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Review

Retinoic acid metabolism blocking agents (RAMBAs) for treatment of cancer and dermatological diseases

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Abstract—The naturally occurring retinoids and their synthetic analogs play a key role in differentiation, proliferation, and apoptosis, and their use/potential in oncology, dermatology and a variety of diseases are well documented. This review focuses on the role of all-*trans*-retinoic acid (ATRA), the principal endogenous metabolite of vitamin A (retinol) and its metabolism in oncology and dermatology. ATRA has been used successfully in differentiated therapy of acute promyelocytic leukemia, skin cancer, Kaposi's sarcoma, and cutaneous T-cell lymphoma, and also in the treatment of acne and psoriasis. However, its usefulness is limited by the rapid emergence of acquired ATRA resistance involving multifactoral mechanisms. A key mechanism of resistance involves ATRA-induced catabolism of ATRA. Thus, a novel strategy to overcome the limitation associated with exogenous ATRA therapy has been to modulate and/or increase the levels of endogenous ATRA by inhibiting the cytochrome P450-dependent ATRA-4-hydroxylase enzymes (particularly CYP26s) responsible for ATRA metabolism. These inhibitors are also referred to as retinoic acid metabolism blocking agents (RAMBAs). This review highlights development in the design, synthesis, and evaluation of RAMBAs. Major emphasis is given to liarozole, the most studied and only RAMBA in clinical use and also the new RAMBAs in development and with clinical potential.

Contents

Keywords: All-*trans* retinoic acid (ATRA); Retinoic acid (RA); CYP26; Retinoic acid metabolism blocking agents (RAMBAs); Differentiation; Retinoid resistance; Cancer; Dermatology.
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1. Introduction

Retinoids (vitamin A and its natural metabolites and synthetic analogs) comprise a family of polyisoprenoid compounds. They are currently the subject of intense biological interest stimulated by the discovery and characterization of retinoid receptor and the realization of these compounds as nonsteroidal small-molecule hormones.[1] All-*trans*-retinoic acid (ATRA), the biologically most active metabolite of vitamin A, plays a major role in the regulation of gene expression, in cellular differentiation, and proliferation of epithelial cells.[2] Differentiating agents redirect cells toward their normal phenotype and therefore may reverse or suppress evolving malignant lesions or prevent cancer, and indeed represent an attractive target for medicinal intervention. ATRA is being used in differentiation therapy of cancer, in cancer chemoprevention, and for the treatment of dermatological diseases, including, acne, psoriasis, and ichthyosis.[3] Recently, ATRA has proven useful in cancer chemotherapy.[4] One of the most impressive effects of ATRA is on acute promyelocytic leukemia. Treatment of acute promyelocytic leukemia patients with high dose of ATRA resulted in complete remission.[5,6] Furthermore, several experiments in animals have demonstrated that ATRA inhibited the induction and caused the disappearance of prostate tumors.[7] In spite of these encouraging results, the effects of prolonged ATRA therapy on human cancers in the clinic have been scarce and disappointing.[8] Although the use of retinoids in the treatment of dermatological diseases has met with relatively better outcomes, side effects constitute a limit to the chronic use of these systemic agents. It has been suggested that the therapeutic effects of ATRA are undermined by its rapid in vivo metabolism and catabolism by cytochrome P450 enzymes.[9] An important consideration is that two cellular retinoic acid-binding proteins (referred to as CRABP-I and CRABP-II) are believed to be involved in the presentation of ATRA to metabolizing CYP enzymes and its channeling to the RAR receptors.[10,11] This topic will be briefly discussed in the next section. It should be stated that the two natural isomers of ATRA, 9-*cis*-retinoic acid (9-CRA) or 13-*cis*-retinoic acid (13-CRA), are also being investigated for cancer chemoprevention and/or therapy. In general, few P450 enzymes are known to be involved in retinoid metabolism.

One of the strategies for preventing in vivo catabolism of ATRA is to inhibit the P450 enzymes responsible for this process. Indeed, this seems to be an emerging approach that may yield effective agents for the chemoprevention and/or treatment of cancers and dermatological diseases.[3a,12] In this review, we will highlight development in the design, synthesis, and evaluation of RAMBAs since 1987. Major emphasis is given to liarozole, the most studied and first RAMBA to undergo clinical investigation and also the recently developed novel and potent 4-azolyl retinoids, the benzeneacetic acid derivatives and the 2,6-disubstituted naphthalenes. The potential role of a new family of cytochrome P450 enzymes, CYP26, with specificity toward ATRA is also discussed. For recent presentations of work in this field, the reviews by Miller[3a] and Njar[12] are recommended. To our knowledge, this represents the second comprehensive review of RAMBAs. Since the last comprehensive review on RAMBAs,[12] several manuscripts and patents on novel RAMBAs have appeared and gratifyingly, a pioneering RAMBA called liarozole was recently (2004) approved in Europe and USA as an orphan drug for the treatment of congenital ichthyosis.[13] Studies were identified for this review by searching the MEDLINE® and PubMed databases for appropriate papers published in the last 15 years up to December 2005 and by reviews of bibliographies from articles identified through that search. This review is complementary to the first comprehensive review on RAMBAs that appeared in 2002.[12] In addition, we include some of our unpublished data.

2. Mechanism of action of retinoids and retinoic acids

2.1. The role of retinoid and retinoic acid receptors

With current knowledge, the pleiotropic action of retinoic acids (RAs) and retinoids might be explained mechanistically by the actions of the six known nuclear receptors, the retinoic acid receptors (RARα, β, and γ) and the retinoid X receptor (also called rexinoids (RXRα, β, and γ)).[1,2,3b,10] Each of these receptors is encoded by distinct genes and are members of the steroid/thyroid hormone receptor superfamily. It is also thought that each receptor mediates a set of unique biological functions in certain cell or tissue types. ATRA is the natural ligand of the RARs, while 9-CRA is the ligand for the RXRs and it also has a high affinity for the RARs. The binding of the other ATRA stereoisomers, 11-*cis*-retinoic acid (11-CRA) and 13-CRA, to these receptors is still unclear. However, because of the reported antitumor efficacy of 13-CRA[14–19] it is plausible that 13-CRA is isomerized intracellularly to ATRA, or it may act without obvious interaction with the known retinoid receptors (Fig. 1). Clearly, more research is needed in this area.

Most of the pleiotropic activities of the RAs and other retinoids are elicited by the binding of these agents to the RAR site of RAR/RXR heterodimers. RXRs are the silent partners of the RARs, as the RXR ligands alone are unable to activate the RAR/RXR heterodimers. However, recent studies using RAR- and RXR-selective ligands have revealed that the RXR ligands allosterically increase the potencies of the RAR ligands.[20–22] Furthermore, RXRs form heterodimers with various nuclear receptors, such as estrogen receptors (ERs), vitamin D_3 receptors (VDRs), thyroid hormone receptors (TRs), and peroxisome proliferator-activated receptors (PPARs). Because of these unique properties of the RXRs, the RXR ligands are able to modulate the activities of other hormone receptors, in addition to their retinoidal activities.[23]

These receptors, as heterodimers (RAR/RXR) or homodimers (RXR/RXR), function as RA-inducible transcriptional regulatory proteins by binding to DNA

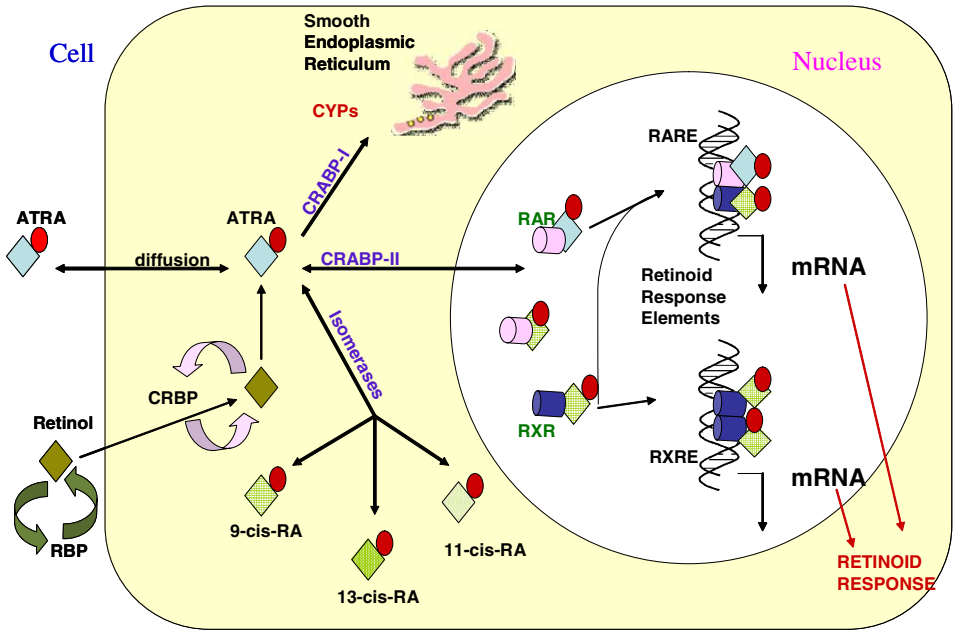


Figure 1. Fate of ATRA in the cell. ATRA enters the cell by simple diffusion or by conversion from retinol that has been absorbed from the gastrointestinal tract, bound in circulating form to retinol-binding proteins (RBPs), and rebound intracellularly to cellular retinol-binding proteins (CRBPs). ATRA can be immediately metabolized upon binding to cellular retinoic acid-binding proteins (CRAPBPs) and oxidized by CYPs located in the endoplasmic reticulum. Alternatively, ATRA and its 9-*cis*-isomer enter the nucleus and bind to RARs or RXRs, respectively. Upon dimerization of these receptors, that is, RAR/RXR heterodimer or RXR/RXR homodimer, the activated receptors bind with high affinity to specific DNA retinoic acid response element (RARE) and effect mRNA transcription. Ultimately, the retinoid response is mediated by primary target genes, by interference with other transcription factors or by control of certain post-transcriptional actions.

