

7TM receptors

Overview: Alongside the 7-transmembrane receptors listed in the Guide to Receptors and Channels, IUPHAR recognises a number of genes, which sequence analysis suggests code for 7-transmembrane receptors and for which an endogenous ligand has yet to be identified (Foord *et al.*, 2006).

Below are listed a number of these genes, for which preliminary evidence for an endogenous ligand has been published.

Gene Symbol (Ensembl ID)	Putative endogenous ligand	Comment
GPR17 (ENSG00000144230)	Dual leukotriene and UDP (Ciana <i>et al.</i> , 2006)	Also known as R12
GPR18 (ENSG00000125245)	N-Arachidonoylglycine, cannabinoid-like (Kohno <i>et al.</i> , 2006)	
GPR34 (ENSG00000171659)	Lysophosphatidylserine (Sugo <i>et al.</i> , 2006)	Has also been reported to respond to the phosphodiesterase inhibitor zaprinast (Taniguchi <i>et al.</i> , 2006)
GPR35 (ENSG00000178623)	Kynurenic acid (Wang <i>et al.</i> , 2006)	
GPR37 (ENSG00000170775)	Head activator (Rezgaoui <i>et al.</i> , 2006)	Also known as PAELR, EDNRLB
GPR39 (ENSG00000183840)	Obestatin (Zhang <i>et al.</i> , 2005) or Zn ²⁺ (Holst <i>et al.</i> , 2007)	
GPR55 (ENSG00000135898)	Cannabinoid-like (Baker <i>et al.</i> , 2006)	Also known as TGR7; potentially exists as a heteromer with MRGPRE (GPR167, ENSG00000184350) (Milasta <i>et al.</i> , 2006)
GPR119 (ENSG00000147262)	N-Oleylethanolamine (Overton <i>et al.</i> , 2006)	
GPR120 (ENSG00000186188)	Free fatty acids (Katsuma <i>et al.</i> , 2005; Hirasawa <i>et al.</i> , 2005)	
MRGPRD (ENSG00000172938)	β-Alanine (Shinohara <i>et al.</i> , 2004)	
MRGPRX1 (ENSG00000170255)	BAM8-22 (Chen and Ikeda, 2004)	Also known as SNSR4
MRGPRX2 (ENSG00000183695)	PAMP (Kamohara <i>et al.</i> , 2005), cortistatin (Robas <i>et al.</i> , 2003)	
OXGR1 (ENSG00000165621)	α-Ketoglutarate (He <i>et al.</i> , 2004)	Also known as GPR80, GPR99, P2Y15; Initially proposed to be a receptor for nucleotides
SUCNR1 (ENSG00000198829)	Succinate (He <i>et al.</i> , 2004)	

Further Reading

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* 57: 279–288.

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Citation Information

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Additional 'orphan' 7-transmembrane receptors

In the table below, putative 7-transmembrane receptors with as-yet unidentified endogenous ligands have been listed.

Symbol	Ensembl ID	Other names	Symbol	Ensembl ID	Other names
GPR1	ENSG00000183671		GPR115	ENSG00000153294	FLJ38076, PGR18
GPR3	ENSG00000181773	ACCA	GPR116	ENSG00000069122	DKFZp564O1923, KIAA0758
GPR4	ENSG00000177464	Proton-sensing, sphingosylphosphorylcholine	GPR123	ENSG00000197177	KIAA1828
			GPR124	ENSG00000020181	Tumour endothelial marker 5
GPR6	ENSG00000146360		GPR126	ENSG00000112414	FLJ14937
GPR10	ENSG00000119973		GPR127	ENSG00000186629	PGR16, EMR4
GPR12	ENSG00000132975	GPCR21	GPR128	ENSG00000144820	FLJ14454
GPR15	ENSG00000154165		GPR132	ENSG00000183484	G2A
GPR19	ENSG00000183150		GPR133	ENSG00000111452	PGR25
GPR20	ENSG00000204882		GPR136	ENSG00000124818	OPN5, neuropsin, PGR14
GPR21	ENSG00000188394		GPR137	ENSG00000173264	GPR137A, TM7SF1L1
GPR22	ENSG00000172209		GPR139	ENSG00000180269	PGR3
GPR25	ENSG00000170128		GPR140	ENSG00000172935	MRGPRE, GPR168, RTA
GPR26	ENSG00000154478		GPR141	ENSG00000187037	PGR13
GPR27	ENSG00000170837	SREB1	GPR142	ENSG00000196169	PGR2, KIF19
GPR31	ENSG00000120436		GPR143	ENSG00000101850	OA1
GPR32	ENSG00000142511		GPR144	ENSG00000180264	PGR24
GPR33	ENSMUSG00000035148	Pseudogene in man	GPR146	ENSG00000164849	PGR8
GPR37	ENSG00000170775	PAELR, EDNRLB	GPR148	ENSG00000173302	PGR6, brain and testis restricted GPCR
GPR45	ENSG00000135973	PSP24			PGR10, IEDA
GPR48	ENSG00000205213	Leucine-rich repeat-containing G-protein coupled receptor 4	GPR149	ENSG00000174948	PGR11
			GPR150	ENSG00000178015	PGR7, GALR4, GPCR-2037
GPR49	ENSG00000139292	LGR5, GPR67, FEX, HG38, MGC117008	GPR151	ENSG00000173250	PGR5
		H9	GPR152	ENSG00000175514	PGR1
GPR50	ENSG00000102195		GPR153	ENSG00000158292	NPS1, PGR14, GPRA
GPR52	ENSG00000203737		GPR154	ENSG00000187258	DEPDC3, DEP.7, FLJ31819, PGR22
GPR56	ENSG00000205336	TM7LN4, TM7XN1	GPR155	ENSG00000163328	PGR28, GABABL
GPR61	ENSG00000156097	BALGR			FLJ12132
GPR62	ENSG00000180929		GPR156	ENSG00000175697	KIAA1136
GPR63	ENSG00000112218	PSP24B	GPR157	ENSG00000180758	GPCR150, GPCR1
GPR64	ENSG00000173698	HE6	GPR158	ENSG00000151025	RE2
GPR65	ENSG00000140030	TDAG8	GPR160	ENSG00000173890	A-2, GRCA
GPR68	ENSG00000119714	OGR1, Proton-sensing	GPR161	ENSG00000143147	Olfactory receptor 51E1, prostate overexpressed G protein-coupled receptor
GPR70	ENSG00000173662	TAS1R1	GPR162	ENSG00000110811	
GPR71	ENSG00000179002	TAS1R2	GPR164	ENSG00000180785	
GPR72	ENSG00000123901	GPR83			
GPR75	ENSG00000119737	WI31133			
GPR77	ENSG00000134830	CSL2	GPR165	ENSMUSG00000031210	
GPR78	ENSG00000155269		GPR169	ENSG00000182170	Mas-related GPR, member G H963
GPR81	ENSG00000196917	TAGPCR, GPR104	GPR171	ENSG00000174946	PAR1, Porcine endogenous retrovirus A receptor 1
GPR82	ENSG00000171657		GPR172A	ENSG00000185803	Super conserved receptor expressed in brain 3
GPR84	ENSG00000139572	EX33			FKSG79
GPR85	ENSG00000164604	SREB2	GPR173	ENSG00000184194	TPRA40
GPR87	ENSG00000138271	GPR95			Gm1012, HB954
GPR88	ENSG00000181656	STRG	GPR174	ENSG00000147138	Protein wtless homolog, putative NFkB-activating protein 373
GPR90	ENSMUSG00000059408	Mas-related GPR, member H	GPR175	ENSG00000163870	KIAA1423, TMEM181
GPR97	ENSG00000182885	Pb99, PGR26	GPR176	ENSG00000166073	GPR158L1
GPR98	ENSG00000164199	VLGR1	GPR177	ENSG00000116729	Intimal thickness-related receptor
GPR101	ENSG00000165370				Epstein-Barr virus induced gene 2, lymphocyte-specific G protein-coupled receptor
GPR107	ENSG00000148358	KIAA1624, RP11-88G17, FLJ20998, LUSTR1	GPR178	ENSG00000146433	
GPR110	ENSG00000153292	hGPCR36, PGR19	GPR179	ENSG00000188888	
GPR111	ENSG00000164393	hGPCR35, PGR20	GPR180	ENSG00000152749	
GPR112	ENSG00000156920	RP1-299I16, PGR17			
GPR113	ENSG00000173567	hGPCR37, PGR23	EBI2	ENSG00000169508	
GPR114	ENSG00000159618	PGR27			

5-HT (5-Hydroxytryptamine)

5-HT receptors [nomenclature as agreed by NC-IUPHAR Subcommittee on 5-HT receptors (Hoyer *et al.*, 1994) and subsequently revised (Hartig *et al.*, 1996)] are, with the exception of the ionotropic 5-HT₃ class, 7TM receptors where the endogenous agonist is 5-HT. The diversity of 5-HT receptors is increased by alternative splicing that produces isoforms of the 5-HT_{2A} (non-functional), 5-HT_{2C} (non-functional), 5-HT₄, 5-HT₆ (non-functional) and 5-HT₇ receptors. RNA editing produces 5-HT_{2C} receptor isoforms that differ in function, such as efficiency and specificity of coupling to Gq/11 (reviewed by Sanders-Bush *et al.*, 2003; Bockaert *et al.*, 2006).

Nomenclature	5-HT _{1A}	5-HT _{1B}	5-HT _{1D}	5-HT _{1E}
Other names	—	5-HT _{1Dβ}	5-HT _{1Dα}	—
Ensembl ID	ENSG00000178394	ENSG00000135321	ENSG00000179546	ENSG00000168830
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Selective agonists (pK _i)	8-OH-DPAT (8.4–9.4), U92016A (9.7)	Sumatriptan (6.5–8.1) eletriptan (8.0), L694247 (9.2)	PNU109291 (9.0—gorilla, Ennis <i>et al.</i> , 1998) sumatriptan (8.0–8.7), eletriptan (8.9), L694247 (9.0, Wurch <i>et al.</i> , 1998) SB714786 (9.1) BRL15572 (7.9)	—
Selective antagonists (pK _i)	(±)WAY100635 (7.9–9.2), (S)-UH301 (7.9–8.6), NAD299 (robalzotan, 9.2)	SB236057 (8.2, inverse agonist, Middelmiss <i>et al.</i> , 1999), SB224289 (inverse agonist, 8.2–8.6), GR55562 (pK _B 7.4, Hoyer <i>et al.</i> , 2002)	—	—
Probes (K _D)	[³ H]WAY100635 (0.3 nM, Khawaja <i>et al.</i> , 1997), [³ H]NAD299 (0.16 nM), [³ H]8-OH-DPAT (0.4 nM), [¹¹ C]WAY100635 (PET ligand), p-[¹⁸ F]MPPF (PET ligand)	[³ H]Alniditan (2.0– 2.4 nM) [³ H]eletriptan (3 nM), [³ H]sumatriptan (11 nM) [¹²⁵ I]GTI, [³ H]GR125743 (2.6 nM, Xie <i>et al.</i> , 1999),	[³ H]Alniditan (1.2– 1.4 nM) [³ H]eletriptan (0.9 nM), [³ H]sumatriptan (7 nM), [¹²⁵ I]GTI, [³ H]GR125743 (2.8 nM, Xie <i>et al.</i> , 1999)	[³ H]5-HT (6 nM)

Nomenclature	5-HT _{1F}	5-HT _{2A}	5-HT _{2B}	5-HT _{2C}
Other names	5-HT _{1EB} , 5-HT ₆	D, 5-HT ₂	5-HT _{2F}	5-HT _{1C}
Ensembl ID	ENSG00000179097	ENSG00000102468	ENSG00000135914	ENSG00000147246
Principal transduction	G _{i/o}	G _{q/11}	G _{q/11}	G _{q/11}
Selective agonists (pK _i)	LY344864 (8.2, Phebus <i>et al.</i> , 1997) LY334370 (8.7)	DOI (7.4–9.2)	DOI (7.6–7.7), Ro600175 (8.3), BW723C86 (7.3–8.6)	DOI (7.2–8.6), Ro600175 (7.7–8.2) WAY163909 (8.0, Dunlop <i>et al.</i> , 2005)
Selective antagonists (pK _i)	—	ketanserin (8.1–9.7), MDL100907 (9.4)	RS127445 (9.0), EGIS- 7625 (9.0)	SB242084 (8.2–9.0), RS102221 (8.3–8.4)
Probes (K _D)	[³ H]LY334370 (0.5 nM), [¹²⁵ I]LSD	[³ H]ketanserin (0.2– 1.3 nM), [³ H]RP62203 (fananserin, 0.13 nM—rat, Malgouris <i>et al.</i> , 1993), [¹¹ C]M100907 (PET ligand), [¹⁸ F]altanserin (PET ligand)	[³ H]5-HT (8 nM—rat)	[³ H]mesulergine (0.5–2.2 nM), [³ H]LSD

Nomenclature	5-HT ₄	5-HT _{5A}	5-HT _{5B}	5-HT ₆
Other names	—	5-HT _{5α}	—	—
Ensembl ID	ENSG00000164270	ENSG00000157219	ENSMUSG00000050534	ENSG00000158748
Principal transduction	G _s	G _i /G _o ?	None identified	G _s
Selective agonists (pK _i)	BIMU8 (7.3), ML10302 (7.9–9.0), RS67506 (8.8—guinea-pig, Eglen <i>et al.</i> , 1995)	—	—	—
Selective antagonists (pK _i)	GR113808 (9.3–10.3), SB204070 (9.8–10.4), RS100235 (8.7–12.2)	SB699551 (8.2)	—	SB271046 (8.9), SB357134 (8.5, Bromidge <i>et al.</i> , 2001), Ro630563 (7.9–8.4)
Probes (K _D)	[³ H]GR113808 (50–200 pM), [¹²⁵ I]SB207710 (86 pM— piglet, Brown <i>et al.</i> , 1993), [³ H]RS57639 (0.25 nM— guinea-pig, Bonhaus <i>et al.</i> , 1997)	[³ H]5-CT (2.5 nM), [¹²⁵ I]LSD (0.2 nM)	[³ H]5-CT, [¹²⁵ I]LSD	[¹²⁵ I]SB258585 (1.0 nM, Hirst <i>et al.</i> , 2000), [³ H]Ro630563 (5 nM, Boess <i>et al.</i> , 1998), [³ H]5-CT, [¹²⁵ I]LSD (2 nM)

Nomenclature	5-HT ₇
Other names	5-HT _X , 5-HT ₁ -like
Ensembl ID	ENSG00000148680
Principal transduction	G _s
Selective agonists	—
Selective antagonists (pK _i)	SB656104 (8.7, Forbes <i>et al.</i> , 2002), SB269970 (8.6–8.9 Thomas <i>et al.</i> , 2000), SB258719 (7.5)
Radioligands (K _D)	[³ H]SB269970 (1.2 nM, Thomas <i>et al.</i> 2000), [³ H]5-CT (0.4 nM, Thomas <i>et al.</i> , 2000) [³ H]LSD (3 nM), [³ H]5-HT (1–8 nM)

Tabulated pK_i and K_D values refer to binding to human 5-HT receptors unless indicated otherwise. Unreferenced values are extracted from the NC-IUPHAR database (<http://www.iuphar-db.org>). The nomenclature of 5-HT_{1B}/5-HT_{1D} receptors has been revised (Hartig *et al.*, 1996). Only the non-rodent form of the receptor was previously called 5-HT_{1D}. The human 5-HT_{1B} receptor (tabulated) displays a different pharmacology to the rodent form of the receptor due to Thr335 of the human sequence being replaced by Asn in rodent receptors. NAS181 is a selective antagonist of the rodent 5-HT_{1B} receptor. Fananserin and ketanserin bind with high affinity to dopamine D₄ and histamine H₁ receptors respectively, in addition to 5-HT_{2A} receptors. The human 5-HT_{5A} receptor has been claimed to couple to several signal transduction pathways when stably expressed in C6 glioma cells (Noda *et al.*, 2003). The human orthologue of the mouse 5-HT_{5B} receptor is non-functional due to interruption of the gene by stop codons. In addition to the receptors listed in the table, an 'orphan' receptor, unofficially termed 5-HT_{1B}, has been described (Gershon, 1999).

Abbreviations: 5-CT, 5-carboxamidotryptamine; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)tetralin; BIMU8, (endo-*N*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dihydro-3-isopropyl-2-oxo-1*H*-benzimidazol-1-carboxamide hydrochloride; BRL15572, 3-[4-(3-chlorophenyl) piperazin-1-yl]-1,1-diphenyl-2-propanol; BW723C86, 1-[5-(2-thienylmethoxy)-1*H*-3-indolyl]propan-2-amine hydrochloride; EGIS-7625, 1-benzyl-4-[(2-nitro-4-methyl-5-amino)-phenyl]-piperazine; GR55562, 3-[3-(dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]benzamide; GR113808, [1-2]-(methylsulphonyl)amino]ethyl]-4-piperidinyl]methyl-1-methyl-1*H*-indole-3-carboxylate; GR125743, *n*-[4-methoxy-3-(4-methyl-1-piperidinyl)phenyl]-3-methyl-4-(4-pyridinyl)benzamide; GTI, 5-hydroxytryptamine-5-*O*-carboxymethylglycyltyrosinamide; L694247, 2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1*H*-indol-3-yl] ethanamine; LY334370, 5-(4-fluorobenzoyl)amino-3-(1-methylpiperidin-4-yl)-1*H*-indole fumarate; LY344864, *N*-[[(6*R*)-6-dimethylamino-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl]-4- fluorobenzamide; MDL100907, (+/-)-2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]; NAD299, (R)-3-*N*,*N*-dicyclobutylamino-8-fluoro-[6-3*H*]-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide; NAS181, (R)-(+)-2-[[[3-(morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl] morpholine methane sulfonate; p-[¹⁸F]MPPE, 4-(2'-methoxyphenyl)-1-[2'-(*N*-2"-pyridinyl)-p-fluorobenzamido]-ethyl piperazine; PNU109291, (S)-3,4-dihydro-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-methyl-1*H*-2-benzopyran-6-carboximide; RP62203, 2-[3-(4-(4-fluorophenyl)-piperazinyl)propyl]naphto[1,8- *ca*]isothiazole-1,1-dioxide; Ro600175, (S)-2-(6-chloro-5-fluoroindol-1-yl)-1-methyl-ethylamine; Ro630563, 4-amino-*N*-[2,6-bis(methylamino)pyridin-4-yl]benzenesulphonamide; RS57639, 4-amino-5-chloro-2-methoxy benzoic acid 1-(3-[2,3-dihydrobenzo[1,4]dioxin-6-yl]-propyl)-piperidin-4-yl methyl ester; RS67506, 1-(4-amino-5-chloro-2-methoxyphenyl)-3-[1-(2-methyl sulphonylamino)ethyl-4-piperidinyl]-1-propanone hydrochloride; RS100235, 1-(8-amino-7-chloro-1,4-benzodioxan-5-yl)-5-((3-(3,4-dimethoxyphenyl)prop-1-yl)piperidin-4-yl)propan-1-one; RS102221, 8-[5-(5-amino 2,4-dimethoxyphenyl) 5-oxopentyl]-1,3,8-triazaspiro[4,5]decane-2,4-dione; RS127445, (2-amino-4-(4-fluoronaphthyl-1-yl)-6-isopropylpyrimidine); SB204070, 1-butyl-4-piperidinylmethyl-8-amino-7-chloro-1,4-benzodioxan-5-carboxylate; SB207710, 1-butyl-4-piperidinylmethyl-8-amino-7-iodo-1,4-benzodioxan-5-carboxylate; SB224289, 1'-methyl-5[[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)]biphenyl-4-yl]carbonyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4'-piperidine]oxalate; SB236057, 1'-ethyl-5-(2'-methyl-4'-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indol-3,4'-piperidine; SB242084, 6-chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-yl carbamoyl]indoline; SB258585, 4-iodo-*N*-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-benzenesulphonamide; SB258719, (R)-3-*N*-dimethyl-*N*-[1-methyl-3-(4-methylpiperidin-1-yl)propyl]benzene sulphonamide; SB269970, (R)-3-(2-(2-(4-methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulphonyl)phenol; SB271046, 5-chloro-*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulphonamide; SB357134, *N*-(2,5-dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulphonamide; SB656104, 6-((R)-2-[2-[4-(4-chloro-phenoxy)-piperidin-1-yl]-ethyl]-pyrrolidine-1-sulphonyl)-1*H*-indole hydrochloride; SB699551, 3-cyclopentyl-*N*-[2-(dimethylamino)ethyl]-*N*-[4'-[(2-phenylethyl)amino]-methyl]-4-biphenyl]methyl]propanamide dihydrochloride; SB714786, 2-methyl-5-((2-[4-(8-quinolinylmethyl)-1-piperazinyl]ethyl)oxy)quinoline; UH301, 5-fluoro-8-hydroxy-2-(dipropylamino) tetralin; U92016A, (+/-)-(R)-2-cyano-*N,N*-dipropyl-8-amino-6,7,8,9-tetrahydro-3*H*-benz[e]indole; WAY100635, *N*-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-*N*-(2-pyridyl)-cyclohexanecarboxamide trichloride; WAY163909, (7*bR*, 10*aR*)-1,2,3,4,8,9,10,10a-octahydro-7*bH*-cyclopenta-[*b*][1,4]diazepino[6,7,1*hi*]indole

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Acetylcholine (muscarinic)

Overview: Muscarinic acetylcholine receptors (nomenclature as agreed by NC-IUPHAR sub-committee on Muscarinic Acetylcholine Receptors, Caulfield and Birdsall, 1998) are 7TM receptors of the rhodopsin-like family where the endogenous agonist is acetylcholine. In addition to the agents listed in the table, AC-42 and desmethylclozapine have been described as selective agonists of the M₁ receptor subtype *via* binding to a site distinct to that recognised by non-selective agonists (Spalding *et al.*, 2002; Sur *et al.*, 2003). There are two allosteric sites on muscarinic receptors, one defined by it binding gallamine, strychnine and brucine and the other binds KT5720, WIN62,577, WIN51,708 and staurosporine (Lazareno *et al.*, 2000, 2002). There are selective enhancers of acetylcholine binding and action; brucine and KT5720 at M₁ receptors, PG135 at M₂ receptors, N-chloromethylbrucine and WIN62,577 at M₃ receptors and thiochrome at M₄ receptors (Birdsall and Lazareno, 2005). The allosteric site for gallamine and strychnine on M₂ receptors can be labelled by [³H]dimethyl-W84 (Tränkle *et al.*, 2003). THRX-160209 is a multivalent ligand that may achieve its selectivity for M₂ receptors by binding both to the orthosteric and a nearby allosteric site (Steinfeld *et al.*, 2007).

Nomenclature	M ₁	M ₂	M ₃
Ensembl ID	ENSG00000168539	ENSG00000181072	ENSG00000133019
Principal transduction	G _{q/11}	G _{i/o}	G _{q/11}
Antagonists	MT7 (11.0), 4-DAMP (9.2), triptamine (8.8), darifenacin (8.3), pirenzepine (6.3–8.3), guanylpirenzepine (7.7), AFDX384 (7.3–7.5), MT3 (7.1), himbacine (6.7–7.1), AFDX116 (6.2)	triptamine (9.6), AFDX384 (8.0–9.0), 4-DAMP (8.4), himbacine (7.9–8.4), darifenacin (7.3–7.6), AFDX116 (6.7–7.3), pirenzepine (4.9–6.4), MT7 (<6), MT3 (<6), guanylpirenzepine (5.6)	4-DAMP (9.3), darifenacin (9.1), AFDX384 (7.2–7.8), triptamine (7.1–7.4), himbacine (6.9–7.2), pirenzepine (5.6–6.7), guanylpirenzepine (6.5), AFDX116 (6.1), MT3 (<6), MT7 (<6)
Probes (K _D)	[³ H]NMS (80–150 pM), [³ H]QNB (15–60 pM), [³ H]pirenzepine (3–15 nM), (R,R)-quinuclidinyl-4-[¹⁸ F]-fluoromethyl-benzilate (PET ligand), [¹¹ C]xanomeline (PET ligand), [¹¹ C]butylthio-TZTP (PET ligand)	[³ H]NMS (200–400 pM), [³ H]QNB (20–50 pM), [¹⁸ F]FP-TZTP (PET ligand),	[³ H]NMS (150–250 pM), [³ H]QNB (30–90 pM), [³ H]darifenacin (300 pM)

Nomenclature	M ₄	M ₅
Ensembl ID	ENSG00000180720	ENSG00000184984
Principal transduction	G _{i/o}	G _{q/11}
Antagonists	4-DAMP (8.9), MT3 (8.7), AFDX384 (8.0–8.7), AFDX116 (7–8.7), himbacine (7.9–8.2), triptamine (7.8–8.2), darifenacin (8.1), pirenzepine (5.9–7.6), guanylpirenzepine (6.5), MT7 (<6)	4-DAMP (9.0), darifenacin (8.6), triptamine (7.3–7.5), guanylpirenzepine (6.8), pirenzepine (6.2–6.9), himbacine (5.4–6.5), AFDX384 (6.3), AFDX116 (5.3–5.6), MT3 (<6), MT7 (<6)
Probes (K _D)	[³ H]NMS (50–100 pM), [³ H]QNB (20–80 pM)	[³ H]NMS (500–700 pM), [³ H]QNB (20–60 pM)

Antagonist data tabulated are pK_i values determined for human recombinant receptors. MT3 (m4-toxin) and MT7 (m1-toxin1) are toxins contained with the venom of the Eastern green mamba (*Dendroaspis augusticeps*) (see Bradley, 2000; Potter *et al.*, 2004).

Abbreviations: **4-DAMP**, 4-diphenylacetoxy-N-methylpiperidine methiodide; **AC-42**, 4-*n*-butyl-1-[4-(2-methylphenyl)-4-oxo-1-butyl]-piperidine hydrogen chloride; **AFDX116**, (otenzepad), 1-[2-[2-(diethylaminomethyl)piperidin-1-yl]acetyl]-5*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one; **AFDX384**, (±)-5,11-dihydro-11-[(2-[2-[dipropylamino)methyl]-1-piperidinyl)ethyl]amino)carbonyl]-6*H*-pyrido[2,3-*b*](1,4)benzodiazepine-6-one; **Butylthio-TZTP**, butylthio-thiadiazolyltetrahydro-1-methyl-pyridine; **Dimethyl-W84**, N,N'-bis[3-(1,3-dihydro-1,3-dioxo-4-methyl-2*H*-isoindol-2-yl)propyl]-N,N',N'-tetramethyl-1,6-hexanediaminium diiodide; **FP-TZTP**, [3-(3-(3-Fluoropropyl)thio)-1,2,5-thiadiazol-4-yl]1,2,5,6-tetrahydro-1-methylpyridine; **KT5720**, (9*S*,10*S*,12*R*)-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-9,12-epoxy-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*l*][1,6]benzodiazocine-10-carboxylic acid hexyl ester; **NMS**, N-methylscopolamine; **PG135**, (3*aS*,12*R*,12*aS*,12*bR*)-2-amino-2,3,3*a*,4,11,12*a*,12*b*-octahydro-10-hydroxyisoquino[2,1,8-*lma*]carbazol-5(1*H*)-one hydrochloride; **QNB**, 3-quinuclidinylbenzilate; **THRX160209**, 4-[N-[7-(3-(*S*)-(1-carbamoyl-1,1-diphenylmethyl)pyrrolidin-1-yl)hept-1-yl]-N-(*n*-propyl)amino]-1-(2,6-dimethoxy-benzyl)piperidine; **WIN51,708**, 17-β-hydroxy-17-α-ethynyl-5-α-androstano[3,2-*b*]pyrimido[1,2-*a*]benzimidazole; **WIN62,577**, 17-β-hydroxy-17-α-ethynyl-Δ⁴-androstano[3,2-*b*]pyrimido[1,2-*a*]benzimidazole

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Adenosine

Overview: Adenosine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adenosine Receptors; Fredholm *et al.*, 2001) are activated by the endogenous ligand adenosine (potentially inosine also at A₃ receptors). NECA is a non-selective agonist, while XAC and CGS15943 display submicromolar affinity at all four adenosine receptors (Klotz *et al.*, 1998; Ongini *et al.*, 1999).

Nomenclature	A ₁	A _{2A}	A _{2B}	A ₃
Ensembl ID	ENSG00000163485	ENSG00000128271	ENSG00000170425	ENSG00000121933
Principal transduction	G _{i/o}	G _s	G _s	G _{i/o}
Selective agonists	CPA, CCPA, S-ENBA, GR79236	CGS21680, HENECA, ATL-146e (Peirce <i>et al.</i> , 2001)	Bay60-6583 (Eckle <i>et al.</i> , 2007)	2-Cl-IB-MECA, IB-MECA
Selective antagonists	DPCPX (8.5)	ZM241385 (9.0), SCH58261 (7.9–9.5)	MRS1754 (8.7), MRS1706 (8.4), PSB1115 (7.7)	MRS1220 (8.8), VUF5574 (8.4, van Muijlwijk-Koezen <i>et al.</i> , 2000), MRS1523 (7.7), MRS1191 (7.0)
Probes	[³ H]-CCPA, [³ H]-DPCPX (0.6–1.2 nM)	[³ H]-CGS21680, [³ H]-ZM241385 (0.8 nM)	[³ H]-MRS1754 (1.1 nM)	[¹²⁵ I]-AB-MECA (0.6 nM)

Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A_{2B} adenosine receptor (ENSG00000182537) with 79% identity to the A_{2B} adenosine receptor cDNA coding sequence, but which is unable to encode a functional receptor (Jacobson *et al.*, 1995). DPCPX also exhibits antagonism at A_{2B} receptors (pK_i ca. 7, Alexander *et al.*, 1996; Klotz *et al.*, 1998). HENECA also shows activity at A₃ receptors (Varani *et al.*, 1998). Antagonists at A₃ receptors exhibit marked species differences, such that only MRS1523 and MRS1191 are selective at the rat A₃ receptor. In the absence of other adenosine receptors, [³H]-DPCPX and [³H]-ZM241385 can also be used to label A_{2B} receptors (K_D ca. 30 and 60 nM, respectively). [¹²⁵I]-AB-MECA also binds to A₁ receptors (Klotz *et al.*, 1998). [³H]-CGS21680 is relatively selective for A_{2A} receptors, but may also bind to other sites in cerebral cortex (Johansson & Fredholm, 1995; Cunha *et al.*, 1996). [³H]-NECA binds to other non-receptor elements, which also recognise adenosine (e.g. Lorenzen *et al.*, 1996). XAC-BY630 has been described as a fluorescent antagonist for labelling A₁ adenosine receptors in living cells, although activity at other adenosine receptors was not examined (Briddon *et al.*, 2004).

Adenosine has also been reported to act as a partial agonist at the ghrelin receptor (Smith *et al.*, 2000), but this has been questioned (Johansson *et al.*, 2005).

