7 TM RECEPTORS

5-HT

Overview: 5-HT receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on 5-HT receptors (Hoyer *et al*., 1994) and subsequently revised (Hartig *et al*., 1996)) are, with the exception of the ionotropic 5-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} (nonfunctional), 5-HT_{2C} (nonfunctional), 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-$HT_{1D\beta}$	5-$HT_{1D\alpha}$	—
Ensembl 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)	SB714786 (9.1, Ward *et al*., 2005) BRL15572 (7.9)	—
Probes	[^{3}H]-WAY100635 (0.3 nM, Khawaja *et al*., 1997), [^{3}H]-8-OH-DPAT, [^{11}C]-WAY100635	[^{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}
Ensembl ID	ENSG00000179097	ENSG00000102468	ENSG00000135914	ENSG00000147246
Principal transduction	$G_{i/o}$	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Selective agonists	LY334370, LY334864	DOI	DOI, Ro600175, BW723C86	DOI, Ro600175
Selective antagonists	—	ketanserin (8.5–9.5), M100907 (9.4)	RS127445 (9.5)	SB242084 (9.0), RS102221 (8.6)
Probes	[^{3}H]-LY334370 (0.5 nM, Wainscott *et al*., 2005), [^{125}I]-LSD	[^{3}H]-ketanserin (0.45 nM, Bonhaus *et al*., 1995), [^{3}H]-RP62203 (fananserin, 0.13 nM, Malgouris *et al*., 1993), [^{11}C]-M100907 [^{18}F]-altanserin	[^{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-$HT_{5\alpha}$	—	—
Ensembl ID	ENSG00000164270	ENSG00000157219	ENSMUSG00000050534	ENSG00000158748
Principal transduction	G_s	$G_{i/o}$	None identified	G_s
Selective agonists	BIMU8, ML10302, RS67506	—	—	—
Selective antagonists	GR113808 (9.0–9.5), SB204070 (10.8), RS100235 (11.2)	SB699551 (8.0; Corbett *et al*., 2005)	—	SB271046 (8.7), SB357134 (7.6), Ro630563 (7.9)
Probes	[^{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
Ensembl ID	ENSG00000148680
Principal transduction	G_s
Selective agonists	—
Selective antagonists	SB656104 (8.5), SB269970 (8.5), SB258719 (7.2)
Probes	[^{3}H]-SB269970 (1.2 nM, Thomas *et al*. 2000), [^{3}H]-5-CT, [^{125}I]-LSD, [^{3}H]-5-HT

Tabulated K_D 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 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 nonfunctional due to interruption of the gene by stop codons. In addition to the receptors listed in the table, an 'orphan' receptor, unofficially termed 5-HT_{1P}, 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; **M100907**, (+/−)2,3-dimethoxyphenyl-1-[2-(4-piperidine)-methanol]; **NAD299**, (*R*)-3-*N*,*N*-dicyclobutylamino-8-fluoro-[6-3*H*]-3,4-dihydro-2*H*-1-benzo pyran-5-carboxamide; **NAS181**, (*R*)-(+)-2-[[[3-(morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl] morpholine methane sulphonate; **PNU109291**, (*S*)-3,4-dihydro-1-[2-[4-(4-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-methyl-1*H*-2-benzopyran-6-carboximide; **Ro600175**, (*S*)-2-(6-chloro-5-fluroindol-1-yl)-1-methyethylamine; **Ro630563**, 4-amino-*N*-[2,6-bis(methylamino)pyridin-4-yl]benzenesulphonamide; **RP62203**, 2-[3-(4-(4-fluorophenyl)-piperazinyl)propyl]naphto[1,8-ca]isothiazole-1,1-dioxide; **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; **SB271046**, 5-chloro-*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulphonamide; **SB357134**, *N*-(2,5-dibromo-3-flurophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulphonamide; **SB656104**, 6-((*R*)-2-[2-[4-(4-Chlorophenoxy)-piperidin-1-yl]-ethyl]-pyrrolidine-1-sulphonyl)-1*H*-indole hydrochloride; **SB699551**, 3-cyclopentyl-*N*-[2-(dimethylamino)ethyl]-*N*-[(4′-{[(2-phenylethyl)amino]methyl}-4-biphenylyl)methyl]propanamide dihydrochloride; **SB714786**, 2-methyl-5-({2-[4-(8-quinolinylmethyl)-1-piperazinyl]ethyl}oxy)quinoline; **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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Acetylcholine (muscarinic)

Overview: Muscarinic acetylcholine receptors (nomenclature as agreed by NC-IUPHAR subcommittee on Muscarinic Acetylcholine Receptors, Caulfield and Birdsall, 1998) are 7TM receptors of the rhodopsin-like family where the endogenous agonist is acetylcholine. In addition to the agents listed in the table, AC-42 and desmethylclozapine have recently been described as selective agonists of the M_1 receptor subtype *via* binding to a site distinct to that recognised by nonselective agonists (Spalding *et al*., 2002; Sur *et al*., 2003). There are two allosteric sites on muscarinic receptors, one defined by the binding of gallamine, strychnine and brucine and the other binds KT5720, WIN62,577, WIN51,708 and staurosporine (Lazareno *et al*., 2000, 2002). There are selective enhancers of acetylcholine binding and action; brucine and KT5720 at 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)
Probes	[^{3}H]-NMS (80–150 pM), [^{3}H]-QNB (15–60 pM), [^{3}H]-pirenzepine (3–15 nM), [^{11}C]-xanomeline [^{11}C]-methylpyridine [^{11}C]-butylthio-TZTP	[^{3}H]-NMS (200–400 pM), [^{3}H]-QNB (20–50 pM), [^{18}F]-FP-TZTP	[^{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)
Probes	[^{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; **Butylthio-TZTP**, butylthio-thiadiazolyltetrahydro-1-methyl-pyridine **Dimethyl-W84**, *N*,*N*′-bis[3-(1,3-dihydro-1,3-dioxo-4-methyl-2*H*-isoindol-2-yl)propyl]-*N*,*N*,*N*′,*N*′-tetramethyl-1,6-hexanediaminium diiodide; **FP-TZTP**, [3-(3-(3-Fluoropropyl)thio)-1,2,5-thiadiazol-4-yl]-1,2,5,6-tetrahydro-1-methylpyridine; **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 nonselective agonist, while XAC and CGS15943 display submicromolar affinity at all four adenosine receptors (Klotz *et al*., 1998; Ongini *et al*., 1999).

Nomenclature	**A_1**	**A_{2A}**	**A_{2B}**	**A_3**
Ensembl ID	ENSG00000163485	ENSG00000128271	ENSG00000170425	ENSG00000121933
Principal transduction	$G_{i/o}$	G_s	G_s	$G_{i/o}$
Selective agonists	CPA, CCPA, S-ENBA	CGS21680, HENECA	—	2-Cl-IB-MECA, IB-MECA
Selective antagonists	DPCPX (8.5)	ZM241385 (9.0), SCH58261 (7.9–9.5)	MRS1754 (8.7), MRS1706 (8.4)	MRS1220 (8.8), VUF8504 (7.8, van Muijlwijk-Koezen *et al*., 1998), MRS1523 (7.7), MRS1191 (7.0)
Probes	[^{3}H]-CCPA, [^{3}H]-DPCPX (0.6–1.2 nM)	[^{3}H]-CGS21680, [^{3}H]-ZM241385 (0.8 nM)	[^{3}H]-MRS1754 (1.1 nM)	[^{125}I]-AB-MECA (0.6 nM)

Adenosine inhibits many intracellular ATP-utilising enzymes, including adenylyl cyclase (P-site). A pseudogene exists for the A_{2B} adenosine receptor (ENSG00000182537) with 79% identity to the A_{2B} adenosine receptor cDNA coding sequence, but which is unable to encode a functional receptor (Jacobson *et al*., 1995). DPCPX also exhibits antagonism at A_{2B} receptors (pK_i ca. 7, Alexander *et al*., 1996; Klotz *et al*., 1998). HENECA also shows activity at 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 (Johansson & Fredholm, 1995; Cunha *et al*., 1996). [^{3}H]-NECA binds to other nonreceptor elements, which also recognise adenosine (e.g. Lorenzen *et al*., 1996).
Adenosine has also been reported to act as a partial agonist at the ghrelin receptor (Smith *et al*., 2000), but this has recently been questioned (Johansson *et al*., 2005).

Abbreviations: **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; **2Cl-IB-MECA**, 2-chloro-N^6-(3-iodobenzyl)adenosine-5′-*N*-methyluronamide; **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**, (2S)-N^6-(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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Adiponectin

Overview: Adiponectin receptors (provisional nomenclature, ENSF00000002482) respond to the 30 kDa complement-related protein hormone adiponectin (also known as adipocyte, C1q and collagen domain-containing protein; ACRP30, adipose most abundant gene transcript 1; apM-1; gelatin-binding protein; ENSG00000181092) originally cloned from adipocytes (Maeda *et al*., 1996). Although sequence data suggest 7TM domains, immunological evidence indicates that, contrary to typical 7TM topology, the carboxyl terminus is extracellular, while the amino terminus is intracellular (Yamauchi *et al*., 2003). Signalling through these receptors appears to avoid G-proteins and rather activates protein phosphorylation *via* AMP-activated protein kinase and MAP kinase pathways (Yamauchi *et al*., 2003).

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

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

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Adrenoceptors, α_1

Overview: α_1-Adrenoceptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Adrenoceptors, Bylund *et al*., 1994) are 7TM receptors, 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 (< 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) and [^{3}H]-RX821002 (0.5 nM and 0.1 nM at α_{2C}) are relatively selective radioligands. There is species variation in the pharmacology of the α_{2A}-adrenoceptor; for example, yohimbine, rauwolscine and oxymetazoline have an ~20-fold lower affinity for rat, mouse and bovine α_{2A}-adrenoceptors. 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
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Selective agonists	Oxymetazoline	—	—
Selective antagonists	BRL44408 (8.0)	ARC239 (8.0), prazosin (7.5), imiloxan (7.3)	ARC239 (8.0), prazosin (7.5)

Oxymetazoline is a partial agonist. Binding sites for imidazolines, distinct from α_2-adrenoceptors, have been identified, 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 the 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 (p*K*i 8.2–9.2) and cyanopindolol (p*K*i 10.0–11.0) are relatively selective antagonists. β_3-Adrenoceptors are relatively resistant to blockade by propranolol (p*K*i 5.8–7.0), but can be blocked with high concentrations of cyanopindolol (p*K*i 9.0).

Nomenclature	β_1	β_2	β_3
Other names	—	—	atypical β
Ensembl ID	ENSG00000043591	ENSG00000169252	ENSG00000147477
Principal 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)
Probes	[^{125}I]-ICYP (20–50 pM) + 70 nM ICI118551	[^{125}I]-ICYP (20–50 pM) + 100 nM CGP20712A	[^{125}I]-ICYP (0.5 nM)

Noradrenaline, xamoterol and RO363 show selectivity for β_1- relative to β_2-adrenoceptors. 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), 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 β4c, t428 SwissProt P43141) has a 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 nonconventional partial agonists at β1-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([1s]-1,2,3,4-tetrahydronaphth-1-ylamino)-2*S*-propanol oxalate

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Anaphylatoxin and chemotactic peptide

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

Nomenclature	**C3a**	**C5a**	**fMLP**
Other names	AZ3B, HNFAG09	CD88	Formyl peptide, FPR
Ensembl ID	ENSG00000171860	ENSG00000134830	ENSG00000171051
Principal transduction	$G_{i/o}$, 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	SB290157 (pIC50 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), CHIPS (Postma *et al*., 2004)	Cyclosporin H (6.3-7.0, Wenzel-Seifert & Seifert, 1993), BOC-PLPLP (6.0-6.5, Wenzel-Seifert and Seifert, 1993), spinorphin (4, Liang *et al*., 2001)
Probes	[^{125}I]-C3a	[^{125}I]-C5a	[^{3}H]-fMLP

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

Abbreviations: **BOC-PLPLP**, Boc-Phe-Leu-Phe-Leu-Phe; **CHIPS**, chemotaxis inhibitory protein of *Staphylococcus aureus*; **SB290157**, 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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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 *AT1* gene, but two related *AT1A* and *AT1B* 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 upregulated in pathological conditions. Endogenous ligands are Ang II and angiotensin III (Ang III), while angiotensin I is weakly active in some systems.

