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Human Cytochrome P450 Enzymes 5-51 as Targets of Drugs and Natural and Environmental Compounds: Mechanisms, Induction, and Inhibition—Toxic Effects and Benefits

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Abstract

Cytochrome P450 (P450, CYP) enzymes have long been of interest due to their roles in the metabolism of drugs, pesticides, pro-carcinogens, and other xenobiotic chemicals. They have also been of interest due to their very critical roles in the biosynthesis and metabolism of steroids, vitamins, and certain eicosanoids. This review covers the 22 (of the total of 57) human P450s in Families 5–51 and their substrate selectivity. Also included is information and references regarding inducibility, inhibition, and (in some cases) stimulation by chemicals. We update and discuss important aspects of each of these 22 P450s and questions that remain open.

Keywords

cytochrome P450; xenobiotics; endogenous compounds; steroids; eicosanoids; vitamin D; vitamin A; retinoids; enzyme inhibition; enzyme induction

Introduction

The significance of the human cytochrome P450 (P450) enzymes in drug metabolism has been reviewed in detail in previous reviews (Guengerich and Rendic 2010; Rendic and Guengerich 2010, 2012; Guengerich 2015; Rendic and Guengerich 2015). In addition to a great number of compounds used as drugs or being found in the environment, and influencing the activity and/or expression of the cytochrome P450 enzymes (Guengerich and Rendic 2010; Rendic and Guengerich 2012), the effects of diseases and environmental factors—including ionizing radiation, UV, γ -rays, X-rays—are also of interest and have been reviewed (Semonin-Holleran 1991; Klammert et al. 2009; Guengerich and Rendic 2010; Rendic and Guengerich 2012). Such factors can have profound effects on enzyme activity and expression and therefore also on the final biological activity, efficacy, and safety of drugs and other chemicals. They can contribute to drug-drug, drug-chemical, or chemical-chemical interactions by modifying the disposition of xeno- and endobiotics and

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consequently their fate in the body. In some cases, analysis of the results on the effects of diseases and different environmental factors on human cytochrome P450 enzymes revealed inconsistency of the reported results, making it difficult to reach conclusions.

The scope of this article is the human P450s in Families 5–51. The topic follows two relevant reviews that one of us wrote in the past four years (Guengerich 2015, 2017) on the P450s involved in metabolism of endogenous compounds. Why are we focusing on these P450s in a journal that deals with drug metabolism? There are several reasons. One is that some of the steroids and vitamins are used as drugs. Another is that most of these P450s have important roles in physiology and are subject to induction and/or inhibition by drugs. Finally, several of these P450s are functional targets for drugs, e.g. 5A1, 11B1, 11B2, 17A1, 19A1. These enzymes synthesize important molecules but over-production may be an issue in some diseases. Families 5–51 were covered in a chapter several years ago (Guengerich 2015), but here we have focused on inhibitors and also updated the information.

Most of the P450 enzymes in Families 5–51 are mainly extrahepatic, with several exceptions (7A1, 8B1, 26A1, 27A1, 39A1, 51A1). In contrast to the “drug-metabolizing” P450s in Families 1–4, the levels of expression of these enzymes are highly regulated and do not vary among individuals as much and, in general, are not very inducible by xenobiotics.

Analyses of clinical tumor samples may link causality with changes in gene expression in some cases. For instance, increases/or downregulation in mRNA and/or protein expression of P450s 5A1, 7B1, 19A1, 26A1, 26B1, 26C1, 27A1, and 27B1 have been observed and suggested as markers of the aggressive biological potential of tumors and association with poor patient survival. It has been suggested that up-regulation of these enzymes might be useful as tumor markers in the diagnosis and prognosis of different malignancies. On the other hand, enhanced or lowered expression and/or activity of P450 enzymes in some diseases could result in clinically significant drug interaction potential, resulting in unfavorable clinical outcome or increased drug/chemical toxicity. Some examples include increased expression of P450 2E1 due to alcohol in healthy subjects and decreased enzyme expression in alcoholic liver disease, increased P450 2E1 expression in livers of transplant patients, high expression of P450 3A4 enzyme in lymphoid carcinoma (proposed as a useful predictor of poor response to the standard peripheral type lung cancer chemotherapy), and high expression of P450 3A enzymes in osteosarcomas (suggested as a predictor of metastasis and poor prognosis) (Guengerich and Rendic 2010).

For each of the 22 P450s we will review, the format will include a brief synopsis followed by a figure showing the main reaction and a table that includes a list of physiological substrates, function, and inhibitors and inducers. We have included references following the section on each P450 for the convenience of the reader. Collectively there is a total of 1,057 references for the entire review (not correcting for multiple entries in different sections).

We have divided the review into several sections, based on the substrates for these P450s. The four sections include eicosanoids, steroids, vitamin D and related secosteroids, and retinoids. A fifth section is for P450 20A1, for which no substrates or functions have yet

been characterized. This P450 remains an “orphan,” in our sense of the word (Guengerich and Cheng 2011).

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Eicosanoid metabolism

Some of the Family 4 P450s are involved in ω - and ω -1 hydroxylation of leukotrienes and prostaglandins (Guengerich 2015), which are generally considered to be deactivating processes. The two P450s discussed here (P450s 5A1 and 8A1) catalyze rearrangements of prostaglandin H_2 and related molecules (Fig. 1). P450s 8A1 and P450 5A1 are the only two human P450s that use an endoperoxide as a physiological substrate. These two enzymes isomerize prostaglandin endoperoxides without the use of molecular oxygen or any external electron donors (Li et al. 2008).

Both prostacyclin synthase (P450 8A1) and thromboxane synthase (P450 5A1) signaling affect a number of tumor cell survival pathways, e.g., cell proliferation, apoptosis, tumor cell invasion and metastasis, and angiogenesis. However, the effects of these respective synthases differ considerably with respect to the pathways described. Prostacyclin (prostaglandin I_2 (PGI_2)) is a potent inhibitor of vasoconstriction, platelet activation, and aggregation. Widely known for its vasoprotective activity, prostacyclin is synthesized mainly in the endothelial and smooth muscle cells via the described isomerization of prostaglandin H_2 , a reaction catalyzed by prostacyclin synthase (CYP8A1; also termed PGI_2 synthase; PGIS). The balance of these oppositely-acting cyclooxygenase-derived prostanoids influences many

processes throughout the body, e.g., blood pressure regulation, clotting, and inflammation. The prostacyclin/thromboxane ratio is important *in vivo*, with the corresponding synthases shown to be differentially regulated in a variety of disease states.

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P450 5A1

P450 5A1 (also termed CYP5A1 and thromboxane synthase, TBXAS1) is expressed in platelets and some other cells (Yokoyama et al. 1991; Guengerich 2015). A 3-dimensional structure is still not available, to our knowledge. In contrast to most P450s, no external source of electrons or molecular oxygen is required. The reaction is an internal rearrangement of the endoperoxide prostaglandin H₂, involving the interaction of the heme iron with the oxygen atoms and high valent intermediates. The most widely accepted mechanism is that proposed by Hecker and Ullrich (1989).

Arachidonic acid metabolites are key mediators involved in the pathogenesis of numerous cardiovascular, pulmonary, inflammatory, and thromboembolic diseases, and one of particular importance is thromboxane A₂. It is produced by the action of thromboxane synthase (P450 5A1) on the prostaglandin endoperoxide H₂ (PGH₂), a product of the enzymatic transformation of arachidonic acid by the cyclooxygenases. Thromboxane A₂ is a potent inducer of platelet aggregation, vasoconstriction, and bronchoconstriction, which are involved in a series of major pathophysiological conditions including myocardial infarction, unstable angina, pregnancy-induced hypertension and preeclampsia, thrombosis and thrombotic disorders, pulmonary hypertension, asthma, septic shock, atherosclerosis, lupus nephritis, and Raynaud's phenomenon. Thromboxane A₂ receptor antagonists, thromboxane synthase inhibitors, and drugs combining both properties have been developed since the 1980s (Dogne et al. 2006; Kontogiorgis and Hadjipavlou-Litina 2010). The activity of the enzyme (and/or transcription of the gene) can be affected by a number of drugs or drug-candidates (particularly azoles), by environmental factors and natural compounds, and even by physiological factors such as illnesses or hypoxia. In some cancers there is a significant increase of P450 5A1 mRNA/protein expression. Tumor progression can occur through modulation of cell motility (prostate cancer) (Nie et al. 2004), development and progression (pituitary tumor) (Onguru et al. 2004), pathogenesis (papillary thyroid carcinoma) (Kajita et al. 2005), or the cancer cell proliferation (human colorectal carcinoma) (Sakai et al. 2006).

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P450 8A1

Prostacyclin synthase activity (P450 8A1) was first found in aorta, and the enzyme was later purified as a 50-kDa hemoprotein with spectroscopic characteristics of a cytochrome P450 (Graf et al. 1983). A P450 8A1 cDNA was cloned from aorta endothelial cells and heterologously expressed (Miyata et al. 1994; Wada et al. 2004). P450 8A1 mRNA is found expressed in many mammalian tissues including ovary, heart, skeletal muscle, lung, prostate (Miyata et al. 1994), umbilical cord, brain, and neurons (Guengerich 2015). Regulation involves a number of factors, including post-translational redox control. Peroxynitrite yields nitration of the Tyr-430 residue and thus steric hindrance to the active site (Bachschmid et al. 2005).

X-ray crystal structures of unliganded P450 8A1 and the enzyme containing a substrate analog (U51605) and inhibitor (minoxidil) have been published (Chiang et al. 2006; Li et al. 2008) (Protein Data Bank structures 3B6H, 3B98, 2IAG, 3B99). The most generally

accepted reaction mechanism, initially proposed by Hecker and Ullrich (1989), involves the key step of an O–O homolytic scission of PGH₂ to generate an alkoxyl radical from the substrate intermediate and a [Fe^{IV}–O–R] species from the enzyme.

Because of the physiology associated with prostacyclin, there is limited practical interest in synthesizing inhibitors of this enzyme. The field of P450 8A1 inhibition is dominated by efforts to avoid use of drugs that might inhibit this enzyme as a side effect. Many common P450 ligands, even imidazole or pyridine derivatives, do not bind P450 8A1. Only a few nitrogen-containing compounds bind P450 8A1 with notable affinity. Thus, the active site of P450 8A1 appears to have a very limited space and is accessible only for nitrogen compounds with side chains rather perpendicular to the Fe–N coordination axis. This hypothesis, which suggests a rigid active site, has not been tested with a wider range of heme ligands.

Prostacyclin synthase overexpression has been shown to be chemopreventive in a murine cancer model (Cathcart et al. 2010).

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Steroid hormone biosynthesis

The sole P450 involved in cholesterol formation, P450 51A1, is the lanosterol 14 α -demethylase (Fig. 4A and Fig. 17, *vide infra*). There are three biologically important pathways from cholesterol catalyzed by P450 enzymes: (1) biosynthesis of steroid hormones, (2) formation of bile acids, and (3) vitamin D₃ metabolism. All mammalian steroids, bile acids, and active forms of vitamin D are formed from cholesterol (Figs. 4A and

4B). Detailed reactions leading to the formation of bile acids and catalyzed by P450 enzymes are presented in Figs. 14A and 15, reactions related to biosynthesis and metabolism of vitamin D₃ in Figs. 19 and 20, and the biosynthesis of steroid hormones in Figs. 7 to 13 and 14B. Clinical experience and studies with transgenic mice have shown the importance of all of these P450s (Nebert and Russell 2002; Auchus and Miller 2015; Auchus 2017). The only other major enzymes involved in steroid hormones biosynthesis are dehydrogenases (Fig. 4B) (plus conjugating enzymes that form methyl ethers, sulfate esters, and glucuronides).

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P450 7A1

Primary bile acids are formed from cholesterol in the liver. The first and rate-limiting reaction in the pathway is 7 α -hydroxylation by the cholesterol 7 α -hydroxylase P450 7A1, an enzyme relatively selective for cholesterol and cholestanol (Ogishima et al. 1987; Jelinek et al. 1990). The conversion of cholesterol to bile acids in the liver (and its subsequent fecal excretion) represents a major route of elimination of cholesterol from the body. Bile acids can be synthesized via a ‘classical pathway’ (P450 7A1, Figs. 4A and 5) or an ‘alternate pathway’ utilizing a different sequence of initial steps (Fig. 4A, P450 39A1 or 7B1, *vide infra*). Compared with the alternative pathway, the classical pathway is more ‘flexible’.

Human P450 7A1, expressed in *Escherichia coli*, is active toward the substrates cholesterol, 20(*S*)-hydroxycholesterol, 25-hydroxycholesterol, 27-hydroxycholesterol, zymostenol, lathosterol, desmosterol, and 7-dehydrocholesterol (Li YC and Chiang 1991; Shinkyo et al. 2011; Acimovic et al. 2016).

The reaction with 7-dehydrocholesterol yields 7-ketocholesterol, an important oxysterol with detrimental properties (Shinkyo et al. 2011). The 7-keto product is formed without an epoxide intermediate, although some 7,8-epoxide is also formed. The reaction also occurs *in vivo* (in humans) (Björkhem et al. 2014) and may be of relevance in Smith-Lemli-Opitz syndrome, in which 7-dehydrocholesterol is elevated due to a genetic deficiency in the reductase.

The 7 α -hydroxylation of cholesterol by human P450 7A1 is one of the faster reactions known with a mammalian P450, with $k_{\text{cat}} > 3 \text{ s}^{-1}$ and specificity constant ($k_{\text{cat}}/K_{\text{m}}$) of $2.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ (Shinkyo et al. 2011). The $k_{\text{cat}}/K_{\text{m}}$ for the oxidation of 7-dehydrocholesterol is considerably lower ($2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$).

X-ray crystal structures of human P450 7A1 are available for the unliganded protein and with cholest-4-en-3-one and 7-ketocholesterol (Protein Data Bank (PDB) 3DZX, 3SN5, 3V8D, <http://www.rscb.org>) (Tempel et al. 2014).

