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Aldo-Keto Reductase Family 1 Member B10 Inhibitors: Potential Drugs for Cancer Treatment

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Abstract: Cytosolic NADPH-dependent reductase AKR1B10 is a member of the aldo-keto reductase (AKR) superfamily. This enzyme is normally expressed in the gastrointestinal tract. However, it is overexpressed in many solid tumors, such as hepatocarcinoma, lung cancer and breast cancer. AKR1B10 may play a role in the formation and development of carcinomas through multiple mechanisms including detoxification of cytotoxic carbonyls, modulation of retinoic acid level, and regulation of cellular fatty acid synthesis and lipid metabolism. Studies have suggested that AKR1B10 may be a useful biomarker for cancer diagnosis and a potential target for cancer treatment. Over the last decade, a number of AKR1B10 inhibitors including aldose reductase inhibitors (ARIs), endogenous substances, natural-based derivatives and synthetic compounds have been developed, which could be novel anticancer drugs. This review provides an overview on related articles and patents about AKR1B10 inhibitors, with a focus on their inhibition selectivity and mechanism of function.

Keywords: AKR1B10, Aldo-keto reductase, ARL-1, cancer, chemoresistance, inhibitors.

1. INTRODUCTION

Aldo-keto reductase family 1 member B10 (AKR1B10), also known as aldose reductase-like-1 (ARL-1), is an important member of the AKR1B subfamily [1, 2]. AKR1B10 is a 36-kDa cytosolic reductase with a high amino acid sequence identity to AKR1B15 (92%) [3] and AKR1B1 (71%), referred to as aldose reductase (AR) [4]. AKR1B10 displays enzymatic activity for substrates such as retinaldehyde [5, 6], lipid peroxidation products [7-9], and xenobiotics [10, 11]. AKR1B10 is primarily expressed in normal epithelial tissues of digestive tract such as colon, small intestine, and stomach, negatively or lowly expressed in non-digestive tract tissues [1, 2]. However, it presents an opposite expression rule in cancer tissues. AKR1B10 is overexpressed in many non-digestive tract solid cancers such as hepatocellular carcinoma [2], various types of lung cancer including lung squamous cell carcinomas [12] and smoking related lung adenocarcinomas [13], cholangiocarcinomas [12], pancreatic carcinomas [14], and breast carcinomas [15]. On the contrary, the expression of AKR1B10 is downregulated in gastrointestinal cancer [16, 17]. AKR1B10 overexpression has been considered as a valuable biomarker and prognostic indicator for some cancers [15, 17, 18], and low expression of AKR1B10 has been used as a biomarker for the diagnosis of bowel diseases (US8551720) [19]. AKR1B10 is a protein secreted through a lysosome-mediated pathway and may serve as a potential serum marker for malignant diseases [20]. Methods based on specific antibodies against AKRIB10 (US8114606, US8685666) [21, 22] were developed for the detection of AKR1B10 in peripheral blood [23].

Since AKR1B10 plays a significant role in cancer development and progression, and has served as a diagnostic biomarker for some certain tumors,targeting AKR1B10 using specific inhibitors should be a desirable cancer treatment strategy. The development of potent and selective AKR1B10 inhibitor as anticancer drugs has attracted growing attentions. Recently, many AKR1B10 inhibitors have been developed rapidly [24-37]. We here, review the recent publications and patents related to AKR1B10 inhibitors.

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2. ROLES OF AKR1B10 IN CANCER FORMATION AND DEVELOPMENT

2.1. Functions of AKR1B10

AKR1B10 is an NADPH-dependent oxidoreductase, which efficiently catalyzes the reduction of various intracellular cytotoxic carbonyl compounds [38] including oxidative stress products [8] and various drugs [39]. AKR1B10 can convert highly reactive carbonyl groups to less toxic hydroxyl groups to protect cells from carbonyl toxic injury, although it also participates in the activation of procarcinogens [40]. AKR1B10 possesses high enzymatic activity to reduce retinaldehyde isomers, especially all-*trans*-retinaldehyde, to their corresponding retinols [5, 6], resulting presumably in a decrease of the cellular levels of retinoic acid, a signal molecule involved in cell proliferation and differentiation [41-44]. AKR1B10 has been shown to promote cell growth and survival via modulating lipid synthesis and membrane function by hindering the degradation of acetyl-CoA carboxylase-α (ACCA), a rate-limiting enzyme in fatty acid synthesis, through the ubiquitination-proteasome pathway [45, 46]. AKR1B10 is also involved in protein prenylation through the farnesyl pathway [38, 47], a crucial event in carcinogenesis [14, 48]. Taken together, these studies suggest that AKR1B10 may play an important role in the development and progression of cancers.

2.2. AKR1B10 in Cancer Formation and Development

2.2.1. AKR1B10 in Cancer Formation

AKR1B10 is mainly confined to the distal gastrointestinal tract [2], where directly exposes toxic carbonyl compounds produced by the gut microbiota and from food intake [49]. AKR1B10 can metabolize carbonyl compounds to less toxic hydroxyl compounds, resulting in a protective effect on the gastrointestinal mucosa. AKR1B10 can also promote the synthesis of fatty acid/lipid in the gastrointestinal mucosa, facilitating the constant renewal of cryptic cells. Thus, a loss of AKR1B10 would have a detrimental outcome as observed in colon, gastric, head and neck cancers, in which AKR1B10 was down-regulated [50]. Moreover, AKR1B10 shares a high sequence identity (82%) with mouse AKR1B8, and both are mainly expressed in the small intestine and colon, and possess similar efficiency in carbonyl detoxification and lipid biosynthesis [2, 51]. Recently, Shen *et al.* [52] have shown an increase in DNA mutations and dysplasia, and an impairment of epithelial cell proliferation in AKR1B8-deficient mice by using the dextran sulfate sodium model of colitis. These reports collectively emphasize that AKR1 isozymes such as AKR1B10 and AKR1B8 may play a vital role in modulating the development of ulcerative colitis and colitis-associated colorectal cancer in mammals. However, the mechanisms underlying AKR1B10 overexpression in many non-digestive tract cancers [12, 13, 15, 18] are still not well elucidated, therefore efforts are needed to discover the relationship between AKR1B10 overexpression and cancer formation.

2.2.2. AKR1B10 in Cancer Development

Numerous studies indicated that AKR1B10 was implicated in the development of various cancers. In colorectal carcinoma HCT-8 cells, knockdown of AKR1B10 by siRNA (small interfering RNA) resulted in growth inhibition and cell susceptibility to reactive carbonyls [10]. In both HCT-8 and lung carcinoma NCI-H460 cells, knockdown of AKR1B10 promoted cell apoptosis, which was mediated through mitochondrial dysfunction and oxidative stress [46]. The growth of hepatocellular carcinoma in xenograft mice was inhibited by AKR1B10 silencing [53]. In MHCC97H hepatoma cell line, knockdown of AKR1B10 decreased the expression of oncogenes such as c-myc, c-fos and N-ras, and the proliferation-associated gene Ki-67, while increased expression of apoptosis-promoting genes bax and caspase-3 [54]. These data suggest that AKRlBl0 might promote cell proliferation, inhibit apoptosis and then induce malignant transformation in hepatocytes via the regulation of oncogene expression. In contrast, silencing of AKR1B10 in tumor cells could inhibit cancer cell growth and cancer progression. AKR1B10 overexpression has shown to increase cell growth in U937 leukemia cells, which was inhibited by an AKR1B10 inhibitor [55]. Similar observations have been reported in pancreatic [56] and breast cancer cells [15, 45].

2.2.3. AKR1B10 and Cancer Chemoresistance

It has been reported that AKR1B10 also shows reduction activity for the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, the antiemetic 5-HT3 (type 3 serotonin) receptor antagonist dolasteron, and the anticancer drugs oracin and daunorubicin [11]. Furthermore, recent studies indicate that the C13 ketonic group in daunorubicin and idarubicin can be reduced by the high level of AKR1B10 protein, leading to drug resistance of cancer cells to carbonyl group-bearing cytostatic drugs [39, 57, 58]. This is a mechanism of chemoresistance in AKR1B10-overexpressed tumors. AKR1B10 was upregulated in doxorubicin-resistant human gastric cancer MKN45 cells [59], mitomycin c-resistant colon cancer HT29 cells [60], and cisplatin-resistant human lung cancer A549 cells [61]. Phenolphthalein and lithocholic acid can decrease the reduction of dolasetron by inhibiting AKR1B10 activity, leading to a potentiation of dolasetron actions [11]. Multiple studies reported that fibrates were able to inhibit AKR1B10 activity [62, 63]. Fibrates and fibrate analogs including fenofibrate, Wy-14,643, and ciprofibrate were reported to inhibit the carbonyl reduction activity of AKR1B10 in a mixed non-competitive manner [62]. These findings suggest that AKR1B10 is well involved in the drug resistance of cancer cells. Recently, Matsunaga *et al*. [55] reviewed that the roles of AKR1B10 in cancer chemoresistance were mainly due to its three capacities, namely, to reduce anticancer drugs into their harmless forms, to protect cancer cells from damage evoked by the drugs, and to offset their lethal effects through activating growth signaling pathways.

3. STRUCTURE OF AKR1B10-INHIBITOR COMPLEXES

AKR1B10 protein folds into an $(\alpha/\beta)_8$ barrel topology, a typical structure for the aldo-keto reductases [43, 64, 65]. AKR1B10 shares high amino acid sequence identity and similar topology with AR, and thus, the structures of these two enzymes in complex with $NADP^+$ and inhibitors are urgently needed for screening selective AKR1B10 inhibitors.