Nomenclature	**AT_1**	**AT_2**
Ensembl ID	ENSG00000144891	ENSG00000180772
Principal transduction	$G_{q/11}$	Tyr & Ser/Thr phosphatases
Selective agonists	L162313	[p-NH_2-Phe^6]-Ang II, CGP42112
Selective antagonists	EXP3174, eprosartan, valsartan, irbesartan, losartan	PD123319, PD123177
Probes	[^{3}H]-A81988, [^{3}H]-L158809, [^{3}H]-eprosartan [^{3}H]-losartan, [^{125}I]-EXP985	[^{125}I]-CGP42112

There is also evidence for an AT_4 receptor that specifically binds angiotensin IV and is located in the 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 B2 receptors have been proposed to form a heterodimeric complex (AbdAlla *et al*., 2000). The antagonist activity of CGP42112 has also been reported (Lokuta *et al*., 1995). Novel AT_1 receptor antagonists bearing substituted 4-phenylquinoline moieties have recently been designed and synthesized. 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*-benzoyl carbonyl-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 derived initially from bovine stomach. Apelin-36, apelin-13 and (Pyr^1)apelin-13 are the predominant endogenous ligands which are cleaved from a 77 amino-acid precursor peptide (ENSG00000171388) by a so far unidentified enzymatic pathway (Tatemoto *et al*., 1998).

Nomenclature	**APJ**
Other names	Apelin receptor, angiotensin receptor-like 1
Ensembl ID	ENSG00000134817
Principal transduction	$G_{i/o}$
Rank order of potency	[Pyr^1]apelin-13 > apelin-13 > apelin-36 (Tatemoto *et al*., 1998)
Selective agonists	[Pyr^1]apelin-13, apelin-13, apelin-17, apelin-36
Probes	[^{125}I]-[Pyr^1]Apelin-13 (0.3 nM, Katugampola *et al*., 2001), [^{3}H]-[Pyr^1][$Met(0)^{11}$]apelin-13 (Medhurst *et al*., 2003), [^{125}I]-[Nle^{75},Tyr^{77}]apelin-36 (Kawatma *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
Ensemble 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},$\psi^{26\text{-}27}$]GRP-20-27, kuwanon H, [dPhe^{6}]bombesin-6-13-ethylester, [dPhe^{6},Cpa^{14},$\psi^{13\text{-}14}$]bombesin-6-14	—
Probes	[^{125}I]-BH-NMB, [^{125}I]-[Tyr^{4}]bombesin	[^{125}I]-[D-Tyr^{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).

Abbreviations: **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 (or kinin) receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on bradykinin (kinin) receptors, Regoli *et al*., 1998b, Leeb-Lundberg *et al*., 2005) are activated by the endogenous peptides bradykinin (BK), [des-Arg^9]BK, Lys-BK (kallidin), Lys-[des-Arg^9]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*., 1998a), R914 (8.6, Gobeil *et al*., 1999), R715 (8.5, Gobeil *et al*., 1996a), Lys-[Leu^8][des-Arg^9]BK (8.0)	Icatibant (8.4, Gobeil *et al*., 1996b), FR173657 (8.2, Rizzi *et al*., 1997), LF160687 (Puneau *et al*., 1999)
Probes	[^{3}H]-Lys-[des-Arg^9]BK (0.4 nM), [^{3}H]-Lys-[Leu^8][des-Arg^9]BK, [^{125}I]-Hpp-desArg^{9}HOE140 (0.1 nM)	[^{3}H]-BK (0.2 nM), [^{3}H]-NPC17731 (50–900 pM), [^{125}I]-[Tyr^8]BK

Abbreviations: **B9958**, Lys-Lys[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; **Icatibant**, DArg[Hyp^3,Thi^5,DTic^7,Oic^8]BK, also known as HOE140; **LF160687**, 1-([2,4-dichloro-3-{([2,4-dimethylquinolin-8-yl]oxy)methyl}phenyl]sulfonyl)-*N*-(3-[{4-(aminoimethyl)phenyl}carbonylamino]propyl)-2(S)-pyrrolidinecarboxamide; **NPC17731**, DArg[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,$\delta-\beta$Nal^7,Ile^8)desArg^{9}BK

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Calcitonin, amylin, CGRP and adrenomedullin

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

Nomenclature	**Calcitonin**	**Amylin**	**CGRP**	**Adrenomedullin**
Composition	*CALCR*	*AMY1: CALCR + RAMP1* *AMY2: CALCR + RAMP2* *AMY3: CALCR + RAMP3*	*CGRP1: CALCRL + RAMP1*	*AM1: CALCRL + RAMP2* *AM2: CALCRL + RAMP3*
Ensemble 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, AM2/IMD	AMY1a: Salmon CT ⩾ AMY ⩾ CGRP > AM2/IMD > human CT > AM AMY3a: Salmon CT ⩾ AMY > CGRP > AM2/IMD > human CT > AM	CGRP > AM ⩾ AM2/IMD > AMY ⩾ salmon CT	AM1: AM ≫ CGRP, AM2/IMD > AMY > salmon CT AM2: AM ⩾ CGRP, AM2/IMD > AMY > salmon CT
Selective agonists	Human CT	AMY	αCGRP	AM
Selective antagonists	—	—	BIBN4096BS (11, Doods *et al*., 2000; Hay *et al*., 2003)	AM-(22–52) (7)
Probes	[^{125}I]-CT (salmon, 0.1 nM), [^{125}I]-CT (human, 0.1–1.0 nM)	[^{125}I]-BH-AMY (rat, 0.1–1.0 nM)	[^{125}I]-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 crossreactivity at *amylin* receptors and some AM receptors. Responsiveness to human CT can be affected by splice variation (at the rat C1b receptor it is very weak, Houssami *et al*., 1994). Particularly for AMY receptors, 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 490 amino-acid 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-RCP (a 148 amino-acid hydrophilic protein, ENSG00000126522) is important for the coupling of the CL receptor to adenylyl cyclase (Evans *et al*., 2000). When coexpressed with RAMP2, the CL receptor produces an AM receptor (AM1). RAMP3 interacts with the CL receptor to give another receptor that is responsive to AM (AM2, Fraser *et al*., 1999). There is some evidence that these AM receptors are pharmacologically distinct (Hay *et al*., 2003). Transfection of hCT(a) with any RAMP can give a receptor with a high affinity for both salmon CT and AMY and varying affinity for different antagonists (Christopoulos *et al*., 1999; Hay *et al*., 2005). hCT(a)–RAMP1 has a high affinity for CGRP, unlike hCT(a)–RAMP3 (Christopoulos *et al*., 1999; Hay *et al*., 2005). However, AMY receptor phenotype is RAMP-type- and cell-line-dependent (Tilakaratne *et al*., 2000).

[^{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 $CGRP_2$ 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, p*K*i 7.0–8.0, Juaneda *et al*., 2000). CL/RAMP1 represents 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, although in some cases it may represent CGRP acting *via* AM2 or *amylin* receptors.

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

Nomenclature	**CaR**
Other names	Parathyroid cell calcium-sensing receptor, CASR
Ensembl ID	ENSG00000036828
Principal transduction	$G_{q/11}$, $G_{i/o}$, $G_{12/13}$ (Ward *et al*., 2004)
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)
Positive allosteric modulators	NPSR568 (Nemeth el al., 1998), calindol (Petrel *et al*., 2004), cinacalcet (Nemeth *et al*., 2004)
Negative allosteric modulators	NPS2143, NPS89636 (Nemeth *et al*., 2001), Calhex-231 (Petrel *et al*., 2004), 2-benzylpyrrolidine derivatives of NPS2143 (Yang *et al*., 2005)

Positive allosteric modulators are termed calcimimetics (Hammerland *et al*., 1998) and can suppress parathyroid hormone secretion, whereas negative allosteric modulators are called calcilytics and can act to increase parathyroid hormone secretion (Nemeth *et al*., 2001).
The central role of CaR in maintaining whole-body extracellular calcium homeostasis is seen in patients with loss-of-function CaR mutations who develop familial hypocalciuric hypercalcaemia (heterozygous mutation) or neonatal severe hyperparathyroidism (homozygous mutation) and in CaR null mice (Ho *et al*., 1995), which exhibit similar increases in PTH secretion and blood Ca^{2+} levels. A gain-of-function mutation in the CaR gene is associated with autosomal dominant hypocalcaemia.

Abbreviations: **Calhex-231**, (1S,2S,1′R)-N^1-(4-chlorobenzoyl)-N^2-[1-(1-naphthyl)ethyl]-1,2-diaminocyclohexane; **calindol**, (R)-2-[1-(1-naphthyl) ethylaminomethyl]-1H-indole; **NPSR568**, (*R*)-*N*-(3-methoxy-α-phenylethyl)-3-(2-chlorophenyl)-1-propylamine hydrochloride; **NPS2143**, *N*-[(R)-2-hydroxy-3-(2-cyano-3-chlorophenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine

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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 endogenous ligands that include *N*-arachidonoylethanolamine (anandamide), *N*-homo-γ-linolenylethanolamine, *N*-docosatetra-7,10,13,16-enylethanolamine, 2-arachidonoylglycerol and 2-arachidonylglyceryl ether (noladin ether). Potency determinations are complicated by the possibility of differential susceptibility of endogenous ligands to enzymatic conversion. Both CB_1 and CB_2 receptors may be labelled with [^{3}H]-HU243 (45-61 pM; Devane *et al*., 1992; Bayewitch *et al*., 1995), [^{3}H]-CP55940 (0.6 nM; Showalter *et al*., 1996) and [^{3}H]-WIN55212-2 (2–12 nM; Slipetz *et al*., 1995; Song & Bonner, 1996).

Nomenclature	**CB_1**	**CB_2**
Ensembl ID	ENSG00000118432	ENSG00000162562
Principal transduction	$G_{i/o}$	$G_{i/o}$
Selective agonists	ACEA (Hillard *et al*., 1999), ACPA (Hillard *et al*., 1999), methanandamide (Khanolkar *et al*., 1996), O1812 (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	AM251 (8.1, Lan *et al*., 1999a), AM281 (7.9, Lan *et al*., 1999b) SR141716A (7.9, Showalter *et al*., 1996), LY320135 (6.9, Felder *et al*., 1998),	SR144528 (9.2, Rinaldi-Carmona *et al*., 1998), AM630 (7.5, Ross *et al*., 1999)
Probes	[^{3}H]-SR141716A (0.6 nM, Rinaldi-Carmona *et al*., 1996)	—

Anandamide is also a vanilloid receptor (TRPV1) agonist (Pertwee, 2004; Ross, 2003). A putative 'CB_3' receptor has been suggested following studies of the orphan 7TM receptor GPR55 (ENSG00000135898; Brown *et al*., 2005; Sjögren *et al*., 2005). Other pharmacological targets for cannabinoids have also been proposed (Begg *et al*., 2005; Pertwee, 2004). All of the compounds listed as antagonists behave as inverse agonists in some bioassay systems (Pertwee, 2005).

