

7 TM RECEPTORS

Acetylcholine (muscarinic)

Overview: Muscarinic acetylcholine receptors (nomenclature as agreed by NC-IUPHAR sub-committee on Muscarinic Acetylcholine Receptors; Caulfield & 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 has recently been described as a selective agonist of the M₁ receptor subtype *via* binding to a site distinct to that recognised by nonselective agonists (Spalding *et al.*, 2002). There are two allosteric sites on muscarinic receptors, one defined by the binding of 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 (Lazareno *et al.*, 1998; 1999; 2000; 2002; 2004). The allosteric site for gallamine and strychnine on M₂ receptors can be labelled by [³H]dimethyl-W84 (Tränkle *et al.*, 2003).

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 (9.8), 4-DAMP (8.6–9.2), triptiramine (8.4–8.8), pirenzepine (7.8–8.5), guanylpirenzepine (7.7), darifenacin (7.5–7.8), AFDX384 (7.3–7.5), MT3 (7.1), himbacine (7.0–7.2), PD102807 (5.3)	triptiramine (9.4–9.6), AFDX384 (8.2–9.0), himbacine (8.0–8.3), 4-DAMP (7.8–8.4), darifenacin (7.0–7.4), pirenzepine (6.3–6.7), MT7 (<6), PD102807(5.7), guanylpirenzepine (5.5)	4-DAMP (8.9–9.3), darifenacin (8.4–8.9), AFDX384 (7.2–7.8), triptiramine (7.1–7.4), himbacine (6.9–7.4), pirenzepine (6.7–7.1), guanylpirenzepine (6.5), PD102807 (6.2), MT3 (<6), MT7 (<6)
Radioligands	[³ H]NMS (80–150 pM), [³ H]QNB (15–60 pM), [³ H]pirenzepine (3–15 nM)	[³ H]NMS (200–400 pM), [³ H]QNB (20–50 pM)	[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	MT3 (8.7), 4-DAMP (8.4–9.4), himbacine (8.0–8.8), AFDX384 (8.0–8.7), triptiramine (7.8–8.2), darifenacin (7.7–8.0), PD102807 (7.3), pirenzepine (7.1–8.1), guanylpirenzepine (6.5), MT7 (<6)	4-DAMP (8.9–9.0), darifenacin (8.0–8.1), triptiramine (7.3–7.5), guanylpirenzepine (6.8), pirenzepine (6.2–7.1), AFDX384 (6.3), himbacine (6.1–6.3), MT3 (<6), MT7 (<6), PD102807 (5.2)
Radioligands	[³ H]NMS (50–100 pM), [³ H]QNB (20–80 pM)	[³ H]NMS (500–700 pM), [³ H]QNB (20–60 pM)

MT3 (m4-toxin) and MT7 (m1-toxin) are toxins contained within the venom of the Eastern green mamba (*Dendroaspis augusticeps*) (see Bradley, 2000; Potter, 2001).

Abbreviations: **AC-42**, 4-*n*-butyl-1-[4-(2-methylphenyl)-4-oxo-1-butyl]-piperidine hydrogen chloride; **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; **dimethyl-W84**, *N,N'*-bis[3-(1,3-dihydro-1,3-dioxo-4-methyl-2*H*-isoindol-2-yl)propyl]-*N,N,N',N'*-tetramethyl-1,6-hexanediaminium diiodide; **4-DAMP**, 4-diphenylacetoxy-*N*-methylpiperidine methiodide; **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-*ij*][1,6]benzodiazocine-10-carboxylic acid hexyl ester; **NMS**, *N*-methylscopolamine; **PD102807**, 9-methoxy-2-methyl-11,12-dihydro-3*H*,6*αH*,13*H*-6-oxa-3,12*α*-diazabenzocyclopenta(*h*)anthracene-1-carboxylic acid ethyl ester; **PG135**, (3*aS*,12*R*,12*aS*,12*bR*)-2-amino-2,3,3*a*,4,11,12*a*,12*b*-octahydro-10-hydroxyisoquinolo[2,1,8-*lma*]carbazol-5(1*H*)-one hydrochloride; **QNB**, 3-quinuclidinylbenzilate; **WIN 51,708**, 17-*β*-hydroxy-17-*α*-ethynyl-5-*α*-androstano[3,2-*b*]pyrimido[1,2-*a*]benzimidazole; **WIN 62,577**, 17-*β*-hydroxy-17-*α*-ethynyl- Δ^4 -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 nonselective 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	CGS21680, HENECA	—	2-Cl-IB-MECA, IB-MECA
Selective antagonists	DPCPX (8.5)	ZM241385 (9.0), SCH58261 (7.9–9.5)	MRS1706 (8.4)	MRS1220 (8.8), MRS1523 (7.7), MRS1191 (7.0)
Radioligands	[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 adenyl 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 nonreceptor elements which also recognise adenosine (e.g. Lorenzen *et al.*, 1996).

Abbreviations: **2Cl-IB-MECA**, 2-chloro-*N*⁶-(3-iodobenzyl)adenosine-5'-*N*-methyluronamide; **AB-MECA**, *N*⁶-(4-aminobenzyl)-adenosine-5'-*N*-methyluronamide; **CCPA**, 2-chloro-*N*⁶-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; **CPA**, *N*⁶-cyclopentyladenosine; **DPCPX**, 8-cyclopentyl-1,3-dipropylxanthine; **HENECA**, 2-(1-(*E*)-hexenyl)adenosine-5'-*N*-ethyluronamide; **MRS1191**, 6-phenyl-1,4-dihydropyridine; **MRS1220**, 9-chloro-2-(2-furyl)5-phenylacetyl amino[1,2,4]triazolo[1,5-*c*]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-1*H*-purin-8-yl]phenoxy)acetamide; **MRS1754**, 8-(4-[(4-cyanophenyl)carbamoylmethyl]oxy)phenyl)-1,3-di(*n*-propyl)xanthine; **NECA**, adenosine-5'-*N*-ethyluronamide; **S-ENBA**, (2*s*)-N⁶-(2-endonorbanyl)adenosine; **SCH58261**, 5-amino-2-(2-furyl)-7-phenylethyl-pyrazolo[4,3-*c*]1,2,4-triazolo[1,5-*c*]pyrimidine; **XAC**, 8-(4-[(2-aminoethyl)amino]carbonylmethyl]oxy)phenyl)-1,3-dipropylxanthine; also known as xanthine amine congener; **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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Adrenoceptors, α_1

Overview: α_1 -Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors, Bylund *et al.*, 1994) are 7TM receptors, where the endogenous agonists adrenaline and noradrenaline display equal potency. Phenylephrine, methoxamine and cirazoline are examples of 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 antagonists for α_1 -adrenoceptors relative to α_2 -adrenoceptors. [³H]prazosin (0.1 nM) and [¹²⁵I]HEAT (0.1 nM; also known as BE2254) are relatively selective radioligands. Numerous splice variants of the α_1 -adrenoceptors exist, whose role is not clear at present.

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	—	—
Selective antagonists	KMD3213 (10.4), (+)niguldipine (10.0), SNAP5089 (9.7), RS17053 (9.2), SNAP5272 (8.4)	—	BMY7378 (8.4)

The clone originally called the α_{1C} -adrenoceptor corresponds to the pharmacologically defined α_{1A} -adrenoceptor (see Hieble *et al.*, 1995). Some tissues possess α_1 -adrenoceptors that have relatively low affinity (less than 1 nM) for prazosin and might represent additional subtypes. (+)Niguldipine also has high affinity for L-type Ca²⁺ channels.

Abbreviations: **A61603**, *N*-(5-[4,5-dihydro-1*H*-imidazol-2-yl]-2-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)methanesulfonamide hydrobromide; **BMY7378**, 8-(2-[4-{2methoxyphenyl}-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-1*H*-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; **RS17053**, *N*-[2-(2-cyclopropylmethoxyphenoxy)ethyl]-5-chloro- α,α -dimethyl-1*H*-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**, 5-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, where the endogenous agonists display a rank order of potency: adrenaline > noradrenaline. UK14304 and BHT920 are examples of agonists selective for α_2 -adrenoceptors relative to α_1 -adrenoceptors. Rauwolscline (9.0) and yohimbine (9.0) are antagonists selective for α_2 -adrenoceptors relative to α_1 -adrenoceptors. [3 H]Rauwolscline (1 nM), [3 H]UK14304, [3 H]RX821002 (0.5 nM) and [3 H]MK912 (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, rauwolscline and oxymetazoline have an ~20-fold lower affinity for rat, mouse and bovine α_{2A} -adrenoceptors. These α_{2A} orthologues are sometimes referred to as α_{2D} -adrenoceptors.

Nomenclature	α_{2A}	α_{2B}	α_{2C}
Other names	α_{2D}	—	—
Ensembl ID	ENSG00000150594	ENSG00000181210	ENSG00000184160
Principle 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 reduced efficacy agonist. Binding sites for imidazolines, distinct from α_2 -adrenoceptors have been identified but their function is not known; catecholamines have a low affinity for these sites.

Abbreviations: **ARC239**, 2-(2-[4-{2-methoxyphenyl}piperazin-1-yl] ethyl)-4,4-dimethyl-1,3-(2*H*,4*H*)-isoquinolindione dihydrochloride **BHT920**, 6-allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo-[4,5-*d*]-azepine; **BRL44408**, 2-(2*H*-[1-methyl-1,3-dihydroisoindole]methyl)-4,5-dihydroimidazole; **MK912**, (2*S*,12*bS*)1',3'-dimethylspiro[1,3,4,5',6,6',7,12*b*-octahydro-2*H*-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

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Adrenoceptors, β

Overview: β -Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors, Bylund *et al.*, 1994) are 7TM receptors, where the endogenous agonists are adrenaline and noradrenaline. Isoprenaline is an example of an 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 labelled with high concentrations of cyanopindolol (pK_i 9.0).