The *CYP7A1* gene is highly regulated, as might be expected for an enzyme with a central role in the clearance of an important sterol (Guengerich 2015, Zhang, Zhao, et al. 2017, Zhang, Jackson, et al. 2017, Zhang, Wang, et al. 2018, Lee et al. 2018). Transcription of the *CYP7A1* gene is stimulated by dietary cholesterol in rodents (Horton et al. 1995). In mammals, however, dietary cholesterol does not stimulate hepatic P450 7A1 expression, resulting in accumulation of peripheral cholesterol and atherosclerosis (Chiang et al. 2001, Goodwin et al. 2003). The regulatory element FXR is responsive to bile acids and inhibits *CYP7A1* gene transcription through the activation of SHP and inhibition of HNF4 α transactivation. An A to C transversion mutation 278 bp upstream (of the *CYP7A1* promoter) has been associated with variations in serum lipid levels in populations with hypertriglyceridemia, combined hyperlipidemia, familial dysbetalipoproteinemia, and familial hypercholesterolemia (Hofman et al. 2004).

Oxysterols are important degradation products of cholesterol and are intermediates in the biosynthesis of steroid hormones and bile acids. These compounds have biology of their own and a broad spectrum of effects, including modulation of the activity of enzymes involved in cholesterol homeostasis (Waterman et al. 1986; Axelson and Sjövall 1990; Björkhem 1992; Janowski et al. 1996; Lala et al. 1997; Lehmann et al. 1997; Janowski et al. 1999; Russell 1999; Schroepfer 2000).

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P450 7B1

P450 7A1 catalyzes the first and rate-limiting step in bile acid synthesis, i.e. cholesterol 7 α -hydroxylation (*vide supra*). P450 7B1 was first described in rodent brain tissue as a dehydroepiandrosterone 7 α -hydroxylase and was originally isolated from the hippocampus (Rose et al. 1997). Later it was identified as a hepatic oxysterol 7 α -hydroxylase (Schwarz et al. 1997).

P450 7B1 mRNA is found not only in liver but also in the steroidogenic tissues testes, ovary, and prostate—as well as in brain, and in colon, kidney, and small intestine—but the tissue specificity is species specific. In humans the highest (mRNA) levels are in kidney and brain.

Much of the literature with this enzyme is based on rodent work. However, Yantsevich et al. (2014) characterized recombinant human P450 7B1 and reported several K_s values for ligand binding and (single-concentration) rates of 7 α -hydroxylation of several steroids. The substrates with the highest rates of 7 α -hydroxylation were 27- and 25-hydroxycholesterol, dehydroepiandrosterone, 5 α -androstane-3 β ,17 β -diol, 5-androsten-3 β ,17 β -diol, and 5 α -androstane-3 β -ol-17-one (EpiA), with lower activity seen with pregnenolone and 21-hydroxypregnenolone.

No crystal structures are available but a homology model based on P450 7A1 has been proposed (Yantsevich et al. 2014).

Although the catalytic specificity is not immediately obvious regarding physiological issues, there are two major clinical issues: (i) liver failure in children due to genetic insufficiency and (ii) a neuropathy in adults, particularly the autosomal recessive disorder spastic paraplegia type 5 (Stiles et al. 2009).

Increased levels of the cholesterol metabolite 27-hydroxycholesterol in breast tissue tumor were correlated with diminished expression of P450 7B1. However, expression of the *CYP7B1* gene in tumors is associated with poorer patient survival (Wu et al. 2013). The

opposite pattern was found in prostatic cancer tissue, where P450 7B1 was overexpressed, and it was suggested that local methylation of the *CYP7B1* promoter region may have a significant effect on gene transcription (Olsson et al. 2007). The latter results correspond to those presented for induction in prostate cancer tissue (Table 4).

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P450 8B1

P450 8B1 is a liver enzyme and a sterol 12 α -hydroxylase. Although it is most closely related to P450 8A1 in its primary sequence, its substrate specificity and function are not at all related (as in the case of P450 27C1 and its relatives, *vide infra*). While P450 8A1 is involved with eicosanoids, P450 8B1 utilizes sterols and is involved in bile acid synthesis. The enzyme controls the ratio of cholic acid to chenodeoxycholic acid. Substrates include 4 β - and 7 α -hydroxycholesterol and also 7 α ,24- and 7 α ,27-dihydroxycholesterol (Pikuleva 2006). The regulation of the enzyme is complex, and much of what has been reported in the literature is based on animal models.

P450 8B1 controls the balance between cholic acid and chenodeoxycholic acid, thus adjusting the hydrophobicity of bile (cholic acid is more hydrophilic), i.e. the neutral pathway and the acidic pathway (Russell 2003; Chiang 2004). This ratio between the bile acids is important for feedback regulation of bile acid synthesis (Ellis E et al. 2003). However, the ratio between these two bile acids does not appear to be sensitive to genetic variations in P450 8B1 (Pikuleva 2006). The enzyme plays a critical role in intestinal cholesterol absorption and pathogenesis of cholesterol gallstone, dyslipidemia, and diabetes (Pathak et al. 2013).

Interestingly, the *CYP8B1* gene is devoid of introns, a unique phenomenon for eukaryotic P450s (Gafvels et al. 1999). No crystal structures have been reported yet and, despite some sequence similarity to P450 8A1, the functional differences make comparisons with homology modeling questionable.

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P450 11A1

Cholesterol is the precursor of all steroid hormones and bile acids, and P450 11A1 is the main cholesterol side chain cleavage enzyme in steroidogenic tissues, yielding pregnenolone as a key intermediate (Fig. 4). The enzyme is localized in steroidogenic tissues (e.g. adrenal cortex, gonads, ovary) consistent with the reaction being the initiating step in steroid synthesis. The enzyme is synthesized on ribosomes in the cytosol and imported into mitochondria.

NADPH-adrenoredoxin reductase and adrenodoxin are used for electron delivery to mitochondrial P450 11A1. The principal intermediate in P450-mediated oxidations has been

identified as Compound I, the high-valent FeO^{3+} species (McQuarters et al. 2014), including the case of P450 11A1 (Davydov et al. 2015). In addition, ^{18}O labeling studies have demonstrated that Compound I reacts with one of the hydroxyl groups of 20(*R*), 22(*R*)-dihydroxycholesterol in the third step of the reaction, as opposed to hydrogen atom abstraction (from one of the alcohols) (Ortiz de Montellano 2015; Yoshimoto et al. 2016).

The substrate specificity of P450 11A1 is not so strict as once thought, i.e. it does not only act on cholesterol. Several other sterols are also substrates including 7-dehydrocholesterol, zymosterol, lathosterol, and desmosterol (Acimovic et al. 2016). Tuckey and his associates have found that vitamin D_3 is hydroxylated on the side chain to multiple products (Guryev et al. 2003; Slominski A et al. 2006; Tuckey, Janjetovic, et al. 2008; Tuckey, Li, et al. 2008; Tuckey et al. 2011; Slominski A. T. et al. 2013). A Bristol-Myers Squibb drug candidate, BMS-A [(*N*-(4-(1H-pyrrolo[2,3-*b*]pyridine-4-yl)oxy)-3-fluorophenyl)2-oxo-1,2-dihydropyridine-3-carboxamide, was also oxidized by rat and human P450 11A1 (Zhang et al. 2012), and this reaction was linked to adrenal toxicity of the compound.

Two groups have reported X-ray crystal structures, both with 22-hydroxycholesterol and one with 20,22-dihydroxycholesterol bound (Mast et al. 2011; Strushkevich et al. 2011) (PDB 3MZS, 3N9Y, 3N9Z, 3NA0, 3NA1).

Because of the importance of this enzyme and its role, there does not seem to be an impetus to develop inhibitory drugs. Deficiencies in the enzyme are debilitating. Another issue is the presence of autoantibodies to P450 11A1 in patients with autoimmune polyglandular syndrome types I and II and Addison's disease, although no causal relationships have been shown (Chen et al. 1996; Seissler et al. 1999; Boe et al. 2004).

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P450 11B1

Steroid production occurs primarily in the adrenal cortex and gonads, and cortisol production is localized mainly in the zona fasciculata region of the adrenal cortex. The production of cortisol is regulated through three major P450s—17A1, 21A2, and 11B1—in the zona glomerulosa and zona fasciculata regions. The last steps in aldosterone biosynthesis are mediated by the mitochondrial cytochrome P450 11B family (Fig. 4), which catalyze (subsequent) oxidation reactions on the C11, C18, and C19 carbons on the β -side of the steroid skeleton (Fig. 9). In cattle, swine, and frogs, aldosterone synthesis is performed by only one P450, 11B, but in humans (Fisher et al. 2001) and mice (Domalik et al. 1991) aldosterone formation involves two P450 genes, P450 11B1 (steroid 11 β -hydroxylase) and 11B2 (aldosterone synthase) (rats have four P450 genes: 11B1, 11B2, 11B3 (only expressed in neonates, similar activity as 11B2), and 11B4 (a pseudogene) (Nonaka and Okamoto 1991)). Human P450s 11B1 and 11B2 differ in only 32 residues. P450 11B1 catalyzes the 11 β -hydroxylation of deoxycortisol to form cortisol, the major glucocorticoid in the body. Deficiencies result in congenital adrenal hyperplasia. In both humans and rats, only P450 11B2 can perform the final oxidation at C18 to produce aldosterone (Nonaka and Okamoto 1991; Fisher et al. 2001). C19 hydroxylation has been reported for rat P450 11B1 but not the human enzyme (Nonaka and Okamoto 1991), and P450 11B1 is known to play an important role in the biosynthesis of glucocorticoids. If an inhibitor of aldosterone synthesis is to be clinically useful, the biosynthesis of glucocorticoids should remain unaffected, indicating that the inhibition must be 11B2-selective (Roumen et al. 2007).

The regulation of the *CYP11B1* gene is very complex, and the animal models have several deficiencies in this regard. A large number of genetic variants in the *CYP11B1* gene have been identified and linked to high 18 β -hydroxycortisol levels and low 11 β -hydroxylation, as well as congenital adrenal hyperplasia and hypertension (Guengerich 2015). No crystal structures of P450 11B1 have been published, to our knowledge.

Although there are medical issues related to P450 11B1 deficiency, there are also reasons to develop inhibitors. Cortisol dysregulation has been associated with diseases such as diabetes, heart failure, hypertension, stroke, obesity, renal failure, and prostate, breast, uterine, and ovarian cancers (Connolly and Wills 1967; Mitrinen et al. 2000; Chiodini et al. 2007; Barugh et al. 2014). In some cases, an excess amount of circulating cortisol is produced. High levels of cortisol are associated with Cushing's syndrome (Bureik, Lisurek, et al. 2002). Metabolic syndrome is also linked to the overproduction of cortisol (Walker 2006).

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P450 11B2

As mentioned earlier under P450 11B1, there are only 32 residues that differ between P450s 11B1 and 11B2, and their catalytic specificities overlap. The *CYP11B2* gene is also highly regulated (Guengerich 2015). Many *CYP11B2* genetic variants are known and related to a number of diseases (Guengerich 2015). “Crossovers” between the *CYP11B1* and *CYP11B2* genes are generally inactivating for both enzymes.

X-ray crystal structures of human P450 11B2 have been published, with the substrate deoxycorticosterone and also with the inhibitor fadrazole, as well as another inhibitor (Strushkevich et al. 2013 Martin, 2015, 59534) (PDB 4DVQ, 4ZGX, 4FDH).

P450 11B2 catalyzes the 3-step conversion of 11-deoxycorticosterone to aldosterone, with 11 β -hydroxylation, 18-hydroxylation, and 2-electron oxidation of the 18-carbinol. Strushkevich et al. (2013) have proposed that this is a processive reaction, with no intermediates released. However, this proposal has not been examined more rigorously, e.g. with time course and pulse-chase experiments. The non-classical substrate methandienone is oxidized to the 11 β - and 20 β -norsteroid products (Parr et al. 2012).

Although a number of cases of genetic insufficiency are known P450 11B2 is a target for intervention in hypertension, with at least two major pharmaceutical firms screening for inhibitors.

P450 11B2 is involved in the biosynthesis of aldosterone, which has a critical role in blood pressure control (maintaining potassium and sodium homeostasis) and in cardiovascular and renal disease (Brown 2005; Cohn and Colucci 2006; Pimenta and Calhoun 2006; Funder and Mihailidou 2009). Excess aldosterone is linked to hypertension onset (Vasan et al. 2004) and is believed to play a critical role in mediating and aggravating resistant hypertension (Whaley-Connell et al. 2010), a common clinical problem for 20–28% of patients (Calhoun et al. 2008; Egan et al. 2011). Lowering aldosterone represents an attractive therapeutic approach to lower blood pressure and reducing the risk of cardiovascular events and end-organ damage.

An alternative approach to attenuating the effects of aldosterone is to decrease circulating levels by inhibiting its synthesis, preferably at the level of P450 11B2, which mediates the rate-limiting conversion of 11-deoxycorticosterone to aldosterone (Karns et al. 2013).

Despite the relatedness of P450s 11B1 and 11B2, it has been possible to identify compounds with > 500-fold selectivity (Voets et al. 2006).

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P450 17A1

P450 17A1 functions at an important branch point in human steroidogenesis (Miller and Auchus 2011). P450 17A1 catalysis leads to either (i) precursors of glucocorticoids (e.g., cortisol) that regulate immune responses or (ii) androgens (e.g., testosterone) that drive the development and maintenance of male characteristics or are converted to estrogens (Gilep et al. 2011).

In addition to 17 α -hydroxylation, P450 17A1 also performs a carbon-carbon bond cleavage, which is unusual for cytochrome P450 enzymes (Zuber et al. 1985; Sohl and Guengerich 2010; Guengerich 2015; Guengerich and Yoshimoto 2018). For human P450 17A1, this 17,20-lyase reaction proceeds less efficiently for the ⁴,3-keto 17 α -hydroxyprogesterone substrate than for its counterpart, the ⁵,3-ol 17 α -hydroxypregnenolone (Fig. 11). As a result, the ⁵,3-ol 17 α -hydroxypregnenolone 17,20-lyase product dehydroepiandrosterone is considered the more physiologically relevant intermediate in the formation of all human androgens and estrogens (Auchus R. J. and Miller 2015; Guengerich 2015), although this should not be assumed to be the case in all species.

