Rhodopsin, Beta-2 Adrenergic Receptor, and Muscarinic Acetylcholine Receptor Micro-Switches

Rhodopsin

1) Ionic Lock

Arg 3.50 (Arg135) (R of (E/D)RY motif)

*Arg 3.50 (Arg 135) and Glu 6.30 (Glu 247) have a salt bridge between them, referred to as the ionic lock, and must be broken upon receptor activation.

-Inactive: Glu 3.49 (Glu 134)

-Active: Tyr 5.58 (Tyr 223)

2) Micro-switch

*Contributes to breaking ionic lock

Trp 6.48 (Trp 268) (W of CWxP motif)

-Inactive: (Chi 1 ~ -60 degrees): Structural H2O

-Active (Chi 1 ~ 180 degrees): Phe 5.47 (Phe 212)

3) Micro-switch

Tyr 7.53 (Tyr 306) (Y of NPxxY motif)

-Inactive: Phe VIII: 04 (Phe 313)

-Active: Hydrophobic Cluster

-Intermediate: Structural H2O (H-bond network)

4) Inactive Salt Bridge

Glu 3.28 (Glu 113) forms a salt bridge in the inactive state with Lys 7.43 (Lys 296) with Lys 7.43 being covalently attached to the retinal

5) Hydrogen Bonding Network

Glu 3.37 (Glu122), Trp 3.41 (Trp 126), and His 5.46 (His 211)

In Meta II: Glu 3.37 and His 5.46 form hydrogen bond

6) Molecular Switch

Glu 3.37 (Glu 122)

Inactive: bb carbonyl His 5.46 (His 211)

Active: S-nitrogen His 5.46 (His 211)

7) Molecular Switch

Asn 7.49 (Asn 302)

Inactive: H2O mediated H-bond Trp 6.48 (Trp 265)

Active: Asp 2.54 (Asp 83)

8) Salt bridge

Glu 6.28 (Glu 249) and Lys 311 (CT)

Beta-2 Adrenergic Receptor

1) Ionic Lock

Arg 3.50 (Arg 131) (R of (E/D)RY motif)

*Arg 3.50 (Arg 131) and Glu 6.30 (Glu 268) also have salt bridge, but not observed in model

-Inactive: Asp 3.49 (Asp 130)

-Active: Tyr 5.58 (Tyr 219)

2) Molecular Switch

Trp 6.48 (Trp 286) (W of CWxP motif)

-Inactive: (Chi 1 ~ -60 degrees): Structural H2O

-Active: (Chi 1 ~ 180 degrees): Phe 5.47 (Phe 208)

3) Molecular Switch

Tyr 7.53 (Tyr 326) (Y of NPxxY motif)

-Inactive: Phe VIII: 04 (Phe 332)

-Active: Hydrophobic Cluster

Intermediate: Structural H2O (H-bond network)

4) Zinc Binding

Asp 113 (salt bridge) and Asn 312 (H-bond) bond ligand's amine group

Asp 113 and Cys 312 allow for Zn2+ binding

Muscarinic Acetylcholine Receptor (M2)

1) Tyrosine Lid

Tyr 7.53 (Tyr 440)

-Active: Tyr 5.58 (Tyr 206) *close enogh for H2O mediated H-bond

*Y206F = No activation

2) Asp 3.49 (Asp 120)

-Active: Asn 2.39 (Asn 58) *Hydrogen bond

3) Asn 6.52 (Asn 404): Hydrogen bond with iperoxo

4) Ligand Binding

Tyr 6.51 (Tyr 403): h-bonds Tyr 3.33 (Tyr 104), h-bonds Tyr 7.39 (Tyr 426)

*Cation-π interaction with ligand amine

Tyr àPhe mutation: impaired agonist binding

5) Molecular Switch

Tyr 177 (ECL2), Trp 7.35 (Trp 422)

-3-layered aromatic stack with LY2119620 (allosteric modulator)