# 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 RAR$\alpha$, $\beta$, or $\gamma$.[3-6] RAR forms heterodimers with one of three isotypes of the retinoid X receptor (RXR): RXR$\alpha$, $\beta$ or $\gamma$.[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 RAR-RXR is considered a non-permissive heterodimer. In addition to RAR, RXR is a heterodimeric partner of many other nuclear receptors including both non-permissive 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) $\alpha$, $\beta/\delta$, and $\gamma$, 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

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*-retinol: 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 RAR$\alpha$ and $\gamma$, while RAR$\beta$ has four isoforms. Combinations of the

## Table 1 | Naturally occurring pan-RAR modulators

| Compound Number | Compound Name | Activity/Specificity | Structure | Cat. No. |
|---|---|---|---|---|
| 1 | Retinoic Acid (tretinoin) | Pan-RAR agonist<br><br>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 | | – |

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-

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 RAR$\alpha$ (*Rara*-null), can be to some extent compensated *in vivo* by the remaining isotypes, in this particular case RAR$\beta$ (*Rarb*), or RAR$\gamma$ (*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.
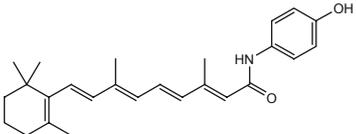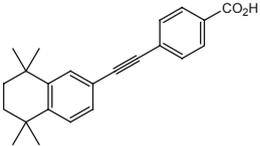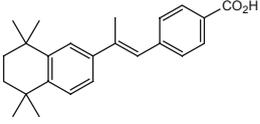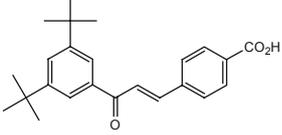
Naturally occurring or synthetic modulators of RARs are known as retinoids while naturally occurring or synthetic modulators of RXR are known as rexinoids. The use of retinoids in therapy has to be balanced with the significant toxicity that is associated with retinoids including teratogenesis, the induction 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, a ligand-free structure of RAR is not currently 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 (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

## Table 2 | Synthetic pan-RAR modulators

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

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.

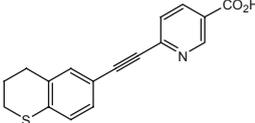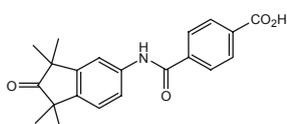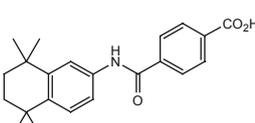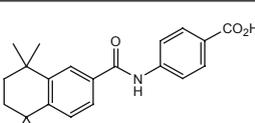## Table 3A | Subtype-selective RAR agonists and antagonists

| Compound Number | Compound Name | Activity/Specificity | Structure | Cat. No. |
|---|---|---|---|---|
| 8 | Tazarotene | RARβ/γ agonist | | 3997 |
| 9 | BMS 753 | RARα agonist | | 3505 |
| 10 | AM 80 | RARα agonist<br><br>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 |
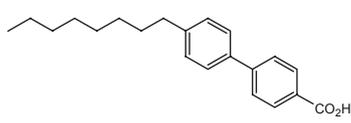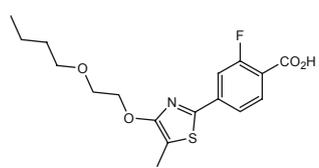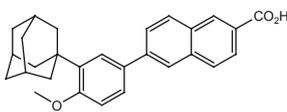
## Table 3B | Subtype-selective RAR agonists and antagonists