The addition of cytochrome *b*₅ has a positive effect on the 17 α -hydroxylation reactions, and it selectively facilitates the 17,20-lyase reaction (Fig. 11). Compartmentalization of cytochrome *b*₅ and developmental changes in cytochrome *b*₅ levels assist in controlling androgen production in humans, in that individuals with nonfunctional cytochrome *b*₅ are impaired in performing the lyase reactions and produce sex steroids, although the

hydroxylase reaction required for glucocorticoid synthesis is operational (Kok et al. 2010; Idkowiak et al. 2012). Facilitation of the lyase reaction by cytochrome *b*₅ occurs without electron transfer (Auchus R.J. et al. 1998). Thus it has been suggested that cytochrome *b*₅ might selectively stabilize the intermediate in the lyase reaction or cause substrates to assume orientations in the P450 17A1 active site more favorable for the lyase chemistry, but the details of the mechanism remain unresolved (Naffin-Olivos and Auchus 2006).

The structural basis for hydroxylase substrate regioselectivity, lyase reaction selectivity for the ⁴,3-keto versus ⁵,3-ol 17-hydroxylated substrate, and cytochrome *b*₅ facilitation of the lyase versus hydroxylase reaction is still largely unknown. X-ray crystal structures of human P45017A1, in the presence of the four steroid substrates (Fig. 11) and the steroidal inhibitors abiraterone and TOK-001, have been published recently (DeVore and Scott 2012; Petrunak et al. 2014). The steroidal inhibitors both orient nearly perpendicular to the heme (DeVore and Scott 2012).

The *CYP17A1* gene is highly regulated, in keeping with its critical role in androgen synthesis (Guengerich 2015). More than 50 deleterious genetic variants have been identified clinically. It is of interest that several of these strongly affect the lyase reaction but have only limited effects on the 17 α -hydroxylation step (E305G, R347C, R347H, R358Q) (Geller et al. 1997; Van Den Akker et al. 2002; Sherbet et al. 2003). In addition, genetic variants that disrupt *b*₅ activity show similar clinical responses (Kok et al. 2010; Idkowiak et al. 2012). However, understanding the basis of the selective loss of the lyase activity has been difficult. In teleost fish (including zebrafish), there are two genes, *CYP17A1* and *CYP17A2*. The former yields a protein with the characteristics of human P450 17A1 (i.e., both 17 α -hydroxylation and lyase activities) but P450 17A2 does only the former reaction, behaving like some of the human clinical variants. Structures of both zebrafish P450s (17A1, 17A2) have been obtained but look remarkably similar (Pallan et al. 2015) and switching the few differing residues near the heme periphery did not restore lyase activity (Gonzalez et al. 2018).

¹⁸O-labeling results are not unambiguous, in contrast to P450 19A1, but the lyase reaction can be supported by oxygen surrogates (iodosylbenzene and 17 α -hydroperoxy steroids) (Yoshimoto et al. 2016; Gonzalez et al. 2018). Results with the 17 α -hydroperoxy steroids support a dioxetane intermediate (Gonzalez et al. 2018).

One question is how processive the two sequential reactions are, i.e. whether the 17 α -hydroxy product dissociates and rebinds (“distributive”) or remains bound to the enzyme through the lyase reaction (“processive”). Recent results indicate that human P450 17A1, in the presence of cytochrome *b*₅, is distributive but that a fraction (~ ¼) of the 17 α -hydroxypregnenolone remains bound to the enzyme for the lyase reaction, as revealed by pulse-chase and pre-steady-state kinetic modeling (Gonzalez and Guengerich 2017). Exactly how this model applies to the progesterone → androstenedione sequence has been addressed but more detail is needed (Gonzalez and Guengerich 2017). This information is highly relevant in efforts to develop selective inhibitors of the lyase step, which in principle might not be possible in a processive reaction.

Even the binding of substrate to P450 17A1 is complex and the data do not fit a simple diffusion-controlled 2-state model (Gonzalez and Guengerich 2017). There is evidence that multiple conformations of both unbound and inhibitor-bound exist, as judged by both NMR spectra and X-ray crystallographic data (Estrada et al. 2014; Petrunak et al. 2017). The kinetic data can be fit to a model in which both unbound and substrate-bound P450 17A1 have two conformations (Gonzalez and Guengerich 2017) but more details about what these conformations are and their relevance to catalysis remain obscure.

Androgens drive prostate cancer development, and estrogens are involved in hormone-responsive breast cancer (Edwards et al. 2014). Thus this enzyme has garnered substantial interest as a relatively new drug target, validated by successful use of the P450 17A1 inhibitor abiraterone in men with castration-resistant prostate cancer (de Bono et al. 2011; Auchus ML and Auchus 2012; Ferraldeschi and de Bono 2013) and its current evaluation in breast cancer patients. Several P450 17A1 inhibitors have been developed over the years, but only abiraterone has been approved by the FDA for treating prostate cancer. Some non-steroidal inhibitors (e.g., galaterone, orteronel, and VT-46411) have been evaluated in clinical trials. Abiraterone improves overall survival in men with metastatic castration-resistant prostate cancer (de Bono et al. 2011; Auchus ML and Auchus 2012; Loriot et al. 2013). The drug binds tightly to the P450 17A1 heme iron (DeVore and Scott 2012), preventing androgen production. However, this inhibition also increases the pool of mineralocorticoid precursors and blocks P450 17A1-mediated production of glucocorticoids. The situation is even more complex. Abiraterone is also an antagonist of the androgen receptor, and metabolites of P450 17A1 inhibitors can have their own biological activities (Alyamani et al. 2017). The resulting steroid imbalances in patients treated with abiraterone can frequently lead to hypertension, hypokalemia, and adrenocortical insufficiency, which must then be monitored and treated (Pia et al. 2013). Furthermore, there is some evidence that the increase in mineralocorticoids associated with complete inhibition of P450 17A1 (Fig. 4) may facilitate the flow of androgen precursors through a “back door” androgen biosynthesis pathway (Attard et al. 2012). Selective inhibition of the P450 17A1-mediated androgen biosynthetic step (second reaction in Fig. 11) has proven to increase overall survival, but sparing P450 17A1-mediated glucocorticoid biosynthesis (preventing corticosteroid imbalances) would ameliorate these issues for prostate cancer patients. P450 17A1 inhibition has also been associated with Cushing’s syndrome (Ogo et al. 1991), some forms of congenital adrenal hyperplasia (Maitra and Shirwalkar 2003), and polycystic ovary syndrome (Qin and Rosenfield 1998; Arlt et al. 2002; Strauss 2003).

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P450 19A1

P450 19A1 is the steroid aromatase and catalyzes the conversion of androstenedione and testosterone to estrone and estradiol, respectively (Figs. 4, 12). In mammals P450 19A1 is mainly expressed in the brain and the gonads, but it is also found in placental, adipose, and bone tissue (Conley and Hinshelwood 2001). While one single aromatase gene exists in humans, it contains at least ten different promoters (Bulun et al. 2003), with different promoters and ligands regulating estrogen synthesis across different tissue types (Means et al. 1991; Simpson et al. 2002; Simpson 2003; Clyne et al. 2004; Kamat et al. 2005; Mendelson et al. 2005). The balance between the different sex steroid hormones, androgens and estrogens, is crucial for the reproductive system as well as for the ontogenic differentiation of sexual phenotype. In mammals, differentiation of the male phenotype depends not only on testosterone but also on estradiol generated from testosterone by neuronal aromatase (in the central nervous system). In transgenic male mice overexpressing aromatase in the testis, the serum estradiol level was increased, and one-half of these animals were infertile and had larger testes and a significantly increased incidence of Leydig cell tumors in testes (Fisher et al. 1998; Robertson et al. 1999).

X-ray crystal structures of P450 19A1 are now available. The first structure was obtained with a full-length protein purified from human placenta (Ghosh et al. 2009); subsequently other structures, with bound ligands, have been obtained with recombinant P450 19A1 (Ghosh et al. 2012; McCammon et al. 2016).

The mechanism of the third reaction in the 3-step sequence (Fig. 12) has been controversial. Multiple catalytic mechanisms were proposed in the 1970s and 1980s (Akhtar et al. 1976; Goto and Fishman 1977; Akhtar et al. 1982; Hahn and Fishman 1984; Caspi et al. 1986) and many of these have been ruled out. Some of the evidence has been equivocal, e.g.

biophysical, theoretical, synthesis and testing of possible intermediates (Hackett et al. 2005; Khatri et al. 2014). For many years the most popular mechanism involved a ferric peroxide ($\text{Fe}^{\text{III}}\text{-O}_2^-$) intermediate (Compound 0), proposed to attack the C19 formyl group (aldehyde) (Fig. 12). The strongest evidence for this mechanism was an $^{18}\text{O}_2$ -labeling study by the Akhtar group, who reported incorporation of a single ^{18}O atom into formic acid (Akhtar et al. 1976; Akhtar et al. 1982). Similar findings were reported by Caspi et al. (1986), without presenting data. The ^{18}O labeling study was repeated with both major substrates, testosterone and androstenedione, using purified P450 19A1, a new method of derivatizing the product formic acid, and higher resolution mass spectrometry. The opposite result was obtained, i.e., no ^{18}O was incorporated into formic acid, leaving only the Compound I (FeO^{3+}) mechanism as being viable (Yoshimoto and Guengerich 2014).

The multiple *CYP19A1* promoters play a different role in benign as opposed to malignant breast tissue; although the 1.4 promoter is the main activator in normal breast tissue, promoters II, 1.3, and 1.7 have been shown to play a role (in addition to 1.4) in breast cancer tissue (Robertson et al. 1999). While circulating androstenedione (as well as testosterone) in postmenopausal women is considered to be of adrenal origin, the ovary seems to provide a minor contribution of circulating testosterone (Sluijmer et al. 1995; Couzin et al. 2001).

Aromatase inhibitors have now become generally standard adjuvant endocrine therapy for postmenopausal breast cancer patients. The collective evidence advocates the use of aromatase inhibitors in the adjuvant treatment of postmenopausal women. There is no consensus in favor of either sequential or monotherapy compared with the alternative treatment strategy. Considering the cost per (quality-adjusted) life-year gained related with each strategy, this depends on the relapse risk and also patient age at diagnosis (Lønning and Eikesdal 2013).

P450 19A1 can be inhibited competitively and reversibly by azole compounds, as in the case of sterol 14 α -demethylase (P450 51A1, *vide infra*). In a rat ovary model, the therapeutic drugs anastrozole, fadrozole, and letrozole exhibited IC_{50} values of 25, 7, and 7 nM, respectively (Odum and Ashby 2002). Not only azoles, including azole fungicides, but also natural plant constituents such as flavonoids are able to significantly inhibit P450 19A1 (Zarn et al. 2003).

Aromatase inhibitors can be divided into two groups, Types I and II. Type I inhibitors are steroidal derivatives of the substrate androstenedione and bind tightly to the heme prosthetic group in the active site. Type II are nonsteroidal and also bind reversibly to the heme group. The third-generation nonsteroidal aromatase inhibitors anastrozole and letrozole have longer half-lives and are the most effective blocking compounds (> 95%) in suppressing the formation of the estrogens (Boeddinghaus and Dowsett 2001). Due to the higher potency of letrozole, a greater increase in the concentrations of gonadotropins and testosterone has been reported in boys treated with letrozole when compared to the group treated with anastrozole (Mauras 2011).

Men with congenital aromatase deficiency have tall stature, associated with delayed fusion of the epiphyseal growth plate, osteoporosis, overweight, glucose intolerance,

hyperlipidemia, and reduction of fertility. In girls, virilization of the external genitalia can result in atypical genitalia. Hypogonadism can also occur, with inappropriate mammary gland development and primary amenorrhea (Morishima et al. 1995; Carani et al. 1997; Diaz-Thomas and Shulman 2010). Aromatase excess syndrome, conversely, is caused by chromosomal recombination of the *CYP19A1* gene (e.g., duplication, deletion, inversion), with recruitment of new promoters. The clinical presentation includes gynecomastia and bone age advancement, with potential reduction of final height (Shozu et al. 2014). Estrogens play a key role in bone maturation (Rochira et al. 2010) and the use of aromatase inhibitors, with the goal of reducing the estrogen-dependent skeletal maturation rate, has been proposed with boys receiving treatment for short stature (McGrath and O'Grady 2015; Ferris and Geffner 2017). These drugs reduce estrogen concentrations at the epiphyseal chondrocyte level and are associated with decreased circulating estrogen concentration and consequent reduction in the secretion of both growth hormone and insulin-like growth factor-1 (Juul et al. 1994; Shim 2015). Estrogen has limited relevance growth regulation in the prepubertal period but increases growth during puberty and, at high concentrations, determines maturation and closure of the epiphyses at the final stage of puberty (Wit et al. 2011).

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P450 21A2

The *CYP21A2* gene is one of the most frequently mutated genes in medicine and has consequences in steroid insufficiency; i.e., the lack of 21-hydroxylation lowers levels of all

steroids downstream of the process (Fig. 4B). The hyperplasia can be one of several forms, depending upon the severity of the disease, either salt-wasting (most severe), simple virilizing (intermediate), or non-classical (least severe).

The (wild-type) enzyme is very efficient and has a specificity constant (k_{cat}/K_m) of $1.3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ (Pallan, Wang, et al. 2015). The two steps that contribute to rate-limitation are substrate binding and the C-H bond-breaking step. It is of interest that the high kinetic deuterium isotope effect is persistent even in the very low activity variants (Wang et al. 2017). There is a general correlation between the catalytic activities of the mutants and the severity of the disease (Wang et al. 2017). However, it is not perfect and there is the possibility that protein stability may be an additional factor (Wang et al. 2017).

Our laboratory first reported a structure for bovine P450 21A2 (Zhao et al. 2012) and subsequently a structure for (wild-type) human P450 21A2 (Pallan, Wang, et al. 2015). Others (Haider et al. 2013) had modeled the human structure based on the bovine enzyme but a careful analysis shows that some critical features may be in error in such an approach (Pallan, Lei, et al. 2015). In analyzing the structure, there is a tendency for the most severe mutations to be located inside of the protein and the changes associated with the least severe disease on the outside of the protein (Pallan, Lei, et al. 2015).

In reviewing the disease and the contribution of the single nucleotide variations (i.e., single amino acid substitutions) (Wang et al. 2017), it is surprising that these seemingly small changes have such dramatic functional effects. Some of this can be attributed to protein stability and some to the fact that, using the Eyring equation, even a $6.4 \text{ kcal mol}^{-1}$ difference (e.g., one of two H-bonds) can be linked to a 50,000-fold change in enzyme activity (Wang et al. 2017).

