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Retinoic Acid Signaling Pathways in Development and Diseases

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Abstract

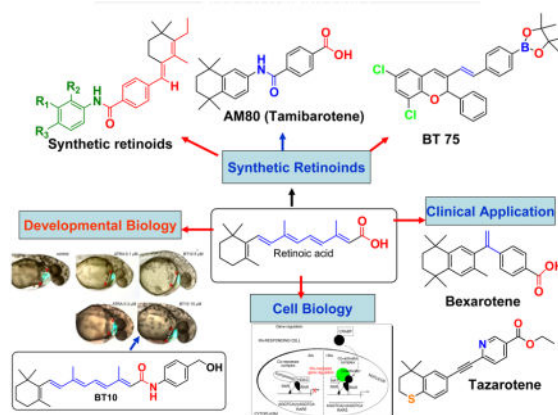
Retinoids comprise a group of compounds each composed of three basic parts: a trimethylated cyclohexene ring that is a bulky hydrophobic group, a conjugated tetraene side chain that functions as a linker unit, and a polar carbon-oxygen functional group. Biochemical conversion of carotenoid or other retinoids to retinoic acid (RA) is essential for normal regulation of a wide range of biological processes including development, differentiation, proliferation, and apoptosis. Retinoids regulate various physiological outputs by binding to nuclear receptors called retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which themselves are DNA-binding transcriptional regulators. The functional response of RA and their receptors are modulated by a host of coactivators and corepressors. Retinoids are essential in the development and function of several organ systems; however, deregulated retinoid signaling can contribute to serious diseases. Several natural and synthetic retinoids are in clinical use or undergoing trials for treating specific diseases including cancer. In this review, we provide a broad overview on the importance of retinoids in development and various diseases, highlighting various retinoids in the drug discovery process, ranging all the way from retinoid chemistry to clinical uses and imaging.

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GRAPHICAL ABSTRACT



1. Introduction

Vitamin A or retinol is a fat-soluble compound derived from [beta]-carotene found in plants and retinyl esters from animal sources. It is stored in the liver and adipose tissue as retinyl esters and circulates in the blood in a protein complex containing retinol binding protein and transthyretin. Retinoic acid, the main derivative of vitamin A, binds to nuclear receptors, retinoic acid receptor (RAR) and retinoic X receptor (RXR) to regulation gene transcription. RA plays an important role in tissue development and differentiation. This review focuses on the role of RA in development and diseases, and the development of synthetic RA compounds for therapy and molecular imaging.

2. Synthesis, chemistry and analysis of RA

Retinoids comprise a group of compounds related to vitamin A, including its natural and synthetic analogues, which contain four isoprenoid units joined in a head-to-tail fashion. The basic structure of a retinoid consists of three parts: a trimethylated cyclohexene ring that is a bulky hydrophobic group, a conjugated tetraene side chain that serves as a linker unit, and a polar carbon-oxygen functional group, typically carboxylic acid as shown in Figure 1.

Retinoids are unstable due to the presence of conjugated double bonds and easily undergo oxidation and/or isomerization in the presence of oxidants, light or excessive heat. Retinoids that contain alcoholic and carboxylic groups are soluble in methanol and ethanol, whereas esterified long-chain fatty acid is only slightly soluble in alcohol but highly soluble in hexane.

Numbering for the retinoids is practiced in either of two ways, starting the numbering from the cyclohexenyl group as shown in Figure 2A, or by designating 1 for the carbon atom bonded to the functional group, as shown in Figure 2B.

Animals are unable to synthesize vitamin A *de novo*, and therefore it must be obtained through the diet. Dietary intake in the form of retinol, retinyl ester, or beta-carotene are good

sources of vitamin A. Carotenoids, the main precursor of fat soluble vitamin A, including α/β -carotene are converted into retinal or apocarotenoids and subsequently to retinoids.¹

Unlike other most biological compounds, carotenoids and retinoids have conjugated polyene systems that absorb light in the visible and ultraviolet spectrums, around 450 nm and 325–380 nm, respectively. Historically, colorimetric assays were widely used for the analysis of vitamin A and carotenoids. In this methodology, the polyene system of a retinoid or carotenoid is protonated by a strong acid such as antimony trichloride or trifluoroacetic acid in organic solvent to give a highly intense characteristic transient blue color, which provides a selective and very sensitive assay for vitamin A analysis.^{2, 3} The reagents used in this method are corrosive and noxious, which is one reason these methods are rarely used today. Still, absorbance spectroscopy remains a major tool for quantification of retinoids and carotenoids. Today, high performance liquid chromatography (HPLC) equipped with absorbance detectors and photodiode-array detectors have become the standard means for quantitative and qualitative analysis of retinoids and carotenoids. Fluorescence spectroscopy, which offers greater specificity than absorbance spectroscopy for analysis of retinol and retinyl esters in biological samples, is another widely used technique. For assignment of cis- and trans-isomers of retinoids, nuclear magnetic resonance (NMR) has been very helpful. Similarly, infrared spectroscopy (IR), though not as important as ultraviolet (UV) and visible light spectroscopy, provides useful information in structural analysis of retinoids. Typically, a combination of techniques including HPLC with NMR and mass spectroscopy (MS) are now used for separation, identification, and quantitation of retinoids.⁴

3. Retinoid and carotenoid metabolism

Carotenoids or other retinoids are biochemically converted to retinoic acid (RA), which is essential for modulating a wide range of biological processes including development, differentiation, proliferation, and apoptosis. The bioconversion takes place successively (Figure 3), first in the intestine, then the liver, and finally in target cells with the support of various binding proteins including cellular retinol-binding proteins (CRBPs), retinol-binding proteins (RBPs), and cellular retinoic acid binding proteins (CRABPs).⁵ β -Carotene and retinyl esters derived from plants or animals, respectively, are good sources of retinol. β -Carotenes are converted to retinal that binds to the cellular retinol-binding protein (CRBP)II. Binding to CRBPII prevents the oxidation of retinal to RA in the intestine and facilitates the reduction into the retinol in support of microsomal retinal reductase.⁶ The retinyl esters from animal source can undergo hydrolysis to give retinol. The retinol binds with CRBPII to give the complex, which acts as a substrate for the conversion of retinol to retinyl esters in the presence of lecithin-retinol acyltransferase (LRAT) enzyme.^{7,8} Most of the retinyl esters are incorporated into the chylomicron, which is then secreted into the lymph and subsequently into general circulation where elimination of triacylglycerol takes place with the help of lipoprotein lipase.^{9,10} This results in the formation of chylomicron remnants, which are taken up via endocytosis by hepatocytes in the liver. Retinyl ester undergoes hydrolysis to give retinol. The free retinol binds with the retinol-binding protein (RBP) and is secreted into plasma where it binds with transthyretin (TTR).¹¹ Binding to TTR prevents the elimination of retinol by the kidney. At the same time, large numbers of unesterified retinols

are transported to another type of liver cell called as “stellate cell”. The retinols are converted to retinyl ester in the presence of LRAT and are packed in cytoplasmic lipid droplets.^{12,13} The retinol-RBP-TTR complex in plasma is taken up by target cells via the RBP receptor, a trans-membrane protein also called “stimulated by retinoic acid 6” (STRA6).¹⁴ After entering the target cell, free retinol either binds with CRBP or undergoes oxidation to give retinal, an aldehyde, in the presence of retinol dehydrogenase (RDH). The retinal is subsequently converted to RA by retinaldehyde dehydrogenase (RALDH).¹⁵ The RA binding with cellular RA binding protein (CRABP) allows it to enter the nucleus where it can bind, and serve as ligand, with various nuclear receptors including RAR and RXR, to mediate genomic and non-genomic mechanisms. At the same time RA can be converted into oxidized metabolites such as 4-hydroxyretinoic acid and 4-oxoretinoic acid by the cytochrome P450 enzyme (CYP26).^{16,17,18}

4. Retinoid receptors and their genomic actions

4.1. Genomic action of retinoids

Retinoids regulate various biological activities by binding RARs and RXRs. Ligand binding to the receptor causes conformational changes that modulate receptor complex function. In addition, these receptor complexes have a range of additional co-activators and co-repressors that modulate receptor activity. The composition of receptor complex is complicated by the presence of distinct subtypes and isoforms. Both RAR and RXR have three subtypes α , β , and γ , each with different isoforms. RAR α and RAR γ both have two isoforms 1 (RAR α 1, RAR γ 1) and 2 (RAR α 2, RAR γ 2) whereas RAR β has five isoforms (RAR β 1–4, and 1'). In the case of RXR, all subtypes have two isoforms 1 and 2.¹⁹ RAR can be activated by both all-*trans* and 9-*cis* RA, whereas RXR is only activated by 9-*cis* RA. Heterodimerization of retinoid receptors, one RAR and one RXR, is essential for the biological activity, although it should be noted that RXRs can heterodimerize with numerous other non-RA associated nuclear receptors to mediate alternative signaling pathways. Availability of several subtypes and isoforms enables the generation of a large group of distinct receptor dimers. As is typical for DNA-binding nuclear receptors, the retinoid receptors have a basic modular domain design. Domains A-F (Figure 4) can be isolated and studied as distinct units without loss of their function.^{20,21,22}

A/B encodes the least conserved N-terminal domain, which contains an autonomous transcriptional activation function, called AF-1. Domain C is highly conserved and contains two zinc finger modules responsible for DNA binding, and therefore it is also called the DNA-binding domain. Domains C and E are separated by a flexible hinge region called domain D. Domain D is also essential for interaction with certain nuclear receptor coregulators. Domain E is a multifunctional domain, comprising the ligand-binding domain (LBD) and activation function-2 (AF-2) domain. This domain is responsible for ligand binding, receptor dimerization, and interaction with other coactivators. When the ligand (retinoid) binds to the LBD, a conformational change in the receptor complex occurs. AF-2 structure includes an amphipathic α -helix that also modulates the conformational change. While unliganded receptor is complexed with transcriptional co-repressors, the conformational changes caused by ligand binding releases these negative regulators and

stimulates the recruitment of distinct coactivators. The C-terminal F domain is present in some but not all receptors, and can participate in the action of AF-2.