regions called retinoic acid response elements (RAREs) or retinoid X response elements (RXREs) located within the promoter of target genes. RAREs consist of direct repeats of the consensus half-site sequence AGGTCA separated most commonly by five nucleotides (DR-5), whereas RXREs are typically direct repeats of AGGTCA with one nucleotide spacing (DR-1). In the absence of ligand (ATRA or 9-CRA), the apo-heterodimer (RAR/RXR) binds to the RARE in the promoter of the target genes and RAR recruits corepressors (CoRs) such as nuclear receptor corepressors (NCoR) or/and silencing mediator for retinoid and thyroid receptors (SMRT). These corepressors by recruiting histone deacetylase complexes (HDACs) cause target gene repression due to compaction of chromatin, causing DNA to be inaccessible to the transcriptional machinery. However, in the presence of ATRA or an agonist, there is a conformational change in the structure of the ligand-binding domain that results in destabilization of the CoR-binding with concomitant recruitment and interaction with coactivators (CoAs). Some coactivators interact directly with the basal transcriptional machinery to enhance transcriptional activation, while others encode histone acetyl transferase (HAT) activity. HAT acetylates histone proteins, causing the opening of the chromatin and activation of transcription of the associated gene. The mechanism of transcriptional repression and activation of RAR/RXR heterodimer is summarized in Figure 2. Other complexes, such as the thyroid receptor associated protein are also involved in this process. It should be stated that whereas the RARα is involved in myeloid leukemias, a growing body of evidence indicate that RARβ is involved in a diverse range of solid tumors.[3b] For more details on the mechanism of action of ATRA, reviews by Chambon[2] and Altucci and Gronemeyer[3b] should be consulted.

2.2. The role of cellular retinoic acid proteins I and II

Two binding proteins, cellular retinoic acid-binding proteins I and II (CRABP-I and CRABP-II), are implicated in the tightly controlled nuclear receptor-mediated mechanism of action of ATRA.[10,11,24] CRABP-I and CRABP-II as well as other retinoid-binding proteins are believed to share a common role, in that they act to solubilize and stabilize their hydrophobic and labile ligands in aqueous milieu. However, in addition to this general role, specific retinoid-binding proteins have distinct functions in regulation of the transport, metabolism, and action of the particular retinoids with which they associate. Furthermore, the distinct patterns of expression of CRABP-I and II suggest that they serve different functions in the biology of ATRA, and/or, perhaps that they allow for accommodating different requirements for ATRA in different tissues.[25] A growing body of information indicates that CRABP-I moderates cellular response to ATRA by facilitating catabolism and/or by sequestering ATRA, rendering it unavailable to nuclear receptors. On the basis of elegant studies by Noy and co-workers,[25–27] it is currently believed that the CRABP-II/RAR complex mediates ligand channeling from the binding protein to the receptor, thereby facilitating the ligation of RAR and potentiating its transcriptional activity (Fig. 3). These investigators have also recently clearly demonstrated that CRABP-II plays a critical role in sensitizing MCF-7 human breast tumors

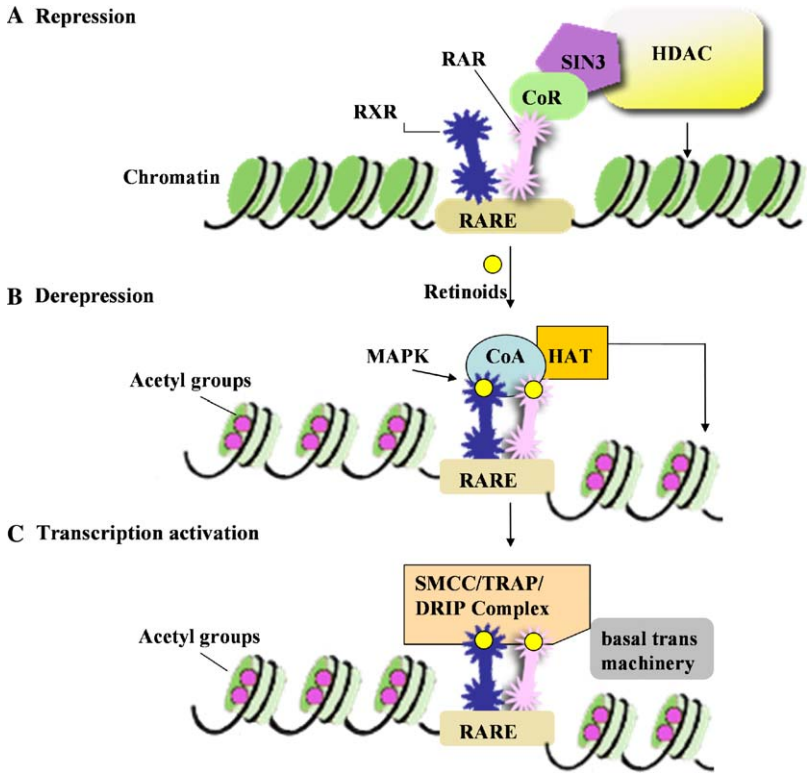


Figure 2. Mechanism of transcriptional repression and activation by RAR–RXR heterodimers. Figure adapted from Ref. 3b.

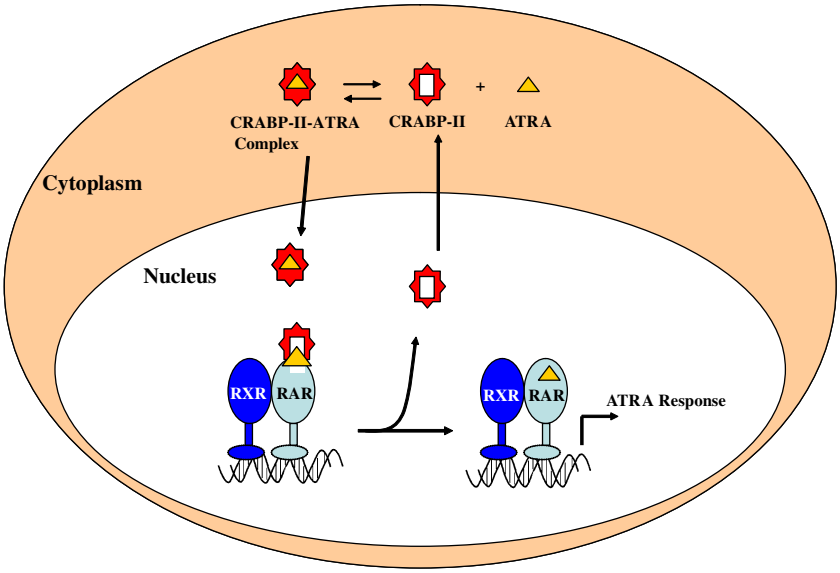


Figure 3. Mechanism of action of cellular RA-binding protein (CRABP-II). Following the binding of ATRA in the cytoplasm, CRABP-II moves into the nucleus where it channels ATRA to the RAR. RAR is then activated, resulting in the up-regulation of multiple target genes. Figure adapted from Ref. 27.

to the growth-suppressive activities of ATRA in vivo.[28] In support of the association between CRABP-II and retinoid receptors, another group has demonstrated that CRABP-II can interact with RARα and RXRα.[29] Taken together, these studies define a novel mechanism of transcriptional control that establish the function of CRABP-II in modulating the RAR-mediated biological activities of ATRA.