Nomenclature	β_1	β_2	β_3
Other names	—	—	atypical β
Ensembl ID	ENSG00000043591	ENSG00000169252	ENSG00000147477
Principle transduction	G _s	G _s	G _s , G _{i/o}
Rank order of potency	NA > adrenaline	Adrenaline > NA	NA = 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)
Radioligands	[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. 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. [³H]-CGP12177 or [³H]-dihydroalprenolol can be used in place of [¹²⁵I]-ICYP. Many agonists at β_3 -adrenoceptors (CL316243, CGP12177A and carazolol) are antagonists at β_1 - and β_2 -adrenoceptors. CGP12177A and carazolol can also show reduced efficacy at β_3 -adrenoceptors. 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 & Molenaar, 1996) and can exhibit agonist properties in some functional assays (Horinouchi & Koike, 2001). 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 (see reviews by Strosberg). 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 pharmacology that is intermediate between β_2 - and β_3 -adrenoceptors (Chen *et al.*, 1994).

There is now convincing evidence that the 'putative β_4 -adrenoceptor' is not a novel receptor but an affinity state of the β_1 -adrenoceptor, since 'putative β_4 -adrenoceptor'-mediated agonist effects of CGP12177A are absent in mice lacking β_1 -adrenoceptors (Konkar *et al.*, 2000).

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-iodobenzenesulphonamide; **L748328**, (s)-N-(4-[2-((3-[3-(aminosulphonyl)phenoxy]-2-hydroxypropyl)-amino)ethyl]phenyl)benzenesulphonamide; **RO363**, (–)-1-(3,4-dimethoxyphenethylamino)-3-(3,4-dihydroxyphenoxy)-2-propanol)oxalate; **SB251023**, (4-[1-(2-(s)-hydroxy-3-(4-hydroxyphenoxy)-propylamino)cyclopentylmethyl]phenoxy)methyl)phenylphosphonic acid lithium salt; **SR59230A**, 3-(2-ethylphenoxy)-1-([1S]-1,2,3,4-tetrahydronaphth-1-ylamino)-2S-propanol oxalate

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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 & 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	[<i>p</i> -NH ₂ -Phe ⁶]-Ang II, CGP42112
Selective antagonists	EXP3174, eprosartan, valsartan, irbesartan, losartan	PD123319, PD123177
Radioligands	[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). Antagonist activity of CGP42112 has also been reported (Lokuta *et al.*, 1995).

Abbreviations: **A81988**, 2(*N*-*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*-butyloxycarbonylsulphonamido)-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 from bovine stomach (Tatemoto *et al.*, 1998). Apelin-36, apelin-13 and (Pyr¹)apelin-13 are the predominant endogenous ligands.

Nomenclature	APJ
Other names	Apelin receptor, angiotensin receptor-like 1
Ensembl ID	ENSG00000134817
Principal transduction	G _i
Rank order of potency	[Pyr ¹]apelin-13 > apelin-13 > apelin-36 (Tatemoto <i>et al.</i> , 1998)
Selective agonists	[Pyr ¹]apelin-13, apelin-13, apelin-17, apelin-36
Radioligands	[¹²⁵ I]-[Pyr ¹]Apelin-13 (0.3 nM, Katugampola <i>et al.</i> , 2001)

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).

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Bombesin

Overview: Bombesin receptors (provisional nomenclature) 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 ,ψ26-27]GRP- (20-27), kuwanon H, [DPhé ⁶]bombesin- (6-13)-ethylester, [DPhé ⁶ ,Cpa ¹⁴ ,ψ13- 14]bombesin-(6-14)	—
Radioligands	[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 the three subtypes may be activated by [DPhé⁶,βAla¹¹,Phe¹³,Nle¹⁴]bombesin-6-14 (Mantey *et al.*, 1997). Replacing DPhé⁶ with (*R*)- or (*S*)-amino-3-phenylpropionic acid gives the selectivity for bb3 receptors (Mantey *et al.*, 2001).

Abbreviation: 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 receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on Bradykinin Receptors, Regoli *et al.*, 1998b) are activated by the endogenous peptides bradykinin (BK), [des-Arg⁹]BK, Lys-BK (kallidin), [des-Arg⁹]Lys-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	B₁	B₂
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)	HOE140 (8.4, Gobeil <i>et al.</i> , 1996b), FR173657 (8.2, Rizzi <i>et al.</i> , 1997), LF160687 (Puneau <i>et al.</i> , 1999)
Radioligands	[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)oxy-methyl} phenyl]-N-methylaminocarbonyl-methyl)acrylamide; **HOE140**, DArg[Hyp³,Thi⁵,DTic⁷,Oic⁸]BK, also known as Icatibant; **LF160687**, 1-([2,4-dichloro-3-{{(2,4-dimethylquinolin-8-yl)oxy)methyl}phenyl)sulphonyl]-N-(3-{{4-(aminomethyl)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-([αMe]Phe⁵,D-βNal⁷,Ile⁸)desArg⁹BK

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Calcitonin, amylin, CGRP and adrenomedullin

Overview: Calcitonin (CT), amylin (AMY), CGRP and adrenomedullin (AM) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Calcitonin Gene-Related Peptides, Adrenomedullin, Amylin, and Calcitonin Receptors, Poyner *et al.*, 2002) are generated by the genes *CALCR* (which codes for the calcitonin 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 aa, identified as a family of three members: RAMP1 (ENSG00000132329), RAMP2 (ENSG00000131477) and RAMP3 (ENSG00000122679). The endogenous agonists are the peptides α calcitonin gene-related peptide (α CGRP; occasionally termed CGRP-I), β CGRP (occasionally termed CGRP-II), amylin (previously termed islet-amyloid polypeptide, diabetes-associated polypeptide) and AM. There are species differences in peptide sequences, particularly for the calcitonins. CGRP-(8–37) acts as an antagonist at CGRP (pK_i 6.5–8.0) and inhibits some AM and AMY responses (7.0). It is inactive at calcitonin receptors. Salmon calcitonin-8–32 is an antagonist at both *amylin* and calcitonin receptors, but not at CGRP receptors. AC187 is also an antagonist at *amylin* and calcitonin receptors but has appreciable affinity at CGRP receptors. AC187, a salmon calcitonin analogue, is also an antagonist at *amylin* and calcitonin receptors. Human AM-(22–52) has some selectivity towards AM receptors, but with modest potency, limiting its use.

Nomenclature Composition	Calcitonin <i>CALCR</i>	Amylin <i>AMY1: CALCR + RAMP1</i> <i>AMY2: CALCR + RAMP2</i> <i>AMY3: CALCR + RAMP3</i>	CGRP <i>CALCRL</i>	Adrenomedullin <i>AM1: CALCRL + RAMP2</i> <i>AM2: CALCRL + 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 $\geq$ human CT $\geq$ AMY, CGRP $>$ AM	Salmon CT $\geq$ AMY $\geq$ CGRP $>$ human CT $>$ AM	CGRP $>$ AM $\geq$ AMY $\geq$ salmon CT	AM1: AM $>$ $>$ CGRP $>$ AMY $>$ salmon CT AM2: AM $\geq$ CGRP $>$ 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)	AM-(22-52) (7)
Radioligands	[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 crossreactivity 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, the 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 coexpressed with RAMP2, the CL receptor produces an AM receptor (AM1). RAMP3 interacts with the CL receptor to give a 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, although the phenotype is RAMP-type- and cell-line-dependent. hCT_(a)-RAMP1 has a high affinity for CGRP, unlike hCT_(a)-RAMP3 (Christopoulos *et al.*, 1999; 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. Although not commercially available, [¹²⁵I]-Tyr⁰-CGRP is widely used as a radioligand.

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 resembles the 'CGRP₁' subtype previously described in native tissues and cell lines (Aiyar *et al.*, 1996; McLatchie *et al.*, 1998).

Abbreviations: AC187, acetyl-[Asn³⁰, Tyr³²]salmon CT; BIBN4096BS, 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 (provisional nomenclature) responds to extracellular calcium, polyamines and, in the presence of millimolar calcium, aromatic L-amino acids (Conigrave *et al.*, 2000).

Nomenclature	CASR
Other names	Parathyroid cell calcium-sensing receptor
Ensembl ID	ENSG00000036828
Principal transduction	$G_{q/11}$, $G_{i/o}$ (Arthur <i>et al.</i> , 1997)
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 $\geq$ L-Ala > L-Ser, L-Pro, L-Glu $\geq$ L-Asp but not L-Lys, L-Arg, L-Leu, and L-Ile (Conigrave <i>et al.</i> , 2000)

Phenylalkylamine calcimetics, such as NPSR-568 (Norcalcine), appear to function as allosteric activators (Hammerland *et al.*, 1998). Loss-of-function mutations appear to underlie the altered calcium homeostasis found in familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. A gain-of-function mutation in the *CASR* gene is associated with autosomal dominant hypocalcemia.

Abbreviations: NPSR-568, (*R*)-*N*-(3-methoxy- α -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; Howlett *et al.*, 2002) are activated by the endogenous ligands arachidonylethanolamide (anandamide), homo- γ -linolenylethanolamide, docosatetra-7,10,13,16-enylethanolamide, 2-arachidonoyl glycerol and 2-arachidonoyl glyceryl ether. Potency determinations are complicated by the possibility of differential susceptibility of endogenous ligands to enzymatic conversion.

Nomenclature	CB₁	CB₂
Ensembl ID	ENSG00000118432	ENSG00000162562
Principal transduction	G _{i/o}	G _{i/o}
Selective agonists	Arachidonoyl-2-chloroethylamide (Hillard <i>et al.</i> , 1999), arachidonoylcyclopropylamide (Hillard <i>et al.</i> , 1999), methanandamide (Khanolkar <i>et al.</i> , 1996), O-1812 (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)
Selective antagonists	SR141716A (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)
Radioligands	[³ H]-HU243 (45 pM, Devane <i>et al.</i> , 1992), [³ H]-CP55940 (0.6 nM, Showalter <i>et al.</i> , 1996), [³ H]-WIN55212-2 (12 nM, Song and Bonner, 1996), [³ H]-SR141716A (0.6 nM, Rinaldi-Carmona <i>et al.</i> , 1996)	[³ H]-HU243 (61 pM Bayewitch <i>et al.</i> , 1995), [³ H]-CP55940 (0.6 nM, Showalter <i>et al.</i> , 1996), [³ H]-WIN55212-2 (2 nM, Slipetz <i>et al.</i> , 1995)

Anandamide is also a vanilloid receptor (TRPV1) agonist.