Receptor dimerization occurs through the interaction of the LBD on each receptor. It is the heterodimeric receptor that is responsible for binding to DNA at specific retinoid acid response elements (RARE) with high affinity. In the presence of ligands (retinoids), the holo-receptor binds to the RARE and activates the histone acetyl transferase (HAT) activity. As a result, histone proteins are acetylated, helping to open the chromatin and activate the transcription machinery. On the other hand, in absence of ligands, the apo receptor pair binds with the RARE in a complex with corepressors and histone deacetylase (HDAC) activity. As a result, histone deacetylation prevails causing chromatin condensation and gene silencing.²³

4.2. Non-genomic actions of retinoids

As described above, retinoids mediate various genomic transcriptional effects via RA nuclear receptors, but they also have non-genomic effects including retinoylation (RA acylation), a post-translational modification of proteins occurring in many eukaryotic cells. Not all target cells for RA contain cellular RA binding proteins. One example is the human acute myeloid leukemia HL-60 cell line. It has been reported that retinoylation in HL-60 occurs through the covalent bonding of RA to perform post-translational modification of proteins. It is believed that RA is first converted into an activated intermediate retinoyl-CoA.²⁴

In another study, it was reported that N-(4-hydroxyphenyl)retinamide (4-HPR) increases the level of retinoylation. It was found that the combination of 4-HPR and RA has a synergistic effect on the differentiation of HL-60 cells and the retinoylation process. RA also mediated retinoylation on proteins of tumoural leydig (MLTC-1) cells.^{25,26} Similarly, when treated with RA, undifferentiated and squamous-differentiated normal human epidermal keratinocytes were found to undergo retinoylation. Retinoylation occurred mainly on the cytokeratin proteins.²⁷

5. RA signaling in normal development

The requirement for retinoids during embryogenesis has been long appreciated, since vitamin A is an essential dietary requirement. Yet for understanding mechanism, it is perplexing that loss of signaling or hyper-activation of the pathway can generate similar phenotypes. For example, excess RA causes many of the same embryonic developmental defects seen with vitamin A deficiency (VAD), which is why vitamin A intake levels should be monitored carefully during pregnancy. Because RA is teratogenic, loss-of-function assays are essential to understand the normal function of the RA-dependent pathways controlling embryonic patterning, growth, and organogenesis. A major tool for this purpose is the targeted knockout of receptors in mouse models. However, interpreting the knockout phenotypes is complicated by partial or total compensation from the related receptor subtypes. For this reason, a valuable approach for studying RA requirements during embryogenesis has been VAD animal models. Complete VAD effectively and specifically eliminates retinoid signaling, since the ligand (in contrast to the receptors) is non-redundant.

The developing embryo normally metabolizes RA from maternal stores of Vitamin A. In a VAD model, the mother remains healthy as long as her diet is supplemented with RA. However, RA is not passed on to the embryo, which develops in the absence of retinoids. Both rodent and avian models have been used effectively, although a quail model developed by Zile and colleagues is arguably the best characterized.²⁸ The VAD quail survives until around day four, and clearly demonstrates the requirements for RA signaling in the formation of the nervous and cardiovascular systems.²⁹ Importantly, the VAD quail is completely rescued if RA is added *in ovo* or to cultured embryos prior to the 5 somite stage, demonstrating specificity for the ligand, and showing that retinoid signaling becomes essential only after this stage of development. The requirements for RA are conserved in mammalian models, shown for example by abnormalities in rats³⁰ or pigs³¹ born from mothers on a VAD diet. VAD animal models have documented clear requirements for RA signaling in a host of organ systems, including the development of the brain, heart, and kidney.

RA contributes to the anteroposterior patterning of the neural plate.³² The neural plate is initially anterior or forebrain-like. RA contributes to the induction of more posterior domains.³³ Hindbrain segments called rhombomeres are transient structures that reflect the evolutionarily conserved segmented nature of positional information, including the ordered pattern of Hox gene expression. In the VAD quail model, there is a failure in the development of posterior regions of the hindbrain (rhombomeres 4–7).³⁴ RA also has an important role in the development of the spinal cord and somites, as VAD quail embryos have fewer spinal cord neurons and smaller somites.³⁵ Eye morphogenesis and differentiation also requires RA signaling. During early stages of eye development, RA activates retinoid receptors present in the perioptic mesenchyme to regulate the development of the anterior eye segment and closure of the optic fissure. RA/RAR regulates the transcription factor Pitx2 that is essential for the morphogenesis of anterior eye segment, and closure of the optic fissure.³⁶ Similarly, RA promotes the differentiation of the neural retina at later stages of development.³⁷

Vitamin A also plays many regulatory roles in the development of mammalian heart, including heart tube patterning and looping, chamber and outflow tract septation, ventricular trabeculation, cardiomyocyte differentiation, and coronary vessel development.^{38,39,40} VAD models have shown the importance of RA in kidney and urinary tract development, including causing embryonic renal hypoplasia. Similarly, rat fetuses that are VAD can display ectopic kidneys, renal fusion and failure of the renal pelvis and calyx to undergo dilatation, and other genitourinary tract defects. Moreover, vitamin A is required for the normal development of diaphragm, lung and upper respiratory tract and airways, somites and skeleton, pancreas, and limb.⁴¹ The VAD quail embryo develops with a significant defect in primitive (yolk sac) erythropoiesis, at least in part due to the failure to properly regulate the GATA2 transcription factor.⁴²

Clearly, RA does not function alone in controlling the development of these organ systems. There is a large literature linking RA functions with other signaling pathways during vertebrate development. For example, the RA signaling pathway interacts with the fibroblast growth factor (FGF),⁴³ Wnt, Nodal,⁴⁴ bone morphogenetic protein (BMP), and sonic

hedgehog (Shh)^{45,46} signaling cascades, which together are essential for the regulation of somitogenesis, heart development, patterning of the central nervous system (CNS), and optic, limb, and pharyngeal differentiation.^{47,48,49,50,51,52}

Despite the value of VAD models, they are limited in terms of understanding temporal and spatial regulation by RA. The RARs are widely expressed in development, and although complicated by functional redundancies and the range of isoforms, mouse knockout models have been generated for each of the RAR/RXR genes and used to describe both developmental and tissue-specific functions for the pathway. This has been reviewed extensively in the literature,⁵³ and the phenotypes described largely support the notion that different heterodimer pairs mediate the developmental functions of RA signaling during development. In coming years, combinations of conditional somatic alleles, for example targeting specific isoforms in defined cell types, will be needed to probe fully the molecular mechanisms by which receptors mediate the myriad developmental functions for the RA signaling pathway during embryogenesis.

6. Retinoids in Diseases

Though RA and its analogs are essential for normal regulation of a wide range of biological processes, while deregulated retinoid signaling can contribute to serious diseases. In this section, we will briefly describe, how aberrant signaling of RA causes diseases, and how synthetic retinoids are used to treat some diseases.

6.1. Retinoids in cancer and control of differentiation

Retinoids can induce differentiation and/or apoptosis in tumor cells and show anti-proliferative and anti-oxidant activity, and therefore have great potential as chemotherapeutic or chemopreventive agents. Depending on the target cells, they can mediate growth inhibitory roles at various stages of carcinogenesis. The use of retinoids for treating cancer was spurred by the critical discovery that the chromosomal translocation t(15:17), a cytogenetic hallmark of acute promyelocytic leukemia (APL), leads to the expression of an oncoprotein consisting of a retinoic acid receptor α (RAR α) fused to a previously unknown protein called PML.^{54,55} The hematopoietic cells expressing RAR-PML are blocked for differentiation. Retinoid or rexinoids act as strong inducers of cell differentiation to overcome this block, and pharmacological doses of RA are used clinically to activate the RA-APL fusion protein, leading to cell cycle arrest and terminal differentiation of leukemic cells. The affect on cell-cycle arrest at G1 is also mediated by increased expression of the p21/WAF1 gene, which is a potential mediator of p53 mediated tumor suppression.⁵⁶ This success story provides a paradigm for differentiation therapy by RA. In addition, retinoids and rexinoids (rexinoids compounds are chemically related to vitamin A, that bind to the retinoid X receptor but not the retinoic acid receptor), alone or in combination with chemotherapeutic agents, are able to induce apoptosis in various other types of cancer cells.^{57,58}

All-*trans* retinoic acid (RA, tretinoin), the most abundant natural retinoid, has been developed for the treatment of various types of cancers including lymphoma, leukemia, cervical cancer, lung cancer, kidney cancer, neuroblastoma, and glioblastoma. As described

above, RA activates only RARs whereas 9-*cis* RA (alitretinoin) can activate both RAR and RXR. 9-*cis* RA has been approved by the US Food Drug Administration (FDA) for the topical treatment of cutaneous lesions of Kaposi's sarcoma⁵⁹ and has also been studied for the prevention of mammary and prostate cancer.^{60,61} Similarly, 13-*cis* RA (isotretinoin) has been in clinical trial for various types of cancers including thyroid cancer, lung cancer, prostate cancer, head-and-neck cancer. Moreover, there are several synthetic retinoids that are in clinical trial for the treatment of different types of cancer. Fenretinide (or 4HPR), tazarotene, MDI 301, R667, Bexarotene, Adapalene, and TAC101 (as shown in Figure 6) are examples of synthetic retinoids that have been tested in clinical trials.^{5,62,70, 104,109,120} Fenretinide, first synthesized in 1960s, is one of the most promising clinically tested retinoids.¹⁰⁴

6.2. Retinoids in metabolic disease

Metabolic disease occurs when there is a disruption in the normal metabolism that regulates the conversion of food into energy used for cellular and physiological processes. Genetic defects that affect expression of key enzymes, transporter proteins, or even channel proteins can be responsible for causing metabolic diseases. Major metabolic disorders that are linked with retinoids are obesity, diabetes, and the metabolic syndrome.