There are currently more than 100 X-ray structures of AR deposited in the PDB (Protein Data Bank). Nevertheless, only 13 different crystallographic structures of AKR1B10 have been released (Table **1**). AKR1B10 and AR have different substrate specificity and inhibitor selectivity mainly due to residue differences in their three external and variable loops [35].

Gallego *et al.* [4] solved the first crystal structure of AKR1B10 in complex with $NADP^+$ and tolrestat (**1**), a powerful inhibitor of AKR1B1 designed to treat type 2 diabetic complications [66]. Subsequently, *in vitro* studies have discovered potent and selective AKR1B10 inhibitors [24, 26-29, 33, 34, 38]. The analysis of interactions between AKR1B10 and tolrestat shows that residues Tyr-49, His-111, and Trp-112 form hydrogen bonds with the carboxyl group in tolrestat, together with the positive charge of cofactor, defining an anion-binding pocket. The so-called "specificity pocket", a hydrophobic subpocket within the active site of AR and AKR1B10, which appears upon the binding of certain inhibitors, causing an induced-fit phenomenon [67], is defined by the nicotinamide moiety of the cofactor and Trp-21, Val-48, Trp-80, Trp-112, Phe-116, Phe-123, Trp-220, Cys-299, Val-301, Gln-303. Tolrestat is bound in the substrate-binding pocket of AKR1B10, a wide and hydrophobic pocket defined by the amino acid residues in the active site and three external loops [68, 69], establishing essentially the same interactions as in AKR1B1 [70]. AKR1B10 shows higher retinaldehyde reductase activity than AKR1B1 [5, 6], especially high activity towards all-*trans*-retinaldehyde [4]. The external part of the substrate-binding site, including positions 125 and 301, where the retinoid cyclohexene ring binds, is responsible for high activity of AKR1B10 to all-*trans*-retinaldehyde, and substitutions in the cyclohexene ring also influence the specificity. In principle, any compound with AKR1B1 inhibitory activity should form key hydrogen bonds with Tyr-48, His-110 and Trp-111 in the catalytic domain [71]. Correspondingly, conserved residues Tyr-49, His-111 and Trp-112 play a key role in AKR1B10 catalytic and inhibitor activity [4]. Two steroidal derivatives were synthesized as potent and selective AKR1B10 inhibitors [30], but they cannot make full use of the three residues to establish hydrogen bonds. Thus, adding a carboxyl group to the steroid ring may help for designing new efficient steroidal derivatives against AKR1B10. The structures of AKR1B10 in complex with tolrestat and AKR1B10 V301L mutant in complex with AKR1B1 inhibitors fidarestat (**6**) or sorbinil (**4**) [72] (PDB ID: 1ZUA, 4GAB and 4GA8, respectively) show almost identical inhibitor binding patterns to those of the corresponding AKR1B1-inhibitor (tolrestat, fidarestat or sorbinil) complex structures (PDB ID: 2FZD, 1EF3, 2PDK, respectively). However, the selectivity of AKR1B10 inhibitors cannot be explained only by the inhibitor binding pattern similarity. Crystal structures of the AKR1B10 holoenzyme and of the ternary complexes with several ARIs or with AKR1B10 inhibitors were reported by Zhang *et al.* [73]. These structures indicated that Trp-112 side-chain flipping at the active site of AKR1B10 and inhibitor-induced "specificity pocket" opening result in a similar geometry of the binding site between AKR1B1-inhibitor and AKR1B10-inhibitor complexes. The inhibitor selectivity between AKR1B10 and AKR1B1 are affected by the native conformations of Trp-112 (Trp-111). The crystal structure of AKR1B10 in complex with caffeic acid phenethyl ester (CAPE, **22**), an efficient AKR1B10 inhibitor *in vitro* [74, 75], not only shows that classical hydrogen bonds are indeed formed between the catechol moiety of CAPE and the active-

Table 1. Crystal Structures for AKR1B10 Deposited in the Protein Data Bank.

AKR1B10	CoFactor	Inhibitor	IC_{50} (μM)	Resolution (Å)	PDB ID	Release Date
Wild type	$NADP^+$	Tolrestat (1)	0.012	1.25	1ZUA	Nov 2006
Val301Leu	$NADP^+$	Fidarestat(6)	33	1.60	4GAB	Mar 2013
Val301Leu	$NADP^+$	Sorbinil (4)	9.6	1.94	4GA8	Aug 2013
Wild type	$NADP^+$	–	–	1.92	4GQG	Aug 2013
Wild type	$NADP^+$	Caffeic acid phenethyl ester(22)	0.08	2.10	4GQ0	Aug 2013
Wild type	$NADP^+$	Flufenamic acid	0.76	2.10	4I5X	Oct 2013
Wild type	$NADP^+$	Zopolrestat (3)	0.62	2.20	4JII	Oct 2013
Wild type	$NADP^+$	Epalrestat (5)	0.33	2.30	4JIH	Oct 2013
AKME2MU	$NADP^+$	JF0064 (29)[a]	1	1.75	4ICC	Feb 2014
AKME2MU	$NADP^+$	Sulindac (34)	0.35	1.45	4WEV	Jan 2015
AKME2MU	$NADP^+$	JF0049 (30)[b]	0.45	1.70	4XZL	Nov 2015
Methylated wild type	$NADP^+$	–	–	1.75	4XZM	Nov 2015
AKME2MU	$NADP^+$	–	–	1.70	4XZN	Nov 2015

[a] JF0064, 2,2',3,3',5,5',6,6'-octafluoro-4,4'-biphenyldiol.
[b] JF0049, 2-(2, 4-dioxo-3-(2, 3, 4, 5-tetrabromo-6-methoxybenzyl)-3, 4-dihydropyrimidin-1 (2H) -yl) acetic acid.
AKME2MU, methylated AKR1B10 K125R/V301L mutant.

site residues of AKR1B10, but also clearly explains the different selectivity of CAPE derivatives towards AKR1B1 and AKR1B10. CAPE induces slight movements of Phe-123 and Leu-302 that favor interactions between the phenethyl tails with the so-called specificity pocket, but does not induce meaningful conformational changes at the active site in AKR1B10. This finding is very different from the AKR1B10/$NADP^+$/tolrestat crystal structure, in which tolrestat induces the movement of the Leu-302-Ser-304 segment, which closes the specificity pocket, and side-chain flip of Trp-112 [4].

By using the surface lysine methylation (SLM) technique, that can improve the success rate of protein crystallization by chemically methylating lysine residues, Cousido-Siah *et al.* solved the structure of the methylated AKR1B10K125R/V301L-JF0064 (**29**) complex [35]. The polyhalogenated compound is characterized as a novel lead, a tetrafluorophenol moiety that targets both AKR1B10 and AR. The same group also solved the methylated AKR1B10K125R/V301L-sulindac complex, which showed that sulindac (**34**) and its sulfone might be a drug lead for selective AKR1B10 and AR inhibitors [32], and the methylated AKR1B10K125R/V301L-JF0049, which explained that the selectivity of JF0049 (**30**) for AKR1B10 is probably due to its bulkier aryl moiety that cannot occupy the AR specificity pocket but fitting into the larger AKR1B10 active site, including a subpocket defined by loop A that does not exist in AR [36]. These studies collectively pave the way for future efforts in structure-guided drug discovery to target AKR1B10.

4. AKR1B10 INHIBITORS

As a novel target for prevention and treatment of cancer, many inhibitors of AKR1B10 have been extensively explored during the past decade. According to their origin, AKR1B10 inhibitors are divided into four main classes: 1) well-known ARIs, 2) endogenous substances, 3) natural-based derivatives and 4) synthetic products. The structures of typical inhibitors from each class and their selectivity of enzymes are shown in Table **2**.

Table 2. The Chemical Structures of AKR1B10 Inhibitors.

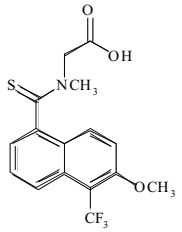
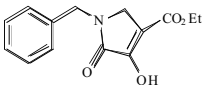
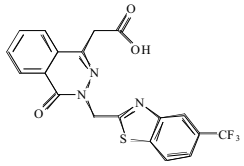
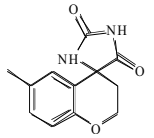
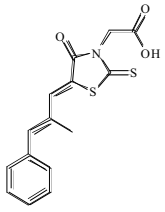
No.	AKR1B10 Inhibitors	Chemical Formula	Selectivity	Ref.
1	Tolrestat		AKR1B1 AKR1B10 AKR1A1	[73]
2	EBPC Ethyl-1-benzyl-3-hydroxy-2(5H)-oxopyrrole-4-carboxylate		AKR1B1 AKR1B10 AKR1A1	[62]
3	Zopolrestat		AKR1B1 AKR1A1 AKR1B10	[62, 73]
4	Sorbinil		AKR1B1 AKR1A1 AKR1B10	[62, 73]
5	Epalrestat		AKR1B1 AKR1A1 AKR1B10	[73]

Table (2) contd….

