Perspective

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Miniperspective

Synthetic Retinoids: Recent Developments Concerning Structure and Clinical Utility

Hiroyuki Kagechika*,† and Koichi Shudo§

School of Biomedical Science, Tokyo Medical and Dental University, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan, and Research Foundation Itsuu Laboratory, 2-28-10 Tamagawa, Setagaya-ku, Tokyo 158-0094, Japan

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Introduction

Small hydrophobic molecules such as steroid hormones and activated vitamins A and D control various biological phenomena, including growth, development, metabolism, and homeostasis, by binding to and activating specific nuclear receptors.[1] Nuclear receptors are ligand-inducible transcription factors that regulate the expression of their target genes. In the past 2 decades, the physiological functions of nuclear receptors and their specific ligands have been clarified in detail. There are reported to be 48 members of the nuclear receptor family encoded in the human genome,[2] and various endogenous and synthetic ligands for nuclear orphan receptors have been reported. Thus, nuclear receptors have become one of the most significant molecular targets for drug discovery in the fields of cancer, metabolic syndrome, autoimmune diseases, and so on.

Retinoids are natural and synthetic analogues of retinoic acid, an active metabolite of vitamin A, and are specific modulators of cell proliferation, differentiation, and morphogenesis in vertebrates.[3,4] The term "retinoid" is first defined by the chemical structure of vitamin A but is now recognized as the biological term for the ligands of two classes of nuclear receptors that mediate the biological activities of retinoic acid, that is, retinoic acid receptors (RARs) and retinoid X receptors (RXRs), as proposed by Sporn et al. in 1985.[5] Modern medicinal chemistry of retinoids started in the 1970s, mainly focusing on their chemopreventive and therapeutic utility in the fields of oncology and dermatology.[6,7] Despite the beneficial activities of retinoids, the scope of retinoid therapy is still limited owing to high toxicity, and only a few retinoids, such as all-trans retinoic acid (ATRA, **1a**, Figure 1) and **2** (etretinate) for the treatment of psoriasis,[8] have been clinically used until recently.

Among various nuclear receptor ligands, retinoids are unique. There are two classes of retinoid nuclear receptors, RARs and RXRs, both having three subtypes (α, β, and γ). Endogenous ligands for RARs and RXRs were identified as ATRA and 9-*cis*-retinoic acid (9cRA, **1b**), respectively, while 9cRA can bind to RARs with as high affinity as to RXRs.[9,10] Thus, 9cRA is a pan-agonist for all six retinoid nuclear receptors. Most of the retinoidal activities are elicited by the binding of retinoids to the RAR site of RXR−RAR heterodimers. RXRs are the silent partners of RARs, and RXR agonists alone cannot activate the RXR−RAR heterodimers, though RXR agonists allosterically increase the potencies of RAR ligands (retinoid synergism).[11−13] Besides so-called retinoidal activities, RXRs have significant roles in nuclear receptor actions by heterodimerizing with various nuclear receptors. The heterodimeric partners of RXRs include endocrine nuclear receptors, such as RARs, vitamin D_3 receptor (VDR), and thyroid hormone receptors (TRs), and some orphan nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), and farnesoid X receptors (FXRs). Nuclear receptors of the latter class have proven to be key

* To whom correspondence should be addressed. Phone: +81 3 5280 8032. Fax: +81 3 5280 8127. E-mail: kage.omc@tmd.ac.jp.
† Tokyo Medical and Dental University.
§ Research Foundation Itsuu Laboratory.

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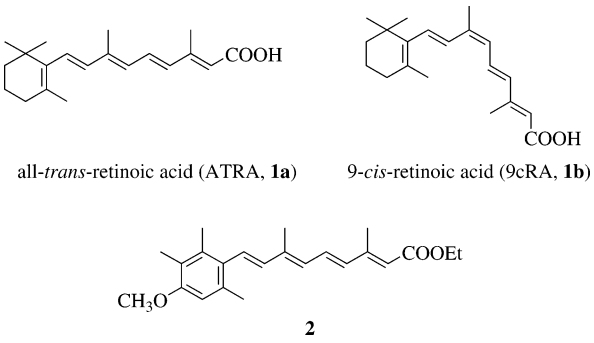
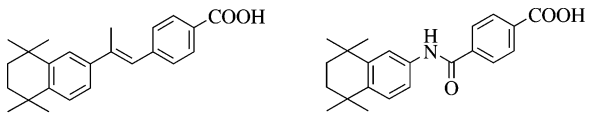


all-*trans*-retinoic acid (ATRA, **1a**) 9-*cis*-retinoic acid (9cRA, **1b**)

2

Figure 1.



