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Pharmacology of Retinoid Receptors

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Contents

Physiology of Vitamin A

Retinol, a form of vitamin A, and its metabolites play important roles in a multitude of physiological processes which include vision and the regulation of immune responses, cellular differentiation, and development in vertebrates. The best characterized bioactive metabolites of vitamin A are 11-*cis*-retinal and all-*trans*-retinoic acid (ATRA, **1**). The 11-*cis*-retinal metabolite mediates photoreception by acting as the visual chromophore.[1] Most of the non-visual functions of vitamin A are mediated by ATRA,[2] which regulates the expression of specific subsets of genes within target tissues via nuclear receptors.[3]

Retinoic Acid and Retinoid X Receptors

Nuclear receptors are ligand-activated transcription factors which bind to specific DNA regulatory elements in the promoter or vicinity of target genes leading to transcriptional activation or repression. The structures of nuclear receptors are modular in nature, being composed of several domains labeled A through F sequentially from the amino terminus. The amino terminal A/B contains the ligand-independent transcriptional activation function, AF-1, which imparts promoter specificity, while the C domain contains the DNA binding domain (DBD). The E/F carboxy terminal domain contains the ligand binding domain (LBD) and is separated from the C domain by a flexible hinge region (D).

ATRA binds the LBD of one of three isotypes of the retinoic acid receptor (RAR), namely RARα, β, or γ.[3–6] RAR forms heterodimers with one of three isotypes of the retinoid X receptor (RXR): RXRα, β or γ.[4,5] While ATRA does not bind or activate RXRs its 9-*cis* isomer does (**2**).[7,8] The RAR-RXR heterodimer associates with retinoic acid response elements (RARE). These elements consist of a direct repeat (DR) of a stretch of DNA that follows the canonical sequence 5′-PuG(G/T)TCA. Two (DR2) or, more often, five nucleotides (DR5) separate the half-sites of a RARE.[9] Considering the direction of transcription of the target gene in relation to the RAR-RXR arrangement, RXR resides upstream of its RAR partner (5′-RXR-RAR-3′). Binding of an agonist to RAR subordinates the role of agonist binding to RXR and therefore RARRXR is considered a non-permissive heterodimer. In addition to RAR, RXR is a heterodimeric partner of many other nuclear receptors including both nonpermissive partners – such as the thyroid receptor, vitamin D_3 receptor and pregnane X receptor – as well as permissive partners, such as peroxisome proliferator activated receptors (PPARs) α, β/δ, and γ, the farnesoid X receptor (FXR) and liver X receptor (LXR). Agonist binding to RXR in the context of permissive heterodimeric partners could influence the activities of such heterodimeric complexes.

Upon agonist binding, the RAR heterodimeric partner undergoes a conformational change in the helical motif H12 (referred to as AF-2) which allows RAR to couple to co-activator proteins that

mediate transcriptional effects.[10,11] Members of the steroid receptor co-activator (SRC-1) family are among the best characterized nuclear receptor co-activators. SRC-1 is required for ligand-dependent transcription of transiently transfected and chromosomally integrated reporter genes by the estrogen receptor (ER) and RAR.[12,13] Co-activators interact with ligand bound nuclear receptors through a central domain that contains three copies of a conserved recognition motif with the consensus sequence LXXLL.[14] The RAR-RXR heterodimer is able to bind RARE in the absence of a ligand, but preferentially associates with co-repressors such as the nuclear receptor co-repressor (N-CoR) 15 proteins and silencer proteins, for example silencing mediator for retinoid and thyroid receptor (SMRT).[16] These co-repressors recruit histone deacetylase and methyl transferase complexes leading to chromatin condensation and sequestration of promoter elements that inhibit transcriptional activity.

Beside the classical ATRA-RAR signaling pathway there are other naturally occurring retinol metabolites that have shown biological activities *in vitro* such as all-*trans*-13,14-dihydroxy-retinol and the retro-retinoids, namely anhydroretinol (AR) and 14-hydroxy-4,14-retro-retinol (14-HRR), which are involved in the regulation of lymphocyte proliferation.[17–20] Meanwhile, saturation of all-*trans*-retinol by the all-*trans*-13,14-dihydroretinol saturase (RetSat) enzyme leads to formation of (13*R*)-all-*trans*-13,14-dihydroretinol[21] that can be further oxidized to (13*R*)-all-*trans*-13,14-dihydroretinoic acid[22], a compound with RAR agonist activity.[23] The activities of these metabolites suggest that there are still other ATRA-independent functions of vitamin A which remain to be discovered.

For every RAR or RXR isotype there are several variants generated by alternative splicing or alternate transcriptional start sites. There are two isoforms for each of the three RXR isotypes and for RARα and γ, while RARβ has four isoforms. Combinations of the 8 RAR and 6 RXR isoforms and isotypes can result in the creation of 48 distinct heterodimers.[3] The ability of a single endogenous ligand to modulate a wide range of specific genes in a temporal and spatial manner may be explained by the large number of possible heterodimers. Genetic ablation of the expression of genes coding for one single isotype as, for example, mice lacking expression of RARα (*Rara*-null), can be to some extent compensated *in vivo* by the remaining isotypes, in this particular case RARβ (*Rarb*), or RARγ (*Rarg*).[24] The redundant and overlapping functions of the various isotypes have added another level of complexity to our understanding of their role and the development of isotype-selective drugs.

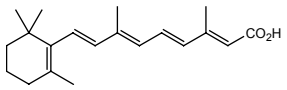
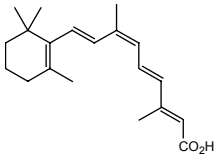
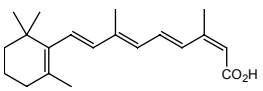
Pharmacology of RAR and RXR

Pharmacologically both RAR and RXR can be modulated in a subtype-specific manner via agonists, inverse agonists, partial agonists and antagonists. Naturally occurring or synthetic modulators of RARs are known as retinoids while naturally occurring or synthetic modulators of RXR are known as rexinoids. The use of retinoids in therapy has to be balanced with the significant toxicity that is associated with retinoids including teratogenesis, the induction of the retinoic acid syndrome characterized by weight gain, elevated white blood cells (WBCs), respiratory distress, interstitial pulmonary infiltrates, pleural and pericardial effusion, dyspnea, episodic hypotension and acute renal failure (ARF). There is hope that by developing more receptor-selective agents, one could circumvent the deleterious effects while obtaining specific responses and therapeutic efficacy.