Abbreviations: **ACEA**, arachidonoyl-2-chloroethylamide; **ACPA**, arachidonoylcyclopropylamide; **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-dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[b,d]-pyran-[7,8-3H]-9-methanol; **HU308**, {4-[4-(1,1-dimethylheptyl)-2,6-dimethoxy-phenyl]-6,6-dimethyl-bicyclo[3.1.1]hept-2-en-2-yl}-methanol; **JWH133**, (3-(1,1-dimethyl-butyl)-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; **O1812**, (*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, also known as rimonabant; **SR144528**, *N*-([1*S*]-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide; **WIN55212-2**, (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate

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Chemokine

Overview: Chemokine receptors (nomenclature agreed by NC-IUPHAR Subcommittee on Chemokine Receptors, Murphy *et al*., 2000; Murphy, 2002) comprise a large subfamily of 7TM receptors activated by one or more of the chemokines, a large family of small cytokines.
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 and 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)
Probes	[^{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)	—	—
Probes	[^{125}I]-LARC	[^{125}I]-ELC, [^{125}I]-SLC	[^{125}I]-I309	[^{125}I]-TECK	—

Nomenclature	**CXCR1**	**CXCR2**	**CXCR3**	**CXCR4**	**CXCR5**	**CXCR6**
Other names	$IL8R_A$, IL-8 receptor type I, IL-8 receptor α	$IL8R_B$, IL-8 receptor type II, IL-8 receptor β	IP10/Mig R, GPR9	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	—	
Probes	[^{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
Probes	[^{125}I]-Fractalkine	SEAP-XCL1

Three human 7TM chemokine binding proteins have been identified that lack a known signalling function: D6 (ENSG00000144648), which binds multiple CC chemokines; a molecule previously inappropriately named CCR11 and now known as CCX CKR or the human homolog of the bovine gustatory receptor PPAR1 (ENSG00000118519, ENSG00000129048), which binds ELC, SLC and TECK; and Duffy, a highly promiscuous CC and CXC chemokine binding protein expressed mainly on erythrocytes. Specific chemokine receptors facilitate cell entry by microbes, such as *Plasmodium vivax*, HIV-1 and the poxvirus myxoma virus. Virally encoded chemokine receptors are known (e.g. US28, a homologue of CCR1 from human cytomegalovirus and ECRF3, a homologue of CXCR2 from *Herpesvirus saimiri*), but their role in viral life cycles is not established. Viruses can exploit or subvert the chemokine system by producing chemokine antagonists and scavengers.

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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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)
Probes	[^{3}H]-Devazepide (0.2 nM)	[^{3}H]-Propionyl-BC264 (0.15 nM), [^{3}H]-PD140376 (0.2 nM), [^{3}H]-L365260 (2 nM), [^{3}H]- or [^{125}I]-gastrin (1 nM), [^{125}I]-PD142308 (0.25 nM)

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

Abbreviations: **A71623**, Boc-Trp-Lys(*O*-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(3.3.1.1D-Trp)-β-Ala; **PD140548**, *N*-(α-methyl-*N*-[{tricyclo(3.3.1.1L-Trp)-D-3-(phenylmethyl)-β-Ala; **PD142308**, iodinated PD140548; **RB400**, HOOC-CH_2-CO-Trp-NMe(Nle)-Asp-Phe-NH_2; **RP73870**, ({[(*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 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*-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-*N*-(2-propynyl)-1,3-thiazol-2-amine hydrochloride

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Dopamine

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

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)	—
Probes	[^{3}H]-SCH23390 (0.2 nM), [^{125}I]-SCH23982 (0.7 nM)	[^{3}H]-Raclopride, [^{3}H]-spiperone	[^{3}H]-7-OH-DPAT, [^{3}H]-PD128907, [^{3}H]-spiperone	[^{3}H]-NGD941 (5 nM, Primus *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, 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 nonpeptide (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**
Ensemble ID	ENSG00000151617	ENSG00000136160
Principal transduction	$G_{q/11}$, G_s	$G_{q/11}$, $G_{i/o}$
Potency order	ET-1, ET-2 > ET-3 (Maguire & 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)
Probes	[^{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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Free fatty acid

Overview: Free fatty acid receptors (FFA, provisional nomenclature) are activated by free fatty acids, such that long chain saturated and unsaturated fatty acids (C16:0, C18:0, C18:1, C18:2, C18:3, n-6, C20:4, C20:5, n-3, C22:6, n-3, Briscoe *et al*., 2003; Itoh *et al*., 2003; Kotarsky *et al*., 2003) activate FFA_1 receptors, while short chain fatty acids (C4, C3 & C2) activate FFA_2 (Brown *et al*., 2003; Le Poul *et al*., 2003; Nilsson *et al*., 2003) and FFA_3 (Brown *et al*., 2003; Le Poul *et al*., 2003) receptors. The thiazolidinedione PPARγ antagonist rosiglitazone has also been suggested to activate FFA_1 (Kotarsky *et al*., 2003).

Nomenclature	**FFA_1**	**FFA_2**	**FFA_3**
Other names	GPR40 (Sawzdargo *et al*., 1997)	GPR43 (Sawzdargo *et al*., 1997). LSSIG (Senga *et al*., 2003)	GPR41 (Sawzdargo *et al*., 1997)
Ensembl ID	ENSG00000126266	ENSG00000185897	ENSG00000126262
Principal transduction	$G_{q/11}$ (Briscoe *et al*., 2003; Itoh *et al.,* 2003; Kotarsky *et al*., 2003)	$G_{q/11}$, $G_{i/o}$ (Brown *et al*., 2003; Le Poul *et al*., 2003; Nilsson *et al*., 2003)	$G_{q/11}$, $G_{i/o}$ (Brown *et al*., 2003; Le Poul *et al*., 2003)
Selective agonists	Elaidic acid (Briscoe *et al*., 2003; Itoh *et al.,* 2003)	—	—

Gpr120 (ENSG00000186188) has also been suggested to be a target for unsaturated long chain free fatty acids (Hirasawa *et al*., 2005; Katsuma *et al*., 2005). GPR42 (ENSG00000126251) is a further member of the family (ENSF00000003273) with as yet undefined characteristics (Brown *et al*., 2003).

Abbreviations: **C16:0**, palmitic acid; **C18:0**, stearic acid; **C18:1**, oleic acid; **C18:2**, linoleic acid; **C18:3,n-6**, γ-linolenic acid; **C2**, acetic acid; **C20:4**, arachidonic acid; **C20:5,n-3**, eicosapenta(5z,8z,11z,14z,17z)enoic acid, EPA; **C22:6,n-3**, docosahexa(4z,7z,10z,13z,16z,19z)enoic acid, DHA; **C3**, propionic acid; **C4**, butyric acid

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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 $GABA_{B2}$ (Bowery *et al*., 2002; Pin *et al*., 2004). The $GABA_{B1}$ subunit, when expressed alone, binds both antagonists and agonists, but the affinity of the latter is generally 10- to 100-fold less than for the native receptor. The $GABA_{B1}$ subunit when expressed alone is not transported to the cell membrane and is nonfunctional. Coexpression 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) (Bowery & Enna, 2000; Bowery *et al*., 2002; Bettler *et al*., 2004). The $GABA_{B1}$ subunit harbours the GABA (orthosteric)-binding site within an extracellular domain (ECD) venus flytrap module (VTM), whereas the $GABA_{B2}$ subunit mediates G-protein coupled signalling (Bowery *et al*., 2002; Pin *et al*., 2004). The two subunits interact allosterically in that $GABA_{B2}$ increases the affinity of $GABA_{B1}$ for agonists and reciprocally $GABA_{B1}$ facilitates the coupling of $GABA_{B2}$ to G-proteins (Pin *et al*., 2004; Kubo & Tateyama, 2005). $GABA_{B1}$ and $GABA_{B2}$ subunits assemble in a 1:1 stoichiometry by means of a coiled-coil interaction between α-helices within their carboxy-termini that masks an endoplasmic reticulum retention motif (RXRR) within the $GABA_{B1}$ subunit but other domains of the proteins also contribute to their heteromerization (Bettler *et al*., 2004; Pin *et al*., 2004). Four isoforms of the human $GABA_{B1}$ subunit have been cloned. The predominant $GABA_{B1(a)}$ and $GABA_{B1(b)}$ isoforms, which are most prevalent in neonatal and adult brain tissue, respectively, differ in their ECD sequences as a result of the use of alternative transcription initiation sites. Isoforms generated by alternative splicing are $GABA_{B1(c)}$ that differs in the ECD, and $GABA_{B1(e)}$, which is a truncated protein that can heterodimerize with the $GABA_{B2}$ subunit but does not constitute a functional receptor. Only the 1a and 1b variants are identified as components of native receptors (Bowery *et al*., 2002). Additional $GABA_{B1}$ subunit isoforms have been described in rodents (reviewed by Bettler *et al*., 2004).

Nomenclature	**$GABA_{B1,2}$**
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)
Positive allosteric modulators	CGP7930, GS39783 (see Bettler *et al*., 2004)
Probes	[^{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 $GABA_{B(1)}$ 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 (Galvez *et al*., 2000). In cerebellar Purkinje neurones, the interaction of Ca^{2+} with the $GABA_B$ receptor enhances the activity of mGlu1, probably *via* a direct association between the two receptors (Tabata *et al*., 2004). Synthetic positive allosteric modulators appear to act on the heptahelical domain of the $GABA_{B2}$ subunit (Pin *et al*., 2004). Knockout of the $GABA_{B1}$ subunit in C57B mice causes the development of severe tonic-clonic convulsions that prove fatal within a month of birth, whereas $GABA_{B1}^{-/-}$ BALB/c mice, although also displaying spontaneous epileptiform activity, are viable. The phenotype of the latter animals additionally includes hyperalgesia, hyperlocomotion, memory impairment and behaviours indicative of anxiety (Enna & Bowery, 2004). A similar phenotype has been found for $GABA_{B2}^{-/-}$ BALB/c mice (Gassmann *et al*., 2004).

Abbreviations: **3-APMPA (CGP35024)**, 3-amino-propyl-(P-methyl)-phosphinic acid; **3-APPA (CGP27492)**, 3-amino-propyl-phosphinic acid; **CGP7930**, 2,6-Di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol; **CGP35348**, p-(3-aminopropyl)-*P*-diethoxymethylphosphinic acid; **CGP44532**, 3-amino-2-hydroxypropylmethylphosphinic acid; **CGP54626**, [*S*-(*R*,*R*)]-[3-[[1-(3,4-dichlorophenyl)ethyl]amino]-2-hydroxypropyl](cyclohexylmethyl)phosphinic acid; **CGP55845**, 3-[-1-(*S*)-(3,4-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*)-hydroxypropyl]amino]ethyl-benzoic acid; **CGP71872**, 3-(1-(*R*)-(3-((5-(4-azido-2-hydroxy-5-iodobenzoylamino)pentyl)hydroxyphosphoryl)-2-(*S*)-hydroxypropylamino)ethyl)-benzoic acid; **GS39783**, *N*,*N*′-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine; **SCH90511**, (+)-(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 and 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 to 1 nM (Skofitsch *et al*., 1986; Smith *et al*., 1997; 1998; Wang *et al*., 1997; Fitzgerald *et al*., 1998). Porcine galanin-(3–29) does not bind to cloned GAL1, GAL2 or GAL3 receptors, but a receptor that is functionally activated by porcine galanin-(3–29) has been reported in pituitary and gastric smooth muscle cells (Wynick *et al*., 1993; Gu *et al*., 1995). Additional galanin receptor subtypes are also suggested from studies with chimeric peptides (e.g M15, M35 and M40), which act as antagonists in functional assays in the cardiovascular system (Ulman *et al*., 1993), spinal cord (Wiesenfeld-Hallin *et al*., 1992), locus coeruleus, hippocampus (Bartfai *et al*., 1991) and hypothalamus (Leibowitz and Kim, 1992; Bartfai *et al*., 1993), but exhibit agonist activity at some peripheral sites (Bartfai *et al*., 1993; Gu *et al*., 1995). The chimeric peptides M15, M32, M35, M40 and C7 are agonists at GAL1 receptors expressed endogenously in Bowes human melanoma cells (Ohtaki *et al*., 1999), and at heterologously expressed recombinant GAL1, GAL2 and GAL3 receptors (Smith *et al*., 1997; Fitzgerald *et al*., 1998; Smith *et al*., 1998).

