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 and desmethylclozapine have recently been described as selective agonists of the M_1 receptor subtype *via* binding to a site distinct to that recognised by non-selective agonists (Spalding *et al*., 2002; Sur *et al*., 2003). There are two allosteric sites on muscarinic receptors, one defined by the binding gallamine, strychnine and brucine and the other binds KT5720, WIN62,577, WIN51,708 and staurosporine (Lazareno *et al*., 2000, 2002). There are selective enhancers of acetylcholine binding and action; brucine and KT5720 at M_1 receptors, PG135 at M_2 receptors, N-chloromethylbrucine and WIN62,577 at M_3 receptors and thiochrome at M_4 receptors (Lazareno *et al*., 1998, 1999, 2000, 2002, 2004). The allosteric site for gallamine and strychnine on M_2 receptors can be labelled by [^{3}H]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), tripitramine (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)	tripitramine (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), MT3 (<6), PD102807(5.7), guanylpirenzepine (5.5)	4-DAMP (8.9–9.3), darifenacin (8.4–8.9), AFDX384 (7.2–7.8), tripitramine (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), tripitramine (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), tripitramine (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-toxin1) are toxins contained with the venom of the Eastern green mamba (*Dendroaspis augusticeps*) (see Bradley, 2000; Potter *et al*., 2004).

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-2H-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-*i*][1,6]benzodiazocine-10-carboxylic acid hexyl ester; **NMS**, N-methylscopolamine; **PD102807**, 9-methoxy-2-methyl-11,12-dihydro-3*H*,6α*H*,13*H*-6-oxa-3,12α-diaza-benzo[*a*]cyclopenta(*h*)anthacene-1-carboxylic acid ethyl ester; **PG135**, (3a*S*,12*R*,12a*S*,12b*R*)-2-amino-2,3,3a,4,11,12a,12b-octahydro-10-hydroxyisoquino[2,1,8-*lma*]carbazol-5(1*H*)-one hydrochloride; **QNB**, 3-quinuclidinylbenzilate; **WIN51,708**, 17-β-hydroxy-17-α-ethynyl-5-α-androstano[3,2-*b*]pyrimido[1,2-*a*]benzimidazole; **WIN62,577**, 17-β-hydroxy-17-α-ethynyl-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 A_3 receptors). NECA is a non-selective agonist, while XAC and CGS15943 display submicromolar affinity at all four adenosine receptors (Klotz *et al*., 1998; Ongini *et al*., 1999).

Nomenclature	**A_1**	**A_{2A}**	**A_{2B}**	**A_3**
Ensembl ID	ENSG00000163485	ENSG00000128271	ENSG00000170425	ENSG00000121933
Principal transduction	$G_{i/o}$	G_s	G_s	$G_{i/o}$
Selective agonists	CPA, CCPA, S-ENBA	CGS21680, HENECA	—	2-Cl-IB-MECA, IB-MECA
Selective antagonists	DPCPX (8.5)	ZM241385 (9.0), SCH58261 (7.9–9.5)	MRS1754 (8.7), MRS1706 (8.4)	MRS1220 (8.8), VUF8504 (7.8, van Muijlwijk-Koezen *et al*., 1998), 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 adenylyl cyclase (P-site). A pseudogene exists for the A_{2B} adenosine receptor (ENSG00000182537) with 79% identity to the A_{2B} adenosine receptor cDNA coding sequence but which is unable to encode a functional receptor (Jacobson *et al*., 1995). DPCPX also exhibits antagonism at A_{2B} receptors (pK_i *ca*. 7, Alexander *et al*., 1996; Klotz *et al*., 1998). HENECA also shows activity at A_3 receptors (Varani *et al*., 1998). Antagonists at A_3 receptors exhibit marked species differences, such that only MRS1523 and MRS1191 are selective at the rat A_3 receptor. In the absence of other adenosine receptors, [^{3}H]-DPCPX and [^{3}H]-ZM241385 can also be used to label A_{2B} receptors (K_D *ca*. 30 and 60 nM, respectively). [^{125}I]-AB-MECA also binds to A_1 receptors (Klotz *et al*., 1998). [^{3}H]-CGS21680 is relatively selective for A_{2A} receptors, but may also bind to other sites in cerebral cortex (Cunha *et al*., 1996; Johansson & Fredholm, 1995). [^{3}H]-NECA binds to other non-receptor 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-phenylacetylamino[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-*e*]-1,2,4-triazolo[1,5*c*]pyrimidine; **VUF8504**, 4-methoxy-*N*-[2-(2-pyridinyl)quinazolin-4-yl]benzamide; **XAC**, 8-(4-[{([{2-aminoethyl}amino]carbonyl)methyl}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 for α_1-adrenoceptors relative to α_2-adrenoceptors. [^{3}H]prazosin (0.25 nM) and [^{125}I]HEAT (0.1 nM; also known as BE2254) are relatively selective radioligands. Numerous splice variants of the α_1-adrenoceptors exist, some of which may display a different spectrum of signalling properties.

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 display relatively low affinity in functional and binding assays (less than 1 nM) for prazosin that might represent different receptor states. (+)Niguldipine also has high affinity for L-type Ca^{2+} channels.

Abbreviations: A61603, *N*-(5-[4,5-dihydro-1*H*-imidazol-2-y]-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-(2,2,2-trifluoroethoxy)-phenoxyl}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. Rauwolscine (9.0) and yohimbine (9.0) are antagonists selective for α_2-adrenoceptors relative to α_1-adrenoceptors. [^{3}H]Rauwolscine (1 nM), [^{3}H]UK14304 (5 nM), [^{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, rauwolscine 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 partial 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-[*O*-methoxyphenyl]-piperazin)-1-yl; **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 (pKi 5.8–7.0) but can be labelled with high concentrations of cyanopindolol (pKi 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. [^{3}H]-CGP12177 or [^{3}H]-dihydroalprenolol can be used in place of [^{125}I]-ICYP. Many antagonists at β_1- and β_2-adrenoceptors are agonists at β_3-adrenoceptors (CL316243, CGP12177A and carazolol). 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 is likely to represent an alternative site of interaction of CGP12177A and other non-conventional partial agonists at β_1-adrenoceptors since 'putative β_4-adrenoceptor'-mediated agonist effects of CGP12177A are absent in mice lacking β_1-adrenoceptors (Konkar *et al*., 2000, Kaumann *et al*., 2001).

Numerous poymorphisms exist for the β_1- and β_2-adrenoceptors and some of these are associated with alterations in signalling in response to agonists. The polymorphisms may be associated with altered responses to drugs.

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-iodobenzenesulfonamide; **L748328**, (*S*)-*N*-(4-[2-{(3-[3-{aminosulfonyl}phenoxy]-2-hydroxypropyl)-amino}ethyl]phenyl)benzenesulfonamide; **RO363**, (−)-1-(3,4-dimethoxyphenethylamino)-3-(3,4-dihdroxyphenoxy)-2-propanol)oxalate; **SB251023**, (4-[1-{2-(*S*)-hydroxy-3-(4-hydroxyphenoxy)-propylamino}cyclopentylmethyl]phenoxymethyl)phenylphosphonic acid lithium salt; **SR59230A**, 3-(2-ethylphenoxy)-1([1*S*]-1,2,3,4-tetrahydronaphth-1-ylamino)-2*S*-propanol oxalate

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Angiotensin

Overview: The actions of angiotensin II (Ang II) are mediated by AT_1 and AT_2 receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Angiotensin Receptors, see de Gasparo *et al*., 2000), which have around 30% sequence similarity. AT_1 receptors are predominantly coupled to $G_{q/11}$. Most species express a single AT_1 gene, but two related AT_{1A} and AT_{1B} receptor genes are expressed in rodents. The AT_2 receptor counteracts several of the growth responses initiated by the AT_1 receptors. The AT_2 receptor is much less abundant than the AT_1 receptor in adult tissues and is up-regulated 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	[*p*-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 AT_4 receptor which specifically binds angiotensin IV and is located in brain and kidney. An additional putative endogenous ligand for the AT_4 receptor has been described (LVV-hemorphin, a globin decapeptide) (Moeller *et al*., 1997). The AT_1 and bradykinin B_2 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). Novel AT_1 receptor antagonists bearing substituted 4-phenylquinoline moieties have recently been designed and synthesised. The best of these compounds bind to AT_1 receptors with nanomolar affinity and are slightly more potent than losartan in functional studies (Cappelli *et al*., 2004).

Abbreviations: A81988, 2(*N*-n-propyl-*N*-[{2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl}methyl]amino)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-5yl}biphenyl-4-yl]methyl)imidazole-5-carboxylate; **EXP985,** *N*-(2-[4-hydroxy-3-iodophenyl]ethyl)-4-chloro-2-propyl-1-([2′-{1*H*-tetrazol-5yl}biphenyl-4-yl]methyl)imidazole-5-carboxamide; **irbesartan,** 2-butyl-3-[[2′-(1H-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-5yl]biphenyl-4-yl)imidazo[4,5-*b*]pyridine; **L162313,** 5,7-dimethyl-2-ethyl-3-[[4-[2(n-butyloxycarbonylsulfonamido)-5-isobutyl-3-thienyl]phenyl]methyl]imidazo[4,5,6]pyridine; **losartan,** 2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]imidazole; also known as Dup 753; **PD123177,** 1-(4-amino-3-methylphenyl)methyl-3-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylate; **PD123319,** (*s*)-1-(4-[dimethylamino]-3-methylphenyl)methyl-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylate; **valsartan,** N-(1-oxopentyl)-N-[[2′-(1H-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 (Pyr^1)apelin-13 are the predominant endogenous ligands, while apelin-17 is exogenous.

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 *et al*., 1998)
Selective agonists	[Pyr^1]apelin-13, apelin-13, apelin-17, apelin-36
Radioligands	[^{125}I]-[Pyr^1]-Apelin-13 (0.3 nM, Katugampola *et al*., 2001)

Potency order determined for heterologously-expressed human APJ receptor (pD_2 values range from 9.5 to 8.6). APJ may also act as a co-receptor with CD4 for isolates of human immunodeficiency virus, with apelin blocking this function (Cayabyab *et al*., 2000).

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Bombesin

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

Nomenclature	**BB1**	**BB2**	**bb3**
Other names	NMB-R	GRP-R	BRS-3
Ensembl ID	ENSG00000135577	ENSG00000126010	ENSG00000102239
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Selective agonists	NMB	GRP	—
Selective antagonists	PD165929, DNal-*cyc*(Cys-Tyr-DTrp-Orn-Val)-Nal-NH_2, DNal-Cys-Tyr-DTrp-Lys-Val-Cys-Nal-NH_2	1-naphthoyl-[DAla^{24},DPro^{26},ψ26–27]GRP-20–27, kuwanon H, [DPhe^{6}]bombesin-6–13-ethylester, [DPhe^{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 three subtypes may be activated by [dPhe^{6}, βAla^{11}, Phe^{13}, Nle^{14}]bombesin-6–14 (Mantey *et al*., 1997). One analogue, [D-Tyr^{6}, Apa-4Cl, Phe^{13}, Nle^{14}] bombesin-6–14 has more than 200 fold selectivity for bb3 receptors over BB1 and BB2. (Mantey *et al*., 2004)

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

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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-Arg^9]BK, Lys-BK (kallidin), [des-Arg^9]Lys-BK, T-kinin (Ile-Ser-BK), [Hyp^3]BK and Lys-[Hyp^3]BK. The variation in affinity or inactivity of B_2 receptor antagonists could reflect the existence of species homologues of B_2 receptors.

Nomenclature	**B_1**	**B_2**
Ensembl ID	ENSG00000100739	ENSG00000168398
Principal transduction	$G_{q/11}$	$G_{q/11}$
Rank order of potency	Lys-[des-Arg^9]BK > [des-Arg^9]BK = Lys-BK > BK	Lys-BK ≥ BK ≫ [des-Arg^9]BK, Lys-[des-Arg^9]BK
Selective agonists	Lys-[des-Arg^9]BK, Sar[DPhe^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 *et al*., 1998), R914 (8.6, Gobeil *et al*., 1999), R715 (8.5, Gobeil *et al*., 1996a), Lys-[Leu^8][des-Arg^9]BK (8.0)	HOE140 (8.4, Gobeil *et al*., 1996b), FR173657 (8.2, Rizzi *et al*., 1997), LF160687 (Puneau *et al*., 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[Hyp^3,Cpg^5,dTic^7,Cpg^8][des-Arg^9]BK; **FR173657,** (*e*)-3-(6-acetamido-3-pyridyl)-*N*-(*N*-[2,4-dichloro-3{(2-methyl-8-quinolinyl)oxymethyl} phenyl]-*N*-methylaminocarbonyl-methyl)acrylamide; **HOE140,** DArg[Hyp^3,Thi^5,DTic^7,Oic^8]BK, also known as Icatibant; **LF160687,** 1-([2,4-dichloro-3-{([2,4-dimethylquinolin-8-yl]oxy)methyl}phenyl]sulfonyl)-*N*-(3-[{4-(aminoimethyl)phenyl}carbonylamino]propyl)-2(*S*)-pyrrolidinecarboxamide; **NPC17731,** DArg[Hyp^3,DHypE(transpropyl)^7,Oic^8]BK; **R715,** AcLys[D Nal^7,Ile^8][des-Arg^9]BK; **R914**, AcLys-Lys-([αMe]Phe^5,δβNal^7,Ile^8)desArg^{9}BK

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Calcitonin, amylin, CGRP and adrenomedullin

Overview: Calcitonin (CT), amylin (AMY), CT gene related-peptide (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 proteins). 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 αCGRP (occasionally termed CGRP-I), *β*CGRP (occasionally termed CGRP-II), amylin (previously termed islet-amyloid polypeptide, diabetes-associated peptide) and AM. There are species differences in peptide sequences, particularly for the calcitonins. CGRP-(8–37) acts as an antagonist of CGRP (pk_i 6.5–8.0) and inhibits some AM and AMY responses (7.0). It is inactive at calcitonin receptors. Salmon calcitonin-(8–32) is an antagonist at both *amylin* and calcitonin receptors but not at CGRP receptors. AC187, a salmon calcitonin-(8–32) analogue, is also an antagonist at *amylin* and calcitonin receptors but has appreciable affinity at CGRP receptors. Human AM-(22–52) has some selectivity towards AM receptors, but with modest affinity, limiting its use.