3 **4**

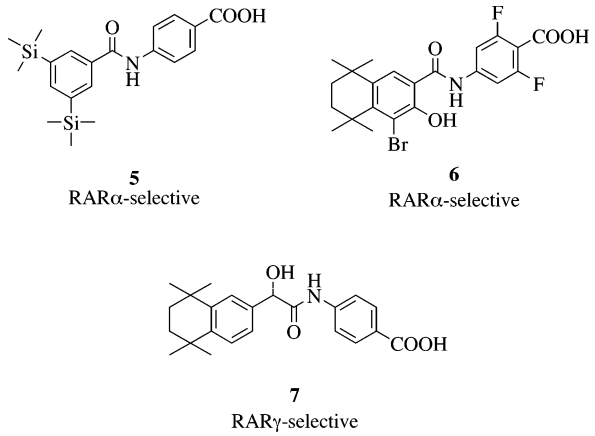
Figure 2.

regulators of carbohydrate, lipid, and cholesterol metabolism.[14] Since RXR agonists alone can activate these heterodimers, RXR agonists act just like the partner receptor's agonists and have potential as drugs for these metabolic diseases. With this background, compounds with various selectivities among RARs and RXRs have been developed in order to separate the pleiotropic retinoidal activities. In this paper, we discuss the structural evolution of RAR- and RXR-specific ligands and their potential utility in clinical applications.

RAR-Selective Ligands: Retinoids

Retinoic acids (**1**) consist of a cyclohexenyl ring, a polyene chain, and a terminal carboxyl group. Earlier work on the development of retinoid analogues afforded aromatic compounds without the unstable polyene structure of retinoic acids, as RAR agonists. Thus, compound **3** (TTNPB, Figure 2) is the first stable and potent RAR-selective agonist (Figure 1). The successful modifications of retinoid structures with aromatic rings and the introduction of heteroatoms afforded potent RAR-selective agonists with remarkable chemical stability and favorable bioavailability, such as compound **4** (Am80, Figure 2).[15] Following the discovery of the three RAR subtypes, retinoids selective to each RAR subtype have been reported. For example, **4** is RARα (and β) selective, and more RARα-selective retinoids, such as **5** (Am555S)[16] and **6** (AGN-193836), have been developed by using **4** as a lead compound (Figure 3).[17] Recent progress in crystallographic studies on nuclear receptor ligand binding domains (LBD) has enabled us to discuss ligand−receptor interactions at the molecular level.[18] Compound **7** (BMS-961) was developed as an RAR-γ-selective retinoid, which distinguishes small differences of amino acid residues in the LBD among the three RAR subtypes.[19]

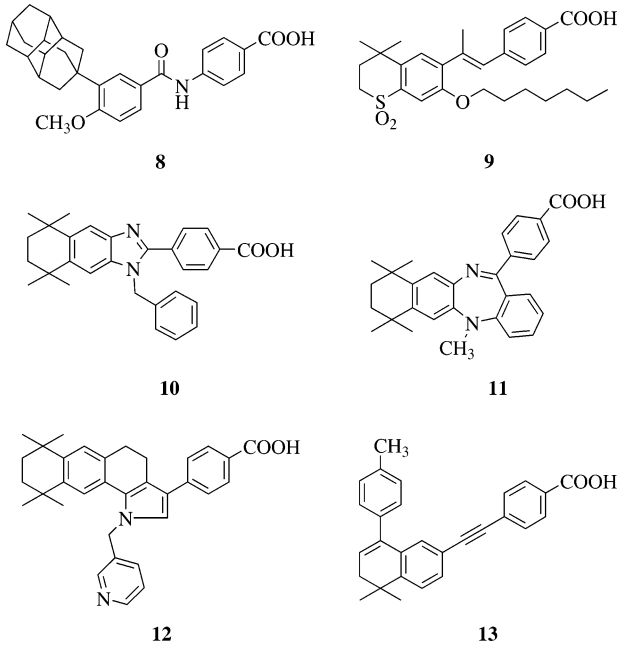
Various RAR antagonists have also been developed (Figure 4).[7] Compound **8** (TD550) bearing a bulky diamantyl group at the hydrophobic part is the first RAR antagonist,[20] and **9** (Ro-41-5253, Figure 3) was reported as the first RARα-subtype selective antagonist.[21] Among two RAR antagonists bearing a heterocyclic ring, **10** and **11** (LE135), a dibenzodiazepine derivative, **11** exhibited RARβ selectivity, although the



5 RARα-selective **6** RARα-selective

7 RARγ-selective

Figure 3. RAR subtype-selective agonists.

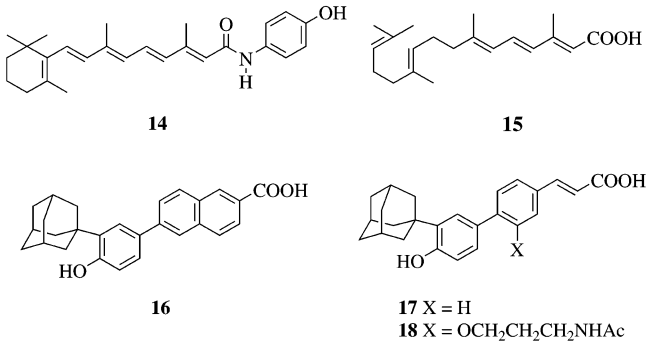


8 **9** **10** **11** **12** **13**

Figure 4. RAR antagonists.

RAR binding affinities of these two subtype-selective antagonists are not high. Several RAR antagonists with high affinity for RARs, similar to that of ATRA, have also been developed. Examples include **12** (ER-27191) and **13** (AGN-193109). These RAR antagonists generally inhibited the biological activities of retinoids, but in some cases, RAR antagonists may act as RAR agonists. For example, **11** exhibited anti-AP-1 activities and inhibition of IL-1-induced IL-6 production, like ATRA or synthetic RAR agonists.[22,23] These activities should be mediated by RARs but not caused by direct regulation of the gene expression at retinoic acid response elements (RARE).