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

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Ghrelin

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

Nomenclature	**Ghrelin**
Other names	GHS-R1a (Growth hormone secretagogue receptor type 1), growth hormone-releasing peptide receptor
Ensembl ID	ENSG00000121853
Principal transduction	$G_{q/11}$
Rank order of potency	Ghrelin = des-Gln-ghrelin (Matsumoto *et al*., 2001; Bedendi *et al*., 2003)
Probes	[^{125}I-His9]-ghrelin (0.4 nM, Katugampola *et al*., 2001), [^{125}I-Tyr^{4}]-ghrelin (0.5 nM, Bedendi *et al*., 2003), [^{125}I]-Tyr^{4}-des-octanoyl (0.7 nM, Bedendi *et al*., 2003)

Des-octanoyl ghrelin has recently been shown to bind (as [^{125}I]-Tyr^{4}-des-octanoyl ghrelin) and have effects in the cardiovascular system (Bedendi *et al*., 2003), which raises the possible existence of different receptor subtypes in peripheral tissues and the central nervous sysytem. One study has reported constitutive activity of the ghrelin receptor and has identified a potent inverse agonist ([D-Arg^{1}, D-Phe^{5}, D-Trp^{7,9},Leu^{11}]-substance P, EC_{50} 5.2 nM; Holst *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), glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory polypeptide or GIP, ENSG00000159224), growth hormone-releasing hormone (GHRH, ENSG00000118702) and secretin (ENSG00000070031). One common precursor (ENSG00000115263) generates glucagon, GLP-1 and GLP-2 peptides (Irwin, 2001).

Nomenclature	**Glucagon**	**GLP-1**	**GLP-2**
Ensembl ID	ENSG00000141558	ENSG00000112164	ENSG00000065325
Principal transduction	G_s	G_s	G_s
Selective agonists	Glucagon	GLP-1-(7-37) (Dillon *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
Selective antagonists	L168049 (Cascieri *et al*., 1999), des-His^{1}-[Glu^{9}]glucagon amide (Post *et al*., 1993), BAY27-9955 (Petersen and Sullivan, 2001), xNNC92-1687 (Madsen *et al*., 1998)	Exendin-(9-39) (Thorens *et al*., 1993); T0632 (Tibaduiza *et al*., 2001)	—
Probes	[^{125}I]-glucagon	[^{125}I]-GLP-1-(7-36) amide, [^{125}I]-exendin, [^{125}I]-exendin-(9-39), [^{125}I]-GLP-1-(7-37)	—

Nomenclature	**GIP**	**GHRH**	**Secretin**
Ensembl ID	ENSG00000010310	ENSG00000106128	ENSG00000080293
Principal transduction	G_s	G_s	G_s
Selective agonists	GIP	BIM28011 (Coy *et al*., 1996)	Secretin
Selective antagonists	—	JV-1-36 (Schally and Varga, 1999), JV-1-38 (Schally and Varga, 1999)	[$(CH_2NH)^{4,5}$]secretin (Kim *et al*., 1993)
Probes	[^{125}I]-GIP	[^{125}I]-GHRH	[^{125}I]-(Tyr^{10})secretin

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

Abbreviations: **BAY27-9955**, (+)-3,5-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; **T0632**, sodium (*S*)-3-(1-[2-fluorophenyl]-2,3-dihydro-3-[{3-isoquinolinyl}-carbonyl]amino-6-methoxy-2-oxo-1*H*-indole)propanoate

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Glutamate, metabotropic

Overview: Metabotropic glutamate (mGlu) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors, Schoepp *et al*., 2000) are activated by the endogenous ligands L-glutamate, L-aspartate, L-serine-*O*-phosphate (LSOP), *N*-acetylaspartylglutamate (NAAG) and L-cysteine sulphonic acid. 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 mGlu 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). 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 Further reading). Group I mGlu receptors may be activated by DHPG and 3HPG (Brabet *et al*., 1995), and antagonized by LY393675 (Baker *et al*., 1998). Group II mGlu receptors may be activated by LY389795 (Monn *et al*., 1999), LY379268 (Monn *et al*., 1999), LY354740 (Schoepp *et al*., 1997; Wu *et al*., 1998), DCG-IV and 2*R*,4*R*-APDC (Schoepp *et al*., 1996), and antagonised by EGLU (4.3, Jane *et al*., 1996) and LY307452 (Escribano *et al*., 1998; Wermuth *et al*., 1996). Group III mGlu receptors may be activated by (*RS*)PPG (Gasparini *et al*., 1999a).

In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as 'potentiators' of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist. Examples of these unique pharmacological agents have been described for $mGlu_1$, $mGlu_2$, $mGlu_4$ and $mGlu_5$.

Nomenclature	**$mGlu_1$**	**$mGlu_2$**	**$mGlu_3$**	**$mGlu_4$**
Other names	$mGluR_1$	$mGluR_2$	$mGluR_3$	$mGluR_4$
Ensembl ID	ENSG00000152822	ENSG00000164082	ENSG00000105781	ENSG00000124493
Principal transduction	$G_{q/11}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Selective agonists	—	—	NAAG (Wroblewska *et al*., 1997)	L-AP4, LSOP (Wu *et al*., 1998),
Selective positive allosteric modulators	Ro01-6128, Ro67-4853, Ro67-7476 (Knoflach *et al*., 2001)	LY487379 (Johnson *et al*., 2003), CBiPES (Johnson *et al*., 2005)	—	(−)-PHCCC (Maj *et al*., 2003), SIB1893, MPEP (Mathiesen *et al*., 2003)
Selective competitive antagonists	3-MATIDA (Moroni *et al*., 2002), AIDA (Moroni *et al*., 1997), (*S*)-(+)-CBPG (Mannaioni *et al*., 1999), LY367385 (Clark *et al*., 1997), (*S*)-TBPG (Constantino *et al*., 2001)	PCCG-4 (Pellicciari *et al*., 1996)	—	MAP4
Selective negative allosteric modulators	CPCCOEt (Litschig *et al*., 1999), BAY36-7620 (Carroll *et al*., 2001), LY456236 (Li *et al*., 2002), 3,5-DMPPP (Micheli *et al*., 2003), EM-TBPC (Malherbe *et al*., 2003), JNJ16259685 (Lavreysen *et al*., 2004)	—	—	—

Nomenclature	**$mGlu_5$**	**$mGlu_6$**	**$mGlu_7$**	**$mGlu_8$**
Other names	$mGluR_5$	$mGluR_6$	$mGluR_7$	$mGluR_8$
Ensembl ID	ENSG00000168959	ENSG00000113262	ENSG00000168160	ENSG00000179603
Principal transduction	$G_{q/11}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Selective agonists	CHPG (Doherty *et al*., 1997), (*S*)-(+)-CBPG (Mannaioni *et al*., 1999)	Homo-AMPA (Bräuner-Osborne *et al*., 1996), 1-benzyl-APDC (Tuckmantel *et al*., 1997)	LSOP (Wu *et al*., 1998), L-AP4	LSOP (Wu *et al*., 1998), L-AP4, (*S*)-3,4-DCPG (Thomas *et al*., 2001)
Selective positive allosteric modulators	DFB (O'Brien *et al*., 2003), CPPHA (O'Brien *et al*., 2004), CDPPB (Kinney *et al*., 2005)	—	AMN082 (Flor *et al*., 2005)	—
Selective competitive antagonists	ACDPP (6.5, Bonnefous *et al*., 2005)	MAP4, THPG (Thoreson *et al*., 1997)	—	MPPG (Wu *et al*., 1998)
Selective negative allosteric modulators	SIB1757 (Varney *et al*., 1999), SIB1893 (Varney *et al*., 1999), MPEP (Gasparini *et al*., 1999b), MTEP (Brodkin *et al*., 2002), fenobam (Porter *et al*., 2005), YM298198 (Kohara *et al*., 2005)	—	—	—

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (for example, [^{3}H]-R214127 (Lavreysen *et al*., 2003) and [^{3}H]-YM298198 (Kohara *et al*., 2005) at $mGlu_1$ receptors and [^{3}H]-methoxyMPEP (Gasparini *et al*., 2002) and [^{3}H]-methoxymethyl-MTEP (Anderson *et al*., 2002) at $mGlu_5$ receptors. Although a number of radioligands have been used to examine binding using native tissues, correlation with individual subtypes is limited. Many pharmacological agents have not been fully tested across all known subtypes of mGlu receptors. Potential differences linked to the species (e.g. human *versus* rat or mouse) of the receptors and the receptor splice variants are generally not known. The influence of receptor expression level on pharmacology and selectivity has not been controlled for in most studies, particularly those involving functional assays of receptor coupling.

(*S*)-(+)-CBPG is an antagonist at $mGlu_1$, 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 (Klein *et al*., 1997; Pellegrini-Giampietro *et al*., 1996).

