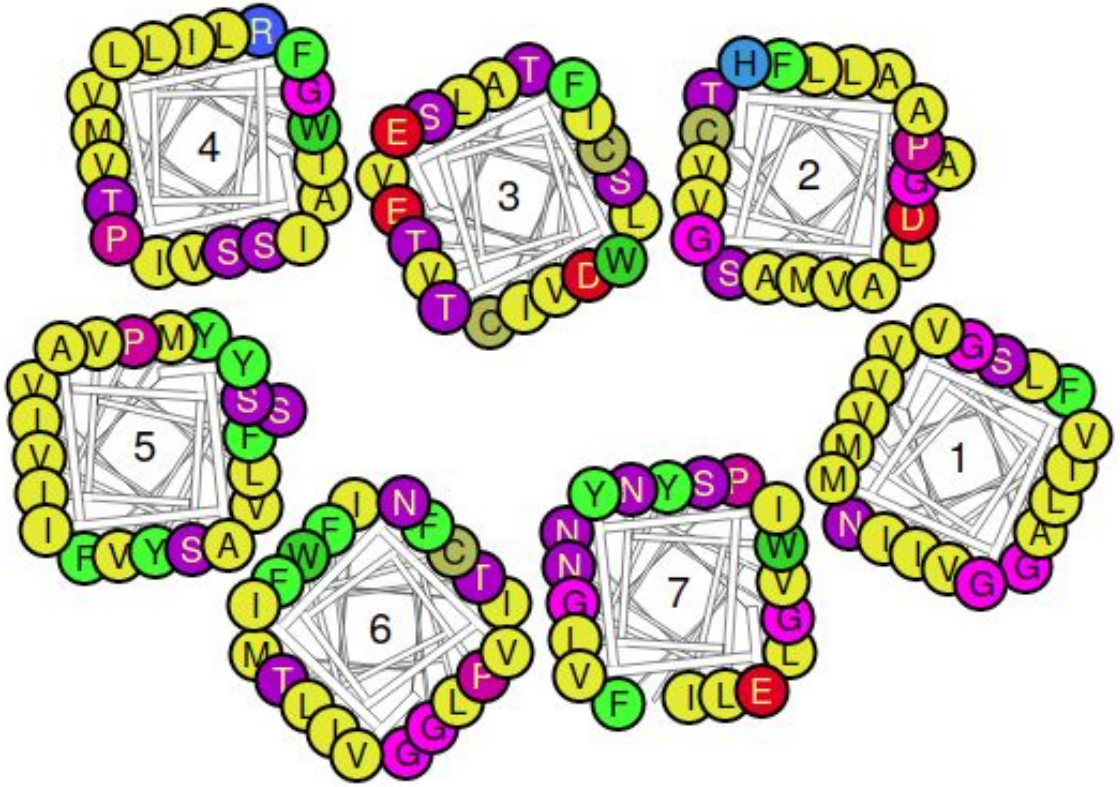


**Extracellular** view

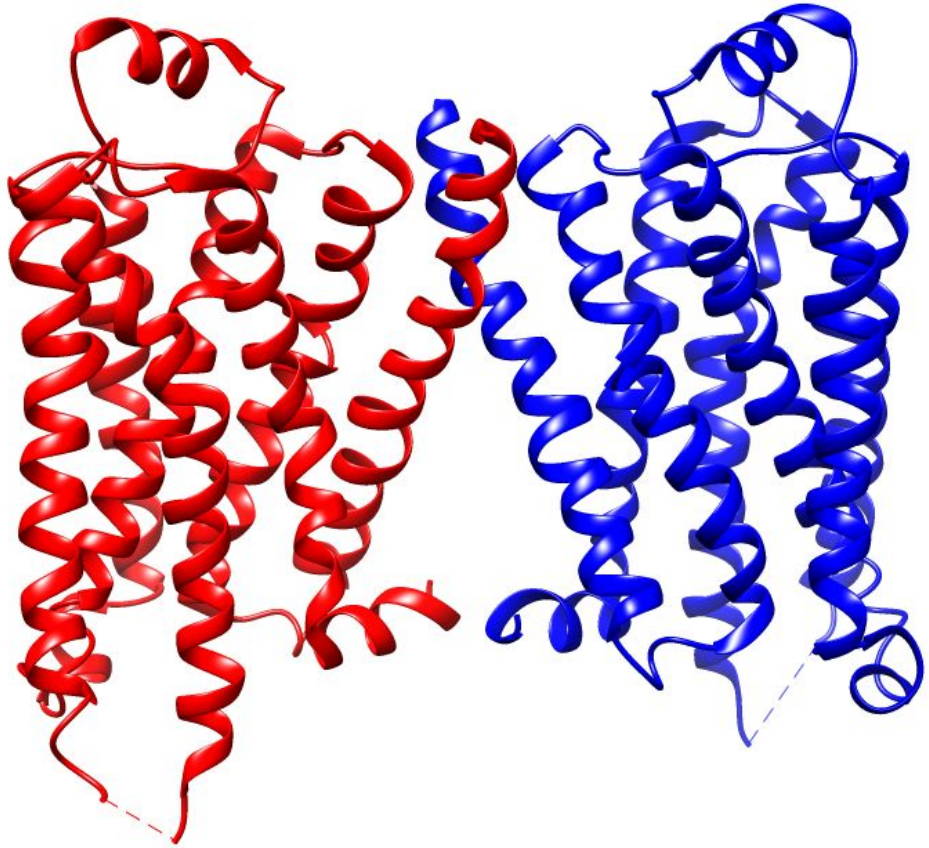


**Intracellular** view

# 2.4. Structure: Membrane binding



# 2.5. Structure: Dimerization



- No scientific consensus
- Highly variable
- **Cholesterol dependent**
- **H1 and H8**

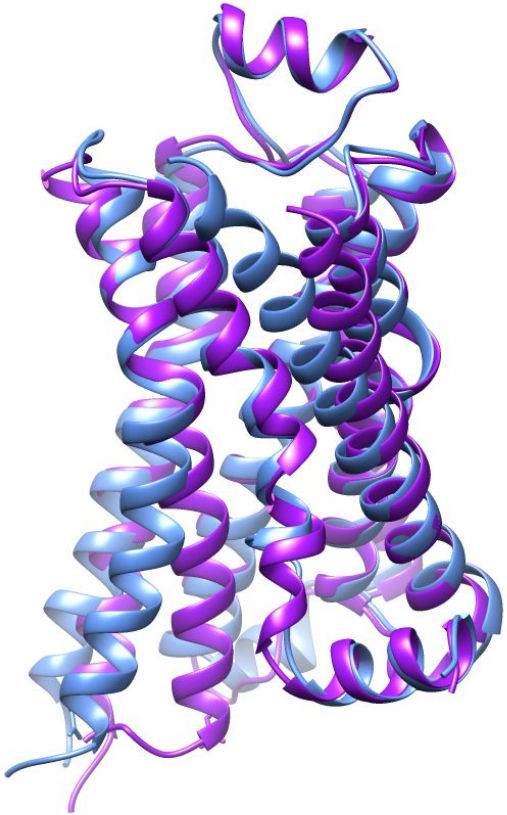
Rhodopsin ChainA

Rhodopsin ChainB

# 2.6. Comparison of active vs inactive conformation

**Active**. 4LDO, adrenaline

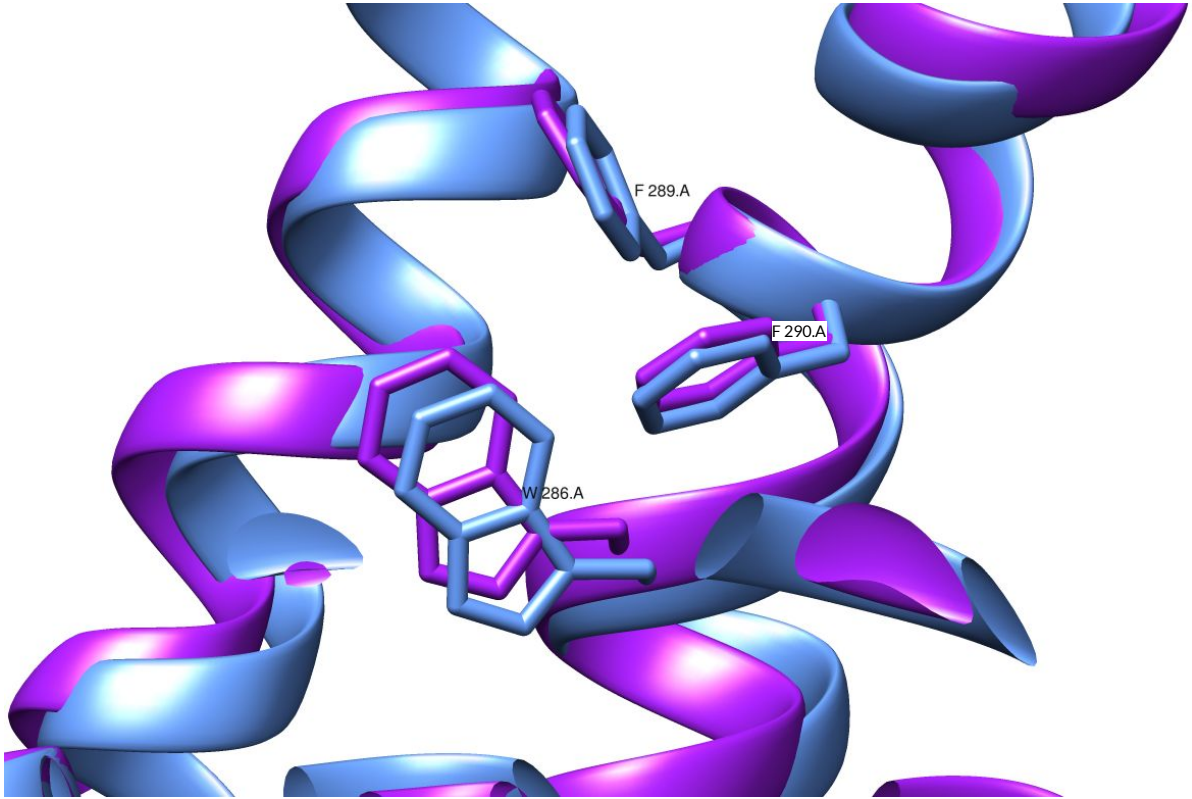
**Inactive**. 2RH1, carazolol



RMSD between 213 atom pairs is 0.999A

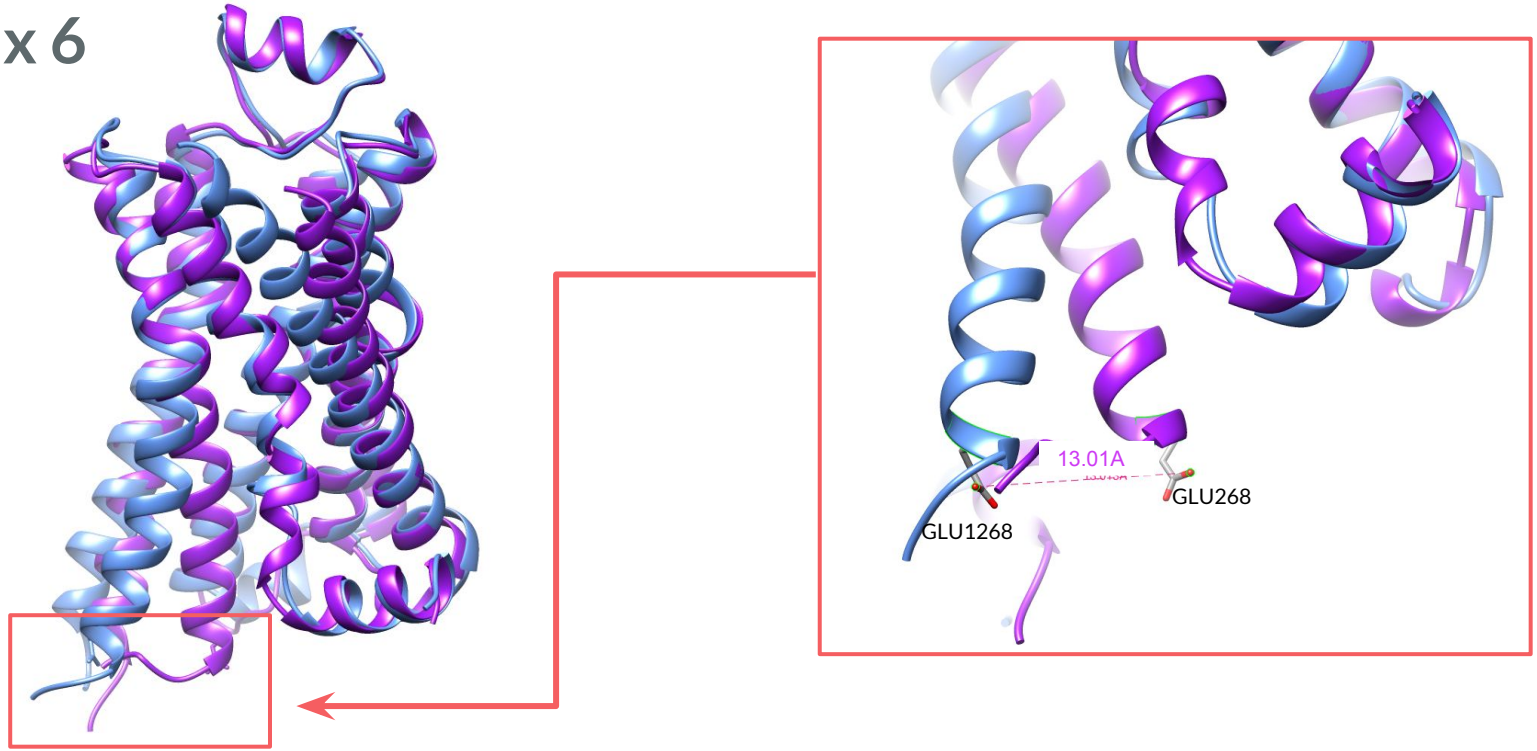
# 2.6. Comparison of active vs inactive conformation

## Toggle Switch



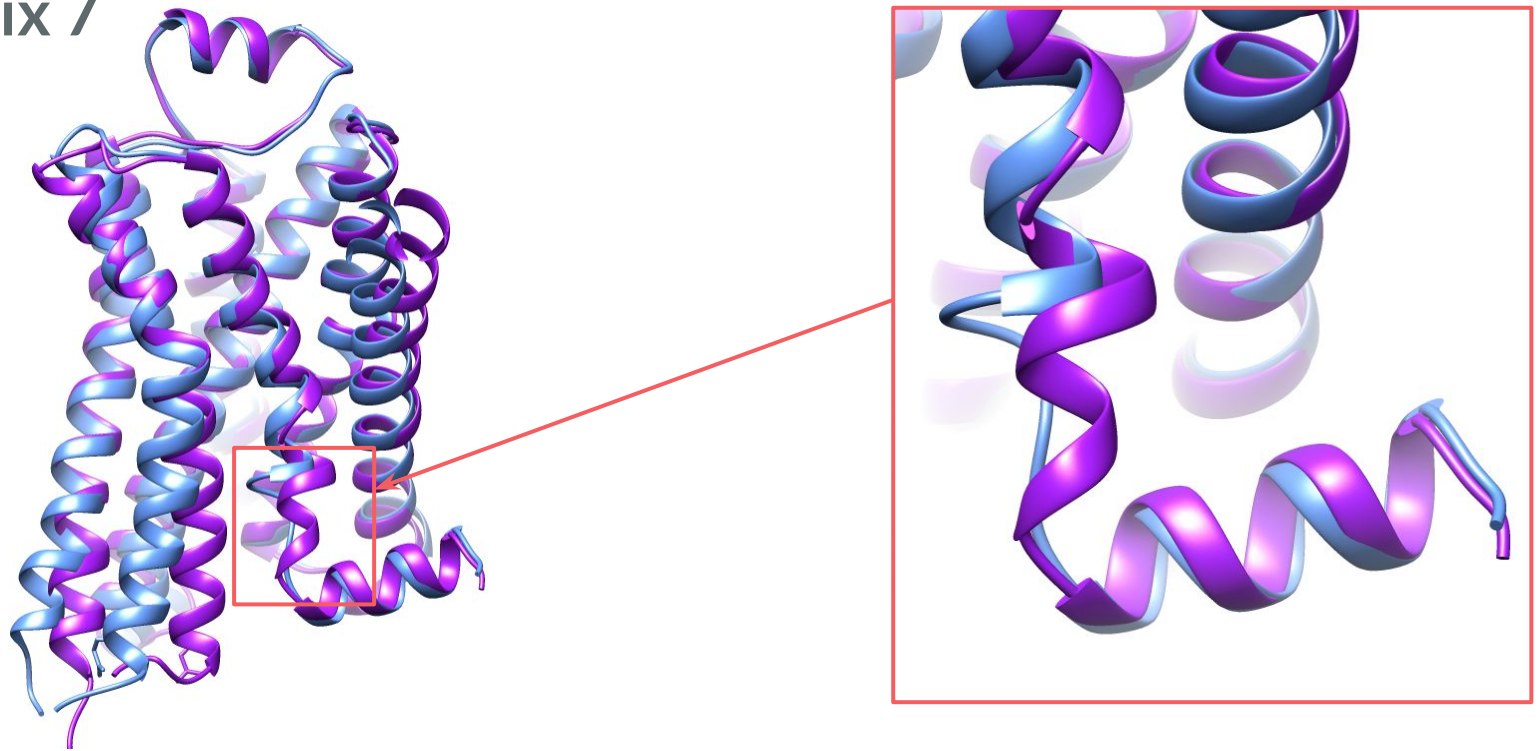
# 2.6. Comparison of active vs inactive conformation

Helix 6



# 2.6. Comparison of active vs inactive conformation

Helix 7

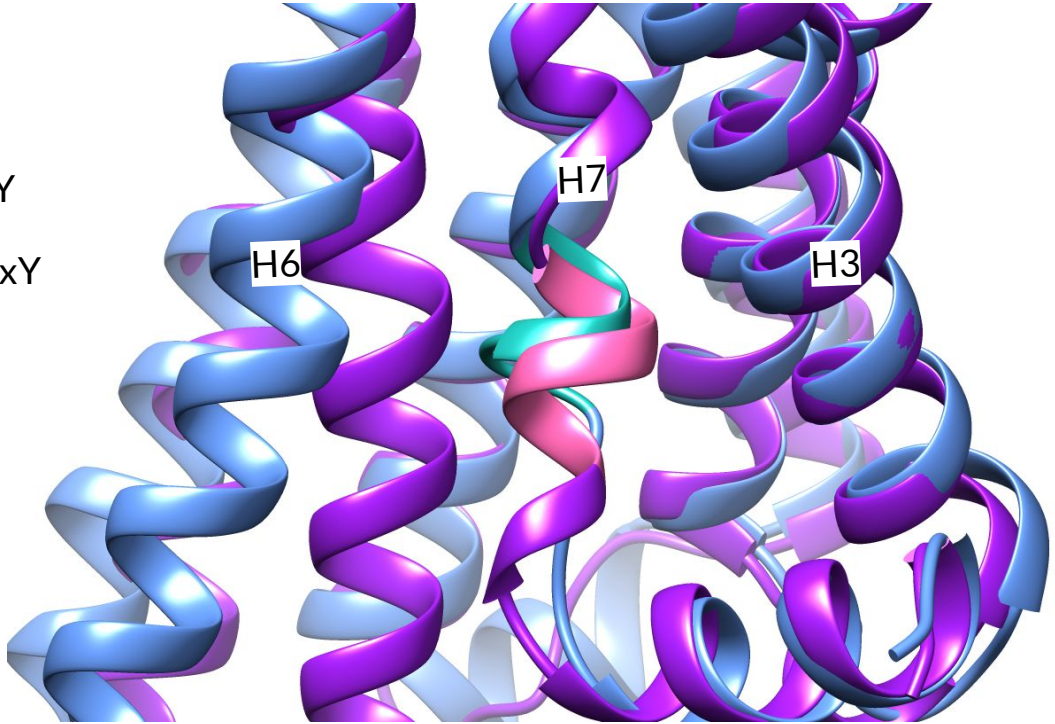


# 2.6. Comparison of active vs inactive conformation

## NPxxY

**Active** NPxxY

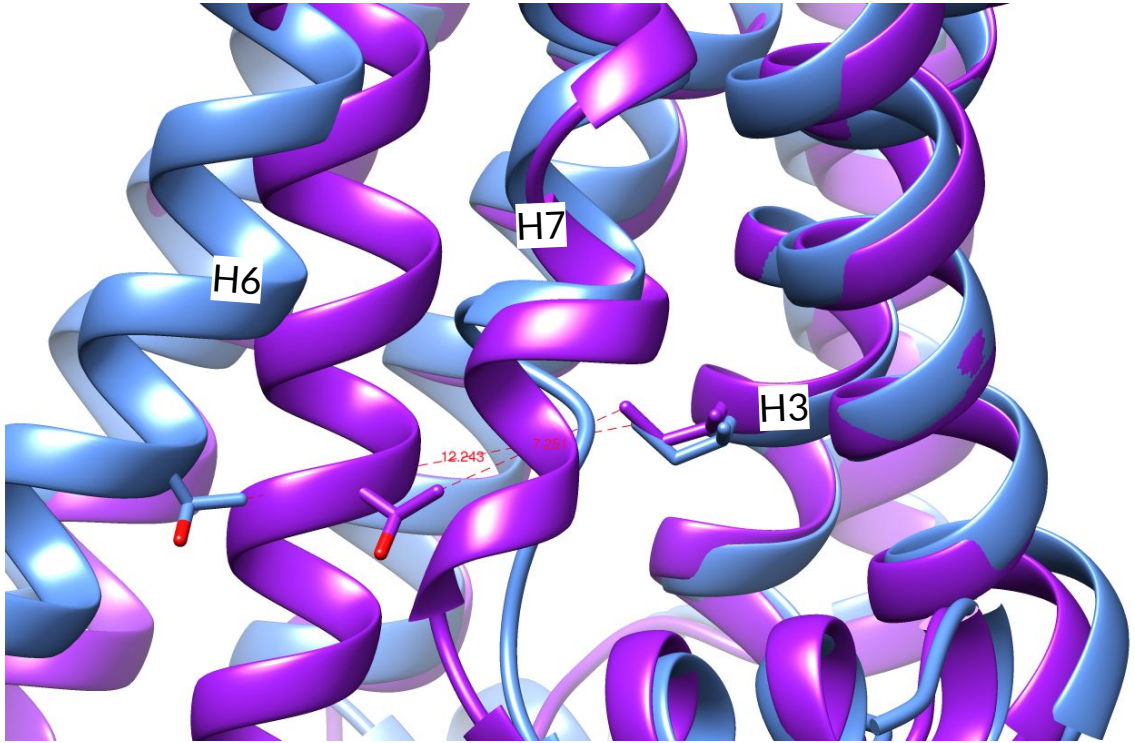
**Inactive** NPxxY




- **Inward movement of NPxxY**
- Increasing distance between H3 and 6

# 2.6. Comparison of active vs inactive conformation

**NPxxY**



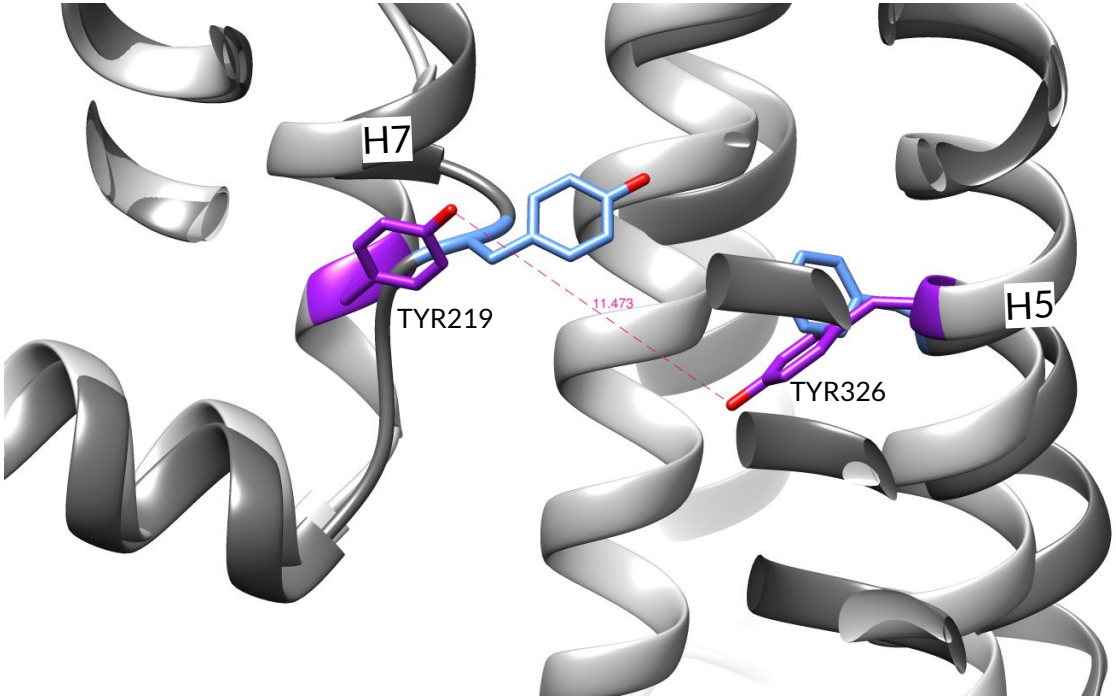

- Inward movement of NPxxY
- **Increasing distance between H3 and H6**

# 2.6. Comparison of active vs inactive conformation

## Hydrogen bond

Hydrogen bond between H7 and H5 is NOT able to form in the inactive state.