3. Cytochrome P450 enzymes (CYPs) involved in retinoic acid metabolism

ATRA is rapidly metabolized by cytochrome P450 (CYP)-dependent enzymes via several routes leading to a variety of polar metabolites (Scheme 1); the immediate products include 4-hydroxy-ATRA (4-OH-ATRA), 18-hydroxy-ATRA (18-OH-ATRA), and 5,6-

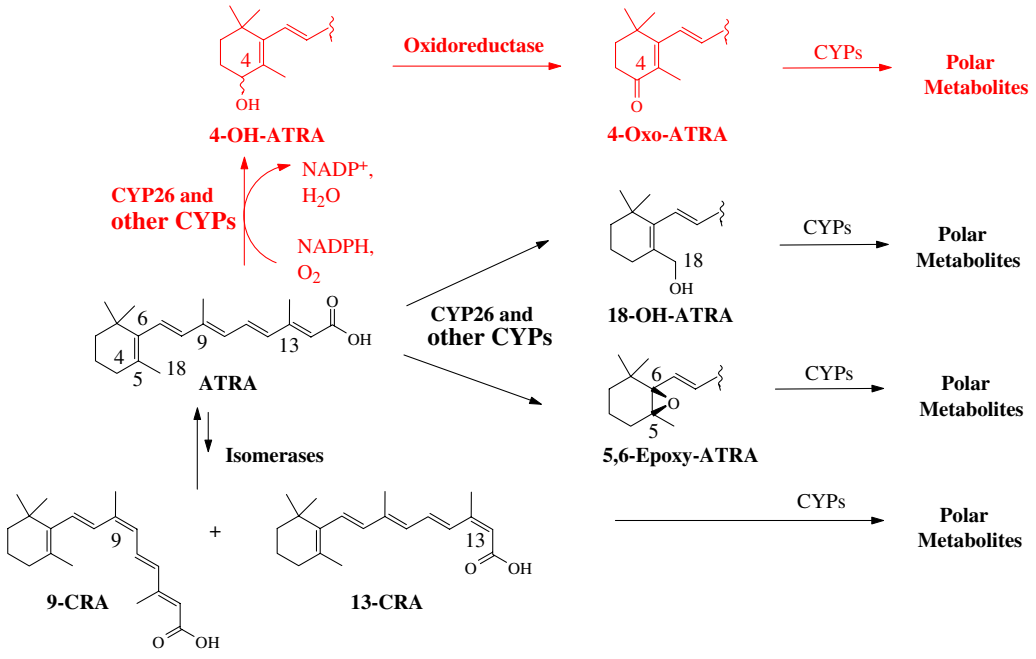
epoxy-ATRA.[30] However, it is believed that the physiologically most prominent pathway starts with the rate-limiting hydroxylation at C-4 position of the cyclohexenyl ring leading to formation of 4-hydroxy-ATRA. It should be stated that the stereochemistry at C-4 of 4-hydroxy-ATRA is yet to be determined. The latter compound is converted by a reductase enzyme into 4-oxo-ATRA that is then further transformed by CYP(s) into more polar metabolites (Scheme 1).[31] Although most of these ATRA metabolism studies have been conducted with rodent liver microsomes, similar results have also been obtained using human liver microsomes.[30,31] Four independent groups have established that of the several human liver CYP isoforms capable of metabolizing ATRA via the 4-hydroxylation route, CYP2C8 is the major contributor, though CYP3A4 and, to a lesser extent CYP2C9, also make contributions.[32–35]

A growing body of experimental data indicates that ATRA is also biotransformed into its isomers, 9-CRA and 13-CRA, but as indicated in Scheme 1, bio-conversions to ATRA are thermodynamically favorable.[36] As expected, these 9-CRA and 13-CRA also undergo CYP metabolism to give their corresponding 4-hydroxy and 4-oxo metabolites. Recent studies by Chabot and co-workers[37] have identified adult human CYPs 2C9, 2C8, and 3A4 to be involved in the 9-CRA metabolism, whereas CYPs 3A4 and 2C8 are active in 13-CRA metabolism. For recent presentations of work in this field, the review by Marill et al.[38] is recommended.

Although several CYPs have been shown to be involved in the catalysis of ATRA 4-hydroxylation, their specificity for ATRA is generally low.[32–34] However, a new family of cytochrome P450 enzymes CYP26A1 has recently been cloned and characterized in zebrafish, human, and mouse tissues.[39–44] In addition to this new enzyme, a second human CYP26 (referred to as CYP2B1) which is 44% identical to CYP26A1 has also been identified.[45] CYP26A1 and CYP26B2 are ATRA-inducible and appear to be the most dedicated ATRA 4-hydroxylase enzymes known. Interestingly, these CYPs do not hydroxylate the closely related isomeric 9-CRA or 13-CRA.[44,46] Of significance also is the recent report of 4-hydroxyphenyl retinamide (4-HPR) induction of CYP26A1 in A2780 human ovarian carcinoma cells, that is responsible for the metabolism of 4-HPR to the biologically active 4-oxo-HPR.[47] A third member of the CYP26 family named CYP26C1 has recently been identified, cloned, and characterized.[48] Although CYP26C1 shares extensive sequence similarity with CYPA1 and CYPB1, its catalytic activity appears distinct from those of other CYP26 family members. Specifically, CYP26C1 can also recognize and metabolize 9-CRA and is much less sensitive than the other CYP26 family members to the inhibitory effects of ketoconazole. These enzymes display high specificity toward ATRA and may function as important regulators of differentiation and as possible modulator of disease states by controlling retinoid concentrations and homeostasis. Recent reviews on the cloning and characterization of CYP26 enzymes[49,50] and also the regulation of CYP genes by nuclear receptors have appeared.[51] It should be noted that the pioneering paper by Petkovich and co-workers[39] opened the way for the recent exciting studies on CYP26 enzymes.

4. Distribution and role of CYP26 in cancer and dermatology

CYP26 is expressed in the liver, heart, pituitary gland, adrenal gland, testis, duodenum, colon, and in specific



Scheme 1. Metabolic pathways of all-*trans*-retinoic acid (ATRA). The major metabolic pathway is shown in red, and partial structures for some metabolites are presented for clarity.

regions of the brain and the placenta [reviewed in Refs. 45, 50, and 52]. Based on recent studies,[50] it is suggested that the major role of CYP26A1 is a protective one, that is, the regulation of intracellular ATRA steady-state levels, exhibiting a similar negative feedback as has been demonstrated for CYP24, which is involved in cholecalciferol catabolism.[53] Although the major retinoid products (4-hydroxy- and 4-oxo-ATRA) of CYP26 were originally considered to be inactive retinoids, there is compelling evidence which suggest that they are highly active modulators of positional specification in amphibian embryonic development and they bind and activate retinoic acid receptors (RAR) subtypes as efficiently as ATRA.[54,55] Thus, in development CYP26A1 may fulfil functions distinct from metabolic inactivation of ATRA.

CYP26 is readily induced by ATRA in a variety of normal and some cancer cells (MCF7, T47D, NB4, HepG2, HPK1A, and LNCaP) and the enzyme efficiently converts ATRA into its oxygenated derivatives. Although the therapeutic potential of ATRA has been demonstrated (reviewed in Refs. 7 and 56) a major drawback to its clinical application is the prompt emergence of resistance, attributed to the induction of oxidative catabolism through CYPs,[9,57–60] and CYP26 could be a major contributor. Because ATRA deficiency is associated with the progression of some cancers,[61–63] it is possible that ATRA-induced CYP26 is involved in rapid metabolism of ATRA in cancer patients. In addition, it is firmly established that inappropriate metabolism of ATRA by CYPs can generate a condition of retinoid deficiency, which is characterized by hyperkeratinization and desquamation as seen in dermatological diseases such as acne, psoriasis, and ichthyosis.[64]

The cloning and characterization of CYP26 represents an important development in ATRA (retinoid) biochemistry and molecular biology. The enzyme's inducibility by ATRA and its ATRA metabolic/catabolic activity define a feedback loop, which may be critical in regulating both normal and therapeutic levels of ATRA. This emphasizes the importance of maintaining stable physiological levels of ATRA. Thus, compounds designed to inhibit CYP26 activity may be useful in elevating normal tissue ATRA levels or maintaining high therapeutic levels of ATRA. As stated earlier, since ATRA has proven useful in the treatment and/or chemoprevention of some cancers and skin disorders, it is now possible to investigate the contributions of the expression/activity of CYP26 (or lack thereof) in various diseases. CYP26A1 has recently been mapped to human chromosome 10q23–q24,[65] a region where several suppressor gene loci have been described[66] as well as the split-hand-split foot syndrome (SHSF-3).[67] Thus, it is possible that mutations in CYP26A1 may play a role in these diseases. On the other hand, CYP26B1 is localized on chromosome 2P12 with 6 exons and codes 512 amino acid proteins.[45,68] CYP26C1 is not widely expressed in the adult but is inducible by ATRA in HPK1a, transformed keratinocyte cell lines, and it is suggested that it may play a specific role in catabolizing both ATRA and 9-CRA.[48]

5. ATRA 4-hydroxylase inhibition—development of retinoic acid metabolism blocking agents (RAMBAs)

The realization that the metabolism of ATRA may be responsible for its limited efficacy in the clinics (CYP26-mediated resistance?) provided the impetus behind the search for inhibitors of the CYP-mediated metabolism of ATRA. As the enzymes responsible for ATRA metabolism are P450 proteins, most of the intial compounds tested for their inhibition were the known P450 inhibitors, such as clotrimazole and ketoconazole. Because the early studies on the inhibitors of these enzymes have recently been discussed,[12] we will focus on the important developments in the design, synthesis, and testing of the newer inhibitors of ATRA 4-hydroxylases (RAMBAs).

