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Aldo-Keto Reductase (AKR) 1C3 inhibitors: a patent review

Trevor M. Penning

Center of Excellence in Environmental Toxicology & Department of Systems Pharmacology & Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Introduction—AKR1C3 is a drug target in hormonal and hormonal independent malignancies and acts as a major peripheral 17β-hydroxysteroid dehydrogenase to yield the potent androgens testosterone and dihydrotestosterone, and as a prostaglandin (PG) F synthase to produce proliferative ligands for the PG FP receptor. AKR1C3 inhibitors may have distinct advantages over existing therapeutics for the treatment of castration resistant prostate cancer, breast cancer and acute myeloid leukemia.

Area covered—This article reviews the patent literature on AKR1C3 inhibitors using SciFinder which identified inhibitors in the following chemical classes: *N*-phenylsulfonylindoles, *N*-(benzimidazoylylcarbonyl)-*N*-(indoylylcarbonyl)- and *N*-(pyridinepyrrolyl)- piperidines, *N*-benzimidazoles and *N*-benzindoles, repurposed nonsteroidal antiinflammatory drugs (indole acetic acids, *N*-phenylanthranilates and aryl propionic acids), isoquinolines, and nitrogen and sulfur substituted estrenes. The article evaluates inhibitor AKR potency, specificity, efficacy in cell-based and xenograft models and clinical utility. The advantage of bifunctional compounds that either competitively inhibit AKR1C3 and block its androgen receptor (AR) coactivator function or act as AKR1C3 inhibitors and direct acting AR antagonists are discussed.

Expert opinion—A large number of potent and selective inhibitors of AKR1C3 have been described however, preclinical optimization, is required before their benefit in human disease can be assessed.

Keywords

Acute myeloid leukemia; aldo-keto reductase; androgen receptor; baccharin; co-activator; estrenes; 17β-hydroxysteroid dehydrogenase; indomethacin; non-steroidal anti-inflammatory drugs; prostate cancer

CONTACT: Trevor M. Penning, penning@upenn.edu, Center of Excellence in Environmental Toxicology & Department of Systems Pharmacology & Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

Declaration of interest

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1. Introduction

Aldo-keto reductase (AKR) 1C3 (type 5 17β-hydroxysteroid dehydrogenase; prostaglandin [PG] $F_{2\alpha}$ synthase; and dihydrodiol dehydrogenase X) belongs to the AKR superfamily of proteins [1–4]. AKR1C3 is a drug target due to its involvement in intratumoral androgen biosynthesis in prostate and breast cancer. In breast cancer, AKR1C3 is a principal source of testosterone (T), the substrate for aromatase. The ability of AKR1C3 to regulate ligand access to the androgen receptor (AR) and estrogen receptor (ER) in a tumor-specific fashion makes it a superior drug target than either AR or ER antagonists [5–8]. By acting as a $PGF_{2\alpha}$ synthase [9,10], it also deprives peroxisome proliferator activating receptor γ(PPARγ) of its putative ligand Δ^{15}-PGJ_2 and generates ligands for the PG FP receptor to stimulate the mitogen activated protein kinase cascade to promote cell proliferation [11,12]. AKR1C3 inhibitors thus offer promise for the treatment of hormonal and hormonal-independent malignancies [11,12].

AKR1C3 inhibitors have been used in clinical trials of castration-resistant prostate cancer (CPRC) [13] and acute myeloid leukemia (AML) [14]. CRPC is the fatal form of prostate cancer. This disease remains androgen dependent despite castrate levels of circulating T. Androgen dependency remains since the tumor undergoes adaptive responses to sustain AR signaling. One mechanism involves adaptive intratumoral androgen biosynthesis and a second mechanism involves changes in the AR itself [15,16]. Intratumoral androgen biosynthesis is targeted by P45017A1 (17α-hydroxylase/17,20-lyase) inhibitors to prevent the conversion of pregnenolone to dehydroepiandrosterone (DHEA) in the adrenal and hence deprive the tumor of its source of androgens. Abiraterone acetate (Abi) **1** is the P45017A1 inhibitor in clinical use and is approved by the US FDA [17–19]. The second mechanism, involving AR, is targeted with the super AR antagonist enzalutamide (ENZ) **2** [20]. To surmount the CNS side effects seen with this drug, a second-generation compound AN-509 (Apalutamide) **3** has been developed (Figure 1) [21]. These antagonists not only bind to the AR but prevent its nuclear translocation and binding to chromatin. Both Abi and ENZ increase median survival time in CRPC patients by only 3–4 months before drug resistance occurs [17–19,22,23]. Thus, a critical clinical unmet need is for better agents. While multiple mechanisms can contribute to drug resistance, both Abi and ENZ resistance can be surmounted in xenograft models using the AKR1C3 inhibitor indomethacin [24,25] first identified by Byrns et al. [26].

AKR1C3 is overexpressed in prostate cancer as part of the adaptive response to androgen deprivation therapy (ADT). AKR1C3 is overexpressed in cell lines deprived of androgens [27,28], in prostate cancer xenografts in castrate mice [24,25,28] and in CRPC patients [29–31]. AKR1C3 is involved in all pathways to T and 5α-dihydrotestosterone (DHT) in the prostate due its 17-ketosteroid reductase activity; it reduces 4-androstene-3,17-dione to T (by the canonical pathway) [32]; it reduces 5α-andros-tane-3,17-dione to DHT (by the alternative pathway) [33]; it reduces androsterone to 5α-androstane-3α,17β-diol (3α-diol) which is then oxidized by 17BHSD6 to DHT (by the backdoor pathway) [34–36]; and it reduces DHEA to 5-androstene-3β,17β-diol which is converted by 3HSDB1 to T. AKR1C3 inhibitors would block all pathways to T and DHT within the tumor and could surmount drug resistance to Abi and ENZ (Figure 2).