Retinoid signaling can induce cellular differentiation or apoptosis, which is particularly relevant in the treatment of cancer. Due to this, there has been a tremendous effort to develop safe and receptor-selective compounds. Structural analysis of various receptors in combination with ATRA, 9-*cis*-RA or synthetic agonists or antagonists has provided the retinoid field with an unprecedented molecular understanding of the subtle changes necessary to produce the desired receptor response and to confer specific activity. Unfortunately, at the time of writing a ligand-free structure of RAR is not available to allow us to fully understand the mechanism of activation. The tables featured throughout this review describe some of the more common retinoids and rexinoids used clinically and in research. The design strategy, approach and history of retinoid research have been thoroughly discussed in several expert reviews.[25–29]

Many retinoids have been used in the treatment of various diseases or disorders. Supplementation with all-*trans*-retinol is used in developing countries to improve vitamin A deficiency (VAD). This is one of the safest and most efficacious therapeutic uses of retinoids and has enormous worldwide impact, saving millions of lives every year.[30] All-*trans*-RA (tretinoin) and 13-*cis*-RA

Table 1 | Naturally occurring pan-RAR modulators

Compound Number	Compound Name	Activity/Specificity	Structure	Cat. No.
1	Retinoic Acid (tretinoin)	Pan-RAR and RXR agonist Ongoing clinical trials in the treatment of cancer		0695
2	9-*cis* RA (alitretinoin)	Pan-RAR and RXR agonist		–
3	13-*cis*-RA (isotretinoin)	Pan-RAR agonist		5513

(isotretinoin, **3**) are used clinically in the treatment of severe acne and other dermatological conditions.[31] In cancer settings, the activation of RAR signaling leads to differentiation of cells and has chemopreventative and chemotherapeutic effects. In the case of Acute Promyelocytic Leukemia (APL), a fusion of RAR with PML (promyelocytic leukemia protein) growth suppressor gene interferes with RAR signaling. Retinoid agonists, for example ATRA, can reverse the effects of PML-RAR. As well as inducing cell differentiation, some retinoids induce apoptosis of tumor cells and provide another mechanism for chemotherapy. Retinoids such as ATRA, 13-*cis*-RA, N-(4-hydroxyphenyl)retinamide (4-HPR or fenretinide, **4**) and synthetic subtype-selective RAR and RXR agonists and modulators are used in the treatment and chemoprevention of various forms of cancer.[32–35] Most retinoids and rexinoids resemble the retinoic acid scaffold and employ a carboxylic acid moiety to make a critical ionic bridge with an arginine residue within the ligand binding domain of the respective receptors.

RAR Agonists and Antagonists

Pan-RAR modulators approved in the clinic include ATRA (tretinoin) and its 9-*cis* (alitretinoin) and 13-*cis* (isotretinoin) isomers. Both ATRA and 13-*cis* compounds act as pan-RAR agonists while 9-*cis*-RA can act as a pan-RAR and pan-RXR agonist. Both 9-*cis* and 13-*cis*-RA can isomerize to ATRA (the more stable isomer) *in vivo* and can be degraded by the same enzymes that regulate the levels of ATRA. EC 23 (**5**), a stable analog of ATRA which does not isomerize, has shown potent activity in the induction of stem cells and neurogenesis.[36,37] Other potent pan-RAR agonists include the arotinoid TTNPB (**6**), which was crystallized in association with RARβ,[38] and the synthetic chalconoid Ch 55 (**7**).[39] Tazarotene (**8**), another stable RAR analog, shows specificity towards RARβ and RARγ[40] and is currently employed as a topically administered treatment of acne and psoriasis.[41]

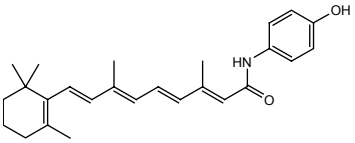
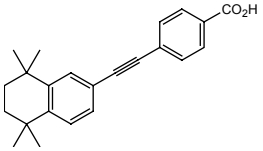
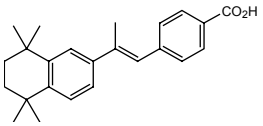
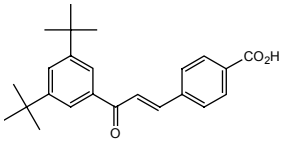
RARα-specific agonists include BMS 753 (**9**),[42] AM 80 (**10**) and related compound AM 580 (**11**).[43] The structure of RARα-LBD in association with a co-activator fragment and complexed with AM 580 was recently determined.[44] These studies show that AM 580 decreases the affinity of all co-repressor motifs for RAR, and describe the structural changes necessary for the repositioning of H12, allowing co-repressor release and co-activator recruitment.

The expression of RARβ is frequently lost in many transformed cells, therefore RARβ agonists would be expected to have potent antiproliferative effects. RARβ-specific agonists include the 4′-octyl-4-biphenylcarboxylic acid, AC 55649 (**12**), discovered using functional high throughput screening, and AC 261066 (**13**), developed by the optimization of AC 55649.[45,46] Adapalene (**14**), which carries the 1-adamantyl substituent, shows agonistic activity against both RARβ and RARγ and is used in the treatment of acne.[47,48]

RARγ-specific agonists include the derivatives of adapalene CD 437 (**15**) and CD 1530 (**16**).[49] The pro-apoptotic and antitumor effects of CD 437 are thought to act independently of the interaction with RARγ[50,51] and possibly via modulation of proapoptotic mitochondrial pathways[52,53] or GADD45A protein.[54] Another adapalene derivative, CD 2665 (**17**), has antagonistic activities against both RARβ and RARγ.[49,52] In general, insertion of a bulky substituent can convert an agonist to an antagonist as demonstrated by the pan-RAR antagonist MM 11253 (**18**)[55] and the RARβ antagonist LE 135 (**19**).[56]

The stilbene arotinoids BMS 493 (**20**) and BMS 453 (**21**) have an interesting profile characterized by either inverse agonist or mixed agonist/antagonist activities. BMS 453 is a potent antagonist of TTNPB-induced activation of RARα or RARγ, and a pan-RAR inverse agonist that enhances the RAR interaction with co-repressors down-regulating RAR-mediated gene transcription.[44] The recently identified pan-RAR inverse agonist SR-0065

Table 2 | Synthetic pan-RAR modulators

Compound Number	Compound Name	Activity/Specificity	Structure	Cat. No.
4	Fenretinide	RAR agonist Exerts antitumor RAR-independent effects		1396
5	EC 23	Pan-RAR agonist Photostable		4011
6	TTNPB (Ro 13-7410)	Pan-RAR agonist		0761
7	Ch 55	Pan-RAR agonist		2020

represents the first non-acid, non-retinoid direct modulator of the RAR receptor subfamily.[58]