A potent RAMBA would be expected to modulate the levels of endogenous or co-administered ATRA, enhancing the 'ATRA-mimetic' effects. In humans, the target enzymes involved in ATRA metabolism are the nonspecific liver CYPs, among which CYP2C8 and 3A4[33–35] are the major contributors, and the ATRA-inducible CYP26.[39–45] Although some investigators[69–72] have targeted inhibition of CYP26, it seems more realistic that both the nonspecific CYPs and specific CYP26 would need to be targeted since without initial ATRA accumulation due to nonspecific CYP action, ATRA levels would be insufficient to induce CYP26. Smith and co-workers[73] have also recently articulated this alternative strategy.

Since the last review on this topic, a large number of new RAMBAs have been reported in the literature and in patent disclosures by researchers from academia, including the University of Cardiff group, and our University of Maryland group and by pharmaceutical companies such as Johnson and Johnson Pharmaceutical Research and Development, Allergan Sales Inc., and OSI Pharmaceuticals, Inc. It should be stated that ATRA hydroxylase inhibition assays are performed differently in various laboratories and inhibitory data reported here are based on assays with hamster or rat liver microsomes, and also cell-based/microsomal assays using ATRA-induced CYP26 in MCF-7 of T47D human breast cancer cells and CYP26 stably transfected HeLa cells. The following is an overview of the different types of RAMBAs and a perspective on the significance of the various classes as potential therapeutic agents in oncology and dermatology.

6. Liarozole (Liazal™) and related compounds—R115866 and R116010

Following extensive studies by researchers of Janssen Research Foundation (now called Johnson and Johnson Pharmaceutical Research and Development) liarozole (**1**, Liazal™, Fig. 4) was identified as a modest inhibitor (IC_{50} 2.2–6.0 μM) of ATRA-4-hydroxylase (CYP26).[69,74–80] On the other hand, the compound was shown to be a good inhibitor of rat CYP17 (IC_{50} = 260 nM) and a potent inhibitor of CYP19.[77]

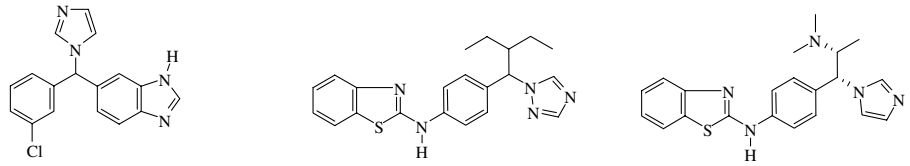


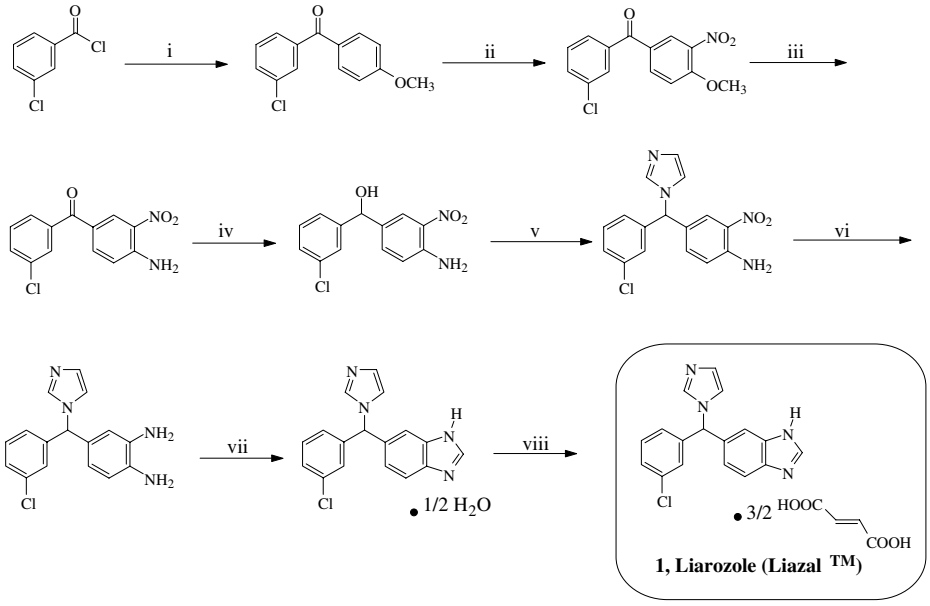
Figure 4. Structures of liarozole (**1**), R115866 (**2**), and R116010 (**3**).

It should be noted that liarozole is the most studied RAMBA and remains to date the only RAMBA to have been evaluated clinically in patients with cancer and also dermatological diseases and, as such, is a standard against which future RAMBAs may be judged. A practical eight-step synthesis of liarozole has been reported (Scheme 2).[69]

Anti-tumoral action was detected in androgen-dependent and androgen-independent rat prostate carcinoma models.[14,78,81] Remarkable anti-tumor activity was observed against prostate cancer xenografts in immunodepressed mice[82,83] and further studies revealed that the anti-tumor properties of liarozole correlate with an increase in tumor differentiation, following accumulation of ATRA.[84] These studies established that the anti-tumoral properties of the compound are related to its inhibition of ATRA metabolism and that the previously demonstrated inhibition of CYP17 (inhibition of androgen synthesis) is marginal in vivo.

A large phase III international study was completed comparing liarozole 300 mg twice daily with cyproterone acetate (CPA) 100 mg twice daily in a total of 321 patients with metastatic prostate cancer in relapse after first-line endocrine therapy.[85] The adjusted hazard ratio for survival was 0.74 in favor of liarozole ($P = 0.039$), indicating a 26% lower risk of death than in patients treated with CPA. Liarozole was superior to CPA in terms of prostate-specific antigen (PSA) response, PSA progression, and survival, and was capable of maintaining patients' quality of life. The observed adverse events were relatively mild to moderate in nature. The results indicate that liarozole might be a possible treatment option for prostate cancer (PCA) following failure of first-line endocrine therapy.

Although most experiences of liarozole as an anti-cancer agent have been limited to prostate cancer, a few experiments with breast cancer have also been conducted. In cultured human breast cancer MCF-7 cells, liarozole potentiated the antiproliferative and differentiative effects of ATRA.[86–89] This enhancement of ATRA effects could be explained by the inhibition of enzymatic degradation of ATRA in these cells. Liarozole has proven antitumor activity in steroid-insensitive TA3-mouse mammary carcinoma and in NUM-induced mammary carcinoma in rats.[90] A recent study of three phase II clinical studies of liarozole in the treatment of ER negative, tamoxifen refractory or chemotherapy-resistant postmenopausal metastatic breast cancer patients only reported a modest response.[91]



Scheme 2. Synthesis of liarozole. Reagents and conditions: (i) $PhOCH_3$, $AlCl_3$, CH_2Cl_2, 5–10 °C; (ii) HNO_3/H_2SO_4, CH_2Cl_2, 10–15 °C, 1 h; (iii) NH_3(g), *i*-PrOH, 100 °C; (iv) $NaBH_4$, *i*-PrOH, reflux, 1 h; (v) CDI, CH_2Cl_2, reflux, 1 h; (vi) H_2, Pt/C, 5% thiophene soln, MeOH, rt; (vii) HCOOH, 4 N HCl, reflux; (viii) EtOH, 50 °C, fumaric acid.

