THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Nuclear hormone receptors

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Abstract

The Concise Guide to PHARMACOLOGY 2021/22 is the fifth in this series of biennial publications. The Concise Guide provides concise overviews, mostly in tabular format, of the key properties of nearly 1900 human drug targets with an emphasis on selective pharmacology (where available), plus links to the open access knowledgebase source of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. Although the Concise Guide constitutes over 500 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at http://onlinelibrary.wiley.com/doi/bph.15540. Nuclear hormone receptors are one of the six major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, catalytic receptors, enzymes and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2021, and supersedes data presented in the 2019/20, 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Conflict of interest

The authors state that there are no conflicts of interest to disclose.

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Overview: Nuclear 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 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 unligand 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 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 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.

### Family structure

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### 1A. Thyroid hormone receptors

Nuclear hormone receptors → 1A. Thyroid hormone receptors

**Overview:** Thyroid hormone receptors (TRs, nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 40]) 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 (triiodothyronine). 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. NHR3 has been described as an antagonist at TRs with modest selectivity for TRβ [108].

**Further reading on 1A. Thyroid hormone receptors**

Elbers LP et al. (2016) Thyroid Hormone Mimetics: the Past, Current Status and Future Challenges. *Curr Atheroscler Rep* **18**, 14 [PMID:26886134]

Flamant F et al. (2006) International Union of Pharmacology. LIX. The pharmacology and classification of the nuclear receptor superfamily: thyroid hormone receptors. *Pharmacol Rev* **58**: 705-11 [PMID:17132849]

Mendoza A et al. (2017) New insights into thyroid hormone action. *Pharmacol Ther* **173**: 135-145 [PMID:28174093]

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1B. Retinoic acid receptors

Nuclear hormone receptors → 1B. Retinoic acid receptors

Overview: Retinoic acid receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 46]) are nuclear hormone receptors of the NR1B family activated by the vitamin A-derived agonists tretinoin (ATRA) and altretinoin, and the RAR-selective synthetic agonists TTNPB and adapalene. BMS493 is a family-selective antagonist [48].

Further reading on 1B. Retinoic acid receptors

Duong V et al. (2011) The molecular physiology of nuclear retinoic acid receptors. From health to disease. *Biochim Biophys Acta* **1812**:1023-31 [PMID:20970498]
Germain P et al. (2006) International Union of Pharmacology. LX. Retinoic acid receptors. *Pharmacol Rev* **58**: 712-25 [PMID:17132850]
Larange A et al. (2016) Retinoic Acid and Retinoic Acid Receptors as Pleiotropic Modulators of the Immune System. *Annu Rev Immunol* **34**: 369-94 [PMID:27168242]
Saeed A et al. (2017) The interrelationship between bile acid and vitamin A homeostasis. *Biochim Biophys Acta* **1862**: 496-512 [PMID:28111285]

Comments: Ro 41-5253 has been suggested to be a PPARγ agonist [127]. LE135 is an antagonist with selectivity for RARα and RARβ compared with RARγ [83].
1C. Peroxisome proliferator-activated receptors

Nuclear hormone receptors → 1C. Peroxisome proliferator-activated receptors

Overview: Peroxisome proliferator-activated receptors (PPARs, nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 99]) 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 [13, 99], including 15-deoxy-Δ12,14-Prostaglandin J2 (15-deoxy-Δ12,14-PGJ2), prostacyclin (PGI2), many fatty acids and their oxidation products, lysophosphatidic acid (LPA) [96], 13-HODE, 15S-HETE, Prostaglandin D2 (PGD2), Bezafibrate acts as a non-selective agonist for the PPAR family [155]. These receptors also bind hypolipidemic 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.