Distance **11.473 A**

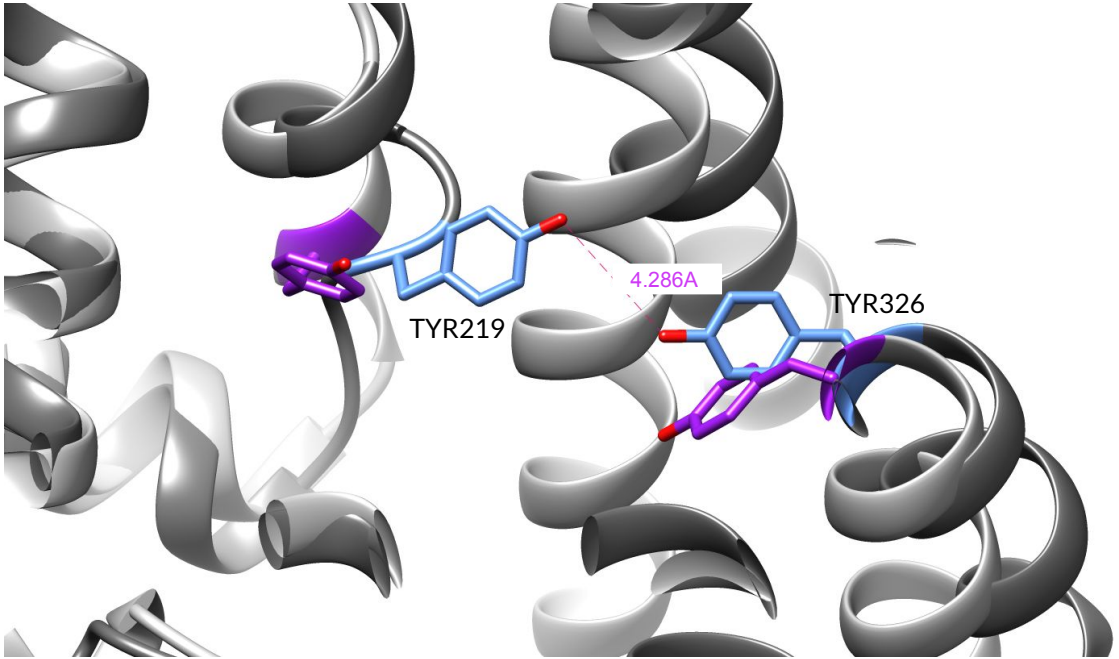


# 2.6. Comparison of active vs inactive conformation

## Hydrogen bond

Hydrogen bond between H7 and H5 is NOT able to form in the inactive state.

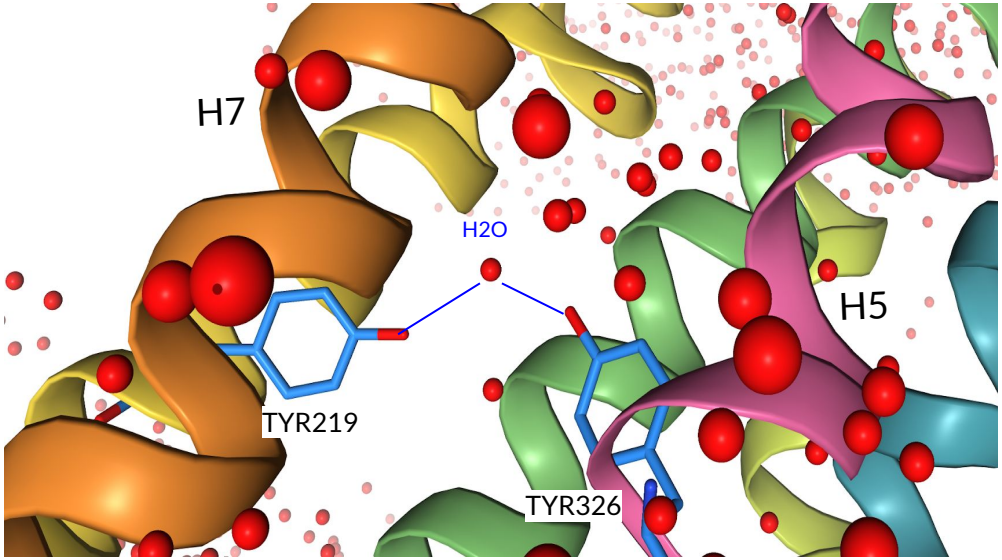
Distance **4.286 A**



# 2.6. Comparison of active vs inactive conformation

## Hydrogen bond

A bridging water molecule mediates the hydrogen bond.




Obtained from GPCRmd

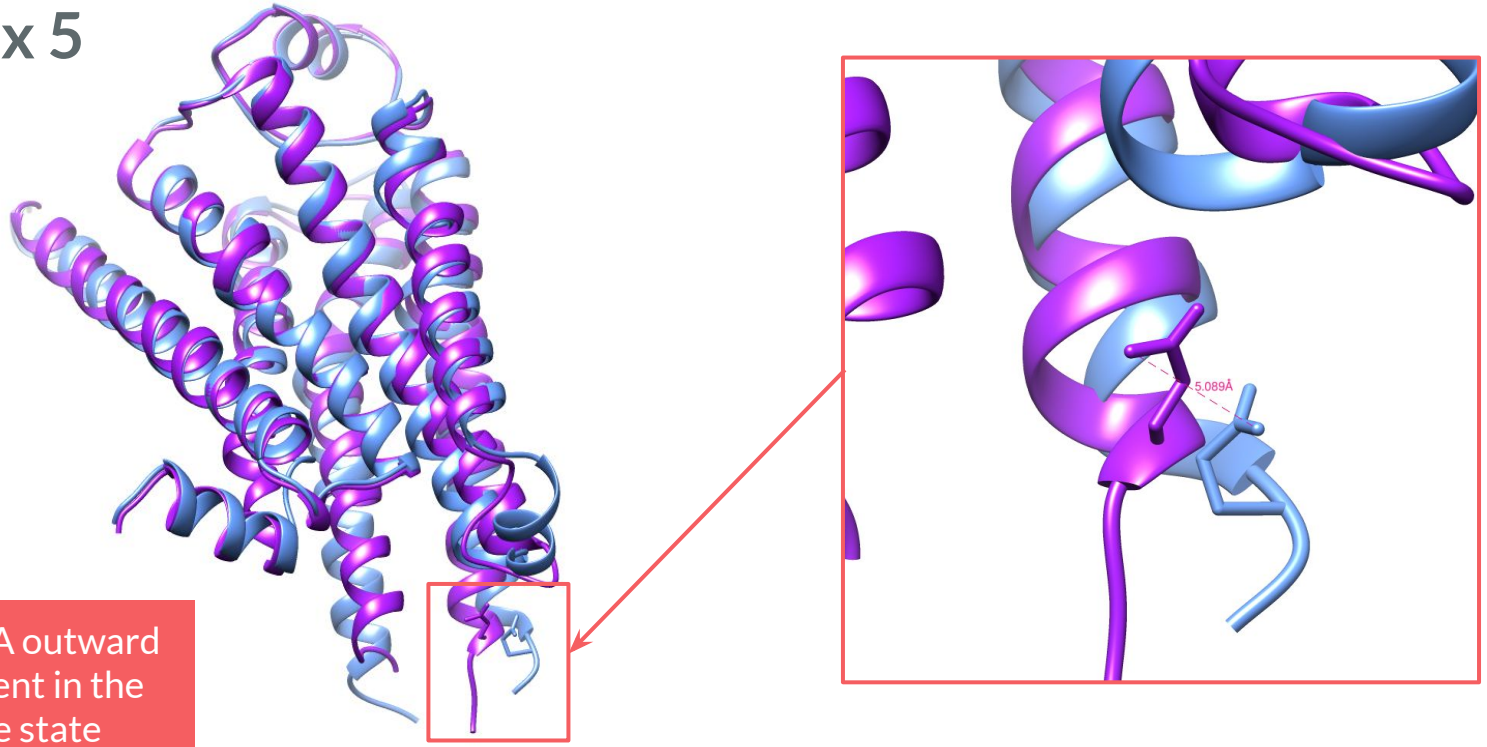
# 2.6. Comparison of active vs inactive conformation

## Helix 3

A 3.54 A inwards movement in the active state

# 2.6. Comparison of active vs inactive conformation

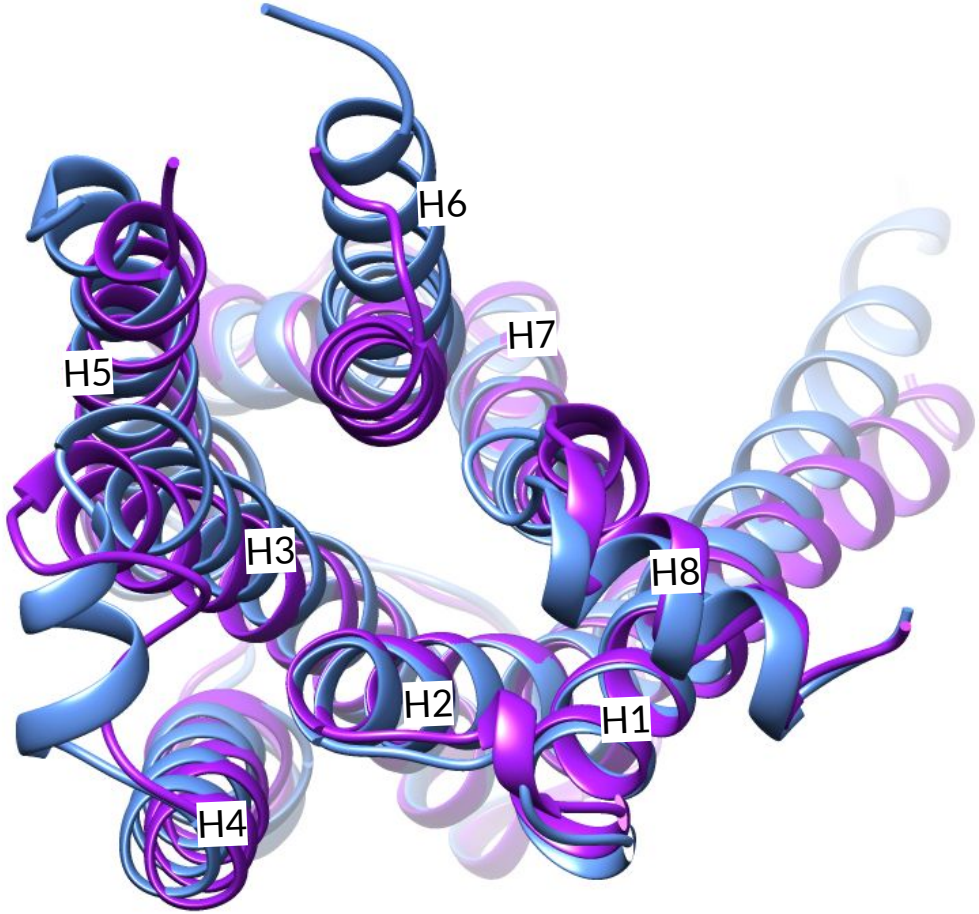
Helix 5




A 5.089 A outward movement in the active state

# 2.6. Comparison of active vs inactive conformation

## Intracellular pocket



# 2.6. Comparison of active vs inactive conformation

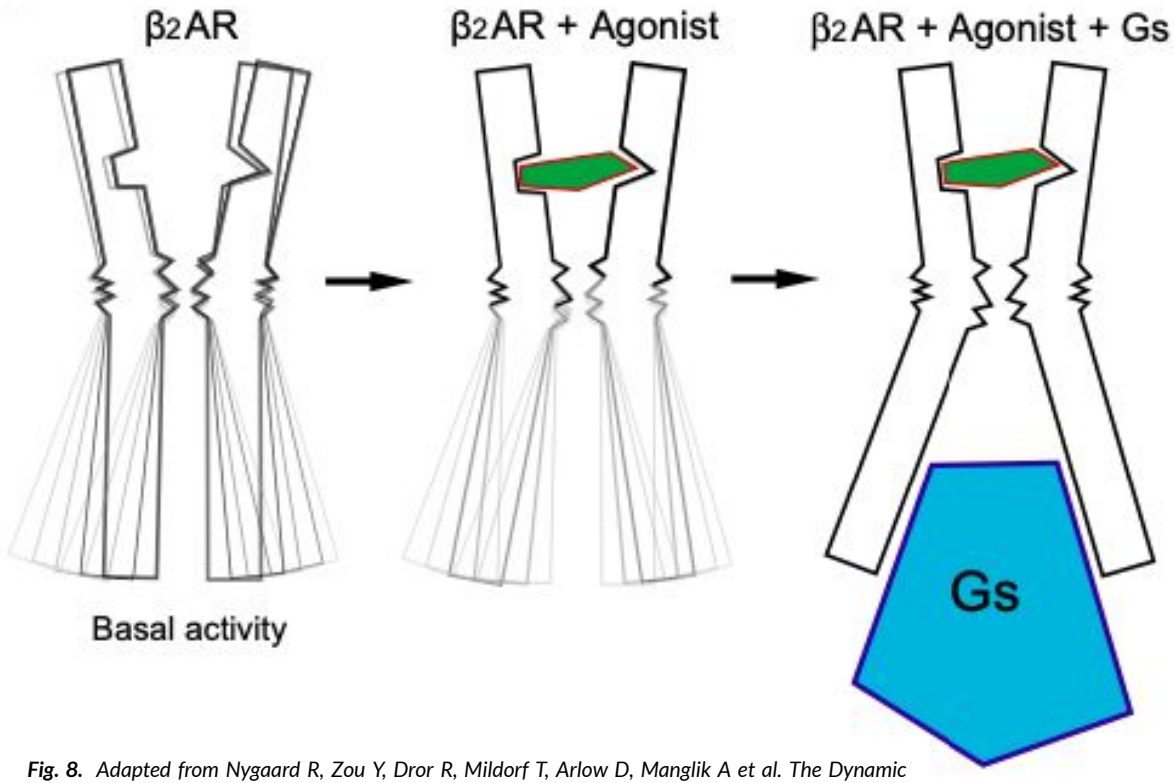
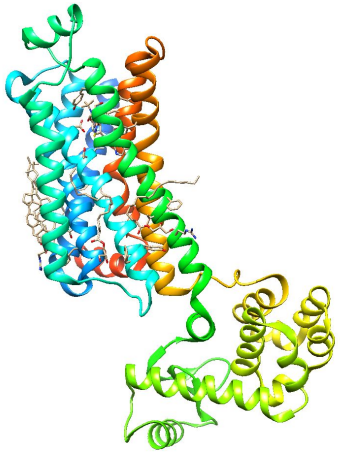
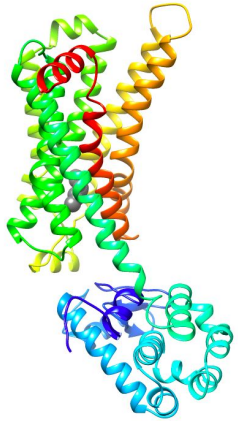
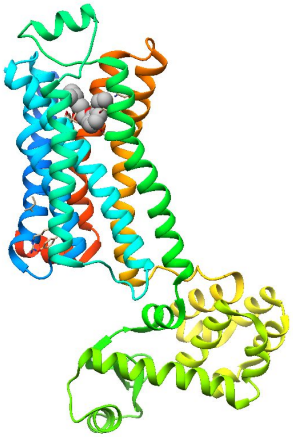
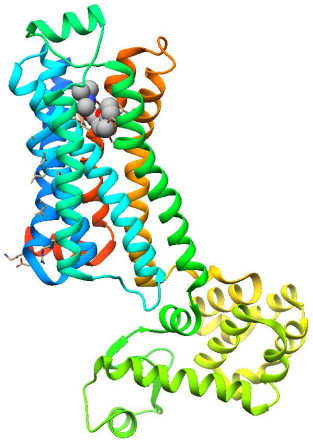
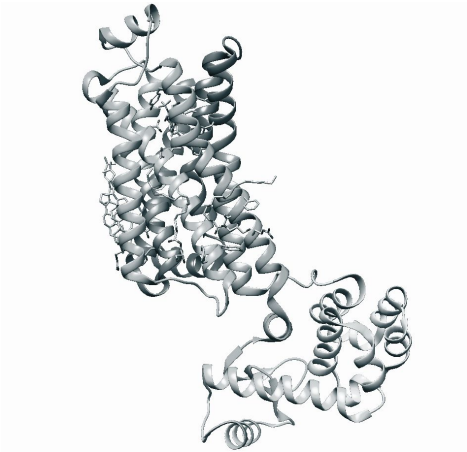


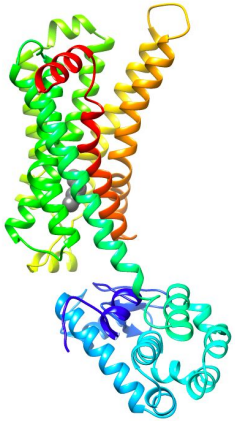
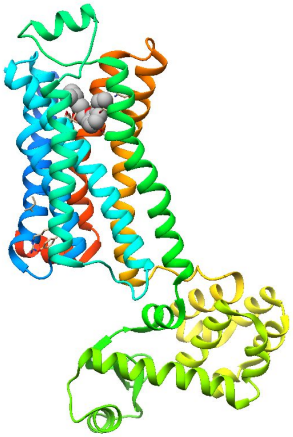
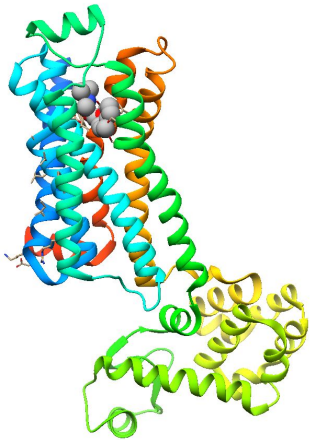

***Fig. 8.*** *Adapted from Nygaard R, Zou Y, Dror R, Mildorf T, Arlow D, Manglik A et al. The Dynamic Process of β2-Adrenergic Receptor Activation. Cell. 2013;152(3):532-542.*

# 3. Ligands

| ALLOSTERIC LIGAND | AGONIST | ANTAGONIST | INVERSE AGONIST |
|---|---|---|---|
| CHOLESTEROL | ADRENALINE | ALPRENOLOL | ICI 118.551 |
|  |  |  |  |
| PDB code: 3d4s | PDB code: 4ldo | PDB code: 3nya | PDB code: 3ny8 |

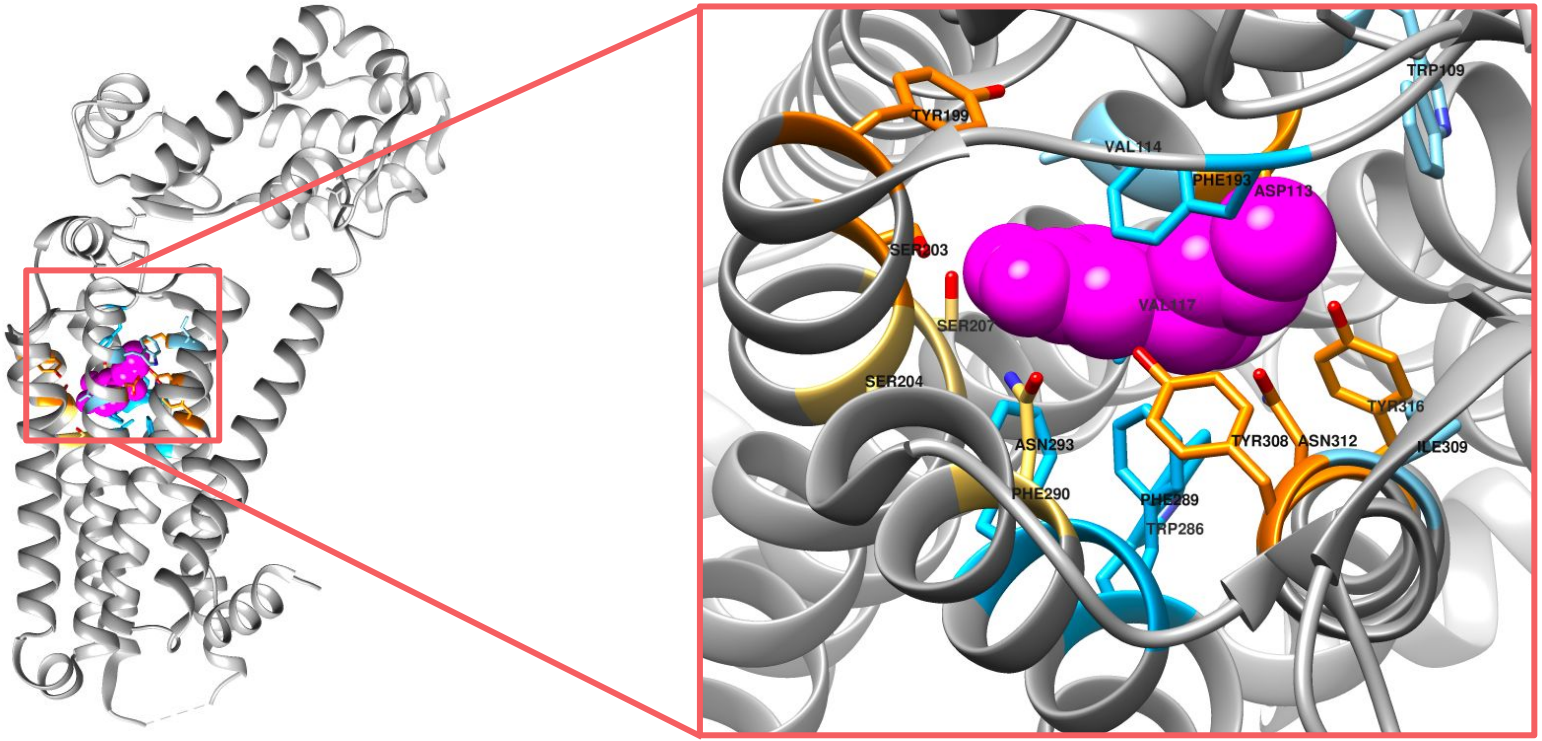
# 3. Ligands

| ALLOSTERIC LIGAND |
| --- |
| CHOLESTEROL |
|  |
| PDB code: 3d4s |

| AGONIST | ANTAGONIST | INVERSE AGONIST |
| --- | --- | --- |
| ADRENALINE | ALPRENOLOL | ICI 118.551 |
|  |  |  |
| PDB code: 4ldo | PDB code: 3nya | PDB code: 3ny8 |