Abbreviations: **AM630**, 6-iodopravadoline; **CP55940**, (1*R*,3*R*,4*R*)-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)cyclohexan-1-ol; **HU243**, [6*aR*-(6*ax*,9*ax*,10*aβ*)]-3-(1,1-dimethylheptyl)-6*a*,7,8,9,10,10*a*-hexahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[b,d]pyran-[7,8-³H]-9-methanol; **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-6*a*,7,10,10*a*-tetrahydro-6*H*-benzo[c]chromene; **L759633**, (6*a*,10*aR*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6,9-trimethyl-6*a*,7,10,10*a*-tetrahydro-6*H*-benzo[c]chromene; **L759656**, (6*a*,10*aR*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6-dimethyl-9-methylene-6*a*,7,8,9,10,10*a*-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; **O-1812**, (*R*)-(20-cyano-16,16-dimethyldocosa-*cis*-5,8,11,14-tetraenyl)-1'-hydroxy-2'-propylamine; **SR141716A**, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride; **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 receptors activated by one or more of the chemokines, a large family of small cytokines.

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. Those human agonists with EC₅₀ values <50 nM in either Ca²⁺ flux or chemotaxis assays at human recombinant receptors expressed in mammalian cell lines are listed. 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 nonchemokine ligands have also been identified for chemokine receptors. The tables include both standard chemokine names (Zlotnik & 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 CKR ₅ , 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), CCL5 (RANTES), CCL4 (MIP-1 β)	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)
Radioligands	[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]-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 I-309	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)	—	—
Radioligands	[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 _α , IL-8 receptor type I, IL-8 receptor α	IL8R _β , 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	ENSG00000180871	SwissProt P49682	ENSG00000121966	ENSG00000160683	ENSG00000172215
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	—	—
Radioligands	[¹²⁵ I]-IL8	[¹²⁵ I]-IL8, [¹²⁵ I]-GRO α , [¹²⁵ I]-NAP-2, [¹²⁵ I]-ENA78	[¹²⁵ I]-IP10	[¹²⁵ I]-SDF-1	—	—

CXCR1 and CXCR2 also couple to phospholipase C when cotransfected 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	CX₃CR1	XCRI
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
Radioligands	[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.

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

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 nonchemokine family includes the cytokine domain of tyrosyl-tRNA synthetase, HBD2, HIV gp120 and HIV Tat.

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Chemotactic peptide

Overview: Chemotactic peptide receptors (provisional nomenclature) are activated by the endogenous anaphylatoxin polypeptides (C3a [ENSG00000125730] and C5a [ENSG00000106804], ~75 aa), generated upon stimulation of the complement cascade. An endogenous ligand for the fMLP receptor has yet to be identified, although it responds to the bacterial product formyl-Met-Leu-Phe.

Nomenclature	C3a	C5a	fMLP
Other names	AZ3B, HNFAG09	CD88	Formyl peptide, FPR
Ensembl ID	ENSG00000171860	ENSG00000134830	ENSG00000171051
Principal transduction	G _{i/o} , G _z	G _{i/o} , G _z , G ₁₆ (Buhl <i>et al.</i> , 1993)	G _{i/o} , G _z
Rank order of potency	C3a > C5a (Ames <i>et al.</i> , 1996)	C5a, C5a des Arg ≥ C3a (Ames <i>et al.</i> , 1996)	—
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, Trp-Lys-Tyr-Met-Val-D-Met (Le <i>et al.</i> , 1999)
Selective antagonists	SB 290157 (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)	Cyclosporin H (6.3–7.0, Wenzel-Seifert and Seifert, 1993), BOC-PLPLP (6.0–6.5, Wenzel-Seifert and Seifert, 1993)
Radioligands	[¹²⁵ I]-C3a	[¹²⁵ I]-C5a	[³ H]-fMLP

A putative chemoattractant receptor termed C5L2 (also known as GPR77, ENSG00000134830) binds [¹²⁵I]-C3a and [¹²⁵I]-C5a, but, as yet, lacks a functional correlate (Cain and Monk, 2002). Binding to this site may be displaced with the rank order C5a, C5a des Arg > C3a, C3a des Arg (Kalant *et al.*, 2003; Okinaga *et al.*, 2003).

Abbreviations: **BOC-PLPLP**, Boc-Phe-Leu-Phe-Leu-Phe; **SB290157**, N²-([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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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	CCK₁	CCK₂
Other names	CCK _A	CCK _B , CCK _B /gastrin
Ensembl ID	ENSG00000163394	ENSG00000110418
Principal transduction	G _{q/11} /G _s (Wu <i>et al.</i> , 1997)	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	Desulphated 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)
Radioligands	[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 on 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*-toluylaminocarbonyl)-Asp-(*N*Me)Phe-NH₂; **BC264**, Tyr(SO₃H)-gNle-mGly-Trp-(*N*Me)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*zS*,5*R*)-2-benzyl-5[*N*-(*tert*-butoxycarbonyl)-L-Trp]amino-1,3-dioxoperhydroprido[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^{3,7})dec-2-yloxy]carbonyl]-D-Trp)- β -Ala; **PD140548**, *N*-(α -methyl-*N*-[tricyclo(3.3.1.1^{3,7})dec-2-yloxy]carbonyl]-L-Trp)-D-3-(phenylmethyl)- β -Ala; **PD142308**, iodinated PD140548; **RB400**, HOOC-CH₂-CO-Trp-NMe(Nle)-Asp-Phe-NH₂; **RP73870**, ({[(*N*-methoxy-3-phenyl)-*N*-(*N*-methyl-*N*-phenyl-carbamoylmethyl)-carbamoylmethyl]-3-ureido}-3-phenyl)-2-ethylsulfonate-(*RS*); **SR27897**, 1-([2-(4-(2-chlorophenyl)thiazole-2-yl)aminocarbonyl]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 aa peptide, ENSG00000147571), urocortin 1 (a 40 aa peptide, ENSG00000163794), urocortin 2 (a 38 aa peptide, ENSG00000145040) and urocortin 3 (a 38 aa peptide, ENSG00000178473). CRF₁ and CRF₂ receptors are activated nonselectively 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 nonselectively antagonized by α -helical CRF-(9–41), D-Phe-CRF-(12–41) and astressin.

Nomenclature	CRF₁	CRF₂
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]-7*H*-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]-7*H*-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},zMeLeu³⁷-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*-[(1*S*)-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.

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 _{ss} , G _{oif}	G _{i/o}	G _{i/o}	G _{i/o}	G _{ss} , G _{oif}
Selective agonists	R(+)SKF81297, R(+)SKF38393, dihydraxedine	(+)PHNO	PD128907	PD168077	—
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)	—
Radioligands	[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)

The selectivity of many of these agonists is less than two orders of magnitude. [³H]-Raclopride exhibits a 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 a 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 to 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]-1*H*-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,10*b*-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazine-9-ol; **PD168077**, *N*-methyl-4-(2-cyanophenyl)piperazinyl-3-methylbenzamide; (+)**PHNO**: 9-hydroxy-4-propyl-naphthoxazine; (+)**S14297**, (+)-7-(*N,N*-dipropylamino)-5,6,7,8-tetrahydro-naphtho(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*-benzopyrano[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, see Masaki *et al.*, 1994; Davenport, 2002) are activated by the endogenous 21-amino-acid peptides endothelin-1 (ET-1, ENSG00000078401), ET-2 (ENSG00000127129) and ET-3 (ENSG00000124205). Nonselective peptide (e.g. TAK044, pA₂ 8.4) and nonpeptide (e.g. bosentan, pA₂ 6.0–7.2; SB209670, pA₂ 9.4) antagonists can block both ET_A and ET_B receptors.

Nomenclature	ET _A	ET _B
Ensembl 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 & 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 & Davenport, 1996), IRL1620 (Watakabe <i>et al.</i> , 1992), BQ3020 (Russell & 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 & Davenport, 1995), BQ123 (6.9–7.4, Maguire & Davenport, 1995)	BQ788 (8.4, Russell & Davenport, 1996), A192621 (8.1, von Geldern <i>et al.</i> , 1999), IRL2500 (7.2, Russell & Davenport, 1996), Ro468443 (7.1, Breu <i>et al.</i> , 1996)
Radioligands	[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-1-(10–21); **IRL2500**, *N*-(3,5-dimethylbenzoyl)-*N*-methyl-(D)-(4-phenylphenyl)-Ala-Trp; **LU135252**, (+)-(-)-(*S*)-2-(4,6-dimethoxypyrimidin-2-yloxy)-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)-benzenesulphonamide; **S0139**, 27-O-3-(2-[3-carboxyacryloylamino]-5-hydroxyphenyl)-acryloyloxymyricone, sodium salt; **SB209670**, (+)-(-)-1*S*,2*R*,3-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxypheyl)-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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GABA_B

Overview: Functional GABA_B receptors (nomenclature agreed by NC-IUPHAR Subcommittee on GABA_B receptors, Bowery *et al.*, 2002; see also Spedding *et al.*, 2002) are formed from the heterodimerisation of two similar subunits termed GABA_{B1} and GABA_{B2} (Kaupmann *et al.*, 1997, 1998; Jones *et al.*, 1998; White *et al.*, 1998; Kuner *et al.*, 1999; Ng *et al.*, 1999). The GABA_{B1} subunit, when expressed alone, binds radiolabelled antagonists but is not transported to the cell membrane and is nonfunctional. 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 inwardly rectifying potassium channels (Marshall *et al.*, 1999; Bowery and Enna, 2000; Couve *et al.*, 2000; Bowery *et al.*, 2002). The GABA_{B1} subunit harbours the ligand-binding site, whereas the GABA_{B2} subunit mediates G-protein-coupled signalling (Bowery *et al.*, 2002). 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 (Margeta-Mitrovic *et al.*, 2000; Pagano *et al.*, 2001). Five splice variants of the human GABA_{B1} subunit exist: isoforms GABA_{B1(a)}, GABA_{B1(b)} and GABA_{B1(c)} differ in their N-terminal sequences; isoform GABA_{B1(d)} differs in its extreme C-terminal sequence and isoform GABA_{B1(e)} is a truncated protein that can heterodimerise with the GABA_{B2} subunit but does not constitute a functional receptor (Schwarz *et al.*, 2000). Only the 1a and 1b variants are identified as components of native receptors (Bowery *et al.*, 2002).