AKR1C3 is also overexpressed in ductal carcinoma *in situ* of the breast [37]; its overexpression is correlated with the expression of ERα [38], and with breast cancer relapse [39]. By acting as a peripheral 17β-hydroxysteroid dehydrogenase that converts 4-androstene-3,17-dione to T, AKR1C3 becomes a peripheral source of T so that aromatase can synthesize 17β-estradiol in the breast [6]. Thus, AKR1C3 inhibitors have a place in the treatment of ERα positive breast cancer and offer an advantage over aromatase inhibitors that would block estrogen biosynthesis systemically.

AKR1C3 inhibitors have been exploited in AML to alter PG signaling. In combination with PPARγ agonists, e.g. bezafibrate (BZF), the AKR1C3 inhibitor 6-medroxyprogesterone acetate (6MPA) **4** gave a superior response than was achieved by either agent alone [15]. In this treatment, BZF could stimulate PPARγ signaling and 6MPA would block the formation of PGs of the F series that would bind to the FP receptor (Figure 3). This is the first clinical example of the use of AKR1C3 inhibitors in a nonhormone-dependent malignancy.

The development of AKR1C3 inhibitors that are potent and selective is challenging since it is highly related to AKR1C1, AKR1C2, and AKR1C4 that share more than 86% sequence identity and their inhibition in the context of prostate cancer would be deleterious. For example, AKR1C1 converts DHT to 5α-androstane-3β,17β-diol (3β-diol) a proapoptotic ligand for ERβ and its inhibition should be avoided [40]. Similarly, AKR1C2 inactivates DHT by forming 3α-diol and its inhibition should be avoided [41,42]. By contrast, AKR1C4 is liver specific and is required for the synthesis of bile-acids and its inhibition would lead to bile-acid deficiency [43]. Despite this challenge, both academic and industrial groups have filed patents on AKR1C3 inhibitors (Table 1).

2. Chemistry

Potent and selective AKR1C3 inhibitors that are based on non-steroidal, steroidal, and natural product scaffolds have been disclosed. Compounds reported but not claimed in patent applications include the *N*-benzoylanthranilates **5** [44], the 2,3-arylpropenic acids **6**–**9** [45], and the natural products stylopne **10** (an isoquinoline alkaloid) [46] and 2′-hydroxyflavone **11** [47]. Compound **5** was synthesized by coupling 3-hydroxybenzoate with 4-bromoaniline and the 2,3-diarylpropenic acids were synthesized by a Perkin reaction between substituted benzal-dehydes and functionalized aryl acetic acids in base (Figure 1).

The synthesis of the lead agent SN33638 **12**, a potent and selective inhibitor of AKR1C3 (IC_{50} = 13 nM), is based on an *N*-phenylsulfonyl-piperidine [48]. SN336381 is also related to the *N*-phenylsulfonyl indoles **13**, developed by Astellas and claimed in patent W02007100066 (Table 1). Building on this lead, a series of *N*-(benzimidazolyl)-, *N*-(indolyl)-, and *N*-(-pyridinelpyroylyl)-carbonyl piperidines **14**–**16** were claimed in JP201202018, W02010101127, and W02010101128, respectively, by Astellas. The *N*-(indolyl)-carbonyl piperdines include ASP9521 **15**, which was taken through to a Phase 1/11b clinical trial [14,49]. A related series of *N*-benzimidazole or *N*-indole benzoic acids **17, 18** were claimed in W02009014150, WO2010087319 (Figure 4).

A screen of existing drugs identified nonsteroidal antiinflammatory drugs (NSAIDs) as selective inhibitors of different AKR1C isoforms [26]. Compounds of interest include indomethacin **19** which was selective for AKR1C3; the *N*-phenylanthranilates (e.g. meclofenamic acid **23**) were pan-AKR1C inhibitors; and aryl pro-pionic acids (e.g. naproxen **25**) displayed equal AKR1C2 and AKR1C3 selectivity and potency. This led to the repurposing of these NSAIDs for AKR1C3 inhibition while eliminating inhibition of the COX-isoforms (PGH synthase I and II). Patent WO2012122208 was issued for *N*-phenylaminobenzoates represented by **24** and patent WO2013059245 was issued for indo-methacin analogs, represented by **20**–**22** [50,51]. This was subsequently followed by patent W02017070448 for β-naphthylacetic acids (*R*-naproxen analogs), **26** [52]. In each case, the NSAID analogs were subjected to medicinal chemistry optimization to remove structural features required for inhibition of COX-1 and COX-2 while inhibition of AKR1C3 was retained. Indomethacin gave rise to three classes of analogs: Class I analogs (retain the core structure of indomethacin, **20**); Class II analogs (are des-methyl indomethacin compounds in which the 2′-methyl group has been removed, **21**); and Class III analogs (are 3′-alkyl derivatives where the acetic acid side chain has been substituted with an alkyl group and the carboxylic acid side chain has been moved to the 2′-position **22** or the 3′ and 2′ positions are cyclized to yield a cyclic carboxylic acid or sulfonamide) [53,54].

Indomethacin analogs with conserved 5′-methoxy groups and *p*-chlorobenzoyl groups at the indole N1 position were synthesized by the method of Yamamoto [55,56**]**. The key reagent for the underlying Fischer indolization is 4-chloro-*N*-(4-methoxyphenyl)-benzohydrazide hydrochloride. Target compounds containing a 3′-propionic acid group or a 2′-des methyl-group were readily obtained from the benzohydrazide hydrochloride by using either a slight excess of 5-oxohexanoic acid (here, R_1 = Me, n = 2) or 4-oxobutanoic acid (R_1 = H, n = 1) in acetic acid, respectively, to give, **20**–**21**. Use of 4-oxohexanoic acid (R_1 = Me, n = 1) quantitatively yielded the reverse 2′-pro-pionic acid/3′-alkyl indole derivative, **22** [57] (Figure 4). Following the issuance of patent WO2013059245 for these indomethacin analogs, a patent claiming the use of indomethacin for CRPC was filed, WO2015065919.