To date we have been unsuccessful in crystallizing any of the low-activity clinically-reported variants.

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P450 27A1

This is another mitochondrial P450, expressed primarily in liver and kidney. It can be regarded as being at an intersection of sterol and vitamin D metabolism, in that it has defined roles in both areas (Fig. 14). The enzyme acts on cholesterol in extrahepatic tissues, bile acid intermediates in the liver, and vitamin D₃ in the kidneys (Wikvall 1984; Masumoto et al. 1988). Despite its broad specificity for sterols, P450 27A1 is also a highly regio- and stereo-specific enzyme producing all of the 27-hydroxycholesterol in humans. Cholesterol 27-hydroxylation enables a means of cholesterol transport from extrahepatic tissues to the liver (Meaney et al. 2002), and 27-hydroxycholesterol is also a bioactive molecule interacting with different regulatory proteins, including liver X receptors (Kalaany and Mangelsdorf 2006).

The regulation of the gene is highly complex, with several pathways involved (Guengerich 2015).

No crystal structures have yet been published.

Clinical issues have been considered with changes in the enzyme in both the areas of vitamin D and sterol metabolism (Guengerich 2015). Complete deficiency of P450 27A1 activity leads to cerebrotendinous xanthomatosis, a progressive autosomal recessive disease characterized by deposition of cholesterol and cholestanol in the brain and other tissues, neurologic dysfunction, and ocular problems. Cerebrotendinous xanthomatosis patients usually have normal or sub-normal levels of plasma cholesterol but often develop premature atherosclerosis and osteoporosis (*CYP27A1*^{+/-} heterozygous individuals do not present with cerebrotendinous xanthomatosis (Björkhem 2013)).

27-Hydroxycholesterol, the reaction product, binds to estrogen receptors and acts as a selective estrogen receptor modulator (SERM), eliciting system-specific adverse effects. The response can take several forms. In the vascular wall 27-hydroxycholesterol can function as an estrogen receptor antagonist and inhibit estrogen-related cardioprotection (Umetani et al. 2007; Umetani and Shaul 2011; Umetani et al. 2014). Conversely, in breast tumors, 27-hydroxycholesterol can serve as a partial estrogen receptor agonist and stimulate tumor growth in mouse breast cancer models of (Nelson et al. 2013). Through its activity with liver X receptors, 27-hydroxycholesterol can also increase breast tumor metastasis (Nelson et al. 2013). In bone, 27-hydroxycholesterol attenuated estrogen action and bone mineralization (DuSell et al. 2010).

Epidemiology studies are consistent with the role of 27-hydroxycholesterol as an SERM. Menopause was accompanied by elevated plasma levels of 27-hydroxycholesterol (Burkard et al. 2007) and is known to dramatically increase the risk of coronary heart disease and ER-positive breast cancer (Lloyd-Jones et al. 2009).

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P450 39A1

The available evidence that the function of this enzyme is the 7 α -hydroxylation of 24(*S*)-hydroxycholesterol, which is a product of oxidation of cholesterol by P450 46A1 (*vide infra*). Almost all of the information about P450 39A1 has come from animal models, mainly mice (Li-Hawkins, Lund, Bronson, et al. 2000; Li-Hawkins, Lund, Bronson, et al. 2000). The enzyme is hepatic. No crystal structures have been reported.

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P450 46A1

P450 46A1 catalyzes cholesterol 24*S*-hydroxylation, the first step in cholesterol elimination from the brain (Lutjohann et al. 1996; Björkhem et al. 1998; Lund et al. 1999), where the concentration of cholesterol is even higher than in liver. This enzymatic reaction produces a membrane-permeable form of cholesterol, 24(*S*)-hydroxycholesterol, that diffuses across cellular membranes and the blood-brain barrier to the systemic circulation and moves to the liver for degradation (Björkhem et al. 1998; Meaney et al. 2002). P450 46A1 is considered to be important for memory and learning, in that *Cyp46a1* knock-out (KO) mice show severe deficiencies in spatial, associative, and motor learning and have impaired cognitive performance (Kotti et al. 2006).

Numerous investigations have been done to assess a possible link between *CYP46A1* genetic variations and neurodegenerative disease, including Alzheimer's disease. The results on an association of *CYP46A1* variants and dementias are still in conflict (for review, see Russell et al. (2009)). Reduced cholesterol biosynthesis does not, however, affect amyloid plaque deposition in *Cyp46a1* KO mice cross-bred with one of the mouse models of

Alzheimer disease but does extend animal life span (Halford and Russell 2009). *Cyp46a1*-expressing transgenic animals also had improved spatial memory (Hudry et al. 2010).

P450 46A1, in addition to using drugs as substrates and being inhibited by drugs (Mast N. et al. 2003; Shafaati et al. 2010), also shows an unexpected phenomenon of enzyme stimulation by drugs (Mast N. et al. 2012; Anderson et al. 2016; Mast N. et al. 2017). These are not inducers; they directly stimulate enzyme activity when added in vitro. Hydrogen-deuterium exchange studies (Mast N. et al. 2008), coupled with the X-ray crystal structure, show that the 'allosteric' site is distinct from the substrate binding site (Mast N. et al. 2014; Anderson et al. 2016). Not only drugs but also some physiological compounds in the brain show this effect (Mast N. et al. 2017). These compounds can enhance rates of reduction by NADPH-P450 reductase, although reduction is not rate-limiting and other factors are probably involved (Mast N. et al. 2017).

The specificity constant ($k_{\text{cat}}/K_{\text{m}}$) for cholesterol 24*S*-hydroxylation is very low ($140 \text{ M}^{-1} \text{ s}^{-1}$) (Goyal et al. 2014), although the significance of the (mouse) enzyme was clearly shown in the behavioral studies by Russell and his associates (Kotti et al. 2006; Russell et al. 2009). Other substrates are zymostenol, lathosterol, 7-dehydrocholesterol, and desmosterol (Goyal et al. 2014; Acimovic et al. 2016). In some cases with these alternate substrates, 25- and 27-hydroxylations occur, as well as epoxidation of desmosterol (Acimovic et al. 2016).

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P450 51A1

Although the liver is generally considered to be the major organ involved in cholesterol synthesis, CYP51A1 mRNA was found to be high in testis, ovary, adrenal, prostate, kidney, and lung as well as liver (Stromstedt et al. 1996). In mouse testis, mRNA levels were high and localized in both round and elongated spermatids (Cotman et al. 2001). This high level has been proposed to lead to the production of steroids for signaling (Rozman and Waterman 1998; Rozman et al. 2002). *Cyp51a1*-knockout mice show a phenotype reminiscent of the Antley-Bixler Syndrome (Keber et al. 2011).

Several X-ray crystal structures of human P450 51A1 have now been published, both ligand-free and with ligands (Strushkevich et al. 2010; Hargrove et al. 2016) (PDB 3JUS, 3JUV, 3LD6, 4UHI, 4UHL). In addition, several X-ray crystal structures of various parasite CYP51 enzymes have also been published (Lepesheva et al. 2010; Hargrove et al. 2015; Hargrove et al. 2017). These structures have potential value in directing the synthesis of inhibitors towards the parasitic 14 α -demethylases and avoiding interactions with human P450 51A1.

The specificity constant ($k_{\text{cat}}/K_{\text{m}}$) for human P450 51A1 has been reported to be only $\sim 300 \text{ M}^{-1} \text{ s}^{-1}$, which is relatively low among P450s and also enzymes in general (Lamb et al. 1998). Nevertheless, the significance of this enzyme is clear, as further demonstrated by the transgenic mouse results (Keber et al. 2011).

An open question is the catalytic mechanism of the third step of the 14 α -demethylase reaction. Obviously this has similarity to the last step of the P450 19A1 reaction (*vide supra*). Although ^{18}O -labeling and other evidence has been presented in favor of a ferric peroxide (FeO_2^-) nucleophilic attack on the C-32 formyl group (Fischer et al. 1991; Shyadehi et al. 1996) instead of the general Compound I (FeO^{3+}) mechanism, the same limitations pointed out in the reassessment of the P450 19A1 mechanism (Yoshimoto and Guengerich 2014) apply (Guengerich and Yoshimoto 2018) and a reassessment with modern mass spectrometry methods is in order.

The oxidative removal of the 14 α -methyl group from sterol precursors by sterol 14 α -demethylase (CYP51 Family genes) is a universal step in the biosynthesis of membrane sterols and steroid hormones. Thus, P450 51A is a primary target in treatment of fungal infections in organisms ranging from humans to plants, and development of more potent and selective inhibitors is an important biological objective in many therapeutic fields. Currently the *CYP51* gene family is found in at least 82 organisms, spread over all biological kingdoms. Several plants and fungi contain multiple *CYP51* genes (e.g. rice (10), black oats (2), tobacco (2), *Arabidopsis thaliana* (2), *Fusarium graminearum* (3), and several of the *Aspergillus* species: e.g., *Aspergillus fumigatus* (2), *A. nidulans* (2), *A. orizae* (3)). As a result, the number of known *CYP51* gene sequences is >100 . All mammalian genomes examined contain only a single *CYP51A1* gene but some have nonfunctional *CYP51* pseudogenes (e.g., three in humans and one in rats, <http://drnelson.uthsc.edu/cytochromeP450.html>).

Azoles (imidazoles and triazoles) play a pivotal role in the treatment of systemic and dermal mycoses. The substrate analogs 7-oxo, 15-keto, 15-oxime, 15-hydroxy, 26-oxo derivatives of lanosterol are effective in blocking cholesterol biosynthesis in humans. 14 α -Amino derivatives of lanosterol were found effective to inhibit *Candida albicans* and *Trypanosoma cruzi* P450 51 orthologs and are effective to cure murine models of leishmania and Chagas disease (Lepesheva and Waterman 2007).

Sterol 14 α -demethylase is one of the hypothetical targets an alternative to classic statin therapy (Kaluzhskiy et al. 2014). Most commercial and experimental inhibitors of microbial P450 51 orthologs (including all clinical antifungals) weakly inhibit human P450 51A1 activity. Only one relatively potent compound, (*R*)-*N*-(1-(3,4'-difluorobiphenyl-4-yl)-2-(1*H*-

imidazol-1-yl)ethyl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)benzamide (VFV), was identified, and it was also found to decrease proliferation of different cancer cell types (Hargrove et al. 2016).

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Vitamin D metabolism

P450s are the major enzymes involved in the conversion of vitamin D₃ to more active products and also in the breakdown of vitamin D and its products (Fig. 18). Because of the many roles of vitamin D, the balance is important and these enzymes are generally highly regulated.

P450 24A1

P450 24A1 is one of the seven human P450s normally localized in mitochondria, and accordingly it receives electrons from NADPH-adrenodoxin reductase and adrenodoxin. This P450 is localized in the kidney, plus a few other places (Guengerich 2015). Its regulation is highly complex, as might be expected for an enzyme involved in a delicate regulation of the amount of an active vitamin (Guengerich 2015).

An X-ray crystal structure of rat P450 24A1 has been published (Annalora et al. 2010) (PDB 3K9V, 3K9Y). No substrate is present, only a molecule of either steroidal detergent 3-[(3-cholamidopropyl)dimethylammonium]-1-propane sulfonate (CHAPS) or the totally synthetic detergent CYMAL-5. Some of the reactions catalyzed by P450 24A1 are shown in Fig. 19, but the human enzyme will also oxidize a number of substrate analogs.

The degradation of 1 α ,25-dihydroxy vitamin D₃ by P450 24A1 occurs through multiple, sequential oxidation reactions targeting specific carbon atoms in the side chain. These multicatalytic activities of P450 24A1 (Makin et al. 1989; Reddy and Tserng 1989; Akiyoshi-Shibata et al. 1994; Beckman et al. 1996) can be divided into two regioselective oxidation pathways, involving an initial attack at C24 to yield a side-chain truncated product, calcitric acid (Makin et al. 1989; Reddy and Tserng 1989), or at C23 to give 1 α , 25-dihydroxy vitamin D₃-26,23-lactone (Sakaki et al. 2000) (Fig. 19). The proportion of these catabolic products is species-dependent, with calcitric acid production predominating in rodents (Hamamoto et al. 2006), 26,23-lactone predominating in the opossum and guinea pig (Pedersen et al. 1988; Horiuchi et al. 1995), and a mixture of the two products being formed in humans (Prosser and Jones 2004). Substrate contact with a species-specific residue in the I-helix adjacent to the heme group of the cytochrome P450 is proposed to control the pathway selection, with Ala-326 directing substrate into the C24 pathway in humans and Gly-326 driving 23-hydroxylation in opossums (Prosser et al. 2007). Other amino acids having a lesser influence on regioselectivity in rat include Thr-416 (Met-416 in humans) and Ile-500 (Thr-500 in humans) (Hamamoto et al. 2006). Thus, the failure of the enzyme to oxidize certain substrates may result from an inability to correctly position the side chain rather than an inherent inability to bind the substrate (Kaufmann et al. 2011).

In melanocytic tumors the level of P450 24A1 was higher than in the normal epidermis, with the highest mean P450 24A1 level found in nevi and early stage melanomas. During

melanoma progression P450 24A1 levels decreased and in the advanced stages was comparable to the normal epidermis and metastases. Lower P450 24A1 levels correlated with the presence of ulceration, necrosis, nodular type, and amelanotic phenotypes. A lack of detectable P450 24A1 expression was related to disease-free survival. Thus, an elevated level of CYP24A1 appears to have an important impact on the formation of melanocytic nevi and melanomagenesis, or progression, in the early stages of tumor development (Brozyna et al. 2014).

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P450 27B1

P450 27B1, a kidney mitochondrial enzyme, is the vitamin D 1 α -hydroxylase, acting on various derivatives of 25-hydroxyvitamin D. This is an activated form of vitamin D, and accordingly the enzyme has a very complex regulatory system (Guengerich 2015). Further, P450 27B1 deficiency is associated with type I vitamin D-dependent rickets, and 20 variants are known (Kitanaka et al. 1998; Wang et al. 1998; Smith et al. 1999; Portale and Miller 2000; Kim et al. 2007; Wu et al. 2007).

No crystal structures have been reported, although roles of several amino acids have been identified through the work with the clinical variants.