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)
Radioligands	[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 & 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).

Abbreviations: **3-APMPA (CGP35024)**, 3-amino-propyl-(P-methyl)-phosphinic acid; **3-APPA (CGP27492)**, 3-amino-propyl-phosphinic acid; **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]carboxamidopentyl]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; **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 aa nonamidated peptide (Evans & Shine, 1991); in other species, it is 29 aa 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	GAL1	GAL2	GAL3
Other names	Galanin-1 receptor, GalR1, GALR1	Galanin-2 receptor, GalR2, GALR2	Galanin-3 receptor, GalR3, 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)	—
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)	—	—

Galanin-(1–11) is a high-affinity agonist at GAL1/GAL2 (pK_i 9) and galanin-(2–11) is selective for GAL2 (pK_i 8.7) compared to GAL1 (pK_i 6.1, Liu *et al.*, 2001). The affinity of GALP, galanin-(1–11) and (2–11) at GAL3 has not been assessed. [¹²⁵I]-[Tyr²⁶]galanin binds to all the 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, 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 & 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; 1998; Fitzgerald *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

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Ghrelin

Overview: Ghrelin receptors (provisional nomenclature) 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 GHS-R 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	GHS-R
Other names	Growth hormone secretagogue receptor type 1, ghrelin-receptor, 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)
Radioligands	[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)

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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), growth hormone-releasing hormone (GHRH, ENSG00000118702) and secretin (ENSG00000115263). One common precursor (ENSG00000115263) generates glucagon, GLP-1 and GLP-2 peptides (Irwin, 2001).

Nomenclature	Glucagon	GLP-1	GLP-2	GHRH	Secretin
Ensembl ID	ENSG00000141558	ENSG00000112164	ENSG000000065325	ENSG00000106128	ENSG00000080293
Principal transduction	G _s	G _s	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) Exendin-(9-39) (Thorens <i>et al.</i> , 1993), T-0632 (Tibaduiza <i>et al.</i> , 2001)	GLP-2	BIM28011 (Coy <i>et al.</i> , 1996)	Secretin
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)	—	—	JV-1-36 (Schally & Varga, 1999), JV-1-38 (Schally & Varga, 1999)	[(CH ₂ NH) ^{4,5}]secretin (Kim <i>et al.</i> , 1993)
Radioligands	[¹²⁵ I]-glucagon	[¹²⁵ I]-GLP-1-(7-36) amide, [¹²⁵ I]-exendin, [¹²⁵ I]-exendin-(9-39), [¹²⁵ I]-GLP-1-(7-37)	—	[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

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Glutamate, metabotropic

Overview: Metabotropic glutamate (mGlu) receptors (nomenclature as agreed by the 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*-acetyl-aspartyl-glutamate (NAAG) and L-cysteine sulphonic acid. 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 Reviews). Many pharmacological agents listed do not distinguish between individual mGlu receptors within each group. 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 metabotropic glutamate 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).

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	DHPG, 3HPG (Brabet <i>et al.</i> , 1995)	LY389795 (Monn <i>et al.</i> , 1999), LY379268 (Monn <i>et al.</i> , 1999), LY354740 (Schoepp <i>et al.</i> , 1997; Wu <i>et al.</i> , 1998), DCG-IV, 2R,4R-APDC (Schoepp <i>et al.</i> , 1996)	LY389795 (Monn <i>et al.</i> , 1999), LY379268 (Monn <i>et al.</i> , 1999), LY354740 (Schoepp <i>et al.</i> , 1997; Wu <i>et al.</i> , 1998), DCG-IV, NAAG (Wroblewska <i>et al.</i> , 1997), 2R,4R-APDC (Schoepp <i>et al.</i> , 1996)	L-AP4, LSOP (Wu <i>et al.</i> , 1998), (RS)PPG (Gasparini <i>et al.</i> , 1999a)
Selective antagonists	AIDA (4,2, Moroni <i>et al.</i> , 1997), (S)-(+)-CBPG (Mannaioni <i>et al.</i> , 1999), CPCCOEt (Litschig <i>et al.</i> , 1999), LY367385 (Clark <i>et al.</i> , 1997), LY393675 (Baker <i>et al.</i> , 1998)	LY341495 (Kingston <i>et al.</i> , 1998), PCCG-4 (Pellicciari <i>et al.</i> , 1996), EGLU (4,3, Jane <i>et al.</i> , 1996), LY307452 (Wermuth <i>et al.</i> , 1996; Escribano <i>et al.</i> , 1998)	LY341495 (Kingston <i>et al.</i> , 1998), EGLU (4,3, Jane <i>et al.</i> , 1996), LY307452 (Wermuth <i>et al.</i> , 1996; Escribano <i>et al.</i> , 1998)	MAP4

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), DHPG, 3HPG (Brabet <i>et al.</i> , 1995), (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), (RS)PPG (Gasparini <i>et al.</i> , 1999a)	LSOP (Wu <i>et al.</i> , 1998), L-AP4, (RS)PPG (Gasparini <i>et al.</i> , 1999a)	LSOP (Wu <i>et al.</i> , 1998), L-AP4, (RS)PPG (Gasparini <i>et al.</i> , 1999a), (S)-3,4-DCPG (Thomas <i>et al.</i> , 2001)
Selective antagonists	SIB1757 (Varney <i>et al.</i> , 1999), SIB1893 (Varney <i>et al.</i> , 1999), MPEP (Gasparini <i>et al.</i> , 1999b), 4CPG, LY393675 (Baker <i>et al.</i> , 1998)	MAP4, THPG (Thoreson <i>et al.</i> , 1997)	—	MPPG (Wu <i>et al.</i> , 1998)

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors. Although many of these 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-methylhomobiotenetic 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). A glutamate-binding protein, of unknown function (r516), has been cloned but exhibits little homology to glutamate receptors.

Abbreviations: 1S,3R-ACPD, 1-aminocyclopentane-1S,3R-dicarboxylate; AIDA, 1-aminoinidan-1,5(RS)-dicarboxylic acid, also known as UPF523; L-AP4, S-2-amino-4-phosphonobutyrate; 2R,4R-APDC, aminopyrrolidine-2R,4R-dicarboxylate, also known as LY314593; (S)-(+)-CBPG, (S)-(1)-2-(39-carboxybicyclo[1.1.1]-pentyl)glycine; L-CCG-I, (2S,3S,4S)-α-(carboxycyclopropyl)glycine; CPCCOEt, cyclopropan[b]chromen-1a-carboxylate; 4CPG, 4-carboxyphenylglycine; DCG-IV, (2S,1'R,2'R,3'R)-2-(2,3-dicarboxycyclopropyl)glycine; (S)-3,4-DCPG, (S)-3,4-dicarboxylphenylglycine; DHPG, S-3,5-dihydroxyphenylglycine; EGLU, (S)-α-ethyl-glutamate; 3HPG, 3-hydroxyphenylglycine; 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; MAP4, (S)-2-methyl-2-amino-4-phosphonobutanoate; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; MPPG, (rs)-α-methyl-4-phosphonophenylglycine; PCCG-4, (2S,1'S,2'S,3'R)-2-(2'-carboxy-3'-phenylcyclopropyl)glycine; (RS)PPG, (R,S)-4-phosphonophenylglycine; SIB1757, 6-methyl-2-(phenylazo)-3-pyrindol; SIB1893, [(phenylazo)-3-pyrindole]-2-methyl-6-(2-phenylethenyl)pyridine; THPG, (RS)-3,4,5-trihydroxyphenylglycine

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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 aa ENSG00000135346), with a unique β chain that confers the biological specificity to follicle-stimulating hormone (FSH, follitropin, 129 aa, ENSG00000131808), luteinizing hormone (LH, lutropin, 141 aa ENSG00000104826), choriogonadotropin (CG, chorionic gonadotropin, 165 aa ENSG00000104818/ENSG00000104827) or thyroid-stimulating hormone (TSH, thyrotropin, 138 aa ENSG00000134200). There is binding crossreactivity 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
Radioligands	[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 Graves 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.*, 1996; 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 & 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 (Sunthorntheparakul *et al.*, 1995). The rat FSH receptor also stimulates phosphoinositide turnover through an unidentified G protein (Quintana *et al.*, 1994).

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Gonadotrophin-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 GnRH II (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Phe-Gly-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 the three ligands exist in amphibians, but only GnRH I and GnRH II and their cognate receptors (type I GnRHRs and type II GnRHRs, provisional nomenclature) have been found in mammals (Sealfon *et al.*, 1997; Millar, 2002). Although thousands of peptide analogues of GnRH I have been synthesised and several (agonists and antagonists) are used therapeutically (Schally, 1999; 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	Luteinizing hormone-releasing hormone 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, leuprolide, nafarelin, hitrelin	—
Selective antagonists	Antide (9.0, Neill, 2002), cetrorelix (8.8, Neill, 2002)	—
Radioligands	[¹²⁵ I]-GnRH I, [¹²⁵ I]-buserelin	[¹²⁵ I]-GnRH II

Coupling of type I GnRHRs to G_s and G_i is evident in some systems (Krsmanovic *et al.*, 2003). 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). The type II GnRHR is expressed by some primates (Grundker *et al.*, 2002), but the human type II GnRHR gene contains a frame shift and internal stop codon and has not yet been shown to encode a functional protein (Millar, 2002; Morgan *et al.*, 2003). GnRHR signalling may be mediated by receptor oligomerisation (Conn *et al.*, 1982; Kroeger *et al.*, 2001).