Further reading on 1C. Peroxisome proliferator-activated receptors

Cheang WS et al. (2015) The peroxisome proliferator-activated receptors in cardiovascular diseases: experimental benefits and clinical challenges. Br J Pharmacol 172: 5512-22 [PMID:25438608]
Gross B et al. (2017) PPARs in obesity-induced T2DM, dyslipidaemia and NALFD. Nat Rev Endocrinol 13: 36-49 [PMID:27636730]
Hallenborg S et al. (2016) The elusive endogenous adipogenic PPARy agonists: Lining up the suspects. Prog Lipid Res 61: 149-62 [PMID:26703188]
Michalik L et al. (2006) International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. Pharmacol Rev 58: 726-41 [PMID:17132851]
Sauer S. (2015) Ligands for the Nuclear Peroxisome Proliferator-Activated Receptor Gamma. Trends Pharmacol Sci 36: 688-704 [PMID:26435213]

Nomenclature

| Nomenclature | Peroxisome proliferator-activated receptor-α | Peroxisome proliferator-activated receptor-β | Peroxisome proliferator-activated receptor-γ |
|--------------|--------------------------------------------|-------------------------------------------|-------------------------------------------|
| Systematic nomenclature | NR1C1 | NR1C2 | NR1C3 |
| HGNC, UniProt | PPARA, Q07869 | PPARD, Q03181 | PPARG, Q37231 |
| Selective agonists | GW7647 [17, 18], CP-775146 [66], pirinixic acid [155], gemfibrozil [29] | GW0742X [51, 140], GW501516 [110] | GW1929 [17], bardoxolone (Partial agonist) [149], rosiglitazone [58, 79, 161], troglitazone [58, 161], pioglitazone [58, 125, 161], cigitazone [58] |
| Selective antagonists | GW6471 (pIC_{50} 6.6) [158] | GSK0660 (pIC_{50} 6.5) [129] | T0070907 (pK_{i} 9) [76], GW9662 (Irreversible inhibition) (pIC_{50} 8.1) [77], CDDO-Me (pK_{i} 6.9) [149] |

Comments: As with the estrogen receptor antagonists, many agents show tissue-selective efficacy (e.g. [12, 107, 122]). Agonists with mixed activity at PPARα and PPARγ have also been described (e.g. [32, 54, 159]).

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1D. Rev-Erb receptors

Overview: Rev-erb receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 7]) have yet to be officially paired with an endogenous ligand, but are thought to be activated by heme.

Further reading on 1D. Rev-Erb receptors

Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]

Gonzalez-Sanchez E et al. (2015) Nuclear receptors in acute and chronic cholestasis. Dig Dis 33: 357-66 [PMID:26045270]

Gustafson CL et al. (2015) Emerging models for the molecular basis of mammalian circadian timing. Biochemistry 54: 134-49 [PMID:25303119]

Sousa EH et al. (2017) Drug discovery targeting heme-based sensors and their coupled activities. J Inorg Biochem 167: 12-20 [PMID:27893989]

| Nomenclature       | Rev-Erb-α               | Rev-Erb-β               |
|--------------------|-------------------------|-------------------------|
| Systematic nomenclature | NR1D1                   | NR1D2                   |
| HGNC, UniProt      | NR1D1, P20393            | NR1D2, Q14995           |
| Endogenous agonists| heme [119, 160]          | heme [95, 119, 160]     |
| Selective agonists | GSK4112 [52], GSK4112 [71] | –                       |
| Selective antagonists| SR8278 (pIC₅₀ 6.5) [71]   | –                       |

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1F. Retinoic acid-related orphans

Nuclear hormone receptors → 1F. Retinoic acid-related orphans

Overview: Retinoic acid receptor-related orphan receptors (ROR, nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 7]) have yet to be assigned a definitive endogenous ligand, although RORα may be synthesized with a ‘captured’ agonist such as cholesterol [64, 65].