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Retinoid metabolism

Several P450 enzymes are involved in oxidations of retinoids (Fig. 21), the regulation of which is very important, as in the case of vitamin D. The 4- and 18-oxidations are considered to be deactivating. The 3,4-desaturation by P450 27C1 in human skin is an efficient reaction but the biological significance has only been established in fish and amphibians.

P450 26A1

Retinoic acid is the endogenous active metabolite of vitamin A₁ (retinol) and acts as an essential regulator of cell growth, cell cycle, and differentiation (Gudas 2012; Napoli 2012). all-*trans*-Retinoic acid is believed to be the main biologically active form, binding predominantly to nuclear retinoic acid receptors (RARs), and plays a critical role in many biological processes including reproduction, maintenance of skin and epithelia, regulation of the immune system and T- and B-cell function, and in fetal development (Maden 2007; Ross 2012; Hogarth and Griswold 2013).

The production of the enzyme P450 26A1 is regulated by its substrate, retinoic acid, via the RXR receptor.

No crystal structures are available for the enzyme.

P450 26A1 has relevance in developmental biology, in that *Cyp26a1*^{-/-} mice show distinct malformations and lethality (Tay et al. 2010). Gudas has demonstrated a role of (mouse) P450 26a1 in stem cell differentiation, and inhibiting P450 26A1 has been considered as an approach in cell/differentiation therapy for neurodegenerative diseases (Ricard and Gudas 2013).

Imbalance in vitamin A and retinoic acid homeostasis have been implicated in development and progression of several human diseases, e.g., acne, psoriasis and ichthyosis, type II diabetes, neurodegenerative diseases, and some cancers (Gudas 2012). The use and long term efficacy of all-*trans* retinoic acid has been limited by its high metabolic clearance, which limits oral administration of this agent, and the resistance that develops towards all-*trans* retinoic acid due to autoinduction of its metabolism (Nelson et al. 2013).

The clearance of all-*trans* retinoic acid is predominantly mediated by P450 Family 26 enzymes (Thatcher and Isoherranen 2009; Ross and Zolfaghari 2011), particularly P450 26A1 in human liver, considered to be responsible for majority of the hepatic clearance (Thatcher et al. 2010). It has been proposed that inhibition of the P450 Family 26 enzymes will increase all-*trans* retinoic acid concentrations in target tissues, and inhibition of P450 26 enzymes during could be used productively (Njar et al. 2006). Many of the existing inhibitors of P450 26 enzymes have not been evaluated for specificity (among the P450 Family 26 enzymes) and therefore the benefits and shortcomings of selective or broad P450 26 inhibition have not been established.

P450 Family 26 enzymes have cell type and tissue specific expression (Topletz et al. 2012) and therefore specific P450 26A1 (or P450 26B1) inhibitors may be beneficial for increasing

retinoic acid concentrations in selected target tissues without causing broad side effects. P450 26A1 is the predominant P450 Family 26 enzyme in the liver, and therefore selective inhibition of P450 26A1 could decrease systemic clearance of retinoic acid and be useful in therapy resistance with individuals being treated with all-*trans* retinoic acid or 13-*cis*-retinoic acid. A P450 26A1 selective inhibitor would avoid side effects of P450 26B1 inhibitors, which have potential reproductive and teratogenic issues, and be more likely to be beneficial than when systemic retinoic acid concentrations are targeted (Diaz et al. 2016).

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P450 26B1

P450 26B1 is expressed in the brain and also in a number of other tissues but not liver (Topletz et al. 2012). It is induced by all-*trans*-retinoic acid and also regulated by certain transcription factors (Guengerich 2015).

The reactions are similar to those catalyzed by P450 26A1, i.e. 4- and 18-hydroxylation of all-*trans*-retinoic acid and further oxidation of the 4-hydroxy product to 4-oxoretinoic acid.

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P450 26C1

In contrast with the other Family 26 P450 enzymes, P450 26C1 is expressed mainly during development, although this conclusion is based largely on animal models (Ross and Zolfaghari 2011). However, P450 26C1 mRNA has been detected not only in human fetal liver and brain but also in adult human brain, lung, liver, spleen, and testis, which are retinoid target tissues (Xi and Yang 2008).

The reactions catalyzed (Fig. 23) are similar as for P450 26B1, although recent work by Zhong et al. (2018) has defined some important differences in both the substrate and product profiles. Zhong et al. (2018) reported that P450 26C1 has a specificity constant (k_{cat}/K_m) up to 10-fold higher than P450 26A1 or 26B1 in oxidizing all-*trans*-4-oxo retinoic acid. There are issues in defining the roles of the three different Family 26 P450s in retinoic acid metabolism, in light of the differences in intrinsic catalytic activity, cellular localization, the concentration of each P450 protein in each tissue, and the potentially different interactions of the P450s with cellular retinoic acid binding proteins (Zhong et al. 2018).

No information about the structure of this protein is available yet, although at least one homology model has been presented (Zhong et al. 2018).

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P450 27C1

Desaturation of retinol to 3,4-dehydroretinol (vitamin A₂) (Figs. 21, 24) has been reported in preparations of human breast skin (Törmä and Vahlquist 1985) and keratinocytes in culture (Rollman et al. 1993; Andersson et al. 1994). UV light exposure was reported to increase the formation of 3,4-dehydroretinol in cultured human keratinocytes (Tafrova et al. 2012). Zebrafish P450 27C1 is an efficient retinol 3,4-desaturase and that this enzyme is expressed in the eyes of fish and amphibians where it acts to red-shift the visual chromophore (Enright

et al. 2015). No bird or mammal has been shown to express P450 27C1 in the eye, but the human *CYP27C1* gene encodes a retinoid 3,4-desaturase, P450 27C1, with selectivity for all-*trans* retinol. This enzyme catalyzes the production of 3,4-dehydroretinoids in human skin (Kramlinger et al. 2016; Johnson et al. 2017).

The specificity constant for human P450 27C1 is relatively high, at least for mammalian P450 enzymes (k_{cat}/K_m 7.7×10^5 M⁻¹ s⁻¹ for all-*trans*-retinol), and clearly indicates that retinoids should be the natural substrates (Kramlinger et al. 2016; Johnson et al. 2017). The rate-limiting steps in the catalytic cycle are the first-electron reduction and C-H bond-breaking, the latter revealed by kinetic deuterium isotope effects (Johnson et al. 2017).

In fish and some amphibians, the enzyme is localized in the retinal epithelium, and synthesis of P450 27C1 allows these animals to change their visual spectra (Enright et al. 2015). However, in humans this (mitochondrial) enzyme is clearly localized in the skin, as shown by extensive proteomic analysis (Johnson et al. 2017).

Although there is little question that P450 27C1 is a skin retinoid desaturase (Kramlinger et al. 2016; Johnson et al. 2017), what is not clear is why such a large fraction of the retinoids in human skin (1/4) is desaturated (Vahlquist 1980, 1982; Vahlquist et al. 1982). Rats and mice are devoid of the 27C1 gene and thus provide no insight into the function.

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An Orphan P450

P450 20A1

The function of P450 20A1 remains unknown; however, the sites of mRNA expression in human brain and the conservation among species may suggest possible neurophysiological function (Stark et al. 2008). P450 20A1 appears to be the only human P450 Family 20 member. P450 20A1 EST sequences have recently been reported from kidney, brain, placenta, and urogenital tissues, according to the NCBI UniGene database (<http://www.ncbi.nlm.nih.gov/UniGene/>). Orthologous nucleotide sequences have been found in a number of mammals, including rat (84% identity), mouse (85%), chimpanzee (99.6%), and chicken (72%) (<http://drnelson.utmem.edu/CytochromeP450.html>). None of these (putative) proteins has been studied to date.

In contrast to our report in Stark *et al.* (Stark et al. 2008), the Protein Atlas Database (www.proteinatlas.org) indicates widespread mRNA expression and possibly higher levels in endocrine tissues. Although expression in *E. coli* has been reported (Stark et al. 2008), the levels were low and in our own hands this has not been easy to repeat. Although there is still no information about a substrate, deletion of the *CYP20A1* gene in zebrafish has been reported to cause a hyperactivity disorder (Lemaire et al. 2016). At this time P450 20A1 remains a true orphan P450 (Guengerich and Cheng 2011) in the sense of not having any identified function.

It has been noted that this protein lacks one amino acid of the conserved heme binding site. It also lacks the conserved I-helix motif AGX(D,E)T, and it has been suggested that its substrate may carry its own oxygen (www.proteinatlas.org). However, there is no actual evidence that this is the case.

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CONCLUSIONS AND OUTLOOK

The human P450 family, which contains 57 members, can be divided into two major groups. Members of the first group are involved largely in the metabolism of xenobiotic compounds such as drugs and environmental chemicals (Families 1–4 with 35 enzymes). Members of the second group are enzymes that predominately catalyze biotransformation and metabolism of endobiotic compounds (Families 5–51 with 22 enzymes). However, there is overlap in these groups, i.e. the Family 5–51 enzymes can oxidize some non-physiological compounds.

The enzymes from the first group have been extensively investigated ever since they were discovered. These enzymes have been the subject of a great number of research publications and review papers. Scientific interest in the enzymes belonging the gene Families *CYP1*, *CYP2*, and *CYP3* was strengthened by the fact that these enzymes were found to be involved in most of the metabolism of clinically relevant drugs and toxicological responses to xenobiotic compounds, with some exceptions (e.g., Family 4 which in addition to some drugs catalyzes reactions in the metabolism of fatty acids and arachidonic acid). The enzymes belonging to the second group (P450s 5–51), reviewed in the present publication, preferentially catalyze biotransformations and metabolism of compounds that are of major importance in the physiological status of humans and consequently for human health. These enzymes catalyze the biosynthesis and metabolism of eicosanoids (P450s 5A1 and 8A1; Figs. 1–3), steroids (P450s 7A1, 11A1, 11B1, 17A1, 19A1, 21A1, 21A2, 27A1; Figs. 4A, 4B, 8, 9, 10, 11, 12), bile acids (P450s 7A1, 7B1, 8B1, 27A1, 39A1, 46A1; Figs 4A, 14A), vitamin D₃ (P450 24A1, 27A1, 27B1; Figs. 4A, 14B) and retinoids (26A1, 26B1, 26C1, 27C1; Fig. 21) and also the formation of cholesterol, the starting material for the biosynthesis of steroids, bile acids, and vitamin D) from lanosterol (Figs. 4A and 17). Also in this group there are exceptions regarding drugs as substrates of the enzymes: P450 11B1, 11B2, 19A1, 21A2, and 46A1. P450 20A1 is considered as orphan enzyme in that its function still remains unknown.

As humans are exposed to a great number of chemicals through food, environmental contamination, and medicines, there may be results with a significant positive or negative effect on catalytic activities of the enzymes or expression of mRNAs or proteins. The data presented in the tables provide information to serve as a guide when considering possible drug-drug, drug-environmental chemicals, or chemical-physiological compounds interactions in clinic or in every day life. The positive effect of inhibition of P450 enzyme activity on human health is exemplified by inhibition of P450 19A1, i.e. lowering estrogen levels by chemicals. Different chemicals can exert such an effect on the enzyme such as drugs (e.g., imidazoles, antiepileptic drugs, cyclooxygenase-selective inhibitors), natural compounds (e.g., flavonoids, polyphenols, and chalcones), physiological compounds (4-hydroxyandrostendione), and environmental chemicals, as well as number of developed drug candidates of different types explored for treatment of breast cancer (Table 10). The following examples illustrate effects provoked by the action of drugs or other chemicals on

the enzymes activity relating to human health: P450 8A1—elevated risk of hypertension and infarction when inhibited, chemo-preventive activity when induced (Table 2); P450 5A1—anti-platelet aggregation and anti-tumor activity when inhibited, pro-carcinogenic role when induced (Table 1); P450 11A1 and 17A1—prostate cancer treatment when inhibited (Tables 6 and 9, respectively). Analysis of the data from clinical samples showed that increases/or down-regulation of mRNA and/or protein expression of P450s 5A1, 7B1, 19A1, 26A1, 26B1, 26C1, 27A1, and 27B1 might be used as markers of the aggressive biological potential of tumors and association with poor patient survival. It has been suggested that up-regulation of these enzymes might be useful as tumor markers in the diagnosis and prognosis of different malignancies.

In summary, the data presented show functional targets of P450 enzymes belonging to the Families 5–51. Of these enzymes, targets for drugs in clinical treatment are P450s 5A1, 11B1, 11B2, 17A1, and 19A1. The enzymes of this group synthesize important physiological molecules but over-production or down-regulation may be an issue in some diseases. The present review brings updated information and has focused on the properties of different chemical entities (drugs, environmental, physiological, and natural compounds, as well as examples of drug candidates under investigation) as inhibitors and/or inducers of the enzymes activity and clinical implications.

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Fig. 1.

Metabolic pathways for arachidonic acid, with participation of P450s 5A1 and 8A1.

Fig. 2.
Conversion of prostaglandin H₂ to thromboxane A₂ by P450 5A1 (thromboxane synthase).

Fig. 3.
Conversion of prostaglandin H₂ to prostacyclin (PGI₂) by P450 8A1.

Fig. 4A.

Formation of bile acids, steroids, and active form of vitamin D from cholesterol. All mammalian steroids, bile acids, and active form of vitamin D are formed from cholesterol.

Fig. 4B. P450 enzymes involved in steroid biosynthesis. P450 51A1, the lanosterol 14 α -demethylase, is involved in the biosynthesis of cholesterol but is not shown. See Figs. 4A and 17.

Fig. 5.
7 α -Hydroxylation of cholesterol by P450 7A1.

Fig. 6.

7 α -Hydroxylation of 25- or 27-hydroxycholesterol by P450 7B1.

Fig. 7.
12 α -Hydroxylation of 4 β - or 7 α -hydroxycholesterol by P450 8B1.

Fig. 8.
Three-step oxidation of cholesterol to pregnenolone by P450 11A1.

Fig. 9.
Steroid oxidations catalyzed by (human) P450 11B1.

Fig. 10.
Steroid oxidations catalyzed by (human) P450 11B2.

Fig. 11.
Two-step oxidations catalyzed by P450 17A1.

Fig. 12.
Three-step oxidation of testosterone to 17 β -estradiol by P450 19A1.