There is another class of compounds, called atypical retinoids. Atypical retinoids have a retinoid-like structure, and some exhibit retinoid activities, but they also have potent retinoid nuclear receptor-independent activities.[24] Compound **14** (4-HPR, Figure 5) is an anilide derivative of ATRA, which was first developed as an RAR ligand and was found to reverse the keratinization of vitamin A deficient tracheal organ cultures. Compound **14** inhibited the growth of ATRA-resistant cells such as HL-60R and also induced the apoptosis of various cancer cell lines independently of RARs. Com-



14 **15** **16**

17 X = H
18 X = $OCH_2CH_2CH_2NHAc$

Figure 5. Atypical retinoids.

pound **14** exhibited significant cancer chemopreventive effects, such as prevention of second breast carcinoma development after surgery. Compound **15** (E5166) is also a unique retinoid-related molecule, called "acyclic retinoid".[25] Compound **15** inhibited experimental liver carcinogenesis and induces the apoptosis of human hepatoma-derived cells.[26] Oral administration of **15** suppressed the development of second primary tumors in cirrhotic patients who underwent potentially curative treatment of hepatocellular carcinoma.[27] There was no severe adverse effect, and the short-term administration of **15** for only 12 months brought a long-term effect over several years. Atypical retinoids have potential as chemopreventive and therapeutic agents against cancers, although their precise mechanisms of action on cell proliferation and apoptosis remain unclear.[28] Various related compounds, such as **16** (AHPN) and **17** (ST1926), have been reported. Compound **16** was first developed as an RARγ-selective retinoid but showed growth inhibition and apoptosis induction with ATRA-resistant cancer cells. Compound **17**, which cannot activate RARs, exhibited antiproliferative effects on a large panel of human tumor cells, as well as inhibition of tumor growth in vivo following oral administration.[29] Further, Dawson et al. reported that compound **18** selectively inhibited cell apoptotic events but not the proliferative events induced by **16**, which suggests that two distinct signaling pathways exist in actions of **16**, that is, suppression of cell proliferation by the induction of cell cycle arrest, and the induction of apoptosis.[30] These retinoid-related compounds would be useful as less toxic drugs in cancer treatment and chemoprevention.

RXR-Selective Ligands: Rexinoids

An endogenous ligand for RXRs was identified as 9cRA, but 9cRA is a potent RAR agonist as ATRA. Compound **19** (SR11237, Figure 6) is the first RXR-selective agonist, and **20** (HX630, Figure 2) was reported as a retinoid synergist, and then its RXR-selective agonistic properties were elucidated. Since then, various RXR-selective agonists have been developed, such as **21** (LGD1069) and **22** (LG268) (Figure 6), and the new term "rexinoid" was proposed for RXR-selective agonists. So far, no RXR ligand with apparent subtype selectivity has been reported. RXRs interact with various factors, including heterodimer partners of nuclear receptors, corepressors, and coactivators. Owing to such complex protein−protein interactions, different RXR agonists do not necessarily exhibit the same biological activities.

Both **20** and **23** (PA024) have been developed as RXR-selective agonists[15] and are inactive alone in the HL-60 cell differentiation assay but strongly enhance the activity of low concentrations of **4**. During the induction of cell differentiation, the combinations of **4** with **20** and with **23** showed different gene expression profiles.[31] Close inspection of DNA microarrays indicated that **20** and **23** had different effects on the apoptosis of HL-60 cells when combined with **4**. Thus, the combination of **4** with **23**, not with **20**, produced a gene expression profile similar to that seen with 9cRA (an RAR−RXR pan-agonist) and increased the induction of HL-60 cell apoptosis. Although the nature of the difference in action mechanisms is unclear, this result seems significant for retinoid therapy using combinations of RAR and RXR agonists.

Another difference between RXR agonists lies in their ability to distinguish heterodimer partner receptors. For example, compound **23** activated both PPARγ−RXR and RXR−LXRα heterodimers, while **20** activated only PPARγ−RXR heterodimer and did not affect the activation of the RXR−LXRα heterodimer even in the presence of an LXRα agonist.[32] Only **23** enhanced the expression of ATP-binding cassette transporter (ABCA1) and apoA-1-dependent cholesterol release in undifferentiated THP-1 cells or RAW264 cells, whereas both RXR agonists are active in differentiated THP-1 cells in which the PPARγ mRNA level is up-regulated. Compound **20** activated the PPARγ−RXR heterodimer, elevating the LXRα level and thereby enhancing ABCA1 expression and the resultant HDL generation.[33] One of the undesirable effects of RXR agonists is an increase of serum triglyceride levels. This effect is considered to be mediated by RXR−LXR heterodimer-enhanced lipogenesis via induction of SREBP-1c expression. If this is the case, **20**, which lacks the ability to activate RXR−LXR heterodimer, may be a promising agent for the treatment of metabolic syndrome.