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; **AMN082**, *N*, *N*′-bis(diphenylmethyl)-1,2-ethanediamine dihydrochloride; **L-AP4**, *S*-2-amino-4-phosphonobutyrate; **2*R*,4*R*-APDC**, aminopyrrolidine-2*R*,4*R*-dicarboxylate; also known as LY314593; **BAY 36-7620**, (3a*S*,6a*S*)-6a-naphtalan-2-ylmethyl-5-methyliden-hexahyrol-cyclopenta[c]furan-1-one; **CBiPES**, *N*-[4′-cyano-biphenyl-3-yl]-*N*-(3-pyridinylmethyl)-ethanesulphonamide hydrochloride; **(*S*)-(+)-CBPG**, (*s*)-(1)-2-(39-carboxybicycle[1.1.1]pentyl)glycine; **L-CCG-I**, (2*S*,3*S*,4*S*)α-(carboxycyclopropyl)glycine; **CDPPB**, 3-cyano-*N*-(1,3-diphenyl-1*H*-[pyrazol-5-yl)benzamide; **CPCCOEt**, cyclopropan[*b*]chromen-1*a*-carboxylate; **4CPG**, 4-carboxyphenylglycine; **CPPHA**, *N*-{4-chloro-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]phenyl}-2-hydroxybenzamide; **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; **DMPPP**, 3,5-dimethyl pyrrole-2,4-dicarboxylic acid 2-propyl ester 4-(1,2,2-tri-methyl-propyl) ester; **EGLU**, (*s*)-α-ethylglutamate; **fenobam**, *N*-(3-chlorophenyl)-*N*′-(4,5-dihydrol-1-methyl-4-oxo-1-*H*-imidazole-2-yl)-urea; **3HPG**, 3-hydroxyphenylglycine; **[^{11}C]-JNJ-16567083**, (3-ethyl-2-[^{11}C]methyl-6-quinolinyl)(*cis*-4-methoxycyclohexyl) methanone; **JNJ16259685**, (3,4-dihydro-2*H*-pyrano[2,3]b-quinolinyl-7-yl)(*cis*-4-methoxycyclohexyl)methanone; **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; **LY456066**, (2-[4-(indan-2-ylamino)-5,6,7,8-tetrahydro-quinazolin-2-ylsulfanyl]-ethanol,hydrochloride; **LY456236**, [(4-methoxy-phenyl)-(6-methoxy-quinazolin-4-yl)-amine hydrochloride; **LY487379**, 2,2,2-trifluoro-*N*-[4-(2-methoxyphenoxy)phenyl]-*N*-(3-pyridinylmethyl)-ethanesulphonamide; **3-MATIDA**, α-amino-5-carboxy-3-methyl-2-thiopheneacetic acid; **MAP4**, (*S*)-2-methyl-2-amino-4-phosphonobutanoate; **MPEP**, 2-methyl-6-(phenylethynyl)-pyridine; **methoxy-MPEP**, 2-methyl-6-((3-methoxyphenyl)ethynyl)-pyridine; **methoxy-PEPy**, 3-methoxy-5-(pyridin-2-yl-ethynyl)-pyridine; **MPPG**, (*RS*)-α-methyl-4-phosphonophenylglycine; **MTEP**, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; **methoxymethyl-MTEP**, 3-(methoxymethyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; **NAAG**, *N*-acetylaspartylglutamate, also known as spaglumic acid; **PCCG-4**, (2*S*,1′*S*,2′*S*,3′*R*)-2-(2′-carboxy-3′-phenylcyclopropyl)glycine; **PHCCC**, *N*-phenyl-7-(hydroxylimino)cyclopropa[b]chromen-1a-carboxamide; **(*RS*)PPG**, (*R*,*S*)-4-phosphonophenylglycine; **R214127**, 1-(3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-2-phenyl-1-ethanone; **Ro01-6128**, diphenylacetyl-carbamic acid ethyl ester; **Ro67-4853**, (9*H*-xanthene-9-carbonyl)-carbamic acid butyl ester **Ro67-7476**, (*S*)-2-(4-fluoro-phenyl)-1-(toluene-4-sulphonyl)-pyrrolidine; **SIB1757**, 6-methyl-2-(phenylazo)-3-pyrindol; **SIB1893**, ([phenylazo]-3-pyrindole)-2-methyl-6-(2-phenylethenyl)pyridine; ***S*-TBPG**, 2-(3′-(1*H*-tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl)glycine; **THPG**, (*RS*)-3,4,5-trihydroxyphenylglycine; **YM298198**, (6-{[(2-methoxyethyl)amino]methyl}-*N*-methyl-*N*-neopentylthiaolo[3,2-a]benzoimidazole-2-carboxamide

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Glycoprotein hormone

Overview: Glycoprotein hormone receptors (provisional nomenclature) are activated by a heterodimeric glycoprotein made up of a common α chain (116 aa ENSG00000135346), with a unique β chain that confers the biological specificity to FSH (follicle-stimulating hormone, follitropin, 129 aa, ENSG00000131808), LH (luteinizing hormone, lutropin, 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
Probes	[^{125}I]-FSH	[^{125}I]-LH, [^{125}I]-CG	[^{125}I]-TSH

Animal follitropins are less potent than the human hormone as agonists at the human FSH receptor. Autoimmune antibodies that act as agonists of the TSH receptor are found in patients with Grave's disease (see Rapoport *et al*., 1998). Gain- and loss-of-function mutations of the FSH receptor are associated with human reproductive disorders (Aittomaki *et al*., 1995; Beau *et al*., 1998; Gromoll *et al*., 1996; Touraine *et al*., 1999). Loss-of-function mutations of the LH receptor are associated with Leydig cell hypoplasia and gain-of-function mutations are associated with male-limited gonadotropin-independent precocious puberty (e.g. Latronico and Segaloff, 1999; Shenker, 2002) and Leydig cell tumours (Liu *et al*., 1999). Mutations of the TSH receptor exhibiting constitutive activity underlie hyperfunctioning thyroid adenomas (Parma *et al*., 1993) and congenital hyperthyroidism (Kopp *et al*., 1995). TSH receptor loss-of-function mutations are associated with thyrotropin resistance (Sunthornthepvarakul *et al*., 1995). The rat FSH receptor also stimulates phosphoinositide turnover through an unidentified G protein (Quintana *et al*., 1994).

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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 related peptides such as 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) have been found in mammals (Sealfon *et al*., 1997; Millar, 2002). GnRH receptors have been cloned from numerous species (most of which express two or three types of GnRHR) and grouped phylogenetically (Silver *et al*., 2005). Type I GnRHRs are expressed primarily by pituitary gonadotrophs in mammals and mediate central control of reproduction. They are selectively activated by GnRH I and all lack the C-terminal tails found in other seven transmembrane region receptors. Type II GnRHRs include all non-mammalian GnRHRs as well as the recently cloned type II primate GnRHRs. They all possess C-teminal tails and (where tested) are selective for GnRH II (over GnRH I). An alternative phylogenetic classification (see Millar et al., 2004) divided these receptors into three classes and includes both GnRH I-selective mammalian type I GnRHRs and GnRH II-selective non-mammalian receptors in type I. Although thousands of peptide analogues of GnRH I have been synthesised and several (agonists and antagonists) are used therapeutically (Kiesel *et al*., 2002), the potency of most of these peptides at type II GnRHRs is unknown.

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

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

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Histamine

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

Nomenclature	H_1	H_2	H_3	H_4
Ensembl ID	ENSG00000171088	ENSG00000168546	ENSG00000146013	ENSG00000125861
Principal transduction	$G_{q/11}$	G_s	$G_{i/o}$	$G_{i/o}$
Selective agonists	Histaprodifen, N^{α}-methylhistaprodifen	Amthamine	*R*-α-Methylhistamine, imetit, immepip	Clobenpropit, 4-methylhistamine
Selective antagonists	Triprolidine (9.9), mepyramine (9.1)	Tiotidine (7.8), ranitidine (7.1)	Clobenpropit (9.9), iodophenpropit (9.6), thioperamide (8.4)	JNJ7777120 (8.1)
Probes	[^{3}H]-Mepyramine (1 nM), [^{11}C]-Mepyramine, [^{11}C]-doxepin	[^{3}H]-Tiotidine (15 nM), [^{125}I]-iodoaminopotentidine (0.3 nM)	[^{3}H]-*R*-α-Methylhistamine (0.5 nM), [^{3}H]-N^{α}-methylhistamine (2 nM), [^{125}I]-iodophenpropit (0.6 nM), [^{125}I]-iodoproxyfan (0.06 nM)	[^{3}H]-JNJ7777120 (3.6 nM)

Histaprodifen and N^{α}-methylhistaprodifen are reduced efficacy agonists. 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). Moreover, 4-methylhistamine is identified as a high affinity, full agonist for the human H_4 receptor (Lim *et al*., 2005). [^{3}H]-Histamine has been used to label the H_4 receptor in heterologous expression systems.

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Leukotriene

Overview: Leukotriene receptors (nomenclature agreed by NC-IUPHAR on Leukotriene and Lipoxin Receptors, Brink *et al*., 2003) are activated by the endogenous ligands leukotriene (LT) 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 nonspecific effects.

Nomenclature	**BLT_1**	**BLT_2**	**$CysLT_1$**	**$CysLT_2$**
Other names	LTB_4	—	HG55, HMTMF81, LTD_4	HPN321, LTC_4
Ensemble ID	ENSG00000116329	ENSG00000082556	ENSG00000112038	ENSG00000125510
Principal transduction	$G_{q/11}$, $G_{i/o}$	$G_{q/11}$, $G_{i/o}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	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)	—
Probes	[^{3}H]-LTB_4 (0.2–0.7 nM), [^{3}H]-CGS23131 (13 nM)	[^{3}H]-LTB_4 (0.2–23 nM)	[^{3}H]-LTD_4, [^{3}H]-ICI198615	[^{3}H]-LTD_4

BAYu9773 is an antagonist at $CysLT_1$ (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 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). In addition, a soluble hydrolytic product of protease action on the urokinase-type plasminogen activator receptor has been reported to activate the ALX receptor (Resnati *et al*., 2002). Furthermore, ALX has been suggested to act as a receptor mediating proinflammatory actions of the acute-phase reactant, serum amyloid A (Su *et al*., 1999; Sodin-Semrl *et al*., 2004).

Nomenclature	**ALX**
Other names	FPRL1, FPR2, FPRH2, RFP
Ensembl ID	ENSG00000171049
Principal transduction	G_i (Maddox *et al*., 1997)
Rank order of potency	$LXA_4 = ATL = ATLa2 > LTC_4 = LTD_4 \gg$ 15-deoxy-$LXA_4 \gg$ fMLP (Clish *et al*., 1999; Fiore *et al*., 1994; Fiore and Serhan, 1995; Gronert *et al*., 2001; Takano *et al*., 1997)
Selective agonists	LXA_4, ATL, ATLa2 (Guilford *et al*., 2004)
Probes	[^{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 and Serhan, 1996; Romano *et al*., 1996; Ariel *et al*., 2003).

Abbreviations: **ANXA1**, annexin 1; **ATL**, aspirin-triggered lipoxin A_4 [15-epi-LXA_4, 5*S*,6*R*,15*R*-trihydroxyl-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid]; **ATLa2**, ATL analog [15-epi-16-(para-fluoro)-phenoxy-LXA_4]; **LTC_4**, leukotriene C_4; **LTD_4**, leukotriene D_4; **LXA_4**, lipoxin A_4 [5*S*,6*R*,15*S*-trihydroxyl-7,9,13-*trans*-11-*cis*-eicosatetraenoic acid]

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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 nonspecific binding, and therefore the relationship between recombinant and endogenously expressed receptors is unclear. Targeted deletion of LPA receptors has clarified signalling pathways and identified physiological and pathophysiological roles. LPA has also been described to be an agonist at PPAR-γ receptors (McIntyre *et al*., 2003), although the physiological significance of this observation is currently unclear (Simon *et al*., 2005).

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. None of the currently available chemical tools have validated specificity *in vivo*.

