Nuclear receptors

Overview: In man, 48 nuclear receptors have been identified from sequence analysis of the genome (see Benoit *et al.*, 2006; Germain *et al.*, 2006), only half of which have been 'assigned' a ligand. The remainder are referred to as 'orphan' nuclear receptors.

Systematic nomenclature	Common nomenclature	Other names	Ensembl ID
NR1D1	Rev-erbα	EAR1, hRev	ENSG00000126368
NR1D2	Rev-erbβ	EAR1β, RVR, BD73	ENSG00000174738
NR2A1	HNF4α	Hepatocyte nuclear factor 4-α, MODY1, TCF14	ENSG00000101076
NR2A2	HNF4γ	Hepatocyte nuclear factor 4-γ	ENSG00000164749
NR2C1	TR2	Testicular receptor 2	ENSG00000120798
NR2C2	TR4	TAK1	ENSG00000177463
NR2E1	TLL	TLX, Tailless homolog	ENSG00000112333
NR2E3	PNR	Photoreceptor-specific nuclear receptor, retina-specific nuclear receptor	ENSG00000031544
NR2F1	COUP-TFI	COUPα, EAR3, SVP44	ENSG00000175745
NR2F2	COUP-TFII	COUPβ, ARP1, SVP40	ENSG00000185551
NR2F6	EAR2	—	ENSG00000160113
NR3B1	ERRα	ESRL1, estrogen-related receptor α, estrogen receptor-like 1	ENSG00000173153
NR3B2	ERRβ	ESRL2, estrogen-related receptor β, estrogen receptor-like 2	ENSG00000119715
NR3B3	ERRγ	ESRL3, estrogen-related receptor γ, estrogen receptor-like 3	ENSG00000196482
NR4A1	NGFI-B	NAK1, ST59, nur77, TR3, HMR	ENSG00000123358
NR4A2	NURR1	Immediate-early response protein NOT, transcriptionally-inducible nuclear receptor, TINUR, RNR-1	ENSG00000153234
NR4A3	NOR1	Neuron-derived orphan receptor, mitogen-induced nuclear orphan receptor	ENSG00000119508
NR5A1	SF1	Steroidogenic factor 1, adrenal 4-binding protein, steroid hormone receptor Ad4BP, Fushi tarazu factor homolog 1	ENSG00000136931
NR5A2	LRH-1	Liver receptor homolog 1, α1-fetoprotein transcription factor, hepatocytic transcription factor, B1-binding factor, CYP7A promoter-binding factor	ENSG00000116833
NR6A1	GCNF	Germ cell nuclear factor, retinoid receptor-related testis-specific receptor, RTR	ENSG00000148200
NR0B1	DAX-1	AHCH	ENSG00000169297
NR0B2	SHP	Small heterodimer partner	ENSG00000131910

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Liver X and farnesoid X

Overview: Liver X and farnesoid X receptors (LXR and FXR, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Moore *et al*., 2006) are members of a steroid analogue-activated nuclear receptor subfamily (ENSF00000000720), which form heterodimers with members of the retinoid X receptor family. Endogenous ligands for LXRs include hydroxycholesterols (OHC), while FXRs appear to be activated by bile acids.

Nomenclature	LXRα	LXRβ	FXRα	FXRβ
Systematic nomenclature	NR1H3	NR1H2	NR1H4	NR1H5
Other names	Oxysterols receptor α	Oxysterols receptor β, ubiquitously expressed nuclear receptor	Bile acid receptor	Lanosterol receptor
Ensembl ID	ENSG00000025434	ENSG00000131408	ENSG00000012504	ENSMUSG00000048938 (pseudogene in man)
Potency order	20*s*-OHC, 22*r*-OHC, 24*s*-OHC >25-OHC, 27-OHC (Lehmann *et al*., 1997)	20*s*-OHC, 22*r*-OHC, 24*s*-OHC >25-OHC, 27-OHC (Lehmann *et al*., 1997)	Chenodeoxycholate >lithocholate, deoxycholate (Makishima *et al*., 1999; Parks *et al*., 1999)	—
Selective agonists	—	—	ECDCA (Pellicciari *et al*., 2002)	Lanosterol (Otte *et al*., 2003)
Selective antagonists	—	—	Guggulsterone (Urizar *et al*., 2002)	—

TO901317 (Repa *et al*., 2000) and GW3965 (Collins *et al*., 2002) are synthetic agonists acting at both LXRα and LXRβ with less than 10-fold selectivity.