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Histamine

Overview: Histamine receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Histamine Receptors, see Hill, 1990; 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	Histaprodifen, <i>N</i> ^z -methylhistaprodifen	Dimaprit, impromidine, amthamine	<i>R</i> - α -Methylhistamine, imetit, immepip	Clobenpropit
Selective antagonists	Triprolidine (9.9, Smit <i>et al.</i> , 1996), mepyramine (9.1, Smit <i>et al.</i> , 1996)	Tiotidine (7.8, Leurs <i>et al.</i> , 1994), ranitidine (7.1, Leurs <i>et al.</i> , 1994)	Clobenpropit (9.9), iodophenpropit (9.6), thioperamide (8.4)	JNJ 7777120 (8.1, Jablonowski <i>et al.</i> , 2003)
Radioligands	[³ H]-Mepyramine (1 nM)	[³ H]-Tiotidine (15 nM), [¹²⁵ I]-iodoaminopotentidine (0.3 nM)	[³ H]- <i>R</i> - α -Methylhistamine (0.5 nM), [³ H]- <i>N</i> ^z -methylhistamine (2 nM), [¹²⁵ I]-iodophenpropit (0.6 nM), [¹²⁵ I]-iodoproxyfan (0.06 nM)	-

Histaprodifen and *N*^z-methylhistaprodifen are reduced efficacy agonists. Impromidine is also an H₃ receptor antagonist. The H₄ receptor appears to exhibit broadly similar pharmacology to the H₃ receptor, although *R*- α -methylhistamine and *N*^z-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). [³H]-histamine has been used to label the H₄ receptor in heterologous expression systems.

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5-Hydroxytryptamine (5-HT)

Overview: 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_{2C} (nonfunctional), 5-HT₄ and 5-HT₇ receptors.

Nomenclature	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{1E}
Other names	—	5-HT _{1Dβ}	5-HT _{1Dα}	—
Ensemble ID	ENSG00000178394	ENSG00000135321	ENSG00000179546	ENSG00000168830
Principal transduction	G _{i/o}	G _{i/o}	G _{i/o}	G _{i/o}
Selective agonists	8-OH-DPAT, (<i>R</i>)-UH301, U92016A	Sumatriptan, L694247	PNU10929, sumatriptan, L694247	—
Selective antagonists	(±)WAY100635 (8.7), (<i>S</i>)-UH301, NAD299 (robalzotan)	SB236057 (8.9), SB224289 (8.5), GR55562 (7.4)	BRL15572 (7.9)	—
Radioligands	[³ H]-WAY100635 (0.3 nM, Khawaja <i>et al.</i> , 1997), [³ H]-8-OH-DPAT (0.8 nM, Albert <i>et al.</i> , 1990)	[³ H]-sumatriptan, [¹²⁵ I]-GTI, [³ H]-GR125743 (2.6 nM, Xie <i>et al.</i> , 1999), [³ H]-L694247	[³ H]-sumatriptan, [¹²⁵ I]-GTI, [³ H]-GR125743 (2.8 nM, Xie <i>et al.</i> , 1999) [³ H]-L694247	[³ H]-5-HT

Nomenclature	5-HT_{1F}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}
Other names	5-HT _{1Eβ} , 5-HT ₆	D, 5-HT ₂	5-HT _{2F}	5-HT _{1C}
Ensemble ID	ENSG00000179097	ENSG00000102468	ENSG00000135914	ENSG00000147246
Principal transduction	G _{i/o}	G _{q/11}	G _{q/11}	G _{q/11}
Selective agonists	LY334370, LY334864	α-Me-5-HT	α-Me-5-HT, BW723C86	α-Me-5-HT, Ro600175
Selective antagonists	—	ketanserin (8.5–9.5), MDL100907 (9.4)	RS127445 (9.5)	SB242084 (9.0), RS102221 (8.6)
Radioligands	[³ H]-LY334370, [¹²⁵ I]-LSD	[³ H]-ketanserin (0.45 nM, Bonhaus <i>et al.</i> , 1995), [³ H]-RP62203 (fananserine, 0.13 nM, Malgouris <i>et al.</i> , 1993)	[³ H]-5-HT	[³ H]-mesulergine (0.67 nM, Bonhaus <i>et al.</i> , 1995), [³ H]-LSD

Nomenclature	5-HT₄	5-HT_{5A}	5-HT_{5B}	5-HT₆
Other names	—	5-HT _{5α}	—	—
Ensemble ID	ENSG00000164270	ENSG00000157219	ENSMUSG00000050534	ENSG00000158748
Principal transduction	G _s	G _i /G _o	none identified	G _s
Selective agonists	BIMU8, ML10302, RS67506	—	—	—
Selective antagonists	GR113808 (9.0–9.5), SB204070 (10.8), RS100235 (11.2)	—	—	SB271046 (8.7), SB357134 (7.6), Ro630563 (7.9)
Radioligands	[³ H]-GR113808 (0.1 nM, Reynolds <i>et al.</i> , 1995), [¹²⁵ I]-SB207710 (86 pM, Brown <i>et al.</i> , 1993), [³ H]-RS57639	[³ H]-5-CT, [¹²⁵ I]-LSD	[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

Nomenclature	5-HT₇
Other names	5-HT _X , 5-HT ₁ -like
Ensemble ID	ENSG00000148680
Principal transduction	G _s
Selective agonists	—
Selective antagonists	SB656104 (8.5), SB269970 (8.5), SB258719 (7.2)
Radioligands	[³ H]-SB269970 (1.2 nM, Thomas <i>et al.</i> , 2000), [³ H]-5-CT, [¹²⁵ I]-LSD, [³ H]-5-HT

Tabulated values refer to binding to human 5-HT receptors, with the exception of SB207710 (piglet) and RP62203 (rat). The nomenclature of 5-HT_{1B}/5-HT_{1D} receptors has been revised (Hartig *et al.*, 1996). Only the nonrodent form of the receptor was previously called 5-HT_{1Dβ}; the human 5-HT_{1B} receptor (tabulated) displays a pharmacology different from the rodent forms of the receptor due to Thr335 of the human sequence being replaced by Asn in rodent receptors. NAS-181 is a selective antagonist of the rodent 5-HT_{1B} receptor. Fananserine binds with high affinity to dopamine D₄, in addition to 5-HT_{2A} receptors. A human orthologue of the mouse 5-HT_{5B} receptor has not been isolated.

Abbreviations: 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; **5-CT**, 5-carboxamidotryptamine; **8-OH-DPAT**, 8-hydroxy-2-(di-*n*-propylamino)tetralin; **GR113808**, [1-2[(methylsulphonyl)amino]ethyl]-4-piperidinylmethyl-1-methyl-1*H*-indole-3-carboxylate; **GR125743**, *n*-[4-methoxy-3-(4-methyl-1-piperizinyl)phenyl]-3-methyl-4-(4-pyridinyl)benzamide; **GR55562**, 3-[3-(dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]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; **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-benzo pyran-5-carboxamide; **NAS181**, (*R*)-(+)-2-[[[3-(morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl] morpholine methane sulphonate; **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-fluorindol-1-yl)-1-methylethylamine; **Ro630563**, 4-amino-*N*-[2,6-bis(methylamino)pyridin-4-yl]benzenesulphonamide; **RS127445**, (2-amino-4-(4-fluoronaphthyl-1-yl)-6-isopropylpyrimidine); **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; **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; **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-tetra-

hydrospiro[furo[2,3-f]indol3-3,4'-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-(4-methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulphonylphenol; **SB357134**, *N*-(2,5-dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulphonamide; **SB271046**, 5-chloro-*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulphonamide; **SR57227**, 4-amino-(6-chloro-2-pyridyl)-1-piperidine hydrochloride; **SB656104**, 6-((*R*)-2-[2-[4-(4-chloro-phenoxy)-piperidin-1-yl]-ethyl]-pyrrolidine-1-sulphonyl)-1*H*-indole hydrochloride; **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

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Leukotriene

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, 12(*R*)-hydroxyeicosa-5*Z*,8*Z*,10*E*,14*Z*-tetraenoic acid (12*R*-HETE) and 12*S*-HETE. LTs 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.

Nomenclature	BLT ₁	BLT ₂	CysLT ₁	CysLT ₂
Other names	LTB ₄	—	HG55, HMTMF81, LTD ₄	HPN321, LTC ₄
Ensembl ID	ENSG00000116329	ENSG000000082556	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	LTB ₄ > 20-hydroxy-LTB ₄ > > 12 <i>R</i> -HETE = 12 <i>S</i> -HETE (Yokomizo <i>et al.</i> , 2001)	LTB ₄ > 12 <i>S</i> -HETE > 12 <i>R</i> -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	—	12 <i>S</i> -HETE	—	BAYu9773
Selective antagonists	SB209247 (9.1), SC53228 (pIC ₅₀ 8.8), CP195543 (8.7), CGS25019C (pIC ₅₀ 8.4), LY293111 (7.6)	—	Zafirlukast (9.5), montelukast (9.3), SR2640 (8.7), pobilukast (8.6), sulukast (8.3)	—
Radioligands	[³ H]-LTB ₄ (0.7–2 nM), [³ H]-CGS23131	[³ H]-LTB ₄ (0.2–22 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.