| 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 135 | 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 |
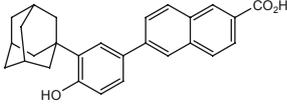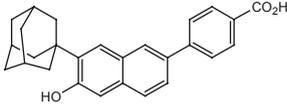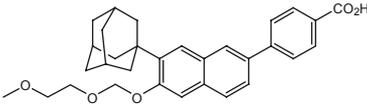
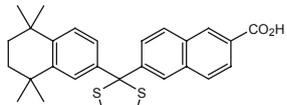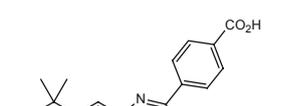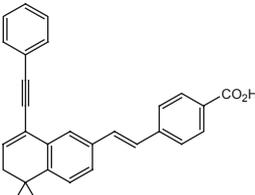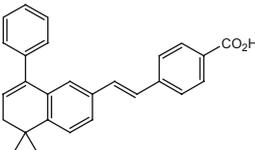The expression of RARβ is frequently lost in many transformed cells, therefore RARβ agonists would be expected to have potent antiproliferative effects. RARβ-specific agonists include the 4´-octyl-4-biphenylcarboxylic acid, AC 55649 (12), discovered using functional high throughput screening, and AC 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 pro-apoptotic 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 weak agonist of RARβ.[57] Meanwhile, BMS 493 is 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 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 biding 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 pharmaceutic 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

## Table 4A | RXR agonists and antagonists

| Compound Number | Compound Name | Activity/Specificity | Structure | Cat. No. |
|---|---|---|---|---|
| **22** | Bexarotene (LGD1069) | Pan-RXR agonist<br><br>Ongoing clinical trials in the treatment of cancer and skin diseases. |  | – |
| **23** | LG 101506 | Selective agonist of a specific set of RXR heterodimers.<br><br>Insulin sensitizer |  | – |
| **24** | CD 3254 | Pan-RXR agonist |  | 3302 |
| **25** | SR 11237 (BMS 649) | Pan-RXR agonist |  | 3411 |
| **26** | UVI 3003 | RXR antagonist |  | 3303 |
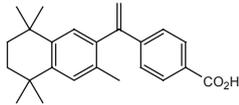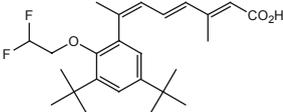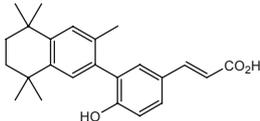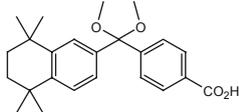
## Table 4B | RXR agonists and antagonists

| 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<br><br>Inhibits activation of RAR-RXR heterodimers | | – |
| 29 | HX 630 | Pan-RXR agonist, weak RAR antagonist<br><br>Synergizes with AM 80 to induce differentiation of HL-60 cells | | – |
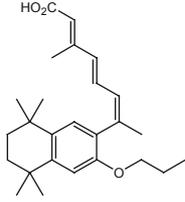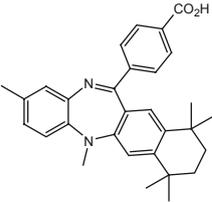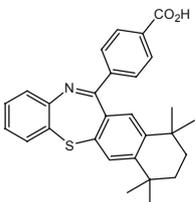
particularly in permissive heterodimers.[64] Another benzoic acid derived RXR ligand, LG 100754, has also been crystallized in association with RXRα and described as a RXR homodimer antagonist and a selective pan-RXR heterodimer agonist. LG 100754 (**27**) acts as an agonist of PPARα/RXR but it does 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 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 interacti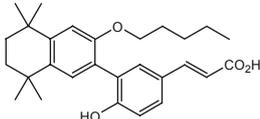on with co-repressors or co-activators within the heterodimer. Instead, LG 100754 mediates activation of RAR through direct binding.[68] Therefore, LG 100754 still acts as an RXR antagonist in the context of RAR-RXR heterodimers.[68] Similar to LG 101506, LG 100754 is also a potent insulin-sensitizer.[66] 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 alternate 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 (non-classical 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 transcription-independent 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 also through 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 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 a 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.

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# Retinoid Receptor Compounds Available from Tocris

## 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

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

## Retinoid X Receptors

### Agonists

3302 **CD 3254**
Potent and selective RXRα agonist

3687 **Docosahexaenoic acid**
RXR agonist

0695 **Retinoic acid**
Endogenous retinoic acid receptor agonist

3411 **SR 11237**
Pan RXR agonist

### Antagonists

3303 **UVI 3003**
RXR antagonist

### Other

3831 **LG 100754**
RXR:PPAR agonist

3508 **LG 101506**
Selective RXR modulator

## Retinoid 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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