Abbreviations: ECDCA, 6α-ethyl-chenodeoxycholate, also known as INT747; **guggulsterone**, *trans*-4,17(20)-pregnadiene-3, 16-dione; **GW3965**, 3-(3-[*N*-{2-chloro-3-trifluoromethylbenzyl}-{2, 2-diphenylethyl}amino]propyloxy)phenylacetic acid hydrochloride; **OHC**, hydroxycholesterol; **TO901317**, *N*-(2,2,2-trifluoroethyl)-*N*-(4-[2,2, 2-trifluoro-1-hydroxy-1-{trifluoromethyl}ethyl]phenyl)-benzenesulfonamide

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Peroxisome proliferator-activated

Overview: Peroxisome proliferator-activated receptors (PPARs, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Michalik *et al*., 2006) are nuclear hormone receptors of the NR1C family, with diverse roles regulating lipid homeostasis, cellular differentiation, proliferation and the immune response. PPARs have many potential endogenous agonists (see Bishop-Bailey and Wray, 2003; Michalik *et al*., 2006), including 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, prostacyclin, many fatty acids and their oxidation products, lysophosphatidic acid (McIntyre *et al*., 2003), 13-HODE, 15-HETE, Paz-PC, azelaoyl-PAF, and leukotriene B4. These receptors also bind hypolipidaemic drugs (PPARα) and anti-diabetic thiazolidinediones (PPARγ), as well as many non-steroidal anti-inflammatory drugs, such as sulindac and indomethacin. Once activated by a ligand, the receptor forms a heterodimer with members of the retinoid X receptor family and can act as a transcription factor. Although radioligand binding assays have been described for all three receptors, the radioligands are not commercially available.

Nomenclature	PPARα	PPARβ	PPARγ
Systematic nomenclature	NR1C1	NR1C2	NR1C3
Other names	—	PPARδ, NUC1, FAAR	—
Ensembl ID	ENSG00000100406	ENSG00000112033	ENSG00000132170
Selective agonists	GW7647, WY14643, clofibrate, fenofibrate, ciprofibrate, gemfibrozil	L165041, GW501516, GW0742	Rosiglitazone, ciglitazone, troglitazone, pioglitazone, CDDO, GW1929
Selective antagonists	GW6471 (Xu *et al*., 2002)	—	GW9662 (Huang *et al*., 1999), CDDO-Me (Wang *et al*., 2000), diclofenac (6.2, Adamson *et al*., 2002), BADGE (4.0, Wright *et al*., 2000), T0070907 (Lee *et al*., 2002)

As with the estrogen receptor antagonists, many agents show tissue-selective efficacy (e.g. Bishop-Bailey *et al*., 2000; Nakamuta *et al*., 2002; Rocchi *et al*., 2001). Agonists with mixed activity at PPARα and PPARγ have recently been described (e.g. Doebber *et al*., 2004; Guo *et al*., 2004; Xu *et al*., 2004).

Abbreviations: 13-HODE, 13-hydroxyoctadecadienoic acid; **15-HETE**, 15-hydroxyeicosatetraenoic acid; azelaoyl-PAF, 1-O-hexadecyl-2-O-(9-carboxyoctanoyl)-sn-glyceryl-3-phosphocholine; **BADGE**, bisphenol A diglycidyl ether; **CDDO**, 2-cyano-3,12-dioxooleana-1, 9-dien-28-oic acid; **CDDO-Me**, 2-cyano-3,12-dioxooleana-1, 9-dien-28-oic acid methyl ester; **GW1929**, (2*S*)-([2-benzoylphenyl]amino)-3-(4-[2-{methylpyridin-2-ylamino}ethoxy]phenyl)propionic acid; **GW501516**, 2-methyl-4([{(4-methyl-2-[4-trifluoromethylphenyl]-1,3-thiazol-5-yl)methyl}sulfanyl]phenoxy)acetic acid; **GW7647**, 2-([4-{2-([{cyclohexylamino}carbonyl][4-cyclohexylbutyl]amino)ethyl}phenyl]thio)-2-methylpropanoic acid; **GW9662**, 2-chloro-5-nitro-*N*-phenylbenzamide; **L165041**, (4-[3-{4-acetyl-3-hydroxy-2-propylphenoxy}propoxyl]phenoxy)acetic acid; **Paz-PC**, 1-palmitoyl-2-azelaoyl-*sn*-glycero-3-phosphocholine; **T0070907**, 2-chloro-5-nitro-*N*-(4-pyridyl)benzamide; **WY14643**, *N*-(3-[2-quinolinylmethoxy]phenyl)-trifluoromethanesulphonamide

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Retinoic acid, retinoid X and retinoic acid-related orphan