RXR Agonists and Antagonists

Development of isotype selective rexinoids has been more challenging due to the highly conserved nature of the residues that delineate the lipid binding pocket of RXR.[25,59] From a subtype perspective, RXRα is the main RXR isotype involved in embryogenesis[6] and RXRα-selective agonists are not very common. Additionally, because of the non-permissive nature of the RAR-RXR heterodimer, activation of RXR alone is not expected to lead to activation of transcription and precludes the use of rexinoid monotherapy to modulate RAR signaling. Activation of RXR in the presence of agonists of RAR can result in synergistic effects and translate into more potent activity. On the other hand, activation of RXR in the context of permissive heterodimers is expected to cause the activation of transcription. The use of RXR agonists might therefore lead to pleiotropic effects by activating multiple permissive heterodimeric complexes. The existence of a multitude of RXR permissive partners provides a potentially important pharmacological tool to target multiple receptors and pathways that converge to obtain a favorable pharmaceutical profile. Dual activation of PPARα and PPARγ leads to increased fatty acid oxidation and increased fat recruitment into adipose stores; both pathways contribute to lowering the levels of ectopic fat and circulating fatty acids and result in increased insulin sensitivity.[60] Such effects were observed very early using the pan-RXR agonist bexarotene (**22**).[61] However, potent pan-RXR agonists can also induce RXR homodimer-dependent transcription which can lead to detrimental effects via suppression of the thyroid axis.[62] In contrast, heterodimer-selective rexinoids, such as LG 101506 (**23**), produce insulin sensitization and do not suppress thyroid signaling.[63]

Other pan-RXR agonists include the pan-RAR/pan-RXR agonist, 9-*cis*-retinoic acid, and benzoic acid derivatives CD 3254 (**24**)[64] and SR 11237 (BMS 649, **25**), which was co-crystallized with RXRα and a co-activator-derived peptide.[59] The related compound UVI 3003 (**26**) acts as a pan-RXR antagonist and provides a useful tool to dissect the contribution of RXR to transactivation in heterodimers and particularly in permissive heterodimers.[64] Another benzoic acid derived RXR ligand, LG 100754, has also been crystallized in association with RXRα and described as a RXR homodimer antagonist and a selective pan-RXR heterodimer agonist. LG 100754 (**27**) acts as an agonist of PPARα/RXR but it does not activate the thyroid receptor (TR)/RXR, vitamin D receptor (VDR)/RXR or LXR/RXR heterodimers.[65,66] The paradoxical result of an RXR antagonist such as LG 100754 acting as an activator of RAR-RXR heterodimers was explained

Table 3A | Subtype-selective RAR agonists and antagonists

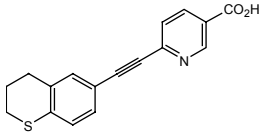
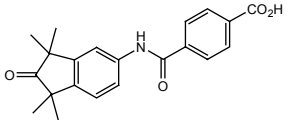
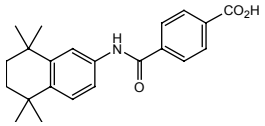
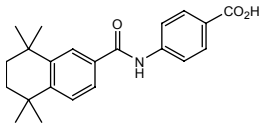
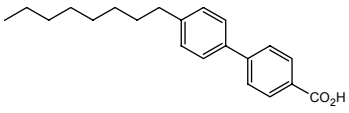
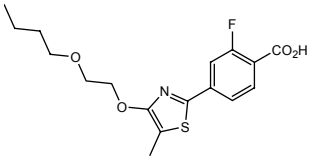
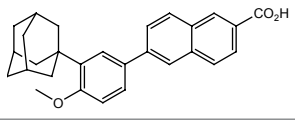
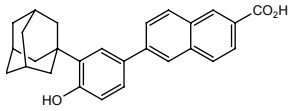
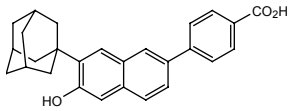
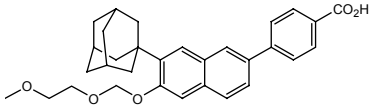
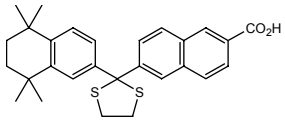
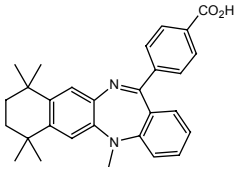
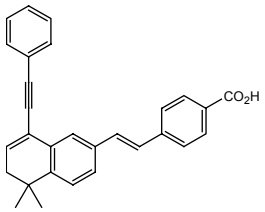
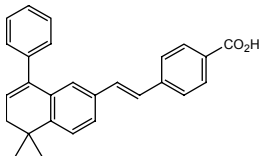
Compound Number	Compound Name	Activity/Specificity	Structure	Cat. No.
8	Tazarotene	RAR β/γ agonist		3997
9	BMS 753	RARα agonist		3505
10	AM 80	RARα agonist Benzoic acid type		3507
11	AM 580	RARα agonist		0760
12	AC 55649	RARβ2 agonist		2436
13	AC 261066	RARβ2 agonist		4046
14	Adapalene	RARβ and γ agonist		2852

Table 3B | Subtype-selective RAR agonists and antagonists

Compound Number	Compound Name	Activity/Specificity	Structure	Cat. No.
15	CD 437	RARγ agonist		1549
16	CD 1530	RARγ agonist		2554
17	CD 2665	RARγ antagonist		3800
18	MM 11253	RAR antagonist		3822
19	LE 185	RARβ antagonist		2021
20	BMS 493	Pan-RAR inverse agonist Strengthens the interaction with repressor CoR		3509
21	BMS 453	Agonist of RARβ Antagonist of RARα or RARγ		3409

though a 'phantom ligand' effect whereby binding of LG 100754 to RXR translates into conformational change in RAR and recruitment of co-activators.[67] More recent studies, however, demonstrate that antagonism of RXR by LG 100754 has no effect on the structure of RAR or its interaction with co-repressors or co-activators within the heterodimer. Instead, LG 100754 mediates activation of RAR through direct binding.[68] Therefore, LG 100754 still acts as an RXR antagonist in the context of RAR-RXR heterodimers.[68] Similar to LG 101506, LG 100754 is also a potent insulin-sensitizer.[66] In contrast, the dibenzodiazepine derivative HX 531 (**28**) is a pan-RXR antagonist that inhibits the activation of both RXR homodimers and RAR-RXR heterodimers. Specifically, HX 531 inhibited the transactivation of RARs induced by the RAR agonist, AM 80.[69] A related derivative of dibenzodiazepine, HX 630 (**29**), acts as a pan-RXR agonist and weak RAR-antagonist.[70] Both HX 630 and HX 531 show weak binding affinity to isolated RXR (with submicromolar K_i values) while exhibiting much better agonist or antagonist activity, respectively, at RAR-RXR heterodimers (with subnanomolar EC_{50} values) suggesting that they are RXR-RAR heterodimer-selective ligands.[70]