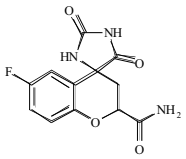
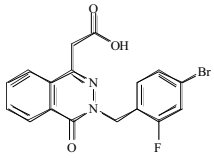
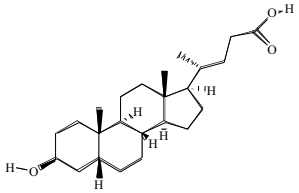
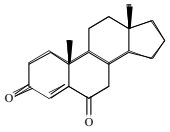
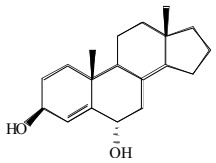
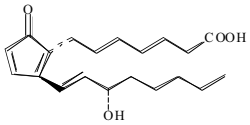
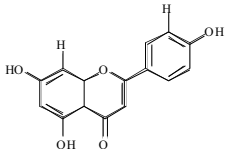
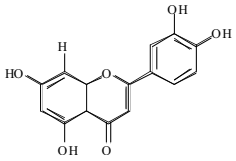
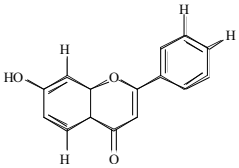
No.	AKR1B10 Inhibitors	Chemical Formula	Selectivity	Ref.
6	Fidarestat		AKR1B1 AKR1A1 AKR1B10	[72, 76]
7	Statil [3-(4-Bromo-2-fluorobenzyl)-4-oxo-3H-phthalazin-1-yl] acetic acid		AKR1B1 AKR1A1 AKR1B10	[77]
8	Isolithocholic acid		AKR1B10 AKR1B1	[38]
9	Androst-4-ene-3,6-dione		AKR1B10 AKR1B1	[30]
10	Androst-4-ene-3β,6α-diol		AKR1B10 AKR1B1	[30]
11	PGA1		AKR1B10 AKR1B1?	[33]
12	Apigenin		AKR1B10 AKR1B1	[78]
13	Luteolin		AKR1B10 AKR1B1	[78]
14	7-Hydroxyflavone		AKR1B10 AKR1B1	[78]

Table (2) contd….

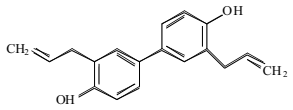
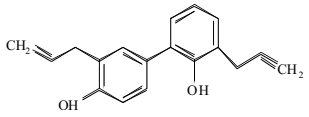
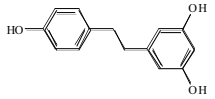
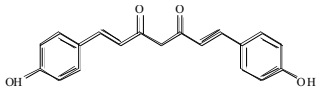
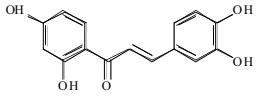
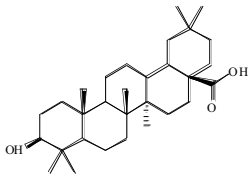
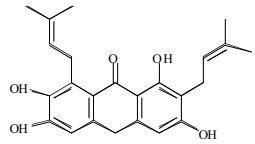
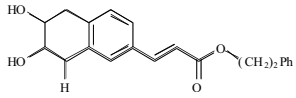
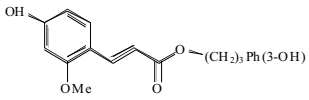
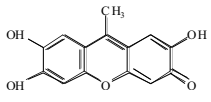
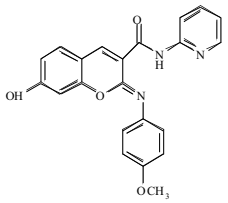
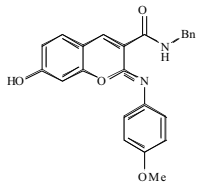
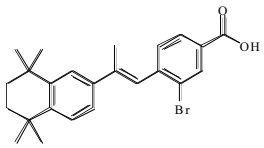
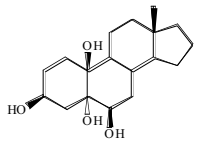
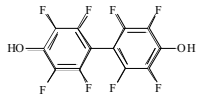
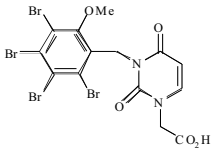
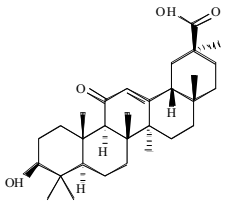
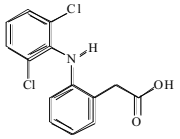
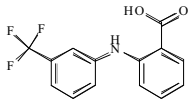
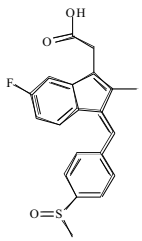
No.	AKR1B10 Inhibitors	Chemical Formula	Selectivity	Ref.
15	Magnolol		AKR1B10 AKR1B1	[24]
16	Honokiol		AKR1B10 AKR1B1	[24]
17	Resveratrol		AKR1B10 AKR1B1	[24]
18	BDMC Bisdemethoxycurcumin		AKR1B10 AKR1B1	[24]
19	Butein		AKR1B10 AKR1B1	[28]
20	Oleanolic acid		AKR1B10 AKR1B1	[29]
21	γ-Mangostin		AKR1B10 AKR1B1 AKR1A1	[34]
22	CAPE		AKR1B10 AKR1B1	[74]
23	3-(4-Hydroxy-2-methoxyphenyl) acrylic acid 3-(3-hydroxyphenyl) propyl ester		AKR1B10 AKR1B1	[74]
24	MTF 9-Methyl-2,3,7-trihydroxy-6- fluorone		AKR1B10 AKR1B1	[25]
25	(Z)-2-(4-Methoxyphenylimino)-7-hydroxy-N -(pyridin-2-yl)-2H-chromene-3 -carboxamide		AKR1B10 AKR1B1 AKR1A1	[27]

Table (2) contd….

No.	AKR1B10 Inhibitors	Chemical Formula	Selectivity	Ref.
26	7-Hydroxy-2-(4-methoxyphenylimino)-2H-chromene-3 - carboxylic acid benzylamide		AKR1B10 AKR1B1	[31]
27	UVI2008		AKR1B10 AKR1B1 AKR1C3?	[79]
28	Androstane-3β,5α, 6β,19-tetraol		AKR1B10 AKR1B1?	[80]
29	JF0064		AKR1B10 AKR1B1	[35]
30	JF0049		AKR1B10 AKR1B1	[36]
31	GA Glycyrrhetic acid		AKR1B10 AKR1B1 AKR1C3	[26]
32	Diclofenac		AKR1B10 AKR1B1 AKR1C3	[26]
33	Flufenamic acid		AKR1B10 AKR1B1 AKR1C3	[26]
34	Sulindac		AKR1B10 AKR1B1 AKR1C3	[48, 81]

4.1. Aldose Reductase Inhibitors (ARIs)

Some of the present ARIs (aldose reductase inhibitors) have various undesirable side effects in their clinic application, which were mainly due to the cross-inhibition of ARIs versus other enzymes. Among them, AKR1A1 has been systematically analyzed as the main cross-inhibition target [65, 82, 83]. Selectivity of ARIs for AKR1B10 also has been attracting an increasing attention for its high similarity to AKR1B1. Tolrestat, a well-known ARI [4, 62, 63], was reported to be the most potent inhibitor for AKR1B10 (**1**). It inhibited the reductase activity of AKR1B10 with an IC_{50} value of approximately 10 nM. In monkey kidney fibroblast COS-1 cells, ectopically expressed AKR1B10 was also completely inhibited by 10 μM tolrestat [4, 5]. Furthermore, ARIs including EBPC (**2**), zopolrestat (**3**) (US4939140) [84] and sorbinil (**4**) (US4130714) [85] also inhibit AKR1B10 activity [62, 63]. Epalrestat (**5**) (US4464382), an ARI [86], has been approved for the treatment of diabetic complications in Japan several years ago [87-89]. To improve its efficiency, various preparations of epalrestat have been introduced such as a potassium anhydrate salt, a sodium anhydrate salt, and a 1-(2-hydroxyethyl)-pyrrolidine anhydrate salt (WO2010011922, US20110275681) [90, 91]. Moreover, novel cocrystal preparations of epalrestat were also reported, including choline hydrogen diepalrestat, betaine hydrogen diepalrestat and choline hydrogen diacid cocrystal of epalrestat (WO2010028132, WO2010011926, US2015057319) [92-94]. Nevertheless, epalrestat was also reported to inhibit AKR1B10 [73]. Except for epalrestat, the ARI fidarestat(**6**) could also be used as a therapeutic drug for its low *in vivo* side effects [95]. Fidarestat showed low inhibitory effect on wild-type AKR1B10, but presented high potency against AKR1B10 V301L mutant [72].Recent studies have indicated that statil (**7**), an ARI, can suppress the growth and proliferation of BT-20 (breast cancer cell lines) and NCI-H460 (lung cancer cell lines), and also shows a good AKR1B10 inhibitory effect [77]. These studies indicated that the overexpression of AKR1B10 in cancers could be eliminated by ARIs. A review about ARIs also suggested that these compounds may be novel antitumor drugs by targeting AKR1B10 [96].