Fig. 13.
Hydroxylations catalyzed by P450 21A2.

Fig. 14.

A, Sterol oxidations catalyzed by P450 27A1 in the synthesis of bile acids. *B*, 25-Hydroxylation of vitamin D₃ by P450 27A1.

Fig. 15.

7 α -Hydroxylation of 24(*S*)-hydroxycholesterol by P450 39A1.

Fig. 16.
24(*S*)-Hydroxylation of cholesterol by P450 46A1.

Fig. 17.
Three-step 14 α -demethylation of lanosterol by P450 51A1.

Fig. 18.
P450s involved in the metabolism of vitamin D₃.

Fig. 19.
Oxidation of vitamin D₃ catalyzed by P450 24A1.

Fig. 20.
1 α -Hydroxylation of 25-hydroxy vitamin D₃ by P450 27B1.

Fig. 21.
Some P450s involved in the metabolism of retinoids.

Fig. 22.
C4-Oxidation of all-*trans*-retinoic acid catalyzed by P450 26A1.

Fig. 23.

C4- and C18-oxidations of all-*trans*-retinol catalyzed by P450s 26B1 and 26C1.

Fig. 24.
3,4-Desaturation of all-*trans*-retinol by P450 27C1.

Table 1.

P450 5A1

Properties	References
Physiological substrates: Prostaglandin (PG) H ₂ , PGH ₁ , 8- <i>iso</i> -PGH ₂ , 13(<i>S</i>)-hydroxy-PGH ₂ , 15-keto-PGH ₂ , PGG ₂ , PGH ₃ 15-hydroperoxyeicosatetraenoic acid, charged lipids (phosphatidylserine and phosphatidylethanolamine)	(Hecker and Ullrich 1989; Ullrich and Hecker 1990; Wang et al. 1996; Yeh et al. 2007; Cathcart et al. 2010; Pan et al. 2016)
Function: Thromboxane A ₂ synthase, conversion of PGH ₂ to TXA ₂ (Figs. 1, 2), stimulates platelet secretion, platelet aggregation and vasoconstriction. Demonstrated to have a pro-carcinogenic role in a variety of cancers.	
Inhibition: Decrease of thromboxane A ₂ levels, antiplatelet aggregation, and thrombosis; increase of PGI ₂ generation <i>in vivo</i> ; antitumor activity by inhibition tumor cell growth, invasion, metastasis, and angiogenesis (de Leval et al. 2003; Dogne et al. 2004)	
Inhibitors^a	
<u>Drugs:</u>	
Cinnamophilin (Yu et al. 1994)	
Furegrelate, ozagrel (Moussa et al. 2008)	
Itraconazole, ketoconazole, terbinafine (Kanda and Watanabe 2006; Kanda et al. 2011)	
Miconazole (Steinhilber et al. 1990)	
Picotamide and derivatives (Dogne et al. 2004; Liu 2015)	
Picotamide, dazoxiben, dazmagrel, pirmagrel, ozagrel, isbogrel, ridogrel, terbogrel, camonagrel, samixogrel, uregrelate, furegrelate (Rowe et al. 2000; Schuster and Bernhardt 2007; Davi et al. 2012)	
Terbogrel (Muck et al. 1998; Soyka et al. 1999; Michaux et al. 2001; Michaux et al. 2003; Dogne et al. 2004)	
Torasemide and derivatives (de Leval et al. 2006)	
<u>Natural compounds:</u>	
<i>Aloe vera</i> glycoprotein fraction (Yagi et al. 2003)	
Cinnamophilin (Yu et al. 1994)	
Nicotine, cotinine and methyl nicotine (Goerig and Habenicht 1988; Goerig et al. 1992; Saareks et al. 1998)	
Onion extract (Moon CH et al. 2000)	
<u>Other compounds, including drug candidates^a</u> (Dogne et al. 2000; Dogne et al. 2004; de Leval et al. 2006; Dogne et al. 2006; Davi et al. 2012)	
(E)-3-(1,4-Benzoquinonyl)-2-[(3-pyridyl)-alkyl]-2-propenoic acid derivatives (Hibi et al. 1996)	
(E)-3-[4-(3-Pyridylmethyl) phenyl]-2-methylacrylate, OKY-1581 (Oketani et al. 2001)	
(E)-3-[p-(1H-Imidazol-1-ylmethyl)phenyl]-2-propenoic acid, OKY-046 (Hiraku et al. 1986)	
1-Imidazolyl(alkyl)-substituted di- and tetrahydroquinolines and pyridines (Ackerley et al. 1995; Hartmann and Frotscher 1999; Jacobs et al. 2000)	
4-(2-Phenyltetrahydrofuran-3-yl) benzene sulfonamide analogs (Sekhar et al. 2009)	
6,6-Disubstituted hex-5-enoic acid derivatives (Soyka et al. 1994)	
Benzene sulfonylurea derivatives (Dogne, Rolin, et al. 2001; Rolin et al. 2001; de Leval et al. 2003; Michaux et al. 2003; Rolin et al. 2004; Ghuysen et al. 2005; Hanson et al. 2005; de Leval et al. 2006; Jarrar et al. 2013)	
Dioxane derivatives (Ackerley et al. 1995; Faull et al. 1995; Hartmann and Frotscher 1999; Jacobs et al. 2000)	
DP-1904, imidazolylmethyl-tetrahydronaphthalene derivative (Trochtenberg et al. 1992)	
E3040, benzothiazole (Oketani et al. 2001)	
FK070 (KDI-792) (pyrrolidine derivative) (Uematsu et al. 1996)	
Guanidine derivatives (Soyka et al. 1999)	
Imidazo[1,5- <i>a</i>]pyridines (Ford et al. 1985)	
Imidazolyl-substituted tetralones (Hartmann et al. 1996)	
MED 27, theophylline derivative (Tubaro et al. 1996)	

Properties	References
NV-52, a synthetic flavonoid derivative (Howes et al. 2007)	
Oxazolecarboxamide-substituted ω -phenyl- ω -(3-pyridyl)alkenoic acid derivatives (Takeuchi et al. 1998)	
Oxazolecarboxamide derivatives (Takeuchi et al. 1998)	
Ridogrel diazine derivatives (Heinisch et al. 1996)	
Sulfonylcyanoguanidine compounds (Dogne, Wouters, et al. 2001; Michaux et al. 2003)	
Tetrahydronaphthalene derivatives (Hartmann et al. 1996; Wachter et al. 1996; Cimetiere et al. 1998)	
Tetrahydroquinolines and analogues (Ackerley et al. 1995; Hartmann and Frotscher 1999; Jacobs et al. 2000)	
ω -Disubstituted alkenoic acid derivatives (Soyka et al. 1994)	
Induction: Enhanced cholesterol biosynthesis	
Inducers:	
<u>Natural compounds:</u>	
Biochanin A ^d (Moon et al. 2007)	
Phorbol ^b (Ihara et al. 1992)	
<u>Physiological compounds:</u>	
Cytotrophoblasts ^c (Ding et al. 2002)	
<u>Physiological conditions and illnesses:</u>	
Human colorectal carcinoma ^d (Sakai et al. 2006)	
Hypoxia ^c (Rowe et al. 2000)	
Papillary thyroid carcinoma ^b (Casey et al. 2004; Kajita et al. 2005)	
Pituitary adenomas and carcinoma ^d (Onguru et al. 2004)	
Prostate carcinoma ^b (Nie et al. 2004)	

Footnotes:

^a Decreased/suppressed/inhibited activity/product formation

^b Increased transcription/mRNA/protein expression/levels /and/or catalytic activity

^c Increased activity, and/or increased product formation

^d Up-regulation of biosynthesis, increased expression of protein

Table 2.

P450 8A1

Properties	References
Physiological substrates: Prostaglandins (PG) (H ₁ , H ₂ , H ₃ , G ₂), 15-keto-prostaglandin H ₂ , 6-keto-prostaglandin F _{1α} , 15-hydroperoxyeicosatetraenoic acid, 10-hydroperoxyoctadeca-8,12-dienoic acid	(Hecker and Ullrich 1989; Ullrich and Hecker 1990; Yeh et al. 2005; Chiang et al. 2006; Yeh et al. 2007; Cathcart et al. 2010; Nakayama 2010; Pan et al. 2016)
Function: Prostacyclin synthase, isomerization of prostaglandin H ₂ to prostacyclin (PGI ₂) (Fig. 3), inhibition of platelet activation and aggregation and induction of vasodilation. Believed to have anti-tumor effects as overexpression has been shown to be chemopreventive in a murine model of the disease, suggesting that the expression and activity of this enzyme may protect against tumor development.	
Inhibition: Risk of essential hypertension, myocardial infarction and cerebral infarction (Chiang et al. 2006)	
Inhibitors:	
<u>Drugs:</u>	
Actinomycin D ^a (Camacho et al. 2008)	
Cycloheximide ^a (Camacho et al. 2008)	
Cyclosporine ^a (Sharanek et al. 2015)	
Miconazole, clotrimazole ^b (Yeh et al. 2005)	
Minoxidil ^b (Yeh et al. 2005; Li et al. 2008)	
Rofecoxib ^c (Griffoni et al. 2007)	
Simvastatin ^a (Skogastierna et al. 2013)	
Tranylcipromine ^b (Ding et al. 2002)	
<u>Other compounds:</u>	
Imidazole derivatives (4-phenylimidazole, 1-phenylimidazole, 1-benzylimidazole) ^b (Yeh et al. 2005)	
U46619, U51605, or U44069 (PGH ₂ analogues) ^b (Wada et al. 2004; Yeh et al. 2005; Li et al. 2008; Chao et al. 2011)	
Induction: Enhanced activity in tumor cells, potential anti-neoplastic and chemopreventive activity	
Inducers:	
<u>Natural compounds:</u>	
13- <i>cis</i> -Retinoic acid, 9- <i>cis</i> -retinoic acid, all- <i>trans</i> - retinoic acid ^d (Camacho et al. 2008)	
13- <i>cis</i> -Retinoic acid, 9- <i>cis</i> -retinoic acid, all- <i>trans</i> - retinoic acid ^d (Camacho et al. 2008)	
Curcumin ^d (Tan et al. 2011)	
Grape seed procyanidin extract ^d (Mao et al. 2016)	
13- <i>cis</i> -Retinoic acid, 9- <i>cis</i> -retinoic acid, all- <i>trans</i> - retinoic acid ^d (Camacho et al. 2008)	
<u>Physiological compounds:</u>	
17β-Estradiol ^d (Korita et al. 2004)	
<u>Physiological condition:</u>	
Hypoxia ^e (Camacho et al. 2011; Wang et al. 2013)	
Pregnancy ^d (Okahara et al. 1998)	

Properties	References
Shear stress ^e (Korita et al. 2002)	

Footnotes:

^a Reduced/suppressed mRNA and/or protein level/expression and activity

^b Competitive inhibition, ligand binding

^c Decreased/suppressed/inhibited activity/product formation

^d Up-regulation of biosynthesis, increased expression of protein

^e Increased transcription/mRNA/protein expression/levels /and/or catalytic activity

Table 3.

P450 7A1

Properties	References
Physiological substrates: Cholesterol, oxysterols, zimosterol, lathosterol, zymostenol, desmosterol, cholestanol, 24(<i>S</i>) and (<i>R</i>)-hydroxycholesterol, 25-hydroxycholesterol, 27-hydroxycholesterol, 20(<i>S</i>)-hydroxycholesterol, 7-dehydrocholesterol, cholest-4-en-3-one, bile acids (taurocholic acid, deoxycholic acid, lithocholic acid, ursodeoxycholic acid)	(Norlin, Andersson, et al. 2000; Norlin, Toll, et al. 2000; Smelt 2010; Shinkyo and Guengerich 2011; Shinkyo et al. 2011; Tempel et al. 2014; Acimovic et al. 2016; Pan et al. 2016)
Function: Cholesterol 7 α -hydroxylase (Figs. 4A, 5), first step in conversion of cholesterol to bile acids	
Inhibition: Causes increased cholesterol saturation of bile, enhanced liver and lower circulating LDL cholesterol content, lowering biosynthesis and excretion of bile acids	
Inhibitors:	
<u>Drugs:</u>	
Cyclosporin A ^a (Sharanek et al. 2015)	
Fibrates ^a (clofibrate, bezafibrate, fenofibrate, gemfibrozil) (Marrapodi and Chiang 2000; Gbaguidi and Agellon 2004; Roglans et al. 2004; Zak et al. 2007; Honda et al. 2013)	
Obeticholic acid ^a (Zhang, Jackson, et al. 2017)	
<u>Natural compounds:</u>	
Guggulsterone ^b (Owsley and Chiang 2003)	
Phorbol 12-myristate-13-acetate ^a (Wang et al. 1996)	
Red grapefruit juice ^a (Davalos et al. 2006)	
α -Tocopherol ^a (Gonzalez, Cruz, Ferrin, Lopez-Cillero, Fernandez-Rodriguez, et al. 2011)	
<u>Physiological compounds:</u>	
25-Hydroxycholesterol ^a (Taniguchi et al. 1994; Gbaguidi and Agellon 2004)	
7-Oxcholesterol ^a (Norlin, Toll, et al. 2000)	
Arachidonic acid ^a (Zhang, Wand, et al. 2017)	
Bile acids (free and glycine conjugated) ^a (chenodeoxycholic acid, deoxycholic acid, glyoursodeoxycholic acid, glycodeoxycholic acid, glycocholic acid) (Chiang et al. 2000; Chen et al. 2001; Ellis E et al. 2003; Li T, Jahan, et al. 2006; Smelt 2010; Gonzalez, Cruz, Ferrin, Lopez-Cillero, Briceno, et al. 2011; Gonzalez, Cruz, Ferrin, Lopez-Cillero, Fernandez-Rodriguez, et al. 2011; Liu J et al. 2014)	
cAMP ^a (Song KH and Chiang 2006)	
Glucagon ^a (Song KH and Chiang 2006)	
Insulin ^a (prolonged treatment) (Wang et al. 1996; Li T, Kong, et al. 2006)	
Proinflammatory cytokines (interleukin-1 β) ^a (Jahan and Chiang 2005; Li T, Jahan, et al. 2006)	
Sitosterol ^c (Nguyen et al. 1998)	
Thyroid hormones (triiodothyronine, T ₃) ^a (Wang et al. 1996; Drover et al. 2002; Drover and Agellon 2004; Ellis EC 2006; Song Y et al. 2015)	
α_1 -Antitrypsin peptide ^a (Gerbod-Giannone et al. 2002)	
<u>Other compounds, including drug candidates:</u>	
WY-14643 (pirinixic acid) ^a (Marrapodi and Chiang 2000; Gbaguidi and Agellon 2004)	
Induction: Causes enhanced biosynthesis of bile acids, cholesterol lowering effect, increased risk of gallstone formation	