Abbreviations: AB-MECA, N⁶-(4-aminobenzyl)-adenosine-5'-N-methyluronamide; ATL-146e, 4-[3-[6-amino-9-(5-ethylcarbamoyl-3,4-dihydroxy-tetrahydro-furan-2-yl)-9H-purin-2-yl]-prop-2-ynyl]-cyclohexanecarboxylic acid methyl ester; Bay 60-6583, 2-(6-amino-3,5-dicyano-4-(4-cyclopropylmethoxy)phenyl) pyridin-2-ylthio)acetamide; CCPA, 2-chloro-N⁶-cyclopentyladenosine; CGS15943, 5-amino-9-chloro-2-(2-furyl)1,2,4-triazolo[1,5-c]quinazoline; CGS21680, 2-[4-[2-carboxyethyl]-phenethylamino]adenosine-5'-N-ethyluronamide; 2Cl-IB-MECA, 2-chloro-N⁶-(3-iodobenzyl)adenosine-5'-N-methyluronamide; CPA, N⁶-cyclopentyladenosine; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; GR79236, N-[(1s,2s)-2-hydroxycyclopentyl adenosine; HENECA, 2-(1-(E)-hexenyl)adenosine-5'-N-ethyluronamide; MRS1191, 1,4-dihydro-2-methyl-6-phenyl-4-(phenylethynyl)-3,5-pyridinedicarboxylic acid,3-ethyl 5-(phenylmethyl) ester; MRS1220, 9-chloro-2-(2-furyl)5-phenylacetylaminol[1,2,4]triazolo[1,5c]quinazoline; MRS1523, 2,3-ethyl-4,5-dipropyl-6-phenylpyridine-3-thiocarboxylate-5-carboxylate; MRS1706, N-(4-acetylphenyl)-2-(4-[2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl]phenoxy)acetamide; MRS1754, 8-(4-[[[(4-cyanophenyl)carbamoyl methyl]oxy]phenyl]-1,3-di(n-propyl)xanthine; NECA, adenosine-5'-N-ethyluronamide; PSB1115, 4-[2,3,6,7-tetrahydro-2,6-dioxo-1-propyl-1H-purin-8-yl]benzenesulphonic acid; S-ENBA, (2S)-N⁶-(2-endonorbanyl)adenosine; SCH58261, 5-amino-2-(2-furyl)-7-phenylethyl-pyrazolo[4,3-e]-1,2,4-triazolo[1,5c]pyrimidine; VUF5574, N-(2-methoxyphenyl)-N-(2-[3-pyridyl]quinazolin-4-yl)urea; XAC, 8-(4-[[[(2-aminoethyl)amino]carboxyl]methyl]oxy]phenyl)-1,3-dipropylxanthine, also known as xanthine amine congener; XAC-BY630, N-(2-aminoethyl)-2-[4-(2,6-dioxo-1,3-dipropyl-7H-purin-8-yl)phenoxy]acetamide; ZM241385, 4-(2-[7-amino-2-(2-furyl)]{1,2,4}triazolo[2,3-a]{1,3,5}triazin-5-yl amino)ethyl)phenol

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Adiponectin

Overview: Adiponectin receptors (provisional nomenclature, ENSF0000002482) respond to the 30 kDa complement-related protein hormone adiponectin (also known as adipocyte, C1q and collagen domain-containing protein; ACRP30, adipose most abundant gene transcript 1; apM-1; gelatin-binding protein; ENSG00000181092) originally cloned from adipocytes (Maeda *et al.*, 1996). Although sequence data suggest 7TM domains, immunological evidence indicates that, contrary to typical 7TM topology, the carboxyl terminus is extracellular, while the amino terminus is intracellular (Yamauchi *et al.*, 2003). Signalling through these receptors appears to avoid G-proteins and rather activates protein phosphorylation *via* AMP-activated protein kinase and MAP kinase pathways (Yamauchi *et al.*, 2003).

Nomenclature	Adipo1	Adipo2
Other names	AdipoR1, progestin and adipoQ receptor family member I, CGI45	AdipoR2, progestin and adipoQ receptor family member II
Ensembl ID	ENSG00000159346	ENSG00000006831
Rank order of potency	gAdipo > flAdipo	gAdipo = flAdipo

T-Cadherin has also been suggested to be a receptor for (hexameric) adiponectin (Hug *et al.*, 2004).

Abbreviations: flAdipo, full-length adiponectin; gAdipo, globular adiponectin

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Adrenoceptors, α_1

Overview: α_1 -Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors, Bylund *et al.*, 1994) are 7TM receptors activated by the endogenous agonists adrenaline and noradrenaline with equal potency. Phenylephrine, methoxamine and cirazoline are agonists selective for α_1 -adrenoceptors relative to α_2 -adrenoceptors, while prazosin (8.5–10.5) and corynanthine (6.5–7.5) are considered selective for α_1 -adrenoceptors relative to α_2 -adrenoceptors. [3 H]-Prazosin (0.25 nM) and [125 I]-HEAT (0.1 nM; also known as BE2254) are relatively selective radioligands. Numerous splice variants of the α_1 -adrenoceptors exist, some of which may display a different spectrum of signalling properties. One polymorphism of the α_{1A} -adrenoceptor has been described but is not associated with disease.

Nomenclature	α_{1A}	α_{1B}	α_{1D}
Other names	α_{1a} , α_{1c}	α_{1b}	$\alpha_{1A/D}$, $\alpha_{1a/d}$
Ensembl ID	ENSG00000120907	ENSG00000170214	ENSG00000171873
Principal transduction	G _{q/11}	G _{q/11}	G _{q/11}
Selective agonists	A61603, dabuzalgron (Blue <i>et al.</i> , 2004)	—	—
Selective antagonists	Tamsulosin (10.5), KMD3213 (10.4), (+)niguldipine (10.0), SNAP5089 (9.7)	—	BMY7378 (8.4)

The clone originally called the α_{1C} -adrenoceptor corresponds to the pharmacologically defined α_{1A} -adrenoceptor (see Ford *et al.*, 1994; Hieble *et al.*, 1995). Some tissues possess α_1 -adrenoceptors that display relatively low affinity in functional and binding assays for prazosin ($pK_i < 9$) that might represent different receptor states (termed α_{1L} -adrenoceptors, Ford *et al.*, 1997; Morishima *et al.*, 2007). α_{1A} -Adrenoceptor C-terminal splice variants form homo and heterodimers, but fail to generate a functional α_{1L} adrenoceptor (Ramsay *et al.*, 2004). α_{1D} -Adrenoceptors form heterodimers with α_{1B} - or β_2 -adrenoceptors that show increased cell-surface expression (Uberti *et al.*, 2005). Heterodimers formed between α_{1D} - and α_{1B} -adrenoceptors have distinct functional properties (Hague *et al.*, 2004). (+)Niguldipine also has high affinity for L-type Ca^{2+} channels.

Abbreviations: A61603, N-(5-[4,5-dihydro-1H-imidazol-2-yl]-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)methanesulfonamide hydrobromide; BMY7378, 8-(2-[4-[2-methoxyphenyl]-1-piperazinyl]ethyl)-8-azaspiro[4,5]decane-7,9-dione dihydrochloride; HEAT, 2- β -4-hydroxy-3-iodophenylethylaminomethyltetralone; ICI118551, (–)-1-(2,3-[dihydro-7-methyl-1H-inden-4-yl]oxy)-3-([1-methylethyl]-amino)-2-butanol; KMD3213, (–)-(R)-1-(3-hydroxypropyl)-5-(2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino]propyl)indoline-7-carboxamide, also known as silodosin; RS17053, N-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro- α , α -dimethyl-1H-indole-3-ethanamide; SNAP5089, 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate-N-[3-(4,4-diphenylpiperidin-1-yl)propyl]amide methyl ester; SNAP5272, carboxamide-2,6-diethyl-1,4-dihydro-3-[N-(3-[4-hydroxy-4-phenylpiperidinyl]propyl)]carboxamido-4-(4-nitrophenyl)

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Adrenoceptors, α_2

Overview: α_2 -Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors; Bylund *et al.*, 1994) are 7TM receptors, activated by endogenous agonists with a relative potency of adrenaline > noradrenaline. UK14304 and BHT920 are agonists selective for α_2 -adrenoceptors relative to α_1 -adrenoceptors. Rauwolscine (9.0) and yohimbine (9.0) are antagonists selective for α_2 -adrenoceptors relative to α_1 -adrenoceptors. [3 H]-rauwolscine (1 nM), [3 H]-UK14304 (5 nM) and [3 H]-RX821002 (0.5 and 0.1 nM at α_{2C}) are relatively selective radioligands. There is species variation in the pharmacology of the α_{2A} -adrenoceptor; for example, yohimbine, rauwolscine and oxymetazoline have an ~20-fold lower affinity for rat, mouse and bovine α_{2A} -adrenoceptors compared to the human receptor. These α_{2A} orthologues are sometimes referred to as α_{2D} -adrenoceptors. Multiple mutations of α_2 -adrenoceptors have been described, some of which are associated with alterations in function.

Nomenclature	α_{2A}	α_{2B}	α_{2C}
Other names	α_{2D}	—	—
Ensembl ID	ENSG00000150594	ENSG00000181210	ENSG00000184160
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}
Selective agonists	Oxymetazoline	—	—
Selective antagonists	BRL44408 (8.0)	ARC239 (8.0), prazosin (7.5), imiloxan (7.3)	ARC239 (8.0), prazosin (7.5)

Oxymetazoline is a partial agonist. Binding sites for imidazolines, distinct from α_2 -adrenoceptors, have been identified and classified as I₁, I₂ and I₃ sites, but with a function other than coupling to G-proteins; catecholamines have a low affinity for these sites.

Abbreviations: **ARC239**, 2-(2,4-[O-methoxyphenyl]-piperazin)-1-yl; **BHT920**, 6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]-azepine; **BRL44408**, 2-(2H-[1-methyl-1,3-dihydroisoindole]methyl)-4,5-dihydroimidazole; **MK912**, (2S,12bS)1',3'-dimethylspiro(1,3,4,5',6,6',7,12b-octahydro-2H-benzo[b]furo[2,3-a]quinolizine)-2,4'-pyrimidin-2'-one; **RX821002**, 2-(2-methoxy-1,4-benzodioxan-2-yl)-2-imidazoline; **UK14304**, 5-bromo-6-[2-imidazolin-2-ylamino]quinoxaline, also known as brimonidine

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Adrenoceptors, β

Overview: β -Adrenoceptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Adrenoceptors, Bylund *et al.*, 1994) are 7TM receptors, activated by the endogenous agonists adrenaline and noradrenaline. Isoprenaline is a synthetic agonist selective for β -adrenoceptors relative to α_1 - and α_2 -adrenoceptors, while propranolol (pK_i 8.2–9.2) and cyanopindolol (pK_i 10.0–11.0) are relatively selective antagonists. β_3 -Adrenoceptors are relatively resistant to blockade by propranolol (pK_i 5.8–7.0), but can be blocked with high concentrations of cyanopindolol (pK_i 9.0). Numerous polymorphisms exist for the β_1 - and β_2 -adrenoceptors and some of these are associated with alterations in signalling in response to agonists. These polymorphisms are likely to be associated with altered responses to drugs.

Nomenclature	β_1	β_2	β_3
Other names	—	—	atypical β
Ensembl ID	ENSG00000043591	ENSG00000169252	ENSG00000147477
Principal transduction	G_s	G_s	G_s
Rank order of potency	Noradrenaline > adrenaline	Adrenaline > noradrenaline	Noradrenaline = adrenaline
Selective agonists	Noradrenaline, xamoterol, RO363, denopamine	Procaterol, zinterol, salmeterol, formoterol, terbutaline, fenoterol	BRL37344, CL316243, CGP12177A, carazolol, L742791, SB251023
Selective antagonists	CGP20712A (8.5–9.3), betaxolol (8.5), atenolol (7.6)	ICI118551 (8.3–9.2)	SR59230A (8.8), L748328 (8.5)
Probes	[125 I]-ICYP (20–50 pM) + 70 nM ICI118551	[125 I]-ICYP (20–50 pM) + 100 nM CGP20712A	[125 I]-ICYP (0.5 nM)

Noradrenaline, xamoterol and RO363 show selectivity for β_1 - relative to β_2 -adrenoceptors. All β -adrenoceptors couple to G_s (activating adenyl cyclase and elevating cyclic AMP levels), but it is also clear that they activate many other signalling pathways, particularly mitogen-activated protein kinases. Many antagonists at β_1 - and β_2 -adrenoceptors are agonists at β_3 -adrenoceptors (CL316243, CGP12177A and carazolol). Many 'antagonists' appear to be able to activate selectively mitogen-activate protein kinase pathways (Baker *et al.*, 2003a; Galandrin and Bouvier, 2006; Sato *et al.*, 2007). SR59230A has reasonably high affinity at β_3 -adrenoceptors (Manara *et al.*, 1996), but does not discriminate well between the three β -adrenoceptor subtypes (Candelore *et al.*, 1999) and has been reported to have lower affinity for the β_3 -adrenoceptor in some circumstances (Kaumann and Molenaar, 1996).

Pharmacological differences exist between human and mouse β_3 -adrenoceptors, and the 'rodent selective' agonists BRL37344 and CL316243 have low efficacy at the human β_3 -adrenoceptor. The β_3 -adrenoceptor has introns, but splice variants have only been described for the mouse (Evans *et al.*, 1999). The β -adrenoceptor cloned from turkey (termed the β_{4c} , t428 SwissProt P43141) has a pharmacology that is intermediate between β_2 - and β_3 -adrenoceptors (Chen *et al.*, 1994). The 'putative β_4 -adrenoceptor' is not a novel receptor but is likely to represent an alternative site of interaction of CGP12177A and other nonconventional partial agonists at β_1 -adrenoceptors, since 'putative β_4 -adrenoceptor'-mediated agonist effects of CGP12177A are absent in mice lacking β_1 -adrenoceptors (Konkar *et al.*, 2000; Kaumann *et al.*, 2001).

Radioligand binding to define β_1 - and β_2 -adrenoceptors can be conducted in the presence of a 'saturating' concentration of the β_1 - or β_2 -adrenoceptor-selective antagonist. [3 H]-CGP12177 or [3 H]-dihydroalprenolol can be used in place of [125 I]-ICYP. Binding of a fluorescent analogue of CGP12177 to β_2 -adrenoceptors in living cells has been described (Baker *et al.*, 2003b).

Abbreviations: BRL37344, sodium 4-(2-[2-hydroxy-3-chlorophenyl]ethylamino)propyl)phenoxyacetate; CGP12177A, (-)-4-(3-tert-butylamino-2-hydroxypropoxy)-benzimidazol-2-one; CGP20712A, 2-hydroxy-5-(2-[[2-hydroxy-3-(4-[1-methyl-4-trifluoromethyl-2-imidazolyl]phenoxy)-propyl]amino]ethoxy)benzamide; CL316243, disodium (*R,R*)-5-(2-[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl)-1,3-benzodioxole-2,2, dicarboxylate; ICYP, iodocyanopindolol; L742791, (*S*)-*N*-(4-[2-[(3-[4-hydroxyphenoxy]-2-hydroxypropyl)amino]ethyl]phenyl)-4-iodobenzene-sulfonamide; L748328, (*S*)-*N*-(4-[2-[(3-[3-[aminosulfonyl]phenoxy]-2-hydroxypropyl)-amino]ethyl]phenyl)benzenesulfonamide; RO363, (-)-1-(3,4-dimethoxyphenethylamino)-3-(3,4-dihydroxyphenoxy)-2-propanol)oxalate; SB251023, (4-[1-(2-(*S*)-hydroxy-3-(4-hydroxyphenoxy)-propyl-amino)cyclopentylmethyl]phenoxy)methyl)phenylphosphonic acid lithium salt; SR59230A, 3-(2-ethylphenoxy)-1-[(1*s*)-1,2,3,4-tetrahydronaphth-1-ylamino]-2*S*-propanol oxalate

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Anaphylatoxin and chemotactic peptide

Overview: Anaphylatoxin and chemotactic peptide receptors (provisional nomenclature) are activated by the endogenous ~75 amino-acid anaphylatoxin polypeptides C3a (ENSG00000125730) and C5a (ENSG00000106804), generated upon stimulation of the complement cascade. The fMLP receptor responds to exogenous ligands such as the bacterial product formyl-Met-Leu-Phe (fMLP) and endogenous ligands such as annexin I (ENSG00000135046), cathepsin G (ENSG00000100448) and spinorphin, derived from β -haemoglobin (ENSG00000188170).

Nomenclature	C3a	C5a	fMLP
Other names	AZ3B, HNFAG09	CD88	Formyl peptide, FPR
Ensembl ID	ENSG00000171860	ENSG00000134830	ENSG00000171051
Principal transduction	Gi/o, Gz	Gi/o, Gz, G16 (Buhl <i>et al.</i> , 1993)	Gi/o, Gz
Rank order of potency	C3a > C5a (Ames <i>et al.</i> , 1996)	C5a, C5a des Arg > C3a (Ames <i>et al.</i> , 1996)	fMLP > Cathepsin G > Annexin I (Le <i>et al.</i> , 2002; Sun <i>et al.</i> , 2004)
Selective agonists	Trp-Trp-Gly-Lys-Lys-Tyr-Arg-Ala-Ser-Lys-Leu-Gly-Leu-Ala-Arg (Ames <i>et al.</i> , 1997)	Phe-Lys-Pro-Cha-Cha-Phe-Lys-D-Cha-Cha-D-Arg (Konteatitis <i>et al.</i> , 1994), S19 (Yamamoto, 2000)	fMLP (Le <i>et al.</i> , 1999)
Selective antagonists	SB290157 (pIC ₅₀ 7.5, Ames <i>et al.</i> , 2001)	NMe-Phe-Lys-Pro-D-Cha-Trp-D-Arg (Konteatitis <i>et al.</i> , 1994), AcPhe-Orn-Pro-D-Cha-Trp-Arg (Wong <i>et al.</i> , 1998), W54011 (8.7, Sumichika <i>et al.</i> , 2002), CHIPS (Postma <i>et al.</i> , 2004)	Cyclosporin H (6.3-7.0, Wenzel-Seifert and Seifert, 1993), BOC-PLPLP (6.0-6.5, Wenzel-Seifert and Seifert, 1993), spinorphin (4, Liang <i>et al.</i> , 2001)
Probes	[¹²⁵ I]-C3a	[¹²⁵ I]-C5a	[³ H]-fMLP

SB290157 has also been reported to have agonist properties (Mathieu *et al.*, 2005). A putative chemoattractant receptor termed C5L2 (also known as GPR77, ENSG00000134830) binds [¹²⁵I]-C5a, with no clear signalling function, but a putative role opposing inflammatory responses (Cain and Monk, 2002; Gao *et al.*, 2005; Gavriluk *et al.*, 2005). Binding to this site may be displaced with the rank order C5a des Arg > C5a (Cain and Monk, 2002; Okinaga *et al.*, 2003), while there is controversy over the ability of C3a and C3a des Arg to compete (Kalant *et al.*, 2003; Okinaga *et al.*, 2003; Honczarenko *et al.*, 2005; Kalant *et al.*, 2005).

Abbreviations: BOC-PLPLP, Boc-Phe-Leu-Phe-Leu-Phe; CHIPS, chemotaxis inhibitory protein of *Staphylococcus aureus*; SB290157, N²-(1,2,2-diphenylethoxy)acetyl-L-arg; W54011, N-([4-dimethylaminophenyl]methyl)-N-(4-isopropylphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-carboxamide hydrochloride

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Angiotensin

Overview: The actions of angiotensin II (Ang II) are mediated by AT₁ and AT₂ receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Angiotensin Receptors; see de Gasparo *et al.*, 2000), which have around 30% sequence similarity. AT₁ receptors are predominantly coupled to G_{q/11}. Most species express a single AT₁ gene, but two related AT_{1A} and AT_{1B} receptor genes are expressed in rodents. The AT₂ receptor counteracts several of the growth responses initiated by the AT₁ receptors. The AT₂ receptor is much less abundant than the AT₁ receptor in adult tissues and is upregulated in pathological conditions. Endogenous ligands are Ang II and angiotensin III (Ang III), while angiotensin I is weakly active in some systems.

Nomenclature	AT ₁	AT ₂
Ensembl ID	ENSG00000144891	ENSG00000180772
Principal transduction	G _{q/11}	Tyr & Ser/Thr phosphatases
Selective agonists	L162313	[p-NH ₂ -Phe ⁶]-Ang II, CGP42112
Selective antagonists	EXP3174, eprosartan, valsartan, irbesartan, losartan	PD123319, PD123177
Probes	[³ H]-A81988, [³ H]-L158809, [³ H]-eprosartan, [³ H]-losartan, [¹²⁵ I]-EXP985	[¹²⁵ I]-CGP42112

There is also evidence for an AT₄ receptor that specifically binds angiotensin IV and is located in the brain and kidney. An additional putative endogenous ligand for the AT₄ receptor has been described (LVV-hemorphin, a globin decapeptide) (Moeller *et al.*, 1997). The AT₁ and bradykinin B2 receptors have been proposed to form a heterodimeric complex (Abdalla *et al.*, 2000). The antagonist activity of CGP42112 has also been reported (Lokuta *et al.*, 1995). Novel AT₁ receptor antagonists bearing substituted 4-phenylquinoline moieties have recently been designed and synthesized. The best of these compounds bind to AT₁ receptors with nanomolar affinity and are slightly more potent than losartan in functional studies (Cappelli *et al.*, 2004).

Abbreviations: **A81988**, 2-(*N*-propyl-*N*-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methylamino)pyridine-3-carboxylate; **CGP42112A**, nicotinic acid-Tyr-(*N*-benzoylcarbonyl-Arg)-Lys-His-Pro-Ile-OH; **eprosartan**, (E)-α-([2-butyl-1-[(4-carboxyphenyl)methyl]-1*H*-imidazol-5-yl]methylene)-2-thiophenepropanoate; **EXP3174**, *n*-butyl-4-chloro-1-[(2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxylate; **EXP985**, *N*-(2-[4-hydroxy-3-iodophenyl]ethyl)-4-chloro-2-propyl-1-[(2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole-5-carboxamide; **irbesartan**, 2-butyl-3-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one; **L158809**, 5,7-dimethyl-2-ethyl-3-(2-[1*H*-tetrazol-5-yl]biphenyl-4-yl)imidazo[4, 5-*b*]pyridine; **L162313**, 5,7-dimethyl-2-ethyl-3-[[4-[2(*n*-butyloxycarbonylsulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl]imidazo[4,5,6]pyridine; **losartan**, 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole, also known as Dup 753; **PD123177**, 1-(4-amino-3-methylphenyl)methyl-3-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylate; **PD123319**, (S)-1-(4-[dimethylamino]-3-methylphenyl)methyl-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylate; **valsartan**, *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine

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Apelin

Overview: The apelin receptor (APJ, provisional nomenclature previously designated as an orphan) responds to apelin, a 36 amino-acid peptide derived initially from bovine stomach. Apelin-36, apelin-13 and (Pyr¹)apelin-13 are the predominant endogenous ligands which are cleaved from a 77 amino-acid precursor peptide (ENSG00000171388) by a so far unidentified enzymatic pathway (Tatemoto *et al.*, 1998).

Nomenclature	APJ
Other names	Apelin receptor, angiotensin receptor-like 1
Ensembl ID	ENSG00000134817
Principal transduction	G _{i/o}
Rank order of potency	[Pyr ¹]apelin-13 ≥ apelin-13 > apelin-36 (Tatemoto <i>et al.</i> , 1998; Fan <i>et al.</i> , 2003)
Selective agonists	[Pyr ¹]apelin-13, apelin-13, apelin-17, apelin-36
Probes	[¹²⁵ I]-[Pyr ¹]Apelin-13 (0.3 nM, Katugampola <i>et al.</i> , 2001), [¹²⁵ I]-apelin-13 (Fan <i>et al.</i> , 2003), [³ H]-[Pyr ¹][Met(0) ¹¹]apelin-13 (Medhurst <i>et al.</i> , 2003), [¹²⁵ I]-[Nle ⁷⁵ ,Tyr ⁷⁷]apelin-36 (Kawamata <i>et al.</i> , 2001)

Potency order determined for heterologously expressed human APJ receptor (pD₂ values range from 9.5–8.6). APJ may also act as a co-receptor with CD4 for isolates of human immunodeficiency virus, with apelin blocking this function (Cayabyab *et al.*, 2000). A modified apelin-13 peptide, apelin-13(F13A) was reported to block the hypotensive response to apelin in rat *in vivo* (Lee *et al.*, 2005), however this peptide exhibits agonist activity in HEK293 cells stably expressing the recombinant APJ receptor (Fan *et al.*, 2003).

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Bile acid

Overview: The bile acid receptor (GPBA, provisional nomenclature) responds to bile acids produced during the liver metabolism of cholesterol.

Nomenclature	GPBA
Other names	BG37, GPCR19, GPR131, M-BAR (Maruyama <i>et al.</i> , 2002), MGC40597, TGR5 (Kawamata <i>et al.</i> , 2003)
Ensembl ID	ENSG00000179921
Principal transduction	G _s (Maruyama <i>et al.</i> , 2002)
Rank order of potency	Lithocholic acid > deoxycholic acid > chenodeoxycholic acid, cholic acid (Maruyama <i>et al.</i> , 2002; Kawamata <i>et al.</i> , 2003)
Selective agonists	Oleanolic acid (Sato <i>et al.</i> , 2007)

Disruption of GPBA expression is reported to protect from cholesterol gallstone formation (Vassileva *et al.*, 2006).

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Bombesin

Overview: Bombesin receptors are activated by the endogenous ligands gastrin-releasing peptide (GRP), neuromedin B (NMB) and GRP-18–27 (previously named neuromedin C). Bombesin is a tetradecapeptide, originally derived from amphibians. These receptors couple, primarily, to the G_{q/11} family of G proteins (but see also Jian *et al.*, 1999). Activation of BB1 and BB2 receptors causes a wide range of physiological actions, including the stimulation of tissue growth, smooth-muscle contraction, secretion and many central nervous system effects (Tokita *et al.*, 2002). A physiological role for the bb3 receptor has yet to be defined.

Nomenclature	BB1	BB2	bb3
Other names	NMB-R	GRP-R	BRS-3
Ensembl ID	ENSG00000135577	ENSG00000126010	ENSG00000102239
Principal transduction	G _{q/11}	G _{q/11}	G _{q/11}
Selective agonists	NMB	GRP	—
Selective antagonists	PD165929, dNal-cyc(Cys-Tyr-dTrp-Orn-Val)-Nal-NH ₂ , dNal-Cys-Tyr-dTrp-Lys-Val-Cys-Nal-NH ₂	1-Naphthoyl-[dAla ²⁴ , dPro ²⁶ , ψ ^{26–27}]GRP-20–27, kuwanon H, [dPhe ⁶]bombesin-6–13-ethylester, [dPhe ⁶ , Cpa ¹⁴ , ψ ^{13–14}]bombesin-6–14	—
Probes	[¹²⁵ I]-BH-NMB, [¹²⁵ I]-[Tyr ⁴]bombesin	[¹²⁵ I]-[DTyr ⁶]bombesin-6–13-methylester, [¹²⁵ I]-GRP, [¹²⁵ I]-[Tyr ⁴]bombesin	[¹²⁵ I]-[Tyr ⁶ , βAla ¹¹ , Phe ¹³ , Nle ¹⁴]bombesin-6–14

All three subtypes may be activated by [dPhe⁶, βAla¹¹, Phe¹³, Nle¹⁴]bombesin-6–14 (Mantey *et al.*, 1997). One analogue, [D-Tyr⁶, Apa-4Cl, Phe¹³, Nle¹⁴] bombesin-6–14, has more than 200-fold selectivity for bb3 receptors over BB1 and BB2 (Mantey *et al.*, 2004).

Abbreviations: PD165929, 2-[3-(2,6-diisopropylphenyl)-ureido]3-(1*H*-indol-3-yl)-2-methyl-*N*-(1-pyridin-2-yl-cyclohexylmethyl)-propionate

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Bradykinin

Overview: Bradykinin (or kinin) receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on bradykinin (kinin) receptors, Leeb-Lundberg *et al.*, 2005) are activated by the endogenous peptides bradykinin (BK), [des-Arg⁹]BK, Lys-BK (kallidin), Lys-[des-Arg⁹]BK, T-kinin (Ile-Ser-BK), [Hyp³]BK and Lys-[Hyp³]BK. The variation in affinity or inactivity of B₂ receptor antagonists could reflect the existence of species homologues of B₂ receptors.

Nomenclature	B ₁	B ₂
Ensembl ID	ENSG00000100739	ENSG00000168398
Principal transduction	G _{q/11}	G _{q/11}
Rank order of potency	Lys-[des-Arg ⁹]BK > [des-Arg ⁹]BK = Lys-BK > BK	Lys-BK ≥ BK > > [des-Arg ⁹]BK, Lys-[des-Arg ⁹]BK
Selective agonists	Lys-[des-Arg ⁹]BK, Sar[D ¹ Phe ⁸][des-Arg ⁹]BK	[Phe ⁸ ,ψ(CH ₂ -NH)Arg ⁹]BK, [Hyp ³ ,Tyr(Me) ⁸]BK
Selective antagonists	B9958 (9.2, Regoli <i>et al.</i> , 1998), R914 (8.6, Gobeil <i>et al.</i> , 1999), R715 (8.5, Gobeil <i>et al.</i> , 1996a), Lys-[Leu ⁸][des-Arg ⁹]BK (8.0)	Icatibant (8.4, Gobeil <i>et al.</i> , 1996b), FR173657 (8.2, Rizzi <i>et al.</i> , 1997), LF160687 (Pruneau <i>et al.</i> , 1999)
Probes	[³ H]-Lys-[des-Arg ⁹]BK (0.4 nM), [³ H]-Lys-[Leu ⁸][des-Arg ⁹]BK, [¹²⁵ I]-Hpp-desArg ⁹ HOE140 (0.1 nM)	[³ H]-BK (0.2 nM), [³ H]-NPC17731 (50–900 pM), [¹²⁵ I]-[Tyr ⁸]BK

Abbreviations: B9958, Lys-Lys[Hyp³,Cpg⁵,dTic⁷,Cpg⁸][des-Arg⁹]BK; FR173657, (E)-3-(6-acetamido-3-pyridyl)-N-(N-[2,4-dichloro-3-((2-methyl-8-quinolinyl)oxymethyl) phenyl]-N-methylaminocarbonyl-methyl)acrylamide; Icatibant, DArg[Hyp³,Thi³,DTic⁷,Oic⁸]BK, also known as HOE140 LF160687, 1-([2,4-dichloro-3-((2,4-dimethylquinolin-8-yl)oxy)methyl]phenyl)sulfonyl)-N-(3-[[4-(aminoimethyl)phenyl]carbonylamino]propyl)-2(S)-pyrrolidinecarboxamide; NPC17731, DArg[Hyp³,DHypE(transpropyl)⁷,Oic⁸]BK; R715, AcLys[D Nal⁷,Ile⁸][des-Arg⁹]BK; R914, AcLys-Lys-([zMe]Phe⁵δ-βNal⁷,Ile⁸)desArg⁹BK

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Calcitonin, amylin, CGRP and adrenomedullin

Overview: Calcitonin (CT), amylin (AMY), calcitonin gene-related peptide (CGRP) and adrenomedullin (AM) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on CGRPs, AM, AMY, and CT receptors, see Poyner *et al.*, 2002) are generated by the genes *CALCR* (which codes for the CT receptor) and *CALCRL* (which codes for the calcitonin receptor-like receptor, CL receptor, previously known as CRLR), whose function and pharmacology are altered in the presence of RAMPs (receptor activity-modifying protein). RAMPs are single TM domain proteins of *ca.* 130 amino acid, identified as a family of three members; RAMP1 (ENSG00000132329), RAMP2 (ENSG00000131477) and RAMP3 (ENSG00000122679). There are splice variants of the CT receptor; these in turn produce variants of the AMY receptor (see Poyner *et al.*, 2002). The endogenous agonists are the peptides CT, α CGRP (also known as CGRP-I), β CGRP (also known as CGRP-II), AMY (also known as islet-amyloid polypeptide, diabetes-associated polypeptide) and AM. There are species differences in peptide sequences, particularly for the CTs. AM2/Intermedin (AM2/IMD) can also activate CGRP1, AM1, AM2 and AMY1 receptors, albeit less potently than the cognate agonists (Ogoshi *et al.*, 2003; Roh *et al.*, 2004; Hay *et al.*, 2005). CT receptor-stimulating peptide (CRSP) is another member of the family with selectivity for the CT receptor; it has not been found in humans (Katafuchi *et al.*, 2003). BIBN4096BS is the most selective antagonist available, having a high selectivity for CGRP1 receptors, with a particular preference for those of primate origin. CGRP-(8–37) acts as an antagonist of CGRP (pK_i 6.5–8.0) and inhibits some AM and AMY responses (7.0). It is inactive at CT receptors. Salmon calcitonin-(8–32) is an antagonist at both *amylin* and CT receptors. AC187, a salmon CT analogue, is also an antagonist at *amylin* and CT receptors. Human AM-(22–52) has some selectivity towards AM receptors, but with modest potency, limiting its use.

Nomenclature	Calcitonin	Amylin	CGRP	Adrenomedullin
Composition	<i>CALCR</i>	AMY1: <i>CALCR</i> + <i>RAMP1</i> AMY2: <i>CALCR</i> + <i>RAMP2</i> AMY3: <i>CALCR</i> + <i>RAMP3</i>	<i>CGRP1</i> : <i>CALCRL</i> + <i>RAMP1</i>	AM1: <i>CALCRL</i> + <i>RAMP2</i> AM2: <i>CALCRL</i> + <i>RAMP3</i>
Ensembl ID	ENSG00000004948	—	ENSG000000064989	—
Principal transduction	G _s /G _q	G _s	G _s /G _q	G _s
Rank order of potency	Salmon CT > human CT > AMY, CGRP > AM, AM2/IMD	AMY1a: Salmon CT > AMY > CGRP > AM2/IMD > human CT > AM AMY3a: Salmon CT > AMY > CGRP > AM2/IMD > human CT > AM	CGRP > AM > AM2/IMD > AMY > salmon CT	AM1: AM > CGRP, AM2/IMD > AMY > salmon CT AM2: AM > CGRP, AM2/IMD > AMY > salmon CT
Selective agonists	Human CT	AMY	α CGRP	AM
Selective antagonists	—	—	BIBN4096BS (11, Doods <i>et al.</i> , 2000; Hay <i>et al.</i> , 2003, 2006)	AM-(22–52) (7)
Probes	[¹²⁵ I]-CT (salmon, 0.1 nM), [¹²⁵ I]-CT (human, 0.1–1.0 nM)	[¹²⁵ I]-BH-AMY (rat, 0.1–1.0 nM)	[¹²⁵ I]- α CGRP (0.1 nM)	[¹²⁵ I]-AM (rat, 0.1–1.0 nM)

The agonists described represent the best available but their selectivity is limited. AM has appreciable affinity for CGRP receptors and some of its effects can be antagonised by CGRP-(8–37). CGRP can show significant cross-reactivity at *amylin* receptors and some AM receptors. Responsiveness to human CT can be affected by splice variation (at the rat C1b receptor it is very weak, Houssami *et al.*, 1994). Particularly for AMY receptors, relative potency can vary with the type and level of RAMP present and can be influenced by other factors such as G-proteins (Tilakaratne *et al.*, 2000).