4.2. Endogenous Substances

Endogenous compounds including steroids and their metabolites were reported to inhibit the reductase activity of AKR1B10 [38]. Cholanic acid derivatives, C21-, C19- and C18-steroids displayed IC_{50} values to AKR1B10 in the range of 0.03-40 μM. Among the cholanic acids and their derivatives, isolithocholic acid (**8**) was the most selective inhibitor for AKR1B10. Docking analysis indicated that tolrestat and isolithocholic acid bind to overlapping sites within the active site. Subsequently, a series of ketosteroids and hydroxysteroids were designed and synthesized to screen out more efficient AKR1B10 inhibitors [30]. Among them, androst-4-ene-3,6-dione (**9**) was the most specific inhibitor for AKR1B10 with an AKR1B10/AKR1B1 selectivity ratio of 195 and androst-4-ene-3β,6α-diol (**10**) was the most potent inhibitor for AKR1B10 with an IC_{50} value of 0.5 μM. Virtual screening multiple binding pocket conformation indicated that the carbonyl oxygen of androst-4-ene-3,6-dione cannot form hydrophobic interactions with Phe-115, Leu-300 and Pro-310, which are important in supporting AKR1B1 inhibition activity [71]. Two hydrogen bonds were formed between carbonyl oxygen of androst-4-ene-3,6-dione with residues Tyr-49 and His-111 of AKR1B10, while only one hydrogen bond was formed between hydroxyl of androst-4-ene-3β,6α-diol and residue Trp-112. This can well explain the function differences between them. Cyclopentenone prostaglandins (cyPG) are endogenous reactive eicosanoids and cyclopentenone prostaglandin A1 (PGA1, **11**) has been reported recently to inhibit AKR1B10 with high efficiency and to increase the efficacy of the antitumor drug doxorubicin [33]. Mutagenesis studies suggested that Cys299 is necessary for PGA1-mediated inhibition of AKR1B10. Inhibition of AKR1B10 by endogenous substances could balance the expression of AKR1B10 and their metabolic regulation *in vivo*.

4.3. Natural-Based Derivatives

Natural-based derivatives are composed of five subclasses: plant polyphenols, pentacyclic triterpenoids, xanthone derivatives, caffeic acid phenethyl ester (CAPE) derivatives, and other compounds extracted from Korean native plants.

Studies have been performed to check the inhibitory effects of plant polyphenols on AKR1B10 and AKR1B1. Flavones could be used as a new structural type of AKR1B10 inhibitor [78]. The strongest flavones, apigenin (**12**), luteolin (**13**), and 7-hydroxyflavone (**14**), can significantly inhibit reductase activities of human recombinant AKR1B10. Curcumin and curcumin-like derivatives were tested to target AKR1B10 with high affinities [97]. Curcuminoids, magnolol (**15**), honokiol (**16**) and resveratrol (**17**) are active substances with higher efficiency for AKR1B10 than for AKR1B1 [24]. Among them, bisdemethoxycurcumin (BDMC, **18**) (CN104591987) [98] is the most prominent one, showing an AKR1B10/AKR1B1 selectivity ratio of 85 and a low IC_{50} value. The related docking and site-directed mutagenesis analyses suggest that Gln-303, Val-301 and Gln-114 are all essential for curcuminoid potency and selectivity against AKR1B10. The above substances were also reported to present antitumor properties [99-102], and the inhibition effect on AKR1B10 might be one of mechanisms on their anticancer activities. Other plant polyphenols, such as butein (WO2014081124) [103] isolated from *Rhus verniciflua*, a medicinal plant, and dicaffeoyl quinic acid (CN104710312) [104] were also reported to can inhibit AKR1B10 [28, 105]. Compounds isolated from *R. verniciflua* showed potent inhibitory effects on AKR1B1 and AKR1B10 [106, 107]. Song *et al.* [28] reported that butein (**19**) extracted from *R. verniciflua* was a potent uncompetitive inhibitor for AKR1B10 and its inhibition pattern was the same as that found against AKR1B1 [106], although its potency against AKR1B1 was slightly higher. Numerous former studies have indicated that human bladder carcinoma and hepatoma could also be suppressed by butein through various mechanisms [108, 109]. Pentacyclic triterpenoids, such as plant-derived betulinic acid, are cytotoxic to various cancer cells [110-113]. Pentacyclic triterpenoids have a variety of functions including hepatoprotective, anti-HIV, anti-inflammatory and immunoregulation. Most Asian countries have used plants containing these triterpenoids as herbal medicines. Pentacyclic triterpene oleanolic acid (**20**) (CN101768201) [114] can

competitively inhibit AKR1B10, which was the most potent and selective inhibitor against AKR1B10 (1370-fold versus AKR1B1) and residues Gln-303 and Val-301 are indispensable for its high efficiency [29]. Xanthones extracted from mangosteen peel, have been reported to exhibit anti-cancer effects [115, 116]. α- and γ-mangostins, are xanthone derivatives, constituents of the pericarp of mangosteen. Both of them showed an inhibitory effect on AKR1B10 in a competitive manner, and γ-mangostin (**21**) was the more potent one [34]. The putative binding model revealed that the high inhibition performance by γ-mangostin was due to its tight binding, which was mainly provided by Gln-303, Val-301, Phe-123 and Trp-220. The reason for the reduced inhibitory potency of α-mangostin was that its 7-methoxy group changed the location of the inhibitor in the substrate-binding site of the enzyme.

Cinnamic acid and analogues of its phenolic, these natural-derived substances, have attracted a lot of attention as antitumor agents [117]. Soda *et al.* [74] compared the inhibitory actions of cinnamic acid derivatives extracted from propolis on AKR1B1 and recombinant AKR1B10, and found that caffeic acid phenethyl ester (CAPE,**22**) and its derivative 3-(4-hydroxy-2-methoxyphenyl) acrylic acid 3-(3-hydroxyphenyl) propyl ester (**23**) were the most potent competitive inhibitors for AKR1B10. Compound **23** displayed an AKR1B10/AKR1B1 selectivity ratio of 790; its high inhibitory selectivity was determined by the interactions between the residues Val-301 and Gln-114 of AKR1B10 and the 2-methoxy and 3-hydroxyl groups of itself, respectively. Pharmaceutical composition containing extracts of many native plants (WO2011052846) [118] could reduce the activation of AKR1B10 in cancer and nutraceutical food containing extracts of *Ligularia fischeri* var. s*piciformis Nakai* (KR20110118748) [119] could be used to prevent or to treat cancer for their inhibitory activity toward AKR1B10. Lead compounds from natural products for AKR1B10 inhibitor discovery are abundant, which could facilitate us to find highly selective inhibitors for AKR1B10.

4.4. Synthetic Products

Synthetic products are divided into two classes. One class is non-drug synthetic compounds, which include a fluorone derivative, chromene derivatives, aromatic retinoids (arotinoids), polybrominated compounds, and so on. The other class includes drugs, such as non-steroidal anti-inflammatory (NSAID).

4.4.1. Non-Drug Synthetic Compounds

Through the approach of selecting chemical complementarity and steric fitting within the active site of the enzyme by *in silico* screening, 9-methyl-2,3,7- trihydroxy-6-fluorone (MTF, **24**), a fluorone derivative, was demonstrated to be a potent competitive inhibitor with 4-fold selectivity for AKR1B10 over AKR1B1 [25]. The molecular docking model and the mutagenesis analysis indicated that Lys-125 and Gln-303 were the residues participating in its binding to AKR1B10. By adopting the virtual screening approach, some chromene-3-carboxamide derivatives were identified as potent competitive inhibitors of AKR1B10. *(Z)*-2-(4-methoxyphenylimino)-7-hydroxy-N-(pyridin-2-yl)-2H chromene-3-carboxamide (**25**), a *(Z)*-2-(phenylimino)-7-hydroxy-N-(pyridin-2-yl)-2H- chromene-3-carboxamide (PHPC) derivative, most potently inhibited AKR1B10, and the 4-methoxy group of **25** on its 2-phenylimino moiety was a necessary for inhibitory activity [27]. Lately, the inhibitory effect of some **25**-based synthetic derivatives on AKR1B10 was evaluated and the most potent inhibitor among them was 7-hydroxy-2-(4-methoxyphenylimino)-2H-chromene-3-carboxylic acid benzylamide (**26**) [31]. Not the 4-methoxy group, but its 7-hydroxyl group in the chromene ring is an essential structure base for inhibitory activity. The interactions between the 7-hydroxyl group and the benzylamide moiety of **26** and the enzyme catalytic residues Tyr-49, His-111 and Trp-220 are necessary for the potent inhibition. Recently, some aromatic retinoid (arotinoids) were synthesized and their inhibitory potency against AKR1B10 and AKR1B1 was explored [79]. Some of them bind to RXR (retinoid X receptors) and others to RAR (retinoic acid receptors), and even exhibit higher selectivity for AKR1B10. UVI2008 (**27**) [120], a retinoic acid receptor (RAR) β/γ agonist, was a potent and selective inhibitor of AKR1B10 with its carboxyl group binding to the anion-binding pocket of the enzyme. It worked as both receptors' ligand and AKR inhibitor, and could be regarded as a lead agent in the design of bifunctional drugs [79]. Androstane-3β,5α,6β,19-tetraol (**28**) (CN104497086)[80], a polyhydroxysterol compound, has high inhibitory activity on AKR1B10 and exhibits good selectivity. It can be used as a selective inhibitor of AKR1B10. Newly, two synthesized polyhalogenated compound 2,2′,3,3′,5,5′,6,6′-octafluoro-4,4′-biphenyldiol (JF0064, **29**) and 2-(2,4-dioxo-3-(2,3,4,5-tetrabromo-6-methoxybenzyl)-3,4-dihydropyrimidin-1(2H)-yl) acetic acid (JF0049, **30**) were reported to be potent AKR1B10 inhibitors [35, 36]. JF0064 is a non-competitive inhibitor for both AR and AKR1B10. The binding structures show that JF0064 does not open the specificity pocket in either of the two structures, however it interacts with the catalytic residues of the enzymes through a negatively charged hydroxyl group (i.e. the acidic phenol) [35]. JF0049 is found to be selective for AKR1B10, which is probably due to its bulkier aryl moiety unable to occupy the AR specificity pocket and its improved fitting into the larger AKR1B10 active site, including a subpocket defined by loop A [36]. The application of 5-carboxymethyl-3-mercapto-1,2,4-triazino-[5,6-B]indoles (WO2015057175) [121], and drug composition containing this compounds was due to their ability to inhibit AKR1B1 and AKR1B10. Compounds with a 2-cyclopentenone structure (WO 2011117453) [122] can also be used as inhibitors for AKR1B10. Based on these effective synthetic compounds, the development of more potent and selective AKR1B10 inhibitors is promising.