Multiple studies have documented that RA regulates adipogenesis.^{63,64,65,66} RA acts as a high affinity ligand for the nuclear receptor peroxisome proliferation-activated receptor β/δ (PPAR β/δ). As PPAR β/δ receptor is a master regulator of lipid metabolism and glucose homeostasis, activation of these receptors increases lipid catabolism in adipose tissue and skeletal muscle to prevent obesity. In one study, obese mice that were treated with RA showed an induction of PPAR β/δ and RAR target genes correlating with weight loss and improved insulin responsiveness.⁶⁷ RA precursors, including β -carotene, β -apo-8'-cartotenal, retinol, and retinal are reported to inhibit adipocyte differentiation.⁶⁸ Moreover, the RAR γ selective retinoid ER36009 has been found to reduce adipose tissue when applied topically in rats.⁶⁹

Similarly, the compound AM80 (Tamibarotene) has been reported as a potential anti-diabetic agent. It was found to inhibit the development of type 1 diabetes in the non-obese diabetic (NOD) mouse model.⁷⁰ RA has also been shown to mediate immune-modulatory effects for the prevention of type I diabetes. Treatment with RA induces T regulatory (Treg) cell-dependent immune tolerance by suppressing both CD4+ and CD8+ T effector cells, while promoting Treg cell expansion.⁷¹

6.3. Retinoids in the eye

As discussed previously, retinoid signaling has an important role in the development of the nervous system including the eye. Studies in the mouse showed a requirement for RA signaling in the normal development of the ventral retina and optic nerve through its activities in the neural crest cell-derived periorbital mesenchyme, dependent on the activities of various retinoid receptors RAR $\alpha/\beta/\gamma$ and RXR $\alpha/\beta/\gamma$. RA-synthesizing enzyme (RALDH) and RA-degrading enzymes (CYP26) also have critical roles in embryonic eye development.⁷² Subsequently, vitamin A is essential throughout life for maintaining normal

vision as shown in Figure 8. The visual cycle occurs in photoreceptor cells and the adjacent retinal pigment epithelium (RPE). Rhodopsin in rod photoreceptors and cone pigment in the cone photoreceptors are the visual pigments that respond to light.^{73,74} In rods, the chromophore 11-*cis*-retinal binds to opsin to form rhodopsin. Photoisomerization of 11-*cis*-retinal changes it to an active conformation, all-*trans*-retinylidene, also known as Meta II. It recruits and binds to intracellular G proteins that facilitate various signaling cascades responsible for transducing vision.⁷⁵

For the visual cycle to function, a continuous supply of 11-*cis*-retinal is necessary. After binding of 11-*cis* retinal with opsin, it undergoes photoisomerization to give 11-*cis*-retinylidene that is further changed to all-*trans*-retinylidene and finally to all-*trans*-retinal. All-*trans*-retinals are then dissociated from the opsin. Most of these products diffuse into the cytoplasm, while those dissociated into the disc lumen are also transferred into cytoplasm by the ATP-binding cassette transporter A4 (ABCA4).⁷⁶ In cytoplasm, all-*trans*-retinal is reduced to all-*trans*-retinol, catalyzed by the NADPH-dependent all-*trans*-retinol dehydrogenases (RDH), RDH8 and RDH12. The all-*trans*-retinol diffuses into the RPE. In the RPE, all-*trans*-retinol is esterified into retinyl esters, as catalyzed by lecithin:retinol acyl transferase (LRAT), and aggregates into lipophilic droplets called retinosomes. These retinyl esters are converted to 11-*cis*-retinol by retinoid isomerase RPE65, and are further oxidized back to 11-*cis*-retinal by various enzymes including RDH5, RDH11, and other RDHs to be ready for next visual cycle.⁷⁷

6.4. Retinoids in neurobiology and aging

Retinoids have essential functions in the CNS throughout life. In addition to controlling development of the hindbrain and the anterior spinal cord, retinoids regulate interneuron and motoneuron development along the dorsoventral axis. In fish and amphibian models, the formation of appropriate numbers of primary neurons is controlled by RA signaling. In vertebrates, various proneural genes, which regulate the process of primary neurogenesis, are regulated by RA signaling.⁷⁸

The wide distribution of different RA receptors throughout the adult brain strongly suggests that retinoid signaling is necessary for neuronal plasticity, neurogenesis, and for cognitive and motor controlling functions. Neuronal plasticity in the brain is the capacity to rearrange the pattern of different neuronal connections that are essential for learning, memory, and promoting rapid response to damage and distress. These processes require synaptic turnover, neurite remodeling, neurogenesis, and changes in synaptic strength, which is measured by long-term potentiation (LTP) and long-term depression (LTD). Because such dynamic processes require transcriptional activation and inactivation of an array of genes in the brain, it is not surprising that neural functions including LTP and LTD are under the control of RA signaling. Individuals with vitamin A deficiency may show defective performances in spatial learning and memory tasks. This can occur in aged individuals who display decreased RA signaling in the brain. Supplementation of diet with RA can help reverse age-related decreases in hippocampal LTP and other brain functions.⁷⁹

In a related sense, vitamin A and its precursor β -carotene may impact neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD). They inhibit the

formation of amyloid- β (A β) fibrils in a dose-dependant manner. Furthermore, they destabilize the preformation of A β fibrils *in vitro*.⁸⁰ Oligomerization of A β 40 and A β 42 can also be prevented by vitamin A and β -carotene.⁸¹ One study showed that 9-*cis*-RA could provide neuroprotection in CNS injury in a transient focal ischemia model due to the activation of bone morphogenetic proteins (BMPs). Retinoid-dependent expression of BMP7 was found to protect neurons against injuries caused or induced by neurotoxins, free radicals, and ischemia *in vitro* and *in vivo*.⁸² Such reports support possibilities for retinoids and their derivatives as therapeutic agents for AD and other neurological diseases.

Various natural and synthetic retinoids have been studied for their anti-aging effects. Most of the studies have focused on patients with the photoaged skin, caused by chronic UV exposure. Tretinoin is the most potent and widely investigated retinoid for treatment of photoaging. Retinol, retinal, RA, adapalene, tazarotene, and aromatic compounds such as etretinate, acitretin, and seletinoid G (Figure 9) have been studied for anti-aging activity.⁸³

6.5. Retinoids in Kidney

Retinoic acid is necessary for renal development and even mild gestational vitamin A deficiency can affect nephron endowment.^{84, 85, 86} This was first demonstrated by feeding pregnant rats a vitamin A-deficient diet that caused reduced vitamin A levels in the fetal circulation leading to a significant reduction in nephron number and severe renal defects in the newborn rats.⁸⁴ Retinoic acid stimulates ureteric bud branching in embryonic kidneys placed in metanephric organ culture,⁸⁷ and this effect on ureteric bud morphogenesis was thought to be mediated by RAR regulation of Ret expression.⁸⁸ Despite compelling evidence for a central role for retinoids in nephrogenesis, it remains unclear if retinoids or RAR/RXR signaling are involved in renal function after birth. Using a RARE reporter mouse, endogenous levels of renal RAR activity were found in collecting duct cells, which are cells derived from the ureteric bud, but not other renal cell types, raising the question of whether vitamin A modulates solute and water homeostasis.⁸⁹ Retinoids have been found to have beneficial effects in some renal diseases⁹⁰ including glomerulosclerosis;⁹¹ however, the cellular mechanisms responsible for these renoprotective effects remain unclear. In a rat model of polycystic kidney disease (PKD), RXR-related genes that are involved in cell proliferation and organ morphogenesis were found to be aberrantly expressed early in disease, suggesting that aberrant RXR signaling may be involved in PKD cystogenesis. Interestingly, retinoic acids activate the human promoter for *PKDI*, the gene when mutated accounts for 85% of the clinical cases.⁹² Recent evidence shows that retinoids have anti-fibrotic and cytoprotective effects in the kidney,^{93, 94} supporting the need for the development of synthetic retinoid derivatives for the treatment of renal disease.

7. Drug discovery and use of Retinoids for treatment of diseases

As described above, several natural and synthetic retinoids have moved to clinical trials for various types of cancer, while several other classes of synthetic retinoids continue to be investigated at the pre-clinical level for anti-cancer activities. A major strategy to develop various synthetic retinoid derivatives with the potential to impart different biological activities is to systematically modify the hydrophobic, linker, or hydrophilic moieties of RA.

Recently, a series of acitretin analogs (Figure 10) was reported to have anti-proliferative activity. In this study, the modification was performed on the lipophilic part of RA using various functional moieties. Among the evaluated derivatives, the compounds **20**, **21**, **22**, and **23** exhibited strong anti-proliferative activity in a dose-dependent manner. Compound **20** containing three methoxy groups in the aromatic ring was compound displaying the most potent anti-proliferative activity.⁹⁵

Similarly, modification at the C-4 position of all-*trans* RA led to the discovery of potent novel retinoic acid metabolism blocking agents (RAMBAs). In this case, the C-4 position of all-*trans* RA was modified with various nucleophilic ligands. Compound **24** (Figure 11, VN/14-1) had inhibitory activity, superior to all-*trans* RA, on growth of the human breast cancer MCF-7 cell line in nude mice. The compound was administered subcutaneously to the mice following implantation of human breast tumor MCF-7 xenografts.⁹⁶

Modifications at position-5 of the lipophilic moiety (cyclohexene ring) have also been tested with various substituents. Such modified analogs of all-*trans* RA and 9-*cis* RA were evaluated for their anti-proliferative and pro-differentiative activities with the human leukemia HL-60 cell line. The all-*trans* analogs **25** and **26** (Figure 11) were found to be potent whereas none of the 9-*cis* analogs showed strong activity.⁹⁷

Modifications on the cyclohexene ring were also used to derive various acyclic demethyl geranylgeranoic acids (GGAs) as retinoid analogs. 3-Demethyl derivative **27** (Figure 12) showed the most significant anti-proliferative activity using the HL-60 cell line, and induced apoptosis more potently than 9-*cis* RA.⁹⁸

In an attempt to modify the hydrophilic moiety, various ferrocenyl retinoates, such as **28** (Figure 13) were developed. These analogues were tested for their cytotoxicity against various human cancer cell lines including a lung cancer cell line (A549), a liver cancer cell line (BEL7404), and a tongue cancer cell line (Tca). The modified compounds showed better cytotoxicity than the standard 13-*cis* RA.⁹⁹

The combination of all-*trans* RA and histone deacetylase inhibitors (HDACIs) resulted in various novel mutual products (MPs). The carboxylic acid group of all-*trans* RA was linked with different HDACIs. These MPs (Figure 14) were tested for growth inhibitory activity against several breast and prostate cancer cell lines. Compounds **29** and **30** performed better than the parental compounds, and showed the most significant growth inhibitory activity against a prostate cancer cell line (PC-3) and a breast cancer cell line (MDA-MB-231), respectively.¹⁰⁰

The substitution of carboxylic acid of all-*trans* RA was carried out to develop a series of retinoate and retinamide derivatives (Figure 15). These derivatives were tested for their anti-tumor activities in NB4 cells using the MTT proliferation assay. Two compounds **31** and **32** showed higher cytotoxicity relative to other derivatives or all-*trans* RA.¹⁰¹

Recently, novel indole retinoid derivatives (Figure 16) were reported with anti-cancer activities. Most of the developed compounds showed strong anti-proliferative activity, with compound **33** being the most potent. Compound **33** showed significant activity especially in

breast cancer cell lines, including estrogen receptor (ER)-positive and ER-negative cell lines.¹⁰²