Nomenclature	**Calcitonin**	**Amylin**	**CGRP**	**Adrenomedullin**
Composition	*CALCR*	*AMY1: CALCR + RAMP1* *AMY2: CALCR + RAMP2* *AMY3: CALCR + RAMP3*	*CALCRL + RAMP1*	*AM1: CALCRL + RAMP2* *AM2: CALCRL + RAMP3*
Ensembl ID	ENSG00000004948	—	ENSG00000064989	—
Principal transduction	G_s/G_q	G_s	G_s/G_q	G_s
Rank order of potency	Salmon CT ⩾ human CT ⩾ AMY, CGRP > AM	Salmon CT ⩾ AMY ⩾ CGRP > human CT > AM	CGRP > AM ⩾ AMY ⩾ salmon CT	AM1: AM ≫ CGRP > AMY > salmon CT AM2: AM ⩾ CGRP > AMY > salmon CT
Selective agonists	Human CT	AMY	αCGRP	AM
Selective antagonists	—	—	BIBN4096BS (11, Doods *et al*., 2000; Hay *et al*., 2003)	AM-(22–52)
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]-αCGRP (0.1 nM)	[^{125}I]-AM (rat, 0.1–1.0 nM)

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

G_s is a prominent route for effector coupling but other pathways (e.g. Ca^{2+} and nitric oxide) and G proteins can be activated. The coupling can be affected by splice variants of the CT receptor (e.g. the 490aa form of the human receptor, $CT_{(b)}$, does not cause an increase in intracellular Ca^{2+} and might have low efficacy in generating cAMP).

There is evidence that CGRP-receptor component protein (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 also 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).

[^{125}I]-Salmon calcitonin is the most common radioligand for calcitonin receptors but it has high affinity for *amylin* receptors and is also poorly reversible. [^{125}I]-Tyr^0-CGRP is widely used as a radioligand for CGRP receptors.

$CGRP_1$ and $CGRP_2$ receptor 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 $CGRP_2$-selective agents) and antagonist CGRP-(8–37) ($CGRP_1$-selective, pk_i 7.0–8.0, Juaneda *et al*., 2000). CL/RAMP1 resembles the '$CGRP_1$' subtype previously described in native tissues and cell lines (Aiyar *et al*., 1996; McLatchie *et al*., 1998). There is not yet a clear molecular correlate for the $CGRP_2$ receptor.

Abbreviations: AC187, acetyl-[Asn^{30},Tyr^{32}]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[2*H*]-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 *et al*., 1997)
Cation rank order of potency	$Gd^{3+} > Ca^{2+} > Mg^{2+}$ (Brown *et al*., 1993)
Polyamine rank order of potency	Spermine > spermidine > putrescine (Quinn *et al*., 1997)
Amino acid rank order of potency	L-Phe, L-Trp, L-His ≥ L–Ala > L-Ser, L-Pro, L-Glu ≥ L-Asp but not L-Lys, L-Arg, L-Leu, and L-Ile (Conigrave *et al*., 2000)

Phenylalkylamine calcimetics, such as NPSR-568 (Norcalcin), 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 arachidonoylethanolamide (anandamide), homo-γ-linolenylethanolamide, docosatetra-7, 10, 13, 16-enylethanolamide, 2-arachidonoyl glycerol and 2-arachidonyl glyceryl ether. Potency determinations are complicated by the possibility of differential susceptibility of endogenous ligands to enzymatic conversion.

Nomenclature	**CB_1**	**CB_2**
Ensembl ID	ENSG00000118432	ENSG00000162562
Principal transduction	$G_{i/o}$	$G_{i/o}$
Selective agonists	Arachidonoyl-2-chloroethylamide (Hillard *et al*., 1999), arachidonoylcyclopropylamide (Hillard *et al*., 1999), methanandamide (Khanolkar *et al*., 1996), O-1812 (Di Marzo *et al.,* 2001)	HU308 (Hanus *et al*., 1999), JWH133 (Huffman *et al*., 1999; Pertwee, 2000), L759633 (Ross *et al*., 1999), L759656 (Ross *et al*., 1999), AM1241 (Ibrahim *et al*., 2003)
Selective antagonists	SR141716A (7.9, Showalter *et al*., 1996), LY320135 (6.9, Felder *et al*., 1998), AM251 (Lan *et al*., 1999a), AM281 (Lan *et al*., 1999b)	SR144528 (9.2, Rinaldi-Carmona *et al*., 1998), AM630 (7.5, Ross *et al*., 1999)
Radioligands	[^{3}H]-HU243 (45 pM, Devane *et al*., 1992), [^{3}H]-CP55940 (0.6 nM, Showalter *et al*., 1996), [^{3}H]-WIN55212-2 (12 nM, Song & Bonner, 1996), [^{3}H]-SR141716A (0.6 nM, Rinaldi-Carmona *et al*., 1996)	[^{3}H]-HU243 (61 pM Bayewitch *et al*., 1995), [^{3}H]-CP55940 (0.6 nM, Showalter *et al*., 1996), [^{3}H]-WIN55212-2 (2 nM, Slipetz *et al*., 1995)

Anandamide is also a vanilloid receptor (TRPV1) agonist.

Abbreviations: **AM251,** *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide**; AM281,** 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-*N*-4-morpholinyl-1*H*-pyrazole-3-carboxamide**; AM630,** 6-iodopravadoline; **AM1241,** (2-iodo-5-nitro-phenyl)-[1-(1-methyl-piperidin-2-ylmethyl)-1*H*-indol-3-yl]-methanone; **CP55940,** (1*R*,3*R*,4*R*)-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)cyclohexan-1-ol; **HU243,** [6a*R*-(6aα,9α,10aβ)]-3-(1,1-dimethylhelptyl)-6a,7,8,9,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[b,d]pyran-[7,8-^{3}H]-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-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromene; **L759633,** (6a*R*,10a*R*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6,9-trimethyl-6a,7,10,10a-tetrahydro-6*H*-benzo[c]chromene; **L759656,** (6a*R*,10a*R*)-3-(1,1-dimethylheptyl)-1-methoxy-6,6-dimethyl-9-methylene-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromene; **LY320135,** (6-methoxy-2-[4-methoxyphenyl]benzo[b]thien-3-yl)(4-cyanophenyl)methanone; **methanandamide,** (*r*)-(+)-arachidonoyl-1′-hydroxy-2′-propylamide; **O-1812,** (*R*)-(20-cyano-16,16-dimethyldocosa-cis-5,8,11,14-tetraenoyl)-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 CX_3C ($n = 1$) chemokines all have four conserved cysteines, with zero, one and three amino acids separating the first two cysteines, respectively. C chemokines ($n = 2$) have only the second and fourth cysteines found in other chemokines. Chemokines can also be classified by function into homeostatic and inflammatory subgroups. Most chemokine receptors are able to bind multiple high affinity chemokine ligands, but the ligands for a given receptor are almost always restricted to the same structural subclass. Most chemokines bind to more than one receptor subtype. Receptors for inflammatory chemokines are typically highly promiscuous with regard to ligand specificity, and may lack a selective endogenous ligand. Listed are those human agonists with EC_{50} values < 50 nM in either Ca^{2+} flux or chemotaxis assays at human recombinant receptors expressed in mammalian cell lines. There can be substantial cross-species differences in the sequences of both chemokines and chemokine receptors, and in the pharmacology and biology of chemokine receptors. Endogenous and HIV-encoded non-chemokine ligands have also been identified for chemokine receptors. The tables include both standard chemokine names (Zlotnik & Yoshie, 2000) and the most commonly used synonyms. Numerical data quoted are typically pKi or pIC_{50} values from radioligand binding to heterologously expressed receptors.

Nomenclature	**CCR1**	**CCR2**	**CCR3**	**CCR4**	**CCR5**
Other names	CKR1, CC CK_1, CC CKR1, MIP-1αR, MIP-1α/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-1α), 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-1α), CCL5 (RANTES), CCL4 (MIP-1β)	CCL3 (MIP-1α), CCL4 (MIP-1β), 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-1β, R5-HIV gp120
Selective antagonists	BX471 (8.3–9), 2b-1 (8.7), UCB35625 (8.0), CP-481,715 (8.0), CCL4 (MIP-1β)	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-1α, [^{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-1α, [^{125}I]-MIP-1β

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-3β), CCL21 (SLC)	CCL1 (I-309), CCL4 (MIP-1β), CCL16 (HCC-4), CCL17 (TARC), HHV8 vMIP-I	CCL25 (TECK)	CCL27 (Eskine, ALP, CTACK), CCL28 (MEC)
Selective agonists	LARC, HBD2	ELC, SLC	I-309	TECK	Eskine, MEC
Selective antagonists	—	—	MCV MC148R (vMCC-I)	—	—
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	$IL8R_A$, IL-8 receptor type I, IL-8 receptor α	$IL8R_B$, IL-8 receptor type II, IL-8 receptor β	IP10/Mig R, GPR9	HUMSTSR, 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 (GROα), CXCL2 (GROβ), CXCL3 (GROγ), CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL7 (NAP-2), CXCL8 (IL-8), HCMV UL146 (vCXC-1)	CXCL9 (Mig), CXCL10 (IP10), CXCL11 (I-TAC)	CXCL12α & β (SDF-1α, SDF-1β	CXCL13 (BLC, BCA-1)	CXCL16 (SR-PSOX)
Selective agonists	—	GROα, GROγ, GROβ, NAP-2, ENA78	IP10, MIG, I-TAC	SDF-1α, SDF-1β, 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]-GROα, [^{125}I]-NAP-2, [^{125}I]-ENA78	[^{125}I]-IP10	[^{125}I]-SDF-1	—	—

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

Nomenclature	CX_3CR1	XCR1
Other names	CMKBRL1, V28	GPR5
Ensembl ID	ENSG00000168329	ENSG00000173578
Principal transduction	$G_{i/o}$	$G_{i/o}$
Agonists	CX3CL1 (Fractalkine)	XCL1 α and β (Lymphotactin α and β)
Selective agonists	Fractalkine	Lymphotactin
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; **SLC**, secondary lymphoid tissue chemokine; **SEAP**, secreted alkaline phosphatase; **TARC,** T-cell and activation-related chemokine; **TECK**, thymus-expressed chemokine

The CC chemokine family (CCL1–28) includes I309 (CCL1), MCP-1 (CCL2), MIP-1α (CCL3), MIP-1β (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 GROα (CXCL1), GROβ (CXCL2), GROγ (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 CX_3C chemokine (CX3CL1) is also known as fractalkine (neurotactin in the mouse). Unlike other chemokines, this molecule is multimodular containing a chemokine domain, an elongated mucin-like stalk, a transmembrane domain and a cytoplasmic tail. Both plasma membrane-associated and shed forms have been identified. The C chemokine (XCL1) is also known as lymphotactin. The non-chemokine family includes the cytokine domain of tyrosyl-tRNA synthetase, HBD2, HIV gp120 and HIV Tat.

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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. The fMLP receptor responds to exogenous ligands such as the bacterial product formyl-Met-Leu-Phe (fMLP) and endogenous ligands such as annexin I (ENSG00000135046), cathepsin G (ENSG00000100448) and spinorphin, derived from β-haemoglobin (ENSG00000188170).