4.4.2. Drugs

NSAIDs are effective for treating breast, prostate, lung and colon cancers [123, 124]. Glycyrrhetic acid (GA) (**31**), as an NSAID, inhibits the growth of liver cancer [125, 126]. Diclofenac (**32**), one kind of NSAID, has been reported as a selective AKR1B10 inhibitor [127]. The inhibitory effect of NSAIDs on ARK1B10 and AKR1B1 were used to screen selective AKR1B10 inhibitors from other drugs applied in clinic [26]. It was found that GA, *N*-phenyl-anthranilic acids, flufenamic acid (**33**), and diclofenac are potent and selective competitive inhibitors of AKR1B10, and the hydrogen-bond

interactions between the NSAIDs and residues Gln-114, Val-301 and Ser-304, together with the side chain of Val-301, are of great importance in the inhibitory potency and selectivity of NSAIDs [26]. The inhibitory potency of NSAIDs against AKR1B10 is comparable or lower than that against AKR1C3 [128-131], while GA is less potent against AKR1C3 [131]. Sulindac **(34)** belongs to the indole acetic acids of NSAIDs and is also a potent competitive inhibitor of AKR1B10. It inhibits the occurrence of pancreatic cancer through suppressing K-ras protein prenylation by targeting AKR1B10 [48]. Consistent with the previous reports [81], sulindac has shown higher inhibitory potency against AR than AKR1B10, which might be illustrated by the two ordered and buried water molecules only existing in AKR1B10 and the different orientation and stacking interaction given by Phe122/Phe123 [Protein Data Bank (PDB) entry 4WEV] [32]. These reports suggest that an alternative way to discover new AKR1B10 inhibitors is to screen currently approved clinical drugs.

5. CURRENT & FUTURE DEVELOPMENTS

The overexpression of AKR1B10 is identified in several human cancers. AKR1B10 is involved in tumor cell growth, cell survival and chemoresistance to antitumor drugs, thus being an attractive target for cancer diagnosis and treatment. Relative to the common expression of AKR1B1, AKR1B10 is a more specific tumor marker with a restricted distribution pattern in normal tissues. The development of highly selective AKR1B10 inhibitors will likely bring great benefits to cancer patients. Thus far, several selective AKR1B10 inhibitors have been developed, such as, BDMC (**18**) [24] Oleanolic acid (**20**) [29], 3-(4-hydroxy-2-methoxyphenyl)acrylic acid 3-(3-hydroxyphenyl) propyl ester (**23**) [74], isolithocholic acid (**8**) [38], and androst -4-ene-3,6-dione (**9**) [30]. They seem to be the most selective inhibitors for AKR1B10. Many *in vitro* studies have indicated that the AKR1B10 inhibitors can suppress cancer cell growth and proliferation [27, 55]. They could be promising anticancer drugs, however, clinical trial based on them has not been approved until now. Owing to the previous efforts on the development of potent inhibitors against AKR1B10, more effective and selective AKR1B10 inhibitors are hopefully to be found.

A potential hurdle which hampers the development and application of AKR1B10 inhibitors is that AKR family members share a structural similar active pocket for inhibitors and substrates. Therefore, the primary task of developing more selective AKR1B10 inhibitors is to identify the important structural differences among these enzymes. The three-dimensional structures of AKR1B10-coenzyme-inhibitor complexes can greatly facilitate the design and screening of AKR1B10 inhibitors. The “specificity pocket” was believed to be essential for inhibitors selectivity between AKR1B1 and AKR1A1, since there is no such a pocket formed in AKR1A1 [67]. The “specificity pocket” is also responsible for inhibitor selectivity between AKR1B1 and AKR1B10. Previous reports suggested that inhibitor-induced "specificity pocket" opening and Trp-112 side-chain flip at the active site of AKR1B10 results in the similar geometry of the binding site between AKR1B1-inhibitor and AKR1B10-inhibitor complexes. The orientation of the native Trp-112 side-chain provides a broader active site of AKR1B10, which facilitates the implant of AKR1B10 inhibitors [73]. Selective AKR1B10 inhibitors indicate that the increased accessibility of the anionic site of AKR1B10 is essential for their selectivity. It suggests that bulky and rigid molecules are more likely to be selective inhibitors.

A comprehensive understanding of AKR1B10 structure and function, as well as elucidation of the specific AKR1B10-inhibitor interactions, will most probably lead to more highly selective and efficient AKR1B10 inhibitors with low toxicity caused by cross-inhibition, which will eventually contribute to effective cancer therapy.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

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REFERENCES

[1] Hyndman DJ, Flynn TG. Sequence and expression levels in human tissues of a new member of the aldo-keto reductase family. Biochim Biophys Acta 1998; 1399 (2-3):198-202.

[2] Cao D, Fan ST, Chung SS. Identification and characterization of a novel human aldose reductase-like gene. J Biol Chem 1998; 273 (19):11429-35.

[3] Gimenez-Dejoz J, Kolar MH, Ruiz FX, Crespo I, Cousido-Siah A, Podjarny A, *et al*. Substrate specificity, inhibitor selectivity and structure-function relationships of aldo-keto reductase 1B15: A novel human retinaldehyde reductase. PLoS One 2015; 10 (7): e0134506.

[4] Gallego O, Ruiz FX, Ardèvol A, Domínguez M, Alvarez R, de Lera AR, *et al*. Structural basis for the high all-*trans*-retinaldehyde reductase activity of the tumor marker AKR1B10. Proc Natl Acad Sci U S A 2007; 104 (52): 20764-9.

[5] Crosas B, Hyndman DJ, Gallego O, Martras S, Parés X, Flynn TG, *et al*. Human aldose reductase and human small intestine aldose reductase are efficient retinal reductases: Consequences for retinoid metabolism. Biochem J 2003; 373 (Pt 3): 973-9.

[6] Gallego O, Belyaeva OV, Porté S, Ruiz FX, Stetsenko AV, Shabrova EV, *et al*. Comparative functional analysis of human medium-chain dehydrogenases, short-chain dehydrogenases/reductases and aldo-keto reductases with retinoids. Biochem J 2006; 399 (1): 101-9.

[7] Spite M, Baba SP, Ahmed Y, Barski OA, Nijhawan K, Petrash JM, *et al*. Substrate specificity and catalytic efficiency of aldo-keto reductases with phospholipid aldehydes. Biochem J 2007; 405 (1): 95-105.

[8] Zhong L, Liu Z, Yan R, Johnson S, Zhao Y, Fang X, *et al*. Aldo-keto reductase family 1 B10 protein detoxifies dietary and lipid-derived alpha, beta-unsaturated carbonyls at physiological levels. Biochem Biophys Res Commun 2009; 387 (2): 245-50.

[9] Shen Y, Zhong L, Johnson S,Cao D. Human aldo-keto reductases 1B1 and 1B10: a comparative study on their enzyme activity toward electrophilic carbonyl compounds. Chem Biol Interact 2011; 191 (1-3): 192-8.

[10] Yan R, Zu X, Ma J, Liu Z, Adeyanju M,Cao D. Aldo-keto reductase family 1 B10 gene silencing results in growth inhibition of co-

lorectal cancer cells: Implication for cancer intervention. Int J Cancer 2007; 121 (10): 2301-6.

[11] Martin HJ, Breyer-Pfaff U, Wsol V, Venz S, Block S, Maser E. Purification and characterization of AKR1B10 from human liver: Role in carbonyl reduction of xenobiotics. Drug Metab Dispos 2006; 34 (3): 464-70.

[12] Heringlake S, Hofdmann M, Fiebeler A, Manns MP, Schmiegel W, Tannapfel A. Identification and expression analysis of the aldo-ketoreductase1-B10 gene in primary malignant liver tumours. J Hepatol 2010; 52 (2): 220-7.

[13] Fukumoto S, Yamauchi N, Moriguchi H, Hippo Y, Watanabe A, Shibahara J, *et al*. Overexpression of aldo-keto reductase family protein AKR1B10 is highly correlated with smokers' non-small cell lung carcinomas. Clin Cancer Res 2005; 11 (5): 1776-85.

[14] Chung YT, Matkowskyj KA, Li H, Bai H, Zhang W, Tsao MS, *et al*. Overexpression and oncogenic function of aldo-keto reductase family 1B10 (AKR1B10) in pancreatic carcinoma. Mod Pathol 2012; 25 (5): 758-66.

[15] Ma J, Luo DX, Huang C, Shen Y, Bu Y, Markwell S, *et al*. AKR1B10 overexpression in breast cancer: Association with tumor size, lymph node metastasis and patient survival and its potential as a novel serum marker. Int J Cancer 2012; 131 (6): E862-71.