For the *N*-phenylaminobenzoates, simple coupling chemistry involving a Buchwald–Hartwig C–N coupling reaction followed by saponification of the formed methyl ester produced an extensive library of compounds that are claimed in patent WO2012122208 and US 20140107085 [50,51]. Compounds in which the arrangement of the amine and carboxylic acid was changed from *ortho*-to *meta*- position followed by introduction of a *para*- electron withdrawing group on the B-ring gave compounds of mid-nanomolar potency and selectivity for AKR1C3 (Figure 4).

For the aryl propionic acids **25**, β-naphthylacetic acids in which the stereochemistry at the alkyl substituent at the alpha carbon was changed from *S*- to *R*- were sufficient to abolish COX-1 and COX-2 inhibition but retain AKR1C3 inhibition; compounds such as **26** are disclosed in WO2017070448 (Figure 4) [52].

Bifunctional AKR1C3 nonsteroidal inhibitors have also been disclosed (Figure 4). Isoquinolines represented by the lead compound GTX-560 **27** not only act as competitive inhibitors of AKR1C3 but also block its AR coactivator function which was previously

unknown [58]. The isoquinolines were claimed in patents WO2013142390 and WO2014039820A1 filed by GTx-Therapeutics. BMT4-158**28**, which is a *N*-naphthylaminobenzoate, is covered by the patent on the *N*-phenylaminobenzoates and acts as a bifunctional AKR1C3 competitive inhibitor and direct acting AR antagonist [59].

Attempts have been made to develop steroidal-based inhibitors for AKR1C3 as it reduces 17-ketosteroids. Extensive nitrogen and sulfur-substituted estrenes with the core structure **30** have been claimed by Bayer in four patents WO201345407, WO2014009274, WO2014128108, and WO02016037956 (Figure 5). The key features of these steroids are the presence of either an amide, amine, or sulfone at the C3 position of the steroid coupled with the presence of either a nitrogen heterocycle or a trifluorosulfone at the C17 position.

Natural products such as baccharin analogs **29** (from the Brazilian propolis) have also be claimed as AKR1C3 inhibitors, and these derivatives contain a phenolic cinammic acid substituted with an isopropyl group and a phenylpropionic ester [60,61]. However, these compounds are likely to hydrolyze *in vivo* to the corresponding alcohol and acid.

3. Structure–activity relationships

Thirty-five crystal structures of AKR1C3·$NADP^+$·inhibitor complexes exist in the PDB. Inspection of these structures shows that if the inhibitor contains a carboxylic acid, it can often form hydrogen bonds with the catalytic tetrad members Tyr55 and His117. Other portions of the inhibitor can occupy one of several subpockets (SP), e.g. SP1 Ser118, Asn167, Phe306, Phe311, and Tyr319 (e.g. occupied by the B-ring of *N*-phenylaminobenzoates). The SP2 sub-pocket refers to Ser129, W227, and F311 (e.g. occupied by the side-chain of PGs), and the SP3 sub-pocket which contains Y24, E192, S217, S221, Q222, Y305, and F306 [62]. While the presence of these sub-pockets can be rationalized to determine binding mode and can be used as the basis of docking studies, some important caveats exist as illustrated by the binding of indomethacin. Two different binding poses for indomethacin exist in the AKR1C3·$NADP^+$·indomethacin depending on pH. In the AKR1C3·$NADP^+$·indomethacin complex at pH 6.0 (PDB ID 1S2A), where indomethacin is fully protonated, the carboxylate is anchored by Q222 and Y24 in SP3, the bridge carbonyl forms a hydrogen bond with Tyr55 through an intervening water molecule, and there is no occupancy of SP1. However, in the AKR1C3·$NADP^+$·indomethacin complex at pH 7.5 (PDB ID 3UG8), where indomethacin is deprotonated, the drug rotates so that the carboxylic acid now forms a hydrogen bond with Tyr55, the SP1 pocket is now occupied by the *p*-chlorobenzoyl ring, and there is interaction between W227 with the methoxyindole in the SP2 pocket (Figure 6) [54]. These structures illustrate the difficulty in performing structure-based inhibitor design for AKR1C3.

4. Biology and action

Tiered screening has been conducted to support patent claims. Tier 1 screening includes *in vitro* inhibition assays on recombinant AKR1C3 to claim compounds with mid-nanomolar affinity. Counterscreens have been performed in many instances versus either AKR1C1 or AKR1C2, to claim compounds that are 40–500-fold selective for the target (see Table 1).

Many compounds have cleared this screen, but often only IC_{50} values are reported and the pattern of inhibition is not given. Since AKR1C3 catalyzes an ordered bi-bi mechanism, in the reduction direction, two inhibitor complexes can form e.g. E·NADPH·I (competitive complex) and $E{\cdot}NADP^{+}{\cdot}I$ (uncompetitive complex) [26]. Thus, depending on the mode of inhibition, the IC_{50} values may not be directly comparable.

Tier 2 screening for repurposed NSAIDs includes a subsequent counter screen against all the human AKRs, and a counter screen against COX-1 and COX-2. This level of screening was conducted for patents WO2012122208 and US 20140107085 and patents WO2013059245 and US 20160303082. In other patents, specificity was assessed by demonstrating the inability of leads to inhibit HSD17B3, the major androgenic 17β-HSD found in the testis and a member of the short-chain dehydrogenase/reductase superfamily [63].

Tier 3 screening includes cell-based assays to determine whether compounds inhibit the conversion of 4-andros-tene-3,17-dione to T in LNCaP-AKR1C3 cells or another prostate cancer cell model in which AKR1C3 is overexpressed. Often HEK-293 cells expressing AKR1C3 have been used as a substitute. These screens determine whether the inhibitor has cell bioavailability and retains potency. Claimed compounds have been shown to be effective in these models, albeit with some loss of potency. Cell-based assays using AR-reporter gene assays and AR-ligand binding assays have also been performed to determine whether compounds act as AR-antagonists or inhibit the co-activator function of AKR1C3, as is the case for GTx-560 [58]. The AR coactivator domain of AKR1C3 was located to amino-acid residues 171–237 by deletion mutagenesis [58], which is distal to the enzyme active site. This region contains a coactivator peptide consensus peptide LXXLL (LEMIL). This suggests that some small molecule competitive inhibitors may have an allosteric effect that radiates to distal portions of the protein to affect AKR1C3–AR interaction. Interestingly, indomethacin does not have this property [58].