Nomenclature	**C3a**	**C5a**	**fMLP**
Other names	AZ3B, HNFAG09	CD88	Formyl peptide, FPR
Ensembl ID	ENSG00000171860	ENSG00000134830	ENSG00000171051
Principal transduction	$G_{i/o}$, G_z	$G_{i/o}$, G_z, G_{16} (Buhl *et al*., 1993)	$G_{i/o}$, G_z
Rank order of potency	C3a > C5a (Ames *et al*., 1996)	C5a, C5a des Arg > C3a (Ames *et al*., 1996)	fMLP > Cathepsin G > Annexin I > (Le *et al*., 2002. Sun *et al*., 2004)
Selective agonists	Trp-Trp-Gly-Lys-Lys-Tyr-Arg-Ala-Ser-Lys-Leu-Gly-Leu-Ala-Arg (Ames *et al*., 1997)	Phe-Lys-Pro-Cha-Cha-Phe-Lys-D-Cha-Cha-D-Arg (Konteatis *et al*., 1994), S19 (Yamamoto, 2000)	fMLP (Le *et al*., 1999)
Selective antagonists	SB 290157 (pIC_{50} 7.5, Ames *et al*., 2001)	NMe-Phe-Lys-Pro-D-Cha-Trp-D-Arg (Konteatis *et al*., 1994), AcPhe-Orn-Pro-D-Cha-Trp-Arg (Wong *et al*., 1998), W54011 (8.7, Sumichika *et al*., 2002)	Cyclosporin H (6.3–7.0, Wenzel-Seifert & Seifert, 1993), BOC-PLPLP (6.0–6.5, Wenzel-Seifert & Seifert, 1993), spinorphin (4, Liang *et al*., 2001)
Radioligands	[^{125}I]-C3a	[^{125}I]-C5a	[^{3}H]-fMLP

A putative chemoattractant receptor termed C5L2 (also known as GPR77, ENSG00000134830) binds [^{125}I]-C3a and [^{125}I]-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**, N^2-([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 CCK_2 receptors distinguished by the relative affinities of the two stereoisomers of devazepide, *R*-L365260 and *S*-L365260, or by the differences in affinity of the agonist BC264 (Durieux *et al*., 1992).

Nomenclature	**CCK_1**	**CCK_2**
Other names	CCK_A	CCK_B, CCK_B/gastrin
Ensembl ID	ENSG00000163394	ENSG00000110418
Principal transduction	$G_{q/11}/G_s$ (Wu *et al*., 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	Desulfated CCK-8, gastrin, CCK-4, BC264, RB400
Selective antagonists	Devazepide (9.8), T0632 (9.6), SR27897 (9.2), IQM95333 (9.2), PD140548 (7.9–8.6), lorglumide (7.2)	YM022 (10.2), L740093 (10.0), GV150013 (9.3), RP73870 (9.3), L365260 (7.5–8.7), LY262691 (7.5)
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 [^{125}I]-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-NH_2; **BC264,** Tyr(SO_3H)-gNle-mGly-Trp-(NMe)Nle-Asp-Phe-NH_2; **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*-(methyoxyphenyl)acetamide; **IQM95333,** (4α*s*,5*r*)-2-benzyl-5[*N*-(*tert*-butoxycarbonyl)-L-Trp]amino-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine; **JMV180,** Boc-Tyr(SO_3H)Ahx-Gly-Trp-Ahx-Asp^{2}phenylethyl 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-pyrrazolidinecarboxamide(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-CH_2-CO-Trp-NMe(Nle)-Asp-Phe-NH_2; **RP73870,** ({[(*N*-methyoxy-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-isoquinolinyl}-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 Subcommittee 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). CRF_1 and CRF_2 receptors are activated non-selectively by CRF and urocortin 1. Binding to CRF receptors can be conducted using [^{125}I]-Tyr^0-CRF or [^{125}I]-Tyr^0-sauvagine with K_d values of 0.1–0.4 nM. CRF_1 and CRF_2 receptors are non-selectively antagonized by α-helical CRF-(9–41), D-Phe-CRF-(12–41) and astressin.

Nomenclature	**CRF_1**	**CRF_2**
Other names	CRF-RA, PC-CRF	CRF-RB, HM-CRF
Ensembl ID	ENSG00000120088	ENSG00000106113
Principal transduction	G_s	G_s
Selective agonists	—	Urocortin 2 (Reyes *et al*., 2001), urocortin 3 (Lewis *et al*., 2001)
Selective antagonists	CP154526 (8.3–9.0, Lundkvist *et al*., 1996), NBI27914 (8.3–9.0, Chen *et al*., 1996), antalarmin (8.3–9.0, Webster *et al*., 1996), CRA1000 (8.3–9.0, Chaki *et al*., 1999), DMP696 (8.3–9.0, He *et al*., 2000), R121919 (8.3–9.0, Zobel *et al*., 2000), SRA125543A (8.7–9.0, Gully *et al*., 2002)	K41498 (9.2, Lawrence *et al*., 2002), K31440 (8.7–8.8, Ruhmann *et al*., 2002), antisauvagine-30 (Ruhmann *et al*., 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-Phe^{12},Nle^{21,38},-Glu^{30},Lys^{33}]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-Phe^{12},Nle^{21,38},αMeLeu^{37}-CRF; **K31440**, Ac-(D-Tyr^{11},His^{12},Nle^{17})sauvagine-(11–40); **K41498**, [D-Phe^{11},His^{12},Nle^{17}]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	ENG00000169676
Principal transduction	G_s, G_{olf}	$G_{i/o}$	$G_{i/o}$ (G_s)	$G_{i/o}$	G_s, G_{olf}
Selective agonists	*R*(+)SKF81297, *R*(+)SKF38393, dihydrexedine	(+)PHNO	PD128907	PD168077	—
Selective antagonists	SCH23390, SKF83566, SCH39166	Raclopride, domperidone	S33084 (9.6, Millan *et al*., 2000), nafadotride (9.5), (+)S14297 (8.7, Millan *et al*., 1994), SB277011 (7.5, Reavill *et al*., 2000)	L745870 (9.3), U101958 (8.9, Schlachter *et al*., 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 *et al*., 1997), [^{125}I]-L750667 (1 nM, Patel *et al*., 1996), [^{3}H]-spiperone	[^{125}I]-SCH23982 (0.8 nM)

The selectivity of many of these agonists is less than two orders of magnitude. [^{3}H]-Raclopride exhibits similar high affinity for D2 and D3 receptors (low affinity for D4), but has been used to label D2 receptors in the presence of a D3-selective antagonist. [^{3}H]-7-OH-DPAT has similar affinity for D2 and D3 receptors, but labels only D3 receptors in the absence of divalent cations. The pharmacological profile of the D5 receptor is similar to, yet distinct from, that of the D1 receptor. The splice variants of the D2 receptor are commonly termed D2S and D2L (short and long). The *DRD4* gene is highly polymorphic in humans, with allelic variations of the protein from amino acid 387 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*-3,4,4*a*,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-tetrahydronaphtho(2,3*b*)dihydro-2,3-furane; **S33084,** (3*aR*,9*bS*)-*N*[4-(8-cyano-1,3*a*,4,9*b*-tetrahydro-3*H*-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,*b*)azepine; ***R*(+)SKF38393,** *R*(+)-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; ***R*(+)SKF81297,** *R*(+)-6-chloro7,8-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, pA_2 8.4) and non-peptide (e.g. bosentan, pA_2 6.0–7.2; SB209670, pA_2 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 *et al*., 1992), sarafotoxin S6c (Russell & Davenport, 1996), IRL1620 (Watakabe *et al*., 1992), BQ3020 (Russell & Davenport, 1996)
Selective antagonists	A127722 (9.2–10.5, Opgenorth *et al*., 1996), LU135252 (8.9, Riechers *et al*., 1996), SB234551 (8.7–9.0, Ohlstein *et al*., 1998), PD156707 (8.2–8.5, Maguire *et al*., 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 *et al*., 1999), IRL2500 (7.2, Russell & Davenport, 1996), Ro468443 (7.1, Breu *et al*., 1996)
Radioligands	[^{3}H]-S0139 (0.6 nM), [^{3}H]-BQ123 (3.2 nM, Ihara *et al*., 1995), [^{125}I]-PD164333(0.2 nM, Davenport *et al*., 1998), [^{125}I]-PD151242 (0.5 nM, Davenport *et al*., 1994)	[^{125}I]-IRL1620 (20 pM, Watakabe *et al*., 1992), [^{125}I]-BQ3020 (0.1 nM, Molenaar *et al*., 1992), [^{125}I]-[$Ala^{1,3,11,15}$]ET-1 (0.2 nM, Molenaar *et al*., 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-methoxycarboyl-D-norleucine; **FR139317,** (*r*)2-([*r*-2-{(*s*)-2-([1-{hexahydro-1*H*-azepinyl}carbonyl]amino)methyl}pentanoyl]amino-3-(3-[methyl-1*H*-indodyl])propionylamino-3-(2-pyridyl))propionate; **IRL1620,** Suc[Glu^9,$Ala^{11,15}$]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-hydroxy-phenyl)-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)-benzenesulfonamide; **S0139,** 27-*O*-3-(2-[3-carboxyacryloylamino]-5-hydroxyphenyl)-acryloyloxymyricone, sodium salt; **SB209670,** (+)-1*s*,2*r*,*s*-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-prop-1-yloxyindane-2-carboxylate; **SB234551,** (*e*)-α-([1-butyl-5-{2-([2-carboxyphenyl]methoxy)-4-methoxyphenyl}-1*H*-pyrazol-4-yl]methylene)-6-methoxy-1,3-benzodioxole-5-propanoic acid; **TAK044,** *cyc*(D-Asp-Asp(Php)-Asp-D-Thg-Leu-D-Trp)-4-oxobut-2-enoate

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$GABA_B$

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 heterodimerization of two similar 7TM 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 non-functional. Co-expression of $GABA_{B1}$ and $GABA_{B2}$ subunits allows transport of $GABA_{B1}$ to the cell surface and generates a functional receptor that can couple to signal transduction pathways such as high-voltage-activated Ca^{2+} channels ($Ca_v2.1$, $Ca_v2.2$), or inwardly rectifying potassium channels (Kir3) (Marshall *et al*., 1999; Bowery & Enna, 2000; Couve *et al*., 2000; Bowery *et al*., 2002; Bettler *et al*., 2004). 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), but other domains of the proteins may also contribute to their heteromerization (Bettler *et al*., 2004). Four human isoforms of the human $GABA_{B1}$ subunit have been cloned. The predominant $GABA_{B1(a)}$ and $GABA_{B1(b)}$ isoforms differ in their extracellular domain (ECD) sequences as a result of the use of alternative transcription initiation sites. Isoforms generated by alternative splicing are $GABA_{B1(c)}$ that differs in the ECD, and $GABA_{B1(e)}$, which is a truncated protein that can heterodimerize with the $GABA_{B2}$ subunit but does not constitute a functional receptor (Schwarz *et al*., 2000). Only the 1a and 1b variants are identified as components of native receptors (Bowery *et al*., 2002). Additional $GABA_{B1}$ subunit isoforms have been described in rodents (reviewed by Bettler *et al*., 2004).

Nomenclature	**$GABA_B$**
Ensembl ID	$GABA_{B1}$ ENSG00000168760; $GABA_{B2}$ ENSG00000136928
Principal transduction	$G_{i/o}$
Selective agonists	3-APPA (CGP27492, 5 nM), 3-APMPA (CGP35024, 16 nM), (*R*)-(−)-baclofen (32 nM), CGP44532 (45 nM)
Selective antagonists	CGP62349 (2.0 nM), CGP55845 (6 nM), SCH50911 (3 μM), 2-hydroxy-S-(−)-saclofen (11 μM), CGP35348 (27 μM)
Radioligands	[^{3}H]-(*R*)-(−)-baclofen, [^{3}H]-CGP54626 (1.5 nM; Bittiger *et al*., 1992), [^{3}H]-CGP62349 (0.9 nM, Kier *et al*., 1999), [^{125}I]-CGP64213 (1 nM, Galvez *et al*., 2000), [^{125}I]-CGP71872 ($K_i = 0.5$ nM, Belley *et al*., 1999)

Potencies of agonists and antagonists listed in the table, quantified as IC_{50} values for the inhibition of [^{3}H]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). In addition to the ligands listed in the table, Ca^{2+} binds to a site on the $GABA_{B1}$ subunit to act as a positive allosteric modulator of GABA. Synthetic positive allosteric modulators with little, or no, intrinsic activity include CGP7930 and GS39783 (reviewed by Bettler *et al*., 2004). Their site of action appears to be on the heptahelical domain of the $GABA_{B2}$ subunit (Pin *et al*., 2004).

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-dichlorphenyl)-ethyl]amino-2(*S*)-hydroxypropyl-(P-benzyl)-phosphinic acid; **CGP62349**, [3-[1-*R*-[[3-(methoxyphenylmethyl)hydroxyphosphinyl]-2(5)-hydroxypropyl]amino]ethyl]-benzoic acid; **CGP64213**, [3-[-(*R*)-[[3-5*N*-[1-[2-[[3-iodo-4-hydroxyphenyl]ethyl]carboxamido]pentyl]hydroxyphosphinyl]-2(*S*)-hydroxy-propyl]amino]ethyl-benzoic acid; **CGP71872**, 3-(1-(*R*)-(3-((5-(4-azido-2-hydroxy-5-iodobenzoylamino)pentyl)hydroxyphosphoryl)-2-(*S*)-hydroxypropylamino)ethyl)benzoic acid; **CGP7930**, 2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol; **GS39783**, *N*,*N*′-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine; **SCH90511**, (+)-(2*S*)-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 non-amidated 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 *et al*., 1999)	GALP > galanin (Ohtaki *et al*., 1999)	—
Selective agonists	—	Galanin-(2–29) (Fathi *et al*., 1997; Wang *et al*., 1997), D-Trp^2-galanin-(1–29) (Smith *et al*., 1997)	—
Selective antagonists	2,3-Dihydro-dithiin and -dithiepine-1,1,4,4-tetroxides (Scott *et al*., 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. [^{125}I]-[Tyr^{26}]galanin binds to all three subtypes with K_d values ranging from 0.05–1 nM, Skofitsch *et al*., 1986; Smith *et al*., 1997; Wang *et al*., 1997; Fitzgerald *et al*., 1998; Smith *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; Fitzgerald *et al*., 1998; Smith *et al*., 1998).