Further reading on 1F. Retinoic acid-related orphans

Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]

Cyr P et al. (2016) Recent progress on nuclear receptor RORγ modulators. Bioorg Med Chem Lett 26: 4387-4393 [PMID:27542908]

Germain P et al. (2006) Overview of nomenclature of nuclear receptors. Pharmacol Rev 58: 685-704 [PMID:17132848]

Guillemot-Legris O et al. (2016) Oxysterols in Metabolic Syndrome: From Bystander Molecules to Bioactive Lipids. Trends Mol Med 22: 594-614 [PMID:27286741]

Mutembezi V et al. (2016) Oxysterols: From cholesterol metabolites to key mediators. Prog Lipid Res 64: 152-169 [PMID:27687912]

| 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 | cholesterol [65, 112] | – | – |
| Selective agonists | 7-hydroxycholesterol [14], cholesterol sulphate [14, 65] | – | – |
| Comments | – | – | – |

The immune system function of RORC proteins most likely resides with expression of the RORγt isoform by immature CD4+/CD8+ cells in the thymus [34, 139] and in lymphoid tissue inducer (LTi) cells [35].

Comments: Tretinoin shows selectivity for RORβ within the ROR family [134]. RORα has been suggested to be a nuclear receptor responding to melatonin [154].

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1H. Liver X receptor-like receptors
Nuclear hormone receptors → 1H. Liver X receptor-like receptors

Overview: Liver X and farnesoid X receptors (LXR and FXR, nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 103]) are members of a steroid analogue-activated nuclear receptor subfamily, 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. In humans and primates, NR1HSP is a pseudogene. However, in other mammals, it encodes a functional nuclear hormone receptor that appears to be involved in cholesterol biosynthesis [111].

Further reading on 1H. Liver X receptor-like receptors
Courtney R et al. (2016) LXR Regulation of Brain Cholesterol: From Development to Disease. Trends Endocrinol Metab 27: 404-414 [PMID:27113081]
El-Gendy BEM et al. (2018) Recent Advances in the Medicinal Chemistry of Liver X Receptors. J Med Chem 61: 10935-10956 [PMID:30004226]
Gadaleta RM et al. (2010) Bile acids and their nuclear receptor FXR: Relevance for hepatobiliary and gastrointestinal disease. Biochim Biophys Acta 1801: 683-92 [PMID:20399894]
Merlen G et al. (2017) Bile acids and their receptors during liver regeneration: ‘Dangerous protectors’. Mol Aspects Med 56: 25-33 [PMID:28302491]
Moore DD et al. (2006) International Union of Pharmacology. LXII. The NR1H and NR1I receptors: constitutive androstane receptor, pregne X receptor, farnesoid X receptor alpha, farnesoid X receptor beta, liver X receptor alpha, liver X receptor beta, and vitamin D receptor. Pharmacol Rev 58: 742-59 [PMID:17132852]
Mouat K et al. (2016) Liver X receptors: from cholesterol regulation to neuroprotection—a new barrier against neurodegeneration in amyotrophic lateral sclerosis? Cell Mol Life Sci 73: 3801-8 [PMID:27510420]
Schulman IG. (2017) Liver X receptors link lipid metabolism and inflammation. FEBS Lett 591: 2978-2991 [PMID:28555747]

| 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, Q96R1 | NR1H5P | NR1H3, Q13133 | NR1H2, Q55055 |
| Potency order | 27-deoxycholesterol acid > lithocholic acid, deoxycholic acid [90, 113] | 20(S)-hydroxycholesterol, 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, 27-hydroxycholesterol [78] | 20(S)-hydroxycholesterol, 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, 27-hydroxycholesterol [78] |
| Endogenous agonists | – | lanosterol [111] – Mouse | – | – |
| Selective agonists | GW4064 [92], obeticholic acid [114], fexaramine [33] | – | – | – |
| Selective antagonists | guggulsterone (pIC50, 5.7–6) [157] | – | – | – |

Comments: T0901317 [120] and GW3965 [25] are synthetic agonists acting at both LXRα and LXRβ with less than 10-fold selectivity.

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11. Vitamin D receptor-like receptors

Nuclear hormone receptors → 11. Vitamin D receptor-like receptors

Overview: Vitamin D (VDR), Pregnane X (PXR) and Constitutive Androstane (CAR) receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 103]) 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 [103].

