THE CONCISE GUIDE TO PHARMACOLOGY 2013/14: NUCLEAR HORMONE RECEPTORS

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Abstract

The Concise Guide to PHARMACOLOGY 2013/14 provides concise overviews of the key properties of over 2000 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full.

Nuclear hormone receptors are one of the seven major pharmacological targets into which the Guide is divided, with the others being G protein-coupled receptors, ligand-gated ion channels, ion channels, catalytic receptors, transporters and enzymes. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. A new landscape format has easy to use tables comparing related targets.

It is a condensed version of material contemporary to late 2013, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in previous Guides to Receptors and Channels. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and the Guide to Receptors and Channels, providing a permanent, citable, point-in-time record that will survive database updates.

An Introduction to Nuclear Hormone Receptors

Nuclear hormone receptors are specialised transcription factors with commonalities of sequence and structure, which bind as homo- or heterodimers to specific consensus sequences of DNA (response elements) in the promoter region of particular target genes. They regulate (either promoting or repressing) transcription of these target genes in response to a variety of endogenous ligands. Endogenous agonists are hydrophobic entities which, when bound to the receptor promote conformational changes in the receptor to allow recruitment (or dissociation) of protein partners, generating a large multiprotein complex.

Two major subclasses of nuclear hormone receptors with identified endogenous agonists can be identified: steroid and non-steroid hormone receptors. Steroid hormone receptors function typically as dimeric entities and are thought to be resident outside the nucleus in the unliganded state in a complex with chaperone proteins, which are liberated upon agonist binding. Migration to the nucleus and interaction with other regulators of gene transcription, including RNA polymerase, acetyltransferases and deacetylases, allows gene transcription to be regulated. Non-steroid hormone receptors typically exhibit a greater distribution in the nucleus in the unliganded state and interact with other nuclear hormone receptors to form heterodimers, as well as with other regulators of gene transcription, leading to changes in gene transcription upon agonist binding.

Selectivity of gene regulation is brought about through interaction of nuclear hormone receptors with particular consensus sequences of DNA, which are arranged typically as repeats or inverted palindromes to allow accumulation of multiple transcription factors in the promoter regions of genes.

Acknowledgements

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Conflict of interest

The authors state that there is no conflict of interest to disclose.

Further reading

Germain P, Staels B, Dacquet C, Spedding M, Laudet V. (2006) Overview of nomenclature of nuclear receptors. *Pharmacol Rev* **58**: 685–704.

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1A. Thyroid Hormone Receptors

Overview: Thyroid hormone receptors (TRs, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, [3]) are nuclear hormone receptors of the NR1A family, with diverse roles regulating macronutrient metabolism, cognition and cardiovascular homeostasis. TRs are activated by thyroxine (T_4) and thyroid hormone (T_3). 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. NH-3 has been described as an antagonist at TRs with modest selectivity for TRβ [4].

Nomenclature	Thyroid hormone receptor-α	Thyroid hormone receptor-β
Systematic nomenclature	NR1A1	NR1A2
HGNC, UniProt	*THRA*, P10827	*THRB*, P10828
Rank order of potency	$T_3 > T_4$	$T_3 > T_4$
Selective agonists (pK_i)	–	GC-1 (pK_d 10.17) [2,5]

Comments: An interaction with integrin αVβ3 has been suggested to underlie plasma membrane localization of TRs and non-genomic signalling [1]. One splice variant, TRα_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.

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1B. Retinoic acid receptors

Overview: Retinoic acid receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, [8]) 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 agonists TTNPB and adapalene.

Nomenclature	Retinoic acid receptor-α	Retinoic acid receptor-β	Retinoic acid receptor-γ
Systematic nomenclature	NR1B1	NR1B2	NR1B3
HGNC, UniProt	*RARA*, P10276	*RARB*, P10826	*RARG*, P13631
Selective agonists (pK_i)	Ro 40-6055 [7,11,18], BMS753 (8.7) [10]	AC261066 (pEC_{50} 7.9 – 8.1) [15], AC55649 (pEC_{50} 6.5 – 7.3) [15]	AHPN [16]
Selective antagonists (pK_i)	Ro 41-5253 (pIC_{50} 6.3 – 7.2) [6,12]	–	MM 11253 [13]

Comments: Ro 41-5253 has been suggested to be a PPARγ agonist [17]. LE135 is an antagonist with selectivity for RARα and RARβ compared with RARγ [14]. [9] is a family-selective antagonist.