[16] Ohashi T, Idogawa M, Sasaki Y, Suzuki H,Tokino T. AKR1B10, a transcriptional target of p53, is downregulated in colorectal cancers associated with poor prognosis. Mol Cancer Res 2013; 11 (12): 1554-63.

[17] Yao HB, Xu Y, Chen LG, Guan TP, Ma YY, He XJ, *et al*. AKR1B10, a good prognostic indicator in gastric cancer. Eur J Surg Oncol 2014; 40 (3):318-24.

[18] Ha SY, Song DH, Lee JJ, Lee HW, Cho SY,Park CK. High expression of aldo-keto reductase 1B10 is an independent predictor of favorable prognosis in patients with hepatocellular carcinoma. Gut Liver 2014; 8 (6): 648-54.

[19] Cao, D.L. Methods for diagnosing bowel disease. US8551720 (**2013**).

[20] Luo DX, Huang MC, Ma J, Gao Z, Liao DF,Cao D. Aldo-keto reductase family 1, member B10 is secreted through a lysosome-mediated non-classical pathway. Biochem J 2011; 438 (1):71-80.

[21] Cao, D.L. ARL-1 specific antibodies. US8114606 (**2012**).

[22] Cao, D.L. ARL-1 specific antibodies and uses thereof. US8685666 (**2014**).

[23] Wang Y, Li Y, Wang T, Gu J, Zhao J,Pan Z. Detection of AKR1B10 in peripheral blood by anti-AKR1B10-conjugated CdTe/CdS quantum dots. Clin Lab 2015; 61 (9): 1267-74.

[24] Matsunaga T, Endo S, Soda M, Zhao HT, El-Kabbani O, Tajima K, *et al*. Potent and selective inhibition of the tumor marker AKR1B10 by bisdemethoxycurcumin: Probing the active site of the enzyme with molecular modeling and site-directed mutagenesis. Biochem Biophys Res Commun 2009; 389 (1):128-32.

[25] Zhao HT, Soda M, Endo S, Hara A, El-Kabbani O. Selectivity determinants of inhibitor binding to the tumour marker human aldose reductase-like protein (AKR1B10) discovered from molecular docking and database screening. Eur J Med Chem 2010; 45 (9):4354-7.

[26] Endo S, Matsunaga T, Soda M, Tajima K, Zhao HT, El-Kabbani O, *et al*. Selective inhibition of the tumor marker AKR1B10 by antiinflammatory *N*-phenylanthranilic acids and glycyrrhetic acid. Biol Pharm Bull 2010; 33 (5):886-90.

[27] Endo S, Matsunaga T, Kuwata K, Zhao HT, El-Kabbani O, Kitade Y, *et al*. Chromene-3-carboxamide derivatives discovered from virtual screening as potent inhibitors of the tumour maker, AKR1B10. Bioorg Med Chem 2010; 18 (7): 2485-90.

[28] Song DG, Lee JY, Lee EH, Jung SH, Nho CW, Cha KH, *et al*. Inhibitory effects of polyphenols isolated from *Rhus verniciflua* on Aldo-keto reductase family 1 B10. BMB Rep 2010; 43 (4):268-72.

[29] Takemura M, Endo S, Matsunaga T, Soda M, Zhao HT, El-Kabbani O, *et al*. Selective inhibition of the tumor marker aldo-keto reductase family member 1B10 by oleanolic acid. J Nat Prod 2011; 74 (5): 1201-6.

[30] Zhang W, Wang L, Zhang L, Chen W, Chen X, Xie M, *et al*. Synthesis and biological evaluation of steroidal derivatives as selective inhibitors of AKR1B10. Steroids 2014; 86: 39-44.

[31] Endo S, Hu D, Suyama M, Matsunaga T, Sugimoto K, Matsuya Y, *et al*. Synthesis and structure-activity relationship of 2-phenyliminochromene derivatives as inhibitors for aldo-keto reductase (AKR) 1B10. Bioorg Med Chem 2013; 21 (21): 6378-84.

[32] Cousido-Siah A, Ruiz FX, Crespo I, Porté S, Mitschler A, Porté X, *et al*. Structural analysis of sulindac as an inhibitor of aldose reductase and AKR1B10. Chem Biol Interact 2015; 234: 290-6.

[33] Díez-Dacal B, Gayarre J, Gharbi S, Timms JF, Coderch C, Gago F, *et al*. Identification of aldo-keto reductase AKR1B10 as a selective target for modification and inhibition by prostaglandin A(1): Implications for antitumoral activity. Cancer Res 2011; 71 (12): 4161-71.

[34] Soda M, Endo S, Matsunaga T, Zhao HT, El-Kabbani O, Iinuma M, *et al*. Inhibition of human aldose reductase-like protein (AKR1B10) by alpha- and gamma-mangostins, major components of pericarps of mangosteen. Biol Pharm Bull 2012; 35 (11): 2075-80.

[35] Cousido-Siah A, Ruiz FX, Mitschler A, Porté S, de Lera AR, Martín MJ, *et al*. Identification of a novel polyfluorinated compound as a lead to inhibit the human enzymes aldose reductase and AKR1B10: Structure determination of both ternary complexes and implications for drug design. Acta Crystallogr D Biol Crystallogr 2014; 70 (Pt 3):889-903.

[36] Ruiz FX, Cousido-Siah A, Porté S, Domínguez M, Crespo I, Rechlin C, *et al*. Structural determinants of the selectivity of 3-benzyluracil-1-acetic acids toward human enzymes aldose reductase and AKR1B10. Chem Med Chem 2015; 10 (12): 1989-2003.

[37] Chatzopoulou M, Alexiou P, Kotsampasakou E,Demopoulos VJ. Novel aldose reductase inhibitors: a patent survey (2006--present). Expert Opin Ther Pat 2012; 22 (11): 1303-23.

[38] Endo S, Matsunaga T, Mamiya H, Ohta C, Soda M, Kitade Y, *et al*. Kinetic studies of AKR1B10, human aldose reductase-like protein: endogenous substrates and inhibition by steroids. Arch Biochem Biophys 2009; 487 (1):1-9.

[39] Zhong L, Shen H, Huang C, Jing H,Cao D. AKR1B10 induces cell resistance to daunorubicin and idarubicin by reducing C13 ketonic group. Toxicol Appl Pharmacol 2011; 255 (1): 40-7.

[40] Quinn AM, Harvey RG, Penning TM. Oxidation of PAH trans-dihydrodiols by human aldo-keto reductase AKR1B10. Chem Res Toxicol 2008; 21 (11): 2207-15.

[41] Dragnev KH, Rigas JR,Dmitrovsky E. The retinoids and cancer prevention mechanisms. Oncologist 2000; 5 (5): 361-8.

[42] Penning TM. AKR1B10: A new diagnostic marker of non-small cell lung carcinoma in smokers. Clin Cancer Res 2005; 11 (5):1687-90.

[43] Ruiz FX, Porté S, Parés X, Farrés J. Biological role of aldo-keto reductases in retinoic acid biosynthesis and signaling. Front Pharmacol 2012; 3: 58.

[44] Liu TA, Jan YJ, Ko BS, Wu YJ, Lu YJ, Liang SM, *et al*. Regulation of aldo-keto-reductase family 1 B10 by 14-3-3epsilon and their prognostic impact of hepatocellular carcinoma. Oncotarget 2015; 6 (36): 38967-82.

[45] Ma J, Yan R, Zu X, Cheng JM, Rao K, Liao DF, *et al*. Aldo-keto reductase family 1 B10 affects fatty acid synthesis by regulating the stability of acetyl-CoA carboxylase-alpha in breast cancer cells. J Biol Chem 2008; 283 (6): 3418-23.

[46] Wang C, Yan R, Luo D, Watabe K, Liao DF, Cao D. Aldo-keto reductase family 1 member B10 promotes cell survival by regulating lipid synthesis and eliminating carbonyls. J Biol Chem 2009; 284 (39): 26742-8.

[47] Endo S, Matsunaga T, Ohta C, Soda M, Kanamori A, Kitade Y, *et al*. Roles of rat and human aldo-keto reductases in metabolism of farnesol and geranylgeraniol. Chem Biol Interact 2011; 191 (1-3): 261-8.

[48] Li H, Yang AL, Chung YT, Zhang W, Liao J,Yang GY. Sulindac inhibits pancreatic carcinogenesis in LSL-KrasG12D-LSL-Trp53R172H-Pdx-1-Cre mice via suppressing aldo-keto reductase family 1B10 (AKR1B10). Carcinogenesis 2013; 34 (9): 2090-8.

[49] Ames BN. Dietary carcinogens and anti-carcinogens. J Toxicol Clin Toxicol 1984; 22 (3): 291-301.

[50] Laffin B, Petrash JM. Expression of the aldo-keto reductases AKR1B1 and AKR1B10 in human cancers. Front Pharmacol 2012; 3: 104.

[51] Joshi A, Rajput S, Wang C, Ma J,Cao D. Murine aldo-keto reductase family 1 subfamily B: Identification of AKR1B8 as an ortholog of human AKR1B10. Biol Chem 2010; 391 (12): 1371-8.

[52] Shen Y, Ma J, Yan R, Ling H, Li X, Yang W, *et al*. Impaired self-renewal and increased colitis and dysplastic lesions in colonic mucosa of AKR1B8-deficient mice. Clin Cancer Res 2015; 21 (6): 1466-76.

[53] Satow R, Shitashige M, Kanai Y, Takeshita F, Ojima H, Jigami T, *et al*. Combined functional genome survey of therapeutic targets for hepatocellular carcinoma. Clin Cancer Res 2010; 16 (9): 2518-28.