Further reading on 11. Vitamin D receptor-like receptors

Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]

Long MD et al. (2015) Vitamin D receptor and RXR in the post-genomic era. J Cell Physiol 230: 758-66 [PMID:25335912]

Moore DD et al. (2006) International Union of Pharmacology: LXII. The NR1H and NR1I receptors: constitutive androstane receptor, pregnene X receptor, farnesoid X receptor alpha, farnesoid X receptor beta, liver X receptor alpha, liver X receptor beta, and vitamin D receptor. Pharmacol Rev 58: 742-59 [PMID:17132852]

| Nomenclature | Vitamin D receptor | Pregnane X receptor | Constitutive androstane receptor |
|--------------|--------------------|--------------------|----------------------------------|
| Systematic nomenclature | NR1I1 | NR1I2 | NR1I3 |
| HGNC, UniProt | VDR, P11473 | NR1I2, Q75469 | NR1I3, Q14994 |
| Endogenous agonists | 1,25-dihydroxyvitamin D3 [11, 38] | 17β-estradiol [63] | – |
| Selective agonists | seocalcitol [26, 153], doxercalciferol | hyperforin [104, 152], 5β-pregnane-3,20-dione [63], lovastatin [80], rifampicin [15, 80] | TCPOBOP [144] – Mouse, CITCO [89] |
| Selective antagonists | TEI-9647 (pIC50 8.2) [124] – Chicken, ZK159222 (pIC50 7.5) [41, 59] | – | – |
| Comments | Clotrimazole [105] and T0901317 [67] although acting at other sites, function as antagonists of the constitutive androstane receptor. | – | – |
2A. Hepatocyte nuclear factor-4 receptors

Overview: The nomenclature of hepatocyte nuclear factor-4 receptors is agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 7]. While linoleic acid has been identified as the endogenous ligand for HNF4α its function remains ambiguous [163]. HNF4γ has yet to be paired with an endogenous ligand.

Further reading on 2A. Hepatocyte nuclear factor-4 receptors

Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]
Garattini E et al. (2016) Lipid-sensors, enigmatic-orphan and orphan nuclear receptors as therapeutic targets in breast-cancer. Oncotarget 7: 42661-42682 [PMID:26894976]
Germain P et al. (2006) Overview of nomenclature of nuclear receptors. Pharmacol Rev 58: 685-704 [PMID:17132848]

Lu H. (2016) Crosstalk of HNF4α with extracellular and intracellular signaling pathways in the regulation of hepatic metabolism of drugs and lipids. Acta Pharm Sin B 6: 393-408 [PMID:27709008]
Walesky C et al. (2015) Role of hepatocyte nuclear factor 4α (HNF4α) in cell proliferation and cancer. Gene Expr 16: 101-8 [PMID:25700366]

| Nomenclature | Hepatocyte nuclear factor-4-α | Hepatocyte nuclear factor-4-γ |
|--------------|--------------------------------|-------------------------------|
| Systematic nomenclature | NR2A1 | NR2A2 |
| HGNC, UniProt | HNF4A, P41235 | HNF4G, Q14541 |
| Endogenous agonists | linoleic acid [163] | – |
| Selective antagonists | B16015 [70] | – |
| Comments | HNF4α has constitutive transactivation activity [163] and binds DNA as a homodimer [62]. | – |
2B. Retinoid X receptors
Nuclear hormone receptors → 2B. Retinoid X receptors

Overview: Retinoid X receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 47]) are NR2B family members activated by allitretinoin and the RXR-selective agonists bexarotene and LG100268, sometimes referred to as retinoids. UV13003 [106] and HX S31 [36] have been described as a pan-RXR antagonists. These receptors form RXR-RAR heterodimers and RXR-RXR homodimers [21, 94].