Tier 4 screening determines whether AKR1C3 inhibitors are effective *in vivo* and cause a reduction in tumor volume or tumor incidence in either xenograft or patient-derived xenografts of prostate cancer. ASP9521 and indomethacin have been shown to inhibit tumor growth in xenografts *ex-vivo* and *in vivo*, respectively [24,25,49]. Similar results have been obtained with GTx-560 [58].

Some attention to the xenograft model is required. Demonstration of reduced tumor incidence and volume in SCID mice transplanted with prostate cancer tumors is not a model of CRPC. CRPC can be modeled if the recipient mouse is castrated after the transplant and the tumor then regrows under castrate conditions. This model has been rarely used. No experiments have been performed with AKR1C3 inhibitors in patient-derived xenografts. Nevertheless, proof-of-principle xenograft data indicate that AKR1C3 inhibitors are effective antitumor agents in animal models [24,25,49].

Based on preclinical data, ASP9521 **15** was advanced to a Phase I/IIb clinical trial by Astellas. ASP9521 was found to be well tolerated but without efficacy [14]. In this small trial, 7/13 patients completed the regimen. Serum levels of ASP9521 reached levels that would be sufficient to inhibit AKR1C3. However, decreases in serum PSA and serum steroid

hormone levels were not achieved. However, inclusion criteria did not screen for AKR1C3 expression and the authors concluded that drug failure may have been due to the exclusion of patients who had been on prior ADT, which is known to upregulate AKR1C3.

The steroid-based estrenes with substitutions at C3 and C17 have been shown to be potent competitive inhibitors *in vitro* using recombinant AKR1C3 and in HEK-293 cells over-expressing AKR1C3. However, counter screens against other human AKRs have not been reported. The presence of the nitrogen heterocycle at C17 is reminiscent of the heterocycle found in Abi and raises issues as to whether they inhibit P45017A1 or other steroid metabolizing P450 isoforms.

5. Expert opinion

As AKR1C3 is a major peripheral 17β-HSD required for the synthesis of T and DHT, inhibitors of the enzyme may have a place for treating endocrinological disorders associated with androgen excess in males and females, e.g. prostate cancer, benign prostatic hyperplasia, alopecia, pattern baldness, hirsutism, polycystic ovarian syndrome, etc. As T synthesized locally is also a substrate for aromatase, AKR1C3 inhibition may also be desirable in breast cancer, endometriosis, and endometrial cancer. However, the major focus has been on prostate cancer.

The majority of AKR1C3 inhibitors claimed are mono-functional agents and act downstream from Abi. Since they do not inhibit P45017A1, they do not have to be coadministered with prednisone to prevent adrenal insufficiency. The monofunctional AKR1C3 inhibitors would be superior to other P45017A1 inhibitors (orterenol and galeterone) since they target an enzyme involved in intratumoral androgen biosynthesis that is overexpressed upon ADT. Even though P45017A1 inhibitors decrease serum DHEA-SO_4 and DHEA by more than 90%, the amount of DHEA-SO_4 that remains leaves a substantial reservoir for intra-crine androgen biosynthesis by AKR1C3 [64,65]. Mechanisms of drug resistance to P45017A1 inhibitors also include *HSD3B1* allelic variants that stabilize the enzyme responsible for the conversion of DHEA to 4-androstene-3,17-dione [66]. The properties of AKR1C3 inhibitors versus other agents that target the AR axis in prostate cancer are presented in Table 2.

AKR1C3 is overexpressed in prostate cancer cells, in xenografts, and in tumors of patients that over undergone ADT [24,25,28–31,67]. But it is likely that the use of these mono-functional AKR1C3 inhibitors will require precision medicine to ensure that the target is expressed in the patient. Interestingly, steroid 5α-reductase inhibitors e.g. finasteride and dutasteride are not approved by the FDA for the treatment of prostate cancer since these may cause the appearance of a more aggressive disease (Table 2).

Few compounds claimed in the patents have undergone a complete counter screen and for many, DMPK studies have yet to be performed limiting their effective use in animal xenograft and human studies. Here, the repurposed NSAIDs hold promise since they are anticipated to retain the properties of the parent drug from which they were derived [5,68].

Monofunctional AKR1C3 inhibitors are ultimately predicted to fail in the clinic due to the issue of drug resistance. However, they could be added to existing regimens, e.g. Abi or ENZ with the prospect of achieving a synergistic effect and more durable drug response. A starting point would be to add indomethacin to patients who progress on Abi or ENZ. Both Abi and ENZ resistance are likely to involve the overexpression of AKR1C3 as a component of drug resistance [24,25].

Mechanisms of drug resistance include AR gene amplification [69], the selection of AR mutants that make it ligand promiscuous [70,71], and the appearance of AR splice variants (AR-SV) that have lost their ligand binding domain and are constitutively active [72–74].

The bifunctional AKR1C3 inhibitors, e.g. GTX-560 **27**, offers promise since it blocks the coactivator function of AKR1C3 on full-length AR (Table 2). Whether AKR1C3 can act as a coactivator of AR-SVs is unknown. The other bifunctional agent claimed is BMT4-158 **28**, which acts as a competitive inhibitor of AKR1C3 and as a direct acting AR antagonist, suggesting that single agents that target intra-tumoral androgen biosynthesis and AR signaling can be developed. Whether these single agents would be superior to a combination treatment of Abi plus prednisone plus ENZ remains to be determined.