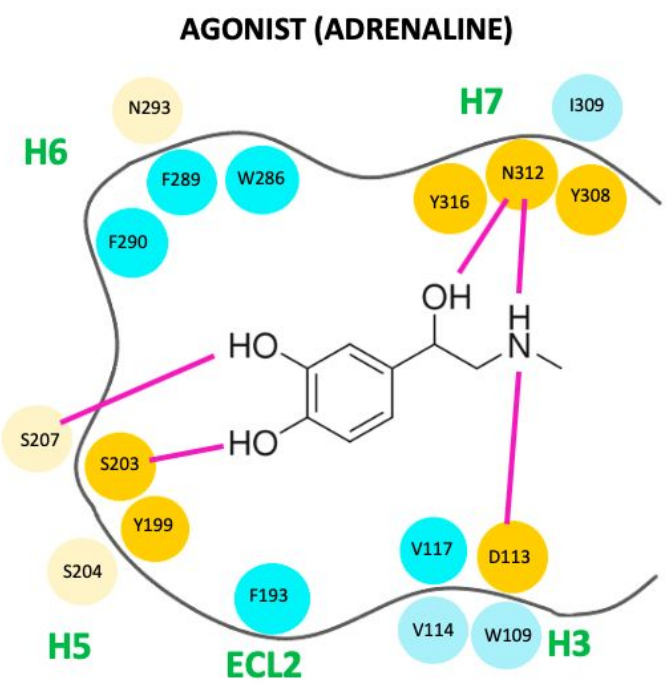
# 3.1. Binding pocket

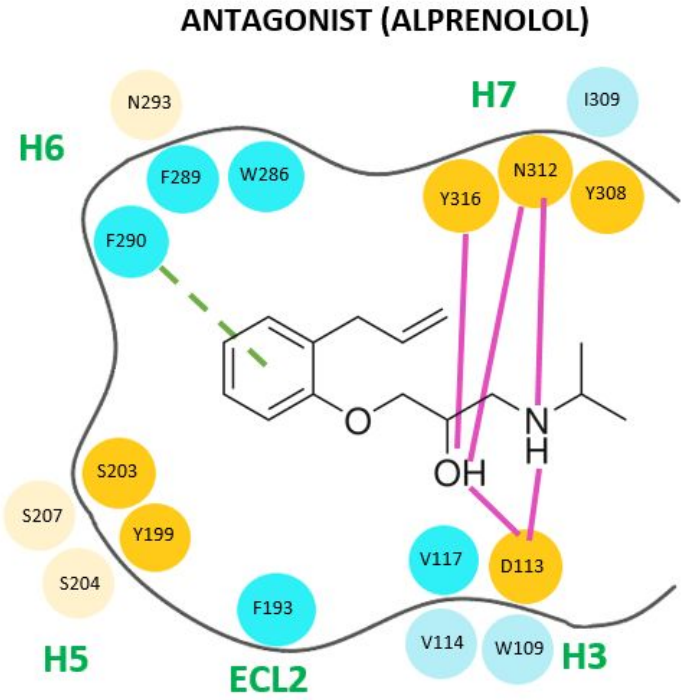
MOST IMPORTANT RESIDUES FOR THE BINDING POCKET OF THE BETA-2 ADRENERGIC RECEPTOR



# 3.1. Binding pocket

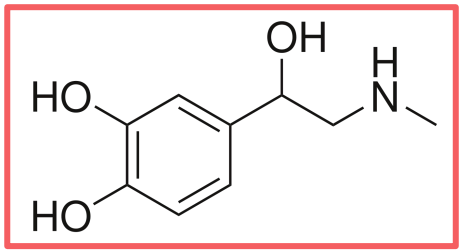
MOST IMPORTANT RESIDUES FOR THE BINDING POCKET OF THE BETA-2 ADRENERGIC RECEPTOR

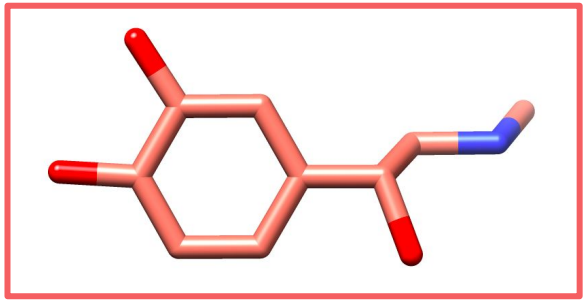


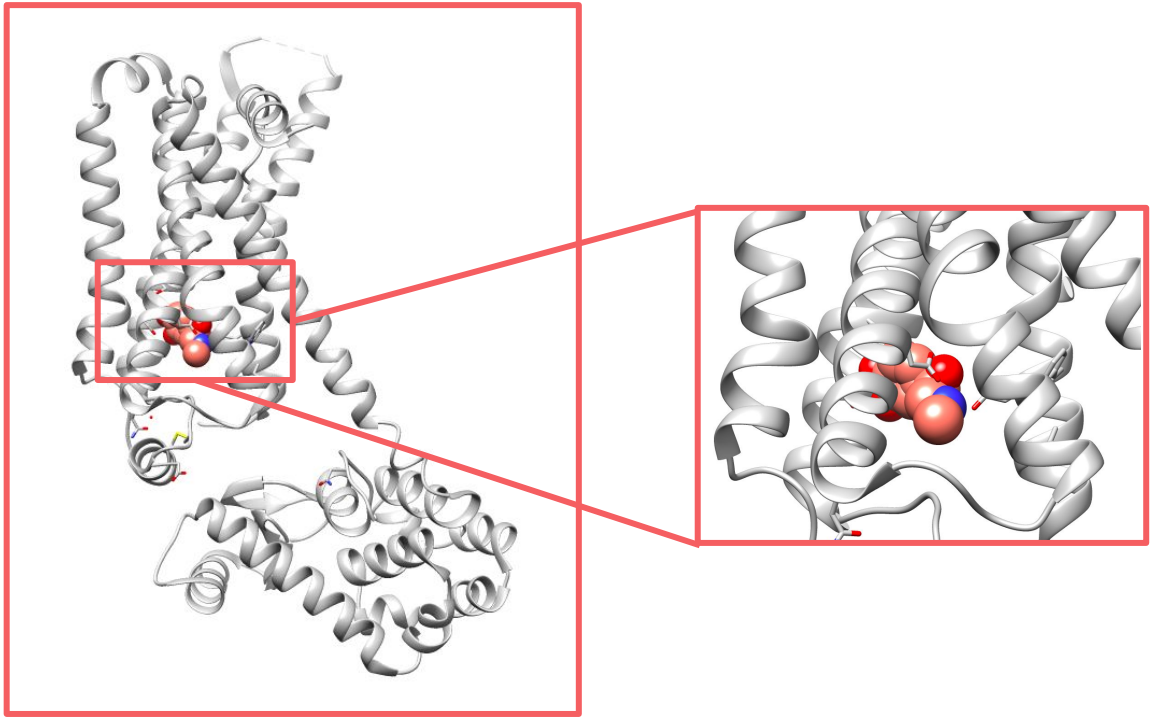



# 3.2. Agonists

## ADRENALINE

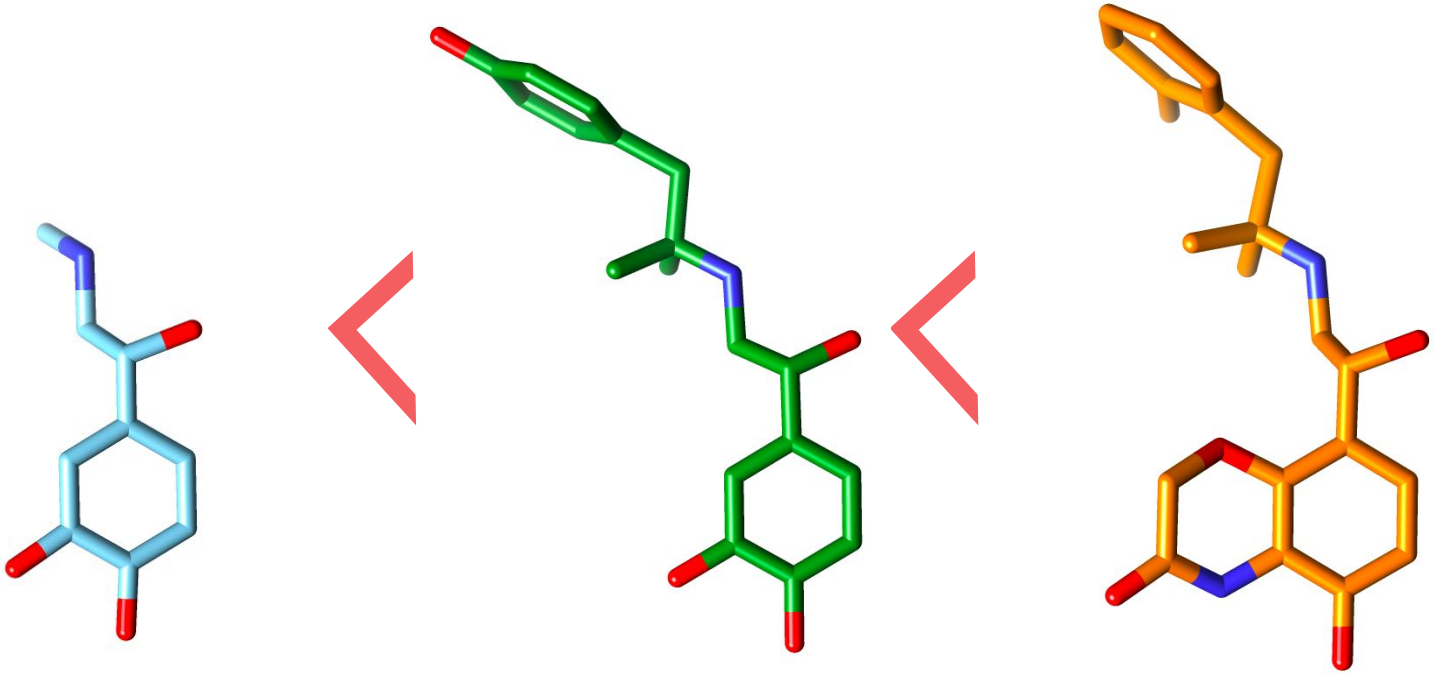




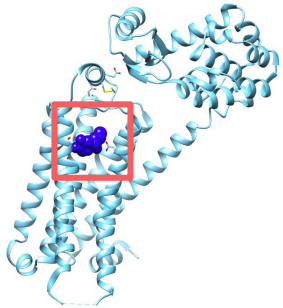
# 3.2. Agonists

## Affinity



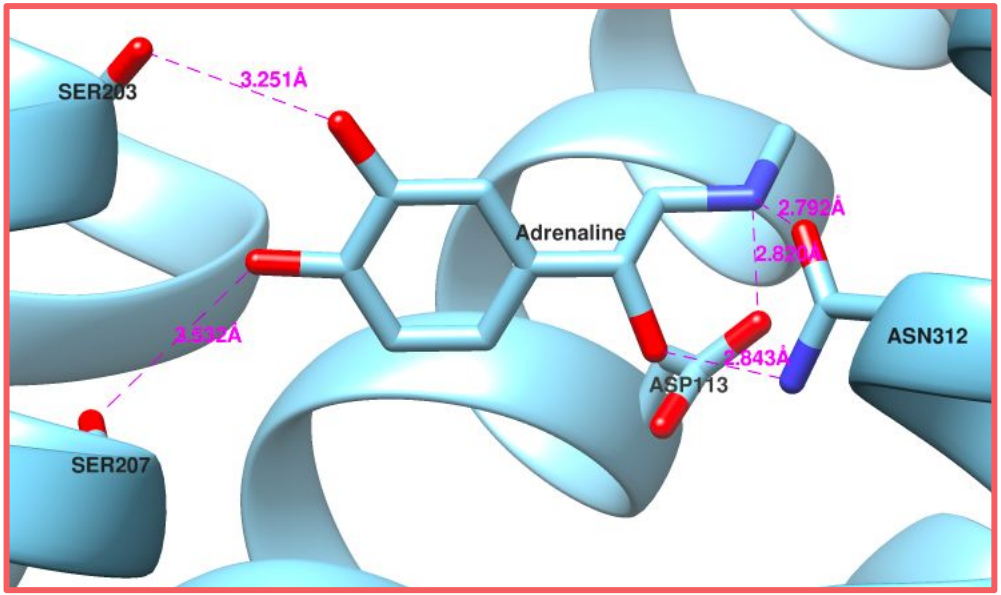
Adrenaline < HBI < BI167107

# 3.2. Agonists



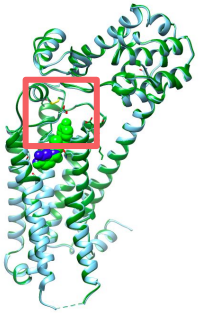
## ADRENALINE

HYDROGEN BONDS IN THE BINDING POCKET




| RECEPTOR'S ATOM | LIGAND'S ATOM | DISTANCE (A) |
|---|---|---|
| SER 203 O1 | O1 | 3.251 |
| SER 207 O1 | O2 | 3.532 |
| ASP 113 O1 | N1 | 2.820 |
| ASN 312 O1 | N1 | 2.792 |
| ASN 312 N1 | O3 | 2.843 |

# 3.2. Agonists

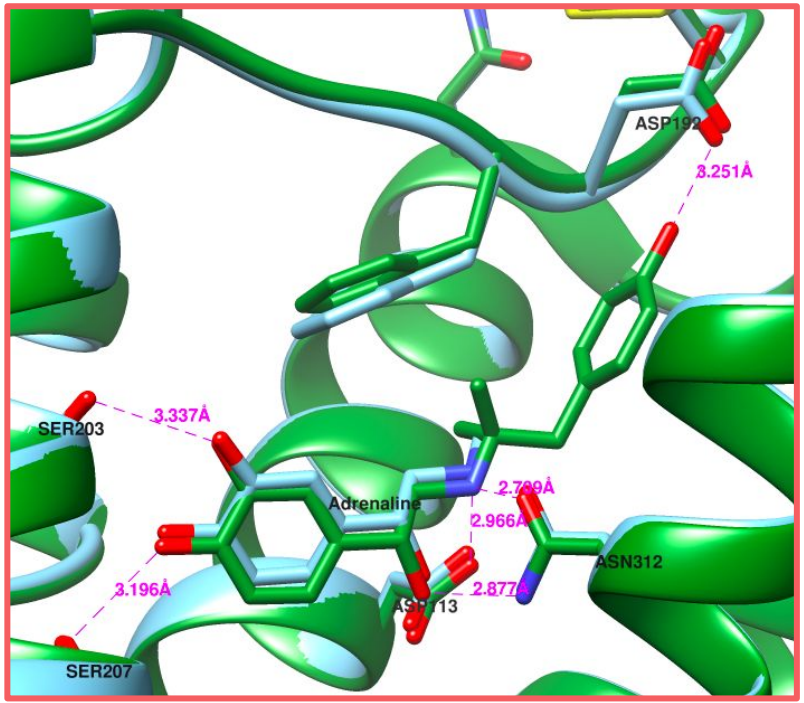


## HBI vs. ADRENALINE

HYDROGEN BONDS IN THE BINDING POCKET

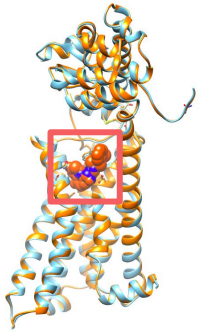
ADR

HBI




| RECEPTOR'S ATOM | LIGAND'S ATOM | DISTANCE (A) | DISTANCE ADREN. (A) |
|---|---|---|---|
| SER 203 O1 | O1 | 3.337 | 3.251 |
| SER 207 O1 | O2 | 3.196 | 3.532 |
| ASP 113 O1 | N1 | 2.966 | 2.820 |
| ASN 312 O1 | N1 | 2.789 | 2.792 |
| ASN 312 N1 | O3 | 2.877 | 2.843 |
| ASP 192 O1 | O4 | 3.251 | No interaction |

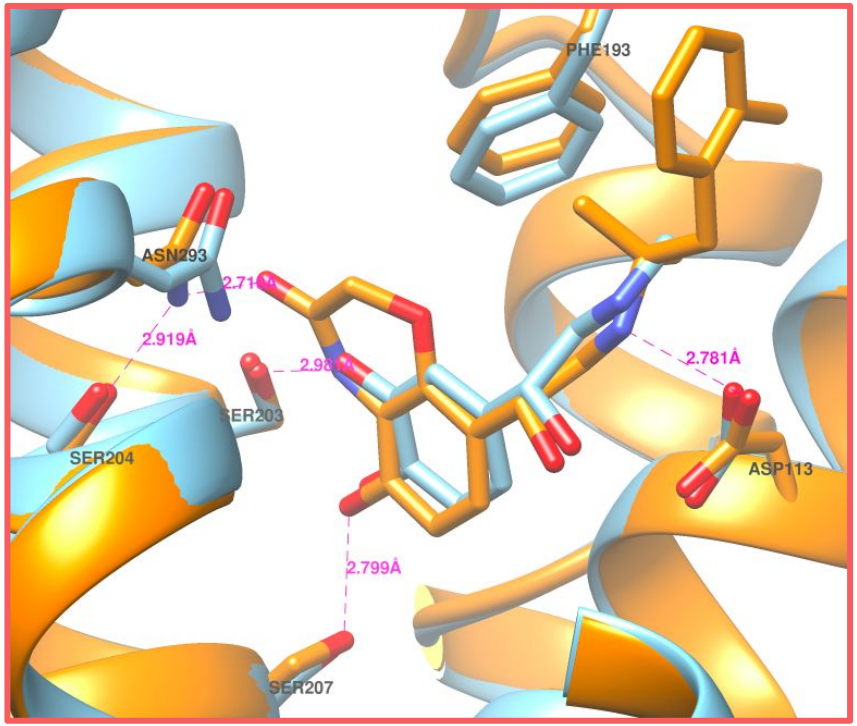
# 3.2. Agonists



## BI 167.107 vs. ADRENALINE

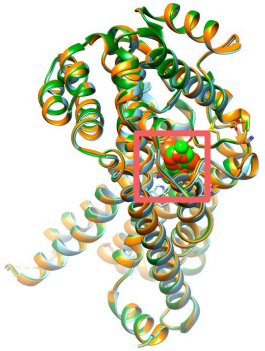
HYDROGEN BONDS IN THE BINDING POCKET

ADR
BI



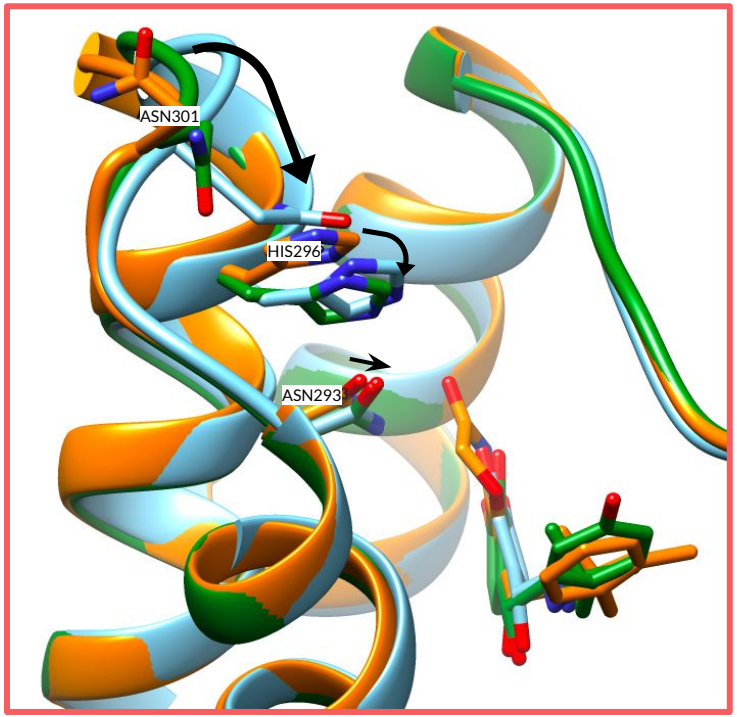

| RECEPTOR'S ATOM | LIGAND'S ATOM | DISTANCE (A) | DISTANCE ADREN. (A) |
|---|---|---|---|
| ASN 293 N1 | O1 | 2.710 | 3.213 |
| ASN 293 N1 | SER 204 O1 | 2.919 | 3.178 |
| SER 203 O1 | N1 | 2.981 | 3.251 |
| SER 207 O1 | O2 | 2.799 | 3.532 |
| ASP 113 O1 | N2 | 2.781 | 2.820 |

# 3.2. Agonists



HYDROGEN BONDS IN THE BINDING POCKET

ADR
BI
HBI



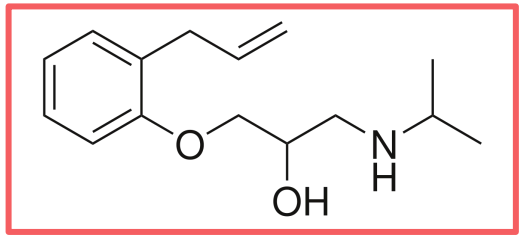

Receptor → **1.2 A shift in H6** extracellular side.

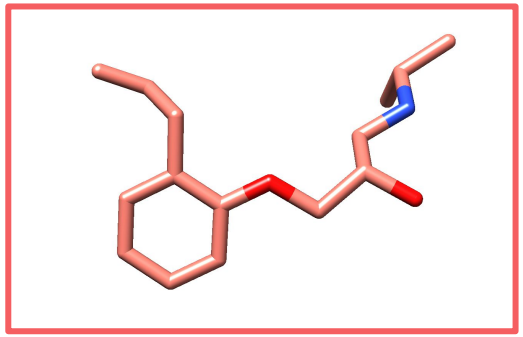
Conformational rearrangement of ECL3, altering the extracellular surface.

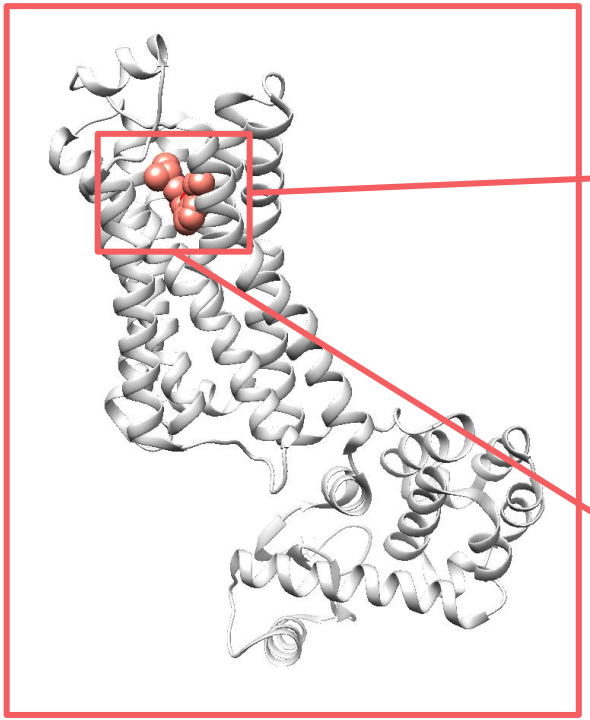
Different agonists stabilize different conformational changes in the receptor, explaining their **different affinities**.

