SnapShot: GPCR-Ligand Interactions

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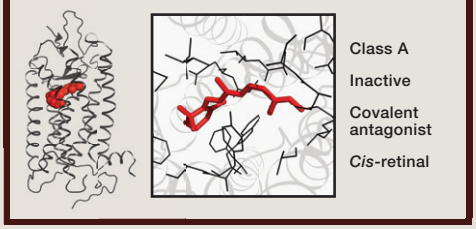
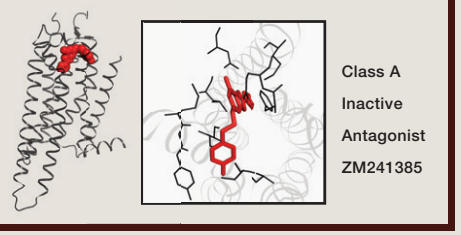
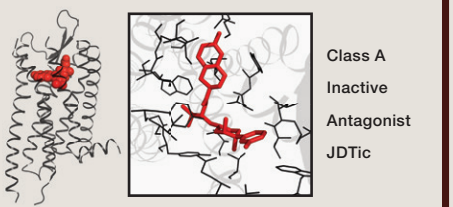
Cell

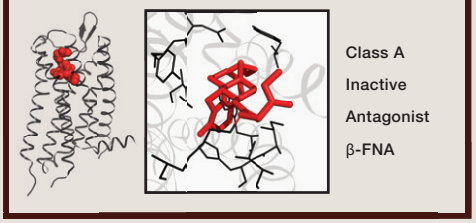
Rhodopsin

Class A
Inactive
Covalent antagonist
Cis-retinal

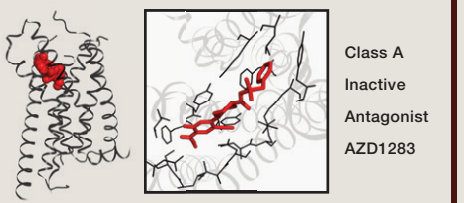
β_2AR

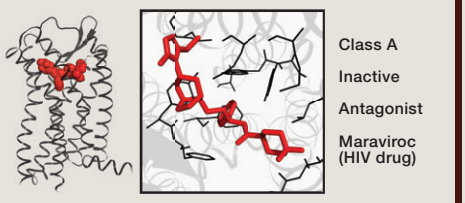
Class A
Inactive
Antagonist
Carazolol

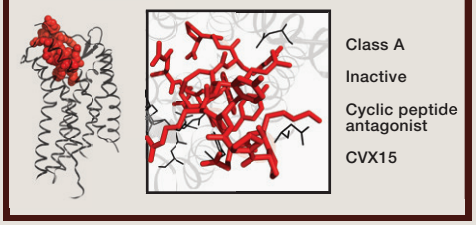
Adenosine A_{2A}R

Class A
Inactive
Antagonist
ZM241385

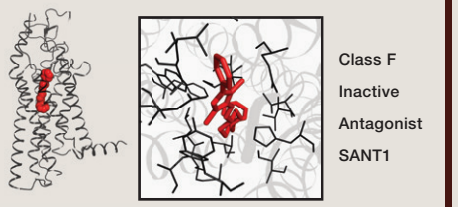
κ-opioid receptor

Class A
Inactive
Antagonist
JDTic

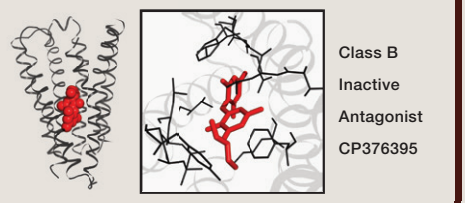
μ-opioid receptor

Class A
Inactive
Antagonist
β-FNA

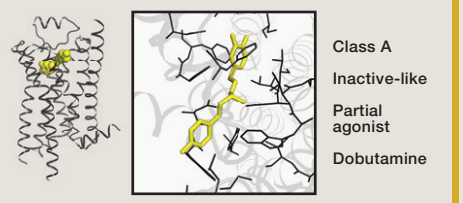
$P2Y_{12}R$

Class A
Inactive
Antagonist
AZD1283

Chemokine receptor CCR5

Class A
Inactive
Antagonist
Maraviroc (HIV drug)

Chemokine receptor CXCR4

Class A
Inactive
Cyclic peptide antagonist
CVX15

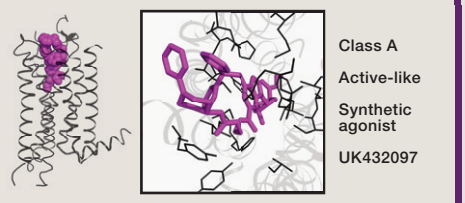
Smoothened receptor

Class F
Inactive
Antagonist
SANT1

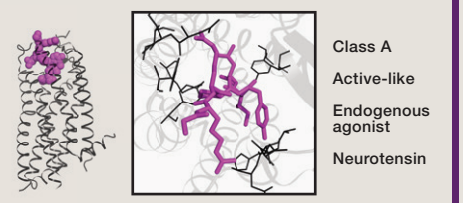
CRF_1R

Class B
Inactive
Antagonist
CP376395

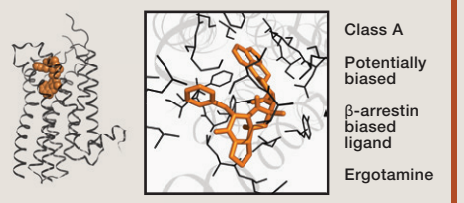
β_1AR

Class A
Inactive-like
Partial agonist
Dobutamine

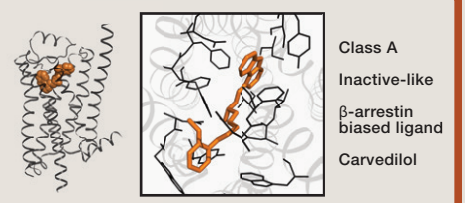
β_2AR

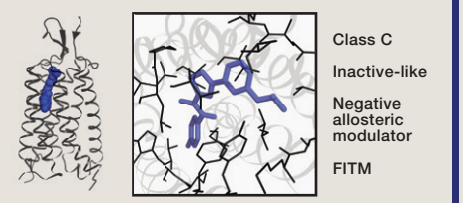
Class A
Active
Covalent agonist
Noradrenaline analog