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Article highlights

- AKR1C3 (type 5 17β-hydroxysteroid dehydrogenase/prostaglandin F2α synthase) is a drug target for hormonal and hormonal independent malignancies
- Nonsteroidal inhibitors, repurposed NSAIDs and steroid based inhibitors have been claimed in multiple patent applications
- Extensive steroidal-based inhibitors based on C3 and C17 substituted estrenes have been developed
- AKR1C3 inhibitors have progressed to clinical trials for castration resistant prostate cancer and acute myeloid leukemia with mixed success
- The majority of inhibitors require optimization for testing in animals and humans

This box summarizes key points contained in the article.

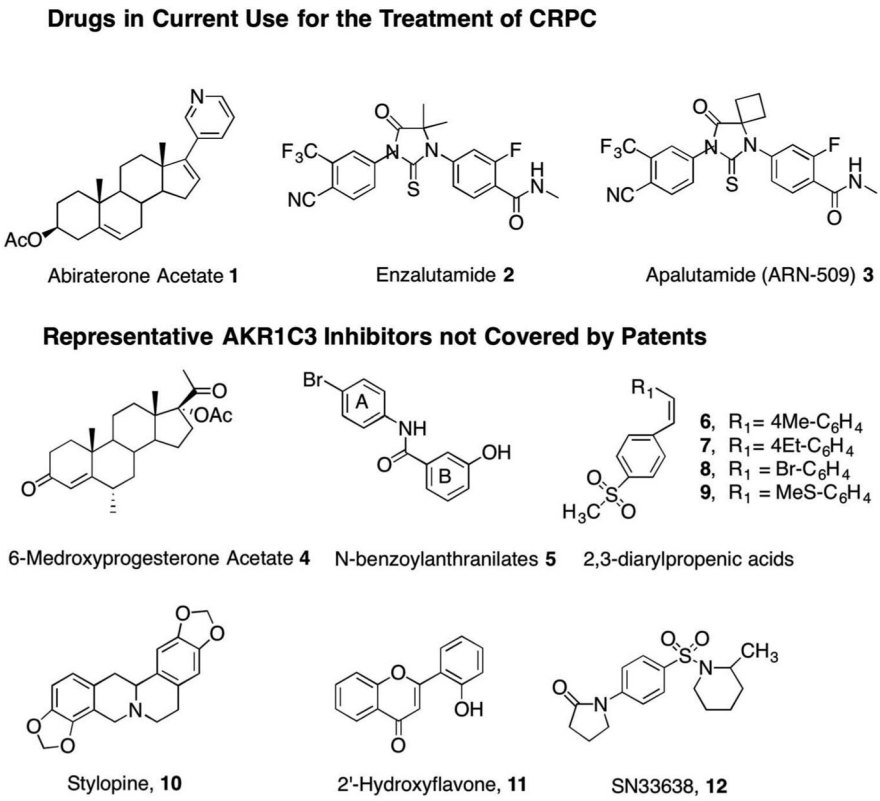

Figure 1.

Drugs in common use for the treatment of CRPC and some representative AKR1C3 inhibitors not covered by patents.

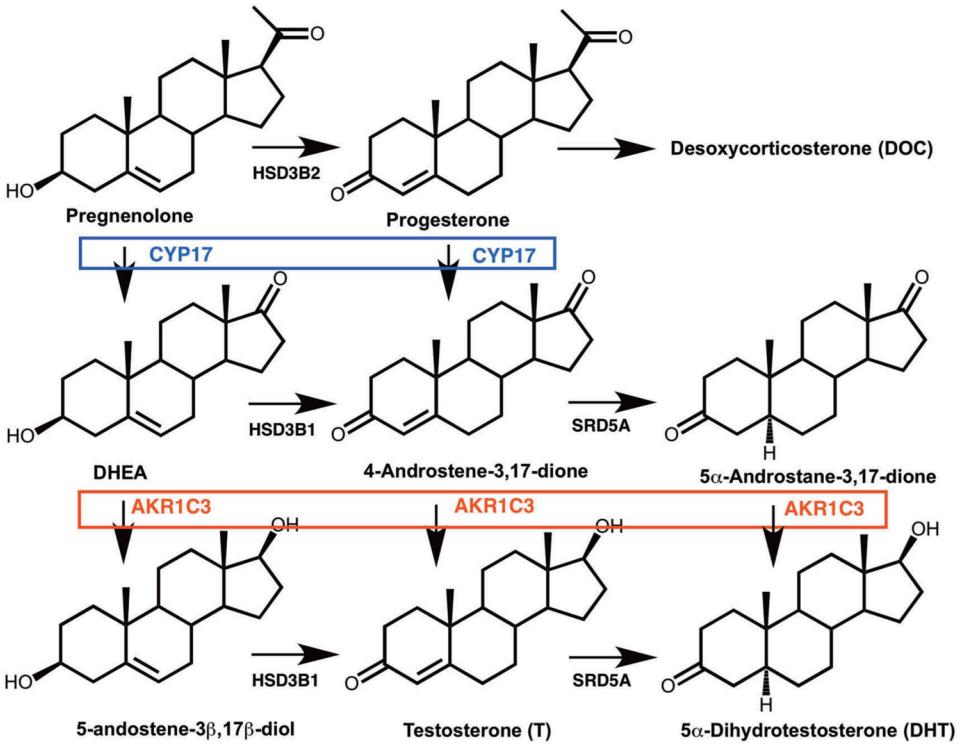

Figure 2.

Role of AKR1C3 in androgen biosynthesis in human prostate. The conversion of C21 steroids pregnenolone and progesterone to the corresponding C19 steroids dehydroepiandrosterone (DHEA) and 4-androstene-3,17-dione is catalyzed by CYP17 (P45017A1); and the preferred route is from pregnenolone. The evidence for intratumoral biosynthesis of C19 steroids from C21 steroids is scant and the reactions occur predominately in the adrenal. The conversion of progesterone to desoxycorticosterone is adrenal specific and is a side effect of abiraterone acetate treatment leading to mineralocorticoid excess. HSD3B1, 3β-hydroxysteroid dehydrogenase type 1, SRD5A, steroid 5α-reductase type 1 and type 2. Reproduced with permission from Adeniji AO, Twenter BM, Byrns MC, Jin, Y, et al. Development of potent and selective inhibitors of aldo-keto reductase 1C3 (type 5 17β-hydroxysteroid dehydrogenase) based on *N*-phenyl-aminobenzoates and their structure-activity relationships. J Med Chem 2012;55:2311–23 Copyright American Chemical Society.