G_s is a prominent route for effector coupling but other pathways (e.g. Ca²⁺ and nitric oxide) and G-proteins can be activated. The coupling can be affected by splice variants of the CT receptor (e.g. the 490 amino-acid form of the human receptor, CT(b), does not cause an increase in intracellular Ca²⁺ and might have low efficacy in generating cAMP).

There is evidence that CGRP-RCP (a 148 amino-acid hydrophilic protein, ENSG00000126522) is important for the coupling of the CL receptor to adenylyl cyclase (Evans *et al.*, 2000). When co-expressed with RAMP2, the CL receptor produces an AM receptor (AM1). RAMP3 interacts with the CL receptor to give another receptor that is responsive to AM (AM2, Fraser *et al.*, 1999). There is some evidence that these AM receptors are pharmacologically distinct (Hay *et al.*, 2003). Transfection of hCT(a) with any RAMP can give a receptor with a high affinity for both salmon CT and AMY and varying affinity for different antagonists (Christopoulos *et al.*, 1999; Hay *et al.*, 2005, 2006). hCT(a)—RAMP1 has a high affinity for CGRP, unlike hCT(a)—RAMP3 (Christopoulos *et al.*, 1999; Hay *et al.*, 2005). However, AMY receptor phenotype is RAMP-type- and cell-line-dependent (Tilakaratne *et al.*, 2000).

[¹²⁵I]-Salmon calcitonin is the most common radioligand for calcitonin receptors but it has high affinity for *amylin* receptors and is also poorly reversible. [¹²⁵I]-Tyr⁰-CGRP is widely used as a radioligand for CGRP receptors.

CGRP₁ and CGRP₂ subtypes have been proposed on the basis of the action of the agonists [Cys(ACM)^{2,7}]CGRP or [Cys(Et)^{2,7}]CGRP (putative CGRP₂-selective agents) and antagonist CGRP-(8–37) (CGRP₁-selective, pK_i 7.0–8.0, Juaneda *et al.*, 2000). CL/RAMP1 represents the CGRP₁ subtype previously described in native tissues and cell lines (Aiyar *et al.*, 1996; McLatchie *et al.*, 1998). There is not yet a clear molecular correlate for the CGRP₂ receptor, although in some cases it may represent CGRP acting via AM2 or *amylin* receptors.

Abbreviations: AC187, acetyl-[Asn³⁰, Tyr³²]salmon CT; AM2/IMD, AM2/intermedin; BIBN409BS, 1-piperidinecarboxamide, N-(2-[[5-amino-1-[(4-{4-pyridinyl}-1-piperazinyl]carbonyl)pentyl]amino]-1-[[3,5-dibromo-4-hydroxyphenyl]methyl]-2-oxoethyl]-4-(1,4-dihydro-2-oxo-3[2H]-quinazolinyl)]; [Cys(ACM)^{2,7}]CGRP, [acetamidomethyl-Cys^{2,7}]CGRP; [Cys(Et)^{2,7}]CGRP, [ethylamide-Cys^{2,7}]CGRP

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Calcium-sensing

Overview: The calcium-sensing receptor (CaR, provisional nomenclature) responds to extracellular calcium and magnesium in the millimolar range and to gadolinium and some polycations in the micromolar range (Brown *et al.*, 1993). The sensitivity of CaR to primary agonists can be increased by aromatic L-amino acids (Conigrave *et al.*, 2000) and also by a rise in extracellular pH (Quinn *et al.*, 2004).

Nomenclature	CaR
Other names	Parathyroid cell calcium-sensing receptor, CASR
Ensembl ID	ENSG00000036828
Principal transduction	G _{q/11} , G _{i/o} , G _{12/13} (Ward <i>et al.</i> , 2004)
Cation rank order of potency	Gd ³⁺ > Ca ²⁺ > Mg ²⁺ (Brown <i>et al.</i> , 1993)
Polyamine rank order of potency	Spermine > spermidine > putrescine (Quinn <i>et al.</i> , 1997)
Amino-acid rank order of potency	L-Phe, L-Trp, L-His > L-Ala > L-Ser, L-Pro, L-Glu > L-Asp but not L-Lys, L-Arg, L-Leu, and L-Ile (Conigrave <i>et al.</i> , 2000)
Positive allosteric modulators	NPS R568 (Nemeth <i>et al.</i> , 1998), calindol (Petrel <i>et al.</i> , 2004), cinacalcet (Nemeth <i>et al.</i> , 2004)
Negative allosteric modulators	NPS 2143, NPS 89636 (Nemeth <i>et al.</i> , 2001), Calhex-231 (Petrel <i>et al.</i> , 2004), 2-benzylpyrrolidine derivatives of NPS 2143 (Yang <i>et al.</i> , 2005)

Positive allosteric modulators are termed Type II calcimimetics and can suppress parathyroid hormone secretion (Nemeth *et al.*, 1998). Negative allosteric modulators are called calcilytics and can act to increase parathyroid hormone secretion (Nemeth *et al.*, 2001).

The central role of CaR in the maintenance of extracellular calcium homeostasis is seen most clearly in patients with loss-of-function CaR mutations who develop familial hypocalciuric hypercalcaemia (heterozygous mutation) or neonatal severe hyperparathyroidism (homozygous mutation) and in CaR null mice (Ho *et al.*, 1995), which exhibit similar increases in PTH secretion and blood Ca²⁺ levels. A gain-of-function mutation in the CaR gene is associated with autosomal dominant hypocalcaemia.

Abbreviations: Calhex-231, (1S,2S,1'R)-N¹-(4-chlorobenzoyl)-N²-[1-(1-naphthyl)ethyl]-1,2-diaminocyclohexane; calindol, (R)-2-[1-(1-naphthyl)ethylaminomethyl]-1H-indole; NPS 2143, N-[(R)-2-hydroxy-3-(2-cyano-3-chlorophenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine; NPS R568, (R)-N-(3-methoxy- ω -phenylethyl)-3-(2-chlorophenyl)-1-propylamine hydrochloride

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Cannabinoid

Overview: Cannabinoid receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Cannabinoid Receptors; see Howlett *et al.*, 2002) are activated by endogenous ligands that include *N*-arachidonylethanolamine (anandamide), *N*-homo- γ -linolenylethanolamine, *N*-docosatetra-7,10,13,16-enylethanolamine and 2-arachidonoylglycerol. Potency determinations are complicated by the possibility of differential susceptibility of endogenous ligands to enzymatic conversion (see Alexander and Kendall, 2007). Both CB₁ and CB₂ receptors may be labelled with [³H]-CP55940 (0.6 nM; Showalter *et al.*, 1996) and [³H]-WIN55212-2 (2–12 nM; Slipetz *et al.*, 1995; Song and Bonner, 1996).

Further cannabinoid-like receptors have been described, including GPR55 (ENSG00000135898), which appears to respond to a wide spectrum of cannabinoid agonists and antagonists (see Brown, 2007; Pertwee, 2007; Ryberg *et al.*, 2007). GPR18 has been described to be a 7-transmembrane receptor for *N*-arachidonoylglycine (Kohno *et al.*, 2006), while GPR119 responds to fatty acid ethanolamides (*N*-oleylethanolamine > *N*-palmitoylethanolamine > anandamide; Overton *et al.*, 2006). Synthetic agonists for this receptor include PSN375963 and PSN632408 (Overton *et al.*, 2006). Other pharmacological targets for cannabinoids have also been proposed (see Baker *et al.*, 2006; Begg *et al.*, 2005; Pertwee, 2005a).

Nomenclature	CB ₁	CB ₂
Ensembl ID	ENSG00000118432	ENSG00000162562
Principal transduction	G _{i/o}	G _{i/o}
Selective agonists	ACEA (Hillard <i>et al.</i> , 1999), ACPA (Hillard <i>et al.</i> , 1999), methanandamide (Khanolkar <i>et al.</i> , 1996), O1812 (Di Marzo <i>et al.</i> , 2001)	HU308 (Hanus <i>et al.</i> , 1999), JWH133 (Huffman <i>et al.</i> , 1999; Pertwee, 2000), L759633 (Ross <i>et al.</i> , 1999), L759656 (Ross <i>et al.</i> , 1999), AM1241 (Ibrahim <i>et al.</i> , 2003)
Selective antagonists	AM251 (8.1, Lan <i>et al.</i> , 1999a), AM281 (7.9, Lan <i>et al.</i> , 1999b) rimonabant (7.9, Showalter <i>et al.</i> , 1996), LY320135 (6.9, Felder <i>et al.</i> , 1998)	SR144528 (9.2, Rinaldi-Carmona <i>et al.</i> , 1998), AM630 (7.5, Ross <i>et al.</i> , 1999)
Probes	[³ H]-rimonabant (0.6 nM, Rinaldi-Carmona <i>et al.</i> , 1996)	—

Anandamide is also an agonist at vanilloid receptors (TRPV1) and PPARs (see O'Sullivan, 2007; Zygmunt *et al.*, 1999). There is evidence for an allosteric site on the CB₁ receptor (Price *et al.*, 2005). All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems (see Pertwee, 2005a, b).

Abbreviations: ACEA, arachidonoyl-2-chloroethylamide; ACPA, arachidonoylcyclopropylamide; **AM1241**, (2-iodo-5-nitro-phenyl)-[1-(1-methyl-piperidin-2-ylmethyl)-1*H*-indol-3-yl]-methanone; **AM251**, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; **AM281**, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-*N*-4-morpholinyl-1*H*-pyrazole-3-carboxamide; **AM630**, 6-iodopravadoline; **CP55940**, (1*R*,3*R*,4*R*)-3-[2-hydroxy-4-(1,1-dimethylheptyl) phenyl]-4-(3-hydroxypropyl)cyclohexan-1-ol; **HU308**, {4-[4-(1,1-dimethylheptyl)-2,6-dimethoxy-phenyl]-6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl}-methanol; **JWH133**, (3-(1,1-dimethylbutyl)-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene; **L759633**, (6*a*,10*a*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromene; **L759656**, (6*a*,10*a*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6-dimethyl-9-methylene-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromene; **LY320135**, (6-methoxy-2-[4-methoxyphenyl]benzo[*b*]thien-3-yl)(4-cyanophenyl)methanone; **methanandamide**, (*R*)-(+)-arachidonoyl-1'-hydroxy-2'-propylamide; **O1812**, (*R*)-(20-cyano-16,16-dimethyldocosa-*cis*-5,8,11,14-tetraenoyl)-1'-hydroxy-2'-propylamine; **PSN375963**, 4-(5-[4-butylcyclohexyl]-1,2,4-oxadiazol-3-yl)pyridine; **PSN632408**, 4-([3-(4-pyridinyl)-1,2,4-oxadiazol-5-yl]methoxy)-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester; **rimonabant**, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride, also known as SR141716A; **SR144528**, *N*-([1*S*]-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide; **WIN55212-2**, (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)-pyrrolo-[1,2,3-*de*]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate

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Chemokine

Overview: Chemokine receptors (nomenclature agreed by NC-IUPHAR Subcommittee on Chemokine Receptors, Murphy *et al.*, 2000; Murphy, 2002) comprise a large subfamily of 7TM receptors activated by one or more of the chemokines, a large family of small cytokines typically possessing chemotactic activity for leukocytes.

Chemokines can be divided by structure into four subclasses by the number and arrangement of conserved cysteines. CC (also known as β -chemokines; $n = 28$), CXC (also known as α -chemokines; $n = 16$) and CX₃C ($n = 1$) chemokines all have four conserved cysteines, with zero, one and three amino acids separating the first two cysteines, respectively. C chemokines ($n = 2$) have only the second and fourth cysteines found in other chemokines. Chemokines can also be classified by function into homeostatic and inflammatory subgroups. Most chemokine receptors are able to bind multiple high affinity chemokine ligands, but the ligands for a given receptor are almost always restricted to the same structural subclass. Most chemokines bind to more than one receptor subtype. Receptors for inflammatory chemokines are typically highly promiscuous with regard to ligand specificity, and may lack a selective endogenous ligand. Listed are those human agonists with EC₅₀ values < 50 nM in either Ca²⁺ flux or chemotaxis assays at human recombinant receptors expressed in mammalian cell lines. There can be substantial cross-species differences in the sequences of both chemokines and chemokine receptors, and in the pharmacology and biology of chemokine receptors. Endogenous and HIV-encoded non-chemokine ligands have also been identified for chemokine receptors. Many chemokine receptors function as HIV co-receptors, and at least two, CCR5 and CXCR4, play prominent roles in pathogenesis. The tables include both standard chemokine names (Zlotnik and Yoshie, 2000) and the most commonly used synonyms. Numerical data quoted are typically pKi or pIC₅₀ values from radioligand binding to heterologously expressed receptors.

Nomenclature	CCR1	CCR2	CCR3	CCR4	CCR5
Other names	CKR1, CC CK ₁ , CC CKR1, MIP-1 α R, MIP-1 α /RANTES	CKR2, CC CK ₂ , CC CKR2, MCP-1	CKR3, CC CK ₃ , CC CKR3	CKR4, CC CK ₄ , CC CKR4	CKR5, CC CK ₅ , CC CKR5, CHEMR13
Ensembl ID	ENSG00000163823	ENSG00000121807	ENSG00000183625	ENSG00000183813	ENSG00000160791
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Agonists	CCL3 (MIP-1 α), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL14a (HCC-1), CCL15 (HCC-2), CCL23 (MPIF-1)	CCL2 (MCP-1), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL16 (HCC-4), HIV-1 Tat	CCL11 (eotaxin), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL15 (HCC-2), CCL24 (eotaxin-2), CCL26 (eotaxin-3), CCL28 (MEC), HIV-1 Tat	CCL22 (MDC), CCL17 (TARC), HHV8 vMIP-III,	CCL3 (MIP-1 α), CCL4 (MIP-1 β), CCL5 (RANTES), CCL8 (MCP-2), CCL11 (eotaxin), CCL14a (HCC-1), CCL16 (HCC-4), R5 HIV-1 gp120
Selective agonists	CCL15 (HCC-2), CCL23 (MPIF-1)	CCL2 (MCP-1)	CCL11 (Eotaxin), CCL24 (eotaxin-2), CCL26 (eotaxin-3),	CCL22 (MDC), CCL17 (TARC)	MIP-1 β , R5-HIV gp120
Selective antagonists	BX471 (8.3-9), 2b-1 (8.7), UCB35625 (8.0), CP-481,715 (8.0), CCL4 (MIP-1 β)	CCL11 (eotaxin), CCL26 (eotaxin-3), GSK Compound 34 (7.6)	Banyu Compound 1b (8.6), SB328437 (8.4), BMS Compound 87b (8.1), CXCL10 (IP10), CXCL9 (Mig), CXCL11 (I-TAC)	—	TAK779 (9.0), CCL7 (MCP-3), SCH C, SCH D, MRK-1, E913 (8.7), maraviroc, aplaviroc
Probes	[¹²⁵ I]-MIP-1 α , [¹²⁵ I]-RANTES, [¹²⁵ I]-MCP-3	[¹²⁵ I]-MCP-1, [¹²⁵ I]-MCP-3	[¹²⁵ I]-RANTES, [¹²⁵ I]-eotaxin, [¹²⁵ I]-MCP-3	[¹²⁵ I]-TARC, [¹²⁵ I]-CTACK/CCL27	[¹²⁵ I]-RANTES, [¹²⁵ I]-MCP-2, [¹²⁵ I]-MIP-1 α , [¹²⁵ I]-MIP-1 β

Nomenclature	CCR6	CCR7	CCR8	CCR9	CCR10
Other names	GPR-CY4, CKR-L3, STRL-22, DRY-6, DCR2, BN-1, GPR29	EBI-1, BLR-2	TER1, CKR-L1, GPR-CY6, ChemR1	GPR 9-6	GPR-2
Ensembl ID	ENSG00000153467	ENSG00000126353	ENSG00000179934	ENSG00000173585	ENSG00000184451
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Agonists	CCL20 (LARC), HBD2	CCL19 (ELC, MIP-3 β), CCL21 (SLC)	CCL1 (I-309), CCL4 (MIP-1 β), CCL16 (HCC-4), CCL17 (TARC), HHV8 vMIP-I	CCL25 (TECK)	CCL27 (Eskine, ALP, CTACK), CCL28 (MEC)
Selective agonists	LARC, HBD2	ELC, SLC	I-309	TECK	Eskine, MEC
Selective antagonists	—	—	MCV MC148R (vMCC-I)	—	—
Probes	[¹²⁵ I]-LARC	[¹²⁵ I]-ELC, [¹²⁵ I]-SLC	[¹²⁵ I]-I309	[¹²⁵ I]-TECK	—

Nomenclature	CXCR1	CXCR2	CXCR3	CXCR4	CXCR5	CXCR6
Other names	IL8R _A , IL-8 receptor type I, IL-8 receptor α	IL8R _B , IL-8 receptor type II, IL-8 receptor β	IP10/Mig R, GPR9	HUMSTR, LESTR, fusin, HM89, LCR1	BLR-1, MDR15	STRL-33, BONZO, TYMSTR
Ensembl ID	ENSG00000163464 ENSG00000172215	ENSG00000180871	SwissProt P49682	ENSG00000121966	ENSG00000160683	
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Agonists	CXCL6 (GCP-2), CXCL8 (IL-8), cytokine domain of tyrosyl tRNA synthetase	CXCL1 (GRO α), CXCL2 (GRO β), CXCL3 (GRO γ), CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL7 (NAP-2), CXCL8 (IL-8), HCMV UL146 (vCXCL-1)	CXCL9 (Mig), CXCL10 (IP10), CXCL11 (I-TAC)	CXCL12 α & β (SDF-1 α , SDF-1 β)	CXCL13 (BLC, BCA-1)	CXCL16 (SR-PSOX)
Selective agonists	—	GRO α , GRO γ , GRO β , NAP-2, ENA78	IP10, MIG, I-TAC	SDF-1 α , SDF-1 β , X4-HIV gp120	BLC	CXCL16
Selective antagonists	—	SB225002 (7.7)	eotaxin, MCP-3	AMD3100, HIV-1 Tat, T134, ALX41-4C	—	—
Probes	[¹²⁵ I]-IL8	[¹²⁵ I]-IL8, [¹²⁵ I]-GRO α , [¹²⁵ I]-NAP-2, [¹²⁵ I]-ENA78	[¹²⁵ I]-IP10, [¹²⁵ I]-I-TAC/CXCL11	[¹²⁵ I]-SDF-1	—	[¹²⁵ I]-CXCL16

CXCR1 and CXCR2 also couple to phospholipase C when co-transfected with members of the G_{q/11} family of G proteins. Mouse CXCR2 binds iodinated mouse KC and mouse MIP-2 with high affinity (mouse KC and MIP-2 are homologues of human GRO chemokines), but shows low affinity for human IL-8.

Nomenclature	CX ₃ CR1	XCR1
Other names	CMKBRL1, V28	GPR5
Ensembl ID	ENSG00000168329	ENSG00000173578
Principal transduction	G _{i/o}	G _{i/o}
Agonists	CX3CL1 (Fractalkine)	XCL1 α and β (Lymphotactin α and β)
Selective agonists	Fractalkine	Lymphotactin
Probes	[¹²⁵ I]-Fractalkine	SEAP-XCL1

Three human 7TM chemokine binding proteins have been identified that lack a known signalling function: D6 (ENSG00000144648), which binds multiple CC chemokines; a molecule previously inappropriately named CCR11 and now known as CCX CKR or the human homolog of the bovine gustatory receptor PPAR1 (ENSG00000118519, ENSG00000129048), which binds ELC, SLC and TECK; and Duffy, a highly promiscuous CC and CXC chemokine binding protein expressed mainly on erythrocytes. Specific chemokine receptors facilitate cell entry by microbes, such as *Plasmodium vivax*, HIV-1 and the poxvirus myxoma virus. Virally encoded chemokine receptors are known (e.g. US28, a homologue of CCR1 from human cytomegalovirus and ECRF3, a homologue of CXCR2 from *Herpesvirus saimiri*), but their role in viral life cycles is not established. Viruses can exploit or subvert the chemokine system by producing chemokine antagonists and scavengers. The CC chemokine family (CCL1–28) includes I309 (CCL1), MCP-1 (CCL2), MIP-1 α (CCL3), MIP-1 β (CCL4), RANTES (CCL5), MCP-3 (CCL7), MCP-2 (CCL8), eotaxin (CCL11), MCP-4 (CCL13), HCC-1 (CCL14), Lkn-1/HCC-2 (CCL15), TARC (CCL17), ELC (CCL19), LARC (CCL20), SLC (CCL21), MDC (CCL22), MPIF-1 (CCL23), eotaxin-2 (CCL24), TECK (CCL25), eotaxin (CCL26), eskine/CTACK (CCL27) and MEC (CCL28). The CXC chemokine family (CXCL1–16) includes GRO α (CXCL1), GRO β (CXCL2), GRO γ (CXCL3), platelet factor 4 (CXCL4), ENA78 (CXCL5), GCP-2 (CXCL6), NAP-2 (CXCL7), IL-8 (CXCL8), MIG (CXCL9), IP10 (CXCL10), I-TAC (CXCL11), SDF-1 (CXCL12), BLC (CXCL13), BRAK (CXCL14), mouse lungkine (CXCL15) and SR-PSOX (CXCL16). The CX₃C chemokine (CX3CL1) is also known as fractalkine (neurotactin in the mouse). Unlike other chemokines, this molecule is multimodular containing a chemokine domain, an elongated mucin-like stalk, a transmembrane domain and a cytoplasmic tail. Both plasma membrane-associated and shed forms have been identified. The C chemokine (XCL1) is also known as lymphotactin. The non-chemokine family includes the cytokine domain of tyrosyl-tRNA synthetase, HBD2, HIV gp120 and HIV Tat.

Abbreviations: BLC, B-lymphocyte chemokine; ELC, Epstein–Barr virus-induced receptor ligand chemokine; ENA-78, epithelial cell-derived neutrophil-activating factor-78 amino acids; GCP-2, granulocyte chemoattractant protein 2; HBD2, human β defensin 2; HCC, hemofiltrate CC chemokine; IL-8, interleukin 8; IP-10, γ -interferon-inducible protein 10; I-TAC, interferon-inducible T-cell α chemoattractant; LARC, liver and activation-related chemokine (CCL20); MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MEC, mucosa expressed chemokine; MIG, monokine-induced by γ -interferon; MIP, macrophage inflammatory protein; MPIF-1, myeloid progenitor inhibitory factor 1; NAP-2, neutrophil-activating peptide 2; RANTES, regulated on activation normal T cell expressed and secreted; SDF, stromal cell-derived factor; SEAP, secreted alkaline phosphatase; SLC, secondary lymphoid tissue chemokine; TARC, T-cell and activation-related chemokine; TECK, thymus-expressed chemokine

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Cholecystokinin

Overview: Cholecystokinin receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on CCK receptors, Noble *et al.*, 1999) are activated by the endogenous peptides cholecystokinin (CCK)-4, CCK-8, CCK-33 and gastrin. There is evidence for species homologues of CCK₂ receptors distinguished by the relative affinities of the two stereoisomers of devazepide, *R*-L365260 and *S*-L365260, or by the differences in affinity of the agonist BC264 (Durieux *et al.*, 1992).

Nomenclature	CCK ₁	CCK ₂
Other names	CCK _A	CCK _B , CCK _B /gastrin
Ensembl ID	ENSG00000163394	ENSG00000110148
Principal transduction	G _{q/11} /G _s	G _s
Rank order of potency	CCK-8 > > gastrin, des-CCK-8 > CCK-4	CCK-8 ≥ gastrin, des-CCK-8, CCK-4
Selective agonists	A71623, JMV180, GW5823	Desulfated CCK-8, gastrin, CCK-4, BC264, RB400
Selective antagonists	Devazepide (9.8), T0632 (9.6), SR27897 (9.2), IQM95333 (9.2), PD140548 (7.9–8.6), lorglumide (7.2)	YM022 (10.2), L740093 (10.0), GV150013 (9.3), RP73870 (9.3), L365260 (7.5–8.7), LY262691 (7.5)
Probes	[³ H]-Devazepide (0.2 nM)	[³ H]-Propionyl-BC264 (0.15 nM), [³ H]-PD140376 (0.2 nM), [³ H]-L365260 (2 nM), [³ H]- or [¹²⁵ I]-gastrin (1 nM), [¹²⁵ I]-PD142308 (0.25 nM)

A mitogenic gastrin receptor, which can be radiolabelled with [¹²⁵I]-gastrin-(1–17) and which appears to couple to the G_s family of G proteins, has been described in human colon cancer cells (Bold *et al.*, 1994) and other cell lines (e.g. pancreatic AR42J and Swiss 3T3 fibroblasts, Seva *et al.*, 1994; Singh *et al.*, 1995).

Abbreviations: A71623, Boc-Trp-Lys(O-toluyllaminocarbonyl)-Asp-(NMe)Phe-NH₂; BC264, Tyr(SO₃H)-gNle-mGly-Trp-(NMe)Nle-Asp-Phe-NH₂; GV150013, (+)-N-(1-[1-adamantane-1-methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-yl)-*N'*-phenylurea; GW5823, 2-[3-(1*H*-indazol-3-ylmethyl)-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]diazepin-1-yl]-*N*-isopropyl-*N*-(methoxyphenyl)acetamide; IQM95333, (4*α*,5*R*)-2-benzyl-5[*N*-(*tert*-butoxycarbonyl)-L-Trp]amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine; JMV180, Boc-Tyr(SO₃H)Ahx-Gly-Trp-Ahx-Asp²phenylethyl ester; L365260, 3*R*(+)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3-methylphenyl)urea; L740093, *N*-([3*R*]-5-[3-azabicyclo[3.2.2]nonan-3-yl]-2,3-dihydro-1-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3-methylphenyl)urea; LY262691, *trans*-*N*-(4-bromophenyl)-3-oxo-4,5-diphenyl-1-pyrazolidinecarboxamide(3.3.1.1^{3,7}); PD140376, L-3-([4-aminophenyl]methyl)-*N*-(α -methyl-*N*-[tricyclo(3.3.1.1*D*-Trp)- β -Ala]; PD140548, *N*-(α -methyl-*N*-[tricyclo(3.3.1.1*L*-Trp)-*D*-3-(phenylmethyl)- β -Ala]; PD142308, iodinated PD140548; RB400, HOOC-CH₂-CO-Trp-NMe(Nle)-Asp-Phe-NH₂; RP73870, ([*R*]); SR27897, 1-([2-{4-(2-chlorophenyl)thiazole-2-yl}amino-carbonyl]indolyl)acetic acid; T0632, sodium (*S*)-3-(1-[2-fluorophenyl]-2,3-dihydro-3-[3-isoquinolyl]-carbonyl)amino-6-methoxy-2-oxo-1*H*-indole)propanoate; YM022, (*R*)-1-(2,3-dihydro-1-[2'-methylphenacyl]-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-3-(3-methylphenyl)urea

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Corticotropin-releasing factor

Overview: Corticotropin-releasing factor (CRF, nomenclature as recommended by the NC-IUPHAR on Corticotropin-releasing Factor Receptors, see Hauger *et al.*, 2003) receptors are activated by the endogenous peptides CRF (also known as corticotropin-releasing hormone [CRH], a 41 amino-acid peptide, ENSG00000147571), urocortin 1 (a 40 amino-acid peptide, ENSG00000163794), urocortin 2 (a 38 amino-acid peptide, ENSG00000145040) and urocortin 3 (a 38 amino-acid peptide, ENSG00000178473). CRF₁ and CRF₂ receptors are activated non-selectively by CRF and urocortin 1. Binding to CRF receptors can be conducted using [¹²⁵I]-Tyr⁰-CRF or [¹²⁵I]-Tyr⁰-sauvagine with K_d values of 0.1–0.4 nM. CRF₁ and CRF₂ receptors are non-selectively antagonized by α -helical CRF-(9-41), D-Phe-CRF-(12-41) and astressin.

Nomenclature	CRF ₁	CRF ₂
Other names	CRF-RA, PC-CRF	CRF-RB, HM-CRF
Ensembl ID	ENSG00000120088	ENSG00000106113
Principal transduction	G _s	G _s
Selective agonists	—	Urocortin 2 (Reyes <i>et al.</i> , 2001), urocortin 3 (Lewis <i>et al.</i> , 2001)
Selective antagonists	CP154526 (8.3–9.0, Lundkvist <i>et al.</i> , 1996), NBI27914 (8.3–9.0, Chen <i>et al.</i> , 1996), antalarmin (8.3–9.0, Webster <i>et al.</i> , 1996), CRA1000 (8.3–9.0, Chaki <i>et al.</i> , 1999), DMP696 (8.3–9.0, He <i>et al.</i> , 2000), R121919 (8.3–9.0, Zobel <i>et al.</i> , 2000), SRA125543A (8.7–9.0, Gully <i>et al.</i> , 2002)	K41498 (9.2, Lawrence <i>et al.</i> , 2002), K31440 (8.7–8.8, Ruhmann <i>et al.</i> , 2002), antisauvagine-30 (Ruhmann <i>et al.</i> , 1998)

A CRF binding protein has been identified (CRF-BP, ENSG00000145708) to which both CRF and urocortin 1 bind with high affinities, which has been suggested to bind and inactivate circulating CRF (Perkins *et al.*, 1995).

Abbreviations: **antalarmin**, N-butyl-N-ethyl-(2,5,6-trimethyl)-7-[2,4,6-trimethylphenyl]-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl-amine; **astressin**, cyc^{30–33}[D-Phe¹²,Nle^{21,38},Glu³⁰,Lys³³]CRF-(12-41); **CP154526**, butyl-ethyl-(2,5-dimethyl-7-[2,4,6-trimethylphenyl]-7H-pyrrolo[2,3-*d*]pyrimidin-4-yl)amine; **CRA1000**, 2-(N-[2-methylthio-4-isopropylphenyl]-N-ethyl-amino-4-[4-(3-fluorophenyl)-1,2,3,6-tetrahydropyridin-1-yl]-6-methylpyrimidine); **DMP696**, 4-(1,3-dimethoxyprop-2-ylamino)-2,7-dimethyl-8-(2,4-dichlorophenyl)pyrazolo[1,5-*a*]-1,3,5-triazine; **D-Phe-CRF-(12-41)**, D-Phe¹²,Nle^{21,38}, α MeLeu³⁷-CRF; **K31440**, Ac-(D-Tyr¹¹,His¹²,Nle¹⁷)sauvagine-(11-40); **K41498**, [D-Phe¹¹,His¹²,Nle¹⁷]sauvagine-(11-40); **NBI27914**, 2-methyl-4-(N-propyl-N-cyclopropanemethylamino)-5-chloro-6-(2,4,6-trichloroanilino)pyrimidine; **R121919**, 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[1,5-*a*]pyrimidin-7-amine; **SRA125543A**, 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-N-(2-propynyl)-1,3-thiazol-2-amine hydrochloride

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Dopamine

Overview: Dopamine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Dopamine Receptors, see Schwartz *et al.*, 1998) are commonly divided into D1-like (D1 and D5) and D2-like (D2, D3 and D4) families, where the endogenous agonist is dopamine. Quinpirole is an agonist with selectivity for D2-like receptors.