Properties	References
Inducers: Decrease of cholesterol levels, alteration of bile acid profiles	
<u>Drugs:</u>	
Dexamethasone ^d	(Andreou and Prokipcak 1998)
NO-1666 (Ibrolipim) ^d	(Li Q et al. 2010)
Rifampicin ^d	(Gonzalez, Cruz, Ferrin, Lopez-Cillero, Briceno, et al. 2011)
Statins ^e (atorvastatin, pitavastatin, pravastatin, simvastatin, lactostatin)	(Fan et al. 2004; Morikawa et al. 2007; Parker et al. 2013)
<u>Natural compounds:</u>	
Dipeptides ^d (Asp-Lys, Glu-Lys, and Trp-Lys)	(Norlin and Wikvall 2007)
Farnesylquinone and derivatives ^e	(Liu D et al. 2014)
Fish oil ^f	(Jonkers et al. 2006; Smelt 2010)
Crocin, chlorogenic acid, geniposide, and quercetin (in combination) ^d	(Leng et al. 2018)
<u>Physiological compounds:</u>	
Cholestyramine ^g	(Norlin, Andersson, et al. 2000; Norlin and Wikvall 2007)
Glucose ^g	(Li T et al. 2010; Li T et al. 2012)
Insulin ^d (short-term treatment)	(Li T, Kong, et al. 2006; Li T et al. 2012)
Taurine ^d	(Guo et al. 2017)
Thyroid hormones ^e	(Lammel Lindemann et al. 2014)
<u>Other compounds:</u>	
2,4,6-Trihydroxyacetophenone ^g	(Charoenteeraboon et al. 2005)
Oleic acid anilide ^d	(An et al. 2008)

Footnotes:

^aReduced/suppressed mRNA and/or protein level/expression and activity^bDecreased/suppressed/inhibited activity/product formation^cCompetitive inhibition, binding to enzyme active site^dIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity^eUp-regulation of biosynthesis, increased expression of protein^fIncreased bile acid synthesis and mRNA levels^gIncreased activity, and/or increased product formation

Table 4.

P450 7B1

Properties	References
Physiological substrates: 25- and 27-Hydroxycholesterol, pregnenolone, dehydroepiandrosterone (DHEA), epiandrosterone, 5 α -androstane-3 β ,17 β -diol, estrone	(Rose et al. 1997; Steckelbroeck et al. 2002; Kim SB et al. 2004; Stiles et al. 2009; Yantsevich et al. 2014; Pan et al. 2016)
Function: 25-Hydroxycholesterol 7 α -hydroxylase, oxysterol and steroid 6 α - or 7 α -hydroxylase (Fig. 6); involved in metabolism of neurosteroids (brain), bile acid synthesis (liver), and metabolism of estrogen receptor ligands (in prostate)	
Inhibition: Possible liver failure and progressive neuropathy	
<u>Inhibitors:</u>	
<u>Drugs:</u>	
Imidazole and triazole drugs (ketoconazole, biconazole, miconazole, clotrimazole, econazole, fluconazole, tioconazole, voriconazole) ^a (Kim SB et al. 2004; Yantsevich et al. 2014)	
Metirapone ^a (Yantsevich et al. 2014)	
<u>Physiological compounds:</u>	
5 α -Androstane-3 β ,17 β -diol, estrone, testosterone, 17 β -estradiol ^b (Kim SB et al. 2004; Tang et al. 2006; Pettersson et al. 2008)	
5 α -Dihydrotestosterone ^b (at high concentrations) (Pettersson et al. 2008)	
Estrogens (estrone, 17 β -estradiol—in the absence of estrogen receptor α) ^b (Tang et al. 2006)	
Triiodothyronine ^c (T ₃) (Ellis 2006)	
β -Amyloid peptide (non-competitive inhibition) (Kim SB et al. 2004)	
<u>Physiological condition and illnesses:</u>	
Breast cancer ^d (Wu et al. 2013)	
Prostatic cancer ^d (in type 2 diabetes) (Lutz et al. 2018)	
<u>Other compounds:</u>	
Pesticides ^a (tebuconazole, propiconazole) (Yantsevich et al. 2014)	
<u>Induction:</u> Immunostimulatory effect of 7 α -hydroxydehydroepiandrosterone (used in rheumatoid arthritis)	
<u>Inducers:</u>	
<u>Drugs:</u>	
Rifampicin (Kim B et al. 2013)	
<u>Physiological compounds:</u>	
17 β -Estradiol ^e (in human embryonic kidney (HEK293) cells transfected with estrogen receptor α) (Dulos, van der Vleuten, et al. 2005; Tang et al. 2006)	
Interleukin-1 β interleukin-1 α , interleukin-7, interleukin-17, activator protein-1, nuclear factor- κ B, tumor necrosis factor- α ^e (Dulos, Kaptein, et al. 2005; Dulos, van der Vleuten, et al. 2005; Dulos and Boots 2006)	
<u>Physiological condition and illnesses:</u>	
Prostatic cancer ^f (Olsson et al. 2007)	
Psoriasis ^f (Sumantran et al. 2016)	
<u>Other compounds:</u>	
Oleic acid anilide ^e (An et al. 2008)	

Footnotes:

^aCompetitive inhibition, ligand binding

^bDecreased/suppressed/inhibited activity/product formation

^cReduced/suppressed mRNA and/or protein level/expression and activity

^dGene downregulated/suppressed

^eIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity

^fUp-regulation of biosynthesis, increased expression of protein

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Table 5.

P450 8B1

Properties	References
Physiological substrates: 27-Hydroxycholesterol, 24-hydroxycholesterol, 7 α -hydroxy-4-cholesten-3-one	
Gafvels et al. 1999; Pan et al. 2016)	
Function: Sterol 12 α -hydroxylase, production of cholic acids (bile acids) in the liver, conversion of 7 α -hydroxy-4-cholesten-3-one into 7 α ,12 α -dihydroxy-4-cholesten-3-one	
Inhibition: Lowered biosynthesis of bile acids	
<u>Inhibitors:</u>	
<u>Drugs:</u>	
Chlorpromazine ^a (Antherieu et al. 2013)	
Cyclosporine A ^b (Sharanek et al. 2015)	
<u>Physiological compounds:</u>	
Bile acids ^b (chenodeoxycholic acid, glycochenodeoxycholic acid, glycodeoxycholic acid) (Zhang and Chiang 2001; Jahan and Chiang 2005)	
Cholesterol ^b (Zhang and Chiang 2001)	
Insulin ^b (Zhang and Chiang 2001)	
Pro-inflammatory cytokines ^b (e.g. interleukin-1 β) (Jahan and Chiang 2005)	
Triiodothyronine (T3) ^b (Andersson et al. 1999; Ellis EC 2006)	
<u>Physiological condition:</u>	
Restricted feeding ^c (Pathak et al. 2013)	
Induction: Enhanced biosynthesis of bile acids, cholesterol lowering effect	
<u>Inducers:</u>	
<u>Drugs:</u>	
Atorvastatin ^d (Parker et al. 2013)	
Cycloheximide ^c (Andreou and Prokipcak 1998)	
Dexamethasone ^c (Andreou and Prokipcak 1998; Mörk et al. 2016)	
<u>Natural compounds:</u>	
Soy isoflavones ^e (genistein, daidzein, equol) (Li et al. 2007)	
<u>Physiological compounds:</u>	
Hepatocyte nuclear factor 4 α (HNF4 α) ^c (Zhang and Chiang 2001)	
<u>Physiological condition:</u>	
Fasting ^c (Pathak et al. 2013)	

Footnotes:

^a Decreased/suppressed/inhibited activity/product formation^b Reduced/suppressed mRNA and/or protein level/expression and activity^c Increased transcription/mRNA/protein expression/levels /and/or catalytic activity^d Up-regulation of biosynthesis, increased expression of protein

^eIncreased bile acid synthesis and mRNA levels

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Table 6.

P450 11A1

Properties	References
Physiological substrate: Cholesterol, cholesterol 25- and 20 ξ -hydroperoxides, cholesterol 25-hydroperoxide	(Tuckey and Cameron 1993b; Tuckey, Janjetovic, et al. 2008; Tuckey, Nguyen, et al. 2008; Mast et al. 2011; Pagotto et al. 2011; Slominski A. T. et al. 2014; Tuckey et al. 2014; Mosa et al. 2015; Slominski Andrzej T. et al. 2015; van Lier et al. 2015; Acimovic et al. 2016; Pan et al. 2016; Schiffer et al. 2016)
Other substrates: Lathosterol, zymostenol, desmosterol, 7-dehydrocholesterol, plant sterols (including campesterol and β -sitosterol), 7-dehydrocholesterol, ergosterol, lumisterol 3, vitamins D ₃ and D ₂ , 1 α -hydroxyvitamin D ₃ , turinabol, androstenedione, deoxycorticosterone, dehydroepiandrosterone, testosterone (6 β -hydroxylation)	
Function: Conversion of cholesterol to pregnenolone (P450 _{sc}) (Figs. 4, 8)	
Inhibition: Block synthesis of androgens (e.g., possible application in prostate cancer therapy)	
Inhibitor:	
Drugs:	
Aminoglutethimide ^a (Fassnacht et al. 2000; Johansson et al. 2002)	
Cisplatin ^a (Garcia et al. 2012)	
Cycloheximide ^b , puromycin ^b (Picado-Leonard et al. 1988)	
Etomidate ^a (Fassnacht et al. 2000)	
Ketoconazole ^c , posaconazole ^c , carbenoxolone ^c , selegiline ^c (Johansson et al. 2002; Mast et al. 2013)	
Metyrapone ^a (Fassnacht et al. 2000)	
Mitotane ^b (Schuster and Bernhardt 2007; Lin et al. 2012)	
Nitric oxide ^a (Drewett et al. 2002)	
Omeprazole ^a (Dowie et al. 1988)	
Turinabol ^b (Schiffer et al. 2016)	
Natural compounds:	
Digoxin, ouabain ^b (Kau et al. 2005)	
Gossypol ^a (Ye et al. 2011)	
Physiological compounds:	
22-Ketocholesterol ^d (Lambeth 1983)	
24-Hydroxycholesterol (at high concentrations) ^d (Tuckey and Cameron 1993b)	
25-Hydroxycholesterol (at high concentrations) ^d (Tuckey and Cameron 1993b, 1993a)	
Interferon- β ^b (van Koetsveld et al. 2013)	
Other compounds:	
2-(4-Pyridylmethyl)-1-indan 15 ^a , HB60 (Hartmann et al. 2003)	
2,3,7,8-Tetrabromodibenzo- <i>p</i> -dioxin	
2,6-Dibromophenol ^b (Ding et al. 2007)	
Dibutyl phthalate ^b (Mauger 1989)	

Properties	References
Lindane ^b (Ye et al. 2011)	
Methoxychlor and its metabolite 2,2-bis(<i>p</i> -hydroxyphenyl)-1,1,1-trichloroethane ^b (Wu et al. 2013)	
Paraquat ^a (Milczarek et al. 2016)	
Pentachlorobenzene ^b (Gregoraszcuk et al. 2014)	
Perfluorooctanoic acid ^c (Kraugerud et al. 2011)	
Induction: Stimulation of androgen biosynthesis	
Inducers:	
Drugs:	
Clobenpropit ^f , dexmedetomidine ^f , desogestrel ^f , pemirolast ^f , tizanidine ^f (Mast et al. 2013)	
Valproate ^g (Nelson-DeGrave et al. 2004)	
Natural compounds:	
Alkylresorcinols ^h (Oskarsson and Ohlsson Andersson 2016)	
<i>Cordyceps sinensis</i> mycelium ^h (Huang et al. 2004)	
Forskolin ^h (Breckwoldt et al. 1996; Sawetawan et al. 1996; Nelson-DeGrave et al. 2004; Asif et al. 2006)	
Physiological compounds:	
17 β -Estradiol ^h (Babishkin et al. 1997)	
25-Hydroxycholesterol ^h (Babishkin et al. 1997)	
Adrenocorticotrophic hormone (ACTH) ^h (Di Blasio et al. 1987; Ghayee and Auchus 2007)	
Cardiolipin ^f (Kisselev et al. 1999)	
Cyclic AMP ^g (Ghayee and Auchus 2007; Aumo et al. 2010)	
Cyclic AMP-inducible factors ^g (Aumo et al. 2010)	
Follicle-stimulating hormone, choriogonadotropin ^g (Breckwoldt et al. 1996)	
Insulin-like growth factors I and II ^h (Mesiano et al. 1997)	
Transcription factors ^g (SF-1, Sp1, AP-2, TRP-132, LBP-1b, LBP-9, AP-1, NF-1, EtsSF-1, c-Jun) (Guo et al. 2003; Guo et al. 2007; Shih et al. 2011)	
Other compounds:	
Bisphenol A ^h (Lan et al. 2015)	
Hexachlorobenzene ^h (Gregoraszcuk et al. 2014)	
Polybrominated biphenyls, brominated flame retardants ^c , polybrominated dibenzofurans ^g (Ding et al. 2007)	
Polybrominated diphenyl ethers (e.g., 2'-hydroxy-2,3',4,5'-tetrabromodiphenyl ether, 2'-hydroxytetrabromodiphenyl ether-68) ^g (Song et al. 2008)	

Footnotes:

^aDecreased/suppressed/inhibited activity/product formation

^bReduced/suppressed mRNA and/or protein level/expression and activity

^cCompetitive inhibition, ligand binding

^dCompetitive inhibition, binding to enzyme active site

^eGene downregulated/suppressed

^fIncreased activity, and/or increased product formation

^gUp-regulation of biosynthesis, increased expression of protein

^hIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity

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Table 7.