Abbreviations: **DGPP 8:0**, dioctanoylglycerol pyrophosphate; **FAP10**, decanol phosphate; **FAP12**, dodecanol phosphate; **Ki16425**, 3-(4-[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)	—
Probes	[^{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	—	—	—
Ensemble ID	ENSG00000141037	ENSG00000185231	ENSG00000124089	ENSG00000166603	ENSG00000176136
Principal transduction	Gs	G_s	G_s	G_s	G_s
Rank order of potency	α-MSH > β-MSH ⩾ACTH, γ-MSH	ACTH	γ-MSH, β-MSH ⩾ACTH, α-MSH	β-MSH ⩾α-MSH, ACTH > γ-MSH	α-MSH ⩾β-MSH ⩾ACTH > γ-MSH
Selective agonists	—	—	D-Trp^8-γ-MSH (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)	—
Probes	[^{125}I]-NDP-MSH	[^{125}I]-ACTH-(1–24)	[^{125}I]-NDP-MSH, [^{125}I]-SHU9119	[^{125}I]-NDP-MSH, [^{125}I]-SHU9119	[^{125}I]-NDP-MSH

Polymorphisms of the 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(6$\beta\rightarrow$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 and Mullins, 1993; Popova and Dubocovich, 1995; Molinari *et al*., 1996; Lucchelli *et al*., 1997), 5MCA-NAT (Popova and 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 and Sugden, 1998)	Prazosin (Lucchelli *et al*., 1997)
Probes	[^{3}H]-melatonin (Browning *et al*., 2000)	[^{3}H]-melatonin (Browning *et al*., 2000)	2-iodo-[^{125}I]-5MCA-NAT (Molinari *et al*., 1996)

Melatonin, 2-iodo-melatonin, S20098, GR196429, LY156735 and TAK375 (Kato *et al*., 2005) are nonselective agonists for MT_1 and MT_2 receptors. 2-Iodo-[^{125}I]-melatonin can be used to label all three melatonin receptor subtypes. (−)-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 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: **4P-PDOT**, 4-phenyl-2-propionamidotetraline; **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; **LY156735**, *β*-methyl-6-chloromelatonin; **5MCA-NAT**, 5-methoxy-carbonylamino-*N*-acetyltryptamine; **S20098**, *N*-(2-[7-methoxy-1-naphthalenyl]ethyl)acetamide; **TAK375**, (S)-N-[2(1,6,7,8-tetrahydro-2H-indeno [5,4-b]furan-8-yl)ethyl]propionamide

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Motilin

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

Nomenclature	**Motilin**
Other names	MTLR1 (Feighner *et al*., 1999), GPR38 (Mckee *et al*., 1997)
Ensembl ID	ENSG00000102539
Principal transduction	$G_{q/11}$ (Depoortere & Peeters, 1995; Feighner *et al*., 1999)
Selective agonists	ABT229 (Lartey *et al*., 1995)
Probes	[^{125}I]-motilin (0.1 nM, Feighner *et al*., 1999)

Abbreviations: **ABT229**, 8,9-anhydro-4″-deoxy-3′-*N*-desmethyl-3′-*N*-ethylerythromycin B 6,9-hemiacetal

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Neuromedin U

Overview: Neuromedin U receptors (provisional nomenclature) are activated by the endogenous 25 aa peptide neuromedin U (NMU), originally isolated from pig spinal cord (Minamino *et al*., 1985). In humans, NMU appears to be the sole product of a precursor (ENSG00000109255) showing a broad tissue distribution, but which is expressed at highest levels in the upper gastrointestinal tract, CNS, bone marrow and fetal liver. Shorter versions of NMU are found in some species, being derived at least in some instances from the proteolytic cleavage of the longer NMU. Despite species differences in NMU structure, the C-terminal region (particularly the C-terminal pentapeptide) is highly conserved and contains biological activity.

Nomenclature	**NMU_1**	**NMU_2**
Other names	GPR66, FM3 (Hedrick *et al*., 2000; Kojima *et al*., 2000; Szekeres *et al*., 2000)	FM4 (Howard *et al*., 2000), TGR1 (Hosoya *et al*., 2000)
Ensembl ID	ENSG00000171596	ENSG00000132911
Principal transduction	$G_{q/11}$ (Hedrick *et al*., 2000)	$G_{q/11}$ (Hosoya *et al*., 2000)
Probes	[^{125}I]-NMU-25, Cy3B-tagged NMU-8 (Brighton *et al*., 2004a)	—

NMU receptors couple predominantly to $G_{q/11}$, although there is evidence of coupling to $G_{i/o}$ (see Hosoya *et al*., 2000; Brighton *et al*., 2004a).

Abbreviations: **NMU**, neuromedin U

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Neuropeptide Y

Overview: Neuropeptide Y (NPY) receptors (nomenclature agreed by NC-IUPHAR on Neuropeptide Y Receptors, see Michel *et al*., 1998) are activated by the endogenous peptides NPY, NPY-(3-36), peptide YY (PYY), PYY-(3-36) and pancreatic polypeptide (PP). The y6 receptor is a functional gene product in mouse, absent in rat, but contains a frame-shift mutation in primates producing a truncated nonfunctional gene (Gregor *et al*., 1996). Many of the agonists exhibit differing degrees of selectivity 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 (Eriksson *et al*., 1998). In addition, many agonists lack selectivity for individual subtypes, but can exhibit comparable potency against pairs of NPY receptor subtypes, or have not been examined for activity at all subtypes. [^{125}I]-PYY or [^{125}I]-NPY can be used to label Y_1, Y_2, Y_5 and y_6 subtypes non-selectively, while [^{125}I]-[hPP1-17,Ala^{31},Aib^{32}]NPY may be used to label Y_5 receptors preferentially.

Nomenclature	**Y_1**	**Y_2**	**Y_4**	**Y_5**	**y_6**
Other names	—	—	PP_1	—	Y_5, PP_2, Y_{2B}
Ensembl ID	ENSG00000164128	ENSG00000185149	ENSG00000169556	ENSG00000164129	ENSG00000159279
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Rank order of potency	NPY ⩾ PYY ≫ PP	NPY ⩾ PYY ≫ PP	PP > NPY = PYY	NPY ⩾ PYY ⩾ PP	NPY = PYY > PP
Selective agonists	[Leu^{31},Pro^{34}]NPY, [Pro^{34}]NPY, [Leu^{31},Pro^{34}]PYY, [Pro^{34}]PYY	NPY-(3-36), PYY-(3-36)	PP	[Ala^{31},Aib^{32}]NPY (Cabrele *et al*., 2000)	—
Selective antagonists	BIBO3304 (9.5, Wieland *et al*., 1998), BIBP3226 (8.2, Gerald *et al*., 1996)	BIIE0246 (8.5, Doods *et al*., 1999)	—	L152804 (7.6, Kanatani *et al*., 2000)	—
Probes	[^{125}I]-[Leu^{31},Pro^{34}] NPY, [^{3}H]-BIBP3226 (2.1 nM)	[^{125}I]-PYY-(3-36)	[^{125}I]-PP	[^{125}I]-[hPP1-17, Ala^{31}, Aib^{32}] NPY (Dumont *et al*., 2003)	—

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 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; **L152804**, 2-(3,3-dimethyl-1-oxo-4H-1*H*-xanthen-9-yl)-5,5-dimethyl-cyclohexane-1,3-dione

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Neuropeptides B and W

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

Nomenclature	**NPBW1**	**NPBW2**
Other names	GPR7	GPR8
Ensembl ID	ENSG00000183729	ENSG00000125522
Principal transduction	$G_{i/0}$ (Mazzocchi *et al*., 2005)	$G_{i/0}$ (Mazzocchi *et al*., 2005)
Rank order of potency	NPB-29 > NPB-23 > NPW-23 > NPW-30 (Brezillon *et al*., 2003)	NPW-23 > NPW-30 > NPB-29 > NPB-23 (Brezillon *et al*., 2003)
Probes	[^{125}I]-NPW-23 (0.44 nM, Singh *et al*., 2004)	[^{125}I]-NPW-23

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

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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)	—
Probes	[^{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 its degradation (Nielsen *et al*., 1999). It has been reported to interact with the NTS1 receptor (Martin *et al*., 2002) and has been implicated in hormone trafficking and/or neurotensin uptake.

Abbreviations: **JMV449**, *H*-Lysψ(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), and endomorphin-1 and -2, although several other opioid-like peptides are found in the CNS. The Greek letter names for the opioid receptors, μ, κ, and δ, are well established and, despite digressions into other nomenclatures (Dhawan *et al*., 1996), IUPHAR appears to now consider these original names most appropriate (Foord *et al*., 2005). 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 receptor**	**Kappa opioid receptor**	**Mu opioid receptor**	**N/OFQ receptor**
Preferred abbreviation	δ	κ	μ	NOP
Other names	OP_1, DOP, DOR	OP_2, KOP, KOR	OP_3, MOP, MOR	ORL1, OP_4
Ensembl ID	ENSG00000116329	ENSG00000082556	ENSG00000112038	ENSG00000125510
Principal transduction	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Rank order of potency	β-End = leu = met > dynA	dynA$\gg\beta$-end > leu > met	β-End > dynA > met = leu	N/OFQ$\gg$dynA
Selective agonists	DPDPE (Mosberg *et al*., 1983), DSBULET (Delay-Goyet *et al*., 1988), [DAla^2]deltorphin I or II (Erspamer *et al*., 1989), SNC80 (Bilsky *et al*., 1995)	U69593 (Lahti *et al*., 1985), CI977 (Hunter *et al*., 1990), Salvinorin A (Roth *et al*., 2002)	Endomorphin-1 and -2 (Zadina *et al*., 1997), morphine (Goldstein & Naidu, 1989), DAMGO (Handa *et al*., 1981), 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), UFP102 (Carra' *et al*., 2005)
Selective antagonists	Naltrindole (Portoghese *et al*., 1988)	Nor-binaltorphimine (Portoghese *et al*., 1987)	CTAP (Pelton *et al*., 1986)	J113397 (8.3, Kawamoto *et al*., 1999), SB612111 (8.5, Zaratin *et al*., 2004), UFP101 (7.2, Calo' *et al*., 2002)
Probes	[^{3}H]-DPDPE (Goldstein & Naidu, 1989), [^{3}H]-naltrindole (Yamamura *et al*., 1992), [^{3}H]-Deltorphin II (Gomes *et al*., 2000)	[^{3}H]-U69593 (Lahti *et al*., 1985), [^{3}H]-CI977 (Simonin *et al*., 2001)	[^{3}H]-DAMGO (Goldstein & Naidu, 1989), [^{3}H]-PL017 (Hawkins *et al*., 1987)	[^{3}H]-N/OFQ (Dooley & Houghten, 1996), [^{3}H]-Leu-N/OFQ, [^{125}I]-Tyr^{14}-N/OFQ

Subtypes of μ (μ1, μ2), δ (δ1, δ2) and κ (κ1, κ2, κ3) receptor have been proposed based primarily on binding studies with poorly selective ligands or *in vivo* studies. Only three naloxone-sensitive opioid receptors have been cloned, and most evidence suggests that these receptors undergo minimal alternative splicing, and certainly none that can be shown to give rise to any of the subtypes proposed. There is at present no molecular basis for any of the opioid receptor subtypes, although it remains possible that they are formed by heterodimerization of opioid receptors with each other or with other 7TM receptors (Jordan & Devi, 1999). 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 hydrochloride; **CTAP**, D-Phe-*cyc*[Cys-Tyr-D-Trp-Arg-Thr-Pen]-Thr-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; **ICI174864**, *N*,*N*-diallyl-Tyr-Aib-Phe-Leu-OH (Aib is aminoisobutyric acid); **J113397**, 1-[(3*r*,4*r*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one; **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; **SB612111**, (−)-*cis*-1-methyl-7-[[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol; **SNC80**, (+)-4-[(αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide; **U69593**, 5α,7α,8β-(−)-*N*-methyl-*N*-(7-[1-pyrrolidinyl]-1-oxaspiro(4,5)-dec-8-yl)benzene acetamide; **UFP101**, [Nphe^1,Arg^{14},Lys^{15}]nociceptin-NH_2; **UFP-102**, [(pF)Phe^4,Arg^{14},Lys^{15}]N/OFQ-NH_2

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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-methyylbenzoxanzol-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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Oxoeicosanoid

Overview: Oxoeicosanoid receptors (OXE, nomenclature agreed by NC-IUPHAR on Oxoeicosanoid Receptors; Brink *et al*., 2004) are activated by endogenous chemotactic eicosanoid ligands oxidised at the C-5 position, with 5-oxo-ETE the most potent agonist identified for this receptor.