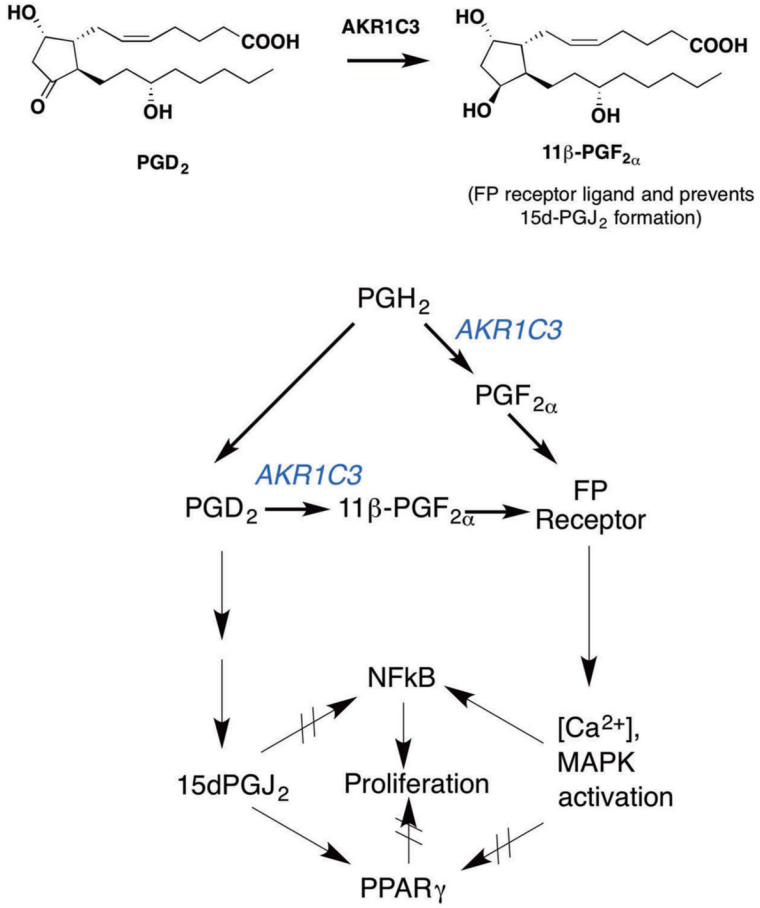

Figure 3.

Role of AKR1C3 in prostaglandin signaling. AKR1C3 catalyzes the conversion of prostaglandin (PG) H_2 and PGD_2 to $PGF_{2\alpha}$ and 11β-$PGF_{2\alpha}$ respectively ($PGF_{2\alpha}$ synthase activity). $PGF_{2\alpha}$ and 11β-$PGF_{2\alpha}$ are ligands for the prostaglandin FP receptor which leads to activation of mitogen activated protein kinase (MAPK) and cell proliferation, as well as activation of NFkB. AKR1C3 prevents the conversion of PGD_2 to $15dPGJ_2$ a peroxisome proliferator activating receptor γ(PPARγ) agonist and inhibitor of NFkB signaling where the former leads to cell-differentiation and inhibition of cell growth. Reproduced with permission form Byrns MC and Penning TM. Type 5 17β-hydroxysteroid dehydrogenase/ prostaglandin F synthase (AKR1C3): Role in breast cancer and inhibition by nonsteroidal anti-inflammatory drugs. Chem Biol Inter 2009: 178: 221–7 Copyright Elsevier.