Further reading on 2B. Retinoid X receptors
Germain P et al. (2006) International Union of Pharmacology. LXIII. Retinoid X receptors. Pharmacol Rev 58: 760-72 [PMID:17132853]

Long MD et al. (2015) Vitamin D receptor and RXR in the post-genomic era. J Cell Physiol 230: 758-66 [PMID:25335912]

Menéndez-Gutiérrez MP et al. (2017) The multi-faceted role of retinoid X receptor in bone remodeling. Cell Mol Life Sci 74: 2135-2149 [PMID:28105491]

| Nomenclature | Retinoid X receptor-α | Retinoid X receptor-β | Retinoid X receptor-γ |
|--------------|-----------------------|-----------------------|-----------------------|
| Systematic   | NR2B1                 | NR2B2                 | NR2B3                 |
| nomenclature | RXRA, P19793          | RXRB, P28702          | RXRG, P48443          |
| HGNC, UniProt| bexarotene [16, 20, 141] | bexarotene [16, 20, 141] | bexarotene [16, 20, 141] |
| Sub/family-selective agonists | CD3254 [49] | – | – |

2C. Testicular receptors
Nuclear hormone receptors → 2C. Testicular receptors

Overview: Testicular receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [7]) have yet to be officially paired with an endogenous ligand, although testicular receptor 4 has been reported to respond to retinoids.

Further reading on 2C. Testicular receptors
Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]

Germain P et al. (2006) Overview of nomenclature of nuclear receptors. Pharmacol Rev 58: 685-704 [PMID:17132848]

Safe S et al. (2014) Mini review: role of orphan nuclear receptors in cancer and potential as drug targets. Mol Endocrinol 28: 157-72 [PMID:24295738]

Wu D et al. (2016) The emerging roles of orphan nuclear receptors in prostate cancer. Biochim Biophys Acta 1866: 23-36 [PMID:27264242]

| Nomenclature | Testicular receptor 2 | Testicular receptor 4 |
|--------------|-----------------------|-----------------------|
| Systematic   | NR2C1                 | NR2C2                 |
| nomenclature | NR2C1, P13056         | NR2C2, P49116         |
| HGNC, UniProt| –                     | retinol [169], allitretinoin [169] |
| Endogenous   | –                     | –                     |
| agonists     | –                     | –                     |
| Comments     | Forms a heterodimer with TR4; gene disruption appears without effect on testicular development or function [130]. | Forms a heterodimer with TR2. |

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2E. Tailless-like receptors

Nuclear hormone receptors → 2E. Tailless-like receptors

Overview: Tailless-like receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [7]) have yet to be officially paired with an endogenous ligand.

Further reading on 2E. Tailless-like receptors

Benod C et al. (2016) TLX: An elusive receptor. J Steroid Biochem Mol Biol 157: 41-7
Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]
Germain P et al. (2006) Overview of nomenclature of nuclear receptors. Pharmacol Rev 58: 685-704 [PMID:17132848]
O’Leary JD et al. (2018) Regulation of behaviour by the nuclear receptor TLX. Genes Brain Behav 17: e12357 [PMID:27790850]

| Nomenclature | TLX          | PNR           |
|--------------|--------------|---------------|
| Systematic nomenclature | NR2E1        | NR2E3         |
| HGNC, UniProt | NR2E1, Q9Y466 | NR2E3, Q9Y5X4 |
| Agonists     | BMS493 [53], tretinoin [53] | –             |
| Comments     | Gene disruption is associated with abnormal brain development [74, 102]. | –             |

2F. COUP-TF-like receptors

Nuclear hormone receptors → 2F. COUP-TF-like receptors

Overview: COUP-TF-like receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 7]) have yet to be officially paired with an endogenous ligand.

Further reading on 2F. COUP-TF-like receptors

Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]
Wu D et al. (2016) The emerging roles of orphan nuclear receptors in prostate cancer. Biochim Biophys Acta 1866: 23-36 [PMID:27264242]
Germain P et al. (2006) Overview of nomenclature of nuclear receptors. Pharmacol Rev 58: 685-704 [PMID:17132848]
Wu SP et al. (2016) Choose your destiny: Make a cell fate decision with COUP-TFII. J Steroid Biochem Mol Biol 157: 7-12 [PMID:26658017]

| Nomenclature | COUP-TF1         | COUP-TF2         | V-erbA-related gene |
|--------------|------------------|------------------|---------------------|
| Systematic nomenclature | NR2F1           | NR2F2            | NR2F6               |
| HGNC, UniProt | NR2F1, P10589   | NR2F2, P24468    | NR2F6, P10588       |
| Comments     | Gene disruption is perinatally lethal [118]. | Gene disruption is embryonically lethal [115]. | Gene disruption impairs CNS development [151]. |

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Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.15540/full
3B. Estrogen-related receptors

Nuclear hormone receptors → 3B. Estrogen-related receptors

Overview: Estrogen-related receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [7]) have yet to be officially paired with an endogenous ligand.