A novel class of retinoid-chalcone hybrids has also been developed and studied for their anti-cancer activities (Figure 17). They were tested against the colon cancer cell line (HT-29), which indicated that compound **34** possessed the most significant proliferation inhibitory activity with an IC₅₀ of 0.66 μM.¹⁰³

4HPR has been studied for activity against a variety of cancer types. Derivatives of 4HPR have been investigated for their growth inhibitory activity against human lung and head-and-neck cancer cells. This resulted in discovery of a more potent compound 2CPR, **35**.¹⁰⁴

Similarly, our research group has reported various synthetic derivatives of 4HPR for inhibition of rhabdoid tumors and for targeting a protein that is over-expressed in prostate carcinoma called mitochondria-associated granulocyte-macrophage colony stimulating factor signaling (Magma). Compound **36** (Figure 19) was found to be a potent Magma inhibitor.¹⁰⁵ Moreover, compound **37** that contains iodo substituted on the phenyl ring showed more potent inhibitory activity (IC₅₀ = 3.14 μM) against rhabdoid tumor cells than the parent compound 4HPR (IC₅₀ = 14.68 μM).¹⁰⁶ Compound **38** also showed significant inhibition of rhabdoid tumor cells when compared with the parent compound 4HPR.¹⁰⁷

There have been reports of diaryl sulfide retinoid analogs that can specifically bind to and transactivate RXRs. Compounds bearing 3-methyl on the tetrahydronaphthalene ring did not show any binding and transactivation of the RARs, indicating the importance of 3-methyl group for the RXR specificity. Compound **39** (Figure 20) was found to be the most potent and specific RXR agonist.¹⁰⁸

Retinoids AM80 (Tamibarotene, **16**), mentioned earlier for its anti-diabetic activity, has also been studied for treatment of AD. For this purpose, AM80 was orally administered to amyloid precursor protein (APP)23 mice, an animal model of AD. The result showed a significant reduction of insoluble Aβ levels, especially Aβ₄₂, in the brain but no effect on the soluble Aβ levels.¹⁰⁹ Similarly all-*trans* RA has been reported as a promising agent for treatment of AD. It was found that treatment of an AD transgenic mouse model with all-*trans* RA resulted in reduction of Aβ accumulation and tau hyperphosphorylation. Interestingly, there was significant reduction in glial activation and neuronal loss in the brain and improvement in spatial learning and memory.¹¹⁰

Finally, retinoids have also been used for the treatment of acne. Tretinoin (all-*trans* RA), isotretinoin (13-*cis* RA), and synthetic retinoids adapalene and tazarotene are FDA approved retinoids for the treatment of acne. Retinaldehyde has shown anti-bacterial effect against the *P. acnes* organism.^{111, 112}

All these above examples are clearly demonstrated the ability and utility of retinoids as novel therapeutic agents for many life threatening diseases.

8. Retinoids in molecular imaging

Molecular imaging plays a very important role in the field of drug discovery. It provides a useful tool to track molecules and identify the molecular targets. Fortunately, an imageable RA derivative has been reported. The imageable compound **40** (Figure 21) was developed by the conjugation of IRdye800cw and N-(aminohexyl)retinoicamide [RA-NH(CH₂)₆NH₂]. This near-infrared (NIR)-labeled agent was used for both *in vitro* and *in vivo* imaging studies. It can be used to detect multiple human cancer xenografts. Interestingly, only retinoid labeled dye was able to internalize in human tumor cells as observed by confocal microscopy. This technique has enabled the analysis of biodistribution, pharmacokinetics, and pharmacodynamics of the experimental agent in real-time. It can be applied to determine an appropriate therapeutic dose to avoid the systemic toxicity caused by high doses of RA.¹¹³

The development of imaging agents of hybrid compounds containing retinoids and HDACs would open a new avenue to study the epigenetic biology in cancer and other neurodisorder diseases.

9. Retinoids in stem cell biology and regenerative medicine

Retinoids regulates the stem cell differentiation via transcription activation. Retinoids are able to activate transcription by binding to the nuclear receptors RAR α , RAR β , and RAR γ . These RARs can form heterodimer with one of the RXRs and can bind with the DNA. This binding facilitates the activation of transcription of RA primary response genes, which are important for stem cell differentiation.¹¹⁴ Stem cells are unspecialized cells that have the ability to self-reproduce and differentiate into functional phenotypes. They can be originated from embryonic, fetal, or adult tissues. Differentiation ability of stem cells into functional cells in the damaged organ has been an important tool in the field of regenerative medicine. Regenerative therapy, emerging field of biomedicine, involves the repair and replacement or regeneration of cells, tissues, or organs. The importance of regenerative therapy has been studied in a wide range of diseases including kidney diseases,¹¹⁵ cardiac/heart diseases,¹¹⁶ skin diseases,¹¹⁷ retinal disorders,¹¹⁸ and neurodegenerative diseases such as AD and PD.¹¹⁹ In another experiments Marder group showed that synthetic retinoids are able to differentiate embryonal carcinoma stem cells to become neurons.¹²⁰ Further studies are needed to define the potential for RA in regenerative medicine.

10. Conclusions

Retinoids comprise a group of natural and synthetic molecules, which regulate a variety of essential biological processes during normal development, help maintain homeostasis, and also mediate protection from diseases such as cancer and age-related disorders of the CNS. Genomic functions of the retinoids are mediated via their nuclear DNA-binding receptors, RARs and RXRs, which regulate gene transcription through recruitment of corepressors and coactivators. Retinoids also have notable non-genomic functions through retinoylation. The synthesis, testing, and development of retinoid derivatives as drugs that target RARs and RXRs is currently an active field for chemical biology. Novel RA derivatives may be useful as therapeutics for the treatment of various malignancies, as well as renal, metabolic and

CNS diseases, while avoiding the teratogenic effects of RA. Synthesis of new retinoids may also serve as useful reagents for molecular imaging. The challenge to synthetic chemists is how to design and synthesize receptor sub-type and isotype specific ligands. Moreover, there are concerns in regard to how receptor isoforms and sub-types function in particular tissue and organ, and how the concentration of RA is spatial, temporal and kinetic controlled in organ development and disease. As regenerative medicine and stem cell biology are the frontier areas of research and RA signaling pathway plays a major role in differentiation, the development of receptor specific ligands may open new avenues for chemical biologists.

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References & Notes

1. Barua AB, Furr HC. *Mol Biotechnol.* 1998; 10:167. [PubMed: 9819815]
2. Carr FH, Price EA. *Biochemical J.* 1926; 20:497.
3. Neeld JB, Pearson WN. *J Nutr.* 1963; 79:454. [PubMed: 13937886]
4. Furr HC. *J Nutr.* 2004; 134:281S. [PubMed: 14704334]
5. Bushue N, Wan YJ. *Adv Drug Deliv Rev.* 2010; 62:1285. [PubMed: 20654663]
6. Kakkad BP, Ong DE. *J Biol Chem.* 1988; 263:12916. [PubMed: 3417642]
7. MacDonald PN, Ong DE. *J Biol Chem.* 1988; 263:12478. [PubMed: 3410848]
8. Harrison EH, Hussain MM. *J Nutr.* 2001; 131:1405. [PubMed: 11340090]
9. Green PH, Glickman RM. *J Lipid Res.* 1981; 22:1153. [PubMed: 7033425]
10. Blomhoff R, Green MH, Berg T, Norum KR. *Science.* 1990; 250:399. [PubMed: 2218545]
11. Noy N, Slosberg E, Scarlata S. *Biochemistry.* 1992; 31:11118. [PubMed: 1445851]
12. MacDonald PN, Ong DE. *Biochem Biophys Res Commun.* 1988; 156:157. [PubMed: 3178828]
13. Blaner WS, O'Byrne SM, Wongsiriroj N, Kluwe J, D'Ambrosio DM, Jiang H, Schwabe RF, Hillman EM, Piantadosi R, Libien J. *Biochim Biophys Acta.* 2009; 1791:467. [PubMed: 19071229]
14. Berry DC, O'Byrne SM, Vreeland AC, Blaner WS, Noy N. *Mol Cell Biol.* 2012; 32:3164. [PubMed: 22665496]
15. Duester G. *Eur J Biochem.* 2000; 267:4315. [PubMed: 10880953]
16. Blomhoff R, Blomhoff HK. *J Neurobiol.* 2006; 66:606. [PubMed: 16688755]
17. Napoli JL. *Clin Immunol Immunopathol.* 1996; 80:S52. [PubMed: 8811064]
18. Theodosiou M, Laudet V, Schubert M. *Cell Mol Life Sci.* 2010; 67:1423. [PubMed: 20140749]
19. Chambon P. *FASEB J.* 1996; 10:940. [PubMed: 8801176]
20. Moras D, Gronemeyer H. *Curr Opin Cell Biol.* 1998; 10:384. [PubMed: 9640540]
21. Renaud JP, Moras D. *Cell Mol Life Sci.* 2000; 57:1748. [PubMed: 11130180]
22. Rastinejad F. *Curr Opin Struct Biol.* 2001; 11:33. [PubMed: 11179889]
23. Wei LN. *Annu Rev Pharmacol Toxicol.* 2003; 43:47. [PubMed: 12142470]
24. Takahashi N, Breitman TR. *J Biol Chem.* 1989; 264:5159. [PubMed: 2925686]
25. Takahashi N, Sausville EA, Breitman TR. *Clin Cancer Res.* 1995; 1:637. [PubMed: 9816026]
26. Cione E, Tucci P, Senatore V, Ioele G, Genchi G. *Mol Cell Biochem.* 2005; 276:55. [PubMed: 16132685]
27. Takahashi N, Jetten AM, Breitman TR. *Biochem Biophys Res Commun.* 1991; 180:393. [PubMed: 1718279]
28. Dong D, Zile MH. *Biochem Biophys Res Commun.* 1995; 217:1026. [PubMed: 8554553]