Nomenclature	D1	D2	D3	D4	D5
Other names	D ₁ , D _{1A}	D ₂	D ₃	D ₄	D ₅ , D _{1B}
Ensembl ID	ENSG00000184845	ENSG00000149295	ENSG00000151577	ENSG00000069696	ENSG00000169676
Principal transduction	G _s , G _{olf}	G _{i/o}	G _{i/o}	G _{i/o}	G _s
Selective agonists	R(+)SKF81297, R(+)SKF38393	—	PD128907	PD168077, A412997 (Moreland <i>et al.</i> , 2005)	—
Selective antagonists	SCH23390, SKF83566, SCH39166	Raclopride, domperidone	S33084 (9.6, Millan <i>et al.</i> , 2000), nafadotride (9.5), (+)S14297 (8.7, Millan <i>et al.</i> , 1994), SB277011 (7.5, Reavill <i>et al.</i> , 2000)	L745870 (9.3), U101958 (8.9, Schlachter <i>et al.</i> , 1997), L741742 (8.5)	—
Probes	[³ H]-SCH23390 (0.2 nM), [¹²⁵ I]- SCH23982 (0.7 nM)	[³ H]-Raclopride, [[³ H]-spiperone	[³ H]-7-OH-DPAT, [³ H]-PD128907, [³ H]-spiperone	[³ H]-NGD941 (5 nM, Primus <i>et al.</i> , 1997), [¹²⁵ I]-L750667 (1 nM, Patel <i>et al.</i> , 1996), [³ H]-spiperone	[¹²⁵ I]-SCH23982 (0.8 nM) [³ H]- SCH23390 (0.5 nM)

The selectivity of many of these agents is less than two orders of magnitude. [³H]-Raclopride exhibits similar high affinity for D2 and D3 receptors (low affinity for D4), but has been used to label D2 receptors in the presence of a D3-selective antagonist. [³H]-7-OH-DPAT has similar affinity for D2 and D3 receptors, but labels only D3 receptors in the absence of divalent cations. The pharmacological profile of the D5 receptor is similar to, yet distinct from, that of the D1 receptor. The splice variants of the D2 receptor are commonly termed D2S and D2L (short and long). The *DRD4* gene is highly polymorphic in humans, with allelic variations of the protein from amino acid 387–515.

Abbreviations: L741742, 5-(4-chlorophenyl)-4-methyl-3-(1-[2-phenethyl]piperidin-4-yl)isoxazole; L745870, 3-[[4-(4-chlorophenyl)piperazin-1-yl]methyl]-1H-pyrrolo[2,3-*b*]pyridine; L750667, iodinated L745870; NGD941, 2-phenyl-4(S)-(4-[2-pyrimidinyl]-[piperazin-1-yl]-methyl)-imidazole dimaleate; (+)-7-OH-DPAT, (+)-7-hydroxy-2-aminopropylaminotetralin; PD128907, R-(+)-*trans*-3,4,4a,10b-tetrahydro-4-propyl-2H,5H-[1]benzopyrano[4,3-*b*]-1,4-oxazine-9-ol; PD168077, N-methyl-4-(2-cyanophenyl)piperazinyl-3-methylbenzamide; (+)S14297, (+)-7-(N,N-dipropylamino)-5,6,7,8-tetrahydronaphtho(2,3*b*)dihydro-2,3-furane; S33084, (3*aR*,9*bS*)-N[4-(8-cyano-1,3*a*,4,9*b*-tetrahydro-3*H*-benzopyran-3,4-*c*]pyrrole-2-yl)-butyl] (4-phenyl)benzamide; SB277011, *trans*-N-(4-[2-[6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl]ethyl]cyclohexyl)-4-quinolininecarboxamide; SCH23390, 7-chloro-8-hydroxy-3-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; SCH23982, 8-iodo-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine; SCH39166, (–)-*trans*-6,7,7*a*,8,9,13*b*-hexahydro-3-chloro-2-hydroxy-N-ethyl-5*H*-benzo[*d*]-naphtho(2,3*b*)azepine; R(+)-SKF38393, R(+)-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; R(+)-SKF81297, R(+)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzazepine; SKF83566, (–)-7-bromo-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-3-benzazepine; U101958, 3-isopropoxy-N-methyl-N-(1-[phenylmethyl]-4-piperidinyl)-2-pyridinylamine

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Endothelin

Overview: Endothelin receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Endothelin Receptors, Davenport, 2002) are activated by the endogenous 21 amino-acid peptides endothelin-1 (ET-1, ENSG00000078401), ET-2 (ENSG00000127129) and ET-3 (ENSG00000124205). Non-selective peptide (e.g. TAK044, pA₂ 8.4) and non-peptide (e.g. bosentan, pA₂ 6.0–7.2; SB209670, pA₂ 9.4) antagonists can block both ET_A and ET_B receptors. Splice variants of the ET_A receptor have been identified in rat pituitary cells; one of these, ET_AR-C13, appeared to show loss of function with comparable plasma membrane expression (Hatae *et al.*, 2007).

Nomenclature	ET _A	ET _B
Ensemble ID	ENSG00000151617	ENSG00000136160
Principal transduction	G _{q/11} , G _s	G _{q/11} , G _{i/o}
Potency order	ET-1, ET-2 > ET-3 (Maguire and Davenport, 1995)	ET-1, ET-2, ET-3
Selective agonists	—	[Ala ^{1,3,11,15}]ET-1 (Molenaar <i>et al.</i> , 1992), sarafotoxin S6c (Russell and Davenport, 1996), IRL1620 (Watakabe <i>et al.</i> , 1992), BQ3020 (Russell and Davenport, 1996)
Selective antagonists	A127722 (9.2–10.5, Opgenorth <i>et al.</i> , 1996), LU135252 (8.9, Riechers <i>et al.</i> , 1996), SB234551 (8.7–9.0, Ohlstein <i>et al.</i> , 1998), PD156707 (8.2–8.5, Maguire <i>et al.</i> , 1997), FR139317 (7.3–7.9, Maguire and Davenport, 1995), BQ123 (6.9–7.4, Maguire and Davenport, 1995)	BQ788 (8.4, Russell and Davenport, 1996), A192621 (8.1, von Geldern <i>et al.</i> , 1999), IRL2500 (7.2, Russell and Davenport, 1996), Ro468443 (7.1, Breu <i>et al.</i> , 1996)
Probes	[³ H]-S0139 (0.6 nM), [³ H]-BQ123 (3.2 nM, Ihara <i>et al.</i> , 1995), [¹²⁵ I]-PD164333 (0.2 nM, Davenport <i>et al.</i> , 1998), [¹²⁵ I]-PD151242 (0.5 nM, Davenport <i>et al.</i> , 1994)	[¹²⁵ I]-IRL1620 (20 pM, Watakabe <i>et al.</i> , 1992), [¹²⁵ I]-BQ3020 (0.1 nM, Molenaar <i>et al.</i> , 1992), [¹²⁵ I]-[Ala ^{1,3,11,15}]ET-1 (0.2 nM, Molenaar <i>et al.</i> , 1992)

Subtypes of the ET_B receptor have been proposed, although gene disruption studies in mice suggest that the heterogeneity results from a single gene product (Mizuguchi *et al.*, 1997).

Abbreviations: A127722, *trans-trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-([N,N-dibutylamino]carbonylmethyl)pyrrolidine-3-carboxylate; A192621, (2*R*,3*R*,4*S*)-2-(4-propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-[2,6-diethylphenyl]acetamido)pyrrolidine-3-carboxylic acid; BQ123, *cyc*(DTrp-DAsp-Pro-D-Val-Leu); BQ3020, *N*-acetyl-Leu-Met-Asp-Lys-Glu-Ala-Val-Tyr-Phe-Ala-His-Leu-Asp-Ile-Ile-Trp; BQ788, *N*-*cis*-2,6-dimethylpiperidinocarbonyl-L-γ-methylleucyl-D-1-methoxycarbonyl-D-norleucine; FR139317, (R)2-([R-2-((S)-2-([1-[hexahydro-1*H*-azepinyl]carbonyl]amino)methyl)pentanoyl]amino-3-(3-[methyl-1*H*-indodolyl]propionylamino-3-(2-pyridyl)propionate; IRL1620, Suc[Glu⁹,Ala^{11,15}]ET-1₁₀₋₂₁; IRL2500, *N*-(3,5-dimethylbenzoyl)-*N*-methyl-(D)-(4-phenylphenyl)-Ala-Trp; LU135252, (+)-(*S*)-2-(4,6-dimethoxypyrimidin-2-yl)-3-methoxy-3,3-propionic acid; PD151242, (N-[[hexahydro-1-azepinyl]carbonyl]Leu(1-Me)-DTrp-DTyr; PD156707, 2-benzo[1,3]dioxol-5-yl-4-(4-methoxyphenyl)-4-oxo-3-(3,4,5-trimethoxybenzyl)-but-2-enoate; PD164333, 2-benzo[1,3]dioxol-5-yl-4-(3-[2-(4-hydroxyphenyl)-ethylcarbamoyl]-propoxy)-4,5-dimethoxy-phenyl-3-(4-methoxy-benzoyl)-but-2-enoate; RES7011, *cyc*(Gly-Asn-Trp-His-Gly-Thr-Ala-Pro-Asp)-Trp-Phe-Phe-Asn-Tyr-Tyr-Trp; Ro468443, (R)-4-*tert*-butyl-*N*-(6-[2,3-dihydroxypropoxy]-5-[2-methoxyphenoxy]-2-[4-methoxyphenyl]-pyrimidin-4-yl)-benzene-sulfonamide; S0139, 27-O-3-(2-[3-carboxyacryloylamino]-5-hydroxyphenyl)-acryloyloxymyricone, sodium salt; SB209670, (+)-1*S*,2*R*,3-*S*-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-prop-1-yloxyindane-2-carboxylate; SB234551, (E)-α-([1-butyl-5-{2-[(2-carboxyphenyl)methoxy]-4-methoxyphenyl}-1*H*-pyrazol-4-yl]methylene)-6-methoxy-1,3-benzodioxole-5-propanoic acid; TAK044, *cyc*(D-Asp-Asp(Php)-Asp-D-Thg-Leu-D-Trp)-4-oxobut-2-enoate

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Free fatty acid

Overview: Free fatty acid receptors (FFA, provisional nomenclature) are activated by free fatty acids, such that long chain saturated and unsaturated fatty acids (C16:0, C18:0, C18:1, C18:2, C18:3,n-6, C20:4, C20:5,n-3, C22:6,n-3, Briscoe *et al.*, 2003; Itoh *et al.*, 2003; Kotarsky *et al.*, 2003) activate FFA₁ receptors, while short chain fatty acids (C4, C3 & C2) activate FFA₂ (Brown *et al.*, 2003; Le Poul *et al.*, 2003; Nilsson *et al.*, 2003) and FFA₃ (Brown *et al.*, 2003; Le Poul *et al.*, 2003) receptors. In addition, the thiazolidinedione PPAR γ agonists rosiglitazone and troglitazone have been suggested to activate FFA₁ (Kotarsky *et al.*, 2003; Stoddart *et al.*, 2007).

Nomenclature	FFA ₁	FFA ₂	FFA ₃
Other names	GPR40 (Sawzdargo <i>et al.</i> , 1997)	GPR43 (Sawzdargo <i>et al.</i> , 1997)	GPR41 (Sawzdargo <i>et al.</i> , 1997). LSSIG (Senga <i>et al.</i> , 2003)
Ensembl ID	ENSG00000126266	ENSG00000126262	ENSG00000185897
Principal transduction	G _{q/11} (Briscoe <i>et al.</i> , 2003; Itoh <i>et al.</i> , 2003; Kotarsky <i>et al.</i> , 2003)	G _{q/11} , G _{i/o} (Brown <i>et al.</i> , 2003; Le Poul <i>et al.</i> , 2003; Nilsson <i>et al.</i> , 2003)	G _{q/11} , G _{i/o} (Brown <i>et al.</i> , 2003; Le Poul <i>et al.</i> , 2003)
Selective agonists	Linoleic acid (Briscoe <i>et al.</i> , 2003; Itoh <i>et al.</i> 2003), GW9508 (pEC ₅₀ 7.3; Briscoe <i>et al.</i> , 2006; Sum <i>et al.</i> , 2007)	—	—
Selective antagonists	GW1100 (Briscoe <i>et al.</i> , 2006; Stoddart <i>et al.</i> , 2007)	—	—

GW1100 is also an oxytocin receptor antagonist (Briscoe *et al.*, 2006).

GPR120 (ENSG00000186188) is an additional target for unsaturated long chain free fatty acids (Hirasawa *et al.*, 2005; Katsuma *et al.*, 2005; Gotoh *et al.*, 2007) and GW9508 (pEC₅₀ 5.7; Briscoe *et al.*, 2006). GPR42 (ENSG00000126251) is a further member of the family (ENSF00000003273) with as yet undefined characteristics (Brown *et al.*, 2003).

Abbreviations: C16:0, palmitic acid; C18:0, stearic acid; C18:1, oleic acid; C18:2, linoleic acid; C18:3, n-6, γ -linolenic acid; C2, acetic acid; C20:4, arachidonic acid; C20:5, n-3, 5z,8z,11z,14z,17z-eicosapentaenoic acid, EPA; C22:6, n-3, 4z,7z,10z,13z,16z,19z-docosahexaenoic acid, DHA; C3, propionic acid; C4, butyric acid; GW1100, ethyl 4-(5-[[2-(ethyloxy)-5-pyrimidinyl]methyl]-2-[[4-(4-fluorophenyl)methyl]thio]-4-oxo-1[4H]-pyrimidinyl)benzoate; GW9508, 3-(4-[[3-[phenyloxy]phenyl)methyl]amino]phenyl)propanoic acid

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Frizzled

Overview: Receptors of the Frizzled class (FZD, provisional nomenclature, see Foord *et al.*, 2005), which also includes Smoothened (Smo, ENSG00000128602), are 7TM receptors originally identified in *Drosophila* (Chan *et al.*, 1992), which are highly conserved across species. FZD are activated by WNTs, which are palmitoylated, cysteine-rich glycoprotein hormones with fundamental functions in ontogeny and tissue homeostasis. FZD signalling was initially divided into two pathways, being either dependent on the accumulation of the transcription factor β -catenin (ENSG00000168036) or being β -catenin-independent (often referred to as canonical vs non-canonical WNT/FZD signaling, respectively). WNT stimulation of FZDs can, in cooperation with the low density lipoprotein receptors (LRP 5, ENSG00000162337 and LRP6, ENSG00000070018), lead to the inhibition of a constitutively active destruction complex, which results in the accumulation of β -catenin. β -Catenin, in turn, modifies gene transcription in concert with TCF/LEF transcription factors. β -Catenin-independent FZD signaling is far more complex with regard to the diversity of the activated pathways. WNT/FZD signalling can lead to the elevation of intracellular calcium (Slusarski *et al.*, 1997) and activation of cGMP-specific PDE6 (Ahumada *et al.*, 2002), which has been implicated to be mediated through heterotrimeric G-proteins. FZD signalling can also occur through Dishevelled phosphoproteins (ENSF00000001536) to RAC-1 and JNK, as well as Rho and ROCK kinases. The pattern of cell signalling is complicated by the presence of additional ligands which can enhance (Norrin or R-spondin) or inhibit FZD function (secreted Frizzled-related proteins [sFRP], Wnt inhibitory factor [WIF], SOST or Dickkopf), as well as modulatory proteins with positive (Ryk, ENSG00000163785; ROR1, ENSG00000185483 and ROR2, ENSG00000169071) and negative (Kremen) regulatory features, which may also function as independent signalling proteins.

Nomenclature	FZD ₁	FZD ₂	FZD ₃	FZD ₄	FZD ₅
Other names	Frizzled-1	Frizzled-2	Frizzled-3	Frizzled-4, CD344	Frizzled-5
Ensembl ID	ENSG00000157240	ENSG00000180340	ENSG00000104290	ENSG00000174804	ENSG00000163251

Nomenclature	FZD ₆	FZD ₇	FZD ₈	FZD ₉	FZD ₁₀
Other names	Frizzled-6	Frizzled-7	Frizzled-8	Frizzled-9, CD349	Frizzled-10, CD350
Ensembl ID	ENSG00000164930	ENSG00000155760	ENSG00000177283	ENSG00000188763	ENSG00000111432

There is limited knowledge about WNT/FZD specificity and which molecular entities determine the signalling outcome of a specific WNT/FZD pair. There is also a scarcity of information on basic pharmacological characteristics of FZDs, such as binding constants, ligand specificity or concentration-response relationships.

Ligands associated with FZD signalling: WNTs: WNT1 (ENSG00000125084), WNT2 (ENSG00000105989, also known as Int-1-related protein), WNT2B (ENSG00000134245, also known as WNT-13), WNT3 (ENSG00000108379), WNT3A (ENSG00000154342), WNT4 (ENSG00000162552), WNT5A (ENSG00000114251), WNT5B (ENSG00000111186), WNT6 (ENSG00000115596), WNT7A (ENSG00000154764), WNT7B (ENSG00000188064), WNT8A (ENSG00000061492), WNT8B (ENSG00000075290), WNT9A (ENSG00000143816, also known as WNT-14), WNT9B (ENSG00000158955, also known as WNT-15 or WNT-14b), WNT10A (ENSG00000135925), WNT10B (ENSG00000169884, also known as WNT-12), WNT11 (ENSG00000085741) and WNT16 (ENSG00000002745).

Proteins that interact with FZDs: Norrin (ENSG00000124479), R-spondin 1 (ENSG00000169218), R-spondin 2 (ENSG00000147655), R-spondin 3 (ENSG00000146374), R-spondin 4 (ENSG00000101282), sFRP 1 (ENSG00000104332), sFRP 2 (ENSG00000145423), sFRP 3 (ENSG00000162998), sFRP 4 (ENSG00000106483), sFRP 5 (ENSG00000120057),

Proteins that interact with WNTs or LRP: Dickkopf 1 (ENSG00000104901), WIF 1 (ENSG00000156076), SOST (ENSG00000167941), Kremen 1 (ENSG00000183762) and Kremen 2 (ENSG00000131650)

Abbreviations: FZD, Frizzled; TCF/LEF, ternary complex factor/lymphoid enhancer binding factor

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GABA_B

Overview: Functional GABA_B receptors (nomenclature agreed by NC-IUPHAR Subcommittee on GABA_B receptors, Bowery *et al.*, 2002; see also Pin *et al.*, 2007) are formed from the heterodimerization of two similar 7TM subunits termed GABA_{B1} and GABA_{B2} (Bowery *et al.*, 2002; Pin *et al.*, 2004, 2007). The GABA_{B1} subunit, when expressed alone, binds both antagonists and agonists, but the affinity of the latter is generally 10–100-fold less than for the native receptor. The GABA_{B1} subunit when expressed alone is not transported to the cell membrane and is non-functional. Co-expression of GABA_{B1} and GABA_{B2} subunits allows transport of GABA_{B1} to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca²⁺ channels (Ca_v2.1, Ca_v2.2), or inwardly rectifying potassium channels (Kir3) (Bowery and Enna, 2000; Bowery *et al.*, 2002; Bettler *et al.*, 2004). The GABA_{B1} subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus flytrap module (VTM), whereas the GABA_{B2} subunit mediates G-protein coupled signalling (Bowery *et al.*, 2002, Pin *et al.*, 2004). The two subunits interact allosterically in that GABA_{B2} increases the affinity of GABA_{B1} for agonists and reciprocally GABA_{B1} facilitates the coupling of GABA_{B2} to G-proteins (Pin *et al.*, 2004; Kubo and Tateyama, 2005). GABA_{B1} and GABA_{B2} subunits assemble in a 1:1 stoichiometry by means of a coiled-coil interaction between α -helices within their carboxy-termini that masks an endoplasmic reticulum retention motif (RXRR) within the GABA_{B1} subunit but other domains of the proteins also contribute to their heteromerization (Bettler *et al.*, 2004; Pin *et al.*, 2004). Four isoforms of the human GABA_{B1} subunit have been cloned. The predominant GABA_{B1(a)} and GABA_{B1(b)} isoforms, which are most prevalent in neonatal and adult brain tissue respectively, differ in their ECD sequences as a result of the use of alternative transcription initiation sites. GABA_{B1(a)}-containing heterodimers localise to distal axons and mediate inhibition of glutamate release in the CA3-CA1 terminals, and GABA release onto the layer 5 pyramidal neurons, whereas GABA_{B1(b)}-containing receptors occur within dendritic spines and mediate slow postsynaptic inhibition (Vigot *et al.*, 2006; Pérez-García *et al.*, 2006). Isoforms generated by alternative splicing are GABA_{B1(c)} that differs in the ECD, and GABA_{B1(e)}, which is a truncated protein that can heterodimerize with the GABA_{B2} subunit but does not constitute a functional receptor. Only the 1a and 1b variants are identified as components of native receptors (Bowery *et al.*, 2002). Additional GABA_{B1} subunit isoforms have been described in rodents (reviewed by Bettler *et al.*, 2004).

Nomenclature	GABA _B
Ensembl ID	GABA _{B1} ENSG00000168760; GABA _{B2} ENSG00000136928
Principal transduction	G _{i/o}
Selective agonists	3-APPA (CGP27492, 5 nM), 3-APMPA (CGP35024, 16 nM), (R)-(-)-baclofen (32 nM), CGP44532 (45 nM)
Selective antagonists	CGP62349 (2.0 nM), CGP55845 (6 nM), SCH50911 (3 μ M), 2-hydroxy-s-(-)-saclofen (11 μ M), CGP35348 (27 μ M)
Probes (K _D)	[³ H](R)-(-)-baclofen, [³ H]CGP54626 (1.5 nM; Bittiger <i>et al.</i> , 1992), [³ H]CGP62349 (0.9 nM, Kier <i>et al.</i> , 1999), [¹²⁵ I]CGP64213 (1 nM, Galvez <i>et al.</i> , 2000), [¹²⁵ I]CGP71872 (K _i = 0.5 nM, Belley <i>et al.</i> , 1999)

Potencies of agonists and antagonists listed in the table, quantified as IC₅₀ values for the inhibition of [³H]CGP27492 binding to rat cerebral cortex membranes, are from Froestl and Mickel (1997) and Bowery *et al.* (2002). Radioligand K_D values relate to binding to rat brain membranes. CGP71872 is a photoaffinity ligand for the GABA_{B1} subunit (Belley *et al.*, 1999). In addition to the ligands listed in the table, Ca²⁺ binds to a site on the GABA_{B1} subunit to act as a positive allosteric modulator of GABA (Galvez *et al.*, 2000). In cerebellar Purkinje neurones, the interaction of Ca²⁺ with the GABA_B receptor enhances the activity of mGlu1, most probably via a direct association between the two receptors (Tabata *et al.*, 2004). Synthetic positive allosteric modulators with little, or no, intrinsic activity include CGP7930 and GS39783 (reviewed by Bettler *et al.*, 2004; Adams and Lawrence, 2007). Their site of action appears to be on the heptahelical domain of the GABA_{B2} subunit (Pin *et al.*, 2004; Dupuis *et al.*, 2006). Knock-out of the GABA_{B1} subunit in C57B mice causes the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas GABA_{B1}^{-/-} BALB/c mice, although also displaying spontaneous epileptiform activity, are viable. The phenotype of the latter animals additionally includes hyperalgesia, hyperlocomotion (in a novel, but not familiar, environment), hyperdopaminergia, memory impairment and behaviours indicative of anxiety (Enna and Bowery, 2004; Vacher *et al.*, 2006). A similar phenotype has been found for GABA_{B2}^{-/-} BALB/c mice (Gassmann *et al.*, 2004).

Abbreviations: 3-APMPA (CGP35024), 3-amino-propyl-(P-methyl)-phosphinic acid; 3-APPA (CGP27492), 3-amino-propyl-phosphinic acid; CGP7930, 2,6-Di-*tert*-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol; CGP35348, p-(3-aminopropyl)-P-diethoxymethylphosphinic acid; CGP44532, 3-amino-2-hydroxypropylmethylphosphinic acid; CGP54626, [S-(R,R)]-[3-[[1-(3,4-dichlorophenyl)ethyl]amino]-2-hydroxypropyl](cyclohexylmethyl)phosphinic acid; CGP55845, 3-[-1-(S)-(3,4-dichlorophenyl)-ethyl]amino-2(S)-hydroxypropyl-(P-benzyl)-phosphinic acid; CGP62349, [3-[-1-R-[[3-(methoxyphenylmethyl)hydroxyphosphinyl]-2(S)-hydroxypropyl]amino]ethyl]-benzoic acid; CGP64213, [3-[-(R)-[[3-5N-[1-[2-[[3-iodo-4-hydroxyphenyl]ethyl]carboxamido]pentyl]hydroxyphosphinyl]-2(S)-hydroxy-propyl]amino]ethyl-benzoic acid; CGP71872, 3-(1-(R)-3-((5-(4-azido-2-hydroxy-5-iodobenzoylamino)pentyl)hydroxyphosphoryl)-2-(S)-hydroxypropylamino)ethyl)benzoic acid; GS39783, N,N'-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine; SCH90511, (+)-(2S)-5,5-dimethyl-2-morpholineacetic acid

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Galanin

Overview: Galanin receptors (provisional nomenclature) are activated by the endogenous peptides galanin (ENSG00000069482) and galanin-like peptide (GALP, ENSG00000105099). Human galanin is a 30 amino-acid non-amidated peptide (Evans and Shine, 1991); in other species, it is 29 amino acids long and C-terminally amidated. Amino acids 1–14 of galanin are highly conserved in mammals, birds, reptiles, amphibia and fish. Shorter peptide species (e.g. human galanin-1–19, (Bersani *et al.*, 1991a) and porcine galanin-5–29 (Sillard *et al.*, 1992)) and N-terminally extended forms (e.g. N-terminally seven and nine residue elongated forms of porcine galanin (Bersani *et al.*, 1991b; Sillard *et al.*, 1992)) have been reported.

Nomenclature	GAL ₁	GAL ₂	GAL ₃
Other names	Galanin-1 receptor, GALR1	Galanin-2 receptor, GALR2	Galanin-3 receptor, GALR3
Ensembl ID	ENSG00000166573	ENSG00000182687	ENSG00000128310
Principal transduction	G _{i/o}	G _{i/o} / G _{q/11}	G _{i/o}
Rank order of potency	Galanin > GALP (Ohtaki <i>et al.</i> , 1999)	GALP ≥ galanin (Ohtaki <i>et al.</i> , 1999)	GALP > galanin (Lang <i>et al.</i> , 2005)
Selective agonists	—	Galanin-(2–29) (Fathi <i>et al.</i> , 1997; Wang <i>et al.</i> , 1997), D-Trp ² -galanin-(1–29) (Smith <i>et al.</i> , 1997)	—
Selective antagonists	2,3-Dihydro-dithiin and -dithiepine-1,1,4,4-tetroxides (Scott <i>et al.</i> , 2000)	M871 (7.9, Sollenberg <i>et al.</i> , 2006)	—

Galanin-(1–11) is a high-affinity agonist at GAL₁/GAL₂ (pK_i 9) and galanin-(2–11) is selective for GAL₂ and Gal₃ compared to GAL₁ (Lu *et al.*, 2005). [¹²⁵I]-[Tyr²⁶]galanin binds to all three subtypes with K_d values ranging from 0.05 to 1 nM (Skofitsch *et al.*, 1986; Smith *et al.*, 1997, 1998; Wang *et al.*, 1997; Fitzgerald *et al.*, 1998). Porcine galanin-(3–29) does not bind to cloned GAL₁, GAL₂ or GAL₃ receptors, but a receptor that is functionally activated by porcine galanin-(3–29) has been reported in pituitary and gastric smooth muscle cells (Wynick *et al.*, 1993; Gu *et al.*, 1995). Additional galanin receptor subtypes are also suggested from studies with chimeric peptides (e.g. M15, M35 and M40), which act as antagonists in functional assays in the cardiovascular system (Ulman *et al.*, 1993), spinal cord (Wiesenfeld-Hallin *et al.*, 1992), locus coeruleus, hippocampus (Bartfai *et al.*, 1991) and hypothalamus (Leibowitz and Kim, 1992; Bartfai *et al.*, 1993), but exhibit agonist activity at some peripheral sites (Bartfai *et al.*, 1993; Gu *et al.*, 1995). The chimeric peptides M15, M32, M35, M40 and C7 are agonists at GAL₁ receptors expressed endogenously in Bowes human melanoma cells (Ohtaki *et al.*, 1999), and at heterologously expressed recombinant GAL₁, GAL₂ and GAL₃ receptors (Smith *et al.*, 1997; Fitzgerald *et al.*, 1998; Smith *et al.*, 1998).

Abbreviations: C7, galanin-(1–13)-spantide; M15, galanin-(1–13)-substance P-5–11 amide^also known as galantide; M32, galanin-(1–13)-neuropeptide Y amide-(25–36) amide; M35, galanin-(1–13)-bradykinin-(2–9) amide; M40, galanin-(1–13)-Pro-Pro-Ala-Leu-Ala-Leu-Ala-Leu-Ala amide; M871, galanin-(2–13)-Glu-His-(Pro)₃-(Ala-Leu)₂-Ala-amide

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Ghrelin

Overview: Ghrelin receptors (see Davenport *et al.*, 2005) are activated by a 28 amino-acid peptide originally isolated from rat stomach, where it is cleaved from a 117 amino-acid precursor (ENSG00000157017). The human gene encoding the precursor peptide has 83% sequence homology to rat prepro-ghrelin, although the mature peptides from rat and human differ by only two amino acids (Matsumoto *et al.*, 2001). Alternative splicing results in the formation of a second peptide, des-Gln¹⁴-ghrelin with equipotent biological activity (Hosoda *et al.*, 2000). A unique post-translational modification (octanoylation of Ser³) occurs in both peptides, essential for full activity in binding to the ghrelin receptors in the hypothalamus and pituitary; and the release of growth hormone release from the pituitary (Kojima *et al.*, 1999). Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding (Bednarek *et al.*, 2000).

Nomenclature	Ghrelin
Other names	GHS-R1a (Growth hormone secretagogue receptor type 1), growth hormone-releasing peptide receptor
Ensembl ID	ENSG00000121853
Principal transduction	G _{q/11}
Rank order of potency	Ghrelin = des-Gln-ghrelin (Matsumoto <i>et al.</i> , 2001; Bedendi <i>et al.</i> , 2003)
Selective antagonists	YIL781 (K _B 11 nM) (Esler <i>et al.</i> , 2007)
Probes	[¹²⁵ I-His ⁹]-ghrelin (0.4 nM, Katugampola <i>et al.</i> , 2001), [¹²⁵ I-Tyr ⁴]-ghrelin (0.5 nM, Bedendi <i>et al.</i> , 2003), [¹²⁵ I]-Tyr ⁴ -des-octanoyl (0.7 nM, Bedendi <i>et al.</i> , 2003)

Des-octanoyl ghrelin has been shown to bind (as [¹²⁵I]-Tyr⁴-des-octanoyl ghrelin) and have effects in the cardiovascular system (Bedendi *et al.*, 2003), which raises the possible existence of different receptor subtypes in peripheral tissues and the central nervous system. One study has reported constitutive activity of the ghrelin receptor and has identified a potent inverse agonist ([D-Arg¹, D-Phe⁵, D-Trp^{7,9}, Leu¹¹]-substance P, EC₅₀ 5.2 nM; Holst *et al.*, 2003).

Abbreviations: YIL781, 6-(4-fluorophenoxy)-3-([(3S)-1-isopropylpiperidin-3-yl]methyl)-2-methylquinazolin-4(3H)-one

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Glucagon, glucagon-like peptide and secretin

Overview: The glucagon family of receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on the Glucagon receptor family, see Mayo *et al.*, 2003) are activated by the endogenous peptide (27–44 aa) hormones glucagon, glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory polypeptide or GIP, ENSG00000159224), growth hormone-releasing hormone (GHRH, ENSG00000118702) and secretin (ENSG00000070031). One common precursor (ENSG00000115263) generates glucagon, GLP-1 and GLP-2 peptides (Irwin, 2001).

Nomenclature	Glucagon	GLP-1	GLP-2
Ensembl ID	ENSG00000141558	ENSG00000112164	ENSG00000065325
Principal transduction	G _s	G _s	G _s
Selective agonists	Glucagon	GLP-1-(7-37) (Dillon <i>et al.</i> , 1993); GLP-1-(7-36)amide (Thorens <i>et al.</i> , 1993), exendin-3 (Raufman <i>et al.</i> , 1991), exendin-4 (Thorens <i>et al.</i> , 1993)	GLP-2
Selective antagonists	L168049 (Cascieri <i>et al.</i> , 1999), des-His ¹ -[Glu ⁹]glucagon amide (Post <i>et al.</i> , 1993), BAY27-9955 (Petersen and Sullivan, 2001), NNC92-1687 (Madsen <i>et al.</i> , 1998)	Exendin-(9-39) (Thorens <i>et al.</i> , 1993); T0632 (Tibaduiza <i>et al.</i> , 2001)	—
Probes	[¹²⁵ I]-glucagon	[¹²⁵ I]-GLP-1-(7-36) amide, [¹²⁵ I]-exendin, [¹²⁵ I]-exendin-(9-39), [¹²⁵ I]-GLP-1-(7-37)	—

Nomenclature	GIP	GHRH	Secretin
Ensembl ID	ENSG00000010310	ENSG00000106128	ENSG00000080293
Principal transduction	G _s	G _s	G _s
Selective agonists	GIP	BIM28011 (Coy <i>et al.</i> , 1996)	Secretin
Selective antagonists	—	JV-1-36 (Schally and Varga, 1999), JV-1-38 (Schally and Varga, 1999)	[(CH ₂ NH) ^{4,5}]secretin (Kim <i>et al.</i> , 1993)
Probes	[¹²⁵ I]-GIP	[¹²⁵ I]-GHRH	[¹²⁵ I]-(Tyr ¹⁰)secretin

The glucagon receptor has been reported to interact with receptor activity modifying proteins (RAMPs), specifically RAMP2, in heterologous expression systems (Christopoulos *et al.*, 2003), although the physiological significance of this has yet to be established.