Overview: Retinoic acid receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Germain *et al*., 2006a) are nuclear hormone receptors of the NR1B family activated by the vitamin A-derived agonists all-*trans* retinoic acid (ATRA) and 9-*cis*-retinoic acid, and the RAR-selective synthetic agonist TTNPB. Retinoid X receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Germain *et al*., 2006b) are NR2B family members activated by 9-*cis*-retinoic acid and the RXR-selective agonists LGD1069 and LG100268. These receptors form RXR–RAR heterodimers and RXR–RXR homodimers (Mangelsdorf and Evans, 1995; Chambon, 1996). Retinoic acid-related orphan receptors (ROR, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Benoit *et al*., 2006) have yet to be assigned a definitive endogenous ligand, although RORα may be synthesised with a 'captured' agonist such as cholesterol (Kallen *et al*., 2002, 2004).
Cytoplasmic cellular retinoid binding proteins I (ENSG00000114115), II (ENSG00000114113), III (ENSG00000139194) and IV (ENSG00000162444) are thought to control the levels of intracellular retinoids available for interaction with their receptors (Li, 1999). [^{3}H]-ATRA and [^{3}H]-9-*cis*-retinoic acid have been used to label RARs and RXRs, respectively.

Nomenclature	RARα	RARβ	RARγ
Systematic nomenclature	NR1B1	NR1B2	NR1B3
Other names	—	HBV-activated protein	—
Ensembl ID	ENSG00000131759	ENSG00000077092	ENSG00000172819
Selective agonists	Ro406055 (Delescluse *et al*., 1991)	—	AHPN (Martin *et al*., 1992)
Selective antagonists	Ro415253 (Apfel *et al*., 1992)	—	—

Ro415253 has been suggested to be a PPARγ agonist (Schupp *et al*., 2007). LE135 is an antagonist with selectivity for RARα and RARβ compared to RARγ (Li *et al*., 1999).

Nomenclature	RXRα	RXRβ	RXRγ
Systematic nomenclature	NR2B1	NR2B2	NR2B3
Ensembl ID	ENSG00000078380	ENSG00000112472	ENSG00000143171

Nomenclature	RORα	RORβ	RORγ
Systematic nomenclature	NR1F1	NR1F2	NR1F3
Other names	RZRα	RZRβ	RZRγ
Ensembl ID	ENSG00000069667	ENSG00000198963	ENSG00000143365
Selective agonists	Cholesterol sulfate, cholesterol, 7-OHC (Bitsch *et al*., 2003)	ATRA (Stehlin-Gaon *et al*., 2003)	—

ATRA shows selectivity for RORβ within the ROR family. RORα has been suggested to be a nuclear receptor responding to melatonin (Wiesenberg *et al*., 1995).

Abbreviations: **AHPN**, 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid, also known as CD437; **ATRA**, all-*trans*-retinoic acid; **CD1530**, 4-(6-hydroxy-7-tricyclo[3.3.1.13,7]dec-1-yl-2-naphthalenyl)benzoic acid; **LE135**, 4-(7,8,9,10-tetrahydro-5,7,7,10,10-pentamethyl-5*H*-benzo[*e*]naphtho[2,3-*b*][1,4]diazepin-13-yl)benzoic acid; **LG100268**, 6-(1-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl]cyclopropyl) nicotinic acid; **LGD1069**, 4-(1-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl]ethenyl) benzoic acid; **OHC**, hydroxycholesterol; **Ro406055**, 4-([5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]carboxamido)benzoic acid (also known as AM580); **Ro415253**, 4-[2-(7-heptoxy-4,4-dimethyl-1,1-dioxo-2,3-dihydrothiochromen-6-yl)prop-1-enyl]benzoic acid, also known as LG629; **TTNPB**, (*E*)-4-(2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]-1-propenyl)benzoic acid

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Steroid hormone

Overview: Steroid hormone receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Dahlman-Wright *et al*., 2006; Lu *et al*., 2006) are nuclear hormone receptors of the NR3 class, with endogenous agonists that include 5α-dihydrotestosterone (DHT), aldosterone, cortisol, corticosterone, progesterone, testosterone and estradiol. These receptors exist as dimers coupled with chaperone molecules (such as HSP90 and immunophilin HSP65), which are shed on binding the steroid hormone. The activated receptors then bind to nuclear hormone response elements of the genome, with a 15-nucleotide consensus sequence AGAACAnnnTGTTCT (i.e. an inverted palindrome) as homo- or heterodimers. They also affect transcription by protein–protein interactions with other transcription factors, such as activator protein 1 (AP-1) and nuclear factor κB (NF-κB). Splice variants of each of these receptors can form functional or nonfunctional monomers that can dimerize to form functional or non-functional receptors. For example, alternative splicing of PR mRNA produces A and B monomers that combine to produce functional AA, AB and BB receptors with distinct characteristics (Vegeto *et al*., 1993).