RXR antagonists also exhibited heterodimer partner receptor-dependent behavior. **24** (LG100754, Figure 6) was first developed as an RXR homodimer antagonist and elicited RXR agonistic activities in RXR−RAR and PPARγ−RXR heterodimers. Thus, compound **24** showed antidiabetic activity mediated by PPARγ−RXR activation, like RXR agonists.[34,35] During investigations on the structure−activity relationships of RXR ligands with the trienecarboxylic acid structure, **25** (LG101506) was recently found as an RXR ligand that selectively activated PPARγ−RXR heterodimer and did not show retinoid synergism in RXR−RAR actions or activation of RXR−LXR heterodimer.[36,37] Compound **25** showed a potent ability to lower the glucose level in db/db mice and did not elevate the triglyceride level in Sprague-Dawley rats, whereas the level was significantly increased when an RXR agonist **22** was used.

Compound **26** (HX531), a derivative of RXR agonist **20**, exhibited RXR antagonistic activity and inhibited both RXR transactivation and HL-60 cell differentiation mediated by RXR−RAR heterodimers. Interestingly, **26** acted as an antagonist toward the PPARγ−RXR heterodimer but not toward the PPARα−RXR heterodimer in an in vitro transactivation assay.[38] Thus, **26** selectively inactivated PPARγ−RXR action in adipocytes and did not affect PPARα−RXR action in liver, consequently eliciting antidiabetic and antiobesity effects in KKAy mice on a high-fat diet. Compound **27** (PA452) is a more

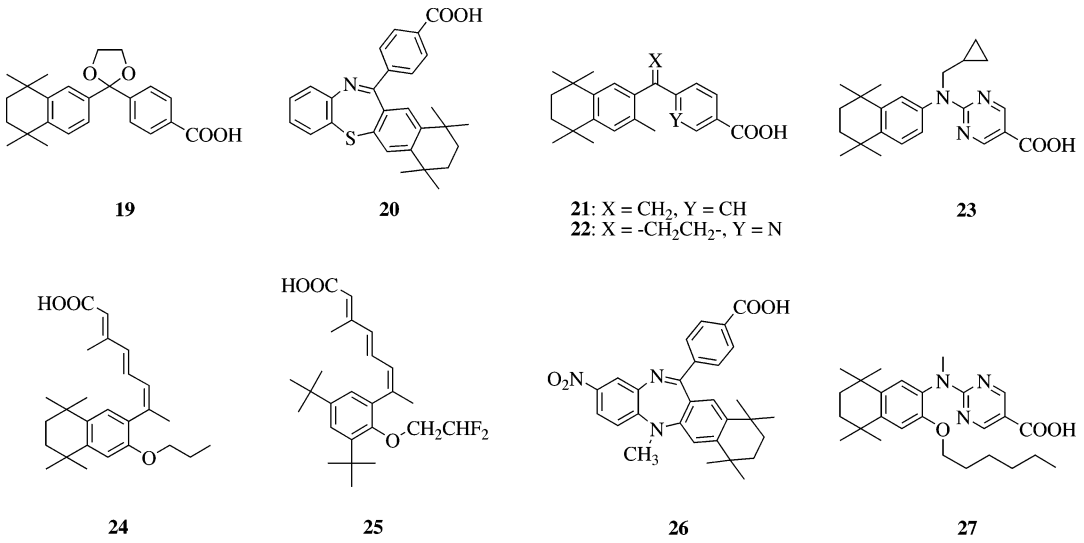


Figure 6. RXR-selective agonists and antagonists

RXR-selective antagonist than **26**.[39] Their antagonistic activities in RAR−RXR heterodimer action are different from each other. Compound **27** did not affect the differentiation-inducing activity of **4** alone but inhibited the retinoid synergistic activity of **23** in combination with a low concentration of **4**. In this case, the inhibition did not reach the basal level, and the percentage of differentiated cells in the presence of a high concentration of **23** was more than that induced by **4** alone. Compound **26** inhibited both **4** alone and the combination of RAR and RXR agonists to the basal level. Thus, some RXR ligands seem to change the agonistic and antagonistic activities, depending on the heterodimer partners and/or related cofactors, even in the case of permissive RXR heterodimers.[40]

Retinoids with Unique Structures: Novel Bioisosters of the Carboxyl Group

As described above, knowledge of the crystal structures of nuclear receptor LBDs enabled the structure-based molecular design of nuclear receptor ligands, although various interactions between nuclear receptors or between nuclear receptors and corepressors/coactivators should be taken into consideration. Various nuclear receptor ligands have been developed by computer-assisted methods using virtual libraries or molecular databases.[41,42] Retinoid antagonism can be understood on the basis of docking studies of the ligand with the crystal structures of LBDs in agonist and/or antagonist binding conformations.[43] Small molecules that inhibit coactivator binding to nuclear receptors (estrogen receptors) were also developed by structure-based design, although the binding constants are still inadequate.[44]