Abbreviations: **BAYu9773**, 6(*R*)-(4'-carboxyphenyl-thio)-5(*S*)-hydroxy-7(*E*),11(*Z*),14(*Z*)-eicosatetraenoic acid; **CGS23131**, (*E*)-5-(3-carboxybenzoyl)-2-([6-{4-methoxyphenyl}-5-hexenyl]oxy)benzene propanoic acid, also known as LY223982; **CGS25019C**, 4-(5-[4-{aminoiminomethyl}phenoxy]pentoxy)-3-methoxy-*N,N*-bis(1-methylethyl)benzamide-(*z*)-2-butenedioate; **CP195543**, (+)-2-(3-benzyl-4-hydroxychroman-7-yl)-4-trifluoromethylbenzoic acid; **ICI198615**, (1-[2-methoxy-4-({[phenylsulfonylamino]carbonyl}phenyl)methyl]-1*H*-indazol-6-yl)carbamic acid cyclopentyl ester; **LY293111**, (2-[2-propyl-3-{2-ethyl-4(4-fluorophenyl)-5-hydroxyphenyl]propoxy]phenoxy)benzoic acid; **SB209247**, (*E*)-3-(6-[(2,6-dichlorophenyl)-thio]methyl)-3-[2-phenylethoxy]-2-pyridinyl-2-propenoic acid; **SC53228**, ((+)-(*S*)-7-[3-{2-cyclopropylmethyl}-3-methoxy-4-(methyldamino)carbonyl]phenoxy]propoxy)-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-propanoic acid; **SR2640**, 2-(3-[2-quinolylmethoxy]phenylamino)benzoic acid

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Lipoxin

Overview: 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 ligands lipoxin A₄ (LXA₄) and 15-epi-LXA₄. 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 and its N-terminal peptides (Perretti *et al.*, 2002). A soluble hydrolytic product of protease action on the urokinase-type plasminogen activator receptor has also been reported to activate the ALX receptor (Resnati *et al.*, 2002).

Nomenclature	ALX
Other names	FPRL1, FPR2, FPRH2, RFP
Ensembl ID	ENSG00000171049
Principal transduction	G _{i/o} (Maddox <i>et al.</i> , 1997)
Rank order of potency	LXA ₄ = 15-epi-LXA ₄ > LTC ₄ = LTD ₄ > > 15-deoxy-LXA ₄ > > fMLP (Fiore <i>et al.</i> , 1994; Fiore & Serhan, 1995; Takano <i>et al.</i> , 1997; Gronert <i>et al.</i> , 2001)
Selective agonists	LXA ₄ , 15-epi-LXA ₄
Radioligands	[³ H]-LXA ₄ (0.2–1.7 nM, Fiore <i>et al.</i> , 1994; Takano <i>et al.</i> , 1997)

A receptor selective for LXB₄ has been suggested from functional studies (Maddox & Serhan, 1996; Romano *et al.*, 1996; Ariel *et al.*, 2003).

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Lysophosphatidic acid

Overview: Lysophosphatidic acid (LPA) receptors (nomenclature as agreed by the 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 physiological 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 is currently unclear. The recently identified LPA₄ is undergoing further characterisation.

Nomenclature	LPA ₁	LPA ₂	LPA ₃	LPA ₄
Other names	VZG-1, Edg2, <i>lp</i> _{A1}	Edg4, <i>lp</i> _{A2}	Edg7, <i>lp</i> _{A3}	p2y9, gpr23
Ensembl ID	ENSG00000119438	ENSG00000064547	ENSG00000171517	ENSG00000147149
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 ₈	G _{q/11} , G ₈ (Noguchi <i>et al.</i> , 2003)

Although subtype-selective agents have been reported (e.g. Heise *et al.*, 2001; Hasegawa *et al.*, 2003), these compounds are not yet generally available and their confirmed specificity, particularly *in vivo*, remains to be demonstrated.

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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 (DFDMLRCMLGRVYRPCWQV) generated from a precursor (ENSG00000183395), which also produces neuropeptides EI and GE. The MCH2 receptor appears to be a nonfunctional 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)	—
Radioligands	[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-dioxooctanoyl)MCH-(6-17); **SNAP7941**, (+)-methyl(4*S*)-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 antagonists	—	—	—	HS014 (8.5, Schiöth <i>et al.</i> , 1998)	—
Radioligands	[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 and MC₅ receptors have been linked to obesity (Chagnon *et al.*, 1997).

Abbreviations: **HS014**, *cyc*(SS)-(Ac-Cys¹¹,D-Nal¹⁴,Cys¹⁸,Asp-NH₂) β -MSH-(11–22); **NDP-MSH**, [Nle⁴,D-Phe⁷] α -MSH; **SHU9119**, Ac-Nle-Asp-His-D-Nal²-Arg-Trp-Lys-NH₂

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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	MT₁	MT₂	MT₃
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	—	IKK7 (Sugden <i>et al.</i> , 1999)	<i>N</i> -acetylserotonin (Eison & Mullins, 1993; Popova & Dubocovich, 1995; Molinari <i>et al.</i> , 1996; Lucchelli <i>et al.</i> , 1997), 5MCA-NAT (Popova & 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; 1998), DH97 (8.0, Teh & Sugden, 1998)	—
Radioligands	[³ H]-melatonin (Browning <i>et al.</i> , 2000), 2-iodo-[¹²⁵ I]-melatonin	[³ H]-melatonin (Browning <i>et al.</i> , 2000), 2-iodo-[¹²⁵ I]-melatonin	2-iodo-[¹²⁵ I]-5MCA-NAT (Molinari <i>et al.</i> , 1996), 2-iodo-[¹²⁵ I]-melatonin

Melatonin, 2-iodo-melatonin, S20098 and GR196429 are nonselective agonists for MT₁ and MT₂ receptors. (–)-AMMTC displays an ~400-fold greater agonist potency than (+)-AMMTC at rat MT₁ receptors (Ting *et al.*, 1999). Luzindole is a nonselective 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 the human quinone reductase 2 (ENSG00000124588, Nosjean *et al.*, 2000; 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 (x420, 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.

Abbreviations: AMMTC, *N*-acetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole; DH97, 2-benzyl-*N*-pentanoyltryptamine; GR196429, *N*-(2-[2,3,7,8-tetrahydro-1*H*-furo(2,3-*g*) indol-1-yl]ethyl)acetamide; IKK7, *N*-butanoyl-2-(2-methoxy-6*H*-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; 5MCA-NAT, 5-methoxy-carbonylamino-*N*-acetyltryptamine; 4P-PDOT, 4-phenyl-2-propionamidotetraline; S20098, *N*-(2-[7-methoxy-1-naphthalenyl]ethyl)acetamide

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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 y6 receptor is a functional gene product in mouse, absent in rat, but contains a frame-shift mutation in primates producing a truncated nonfunctional gene (Gregor *et al.*, 1996). Many of the agonists exhibit differing degrees of selectivity, depending on the species examined. For example, the relative potency of PP is greater at the rat Y₄ receptor than at the human receptor. 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 nonselectively.

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-(13–36), PYY-(3–36)	PP	PYY-(3–36)	—
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)	—	CGP71683A (9.0, Criscione <i>et al.</i> , 1998)	—
Radioligands	[¹²⁵ I]-[Leu ³¹ ,Pro ³⁴] NPY, [³ H]-BIBP3226 (2.1 nM)	[¹²⁵ I]-PYY (3–36)	[¹²⁵ I]-PP	—	—

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 and Y₄ selective relative to Y₁ receptors.

Abbreviations: **BIBO3304**, (*R*)-*N*-([4-{aminocarbonylaminoethyl}-phenyl]methyl)-*N*²-(diphenylacetyl)-argininamide trifluoroacetate; **BIBP3226**, *R*-*N*²-(diphenylacetyl)-*N*-(4-hydroxyphenyl)methyl-argininamide; **BIIE0246**, (*S*)-*N*²-([1-{2-(4-[(*R,S*)-5,11-dihydro-6(6*H*)-oxodibenz[*b,e*]azepin-11-yl]-1-piperazinyl)-2-oxoethyl}cyclopentyl)acetyl]-*N*-(2-[1,2-dihydro-3,5(4*H*)-dioxo-1,2-diphenyl-3*H*-1,2,4-triazol-4-yl]ethyl)-argininamide; **CGP71683A**, *trans*-naphthalene-1-sulfonic acid(4-[4-amino-quinazolin-2-ylamino]-methyl)-cyclohexylmethyl-amide hydrochloride

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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)	Levocobastine (Mazella <i>et al.</i> , 1996)
Selective antagonists	SR48692 (7.5–8.2, Gully <i>et al.</i> , 1997)	—
Radioligands	[^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 recently 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*-Lys ω [(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-quinoliny]-5-{2,6-dimethoxyphenyl}pyrazol-3-yl]carboxylamino)tricyclo(3.3.1.1.¹[3.7])decan-2-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 -neodynorphin, dynorphin A (dynA), dynorphin B, nociceptin/orphanin FQ (N/OFQ), endomorphin-1 and -2, although several other opioid-like peptides are found in the CNS. The Greek names (μ , δ , κ) for the opioid receptors have been well established; however, the IUPHAR nomenclature committee is currently considering several proposals to revise and standardize opioid receptor names based on endogenous ligands. The OP_1 , OP_2 , etc. nomenclature (Dhawan *et al.*, 1996) has not been widely accepted. The human N/OFQ receptor is considered 'opioid-related' rather than opioid, as it exhibits a high degree of structural homology with the conventional opioid receptors (Mollereau *et al.*, 1994), but displays a distinct pharmacology.