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

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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 2 amino acids (Matsumoto *et al*., 2001). Alternative splicing results in the formation of a second peptide, des–Gln^{14}-ghrelin with equipotent biological activity (Hosoda *et al*., 2000). A unique post-translational modification (octanoylation of Ser^{3}) occurs in both peptides, essential for full activity in binding to GHS-R in hypothalamus and pituitary and the release of growth hormone 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 *et al*., 2001; Bedendi *et al*., 2003)
Radioligands	[^{125}I-His^{9}]-ghrelin (0.4 nM, Katugampola *et al*., 2001), [^{125}I-Tyr^{4}]-ghrelin (0.5 nM, Bedendi *et al*., 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 (ENSG00000070031). 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	ENSG00000065325	ENSG00000106128	ENSG00000080293
Principal transduction	G_s	G_s	G_s	G_s	G_s
Selective agonists	Glucagon	GLP-1-(7–37) (Dillon *et al*., 1993); GLP-1-(7–36)amide (Thorens *et al*., 1993), exendin-3 (Raufman *et al*., 1991), exendin-4 (Thorens *et al*., 1993)	GLP-2	BIM28011 (Coy *et al*., 1996)	Secretin
Selective antagonists	L168049 (Cascieri *et al*., 1999); des-His^{1}-[Glu^{9}]glucagon amide (Post *et al*., 1993), BAY27-9955 (Petersen & Sullivan, 2001); NNC92-1687 (Madsen *et al*., 1998)	Exendin-(9–39) (Thorens *et al*., 1993); T-0632 (Tibaduiza *et al*., 2001)	—	JV-1–36 (Schally & Varga, 1999), JV-1–38 (Schally & Varga, 1999)	[$(CH_2NH)^{4,5}$]secretin (Kim *et al*., 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-diiospropyl-2-(1-hydroxyethyl)-6-propyl-4′-fluoro-1,1′-biphenyl; **BIM28011**, [D-Ala^{2},Ala^{8,9,15,27},D-Arg^{29}]hGHRH-(1–29)NH_2; **JV-1-36,** [PhAc-Tyr^{1},D-Arg^{2},Phe(4-Cl)^{6},Arg^{9},Abu^{15},Nle^{27},D-Arg^{28},Har^{29}]hGHRH(1–29)NH_2**; JV-1-38,** [PhAc-Tyr^{1},D-Arg^{2},Phe(4-Cl)^{6},Har^{9},Tyr(Me)^{10},Abu^{15},Nle^{27},D-Arg^{28},Har^{29}]hGHRH(1–29)NH_2; **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 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 ($mGlu_1$ and $mGlu_5$); Group II ($mGlu_2$ and $mGlu_3$); and Group III ($mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$) (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 1*S*,3*R*-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 $mGlu_2$ and $mGlu_3$ at low nanomolar concentrations, $mGlu_8$ at high nanomolar concentrations, and $mGlu_1$, $mGlu_4$, $mGlu_5$ and $mGlu_7$ 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 *et al*., 1995)	LY389795 (Monn *et al*., 1999), LY379268 (Monn *et al*., 1999), LY354740 (Schoepp *et al*., 1997; Wu *et al*., 1998), DCG-IV, 2*R*,4*R*-APDC (Schoepp *et al*., 1996)	LY389795 (Monn *et al*., 1999), LY379268 (Monn *et al*., 1999), LY354740 (Schoepp *et al*., 1997; Wu *et al*., 1998), DCG-IV, NAAG (Wroblewska *et al*., 1997), 2*R*,4*R*- APDC (Schoepp *et al*., 1996)	L-AP4, LSOP (Wu *et al*., 1998), (*RS*)PPG (Gasparini *et al*., 1999a)
Selective antagonists	AIDA (4.2, Moroni *et al*., 1997), (*S*)-(+)-CBPG (Mannaioni *et al*., 1999), CPCCOEt (Litschig *et al*., 1999), LY367385 (Clark *et al*., 1997), LY393675 (Baker *et al*., 1998)	LY341495 (Kingston *et al*., 1998), PCCG-4 (Pellicciari *et al*., 1996), EGLU (4.3, Jane *et al*., 1996), LY307452 (Escribano *et al*., 1998; Wermuth *et al*., 1996)	LY341495 (Kingston *et al*., 1998), EGLU (4.3, Jane *et al*., 1996), LY307452 (Escribano *et al*., 1998; Wermuth *et al*., 1996)	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 *et al*., 1997), DHPG, 3HPG (Brabet *et al*., 1995), (*S*)-(+)-CBPG (Mannaioni *et al*., 1999)	homo-AMPA (Bräuner-Osborne *et al*., 1996), 1-benzyl-APDC (Tuckmantel *et al*., 1997), (*RS*)PPG (Gasparini *et al*., 1999a)	LSOP (Wu *et al*., 1998), L-AP4, (*RS*)PPG (Gasparini *et al*., 1999a)	LSOP (Wu *et al*., 1998), L-AP4, (*RS*)PPG (Gasparini *et al*., 1999a), (*S*)-3,4-DCPG (Thomas *et al*., 2001)
Selective antagonists	SIB1757 (Varney *et al*., 1999), SIB1893 (Varney *et al*., 1999), MPEP (Gasparini *et al*., 1999b), 4CPG, LY393675 (Baker *et al*., 1998)	MAP4, THPG (Thoreson *et al*., 1997)	—	MPPG (Wu *et al*., 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 $mGlu_1$ but is an agonist (albeit of reduced efficacy) at $mGlu_5$ 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-methylhomoibotenic 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: **1*S*,3*R*-ACPD,** 1-aminocyclopentane-1*S*,3*R*-dicarboxylate; **AIDA,** 1-aminoindan-1,5(*RS*)-dicarboxylic acid; also known as UPF523; **L-AP4,** *S*-2-amino-4-phosphonobutyrate; **2*R*,4*R*-APDC,** aminopyrrolidine-2*R*,4*R*-dicarboxylate; also known as LY314593; **(*S*)-(+)-CBPG,** (*S*)-(1)-2-(39-carboxybicyclo[1.1.1]-pentyl)glycine; **L-CCG-I,** (2*S*,3*S*,4*S*)α-(carboxycyclopropyl)glycine; **CPCCOEt,** cyclopropan[*b*]chromen-1*a*-carboxylate; **4CPG,** 4-carboxyphenylglycine; **DCG-IV,** (2*S*,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,** 2*S*,4*S*-2-amino-4-(4,4-diphenylbut-1-yl)pentan-1,5-dioc acid; **LY341495,** 2*S*-2-amino-2-(1*S*,2*S*-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl)propanoic acid; **LY354740,** (+)-2-aminobicyclic[3.1.0]hexane-2,6-dicarboxylate; **LY367385,** (+)-2-methyl-4-carboxyphenylglycine; **LY379268,** (−)-2-oxa-4-aminobicylco[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,** (2*S*,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 FSH (follitropin, follicle-stimulating hormone, 129 aa, ENSG00000131808), LH (lutropin, luteinizing hormone, 141 aa ENSG00000104826), CG (choriogonadotropin, chorionic gonadotropin, 165 aa ENSG00000104818/ENSG00000104827) or TSH (thyrotropin, thyroid-stimulating hormone, 138 aa ENSG00000134200). There is binding cross-reactivity across the endogenous agonists for each of the glycoprotein hormone receptors. The deglycosylated hormones appear to exhibit reduced efficacy at these receptors (Sairam, 1989).

Nomenclature	**FSH**	**LH**	**TSH**
Ensembl ID	ENSG00000170820	ENSG00000168546	ENSG00000146013
Principal transduction	G_s	G_s, $G_{q/11}$ and G_i	All four families of G proteins can be activated by this receptor
Selective agonists	FSH	LH, CG	TSH
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 Grave's disease (see Rapoport *et al*., 1998). Gain- and loss-of-function mutations of the FSH receptor are associated with human reproductive disorders (Aittomaki *et al*., 1995; Gromoll *et al*., 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 (Sunthornthepvarakul *et al*., 1995). The rat FSH receptor also stimulates phosphoinositide turnover through an unidentified G protein (Quintana *et al*., 1994).

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Gonadotrophin-releasing Hormone (GnRH)

Overview: Gonadotropin-releasing hormone (GnRH) is a hypothalamic decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pr-Gly-NH_2, 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-Plo-Gly-NH_2, also known as chicken GnRH-II, ENSG00000180290) and GnRH III (pGlu-His-Trp-Ser-His-Asp-Trp-Lys-Pro-Gly-NH_2 also known as lamprey GnRH III). Receptors for all three ligands exist in amphibians but only GnRH I and GnRH II and their cognate receptors (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 non peptide 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, N^{α}-methylhistaprodifen	Dimaprit, impromidine, amthamine	*R*-α-Methylhistamine, imetit, immepip	Clobenpropit
Selective antagonists	Triprolidine (9.9, Smit *et al*., 1996), mepyramine (9.1, Smit *et al*., 1996)	Tiotidine (7.8, Leurs *et al*., 1994), ranitidine (7.1, Leurs *et al*., 1994)	Clobenpropit (9.9), iodophenpropit (9.6), thioperamide (8.4)	JNJ 7777120 (8.1, Jablonowski *et al*., 2003)
Radioligands	[^{3}H]-Mepyramine (1 nM)	[^{3}H]-Tiotidine (15 nM), [^{125}I]-iodoaminopotentidine (0.3 nM)	[^{3}H]-*R*-α-Methylhistamine (0.5 nM), [^{3}H]-N^{α}-methylhistamine (2 nM), [^{125}I]-iodophenpropit (0.6 nM), [^{125}I]-iodoproxyfan (0.06 nM)	—

Histaprodifen and N^{α}-methylhistaprodifen are reduced efficacy agonists. Impromidine is also an H_3 receptor antagonist. The H_4 receptor appears to exhibit broadly similar pharmacology to the H_3 receptor, although *R*-α-methylhistamine and *N*-α-methylhistamine are less potent, while clobenpropit acts as a reduced efficacy agonist (Nakamura *et al*., 2000; Oda *et al*., 2000; Liu *et al*., 2001; Nguyen *et al*., 2001; Zhu *et al*., 2001). [^{3}H]-Histamine has been used to label the H_4 receptor in heterologous expression systems.

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5-HT (5-Hydroxytryptamine)

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-HT_3 class, 7TM receptors where the endogenous agonist is 5-HT. The diversity of 5-HT receptors is increased by alternative splicing that produces isoforms of the 5-HT_{2A} (non-functional), 5-HT_{2C} (non-functional), 5-HT_4 and 5-HT_7 receptors. RNA editing produces 5-HT_{2C} receptor isoforms that differ in function, such as efficiency and specificity of coupling to $G_{q/11}$ (reviewed by Sanders-Bush *et al*., 2003).

Nomenclature	**5-HT_{1A}**	**5-HT_{1B}**	**5-HT_{1D}**	**5-ht_{1E}**
Other names	—	5-HT1Dβ	5-HT_{1Dz}	—
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, (*R*)-UH301, U92016A	Sumatriptan, L694247	PNU10929, sumatriptan, L694247	—
Selective antagonists	(±)WAY100635 (8.7), (*S*)-UH301, NAD299 (robalzotan)	SB236057 (8.9), SB224289 (8.5), GR55562 (7.4)	BRL15572 (7.9)	—
Radioligands	[^{3}H]-WAY100635 (0.3 nM, Khawaja *et al*., 1997), [^{3}H]-8-OH-DPAT (0.8 nM, Albert *et al*., 1990)	[^{3}H]-sumatriptan, [^{125}I]-GTI, [^{3}H]-GR125743 (2.6 nM, Xie *et al*., 1999), [^{3}H]-L694247	[^{3}H]-sumatriptan, [^{125}I]-GTI, [^{3}H]-GR125743 (2.8 nM, Xie *et al*., 1999) [^{3}H]-L694247	[^{3}H]-5-HT

Nomenclature	**5-ht_{1F}**	**5-HT_{2A}**	**5-HT_{2B}**	**5-HT_{2C}**
Other names	5-$HT_{1E\beta}$, 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 *et al*., 1995), [^{3}H]-RP62203 (fananserin, 0.13 nM, Malgouris *et al*.,1993)	[^{3}H]-5-HT	[^{3}H]-mesulergine (0.67 nM, Bonhaus *et al*., 1995), [^{3}H]-LSD

Nomenclature	**5-HT_4**	**5-ht_{5A}**	**5-ht_{5B}**	**5-ht_6**
Other names	—	5-HT_{5z}	—	—
Ensemble ID ENSG00000158748	ENSG00000164270	ENSG00000157219		ENSMUSG00000050534
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 *et al*., 1995), [^{125}I]-SB207710 (86 pM, Brown *et al*., 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 *et al*., 2000), [^{3}H]-Ro630563 (5 nM, Boess *et al*., 1998), [^{3}H]-5-CT, [^{125}I]-LSD

Nomenclature	**5-HT_7**
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 *et al*., 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 non-rodent form of the receptor was previously called 5-$HT_{1D\beta}$: The human 5-HT_{1B} receptor (tabulated) displays a different pharmacology to 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. Fananserin binds with high affinity to dopamine D4, in addition to 5-HT_{2A} receptors. The human 5-ht_{5A} receptor has recently been claimed to couple to several signal transduction pathways when stably expressed in C6 glioma cells (Noda *et al*., 2003). The human orthologue of the mouse 5-ht_{5B} receptor is non-functional due to interruption of the gene by stop codons. In addition to the receptors listed in the table, an 'orphan' receptor, unofficially termed 5-HT1P, has been described (Gershon, 1999).