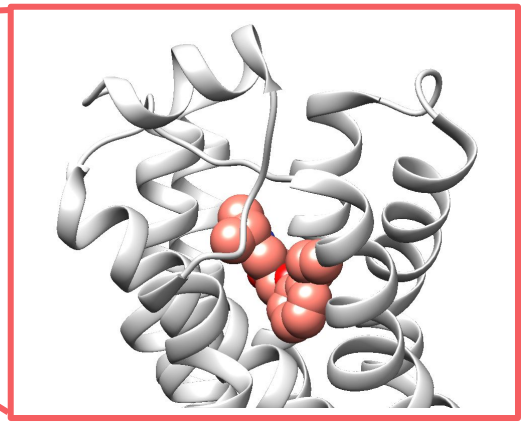
# 3.3. Antagonists

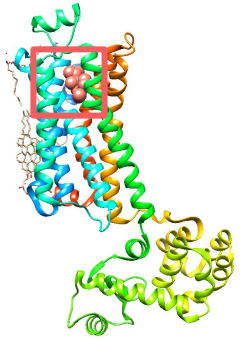
## ALPRENOLOL



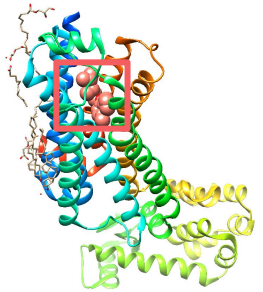







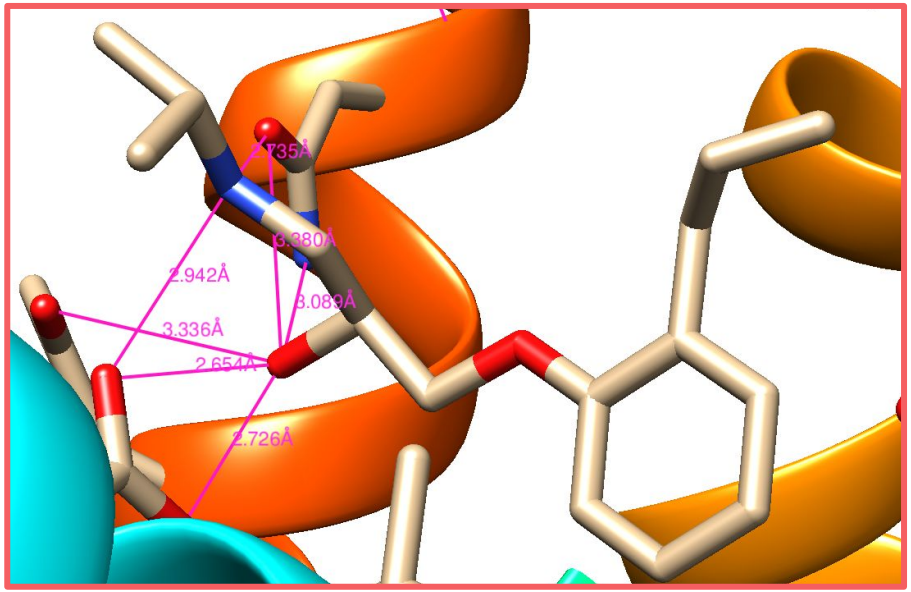


# 3.3. Antagonists



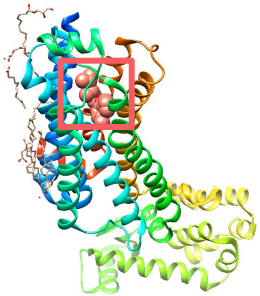
## ALPRENOLOL

HYDROGEN BONDS IN THE BINDING POCKET



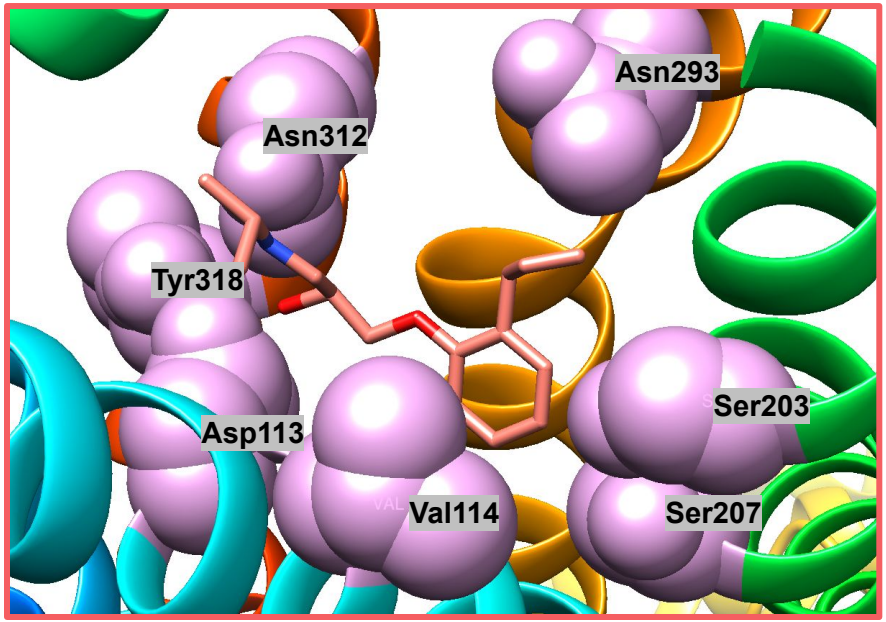

| RECEPTOR'S ATOM | LIGAND'S ATOM | DISTANCE (A) |
|---|---|---|
| TYR 316 OH | O1 | 3.336 A |
| ASP 113 O2 | O1 | 2.654 A |
| ASP 113 O1 | O1 | 2.726 A |
| ASP 113 O2 | N1 | 2.942 A |
| ASN 312 O1 | N1 | 2.735 A |
| ASN 312 O1 | O1 | 3.380 A |
| ASN 312 N2 | O1 | 3.089 A |

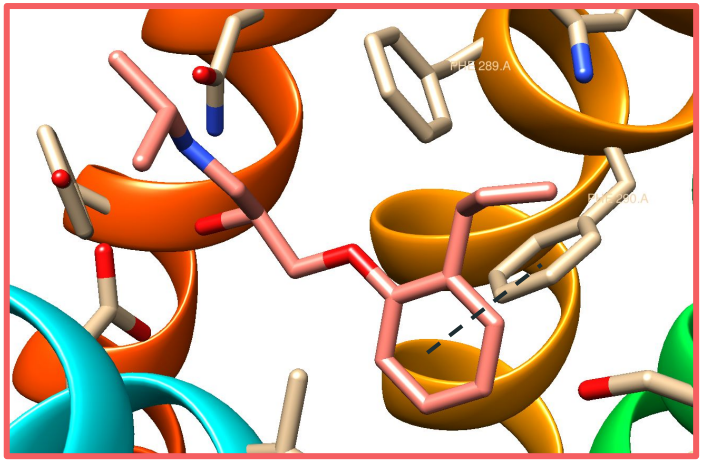
# 3.3. Antagonists



## ALPRENOLOL

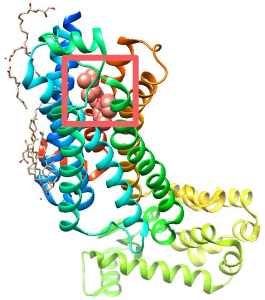
HYDROPHOBIC AND AROMATIC INTERACTIONS



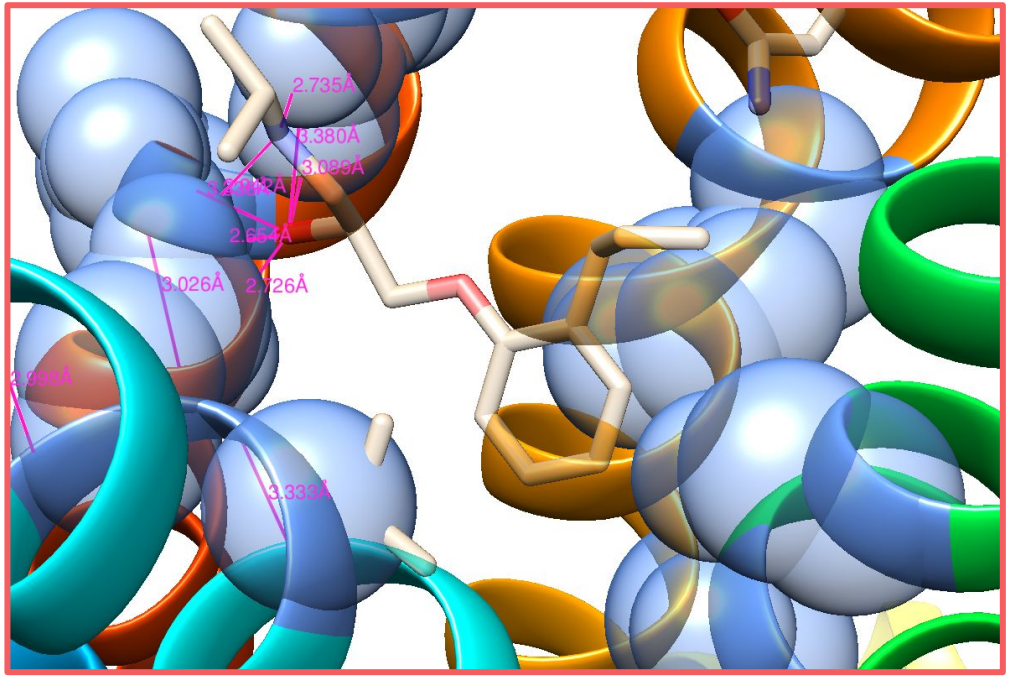
**Pi interactions:** Phe290 of the receptor.

# 3.3. Antagonists



## ALPRENOLOL

SUMMARY OF THE MOST IMPORTANT INTERACTIONS FOR THIS LIGAND



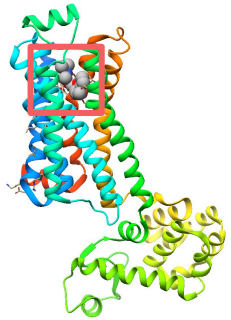

**SUMMARY**

- **Hydrogen bond network:**
  - Asp113, Tyr316 and Asn312 in the "front" of the pocket.
- **Aromatic interactions:**
  - Phe290 in the "back" of the pocket.

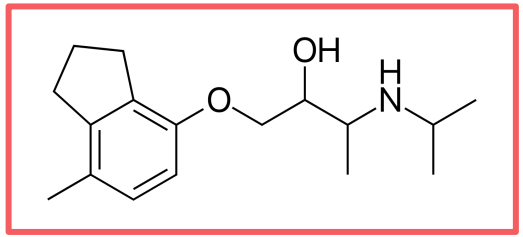
**Antagonist:**

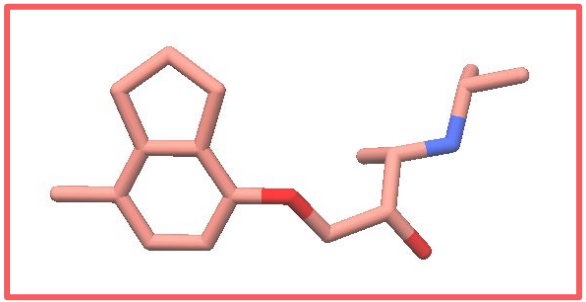
- Blocks the biological response unleashed by the receptor.
- It is bound to the same spot as the agonist.

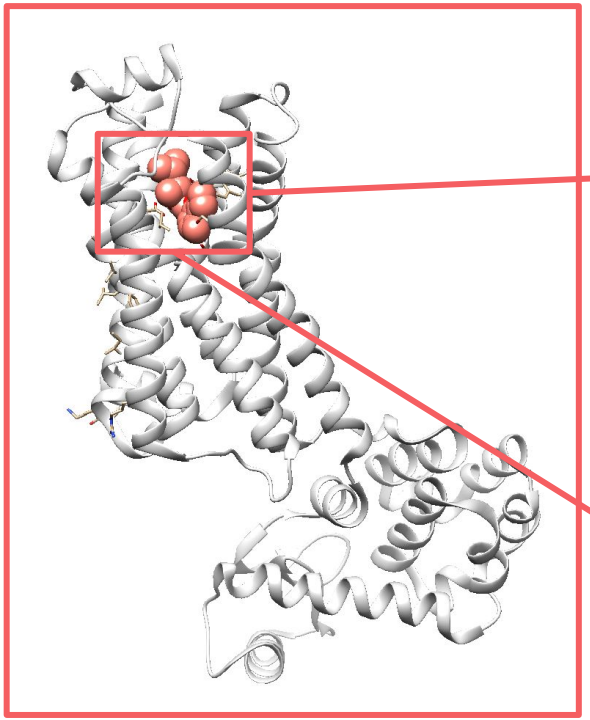
# 3.4. Inverse agonists

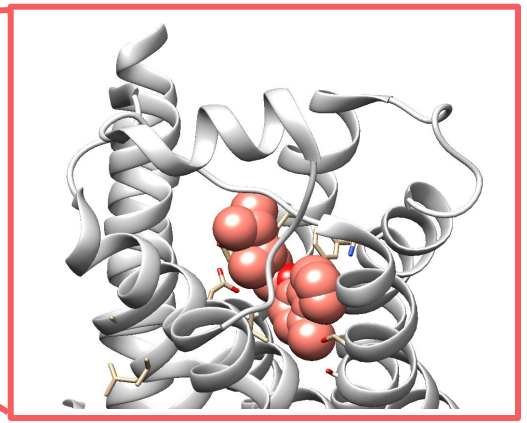


## ICI 118.551

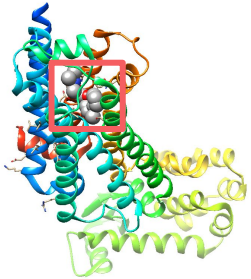




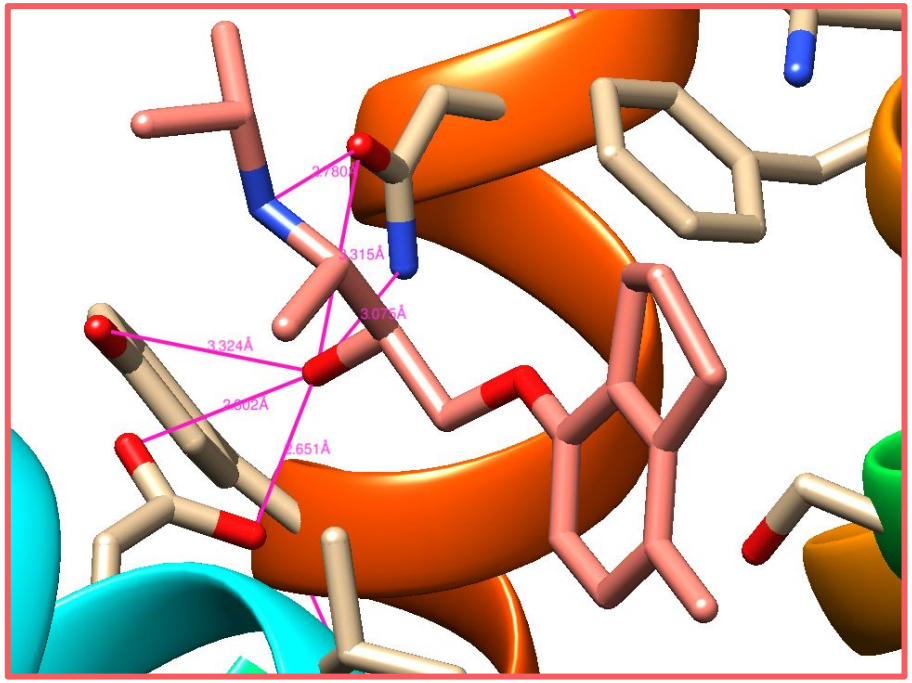


# 3.4. Inverse agonists



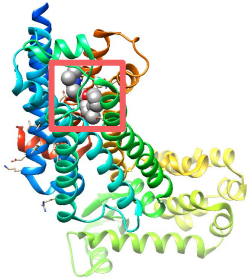
## ICI 118.551

HYDROGEN BONDS IN THE BINDING POCKET



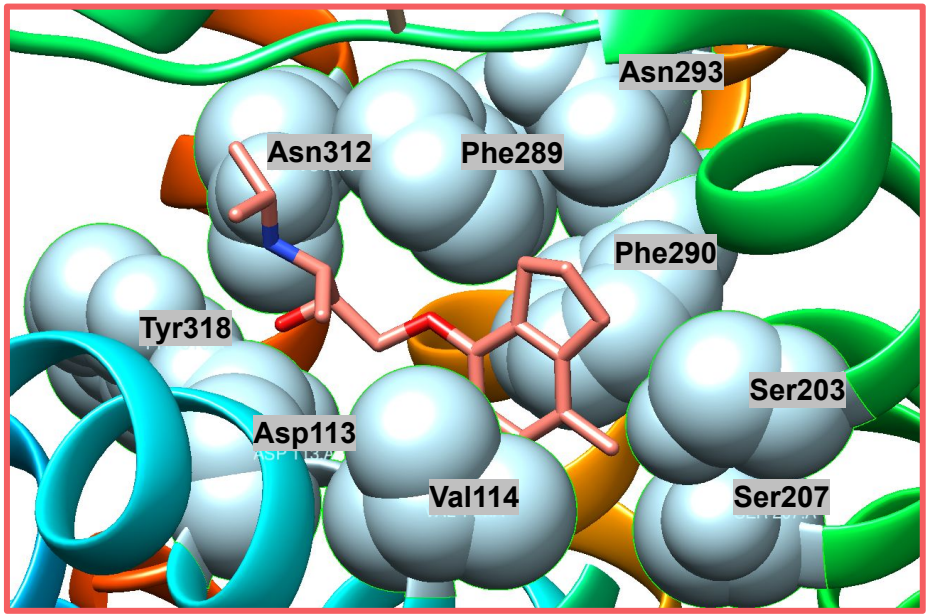

| RECEPTOR'S ATOM | LIGAND'S ATOM | DISTANCE (A) |
|---|---|---|
| TYR 316 OH | O2 | 3.324 A |
| ASP 113 O2 | O2 | 2.802 A |
| ASP 113 O1 | O2 | 2.651 A |
| ASN 312 O1 | N1 | 2.780 A |
| ASN 312 O1 | O2 | 3.315 A |
| ASN 312 N2 | O2 | 3.075 A |

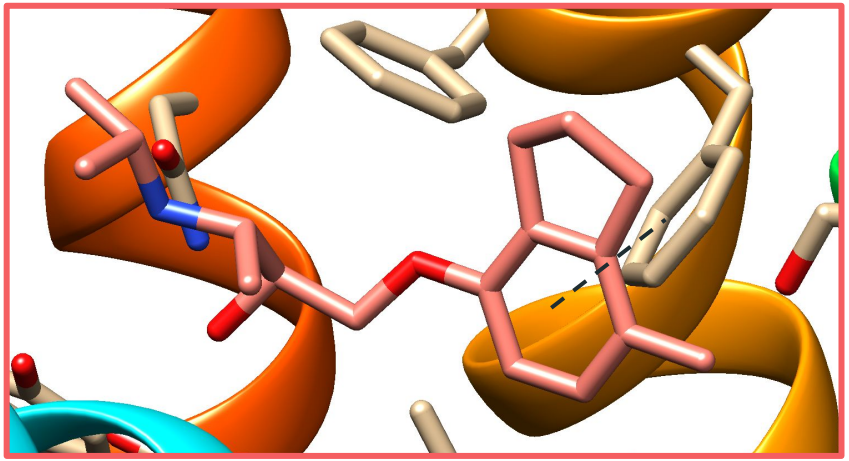
# 3.4. Inverse agonists



## ICI 118.551

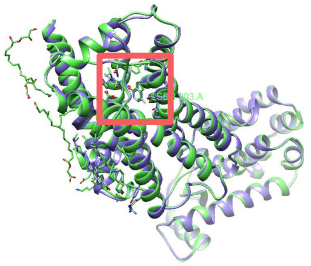
HYDROPHOBIC AND AROMATIC INTERACTIONS



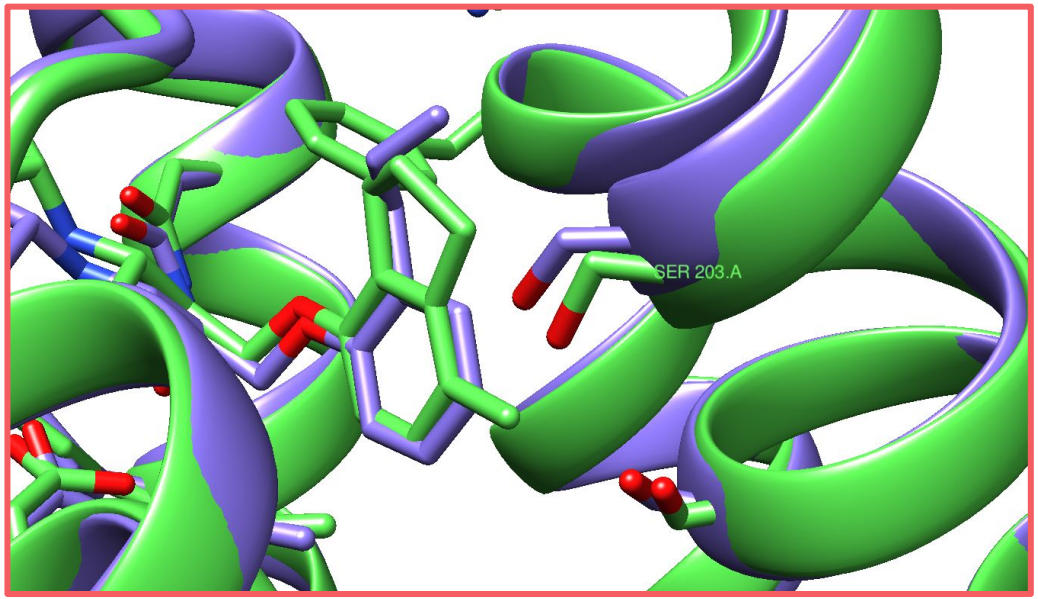
**Pi interactions:** Phe290 of the receptor.

# 3.4. Inverse agonists



## ICI 118.551

CHANGES IN CONFORMATION

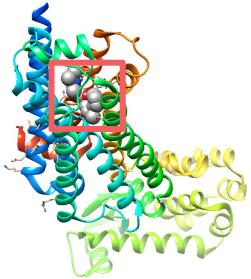



ICI 118.551

Alprenolol

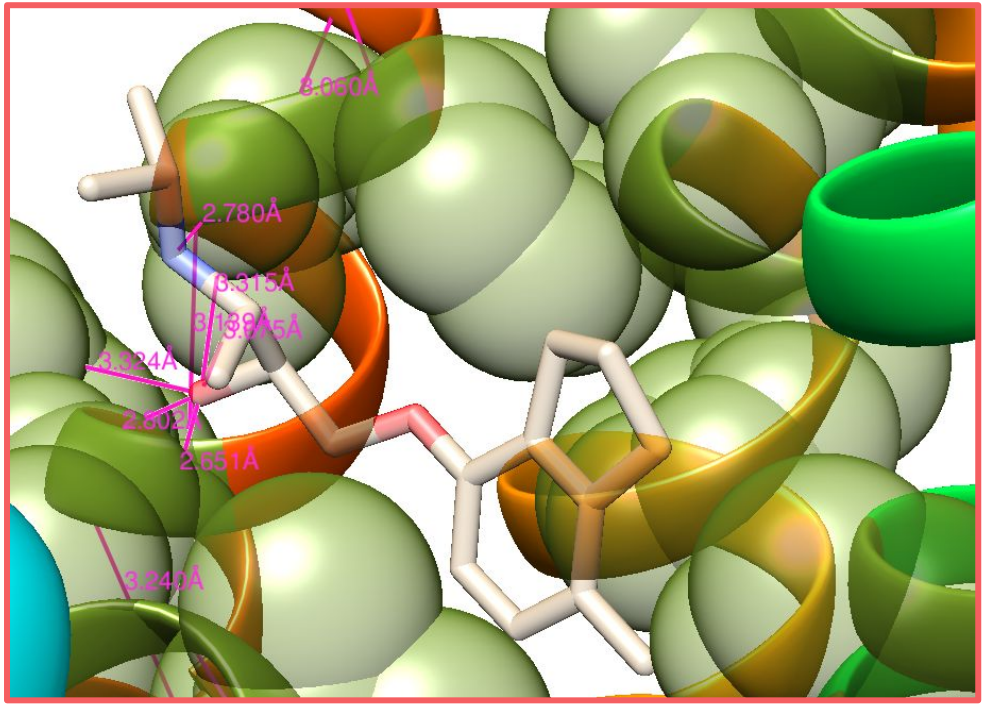
The extra methyl group in ICI 118.551 makes the Serine203 to rearrange 0.4 A in the H5.

# 3.4. Inverse agonists



## ICI 118.551

SUMMARY OF THE MOST IMPORTANT INTERACTIONS FOR THIS LIGAND




### SUMMARY

- **Hydrogen bond network:**
  - Asp113, Tyr316 and Asn312 in the "front" of the pocket.
- **Aromatic interactions:**
  - Phe290 in the "back" of the pocket.