29. Zile MH. *Exp Biol Med.* 2004; 229:598.
30. Li Z, Shen J, Wu WK, Wang X, Liang J, Qiu G, Liu J. *PLoS One.* 2012; 1:e46565. [PubMed: 23071590]
31. Hale F. *J Hered.* 1933; 24:105.
32. Glover JC, Renaud JS, Rijli FM. *J Neurobiol.* 2006; 66:705. [PubMed: 16688767]
33. Maden M. *J Neurobiol.* 2006; 66:726. [PubMed: 16688770]
34. Maden M, Gale E, Kostetskii I, Zile M. *Curr Biol.* 1996; 6:417. [PubMed: 8723346]
35. Diez del Corral R, Olivera-Martinez I, Goriely A, Gale E, Maden M, Storey K. *Neuron.* 2003; 40:65. [PubMed: 14527434]
36. Lupo G, Gestri G, O'Brien M, Denton RM, Chandraratna RA, Ley SV, Harris WA, Wilson SW. *Proc Natl Acad Sci U S A.* 2011; 108:8698. [PubMed: 21555593]
37. Kelley MW, Turner JK, Reh TA. *Development.* 1994; 120:2091. [PubMed: 7925013]
38. Niederreither K, Vermot J, Messaddeq N, Schuhbauer B, Chambon P, Dollé P. *Development.* 2001; 128:1019. [PubMed: 11245568]
39. Collop AH, Broomfield JA, Chandraratna RA, Yong Z, Deimling SJ, Kolker SJ, Weeks DL, Drysdale TA. *Dev Biol.* 2006; 291:96. [PubMed: 16423341]
40. Lin SC, Dollé P, Ryckebusch L, Nosedá M, Zaffran S, Schneider MD, Niederreither K. *Proc Natl Acad Sci U S A.* 2010; 107:9234. [PubMed: 20439714]
41. Clagett-Dame M, Knutson D. *Nutrients.* 2011; 3:385. [PubMed: 22254103]
42. Ghatpande S, Ghatpande A, Sher J, Zile MH, Evans T. *Blood.* 2002; 99:2379. [PubMed: 11895770]
43. Stavridis MP, Collins BJ, Storey KG. *Development.* 2010; 137:881. [PubMed: 20179094]
44. Engberg N, Kahn M, Petersen DR, Hansson M, Serup P. *Stem Cells.* 2010; 28:1498. [PubMed: 20665854]
45. Metallo CM, Ji L, de Pablo JJ, Palecek SP. *Stem Cells.* 2008; 26:372. [PubMed: 17962700]
46. Liu L, Suzuki K, Nakagata N, Mihara K, Matsumaru D, Ogino Y, Yashiro K, Hamada H, Liu Z, Evans SM, Mendelsohn C, Yamada G. *Birth Defects Research (Part B).* 2012; 95:79.
47. Duester G. *Birth Defects Res C Embryo Today.* 2007; 81:84. [PubMed: 17600781]
48. Sirbu IO, Zhao X, Duester G. *Dev Dyn.* 2008; 237:1627. [PubMed: 18498088]
49. Gavalas A, Krumlauf R. *Curr Opin Genet Dev.* 2000; 10:380. [PubMed: 10889064]
50. Maden M, Blentic A, Reijntjes S, Seguin S, Gale E, Graham A. *Int J Dev Biol.* 2007; 51:191. [PubMed: 17486539]
51. Lewandoski M, Mackem S. *Curr Biol.* 2009; 19:R558. [PubMed: 19640492]
52. Wendling O, Dennefeld C, Chambon P, Mark M. *Development.* 2000; 127:1553. [PubMed: 10725232]
53. Mark M, Ghyselinck NB, Chambon P. *Nucl Recept Signal.* 2009; 7:e002. [PubMed: 19381305]
54. de Thé H, Chomienne C, Lanotte M, Degos L, Dejean A. *Nature.* 1990; 347:558. [PubMed: 2170850]
55. Borrow J, Goddard AD, Sheer D, Solomon E. *Science.* 1990; 249:1577. [PubMed: 2218500]
56. el-Deiry WS, Tokino T, Velculescu VE, Levy DB, Parsons R, Trent JM, Lin D, Mercer WE, Kinzler KW, Vogelstein B. *Cell.* 1993; 75:817. [PubMed: 8242752]
57. Altucci L, Gronemeyer H. *Nat Rev Cancer.* 2001; 1:181. [PubMed: 11902573]
58. Niles RM. *Nutrition.* 2000; 16:1084. [PubMed: 11118831]
59. Baumann L, Vujevich J, Halem M, Martin LK, Kerdel F, Lazarus M, Pacheco H, Black L, Bryde J. *Cutis.* 2005; 76:69. [PubMed: 16144296]
60. Wu K, Kim HT, Rodriguez JL, Munoz-Medellin D, Mohsin SK, Hilsenbeck SG, Lamph WW, Gottardis MM, Shirley MA, Kuhn JG, Green JE, Brown PH. *Clin Cancer Res.* 2000; 6:3696. [PubMed: 10999763]
61. Christov KT, Moon RC, Lantvit DD, Boone CW, Steele VE, Lubet RA, Kelloff GJ, Pezzuto JM. *Cancer Res.* 2002; 62:5178. [PubMed: 12234981]

62. Altucci L, Leibowitz MD, Ogilvie KM, de Lera AR, Gronemeyer H. *Nat Rev Drug Discov.* 2007; 6:793. [PubMed: 17906642]
63. Schwarz EJ, Reginato MJ, Shao D, Krakow SL, Lazar MA. *Mol Cell Biol.* 1997; 17:1552. [PubMed: 9032283]
64. Sato M, Hiragun A, Mitsui H. *Biochem Biophys Res Commun.* 1980; 95:1839. [PubMed: 6998485]
65. Pairault J, Quignard-Boulangé A, Dugail I, Lasnier F. *Exp Cell Res.* 1988; 177:27. [PubMed: 2455651]
66. Kuri-Harcuch W. 1982; 23:164.
67. Berry DC, Noy N. *Mol Cell Biol.* 2009; 29:3286. [PubMed: 19364826]
68. Kawada T, Kamei Y, Fujita A, Hida Y, Takahashi N, Sugimoto E, Fushiki T. *Biofactors.* 2000; 13:103. [PubMed: 11237167]
69. Sakuta T, Uchiyama T, Kanayama T. *Endocrine.* 2006; 30:113. [PubMed: 17185799]
70. Miwako I, Shudo K. *Biol Pharm Bull.* 2009; 32:157. [PubMed: 19122301]
71. Van YH, Lee WH, Ortiz S, Lee MH, Qin HJ, Liu CP. *Diabetes.* 2009; 58:146. [PubMed: 18984738]
72. Cvekl A, Wang WL. *Exp Eye Res.* 2009; 89:280. [PubMed: 19427305]
73. Khorana HG. *J Biol Chem.* 1992; 267:1. [PubMed: 1730574]
74. Kefalov VJ. *J Biol Chem.* 2012; 287:1635. [PubMed: 22074928]
75. von Lintig J, Kiser PD, Golczak M, Palczewski K. *Trends Biochem Sci.* 2010; 35:400. [PubMed: 20188572]
76. Molday RS. *J Bioenerg Biomembr.* 2007; 39:507. [PubMed: 17994272]
77. Palczewski K. *Trends Pharmacol Sci.* 2010; 31:284. [PubMed: 20435355]
78. Maden M. *Nat Rev Neurosci.* 2002; 3:843. [PubMed: 12415292]
79. Etchamendy N, Enderlin V, Marighetto A, Vouimba RM, Pallet V, Jaffard R, Higuieret P. *J Neurosci.* 2001; 21:6423. [PubMed: 11487666]
80. Ono K, Yoshiike Y, Takashima A, Hasegawa K, Naiki H, Yamada M. *Exp Neurol.* 2004; 189:380. [PubMed: 15380488]
81. Takasaki J, Ono K, Yoshiike Y, Hirohata M, Ikeda T, Morinaga A, Takashima A, Yamada M. *J Alzheimers Dis.* 2011; 27:271. [PubMed: 21811022]
82. Shen H, Luo Y, Kuo CC, Deng X, Chang CF, Harvey BK, Hoffer BJ, Wang Y. *J Neurosci Res.* 2009; 87:545. [PubMed: 18803283]
83. Mukherjee S, Date A, Patravale V, Korting HC, Roeder A, Weindl G. *Clin Interv Aging.* 2006; 1:327. [PubMed: 18046911]
84. Wilson JG, Warkany J. *Am J Anat.* 1948; 83:357. [PubMed: 18098411]
85. Lelièvre-Pégorier M, Vilar J, Ferrier ML, Moreau E, Freund N, Gilbert T, Merlet-Bénichou C. *Kidney Int.* 1998; 54:1455. [PubMed: 9844121]
86. Merlet-Bénichou C, Vilar J, Lelièvre-Pégorier M, Gilbert T. *Curr Opin Nephrol Hypertens.* 1999; 8:39. [PubMed: 9914859]
87. Gilbert T. *Nephrol Dial Transplant.* 2002; 17:78. [PubMed: 12386298]
88. Batourina E, Gim S, Bello N, Shy M, Clagett-Dame M, Srinivas S, Costantini F, Mendelsohn C. *Nat Genet.* 2001; 27:74. [PubMed: 11138002]
89. Wong YF, Kopp JB, Roberts C, Scambler PJ, Abe Y, Rankin AC, Dutt N, Hendry BM, Xu Q. *PLoS One.* 2011; 6:e16770. [PubMed: 21326615]
90. Zhou TB, Qin YH, Lei FY, Su LN, Zhao YJ, Huang WF. *Exp Mol Pathol.* 2011; 90:287. [PubMed: 21385580]
91. Zhang J, Pippin JW, Vaughan MR, Kroffit RD, Taniguchi Y, Romagnani P, Nelson PJ, Liu ZH, Shankland SJ. *Nephron Exp Nephrol.* 2012; 121:e23. [PubMed: 23107969]
92. Islam MR, Puri S, Rodova M, Magenheimer BS, Maser RL, Calvet JP. *Am J Physiol Renal Physiol.* 2008; 295:F1845. [PubMed: 18922886]
93. Xu Q, Lucio-Cazana J, Kitamura M, Ruan X, Fine LG, Norman JT. *Kidney Int.* 2004; 66:2119. [PubMed: 15569301]