[54] Wei W, Liang HJ, Cui JF, Guo K, Kang XN, Cao J, *et al*. [Effects of AKR1B10 gene silence on the growth and gene expression of HCC cell line MHCC97H]. Zhonghua Gan Zang Bing Za Zhi 2010; 18 (9): 666-71.

[55] Matsunaga T, Wada Y, Endo S, Soda M, El-Kabbani O,Hara A. aldo-keto reductase 1B10 and its role in proliferation capacity of drug-resistant cancers. Front Pharmacol 2012; 3: 5.

[56] Zhang W, Li H, Yang Y, Liao J,Yang GY. Knockdown or inhibition of aldo-keto reductase 1B10 inhibits pancreatic carcinoma growth via modulating Kras-E-cadherin pathway. Cancer Lett 2014; 355 (2): 273-80.

[57] Martin HJ, Maser E. Role of human aldo-keto-reductase AKR1B10 in the protection against toxic aldehydes. Chem Biol Interact 2009; 178 (1-3): 145-50.

[58] Balendiran GK. Fibrates in the chemical action of daunorubicin. Curr Cancer Drug Targets 2009; 9 (3): 366-9.

[59] Morikawa Y, Kezuka C, Endo S, Ikari A, Soda M, Yamamura K, *et al*. Acquisition of doxorubicin resistance facilitates migrating and invasive potentials of gastric cancer MKN45 cells through up-regulating aldo-keto reductase 1B10. Chem Biol Interact 2015; 230: 30-9.

[60] Matsunaga T, Yamane Y, Iida K, Endo S, Banno Y, El-Kabbani O, *et al*. Involvement of the aldo-keto reductase, AKR1B10, in mitomycin-C resistance through reactive oxygen species-dependent mechanisms. Anticancer Drugs 2011; 22 (5): 402-8.

[61] Matsunaga T, Yamaji Y, Tomokuni T, Morita H, Morikawa Y, Suzuki A, *et al*. Nitric oxide confers cisplatin resistance in human lung cancer cells through upregulation of aldo-keto reductase 1B10 and proteasome. Free Radic Res 2014; 48 (11): 1371-85.

[62] Verma M, Martin HJ, Haq W, O'Connor TR, Maser E, Balendiran GK. Inhibiting wild-type and C299S mutant AKR1B10; a homologue of aldose reductase upregulated in cancers. Eur J Pharmacol 2008; 584 (2-3): 213-21.

[63] Balendiran GK, Martin HJ, El-Hawari Y, Maser E. Cancer biomarker AKR1B10 and carbonyl metabolism. Chem Biol Interact 2009; 178 (1-3): 134-7.

[64] Jin Y,Penning TM. Aldo-keto reductases and bioactivation/detoxication. Annu Rev Pharmacol Toxicol 2007; 47:263-92.

[65] Barski OA, Tipparaju SM, Bhatnagar A. The aldo-keto reductase superfamily and its role in drug metabolism and detoxification. Drug Metab Rev 2008; 40 (4): 553-624.

[66] Foppiano M, Lombardo G. Worldwide pharmacovigilance systems and tolrestat withdrawal. Lancet 1997; 349 (9049): 399-400.

[67] Urzhumtsev A, Tete-Favier F, Mitschler A, Barbanton J, Barth P, Urzhumtseva L, *et al*. A 'specificity' pocket inferred from the crystal structures of the complexes of aldose reductase with the pharmaceutically important inhibitors tolrestat and sorbinil. Structure 1997; 5 (5): 601-12.

[68] Rondeau JM, Tete-Favier F, Podjarny A, Reymann JM, Barth P, Biellmann JF, *et al*. Novel NADPH-binding domain revealed by the crystal structure of aldose reductase. Nature 1992; 355 (6359): 469-72.

[69] Wilson DK, Bohren KM, Gabbay KH, Quiocho FA. An unlikely sugar substrate site in the 1.65 Å structure of the human aldose reductase holoenzyme implicated in diabetic complications. Science 1992; 257 (5066): 81-4.

[70] Steuber H, Zentgraf M, Gerlach C, Sotriffer CA, Heine A, Klebe G. Expect the unexpected or caveat for drug designers: multiple structure determinations using aldose reductase crystals treated under varying soaking and co-crystallisation conditions. J Mol Biol 2006; 363 (1): 174-87.

[71] Wang L, Gu Q, Zheng X, Ye J, Liu Z, Li J, *et al*. Discovery of new selective human aldose reductase inhibitors through virtual screening multiple binding pocket conformations. J Chem Inf Model 2013; 53 (9): 2409-22.

[72] Ruiz FX, Cousido-Siah A, Mitschler A, Farrés J, Parés X, Podjarny A. X-ray structure of the V301L aldo-keto reductase 1B10 complexed with NADP(+) and the potent aldose reductase inhibitor fidarestat: implications for inhibitor binding and selectivity. Chem Biol Interact 2013; 202 (1-3): 178-85.

[73] Zhang L, Zhang H, Zhao Y, Li Z, Chen S, Zhai J, *et al*. Inhibitor selectivity between aldo-keto reductase superfamily members AKR1B10 and AKR1B1: Role of Trp112 (Trp111). FEBS Lett 2013; 587 (22): 3681-6.

[74] Soda M, Hu D, Endo S, Takemura M, Li J, Wada R, *et al*. Design, synthesis and evaluation of caffeic acid phenethyl ester-based inhibitors targeting a selectivity pocket in the active site of human aldo-keto reductase 1B10. Eur J Med Chem 2012; 48: 321-9.

[75] Zhang L, Zhang H, Zheng X, Zhao Y, Chen S, Chen Y, *et al*. Structural basis for the inhibition of AKR1B10 by caffeic acid phenethyl ester (CAPE). Chem Med Chem 2014; 9 (4): 706-9.

[76] El-Kabbani O, Carbone V, Darmanin C, Oka M, Mitschler A, Podjarny A, *et al*. Structure of aldehyde reductase holoenzyme in complex with the potent aldose reductase inhibitor fidarestat: Implications for inhibitor binding and selectivity. J Med Chem 2005; 48 (17): 5536-42.

[77] Cao Z, Zhou B, Chen X, Huang D, Zhang X, Wang Z, *et al*. Statil suppresses cancer cell growth and proliferation by the inhibition of tumor marker AKR1B10. Anticancer Drugs 2014; 25 (8): 930-7.

[78] Zemanova L, Hofman J, Novotna E, Musilek K, Lundova T, Havrankova J, *et al*. Flavones inhibit the activity of AKR1B10, a promising therapeutic target for cancer treatment. J Nat Prod 2015; 78 (11): 2666-74.

[79] Porté S, Ruiz FX, Giménez J, Molist I, Alvarez S, Domínguez M, *et al*. Aldo-keto reductases in retinoid metabolism: Search for substrate specificity and inhibitor selectivity. Chem Biol Interact 2013; 202 (1-3): 186-94.

[80] Zhang, J.X., Chen, W.L., Yan, G.M. Androstane-3beta, 5alpha, 6beta,19-tetraol as well as preparation method and application thereof. CN104497086 (**2015**).

[81] Ratliff DM, Martinez FJ, Vander Jagt TJ, Schimandle CM, Robinson B, Hunsaker LA, *et al*. Inhibition of human aldose and aldehyde reductases by non-steroidal anti-inflammatory drugs. Adv Exp Med Biol 1999; 463: 493-9.

[82] El-Kabbani O,Podjarny A. Selectivity determinants of the aldose and aldehyde reductase inhibitor-binding sites. Cell Mol Life Sci 2007; 64 (15): 1970-8.

[83] Steuber H, Heine A, Podjarny A, Klebe G. Merging the binding sites of aldose and aldehyde reductase for detection of inhibitor selectivity-determining features. J Mol Biol 2008; 379 (5):991-1016.

[84] Larson, E.R., Mylari, B.L. Heterocyclic oxophthalazinyl acetic acids. US4939140 (**1990**).

[85] Sarges, R. Hydantoin therapeutic agents. US4130714 (**1978**).

[86] Tanouchi, T., Kawamura, M., Ajima, A., Mohri, T., Hayashi, M., Terashima, H., Hirata, F., Morimura, T. Rhodanine derivatives, process for their preparation,and aldose reductase inhibitor containing the rhodanine derivatives as active ingredient. US4464382 (**1984**).

[87] Ramirez MA, Borja NL. Epalrestat: an aldose reductase inhibitor for the treatment of diabetic neuropathy. Pharmacotherapy 2008; 28 (5): 646-55.

[88] Ziegler D. Treatment of diabetic polyneuropathy: Update 2006. Ann N Y Acad Sci 2006; 1084: 250-66.

[89] Hotta N, Kawamori R, Atsumi Y, Baba M, Kishikawa H, Nakamura J, *et al*. Stratified analyses for selecting appropriate target patients with diabetic peripheral neuropathy for long-term treatment with an aldose reductase inhibitor, epalrestat. Diabet Med 2008; 25 (7): 818-25.

[90] Kalofonos, I., Stahly, G.P., Martin-Doyle, W., Kalofonos, D., Stults, G.S., Houston, T.L. Preparation of crystalline anhydrate salts of epalrestat. WO2010011922 (**2010**).

[91] Kalofonos, I., Stahly, G.P., Martin-Doyle, W., Kalofonos, D., Stults, G.S., Houston, T.L. Novel solid forms of epalrestat. US20110275681 (**2011**).