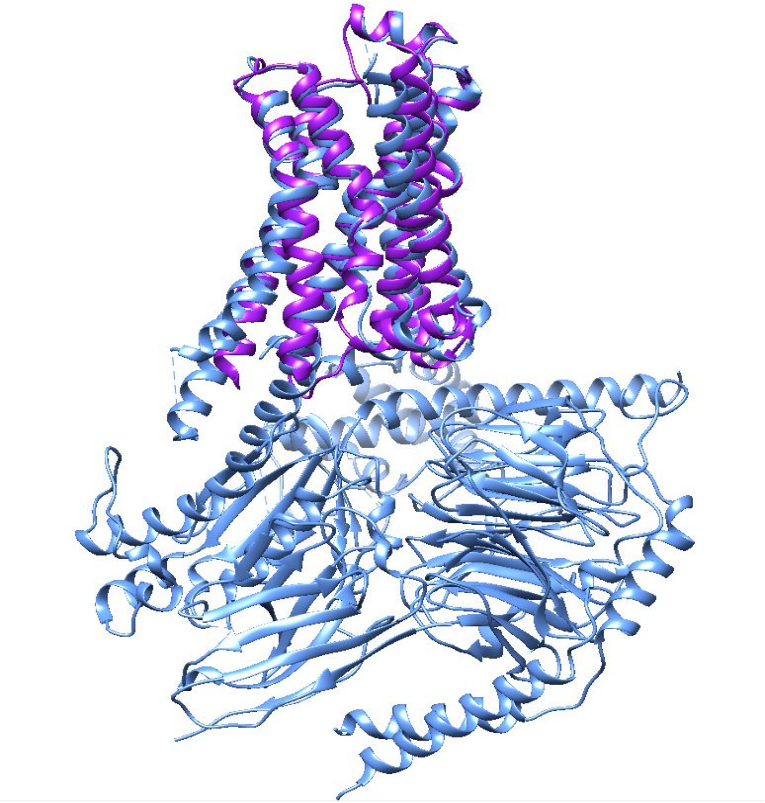
**Inverse agonist:**

- Binds to the same place as the agonist in the receptor.
- The extra methyl group causes a shift in the conformation of the receptor.

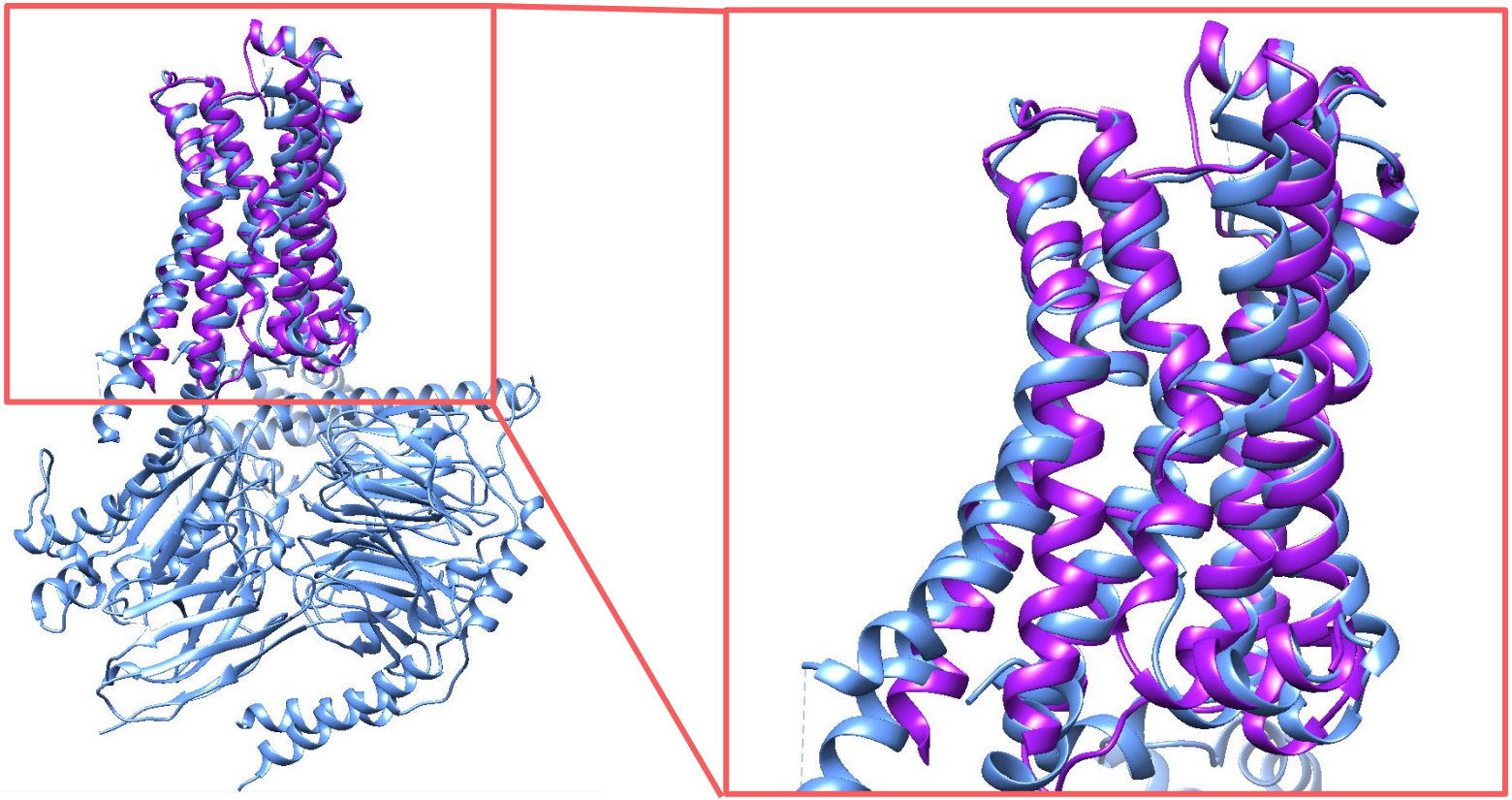
# 4. Gs-Protein binding

Active

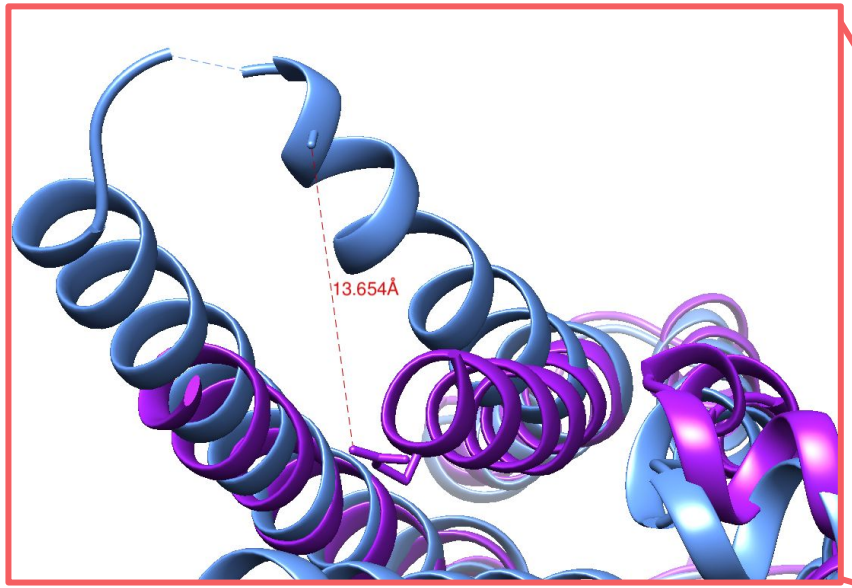
Inactive

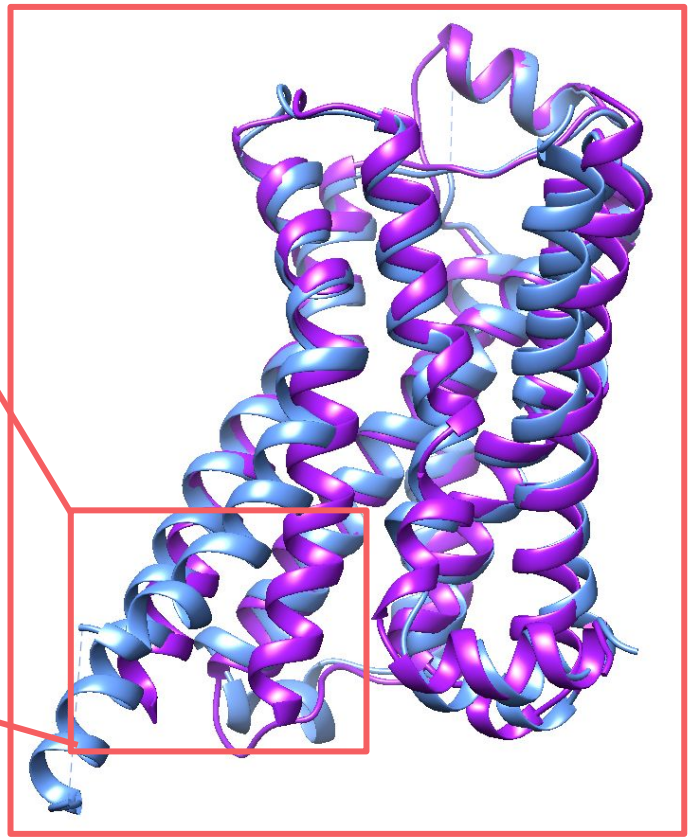


# 4.1 Conformational changes



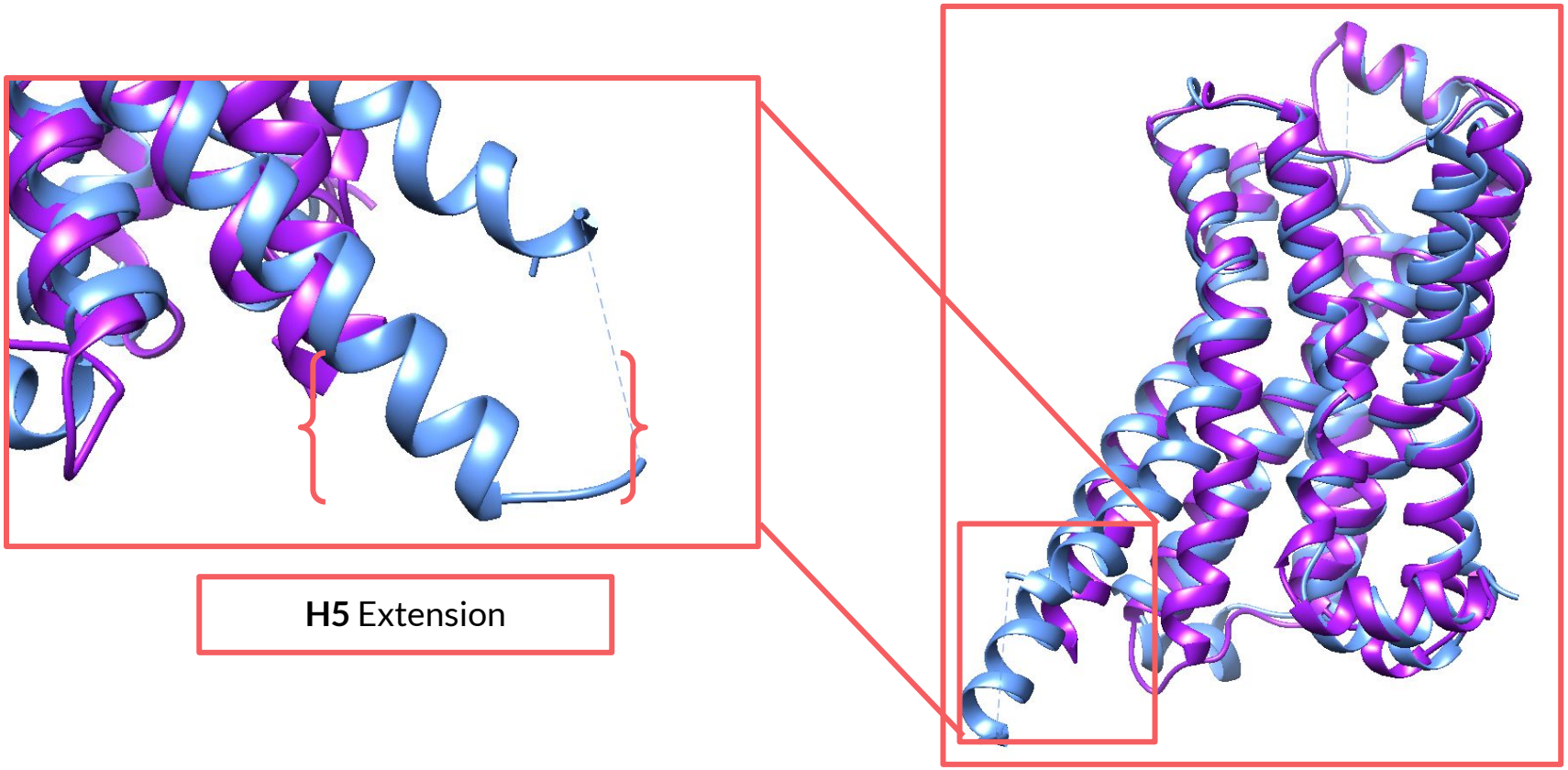
# 4.1 Conformational changes



**H6** Outward movement

# 4.1 Conformational changes



**H5** Extension

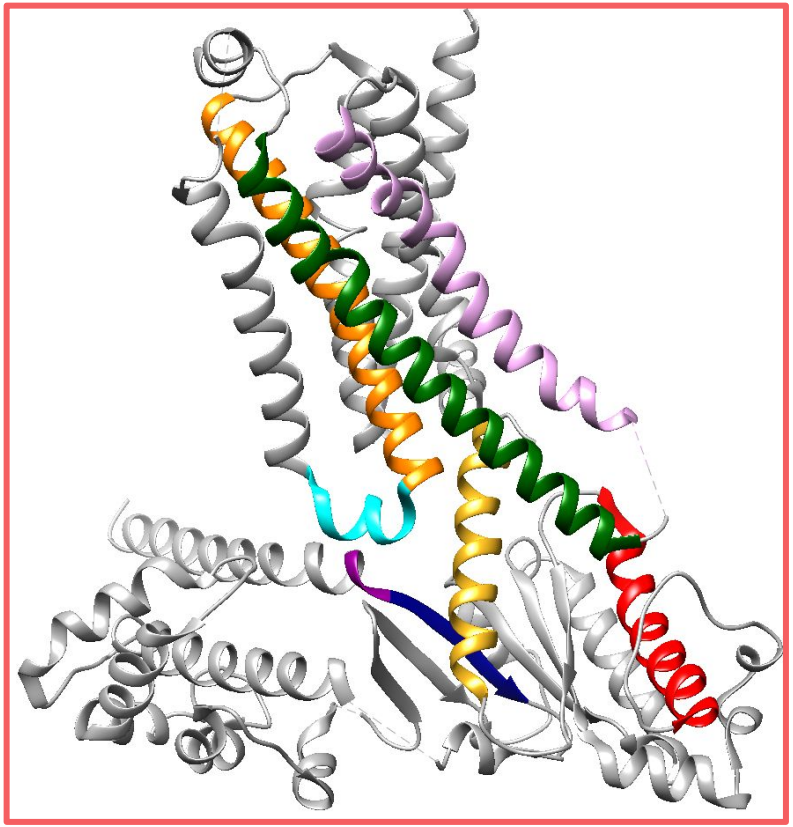
# 4.2 Coupling interface

RECEPTOR-Gs PROTEIN INTERACTIONS

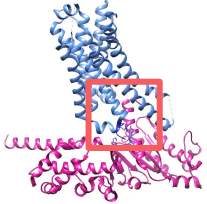
**B2 RC** | **Gs PROTEIN**

| | |
|---|---|
| ICL 2 | Alpha 5 helix |
| H3 | Alpha 4 helix |
| H5 | Beta 1 strand |
| H6 | Alpha-N Beta 1 junction |

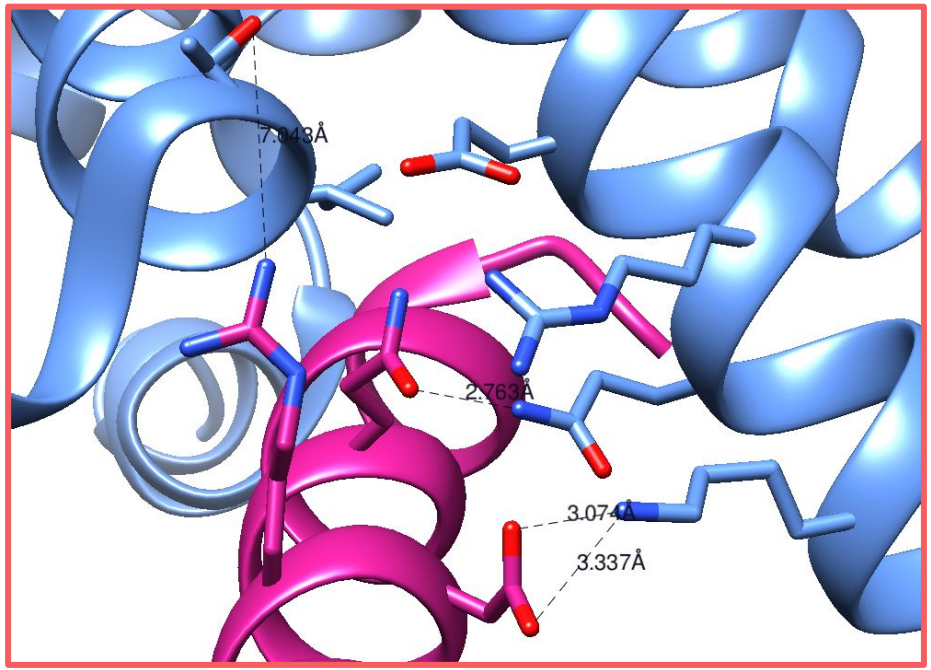
**Gs** coupling interface



# 4.2 Coupling interface



HYDROGEN BONDS B2AR-Gs

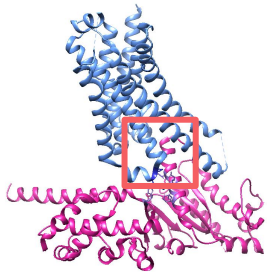



| RECEPTOR'S ATOM | Gs PROTEIN ATOM | DISTANCE (A) |
|---|---|---|
| THR 136 O | ARG 380 NH2 | 3.0 |
| ILE 135 O | GLN 384 N2 | 2.9 |
| GLN 229 N2 | GLN 384 O1 | 2.8 |
| LYS 232 N1 | ASP 381 O1 | 3.1 |

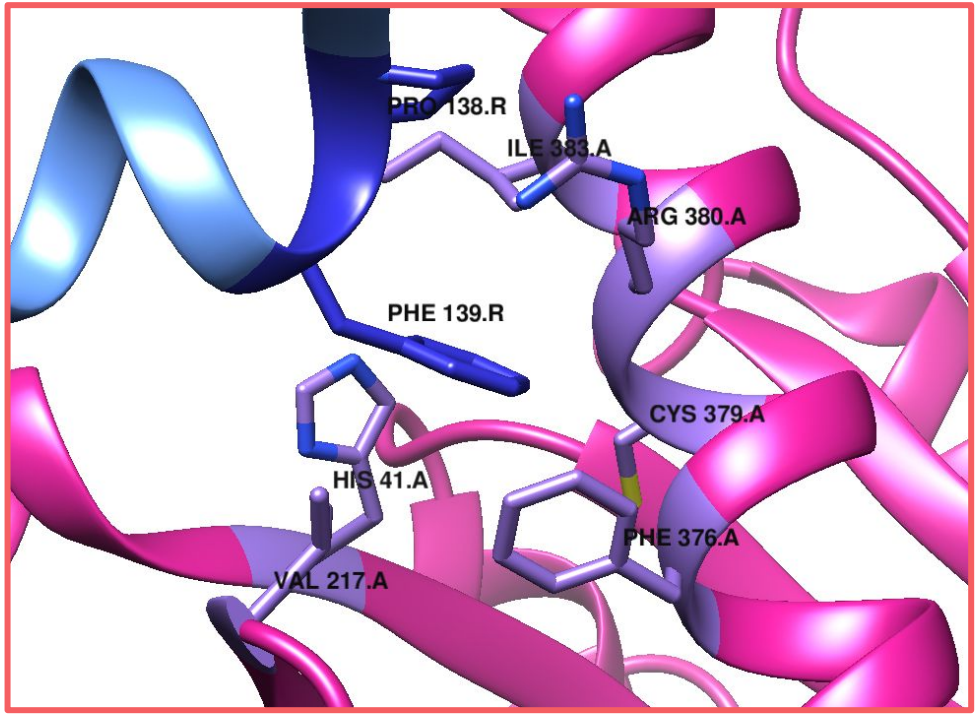
## Salt bridges

| RECEPTOR'S ATOM | Gs PROTEIN ATOM | DISTANCE (A) |
|---|---|---|
| LYS 232 N1 | ASP 381 O1 | 3.1 |

# 4.2 Coupling interface



HYDROPHOBIC INTERACTIONS B2AR-Gs




| RECEPTOR'S ATOM | Gs PROTEIN ATOM |
|---|---|
| PRO 138 O | ILE 383 C1 |
| PHE 139 C | PHE 376 C |
| PHE 139 C | CYS 379 C |
| PHE 139 C | ARG 380 N |
| PHE 139 C | HIS 41 N |
| PHE 139 C | VAL 217 C |

# 5. Evolution

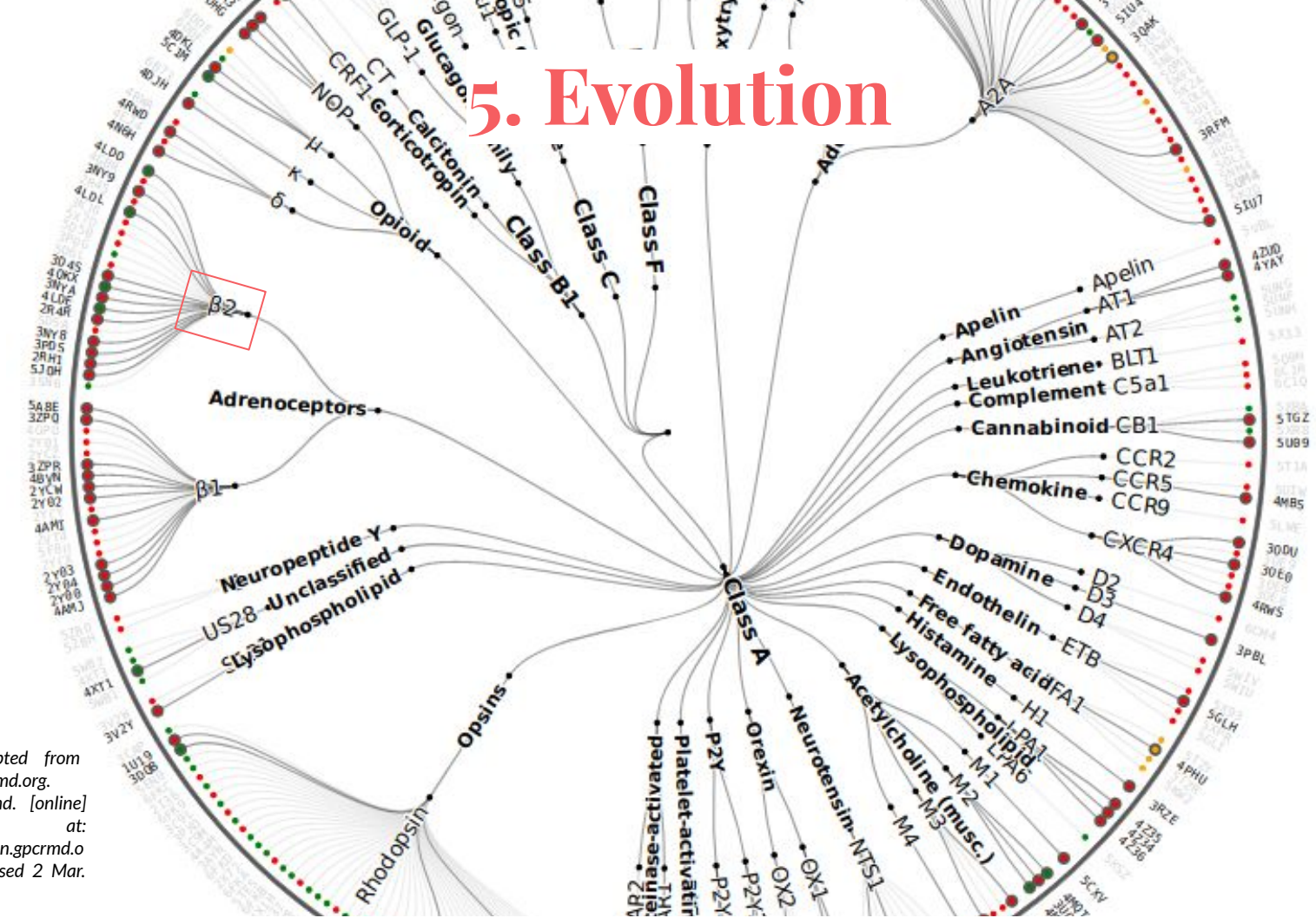
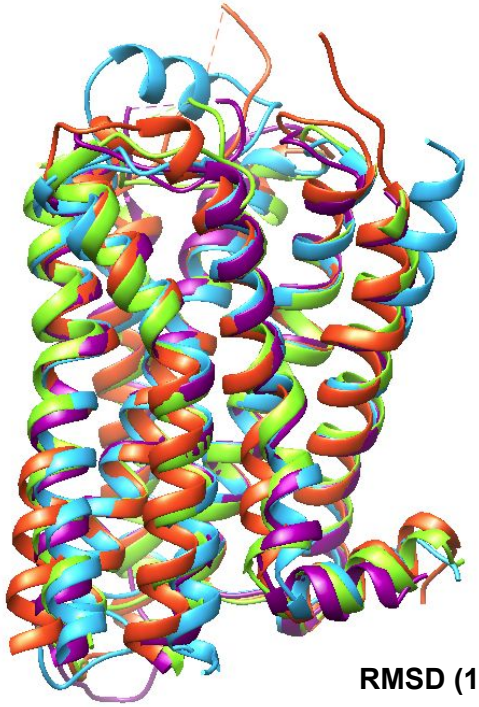



***Fig. 9.*** *Adapted from Submission.gpcrmd.org. (2020). GPCRmd. [online] Available at: https://submission.gpcrmd.org/home/ [Accessed 2 Mar. 2020].*

# 5.1. Evolution: comparison between GPCRs

Various human GPCRs with different functions have the same structure.