Despite these encouraging preclinical and clinical results, the usefulness of liarozole cancer therapy is considered limited due to adverse side effects that are attributed to its lack of CYP isozyme specificity and its moderate potency of ATRA 4-hydroxylases. Consequently, Janssen have since discontinued clinical development of liarozole as an anti-cancer agent.[91,92]

Inappropriate metabolism of ATRA could generate a condition of retinoid deficiency, which is characterized by hyperkeratinization and desquamation as seen in acne, psoriasis, and ichthyosis.[64] Because of these reasons, liarozole has also been extensively investigated as a potential agent for the treatment of dermatological diseases.[3d,3e,76] Studies in mice revealed that liarozole is able to mimic the antikeratinizing effects of ATRA.[76] In open clinical studies, liarozole was found to be therapeutically effective in patients with psoriasis[93,94] and with ichthyosis.[95] A double-blind, randomized clinical study involving 20 patients with severe plaque-type psoriasis was conducted where half of the patients were treated with oral liarozole (75 mg, twice daily) and the other half were treated with oral acitretin (25 mg/day).[3d] After 12 weeks of treatment, both groups responded with a similar decrease in the PASI (psoriasis area severity index) score from ~20 to ~10. It is gratifying to state that liarozole was recently (2004) approved in Europe and USA as an orphan drug for the treatment of congenital ichthyosis.[13,96] Finally, in a most recent (2005) paper, Lucker and co-workers reported that topical liarozole was effective in the treatment of ichthyosis.[96]

6.1. R115866 and R116010

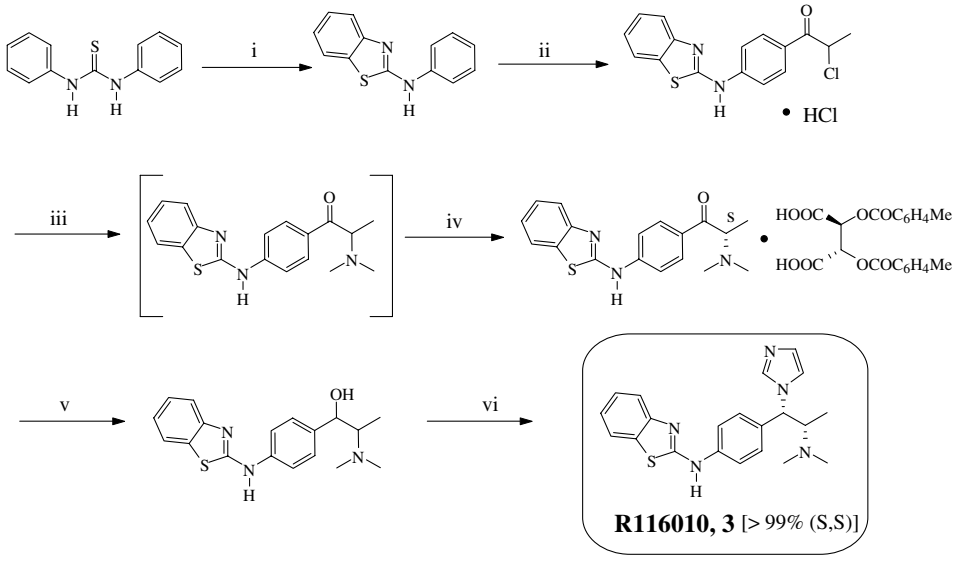
Recently, researchers of this same company have identified two novel benzothiazolamines, R115866, **2**[70] and R116010, **3**[71] (Fig. 4) as highly potent and selective second-generation inhibitors of ATRA metabolism. R115866 is a potent inhibitor of human CYP26A1 (IC_{50}, 4 nM), being 750 times as potent as liarozole (IC_{50}, 3 μM).[70] R115866 is highly selective for CYP26 as it exhibited mediocre inhibitory effects on aromatase, CYP17, CYP211, CYP3A, and CYP2A1, respectively. In vivo administration of R115866 (2.5 mg/kg po) to rats induced significant and transient increase of endogenous ATRA levels in plasma, skin, fat, kidney, and testis. Consequently, the compound exerted retinoidal effects, for example, inhibition of vaginal keratinization in rats. Although these studies with R115866 seem to be focused on dermatological therapy,[3e,70] their potential as agents for the treatment of cancers is warranted.

R116010 (**3**) is a dimethylamino derivative of R115866 and it has only been investigated as an anti-cancer agent.[71a,b] In vitro R116010 inhibits ATRA metabolism in intact T47D human breast cancer cells with an IC_{50} value of 8.7 nM and was selective against several CYPs. In combination with ATRA, R116011 enhanced ATRA-mediated antiproliferative activity in a concentration-dependent manner. In vivo, the growth of murine estrogen-independent TA3-Ha mammary tumors was significantly inhibited by R116010 at a dose as low as 0.16 mg/kg. A facile and large-scale preparation (commercial process) of R116010 (3) has recently been developed (Scheme 3).[71b]

Although these two agents are clearly superior to liarozole, it is unclear whether they are being developed further given that the last publication on R115866 and R116011 appeared in 2000 and 2002, respectively. Because of these compounds, high inhibitory potencies and selectivity for CYP26A1, they should be considered less likely to produce unwanted side effects as those experienced with liarozole therapy.

7. Azolyl retinoids and related compounds

The emerging role of RAMBAs as potential agents in the treatment of both hormone-dependent and

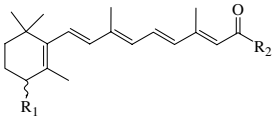


Scheme 3. Synthesis of R116010. Reagents and conditions: (i) aq HBr, Br_2; (ii) $ClCOCHClCH_3$, $AlCl_3$, CH_2Cl_2; (iii) aq Me_2NH, *i*-PrOH; (iv) (+)(D)-ditoluoyl tartaric acid, MeOH, refux, 6 h; (v) $NaBH_4$, *i*-PrOH, NaOH; (vi) CDI, imidazole, EtOAc.

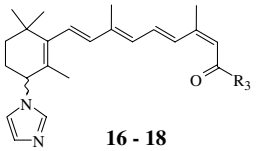
hormone-independent cancers[3a,12,97] has led to our interest in this area. Given the significance of azole group of many drugs that are P450 enzyme inhibitors,[98–100] we reasoned that introducing azole group at C-4 (the site of initial enzymatic hydroxylation) of ATRA should yield specific and potent inhibitors of ATRA 4-hydroxylase. Indeed, we very recently described the synthesis of a number of novel 4-azolyl ATRA derivatives, some of which are amongst the most potent inhibitors of this enzyme (Table 1, **4**–**14**, **16**–**18**).[12,101–103] This series of compounds were evaluated against microsomal preparations of male hamster liver (ATRA 4-hydroxylase CYPs) and microsomal preparations from T47D cells induced to express CYP26[103]. As shown in Table 1, all of our compounds exhibited potent inhibitory activity versus hamster liver microsomal CYPs at nanomolar concentration with IC_{50} values ranging from 0.009 to 119.00 nM. Our best compound **4** showed a 666,667-fold stronger inhibitory activity (IC_{50} = 0.009 nM) than liarozole (IC_{50} = 6000 nM) in the same assay. As expected, compounds with ATRA scaffold (**4**–**14**) were more potent than those with 13-CRA scaffold (**16**–**18**). Furthermore, the results suggest that the nature of C-4 substituent is important in determining affinity for the enzyme (compare IC_{50} values of **5**, **6**, **7** vs **12** and **13**; see Table 1) and also reveal that the corresponding methyl esters (**4**, **6**, and **7**) and imidazole amide (**10**) are significantly (24- to 48-fold) more potent than the corresponding free acids (**6**, **9**, and **10**). Compounds with 4-imidazole substitutions (**4**, **5**, and **10**) are most potent three inhibitors. Thus, it would appear that the imidazolyl nitrogen lone pair makes the strongest coordination to the iron atom of the heme in the active site of the enzyme. Compound **11** (IC_{50} = 43.7 nM) was synthesized to determine the effect of increasing the size of the terminal amide group. The modification resulted in a considerable 875-fold decreased potency compared to **10** (IC_{50} = 0.05 nM), suggesting limited steric tolerance at the active site of the enzyme. Because ketoconazole is used as a standard inhibitor of ATRA metabolism and 4-hydroxyphenyl retinamide (4-HPR, **15**) has recently been suggested as an inhibitor of ATRA metabolism,[104] we also tested these two compounds for comparison. As shown in Table 1, ketoconazole and 4-HPR are very weak inhibitors of this enzyme. Some compounds were further tested against microsomal preparations from T47D cells induced to express CYP26. The trend in activity against T47D CYP26 is different from those observed in the hamster liver microsomal CYPs. For example, **5** is the most active of the series against T47D CYP26, but it was less active than **4** against the hamster liver CYPs. Another interesting and surprising observation was that the racemate **4** was considerably more potent than the enantiomers (−)-**4** and (+)-**4** and quite unexpectedly, there was essentially no difference in activity between the two enantiomers.