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1C. Peroxisome proliferator-activated receptors

Overview: Peroxisome proliferator-activated receptors (PPARs, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, [33]) 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 [21,33], including 15-deoxy-$\Delta^{12,14}$-PGJ_2, prostacyclin (PGI_2), many fatty acids and their oxidation products, lysophosphatidic acid (LPA) [32], 13-HODE, 15S-HETE, Paz-PC, azelaoyl-PAF and leukotriene B4 (LTB_4). bezafibrate acts as a non-selective agonist for the PPAR family [41]. 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. Commonly, receptor occupancy studies are conducted using fluorescent ligands and truncated forms of the receptor limited to the ligand binding domain.

Nomenclature	Peroxisome proliferator-activated receptor-α	Peroxisome proliferator-activated receptor-β/δ	Peroxisome proliferator-activated receptor-γ
Systematic nomenclature	NR1C1	NR1C2	NR1C3
HGNC, UniProt	*PPARA*, Q07869	*PPARD*, Q03181	*PPARG*, P37231
Selective agonists (pK_i)	ciprofibrate, GW7647 (pEC_{50} 8.2) [22–23], CP-775146 (pEC_{50} 7.3) [28], pirinixic acid (pEC_{50} 5.3) [41]	GW501516 (pEC_{50} 9.0) [35], GW0742X (pIC_{50} 9.0) [25,39]	rosiglitazone (pK_d 7.4) [27,31,44], GW1929 (8.8) [22], CDDO (Partial agonist) (8.0) [40], troglitazone (5.8) [19], ciglitazone (pEC_{50} 4.6) [27], troglitazone (pIC_{50} 6.3) [27,44], pioglitazone (pIC_{50} 6.2) [27,37,44]
Selective antagonists (pK_i)	GW6471 (pIC_{50} 6.6) [42]	GSK0660 (pIC_{50} 6.5) [38]	T0070907 (9.0) [29], CDDO-Me (6.9) [40], GW9662 (Irreversible inhibition) (pIC_{50} 8.1) [30]

Comments: As with the estrogen receptor antagonists, many agents show tissue-selective efficacy (*e.g.* [20,34,36]). Agonists with mixed activity at PPARα and PPARγ have also been described (*e.g* [24,26,43]).

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1D. Rev-Erb receptors

Overview: Rev-erb receptors (nomenclature as agreed by NC-IUPHAR committee on nuclear hormone receptors [45]) have yet to be officially paired with an endogenous ligand, but are thought to be activated by heme.

Nomenclature	Rev-Erb-α	Rev-Erb-β
Systematic nomenclature	NR1D1	NR1D2
HGNC, UniProt	*NR1D1*, P20393	*NR1D2*, Q14995
Endogenous agonists (pK_i)	heme (Selective) [48–49]	heme (Selective) [48–49]
Selective agonists (pK_i)	GSK4112 (pEC_{50} 6.4) [46], GSK4112 (pIC_{50} 5.6) [47]	–
Selective antagonists (pK_i)	SR8278 (pIC_{50} 6.5) [47]	–

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1F. Retinoic acid-related orphans

Overview: Retinoic acid receptor-related orphan receptors (ROR, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, [50]) have yet to be assigned a definitive endogenous ligand, although RORα may be synthesized with a 'captured' agonist such as cholesterol [52–53].

Nomenclature	RAR-related orphan receptor-α	RAR-related orphan receptor-β	RAR-related orphan receptor-γ
Systematic nomenclature	NR1F1	NR1F2	NR1F3
HGNC, UniProt	*RORA*, P35398	*RORB*, Q92753	*RORC*, P51449
Endogenous agonists (pK_i)	cholesterol (Selective) [53–54]	–	–
Selective agonists (pK_i)	7-hydroxycholesterol [51], cholesterol sulphate [51,53]	–	–

Comments: all-trans-retinoic acid shows selectivity for RORβ within the ROR family [55]. RORα has been suggested to be a nuclear receptor responding to melatonin [56].