94. Kishimoto K, Kinoshita K, Hino S, Yano T, Nagare Y, Shimazu H, Nozaki Y, Sugiyama M, Ikoma S, Funauchi M. *Nephron Exp Nephrol*. 2011; 118:e69. [PubMed: 21228601]
95. Magoulas GE, Bariamis SE, Athanassopoulos CM, Haskopoulos A, Dedes PG, Krokidis MG, Karamanos NK, Kletsas D, Papaioannou D, Maroulis G. *Eur J Med Chem*. 2011; 46:721. [PubMed: 21208698]
96. Patel JB, Huynh CK, Handratta VD, Gediya LK, Brodie AM, Goloubeva OG, Clement OO, Nanne IP, Soprano DR, Njar VC. *J Med Chem*. 2004; 47:6716. [PubMed: 15615521]
97. Wada A, Matsuura N, Mizuguchi Y, Nakagawa K, Ito M, Okano T. *Bioorg Med Chem*. 2008; 16:8471. [PubMed: 18760926]
98. Wada A, Wang F, Suhara Y, Yamano Y, Okitsu T, Nakagawa K, Okano T. *Bioorg Med Chem*. 2010; 18:5795. [PubMed: 20673632]
99. Long B, Liang S, Xin D, Yang Y, Xiang J. *Eur J Med Chem*. 2009; 44:2572. [PubMed: 19231037]
100. Gediya LK, Khandelwal A, Patel J, Belosay A, Sabnis G, Mehta J, Purushottamachar P, Njar VC. *J Med Chem*. 2008; 51:3895. [PubMed: 18543902]
101. Shen J, Shi JB, Chen FH, Wang Y, Ruan JJ, Huang Y. *Chin Chem Lett*. 2009; 20:809.
102. Gurkan-Alp AS, Mumcuoglu M, Andac CA, Dayanc E, Cetin-Atalay R, Buyukbingol E. *Eur J Med Chem*. 2012; 58:346. [PubMed: 23142674]
103. Mizuno CS, Paul S, Suh N, Rimando AM. *Bioorg Med Chem Lett*. 2010; 20:7385. [PubMed: 21041085]
104. Sun SY, Yue P, Kelloff GJ, Steele VE, Lippman SM, Hong WK, Lotan R. *Cancer Epidemiol Biomarkers Prev*. 2001; 10:595. [PubMed: 11401908]
105. Jubinsky PT, Short MK, Ghanem M, Das BC. *Bioorg Med Chem Lett*. 2011; 21:3479. [PubMed: 21514823]
106. Das BC, Smith ME, Kalpana GV. *Bioorg Med Chem Lett*. 2008; 18:4177. [PubMed: 18556204]
107. Das BC, Smith ME, Kalpana GV. *Bioorg Med Chem Lett*. 2008; 18:3805. [PubMed: 18515102]
108. Beard RL, Colon DF, Song TK, Davies PJA, Kochhar DM, Chandraratna RAS. *J Med Chem*. 1996; 39:3556. [PubMed: 8784454]
109. Kawahara K, Nishi K, Suenobu M, Ohtsuka K, Maeda A, Nagatomo K, Kuniyasu A, Staufenbiel M, Nakagomi M, Shudo K, Nakayama H. *Biol Pharm Bull*. 2009; 32:1307. [PubMed: 19571405]
110. Ding Y, Qiao A, Wang Z, Goodwin JS, Lee ES, Block ML, Allsbrook M, McDonald MP, Fan GH. *J Neurosci*. 2008; 28:11622. [PubMed: 18987198]
111. Thielitz A, Abdel-Naser MB, Fluhr JW, Zouboulis CC, Gollnick H. *J Dtsch Dermatol Ges*. 2008; 6:1023. [PubMed: 18479477]
112. Pechère M, Pechère JC, Siegenthaler G, Germanier L, Saurat JH. *Dermatology*. 1999; 199:29. [PubMed: 10473957]
113. Wang W, Qiu X, Zhang F, Sun J, Cameron AG, Wendt JA, Mawad ME, Ke S. *Contrast Media Mol Imaging*. 2011; 6:200. [PubMed: 21861280]
114. Gudas LJ, Wagner JA. *J Cell Physiol*. 2011; 226:322. [PubMed: 20836077]
115. Yokoo T, Fukui A, Kobayashi E. *Organogenesis*. 2007; 3:34. [PubMed: 19279698]
116. Ptaszek LM, Mansourm M, Ruskin JN, Chien KR. *Lancet*. 2012; 379:933. [PubMed: 22405796]
117. Uitto J. *J Invest Dermatol*. 2011; 131:812. [PubMed: 21407233]
118. Daftarian N, Kiani S, Zahabi A. *J Ophthalmic Vis Res*. 2010; 5:250. [PubMed: 22737370]
119. Peng J, Zeng X. *Stem Cell Res Ther*. 2011; 2:32. [PubMed: 21861938]
120. Christie B, Barnard H, Batsanov A, Bridgens C, Cartmell B, Collings J, Maltman D, Redfern C, Marder T, Przyborski S, Whiting A. *Org Biomol Chem*. 2008; 6:3497–3507. [PubMed: 19082150]

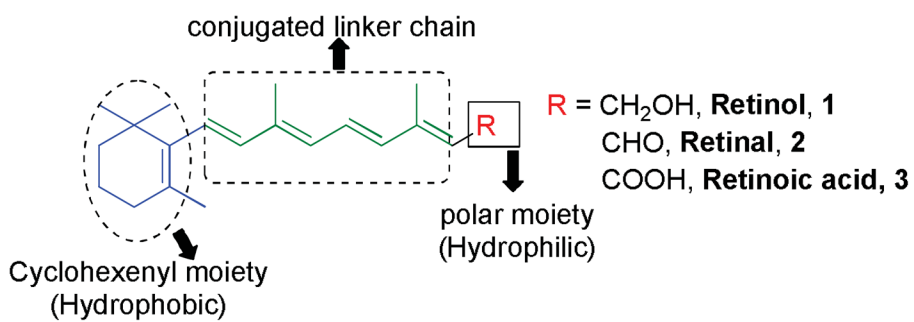


Figure 1.
Basic structure of retinoids.

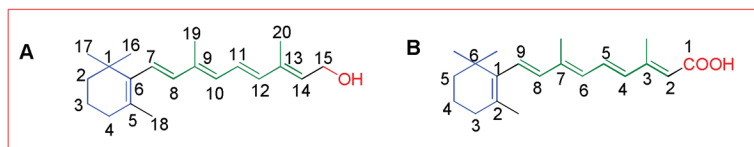


Figure 2.
Numbering of retinoids.

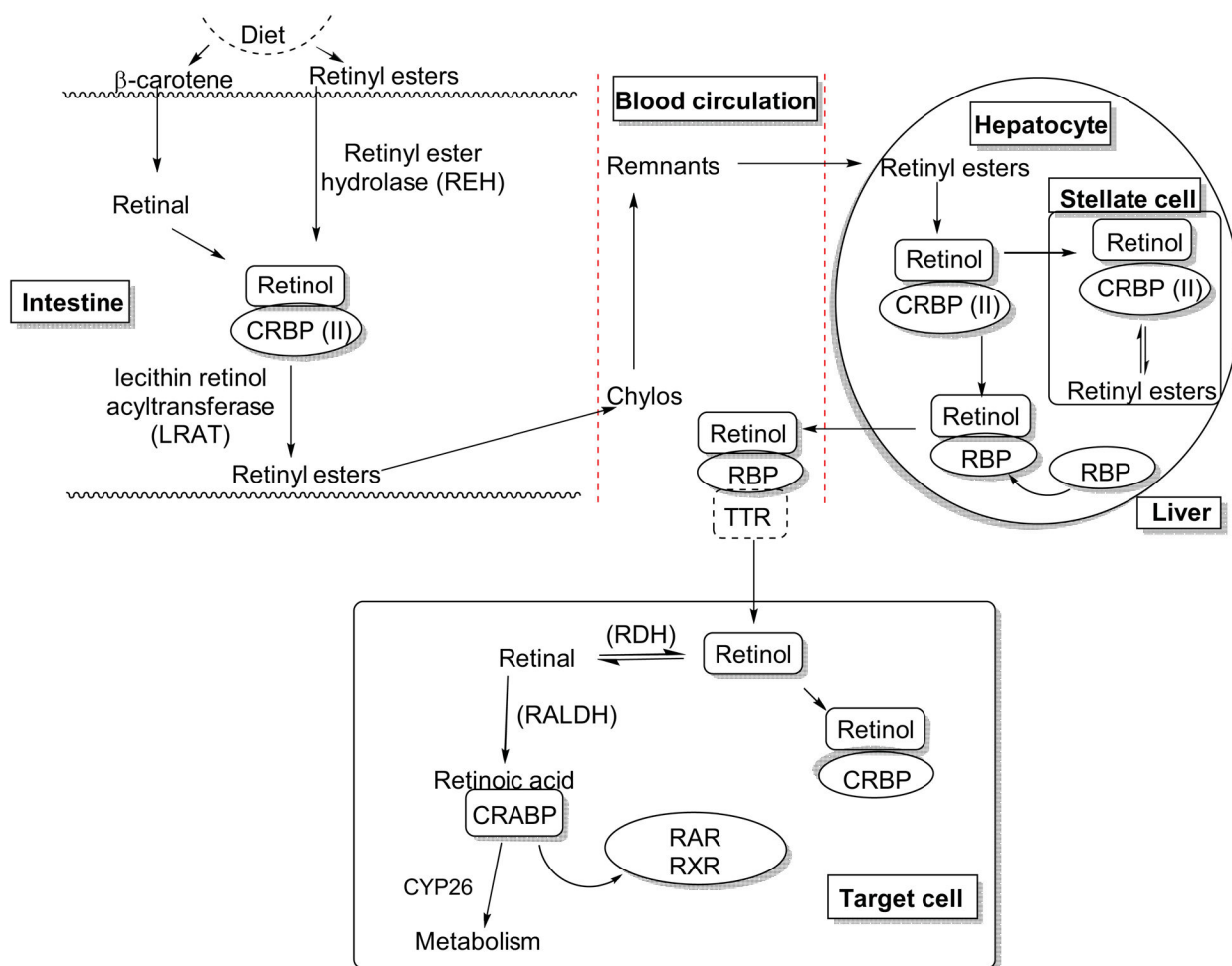


Figure 3. Biochemical conversion of carotenoids and retinoids to form retinoic acid.^{5,16,17,18}

