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Supplementary information

GPCR activation mechanisms across classes and macro/microscales

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Supplementary Table 1 | Representative structures of GPCRs and inactive and active states used as templates.

The structure annotation and criteria-based filtering to select these templates is shown in Supplementary Spreadsheet 1.

Cl	Receptor family	UniProt	IUPHAR	Inactive PDB ID	Active PDB ID	Inactive Ref.	Active Ref.
A	Adrenoceptors	ADA2B	α_{2B}		6K41		[1]
A	Cannabinoid	CNR1	CB_1		6N4B		[2]
A	Chemokine	CCR6	CCR6		6WWZ		[3]
A	Formylpeptide	FPR2	FPR2/ALX		6OMM		[4]
A	Neurotensin	NTR1	NTS1		6OS9		[5]
A	Adrenoceptors	ADRB2	β_2	2RH1	3SN6	[6]	[7]
A	Dopamine	DRD3	D_3	3PBL		[8]	
A	Histamine	HRH1	H_1	3RZE		[9]	
A	Lysophospholipid (S1P)	S1PR1	$S1P_1$	3V2Y		[10]	
A	Opioid	OPRK	κ	4DJH		[11]	
A	Opioid	OPRM	μ	4DKL	6DDE	[12]	[13]
A	Opioid	OPRD	δ	4N6H		[14]	
A	Acetylcholine (muscarinic)	ACM3	M_3	4U15		[15]	
A	Lysophospholipid (LPA)	LPAR1	LPA_1	4Z36		[16]	
A	Angiotensin	AGTR1	AT_1	4ZUD		[17]	
A	Acetylcholine (muscarinic)	ACM1	M_1	5CXV	6OIJ	[18]	[19]
A	Opioid	OPRX	NOP	5DHH		[20]	
A	Acetylcholine (muscarinic)	ACM4	M_4	5DSG		[18]	
A	Adenosine	AA2AR	A_{2A}	5NM4	5G53	[21]	[22]
A	Adenosine	AA1R	A_1	5UEN	6D9H	[23]	[24]
A	Dopamine	DRD4	D_4	5WIU		[25]	
A	Orexin	OX2R	OX_2	5WQC		[26]	
A	Endothelin	EDNRB	ETB	5X93		[27]	
A	Neuropeptide Y	NPY1R	Y_1	5ZBQ		[28]	
A	Acetylcholine (muscarinic)	ACM2	M_2	5ZKC	6OIK	[29]	[19]
A	Cannabinoid	CNR2	CB_2	5ZTY	6KPF	[30]	[31]
A	5-Hydroxytryptamine	5HT2A	$5\text{-}HT_{2A}$	6A94		[32]	
A	5-Hydroxytryptamine	5HT2C	$5\text{-}HT_{2C}$	6BQH		[33]	
A	Complement peptide	C5AR1	$C5a_1$	6C1R		[34]	
A	Dopamine	DRD2	D_2	6CM4		[35]	
A	Tachykinin	NK1R	NK_1	6HLP		[36]	
A	Ghrelin	GHSR	Ghrelin	6KO5		[37]	
A	Adrenoceptors	ADA2C	α_{2C}	6KUW		[38]	
A	Chemokine	CXCR2	CXCR2	6LFL	6LFO	[39]	[39]
A	Acetylcholine (muscarinic)	ACM5	M_5	6OL9		[40]	
A	Melatonin	MTR1A	MT_1	6PS8		[41]	
A	Orexin	OX1R	OX_1	6TOD		[42]	
A	Vasopressin and oxytocin	OXYR	OT	6TPK		[43]	
B1	Calcitonin	CALCR	CT		6NIY		[44]
B1	Calcitonin	CALRL	Calcitonin-like		6UVA		[45]
B1	Corticotropin-releasing factor	CRFR2	CRF2		6PB1		[46]
B1	Glucagon	SCTR	Secretin		6WZG		[47]
B1	VIP and PACAP	PACR	PAC1		6M1I		[48]
B1	VIP and PACAP	VIPR1	VPAC1		6VN7		[49]
B1	Corticotropin-releasing factor	CRFR1	CRF1	4K5Y	6P9X	[46]	[50]
B1	Glucagon	GLR	Glucagon	5EE7	6WPW	[51]	[52]
B1	Parathyroid hormone	PTH1R	PTH1		6NBH		[53]
B1	Glucagon	GLP1R	GLP-1	6LN2	6X18	[54]	[55]
C	Metabotropic glutamate	GRM1	$mGlu_1$	4OR2		[56]	
C	Metabotropic glutamate	GRM2	$mGlu_2$		7E9G		[57]
C	Metabotropic glutamate	GRM5	$mGlu_5$	6FFI		[58]	
C	GABAB	GABR1	$GABA_{B1}$	7C7S		[59]	
C	GABAB	GABR2	$GABA_{B2}$	7C7S	7C7Q	[59]	[59]
F	Frizzled	SMO	SMO	4JKV	6XBK	[60]	[61]
F	Frizzled	FZD4	FZD_4	6BD4		[62]	
F	Frizzled	FZD7	FZD_7	7EVW			[63]

Supplementary Table 2 | State-changing residue mutation potency and Emax values. Individual data points for the potency reduction and Emax values plotted and visualised in Figure 5.

Generic residue number	State contact difference	Gs pEC50 reduction (log units)	G15 pEC50 reduction (log units)	Gs Emax (%)	G15 Emax (%)
7x50	151	1.2	1.5	83	75
5x58	92	2.0	1.7	93	17
23x52	90	0.5	1.1	50	58
7x46	86	0.8	1.1	107	90
2x42	84	1.1	1.2	60	77
3x41	81	0.8	0.9	117	101
1x51	1	-0.2	0.1	99	99
3x42	1	0.0	0.2	47	39
4x51	1	0.4	0.4	85	91
4x52	1	0.7	0.6	76	93
6x61	1	-0.4	-0.1	102	98
3x51	0	0.8	0.3	73	87

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