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1H. Liver X receptor-like receptors

Overview: Liver X and farnesoid X receptors (LXR and FXR, nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, [62]) are members of a steroid analogue-activated nuclear receptor subfamily (ENSFM00500000269785), 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	Farnesoid X receptor	Farnesoid X receptor-β	Liver X receptor-α	Liver X receptor-β
Systematic nomenclature	NR1H4	NR1H5	NR1H3	NR1H2
HGNC, UniProt	*NR1H4*, Q96RI1	*NR1H5P*, -	*NR1H3*, Q13133	*NR1H2*, P55055
Potency order	chenodeoxycholic acid > lithocholic acid, deoxycholic acid [60,64]	–	20S-hydroxycholesterol, 22R-hydroxycholesterol, 24(S)-hydroxycholesterol > 25-hydroxycholesterol, 27-hydroxycholesterol [59]	20S-hydroxycholesterol, 22R-hydroxycholesterol, 24(S)-hydroxycholesterol > 25-hydroxycholesterol, 27-hydroxycholesterol [59]
Selective agonists (pK_i)	GW4064 (pEC_{50} 7.8) [61], ECDCA (pEC_{50} 7.0) [65], fexaramine (pEC_{50} 6.6) [58]	–	–	–
Selective antagonists (pK_i)	guggulsterone (pIC_{50} 5.7 – 6.0) [67]	–	–	–
Endogenous agonists (pK_i)	–	lanosterol (pEC_{50} 6.0 - Mouse) [63]	–	–

Comments: T0901317 [66] and GW3965 [57] are synthetic agonists acting at both LXRα and LXRβ with less than 10-fold selectivity. NR1H5P (FXRβ) is a pseudogene in man, but active in the mouse.

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1I. Vitamin D receptor-like receptors

Overview: Vitamin D (VDR), Pregnane X (PXR) and Constitutive Androstane (CAR) receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, [79]) 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 PXR and CAR[79].

Nomenclature	Vitamin D receptor	Pregnane X receptor	Constitutive androstane receptor
Systematic nomenclature	NR1I1	NR1I2	NR1I3
HGNC, UniProt	*VDR*, P11473	*NR1I2*, O75469	*NR1I3*, Q14994
Endogenous agonists (pK_i)	1,25-dihydroxyvitamin D3 (pK_d 8.9 – 9.2) [68,71]	17β-estradiol (Selective) [74]	–
Selective agonists (pK_i)	EB1089 (pK_d 9.57) [70,84]	hyperforin (pEC_{50} 7.6) [80,83], rifampicin (pEC_{50} 5.5 – 6.0) [69,76], lovastatin (pEC_{50} 5.3 – 6.0) [76], pregnanedione (pIC_{50} 6.4) [74]	TCPOBOP (pEC_{50} 7.7 - Mouse) [82], CITCO (pEC_{50} 7.3) [77]
Selective antagonists (pK_i)	TEI-9647 [78], ZK159222 (pIC_{50} 7.5) [72–73]	–	–
Comment	–	–	clotrimazole [81] and T0901317 [75] although acting at other sites, function as antagonists of the constitutive androstane receptor

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2A. Hepatocyte nuclear factor-4 receptors

Overview: Hepatocyte nuclear factor-4 receptors (nomenclature as agreed by NC-IUPHAR committee on nuclear hormone receptors [85]) have yet to be officially paired with an endogenous ligand, although linoleic acid has been described to activate HNF4α receptors.

Nomenclature	Hepatocyte nuclear factor-4-α	Hepatocyte nuclear factor-4-γ
Systematic nomenclature	NR2A1	NR2A2
HGNC, UniProt	*HNF4A*, P41235	*HNF4G*, Q14541
Endogenous agonists (pK_i)	linoleic acid (Selective) [87]	–
Selective antagonists (pK_i)	BI6015 [86]	–

Further reading

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2B. Retinoid X receptors

Overview: Retinoid X receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, [90]) are NR2B family members activated by 9-cis-retinoic acid and the RXR-selective agonists bexarotene and LG100268, sometimes referred to as rexinoids. UVI3003 [93] and HX531 [89] have been described as a pan-RXR antagonists. These receptors form RXR–RAR heterodimers and RXR–RXR homodimers [88,92].

Nomenclature	Retinoid X receptor-α	Retinoid X receptor-β	Retinoid X receptor-γ
Systematic nomenclature	NR2B1	NR2B2	NR2B3
HGNC, UniProt	*RXRA*, P19793	*RXRB*, P28702	*RXRG*, P48443
Selective agonists (pK_i)	CD3254 (pIC_{50} 8.5) [91]	–	–

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2C. Testicular receptors

Overview: Testicular receptors (nomenclature as agreed by NC-IUPHAR committee on nuclear hormone receptors [94]) have yet to be officially paired with an endogenous ligand, although testicular receptor 4 has been reported to respond to retinoids.