Most of the classical RAR and RXR ligands (Figures 1−6) are derivatives of polyenecarboxylic acids or aromatic carboxylic acids. For example, retinoidal benzoic acids are represented by the general structure **28**, which consists of three parts, that is, the hydrophobic aromatic ring, benzoic acid moiety, and the linking group between them (Figure 7). Earlier studies by us and others indicated that the carboxyl group in the retinoid structure cannot be replaced by typical bioisosteric functional groups, such as sulfonamide, tetrazole, and so on, without a significant decrease or loss of activity.[15,45] Computer-assisted design of RAR and RXR ligands using a focused virtual library showed that some thiazolidinediones can bind to RAR and RXR LBDs. Thiazolidinedione is a useful structural moiety for antidiabetic agents, such as pioglytazone and rosiglytazone, whose molecular target is PPARγ.[46,47] As other types of PPARγ ligands, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 and some nonsteroidal antiinflammatory drugs (NSAIDs) were identified. Recently, synthetic (putative metabolic) analogues of docosahexaenoic acid were reported to be potent PPARγ agonists and to exhibit antidiabetic activity in vivo.[48] These studies indicated that the carboxyl group of these PPARγ ligands can mimic the thiazolidinedione moiety of pioglytazone and rosiglytazone at the ligand binding pocket. On this basis, thiazolidinedione was introduced into the retinoid structure. Since the compounds bearing all-trans and 9-cis types of polyene thiazolidinediones showed weak but significant retinoidal activities, a more efficient virtual library screening using software developed by Itai et al. was conducted.[49] Construction of a virtual library of thiazolidinediones whose general structure is **29** (Figure 7), including about 30 000 molecules with different substituents (R_1−R_5 and X groups), followed by computational three-dimensional docking with each RXR LBD, afforded about 300 thiazolidinediones as RXR agonist candidates. Among them, **30** (TZ335) was proven to be a potent RXR agonist by synthesis and biological evaluation.[50] Similar computer-assisted ligand search by using a database of commercially available molecules also afforded a unique RAR ligand candidate **31** without a carboxyl group.[51] The docking study showed that the benzofloxane ring may mimic the benzoic acid group of retinoids. Although **31** had weak RAR binding affinity, the benzofloxane **32** bearing a hydrophobic aromatic ring exhibited significant RAR agonistic activity.

Another unique non-carboxylic-acid-type retinoid is a tropolone derivative, **33** (Tp80).[52] Tropolone, 2-hydroxy-2,4,6-cycloheptatrien-1-one, is an isomer of benzoic acid and is a seven-membered, nonbenzenoid aromatic molecule possessing three double bonds conjugated with a carbonyl group. Compound **33**, an isomer

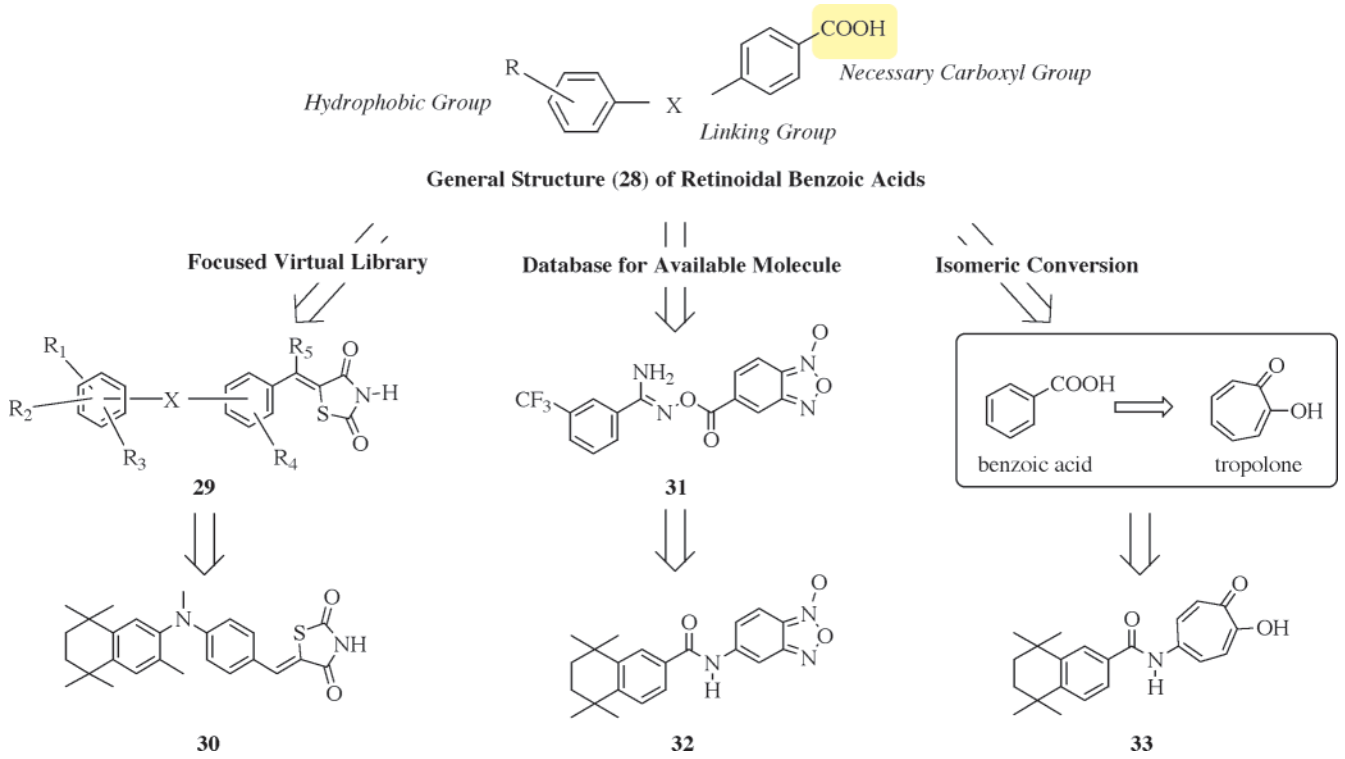


Figure 7. Bioisosteric conversion of the carboxyl group of retinoid structure.

of **4**, induced HL-60 cell differentiation into mature granulocytes in a manner similar to **4** except that the maximum response induced by a high concentration of **33** was about half of that by **4**. The potency of **33** was remarkably enhanced by combination with an RXR agonist, **20**, the degree being larger than that expected from the combination of **4** with **20**. The partial agonistic activity of **33** seems to arise from its dual function as an RAR agonist and RXR antagonist.