The structure of RXR in combination with various agonists revealed that the RXR lipid binding pocket is more accommodating than the one of RAR, allowing RXR to bind several ligands such as the proposed endogenous ligand, 9-*cis*-RA, as well as other long-chain unsaturated fatty acids. It is possible that RXR does not have a truly dedicated endogenous ligand and that it evolved to respond to several molecular signatures depending on the cellular and metabolic context and the local concentration and supply of each potential ligand. Using genetic and pharmacological evidence it has been possible to exclude a physiological role for 9-*cis*-RA as a ligand of RXR in mouse keratinocytes.[71] Taken together with the opportunistic nature of RXR, this questions the nature of its endogenous ligand. Before its recent detection in mouse pancreas using a sensitive analytical LC-MS/MS technique,[72] 9-*cis*-RA could not be detected in tissues of animals unless they were first supplemented with pharmacological doses of vitamin A. The difficulties encountered in detecting endogenous 9-*cis*-RA prompted the search for alternate ligands. Other possible endogenous RXR ligands include docosahexaenoic acid (DHA),[73] the most abundant essential omega-3 fatty acid present in the brain, and phytanic acid, derived from the degradation of chlorophyll by α-oxidation.[74] Both DHA and phytanic acid have many other potential cellular receptors or mediators which

preclude their use as selective rexinoids. DHA can also activate PPARγ[75] and can have many other possible effects (reviewed by Niemoller *et al.*[76]) while phytanic acid can also activate PPARα.[77]

Off-target Effects of Retinoids and Rexinoids

One important consideration in the use of retinoids and rexinoids is the possibility for off-target effects. Our understanding of the behavior of such retinoids or rexinoids is, in some cases, limited to *in vitro* assays where the response of an isolated receptor is interrogated one ligand at a time. The use of such compounds in cell-based assays or *in vivo* (based solely on reported *in vitro* activity) is fraught with the possibility of off-target effects, as seen in the case of the widely used RARα-specific antagonist Ro 41-5253, which is also an agonist of PPARγ.[78] Current methodologies make it possible to screen a given ligand for agonistic or antagonistic effects against a large panel of nuclear receptors reducing the risk of off-target effects. In one such study, screening 25 human nuclear receptors allowed the authors to conclude that all-*trans*-13,14-dihydroretinoic acid displays RAR-specificity.[23]

When developing better drugs, a good understanding of retinoid and rexinoid pharmacology – beyond RAR and RXR – and screening for off-target effects is crucial. Off-target effects may provide alternative avenues of research for retinoid compounds with established antitumor activity. An example of this is the atypical retinoids, which have been shown to bind and activate RAR or RXR *in vitro*; however, this does not fully explain their *in vivo* antitumor effects. In the case of CD 437 and fenretinide, both appear to be effective in retinoid-resistant cells and their effects cannot be blocked using RAR antagonists.[79] Fenretinide lacks the carboxylic acid which would allow it to interact with the RAR LBD but can be converted to ATRA, however, this is not a prerequisite for inducing apoptosis[80] and both drugs are promising therapeutic agents. CD 437 and fenretinide are currently in preclinical studies for the treatment of various cancers.

In addition to activating the RAR/RXR heterodimer, ATRA has also been proposed to modulate cell signaling through RAR-independent pathways (nonclassical pathways) which were shown to occur in many settings including neural development,[81] mucous cell differentiation[82] and dendritic cell maturation.[83] Several receptor molecules have been proposed to mediate the non-classical effects of ATRA including non-RAR nuclear transcription factors such as the retinoic acid orphan receptor γ (RORγ),[84] PPARβ/δ,[85] testicular receptor 4 (TR4)[86] and chicken ovalbumin upstream promoter-transcription factors II (COUP-TFII)[87] as well as other cellular signaling mediators, such as the mannose-6-phosphate receptor/IGF2R[88,89] and extracellular signal-regulated kinase (ERK). Even though RAR is considered as a classical nuclear receptor, it continues to reveal new facets of its complexity and its potential may have been overlooked. RARα, in response to ATRA, can carry out transcriptionindependent effects by regulating the translation of neuronal proteins such as the glutamate receptor 1 (GluR1) mRNA and mediating synaptic plasticity.[90–93]

Modulators of ATRA Metabolism

Retinoid signaling is controlled via the isotype of nuclear receptor present, the levels of nuclear receptors, and the amount of available ligand. Both excess and deficiency of ligand can lead to severe developmental abnormalities. The levels of ATRA are exquisitely well controlled *in vivo* in a temporal and spatial manner by the enzymes and binding proteins involved in its

Table 4A | RXR agonists and antagonists

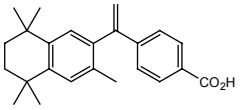
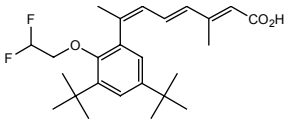
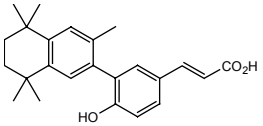
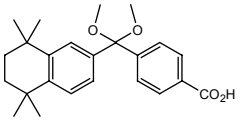
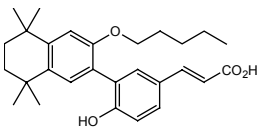
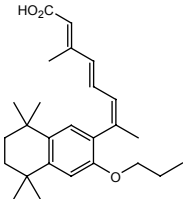
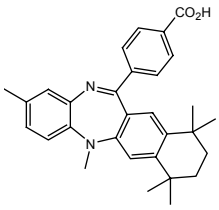
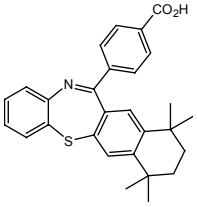
Compound Number	Compound Name	Activity/Specificity	Structure	Cat. No.
22	Bexarotene (LGD1069)	Pan-RXR agonist Ongoing clinical trials in the treatment of cancer and skin diseases		5819
23	LG 101506	Selective agonist of a specific set of RXR heterodimers Insulin sensitizer		3508
24	CD 3254	Pan-RXR agonist		3302
25	SR 11237 (BMS 649)	Pan-RXR agonist		3411
26	UVI 3003	RXR antagonist		3303

Table 4B | RXR agonists and antagonists

Compound Number	Compound Name	Activity/Specificity	Structure	Cat. No.
27	LG 100754	RXR homodimer antagonist, RXR heterodimer agonist		3831
28	HX 531	Pan-RXR antagonist dibenzodiazepine derivative Inhibits activation of RAR-RXR heterodimers		3912
29	HX 630	Pan-RXR agonist, weak RAR antagonist Synergizes with AM 80 to induce differentiation of HL-60 cells		3913

synthesis and catabolism. The enzymes involved in the synthesis and degradation of retinoic acid (RA) have been extensively described. Retinol (ROL) and retinaldehyde (RAL) can be interconverted by microsomal short-chain dehydrogenase/reductase (SDR)[94,95] and by class I, II, and IV medium-chain alcohol dehydrogenases (ADH).[96] Irreversible oxidation of RAL to RA is carried out by retinal dehydrogenase (RALDH) types 1, 2, 3, and 4.[97–102] Cytochrome P450 enzymes CYP26A1, CYP26B1, and CYP26C1 carry out the catabolism of RA to 4-hydroxy-RA, 4-oxo-RA, and 18-hydroxy-RA.[103–106]