Abbreviations: BAY27-9955, (+)-3,5-diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-1,1'-biphenyl; BIM28011, [D-Ala²,Ala^{8,9,15,27},D-Arg²⁹]hGHRH-(1-29)NH₂; JV-1-36, [PhAc-Tyr¹,D-Arg²,Phe(4-Cl)⁶,Arg⁹,Abu¹⁵,Nle²⁷,D-Arg²⁸,Har²⁹]hGHRH(1-29)NH₂; JV-1-38, [PhAc-Tyr¹,D-Arg²,Phe(4-Cl)⁶,Har⁹,Tyr(Me)¹⁰,Abu¹⁵,Nle²⁷,D-Arg²⁸,Har²⁹]hGHRH(1-29)NH₂; L168049, 2-(4-pyridyl)-5-(4-chlorophenyl)-3-(5-bromo-2-propyloxyphenyl)pyrrole; NNC92-1687, 2-(benzimidazol-2-ylthio)-1-(3,4-dihydroxyphenyl)-1-ethanone|T0632, sodium (S)-3-(1-[2-fluorophenyl]-2,3-dihydro-3-[[3-isoquinolinyl]-carbonyl]amino-6-methoxy-2-oxo-1H-indole)propanoate

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Glutamate, metabotropic

Overview: Metabotropic glutamate (mGlu) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors, Schoepp *et al.*, 2000) are activated by the endogenous ligands L-glutamate, L-aspartate, L-serine-O-phosphate (LSOP), N-acetylaspartylglutamate (NAAG) and L-cysteine sulphonc acid. Examples of agonists selective for mGlu receptors compared with ionotropic glutamate receptors are 1S,3R-ACPD and L-CCG-I, which show limited selectivity for Group II receptors. An example of an antagonist selective for mGlu receptors is LY341495, which blocks mGlu₂ and mGlu₃ at low nanomolar concentrations, mGlu₈ at high nanomolar concentrations, and mGlu₁, mGlu₄, mGlu₅ and mGlu₇ in the micromolar range (Kingston *et al.*, 1998). Currently, three groups of native receptors are distinguishable on the bases of similarities of agonist pharmacology, primary sequence and G-protein effector coupling: Group I (mGlu₁ and mGlu₅); Group II (mGlu₂ and mGlu₃) and Group III (mGlu₄, mGlu₆, mGlu₇ and mGlu₈) (see Further reading). Group I mGlu receptors may be activated by DHPG and 3HPG (Brabet *et al.*, 1995), and antagonized by LY393675 (Baker *et al.*, 1998). Group II mGlu receptors may be activated by LY389795 (Monn *et al.*, 1999), LY379268 (Monn *et al.*, 1999), LY354740 (Schoepp *et al.*, 1997; Wu *et al.*, 1998), DCG-IV and 2R,4R-APDC (Schoepp *et al.*, 1996), and antagonised by EGLU (4.3, Jane *et al.*, 1996) and LY307452 (Wermuth *et al.*, 1996; Escribano *et al.*, 1998). Group III mGlu receptors may be activated by (RS)PPG (Gasparini *et al.*, 1999a).

In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as 'potentiators' of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist. Examples of these unique pharmacological agents have been described for mGlu₁, mGlu₂, mGlu₄ and mGlu₅.

Nomenclature	mGlu ₁	mGlu ₂	mGlu ₃	mGlu ₄
Other names	mGluR ₁	mGluR ₂	mGluR ₃	mGluR ₄
Ensembl ID	ENSG00000152822	ENSG00000164082	ENSG00000105781	ENSG00000124493
Principal transduction	G _{q/11}	G _{i/o}	G _{i/o}	G _{i/o}
Selective agonists	—	—	NAAG (Wroblewska <i>et al.</i> , 1997)	L-AP4, LSOP (Wu <i>et al.</i> , 1998), (–)-PHCCC (Maj <i>et al.</i> , 2003), SIB1893, MPEP (Mathiesen <i>et al.</i> , 2003)
Selective positive allosteric modulators	Ro01-6128, Ro67-4853, Ro67-7476 (Knoflach <i>et al.</i> , 2001)	LY487379 (Johnson <i>et al.</i> , 2003), CBiPES (Johnson <i>et al.</i> , 2005)	—	—
Selective competitive antagonists	3-MATIDA (Moroni <i>et al.</i> , 2002), AIDA (Moroni <i>et al.</i> , 1997), (S)-(+)-CBPG (Mannaioni <i>et al.</i> , 1999), LY367385 (Clark <i>et al.</i> , 1997), (S)-TBPG (Costantino <i>et al.</i> , 2001)	PCCG-4 (Pellicciari <i>et al.</i> , 1996)	—	MAP4
Selective negative allosteric modulators	CPCCOEt (Litschig <i>et al.</i> , 1999), BAY36-7620 (Carroll <i>et al.</i> , 2001), LY456236 (Li <i>et al.</i> , 2002), 3,5-DMPPP (Micheli <i>et al.</i> , 2003), EM-TBPC (Malherbe <i>et al.</i> , 2003), JNJ16259685 (Lavreysen <i>et al.</i> , 2004)	—	—	—

Nomenclature	mGlu ₅	mGlu ₆	mGlu ₇	mGlu ₈
Other names	mGluR ₅	mGluR ₆	mGluR ₇	mGluR ₈
Ensembl ID	ENSG00000168959	ENSG00000113262	ENSG00000168160	ENSG00000179603
Principal transduction	G _{q/11}	G _{i/o}	G _{i/o}	G _{i/o}
Selective agonists	CHPG (Doherty <i>et al.</i> , 1997), (S)-(+)-CBPG (Mannaioni <i>et al.</i> , 1999)	Homo-AMPA (Bräuner-Osborne <i>et al.</i> , 1996), 1-benzyl-APDC (Tuckmantel <i>et al.</i> , 1997)	LSOP (Wu <i>et al.</i> , 1998), L-AP4	LSOP (Wu <i>et al.</i> , 1998), L-AP4, (S)-3,4-DCPG (Thomas <i>et al.</i> , 2001)
Selective positive allosteric modulators	DFB (O'Brien <i>et al.</i> , 2003), CPPHA (O'Brien <i>et al.</i> , 2004), CDPPB (Kinney <i>et al.</i> , 2005)	—	AMN082 (Flor <i>et al.</i> , 2005)	—
Selective competitive antagonists	ACDPP (6.5, Bonnefous <i>et al.</i> , 2005)	MAP4, THPG (Thoreson <i>et al.</i> , 1997)	—	MPPG (Wu <i>et al.</i> , 1998)
Selective negative allosteric modulators	SIB1757 (Varney <i>et al.</i> , 1999), SIB1893 (Varney <i>et al.</i> , 1999), MPEP (Gasparini <i>et al.</i> , 1999b), MTEP (Brodin <i>et al.</i> , 2002), fenobam (Porter <i>et al.</i> , 2005), YM298198 (Kohara <i>et al.</i> , 2005)	—	—	—

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [³H]-R214127 (Lavreysen *et al.*, 2003) and [³H]-YM298198 (Kohara *et al.*, 2005) at mGlu₁ receptors and [³H]-methoxymPEP (Gasparini *et al.*, 2002) and [³H]-methoxymethyl-MTEP (Anderson *et al.*, 2002) at mGlu₅ receptors. Although a number of radioligands have been used to examine binding using native tissues, correlation with individual subtypes is limited. Many pharmacological agents have not been fully tested across all known subtypes of mGlu receptors. Potential differences linked to the species (e.g. human versus rat or mouse) of the receptors and the receptor splice variants are generally not known. The influence of receptor expression level on pharmacology and selectivity has not been controlled for in most studies, particularly those involving functional assays of receptor coupling.

(S)-(+)-CBPG is an antagonist at mGlu₁, but is an agonist (albeit of reduced efficacy) at mGlu₅ receptors. DCG-IV also exhibits agonist activity at NMDA glutamate receptors (Uyama *et al.*, 1997). A potential novel metabotropic glutamate receptor coupled to phosphoinositide turnover has been observed in rat brain; it is activated by 4-methylhomobiotenic acid (ineffective as an agonist at recombinant Group I metabotropic glutamate receptors), but resistant to LY341495 (Chung *et al.*, 1997). There are also reports of a novel metabotropic glutamate receptor coupled to phospholipase D in rat brain, which does not readily fit into the current classification (Pellegrini-Giampietro *et al.*, 1996; Klein *et al.*, 1997).

Abbreviations: **1S,3R-ACPD**, 1-aminocyclopentane-1S,3R-dicarboxylate; **AIDA**, 1-aminoindan-1,5(RS)-dicarboxylic acid; also known as UPF523; **AMN082**, N,N'-bis(diphenylmethyl)-1,2-ethanediamine dihydrochloride; **L-AP4**, S-2-amino-4-phosphonobutyrate; **2R,4R-APDC**, aminopyrrolidine-2R,4R-dicarboxylate; also known as LY314593; **BAY 36-7620**, (3aS,6aS)-6a-naphthalen-2-ylmethyl-5-methyliden-hexahydrocyclopenta[c]furan-1-one; **CBiPES**, N-[4'-cyano-biphenyl-3-yl]-N-(3-pyridinylmethyl)-ethanesulphonamide hydrochloride; **(S)-(+)-CBPG**, (s)-(1)-2-(39-carboxybicyclo[1.1.1]pentyl)glycine; **L-CCG-I**, (2S,3S,4S)- α -(carboxycyclopropyl)glycine; **CDPPB**, 3-cyano-N-(1,3-diphenyl-1H-[pyrazol-5-yl]benzamide; **CHPG**, 2-chloro-5-hydroxyphenylglycine; **CPCCOEt**, cyclopropan[b]chromen-1a-carboxylate; **4CPG**, 4-carboxyphenylglycine; **CPPHA**, N-[4-chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl]-2-hydroxybenzamide; **DCG-IV**, (2S,1'R,2'R,3'R)-2-(2,3-dicarboxycyclopropyl)glycine; **(S)-3,4-DCPG**, (S)-3,4-dicarboxylphenylglycine; **DFB**, 3,3'-difluorobenzaldazine; **DHPG**, S-3,5-dihydroxyphenylglycine; **DMPPP**, 3,5-dimethyl pyrrole-2,4-dicarboxylic acid 2-propyl ester 4-(1,2,2-trimethyl-propyl) ester; **EGLU**, (s)- α -ethylglutamate; **fenobam**, N-(3-chlorophenyl)-N'-(4,5-dihydro-1-methyl-4-oxo-1H-imidazole-2-yl)-urea; **3HPG**, 3-hydroxyphenylglycine; **[¹¹C]-JNJ-16567083**, (3-ethyl-2-[¹¹C]methyl-6-quinolinyl)(cis-4-methoxycyclohexyl) methanone; **JNJ16259685**, (3,4-dihydro-2H-pyrano[2,3]b-quinolinyl-7-yl)(cis-4-methoxycyclohexyl)methanone; **LY307452**, 2S,4S-2-amino-4-(4,4-diphenylbut-1-yl)pentan-1,5-dioic acid; **LY341495**, 2S-2-amino-2-(1S,2S-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl)propanoic acid; **LY354740**, (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate; **LY367385**, (+)-2-methyl-4-carboxyphenylglycine; **LY379268**, (-)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid; **LY389795**, (-)-2-thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid; **LY393675**, α -substituted-cyclobutylglycine; **LY456066**, (2-[4-(indan-2-ylamino)-5,6,7,8-tetrahydro-quinazolin-2-ylsulfanyl]-ethanol,hydrochloride; **LY456236**, [(4-methoxy-phenyl)-(6-methoxy-quinazolin-4-yl)-amine hydrochloride; **LY487379**, 2,2,2-trifluoro-N-[4-(2-methoxyphenoxy)phenyl]-N-(3-pyridinylmethyl)-ethanesulphonamide; **3-MATIDA**, α -amino-5-carboxy-3-methyl-2-thiopheneacetic acid; **MAP4**, (S)-2-methyl-2-amino-4-phosphonobutanoate; **MPEP**, 2-methyl-6-(phenylethynyl)-pyridine; **methoxy-MPEP**, 2-methyl-6-((3-methoxyphenyl)ethynyl)-pyridine; **methoxy-PEPy**, 3-methoxy-5-(pyridin-2-yl-ethynyl)-pyridine; **MPPG**, (RS)- α -methyl-4-phosphonophenylglycine; **MTEP**, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; **methoxymethyl-MTEP**, 3-(methoxymethyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; **NAAG**, N-acetylaspartylglutamate, also known as spaglumic acid; **PCCG-4**, (2S,1'S,2'S,3'R)-2-(2'-carboxy-3'-phenylcyclopropyl)glycine; **PHCCC**, N-phenyl-7-(hydroxylimino)cyclopropa[b]chromen-1a-carboxamide; **(RS)PPG**, (R,S)-4-phosphonophenylglycine; **R214127**, 1-(3,4-dihydro-2H-pyrano[2,3-b]quinolin-7-yl)-2-phenyl-1-ethanone; **Ro01-6128**, diphenylacetyl-carbamic acid ethyl ester; **Ro67-4853**, (9H-xanthene-9-carbonyl)-carbamic acid butyl ester; **Ro67-7476**, (S)-2-(4-fluoro-phenyl)-1-(toluene-4-sulphonyl)-pyrrolidine; **SIB1757**, 6-methyl-2-(phenylazo)-3-pyrindol; **SIB1893**, [(phenylazo)-3-pyrindole]-2-methyl-6-(2-phenylethenyl)pyridine; **S-TBPG**, 2-(3'-(1H-tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl)glycine; **THPG**, (RS)-3,4,5-trihydroxyphenylglycine; **YM298198**, (6-[(2-methoxyethyl)amino]methyl)-N-methyl-N-neopentylthiaolo[3,2-a]benzimidazole-2-carboxamide

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Glycoprotein hormone

Overview: Glycoprotein hormone receptors (provisional nomenclature) are activated by a heterodimeric glycoprotein made up of a common α chain (116 amino-acid ENSG00000135346), with a unique β chain that confers the biological specificity to FSH (follicle-stimulating hormone, follitropin, 129 amino-acid, ENSG00000131808), LH (luteinizing hormone, lutropin, 141 amino-acid ENSG00000104826), CG (choriogonadotropin, chorionic gonadotropin, 165 amino-acid, ENSG00000104818/ENSG00000104827) or TSH (thyrotropin, thyroid-stimulating hormone, 138 amino-acid ENSG00000134200). There is binding cross-reactivity across the endogenous agonists for each of the glycoprotein hormone receptors. The deglycosylated hormones appear to exhibit reduced efficacy at these receptors (Sairam, 1989).

Nomenclature	FSH	LH	TSH
Ensembl ID	ENSG00000170820	ENSG00000168546	ENSG00000146013
Principal transduction	G _s	G _s , G _{q/11} and G _i	All four families of G-proteins can be activated by this receptor
Selective agonists	FSH	LH, CG	TSH
Probes	[¹²⁵ I]-FSH	[¹²⁵ I]-LH, [¹²⁵ I]-CG	[¹²⁵ I]-TSH

Animal follitropins are less potent than the human hormone as agonists at the human FSH receptor. Autoimmune antibodies that act as agonists of the TSH receptor are found in patients with Grave's disease (see Rapoport *et al.*, 1998). Gain- and loss-of-function mutations of the FSH receptor are associated with human reproductive disorders (Aittomaki *et al.*, 1995; Gromoll *et al.*, 1998; Beau *et al.*, 1998; Touraine *et al.*, 1999). Loss-of-function mutations of the LH receptor are associated with Leydig cell hypoplasia and gain-of-function mutations are associated with male-limited gonadotropin-independent precocious puberty (e.g. Latronico and Segaloff, 1999; Shenker, 2002) and Leydig cell tumours (Liu *et al.*, 1999). Mutations of the TSH receptor exhibiting constitutive activity underlie hyperfunctioning thyroid adenomas (Parma *et al.*, 1993) and congenital hyperthyroidism (Kopp *et al.*, 1995). TSH receptor loss-of-function mutations are associated with thyrotropin resistance (Sunthornthepvarakul *et al.*, 1995). The rat FSH receptor also stimulates phosphoinositide turnover through an unidentified G protein (Quintana *et al.*, 1994).

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Gonadotropin-releasing hormone (GnRH)

Overview: Gonadotropin-releasing hormone (GnRH) is a hypothalamic decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pr-Gly-NH₂, also known as luteinising hormone-releasing hormone, gonadoliberin, luliberin, gonadorelin, ENSG00000147437) designated GnRH I, to distinguish it from related peptides such as GnRH II (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Phe-NH₂, also known as chicken GnRH-II, ENSG00000180290) and GnRH III (pGlu-His-Trp-Ser-His-Asp-Trp-Lys-Pro-Gly-NH₂ also known as lamprey GnRH III). Receptors for all three ligands exist in amphibians but only GnRH I and GnRH II (and their cognate receptors) have been found in mammals (Sealfon *et al.*, 1997; Millar, 2002). Type I and Type II GnRH receptors (provisional nomenclature) have been cloned from numerous species (most of which express two or three types of GnRHR) and grouped phylogenetically (Silver *et al.*, 2005). Type I GnRHRs are expressed primarily by pituitary gonadotrophs in mammals and mediate central control of reproduction. They are selectively activated by GnRH I and all lack the C-terminal tails found in other seven transmembrane region receptors. Type II GnRHRs include all non-mammalian GnRHRs as well as the recently cloned type II primate GnRHRs. They all possess C-terminal tails and (where tested) are selective for GnRH II (over GnRH I). An alternative phylogenetic classification (see Millar *et al.*, 2004) divided these receptors into three classes and includes both GnRH I-selective mammalian type I GnRHRs and GnRH II-selective non-mammalian receptors in type I. Although thousands of peptide analogues of GnRH I have been synthesised and several (agonists and antagonists) are used therapeutically (Kiesel *et al.*, 2002), the potency of most of these peptides at type II GnRHRs is unknown.

Nomenclature	Type I GnRHR	Type II GnRHR
Other names	LHRH receptor, GnRH I receptor	—
Ensembl ID	ENSG00000109163	ENSG00000180290
Principal transduction	G _{q/11}	G _{q/11}
Rank order of potency	GnRH I > GnRH II	GnRH II > GnRH I
Selective agonists	Triptorelin, buserelin, leuprorelin, nafarelin, histrelin, goserelin	—
Selective antagonists	Antide (9.0, Neill, 2002), cetrorelix (8.8, Neill, 2002), ganirelix, abarelix	Trptorelix-1 (Maiti <i>et al.</i> , 2003)
Probes	[¹²⁵ I]-GnRH I, [¹²⁵ I]-buserelin	[¹²⁵ I]-GnRH II

Type I (and type II) GnRHRs couple primarily to G_{q/11} (Grosse *et al.*, 2000) but coupling to G_s and G_i is evident in some systems (Krsmanovic *et al.*, 2003). Type II GnRHRs may also mediate (heterotrimeric) G protein-independent signalling to protein kinases (see Caunt *et al.*, 2006). There is increasing evidence for expression of GnRHRs on hormone-dependent cancer cells where they can exert antiproliferative and/or proapoptotic effects and mediate effects of cytotoxins conjugated to GnRH analogues (Limonta *et al.*, 2003; Harrison *et al.*, 2004; Schally and Nagy, 2004; Cheng and Leung, 2005). In some human cancer cell models GnRH II is more potent than GnRH I, implying mediation by a type II GnRHR (Grundker *et al.*, 2002). However, type II GnRHRs that are expressed by some primates are probably not expressed in humans because the human type II GnRHR gene contains a frame shift and internal stop codon (Morgan *et al.*, 2003). The possibility remains that this gene expresses type II GnRHR-related proteins (other than the full-length receptor) that mediate responses to GnRH II (see Neill *et al.*, 2004). Alternatively, there is evidence for multiple active GnRHR conformations (Caunt *et al.*, 2004; Maudsley *et al.*, 2004; Millar *et al.*, 2004) raising the possibility that type I GnRHR-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon different conformations (with different ligand specificity) than effects on G_{q/11} in pituitary cells (Maudsley *et al.*, 2004). Loss-of-function mutations in the type I GnRHR and deficiency of GnRH I are associated with hypogonadotropic hypogonadism although some 'loss of function' mutations may actually prevent trafficking of 'functional' type I GnRHRs to the cell surface, as evidenced by recovery of function by nonpeptide antagonists (Leanos-Miranda *et al.*, 2003). GnRHR signalling may be dependent upon receptor oligomerisation (Conn *et al.*, 1982; Kroeger *et al.*, 2001).

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G-protein-coupled estrogen (GPE)

Overview: The G-protein-coupled estrogen receptor (GPE, provisional nomenclature) was identified following observations of estrogen-evoked cyclic AMP signalling in breast cancer cells (Aronica *et al.*, 1994), which mirrored the differential expression of an orphan 7-transmembrane receptor GPR30 (Carmeci *et al.*, 1997). There are observations of both cell-surface and intracellular expression of the GPE receptor (Revankar *et al.*, 2005; Thomas *et al.*, 2005).

Nomenclature	GPE
Other names	GPR30, IL8-related receptor DRY12, flow-induced endothelial G-protein coupled receptor, GPCR-BR, CMKRL2 (Owman <i>et al.</i> , 1996)
Ensembl ID	ENSG00000164850
Principal transduction	G _s (Filardo <i>et al.</i> , 2000), G _{i/o} (Revankar <i>et al.</i> , 2005)
Selective agonists	G1 (Bologa <i>et al.</i> , 2006)
Probes	[³ H]-Estrogen (Revankar <i>et al.</i> , 2005)

Antagonists at the nuclear estrogen receptor, such as ICI182780 and tamoxifen (Filardo *et al.*, 2000), as well as the flavonoid 'phytoestrogens' genistein and quercetin (Maggiolini *et al.*, 2004), are agonists at GPE receptors.

Abbreviations: G1, 1-(4-[6-bromo-benzo[1,3]dioxol-5-yl]-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-8-yl)ethanone; ICI182780, 7 α -(9-[[4,4,5,5,5-pentafluoropentyl]sulphinyl]nonyl)estra-1,3,5(10)-triene-3,17 β -diol

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Histamine

Overview: Histamine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Histamine Receptors, see Hill *et al.*, 1997) are activated by the endogenous ligand histamine. Marked species differences exist between histamine receptor orthologues (see Hill *et al.*, 1997).

Nomenclature	H ₁	H ₂	H ₃	H ₄
Ensembl ID	ENSG00000171088	ENSG00000168546	ENSG00000146013	ENSG00000125861
Principal transduction	G _{q/11}	G _s	G _{i/o}	G _{i/o}
Selective agonists	Histaprofiden, N ¹ -methylhistaprofiden	Amthamine	Methimnapip (Kitbunnadaj <i>et al.</i> , 2005),	Clobenpropit, 4-methylhistamine, VUF8430 (Lim <i>et al.</i> , 2006)
Selective antagonists	Triprolidine (9.9), mepyramine (9.1)	Tiotidine (7.8), ranitidine (7.1)	Clobenpropit (9.9), iodophenpropit (9.6), A331440 (8.5, Hancock <i>et al.</i> , 2004), thioperamide (8.4)	JNJ7777120 (8.1)
Probes	[³ H]-Mepyramine (1 nM), [¹¹ C]-mepyramine, [¹¹ C]-doxepin	[³ H]-Tiotidine (15 nM), [¹²⁵ I]-iodoaminopotentidine (0.3 nM)	[³ H]-R- α -Methylhistamine (0.5 nM), [³ H]-N ² -methylhistamine (2 nM), [¹²⁵ I]-iodophenpropit (0.6 nM), [¹²⁵ I]-iodoproxyfan (0.06 nM)	[³ H]-JNJ7777120 (3.6 nM)

Histaprofiden and N¹-methylhistaprofiden are reduced efficacy agonists. The H₄ receptor appears to exhibit broadly similar pharmacology to the H₃ receptor for imidazole-containing ligands, although R- α -methylhistamine and N- α -methylhistamine are less potent, while clobenpropit acts as a reduced efficacy agonist (Nakamura *et al.*, 2000; Oda *et al.*, 2000; Liu *et al.*, 2001; Nguyen *et al.*, 2001; Zhu *et al.*, 2001). Moreover, 4-methylhistamine is identified as a high affinity, full agonist for the human H₄ receptor (Lim *et al.*, 2005). [³H]-Histamine has been used to label the H₄ receptor in heterologous expression systems.

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KISS1, Neuropeptide FF, Prolactin-releasing peptide and QRFP

Overview: KISS1, neuropeptide FF (NPFF), prolactin-releasing peptide (PrP) and QRFP receptors (provisional nomenclature) respond to endogenous peptides with an arginine-phenylalanine-amide (RFamide) motif. Kisspeptin-54 (KP54, originally named metastin), KP13 and KP10 are biologically-active peptides cleaved from the *KISS1* gene product (ENSG00000170498), while a single propeptide precursor (ENSG00000139574) generates the octapeptides NPFF (FLQPQRF-NH₂, neuropeptide FF or F-8-F-amide) and NPSF (SLAAPQRF-NH₂, neuropeptide SF) and the octadecapeptide NPAF (AGEGLSPFWSLAAPQRF-NH₂, neuropeptide AF or A-18-F-amide). NPFF and NPAF were originally isolated from bovine brain (Yang *et al.*, 1985). The precursor (ENSG00000071677) for PrRP generates 31 and 20-amino-acid versions. QRFP (named after a pyroglutamylated arginine-phenylalanine-amide peptide) is a 43 amino acid peptide derived from ENSG00000188710, and is also known as P518 or 26RfA. RFRP is an RF amide-related peptide (Hinuma *et al.*, 1998) derived from a FMRFamide-related peptide precursor (ENSG00000105954), which is cleaved to generate neuropeptide NPSF (Neuropeptide RFRP-1), neuropeptide RFRP-2 and neuropeptide NPVF (neuropeptide RFRP-3).

Nomenclature	KISS1	NPFF1	NPFF2	PrRP	QRFP
Other names	hOT7T175 (Ohtaki <i>et al.</i> , 2001), GPR54, metastin, hypogonadotropin	Neuropeptide FF 1, GPR147 (Bonini <i>et al.</i> , 2000), OT7T022	Neuropeptide FF 2, GPR74 (Bonini <i>et al.</i> , 2000), HLWAR77	Prolactin-releasing peptide, GPR10 (Hinuma <i>et al.</i> , 1998), hGR3, UHR-1	SP9155 (Jiang <i>et al.</i> , 2003), AQ27 (Fukusumi <i>et al.</i> , 2003), P518
Ensembl ID	ENSG00000116014	ENSG00000148734	ENSG00000056291	ENSG00000119973	ENSG00000186867
Principal transduction	G _{q/11} (Kotani <i>et al.</i> , 2001; Muir <i>et al.</i> , 2001)	G _{q/11}	G _{i/o} (Mollereau <i>et al.</i> , 2005)	G _{q/11} (Langmead <i>et al.</i> , 2000)	G _{q/11} , G _{i/o} (Fukusumi <i>et al.</i> , 2003)
Potency order	—	FMRF, NPFF > NPAF > NPSF, QRFP, PrP31 (Gouardères <i>et al.</i> , 2007)	NPAF, NPFF > PrP31 > FMRF, QRFP > NPSF (Gouardères <i>et al.</i> , 2007)	PrRP20, PrRP31 (Langmead <i>et al.</i> , 2000)	—
Selective agonists	KP54, KP13, KP10 (Kotani <i>et al.</i> 2001; Ohtaki <i>et al.</i> , 2001)	NPFF	NPFF	PrRP	QRFP
Selective antagonists	—	—	—	Neuropeptide Y (Lagerstrom <i>et al.</i> , 2005)	—
Probes	[¹²⁵ I]-KP10 (Kotani <i>et al.</i> , 2001); [¹²⁵ I]-KP13 (Mead <i>et al.</i> , 2007)	[¹²⁵ I]-NPFF, [¹²⁵ I]-YVP (Gouardères <i>et al.</i> , 2002)	[¹²⁵ I]-NPFF, [¹²⁵ I]-EYF (Gouardères <i>et al.</i> , 2002)	[¹²⁵ I]-PrRP20 (Langmead <i>et al.</i> , 2000)	[¹²⁵ I]-QRFP (Takayasu <i>et al.</i> , 2006)

An orphan receptor GPR83 (ENSG00000123901) shows sequence similarities with NPFF1, NPFF2, PrRP and QRFP receptors.

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Leukotriene, lipoxin, oxoeicosanoid and resolvin E1

Overview: Leukotriene receptors (nomenclature agreed by NC-IUPHAR on Leukotriene and Lipoxin Receptors, Brink *et al.*, 2003) are activated by the endogenous ligands leukotriene (LT) B₄, LTC₄, LTD₄, LTE₄, 12R-HETE and 12S-HETE. Lipoxin A₄ receptors (ALX, nomenclature agreed by NC-IUPHAR on Leukotriene and Lipoxin Receptors; Brink *et al.*, 2003) are activated by the endogenous lipid-derived, anti-inflammatory ligands lipoxin A₄ (LXA₄) and 15-epi-LXA₄ (aspirin-triggered lipoxin A₄, ATL). Oxoeicosanoid receptors (OXE, nomenclature agreed by NC-IUPHAR on Oxoeicosanoid Receptors; Brink *et al.*, 2004) are activated by endogenous chemotactic eicosanoid ligands oxidised at the C-5 position, with 5-oxo-EETE the most potent agonist identified for this receptor. Resolvin receptors (provisional nomenclature) are activated by the lipid-derived, anti-inflammatory ligand resolvin E1 (RvE1), which is the result of sequential metabolism of EPA by aspirin-modified cyclooxygenase and lipoxygenase (Arita *et al.*, 2005a, b).

CysLT₁ and CysLT₂ are co-expressed by most myeloid cells. However, the function of CysLT₂ remains unclear. CysLT₂ has been demonstrated to exert a suppressive influence on CysLT₁ expression, suggesting an autoregulatory function which is indicated by a reported up-regulation of CysLT-mediated responses in mice lacking CysLT₂ receptors (Jiang *et al.*, 2007).

Leukotrienes bind extensively to enzymes in their metabolic pathways (glutathione-S-transferase/LTC₄ synthase, γ -glutamyltranspeptidase and several aminopeptidases) and can also bind to peroxisome proliferator-activated receptor α (PPAR α , Lin *et al.*, 1999) and the ALX lipoxin receptor (Fiore *et al.*, 1994), complicating the interpretation of radioligand binding and functional studies (e.g. LTC₄ is rapidly converted in many systems to LTD₄). Metabolic inhibitors (e.g. serine-borate complex) reduce this problem but can also have nonspecific effects. The ALX receptor also interacts with endogenous peptide and protein ligands, such as MHC binding peptide (Chiang *et al.*, 2000) as well as annexin 1 (ANXA1) and its N-terminal peptides (Perretti *et al.*, 2002). In addition, a soluble hydrolytic product of protease action on the urokinase-type plasminogen activator receptor has been reported to activate the ALX receptor (Resnati *et al.*, 2002). Furthermore, ALX has been suggested to act as a receptor mediating proinflammatory actions of the acute-phase reactant, serum amyloid A (Su *et al.*, 1999; Sodin-Semrl *et al.*, 2004).