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; **GR55562**, 3-[3-(dimethylamino)propyl]-4-hydroxy-*N*-[4-(4-pyridinyl)phenyl]benzamide; **GR113808**, [1-2[(methylsuphonyl)amino]ethyl]-4-piperidinyl]methyl-1-methyl-1*H*-indole-3-carboxylate; **GR125743**, *n*-[4-methoxy-3-(4-methyl-1-piperizinyl)phenyl]-3-methyl-4-(4-pyrindinyl)benzamide; **GTI**, 5-hydroxytryptamine-5-*O*-carboxymethylglycyltyrosinamide; **L694247**, 2-[5-[3-(4-methylsulphonylamino)benzyl-1,2,4-oxadiazol-5-yl]-1*H*-indol-3yl] ethanamine; **LY334370**, 5-(4-flurobenzoyl)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-[6-3H]-3,4-dihydro-2H-1-benzo pyran-5-carboxamide; **NAS181,** (*R*)-(+)-2-[[[3-(morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl] morpholine methane sulfonate; **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-fluroindol-1-yl)-1-methyethylamine; **Ro630563**, 4-amino-*N*-[2,6-bis(methylamino)pyridin-4-yl]benzenesulphonamide; **RS127445**, (2-amino-4-(4-fluoronaphthyl-1-yl)-6-isopropylpyrimidine); **RS57639**, 4-amino-5-chloro-2-methoxy benzoic acid 1-(3-[2,3-dihydrobenzo[1,4]dioxin-6yl)-propyl]-piperidin-4yl methyl ester; **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; **SB204070**, 1-butyl-4-piperidinylmethyl-8-amino-7-chloro-1-4-benzoioxan-5-carboxylate; **SB207710**, 1-butyl-4-piperidinylmethyl-8-amino-7-iodo-1,4-benzodioxan-5-carboxylate; **SB224289**,1′-methyl-5[[2′-methyl-4′-)5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl-2,3,6,7-tetrahydrospiro[furo[2,3-*f*]indole-3,4′-piperidine]oxalate; **SB236057**,1′-ethyl-5-(2′-methyl-4′-(5-methyl-1,3,4-oxadiazol-2-yl)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro[furo[2,3-f]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-(2-(4-methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulphonyl)phenol; **SB357134**, *N*-(2,5-dibromo-3-flurophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulphonamide; **SB656104**, 6-((*R*)-2-[2-[4-(4-Chloro-phenoxy)-piperidin-1-yl]-ethyl]-pyrrolidine-1-sulphonyl)-1*H*-indole hydrochloride; **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; **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 Subcommittee on Leukotriene and Lipoxin Receptors, Brink *et al*., 2003) are activated by the endogenous ligands leukotriene (LT) B_4, LTC_4, LTD_4, LTE_4, 12*R*-HETE and 12*S*-HETE. Leukotrienes bind extensively to enzymes in their metabolic pathways (glutathione-*S*-transferase/LTC_4 synthase, γ-glutamyltranspeptidase and several aminopeptidases) and can also bind to peroxisome proliferator activated receptor α (PPARα, Lin *et al*., 1999) and the ALX lipoxin receptor (Fiore *et al*., 1994), complicating the interpretation of radioligand binding and functional studies (e.g. LTC_4 is rapidly converted in many systems to LTD_4). Metabolic inhibitors (e.g. serine-borate complex) reduce this problem but can also have non-specific effects.

Nomenclature	**BLT_1**	**BLT_2**	**$CysLT_1$**	**$CysLT_2$**
Other names	LTB_4	—	HG55, HMTMF81, LTD_4	HPN321, LTC_4
Ensembl ID	ENSG00000116329	ENSG00000082556	ENSG00000112038	ENSG00000125510
Principal transduction	$G_{q/11}$, $G_{i/o}$	$G_{q/11}$, $G_{i/o}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	LTB_4 > 20-hydroxy-LTB_4 ≫ 12*R*-HETE (Yokomizo *et al*., 2001)	LTB_4 > 12*S*-HETE = 12*S*-HPETE > 15*S*-HETE > 12*R*-HETE = 15*S*-HETE > 20-hydroxy-LTB_4 (Yokomizo *et al*., 2001)	LTD_4 > LTC_4 > LTE_4 (Sarau *et al*., 1999)	LTC_4 = LTD_4 ≫ LTE_4 (Nothacker *et al*., 2000)
Selective agonists	—	12*S*-HETE	—	BAYu9773
Selective antagonists	CP105696 (pIC_{50} 7.2), U75302 (pIC_{50} 6.9)	LY255283 (pIC_{50} 6.0)	Zafirlukast (9.5), montelukast (9.3), SR2640 (8.7), pobilukast (8.6), sulukast (8.3)	—
Radioligands	[^{3}H]-LTB_4 (0.2–0.7 nM), [^{3}H]-CGS23131 (13 nM)	[^{3}H]-LTB_4 (0.2–23 nM)	[^{3}H]-LTD_4, [^{3}H]-ICI198615	[^{3}H]-LTD_4

BAYu9773 is an antagonist at $CysLT_1$ (6.8–7.7) and a reduced efficacy agonist at $CysLT_2$ receptors.

Abbreviations: 12*R*-HETE, 12(*R*)-hydroxyeicosa-5*Z*,8*Z*,10*E*,14*Z*-tetraenoic acid; **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; **CP105696,** (+)-1-(3S,4R)-[3-(4-phenylbenzyl)-4-hydroxy-chroman-7-yl]cyclopentane carboxylic acid; **ICI198615,** (1-[2-methoxy-4-{([phenylsulfonylamino]carbonyl)phenyl}methyl]-1*H*-indazol-6-yl)carbamic acid cyclopentyl ester; **LY255283,** 1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)-heptyl]-oxy]-phenyl]-ethanone; **SR2640,** 2-(3-[2-quinolylmethoxy]phenylamino)benzoic acid; **U75302,** 6-(6-(3-hydroxy-1E,5Z-undecadien-1-yl)-2-pyridinyl)-1,5-hexanediol

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Lipoxin

Overview: Lipoxin A_4 receptors (ALX, nomenclature agreed by NC-IUPHAR Subcommittee on Leukotriene and Lipoxin Receptors, Brink *et al*., 2003) are activated by the endogenous lipid-derived, anti-inflammatory ligands lipoxin A_4 (LXA_4) and 15-epi-LXA_4 (aspirin-triggered lipoxin A_4, ATL). The ALX receptor also interacts with endogenous peptide and protein ligands, such as MHC binding peptide (Chiang *et al*., 2000) as well as annexin-1 (ANXA1) and its *N*-terminal peptides (Perretti *et al*., 2002). 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). Furthermore, ALX has been suggested to act as a receptor mediating pro-inflammatory actions of the acute-phase reactant, serum amyloid A (Sodin-Semrl *et al*., 2004).

Nomenclature	**ALX**
Other names	FPRL1, FPR2, FPRH2, RFP
Ensembl ID	ENSG00000171049
Principal transduction	G_i, G_q (Maddox *et al*., 1997)
Rank order of potency	$LXA_4 = ATL = ATLa2 > LTC_4 = LTD_4 \gg 15\text{-deoxy-}LXA_4 \gg$ fMLP (Clish *et al*., 1999; Fiore *et al*., 1994; Fiore & Serhan, 1995; Gronert *et al*., 2001; Takano *et al*., 1997)
Selective agonists	LXA_4, ATL, ATLa2 (Guilford *et al*., 2004)
Radioligands	[^{3}H]-LXA_4 (0.2–1.7 nM, Fiore *et al*., 1994; Takano *et al*., 1997)

A receptor selective for LXB_4 has been suggested from functional studies (Maddox & Serhan, 1996; Romano *et al*., 1996; Ariel *et al*., 2003).

Abbreviations: ATL, aspirin-triggered lipoxin A_4 (15-epi-LXA_4); **ATLa2**, 15-epi-16-(para-fluoro)-phenoxy-LXA_4

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Lysophosphatidic acid

Overview: Lysophosphatidic acid (LPA) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Lysophospholipid receptors, Chun *et al*., 2002) are activated by the endogenous lipid derivative LPA. The identified receptors can account for most, although not all, LPA-induced phenomena in the literature, indicating that a majority of LPA-dependent phenomena are receptor-mediated. Radioligand binding has been conducted in heterologous expression systems using [^{3}H]-LPA (e.g. Fukushima *et al*., 1998). In native systems, analysis of binding data is complicated by metabolism and high levels of non-specific 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.

Nomenclature	**LPA_1**	**LPA_2**	**LPA_3**	**LPA_4**
Other names	VZG-1, Edg2, lp_{A1}	Edg4, lp_{A2}	Edg7, lp_{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_s	$G_{q/11}$, G_s (Noguchi *et al*., 2003)
Selective agonists	—	FAP10, FAP12 (Virag *et al*., 2003)	—	—
Selective antagonists	Ki16425 (Ohta *et al*., 2003)	—	DGPP 8:0 (Ohta *et al*., 2003)	—

FAP12 has antagonist activity at LPA_1 and LPA_3 receptors (Virag *et al*., 2003). The selectivity of these antagonists is less than two orders of magnitude: the recently identified LPA_4 is undergoing further characterization.

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

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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 non-functional pseudogene in rodents (Tan *et al*., 2002).

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

Abbreviations: S36057, 3-iodo-tyr-(8-amino-3,6-dioxyoctanoyl)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 $\geqslant$ ACTH, γ-MSH	ACTH	γ-MSH, β-MSH $\geqslant$ ACTH, α-MSH	β-MSH $\geqslant$ α-MSH, ACTH > γ-MSH	α-MSH $\geqslant$ β-MSH $\geqslant$ ACTH > γ-MSH
Selective agonists	—	—	D-Trp^8-γMSH (Grieco *et al*., 2000)	THIQ (Van der Ploeg *et al*., 2002)	—
Selective antagonists	—	—	—	HS014 (8.5, Schiöth *et al*., 1998), MBP10 (Bednarek *et al*., 2001)	—
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 MC_1 receptor have been linked to variations in skin pigmentation. Defects of the MC_2 receptor underlie familial glucocorticoid deficiency. Polymorphisms of the MC_4 and MC_5 receptors have been linked to obesity (Chagnon *et al*., 1997).

Abbreviations: **HS014,** *cyc*(*S*–*S*)-(Ac-Cys^{11},D-Nal^{14},Cys^{18},Asp-NH$_2$)β-MSH-(11 – 22); **MBP10**, cyclo(6β- > 10ε)(succinyl(6)-D-(2′)Nal^7-Arg^8-Trp^9-Lys^{10})-NH$_2$; **NDP-MSH,** [Nle^4,D-Phe^7]α-MSH; **SHU9119,** Ac-Nle-Asp-His-D-Nal^2-Arg-Trp-Lys-NH$_2$; **THIQ**, *N*-([3R]-1,2,3,4-tetrahydroisoquinolinium-3-ylcarbonyl)-(1R)-1-(4-chlorobenzyl)-2-(4-cyclohexyl-4-[1*H*-1,2,4-triazol-1ylmethyl]piperidin-1-yl)-2-oxoethylamine

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Melatonin

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

Nomenclature	**MT_1**	**MT_2**	***MT_3***
Other names	MEL_{1A}, ML_{1A}, Mel_{1a}	MEL_{1B}, ML_{1B}, Mel_{1b}	ML_2
Ensembl ID	ENSG00000168412	ENSG00000134640	—
Principal transduction	$G_{i/o}$	$G_{i/o}$	—
Selective agonists	—	IIK7 (Sugden *et al*., 1999)	*N*-acetylserotonin (Eison & Mullins, 1993; Lucchelli *et al*., 1997; Molinari *et al*., 1996; Popova & Dubocovich, 1995), 5MCA-NAT (Popova & Dubocovich, 1995)
Selective antagonists	—	K185 (9.3, Sugden *et al*., 1999), 4P-PDOT (8.8, Dubocovich *et al*., 1997; Dubocovich *et al*., 1998), DH97 (8.0, Teh & Sugden, 1998)	Prazosin (Lucchelli *et al*., 1997)
Radioligands	[^{3}H]-melatonin (Browning *et al*., 2000), 2-iodo-[^{125}I]-melatonin	[^{3}H]-melatonin (Browning *et al*., 2000), 2-iodo-[^{125}I]-melatonin	2-iodo-[^{125}I]-5MCA-NAT (Molinari *et al*., 1996), 2-iodo-[^{125}I]-melatonin

Melatonin, 2-iodo-melatonin, S20098 and GR196429 are nonselective agonists for MT_1 and MT_2 receptors. (−)-AMMTC displays an ∼400-fold greater agonist potency than (+)-AMMTC at rat MT_1 receptors (Ting *et al*., 1999). Luzindole is a non-selective melatonin receptor antagonist with some selectivity for the MT_2 receptor (Dubocovich *et al*., 1998). The *MT_3* binding site of hamster kidney was identified as the hamster homologue of the human quinone reductase 2 (ENSG00000124588, Nosjean *et al*., 2000; Nosjean *et al*., 2001). Pharmacological investigations of *MT_3* binding sites have primarily been conducted in hamster and guinea-pig tissues. A suggested physiological function of the *MT_3* 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. MT_1/MT_2 heterodimers present different pharmacological profiles from MT_1 and MT_2 receptors (Ayoub *et al*., 2004).