In these non-carboxylic-acid-type ligands, the acidic property of the bioisosteric functional groups is important, besides their molecular shape. Thiazolidinedione and tropolone have pK_a values of about 6.7−7.0. Other cyclic imide derivatives, such as phthalimide, succinic imide, and uracil groups having larger pK_a values (8−11), cannot replace the carboxyl group of the retinoid structure without loss of activity. These non-carboxylic-acid-type RAR−RXR ligands shown in Figure 7 may exhibit different pharmacological behaviors from classical compounds, as well as unique biological activity, and they may provide further scope for clinical applications.

Carborane, New Hydrophobic Pharmacophore

The hydrophobic part of the RAR and RXR ligand structures is important, since it interacts directly with the LBD helix 12 (known as the AF-2 region) of the receptors. The helix 12 of nuclear receptors dramatically changes its conformation upon binding of an agonist, covering the ligand-occupied ligand binding pocket.[18] In retinoid receptors, the interaction between the inside of helix 12 and the hydrophobic moiety of the agonist ensures the proper conformation of helix 12 for the nuclear receptor−coactivator interactions. Introduction of larger substituents into the hydrophobic part of agonists usually results in loss of activity or in some cases affords antagonists, as shown by **8** and **13** (Figure 4).

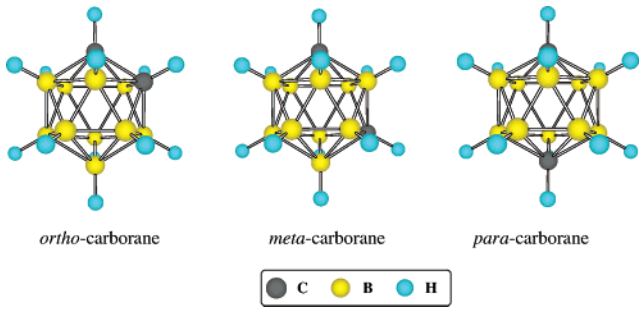


Figure 8. Structures of carboranes.

Carborane ($C_2B_{10}H_{12}$, Figure 8) is a boron cluster with icosahedral geometry in which 2 carbon and 10 boron atoms are hexacoordinated. There are three isomers, ortho, meta, and para carboranes, corresponding to the possible positions of the two-carbon atoms. Besides the unique structure and chemical properties, carboranes have attracted attention as an efficient tool for boron neutron capture therapy (BNCT) of cancer in the field of medicinal chemistry.[53] In most of the compounds so far examined, the carboranes are simply linked to less important sites of bioactive substances. On the other hand, carboranes are bulky and have exceptional hydrophobicity[54] and might be applicable as the hydrophobic part of retinoid structures. Although the replacement of the hydrophobic cyclic alkyl group of **4** with ortho carborane, yielding compound **34**, caused a decrease of retinoidal activity, **35** (BR403), having a shorter linking group than compound **34**, is as potent an RAR agonist as ATRA (Figure 9).[55] Since carborane has a rigid icosahedral structure and plural substituents can be placed in precisely defined spatial positions and orientations, it is expected to be widely useful as a hydrophobic pharmacophore. Indeed, several nuclear receptor agonists and antagonists have been

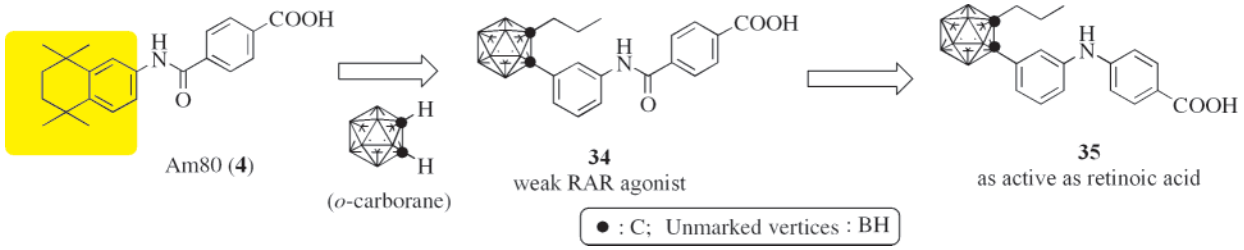


Figure 9. Design of retinoid bearing an ortho carborane moiety as the hydrophobic pharmacophore.