RMSD (176) = 1.103

- Beta-2 AR
- 5-HT2B
- Histamine H1
- Dopamine D4

# 5.1. Evolution: comparison between GPCRs

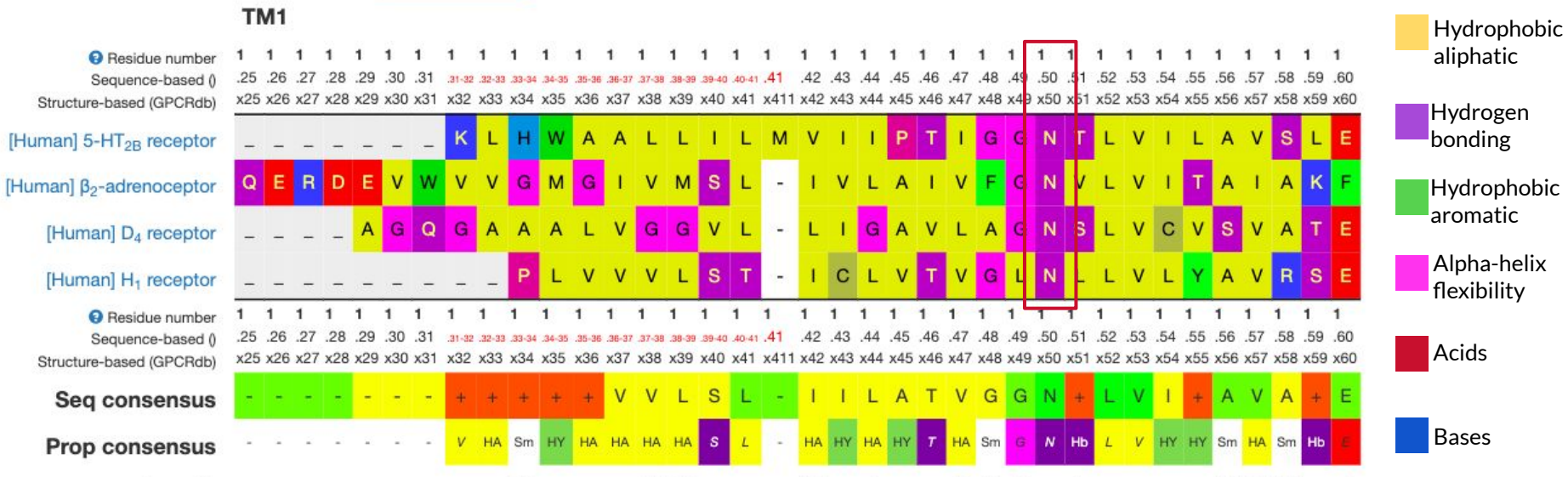
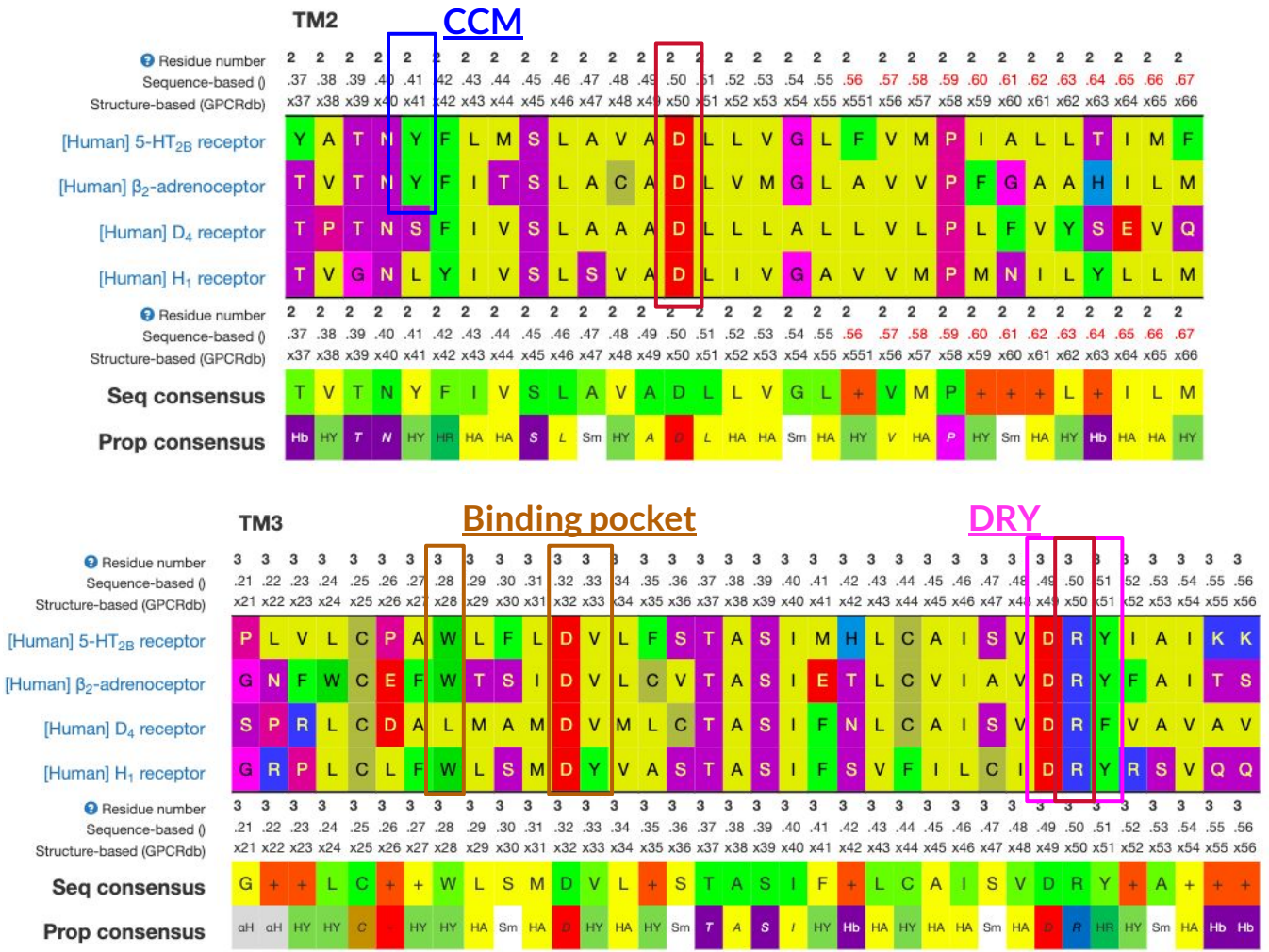
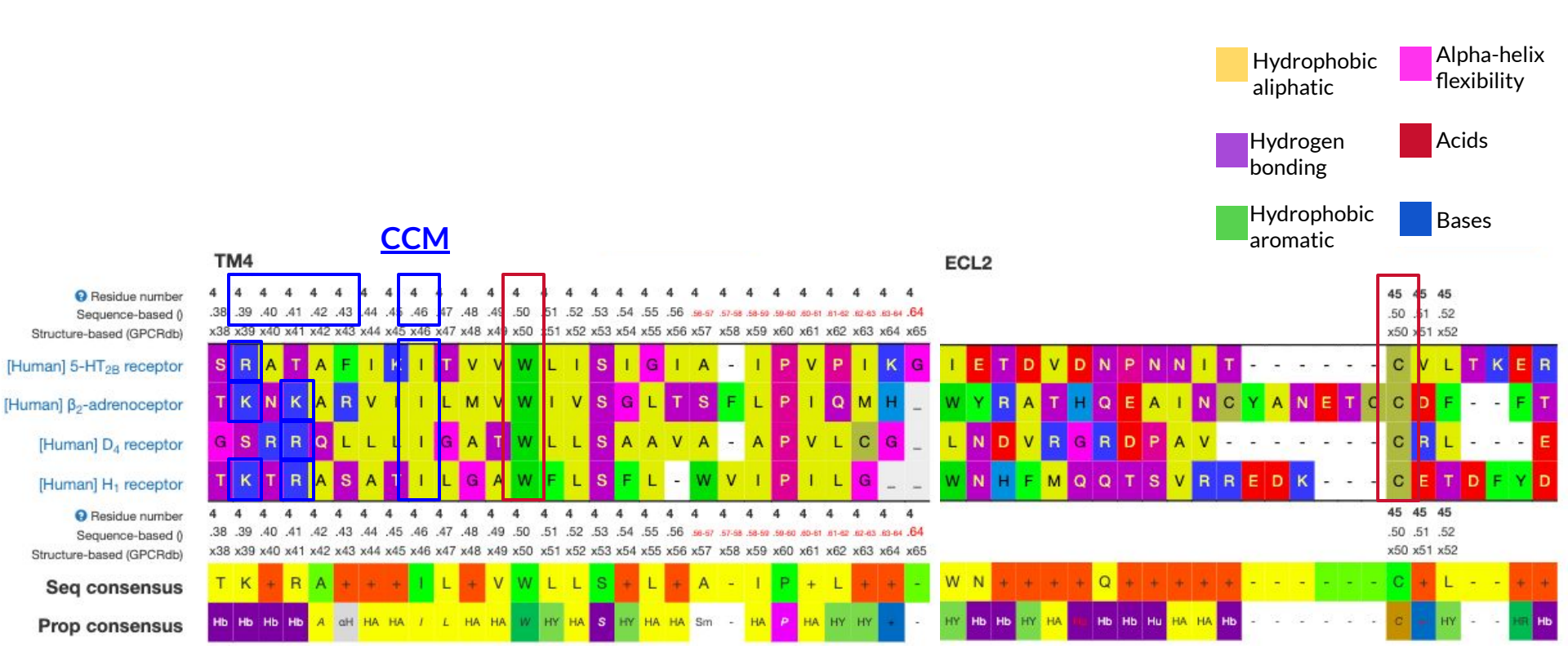
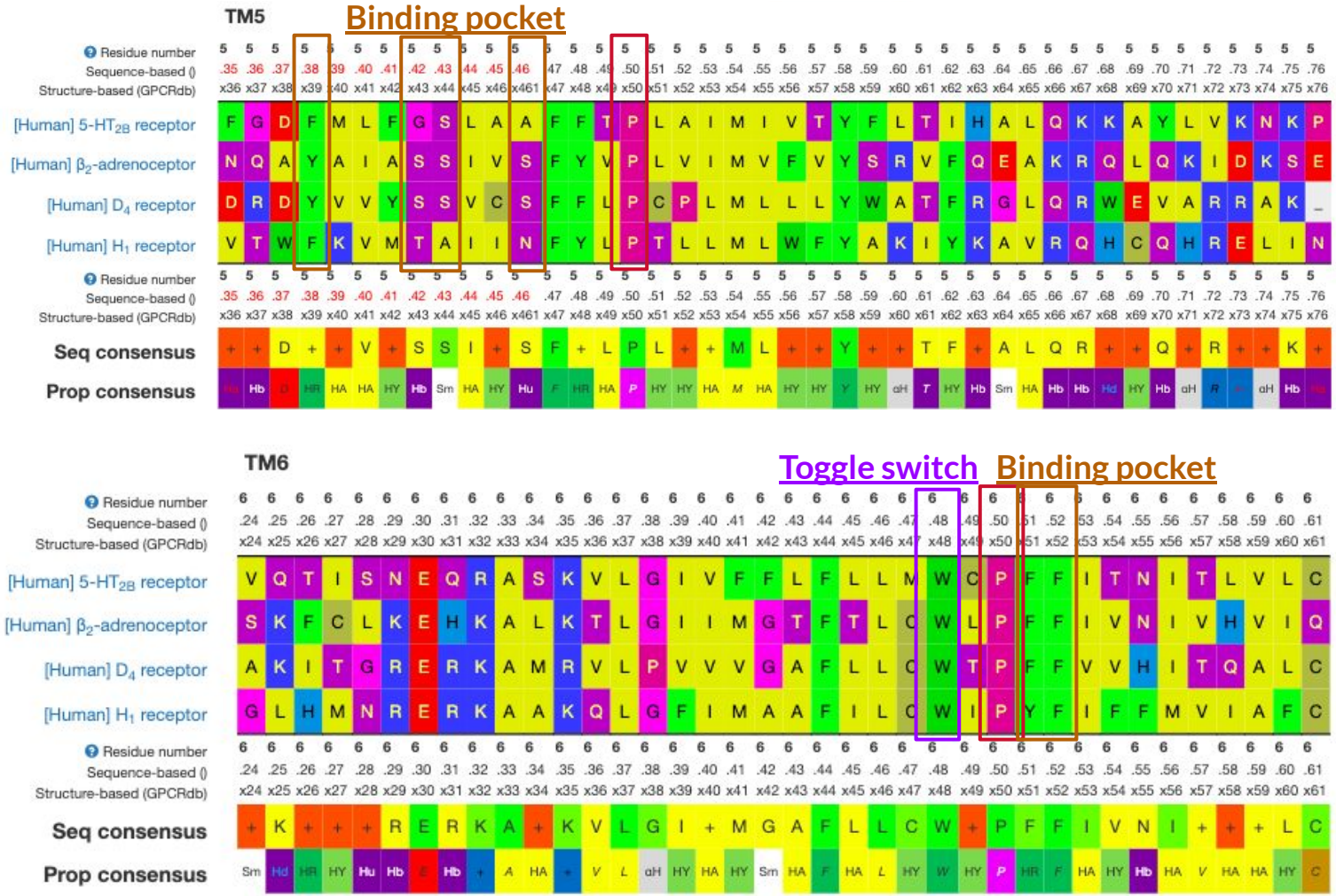



***Fig. 10A, 10B, 10D and 10E.*** *Adapted from Submission.gpcrmd.org. (2020). GPCRmd. [online] Available at: https://submission.gpcrmd.org/home/ [Accessed 2 Mar. 2020].*


TM2
CCM
Residue number
Sequence-based ()
Structure-based (GPCRdb)
[Human] 5-HT2B receptor
[Human] β2-adrenoceptor
[Human] D4 receptor
[Human] H1 receptor
Seq consensus
Prop consensus
TM3
Binding pocket
DRY
Hydrophobic aliphatic
Hydrogen bonding
Hydrophobic aromatic
Alpha-helix flexibility
Acids
Bases


Hydrophobic aliphatic
Alpha-helix flexibility
Hydrogen bonding
Acids
Hydrophobic aromatic
Bases
CCM
TM4
ECL2
Residue number
Sequence-based ()
Structure-based (GPCRdb)
[Human] 5-HT2B receptor
[Human] β2-adrenoceptor
[Human] D4 receptor
[Human] H1 receptor
Seq consensus
Prop consensus


TM5
Binding pocket
Residue number
Sequence-based ()
Structure-based (GPCRdb)
[Human] 5-HT2B receptor
[Human] β2-adrenoceptor
[Human] D4 receptor
[Human] H1 receptor
Seq consensus
Prop consensus
TM6
Toggle switch
Binding pocket
Hydrophobic aliphatic
Hydrogen bonding
Hydrophobic aromatic
Alpha-helix flexibility
Acids
Bases