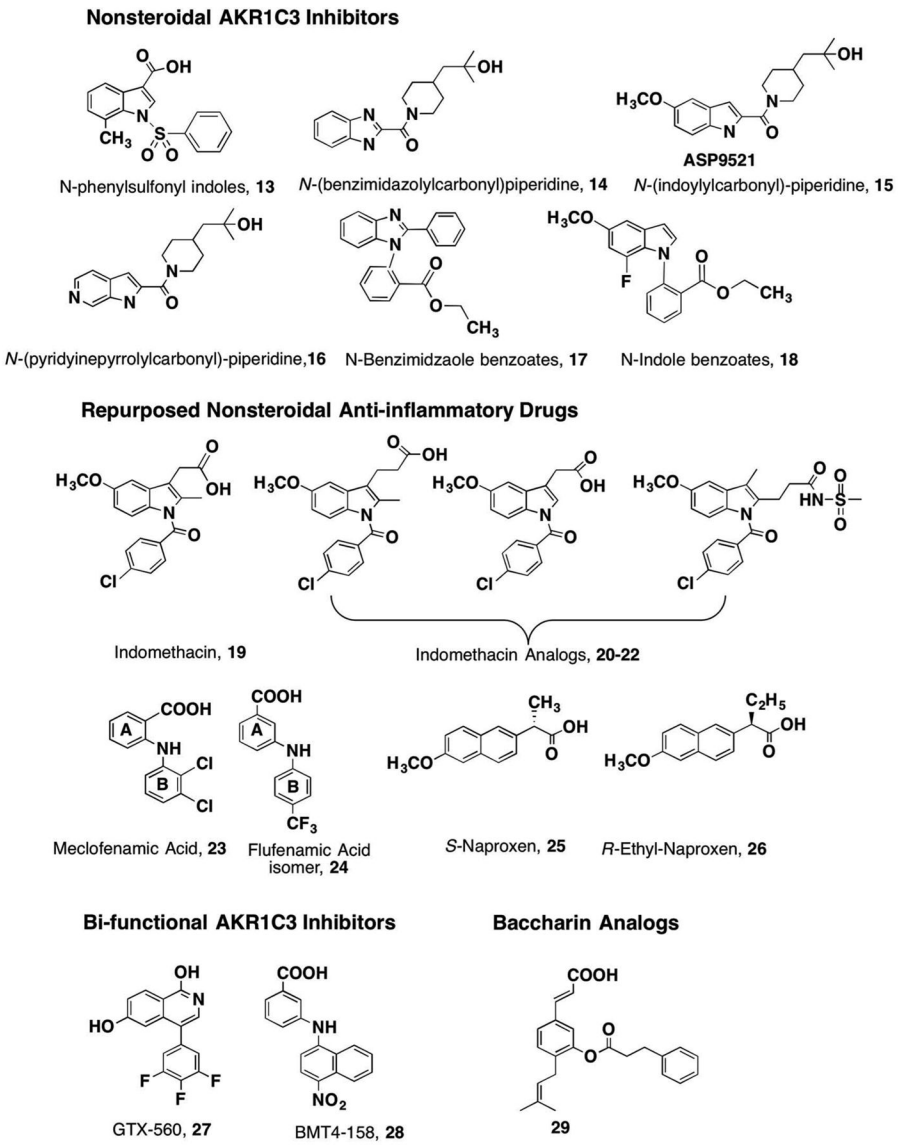

Figure 4.
AKR1C3 nonsteroidal inhibitors under patent.

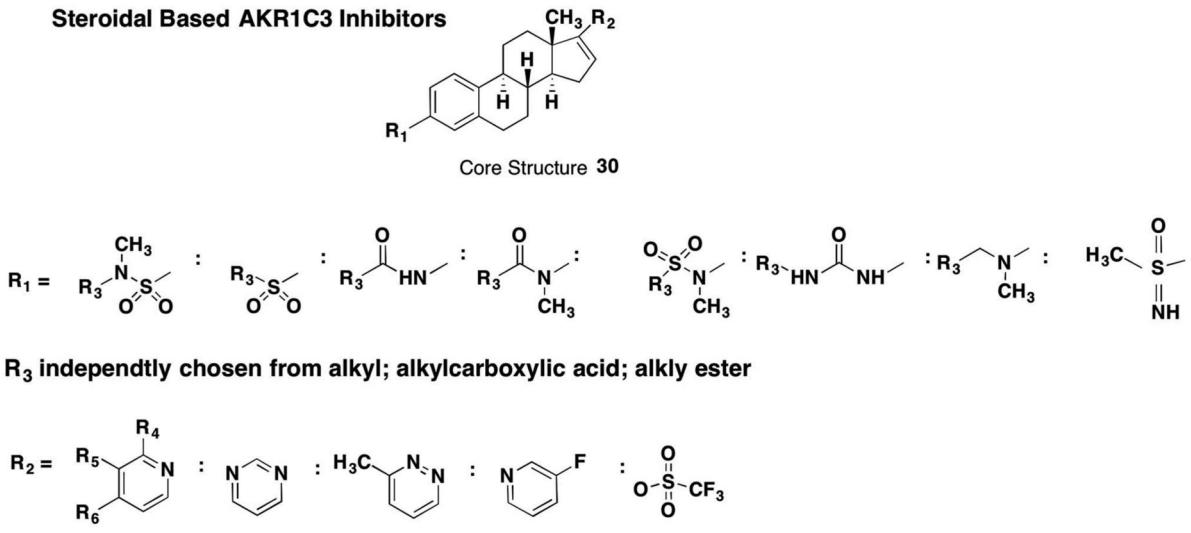

Figure 5.
AKR1C3 steroidal inhibitors under patent.

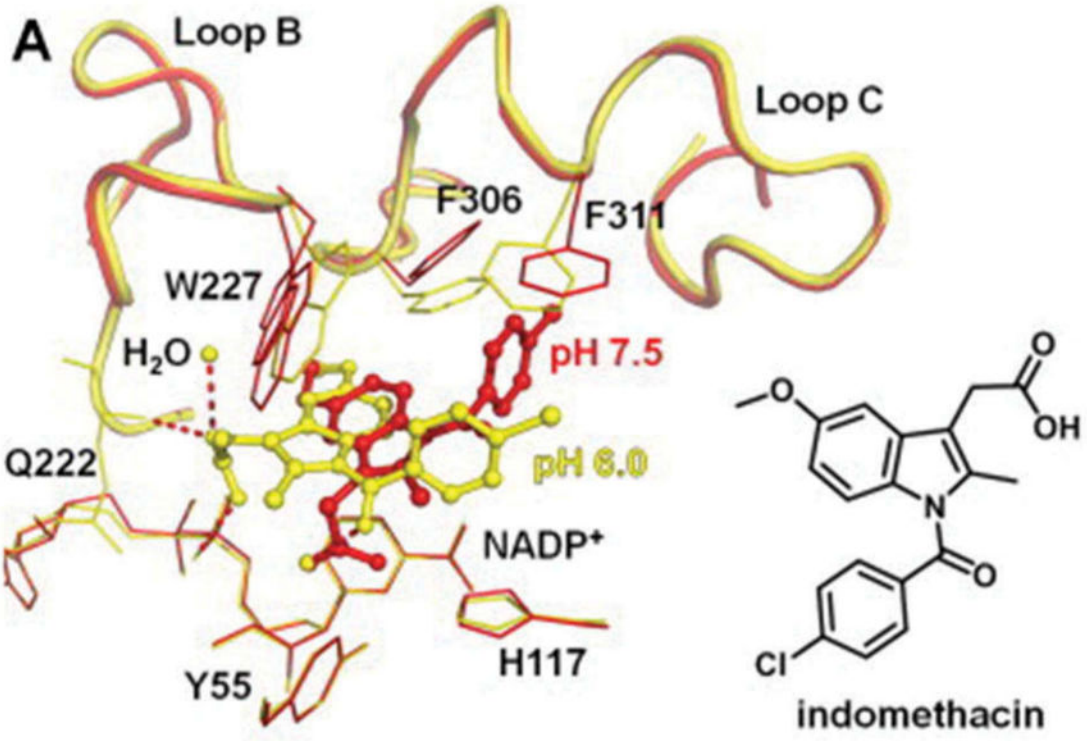

Figure 6.