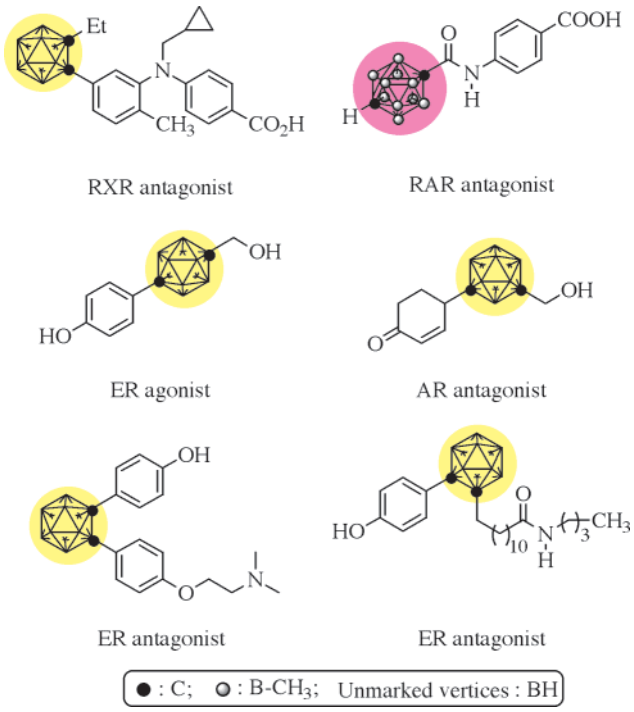


Figure 10. Synthetic nuclear receptor ligands bearing a carborane moiety.

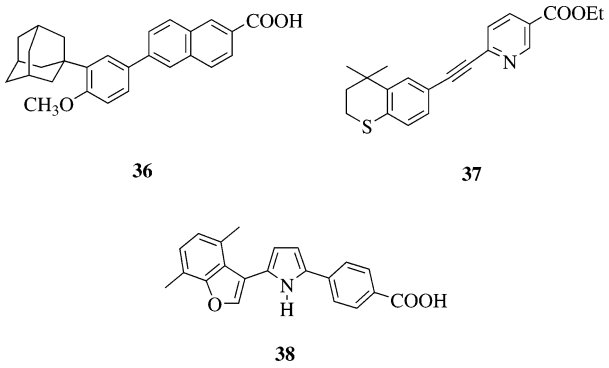


Figure 11. Synthetic retinoids examined for their clinical utilities.

developed recently, including RAR antagonist,[56] RXR antagonist,[57] and steroid hormone receptor agonists/antagonists (Figure 10).[58,59] Besides their biological functions as agonists/antagonists, these carborane derivatives may have useful applications for BNCT targeting nuclear receptors.

Prospects for Retinoid Therapy

Retinoid therapy using synthetic retinoids has already been realized in the fields of dermatology and oncology. Some synthetic retinoids, such as **36** (adapalene), **37** (tazalotene), and **4** (Figure 11), have been proven to be clinically useful in the treatment of acne and psoriasis.[7,60,61] The most successful clinical application of retinoids is ATRA therapy of APL.[62,63] More than 90% of APL patients achieved complete remission (CR) with ATRA treatment. ATRA is less effective in APL patients who relapsed after complete remission induced by ATRA (less than 20% CR), while a synthetic retinoid, **4**, was shown to be effective (about 60% CR) in such patients.[64] On the basis of this preliminary clinical examination, the efficacy of Am80 (**4**) in relapsed APL was confirmed by clinical trials in Japan. Compound **4** is less toxic than ATRA or conventional retinoids, partially because of the lack of binding affinity to RARγ.[65−68] Besides RAR subtype-selectivity, **4** exhibits poor affinity for cellular retinoic acid binding protein (CRABP), which sometimes causes retinoid resistance. The less hydrophobic properties of **4** result in proper clearance of **4** from the body. Because of these advantages, several clinical trials using **4** toward several diseases (described below) are going to start.

In the fields of cancer therapy and chemoprevention, various types of retinoids have been examined, including atypical retinoids and RXR agonists,[24,27,28,69] as well as combination therapy of classical retinoids with these or other factors, such as HDAC inhibitors.[70] Although the action mechanisms of RXR agonists in cancer therapy and chemoprevention are poorly understood, clinical examination of RXR agonists is in progress. For example, compound **21** effectively prevented primary and secondary rat mammary carcinoma induced by *N*-nitroso-*N*-methylurea. In a clinical trial for the treatment of refractory advanced-stage cutaneous T-cell lymphoma, **21** showed 2% CR and 43% partial response (PR)[71] and is clinically marketed as bexarotene (Targretin).

The clinical utility of RXR ligands is also attractive in the field of metabolic syndrome. RXRs form heterodimers with nuclear receptors related to lipid physiology, such as PPARs, LXRs, and FXRs, and RXR agonists can elicit similar activities to ligands of the heterodimer partner receptors, since these heterodimers can be activated by each ligand alone.[14] Thus, compound **22** showed antidiabetic activity in db/db or ob/ob mice, mediated by the activation of PPARγ−RXR heterodimers.[72] Compound **22** also inhibited cholesterol absorption by RXR−LXR mediated increase of cholesterol efflux and by FXR−RXR mediated reduction of the bile acid pool.[73] Further, LG101315, a fluorinated analogue of **22** reduced atherosclerotic progression in apolipoprotein E knockout mice, mediated by the PPARγ−LXR−ABCA1 pathway.[74,75] On the other hand, the RXR antagonist **26** has potential antidiabetic and antiobesity activities. At present, more detailed studies are needed to clarify what kinds of RXR ligands are most useful,

such as agonist vs antagonist, and heterodimer partner-selective vs nonselective, but RXR ligands appear promising for the treatment of metabolic syndrome.