Further reading on 3B. Estrogen-related receptors

Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]
Divekar SD et al. (2016) Estrogen-related receptor β (ERR β) - renaissance receptor or receptor renaissance? Nucl Recept Signal 14: e002 [PMID:27507929]
Germain P et al. (2006) Overview of nomenclature of nuclear receptors. Pharmacol Rev 58: 685-704 [PMID:17132848]

Tam IS et al. (2016) There and back again: The journey of the estrogen-related receptors in the cancer realm. J Steroid Biochem Mol Biol 157: 13-9 [PMID:26151739]
Wu D et al. (2016) The emerging roles of orphan nuclear receptors in prostate cancer. Biochim Biophys Acta 1866: 25-36 [PMID:27264242]

| 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 |
| Comments | Activated by some dietary flavonoids [136]; activated by the synthetic agonist GSK4716 [172] and blocked by XCT790 [156]. | May be activated by DY131 [162]. | May be activated by DY131 [162]. |

4A. Nerve growth factor IB-like receptors

Nuclear hormone receptors → 4A. Nerve growth factor IB-like receptors

Overview: Nerve growth factor IB-like receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [7]) have yet to be officially paired with an endogenous ligand.

Further reading on 4A. Nerve growth factor IB-like receptors

Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]
Germain P et al. (2006) Overview of nomenclature of nuclear receptors. Pharmacol Rev 58: 685-704 [PMID:17132848]
Ranhotra HS. (2015) The NR4A orphan nuclear receptors: mediators in metabolism and diseases. J Recept Signal Transduct Res 35: 184-8 [PMID:25089663]

Rodríguez-Calvo R et al. (2017) The NR4A subfamily of nuclear receptors: potential new therapeutic targets for the treatment of inflammatory diseases. Expert Opin Ther Targets 21: 291-304 [PMID:28055275]
Safe S et al. (2016) Nucleor receptor 4A (NR4A) family - orphans no more. J Steroid Biochem Mol Biol 157: 48-60 [PMID:25917081]
5A. Fushi tarazu F1-like receptors

Nuclear hormone receptors → 5A. Fushi tarazu F1-like receptors

**Overview:** Fushi tarazu F1-like receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [7]) have yet to be officially paired with an endogenous ligand.

**Further reading on 5A. Fushi tarazu F1-like receptors**

Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. *Pharmacol Rev* **58**: 798-836 [PMID:17132836]

Garattini E et al. (2016) Lipid-sensors, enigmatic-orphan and orphan nuclear receptors as therapeutic targets in breast-cancer. *OncoTargets* **7**: 42661-42682 [PMID:26894976]

Germain P et al. (2006) Overview of nomenclature of nuclear receptors. *Pharmacol Rev* **58**: 685-704 [PMID:17132848]

Zhi X et al. (2016) Structures and regulation of non-X orphan nuclear receptors: A retinoid hypothesis. *J Steroid Biochem Mol Biol* **157**: 27-40 [PMID:26159912]

Zimmer V et al. (2015) Nuclear receptor variants in liver disease. *Dig Dis* **33**: 415-9 [PMID:26045277]

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**Nomenclature**

| Steroidogenic factor 1 | Liver receptor homolog-1 |
|------------------------|--------------------------|
| NRS1A                  | NRS2A                    |
| NRS1A, Q13285          | NRS2A, O00482            |
| Comments               |                          |
| Reported to be inhibited by AC45594 [30] and SID7969543 [88]. | – |
6A. Germ cell nuclear factor receptors

Overview: Germ cell nuclear factor receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [7]) have yet to be officially paired with an endogenous ligand.