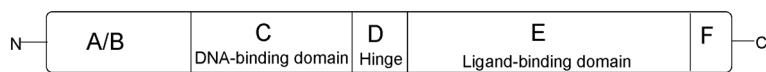


Figure 4. Functional domains of retinoid receptors. ^{20,21,22}

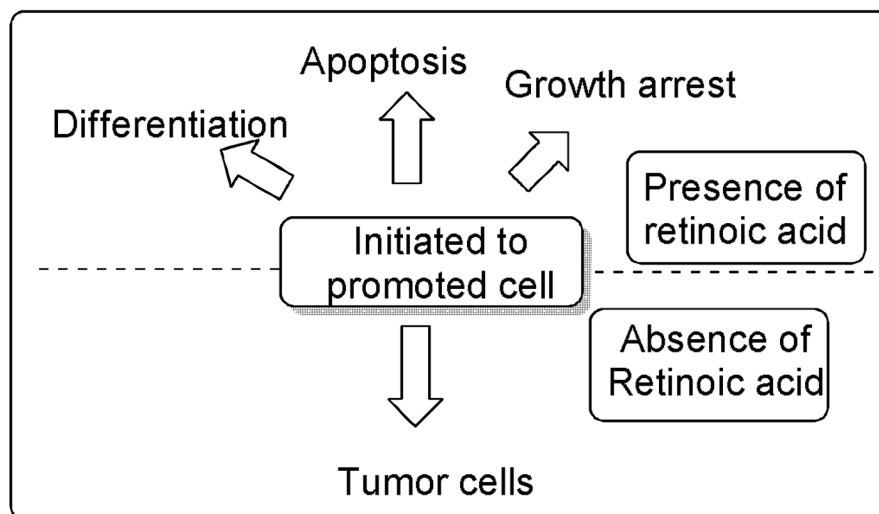


Figure 5.
Role of retinoic acid in inhibiting cancer development. ^{57,58}

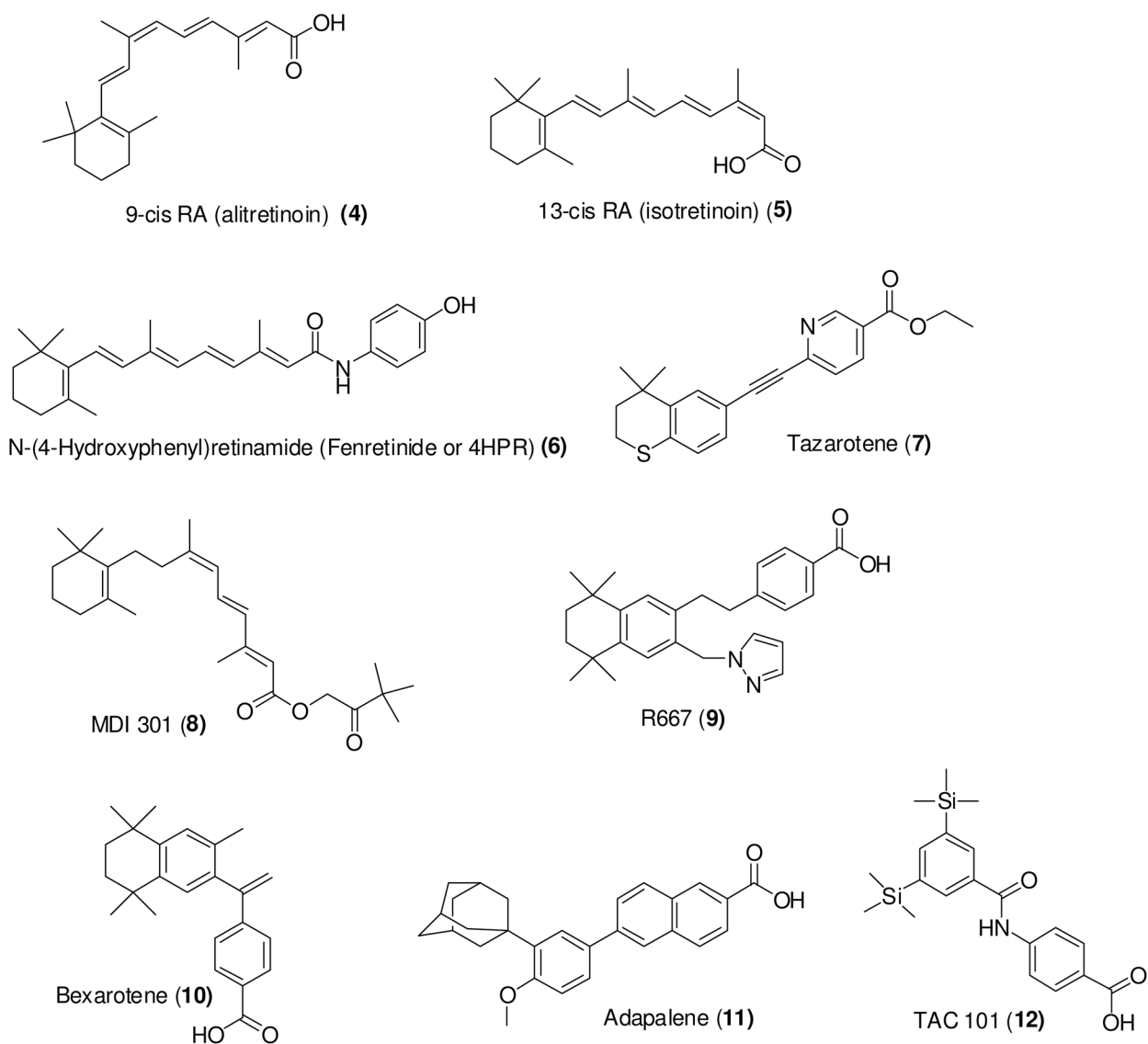


Figure 6.
Structure of natural or synthetic retinoids previously developed for clinical testing.

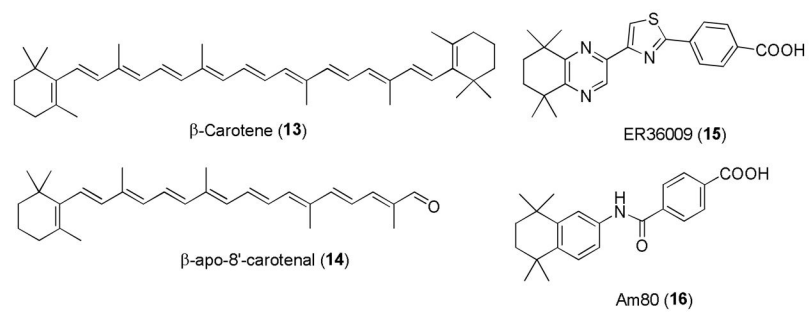


Figure 7.
Retinoids for treatment of metabolic disease

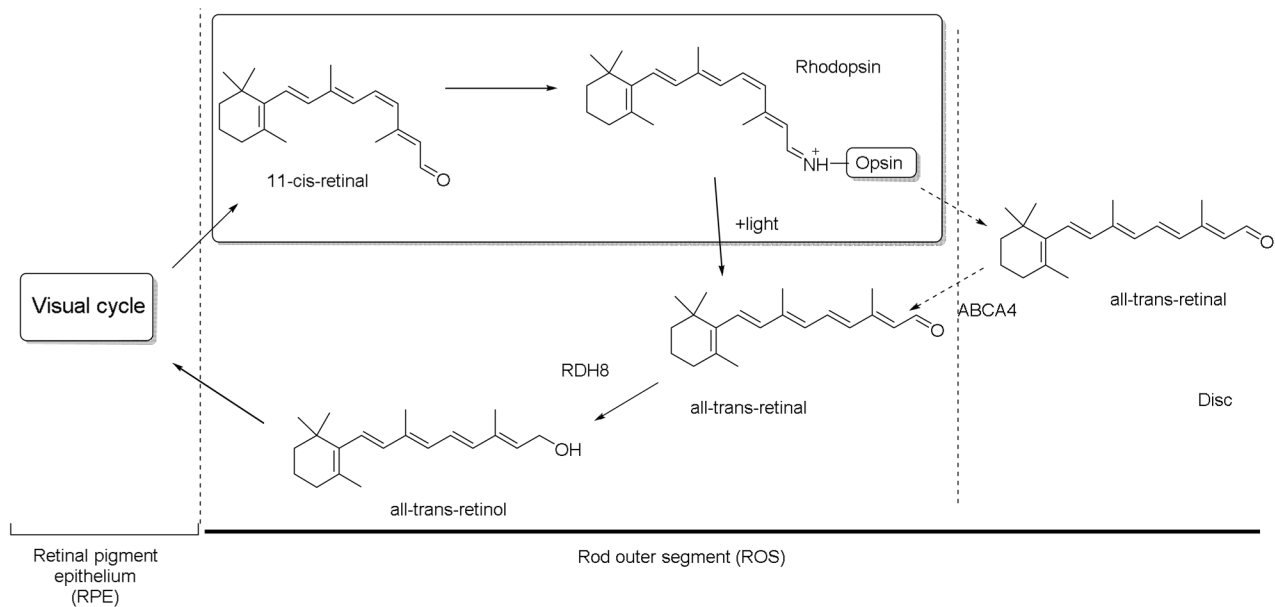


Figure 8.
Involvement of retinoids in the visual cycle.⁷⁷

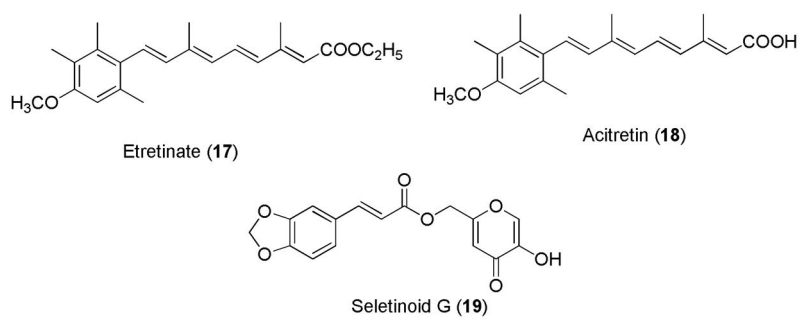


Figure 9.
Aromatic retinoids for anti-aging activity.

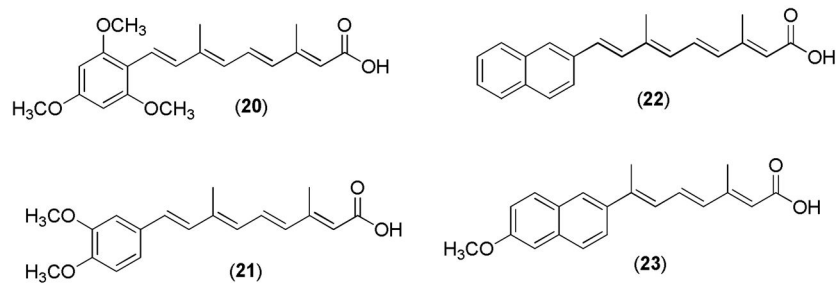


Figure 10.
Acitretin derivatives.