Retinoids have the ability to ameliorate the symptoms in various immunological disease models. Retinoids, such as ATRA and **4**, are potent inhibitors of IL-6 producton.[23] IL-6 is a multifunctional cytokine produced by various cells, and abnormal expression of IL-6 is related to the pathogenesis of several diseases such as psoriasis, multiple myeloma, and rheumatoid arthritis. In fact, **4** inhibited the IL-6-dependent growth of multiple myeloma cells.[76] ATRA is effective in rat adjuvant arthritis and experimental allergic encephalomyelitis.[77] In the ameliorative effects toward these immunological diseases, **4** and **5** were more potent than ATRA in various animal models. Thus, **4** and **5** inhibited the development of collagen-induced arthritis in mice and delayed the onset and development of experimental allergic encephalomyelitis in rats.[78−80] Recently, RARα-selective retinoids, **4** and **38** (ER-38925), were reported to inhibit allospecific murine T lymphocyte activation more efficiently than ATRA or other RAR subtype-selective retinoids.[81] Further, oral administration of **38** inhibited the acute rejection of cardiac allograft in mice by inhibiting the induction of cytotoxic T lymphocyte and Th1-related cytokines, such as IL-2, IL-12, and IFN-γ. The effect of **38** was enhanced by tacrolimus (FK506). The result indicated that RARα-selective retinoids may have possible utility as immunosuppressants in human organ.

On the other hand, ATRA was recently identified as the first molecule responsible for the imprinting of gut-homing T cells.[82] Native T cell exposure to ATRA induced gut-homing receptors, $\alpha4\beta7$ integrin and CCR9, and the ability to migrate to the small intestine. Simultaneously, ATRA suppressed the expression of skin-homing molecules, E-selectin ligands. Vitamin A deficiency in mice caused a reduction of $\alpha4\beta7^+$ effector/memory T cells in lymphoid organs and depletion of $CD4^+$ T cells from the intestinal lamina. These activities are due to the biosynthesis of ATRA mediated by RARs, since they were inhibited by inhibitors of retinal dehydrogenase, an enzyme involved in ATRA biosynthesis, or RAR antagonists. Thus, retinoid have significant roles in the treatment and prevention of T-cell-mediated diseases.[83] Since the retinoid action depends on the type of T cell and tissue, further investigations on the clinical utilities of retinoids and retinoid antagonists in each immunological disease are warranted.

ATRA limits restenosis after balloon angioplasty in the focally atherosclerotic rabbit.[84] Krüppel-like zinc-finger transcription factor 5 (KLF5/BTEB2) is a transcription factor whose expression is strongly induced in activated vascular smooth muscle and fibroblasts, and it plays key roles in cardiovascular remodeling. Recently, the function of KLF5 was found to be regulated by retinoids and RARs.[85] Compound **4** regulated the activities of KLF5 through RARs both in vitro and in vivo. Compound **4** repressed the formation of granulation tissue and the neointima in wild-type mice with cuffed femoral arteries, as observed in KLF5-knockout mice ($klf^{+/-}$). In contrast, the RAR antagonist **11** enhanced the formation of granulation tissue and the neointima in $klf^{+/-}$ mice to the level observed in wild-type mice. Thus, retinoids have potential for clinical use as KLF5 inhibitors in various cardiovascular diseases.

In conclusion, recent development of RAR and RXR ligands with a wide variety of structures and biological functions has opened up new areas of potential retinoid treatment in many clinical fields. Besides those described above, retinoids may also prove to be useful in the treatment of neurodegenerative and neuropsychiatric disorders, such as Alzheimer's disease, schizophrenia, Parkinson's disease, and so on.[86,87] We also found that several synthetic retinoids rescued memory deficit in rats treated with scopolamine in mice[88] and reduced haloperidol-induced dyskinesias in mice.[89] Retinoids play significant roles in the development of the central nervous system[90] and regulate expression of various genes mediated by RARs and RXRs in adult brain. Thus, even though more than 30 years have passed since the medicinal−chemical study of retinoids was started, retinoid nuclear receptors, RARs and RXRs, remain among the most significant molecular targets for drug discovery in the 21st century.

Biographies

Hiroyuki Kagechika received his Bachelor and Ph.D. degrees from The University of Tokyo (Pharmaceutical Sciences), Japan, in 1989 and was an Associate Professor at the same university until 2004. Then he moved to Tokyo Medical and Dental University, where he is currently a Professor in School of Biomedical Science. His major research interest is the medicinal chemistry of nuclear receptors. He is also interested in the chemistry of aromatic amides with unique structures, which is useful for construction of functional aromatic molecules.

Koichi Shudo received his Bachelor and Ph.D. degrees from The University of Tokyo (Pharmaceutical Sciences). He was a Professor of the same university until 2000. One of his major research fields is bioorganic chemistry related to oncology. Retinoid research has been conducted since 1979. His research on the structure elucidation of heterocyclic mutacarcinogens and their interactions with DNA contributed to cancer biology. Another major field is research on cationic reactive species. He proposed that various dications are involved in aromatic electrophilic reactions.

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