Nomenclature	**OXE**
Other names	TG1019 (Hosoi *et al*., 2002), R527 (Jones *et al*., 2003)
Ensembl ID	ENSG00000162881
Principal transduction	$G_{i/o}$ (O'Flaherty *et al*., 2000; Hosoi *et al*., 2002; Jones *et al*., 2003; Hosoi *et al*., 2005)
Rank order of potency	5-Oxo-ETE≫5(*S*)-HpETE > 5(*S*)-HETE (Hosoi *et al*., 2002; Jones *et al*., 2003)
Selective agonists	5-Oxo-ETE
Probes	[^{3}H]-5-oxo-ETE (3.8 nM; O'Flaherty *et al*., 1998)

Initial characterization of the heterologously expressed receptor suggested that polyunsaturated fatty acids, such as DHA and EPA, acted as receptor antagonists (Hosoi *et al*., 2002).

Abbreviations: **DHA**, 4*z*,7*z*,10*z*,13*z*,16*z*,19*z*-docosahexaenoic acid, **EPA**, 5*z*,8*z*,11*z*,14*z*,17*z*-eicosapentaenoic acid, **OXE**, oxoeicosanoid; **5-oxo-ETE**, 5-oxo-6*E*,8*z*,11*z*,14*z*-eicosatetraenoic acid; **5(*S*)-HpETE**, 5(*s*)-hydroperoxy-6*E*,8*z*,11*z*,14*z*-eicosatetraenoic acid; **5(*S*)-HETE**, 5(*s*)-hydroxy-6*E*,8*z*,11*z*,14*z*-eicosatetraenoic acid

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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)	MRS2578 (pIC_{50} 7.4, Mamedova *et al*., 2004)
Probes	[^{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 (see Abbracchio *et al*., 2005), but rather responds to dicarboxylic acids (He *et al*., 2004). Further P2Y-like receptors have been cloned from nonmammalian 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 (King & Townsend-Nicholson, 2000; Webb *et al*., 1996b). 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 (×l537 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-$\beta\gamma$-difluoromethylene 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; **MRS2578**, *N*,*N*″-1,4-butanediyl *bis*(*N*′-[3-isothiocynatophenyl)] thiourea; **PIT**, 2,2′-pyridylisatogen tosylate

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Platelet-activating factor

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

Nomenclature	**PAF-R**
Ensembl ID	ENSG00000169403
Principal transduction	$G_{q/11}$, G_i, G_o
Selective agonists	mc-PAF
Selective antagonists	CV-6209 (9.5), SR27417 (10.0), WEB2086 (8.0), L659989 (8.1), ginkgolide B (6.4)
Radioligand	[^{3}H]-PAF (1.6 nM, Fukunaga *et al*., 2001)

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

Abbreviations: **CV-6209**, 2-(*N*-acetyl-*N*-[2-methoxy-3-octadecylcarbamoyloxypropoxycarbamoyl]aminomethyl)-1-ethylpyridinium chloride; **L659989**, *trans*-2-(3-methoxy-5-methylsulphonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran; **mc-PAF**, 1-*O*-alkyl-2-*N*-methylcarbamoyl-*sn*-glycero-3-phosphocholine; also known as (methyl)carbam(o)yl-PAF or c-PAF; **SR27417**, *N*-(2-dimethylaminoethyl)-*N*-(3-pyridinylmethyl)(4-[2,4,6-triisopropylphenyl]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 U46619, respectively, in receptor characterization studies.

Nomenclature	**DP**	**FP**	**IP**	**TP**
Ensembl ID	ENSG00000168229	ENSG00000122420	ENSG00000160013	ENSG00000006638
Principal transduction	G_s	$G_{q/11}$	G_s	$G_{q/11}$
Rank order of potency	D≫E>F>I,T	F>D>E>I,T	I≫D,E,F>T	T=H≫D,E,F,I
Selective agonists	L644698, BW245C, ZK118182, RS93520, SQ27986	Fluprostenol, latanoprost	Cicaprost, AFP-07, BMY45778 (Seiler *et al*., 1997)	U46619, STA_2, I-BOP, AGN192093
Selective antagonists	BWA868C (9.3, Giles, 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)
Probes	[^{3}H]-PGD_2 (13–34 nM)	[^{3}H]-$PGF2_\alpha$ (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)	—	L798106 (7.7)	GW627368 (9.2), ONO-AE3–208 (8.5), L161982 (7.6)
Probes	[^{3}H]-PGE_2 (1–25 nM)	[^{3}H]-PGE_2 (5–22 nM)	[^{3}H]-PGE_2 (0.3–7 nM)	[^{3}H]-PGE_2 (0.6–24 nM)

17-Ph-ω-trinor-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. There is evidence for subtypes of FP (Liljebris *et al*., 1995), IP (Takechi *et al*., 1996; Wise *et al*., 1995) 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; **L161982**, 5-butyl-2,4-dihydro-[[2′-[*N*-(5-methyl-2-thiophenecarbonyl)sulphamoyl]biphenyl-4-yl]methyl]-2-[(2-trifluoromethyl)phenyl]-1,2,4-triazol-3-one; **L644698**, 4-(3-{3-[3-hydroxyoctyl]-4-oxo-2-thiazolidinyl}propyl)benzoate racemate; **L798106**, 5-bromo-2-methoxy-*N*-[3-(naphthalen-2-yl-methylphenyl)-acryloyl]-benzenesulphonamide; **ONO3708**, (9,11)-(11,12)-dideoxa-9α,11α-dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14-oxo-15-cyclopentyl-16,17,18,19,20-pentanor-15-epi-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-benzenesulphonamino-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*,4*β*])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,11*β*-thia-Txa_2; **U46619**, 11α,9α-epoxymethano-PGH_2; **ZK 118182**, (5*Z*,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 Protease-activated Receptors, see Hollenberg & Coughlan, 2002) are activated by proteolytic cleavage of their amino terminal exodomains. Alternative endogenous proteinases or ligands to thrombin for PAR1, PAR3 or PAR4 have not been demonstrated. Activation of PAR2 by trypsin or tryptase release *in vivo* is yet to be demonstrated. Several proteases, including cathepsin G and chymotrypsin, have an inhibitory effect at the PAR1 receptor such that they cleave the exodomain of the receptor without inducing activation, thereby preventing activation by thrombin but not by agonist peptides. The role of such an action *in vivo* is unclear. Agonist protease-induced hydrolysis is thought to unmask a tethered ligand at the exposed amino terminus, which acts intramolecularly at the binding site in the body of the receptor to effect transmembrane signalling. Tethered ligand sequences at human PAR1–4 are SFLLRN, SLIGKV, TFRGAP and GYPGQV, respectively. With the exception of PAR3, these synthetic peptide sequences (as carboxyl terminal amides) are able to act as agonists at their respective receptors.

Nomenclature	**PAR_1**	**PAR_2**	**PAR_3**	**PAR_4**
Other names	Thrombin receptor, PAR-1, PAR_1	PAR-2, PAR_2	Thrombin receptor, PAR-3, PAR_3	Thrombin receptor, PAR-4, PAR_4
Ensembl ID	ENSG00000181104	ENSG00000164251	ENSG00000164220	ENSG00000127533
Principal transduction	$G_{q/11}/G_{i/o}/G_{12/13}$	$G_{q/11}/G_{i/o}$	$G_{q/11}/G_{i/o}$	$G_{q/11}/G_{i/o}$
Agonist proteases	Thrombin, trypsin	Trypsin, tryptase	Thrombin, trypsin, factor Xa	Thrombin, trypsin
Selective agonists	TFLLR-NH_2	SLIGRL, SLIGKV	—	GYPGQV, GYPGKF
Selective antagonists	RWJ56110 (Andrade-Gordon *et al*., 1999)	—	—	—
Probes	[^{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 PAR2 receptor (Blackhart *et al*., 1996; Kawabata *et al*., 1999). Thrombin is inactive at the PAR_2 receptor.

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

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Relaxin family peptide

Overview: Relaxin family peptide receptors (provisional nomenclature) are activated by heterodimeric peptide hormones analogous to insulin (H1 relaxin [OTTHUMG00000019495*], H2 relaxin [ENSG00000107014], H3 relaxin [also known as INSL7, ENSG00000171136] in higher primates, INSL3, Leydig insulin-like peptide [OTTHUMG00000070952*]) and INSL5 [ENSG00000172410]. Species homologs of relaxin have distinct pharmacology – H2 relaxin interacts with RXFP1 and RXFP2, mouse and rat relaxin selectively bind to and activate RXFP1 (Scott *et al*., 2005a) and porcine relaxin may have a higher efficacy than H2 relaxin (Halls *et al*., 2005). H3 relaxin has differential affinity for RXFP2 receptors between species; mouse and rat RXFP2 have a higher affinity for H3 relaxin (Scott *et al*., 2005b). At least two binding sites have been identified on the RXFP1 and RXFP2 receptors: a high-affinity site in the leucine-rich repeat region of the ectodomain and a somewhat lower-affinity site located in the surface loops of the transmembrane (Halls *et al*., 2005). The unique LDLa module of RXFP1 and RXFP2 directs cAMP signalling by an unknown mechanism (Scott *et al*., 2003c).

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, $G_{i/o}$	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 (Liu *et al*., 2003a)	INSL5 = H3 relaxin > H3 relaxin B chain (Liu *et al*., 2003b, 2005a)
Antagonists	LGR7-truncate (Scott *et al*., 2005c)	INSL3 B-chain analog (Del Borgo *et al*., 2004) (des 1-8) A-chain INSL3 analog (Bullesbach & Schwabe, 2005)	INSL5 (Liu *et al*., 2005a)	—
Probes	[^{33}P]-H2 relaxin (0.2 nM, Sudo *et al*., 2003)	[^{33}P]-H2 relaxin (1.06 nM; Sudo *et al*., 2003) [^{125}I]-INSL3 (0.1 nM; Muda *et al*., 2005)	[^{125}I]-H3 relaxin (0.3 nM; Liu *et al*., 2003a) [^{125}I]-H3-B/INSL5 A chimera (0.5 nM; Liu *et al*., 2005b)	[^{125}I]-H3 relaxin (0.2 nM; Liu *et al*., 2003b) [^{125}I]-H3-B/INSL5 A chimera (1.2 nM; Liu *et al*., 2005b)

Mutations in *INSL3* and *LGR8* (RXFP2) have been reported in populations of patients with cryptorchidism (Ferlin *et al*., 2003). Numerous splice variants of the human RXFP1 and RXFP2 receptors have been identified, none of which bind relaxin family peptides (Muda *et al*., 2005).
*VEGA access numbers provided for H1 relaxin and INSL3 (no longer in ENSEMBL).

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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Resolvin

Overview: Resolvin receptors (provisional nomenclature) are activated by the lipid-derived, anti-inflammatory ligand resolvin E1 (RvE1), which is the result of sequential metabolism of EPA by aspirin-modified cyclooxygenase and lipoxygenase (Arita *et al*., 2005).