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; **IIK7,** *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 Subcommittee 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 non-functional gene (Gregor *et al*., 1996). Many of the agonists exhibit differing degrees of selectivity dependent on the species examined. For example, the relative potency of PP is greater at the rat Y_4 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. [^{125}I]-PYY or [^{125}I]-NPY can be used to label Y_1, Y_2, Y_5 and y_6 subtypes non-selectively.

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 *et al*., 1998), BIBP3226 (8.2, Gerald *et al*., 1996)	BIIE0246 (8.5, Doods *et al*., 1999)	—	CGP71683A (9.0, Criscione *et al*., 1998)	—
Radioligands	[^{125}I]-[Leu^{31},Pro^{34}] NPY, [^{3}H]-BIBP3226 (2.1 nM)	[^{125}I]-PYY_{3-36}	[^{125}I]-PP	—	—

The Y_1 agonists indicated are selective relative to Y_2 receptors. BIBP3226 is selective relative to Y_2, Y_4 and Y_5 receptors (Gerald *et al*., 1996). NPY-(13–36) is Y_2 selective relative to Y_1 and Y_5 receptors. PYY-(3–36) is Y_2 and Y_4 selective relative to Y_1 receptors.

Abbreviations: BIBO3304, (*R*)-*N*-([4-{aminocarbonylaminomethyl}-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). [^{3}H]-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 *et al*., 1997)	Neurotensin = neuromedin N (Mazella *et al*., 1996)
Selective agonists	JMV449 (Souaze *et al*., 1997)	Levocobastine (Mazella *et al*., 1996)
Selective antagonists	SR48692 (7.5–8.2, Gully *et al*., 1997)	—
Radioligands	[^{3}H]-SR48692 (3.4 nM, Labbe-Jullie *et al*., 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 it's degradation (Nielsen *et al*., 1999). It has been reported to interact with the NTS1 receptor (Martin *et al*., 2002) and has been implicated in hormone trafficking and/or neurotensin uptake.

Abbreviations: JMV449, *H*-LysΨ(CH_2NH)-Lys-Pro-Tyr-Ile-Leu; **SR142948A,** 2-([5-{2,6-dimethoxyphenyl}-1-{4-(*N*-[3-dimethylaminopropyl]-*N*-methylcarbamoyl)-2-isopropylphenyl}-1*H*-pyrazole-3-carbonyl]amino)adamantane-2-carboxylic acid hydrochloride; **SR48692,** 2-([1-{7-chloro-4-quinolinyl}-5-{2,6-dimethoxyphenyl}-pyrazol-3-yl]carboxylamino)tricyclo(3.3.1.1.[3.7])decan-2-carboxylic acid

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Opioid and opioid-like

Overview: Opioid and opioid-like receptors are activated by the endogenous peptides [Met]enkephalin (met), [Leu]enkephalin (leu), β-endorphin (β-end), α-neo-dynorphin, dynorphin A (dynA), dynorphin B (dynB), 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	DADL (Befort *et al*., 1996), DPDPE (Delay-Goyet *et al*., 1988), DSLET (Delay-Goyet *et al*., 1988), DSBULET (Delay-Goyet *et al*., 1988), [DAla^2]deltorphin I or II (Befort *et al*., 1996)	Bremazocine (Evans *et al*., 2000), U69593 (Emmerson *et al*., 1994), CI977 (Hjorth *et al*., 1996), ICI197067 (Wang *et al*., 1993)	Endomorphin-1 and -2 (Zadina *et al*., 1997), morphine (Goldberg *et al*., 1998), DAMGO (Zadina *et al*., 1997), sufentanil (Yeadon & Kitchen, 1988), PL017 (Costa *et al*., 1992)	N/OFQ, N/OFQ-(1–13)-NH_2 (Guerrini *et al*., 1997), Ro646198 (Jenck *et al*., 2000)
Selective antagonists	Naltrindole (9.6, Kim *et al*., 2001), NNDT (9.4), naltriben (8.9, Kim *et al*., 2001), TIPP-psi (8.5, Martin *et al*., 2002)	Nor-binaltorphine (Heyliger *et al*., 1999)	Naloxone (Romero *et al*., 1999), CTOP (Hawkins *et al*., 1989)	J113397 (pIC_{50} = 8.3, Kawamoto *et al*., 1999), [Nphe^1]N/OFQ-(1–13)-NH_2 (6.2, Calo *et al*., 2000)
Radioligands	[^{3}H]-diprenorphine (0.6 nM, Befort *et al*., 1996), [^{3}H]-DPDPE (2.7 nM, Kim *et al*., 2001), [^{3}H]-TIPP-psi (Nevin *et al*., 1995), [^{3}H]-naltrindole (Bot *et al*., 1997), [^{3}H]-deltorphin II (Gomes *et al*., 2000)	[^{3}H]-U69593 (0.75 nM, Izenwasser *et al*., 1999), [^{3}H]-CI977 (0.29 nM, Simonin *et al*., 2001)	[^{3}H]-DAMGO (2.8 nM, Gomes *et al*., 2000), [^{3}H]-PL017 (Hawkins *et al*., 1987)	[^{3}H]-N/OFQ (5 nM, Dooley & Houghten, 1996), [^{3}H]-Leu-N/OFQ, [^{125}I]-Tyr^{14}-N/OFQ

The existence of μ1 and μ2 opioid receptor subtypes has been proposed; μ1 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-benzylidine-7-dehydronaltrexone are selective for δ1 sites; [dAla^2]deltorphin II and the antagonist, naltriben, are selective for δ2 sites. Subtypes of the κ receptor have also been proposed. Arylacetamides (e.g. U69593) bind to a subset of sites labelled by ethylketocyclazocine (κ1). κ2 sites have moderate affinity for ethylketocyclazocine and bremazocine; under κ-selective conditions, naloxone benzoylhydrazone labels a population of distinct sites (κ3). It has been suggested that κ2 sites result from a heterodimer of κ and δ receptors (Jordan & Devi, 1999). The cloned μ, δ and κ receptors correspond to the μ1, δ2 and κ1 subtypes. A distinct met-enkephalin receptor lacking structural resemblence 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*)-(5α,7α,8β)-(−)-*N*-methyl-*N*-(7-[1-pyrrolidinyl]-1-oxaspiro[4,5]dec-8-yl)-4-benzofuranacetamide monohydrochloride; **CTOP,** DPhe-*cyc*[Cys-Tyr-DTrp-Lys-Thr-Pen]-The-NH_2; **DAMGO,** Tyr-DAla-Gly-[*N*MePhe]-NH$(CH_2)_2$; **DPDPE,** *cyc*[DPen^2,DPen^5]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*$(CH_3)_2$-(2′,6′-CH_3)-Tyr-Tic; **PL017,** [*N*-MePhe^3,DPro^4]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,** 5α,7α,8β-(−)-*N*-methyl-*N*-(7-[1-pyrrolidinyl]-1-oxasipro(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 [^{125}I]-orexin A (Holmqvist *et al*., 2001).

Nomenclature	**OX_1**	**OX_2**
Other names	Hypocretin receptor type 1	Hypocretin receptor type 2
Ensembl ID	ENSG00000121764	ENSG00000137252
Principal transduction	$G_{q/11}$	$G_{q/11}$
Rank order of potency	Orexin-A > orexin-B	Orexin-A = orexin-B
Selective agonists	—	[Ala^{11},D-Leu^{15}]orexin-B (Asahi *et al*., 2003)
Selective antagonists	SB408124 (7.5, Langmead *et al*., 2004), SB334867A (7.2–7.3, Smart *et al*., 2001)	—

The *HCRTR2* gene encoding the OX_2 receptor has been identified as a possible candidate for inherited narcolepsy (Chemelli *et al*., 1999; Lin *et al*., 1999; Siegel, 1999).

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

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P2Y

Overview: P2Y receptors (provisional nomenclature as agreed by NC-IUPHAR Subcommittee on P2Y Receptors, 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 wording such as 'UTP-preferring (or ATP-, etc.) P2Y receptor' or '$P2Y_1$-like', etc., until further, as yet undefined, corroborative critieria can be applied.

Nomenclature	**$P2Y_1$**	**$P2Y_2$**	**$P2Y_4$**	**$P2Y_6$**
Ensembl ID	ENSG00000169860	ENSG00000175591	ENSG00000	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 *et al*., 1996), Ap_4A (Castro *et al*., 1992)	UTPγS (Lazarowski *et al*., 1996)	UDP
Selective antagonists	MRS2279 (8.0, Waldo *et al*., 2002), MRS2179 (7.0, Boyer *et al*., 1996), PIT (6.8, Gao *et al*., 2004)	—	ATP (6.2, Kennedy *et al*., 2000)	—
Radioligands	[^{3}H]-MRS2279 (8 nM, Waldo *et al*., 2002) [^{35}S]-ADPβS, [^{35}S]-ATPαS, [^{35}S]-dATPαS	—	—	—

Nomenclature	**$P2Y_{11}$**	**$P2Y_{12}$**	**$P2Y_{13}$**	**$P2Y_{14}$**
Other names	—	$P2Y_{ADP}$, P_{2T}	GPR86, GPR94, SP174	KIAAA00001, gpr105
Ensembl ID	ENSG00000176130	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 *et al*., 1995)	—	—

The recently-described '$P2Y_{15}$' receptor (Inbe *et al*., 2004) appears not to be a genuine nucleotide receptor, but rather responds to dicarboxylic acids (He *et al*., 2004). Further P2Y-like receptors have been cloned from non-mammalian sources; a clone from chick brain, termed a $p2y_3$ 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 & 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 (xl537 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 Ca^{2+}-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 $Ap_4A > Ap_5A > Ap_3A$, coupling *via* $G_{q/11}$ (Castro *et al*., 1992). P2Y-like receptors have recently been described on mitochondria (Belous *et al*., 2004).

Abbreviations: **2-MeSADP**, 2-methylthio-adenosine-5′-diphosphate; **2-MeSATP**, 2-methylthio-adenosine-5′-triphosphate; **ARL66096**, 2-propylthio-$\beta\gamma$-difluoro-methylene ATP (previously FPL66096); **ATPγS**, adenosine 5′-(3-thio)triphosphate; **MRS2179**, N^6-methyl-2′-deoxyadenosine-3′,5′-bisphosphate; **MRS2279**, 2-chloro-N^6-methyl-(*N*)-methanocarba-2′-deoxyadenosine-3′,5′- bisphosphate; **PIT**, 2,2′-pyridylisatogen tosylate

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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 TM 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	CV6209 (9.5), SR27417 (10.0), WEB2086 (8.0), L659989 (8.1), ginkgolide B (6.4)
Radioligand	[^{3}H]-PAF (K_d 1.6 nM, Fukanaga *et al*., 2001)

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

Abbreviations: CV6209, 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]thoiazol-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) D_2 (D), PGE_2 (E), $PGF_{2\alpha}$ (F), PGH_2 (H), prostacyclin [PGI_2 (I)] and thromboxane A_2 (T). Measurement of the potency of PGI_2 and TXA_2 is hampered by their instability in physiological salt solution; they are often replaced by cicaprost and U-46619, 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 *et al.*, 1997)	U46619, STA_2, I-BOP, AGN192093
Selective antagonists	BWA868C (9.3, Giles *et al.*, 1989), S5751 (8.8 Arimura *et al.*, 2001), ZK138357 (7.3, Lydford *et al.*, 1996)	—	—	BMS180291 (9.3 – 10.0), ONO3708 (8.9), GR32191 (8.3 – 9.4, Lumley *et al.*, 1989), SQ29548 (8.1 – 9.1, Swayne *et al.*, 1988)
Radioligands	[^{3}H]-PGD_2 (13 – 34 nM)	[^{3}H]-$PGF_{2\alpha}$ (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 PGD_2-sensitive receptor related to the classical chemotactic peptide receptors has also been characterised (Hirai *et al.*, 2001; Monneret *et al.*, 2001). Cicaprost exhibits moderate EP_4 receptor agonist potency (Abramovitz *et al.*, 2000). Iloprost also binds to EP_1 receptors. The TP receptor exists in α and β isoforms due to alternative splicing of the cytoplasmic tail (Raychowdhury *et al.*, 1994).