The exceptionally potent inhibitory activities versus hamster liver microsomal CYPs of our RAMBAs have

Table 1. Structures and activities of novel azolyl RAMBAs (**4**–**18**)



4 - 15



16 - 18

Compound	R_1	R_2	R_3	IC_{50} value[a] (nM)	
				Hamster liver	T47D cells
4	–1*H*-Imidazole	–OMe	—	0.009 ± 0.0007	40.00 ± 3.00
(−)-**4**	–1*H*-Imidazole	–OMe	—	—	680.00 ± 20.00
(+)-**4**	–1*H*-Imidazole	–OMe	—	—	800.00 ± 25.00
5	–1*H*-Imidazole	–OH	—	2.33 ± 0.72	2.40 ± 0.12
6	–1*H*-1,2,4-Triazole	–OMe	—	2.00 ± 0.05	—
7	–4*H*-1,2,4-Triazole	–OMe	—	21.67 ± 0.30	—
8	–1*H*-1,2,4-Triazole	–OH	—	5.84 ± 0.48	—
9	–4*H*-1,2,4-Triazole	–OH	—	46.67 ± 3.30	—
10	–1*H*-Imidazole	–1*H*-imidazole	—	0.050 ± 0.002	5.20 ± 0.32
11	–1*H*-Imidazole	–4-Aminophenol	—	43.73 ± 4.70	—
12	–H	–1*H*-Imidazole	—	61.25 ± 6.50	—
13	–H	–1*H*-1,2,4-Triazole	—	51.67 ± 4.40	—
14	–Keto-oxime	–OMe	—	23.00 ± 1.63	—
16	—	—	–OH	119.0 ± 20.2	—
17	—	—	–1*H*-Imidazole	57.50 ± 8.5	—
18	—	—	–4-Aminophenol	176.67 ± 13.36	—
For comparison					
Liarozole (**1**)				6000.00 ± 30.00	—
Ketoconazole				34000.00 ± 170	—
4-HPR (**15**)	–H	–4-Aminophenol	—	31850.00 ± 150	—

'—,' not determined.

[a] Means ± SDM of at least two experiments.

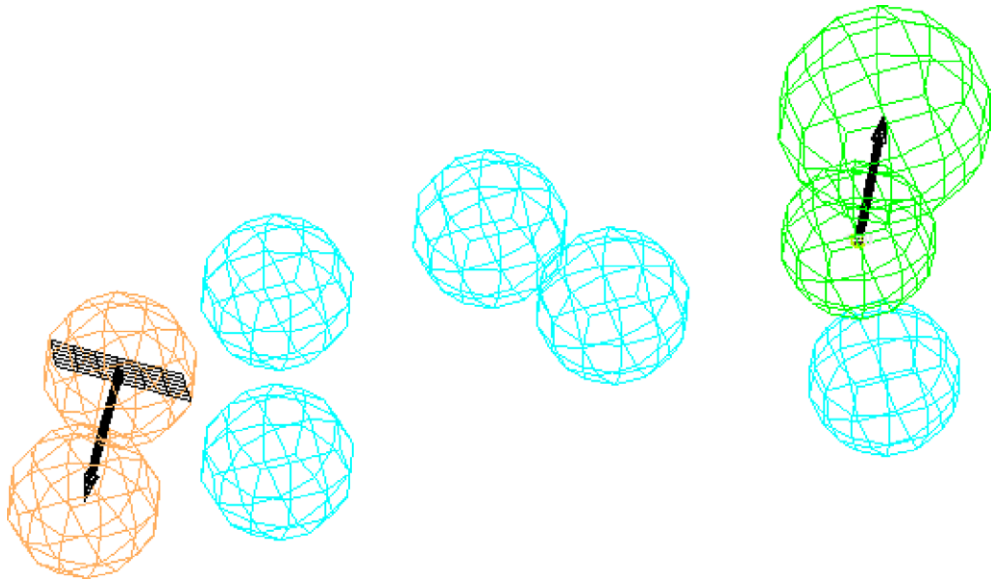


Figure 5. Common feature-based (catalyst/HipHop) pharmacophore model of novel RAMBAs. The model contains seven features: five hydrophobes (cyan), one hydrogen bond acceptor (green), and one aromatic ring (brown).

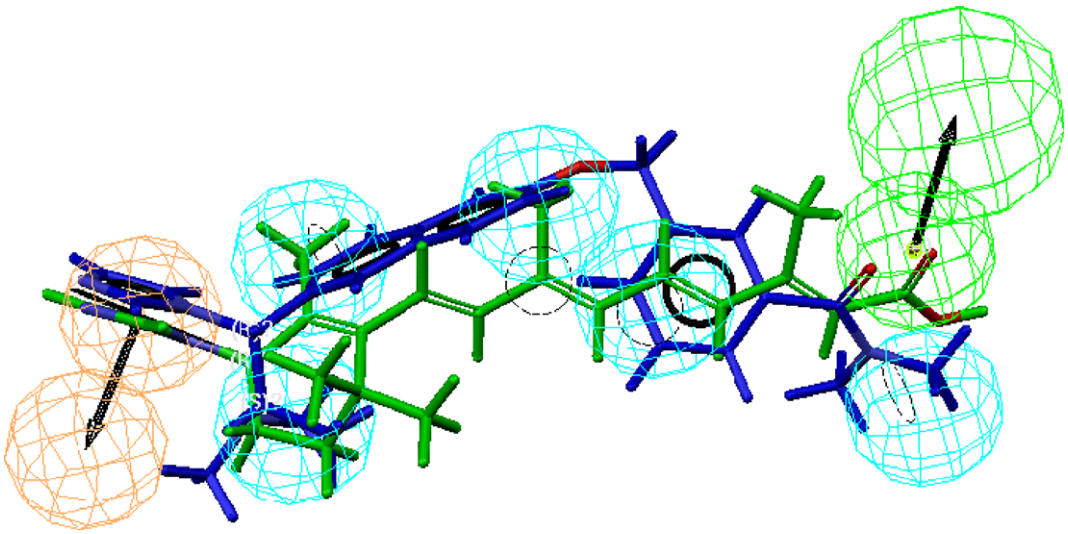
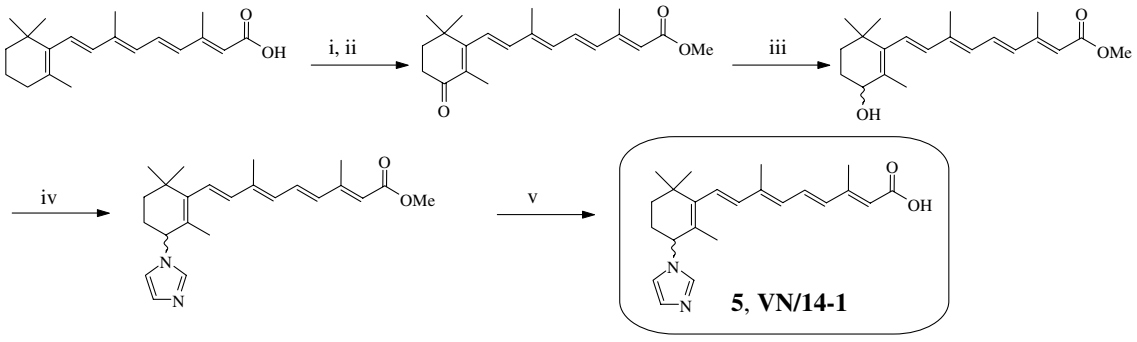


Figure 6. Alignment of common-feature pharmacophore model with compounds **4** (green) and **39** (blue).

enabled us to utilize the Catalyst molecular modeling program to create a common feature-based pharmacophore model (Fig. 5; consisting of five hydrophobic groups, one hydrogen bond acceptor, and one ring aromatic group) that can differentiate compounds as active or inactive inhibitors of this enzyme.[105] It is interesting to note that a recently identified RAMBA (**39**, IC_{50} = 14.4 nM, vide supra) by OSI Pharmaceuticals Inc. researchers[106] overlays perfectly with our most potent RAMBA, **4** (an isosteric relationship between the two compounds) and maps all the seven pharmacophores of our model (Fig. 6). Their current lead compound **35** (IC_{50} = 20.0 nM) maps to six of our seven pharmacophores.

The novel atypical RAMBAs, in addition to being highly potent inhibitors of ATRA metabolism in microsomal preparations and in intact human cancer cells (MCF-7, T47D, and LNCaP), also exhibit multiple biological activities, including induction of apoptosis and differentiation, retinoic acid receptor binding, and potent antiproliferative activity on a number of human cancer cells.[103,107–110] The combination of **11** with SAHA [a histone deacetylase inhibitor (HDACI)] inhibited LNCaP cell proliferation in an additive manner compared with single agents.[111] In a recent study, **5** was shown to be a potent microsomal human placental aromatase inhibitor (IC_{50} = 8.0 pM) and it significantly inhibited the growth of MCF-7Ca and LTLC (letrozole-resistant MCF-7Ca) with IC_{50} values of 8.5 and 0.83 nM, respectively.[108] Amongst these RAMBAs, compound **5** has been shown to significantly suppress MCF-7 tumor growth (~90.4% vs control, $P < 0.0005$ at 66.0 μM/kg/day dose) in female ovariectomized nude mice. In addition, the molecular mechanisms underlying the activities of these novel RAMBAs in



Scheme 4. Synthesis of compound **5** (**VN/14–1**). Reagents and conditions: (i) $TMSCHN_2$/benzene, MeOH, Ar, rt; (ii) activated MnO_2/CH_2Cl_2, rt; (iii) $NaBH_4$, MeOH, rt; (iv) CDI, CH_3CN, rt; (v) 10% KOH/MeOH, Ar, reflux.

human breast and prostate cancer models have been reported.[107–110] These atypical RAMBAs are yet to be tested as potential agents for the treatment of dermatological diseases. In this series of novel RAMBAs, compound **5** (code name **VN/14–1**) has been identified as the lead anticancer agent, and its synthesis has been reported (Scheme 4).[101a,102,103] An Australian patent[112] has recently been insured to protect these compounds and several other patents are pending.