Nomenclature	Testicular receptor 2	Testicular receptor 4
Systematic nomenclature	NR2C1	NR2C2
HGNC, UniProt	*NR2C1*, P13056	*NR2C2*, P49116
Endogenous agonists (pK_i)	–	all-trans-retinoic acid (Selective) [96], retinol (Selective) [96]
Comment	Forms a heterodimer with TR4; gene disruption appears without effect on testicular development or function [95]	Forms a heterodimer with TR2

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2E. Tailless-like receptors

Overview: Tailless-like receptors (nomenclature as agreed by NC-IUPHAR committee on nuclear hormone receptors [97]) have yet to be officially paired with an endogenous ligand.

Nomenclature	TLX	PNR
Systematic nomenclature	NR2E1	NR2E3
HGNC, UniProt	*NR2E1*, Q9Y466	*NR2E3*, Q9Y5X4
Comment	Gene disruption is associated with abnormal brain development [98–99]	–

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2F. COUP-TF-like receptors

Overview: COUP-TF-like receptors (nomenclature as agreed by NC-IUPHAR committee on nuclear hormone receptors [100]) have yet to be officially paired with an endogenous ligand.

Nomenclature	COUP-TF1	COUP-TF2	V-erbA-related gene
Systematic nomenclature	NR2F1	NR2F2	NR2F6
HGNC, UniProt	*NR2F1*, P10589	*NR2F2*, P24468	*NR2F6*, P10588
Comment	Gene disruption is perinatally lethal [102]	Gene disruption is embryonically lethal [101]	Gene disruption impairs CNS development [103]

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3B. Estrogen-related receptors

Overview: Estrogen-related receptors (nomenclature as agreed by NC-IUPHAR committee on nuclear hormone receptors [104]) have yet to be officially paired with an endogenous ligand.

Nomenclature	Estrogen-related receptor-α	Estrogen-related receptor-β	Estrogen-related receptor-γ
Systematic nomenclature	NR3B1	NR3B2	NR3B3
HGNC, UniProt	*ESRRA*, P11474	*ESRRB*, O95718	*ESRRG*, P62508
Comment	Activated by some dietary flavonoids [105]; activated by the synthetic agonist GSK4716 [108] and blocked by XCT790 [106]	May be activated by DY131 [107]	May be activated by DY131 [107]

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4A. Nerve growth factor IB-like receptors

Overview: Nerve growth factor IB-like receptors (nomenclature as agreed by NC-IUPHAR committee on nuclear hormone receptors [110]) have yet to be officially paired with an endogenous ligand.

Nomenclature	Nerve Growth factor IB	Nuclear receptor related 1	Neuron-derived orphan receptor 1
Systematic nomenclature	NR4A1	NR4A2	NR4A3
HGNC, UniProt	*NR4A1*, P22736	*NR4A2*, P43354	*NR4A3*, Q92570
Comment	An endogenous agonist, cytosporone B, has been described [113], although structural analysis and molecular modelling has not identified a ligand binding site [109,111–112]	–	–

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5A. Fushi tarazu F1-like receptors

Overview: Fushi tarazu F1-like receptors (nomenclature as agreed by NC-IUPHAR committee on nuclear hormone receptors [114]) have yet to be officially paired with an endogenous ligand.

Nomenclature	Steroidogenic factor 1	Liver receptor homolog-1
Systematic nomenclature	NR5A1	NR5A2
HGNC, UniProt	*NR5A1*, Q13285	*NR5A2*, O00482
Comment	Reported to be inhibited by AC45594 [115] and SID7969543 [116]	–

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6A. Germ cell nuclear factor receptors

Overview: Germ cell nuclear factor receptors (nomenclature as agreed by NC-IUPHAR committee on nuclear hormone receptors [117]) have yet to be officially paired with an endogenous ligand.

Nomenclature	Germ cell nuclear factor
Systematic nomenclature	NR6A1
HGNC, UniProt	*NR6A1*, Q15406

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0B. DAX-like receptors

Overview: Dax-like receptors (nomenclature as agreed by NC-IUPHAR committee on nuclear hormone receptors [118]) have yet to be officially paired with an endogenous ligand.