Nomenclature	Delta opioid peptide	Kappa opioid peptide	Mu opioid peptide	N/OFQ peptide
Preferred abbreviation	DOP	KOP	MOP	NOP
Other names	δ , OP_1 , DOR	κ , OP_2 , KOR	μ , OP_3 , MOR	ORL1, OP_4 , NOR
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	dynA > β -end > leu > met	β -End > dynA > met = leu	N/OFQ > > dynA
Selective agonists	DPDPE, DSBULET, [dAla ²]deltorphin I or II	U69593, CI977, ICI197067	Endomorphin-1 and -2 (Zadina <i>et al.</i> , 1997), DAMGO, sufentanil, PL017	N/OFQ, N/OFQ-(1-13)-NH ₂ (Guerrini <i>et al.</i> , 1997), Ro646198 (Jenck <i>et al.</i> , 2000)
Selective antagonists	Naltrindole (9.7), NNDT (9.4), TIPP (8.8)	Nor-binaltorphine (10.3)	CTOP (9.7)	J113397 (pIC ₅₀ = 8.3, Kawamoto <i>et al.</i> , 1999), [Nphe ¹]N/OFQ-(1-13)-NH ₂ (6.2, Calo <i>et al.</i> , 2000)
Radioligands	[³ H]-DPDPE, [³ H]-TIPP (0.64 nM), [³ H]-naltrindole	[³ H]-U69593, [³ H]-CI977	[³ H]-DAMGO, [³ H]-PL017	[³ H]-N/OFQ (5 nM, Dooley and Houghten, 1996), [³ H]-Leu-N/OFQ, [¹²⁵ I]-Tyr ¹⁴ -N/OFQ

The existence of μ_1 and μ_2 opioid receptor subtypes has been proposed; μ_1 receptors exhibit high affinity for many δ receptor agonists, with the notable exception of DPDPE. The existence of δ receptor subtypes has been suggested on the basis of *in vivo* studies using δ -receptor-selective ligands: DPDPE and the antagonist 7-benzylidene-7-dehydronaltrexone are selective for δ_1 sites; [dAla²]deltorphin II and the antagonist naltriben are selective for δ_2 sites. Subtypes of the κ receptor have also been proposed. Arylacetamides (e.g. U69593) bind to a subset of sites labelled by ethylketocyclazocine (κ_1). κ_2 sites have moderate affinity for ethylketocyclazocine and bremazocine; under κ -selective conditions, naloxone benzoylhydrazone labels a population of distinct sites (κ_3). It has been suggested that κ_2 sites result from a heterodimer of κ and δ receptors (Jordan & Devi, 1999). The cloned μ , δ and κ receptors correspond to the μ_1 , δ_2 and κ_1 subtypes. 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).

Abbreviations: **CI977**, (5*R*)-(5*α*,7*α*,8*β*)-(–)-*N*-methyl-*N*-(7-[1-pyrrolidinyl]-1-oxaspiro[4.5]dec-8-yl)-4-benzofuranacetamide monohydrochloride; **CTOP**, DPhcyc[Cys-Tyr-DTrp-Lys-Thr-Pen]-The-NH₂; **DAMGO**, Tyr-DAla-Gly-[NMePhe]-NH(CH₂)₂; **DPDPE**, cyc[DPen²,DPen⁵]enkephalin; **DSBULET**, Tyr-DSer(OtBu)-Gly-Phe-Leu-Thr; **ICI197067**, (2*S*)-*N*-([2*N*-methyl-3,4-dichlorophenylacetamido]-3-methylbutyl)pyrrolidone hydrochloride; **J113397**, 1-[(3*R*,4*R*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one; **NNDT**, *N*-(CH₃)₂-(2',6'-CH₃)-Tyr-Tic; **PL017**, [*N*-MePhe³,DPro⁵]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; **TIPP**, Tyr-Tic-Phe-Phe; **U69593**, 5*α*,7*α*,8*β*-(–)-*N*-methyl-*N*-(7-[1-pyrrolidinyl]-1-oxaspiro[4.5]dec-8-yl)benzene acetamide

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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	OX₁	OX₂
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 antagonists	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

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P2Y

Overview: P2Y receptors (provisional nomenclature as agreed by NC-IUPHAR Subcommittee on P2Y Receptors, Abbracchio *et al.*, 2003) 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 wordings 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	ENSG000000	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	UTPγS (Lazarowski <i>et al.</i> , 1996), Ap ₄ A (Castro <i>et al.</i> , 1992)	UTPγS (Lazarowski <i>et al.</i> , 1996)	UDP
Selective antagonists	MRS2179 (7.0, Boyer <i>et al.</i> , 1996)	-	ATP (6.2, Kennedy <i>et al.</i> , 2000)	-
Radioligands	[³⁵ S]-ADPβS, [³⁵ S]-ATPαS, [³⁵ S]-dATPαS	-	-	-

Nomenclature	P2Y ₁₁	P2Y ₁₂	P2Y ₁₃	P2Y ₁₄
Other names	—	P2Y _{ADP} , P2T	GPR86, GPR94, SP174	KIAA00001, gpr105
Ensembl ID	ENSG00000176130	ENSG00000169313	ENSG00000181631	ENSG00000174944
Principal transduction	G _s , G _{q/11}	G _{i/o}	G _{i/o}	G _{q/11}
Rank order of potency	ATP	ADP > > ATP	ADP > > ATP	UDP-glucose
Selective agonists	—	ADP, 2-MeSADP	—	UDP-glucose
Selective antagonists	—	ATP, ARL66096 (Humphries <i>et al.</i> , 1995)	—	—

Further P2Y-like receptors have been cloned from non-mammalian sources; a clone from chick brain, termed a p2y₃ receptor (ch328 aa Q98907), 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 (h328 P43657) and contradictory evidence of responses to ATP (Webb *et al.*, 1996b; King and Townsend-Nicholson, 2000). The clone p2y7 (h352 Q15722), 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 (x1537 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 (AF000545) 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).

Abbreviations: ARL66096, 2-propylthio-βγ-difluoromethylene ATP (previously FPL66096); ATPγS, adenosine 5'-(3-thio)triphosphate; 2-MeSADP, 2-methylthio-adenosine-5'-diphosphate; 2-MeSATP, 2-methylthio-adenosine-5'-triphosphate; MRS2179, N⁶-methyl-2'-deoxyadenosine-3',5'-bisphosphate

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Platelet-activating factor (PAF)

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) (Fukanaga <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-octadecylcarbamoyloxypropoxycarbamoyl]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*-methylcarbamoyl-sn-glycero-3-phosphocholine, also known as (methyl)carbam(o)yl-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-6*H*-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	FP	IP	TP
Ensembl ID	ENSG00000168229	ENSG00000122420	ENSG00000160013	ENSG00000006638
Principal transduction	G _s	G _{q/11}	G _s	G _{q/11}
Rank order of potency	D > E > F > 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	Fluprostenol, latanoprost	Cicaprost, AFP-07, BMY45778 (Seiler <i>et al.</i> , 1997)	U46619, STA ₂ , I-BOP, AGN192093
Selective antagonists	BWA868C (9.3, Giles <i>et al.</i> , 1989), S5751 (8.8 Arimura <i>et al.</i> , 2001), ZK138357 (7.3, Lydford <i>et al.</i> , 1996)	—	—	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)
Radioligands	[³ H]-PGD ₂ (13–34 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)

A PGD₂-sensitive receptor related to the classical chemotactic peptide receptors has also been characterised (Hirai *et al.*, 2001; Monneret *et al.*, 2001). 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 -trilor-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)	—	—	GW627368 (9.2), ONO-AE3-208 (8.5), L-161982 (7.6)
Radioligands	[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 -trilor-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. EP₃ antagonists are under development (Gallant *et al.*, 2002). There is evidence for subtypes of FP (Liljebriis *et al.*, 1995), IP (Wise *et al.*, 1995; Takechi *et al.*, 1996) 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 G₁₂₊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-[(1 α ,5 α ,6 α ,7 β)-7-[(1E,3S)-3-hydroxy-1-octenyl]-3-oxo-2,4-dioxo-bicyclo[3.2.1]oct-6-yl)-5-heptenol; AH13205, *trans*-2-(4-[1-hydroxyhexyl]phenyl)-5-oxocyclopentane-heptanoic acid; AH23848, (1 α [z],2 β ,5 α)-(±)-7-(5-[(1,1'-biphenyl)-4-yl]methoxy)-2-[4-morpholinyl]-3-oxocyclopentyl)-4-heptenoate; BMS180291, (1S-(1 α ,2 α ,3 α ,4 α)-2-[(3-{4-[(pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl)methyl]benzenepropanoic acid, also known as ifetroban; BMY45778, 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; GR32191, [1R-(1(Z),2 β ,3 β ,5)]-(+)-7-[5-[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid; GW627368, N-(2-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzof[isoindol-2-yl]phenyl)-acetyl]benzenesulphonamide; I-BOP, (1S-[1 α ,2 β {5z},3 α [1E,3S*],4 α]-7-(3-[hydroxy-4-(4'-iodophenoxy)-1-butenyl]-7-oxabicyclo[2.2.1]hept-2-yl)-5-heptanoate; L-161982, 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; ONO3708, (9,11)-(11,12)-dideoxa-9 α ,11 α -dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14-oxo-15-cyclopentyl-16,17,18,19,20-pentano-15-epi-TXA₂; ONO8711, 6-[(2S,3S)-3-(4-chloro-2-methylphenylsulphonylaminomethyl)-bicyclo[2.2.2]octan-2-yl]-5Z-hexenoic acid; ONO-DI-004, 17S-17,20-dimethyl-2,5-ethano-6-oxo PGE₂; ONO-AE-248, 11,15-O-dimethyl-PGE₂; ONO-AE1-259, 16S-9-deoxy-9 β -chloro-15-deoxy-16-hydroxy-17,17-propano-19,20-didehydro-PGE₂; ONO-AE1-329, 16-(3-methoxymethyl)phenyl- ω -tetranor-3,7-dithia-PGE₂; ONO-AE3-208, 2-(2-(2-methyl-2-naphth-1-ylacetylaminophenyl)methyl)-benzoic acid; 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-benzenesulfonamino-bicyclo[3.1.1]hept-2-yl)-5Z-heptenoic acid; SC46275, methyl-7-(2 β -[6-{1-cyclopenten-1-yl}-4R-hydroxy-4-methyl-1E,5E-hexadienyl]-3 α -hydroxy-5-oxo-1R,1 α -cyclopentyl)-4Z-heptenoic acid; SC51322, 8-chlorodibenz[b,f][1,4]oxazepine-10(1H)-carboxylic acid, 2-[3-[furanylmethyl]-thio]-1-oxopropyl]hydrazide; SQ29548, (1S-[1 α ,2 β {5z},3 β ,4 α]-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 α -thia-txa₂; U46619, 1 α ,9 α -epoxymethano-PGH₂; ZK118182, (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-[(2RS,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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Protease-activated

Overview: Protease-activated receptors (PARs, nomenclature as agreed by NC-IUPHAR Subcommittee on Protease-activated Receptors, see Hollenberg & Compton, 2002) are activated by proteolytic cleavage of their amino-terminal exodomains. Alternative endogenous proteases or ligands to thrombin for PAR1, PAR3 or PAR4 have not been demonstrated. Activation of PAR2 by trypsin or tryptase release *in vivo* has 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	PAR1	PAR2	PAR3	PAR4
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)	—	—	—
Radioligands	[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]carbonylamino)-3,4-difluoro-benzenepropanamide

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Relaxin

Overview: Relaxin receptors (provisional nomenclature) are activated by heterodimeric peptide hormones analogous to insulin (relaxin-1 (ENSG000010718), relaxin-2 (ENSG0000107014), relaxin-3 (also known as INSL7, ENSG0000171136) in higher primates and possibly INSL3, Leydig insulin-like peptide (ENSG0000171717)).