Nomenclature	BLT ₁	BLT ₂	CysLT ₁	CysLT ₂
Other names	LTB ₄	—	HG55, HMTMF81, LTD ₄	HPN321, LTC ₄
Ensemble ID	ENSG00000116329	ENSG00000082556	ENSG00000112038	ENSG00000125510
Principal transduction	G _{q/11} , G _{i/o}	G _{q/11} , G _{i/o}	G _{q/11}	G _{q/11}
Rank order of potency	LTC ₄ > 20-hydroxy-LTB ₄ > 12R-HETE (Yokomizo <i>et al.</i> , 2001)	LTC ₄ > 12S-HETE = 12S-HPETE > 15S-HETE > 12R-HETE = 15S-HETE > 20-hydroxy-LTB ₄ (Yokomizo <i>et al.</i> , 2001)	LTD ₄ > LTC ₄ > LTE ₄ (Sarau <i>et al.</i> , 1999)	LTC ₄ = LTD ₄ > LTE ₄ (Nothacker <i>et al.</i> , 2000)
Selective agonists	—	12S-HETE	—	BAYu9773
Selective antagonists	CP105696 (pIC ₅₀ 7.2), U75302 (pIC ₅₀ 6.9)	LY255283 (pIC ₅₀ 6.0)	Zafirlukast (9.5), montelukast (9.3), SR2640 (8.7), pobilukast (8.6), sulukast (8.3)	—
Probes	[³ H]-LTB ₄ (0.2–0.7 nM), [³ H]-CGS23131 (13 nM)	[³ H]-LTB ₄ (0.2–23 nM)	[³ H]-LTD ₄ , [³ H]-ICI198615	[³ H]-LTD ₄

BAYu9773 is an antagonist at CysLT₁ (6.8–7.7) and a reduced efficacy agonist at CysLT₂ receptors. The CysLT₁ and CysLT₂ receptors also respond to uracil nucleotides (Mellor *et al.*, 2001, 2003). GPR17 has been described as a 'dualistic' receptor responding to both uracil nucleotides and cysteinyl leukotrienes, responses which may be inhibited by antagonists of either P2 or CysLT receptors (Ciana *et al.*, 2006).

Nomenclature	ALX	OXE	RvE1
Other names	FPRL1, FPR2, FPRH2, RFP	TG1019 (Hosoi <i>et al.</i> , 2002), R527 (Jones <i>et al.</i> , 2003), hGPCR48 (Koike <i>et al.</i> , 2006)	ChemR23, chemokine receptor-like 1, DEZ
Ensemble ID	ENSG00000171049	ENSG00000162881	ENSG00000174600
Principal transduction	G _i (Maddox <i>et al.</i> , 1997)	G _{i/o} (O'Flaherty <i>et al.</i> , 2000; Hosoi <i>et al.</i> , 2002; Jones <i>et al.</i> , 2003; Hosoi <i>et al.</i> , 2005)	Not yet established
Rank order of potency	LXA ₄ = ATL = ATLa2 > LTC ₄ = LTD ₄ > 15-deoxy-LXA ₄ > fMLP (Clish <i>et al.</i> , 1999; Fiore <i>et al.</i> , 1994; Fiore and Serhan, 1995; Gronert <i>et al.</i> , 2001; Takano <i>et al.</i> , 1997)	5-Oxo-EETE > 5(S)-HpETE > 5(S)-HETE (Hosoi <i>et al.</i> , 2002; Jones <i>et al.</i> , 2003)	RvE1 > chemerin C-terminal peptide (Arita <i>et al.</i> , 2005a, b)
Selective agonists	LXA ₄ , ATL, ATLa2 (Guilford <i>et al.</i> , 2004)	5-Oxo-EETE	—
Probes	[³ H]-LXA ₄ (0.2–1.7 nM; Fiore <i>et al.</i> , 1994; Takano <i>et al.</i> , 1997)	[³ H]-5-oxo-EETE (3.8 nM; O'Flaherty <i>et al.</i> , 1998)	[³ H]-RvE1 (48 nM; Arita <i>et al.</i> , 2007)

A receptor selective for LXB₄ has been suggested from functional studies (Maddox and Serhan, 1996; Romano *et al.*, 1996; Ariel *et al.*, 2003). Initial characterization of the heterologously expressed OXE receptor suggested that polyunsaturated fatty acids, such as DHA and EPA, acted as receptor antagonists (Hosoi *et al.*, 2002).

Abbreviations: 12R-HETE, 12(R)-hydroxyeicosa-5z, 8z, 10E, 14z-tetraenoic acid; 5(S)-HETE, 5(S)-hydroxy-6E, 8z, 11z, 14z-eicosatetraenoic acid; 5(S)-HpETE, 5(s)-hydroperoxy-6E, 8z, 11z, 14z-eicosatetraenoic acid; 5-oxo-EETE, 5-oxo-6E, 8z, 11z, 14z-eicosatetraenoic acid; ANXA1, annexin 1; ATL, aspirin-triggered lipoxin A₄ [15-*epi*-LXA₄, 5S, 6R, 15R-trihydroxyl-7E, 9E, 13E, 11z-eicosatetraenoic acid]; ATLa2, ATL analog [15-*epi*-16-(para-fluoro)-phenoxy-LXA₄]; BAYu9773, 6(R)-(4'-carboxyphenyl-thio)-5(S)-hydroxy-7E, 11z, 14z-eicosatetraenoic acid; CGS23131, (E)-5-(3-carboxybenzoyl)-2-([6-[4-methoxyphenyl]-5-hexenyl]oxy)benzene propanoic acid, also known as LY223982; CP105696, (+)-1-(3S, 4R)-[3-(4-phenylbenzyl)-4-hydroxy-chroman-7-yl]cyclopentane carboxylic acid; DHA, 4z, 7z, 10z, 13z, 16z, 19z-docosahexaenoic acid; EPA, 5z, 8z, 11z, 14z, 17z-eicosapentaenoic acid; ICI198615, (1-[2-methoxy-4-([phenylsulfonylamino]carbonyl)phenyl]methyl)-1H-indazol-6-yl)carbamic acid cyclopentyl ester; LTC₄, leukotriene C₄; LTD₄, leukotriene D₄; LXA₄, lipoxin A₄ [5S, 6R, 15S-trihydroxyl-7E, 9E, 13E-11z-eicosatetraenoic acid]; LY255283, 1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)-heptyl]-oxy]-phenyl]-ethanone; OXE, oxoeicosanoid; RvE1, resolvin E1 or 5S, 12R, 18R-trihydroxy-6z, 8E, 10E, 14z, 16E-EPA[SR2640, 2-(3-[2-quinolylmethoxy]phenylamino)benzoic acid; U75302, 6-(6-(3-hydroxy-1E, 5z-undecadien-1-yl)-2-pyridinyl)-1, 5-hexanediol

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Lysophosphatidic acid

Overview: Lysophosphatidic acid (LPA) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid Receptors; Chun *et al.*, 2002) are activated by the endogenous lipid derivative LPA. The identified receptors can account for most, although not all, LPA-induced phenomena in the literature, indicating that a majority of LPA-dependent phenomena are receptor-mediated. Radioligand binding has been conducted in heterologous expression systems using [³H]-LPA (e.g. Fukushima *et al.*, 1998). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding, and therefore the relationship between recombinant and endogenously expressed receptors is unclear. Targeted deletion of LPA receptors has clarified signalling pathways and identified physiological and pathophysiological roles. LPA has also been described to be an agonist at PPAR γ receptors (McIntyre *et al.*, 2003), although the physiological significance of this observation remains unclear (Simon *et al.*, 2005).

Nomenclature	LPA ₁	LPA ₂	LPA ₃	LPA ₄	LPA ₅
Other names	VZG-1, Edg2, <i>lp</i> _{A1}	Edg4, <i>lp</i> _{A2}	Edg7, <i>lp</i> _{A3}	p2y9, gpr23	GPR92
Ensembl ID	ENSG00000119438	ENSG00000064547	ENSG00000171517	ENSG00000147149	ENSG00000184574
Principal transduction	G _{i/o} , G _{q/11} , G _{12/13}	G _{i/o} , G _{q/11} , G _{12/13}	G _{i/o} , G _{q/11} , G _s	G _{i/o} , G _{q/11} , G _s , G _{12/13} (Lee <i>et al.</i> , 2007)	G _q , G _{12/13} (Kotarsky <i>et al.</i> , 2006; Lee <i>et al.</i> , 2006)
Selective agonists	—	FAP10, FAP12 (Virag <i>et al.</i> , 2003)	OMPT (Hasegawa <i>et al.</i> , 2003)	—	—
Selective antagonists	Ki16425 (Ohta <i>et al.</i> , 2003)	—	DGPP 8:0 (Ohta <i>et al.</i> , 2003)	—	—

FAP12 has antagonist activity at LPA₁ and LPA₃ receptors (Virag *et al.*, 2003). The selectivity of these antagonists is less than two orders of magnitude. None of the currently available chemical tools have validated specificity *in vivo*.

Abbreviations: DGPP 8:0, dioctanoylglycerol pyrophosphate; FAP10, decanol phosphate; FAP12, dodecanol phosphate; Ki16425, 3-(4-[(1-[2-chlorophenyl]ethoxy)carbonylamino]-3-methyl-5-isoxazolyl]benzylsulfanyl)propanoic acid; OMPT, 1-oleoyl-2-O-methyl-rac-glycerophosphothionate

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Melanin-concentrating hormone

Overview: Melanin-concentrating hormone (MCH) receptors (provisional nomenclature) are activated by an endogenous nonadecameric cyclic peptide identical in humans and rats (DFDMLRCMLGRVYRQWQV) generated from a precursor (ENSG00000183395), which also produces neuropeptides EI and GE. The MCH2 receptor appears to be a non-functional pseudogene in rodents (Tan *et al.*, 2002).

Nomenclature	MCH1	MCH2
Other names	SLC-1, GPR24	SLT, GPRv17
Ensembl ID	ENSG00000128285	ENSG00000152034
Principal transduction	G _{q/11} , G _{i/o}	G _{q/11} (Hill <i>et al.</i> , 2001; Mori <i>et al.</i> , 2001; Rodriguez <i>et al.</i> , 2001)
Rank order of potency	Human MCH > salmon MCH	Human MCH = salmon MCH (Hill <i>et al.</i> , 2001)
Selective antagonists	SNAP7941 (9.2, Borowsky <i>et al.</i> , 2002), T226296 (7.5, Takekawa <i>et al.</i> , 2002)	—
Probes	[³ H]-MCH (Burgaud <i>et al.</i> , 1997), [Phe ¹³ , [125I]-Tyr ¹⁹] MCH (Burgaud <i>et al.</i> , 1997), [125I]-S36057 (0.04 nM, Audinot <i>et al.</i> , 2001)	—

Abbreviations: S36057, 3-iodo-tyr-(8-amino-3,6-dioxyoctanoyl)MCH-(6-17); SNAP7941, (+)-methyl(4S)-3-([3-(4-[3-(acetylamino)phenyl]-1-piperidinyl)propyl]amino)carbonyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate hydrochloride; T226296, (–)-N-[6-(dimethylamino)-methyl]-5,6,7,8-tetrahydro-2-naphthalenyl]-4'-fluoro[1,1'-biphenyl]-4-carboxamide

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Melanocortin

Overview: Melanocortin receptors (provisional nomenclature) are activated by members of the melanocortin family (MSH— α , β , and γ forms— δ form is not found in mammals) and adrenocorticotrophin (ACTH). Endogenous antagonists include agouti and agouti-related protein (AGRP).

Nomenclature	MC ₁	MC ₂	MC ₃	MC ₄	MC ₅
Other names	—	ACTH receptor	—	—	—
Ensembl ID	ENSG00000141037	ENSG00000185231	ENSG00000124089	ENSG00000166603	ENSG00000176136
Principal transduction	G _s	G _s	G _s	G _s	G _s
Rank order of potency	α -MSH > β -MSH $\geq$ ACTH, γ -MSH	ACTH	γ -MSH, β -MSH $\geq$ ACTH, α -MSH	β -MSH $\geq$ α -MSH, ACTH > γ -MSH	α -MSH $\geq$ β -MSH $\geq$ ACTH > γ -MSH
Selective agonists	—	—	D-Trp ⁸ - γ -MSH (Grieco <i>et al.</i> , 2000)	THIQ (Van der Ploeg <i>et al.</i> , 2002)	—
Selective antagonists	—	—	—	HS014 (8.5, Schiöth <i>et al.</i> , 1998), MBP10 (Bednarek <i>et al.</i> , 2001)	—
Probes	[¹²⁵ I]-NDP-MSH	[¹²⁵ I]-ACTH-(1–24)	[¹²⁵ I]-NDP-MSH, [¹²⁵ I]-SHU9119	[¹²⁵ I]-NDP-MSH, [¹²⁵ I]-SHU9119	[¹²⁵ I]-NDP-MSH

Polymorphisms of the MC₁ receptor have been linked to variations in skin pigmentation. Defects of the MC₂ receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC₄ receptor have been linked to obesity (Chagnon *et al.*, 1997).

Abbreviations: **HS014**, cyc(S-S)-(Ac-Cys¹¹,D-Nal¹⁴,Cys¹⁸,Asp-NH₂) β -MSH-(11-22); **MBP10**, cyclo(6 β →10 ϵ)(succinyl(6)-D-(2')Nal⁷-Arg⁸-Trp⁹-Lys¹⁰)-NH₂; **NDP-MSH**, [Nle⁴,d-Phe⁷] α -MSH; SHU9119, Ac-Nle-Asp-His-d-Nal²-Arg-Trp-Lys-NH₂; **THIQ**, N-([3R]-1,2,3,4-tetrahydroisquinolinium-3-ylcarbonyl)-(1R)-1-(4-chlorobenzyl)-2-(4-cyclohexyl-4-[1H-1,2,4-triazol-1-ylmethyl]piperidin-1-yl)-2-oxoethylamine

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Melatonin

Overview: Melatonin receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on melatonin receptors (see Dubocovich *et al.*, 1998, 2000) are activated by the endogenous ligands melatonin and N-acetylserotonin.

Nomenclature	MT ₁	MT ₂	MT ₃
Other names	MEL _{1A} , ML _{1A} , Mel _{1a}	MEL _{1B} , ML _{1B} , Mel _{1b}	ML ₂
Ensembl ID	ENSG00000168412	ENSG00000134640	—
Principal transduction	G _{i/o}	G _{i/o}	—
Selective agonists	—	IIK7 Sugden <i>et al.</i> (1999), 5-methoxyluzindole Dubocovich <i>et al.</i> (1998)	N-acetylserotonin (Eison and Mullins (1993); Popova and Dubocovich (1995); Molinari <i>et al.</i> (1996); Lucchelli <i>et al.</i> (1997), 5MCA-NAT Popova and Dubocovich (1995) Prazosin Lucchelli <i>et al.</i> (1997)
Selective antagonists	—	K185 (9.3, Sugden <i>et al.</i> , 1999), 4P-PDOT (8.8, Dubocovich <i>et al.</i> (1997); Dubocovich <i>et al.</i> , 1998), DH97 (8.0, Teh and Sugden, 1998)	—
Probes	[³ H]-melatonin Browning <i>et al.</i> (2000)	[³ H]-melatonin Browning <i>et al.</i> (2000)	2-iodo-[¹²⁵ I]-5MCA-NAT Molinari <i>et al.</i> (1996)

Melatonin, 2-iodo-melatonin, S20098, GR196429, LY156735 and TAK375 (Kato *et al.*, 2005) are nonselective agonists for MT₁ and MT₂ receptors. 2-Iodo-[¹²⁵I]-melatonin can be used to label all three melatonin receptor subtypes. (–)-AMMTC displays an ~400-fold greater agonist potency than (+)-AMMTC at rat MT₁ receptors (Ting *et al.*, 1999). Luzindole is a non-selective melatonin receptor antagonist with some selectivity for the MT₂ receptor (Dubocovich *et al.*, 1998). The MT₃ binding site of hamster kidney was identified as the hamster homologue of human quinone reductase 2 (ENSG00000124588, Nosjean *et al.*, 2000; Nosjean *et al.*, 2001). Pharmacological investigations of MT₃ binding sites have primarily been conducted in hamster and guinea-pig tissues. A suggested physiological function of the MT₃ receptor is in the control of intraocular pressure in rabbits (Pintor *et al.*, 2003). *Xenopus* melanophores and chick brain express a distinct receptor (×420, P49219; c346, P49288, initially termed Mel_{1C}) coupled to the G_{i/o} family of G proteins, for which a mammalian counterpart has not yet been defined. MT₁/MT₂ heterodimers present different pharmacological profiles from MT₁ and MT₂ receptors (Ayoub *et al.*, 2004).

Abbreviations: 4P-PDOT, 4-phenyl-2-propionamidotetraline; AMMTC, N-acetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydro-carbazole; DH97, 2-benzyl-N-pentanoyltryptamine; GR196429, N-(2-[2,3,7,8-tetrahydro-1H-furo(2,3-g)indol-1-yl]ethyl)acetamide; IIK7, N-butanoyl-2-(2-methoxy-6H-isoindolo [2,1-a]indol-11-yl)ethanamine; K185, N-butanoyl-2-(5,6,7-trihydro-11-methoxybenzo[3,4]cyclohept[2,1-a]indol-13-yl)ethanamine; LY156735, β-methyl-6-chloromelatonin; 5MCA-NAT, 5-methoxy-carbonylamino-N-acetyltryptamine; S20098, N-(2-[7-methoxy-1-naphthalenyl]ethyl)acetamide; TAK375, (S)-N-[2(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide

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Motilin

Overview: Motilin receptors (provisional nomenclature) are activated by a 22 amino-acid peptide derived from a precursor (ENSG00000096395), which also generates motilin-associated peptide. These receptors are suggested to be responsible for the gastrointestinal prokinetic effects of motilides (particular macrolide antibiotics, see Abu-Gharbieh *et al.*, 2004; Inui *et al.*, 2004; Xu *et al.*, 2005).

Nomenclature	Motilin
Other names	MTLR1 (Feighner <i>et al.</i> , 1999), GPR38 (McKee <i>et al.</i> , 1997)
Ensembl ID	ENSG00000102539
Principal transduction	G _{q/11} (Depoortere and Peeters, 1995; Feighner <i>et al.</i> , 1999)
Rank order of potency	Motilin > ABT229, mitemcinal > erythromycin (Clark <i>et al.</i> , 1999)
Selective agonists	ABT229 (Lartey <i>et al.</i> , 1995), mitemcinal (Koga <i>et al.</i> , 1994; Takanashi <i>et al.</i> , 2007)
Selective antagonists	GM109 (Takanashi <i>et al.</i> , 1995; pA ₂ 7.2–7.5 Clark <i>et al.</i> , 1999)
Probes	[¹²⁵ I]-motilin (0.1 nM, Feighner <i>et al.</i> , 1999)

Abbreviations: ABT229, 8,9-anhydro-4''-deoxy-3'-N-desmethyl-3'-N-ethylerythromycin B 6,9-hemiacetal; GM109, phe-cyclo[Lys-Tyr(3-tBu)-β-Ala].trifluoroacetate; mitemcinal, de(N-methyl)-11-deoxy-N-isopropyl-12-O-methyl-11-oxo-8,9-anhydroerythromycin A 6,9-hemiacetal fumaric acid, also known as GM611

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Neuromedin U

Overview: Neuromedin U receptors (provisional nomenclature) are activated by the endogenous 25 amino-acid peptide neuromedin U (NMU), with an indeterminate protein distribution, although mRNA levels indicate a predominant distribution of NMU₁ receptors in the periphery, particularly the gastrointestinal tract, while NMU₂ receptors appear expressed predominantly in localised regions of the CNS. NMU was originally isolated from pig spinal cord (Minamino *et al.*, 1985). In humans, NMU appears to be the sole product of a precursor (ENSG00000109255) showing a broad tissue distribution, but which is expressed at highest levels in the upper gastrointestinal tract, CNS, bone marrow and fetal liver. Shorter versions of NMU are found in some species, being derived at least in some instances from the proteolytic cleavage of the longer NMU. Despite species differences in NMU structure, the C-terminal region (particularly the C-terminal pentapeptide) is highly conserved and contains biological activity. Neuromedin S (NMS), an endogenous 36 amino-acid peptide (ENSG00000204640), which contains an amidated C-terminal heptapeptide identical to NMU, appears to activate NMU receptors with equivalent potency (Mori *et al.*, 2005).

Nomenclature	NMU ₁	NMU ₂
Other names	GPR66, FM3 (Hedrick <i>et al.</i> , 2000; Kojima <i>et al.</i> , 2000; Szekeres <i>et al.</i> , 2000)	FM4 (Howard <i>et al.</i> , 2000), TGR1 (Hosoya <i>et al.</i> , 2000)
Ensembl ID	ENSG00000171596	ENSG00000132911
Principal transduction	G _{q/11} (Hedrick <i>et al.</i> , 2000)	G _{q/11} (Hosoya <i>et al.</i> , 2000)
Probes	[¹²⁵ I]-NMU-25, Cy3B-tagged NMU-8 (Brighton <i>et al.</i> , 2004a)	—

Although NMU₁ and NMU₂ receptors couple predominantly to G_{q/11}, there is evidence of coupling to G_{i/o} (see Hosoya *et al.*, 2000; Brighton *et al.*, 2004b).

Abbreviations: NMS, neuromedin S; NMU, neuromedin U

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Neuropeptide S

Overview: The neuropeptide S receptor (NPS, provisional nomenclature) responds to the 20 amino-acid peptide neuropeptide S derived from a precursor (ENSG00000205730). The NPS receptor was initially identified as a G protein-coupled receptor for asthma susceptibility (GPRA, Laitinen *et al.*, 2004).

Nomenclature	NPS
Other names	GPRA (Laitinen <i>et al.</i> , 2004), GPR154, vasopressin receptor-related receptor 1, PGR14
Ensembl ID	ENSG00000187258
Principal transduction	G _s , G _{q/11} (Gupte <i>et al.</i> , 2004; Vendelin <i>et al.</i> , 2005)
Selective agonists	NPS
Probes	[¹²⁵ I-Tyr ¹⁰]-NPS

Polymorphisms in the NPS receptor have been suggested to be associated with asthma (Laitinen *et al.*, 2004; Vendelin *et al.*, 2005) and irritable bowel syndrome (D'Amato *et al.*, 2007).

Abbreviation: NPS, neuropeptide S

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Neuropeptide Y

Overview: Neuropeptide Y (NPY) receptors (nomenclature agreed by NC-IUPHAR on Neuropeptide Y Receptors, see Michel *et al.*, 1998) are activated by the endogenous peptides NPY, NPY-(3–36), peptide YY (PYY), PYY-(3–36) and pancreatic polypeptide (PP). The receptor originally identified as the Y3 receptor has been identified as the CXCR4 chemokine receptor (originally named LESTR, Loetscher *et al.*, 1994). The y6 receptor is a functional gene product in mouse, absent in rat, but contains a frame-shift mutation in primates producing a truncated non-functional gene (Gregor *et al.*, 1996). Many of the agonists exhibit differing degrees of selectivity dependent on the species examined. For example, the relative potency of PP is greater at the rat Y₄ receptor than at the human receptor (Eriksson *et al.*, 1998). In addition, many agonists lack selectivity for individual subtypes, but can exhibit comparable potency against pairs of NPY receptor subtypes, or have not been examined for activity at all subtypes. [¹²⁵I]-PYY or [¹²⁵I]-NPY can be used to label Y₁, Y₂, Y₅ and y₆ subtypes non-selectively, while [¹²⁵I]-cPP(1–7), NPY(19–23), Ala³¹, Aib³², Gln³⁴]hPP may be used to label Y₅ receptors preferentially.

Nomenclature	Y ₁	Y ₂	Y ₄	Y ₅	Y ₆
Other names	—	—	PP ₁	—	Y ₅ , PP ₂ , Y _{2B}
Ensembl ID	ENSG00000164128	ENSG00000185149	ENSG00000169556	ENSG00000164129	ENSG00000159279
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Rank order of potency	NPY ≥ PYY > > PP	NPY ≥ PYY > > PP	PP > NPY = PYY	NPY ≥ PYY ≥ PP	NPY = PYY > PP
Selective agonists	[Leu ³¹ ,Pro ³⁴]NPY, [Pro ³⁴]NPY, [Leu ³¹ ,Pro ³⁴]PYY, [Pro ³⁴]PYY	NPY-(3–36), PYY-(3–36)	PP	[Ala ³¹ ,Aib ³²]NPY (Cabrele <i>et al.</i> , 2000)	—
Selective antagonists	BIBO3304 (9.5, Wieland <i>et al.</i> , 1998), BIBP3226 (8.2, Gerald <i>et al.</i> , 1996)	BIIE0246 (8.5, Doods <i>et al.</i> , 1999), JNJ5207787 (Bonaventure <i>et al.</i> , 2004)	—	L152804 (7.6, Kanatani <i>et al.</i> , 2000)	—
Probes	[¹²⁵ I]-[Leu ³¹ ,Pro ³⁴] NPY, [³ H]-BIBP3226 (2.1 nM)	[¹²⁵ I]-PYY-(3–36)	[¹²⁵ I]-PP	[¹²⁵ I]-[cPP(1–7),NPY(19–23),Ala ³¹ ,Aib ³² ,Gln ³⁴]hPP (Dumont <i>et al.</i> , 2004)	—

The Y₁ agonists indicated are selective relative to Y₂ receptors. BIBP3226 is selective relative to Y₂, Y₄ and Y₅ receptors (Gerald *et al.*, 1996). NPY-(13–36) is Y₂ selective relative to Y₁ and Y₅ receptors. PYY-(3–36) is Y₂ selective relative to Y₁ receptors.

Abbreviations: **BIBO3304**, (R)-N-([4-{aminocarbonylaminoethyl}-phenyl]methyl)-N²-(diphenylacetyl)-argininamide trifluoroacetate; **BIBP3226**, R-N²-(diphenylacetyl)-N-(4-hydroxyphenyl)methyl-argininamide; **BIIE0246**, (S)-N²-([1-[2-(4-[(R,S)-5,11-dihydro-6(6H)-oxodibenz[b,e]azepin-11-yl]-1-piperazinyl)-2-oxoethyl]cyclopentyl]acetyl)-N-(2-[1,2-dihydro-3,5(4H)-dioxo-1,2-diphenyl-3H-1,2, 4-triazol-4-yl]ethyl)-argininamide; **JNJ5207787**, N-(1-acetyl-2,3-dihydro-1H-indol-6-yl)-3-(3-cyano-phenyl)-N-[1-(2-cyclopentylethyl)piperidin-4-yl]acrylamide; **L152804**, 2-(3,3-dimethyl-1-oxo-4H-1H-xanthen-9-yl)-5,5-dimethyl-cyclohexane-1,3-dione

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Neuropeptides B and W

Overview: The neuropeptide BW receptor 1 (NPBW1, provisional nomenclature) is activated by two 23-amino-acid peptides, neuropeptide W (NPW-23) and neuropeptide B (NPB-23) (Fujii *et al.*, 2002; Shimomura *et al.*, 2002). C-terminally extended forms of the peptides (NPW-30 and NPB-29) also activate NPBW1 (Brezillon *et al.*, 2003). Unique to both forms of NPB is the *N*-terminal bromination of the first tryptophan residue. des-Br-NPB-23 and des-Br-NPB-29 were not found to be major components of bovine hypothalamic tissue extracts. The NPBW2 receptor is activated by the short and C-terminal extended forms of NPB and NPW (Brezillon *et al.*, 2003).

Nomenclature	NPBW1	NPBW2
Other names	GPR7	GPR8
Ensembl ID	ENSG00000183729	ENSG00000125522
Principal transduction	G _{i/o} (Mazzocchi <i>et al.</i> , 2005)	G _{i/o} (Mazzocchi <i>et al.</i> , 2005)
Rank order of potency	NPB-29 > NPB-23 > NPW-23 > NPW-30 (Brezillon <i>et al.</i> , 2003)	NPW-23 > NPW-30 > NPB-29 > NPB-23 (Brezillon <i>et al.</i> , 2003)
Selective agonists	Ava-3, Ava-5 (Kanesaka <i>et al.</i> , 2007)	—
Probes	[¹²⁵ I]-NPW-23 (0.44 nM, Singh <i>et al.</i> , 2004)	[¹²⁵ I]-NPW-23

Potency measurements were conducted with heterologously-expressed receptors with a range of 0.14–0.57 nM (NPBW1) and 0.98–21 nM (NPBW2).

Abbreviations: Ava3, TrpTyrLysAvaAvaAvaGlyArgAlaAlaGlyLeuLeuSerGlyLeu-NH₂; Ava5, TrpTyrLysAvaAvaAvaAvaAvaAvaGlyArgAlaAlaGly-LeuLeuSerGlyLeu-NH₂, respectively

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Neurotensin

Overview: Neurotensin receptors (provisional nomenclature) are activated by the endogenous tridecapeptide neurotensin (pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu) derived from a precursor (ENSG00000133636), which also generates neuromedin N, an agonist at the NTS2 receptor. A nonpeptide antagonist, SR142948A, shows high affinity ($pK_i \sim 9$) at both NTS1 and NTS2 receptors (Gully *et al.*, 1997). [^3H]-Neurotensin and [^{125}I]-neurotensin may be used to label NTS1 and NTS2 receptors at 0.1–0.3 and 3–5 nM concentrations, respectively.

Nomenclature	NTS1	NTS2
Other names	High-affinity neurotensin receptor, NTRH, NTR-1, NT ₁	Low-affinity neurotensin receptor, NTRL, NTR-1, NT ₂
Ensembl ID	ENSG00000101188	ENSG00000169006
Principal transduction	G _{q/11}	G _{q/11}
Rank order of potency	Neurotensin > neuromedin N (Hermans <i>et al.</i> , 1997)	Neurotensin = neuromedin N (Mazella <i>et al.</i> , 1996)
Selective agonists	JMV449 (Souaze <i>et al.</i> , 1997)	Levocabastine (Mazella <i>et al.</i> , 1996)
Selective antagonists	SR48692 (7.5–8.2; Gully <i>et al.</i> , 1997)	—
Probes	[^3H]-SR48692 (3.4 nM; Labbe-Jullie <i>et al.</i> , 1995)	—

Neurotensin appears to be a low-efficacy agonist at the NTS2 receptor (Vita *et al.*, 1998). An additional protein, provisionally termed NTS3 (also known as NTR3, gp95 and sortilin; ENSG00000134243), has been suggested to bind lipoprotein lipase and mediate its degradation (Nielsen *et al.*, 1999). It has been reported to interact with the NTS1 receptor (Martin *et al.*, 2002) and has been implicated in hormone trafficking and/or neurotensin uptake.

Abbreviations: JMV449, *H*-Lysψ (CH₂NH)-Lys-Pro-Tyr-Ile-Leu; **SR142948A**, 2-([5-[2,6-dimethoxyphenyl]-1-{4-(*N*-[3-dimethylaminopropyl]-*N*-methylcarbamoyl)-2-isopropylphenyl]-1*H*-pyrazole-3-carbonyl]amino)adamantane-2-carboxylic acid hydrochloride; **SR48692**, 2-([1-[7-chloro-4-quinolinyl]-5-[2,6-dimethoxyphenyl]pyrazol-3-yl]carboxylamino)tricyclo(3.3.1.1.[3.7])decan-2-carboxylic acid

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Nicotinic acid

Overview: Nicotinic acid receptors (provisional nomenclature) respond to the lipid lowering agents nicotinic acid (niacin), acipimox and acifran (Soga *et al.*, 2003; Tunaru *et al.*, 2003; Wise *et al.*, 2003). Although GPR109A and GPR109B are over 95 % homologous at the protein level, the former is activated by submicromolar concentrations of nicotinic acid, while the latter is only activated at millimolar concentrations (Wise *et al.*, 2003).

Nomenclature	GPR109A	GPR109B
Other names	High affinity, HM74A, Nic1, Puma-G	Low affinity, HM74, Nic2
Ensembl ID	ENSG00000182782	ENSG00000182442
Principal transduction	$G_{i/o}$ (Soga <i>et al.</i> , 2003; Wise <i>et al.</i> , 2003; Tunaru <i>et al.</i> , 2003)	$G_{i/o}$ (Soga <i>et al.</i> , 2003; Wise <i>et al.</i> , 2003)
Selective agonists	Nicotinic acid (Soga <i>et al.</i> , 2003; Wise <i>et al.</i> , 2003; Tunaru <i>et al.</i> , 2003), acipimox, 3-hydroxybutyrate (Taggart <i>et al.</i> , 2005)	IBC293 (Semple <i>et al.</i> , 2006)
Probes	[³ H]-Nicotinic acid (Soga <i>et al.</i> , 2003)	—

GPR109A and GPR109B belong to a family of 7TM receptors (ENSF00000004244), which also includes the 5-oxoeicosanoic acid receptor and GPR31 and GPR81. Although the latter is the most closely related receptor to GPR109A and GPR109B, it fails to respond to nicotinic acid (Tunaru *et al.*, 2003).