Two different binding poses for indomethacin in the AKR1C3.NADP$^+$ complex. AKR1C3.NADP$^+$.Indomethacin complex (yellow) at pH 6.0 (PDB ID 1S2A) and AKR1C3.NADP$^+$.Indomethacin complex (red) at pH 7.5 (PDB ID 3UG8). Full color available online.

Table 1

Summary of patent applications reviewed on AKR1C3 inhibitors.

Compound class	Patent number	Mode of action	Assay method	IC_{50} value for AKR1C3[a]	Specificity for AKR1C3[b]	Status
N-phenylsulfonyl indoles	CA 2644809 W02007100066	Enzyme inhibition	4-AD to testosterone	90 nM	Counter screen against 17BHSD3 selectivity > 100-fold	Preclinical (Astellas)
N-(benzimidazolylcarbonyl)-piperidines	JP201202018	Enzyme inhibition	4-AD to testosterone	110 nM	Counter screen against 17BHSD3	Preclinical (Astellas)
N-(indolylcarbonyl)-piperidines	WO2010101127 JP2012102017 JP2010222350	Enzyme inhibition	4-AD to testosterone	3.7 nM	AKR1C3 > AKR1C1	Lead ASP9521 (Astellas) Phase 1 clinical trial
N-(pyridinepyrroylylcarbonyl)-piperidines	W02010101128	Enzyme inhibition	4-AD to testosterone	24 nM	Not determined	Preclinical (Astellas)
N-(benzimidazoles or indole) benzoic acids	CA02694216 WO2009014150 WO2010087319	Enzyme inhibition	4-AD to testosterone	40–50 nM	Counter screen against 17BHSD3 Selectivity > 40–250-fold LNCaP-AKR1C3 cells	Preclinical
N-(phenylamino)-benzoates	WO2012122208 US 2014/0107085	COMP	Inhibits *S*-tetralol oxidation	60 nM	Counter screen against AKR1C1, 1C2, 1C4 Selectivity > 250-fold	Flufenamic acid isomer Preclinical
N-(naphthylamino)-benzoates	WO2012142208 US 20140107085	COMP; AR antagonist	Inhibits *S*-tetralol oxidation	80 nM	Counter screen against AKR1C1, 1C2, 1C4 Selectivity > 100-fold	BMT4-158 Preclinical
Isoquinolones	WO2013142390 WO2014039820	COMP; blocks AKR1C3-AR coactivator function	4-AD to testosterone	770 nM	AKR1C3 > AKR1C1	GTx-560 (GTx-Therapeutics) Preclinical
Indomethacin analogs	WO2013/059245 US 2016/0303082 WO2015065919[c]	COMP	Inhibits *S*-tetralol oxidation	90 nM	Counter screen against AKR1C1, 1C2, 1C4 Selectivity > 500-fold	Preclinical
Nitrogen or sulfur-substituted estrenes	WO2013045407 WO2014009274 WO2014128108 WO2016/037956	Enzyme inhibition	NADPH reduction of cumberone to cumberol and 4-AD to testosterone	1 nM	HEK-293-AKR1C3 cells	Preclinical (Bayer)
β-Naphthylacetic acids	W02017/070448-A120170427	COMP	Inhibits *S*-tetralol oxidation	110 nM	Counter screen AKR1C2 Selectivity > 400 fold	*R*-Ethyl-naproxen Preclinical
Baccharin	JP2015020966	COMP	Inhibits *S*-tetralol oxidation	100 nM	Counter screen	Preclinical
Baccharin analogs	Provisional patent				AKR1C2 Selectivity > 500-fold	

COMP: Competitive inhibition; 4-AD: 4-androstene-3,17-dione; AR: androgen receptor; ND: not determined.

[a] IC_{50} value for the most potent inhibitor in the series.

[b] Fold selectivity for most specific compound in the series in counterscreens.

[c] Use patent.

Table 2

Comparison of AKR1C3 inhibitors with other therapeutic agents for castration-resistant prostate cancer.

Drug	Target	Resistance mechanism	Status	Company
Abiraterone acetate/prednisone	P45017A1	DHEA-SO_4 depot remains AR upregulation AR-SV HSDB1 variants AKR1C3 upregulation	FDA Approval 12 December 2012 Off patent 2019	Johnson & Johnson
Orteronel (TAK-700)	P45017A1	DHEA-SO_4 depot remains AR upregulation AR-SV HSDB1 variants AKR1C3 upregulation	Takeda terminates drug June 2014. No clinical benefit in terms of overall survival in Phase III clinical trial	Takeda
Galeterone (TOK-001)	P45017A1 (lyase specific) and degrades AR-SV	DHEA-SO_4 depot remains AR upregulation HSDB1 variants AKR1C3 upregulation	Phase III clinical trial. No benefit over ENZ in AR-V7 expressing CRPC. Drug terminated July 2016	Tokai Pharmaceuticals
Dutasteride	SRD5A1/SRD5A2	Intratumoral T bisosynthesis AKR1C3 upregulation	FDA warning for use in prostate cancer	Glaxo-Smith Kline
Enzalutamide	AR	Adaptive tumor androgen synthesis AKR1C3 upregulation AR-SV CNS-seizures	FDA Approval 12 September 2012 Off patent 2026	Medivation and now Astellas
Apalutamide	AR	Adaptive tumor androgen synthesis AKR1C3 upregulation AR-SV		Aragon and now Johnson & Johnson
ASP9521	AKR1C3	AR-SV	Phase I/IIb trial lack of efficacy in limited no of patients	Astellas

SRD5A1/SRD5A2: Steroid 5α-reductase; AR: androgen receptor.