Retinoids are very labile and poorly soluble in aqueous solutions. Transport proteins play important roles *in vivo* by protecting retinoids from oxidation or isomerization and by ensuring their delivery to target tissues, enzymes or receptors.[107] Transport of retinol in serum is mediated by retinol binding protein (RBP)[108] which circulates bound to transthyretin (TTR).[109] Cellular uptake and efflux of retinol occurs via receptors such as those stimulated by retinoic acid 6 (STRA6) found on vascular-endothelial cells and retinal pigmented epithelial cells.[110–112] Cellular uptake is driven by esterification of retinol by the enzyme lecithin:retinol acyltransferase to form highly insoluble retinyl esters. Delivery of ATRA to the nucleus is achieved by accessory proteins CRABP (cellular retinoic acid binding proteins) I and II, soluble proteins that belong to the intracellular ligand-binding protein family (iLBPs).[113] Both CRABPI and II remain in the cytosol in the absence of ligand but translocate to the nucleus in its presence. CRABPII delivers the ligand by associating directly with RARs[114] and enhancing their activity.[115] The type of accessory protein can determine the fate of the ligand: for example retinoic acid, which, depending on the accessory protein present, can be shuttled to the nucleus by CRABPI or II or fatty acid binding protein 4 (FABP4 or aP2) to bind either RAR or PPARβ/δ, respectively.[116] The presence of specific accessory molecules can therefore modulate the binding of a given ligand to alternate receptors and this is an important consideration when studying the activity of such a ligand *in vivo* or in cell culture. Modulation of retinoid metabolism or transport can affect the precursor pool of ATRA or result in pharmacokinetic enhancement of ATRA. Inhibitors of the CYP26A1 enzymes such as liarozole hydrochloride increase the levels of ATRA in cells resulting in augmentation of RAR signaling in pan-RAR fashion. Fenretinide, in addition to its pro-apoptotic effects, interferes with RBP binding to transthyretin, which results in the excretion of RBP via glomerular filtration and resulting in a depletion of the precursor pool of retinol for ATRA synthesis.[117]

Conclusion

Advances in structural biology started with the elucidation of a fragment of RXR that encompassed the LBD,[118] then the ligand bound LBD of RARs[119] and the DBD of RAR-RXR on DNA.[120] This was followed by many structures showing the RAR or RXR LBD complexed with agonists, antagonists and co-activator and co-repressor peptides (reviewed by de Lera *et al*[25]). This has led to a much better understanding of the molecular details of receptor activation, repression, and the role of specific domains in the association with co-activator and co-repressor. Due to the unstructured and flexible nature of the hinge separating the DBD and LBD there has been a paucity of full-length receptor structures. The elucidation of the structure of an intact receptor, containing both the LBD and DBD, has become an essential step in understanding how the two domains interact and how activation translates into global changes. The first crystal structure of a full-length nuclear receptor complex on DNA was reported by Chandra *et al*[121] showing the assembly of full-length PPARγ-RXRα heterodimers on DNA. Such an understanding of RAR-RXR will lead to an improvement in the selectivity of retinoids and rexinoids and the possible development of allosteric modulators. These allosteric modulators would most likely not be

based on the retinoid scaffold and would bind to a distinct site from the LBD to mediate the interaction of nuclear receptors with co-activators and co-repressors in a ligand-dependent manner. Allosteric modulators would also be expected to act in a more isotype-selective manner in comparison to current retinoids and rexinoids which are constrained to bind the highly conserved LBD. Unfortunately, the development of allosteric modulators generally occurs through structure guided design or fragment-based drug discovery efforts. Both approaches have proved to be major obstacles in the case of nuclear receptors since they require high resolution structures of intact receptors and very reproducible crystallization conditions. Future integration of screens for co-activator binding and structural biology could lead to new classes of modulators and major advances in the retinoid and rexinoid field.