Hydrophobic aliphatic

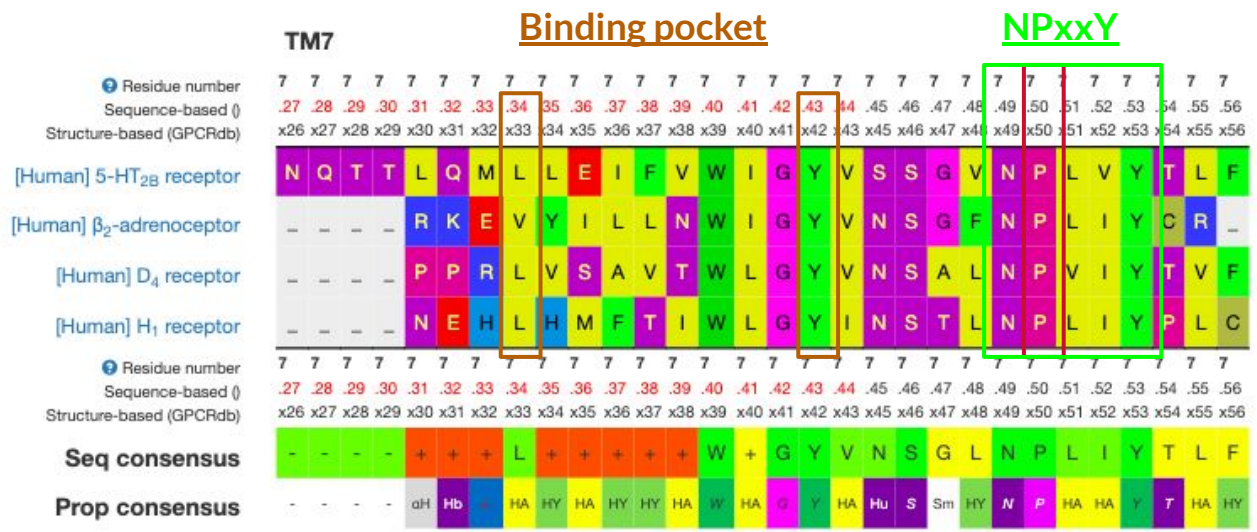
Alpha-helix flexibility

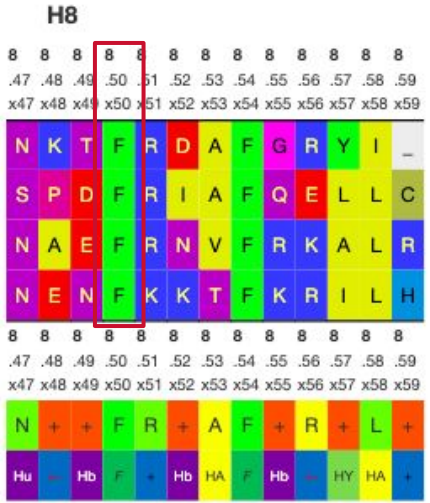
Hydrogen bonding

Acids

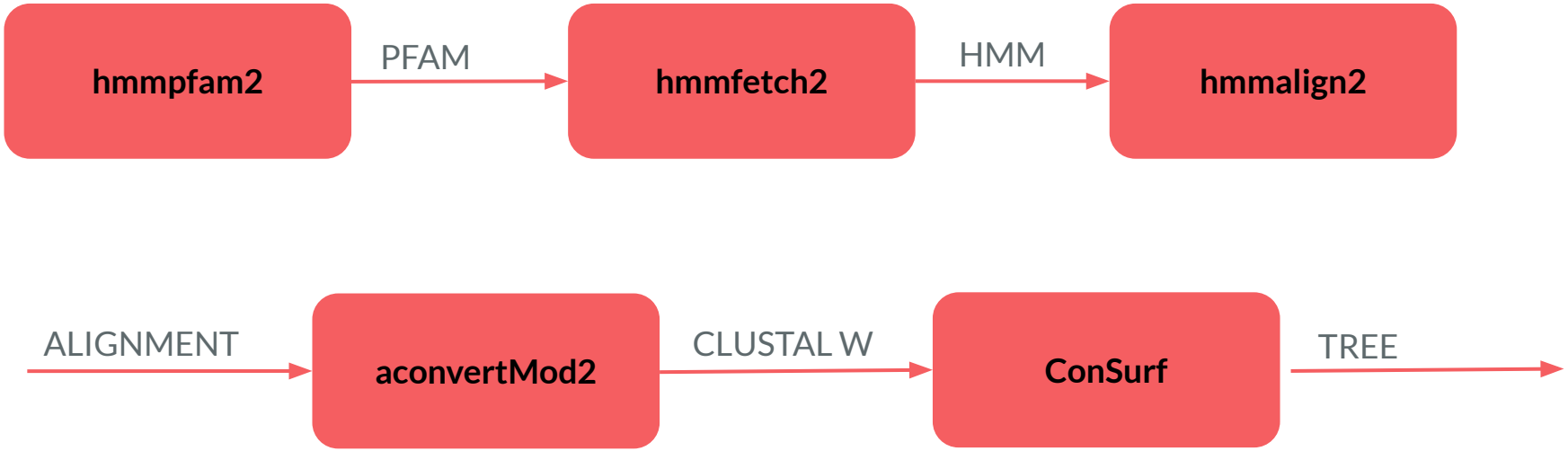
Hydrophobic aromatic

Bases

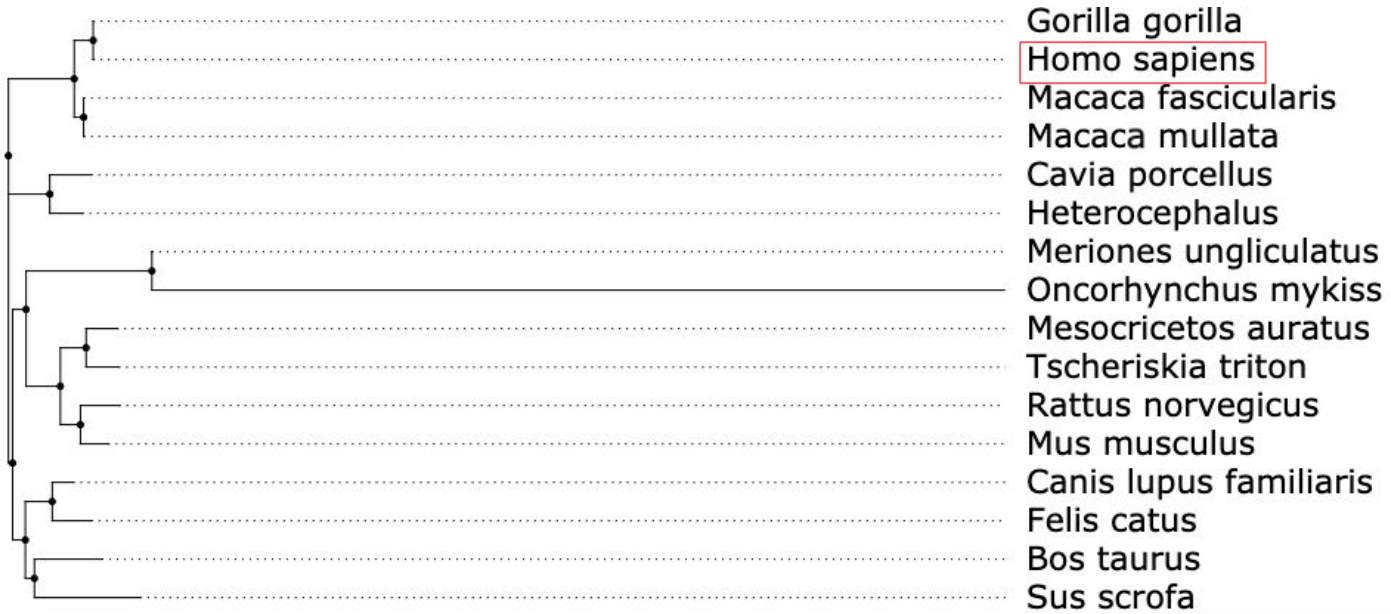


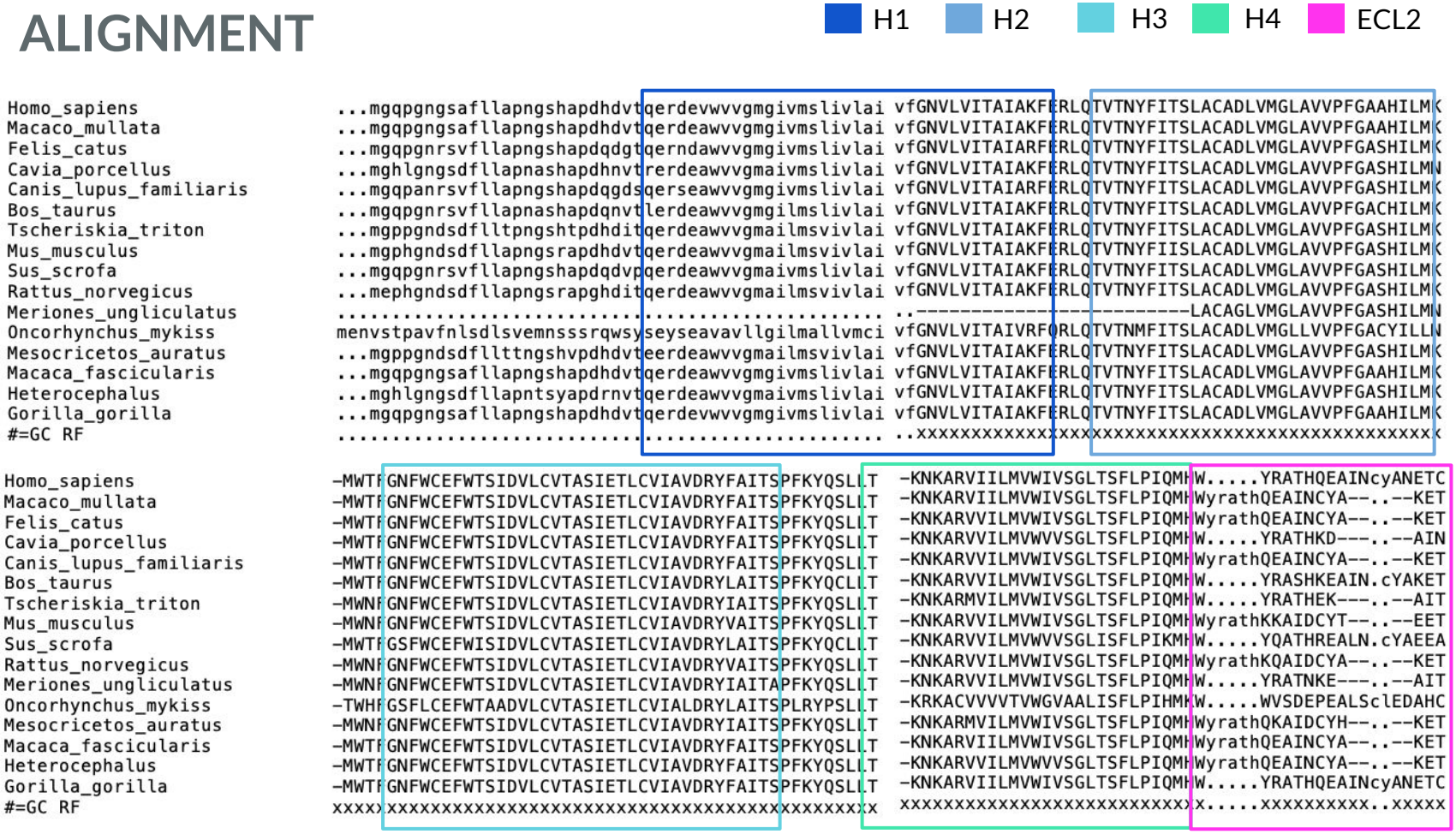
# 5.2. Evolution: β2-AR



# 5.2. Evolution: β2-AR

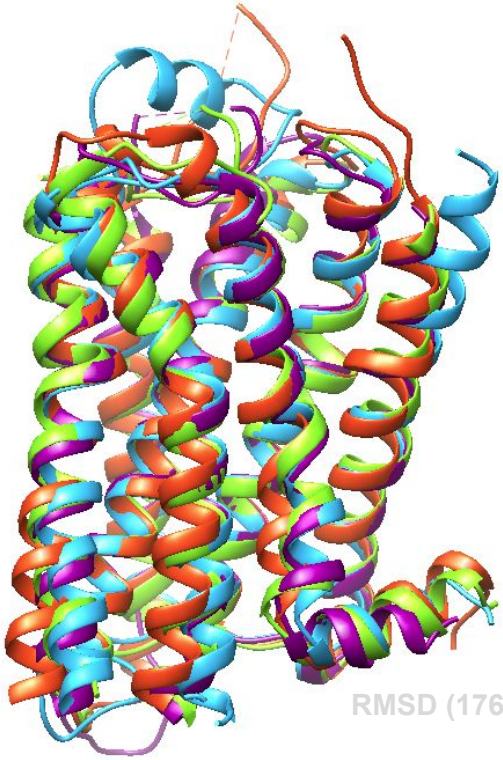


# ALIGNMENT

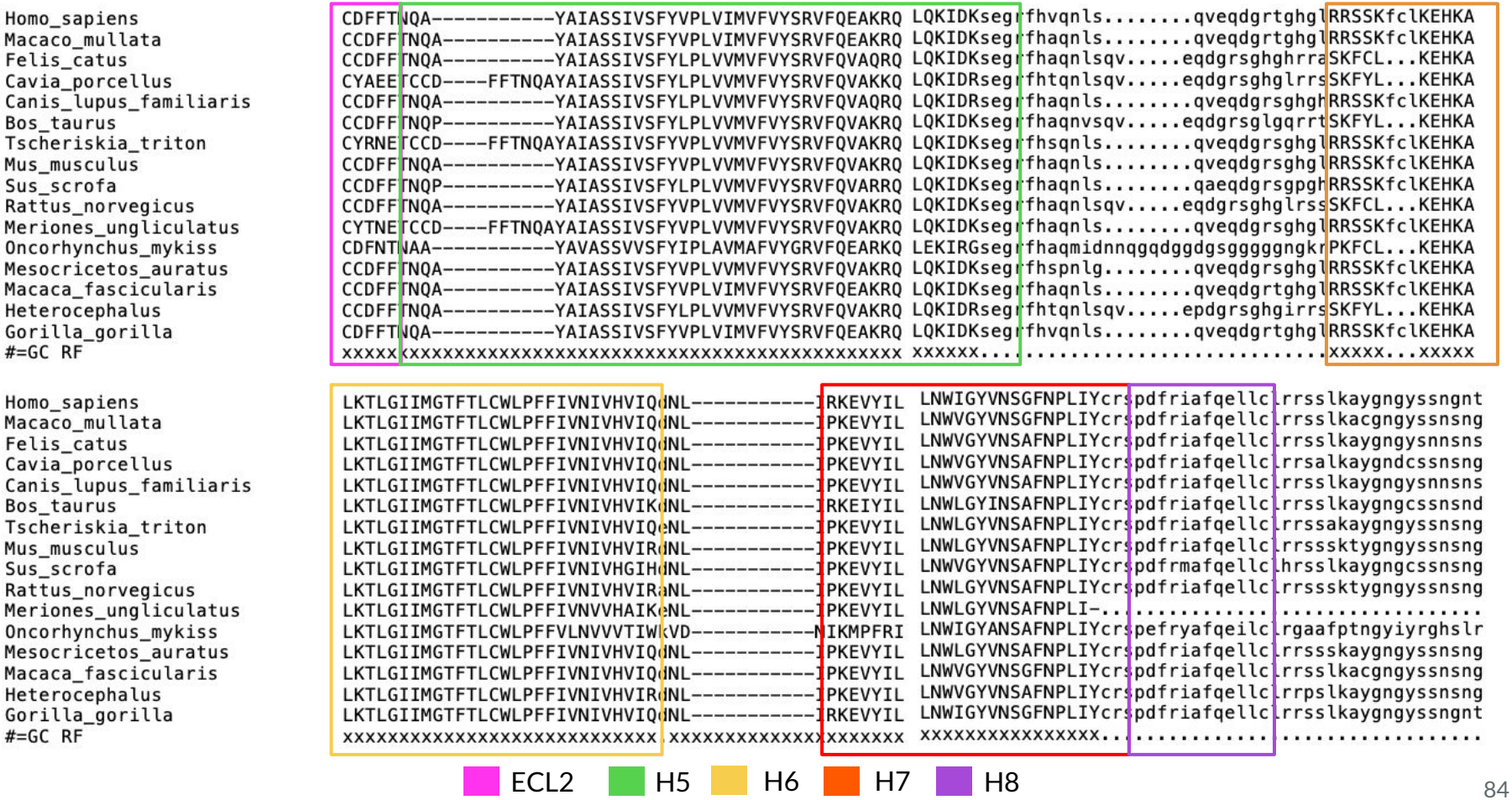

H1
H2
H3
H4
ECL2
Homo_sapiens ...mgqpgngsafllapngshapdhdvtqerdevwvvgmgivmslivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGAAHILMK
Macaco_mullata ...mgqpgngsafllapngshapdhdvtqerdeawvvgmgivmslivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGAAHILMK
Felis_catus ...mgqpgnrsvfllapngshapdqdgtqerndawvvgmgivmslivlai vfGNVLVITAIARFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Cavia_porcellus ...mghlgngsdfllapnashapdhnvtrerdeawvvgmaivmslivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMN
Canis_lupus_familiaris ...mgqpanrsvfllapngshapdqgdsqerseawvvgmgivmslivlai vfGNVLVITAIARFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Bos_taurus ...mgqpgnrsvfllapnashapdqnvtlerdeawvvgmgilmslivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGACHILMK
Tscheriskia_triton ...mgppgndsdflltpngshtpdhditqerdeawvvgmailmsvivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Mus_musculus ...mgphgndsdfllapngsrapdhdvtqerdeawvvgmailmsvivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Sus_scrofa ...mgqpgnrsvfllapngshapdqdvpqerdeawvvgmaivmslivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Rattus_norvegicus ...mephgndsdfllapngsrapghditqerdeawvvgmailmsvivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Meriones_ungliculatus ..... ..----------LACAGLVMGLAVVPFGASHILMN
Oncorhynchus_mykiss menvstpavfnlsdlsvemnsssrqwsyseyseavavllgilmallvmci vfGNVLVITAIVRFQRLQTVTNMFITSLACADLVMGLLVVPFGACYILLN
Mesocricetos_auratus ...mgppgndsdfllttngshvpdhdvteerdeawvvgmailmsvivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Macaca_fascicularis ...mgqpgngsafllapngshapdhdvtqerdeawvvgmgivmslivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGAAHILMK
Heterocephalus ...mghlgngsdfllapntsyapdrnvtqerdeawvvgmaivmslivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Gorilla_gorilla ...mgqpgngsafllapngshapdhdvtqerdevwvvgmgivmslivlai vfGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGAAHILMK
#=GC RF ..... ..xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Homo_sapiens -MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLT -KNKARVIILMVWIVSGLTSFLPIQMHWyrathQEAINCYA--..--KET
Macaco_mullata -MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLT -KNKARVIILMVWIVSGLTSFLPIQMHWyrathQEAINCYA--..--KET
Felis_catus -MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLT -KNKARVVILMVWVVSGLTSFLPIQMHW.....YRATHKD---..--AIN
Cavia_porcellus -MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLT -KNKARVVILMVWIVSGLTSFLPIQMHWyrathQEAINCYA--..--KET
Canis_lupus_familiaris -MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYLAITSPFKYQCLLT -KNKARVVILMVWIVSGLTSFLPIQMHW.....YRASHKEAIN.cYAKET
Bos_taurus -MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYIAITSPFKYQSLLT -KNKARMVILMVWIVSGLTSFLPIQMHW.....YRATHEK---..--AIT
Tscheriskia_triton -MWNFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYVAITSPFKYQSLLT -KNKARVVILMVWIVSGLTSFLPIQMHWyrathKKAIDCYT--..--EET
Mus_musculus -MWNFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYLAITSPFKYQCLLT -KNKARVVILMVWVVSGLISFLPIKMHW.....YQATHREALN.cYAEEA
Sus_scrofa -MWTFGSFWCEFWISIDVLCVTASIETLCVIAVDRYVAITSPFKYQSLLT -KNKARVVILMVWIVSGLTSFLPIQMHWyrathKQAIDCYA--..--KET
Rattus_norvegicus -MWNFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYIAITAPFKYQSLLT -KNKARVVILMVWIVSGLTSFLPIQMHW.....YRATNKE---..--AIT
Meriones_ungliculatus -MWNFGNFWCEFWTSIDVLCVTASIETLCVIALDRYLAITSPLRYPSLLT -KRKACVVVVTVWGVAALISFLPIHMHW.....WVSDEPEALSclEDAHC
Oncorhynchus_mykiss -TWHFGSFLCEFWTAADVLCVTASIETLCVIAVDRYIAITSPFKYQSLLT -KNKARMVILMVWIVSGLTSFLPIQMHWyrathQKAIDCYH--..--KET
Mesocricetos_auratus -MWNFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYIAITSPFKYQSLLT -KNKARVIILMVWIVSGLTSFLPIQMHWyrathQEAINCYA--..--KET
Macaca_fascicularis -MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLT -KNKARVIILMVWVVSGLTSFLPIQMHWyrathQEAINCYA--..--KET
Heterocephalus -MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLT -KNKARVIILMVWIVSGLTSFLPIQMHW.....YRATHQEAINcyANETC
Gorilla_gorilla -MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLT -KNKARVIILMVWIVSGLTSFLPIQMHW.....YRATHQEAINcyANETC
#=GC RF xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxx.....xxxxxxxxxx..xxxxx

# 5.1. Evolution: comparison between GPCRs

Various human GPCRs with different functions have the same structure.




Beta-2 AR
5-HT2B
Histamine H1
Dopamine D4


Homo_sapiens
Macaco_mullata
Felis_catus
Cavia_porcellus
Canis_lupus_familiaris
Bos_taurus
Tscheriskia_triton
Mus_musculus
Sus_scrofa
Rattus_norvegicus
Meriones_ungliculatus
Oncorhynchus_mykiss
Mesocricetos_auratus
Macaca_fascicularis
Heterocephalus
Gorilla_gorilla
#=GC RF
ECL2
H5
H6
H7
H8

# 5. Conclusions

1. The active vs inactive model is not accurate because there are intermediate states of the receptor which explain its basal activity.
2. Agonists have different interactions with the receptor than antagonists and inverse agonists and because of this they have different functions.
3. Residues implied in important functions (CCM, NPxxY, binding pocket, etc.) are very conserved both amongst species as amongst different GPCRs.

# 6. References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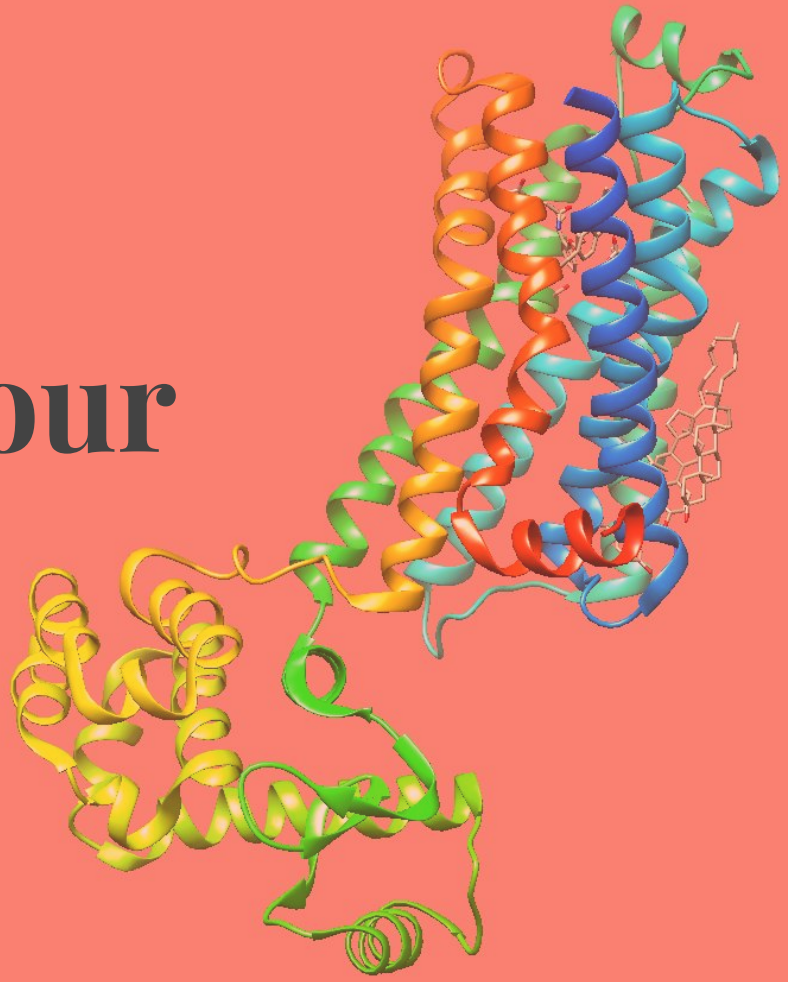
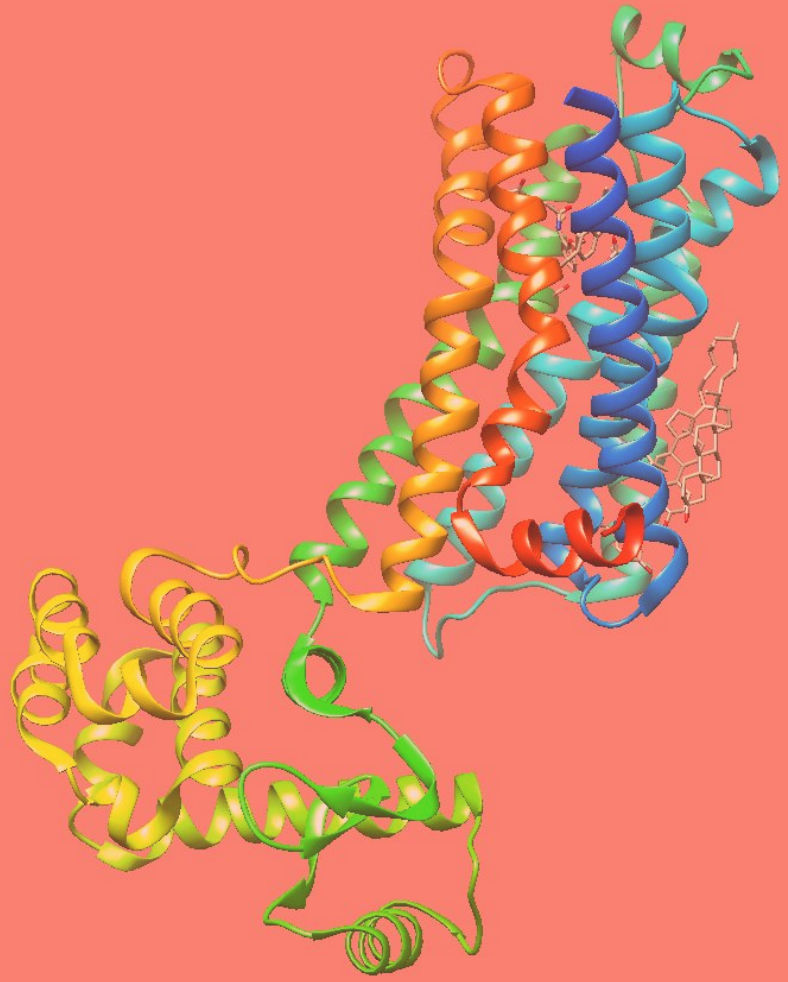
# Thank you for your attention.