Further reading on 6A. Germ cell nuclear factor receptors

Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]
Garattini E et al. (2016) Lipid-sensors, enigmatic-orphan and orphan nuclear receptors as therapeutic targets in breast-cancer. Oncotarget 7: 42661-42682 [PMID:26894976]
Germain P et al. (2006) Overview of nomenclature of nuclear receptors. Pharmacol Rev 58: 685-704 [PMID:17132848]

Safe S et al. (2014) Minireview: role of orphan nuclear receptors in cancer and potential as drug targets. Mol Endocrinol 28: 157-72 [PMID:24295738]
Zhi X et al. (2016) Structures and regulation of non-X orphan nuclear receptors: A retinoid hypothesis. J Steroid Biochem Mol Biol 157: 27-40 [PMID:26159912]

0B. DAX-like receptors

Overview: DAX-like receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [7]) have yet to be officially paired with an endogenous ligand.

Further reading on 0B. DAX-like receptors

Benoit G et al. (2006) International Union of Pharmacology. LXVI. Orphan nuclear receptors. Pharmacol Rev 58: 798-836 [PMID:17132856]
Garattini E et al. (2016) Lipid-sensors, enigmatic-orphan and orphan nuclear receptors as therapeutic targets in breast-cancer. Oncotarget 7: 42661-42682 [PMID:26894976]
Germain P et al. (2006) Overview of nomenclature of nuclear receptors. Pharmacol Rev 58: 685-704 [PMID:17132848]

Safe S et al. (2014) Minireview: role of orphan nuclear receptors in cancer and potential as drug targets. Mol Endocrinol 28: 157-72 [PMID:24295738]
Wu D et al. (2016) The emerging roles of orphan nuclear receptors in prostate cancer. Biochim Biophys Acta 1866: 23-36 [PMID:27264242]

Nomenclature | Systematic nomenclature | HGNC, UniProt
--- | --- | ---
DAX1 | NR0B1 | NR0B1, P51843
SHP | NR0B2 | NR0B2, Q15466
Steroid hormone receptors

Overview: Steroid hormone receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 28, 85]) 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, P98238] and immunophilin FKBP52:FKBP4, Q02790), which are shed on binding the steroid hormone. Although rapid signalling phenomena are observed [82, 117], 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 [145].

A 7TM receptor responsive to estrogen (GPER1, Q99527, also known as GPR30, see [116]) has been described. Human orthologues of 7TM ‘membrane progestin receptors’ (PAQR7, PAQR8 and PAQR5), initially discovered in fish [170, 171], appear to localize to intracellular membranes and respond to ‘non-genomic’ progesterone analogs independently of G proteins [132].

3A. Estrogen receptors

Overview: Estrogen receptor (ER) activity regulates diverse physiological processes via transcriptional modulation of target genes [1]. The selection of target genes and the magnitude of the response, be it induction or repression, are determined by many factors, including the effect of the hormone ligand and DNA binding on ER structural conformation, and the local cellular regulatory environment. The cellular environment defines the specific complement of DNA enhancer and promoter elements present and the availability of coregulators to form functional transcription complexes. Together, these determinants control the resulting biological response.

Further reading on 3A. Estrogen receptors

Coons LA et al. (2017) DNA Sequence Constraints Define Functionally Active Steroid Nuclear Receptor Binding Sites In Chromatin. Endocrinology 158: 3212-3234 [PMID:28977594] Dahlman-Wright K et al. (2006) International Union of Pharmacology. LXIV. Estrogen receptors. Pharmacol Rev 58: 773-81 [PMID:17132854] Gonzalez-Sanchez E et al. (2015) Nuclear receptors in acute and chronic cholestasis. Dig Dis 33: 357-66 [PMID:26043276] Hewitt SC et al. (2016) What’s new in estrogen receptor action in the female reproductive tract. J Mol Endocrinol 56: R55-71 [PMID:26826253] Jameera Begam A et al. (2017) Estrogen receptor agonists/antagonists in breast cancer therapy: A critical review. Bioorg Chem 71: 257-274 [PMID:28274582] Warner M et al. (2017) Estrogen Receptor β as a Pharmaceutical Target. Trends Pharmacol Sci 38: 92-99 [PMID:27979317]
3C. 3-Ketosteroid receptors

Nuclear hormone receptors → Steroid hormone receptors → 3C. 3-Ketosteroid receptors

Overview: Steroid hormone receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on Nuclear Hormone Receptors [1, 28, 85]) 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). For rodent GR and MR, the physiological ligand is corticosterone rather than cortisol.