References

1. **Wald** (1968) Molecular basis of visual excitation. *Science* **162** 230.
2. **Dowling and Wald** (1981) Nutrition classics. Proceeding of the National Academy of Sciences of the United States of America, Volume 46, 1960: The biological function of vitamin A acid. *Nutr.Rev.* **39** 13.
3. **Chambon** (1996) A decade of molecular biology of retinoic acid receptors. *FASEB J.* **10** 940.
4. **Petkovich** *et al.* (1987) A human retinoic acid receptor which belongs to the family of nuclear receptors. *Nature* **330** 444.
5. **Giguere** *et al.* (1987) Identification of a receptor for the morphogen retinoic acid. *Nature* **330** 624.
6. **Mark** *et al.* (2006) Function of retinoid nuclear receptors: Lessons from genetic and pharmacological dissections of the retinoic acid signaling pathway during mouse embryogenesis. *Annu.Rev.Pharmacol.Toxicol.* **46** 451.
7. **Heyman** *et al.* (1992) 9-*cis* retinoic acid is a high affinity ligand for the retinoid X receptor. *Cell* **68** 397.
8. **Egea** *et al.* (2000) Crystal structure of the human RXRα ligand-binding domain bound to its natural ligand: 9-*cis* retinoic acid. *EMBO J.* **19** 2592.
9. **Predki** *et al.* (1994) Ordered binding of retinoic acid and retinoid-X receptors to asymmetric response elements involves determinants adjacent to the DNA-binding domain. *Mol.Endocrinol.* **8** 31.
10. **Darimont** *et al.* (1998) Structure and specificity of nuclear receptorcoactivator interactions. *Genes.Dev.* **12** 3343.
11. **Nolte** *et al.* (1998) Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-γ. *Nature* **395** 137.
12. **Onate** *et al.* (1995) Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science* **270** 1354.
13. **Llopis** *et al.* (2000) Ligand-dependent interactions of coactivators steroid receptor coactivator-1 and peroxisome proliferator-activated receptor binding protein with nuclear hormone receptors can be imaged in live cells and are required for transcription. *Proc.Natl.Acad.Sci.USA* **97** 4363.
14. **Ding** *et al.* (1998) Nuclear receptor-binding sites of coactivators glucocorticoid receptor interacting protein 1 (GRIP1) and steroid receptor coactivator 1 (SRC-1): multiple motifs with different binding specificities. *Mol.Endocrinol.* **12** 302.
15. **Kurokawa** *et al.* (1995) Polarity-specific activities of retinoic acid receptors determined by a co-repressor. *Nature* **377** 451.
16. **Chen and Evans** (1995) A transcriptional co-repressor that interacts with nuclear hormone receptors. *Nature* **377** 454.
17. **Buck** *et al.* (1991) Intracellular signaling by 14-hydroxy-4,14-retroretinol. *Science* **254** 1654.
18. **Buck** *et al.* (1993) Anhydroretinol: a naturally occurring inhibitor of lymphocyte physiology. *J.Exp.Med.* **178** 675.
19. **Derguini** *et al.* (1994) Intracellular signaling activity of synthetic (14R)-, (14S)-, and (14RS)-14-hydroxy-4,14-retro-retinol. *Biochemistry* **33** 623.
20. **Derguini** *et al.* (1995) 13,14-Dihydroxy-retinol, a new bioactive retinol metabolite. *J.Biol.Chem.* **270** 18875.
21. **Moise** *et al.* (2004) Identification of all-*trans*-retinol:all-*trans*-13,14-dihydroretinol saturase. *J.Biol.Chem.* **279** 50230.
22. **Moise** *et al.* (2005) Metabolism and transactivation activity of 13,14-dihydroretinoic acid. *J.Biol.Chem.* **280** 27815.
23. **Moise** *et al.* (2009) Activation of retinoic acid receptors by dihydroretinoids. *Mol.Pharmacol.* **76** 1228.
24. **Lufkin** *et al.* (1993) High postnatal lethality and testis degeneration in retinoic acid receptor α mutant mice. *Proc.Natl.Acad.Sci.USA* **90** 7225.
25. **de Lera** *et al.* (2007) Design of selective nuclear receptor modulators: RAR and RXR as a case study. *Nat.Rev.Drug Discov.* **6** 811.
26. **Altucci** *et al.* (2007) RAR and RXR modulation in cancer and metabolic disease. *Nat.Rev.Drug Discov.* **6** 793.
27. **Germain** *et al.* (2006) International Union of Pharmacology. LX. Retinoic acid receptors. *Pharmacol.Rev.* **58** 712.
28. **Dawson** (2004) Synthetic retinoids and their nuclear receptors. *Curr.Med.Chem.Anticancer Agents* **4** 199.
29. **Thacher** *et al.* (2000) Therapeutic applications for ligands of retinoid receptors. *Curr.Pharm.Des.* **6** 25.
30. **Humphrey** *et al.* (1992) Vitamin A deficiency and attributable mortality among under-5-year-olds. *Bull.World Health Organ.* **70** 225.
31. **Chivot** (2005) Retinoid therapy for acne. A comparative review. *Am.J.Clin.Dermatol.* **6** 13.
32. **Chomienne** *et al.* (1989) Retinoic acid therapy for promyelocytic leukaemia. *Lancet* **2** 746.
33. **Hong and Sporn** (1997) Recent advances in chemoprevention of cancer. *Science* **278** 1073.
34. **Simeone and Tari** (2004) How retinoids regulate breast cancer cell proliferation and apoptosis. *Cell.Mol.Life Sci.* **61** 1475.
35. **Hail** *et al.* (2006) Mechanisms of fenretinide-induced apoptosis. *Apoptosis* **11** 1677.
36. **Christie** *et al.* (2010) Retinoid supplementation of differentiating human neural progenitors and embryonic stem cells leads to enhanced neurogenesis *in vitro*. *J.Neurosci.Methods* **193** 239.
37. **Christie** *et al.* (2008) Synthesis and evaluation of synthetic retinoid derivatives as inducers of stem cell differentiation. *Org.Biomol.Chem.* **6** 3497.
38. **Germain** *et al.* (2004) Rational design of RAR-selective ligands revealed by RARβ crystal structure. *EMBO Rep.* **5** 877.
39. **Nervi** *et al.* (1989) Identification and characterization of nuclear retinoic acid-binding activity in human myeloblastic leukemia HL-60 cells. *Proc.Natl. Acad.Sci.USA* **86** 5854.
40. **Chandraratna** (1996) Tazarotene - first of a new generation of receptor-selective retinoids. *Br.J.Dermatol.* **135** (Suppl 49) 18.
41. **Talpur** *et al.* (2009) Efficacy and safety of topical tazarotene: a review. *Expert.Opin.Drug Metab.Toxicol.* **5** 195.
42. **Gehin** *et al.* (1999) Structural basis for engineering of retinoic acid receptor isotype-selective agonists and antagonists. *Chem.Biol.* **6** 519.
43. **Kagechika** *et al.* (1988) Retinobenzoic acids. 1. Structure-activity relationships of aromatic amides with retinoidal activity. *J.Med.Chem.* **31** 2182.
44. **le Maire** *et al.* (2010) A unique secondary-structure switch controls constitutive gene repression by retinoic acid receptor. *Nat.Struct.Mol.Biol.* **17** 801.
45. **Lund** *et al.* (2005) Discovery of a potent, orally available, and isoform-selective retinoic acid β2 receptor agonist. *J.Med.Chem.* **48** 7517.
46. **Lund** *et al.* (2009) Design, synthesis, and structure-activity analysis of isoform-selective retinoic acid receptor β ligands. *J.Med.Chem.* **52** 1540.
47. **Hensby** *et al.* (1990) The *in vivo* and *in vitro* anti-inflammatory activity of CD271: a new retinoid-like modulator of cell differentiation. *Agents Actions* **29** 56.
48. **Bernard** (1993) Adapalene, a new chemical entity with retinoid activity. *Skin Pharmacol.* **6** 61.
49. **Bernard** *et al.* (1992) Identification of synthetic retinoids with selectivity for human nuclear retinoic acid receptor γ. *Biochem.Biophys.Res.Commun.* **186** 977.
50. **Shao** *et al.* (1995) p53 independent G0/G1 arrest and apoptosis induced by a novel retinoid in human breast cancer cells. *Oncogene* **11** 493.
51. **Sun** *et al.* (2000) Dual mechanisms of action of the retinoid CD437: nuclear retinoic acid receptor-mediated suppression of squamous differentiation and receptor-independent induction of apoptosis in UMSCC22B human head and neck squamous cell carcinoma cells. *Mol.Pharmacol.* **58** 508.
52. **Sun** *et al.* (1997) Induction of apoptosis in human non-small cell lung carcinoma cells by the novel synthetic retinoid CD437. *J.Cell.Physiol.* **173** 279.
53. **Gonda** *et al.* (2008) Synthetic retinoid CD437 induces mitochondriamediated apoptosis in hepatocellular carcinoma cells. *Biochem. Biophys.Res.Commun.* **370** 629.
54. **Jiang** *et al.* (2007) GADD45A is a mediator of CD437 induced apoptosis in ovarian carcinoma cells. *J.Cell.Physiol.* **212** 771.
55. **Holmes** *et al.* (2000) Induction of apoptosis in ovarian carcinoma cells by AHPN/CD437 is mediated by retinoic acid receptors. *J.Cell.Physiol.* **185** 61.
56. **Eyrolles** *et al.* (1994) Retinobenzoic acids. 6. Retinoid antagonists with a heterocyclic ring. *J.Med.Chem.* **37** 1508.
57. **Alvarez** *et al.* (2009) C3 halogen and C8″ substituents on stilbene arotinoids modulate retinoic acid receptor subtype function. *ChemMedChem.* **4** 1630.
58. **Busby** *et al.* (2011) Identification of a novel non-retinoid pan inverse agonist of the retinoic acid receptors. *ACS Chem.Biol.* **6** 618.
59. **Egea** *et al.* (2002) Molecular recognition of agonist ligands by RXRs. *Mol.Endocrinol.* **16** 987.