Nomenclature	DAX1	SHP
Systematic nomenclature	NR0B1	NR0B2
HGNC, UniProt	*NR0B1*, P51843	*NR0B2*, Q15466

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Steroid hormone receptors

Overview: Steroid hormone receptors (nomenclature as agreed by NC-IUPHAR Committee on Nuclear Receptors, [120,132]) are nuclear hormone receptors of the NR3 class, with endogenous agonists that may be divided into 3-hydroxysteroids (estrone and 17β-estradiol) and 3-ketosteroids (dihydrotestosterone [DHT], aldosterone, cortisol, corticosterone, progesterone and testosterone). These receptors exist as dimers coupled with chaperone molecules (such as hsp90 (*HSP90AB1*, P08238) and immunophilin FKBP52:*FKBP4*, Q02790), which are shed on binding the steroid hormone. Although rapid signalling phenomena are observed [130,138], the principal signalling cascade appears to involve binding of the activated receptors 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 non-functional 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 [148].

A 7TM receptor responsive to estrogen (*GPER1*, Q99527, also known as GPR30, see [137]) has been described. Human orthologues of 7TM 'membrane progestin receptors' (*PAQR7*, *PAQR8* and *PAQR5*), initially discovered in fish [151–152], appear to localize to intracellular membranes and respond to 'non-genomic' progesterone analogues independently of G proteins [142].

3A. Estrogen receptors

Nomenclature	Estrogen receptor-α	Estrogen receptor-β
Systematic nomenclature	NR3A1	NR3A2
HGNC, UniProt	*ESR1*, P03372	*ESR2*, Q92731
Selective agonists (pK_i)	PPT (9.64) [128,143]	ERB 041 [133], diarylpropionitril (8.6) [135,143], WAY200070 (pIC_{50} 8.52 – 9.0) [133]
Selective antagonists (pK_i)	methyl-piperidino-pyrazole (8.57) [145]	PHTPP [119], R,R-THC (8.44) [134,146]

Comments: R,R-THC exhibits partial agonist activity at ERα [134,146]. Estrogen receptors may be blocked non-selectively by tamoxifen and raloxifene and labelled by [^{3}H]17β-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 [136].

3C. 3-Ketosteroid receptors

Nomenclature	Androgen receptor	Glucocorticoid receptor	Mineralocorticoid receptor	Progesterone receptor
Systematic nomenclature	NR3C4	NR3C1	NR3C2	NR3C3
HGNC, UniProt	*AR*, P10275	*NR3C1*, P04150	*NR3C2*, P08235	*PGR*, P06401
Rank order of potency	dihydrotestosterone>testosterone	cortisol,corticosterone>>aldosterone, deoxycortisone [139]	corticosterone,cortisol,aldosterone, progesterone [139]	progesterone
Endogenous agonists (pK_i)	dihydrotestosterone (pK_d 9.3) [147]	–	aldosterone (Selective) (pIC_{50} 9.8 – 10.0) [126,139]	progesterone (Selective)
Selective agonists (pK_i)	methyltrienolone (pEC_{50} < 5.0) [149], mibolerone (pIC_{50} 8.96) [124]	fluticasone, RU26988, RU28362	–	levonorgestrel [140], ORG2058
Selective antagonists (pK_i)	hydroxyflutamide (pEC_{50} 6.6) [149], PF0998425 (pIC_{50} 7.1 – 7.5) [131], nilutamide (pIC_{50} 7.07 – 7.12) [141]	onapristone, ZK112993, mifepristone (pK_d 9.4) [125,139]	onapristone, RU28318, ZK112993, eplerenone (pIC_{50} 1.0) [121,127]	mifepristone, onapristone, ZK112993
Radioligands (K_d)	[^{3}H]dihydrotestosterone (Agonist), [^{3}H]mibolerone (Agonist), [^{3}H]R1881 (Agonist)	[^{3}H]dexamethasone (Agonist)	[^{3}H]aldosterone (Agonist) ($3x10^{-10}$ – $4x10^{-10}$ M - Rat) [123,144]	[^{3}H]ORG2058 (Agonist)

Comments: [^{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 [122,129]. Mutations in AR underlie testicular feminization and androgen insensibility syndromes, spinal and bulbar muscular atrophy (Kennedy's disease).

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