Nomenclature	**EP_1**	**EP_2**	**EP_3**	**EP_4**
Ensembl ID	ENSG00000160951	ENSG00000125384	ENSG00000050628	ENSG00000171522
Principal transduction	$G_{q/11}$	G_s	$G_{i/o}$	G_s
Rank order of potency	E > F,I > D,T	E > F,I > D,T	E > F,I > D,T	E > F,I > D,T
Selective agonists	17-Ph-ω-trinor-PGE_2, ONO-DI-004	Butaprost, AH13205, ONO-AE1-259	Sulprostone, SC46275, ONO-AE-248	ONO-AE1-329
Selective antagonists	ONO8711 (9.2), SC51322 (8.8)	—	—	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-trinor-PGE_2 also shows agonist activity at EP_3 receptors. Sulprostone also has affinity for EP_1 receptors. Butaprost and SC46275 may require de-esterification within tissues to attain full agonist potency. EP_3 antagonists are under development (Gallant *et al.*, 2002). There is evidence for subtypes of FP (Liljebris *et al.*, 1995), IP (Wise *et al.*, 1995; Takechi *et al.*, 1996) and TP (Krauss *et al.*, 1996) receptors. mRNA for the EP_1 and EP_3 receptors undergo alternative splicing to produce two (Okuda-Ashitaka *et al.*, 1996) and at least six variants, respectively, which can interfere with signalling (Okuda-Ashitaka *et al.*, 1996) or generate complex patterns of G-protein ($G_{i/o}$, $G_{q/11}$, G_s and $G_{12,13}$) coupling (e.g. Kotani *et al.*, 1995; Negishi *et al.*, 1995). The possibility of additional receptors for the isoprostanes has been suggested (Pratico *et al.*, 1996).

Abbreviations: AFP-07, 7,7-difluoro-16*S*,20-dimethyl-18,19-didehydro-PGI_2; **AGN192093,** (*Z*)-7-([1α,5α,6α,7*β*]-7-[{1*E*,3*S*}-3-hydroxy-1-octenyl]-3-oxo-2,4-dioxobicyclo[3.2.1]oct-6-yl)-5-heptenol; **AH13205,** *trans*-2-(4-[1-hydroxyhexyl]phenyl)-5-oxocyclopentane-heptanoic acid; **AH23848,** (1α[*z*],2*β*,5α)-(±)-7-(5-[{(1,1′-biphenyl)-4-yl}methoxy]-2-[4-morpholinyl]-3-oxocyclopentyl)-4-heptenoate; **BMS180291,** (1*s*-(1α,2α,3α,4α)-2-([3-{4-([pentylamino]carbonyl)-2-oxazolyl}-7-oxabicyclo{2.2.1}-hept-2-yl]methyl)benzenepropanoic acid; also known as ifetroban; **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,** [1*r*-[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-benzo[f]isoindol-2-yl}phenyl]-acetyl)benzenesulphonamide; **I-BOP,** (1*s*-[1α,2*β*{5*z*},3α[1*e*,3*s**],4α])-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-9α,11α-dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14-oxo-15-cyclopentyl-16,17,18,19,20-pentanor-15-epi-TXA_2; **ONO8711**, 6-[(2*S*,3*S*)-3-(4-chloro-2-methylphenylsulphonylaminomethyl)-bicyclo[2.2.2]octan-2-yl]-5*Z*-hexenoic acid; **ONO-DI-004**, 17*S*-17,20-dimethyl-2,5-ethano-6-oxo PGE_1; **ONO-AE-248**, 11,15-O-dimethyl-PGE_2; **ONO-AE1-259**, 16*S*-9-deoxy-9*β*-chloro-15-deoxy-16-hydroxy-17,17-propano-19,20-didehydro-PGE_2; **ONO-AE1-329**, 16-(3-methoxymethyl)phenyl-ω-tetranor-3,7-dithia-PGE_1; **ONO-AE3-208**, 2-(2-(2-methyl-2-naphth-1-ylacetylamino)-phenylmethyl)-benzoic acid; **RS93520,** *Z*-4-([C3′*S*,1*R*,2*R*,3*S*,6*R*]-2C3′-cyclohexyl-3′-hydroxyprop-1-ynyl)-3-hydroxybicyclo(4.2.0)oct-7-ylidene butyrate; **SAP,** 7-([1*R*,2*S*,3*S*,5*R*]-6,6-dimethyl-3-benzenesulfonamino-bicyclo[3.1.1]hept-2-yl)-5*Z*-heptenoic acid; **SC46275,** methyl-7-(2*β*-[6-{1-cyclopenten-1-yl}-4*R*-hydroxy-4-methyl-1*E*,5*E*-hexadienyl]-3α-hydroxy-5-oxo-1*R*,1α-cyclopentyl)-4*z*-heptenoic acid; **SC51322,** 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[3-[furanylmethyl)-thio]-1-oxopropyl]hydrazide; **SQ29548,** (1*S*-[1α,2*β*{5*Z*},3*β*,4α])7-(3-[{2-(phenylamino)carbonyl}hydrazino]methyl)-7-oxabicyclo[2.2.1]hept-2-yl-5-heptenoate; **S5751,** ((*Z*)-7-[1*R*,2*R*,3*S*,5*S*)-2-(5-hydroxybenzo[b]thiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid); **SQ27986**, [1*S*-[1B,2B(5*Z*),3A(1*E*,3*S*)4B]]7-[3-(3-cyclohexyl-3-hydroxy-1-propenyl)-7-oxabicyclo[2.2.1]hept-2-y]5-heptenoic acid**; STA_2,** 11α-carba-9α,11α-thia-txa_2; **U46619,** 11α,9α-epoxymethano-PGH_2; **ZK 118182**, (5Z,13E)-(9*R*,11*R*,15*S*)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid; **ZK138357,** (5*Z*)-7-([2*RS*,4*S*,5*S*]-2-[2-chlorophenyl]-5-[{1*E*}-{3*R*,*S*}-3-hydroxy-3-cyclohexyl-1-propenyl]-1,3-dioxolan-4-yl)-5-heptanoic acid

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Proteinase-activated

Overview: Proteinase-activated receptors (PARs, nomenclature as agreed by NC-IUPHAR Subcommittee on Proteinase-activated Receptors, see Hollenberg & Compton, 2002) are activated by the intramolecular binding of a cryptic tethered ligand revealed (or unmasked) following the proteolytic cleavage of their amino terminal sequence by serine proteinases such as thrombin and trypsin. Other members of this class of proteinases can either unmask or remove the tethered ligand (see table) to either activate or disarm the PARs. Activation of PAR_2 by trypsin or by tryptase release *in vivo* and alternative endogenous ligands for PARs, other than serine proteinases, has yet to be demonstrated. Interestingly, with the exception of PAR_3, synthetic peptide sequences (as carboxyl terminal amides) based on the proteolytically revealed thethered ligand sequences of human PAR_{1-4} (SFLLRN, SLIGKV, TFRGAP and GYPGQV, respectively) are able to act as agonists at their respective receptors. TFRGAP-NH_2 can activate PAR_1 and PAR_2, but not PAR_3. Of importance for experimental studies, these agonist peptides can activate receptors that were previously disarmed (i.e. the tethered ligand sequence cleaved, hence preventing activation by agonist proteinases) by inactivating proteinases. The role of such inactivating proteinases (e.g. elastase) *in vivo* is as yet unclear.

Nomenclature	**PAR_1**	**PAR_2**	**PAR_3**	**PAR_4**
Other names	Thrombin receptor, protease-activated receptor 1, PAR-1, coagulation factor 2 receptor	Protease-activated receptor 2, PAR-2, thrombin receptor-like 1, coagulation factor 2 receptor-like 1,	Protease-activated receptor 3, PAR-3, thrombin receptor-like 2, coagulation factor 2 receptor-like 2,	Protease-activated receptor 4, PAR-4, thrombin receptor-like 3, coagulation factor 2 receptor-like 3,
Ensembl ID; SwissProt Accession	ENSG00000181104; P25116	ENSG00000164251; P55085	ENSG00000164220; O00254	ENSG00000127533; Q96R10
Principal transduction	$G_{q/11}/G_{i/o}/G_{12/13}$	$G_{q/11}/G_{i/o}$	Coupling not yet established	$G_{q/11}/G_{i/o}$
Agonist proteinases	Thrombin, trypsin, Tisssue Factor-VIIa-Xa complex, activated protein C, plasmin	Trypsin, tryptase, Tissue Factor-VIIa $\pm$ Xa complex, membrane-type serine protease 1	Thrombin, trypsin, factor Xa (cleave, but fail to activate)	Thrombin, trypsin, cathepsin G, plasmin
Selective agonists	TFLLR-NH_2	SLIGRL, SLIGKV, 2-furoyl-LIGRLO-NH_2, 2-furoyl-LIG-RL-NH_2	—	AYPGKF-NH_2, GYPGQV-NH_2, GYPGKF-NH_2
Selective antagonists	RWJ56110 (Andrade-Gordon *et al*., 1999); SCH79797 (Ahn *et al*., 2000)	—	—	Trans-cinnamoyl-YPGKF-NH_2; *N*-palmitoyl-SGRRYG-HALR-NH_2
Radioligands	[^{3}H]-haTRAP (Ahn *et al*., 1997)	*trans*-cinnamoyl-LIGRLO[*N*-[^{3}H]-propionyl]-NH_2 (Al Ani *et al*., 1999)	—	—

TFLLR-NH_2 is selective relative to the PAR_2 receptor (Blackhart *et al*., 1996; Kawabata *et al*., 1999). Thrombin is inactive at the PAR_2 receptor. Peptides acting as inactive controls for PAR_1 (FTLLR-NH_2 and FSLLR-NH_2), PAR2 (LSIGRL-NH_2 and LRGILS-NH_2) and PAR3 (YAPGKF-NH_2 and N-palmitoyl-RLAHGYRRGS-NH_2) have been described.

Abbreviations: [^{3}H]-haTRAP, Ala-*p*-fluoroPhe-Ala-Arg-cyclohexylAla-homoArg-[^{3}H]Tyr-amide; **RWJ56110,** (α*S*)-*N*-([1*S*]-3-amino-1-[{(phenylmethyl)amino}propyl]-α-[{(1-[{2,6-dichlorophenyl}methyl]-3-[1-pyrrolidinylmethyl]-1*H*-indol-6-yl)amino}carbonyl]amino)-3,4-difluoro-benzenepropanamide; **SCH79797,** N3-cyclopropyl-7-[[4-(1-methylethyl)phenyl]methyl]-7H-pyrrolo[3, 2-f]quinazoline-1,3-diamine.

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Relaxin family peptide

Overview: Relaxin family peptide receptors (provisional nomenclature) are activated by heterodimeric peptide hormones analogous to insulin (relaxin 1 [ENSG0000010718], relaxin 2 [ENSG0000107014], relaxin 3 [also known as INSL7, ENSG0000171136] in higher primates, INSL3, Leydig insulin-like peptide [ENSG0000171717]) and INSL5 [ENSG00000172410].

Nomenclature	**RXFP1**	**RXFP2**	**RXFP3**	**RXFP4**
Other names	Relaxin receptor, LGR7, Leucine-Rich Repeat-Containing G Protein-Coupled Receptor 7, RX1	INSL3 receptor, LGR8, Leucine-Rich Repeat-Containing G Protein-Coupled Receptor 8, GREAT, RX2	Relaxin 3 receptor, GPCR135, Somatostatin and angiotensin-like peptide receptor SALPR, RX3	INSL5 receptor, GPCR142, GPR100, relaxin 3 receptor 2, RX4
Ensembl ID	ENSG00000171509	ENSG00000133105	ENSG00000182631	ENSG00000173080
Principal transduction	G_s	G_s, $G_{i/o}$ (Kawamura *et al*., 2004)	$G_{i/o}$ (Matsumoto *et al*., 2000)	$G_{i/o}$ (Liu *et al*., 2003b)
Rank order of potency	H2 relaxin > H3 relaxin ≫ INSL3 (Sudo *et al*., 2003)	INSL3 > H2 relaxin ≫ H3 relaxin (Kumagai *et al*., 2002, Sudo *et al*., 2003)	H3 relaxin > H3 relaxin B chain ≫ INSL5 (Liu *et al*., 2003a)	INSL5 = H3 relaxin > H3 relaxin B chain (Liu *et al*., 2003b, 2004)
Radioligands	[^{33}P]-H2 relaxin (0.1–0.5 nM, Kumagai *et al*., 2002)	[^{33}P]-H2 relaxin	[^{125}I]-H3 relaxin (0.3 nM, Liu *et al*., 2003a)	[^{125}I]-H3 relaxin (0.2 nM, Liu *et al*., 2003b)

Mutations in *INSL3* and *LGR8* (RXFP2) have been reported in populations of patients with cryptorchidism (Ferlin *et al*., 2003).