60. **Artis** *et al.* (2009) Scaffold-based discovery of indeglitazar, a PPAR pan-active anti-diabetic agent. *Proc.Natl.Acad.Sci.USA* **106** 262.
61. **Mukherjee** *et al.* (1997) Sensitization of diabetic and obese mice to insulin by retinoid X receptor agonists. *Nature* **386** 407.
62. **Liu** *et al.* (2002) Mechanism of selective retinoid X receptor agonistinduced hypothyroidism in the rat. *Endocrinology* **143** 2880.
63. **Leibowitz** *et al.* (2006) Biological characterization of a heterodimerselective retinoid X receptor modulator: potential benefits for the treatment of type 2 diabetes. *Endocrinology* **147** 1044.
64. **Nahoum** *et al.* (2007) Modulators of the structural dynamics of the retinoid X receptor to reveal receptor function. *Proc.Natl.Acad.Sci.USA* **104** 17323.
65. **Lala** *et al.* (1996) Activation of specific RXR heterodimers by an antagonist of RXR homodimers. *Nature* **383** 450.
66. **Cesario** *et al.* (2001) The rexinoid LG100754 is a novel RXR:PPARγ agonist and decreases glucose levels *in vivo*. *Mol.Endocrinol.* **15** 1360.
67. **Schulman** *et al.* (1997) The phantom ligand effect: allosteric control of transcription by the retinoid X receptor. *Genes Dev.* **11** 299.
68. **Sato** *et al.* (2010) The "phantom effect" of the rexinoid LG100754: structural and functional insights. *PLoS One* **5** e15119.
69. **Ebisawa** *et al.* (1999) Retinoid X receptor-antagonistic diazepinylbenzoic acids. *Chem.Pharm.Bull.* (Tokyo) **47** 1778.
70. **Umemiya** *et al.* (1997) Action mechanism of retinoid-synergistic dibenzodiazepines. *Biochem.Biophys.Res.Commun.* **233** 121.
71. **Calleja** *et al.* (2006) Genetic and pharmacological evidence that a retinoic acid cannot be the RXR-activating ligand in mouse epidermis keratinocytes. *Genes Dev.* **20** 1525.
72. **Kane** *et al.* (2010) Identification of 9-*cis*-retinoic acid as a pancreas-specific autacoid that attenuates glucose-stimulated insulin secretion. *Proc.Natl. Acad.Sci.USA.* **107** 21884.
73. **de Urquiza** *et al.* (2000) Docosahexaenoic acid, a ligand for the retinoid X receptor in mouse brain. *Science* **290** 2140.
74. **LeMotte** *et al.* (1996) Characterization of synthetic retinoids with selectivity for retinoic acid or retinoid X nuclear receptors. *Biochim.Biophys.Acta.Gen. Subjects* **1289** 298.
75. **Itoh** *et al.* (2008) Structural basis for the activation of PPARγ by oxidized fatty acids. Nat.Struct.Mol.Biol. **15** 924.
76. **Niemoller and Bazan** (2009) Docosahexaenoic acid neurolipidomics. *Prostaglandins Other Lipid Mediat.* **91** 85.
77. **Zomer** *et al.* (2000) Pristanic acid and phytanic acid: naturally occurring ligands for the nuclear receptor peroxisome proliferatoractivated receptor α. *J.Lipid.Res.* **41** 1801.
78. **Schupp** *et al.* (2007) A widely used retinoic acid receptor antagonist induces peroxisome proliferator-activated receptor-γ activity. *Mol.Pharmacol.* **71** 1251.
79. **Dawson** *et al.* (2001) Apoptosis induction in cancer cells by a novel analogue of 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalenecarboxylic acid lacking retinoid receptor transcriptional activation activity. *Cancer Res.* **61** 4723.
80. **Chapman** *et al.* (2003) Hydrolysis of 4-HPR to atRA occurs *in vivo* but is not required for retinamide-induced apoptosis. *Arch.Biochem.Biophys.* **419** 234.
81. **Cammas** *et al.* (2010) Retinoic acid receptor (RAR)-α is not critically required for mediating retinoic acid effects in the developing mouse retina. *Invest.Ophthalmol.Vis.Sci.* **51** 3281.
82. **Kim** *et al.* (2007) Regulation of mucin gene expression by CREB via a nonclassical retinoic acid signaling pathway. *Mol.Cell.Biol.* **27** 6933.
83. **Geissmann** *et al.* (2003) Retinoids regulate survival and antigen presentation by immature dendritic cells. *J.Exp.Med.* **198** 623.
84. **Stehlin-Gaon** *et al.* (2003) All-*trans* retinoic acid is a ligand for the orphan nuclear receptor ROR beta. *Nat.Struct.Biol.* **10** 820.
85. **Shaw** *et al.* (2003) Retinoic acid is a high affinity selective ligand for the peroxisome proliferator-activated receptor β/δ. *J.Biol.Chem.* **278** 41589.
86. **Zhou** *et al.* (2010)The orphan nuclear receptor TR4 is a vitamin A-activated nuclear receptor. *J.Biol.Chem.* **286** 2877.
87. **Kruse** *et al.* (2008) Identification of COUP-TFII orphan nuclear receptor as a retinoic acid-activated receptor. *PLoS Biol.* **6** e227.
88. **Kang** *et al.* (1999) Mannose 6-phosphate/insulin-like growth factor II receptor mediates the growth-inhibitory effects of retinoids. *Cell Growth Differ.* **10** 591.
89. **Rajawat** *et al.* (2010) Autophagy: a target for retinoic acids. *Autophagy* **6** 1224.
90. **Poon and Chen** (2008) Retinoic acid-gated sequence-specific translational control by RARα. *Proc.Natl.Acad.Sci.USA* **105** 20303.
91. **Maghsoodi** *et al.* (2008) Retinoic acid regulates RARα-mediated control of translation in dendritic RNA granules during homeostatic synaptic plasticity. *Proc.Natl.Acad.Sci.USA* **105** 16015.
92. **Aoto** *et al.* (2008) Synaptic signaling by all-trans retinoic acid in homeostatic synaptic plasticity. *Neuron* **60** 308.
93. **Chen and Napoli** (2008) All-trans-retinoic acid stimulates translation and induces spine formation in hippocampal neurons through a membrane-associated RARα. *FASEB J.* **22** 236.
94. **Duester** (2000) Families of retinoid dehydrogenases regulating vitamin A function: production of visual pigment and retinoic acid. *Eur. J.Biochem.* **267** 4315.
95. **Haeseleer** *et al.* (2002) Dual-substrate specificity short chain retinol dehydrogenases from the vertebrate retina. *J.Biol.Chem.* **277** 45537.
96. **Duester** *et al.* (2003) Cytosolic retinoid dehydrogenases govern ubiquitous metabolism of retinol to retinaldehyde followed by tissue-specific metabolism to retinoic acid. *Chem.Biol.Interact.* **143** 201.
97. **Bhat** *et al.* (1995) Cloning of a cDNA encoding rat aldehyde dehydrogenase with high activity for retinal oxidation. *Gene* **166** 303.
98. **Penzes** *et al.* (1997) Cloning of a rat cDNA encoding retinal dehydrogenase isozyme type I and its expression in *E. coli. Gene* **191** 167.
99. **Wang** *et al.* (1996) Cloning of a cDNA encoding an aldehyde dehydrogenase and its expression in *Escherichia coli*. Recognition of retinal as substrate. *J.Biol.Chem.* **271** 16288.
100. **Zhao** *et al.* (1996) Molecular identification of a major retinoic-acid-synthesizing enzyme, a retinaldehyde-specific dehydrogenase. *Eur.J.Biochem.* **240** 15.
101. **Mic** *et al.* (2000) RALDH3, a retinaldehyde dehydrogenase that generates retinoic acid, is expressed in the ventral retina, otic vesicle and olfactory pit during mouse development. *Mech.Dev.* **97** 227.
102. **Lin** *et al.* (2003) Mouse retinal dehydrogenase 4 (RALDH4), molecular cloning, cellular expression, and activity in 9-*cis*-retinoic acid biosynthesis in intact cells. *J.Biol.Chem.* **278** 9856.
103. **Fujii** *et al.* (1997) Metabolic inactivation of retinoic acid by a novel P450 differentially expressed in developing mouse embryos. *EMBO J.* **16** 4163.
104. **White** *et al.* (1997) cDNA cloning of human retinoic acid-metabolizing enzyme (hP450RAI) identifies a novel family of cytochromes P450. *J.Biol.Chem.* **272** 18538.
105. **White** *et al.* (2000) Identification of the human cytochrome P450, P450RAI-2, which is predominantly expressed in the adult cerebellum and is responsible for all-*trans*-retinoic acid metabolism. *Proc.Natl. Acad.Sci.USA* **97** 6403.
106. **Taimi** *et al.* (2004) A novel human cytochrome P450, CYP26C1, involved in metabolism of 9-*cis* and all-*trans* isomers of retinoic acid. *J.Biol.Chem.* **279** 77.
107. **Soprano and Blaner** (1994) Plasma retinol-binding protein. In: *The Retinoids: Biology, Chemistry, and Medicine.* New York. Raven Press 257.
108. **Kanai** *et al.* (1968) Retinol-binding protein: the transport protein for vitamin A in human plasma. *J.Clin.Invest.* **47** 2025.
109. **Benson and Dwulet** (1983) Prealbumin and retinol binding protein serum concentrations in the Indiana type hereditary amyloidosis. *Arthritis Rheum.* **26** 1493.
110. **Isken** *et al.* (2008) RBP4 disrupts vitamin A uptake homeostasis in a STRA6-deficient animal model for Matthew-Wood syndrome. *Cell Metab.* **7** 258.
111. **Blaner** (2007) STRA6, a cell-surface receptor for retinol-binding protein: The plot thickens. *Cell Metab.* **5** 164.
112. **Kawaguchi** *et al.* (2007) A membrane receptor for retinol binding protein mediates cellular uptake of vitamin A. *Science* **315** 820.
113. **Ong and Chytil** (1975) Specificity of cellular retinol-binding protein for compounds with vitamin A activity. *Nature* **255** 74.
114. **Delva** *et al.* (1999) Physical and functional interactions between cellular retinoic acid binding protein II and the retinoic acid-dependent nuclear complex. *Mol.Cell.Biol.* **19** 7158.
115. **Budhu and Noy** (2002) Direct channeling of retinoic acid between cellular retinoic acid-binding protein II and retinoic acid receptor sensitizes mammary carcinoma cells to retinoic acid-induced growth arrest. *Mol.Cell.Biol.* **22** 2632.
116. **Schug** *et al.* (2007) Opposing effects of retinoic acid on cell growth result from alternate activation of two different nuclear receptors. *Cell* **129** 723.
117. **Formelli** *et al.* (1989) Plasma retinol level reduction by the synthetic retinoid fenretinide: a one year follow-up study of breast cancer patients. *Cancer Res.* **49** 6149.
118. **Bourguet** *et al.* (1995) Crystal structure of the ligand-binding domain of the human nuclear receptor RXR-α. *Nature* **375** 377.
119. **Renaud** *et al.* (1995) Crystal structure of the RAR-γ ligand-binding domain bound to all-*trans* retinoic acid. *Nature* **378** 681.
120. **Rastinejad** *et al.* (2000) Structure of the RXR-RAR DNA-binding complex on the retinoic acid response element DR1. *EMBO J.* **19** 1045.
121. **Chandra** *et al.* (2008) Structure of the intact PPAR-γ-RXR- nuclear receptor complex on DNA. *Nature* **456** 350.