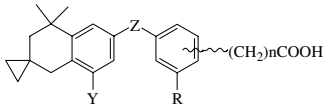
8. Benzeneacetic acid derivatives

Researchers at Allergan Sales Inc. have described in about 12 US patents on the synthesis and evaluation of several new benzeneacetic acid derivatives as inhibitors of human CYP26 stably transfected in HeLa cells.[72] Although they did not disclose the inhibitor design strategy, their compounds appear to overlay in a complementary fashion with the structure of ATRA. The structures and CYP26 inhibitory activities of their most potent inhibitors (**19–27**) are presented in Table 2. These compounds have a linker or tethering group designated Z covalently connecting an aromatic moiety and substituted chromain. The most potent CYP26 inhibitor was **23** (IC_{50} = 14 nM). The synthesis of this compound has also been reported (Scheme 5).[72] With regard to structure–activity relationship the preferred linker is the acetylene moiety and aromatic *para* substitution of terminal carboxylic acid with a one-carbon spacer. Introduction of fluorine in the aromatic ring and substitution of cyclopropyl ring at position Y of chromain moiety result in increase in potency. These researchers also demonstrated that their RAMBAs are not agonists or antagonists for both the RAR and RXR receptors. In addition, topical application of some of these agents caused an increase in the endogenous levels of ATRA that resulted in ATRA-induced irritation in skin of hairless mice. To the best of our knowledge, these agents have not been investigated in preclinical in vitro or in vivo cancer models. Because of the potent CYP26 inhibitory activities of these agents, they may be considered as potential therapeutics that may be useful in dermatology.

9. 2,6-Disubstituted naphthalenes

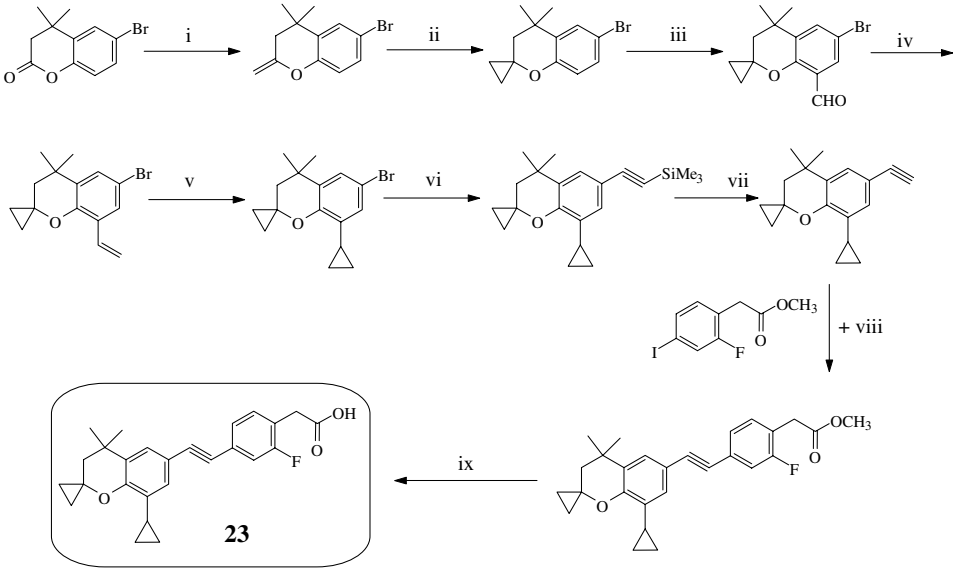
In the most recent publication on novel RAMBAs, researchers of OSI Pharmaceuticals Inc. reported the synthesis of a series of 2,6-disubstituted naphthalenes (**28–42**, Table 3) as inhibitors of microsomal preparations

Table 2. Structures and activities of benzeneacetic acid derivatives (**19–27**)



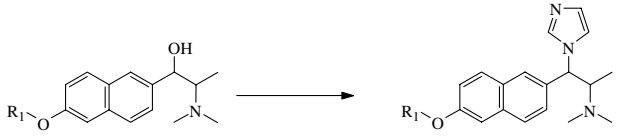
19 - 27

Compound	Y	Z	R	*n*	Position of $(CH_2)_nCOOH$	CYP26, IC_{50} (nM)
19	H	—≡—	H	0	4	1700
20	H	—≡—	H	1	4	190
21	H	—≡—	F	0	4	270
22	Cyclopropyl	—≡—	H	1	4	33
23	Cyclopropyl	—≡—	F	1	4	14
24	Cyclopropyl	—≡—	H	0	4	50
25	Cyclopropyl	—≡—	F	0	4	22
26	Cyclopropyl		H	1	3	1600
27	Cyclopropyl		H	1	4	180



Scheme 5. Synthesis of compound **23**. Reagents and conditions: (i) Tebbe reagent; (ii) CH_2I_2, Et_2Zn, CH_2Cl_2; (iii) $TiCl_4$, $Cl_2CH(OCH_3)$, CH_2Cl_2, $PhCH_3$; (iv) $CH_2{=}PPh_3$, THF; (v) CH_2N_2, $Pd(OAc)_2$, ether; (vi) $Pd(PPh_3)_2Cl_2$, HCC–TMS, CuI, NEt_3, THF, 70 °C; (vii) K_2CO_3, MeOH; (viii) $Pd(PPh_3)_2Cl_2$, THF, NEt_3, CuI; (ix) IM NaOH, EtOH, 80 °C.

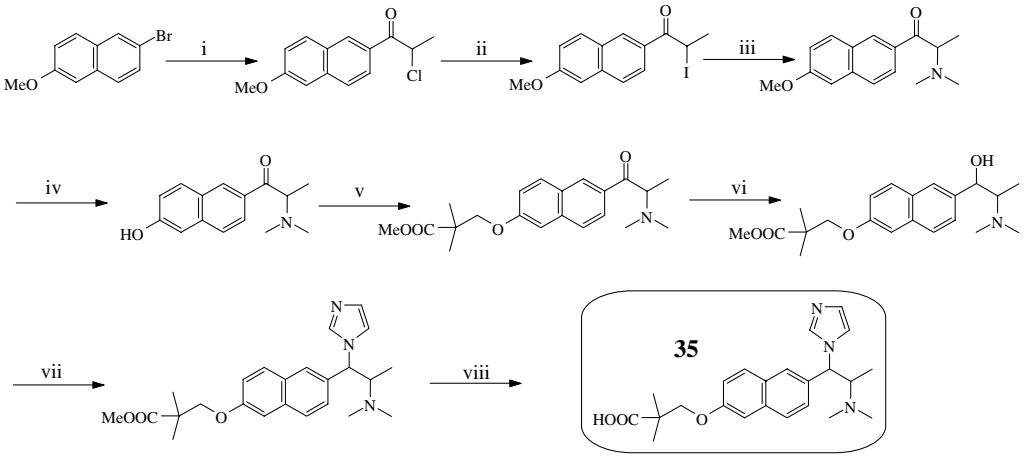
Table 3. Structures and activities of 2,6-disubstituted naphthalenes (**28**–**42**)



Aminoalcohol **28 - 42**

Compound	OR^1/O–Z–CO_2H/–O–Z–$CONR^2R^3$	Stereochemistry	CYP26 in T47D (IC_{50}, nM)
28	(O)–CH_2CO_2H	Mix	335
29	(O)–CH_2–Ph–4-(CH_2CO_2H)	Mix	25.0
30	(O)–CH_2–Ph–4-(OCH_2CO_2H)	*syn*	8.00
31	(O)–CH_2–Ph–3-(CO_2H)	*syn*	3.50
32	(O)–CH_2–Ph–3-(CO_2H)	*anti*	6.30
33	(O)–CH_2–Ph–4-(CO_2H)	*syn*	3.30
34	(O)–CH_2–Ph–4-(CO_2H)	*anti*	12.0
35	(O)–$CH_2C(CH_3)_2CO_2H$	*syn*	20.0
36	(O)–$CH_2C(CH_3)_2CO_2H$	*anti*	46.0
37	(O)–CH_2–Ph–3-($CONH_2$)	*syn*	48.0
38	(O)–CH_2–Ph–3-($CONHCH_3$)	*syn*	37.0
39	(O)–CH_2–Ph–3-($CON(CH_3)_2$)	*syn*	14.4
40	(O)–$CH_2C(CH_3)_2CONH_2$	*syn*	47.0
41	(O)–$CH_2C(CH_3)_2$–($CONHCH_3$)	*syn*	54.0
42	(O)–$CH_2C(CH_3)_2$–($CON(CH_3)_2$)	*syn*	35.0

from T47D cells induced to express CYP26.[106] These compounds are based on fusion of the imidazolyl propylamino moiety of R116010 (**3**)[71] with naphthalene core with a substitution (called CYP26 selectivity handle) at the 6-position. This series of compounds (Table 3) demonstrated that the *syn*-isomers were generally more potent than the *anti*-isomers. The imidazolyl moiety proved to be a critical element for CYP26 activity as seen by the lack of activity in the aminoalcohol precursors (Table 3), but a variety of tethers and substituents were tolerated. While in some cases only a moderate degree of selectivity for CYP3A4 was observed, the terminal carboxylate moiety in their lead compounds, **33** and **35**, afforded a large degree of selectivity (CYP3A4 IC_{50} values for **33** and **35** were 640 and 6300 nM, respectively). Conversion of the carboxylate moieties of **33** and **35** to their corresponding amides, **37**–**42**, caused a reduction in both CYP26 inhibitory potency and selectivity for CYP3A4. These two compounds also inhibited (nanomolar range) the growth of T47D breast cancer cells as well as the AT6.1 rat prostate cancer cells. The excellent pharmacokinetic properties of **35** (IC_{50} = 20 nM) and