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

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Somatostatin

Overview: Somatostatin (somatotropin release inhibiting factor) is an abundant neuropeptide, which acts on five subtypes of somatostatin receptor (sst1 – sst5; nomenclature approved by the NC-IUPHAR Subcommittee on Somatostatin Receptors, see Hoyer *et al*., 2000). Activation of these receptors produces a wide range of physiological effects throughout the body. The relationship of the cloned receptors to endogenously expressed receptors is not yet well established in some cases. Endogenous ligands for these receptors are somatostatin-14 (SRIF-14) and somatostatin-28 (SRIF-28). Cortistatin (CST-14) has also been suggested to be an endogenous ligand for somatostatin receptors (Delecea *et al*., 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	des-$Ala^{1,2,5}$-[$DTrp^8$,$Iamp^9$] SRIF, L797591	Octreotide, seglitide BIM23027, L054522	L796778	NNC269100 L803087	BIM23268, BIM23052, L817818
Selective antagonists	—	Cyanamid 154806 (7.7 – 8.0)	—	—	BIM23056 (7.4 – 8.3)
Radioligands	—	[^{125}I]-[Tyr^3]octreotide (0.13 nM) [^{125}I]-BIM23027	—	—	[^{125}I]-[Tyr^3]octreotide (0.23 nM)

[^{125}I]-[Tyr^{11}]-SRIF-14, [^{125}I]-LTT-SRIF-28, [^{125}I]-CGP23996 and [^{125}I]-[Tyr^{10}]CST-14^6 may be used to label somatostatin receptors non-selectively; BIM23052 is said to be selective at rat but not human receptor (Patel & Srikant, 1994). A number of non-peptide 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-DTrp-Lys-Thr-Phe-Thr-NH_2; **BIM23056,** DPhe-Phe-Tyr-DTrp-Lys-Val-Phe-dNal-NH_2; **BIM23268,** *cyc*(Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys)-NH_2; **CGP23996,** *cyc*(Asn-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser); **Cyanamid 154806,** Ac-(4-NO_2-Phe)-*cyc*(D-Cys-Tyr-D-Trp-Lys-Thr-Cys)-D-Tyr-NH_2; **L797591,** (2R)-N-(6-amino-2,2,4-trimethylhexyl)-3-(1-naphthyl)-2-({[(2-phenylethyl)2-pyridin-2-ylethyl)amino]carbonyl}amino)propanamide; **L054522,** tert-butyl (bS)-b-methyl-N{[4-(2-oxo-2,3,-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]carbonyl}-D-tryptophyl-L-lysinate; **L796778,** methyl (2S)-6-amino-2-[((2R)-2-{[({(1S)-1-benzyl-2-[(4-nitrophenyl)amino]-2-oxoethyl}amino)carbonyl]amino}hexanoyl)amino]hexanoate; **L803087,** methyl (2S)-5-{[amino(imino)methyl]amino}-2-{[4-(5,7-difluoro-2-phenyl-1H-indol-3-yl)butanoyl]amino}pentanoate; **L817818,** (2R)-2-aminopropyl N2-{[2-(2-naphthyl)-1H-benzo[g]indo-3-yl]acetyl}-L-lysinat; **LTT-SRIF-28,** [Leu^8,$DTrp^{22}$,$DTyr^{25}$]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 & Milstien, 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 [^{32}P]-S1P (e.g. Okamoto *et al*., 1998). In native systems, analysis of binding data is complicated by metabolism and high levels of non-specific binding. Targeted deletion of several S1P receptors has clarified signalling pathways and physiological roles.

Nomenclature	**$S1P_1$**	**$S1P_2$**	**$S1P_3$**	**$S1P_4$**	**$S1P_5$**
Other names	edg1, lp_{B1}	edg5, lp_{B2}, AGR16, H218	edg3, lp_{B3}	*edg6*, lp_{C1}	*edg8*, lp_{B4}, NRG-1
Ensembl ID	ENSG00000170989	ENSG00000175898	ENSG00000186354	ENSG00000125910	ENSG00000180739
Principal transduction	$G_{i/o}$	G_q, $G_{12/13}$, G_s	G_q, $G_{i/o}$, G_s	$G_{i/o}$, $G_{12/13}$, G_s	$G_{i/o}$, $G_{12/13}$
Rank order of potency	S1P > SPC	S1P > SPC (Okamoto *et al*., 1998)	S1P > SPC (Okamoto *et al*., 1998)	S1P, SPC	S1P, SPC
Selective agonists	SEW2871 (Sanna *et al*., 2004)	—	—	—	—
Selective antagonists	—	JTE013 (Osada *et al*., 2002)	—	—	—

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

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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 non-peptide ligands.

Nomenclature	**NK_1**	**NK_2**	**NK_3**
Other names	Substance P	Substance K	Neurokinin B, neuromedin K
Ensembl ID	ENSG00000115353	ENSG00000075073	ENSG00000169836
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	SP > NKA > NKB	NKA > NKB ≫ SP	NKB > NKA > SP
Selective agonists	SP methylester, [Sar^9,Met(O$_2$)^{11}]SP, [Pro^9]SP, septide	[β-Ala^8]NKA-(4–10),[Lys^5,MeLeu^9,Mle^{10}] NKA-(4–10), GR64349	Senktide, [MePhe^7]NKB
Selective antagonists	L742694 (10.0, Hale *et al*., 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 *et al*., 1998)	SR142802 (9.2), SB223412 (9.0, Sarau *et al*., 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 NK_1 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 non-identical site to SP on the NK_1 receptor. There are suggestions for additional subtypes of tachykinin receptor; an orphan receptor (SwissProt P30098) with structural similarities to the NK_3 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-NMe$_2$; **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-NH$_2$; **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]acetylamino)-3-(1*H*-indol-3yl)-2-(*N*-[2-{4-(piperidin-1-yl)piperidin-1-yl}acetyl]amino)propane; also known as lanepitant; **MEN10627,** *cyc*(2β–5β)(Met-Asp-Trp-Phe-Dap-Leu); **MEN11420,** *cyc*(2β–5β)[Asn(2-AcNH-β-D-Glc)-Asp-Trp-Phe-Dap-Leu]; also known as nepadutant; **PD157672,** Boc-(*S*)Phe-(*R*)αMePheNH(CH$_2$)$_7$NHCONH$_2$; **RP67580,** 3α*R*,7α*R*-(1-imino-2-[2-methoxyphenyl]ethyl)-7,7-diphenyl-4-perhydroisoindolone; **SB223412,** (*S*)-(−)-*N*-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide; **SR140333,** (*S*)-1-(2-[3-{3,4-dichlorophenyl}-1-{3-isopropoxyphenylacetyl}piperidin-3-yl]ethyl)-4-phenyl-1-azoniabicyclo(2.2.2)octane chloride; **SR142801,** (*S*)-(*N*)-(1-[3-{1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl}propyl]-4-phenylpiperidin-4-yl)-*N*-methylacetamide; **SR48968,** (*S*)-*N*-methyl-*N*-(4-acetylamino-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-ProNH$_2$). TRH and TRH analogues fail to distinguish TRH_1 and TRH_2 receptors (see Sun *et al*., 2003).

Nomenclature	**TRH_1**	**TRH_2**
Other names	TRH receptor	—
Ensembl ID	ENSG00000163485	ENSMUSG00000039079, ENSRNOG00000012789
Principal transduction	G_q	G_q
Selective antagonists	Midazolam (Drummond *et al*., 1989), chlordiazepoxide (Straub *et al*., 1990), diazepam	—
Radioligands	[^{3}H]-MeTRH, [^{3}H]-TRH (13 nM)	[^{3}H]-TRH (9 nM)

The human orthologue of the rodent TRH_2 receptor has yet to be identified.

Abbreviations: MeTRH: pGlu-[N^{π}-methyl]His-ProNH$_2$

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Urotensin-II

Overview: The urotensin-II receptor (UT, see Douglas and 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). In human tissues, furin and trypsin are reported to act as urotensin-II-converting enzymes (Russell *et al*., 2004).

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 *et al*., 2002)
Radioligands	[^{125}I]-hU-II (0.24 nM, Maguire *et al*., 2000)

In human vasculature, human urotensin-II elicits both vasoconstrictor (pD_2 9.3–10.1, Maguire *et al*., 2000) and vasodilator (pIC_{50} 10.3–10.4, Stirrat *et al*., 2001) responses. BIM23127, a neuromedin B receptor antagonist, has been shown to antagonise human recombinant UT receptors (pA_2 7.5) and to reverse U-II contraction of rat aorta (pIC_{50} 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). Antagonists reported to be selective for the U-II receptor include Urantide (pK_B 8.3 in rat aorta, Patacchini *et al*., 2003) and Palosuran (pIC_{50} 7.8 at human recombinant receptor, Clozel *et al*., 2004).

Abbreviations: BIM23127, D-Nal-*cyc*[Cys-Tyr-D-Trp-Orn-Val-Cys]-Nal-NH_2; **Palosuran**, 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl-ethyl]-3-(2-methyl-quinolin-4yl)-urea sulphate salt, also known as ACT058362; **[Pen^5]U-II-(4-11),** [pencillamine, β,β-dimethylcysteine]^{5}U-II-(4–11); **SB710411,** Cpa-*cyc*[D-Cys-Pal-D-Trp-Lys-Val-Cys]-Cpa-NH_2; **Urantide**, [Pen^5, DTrp^7, Orn^8]hU-II(4–11)

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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 as agreed 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 $VPAC_1$ and $VPAC_2$ meet this definition. [Arg^{16}]chicken secretin is an agonist at both $VPAC_1$ and secretin receptors, but can be used as an agonist at $VPAC_1$ receptors in tissues that do not express secretin receptors (Gourlet *et al*., 1997a). $PACAP_{6-38}$ also shows significant affinity for $VPAC_2$ receptors. Helodermin discriminates $VPAC_1$ and $VPAC_2$ 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 *et al*., 1997a; Gourlet *et al*., 1997b), Ro251392 (Xia *et al*., 1997)	Maxadilan (Moro & Lerner, 1997)
Selective antagonists	[Ac-His^1,D-Phe^2,Lys^{15}, Arg^{16}]VIP-(3–7)-GRF-(8–27)-NH_2 (Gourlet *et al*., 1997a)	—	PACAP-(6–38)
Radioligands	[^{125}I]-VIP, [^{125}I]-PACAP	[^{125}I]-VIP, [^{125}I]-PACAP	[^{125}I]-PACAP

Subtypes of PAC_1 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 PAC_1 receptor mRNA (Spengler *et al*., 1993).

Abbreviations: **Ro251392,** Ac-His^1[Glu^8,OCH_3-Tyr^{10},Lys^{12},Nle^{17},Ala^{19},Asp^{25},Leu^{26},$Lys^{27,28}$]VIP (*cyclo* 21–25); **Ro251553,** Ac-His^1[Glu^8,Lys^{12},Nle^{17},Ala^{19},Asp^{25},Leu^{26},$Lys^{27,28}$,$Gly^{29,30}$,Thr^{31}]VIP-NH_2 (*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 *et al*., 2002)	d[Val^4,DArg^8]VP, OPC51803, VNA932	[Thr^4,Gly^7]OT (Elands *et al*., 1988)
Selective antagonists	d(CH$_2$)$_5$[Tyr(Me)^2,Arg^8]VP (9.0), SR49059 (8.9), YM087 (8.2)	SSR149415 (8.4, Griebel *et al*., 2002; Serradeil-Le Gal *et al*., 2002)	VPA985 (8.9, Albright *et al*., 1998), d(CH$_2$)$_5$[D-Ile^2, Ile^4]AVP (8.4), SR121463A (8.4, Serradeil-Le Gal *et al*., 1996), OPC31260 (7.6, Yamamura *et al*., 1992), YM087 (8.96)	SSR126768A (9.3, Serradeil-Le Gal *et al*., 2004) 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 *et al*., 2002), [^{125}I]-d(CH$_2$)$_5$[Tyr(Me)^2,Thr^4,Orn^8, Tyr-NH$_2^9$]OVT (90 pM), [^{111}In]-DOTA-dLVT (4.5 nM, Chini *et al*., 2003)

The V_2 receptor exhibits marked species differences, such that many ligands (d(CH$_2$)$_5$[D-Ile^2,Ile^4]VP and [^{3}H]-desGly-NH$_2$[D-Ile^2,Ile^4]VP) exhibit low affinity at human V_2 receptors (Ala *et al*., 1997). Similarly, [^{3}H]-d[D-Arg^8]VP is V_2 selective in the rat, not in the human (Saito *et al*., 1997). The gene encoding the V_2 receptor is polymorphic in man, underlying nephrogenic diabetes insipidus (Bichet, 1998). YM087 display high affinity for both human V_{1a} and V_2 receptors (Tahara *et al*., 1998).

Abbreviations: [^{111}In]-DOTA-dLVT, [^{111}In]-DOTA-Lys^8-deamino-vasotocin; **[^{35}S] Non Peptide OT Antagonist**, [^{35}S]-(1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-methylsulfonyl-4-piperidinyloxy)phenylacetyl)-4-piperidinyl)-3,4-dihydro-2(1*H*)-quinolinone); **F180,** Hmp-Phe-Ile-Hgn-Asn-Cys-Pro-Dab(Abu)-Gly-NH$_2$; **L372662,** 1-(1-{4-[1-(2-methyl-1-oxidopyridin-3-ylmethyl)piperidin-4-yloxyl]-2-methoxybenzoyl}piperidin-4-yl)-1,4-dihydrobenz[*d*][1,3]]oxazin-2one; **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; **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; **SSR126768A**, 4-chloro-3-[(3R)-(+)-5-chloro-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-*N*-ethyl-*N*-(3-pyridylmethyl)-benzamide, hydrochloride; **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; **YM087**, (4′-[(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepin -6-yl) carbonyl]-2-phenylbenzanilide monohydrochloride)

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