Retinoid Receptor Compounds Available from Tocris

Cat. No.	Product Name	Primary Action
Retinoic Acid Receptors		
Agonists		
2436	AC 55649	Selective RARβ2 agonist
4046	AC 261066	RARβ2 agonist
2852	Adapalene	RARβ and RARγ agonist
3507	AM 80	RARα agonist; anticancer agent
0760	AM 580	Retinoic acid analog; RARα agonist
3505	BMS 753	RARα-selective agonist
1549	CD 437	RARγ-selective agonist
2554	CD 1530	Potent and selective RARγ agonist
2020	Ch 55	Potent RAR agonist
5513	Isotretinoin	Endogenous agonist for retinoic acid receptors
0695	Retinoic acid	Endogenous retinoic acid receptor agonist
3997	Tazarotene	Receptor-selective retinoid; binds RARβ and -γ
0761	TTNPB	Retinoic acid analog; RAR agonist
Antagonists		
3509	BMS 493	Pan-RAR inverse agonist
3800	CD 2665	Selective RARβ/γ antagonist
2021	LE 135	Selective RARβ antagonist
3822	MM 11253	RARγ-selective antagonist
Other		
3409	BMS 453	RARβ agonist; also RARα agonist and RARγ antagonist
4011	EC 23	Synthetic retinoid; induces differentiation of stem cells
Retinoic X Receptors		
Agonists		
5819	Bexarotene	Potent and selective RXR agonist
3302	CD 3254	Potent and selective RXRα agonist
3687	Docosahexaenoic acid	RXR agonist
3913	HX 630	pan-RXR agonist; synergizes with AM 80 (Cat. No. 3507) to promote differentiation of HL-60 cells; also weak RAR antagonist
0695	Retinoic acid	Endogenous retinoic acid receptor agonist
3411	SR 11237	Pan RXR agonist
Antagonists		
3912	HX 531	Potent RXR antagonist
3303	UVI 3003	RXR antagonist
Other		
3831	LG 100754	RXR:PPAR agonist
3508	LG 101506	Selective RXR modulator
Retinoic Related		
3793	A 1120	High Affinity retinol-binding protein 4 (RBP4) ligand
1396	Fenretinide	Synthetic retinoid; potent anticancer agent
2705	Liarozole hydrochloride	Blocks retinoic acid metabolism

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- G Protein-Coupled Receptors
- Pain Research
- Ion Channels

Life Science Posters

- Multiple Sclerosis
- Pain
- Parkinson's Disease
- Schizophrenia

Scientific Reviews

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