A 7TM receptor responsive to estrogen (GPER, also known as GPR30, ENSG00000164850, see Filardo and Thomas, 2005; Prossnitz *et al*., 2007) has been described. Human orthologues of 7TM 'membrane progestin receptors' (ENSG00000182749, ENSG00000170915 and ENSG00000137819), initially discovered in fish (Zhu *et al*., 2003a, b), appear to localize to intracellular membranes and fail to respond to progesterone (Krietsch *et al*., 2006).

Nomenclature	Glucocorticoid	Mineralocorticoid	Progesterone	Androgen
Preferred abbreviation	GR	MR	PR	AR
Systematic nomenclature	NR3C1	NR3C2	NR3C3	NR3C4
Other names	Type II glucocorticoid receptor	Type I glucocorticoid receptor, aldosterone receptor	—	dihydrotestosterone receptor
Ensembl ID	ENSG00000113580	ENSG00000151623	ENSG00000082175	ENSG00000169083
Rank order of potency	Cortisol, corticosterone >> aldosterone, deoxycortisone Rupprecht *et al*. (1993)	Corticosterone, cortisol, aldosterone, progesterone Rupprecht *et al*. (1993)	Progesterone	DHT > testosterone
Selective agonists	RU28362, RU26988	Aldosterone	ORG2058, progesterone	DHT, mibolerone, R1881
Selective antagonists	Mifepristone, ZK112993, onapristone	RU28318, ZK112993, onapristone	Mifepristone, ZK112993, onapristone	Hydroxyflutamide, nilutamide
Probes	[^{3}H]-Dexamethasone	[^{3}H]-Aldosterone	[^{3}H]-ORG2058	[^{3}H]-DHT, [^{3}H]-mibolerone, [^{3}H]-R1881

[^{3}H]-Dexamethasone also binds to MR *in vitro*. PR antagonists have been suggested to subdivide into Type I (e.g. onapristone) and Type II (e.g. ZK112993) groups. These groups appear to promote binding of PR to DNA with different efficacies and evoke distinct conformational changes in the receptor, leading to a transcription-neutral complex (Gass *et al*., 1998; Leonhardt *et al*., 1998). Mutations in AR underlie testicular feminization and androgen insensibility syndromes, spinal and bulbar muscular atrophy (Kennedy's disease).

Nomenclature	Estrogen α	Estrogen β
Preferred abbreviation	ERα	ERβ
Systematic nomenclature	NR3A1	NR3A2
Other names	Estradiol	Estradiol
Ensembl ID	ENSG00000091831	ENSG00000140009
Selective agonists	PPT Kraichely *et al*. (2000); Stauffer *et al*. (2000)	DPN Meyers *et al*. (2001)
Selective antagonists	MPP Sun *et al*. (2002)	PHTPP Compton *et al*. (2004), *R,R*-THC Meyers *et al*. (1999); Sun *et al*. (1999)

R,R-THC exhibits partial agonist activity at ERα. Estrogen receptors may be blocked non-selectively by tamoxifen and raloxifene, and labelled by [^{3}H]-estradiol and [^{3}H]-tamoxifen. Many agents thought initially to be antagonists at estrogen receptors appear to have tissue-specific efficacy (e.g. tamoxifen is an antagonist at estrogen receptors in the breast, but is an agonist at estrogen receptors in the uterus), hence the descriptor SERM (selective estrogen receptor modulator) or SnuRM (selective nuclear receptor modulator). Y134 has been suggested to be an ERα-selective estrogen receptor modulator (Ning *et al*., 2007).
Additional 'orphan' estrogen-receptor-related proteins have been described (ERRα ENSG00000173153; ERRβ ENSG00000119715; ERRγ ENSG00000057103); DY131 is an agonist with selectivity for ERRβ and ERRγ compared to ERRα, ERα and ERβ (Yu and Forman, 2005).