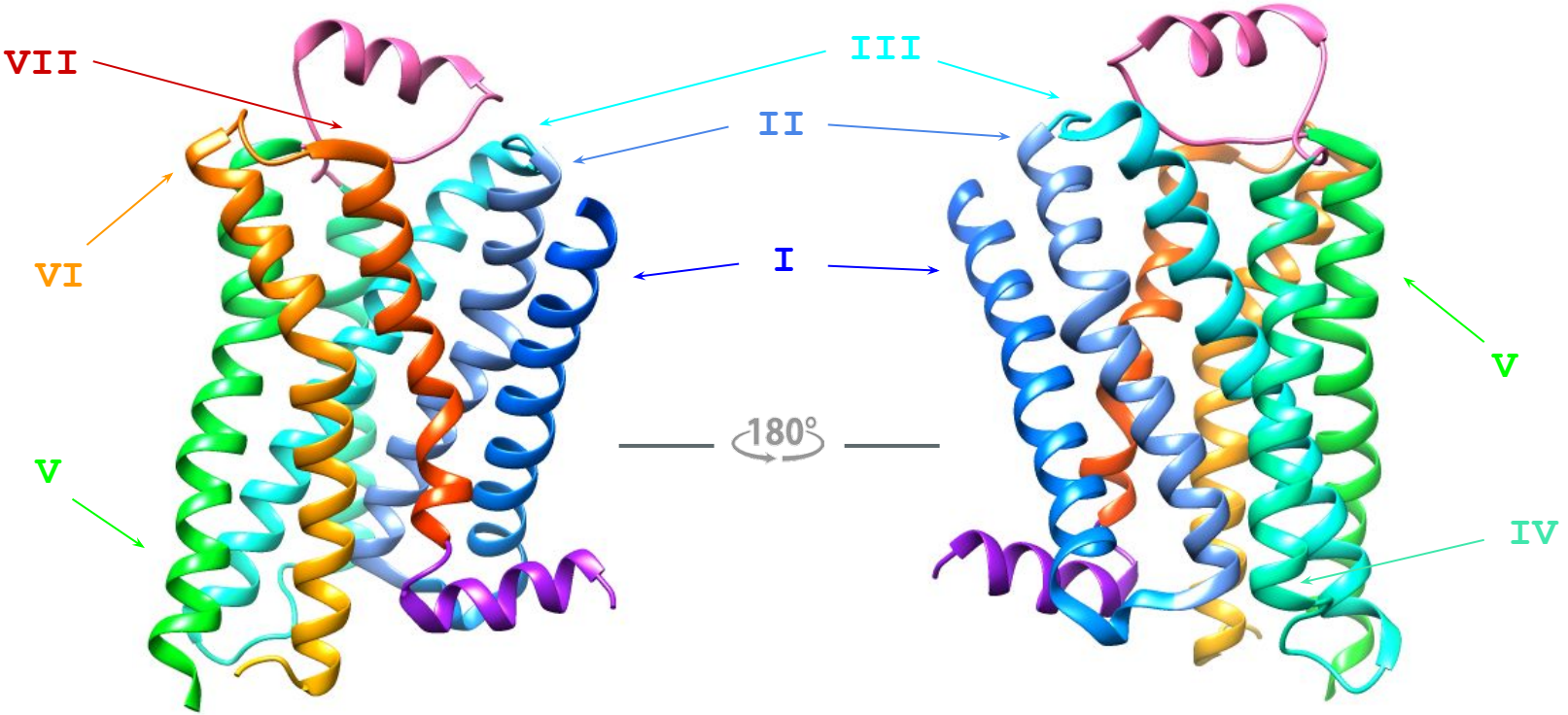
# Extra slides



# Multiple Choice Questions

1. How many Transmembrane domains does the ß-2 AR have?
   a. 1
   b. 3
   c. 4
   d. **7**
   e. 10
2. Which ß-2AR has the most similar sequence to the human? **Gorilla gorilla**
   a. Mouse
   b. Dog
   c. **Gorilla**
   d. Macaque
   e. Hamster
3. Which helix undergoes a distortion in the active state? **H7**
   a. H1
   b. ECL2
   c. H8
   d. H2
   e. **H7**
4. Which agonist has less affinity for the ß-2AR? **Adrenaline**
   a. **Adrenaline**
   b. HBI
   c. BI167107
   d. Alprenelol
   e. ICI 118.551
5. Which moiety does BI167107 lack despite being the agonist with most affinity for ß-2AR?
   a. Pyrrole
   b. Carbamate
   c. Phenyl
   d. **Catechol**
   e. Lactone
6. Which kind of interaction is established between the Phe290 of the receptor and the aromatic ring of alprenolol?
   a. Hydrogen bond
   b. **Pi interaction**
   c. Salt bridge
   d. Ionic bond
   e. Covalent bond
7. Which region is not implied in the interactions between the receptor and the Gs protein?
   a. H6
   b. ICL2
   c. **H8**
   d. H5
   e. H3
8. Which residues form the Hydrogen Bond Network of the binding pocket of the receptor?
   a. Asp 113
   b. Tyr 316
   c. Les dues anteriors són correctes
   d. Asn 312
   e. **Totes les anteriors són correctes**
9. In which superfamily does SCOP include ß2AR? **GPCRs**
   a. Adrenergic receptors
   b. **GPCRs**
   c. SPFHs
   d. Ras
   e. Secretins
10. Which is not an attribute of ß2AR?
    a. It has basal activity
    b. It is tilted 20° in the plane of the membrane
    c. It has 7 transmembrane domains
    d. **It has interactions between its N-terminus and ECL2 domain**
    e. It binds different ligands

# 2.2. Structure: Fold explanation



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CLUSTAL 2.1 multiple sequence alignment


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Mesocricetos_auratus        ---MGPPGNDSDFLLTTNGSHVPDHDVTEERDEAWVVGMAILMSVIVLAI
Mus_musculus                ---MGPHGNDSDFLLAPNGSRAPDHDVTQERDEAWVVGMAILMSVIVLAI
Rattus_norvegicus           ---MEPHGNDSDFLLAPNGSRAPGHDITQERDEAWVVGMAILMSVIVLAI
Homo_sapiens                ---MGQPGNGSAFLLAPNGSHAPDHDVTQERDEVWVVGMGIVMSLIVLAI
Gorilla_gorilla             ---MGQPGNGSAFLLAPNGSHAPDHDVTQERDEVWVVGMGIVMSLIVLAI
Macaco_mullata              ---MGQPGNGSAFLLAPNGSHAPDHDVTQERDEAWVVGMGIVMSLIVLAI
Macaca_fascicularis         ---MGQPGNGSAFLLAPNGSHAPDHDVTQERDEAWVVGMGIVMSLIVLAI
Cavia_porcellus             ---MGHLGNGSDFLLAPNASHAPDHNVTRERDEAWVVGMAIVMSLIVLAI
Heterocephalus              ---MGHLGNGSDFLLAPNTSYAPDRNVTQERDEAWVVGMAIVMSLIVLAI
Felis_catus                 ---MGQPGNRSVFLLAPNGSHAPDQDGTQERNDAWVVGMGIVMSLIVLAI
Canis_lupus_familiaris      ---MGQPANRSVFLLAPNGSHAPDQGDSQERSEAWVVGMGIVMSLIVLAI
Bos_taurus                  ---MGQPGNRSVFLLAPNASHAPDQNVTLERDEAWVVGMGILMSLIVLAI
Sus_scrofa                  ---MGQPGNRSVFLLAPNGSHAPDQDVPQERDEAWVVGMAIVMSLIVLAI
Meriones_ungliculatus       ------------------------------------------------------
Oncorhynchus_mykiss         MENVSTPAVFNLSDLSVEMNSSSRQWSYSEYSEAVALLGILMALLVMCI


Tscheriskia_triton          VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Mesocricetos_auratus        VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Mus_musculus                VFGNVLVITAIAKFERLQTVTNYFIISLACADLVMGLAVVPFGASHILMK
Rattus_norvegicus           VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Homo_sapiens                VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGAAHILMK
Gorilla_gorilla             VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGAAHILMK
Macaco_mullata              VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGAAHILMK
Macaca_fascicularis         VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGAAHILMK
Cavia_porcellus             VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMN
Heterocephalus              VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Felis_catus                 VFGNVLVITAIARFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Canis_lupus_familiaris      VFGNVLVITAIARFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Bos_taurus                  VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGACHILMK
Sus_scrofa                  VFGNVLVITAIAKFERLQTVTNYFITSLACADLVMGLAVVPFGASHILMK
Meriones_ungliculatus       ----------------------------LACAGLVMGLAVVPFGASHILMN
Oncorhynchus_mykiss         VFGNVLVITAIVRFQRLQTVTNMFITSLACADLVMGLLVVPFGACYILLN
                                                         ****.***** ******.:**::


Tscheriskia_triton          MWNFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYIAITSPFKYQSLLTK
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Mus_musculus                MWNFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYVAITSPFKYQSLLTK
Rattus_norvegicus           MWNFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYVAITSPFKYQSLLTK
Homo_sapiens                MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLTK
Gorilla_gorilla             MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLTK
Macaco_mullata              MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLTK
Macaca_fascicularis         MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLTK
Cavia_porcellus             MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLTK
Heterocephalus              MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLTK
Felis_catus                 MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLTK
Canis_lupus_familiaris      MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYFAITSPFKYQSLLTK
Bos_taurus                  MWTFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYLAITSPFKYQCLLTK
Sus_scrofa                  MWTFGSFWCEFWISIDVLCVTASIETLCVIAVDRYLAITSPFKYQCLLTK
Meriones_ungliculatus       MWNFGNFWCEFWTSIDVLCVTASIETLCVIAVDRYIAITAPFKYQSLLTK
Oncorhynchus_mykiss         TWHFGSFLCEFWTAADVLCVTASIETLCVIALDRYLAITSPLRYPSLLTK
                             * **.* **** : ****************:***.***:*::* .****


Tscheriskia_triton          NKARMVILMVWIVSGLTSFLPIQMHWYRATHEKAITCYRNETCCDFFTNQ
Mesocricetos_auratus        NKARMVILMVWIVSGLTSFLPIQMHWYRATHQKAIDCYHKETCCDFFTNQ
Mus_musculus                NKARVVILMVWIVSGLTSFLPIQMHWYRATHKKAIDCYTEETCCDFFTNQ
Rattus_norvegicus           NKARVVILMVWIVSGLTSFLPIQMHWYRATHKQAIDCYAKETCCDFFTNQ
Homo_sapiens                NKARVIILMVWIVSGLTSFLPIQMHWYRATHQEAINCYANETCCDFFTNQ
Gorilla_gorilla             NKARVIILMVWIVSGLTSFLPIQMHWYRATHQEAINCYANETCCDFFTNQ
Macaco_mullata              NKARVIILMVWIVSGLTSFLPIQMHWYRATHQEAINCYAKETCCDFFTNQ
Macaca_fascicularis         NKARVIILMVWIVSGLTSFLPIQMHWYRATHQEAINCYAKETCCDFFTNQ
Cavia_porcellus             NKARVVILMVWVVSGLTSFLPIQMHWYRATHKDAINCYAEETCCDFFTNQ
Heterocephalus              NKARVVILMVWVVSGLTSFLPIQMHWYRATHQEAINCYAKETCCDFFTNQ
Felis_catus                 NKARVVILMVWIVSGLTSFLPIQMHWYRATHQEAINCYAKETCCDFFTNQ
Canis_lupus_familiaris      NKARVVILMVWIVSGLTSFLPIQMHWYRATHQEAINCYAKETCCDFFTNQ
Bos_taurus                  NKARVVILMVWIVSGLTSFLPIQMHWYRASHKEAINCYAKETCCDFFTNQ
Sus_scrofa                  NKARVVILMVWVVSGLISFLPIKMHWYQATHREALNCYAEEACCDFFTNQ
Meriones_ungliculatus       NKARVVILMVWIVSGLTSFLPIQMHWYRATNKEAITCYTNETCCDFFTNQ
Oncorhynchus_mykiss         RKACVVVVTVWGVAALISFLPIHMKWWVSDEPEALSCLEDAHCCDFNTNA
                            .** :::: ** *:.* *****:*:*: : . .*: *  .  **** **


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Mesocricetos_auratus        AYAIASSIVSFYVPLVVMVFVYSRVFQVAKRQLQKIDKSEGRFHSPNLGQ
Mus_musculus                AYAIASSIVSFYVPLVVMVFVYSRVFQVAKRQLQKIDKSEGRFHAQNLSQ
Rattus_norvegicus           AYAIASSIVSFYVPLVVMVFVYSRVFQVAKRQLQKIDKSEGRFHAQNLSQ
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Gorilla_gorilla             AYAIASSIVSFYVPLVIMVFVYSRVFQEAKRQLQKIDKSEGRFHVQNLSQ
Macaco_mullata              AYAIASSIVSFYVPLVIMVFVYSRVFQEAKRQLQKIDKSEGRFHAQNLSQ
Macaca_fascicularis         AYAIASSIVSFYVPLVIMVFVYSRVFQEAKRQLQKIDKSEGRFHAQNLSQ
Cavia_porcellus             AYAIASSIVSFYLPLVVMVFVYSRVFQVAKKQLQKIDRSEGRFHTQNLSQ
Heterocephalus              AYAIASSIVSFYLPLVVMVFVYSRVFQVAKRQLQKIDRSEGRFHTQNLSQ
Felis_catus                 AYAIASSIVSFYLPLVVMVFVYSRVFQVAQRQLQKIDKSEGRFHAQNLSQ
Canis_lupus_familiaris      AYAIASSIVSFYLPLVVMVFVYSRVFQVAQRQLQKIDRSEGRFHAQNLSQ
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Sus_scrofa                  PYAIASSIVSFYLPLVVMVFVYSRVFQVARRQLQKIDKSEGRFHAQNLSQ
Meriones_ungliculatus       AYAIASSIVSFYVPLVVMVFVYSRVFQVAKRQLQKIDKSEGRFHAQNLSQ
Oncorhynchus_mykiss         AYAVASSVVSFYIPLAVMAFVYGRVFQEARKQLEKIRGSEGRFHAQMIDN
                            .**:***:****:**.:*.***.**** *::**:**  ******   :.:


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Homo_sapiens                VE-----QDGRTGHGLRRSSKFCLKEHKALKTLGIIMGTFTLCWLPFFIV
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Macaco_mullata              VE-----QDGRTGHGLRRSSKFCLKEHKALKTLGIIMGTFTLCWLPFFIV
Macaca_fascicularis         VE-----QDGRTGHGLRRSSKFCLKEHKALKTLGIIMGTFTLCWLPFFIV
Cavia_porcellus             VE-----QDGRSGHGLRRSSKFYLKEHKALKTLGIIMGTFTLCWLPFFIV
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Felis_catus                 VE-----QDGRSGHGHRRASKFCLKEHKALKTLGIIMGTFTLCWLPFFIV
Canis_lupus_familiaris      VE-----QDGRSGHGHRRSSKFCLKEHKALKTLGIIMGTFTLCWLPFFIV
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Sus_scrofa                  AE-----QDGRSGPGHRRSSKFCLKEHKALKTLGIIMGTFTLCWLPFFIV
Meriones_ungliculatus       VE-----QDGRSGHGLRRSSKFCLKEHKALKTLGIIMGTFTLCWLPFFIV
Oncorhynchus_mykiss         NQGQDGGDGSGGGGGNGKRPKFCLKEHKALKTLGIIMGTFTLCWLPFFVL
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Tscheriskia_triton          NIVHVIQENLIPKEVYILLNWLGYVNSAFNPLIYCRSPDFRIAFQELLCL
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Mus_musculus                NIVHVIRDNLIPKEVYILLNWLGYVNSAFNPLIYCRSPDFRIAFQELLCL
Rattus_norvegicus           NIVHVIRANLIPKEVYILLNWLGYVNSAFNPLIYCRSPDFRIAFQELLCL
Homo_sapiens                NIVHVIQDNLIRKEVYILLNWIGYVNSGFNPLIYCRSPDFRIAFQELLCL
Gorilla_gorilla             NIVHVIQDNLIRKEVYILLNWIGYVNSGFNPLIYCRSPDFRIAFQELLCL
Macaco_mullata              NIVHVIQDNLIPKEVYILLNWVGYVNSGFNPLIYCRSPDFRIAFQELLCL
Macaca_fascicularis         NIVHVIQDNLIPKEVYILLNWVGYVNSGFNPLIYCRSPDFRIAFQELLCL
Cavia_porcellus             NIVHVIQDNLIPKEVYILLNWVGYVNSAFNPLIYCRSPDFRIAFQELLCL
Heterocephalus              NIVHVIRDNLIPKEVYILLNWVGYVNSAFNPLIYCRSPDFRIAFQELLCL
Felis_catus                 NIVHVIQDNLIPKEVYILLNWVGYVNSAFNPLIYCRSPDFRIAFQELLCL
Canis_lupus_familiaris      NIVHVIQDNLIPKEVYILLNWVGYVNSAFNPLIYCRSPDFRIAFQELLCL
Bos_taurus                  NIVHVIKDNLIRKEIYILLNWLGYINSAFNPLIYCRSPDFRIAFQELLCL
Sus_scrofa                  NIVHGIHDNLIPKEVYILLNWVGYVNSAFNPLIYCRSPDFRMAFQELLCL
Meriones_unglicul atus      NVVHAIKENLIPKEVYILLNWLGYVNSAFNPLI----------------
Oncorhynchus_mykiss         NVVVTIWKVDNIKMPFRILNWIGYANSAFNPLIYCRSPEFRYAFQEILCL
                            *:*  *      *  : :***:** **.*****

Tscheriskia_triton          RRSSAKAYGNGYSSNSNGKSDYMGEASECQLRQEKESELLCEDPPGMESF
Mesocricetos_auratus        RRSSSKAYGNGYSSNSNGKTDYMGEASGCQLGQEKESERLCEDPPGTESF
Mus_musculus                RRSSSKTYGNGYSSNSNGRTDYTGEPNTCQLGQEREQELLCEDPPGMEGF
Rattus_norvegicus           RRSSSKTYGNGYSSNSNGRTDYTGEQSAYQLGQEKENELLCEEAPGMEGF
Homo_sapiens                RRSSLKAYGNGYSSN-----GNTGEQSGYHVEQEKENKLLCEDLPGTEDF
Gorilla_gorilla             RRSSLKAYGNGYSSN-----GNTGEQSGYHVEQEKENKLLCEDLPGTEDF
Macaco_mullata              RRSSLKACGNGYSSNSN---GNTGEQSGYHLEQEKENKLLCEDLPGTEDF
Macaca_fascicularis         RRSSLKACGNGYSSNSN---GNTGEQSGYHLEQEKENKLLCEDLPGTEDF
Cavia_porcellus             RRSALKAYGNDCSSNSNGKTDYTGEPNVCHQGQEKERELLCEDPPGTEDL
Heterocephalus              RRPSLKAYGNGYSSNSNGKTNYTGEPSVCHQGQEKERELLCEDPPGTEDF
Felis_catus                 RRSSLKAYGNGYSNNSNSRTDYAGEHSGGPLGQEKDSEVLCEDPPGTENL
Canis_lupus_familiaris      RRSSLKAYGNGYSNNSNSRSDYAGEHSGCHLGQEKDSELLCEDPPGTE--
Bos_taurus                  RRSSLKAYGNGCSSNSNDRTDYTGEQSGYHLGEEKDSELLCEDPPGTENF
Sus_scrofa                  HRSSLKAYGNGCSSNSNGRTDYTGEQSGCYLGEEKDSERLCEDAPGPEGC
Meriones_unglicul atus      ----------------------------------------------------
Oncorhynchus_mykiss         RGAAFPTNG--------------------YIYRGHSLRLSPKDKPGSLSN

Tscheriskia_triton          ANCQGTVPSLSLDSQGRNCSTNDSPL---
Mesocricetos_auratus        VNCQGTVPSLSLDSQGRNCSTNDSPL---
Mus_musculus                VNCQGTVPSLSVDSQGRNCSTNDSPL---
Rattus_norvegicus           VNCQGTVPSLSIDSQGRNCNTNDSPL---
Homo_sapiens                VGHQGTVPSDNIDSQGRNCSTNDSLL---
Gorilla_gorilla             VGHQGTVPSDNIDSQGRNCSTNDSLL---
Macaco_mullata              VGHQGTVPSDNIDSQGRSCSTNDSLL---
Macaca_fascicularis         VGHQGTVPSDNIDSQGRSCSTNDSLL---
Cavia_porcellus             VSCPGTVPSDSIDSQGRNYSTNDSLL---
Heterocephalus              VTCPGTVPSDSIDSQGRNCSTNDSLL---
Felis_catus                 ANRQGTVPNDSIDSQGQNGSTNDSLL---
Canis_lupus_familiaris      -DRQGTVPSDSVDSQGRNCSTNDSLL---
Bos_taurus                  VNQQGTVPSDSIDSQGRNCSTNDSLL---
Sus_scrofa                  AHRQGTVPDDSTDSQGRNCSTNDSML---
Meriones_unglicul atus      ----------------------------
Oncorhynchus_mykiss         NVGTVELGSLSSVTNINGYCNNPPLASIV
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BLAST result

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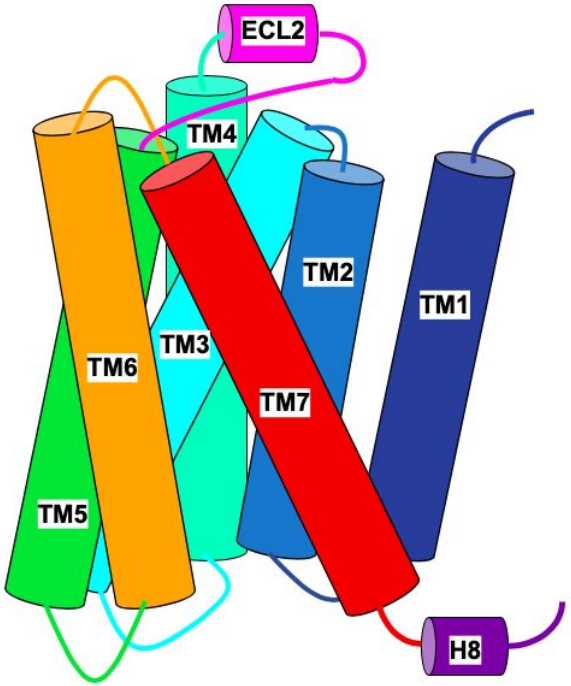
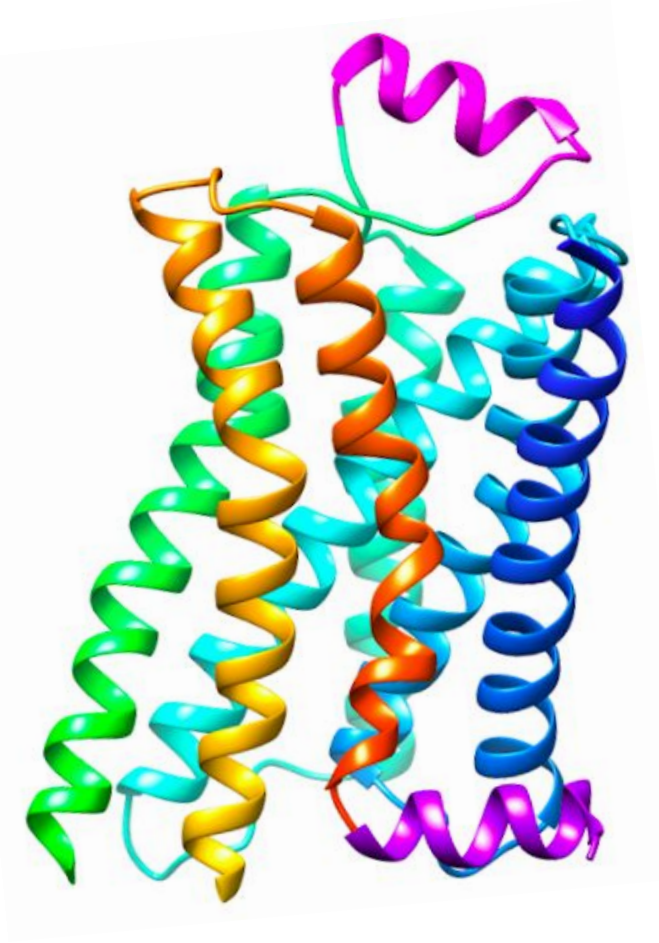
DRD1_HUMAN/40-331
5HT6R_RAT/43-320
ADRB1_HUMAN/75-377
AA1R_BOVIN/26-288
BRS3_CAVPO/64-330

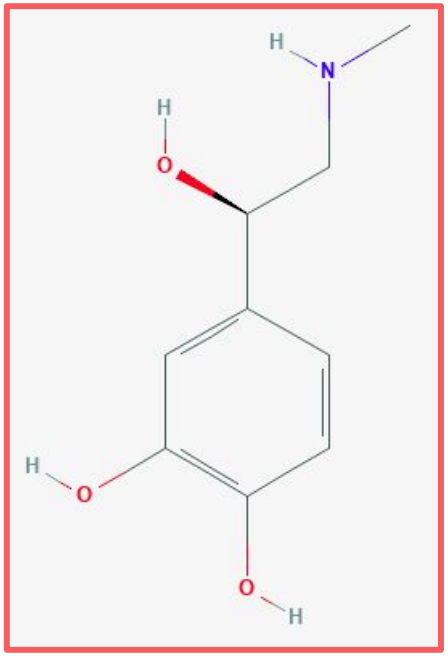



| Helix | Residue |
|---|---|
| I | 29-60 |
| II | 67-96 |
| III | 103-136 |
| IV | 147-171 |
| ECL2 | 172-196 |
| V | 197-229 |
| VI | 267-298 |
| VII | 305-328 |
| VIII | 330-341 |

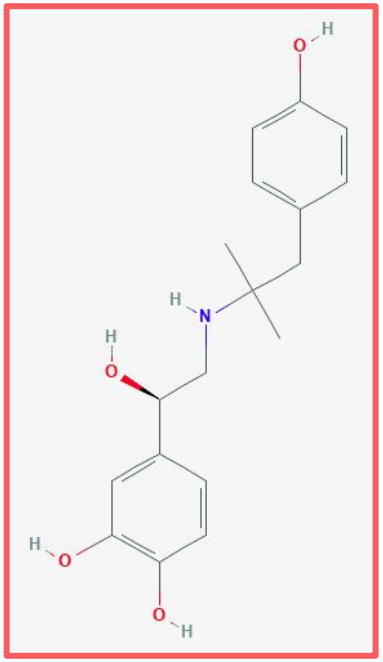


# 3.2. Agonists

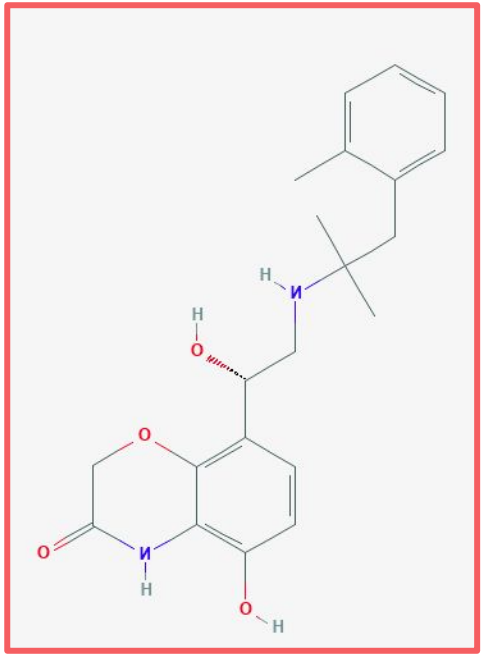
## Affinity



Adrenaline



HBI



BI167107