[92] Kalofonos, I., Stahly, G.P., Martin-Doyle, W., Kalofonos, D., Stults, G.S., Houston, T.L. Preparation of novel choline cocrystal of epalrestat and therapeutic uses thereof. WO2010028132 **(2010)**.

[93] Kalofonos, I., Stahly, G.P., Martin-Doyle, W., Kalofonos, D., Stults, G.S., Houston, T.L. Betaine co-crystal of epalrestat. WO2010011926 (**2010**).

[94] Kalofonos, I., Stahly, G.P., Martin-Doyle, W., Kalofonos, D., Houston, T.L., Stults, J.S. Novel choline cocrystal of epalrestat. US2015057319 (**2015**).

[95] Yadav UC, Aguilera-Aguirre L, Ramana KV, Boldogh I,Srivastava SK. Aldose reductase inhibition prevents metaplasia of airway epithelial cells. PLoS One 2010; 5 (12): e14440.

[96] Liu J, Wen G,Cao D. Aldo-keto reductase family 1 member B1 inhibitors: old drugs with new perspectives. Recent Pat Anticancer Drug Discov 2009; 4 (3): 246-53.

[97] Parsai S, Keck R, Skrzypczak-Jankun E, Jankun J. Analysis of the anticancer activity of curcuminoids, thiotryptophan and 4-phenoxyphenol derivatives. Oncol Lett 2014; 7 (1): 17-22.

[98] Huai, Q.Y., Li, Y., Ma, Q.L. Preparation method for curcumin, demethoxycurcumin and bisdemethoxycurcumin. CN104591987 (**2015**).

[99] Sa G, Das T. Anti cancer effects of curcumin: cycle of life and death. Cell Div 2008; 3: 14.

[100] Itokawa H, Shi Q, Akiyama T, Morris-Natschke SL,Lee KH. Recent advances in the investigation of curcuminoids. Chin Med 2008; 3: 11.

[101] Aggarwal BB, Sethi G, Ahn KS, Sandur SK, Pandey MK, Kunnumakkara AB, *et al*. Targeting signal-transducer-and-activator-of-transcription-3 for prevention and therapy of cancer: modern target but ancient solution. Ann N Y Acad Sci 2006; 1091: 151-69.

[102] Liu H, Zang C, Emde A, Planas-Silva MD, Rosche M, Kuhnl A, *et al*. Anti-tumor effect of honokiol alone and in combination with other anti-cancer agents in breast cancer. Eur J Pharmacol 2008; 591 (1-3): 43-51.

[103] Kim, Y.C., Kim, E.C., Lee, D.S., Kim, K.S., Jeong, G.S. Composition for treating or alleviating dental pulp diseases, containing butein as active ingredient. WO2014081124 (**2014**).

[104] Xiao, H.B., Gao, M.Z., Liu, D., Hong, Z.L. Method for separating dicaffeoyl quinic acid from jerusalem artichoke leaf. CN104710312 (**2015**).

[105] Lee JY, Song DG, Lee EH, Jung SH, Nho CW, Cha KH, *et al*. Inhibitory effects of 3,5-O-dicaffeoyl-epi-quinic acid from *Gymnaster koraiensis* on AKR1B10. J. Korean. Soc. Appl. Biol. Chem 2009; 52 (6): 731-4.

[106] Lee EH, Song DG, Lee JY, Pan CH, Um BH, Jung SH. Inhibitory effect of the compounds isolated from *Rhus verniciflua* on aldose reductase and advanced glycation endproducts. Biol Pharm Bull 2008; 31 (8): 1626-30.

[107] Pan CH, Lee JY, Song DG, Kim GH, Ahn SY, Bae DS, *et al*. Antioxidant and Aldo-keto reductase family 1 B10 inhibition activities of Korean local plant extracts. J Appl Biol Chem 2009; 52 (4): 216-20.

[108] Zhang L, Chen W,Li X. A novel anticancer effect of butein: inhibition of invasion through the ERK1/2 and NF-kappa B signaling pathways in bladder cancer cells. FEBS Lett 2008; 582 (13): 1821-8.

[109] Moon DO, Kim MO, Choi YH, Hyun JW, Chang WY, Kim GY. Butein induces G(2)/M phase arrest and apoptosis in human hepatoma cancer cells through ROS generation. Cancer Lett 2010; 288 (2): 204-13.

[110] Dzubak P, Hajduch M, Vydra D, Hustova A, Kvasnica M, Biedermann D, *et al*. Pharmacological activities of natural triterpenoids and their therapeutic implications. Nat Prod Rep 2006; 23 (3): 394-411.

[111] Ovesna Z, Vachalkova A, Horvathova K, Tothova D. Pentacyclic triterpenoic acids: New chemoprotective compounds. Minireview. Neoplasma 2004; 51 (5): 327-33.

[112] Laszczyk MN. Pentacyclic triterpenes of the lupane, oleanane and ursane group as tools in cancer therapy. Planta Med 2009; 75 (15): 1549-60.

[113] Liu J. Pharmacology of oleanolic acid and ursolic acid. J Ethnopharmacol 1995; 49 (2): 57-68.

[114] Liu, D.F., Zhang, Y. Preparation method of oleanolic acid. CN101768201 (**2010**).

[115] Akao Y, Nakagawa Y, Iinuma M,Nozawa Y. Anti-cancer effects of xanthones from pericarps of mangosteen. Int J Mol Sci 2008; 9 (3): 355-70.

[116] Shan T, Ma Q, Guo K, Liu J, Li W, Wang F, *et al*. Xanthones from mangosteen extracts as natural chemopreventive agents: Potential anticancer drugs. Curr Mol Med 2011; 11 (8): 666-77.

[117] De P, Baltas M, Bedos-Belval F. Cinnamic acid derivatives as anticancer agents-a review. Curr Med Chem 2011; 18 (11): 1672-703.

[118] Pan, C.-H., Song, D.-G., Lee, J.Y. Pharmaceutical composition containing extracts of native plants as active ingredients for preventing or treating cancer. WO2011052846 (**2011**).

[119] Pan, C.-H., Song, D.-G., Lee, J.Y. Compositions for prevention and improvement of cancer cotaining the extracts of ligularia fischeri var.spiciformis nakai as an active ingredient. KR20110118748 (**2011**).

[120] Germain P, Kammerer S, Perez E, Peluso-Iltis C, Tortolani D, Zusi FC, *et al*. Rational design of RAR-selective ligands revealed by RARbeta crystal stucture. EMBO Rep 2004; 5 (9): 877-82.

[121] Consejo, S.D.I.S.T.S., Centrum, V.-T.I.S., Štefek, M., MILÁČKOVÁ, I., Diez-Dacal, B., PÉREZ-Sala, G.D., ŠOLTÉSOVÁ, P.M. Use of 5-carboxymethyl-3-mercapto-1,2,4-triazino-[5,6-B]indoles and their pharmaceutical composition. WO2015057175 (**2015**).

[122] Pérez-Sala, G.M.D., Díez, D.B. Use of compouds with a 2-cyclopentenone structure for the inhibition of enzymes of the family aldo-keto reductases. WO2011117453 (**2011**).

[123] Thun MJ, Henley SJ,Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst 2002; 94 (4): 252-66.

[124] Rao CV, Reddy BS. NSAIDs and chemoprevention. Curr Cancer Drug Targets 2004; 4 (1): 29-42.

[125] Kelloff GJ, Boone CW, Crowell JA, Steele VE, Lubet R,Sigman CC. Chemopreventive drug development: Perspectives and progress. Cancer Epidemiol Biomarkers Prev 1994; 3 (1): 85-98.

[126] Hibasami H, Iwase H, Yoshioka K, Takahashi H. Glycyrrhetic acid (a metabolic substance and aglycon of glycyrrhizin) induces apoptosis in human hepatoma, promyelotic leukemia and stomach cancer cells. Int J Mol Med 2006; 17 (2): 215-9.

[127] Suzen S,Buyukbingol E. Recent studies of aldose reductase enzyme inhibition for diabetic complications. Curr Med Chem 2003; 10 (15): 1329-52.

[128] Bauman DR, Rudnick SI, Szewczuk LM, Jin Y, Gopishetty S, Penning TM. Development of nonsteroidal anti-inflammatory drug analogs and steroid carboxylates selective for human aldo-keto reductase isoforms: potential antineoplastic agents that work independently of cyclooxygenase isozymes. Mol Pharmacol 2005; 67 (1): 60-8.

[129] Gobec S, Brozic P, Rizner TL. Nonsteroidal anti-inflammatory drugs and their analogues as inhibitors of aldo-keto reductase AKR1C3: New lead compounds for the development of anticancer agents. Bioorg Med Chem Lett 2005; 15 (23): 5170-5.

[130] Byrns MC, Steckelbroeck S, Penning TM. An indomethacin analogue, N-(4-chlorobenzoyl)-melatonin, is a selective inhibitor of aldo-keto reductase 1C3 (type 2 3alpha-HSD, type 5 17beta-HSD, and prostaglandin F synthase), a potential target for the treatment of hormone dependent and hormone independent malignancies. Biochem Pharmacol 2008; 75 (2): 484-93.

[131] Higaki Y, Usami N, Shintani S, Ishikura S, El-Kabbani O, Hara A. Selective and potent inhibitors of human 20alpha-hydroxysteroid dehydrogenase (AKR1C1) that metabolizes neurosteroids derived from progesterone. Chem Biol Interact 2003; 143-144: 503-13.