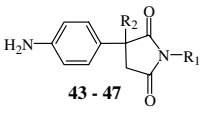
Scheme 6. Synthesis of compound **35**. Reagents and conditions: (i) Mg/THF, $CH_3CHClCOCl$, −78 °C; (ii) NaI, acetone; (iii) Me_2NH, MeOH; (iv) HBr/AcOH, 120 °C; (v) DIAD, Ph_3P, $MeOOC(CH_3)_2CH_2Br$; (vi) $NaBH_4$, MeOH; (vii) CDI, CH_3CN, 65 °C; (viii) NaOH, THF/H_2O.

its favorable selectivity for CYP26 over CYP3A4, 1A2, 2D6, and 2C9 make it a suitable candidate for further development as a therapeutic agent in oncology and dermatology. The synthesis of compound **35** is outlined in Scheme 6.

10. Miscellaneous structures

Researchers at the University of Cardiff, UK, have had a long interest in the development of inhibitors of ATRA metabolism. These investigators first reported on a series of (±)-3-(4-aminophenyl)pyrrolidine-2,5-diones substituted in the 1-, 3-, or 1,3-position with an aryl or long chain alkyl function and found them to be relatively weak inhibitors of ATRA metabolism by rat liver microsomes (68-80% inhibition at 100 μM) compared to ketoconazole (85% inhibition) (Table 4: **43-47**).[113] Although there appears to be no obvious structure activity relationship (SAR) in the limited series of compounds, the unsubstituted compounds were found to be inactive. A related phenylamine compound [(±) teralone A, **48**, Fig. 7] based on the teralin structure was found to be 2-fold more potent than ketoconazole (i.e., IC_{50} = 12.75 vs 22.15 μM).[114] Interestingly, the (+)- and (−)- forms of **48** had similar activity, and it was ~8-fold more potent than the previously reported compound **43**. In a recent study, Angotti et al. showed that intraperitoneal administration of **48** (100 mg/kg) to rats induced a marked and transient increase (from 0.11 to 0.15 ng/ml) of endogenous ATRA levels in plasma.[115] Another recent related study by the University of Cardiff group reported on a series of tetralone derivatives. The most potent compounds versus cellular MCF-7 CYP26 were 2-(hydroxybenzyl)-6-methoxytetralone (**49**) and the corresponding benzylidene (**50**) with IC_{50} values of 7 and 5 μM, respectively, which were comparable with liarozole (IC_{50} = 7 μM).[116] These compounds were further investigated with a CYP26A1 homology model.

Table 4. Structures and activities of aminophenyl pyrrolidines (**43–47**)



43 - 47

Compound	R_1	R_2	% inhibition[a]
43	Ph–	H	75
44	C_6H_{13}	H	79
45	H	C_5H_{11}	71
46	C_7H_{15}	H	80
47	C_6H_{13}	Ph–NH_2	68
Ketoconazole			85

[a] % inhibition versus rat liver microsomal CYPs.

From another series of 70 azoles, compound **51** (Fig. 7) was the most potent and was equipotent with ketoconazole.[117] The same group also examined some 1,2-ethanediones, 2-hydroxyethanones, and 1-ethylenedioxyethanones based on aryl-substituted 1,2-diphenylethane.[118] This study identified the 2-hydroxy ethanone (**52**, Fig. 7) with a 1-(4-dimethylaminophenyl) substituent as the most potent compound for rat liver microsomal enzyme (IC_{50} = 52.1 μM; ketoconazole, 2.8 μM). However, some compounds in this series were found to be moderate inhibitors of the ATRA-induced enzymes in cultured human genital fibroblasts. Finally, another recent report identified seven compounds (**53–59**, Fig. 7) that were equipotent with ketoconazole.[73]

It should be stated that this group has investigated several compounds so far, with at least five different scaffolds as inhibitors of ATRA metabolism. As their most potent inhibitors are at best equipotent with ketoconazole (a weak inhibitor of ATRA-hydroxylase, cf. Table 1), it would appear that these series of compounds and possibly their derivatives are unlikely to yield potent inhibitors of this enzyme complex. Therefore, future inhibitor design strategies with these scaffolds would not be wise.

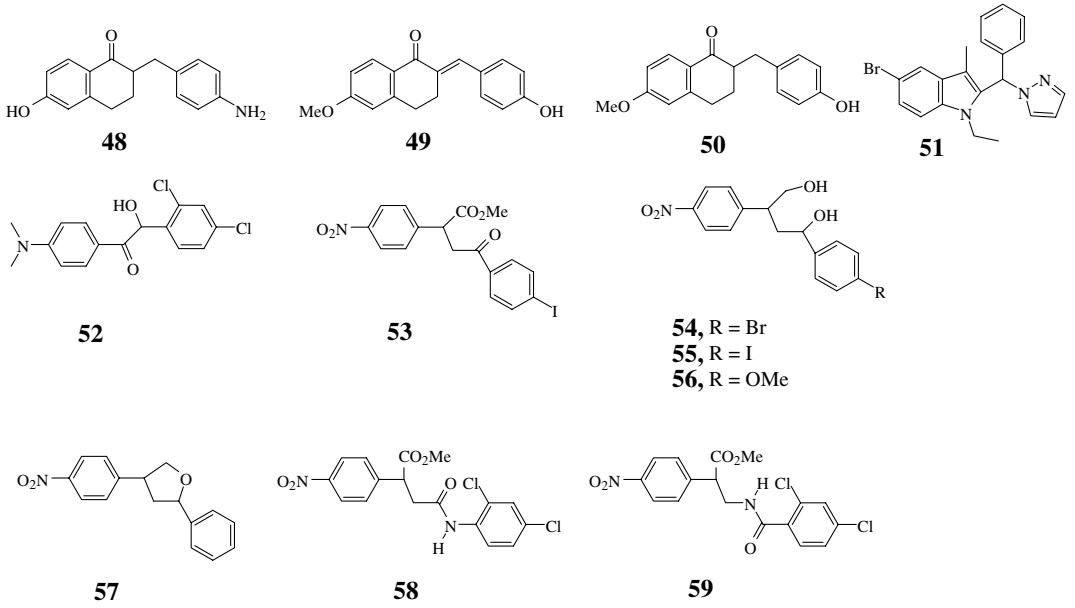


Figure 7. Structures and activities of **48**–**59**.

11. Concluding remarks

Retinoid therapy is based on differentiation of premalignant and malignant cells with the potential of redirecting the cells toward their normal phenotype. However, exogenous retinoid therapy is yet to fulfill the expectations raised by in vitro and in vivo studies in cancer models in the clinics. It is evident from this review that there is currently a high level of interest in the rational design of new RAMBAs, several of which have IC_{50} values in the nanomolar range. The recent approval of a first-generation RAMBA, liarozole, for the treatment of congenital ichthyosis will undoubtedly boost research efforts to develop other potentially useful RAMBAs. Modulation of endogenous ATRA and possibly its natural sterioisomers with the use of new RAMBAs may present an additional cancer therapy strategy and treatment of dermatological diseases. Just as with ATRA, it will be of interest to study RAMBA-HDACI synergy and the possibility of restoring retinoid signaling in ATRA-resistant cells. In addition to HDAC (particularly HDACs 3 and 4) inhibition, reversal of DNA hypermethylation by demethylating agents has been shown to restore ATRA-mediated differentiation/growth inhibition in some leukemia and solid tumor cells in vitro. Thus, studies on the molecular basis and selectivity of the complexes that modulate epigenetic events during tumorigenesis/dermatological insults and their effects on differentiation and apoptogenic pathways might provide new tools to fight cancer and dermatological diseases.

Acknowledgments

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