Abbreviations: IBC293, 1-(1-methylethyl)-1H-benzotriazole-5-carboxylic acid

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Opioid and opioid-like

Overview: Opioid and opioid-like receptors are activated by the endogenous peptides [Met]enkephalin (met), [Leu]enkephalin (leu), β -endorphin (β -end), α -neo-dynorphin, dynorphin A (dynA), dynorphin B (dynB), Big dynorphin (Big dyn), nociceptin/orphanin FQ (N/OFQ), and endomorphin-1 and -2, although several other opioid-like peptides are found in the CNS. The Greek letter names for the opioid receptors, μ , κ , and δ , are well established and, despite digressions into other nomenclatures (see Dhawan *et al.*, 1996), IUPHAR considers these original names most appropriate (Foord *et al.*, 2005). The human N/OFQ receptor is considered 'opioid-related' rather than opioid because while it exhibits a high degree of structural homology with the conventional opioid receptors (Mollereau *et al.*, 1994), it displays a distinct pharmacology.

Nomenclature Preferred abbreviation	Delta opioid receptor δ	Kappa opioid receptor κ	Mu opioid receptor μ	N/OFQ receptor NOP
Other names	OP ₁ , DOP, DOR	OP ₂ , KOP, KOR	OP ₃ , MOP, MOR	ORL1, OP ₄
Ensembl ID	ENSG00000116329	ENSG00000082556	ENSG00000112038	ENSG00000125510
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Rank order of potency	β -End = leu = met > dynA	Big dyn > dynA > β -end > leu > met	β -End > dynA > met = leu	N/OFQ >> dynA
Selective agonists	DPDPE (Mosberg <i>et al.</i> , 1983), DSBULET (Delay-Goyet <i>et al.</i> , 1988), [DALA ²]deltorphin I or II (Erspamer <i>et al.</i> , 1989), SNC80 (Bilsky <i>et al.</i> , 1995)	U69593 (Lahti <i>et al.</i> , 1985), CI977 (Hunter <i>et al.</i> , 1990), Salvinorin A (Roth <i>et al.</i> , 2002)	Endomorphin-1 and -2 (Zadina <i>et al.</i> , 1997), morphine (Goldstein and Naidu, 1989), DAMGO (Handa <i>et al.</i> , 1981), sufentanil (Yeadon and Kitchen, 1988), PL017 (Costa <i>et al.</i> , 1992)	N/OFQ, N/OFQ-(1-13)-NH ₂ (Guerrini <i>et al.</i> , 1997), Ro646198 (Jenck <i>et al.</i> , 2000), UFP-112 (Rizzi <i>et al.</i> , 2007)
Selective antagonists	Naltrindole (Portoghese <i>et al.</i> , 1988), naltriben (Sofuoglu <i>et al.</i> , 1991)	Nor-binaltorphimine (Portoghese <i>et al.</i> , 1987), GNTI (Stevens <i>et al.</i> , 2000)	CTAP (Pelton <i>et al.</i> , 1986)	J113397 (8.3, Kawamoto <i>et al.</i> , 1999), SB612111 (8.5, Zaratini <i>et al.</i> , 2004), UFP101 (7.2, Calo <i>et al.</i> , 2002)
Probes	[³ H]-DPDPE (Goldstein and Naidu, 1989), [³ H]-naltrindole (Yamamura <i>et al.</i> , 1992), [³ H]-deltorphin II, [³ H]-naltriben (Lever and Scheffel, 1998)	[³ H]-U69593 (Lahti <i>et al.</i> , 1985), [³ H]-CI977 (Simonin <i>et al.</i> , 2001)	[³ H]-DAMGO (Goldstein and Naidu, 1989), [³ H]-PL017	[³ H]-N/OFQ (Dooley and Houghten, 1996), [³ H]-Leu-N/OFQ, [¹²⁵ I]-Tyr ¹⁴ -N/OFQ

Subtypes of μ (μ 1, μ 2), δ (δ 1, δ 2) and κ (κ 1, κ 2, κ 3) receptor have been proposed based primarily on binding studies with poorly selective ligands or *in vivo* studies. Only three naloxone-sensitive opioid receptors have been cloned, and while the μ -receptor in particular may be subject to extensive alternative splicing, this has not been functionally correlated with any of the proposed subtypes.. Thus, there is at present no molecular basis for any of the opioid receptor subtypes, although it remains possible that they are formed by hetero-dimerization of opioid receptors with each other or with other 7TM receptors (Jordan and Devi, 1999). A distinct met-enkephalin receptor lacking structural resemblance to the opioid receptors listed has been identified (ENSG00000060491) and termed an opioid growth factor receptor (see Zagon *et al.*, 2002).

A recent study has observed κ -opioid receptor-dependent phosphorylation of c-Jun terminal kinase by long-lasting κ -opioid antagonists, such as nor-binaltorphimine and GNTI, which may reflect 'collateral agonist efficacy' (Bruchas *et al.*, 2007).

Abbreviations: CI977, (5R)-(5 α , 7 α , 8 β)-(-)-N-methyl-N-(7-[1-pyrrolidinyl]-1-oxaspiro[4,5]dec-8-yl)-4-benzofuranacetamide hydrochloride; CTAP, D-Phe-cyc[Cys-Tyr-D-Trp-Arg-Thr-Pen]-Thr-NH₂; DAMGO, Tyr-DALA-Gly-[NMePhe]-NH(CH₂)₂; DPDPE, cyc[DPen², DPen⁵]enkephalin; DSBULET, Tyr-DSer(OtBu)-Gly-Phe-Leu-Thr; GNTI, 5'-guanidinyl-17-(cyclopropylmethyl)-6,7-dehydro-4, 5 α -epoxy-3, 14-dihydroxy-6, 7-2', 3'-indolomorphinan; ICI174864, N, N-diallyl-Tyr-Aib-Phe-Leu-OH (Aib is aminoisobutyric acid); J113397, 1-[(3*r*, 4*r*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one; PL017, [N-MePhe³, DPro⁴]morphiceptin; Ro646198, (1*S*, 3*aS*)-8-(2, 3, 3*a*, 4,5,6-hexahydro-1*H*-phenalen-1-yl)-1-phenyl-1, 3, 8-triazaspiro[4.5]decan-4-one; SB612111, (-)-cis-1-methyl-7-[[4-(2, 6-dichlorophenyl)piperidin-1-yl]methyl]-6, 7, 8, 9-tetrahydro-5H-benzocyclohept-5-ol; SNC80, (+)-4-[(α R)- α -(2*S*, 5*R*)-4-allyl-2, 5-dimethyl-1-piperazinyl]-3-methoxybenzyl]-N, N-diethylbenzamide; U69593, 5 α , 7 α , 8 β -(+)-N-methyl-N-(7-[1-pyrrolidinyl]-1-oxaspiro(4, 5)dec-8-yl)benzene acetamide; UFP101, [Nphe¹, Arg¹⁴, Lys¹⁵]nociceptin-NH₂; UFP-112, [(pF)Phe⁴Aib⁷Arg¹⁴Lys¹⁵]N/OFQ-NH₂

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Orexin

Overview: Orexin receptors (provisional nomenclature) are activated by the endogenous polypeptides orexin-A and orexin-B (also known as hypocretin-1 and -2; 33 and 28 aa) derived from a common precursor, orexin (ENSG00000161610), by proteolytic cleavage (Sakurai *et al.*, 1998). Binding to both receptors may be accomplished with [¹²⁵I]-orexin A (Holmqvist *et al.*, 2001).

Nomenclature	OX ₁	OX ₂
Other names	Hypocretin receptor type 1	Hypocretin receptor type 2
Ensembl ID	ENSG00000121764	ENSG00000137252
Principal transduction	G _{q/11}	G _{q/11}
Rank order of potency	Orexin-A > orexin-B	Orexin-A = orexin-B
Selective agonists	—	[Ala ¹¹ ,D-Leu ¹⁵]orexin-B (Asahi <i>et al.</i> , 2003)
Selective antagonists	SB408124 (7.5, Langmead <i>et al.</i> , 2004), SB334867A (7.2–7.3, Smart <i>et al.</i> , 2001)	—

The *HCRT2* gene encoding the OX₂ receptor has been identified as a possible candidate for inherited narcolepsy (Chemelli *et al.*, 1999; Lin *et al.*, 1999; Siegel, 1999).

Abbreviations: SB334867A, 1-(2-methylbenzoxanzol-6-yl)-3-[1,5]naphthyridin-4-yl-urea hydrochloride; SB408124, 1-(6,8-difluoro-2-methylquinolin-4-yl)-3-(4-dimethylamino-phenyl)-urea

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P2Y

Overview: P2Y receptors (provisional nomenclature as agreed by NC-IUPHAR Subcommittee on P2Y Receptors, Abbraccio *et al.*, 2003; 2006) are activated by the endogenous ligands ATP, ADP, UTP, UDP and UDP-glucose. The relationship of many of the cloned receptors to endogenously expressed receptors is not yet established and so it might be appropriate to use wording such as 'UTP-preferring (or ATP-, etc.) P2Y receptor' or 'P2Y₁-like', etc., until further, as yet undefined, corroborative criteria can be applied.

Nomenclature	P2Y ₁	P2Y ₂	P2Y ₄	P2Y ₆
Ensembl ID	ENSG00000169860	ENSG00000175591	ENSG00000186912	ENSG00000171361
Principal transduction	G _{q/11}	G _{q/11}	G _{q/11}	G _{q/11}
Rank order of potency	ADP > ATP	UTP = ATP	UTP > ATP (at rat recombinant receptors, UTP = ATP)	UDP > > UTP > ATP
Selective agonists	2-MeSADP, ADPβS, MRS2365 (Bourdon <i>et al.</i> , 2006)	UTPγS (Lazarowski <i>et al.</i> , 1996), Ap ₄ A (Castro <i>et al.</i> , 1992)	UTPγS (Lazarowski <i>et al.</i> , 1996)	UDP, 2-phenacylUDP (El-Tayeb <i>et al.</i> , 2006)
Selective antagonists	MRS2500 (8.8, Kim <i>et al.</i> , 2003), MRS2279 (8.0, Waldo <i>et al.</i> , 2002), MRS2179 (7.0, Boyer <i>et al.</i> , 1996), PIT (6.8, Gao <i>et al.</i> , 2004)	—	ATP (6.2, Kennedy <i>et al.</i> , 2000)	MRS2578 (pIC ₅₀ 7.4, Mamedova <i>et al.</i> , 2004)
Probes	[³ H]-MRS2279 (8 nM, Waldo <i>et al.</i> , 2002) [³⁵ S]-ADPβS, [³⁵ S]-ATPαS, [³⁵ S]-dATPαS	—	—	—

Nomenclature	P2Y ₁₁	P2Y ₁₂	P2Y ₁₃	P2Y ₁₄
Other names	—	P2Y _{ADP} P _{2T}	GPR86, GPR94, SP174	KIAAA00001, gpr105
Ensembl ID	ENSG00000176130 ENSG00000174944	ENSG00000169313	ENSG00000181631	
Principal transduction	G _s , G _{q/11}	G _{i/o}	G _{i/o}	G _{q/11}
Rank order of potency	ATP > UTP	ADP > > ATP	ADP > > ATP	UDP-glucose
Selective agonists	ARC67085 (Communi <i>et al.</i> , 1999), NAD ⁺ (Moreschi <i>et al.</i> , 2006), NAADP ⁺ (Moreschi <i>et al.</i> , 2007)	ADP, 2-MeSADP	—	MRS2690 (Ko <i>et al.</i> , 2007)
Selective antagonists	—	ATP, ARL66096 (Humphries <i>et al.</i> , 1995)	MRS2211 (Kim <i>et al.</i> , 2005)	—

ARC69931MX shows selectivity for P2Y₁₂ and P2Y₁₃ receptors compared to other P2Y receptors (Takasaki *et al.*, 2001; Marteau *et al.*, 2003).

A 7TM orphan receptor suggested to be a 'P2Y₁₅' receptor (Inbe *et al.*, 2004) appears not to be a genuine nucleotide receptor (see Abbraccio *et al.*, 2006), but rather responds to dicarboxylic acids (He *et al.*, 2004). Further P2Y-like receptors have been cloned from non-mammalian sources; a clone from chick brain, termed a p2y₃ receptor (ENSGALG00000017327), couples to the G_{q/11} family of G proteins and shows the rank order of potency ADP > UTP > ATP = UDP (Webb *et al.*, 1996a). In addition, human sources have yielded a clone with a preliminary identification of p2y5 (ENSG00000139679) and contradictory evidence of responses to ATP (Webb *et al.*, 1996b; King and Townsend-Nicholson, 2000). The clone p2y7 (ENSG00000196943), originally suggested to be a P2Y receptor (Akbar *et al.*, 1996), has been shown to encode a leukotriene receptor (Yokomizo *et al.*, 1997). A P2Y receptor that was initially termed a p2y8 receptor (P79928) has been cloned from *Xenopus laevis*; it shows the rank order of potency ADPβS > ATP = UTP = GTP = CTP = TTP = ITP > ATPγS and elicits a Ca²⁺-dependent Cl⁻ current in *Xenopus* oocytes (Bogdanov *et al.*, 1997). The clone termed p2y9 has recently been described as an LPA receptor (Noguchi *et al.*, 2003), while the p2y10 (ENSG00000078589) clone lacks functional data. Diadenosine polyphosphates also have effects on as yet uncloned P2Y-like receptors with the rank order of potency of Ap₄A > Ap₅A > Ap₃A, coupling via G_{q/11} (Castro *et al.*, 1992). P2Y-like receptors have recently been described on mitochondria (Belous *et al.*, 2004). CysLT₁ and CysLT₂ leukotriene receptors respond to nanomolar concentrations of UDP, although they are activated principally by leukotrienes C₄ and D₄ (Mellor *et al.*, 2001, 2003); Human (ENSG00000144230) and rat GPR17, which are structurally related to CysLT and P2Y receptors, are also activated by leukotrienes as well as UDP and UDP-glucose (Ciana *et al.*, 2006). Activity at the rat GPR17 is inhibited by submicromolar concentrations of MRS2179 and ARL69931 (Ciana *et al.*, 2006).

Abbreviations: ARC67085, 2-propylthio-βγ-dichloromethylene-ATP; AR-C69931MX, N⁶-(2-methylthioethyl)-2-(3,3,3-trifluoropropylthio)-βγ-dichloromethylene-ATP, also known as cangrelor; 2-MeSADP, 2-methylthio-adenosine-5'-diphosphate; 2-MeSATP, 2-methylthio-adenosine-5'-triphosphate; ARL66096, 2-propylthio-βγ-difluoromethylene ATP (previously FPL66096); ATPγS, adenosine 5'-(3-thio)triphosphate; MRS2179, N⁶-methyl-2'-deoxyadenosine-3',5'-bisphosphate; MRS2211, pyridoxal-5'-phosphate-6-azo (2-chloro-5-nitrophenyl)-2,4-disulfonate; MRS2279, 2-chloro-N⁶-methyl-(N)-methanocarba-2'-deoxyadenosine-3',5'-bisphosphate; MRS2365, (N)-methanocarba-2-MeSADP; MRS2500, N⁶-methyl-(N)-methanocarba-2'-deoxyadenosine-3',5-bisphosphate; MRS2578, N,N'-1,4-butanediyl bis(N'-[3-isothiocyantophenyl]) thiourea; MRS2690, 2-thiouridine-5'-diphosphoglucose; PIT, 2,2'-pyridylisatogen tosylate

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Parathyroid hormone and parathyroid hormone-related peptide

Overview: Parathyroid hormone (PTH) and parathyroid hormone-related peptide (PTHrP) receptors (provisional nomenclature) are activated by precursor-derived peptides: PTH (84 amino acids, ENSG00000152266), PTHrP (141 amino-acids and related peptides (PTHrP-1–36, PTHrP-38–94 and osteostatin (PTHrP-107–139) (ENSG0000087494) and TIP39 (39 amino acids, ENSG00000142538). [¹²⁵I]-PTH may be used to label both PTH₁ and PTH₂ receptors. Although PTH is an agonist at human PTH₂ receptors, it fails to activate the rodent orthologues. TIP39 is a weak antagonist at PTH₁ receptors (Jonsson *et al.*, 2001).

Nomenclature	PTH ₁	PTH ₂
Other names	PTH/PTHrP	—
Ensembl ID	ENSG00000160801	ENSG00000144407
Principal transduction	G _s , G _{q/11}	G _s , G _{q/11}
Rank order of potency	PTH = PTHrP	TIP39, PTH » PTHrP
Selective agonists	—	TIP39 (Hoare <i>et al.</i> , 2000)
Selective antagonists	—	TIP-9-39 (Jonsson <i>et al.</i> , 2001)

Abbreviations: PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; TIP39, tuberoinfundibular protein of 39 residues

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Platelet-activating factor

Overview: Platelet-activating factor (PAF, 1-O-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) is a biologically active phospholipid mediator. PAF acts by binding to a unique G-protein-coupled seven transmembrane receptor (PAF-R) and activates multiple intracellular signaling pathways by coupling to the G_{q/11} and G_{i/o} families of G-proteins. PAF-R is activated by PAF and its metabolically stable analogue mc-PAF. Other suggested endogenous ligands are oxidized phosphatidylcholine (Marathe *et al.*, 1999) and lysophosphatidylcholine (Ogita *et al.*, 1997). It may also be activated by bacterial lipopolysaccharide (Nakamura *et al.*, 1992).

Nomenclature	PAF-R
Ensembl ID	ENSG00000169403
Principal transduction	G _{q/11} , G _i , G _o
Selective agonists	mc-PAF
Selective antagonists	CV-6209 (9.5), SR27417 (10.0), WEB2086 (8.0), L659989 (8.1), ginkgolide B (6.4)
Radioligand	[³ H]-PAF (1.6 nM, Fukunaga <i>et al.</i> , 2001)

Note that a previously recommended radioligand ([³H]-WEB2086; K_d 44.6 nM) is currently unavailable.

Abbreviations: CV-6209, 2-(N-acetyl-N-[2-methoxy-3-octadecylcarbamoxyloxypropoxycarbamoyl]aminomethyl)-1-ethylpyridinium chloride; L659989, *trans*-2-(3-methoxy-5-methylsulphonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran; mc-PAF, 1-O-alkyl-2-N-methylcarbamoxy-*sn*-glycero-3-phosphocholine; also known as (methyl)carbamoxyyl-PAF or c-PAF; SR27417, N-(2-dimethylaminoethyl)-N-(3-pyridinylmethyl)(4-[2,4,6-triisopropylphenyl]thiazol-2-yl)amine; WEB2086, 3-(4-[2-chlorophenyl]-9-methyl-6H-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine-2-yl)-1-(4-morpholinyl)-1-propanone; also known as apafant

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Prostanoid

Overview: Prostanoid receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors, see Coleman *et al.*, 1994) are activated by the endogenous ligands prostaglandin (PG) D₂ (D), PGE₂ (E), PGF_{2α} (F), PGH₂ (H), prostacyclin [PGI₂ (I)] and thromboxane A₂ (T). Measurement of the potency of PGI₂ and TXA₂ is hampered by their instability in physiological salt solution; they are often replaced by cicaprost and U46619, respectively, in receptor characterization studies.

Nomenclature	DP ₁	DP ₂	FP	IP	TP
Other names	—	CRTh2, GPR44	—	—	—
Ensembl ID	ENSG00000168229	ENSG00000183134	ENSG00000122420	ENSG00000160013	ENSG00000006638
Principal transduction	G _s	G _{i/o}	G _{q/11}	G _s	G _{q/11}
Rank order of potency	D > E > F > I, T	D > E, E > I, T	F > D > E > I, T	I > D, E, F > T	T = H > D, E, F, I
Selective agonists	L644698, BW245C, ZK118182, RS93520, SQ27986	13,14-dihydro-15-oxoPGD ₂ , 15R-15-methyl PGD ₂ (Hata <i>et al.</i> , 2003; Monneret <i>et al.</i> , 2003)	Fluprostenol, latanoprost	Cicaprost, AFP-07, BMV45778 (Seiler <i>et al.</i> , 1997)	U46619, STA ₂ , I-BOP, AGN192093
Selective antagonists	BWA868C (9.3, Giles, 1989), SS751 (8.8, Arimura <i>et al.</i> , 2001), ZK138357 (7.3, Lydford <i>et al.</i> , 1996)	Ramatroban (Sugimoto <i>et al.</i> , 2003), CAY10471 (Mathiesen <i>et al.</i> , 2006)	—	RO1138452 (8.8, Bley <i>et al.</i> , 2006)	BMS180291 (9.3–10.0), ONO3708 (8.9), GR32191 (8.3–9.4, Lumley <i>et al.</i> , 1989), SQ29548 (8.1–9.1, Swayne <i>et al.</i> , 1988)
Probes	[³ H]-PGD ₂ (13–34 nM)	[³ H]-PGD ₂ (6–11 nM)	[³ H]-PGF _{2α} (2–4 nM), [³ H]-(+)-fluprostenol (34 nM)	[³ H]-Iloprost (1–20 nM)	[³ H]-SQ29548 (5–40 nM), [¹²⁵ I]-SAP (0.2–1.0 nM), [¹²⁵ I]-I-BOP (0.3–5.0 nM)

Ramatroban is also a TP receptor antagonist. Cicaprost exhibits moderate EP₄ receptor agonist potency (Abramovitz *et al.*, 2000). Iloprost also binds to EP₁ receptors. The TP receptor exists in α and β isoforms due to alternative splicing of the cytoplasmic tail (Raychowdhury *et al.*, 1994).

Nomenclature	EP ₁	EP ₂	EP ₃	EP ₄
Ensembl ID	ENSG00000160951	ENSG00000125384	ENSG00000050628	ENSG00000171522
Principal transduction	G _{q/11}	G _s	G _{i/o}	G _s
Rank order of potency	E > F, I > D, T	E > F, I > D, T	E > F, I > D, T	E > F, I > D, T
Selective agonists	17-Ph-ω-trinor-PGE ₂ , ONO-DI-004	Butaprost, AH13205, ONO-AE1-259	Sulprostone, SC46275, ONO-AE-248	ONO-AE1-329
Selective antagonists	ONO8711 (9.2), SC51322 (8.8)	—	L798106 (7.7)	GW627368 (9.2), ONO-AE3-208 (8.5), L161982 (7.6)
Probes	[³ H]-PGE ₂ (1–25 nM)	[³ H]-PGE ₂ (5–22 nM)	[³ H]-PGE ₂ (0.3–7 nM)	[³ H]-PGE ₂ (0.6–24 nM)

17-Ph-ω-trinor-PGE₂ also shows agonist activity at EP₃ receptors. Sulprostone also has affinity for EP₁ receptors. Butaprost and SC46275 may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP (Liljebriis *et al.*, 1995), IP (Takechi *et al.*, 1996; Wise *et al.*, 1995) and TP (Krauss *et al.*, 1996) receptors. mRNA for the EP₁ and EP₃ receptors undergo alternative splicing to produce two (Okuda-Ashitaka *et al.*, 1996) and at least six variants, respectively, which can interfere with signalling (Okuda-Ashitaka *et al.*, 1996) or generate complex patterns of G-protein (G_{i/o}, G_{q/11}, G_s and G_{12/13}) coupling (e.g. Kotani *et al.*, 1995; Negishi *et al.*, 1995). The possibility of additional receptors for the isoprostanes has been suggested (Pratico *et al.*, 1996).

Abbreviations: AFP-07, 7,7-difluoro-16S,20-dimethyl-18,19-didehydro-PGI₂; AGN192093, (Z)-7-[(1α,5α,6α,7β)-7-[[1E,3S]-3-hydroxy-1-octenyl]-3-oxo-2,4-dioxobicyclo[3.2.1]oct-6-yl]-5-heptenol; AH13205, *trans*-2-(4-[1-hydroxyhexyl]phenyl)-5-oxocyclopentane-heptanoic acid; AH23848, (1α[z],2β,5α)-(±)-7-(5-[[[1,1'-biphenyl]-4-yl]methoxy]-2-[4-morpholinyl]-3-oxocyclopentyl)-4-heptenoate; BMS180291, (1S-(1α,2α,3α,4α)-2-[[3-[4-([pentylamino]carbonyl)-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid, also known as ifetroban; BMV45778, 3-(4-[4,5-diphenyl-2-oxazolyl]-5-oxazolyl)phenoxyacetic acid; BW245C, 5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl)hydantoin; BWA868C, 3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino)hydantoin; CAY10471, (+)-3-[[[4-fluorophenyl]-sulfonyl]methylamino]-1,2,3,4-tetrahydro-9H-carbazole-9-acetic acid; GR32191, [1R-[1(2Z),2α,3β,5]]-(+)-7-[5-[[[1,1'-biphenyl]-4-yl]methoxyl]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid; GW627368, N-(2-[4-[4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl]-acetyl)benzenesulphonamide; I-BOP, (1S-[1α,2β[Sz],3α[1e,3s], 4α])-7-(3-[hydroxy-4-[4'-iodophenoxy]-1-butenyl]-7-oxabicyclo[2.2.1]hept-2-yl)-5-heptanoate; L161982, 5-butyl-2,4-dihydro-[[2'-[N-(5-methyl-2-thiophenecarbonyl)sulphamoyl]biphenyl-4-yl]methyl]-2-[(2-trifluoromethyl)phenyl]-1,2,4-triazol-3-one; L644698, 4-(3-[3-[3-hydroxyoctyl]-4-oxo-2-thiazolidinyl]propyl)benzoate racemate; L798106, 5-bromo-2-methoxy-N-[3-(naphthalen-2-yl-methylphenyl)-acryloyl]-benzenesulphonamide; ONO3708, (9,11)-(11,12)-dideoxa-9α,11α-dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14-oxo-15-cyclopentyl-16,17,18,19,20-pentanor-15-epi-TXA₂; ONO8711, 6-[(2S,3S)-3-(4-chloro-2-methylphenyl)sulphonylaminomethyl]-bicyclo[2.2.2]octan-2-yl]-5Z-hexenoic acid; ONO-DI-004, 17S-17,20-dimethyl-2,5-ethano-6-oxo PGE₁; ONO-AE-248, 11,15-O-dimethyl-PGE₂; ONO-AE1-259, 16S-9-deoxy-9β-chloro-15-deoxy-16-hydroxy-17,17-propano-19,20-didehydro-PGE₂; ONO-AE1-329, 16-(3-methoxymethyl)phenyl-ω-tetranor-3,7-dithia-PGE₁; ONO-AE3-208, 2-(2-(2-methyl-2-naphth-1-ylacetylaminomethyl)-phenylmethyl)-benzoic acid; RO1138452, 4,5-dihydro-1H-imidazol-Z-yl)-[4-(4-isopropoxybenzyl)phenyl]amine; RS93520, Z-4-[(C3'S,1R,2R,3S,6R)-2C3'-cyclohexyl-3'-hydroxyprop-1-ynyl]-3-hydroxybicyclo(4.2.0)oct-7-ylidene butyrate; SAP, 7-[(1R,2S,3S,5R)-6,6-dimethyl-3-benzenesulphonamino-bicyclo[3.1.1]hept-2-yl]-5Z-heptenoic acid; SC46275, methyl-7-(2β-[6-[1-cyclopenten-1-yl]-4R-hydroxy-4-methyl-1e,5e-hexadienyl]-3α-hydroxy-5-oxo-1R,1α-cyclopentyl)-4Z-heptenoic acid; SC51322, 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[3-[furanlylmethyl]-thio]

1-oxopropyl]hydrazide; **SQ29548**, (1S-[1 α ,2 β [5Z],3 β ,4 β])7-(3-[[2-(phenylamino)carbonyl]hydrazino]methyl)-7-oxabicyclo[2.2.1]hept-2-yl-5-heptenoate; **S5751**, ((Z)-7-[1R,2R,3S,5S]-2-(5-hydroxybenzo[b]thiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid); **SQ27986**, [1S-[1B,2B(5Z),3A(1E,3S)4B]]7-[3-(3-cyclohexyl-3-hydroxy-1-propenyl)-7-oxabicyclo[2.2.1]hept-2-yl]5-heptenoic acid; **STA₂**, 11 α -carba-9 α ,11 β -thia-Txa₂; **U46619**, 11 α ,9 α -epoxymethano-PGH₂; **ZK 118182**, (5Z,13E)-(9R,11R,15S)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentano-5,13-prostadienoic acid; **ZK138357**, (5Z)-7-([2R,4S,5S]-2-[2-chlorophenyl]-5-[[1E]-{3R,S}-3-hydroxy-3-cyclohexyl-1-propenyl]1,3-dioxolan-4-yl)-5-heptanoic acid

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Proteinase-activated

Overview: Proteinase-activated receptors (PARs, nomenclature as agreed by NC-IUPHAR Subcommittee on Protease-activated Receptors, see Hollenberg & Coughlan, 2002) are activated by proteolytic cleavage of their amino terminal exodomains. Alternative endogenous proteinases or ligands to thrombin for PAR1, PAR3 or PAR4 have not been demonstrated. Activation of PAR2 by trypsin or tryptase release *in vivo* is yet to be demonstrated. Several proteases, including cathepsin G and chymotrypsin, have an inhibitory effect at the PAR1 receptor such that they cleave the exodomain of the receptor without inducing activation, thereby preventing activation by thrombin but not by agonist peptides. The role of such an action *in vivo* is unclear. Agonist protease-induced hydrolysis is thought to unmask a tethered ligand at the exposed amino terminus, which acts intramolecularly at the binding site in the body of the receptor to effect transmembrane signalling. Tethered ligand sequences at human PAR1–4 are SFLLRN, SLIGKV, TFRGAP and GYPGQV, respectively. With the exception of PAR3, these synthetic peptide sequences (as carboxyl terminal amides) are able to act as agonists at their respective receptors.

Nomenclature	PAR ₁	PAR ₂	PAR ₃	PAR ₄
Other names	Thrombin receptor, PAR-1, PAR ₁	PAR-2, PAR ₂	Thrombin receptor, PAR-3, PAR ₃	Thrombin receptor, PAR-4, PAR ₄
Ensembl ID	ENSG00000181104	ENSG00000164251	ENSG00000164220	ENSG00000127533
Principal transduction	G _{q/11} /G _{i/o} /G _{12/13}	G _{q/11} /G _{i/o}	G _{q/11} /G _{i/o}	G _{q/11} /G _{i/o}
Agonist proteases	Thrombin, trypsin	Trypsin, tryptase	Thrombin, trypsin, factor Xa	Thrombin, trypsin
Selective agonists	TFLLR-NH ₂	SLIGRL, SLIGKV	—	GYPGQV, GYPGKF
Selective antagonists	RWJ56110 (Andrade-Gordon <i>et al.</i> , 1999)	—	—	—
Probes	[³ H]-haTRAP (Ahn <i>et al.</i> , 1997)	<i>Trans</i> -cinnamoyl-LIGRLO[N- ³ H]-propionyl]-NH ₂ (Al Ani <i>et al.</i> , 1999)	—	—

TFLLR-NH₂ is selective relative to the PAR2 receptor (Blackhart *et al.*, 1996; Kawabata *et al.*, 1999). Thrombin is inactive at the PAR₂ receptor.

Abbreviations: [³H]-haTRAP, Ala-*p*-fluoroPhe-Ala-Arg-cyclohexylAla-homoArg-[³H]-Tyr-amide; RWJ56110, (αS)-N-([1S]-3-amino-1-[(phenylmethyl)amino]propyl)-α-[(1-[[2,6-dichlorophenyl]methyl]-3-[1-pyrrolidinylmethyl]-1*H*-indol-6-yl)amino]carbonyl]amino)-3,4-difluoro-benzene-propanamide

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Prokineticin

Overview: Prokineticin receptors (PKR, provisional nomenclature) respond to the cysteine-rich 81–86 amino-acid peptides prokineticin-1 (PK1, also known as endocrine-gland-derived vascular endothelial growth factor, mambakine, ENSG00000143125) and prokineticin-2 (PK2, protein Bv8 homolog, ENSG00000163421). An orthologue of PK1 from black mamba (*Dendroaspis polylepis*) venom, mamba intestinal toxin 1 (MIT1, Schweitz *et al.*, 1999) is a potent, non-selective agonist at PKR receptors (Masuda *et al.*, 2002), while Bv8, an orthologue of PK2 from amphibians (*Bombina sp.*, Mollay *et al.*, 1999), is equipotent at recombinant PKR₁ and PKR₂ receptors (Negri *et al.*, 2005), and has high potency in macrophage chemotaxis assays, which are lost in PKR₁-null mice (Martucci *et al.*, 2006).