Nomenclature	**RvE1**
Other names	ChemR23, chemokine receptor-like 1, DEZ
Ensembl ID	ENSG00000174600
Principal transduction	Not yet established
Rank order of potency	RvE1 > chemerin C-terminal peptide (Arita *et al*., 2005)

Abbreviations: **EPA**, eicosapentaenoic acid; **RvE1**, resolvin E1 or 5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-EPA

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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, $SRIF_1$, $SRIF_{1B}$
Ensemble ID	ENSG00000139874	ENSG00000180616	ENSG00000183473	ENSG00000132671	ENSG00000162009
Principal transduction	G_i	G_i	G_i	G_i	G_i
Selective agonists	des-Ala^{1,2,5}-[DTrp^8,Iamp^9]SRIF, L797591	Octreotide, seglitide, BIM23027, L054522	L796778	NNC269100, L803087	BIM23268, BIM23052, L817818
Selective antagonists	—	Cyanamid 154806 (7.7–8.0)	—	—	BIM23056 (7.4–8.3)
Probes	—	[^{125}I]-[Tyr^3]octreotide (0.13 nM) [^{125}I]-BIM23027	—	—	[^{125}I]-[Tyr^3]octreotide (0.23 nM)

[^{125}I]-[Tyr^{11}]SRIF-14, [^{125}I]-LTT-SRIF-28, [^{125}I]-CGP23996 and [^{125}I]-[Tyr^{10}]CST-14 may be used to label somatostatin receptors nonselectively; BIM23052 is said to be selective in rat but not human receptor (Patel & Srikant, 1994). A number of nonpeptide subtype-selective agonists have been synthesised (see Rohrer *et al*., 1998).

Abbreviations: **BIM23027**, *cyc*(*N*-Me-Ala-Tyr-D-Trp-Lys-Abu-Phe); **BIM23052**, DPhe-Phe-Phe-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 (b*S*)-b-methyl-*N*{[4-(2-oxo-2,3,-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]carbonyl}-D-tryptophyl-L-lysinate; **L796778**, methyl (2*S*)-6-amino-2-[((2*R*)-2-{[({(1*S*)-1-benzyl-2-[(4-nitrophenyl)amino]-2-oxoethyl}amino)carbonyl]amino}hexanoyl)amino]hexanoate; **L803087**, methyl (2*S*)-5-{[amino(imino)methyl]amino}-2-{[4-(5,7-difluoro-2-phenyl-1H-indol-3-yl)butanoyl]amino}pentanoate; **L817818**, (2*R*)-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 & Milstein, 2003), although most cellular phenomena ascribed to S1P can be explained by receptor-mediated mechanisms. The relationship between recombinant and endogenously expressed receptors is unclear. Radioligand binding has been conducted in heterologous expression systems using [^{32}P]-S1P (e.g. Okamoto *et al*., 1998). In native systems, analysis of binding data is complicated by metabolism and high levels of nonspecific binding. Targeted deletion of several S1P receptors has clarified signalling pathways and physiological roles.

Nomenclature	**$S1P_1$**	**$S1P_2$**	**$S1P_3$**	**$S1P_4$**	**$S1P_5$**
Other names	edg1, 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: **JTE013**, pyrazolopyridine analog; **SEW2871**, 5-(4-phenyl-5-trifluoromethylthiophen-2-yl)-3-(3-trifluoromethylphenyl)-(1,2,4)-oxadiazole

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Tachykinin

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

Nomenclature	**NK_1**	**NK_2**	**NK_3**
Other names	Substance P	Substance K	Neurokinin B, neuromedin K
Ensembl ID	ENSG00000115353	ENSG00000075073	ENSG00000169836
Principal transduction	$G_{q/11}$	$G_{q/11}$	$G_{q/11}$
Rank order of potency	SP > NKA > NKB	NKA > NKB ≫ SP	NKB > NKA > SP
Selective agonists	SP methylester, [Sar^9,Met(O$_2$)^{11}]SP, [Pro^9]SP, septide	[β-Ala^8]NKA-(4-10),[Lys^5,Me-Leu^9,Mle^{10}] NKA-(4-10), GR64349	Senktide, [MePhe^7]NKB
Selective antagonists	Aprepitant (10.7; Hale *et al*., 1998), SR140333 (9.5), LY303870 (9.4), CP99994 (9.3), RP67580 (7.6)	GR94800 (9.6), GR159897 (9.5), MEN10627 (9.2), SR48968 (9.0), MEN11420 (8.6; Catalioto *et al*., 1998)	SR142802 (9.2), SB223412 (9.0, Sarau *et al*., 1997), PD157672 (7.8)
Probes	[^{3}H]- or [^{125}I]-SP, [^{3}H]- or [^{125}I]-BH-[Sar^9,Met(O$_2$)^{11}]SP, [^{125}I]-L703606 (0.3 nM), [^{18}F]-SPA-RQ	[^{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 and Kwatra, 1998). The hexapeptide agonist septide appears to bind to an overlapping but nonidentical 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: **Aprepitant**, 5-[[(2*R*,3*S*]-2-[(1*R*)-1-[3,5-bis(trifluoromethyl) phenyl]ethoxy]-3-(4-fluorphenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one; **CP99994**, (+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine; **[^{18}F]-SPA-RQ**, ([[^{18}F]-2-fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]([2*S*,3*S*] 2-phenyl-piperidin-3-yl)-amine; **GR100679**, cyclohexylcarbonyl-Gly-Ala-D-Trp-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-D-Trp-Phe-D-Pro-Pro-Nle-NH$_2$; **L-703606**, *cis*-2(diphenylmethyl)-*N*-([2-iodophenyl]methyl)-1-azabicyclo[2.2.2]octan-3-amide; **L-742694**, 2(*s*)-([3,5-bis{trifluoromethyl}benzyl]-oxy)-3(*S*)-phenyl-4-([3-oxo-1,2,4-triazol-5-yl]methyl)morpholine; **LY303870**, (*r*)-1-(*N*-[2-methoxybenzyl]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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Trace amine-associated

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

Nomenclature	**TA_1**	**TA_2**
Other names	TAA1, TaR-1, BO111	TAA2, GPR58
Ensembl ID	ENSG00000146399	ENSG00000146378
Principal transduction	G_s	G_s
Potency order	Tyramine $\geqslant$ PEA > octopamine = dopamine (Borowsky *et al*., 2001)	PEA > tryptamine (Borowsky *et al*., 2001)
Probes	[^{3}H]-Tyramine (20 nM, Borowsky *et al*., 2001)	—

TAA_3 (BO107) and TAA_4 are pseudogenes. The signalling characteristics and pharmacology of TAA_5 (PNR, Putative Neurotransmitter Receptor, ENSG00000135569), TAA_6 (Trace amine receptor 4, TaR-4, ENSG00000146383), TAA_8 (Trace amine receptor 5, GPR102, ENSG00000146385) and TAA_9 (trace amine associated receptor 9, ENSG00000188604) are lacking.

Abbreviations: **PEA**, 2-phenylethylamine

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TRH

Overview: Thyrotropin-releasing hormone (TRH) receptors (provisional nomenclature) are activated by the endogenous tripeptide TRH (pGlu-His-ProNH$_2$). TRH and TRH analogues fail to distinguish TRH$_1$ and TRH$_2$ receptors (see Sun *et al*., 2003). [^{3}H]-TRH is able to label both TRH$_1$ and TRH$_2$ receptors with K_d values of 13 and 9 nM, respectively.

Nomenclature	**TRH$_1$**	**TRH$_2$**
Other names	TRH receptor	—
Ensembl ID	ENSG00000163485	ENSMUSG00000039079, ENSRNOG00000012789
Principal transduction	G_q	G_q
Selective antagonists	Midazolam (Drummond *et al*., 1989), chlordiazepoxide (Straub *et al*., 1990), diazepam	—

The human orthologue of the rodent TRH$_2$ receptor has yet to be identified.

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

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Urotensin-II

Overview: The urotensin-II (U-II) receptor (UT, nomenclature as agreed by NC-IUPHAR, 2005, Douglas and Ohlstein, 2000a) is activated by the endogenous dodecapeptide U-II, originally isolated from the urophysis, the endocrine organ of the caudal neurosecretory system of teleost fish (Bern *et al*., 1985). Several structural forms of U-II exist in fish and amphibians. The Goby orthologue was used to identify U-II as the cognate ligand for the predicted receptor encoded by the rat gene *gpr14* (Coulouarn *et al*., 1998; Liu *et al*., 1999; Mori *et al*., 1999; Nothacker *et al*., 1999). Human U-II (derived from ENSG00000049247), an 11-amino-acid peptide (Coulouarn *et al*., 1998), retains the cyclohexapeptide sequence of goby U-II that is thought to be important in ligand binding (Kinney *et al*., 2002; Brkovic *et al*., 2003). This sequence is also conserved in the deduced amino-acid sequence of rat (14 aa) and mouse (14 aa) U-II, although the *N*-terminal is more divergent from the human sequence (Coulouarn *et al*., 1999).

Nomenclature	**UT**
Other names	GPR14, SENR, UR-IIR
Ensembl ID	ENSG00000181408
Principal transduction	$G_{q/11}$
Selective agonists	[Pen^5]U-II-(4–11), U-II-(4–11), U-II (Grieco *et al*., 2002), AC7954 (Lehmann *et al.,* 2005)
Selective antagonists	Urantide (8.3, Patacchini *et al.,* 2003), SB706375 (7.5-8.0, Douglas *et al.,* 2005), palosuran (pIC_{50} 7.1, Clozel *et al.,* 2004), SB436811 (6.7, Jin *et al,* 2005)
Probes	[^{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.

Abbreviations: **AC7954**, 3-(4-chlorophenyl)-3-(2-dimethyl-aminoethyl)-isochroman-1-one HCl; **palosuran**, 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-methyl-quinolin-4-yl)-urea sulphate, also known as ACT058362; **[Pen^5]U-II-(4-11)**, [pencillamine, β,β-dimethylcysteine]^{5}U-II-(4-11); **SB436811**; **SB706375**, 2-bromo-4,5-dimethoxy-*N*-[3-(R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluromethyl-phenyl]-benzenesulphonamide HCl; **urantide**, [Pen^5,DTrp^7,Orn^8]hU-II(4-11)

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Vasopressin & Oxytocin

Overview: Vasopressin (AVP) and oxytocin (OT) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on vasopressin and oxytoxcin 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),
Probes	[^{3}H]-AVP, [^{3}H]-SR49059 (1.5 nM), [^{3}H]-d(CH$_2$)$_5$[Tyr(Me)^2, Arg^8]AVP (1.1 nM), [^{125}I]-HO-Phaa,D-Tyr(Me)-Phe-Gln-Asn-Arg-Pro-Arg-NH$_2$ (50 pM)	[^{3}H]-AVP	[^{3}H]-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: **F180**, Hmp-Phe-Ile-Hgn-Asn-Cys-Pro-Dab(Abu)-Gly-NH$_2$; **[^{111}In]-DOTA-dLVT**, [^{111}In]-DOTA-Lys^8-deamino-vasotocin; **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; **[^{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); **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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VIP & PACAP

Overview: Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) receptors (nomenclature recommended by the NC-IUPHAR Subcommittee on Vasoactive Intestinal Peptide Receptors, Harmar *et al*., 1998) are activated by the endogenous peptides VIP, $PACAP_{1-38}$, $PACAP_{1-27}$, peptide histidine isoleucineamide (PHI), peptide histidine methionineamide (PHM), peptide histidine valine and growth hormone-releasing factor (GRF). PACAP type II receptors have been defined as those for which PACAP and VIP display comparable affinity. Both $VPAC_1$ 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, b), Ro251392 (Xia *et al*., 1997)	Maxadilan (Moro and Lerner, 1997)
Selective antagonists	[Ac-His^1,D-Phe^2,Lys^{15}, Arg^{16}]VIP-(3–7)-GRF-(8–27)-NH_2 (Gourlet *et al*., 1997a)	—	PACAP-(6–38)
Probes	[^{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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