Further reading on 3C. 3-Ketosteroid receptors

Baker ME et al. (2017) 30 YEARS OF THE MINERALOCORTICOID RECEPTOR: Evolution of the mineralocorticoid receptor: sequence, structure and function. J Endocrinol 234: T1-T16 [PMID:28468932]
Carroll JS et al. (2017) Deciphering the divergent roles of progestogens in breast cancer. Nat Rev Cancer 17: 54-64 [PMID:27885264]
Cohen DM et al. (2017) Nuclear Receptor Function through Genomics: Lessons from the Glucocorticoid Receptor. Trends Endocrinol Metab 28: 531-540 [PMID:28495406]
de Kloet ER et al. (2017) Brain mineralocorticoid receptor function in control of salt balance and stress-adaptation. Physiol Behav 178: 13-20 [PMID:28089704]
Garg D et al. (2017) Progesterone-Mediated Non-Classical Signaling. Trends Endocrinol Metab 28: 656-668 [PMID:28651856]

S.N. Alexander et al. The Concise Guide to PHARMACOLOGY 2021/22: Nuclear hormone receptors. British Journal of Pharmacology (2021) 178, S246-S263
Nomenclature

Androgen receptor

Glucocorticoid receptor

Systematic nomenclature

NR3C4

NR3C1

HGNC, UniProt

AR, P10275

NR3C1, P04150

Rank order of potency

dihydrotestosterone > testosterone

cortisol, corticosterone > aldosterone, deoxycorticosterone

Endogenous agonists

dihydrotestosterone [142]

Selective agonists

testosterone propionate [93], mibolerone [50], fluoxymesterone [60], methyltrienolone [148], dromostanolone propionate [56], fluticasone propionate [10], flunisolide [3], beclometasone [3], methylprednisolone [3], betamethasone [3], budesonide [100]

Selective antagonists

bicalutamide (pKi 7.7) [69], PF0998425 (pIC50 7.1–7.5) [84], enzalutamide (pIC50 7.4) [143], nilutamide (pIC50 7.1–7.1) [131], hydroxylflutamide (pEC50 6.6) [148], galetone (pIC50 6.4) [56], flutamide (Displacement of 3H testosterone from wild-type androgen receptors) (pKi 5.4) [147]

Labelled ligands

[3H]dihydrotestosterone (Selective Agonist), [3H]mibolerone (Agonist)

[3H]dexamethasone (Agonist)

Progestosterone receptor

NR3C3

HGNC, UniProt

NR3C2, P08235

Rank order of potency

corticosterone, cortisol, aldosterone, progesterone [123]

deoxyxycorticosterone [123], aldosterone [57, 123], cortisol [57, 123], corticosterone

deoxyxycorticosterone [123], aldosterone [57, 123], cortisol [57, 123], corticosterone

Selective agonists

finerenone (pIC50 7.7) [5], eplerenone (pKi 6.9) [6], onapristone (pIC50 6.3) [165], RU28318, ZK112993

Selective antagonists

finerenone (pIC50 7.7) [5], eplerenone (pKi 6.9) [6], onapristone (pKi 7.7) [55], ZK112993

Labelled ligands

[3H]aldosterone (Selective Agonist) [44, 135] – Rat

[3H]ORC2058 (Selective Agonist)

Comments: [3H]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 [43, 81]. Mutations in AR underlie testicular feminization and androgen insensitivity syndromes, spinal and bulbar muscular atrophy (Kennedy’s disease).