Nomenclature	RX1	RX2	RX3	RX4
Other names	Relaxin receptor 1, LGR7, leucine-rich repeat-containing G protein-coupled receptor 7	Relaxin receptor 2, LGR8, leucine-rich repeat-containing G protein-coupled receptor 8, GREAT	GPCR135, SALPR1, relaxin 3 receptor 1	GPCR142, relaxin 3 receptor 2
Ensembl ID	ENSG00000171509	ENSG00000133105	ENSG00000182631	AAQ92316
Principal transduction	G _s	G _s	G _{i/o} (Matsumoto <i>et al.</i> , 2000)	G _{i/o} (Liu <i>et al.</i> , 2003a)
Rank order of potency	H2RLX > H3RLX > > INSL3 (Sudo <i>et al.</i> , 2003)	INSL3 > H2RLX > > H3RLX (Kumagai <i>et al.</i> , 2002)	H3RLX > H3RLX B chain > > INSL3 = PRLX (Liu <i>et al.</i> , 2003a)	H3RLX > H3RLX B chain > > INSL3 = PRLX (Liu <i>et al.</i> , 2003a)
Radioligands	[³³ P]-H2RLX (0.1–0.5 nM, Osheroff & Ho, 1993; Kumagai <i>et al.</i> , 2002)	[³³ P]-H2RLX	[¹²⁵ I]-H3RLX (0.3 nM, Liu <i>et al.</i> , 2003b)	[¹²⁵ I]-H3RLX (0.2 nM, Liu <i>et al.</i> , 2003a)

Mutations in INSL3 and LGR8 have been reported in populations of patients with cryptorchidism (Ferlin *et al.*, 2003).

Abbreviations: **H2RLX**, human gene 2 relaxin; **H3RLX**, human gene 3 relaxin; **INSL3**, insulin-like peptide 3; **PRLX**, porcine relaxin

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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.*, 2000).

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	G _i des-Ala ^{1,2,5} - [DTrp ⁸ ,Iamp ⁹]SRIF				
L-797591	Octreotide, seglitide, BIM23027, L-054522	L-796778	NNC269100, L-803087	L-817818	BIM23268, BIM23052,
Selective antagonists	—	Cyanamid 154806 (7.7–8.0),	—	—	BIM23056 (7.4–8.3)
Radioligands	—	[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-14⁶ may be used to label somatostatin receptors nonselectively; BIM23052 is said to be selective at rat but not human receptor (Patel & 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-Tyr-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-Ser); **cyanamid 154806**, Ac-(4-NO₂-Phe)-cyc(D-Cys-Tyr-D-Trp-Lys-Thr-Cys)-D-Tyr-NH₂; **L-797591**, (2R)-N-(6-amino-2,2,4-trimethylhexyl)-3-(1-naphthyl)-2-({[(2-phenylethyl)2-pyridin-2-ylethyl]amino}carbonyl)amino)propanamide; **L-054522**, tert-butyl (bS)-b-methyl-N-[[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]carbonyl]-D-tryptophyl-L-lysinate; **L-796778**, methyl (2S)-6-amino-2-[[[(2R)-2-[[[(1S)-1-benzyl-2-[(4-nitrophenyl)amino]-2-oxoethyl]amino]carbonyl]amino]hexanoyl]amino]hexanoate; **L-803087**, methyl (2S)-5-[[amino(imino)methyl]amino]-2-[[4-(5,7-difluoro-2-phenyl-1H-indol-3-yl)butanoyl]amino]pentanoate; **L-817818**, (2R)-2-aminopropyl N2-[[2-(2-naphthyl)-1H-benzol[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 & 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	S1P1	S1P2	S1P3	S1P4	S1P5
Other names	edg1, <i>lp_{B1}</i>	edg5, <i>lp_{B2}</i> , AGR16, H218	edg3, <i>lp_{B3}</i>	<i>edg6</i> , <i>lp_{C1}</i>	<i>edg8</i> , <i>lp_{B4}</i> , 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

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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 non-mammalian 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 ⁶]NKA-(4–10), [Lys ⁵ ,MeLeu ⁹ ,Mle ¹⁰] NKA-(4–10), GR64349	Senktide, [MePhe ⁷]NKB
Selective antagonists	L742694 (10.0, Hale <i>et al.</i> , 1996), 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)
Radioligands	[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)	[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 & Kwatra, 1998). The hexapeptide agonist septide appears to bind to an overlapping but nonidentical 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: **CP99994**, (+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine; **GR100679**, cyclohexylcarbonyl-Gly-Ala-DTrp-Phe-NMe₂; **GR159897**, (*R*)-1-(2-[5-fluoro-1*H*-indol-3-yl]ethyl)-4-methoxy-4-[(phenylsulfinyl)methyl]piperidine; **GR64349**, Lys-Asp-Ser-Phe-Val-Gly-(*R*- γ -lactam); **GR94800**, *N*- α -benzoyl-Ala-Ala-DTrp-Phe-DPro-Pro-Nle-NH₂; **L703606**, *cis*-2-(diphenylmethyl)-*N*-([2-iodophenyl]methyl)-1-azabicyclo[2.2.2]octan-3-amide; **L742694**, 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]acetylaminio)-3-(1*H*-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-perhydroisindolone; **SB223412**, (*S*)-(-)-*N*-(α -ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide; **SR140333**, (*S*)-1-(2-[3-{3,4-dichlorophenyl}-1-{3-isopropoxyphenyl}acetyl]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-acetylaminio-4-phenylpiperidino)-2-(3,4-dichlorophenyl)butylbenzamide, also known as saredutant

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Thyrotropin-releasing hormone

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 between TRH₁ and TRH₂ receptors (see Sun *et al.*, 2003).

	TRH ₁	TRH ₂
Nomenclature	TRH receptor	—
Other names	—	—
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	—
Radioligands	[³ H]-MeTRH, [³ H]-TRH (13 nM)	[³ H]-TRH (9 nM)

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 receptor (UT, provisional nomenclature, see Douglas & Ohlstein, 2000a) is activated by the endogenous dodecapeptide urotensin-II (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, 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. This sequence is also conserved in the deduced amino-acid sequence of rat (14 aa) and mouse (14 aa) 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)
Radioligands	[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. BIM23127, a neuromedin B receptor antagonist, has been shown to antagonise human recombinant UT receptors (pA₂ 7.5) and to reverse U-II contraction of rat aorta (pIC₅₀ 6.7, Herold *et al.*, 2003). SB710411, a somatostatin receptor antagonist, also antagonises hU-II constriction in rat aorta (pK_B 6.3, Behm *et al.*, 2002).

Abbreviations: **BIM23127**, D-Nal-cyc[Cys-Tyr-D-Trp-Orn-Val-Cys]-Nal-NH₂; **[Pen⁵]U-II-(4-11)**, [pencillamine, β,β-dimethylcysteine]⁵U-II-(4-11); **SB710411**, Cpa-cyc[D-Cys-Pal-D-Trp-Lys-Val-Cys]-Cpa-NH₂

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Vasoactive intestinal peptide and pituitary adenylate cyclase activating peptide

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, b), 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)
Radioligands	[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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Vasopressin and 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[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)	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)	desGlyNH ₂ -d(CH ₂) ₅ [Tyr(Me) ² , Thr ⁴ , Orn ⁸]OT (8.5), L372662 (8.4)
Radioligands	[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]-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] ³ 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).

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-pyridin-3-ylmethyl)piperidin-4-yloxy]-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-1*H*-benzazepine; **OPC51803**, (5*R*)-2-(1-[2-chloro-4-{1-pyrrolidinyl}benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl)-*N*-isopropylacetamide; [³⁵S] **nonpeptide OT antagonist**, [³⁵S]-(1-(1-(2-(2,2-trifluoroethoxy)-4-(1-methylsulfonyl-4-piperidinyl)oxy)phenylacetyl)-4-piperidinyl)-3,4-dihydro-2(1*H*)-quinolinone); **SR121463A**, 1-(4-Boc-2-methoxybenzenesulfonyl)-5-ethoxy-3-spiro-(4-[2-morpholinoethoxy]cyclohexane)indol-2-one fumarate; equatorial isomer; **SR49059**, (2*S*)-1-[(2*R*,3*S*)-5-chloro-3-(chlorophenyl)-1-{3,4-dimethoxysulfonyl}-3-hydroxy]-2,3-dihydro-1*H*-indole-2-carbonyl]-pyrrolidine-2-carboxamide; **SSR149415**, (2*S*,4*R*)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-*N,N*-dimethyl-2-pyrrolidine carboxamide; **VNA932**, (2-chloro-4-[3-methyl-pyrazol-1-yl]-phenyl)-(5*H*,11*H*)-pyrrolo(2,1-*c*)(1,4)benzodiazepin-10-yl-methanone; **VPA985**, 5-fluoro-2-methyl-*N*-(4-[5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ylcarbonyl]-3-chlorophenyl)benzamide

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