Nomenclature	PKR ₁	PKR ₂
Other names	PK-R1, GPR73 (Lin <i>et al.</i> , 2002; Soga <i>et al.</i> , 2002), G-protein coupled receptor ZAQ (Masuda <i>et al.</i> , 2002)	PK-R2, GPR73a (Lin <i>et al.</i> , 2002), GPRg2 (Soga <i>et al.</i> , 2002), I5E (Masuda <i>et al.</i> , 2002)
Ensembl ID	ENSG00000169618	ENSG00000101292
Principal transduction	G _{q/11} (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002)	G _{q/11} (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002)
Rank order of potency	PK2 ≥ PK1 (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002; Soga <i>et al.</i> , 2002)	PK2 ≥ PK1 (Lin <i>et al.</i> , 2002; Masuda <i>et al.</i> , 2002; Soga <i>et al.</i> , 2002)

Abbreviations: PK1, prokineticin 1; PK2, prokineticin 2

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Relaxin family peptide

Relaxin family peptide receptors (RXFP, nomenclature as approved by the NC-IUPHAR committee on relaxin family peptide receptors, Bathgate *et al.* 2006) may be divided into two groups RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are a number of heterodimeric peptide hormones analogous to insulin: H1 relaxin [ENSG00000107018], H2 relaxin [ENSG00000107014], H3 relaxin [also known as INSL7, ENSG00000171136], insulin-like peptide (INSL) 3 [OTTHUMG00000070952] and INSL5 [ENSG00000172410].

Species homologues of relaxin have distinct pharmacology—H2 relaxin interacts with RXFP1 and RXFP2, mouse and rat relaxin selectively bind to and activate RXFP1 (Scott *et al.*, 2005a) and porcine relaxin may have a higher efficacy than H2 relaxin (Halls *et al.*, 2005). H3 relaxin has differential affinity for RXFP2 receptors between species; mouse and rat RXFP2 have a higher affinity for H3 relaxin (Scott *et al.*, 2005b). At least two binding sites have been identified on the RXFP1 and RXFP2 receptors: a high-affinity site in the leucine-rich repeat region of the ectodomain and a somewhat lower-affinity site located in the surface loops of the transmembrane (Sudo *et al.*, 2003; Halls *et al.*, 2005). The unique *N*-terminal LDLa module of RXFP1 and RXFP2 directs receptor signalling (Scott *et al.*, 2007).

Nomenclature	RXFP1	RXFP2
Other names	Relaxin receptor, LGR7, leucine-rich repeat-containing G-protein-coupled receptor 7, RX1	INSL3 receptor, LGR8, leucine-rich repeat-containing G-protein-coupled receptor 8, GREAT, RX2
Ensembl ID	ENSG00000171509	ENSG00000133105
Principal transduction	G _s , G _{zoB} , G ₂₁₃ (Halls <i>et al.</i> , 2006; Hsu <i>et al.</i> , 2002)	G _s , G _{zoB} (Halls <i>et al.</i> , 2006; Kumagai <i>et al.</i> , 2002)
Rank order of potency	H2 relaxin > H3 relaxin > > INSL3 (Sudo <i>et al.</i> , 2003)	INSL3 > H2 relaxin > > H3 relaxin (Kumagai <i>et al.</i> , 2002; Sudo <i>et al.</i> , 2003)
Antagonists	LGR7-truncate (Scott <i>et al.</i> , 2007)	INSL3 B-chain analog (Del Borgo <i>et al.</i> , 2006), (des 1-8) A-chain INSL3 analog (Bullesbach and Schwabe, 2000)
Probes	[³³ P]-H2 relaxin (0.2 nM; Sudo <i>et al.</i> , 2003)	[³³ P]-H2 relaxin (1.06 nM; Sudo <i>et al.</i> , 2003), [¹²⁵ I]-INSL3 (0.1 nM; Muda <i>et al.</i> , 2005)

Mutations in *INSL3* and *LGR8* (RXFP2) have been reported in populations of patients with cryptorchidism (Ferlin *et al.*, 2003). Numerous splice variants of the human RXFP1 and RXFP2 receptors have been identified, none of which bind relaxin family peptides (Muda *et al.*, 2005). Splice variants of RXFP1 encoding the *N*-terminal LDLa module act as antagonists of RXFP1 signalling (Scott *et al.*, 2005b). Gain-of-function receptor mutants increase cAMP accumulation in cell lines (Hsu *et al.*, 2000; Hsu *et al.*, 2002).

Nomenclature	RXFP3	RXFP4
Other names	Relaxin 3 receptor, GPCR135, somatostatin and angiotensin-like peptide receptor SALPR, RX3	INSL5 receptor, GPCR142, GPR100, relaxin 3 receptor 2, RX4
Ensembl ID	ENSG00000182631	ENSG00000173080
Principal transduction	G _{i/o} (Matsumoto <i>et al.</i> , 2000; van der Westhuizen <i>et al.</i> , 2005)	G _{i/o} (Liu <i>et al.</i> , 2003b; van der Westhuizen <i>et al.</i> , 2007)
Rank order of potency	H3 relaxin > H3 relaxin B chain (Liu <i>et al.</i> , 2003a)	INSL5 = H3 relaxin > H3 relaxin B chain (Liu <i>et al.</i> , 2003b, 2005a)
Antagonists	INSL5 (Liu <i>et al.</i> , 2005a), R3(BA23-27)R/I5 chimeric peptide (Kuei <i>et al.</i> , 2007)	R3(BA23-27)R/I5 chimeric peptide (Kuei <i>et al.</i> , 2007)
Probes	[¹²⁵ I]-H3 relaxin (0.3 nM; Liu <i>et al.</i> , 2003a), [¹²⁵ I]-H3-B/INSL5 A chimera (0.5 nM; Liu <i>et al.</i> , 2005b)	[¹²⁵ I]-H3 relaxin (0.2 nM; Liu <i>et al.</i> , 2003b), [¹²⁵ I]-H3-B/INSL5 A chimera (1.2 nM; Liu <i>et al.</i> , 2005b)

H3 relaxin acts as an agonist at both RXFP3 and RXFP4 whereas INSL5 is an agonist at RXFP4 and an antagonist at RXFP3. Current studies indicate that other relaxins and related peptides have little or no action at RXFP3 and RXFP4. Unlike RXFP1 and RXFP2 both RXFP3 and RXFP4 are encoded by a single exon and therefore no splice variants exist. The rat RXFP3 sequence has two potential start codons that encode RXFP3L and RXFP3S with the longer variant having an additional 7 amino-acids at the *N*-terminus. It is not known which variant is expressed. Rat and dog RXFP4 sequences are pseudogenes (Wilkinson *et al.*, 2005).

Abbreviations: H2 relaxin, human gene 2 relaxin; H3 relaxin, human gene 3 relaxin; INSL3, insulin-like peptide 3; INSL5, insulin-like peptide 5

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Somatostatin

Overview: Somatostatin (somatotropin release inhibiting factor) is an abundant neuropeptide, which acts on five subtypes of somatostatin receptor (sst1 – sst5; nomenclature approved by the NC-IUPHAR Subcommittee on Somatostatin Receptors, see Hoyer *et al.*, 2000). Activation of these receptors produces a wide range of physiological effects throughout the body. The relationship of the cloned receptors to endogenously expressed receptors is not yet well established in some cases. Endogenous ligands for these receptors are somatostatin-14 (SRIF-14) and somatostatin-28 (SRIF-28). Cortistatin (CST-14) has also been suggested to be an endogenous ligand for somatostatin receptors (Delecea *et al.*, 1996).

Nomenclature	sst ₁	sst ₂	sst ₃	sst ₄	sst ₅
Alternative names	SSTR1, SRIF ₂ , SRIF _{2A}	SSTR2, SRIF ₁ , SRIF _{1A}	SSTR3, SRIF ₁ , SRIF _{1C}	SSTR4, SRIF ₂ , SRIF _{2B}	SSTR5, SRIF ₁ , SRIF _{1B}
Ensembl ID	ENSG00000139874	ENSG00000180616	ENSG00000183473	ENSG00000132671	ENSG00000162009
Principal transduction	G _i	G _i	G _i	G _i	G _i
Selective agonists	des-Ala ^{1,2,5} -[DTrp ⁸ ,Iamp ⁹]SRIF, L797591	Octreotide, seglitide, BIM23027, L054522	L796778	NNC269100, L803087	BIM23268, BIM23052, L817818
Selective antagonists	—	Cyanamid 154806 (7.7–8.0)	—	—	BIM23056 (7.4–8.3)
Probes	—	[¹²⁵ I]-[Tyr ³]octreotide (0.13 nM) [¹²⁵ I]-BIM23027	—	—	[¹²⁵ I]-[Tyr ³]octreotide (0.23 nM)

[¹²⁵I]-[Tyr¹¹]SRIF-14, [¹²⁵I]-LTT-SRIF-28, [¹²⁵I]-CGP23996 and [¹²⁵I]-[Tyr¹⁰]CST-14 may be used to label somatostatin receptors nonselectively; BIM23052 is said to be selective in rat but not human receptor (Patel and Srikant, 1994). A number of nonpeptide subtype-selective agonists have been synthesised (see Rohrer *et al.*, 1998).

Abbreviations: **BIM23027**, cyc(N-Me-Ala-Tyr-D-Trp-Lys-Abu-Phe); **BIM23052**, DPhe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂; **BIM23056**, DPhe-Phe-Thr-D-Trp-Lys-Val-Phe-D-Nal-NH₂; **BIM23268**, cyc(Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys)-NH₂; **CGP23996**, cyc(Asn-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser); **Cyanamid 154806**, Ac-(4-NO₂-Phe)-cyc(D-Cys-Tyr-D-Trp-Lys-Thr-Cys)-D-Tyr-NH₂; **L797591**, (2R)-N-(6-amino-2,2,4-trimethylhex-yl)-3-(1-naphthyl)-2-(((2-phenylethyl)2-pyridin-2-ylethyl)amino)carbonyl)amino)propanamide; **L054522**, tert-butyl (bS)-b-methyl-N[[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]carbonyl]-D-tryptophyl-L-lysinate; **L796778**, methyl (2S)-6-amino-2-(((2R)-2-(((1S)-1-benzyl-2-[[4-nitrophenyl]amino]-2-oxoethyl)amino)carbonyl]amino)hexanoyl)amino]hexanoate; **L803087**, methyl (2S)-5-[[amino(imino)methyl]amino]-2-[[4-(5,7-difluoro-2-phenyl-1H-indol-3-yl)butanoyl]amino]pentanoate; **L817818**, (2R)-2-aminopropyl N2-[[2-(2-naphthyl)-1H-benzo[g]indol-3-yl]acetyl]-L-lysinate; **LTT-SRIF-28**, [Leu⁸,DTrp²²,DTyr²⁵]SRIF-28; **NNC269100**, 1-[3-[N-(5-bromopyridin-2-yl)-N-(3,4-dichlorobenzyl)amino]propyl]-3-[3-(¹H-imidazol-1-yl)propyl]thiourea

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Sphingosine-1-phosphate

Overview: Sphingosine-1-phosphate (S1P) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid receptors; see Chun *et al.*, 2002) are activated by the endogenous lipid derivatives S1P and sphingosylphosphorylcholine (SPC). S1P has also been described to act at intracellular sites (see Hla *et al.*, 1999; Spiegel and Milstein, 2003), although most cellular phenomena ascribed to S1P can be explained by receptor-mediated mechanisms. The relationship between recombinant and endogenously expressed receptors is unclear. Radioligand binding has been conducted in heterologous expression systems using [³²P]-S1P (e.g. Okamoto *et al.*, 1998). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding. Targeted deletion of several S1P receptors has clarified signalling pathways and physiological roles.

Nomenclature	S1P ₁	S1P ₂	S1P ₃	S1P ₄	S1P ₅
Other names	edg1, <i>lp</i> _{B1}	edg5, <i>lp</i> _{B2} , AGR16, H218	edg3, <i>lp</i> _{B3}	<i>edg6</i> , <i>lp</i> _{C1}	<i>edg8</i> , <i>lp</i> _{B4} , NRG-1
Ensembl ID	ENSG00000170989	ENSG00000175898	ENSG00000186354	ENSG00000125910	ENSG00000180739
Principal transduction	G _{i/o}	G _q , G _{12/13} , G _s	G _q , G _{i/o} , G _s	G _{i/o} , G _{12/13} , G _s	G _{i/o} , G _{12/13}
Rank order of potency	S1P > SPC	S1P > SPC (Okamoto <i>et al.</i> , 1998)	S1P > SPC (Okamoto <i>et al.</i> , 1998)	S1P, SPC	S1P, SPC
Selective agonists	SEW2871 (Sanna <i>et al.</i> , 2004)	—	—	—	—
Selective antagonists	—	JTE013 (Osada <i>et al.</i> , 2002)	—	—	—

The novel immunomodulator fingolimod (FTY720) may be phosphorylated *in vivo* (Albert *et al.*, 2005) to generate a relatively potent agonist with activity at S1P₁, S1P₃, S1P₄ and S1P₅ receptors (Brinkmann *et al.*, 2002; Mandala *et al.*, 2002).

Abbreviations: JTE013, pyrazolopyridine analog; SEW2871, 5-(4-phenyl-5-trifluoromethylthiophen-2-yl)-3-(3-trifluoromethylphenyl)-(1,2,4)-oxadiazole

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Tachykinin

Overview: Tachykinin receptors (provisional nomenclature) are activated by the endogenous peptides substance P (SP), neurokinin A (NKA; previously known as substance K, neurokinin α , neuromedin L), neurokinin B (NKB; previously known as neurokinin β , neuromedin K), neuropeptide K and neuropeptide γ (N-terminally extended forms of neurokinin A). The neurokinins (A and B) are mammalian members of the tachykinin family, which includes peptides of mammalian and nonmammalian origin containing the consensus sequence: Phe-x-Gly-Leu-Met. Marked species differences in pharmacology exist for all three receptors, in particular with nonpeptide ligands.

Nomenclature	NK ₁	NK ₂	NK ₃
Other names	Substance P	Substance K	Neurokinin B, neuromedin K
Ensembl ID	ENSG00000115353	ENSG00000075073	ENSG00000169836
Principal transduction	G _{q/11}	G _{q/11}	G _{q/11}
Rank order of potency	SP > NKA > NKB	NKA > NKB > > SP	NKB > NKA > SP
Selective agonists	SP methylester, [Sar ⁹ ,Met(O ₂) ¹¹]SP, [Pro ⁹]SP, septide	[β -Ala ⁸]NKA-(4-10), [Lys ⁵ , Me-Leu ⁹ ,Mle ¹⁰] NKA-(4-10), GR64349	Senktide, [MePhe ⁷]NKB
Selective antagonists	Aprepitant (10.7; Hale <i>et al.</i> , 1998), SR140333 (9.5), LY303870 (9.4), CP99994 (9.3), RP67580 (7.6)	GR94800 (9.6), GR159897 (9.5), MEN10627 (9.2), SR48968 (9.0), MEN11420 (8.6; Catalioto <i>et al.</i> , 1998)	SR142802 (9.2), SB223412 (9.0, Sarau <i>et al.</i> , 1997), PD157672 (7.8)
Probes	[³ H]- or [¹²⁵ I]-SP, [³ H]- or [¹²⁵ I]-BH-[Sar ⁹ ,Met(O ₂) ¹¹]SP, [¹²⁵ I]-L703606 (0.3 nM), [¹⁸ F]-SPA-RQ (Bergstrom <i>et al.</i> , 2004)	[³ H]-SR48968 (0.5 nM), [³ H]-GR100679, [¹²⁵ I]-NKA	[³ H]-Senktide, [¹²⁵ I]-[MePhe ⁷]NKB, [³ H]-SR142801 (0.13 nM)

The NK₁ receptor has also been described to couple to other G proteins (Roush and Kwatra, 1998). The hexapeptide agonist septide appears to bind to an overlapping but non-identical site to SP on the NK₁ receptor. There are suggestions for additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK₃ receptor was found to respond to NKB when expressed in *Xenopus* oocytes or Chinese hamster ovary cells (Donaldson *et al.*, 1996; Krause *et al.*, 1997).

Abbreviations: Aprepitant, 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl) phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (also known as Emend); CP99994, (+)-(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine; [¹⁸F]-SPA-RQ, ([¹⁸F]-2-fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl)([2S,3S]-2-phenyl-piperidin-3-yl)-amine; GR100679, cyclohexylcarbonyl-Gly-Ala-DTrp-Phe-NMe₂; GR159897, (R)-1-(2-[5-fluoro-1H-indol-3-yl]ethyl)-4-methoxy-4-([phenylsulfanyl]methyl)piperidine; GR64349, Lys-Asp-Ser-Phe-Val-Gly-(R- γ -lactam); GR94800, N- α -benzoyl-Ala-Ala-DTrp-Phe-DPro-Pro-Nle-NH₂; L-703606, *cis*-2-(diphenylmethyl)-N-([2-iodophenyl]-methyl)-1-azabicyclo[2.2.2]octan-3-amide; L-742694, 2(s)-([3,5-bis(trifluoromethyl)benzyl]-oxy)-3(S)-phenyl-4-([3-oxo-1,2,4-triazol-5-yl]methyl)-morpholine; LY303870, (r)-1-(N-[2-methoxybenzyl]acetylamin)-3-(1H-indol-3-yl)-2-(N-[2-[4-(piperidin-1-yl)piperidin-1-yl]acetyl]amino)propane; also known as lanepitant; MEN10627, *cyc*(2 β -5 β)(Met-Asp-Trp-Phe-Dap-Leu); MEN11420, *cyc*(2 β -5 β)[Asn(2-AcNH- β -D-Glc)-Asp-Trp-Phe-Dap-Leu]; also known as nepadutant; PD157672, Boc-(s)Phe-(r) α MePheNH(CH₂)₇NHCONH₂; RP67580, 3 α R,7 α R-(1-imino-2-[2-methoxyphenyl]ethyl)-7,7-diphenyl-4-perhydroisoindolone; SB223412, (s)-(-)-N-(α -ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide; SR140333, (s)-1-(2-[3,4-dichlorophenyl]-1-[3-isopropoxyphenylacetyl]piperidin-3-yl]ethyl)-4-phenyl-1-azoniabicyclo(2.2.2)octane chloride; SR142801, (S)-(N)-(1-[3-(1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl]propyl)-4-phenylpiperidin-4-yl)-N-methylacetamide; SR48968, (S)-N-methyl-N-(4-acetylamin-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butylbenzamide; also known as saredutant

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Trace amine-associated

Overview: Trace amine-associated receptors (provisional nomenclature) were initially discovered as a result of a search for novel 5-HT receptors (Borowsky *et al.*, 2001), where 15 mammalian orthologues were identified and divided into two families.

Nomenclature	TA ₁	TA ₂
Other names	TAA1, TaR-1, BO111	TAA2, GPR58
Ensembl ID	ENSG00000146399	ENSG00000146378
Principal transduction	G _s	G _s
Potency order	Tyramine ≥ PEA > octopamine = dopamine (Borowsky <i>et al.</i> , 2001)	PEA > tryptamine (Borowsky <i>et al.</i> , 2001)
Probes	[³ H]-Tyramine (20 nM, Borowsky <i>et al.</i> , 2001)	—

TAA₃ (BO107) and TAA₄ are pseudogenes. The signalling characteristics and pharmacology of TAA₅ (PNR, Putative Neurotransmitter Receptor, ENSG00000135569), TAA₆ (Trace amine receptor 4, TaR-4, ENSG00000146383), TAA₈ (Trace amine receptor 5, GPR102, ENSG00000146385) and TAA₉ (trace amine associated receptor 9, ENSG00000188604) are lacking.

Abbreviation: PEA, 2-phenylethylamine

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TRH

Overview: Thyrotropin-releasing hormone (TRH) receptors (provisional nomenclature) are activated by the endogenous tripeptide TRH (pGlu-His-ProNH₂). TRH and TRH analogues fail to distinguish TRH₁ and TRH₂ receptors (Sun *et al.*, 2003). [³H]-TRH is able to label both TRH₁ and TRH₂ receptors with *K_d* values of 13 and 9 nM, respectively.

Nomenclature	TRH ₁	TRH ₂
Other names	TRH receptor	—
Ensembl ID	ENSG00000163485	ENSMUSG00000039079, ENSRNOG00000012789
Principal transduction	G _q	G _q
Selective antagonists	Midazolam (Drummond <i>et al.</i> , 1989), chlordiazepoxide (Straub <i>et al.</i> , 1990), diazepam	—

The human orthologue of the rodent TRH₂ receptor has yet to be identified.

Abbreviation: MeTRH, pGlu-[N^ε-methyl]His-ProNH₂

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Urotensin-II

Overview: The urotensin-II (U-II) receptor (UT, nomenclature as agreed by NC-IUPHAR, see Foord *et al.*, 2005, Douglas and Ohlstein, 2000a) is activated by the endogenous dodecapeptide U-II, originally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish (Bern *et al.*, 1985). Several structural forms of U-II exist in fish and amphibians. The Goby orthologue was used to identify U-II as the cognate ligand for the predicted receptor encoded by the rat gene *gpr14* (Coulouarn *et al.*, 1998; Liu *et al.*, 1999; Mori *et al.*, 1999; Nothacker *et al.*, 1999). Human U-II (derived from ENSG0000049247), an 11-amino-acid peptide (Coulouarn *et al.*, 1998), retains the cyclohexapeptide sequence of goby U-II that is thought to be important in ligand binding (Kinney *et al.*, 2002; Brkovic *et al.*, 2003). This sequence is also conserved in the deduced amino-acid sequence of rat (14 amino-acids) and mouse (14 amino-acids) U-II, although the N-terminal is more divergent from the human sequence (Coulouarn *et al.*, 1999).

Nomenclature	UT
Other names	GPR14, SENR, UR-IIR
Ensembl ID	ENSG00000181408
Principal transduction	G _{q/11}
Selective agonists	[Pen ⁵]U-II-(4–11), U-II-(4–11), U-II (Grieco <i>et al.</i> , 2002), AC7954 (Lehmann <i>et al.</i> , 2005), FL104 and analogues (Lehmann <i>et al.</i> , 2006; 2007)
Selective antagonists	Urantide (8.3, Patacchini <i>et al.</i> , 2003), SB706375 (7.5–8.0, Douglas <i>et al.</i> , 2005), palosuran (pIC ₅₀ 7.1, Clozel <i>et al.</i> , 2004), SB436811 (6.7, Jin <i>et al.</i> , 2005)
Probes	[¹²⁵ I]-hU-II (0.24 nM, Maguire <i>et al.</i> , 2000)

In human vasculature, human urotensin-II elicits both vasoconstrictor (pD₂ 9.3–10.1, Maguire *et al.*, 2000) and vasodilator (pIC₅₀ 10.3–10.4, Stirrat *et al.*, 2001) responses.

Abbreviations: [Pen⁵]U-II-(4–11), [pencillamine, β,β-dimethylcysteine]⁵U-II-(4–11); **AC7954**, 3-(4-chlorophenyl)-3-(2-dimethyl-aminoethyl) isochroman-1-one HCl; **FL104**, (+)N-(1-[4-chlorophenyl]-3-dimethylaminopropyl)-4-phenylbenzamide oxalate; **palosuran**, 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulphate, also known as ACT058362; **SB436811**|**SB706375**, 2-bromo-4,5-dimethoxy-N-[3-(R)-1-methyl-pyrrolidin-3-yloxy]-4-trifluoromethyl-phenyl-benzenesulphonamide HCl; **urantide**, [Pen⁵,DTrp⁷,Orn⁸]hU-II(4–11)

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Vasopressin & oxytocin

Overview: Vasopressin (AVP) and oxytocin (OT) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on vasopressin and oxytocin receptors) are activated by the endogenous cyclic nonapeptides AVP and OT. These peptides are derived from precursors (ENSG00000101200 and ENSG00000101405, respectively), which also produce neurophysins.

Nomenclature	V _{1a}	V _{1b}	V ₂	OT
Ensembl ID	ENSG00000166148	P47901	ENSG00000126895	ENSG00000180914
Principal transduction	G _{q/11}	G _{q/11}	G _s	G _{q/11} , G _{i/o}
Rank order of potency	AVP > OT	AVP > OT	AVP > OT	OT ≥ AVP
Selective agonists	F180, [Phe ² , Orn ⁸]VT	d[D-3-Pal ²]VP, d[Cha ⁴]AVP (Derick <i>et al.</i> , 2002), d[Leu ⁴ , Lys ⁸]VP (Pena <i>et al.</i> , 2007)	d[Val ⁴ , DArg ⁸]VP, OPC51803, VNA932	[Thr ⁴ , Gly ⁷]OT (Elands <i>et al.</i> , 1988)
Selective antagonists	d(CH ₂) ₅ [Tyr(Me) ² , Arg ⁸]VP, (9.0), SR49059 (8.9), YM087 (8.2)	SSR149415 (8.4; Griebel <i>et al.</i> , 2002; Serradeil-Le Gal <i>et al.</i> , 2002)	VPA985 (8.9, Albright <i>et al.</i> , 1998), d(CH ₂) ₅ [D-Ile ² , Ile ⁴]AVP (8.4), SR121463A (8.4; Serradeil-Le Gal <i>et al.</i> , 1996), OPC31260 (7.6; Yamamura <i>et al.</i> , 1992), YM087 (8.96)	SSR126768A (9.3; Serradeil-Le Gal <i>et al.</i> , 2004), desGlyNH ₂ -, d(CH ₂) ₅ [Tyr(Me) ² , Thr ⁴ , Orn ⁸]OT (8.5), L372662 (8.4)
Probes	[³ H]-AVP, [³ H]-SR49059 (1.5 nM), [³ H]-d(CH ₂) ₅ [Tyr(Me) ² , Arg ⁸]AVP (1.1 nM), [¹²⁵ I]-HO-Phaa, D-Tyr(Me)-, Phe-Gln-Asn-Arg-Pro-Arg-NH ₂ (50 pM)	[³ H]-AVP, [³ H]-SSR149415 (1 nM; Serradeil-Le Gal <i>et al.</i> , 2007)	[³ H]-AVP, [³ H]-desGly-NH ₂ [D-Ile ² , Ile ⁴]AVP (2.8 nM), [³ H]-d[D-Arg ⁸]AVP (0.8 nM), [³ H]-SR121463A (4.1 nM)	[³ H]-OT, [³⁵ S]-Non Peptide OT, Antagonist (42 pM; Lemaire <i>et al.</i> , 2002), [¹²⁵ I]-d(CH ₂) ₅ [Tyr(Me) ² , Thr ⁴ , Orn ⁸ , Tyr-NH ₂ ⁹]OVT (90 pM), [¹¹¹ In]-DOTA-dLVT (4.5 nM; Chini <i>et al.</i> , 2003)

The V₂ receptor exhibits marked species differences, such that many ligands (d(CH₂)₅[D-Ile², Ile⁴]VP and [³H]-desGly-NH₂[D-Ile², Ile⁴]VP) exhibit low affinity at human V₂ receptors (Ala *et al.*, 1997). Similarly, [³H]-d[D-Arg⁸]VP is V₂ selective in the rat, not in the human (Saito *et al.*, 1997). The gene encoding the V₂ receptor is polymorphic in man, underlying nephrogenic diabetes insipidus (Bichet, 1998). YM087 display high affinity for both human V_{1a} and V₂ receptors (Tahara *et al.*, 1998). d[Cha⁴]AVP is selective only for the human and bovine V_{1b} receptors (Derick *et al.*, 2002), while d[Leu⁴, Lys⁸]VP has high affinity for the rat V_{1b} receptor (Pena *et al.*, 2007).

Abbreviations: F180, Hmp-Phe-Ile-Hgn-Asn-Cys-Pro-Dab(Abu)-Gly-NH₂; [¹¹¹In]-DOTA-dLVT, [¹¹¹In]-DOTA-Lys⁸-deamino-vasotocin; L372662, 1-(1-{4-[1-(2-methyl-1-oxido-2-pyridin-3-ylmethyl)piperidin-4-yl]oxy}-2-methoxybenzoyl)piperidin-4-yl)-1,4-dihydrobenz[d][1,3]oxazin-2-one; OPC31260, 5-dimethylamino-1-(4-[2-methylbenzoylamino]benzoyl)-2,3,4,5-tetrahydro-1H-benzazepine; OPC51803, (5R)-2-(1-{2-chloro-4-[1-pyrrolidinyl]benzoyl}-2,3,4,5-tetrahydro-1H-1-benzazepin-5-yl)-N-isopropylacetamide; [³⁵S]-non-peptide OT antagonist, [³⁵S]-(1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-methylsulfonyl-4-piperidinyl)oxy)phenylacetyl)-4-piperidinyl)-3,4-dihydro-2(1H)-quinolinone); SR121463A, 1-(4-Boc-2-methoxybenzenesulfonyl)-5-ethoxy-3-spiro-(4-[2-morpholinoethoxy]cyclohexane)indol-2-one fumarate; equatorial isomer; SR49059, (2S)-1-([2,3S]-[5-chloro-3-(chlorophenyl)-1-{3,4-dimethoxysulfonyl}-3-hydroxy]-2,3-dihydro-1H-indole-2-carbonyl)-pyrrolidine-2-carboxamide; SSR149415, (2S,4R)-1-[2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidine carboxamide; SSR126768A, 4-chloro-3-[(3R)-(+)-5-chloro-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-N-ethyl-N-(3-pyridylmethyl)-benzamide, hydrochloride; VNA932, (2-chloro-4-[3-methyl-pyrazol-1-yl]-phenyl)-(5H,11H)-pyrrolo(2,1-c)(1,4)benzodiazepin-10-yl-methanone; VPA985, 5-fluoro-2-methyl-N-(4-[5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11H)-yl-carbonyl]-3-chlorophenyl)benzamide; YM087, (4'-[(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepin-6-yl) carbonyl]-2-phenylbenzanilide monohydrochloride)

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VIP & PACAP

Overview: Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on Vasoactive Intestinal Peptide Receptors, Harmar *et al.*, 1998) are activated by the endogenous peptides VIP, PACAP_{1–38}, PACAP_{1–27}, peptide histidine isoleucineamide (PHI), peptide histidine methionineamide (PHM), peptide histidine valine and growth hormone-releasing factor (GRF). PACAP type II receptors have been defined as those for which PACAP and VIP display comparable affinity. Both VPAC₁ and VPAC₂ meet this definition. [Arg¹⁶]chicken secretin is an agonist at both VPAC₁ and secretin receptors, but can be used as an agonist at VPAC₁ receptors in tissues that do not express secretin receptors (Gourlet *et al.*, 1997a). PACAP_{6–38} also shows significant affinity for VPAC₂ receptors. Helodermin discriminates VPAC₁ and VPAC₂ in a species-dependent manner (Gourlet *et al.*, 1998).

Nomenclature	VPAC ₁	VPAC ₂	PAC ₁
Other names	VIP ₁ /PACAP, VIP, VIP ₁ , PACAP type II, PVR2	VIP ₂ /PACAP, VIP ₂ , PACAP ₃ , PVR2	PACAP, PACAP type I, PVR1
Ensembl ID	ENSG00000114812	ENSG00000106018	ENSG00000078549
Principal transduction	G _s	G _s	G _s
Rank order of potency	VIP, PACAP-(1–27) = PACAP-(1–38) > GRF > > PHI > > secretin	VIP, PACAP-(1–38) > PACAP-(1–27) > PHI > > GRF, secretin	PACAP-(1–27), PACAP-(1–38) > > VIP > PHI
Selective agonists	[Arg ¹⁶]chicken secretin, [Lys ¹⁵ , Arg ¹⁶ , Leu ²⁷] VIP-(1–7)-GRF-(8–27)-NH ₂	Ro251553 (Gourlet <i>et al.</i> , 1997a, 1997b), Ro251392 (Xia <i>et al.</i> , 1997)	Maxadilan (Moro and Lerner, 1997)
Selective antagonists	[Ac-His ¹ , D-Phe ² , Lys ¹⁵ , Arg ¹⁶]VIP-(3–7)-GRF-(8–27)-NH ₂ (Gourlet <i>et al.</i> , 1997a)	—	PACAP-(6–38)
Probes	[¹²⁵ I]-VIP, [¹²⁵ I]-PACAP	[¹²⁵ I]-VIP, [¹²⁵ I]-PACAP	[¹²⁵ I]-PACAP

Subtypes of PAC₁ receptors have been proposed based on tissue differences in the potencies of PACAP_{1–27} and PACAP_{1–38}; these might result from differences in G-protein coupling and second messenger mechanisms (Van Ramplebergh *et al.*, 1996), or from alternative splicing of PAC₁ receptor mRNA (Spengler *et al.*, 1993).

Abbreviations: Ro251392, Ac-His¹[Glu⁸, OCH₃-Tyr¹⁰, Lys¹², Nle¹⁷, Ala¹⁹, Asp²⁵, Leu²⁶, Lys^{27,28}]VIP (*cyclo* 21–25); Ro251553, Ac-His¹[Glu⁸, Lys¹², Nle¹⁷, Ala¹⁹, Asp²⁵, Leu²⁶, Lys^{27,28}, Gly^{29,30}, Thr³¹]VIP-NH₂ (*cyclo* 21–25)

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