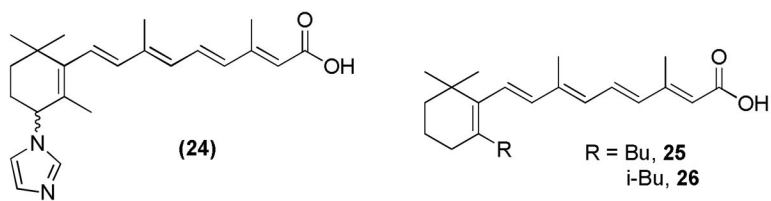
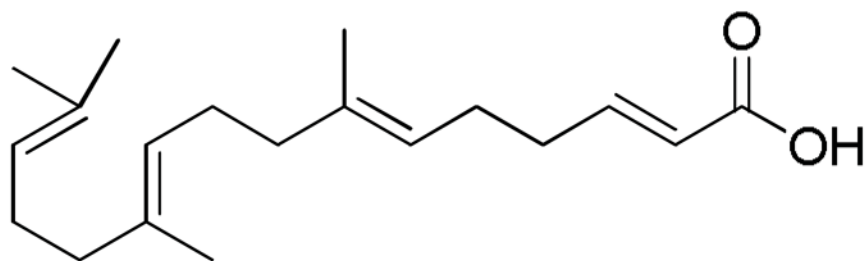


Figure 11.
Retinoid derivatives



(27)

Figure 12.
Acyclic demethyl geranylgeranoic acid (GGA)

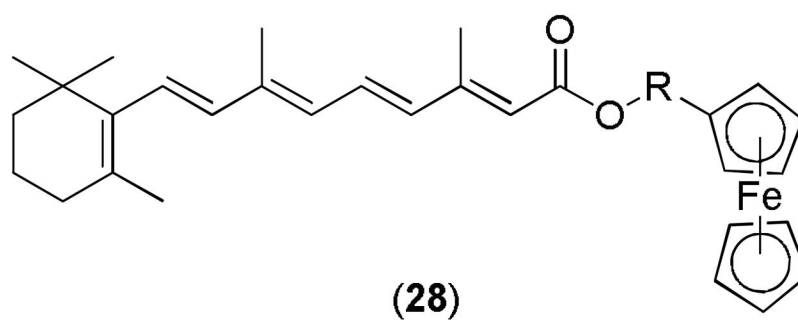


Figure 13.
Ferrocenyl retinoate

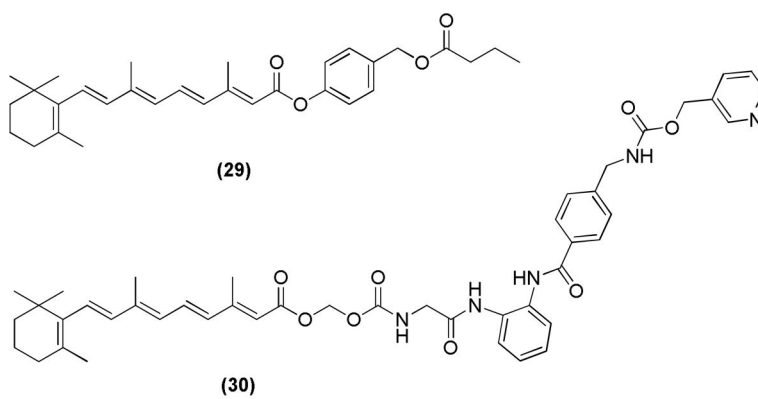


Figure 14.
Novel mutual products (MPs)

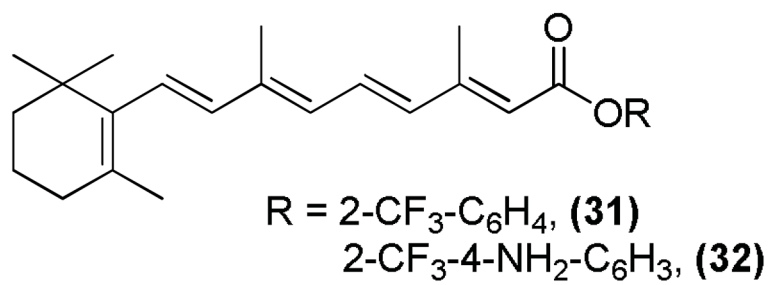


Figure 15.
All-*trans* RA derivatives

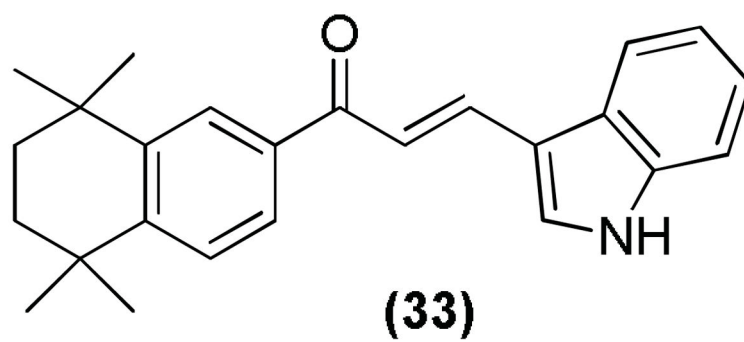


Figure 16.
Indole retinoid derivative

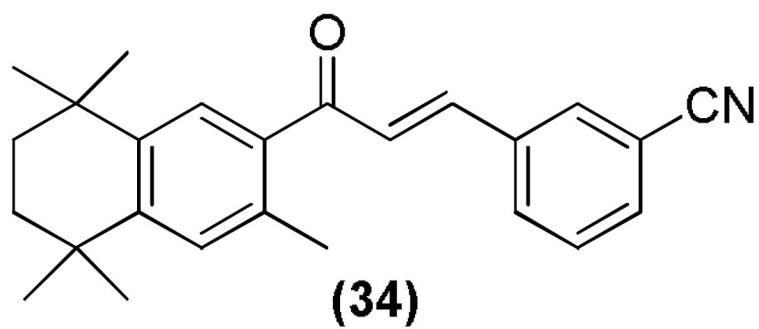


Figure 17.
Retinoid-chalcone hybrid

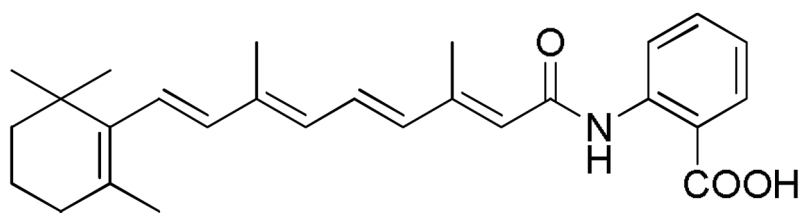
**2CPR (35)**

Figure 18.
Discovery of a 4HPR derivative

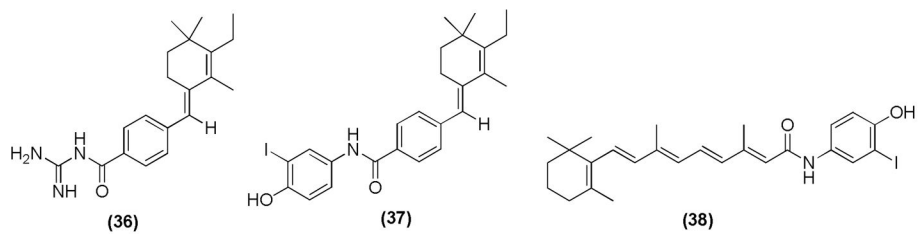
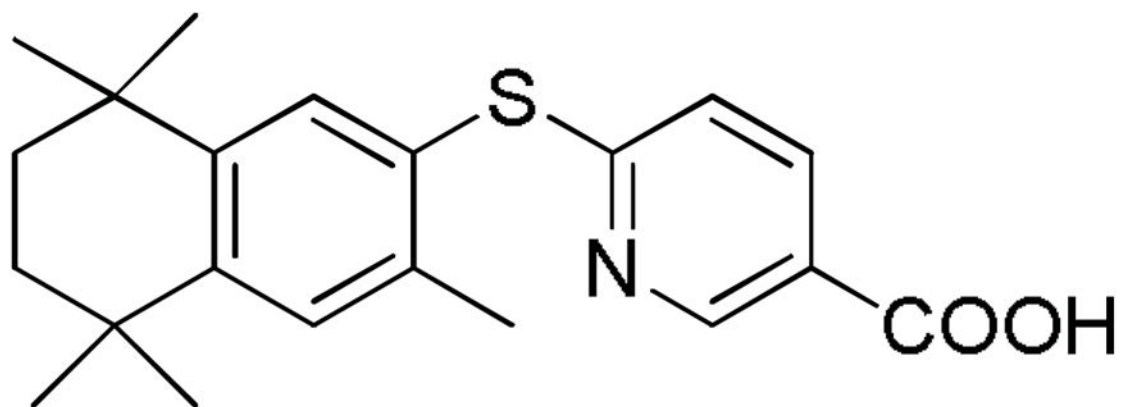


Figure 19.
4HPR derivatives as inhibitors of Magma and rhabdoid tumors.



(39)

Figure 20.
Diaryl sulfide retinoid.

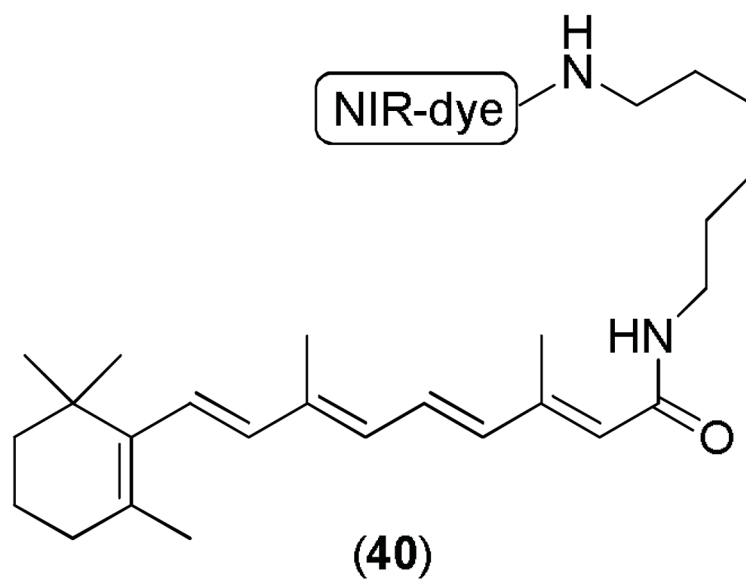


Figure 21.
An imageable RA derivative.