Abbreviations: **DPN**, 2,3-*bis*(4-hydroxyphenyl)propionitrile; **DY131**, *N*′-([1E]-[4-(diethylamino)phenyl]methylene)-4-hydroxybenzohydrazide; **MPP**, 1,3-*bis*(4-hydroxyphenyl)-4-methyl-5-(4-[2-piperidinylethoxy]phenol)-1*H*-pyrazole; **ORG2058**, 16-α-ethyl-21-hydroxy-19-norpregn-4-ene-3,20-dione; **PPT**, 4,4′,4″-(4-propyl-[1*H*]-pyrazole-1,3,5-triyl)trisphenol; **PHTPP**, 4-(2-phenyl-5,7-bis[trifluoromethyl]pyrazolo[1,5-a]pyrimidin-3-yl)phenol; **R1881**, 17β-hydroxy-17α-methyl-estra-4,9,11-triene-3-one, also known as methyltrienolone; ***R,R*-THC**, *R,R*-tetrahydrochrysene; **RU26988**, 11β,17β-dihydroxy-21-methyl-17α-pregna-1,4,6-trien-20-yl-3-on; **RU28318**, 3-oxo-7-propyl-17-hydroxy-androstan-4-en-17-yl; **RU28362**, 11β,17β-dihydroxy-6-methyl-17-(1-propionyl)androsta-1,4,6-triene-3-one; **Y134**, (6-hydroxy-2-[4-hydroxyphenyl]-benzo[b]thiophen-3-yl)-(4-[4-isopropylpiperazin-1-yl]-phenyl)methanone; **ZK112993**, 11β-(4-acetylphenyl)-17β-hydroxyl-17α-(1-propinyl)-4,8-estradiene-3-one

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Thyroid hormone

Overview: Thyroid hormone receptors (TRs, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, see Flamant *et al*., 2006) are nuclear hormone receptors of the NR1A family, with diverse roles regulating macronutrient metabolism, cognition and cardiovascular homeostasis. TRs are activated by thyroxine (T4) and thyroid hormone (T3). Once activated by a ligand, the receptor acts as a transcription factor either as a monomer, homodimer or heterodimer with members of the retinoid X receptor family.
An interaction with integrin αVβ3 has been suggested to underlie plasma membrane localization of thyroid hormone receptors and non-genomic signalling (Bergh *et al*., 2005).

Nomenclature	TRα	TRβ
Systematic nomenclature	NR1A1	NR1A2
Other names	THRA, erbAα, erbA1, EAR7	THRB, erbAβ, erbA2
Ensemble ID	ENSG00000126351	ENSG00000151090
Rank order of potency	T3 > T4	T3 > T4
Selective agonists	—	GC1 (Chiellini *et al*., 1998)

One splice variant, $TR\alpha_2$, lacks a functional DNA-binding domain and appears to act as a transcription suppressor.
Although radioligand binding assays have been described for these receptors, the radioligands are not commercially available. NH-3 has been described as an antagonist at thyroid hormone receptors with modest selectivity for TRβ (Nguyen *et al*., 2002).

Abbreviations: GC1, (3,5-dimethyl-4-[4-hydroxy-3-isopropylbenzyl]phenyloxy)acetate; **NH-3**, (4-[4-hydroxy-3-isopropyl-5-{4-nitrophenyl-ethynyl}-benzyl]-3,5-dimethylphenoxy)acetate

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Vitamin D, pregnene X and constitutive androstane

Overview: Vitamin D (VDR), Pregnene X (PXR) and Constitutive Androstane (CAR) receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, Moore *et al.*, 2006) are members of the NR1I family of nuclear receptors, which form heterodimers with members of the retinoid X receptor family. PXR and CAR are activated by a range of exogenous compounds, with no established endogenous physiological agonists, although high concentrations of bile acids and bile pigments activate CAR (see Moore *et al.*, 2006).

Nomenclature	Vitamin D	Pregnene X	Constitutive androstane
Systematic nomenclature	NR1I1	NR1I2	NR1I3
Other names	1,25-dihydroxyvitamin D3 receptor	Orphan nuclear receptor PAR1, pregnane-activated receptor, steroid and xenobiotic receptor, SXR	Constitutive activator of retinoid response, constitutive active response, orphan nuclear receptor MB67
Ensembl ID	ENSG00000111424	ENSG00000144852	ENSG00000143257
Selective agonists	1,25-Dihydroxyvitamin D_3	5β-Pregnane-3,20-dione, estradiol (Jones *et al.*, 2000), hyperforin (Wentworth *et al.*, 2000), lovastatin (Lehmann *et al.*, 1998), rifampicin (Blumberg *et al.*, 1998; Lehmann *et al.*, 1998)	TCPOBOP (Tzameli *et al.*, 2000)
Selective antagonists	TEI9647 (Miura *et al.*, 1999)	—	—

Abbreviations: **TCPOBOP**, 1,4-bis-[2-(3,5-dichloropyridyloxy)]benzene; **TEI9647**, (23*S*)-25-dehydro-1α hydroxyvitamin D_3-26,23-lactone

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