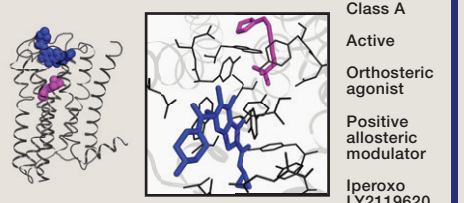
Adenosine A_{2A}R

Class A
Active-like
Synthetic agonist
UK432097

$NTSR_1$

Class A
Active-like
Endogenous agonist
Neurotensin

5-HT_{2B}

Class A
Potentially biased
β-arrestin biased ligand
Ergotamine

β_1AR

Class A
Inactive-like
β-arrestin biased ligand
Carvedilol

$mGluR_1$

Class C
Inactive-like
Negative allosteric modulator
FITM

M_2AchR

Class A
Active
Orthosteric agonist
Positive allosteric modulator
Iperoxo
LY2119620

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SnapShot: GPCR-Ligand Interactions

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Cell

G-protein-coupled receptors (GPCRs) are transmembrane proteins that participate in almost every physiological process, directly or indirectly. They constitute the largest class of drug targets in the human genome and yet eluded structural characterization for decades. High-resolution structure determination of GPCRs has undoubtedly been one of the key recent advances in the field of GPCR biology. In 2007, the human β_2 adrenergic receptor (β_2AR) was the first non-rhodopsin GPCR to be crystallized. The high-resolution crystal structure of β_2AR resulted from a decade of effort enabled by monumental methodological innovations. Since then, a number of GPCRs have been crystallized in inactive and active conformations. GPCRs can be divided into six subfamilies based on their sequence homology and functional similarity. Of these, subfamilies A, B, and C encompass the majority of GPCRs, and there are now structures from each of these subfamilies. Taken together, these crystallographic snapshots provide extensive structural coverage of the GPCR superfamily and allow direct comparison of structural features across its different members.

All GPCRs display a highly conserved seven transmembrane core architecture. However, they utilize a remarkably diverse ligand binding pocket architecture and ligand-receptor interactions. The chemical nature of the ligands bound to the crystallized GPCRs includes a covalently attached chromophore, small molecule synthetic ligands, peptides, a lipid mimetic, and clinically used drugs. In vivo, these ligands act as inverse agonists, partial agonists, full agonists, biased agonists, and allosteric modulators. The divergent chemical structure and functional attributes of these ligands are reflected in their remarkably different binding modes, which range from superficial association with the binding pocket to being deeply embedded in the core of the receptor. For example, the antagonist binding pocket in the CRF1 receptor differs remarkably from other GPCRs, and it is located very deep in the receptor core, almost in the cytoplasmic half of the receptor.

Once a ligand interacts with its target GPCR, it kicks off downstream signaling either through G-protein- or through β-arrestin-mediated pathways. Biased GPCR signaling, the ability of GPCRs to signal through either of these pathways, has opened up new potential avenues for therapeutics. First steps toward understanding the structural details of biased ligand-GPCR interactions have been provided by analysis of β1 adrenergic receptor (β_1AR) bound to a β-arrestin-biased ligand Carvedilol and 5-hydroxyltryptamine serotonin receptor 5-HT_{2B} bound to a β-arrestin-biased ligand Ergotamine. These structures have started to illuminate the ligand-receptor interactions that may contribute to generating bias at the receptor level, thereby dictating distinct signaling outcomes.

A major source of excitement with respect to structure determination of GPCRs has been the potential implications for better drug design and novel drug discovery. Interestingly, several GPCRs have been crystallized in complex with clinically used drugs. These drug-receptor complexes reveal atomic details of drug binding to their target GPCRs for the first time and provide a framework for further fine tuning potential drug candidates.

In addition to the ligands that occupy the conventional orthosteric binding pocket, crystal structures of a few GPCRs have been determined in the presence of allosteric ligands as well. These ligands bind at sites remote from the orthosteric ligand binding pocket and their binding influences affinities of orthosteric ligands and downstream, signaling outcomes either positively (positive allosteric modulators) or negatively (negative allosteric modulators). A particularly exciting example is the muscarinic acetylcholine M2 receptor ($mAchM_2R$) that is crystallized in complex with an orthosteric agonist and an allosteric modulator together.

Crystal structures of GPCRs have yielded long-awaited molecular snapshots of inactive and active signaling conformations. Visualization of ligand binding pockets at high resolution has opened up new avenues for structure-based novel drug design. In coming years, structure determination of GPCRs in additional activated conformations that are functionally distinct and high-resolution visualization of receptor-effector signaling complexes are likely to be at the forefront of research in GPCR biology. Here, we showcase selected GPCR structures that highlight the differences in mode of ligand binding and cover the diversity in pharmacological efficacy of bound ligands. The image displays representative structures from different subfamilies of GPCRs and also highlights key receptor-ligand interactions in the binding pocket.

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