P450 11B1

Properties	References
Physiological substrate: 11 β -Deoxycortisol	(Denner et al. 1996; Coulter and Jaffe 1998; Parr et al. 2012; Bernhardt 2016; Pan et al. 2016; Schiffer, Brixius-Anderko, et al. 2016; Schiffer, Müller, et al. 2016)
Other substrates: Turinabol and metandienone (doping agents in sports), spironolactone, canrenone	
Function: Steroid 11 β - and 18-hydroxylation, cortisol formation (Figs. 4, 9)	
Inhibition: Block synthesis of cortisol in Cushing's syndrome and in chronic skin wounds, treating diseases caused by cortisol overproduction, interfere with the biosynthesis of aldosterone, possible application in treatment of adrenocortical carcinoma	
Inhibitors: (Ehmer et al. 2002; Hartmann et al. 2003; Bureik et al. 2004; Muller-Vieira et al. 2005; Papillon et al. 2015)	
Drugs:	
Aminoglutethimide ^b (at high concentrations) (Vermeulen et al. 1983)	
Canrenone, potassium canrenoate ^b (Cheng et al. 1976)	
Cimetidine ^a (Kenyon et al. 1986)	
Clotrimazole, miconazole, fluconazole ^a (Ayub and Levell 1989; Denner et al. 1995);	
Etomidate ^a (Engelhardt and Weber 1994; Fassnacht et al. 2000)	
Digoxin ^c (Kau et al. 2005)	
(<i>R</i>)-Etomidate ^a (Roumen et al. 2007)	
Fadrozole ^a (weak inhibitor) (Muller-Vieira et al. 2005)	
(<i>R</i>)- and (<i>S</i>)-Fadrozole ^a (Roumen et al. 2007)	
Iodometomidate, metomidate, fluoroetomidate ^c (Hahner et al. 2008)	
Ketoconazole ^d (Ayub and Levell 1989; Denner et al. 1995; Johansson MK et al. 2002)	
Metyrapone ^b (Fassnacht et al. 2000; Johansson MK et al. 2002; Roumen et al. 2007; Yin et al. 2012; Denner et al. 1995; Okahara et al. 1998)	
Mitotane ^c (Lin CW et al. 2012)	
Spironolactone ^b (Cheng et al. 1976; Denner et al. 1995)	
Trilostane ^b (Johansson MK et al. 2002)	
Turinabol ^c (Schiffer, Brixius-Anderko, et al. 2016)	
Natural compounds:	
Bufalin, cinobufagin ^b (Kau et al. 2012)	
Chelerythrine, rottlerin ^b (Bureik, Zehe, et al. 2002)	
Ouabain ^c (Kau et al. 2005)	
Physiological compounds:	
Interferon- β ^c (van Koetsveld et al. 2013)	
Other compounds, including drug candidates (only some examples are presented because of the large number of synthetic derivatives):	
Abiraterone analogues ^a (Pinto-Bazurco Mendieta et al. 2008)	
4,5-Dihydro-[1,2,4]triazolo[4,3- <i>a</i>]quinolines ^a (Hu et al. 2015)	

Properties	References
Arylsulfonyltetrahydroquinolines ^b	(Zhu et al. 2014)
Biphenylmethylene 4-pyridines ^b	(Hu et al. 2010)
Gö 6976 ^b	(Bureik, Zeeh, et al. 2002)
Heteroaryl-substituted dihydronaphthalenes and indenenes ^b	(Voets et al. 2006)
Heteroaryl-substituted naphthalenes ^b	(Voets et al. 2005)
Imidazol-1-ylmethyl substituted 1,2,5,6-tetrahydropyrrolo[3,2,1- <i>ij</i>]quinolin-4-ones, pyridylmethyl pyridine compounds ^b	(Yin et al. 2012)
Imidazolylmethylenetetrahydronaphthalenes and imidazolylmethyleneindanes ^b	(Ulmschneider et al. 2005)
Imidazolylmethylxanthenes ^b	(Otton et al. 1993; Gobbi et al. 2016, 2017)
3-MeSO ₂ -DDE ^d	(Johansson MK et al. 2002)
3-Methylsulfonyl-DDE, MeSO ₂ -PCBs (4-MeSO ₂ -2,3,6,4'-tetrachlorobiphenyl, and 4-MeSO ₂ -2,3,6,3',4'-pentachlorobiphenyl ^b	(Johansson M et al. 1998; Johansson MK et al. 2002);
5-(Phenoxymethyl)-1,3-dioxane analogs ^b	(Schroeder et al. 2016)
1-Phenylsulfinyl-3-(pyridin-3-yl)naphthalen-2-ols ^b	(Grombein et al. 2015)
Pyridyl substituted arylsulfonyltetrahydroquinolines ^b	(Zhu et al. 2014)
Pyridylmethyl isoxazoles ^b	(Emmerich et al. 2017)
Pyridylmethyl pyridine compounds ^b	(Emmerich et al. 2018)
2,3,7,8-Tetrabromodibenzo- <i>p</i> -dioxin, TBDD ^c	(Ding et al. 2007)
Tetralins ^b	(Ehmer et al. 2002; Muller-Vieira et al. 2005)
Induction: Overproduction of cortisol is associated with Cushing's syndrome and chronic wound diseases	
Inducer:	
Drugs:	
Metyrapone ^e	(Coulter and Jaffe 1998)
Mitotane ^f	(Lin CW et al. 2012)
Rifampicin ^f	(Kim et al. 2013)
Natural compounds:	
3',4'-Dimethoxyflavone ^f	(Lin TC et al. 2006)
Forskolin ^e	(Denner et al. 1996)
Physiological compounds:	
Adrenocorticotrophic hormone ^g	(Vukelic et al. 2011)
Angiotensin II ^e	(Denner et al. 1996)
Dibutryl cAMP ^e	(Denner et al. 1996)
Other compounds:	
2,3,7,8-Tetrabromodibenzo- <i>p</i> -dioxin, TBDD ^e	(Ding et al. 2007)
3',4'-Dimethoxyflavone ^f	(Lin TC et al. 2006)

Properties	References
3-Methylsulfonyl-DDE (<i>o</i> , <i>p</i> '-DDT metabolite, at lower concentrations) ^{<i>f</i>} (at lower concentrations) (Asp et al. 2010)	
Heteroaryl-substituted naphthalenes ^{<i>b</i>} (Voets et al. 2005)	
Polychlorinated biphenyls (PCBs) –39, –77, –126, –132, –156, and –169) ^{<i>f</i>} (Lin TC et al. 2006)	

Footnotes:

^{*a*} competitive inhibition, ligand binding

^{*b*} decreased/suppressed/inhibited activity/product formation

^{*c*} reduced/suppressed mRNA and/or protein level/expression and activity

^{*d*} competitive inhibition, binding to enzyme active site

^{*e*} Increased transcription/mRNA/protein expression/levels /and/or catalytic activity

^{*f*} Up-regulation of biosynthesis, increased expression of protein

^{*g*} Increased activity, and/or increased product formation

Table 8.

P450 11B2

Properties	References
Physiological substrate: 11-Deoxycorticosterone	(Denner et al. 1996; Coulter and Jaffe 1998; Roumen et al. 2011; Parr et al. 2012; Bernhardt 2016; Pan et al. 2016; Schiffer, Brixius-Anderko, et al. 2016; Schiffer, Müller, et al. 2016)
Other substrates: Turinabol and metandienone (doping agents misused in sports), spironolactone, canrenone	
Function: Aldosterone synthase, conversion of 11-deoxycorticosterone to aldosterone <i>via</i> corticosterone and 18-hydroxycorticosterone (Figs. 4, 10)	
Inhibition: Lower level of aldosterone, hypertension and heart failure treatment (Azizi et al. 2013; Karns et al. 2013)	
Inhibitors: (Ehmer et al. 2002; Hartmann et al. 2003; Bureik et al. 2004; Muller-Vieira et al. 2005; Lucas, Heim, Negri, et al. 2008; Lucas, Heim, Ries, et al. 2008; Hakki et al. 2011; Papillon et al. 2015)	
Drugs:	
(<i>R</i>)- and (<i>S</i>)-Fadrozole ^a (Roumen et al. 2007)	
(<i>R</i>)-Etomidate ^a (Roumen et al. 2007) Aminoglutethimide ^b (Schuster and Bernhardt 2007)	
Aminoglutethimide ^b (Schuster and Bernhardt 2007)	
Digoxin ^c (Kau et al. 2005)	
Eplerone ^b (Moore et al. 2003; White et al. 2003)	
Etomidate, iodometomidate, metomidate, fluoroetomidate ^c (Roumen et al. 2007; Hahner et al. 2008)	
Fadrozole ^b (Muller-Vieira et al. 2005)	
LCI699, silodrostat ^b (Amar et al. 2010; Karns et al. 2013))	
Metyrapone (weak inhibitor) ^a (Roumen et al. 2007)	
Miconazole, ketoconazole, clotrimazole, isoconazole ^a (Bureik et al. 2004; Hakki et al. 2011);	
Mitotane ^b (Hakki et al. 2011)	
Nifedipine ^c (Denner et al. 1996)	
Phenelzine ^b (Hakki et al. 2011)	
Staurosporine ^b (Bureik et al. 2002; Bureik et al. 2005)	
Natural compounds:	
Bufalin, cinobufagin ^c (Kau et al. 2012)	
Chelerythrine, rottlerin ^b (Bureik et al. 2002)	
Ellipticine ^b (Hakki et al. 2011)	
Ouabain ^c (Kau et al. 2005)	
Physiological compounds:	
4-Androstene-3,17-dione ^b (Hakki et al. 2011)	
Other compounds and drug candidates:	
12- <i>O</i> -Tetradecanoylphorbol-13-acetate (TPA) ^c (LeHoux et al. 2001; LeHoux and Lefebvre 2004)	
Phenylsulfinyl-3-(pyridin-3-yl)naphthalen-2-ols ^b (Grombein et al. 2015)	

Properties	References
20-Hydroxyiminopregna-5,14-diene-3 β -ol ^b	(Ehmer et al. 2002)
1–3-Methylsulfonyl-DDE (at high concentrations)	
4,5-Dihydro-[1,2,4]triazolo[4,3- <i>a</i>]quinolines ^b	(Hu et al. 2015)
4-Anilino-pyrimidines ^b	(Meguro et al. 2017)
Abiraterone analogues ^b	(Pinto-Bazurco Mendieta et al. 2008)
Biphenylmethylene 4-pyridines ^b	(Hu et al. 2010)
Calmidazolium ^b	(Condon et al. 2002)
D, L- <i>p</i> -Chlorophenylalanine methyl ester ^b	(Hakki et al. 2011)
FAD286 ^b	(Brunssen et al. 2017)
Gö 6976 ^b	(Bureik et al. 2002)
Heteroaryl-substituted dihydronaphthalenes and indenenes ^b	(Voets et al. 2006)
Heteroaryl-substituted naphthalenes ^b	(Voets et al. 2005; Lucas, Heim, Negri, et al. 2008)
Imidazolylmethylenetetrahydronaphthalenes and imidazolylmethyleindanes ^b	(Ulmschneider et al. 2005)
Imidazolylmethylxanthenes ^b	(Gobbi et al. 2016)
Imidazopyridyl compounds (e.g. RO6836191) ^d	(Bogman et al. 2017; Whitehead et al. 2017)
Indazole compounds ^b	(Hoyt et al. 2017)
KN93 ^b	(Condon et al. 2002)
Naphthalene based phenyl or benzyl derivatives ^a	(Lucas, Heim, Negri, et al. 2008)
PA024 ^c	(Suzuki et al. 2017)
Pyridine substituted 3,4-dihydro-1 <i>H</i> -quinolin-2-one derivatives ^b	(Lucas, Heim, Negri, et al. 2008)
Pyridyl- or isoquinolyl-substituted indolines and indoles ^b	(Yin et al. 2014)
Pyridyl substituted 4,5-dihydro-[1,2,4]triazolo[4,3- <i>a</i>]quinolines ^b	(Hu et al. 2015)
Pyridyl substituted acenaphthene derivatives ^b	(Ulmschneider et al. 2006)
Tetralins ^a	(Ehmer et al. 2002; Muller-Vieira et al. 2005)
Triazoloquinolines ^b	(Hu et al. 2015)
Turinabol ^c	(Schiffer, Brixius-Anderko, et al. 2016)
Induction: affects sex hormone production, overproduction of aldosterone leads to hypertension and end-organ damage such as cardiac and renal hypertrophy	
Inducers:	
<u>Drug(s):</u>	
BAYK 8644	
Rifampicin ^e	
(Kim et al. 2013)	
Telmisartan ^e	
(Matsuda et al. 2014)	
<u>Natural compounds:</u>	

Properties	References
3',4'-Dimethoxyflavone ^e	(Lin et al. 2006)
Calneuron 1 ^e	(Kobuke et al. 2018)
Forskolin ^f (weak induction)	(Denner et al. 1996)
Glucose (high concentrations) ^e	(Shimada et al. 2017)
<u>Physiological compounds:</u>	
Angiotensin II ^g	(Denner et al. 1996; Gennari-Moser et al. 2013; Matsuda, 2014, 59503}
Vascular endothelial growth factor (VEGF) ^g	(Gennari-Moser et al. 2013)
Very low-density lipoprotein ^f	(Tsai et al. 2017)
<u>Other compounds:</u>	
2,4-Dibromophenol ^e	(Ding et al. 2007)
3-Methylsulfonyl-DDE (<i>o</i> , <i>p</i> '-DDT metabolite, at lower concentrations) ^e	(Asp et al. 2010)
BAYK 8644 ^f	(Denner et al. 1996)
Benzo[<i>a</i>]pyrene ^e	(Keshava et al. 2005)
Brominated flame retardants ^e (e.g., 2,4-dibromophenol, pentabromophenol, 2,3,7,8-tetrabromodibenzofuran, TBDF)	(Ding et al. 2007)
Calcium ^e	(Shimada et al. 2017; Kobuke et al. 2018)
Organic sediment contaminants ^e	(Blaha et al. 2006)
PD98059 ^e	(LeHoux and Lefebvre 2004)
Polybrominated diphenyl ethers (e.g. 2'-OH-BDE-68) ^f	(Song et al. 2008)
Polychlorinated and polybrominated biphenyls ^e (PCB- and PBD-39, -77, -126, -132, -156, and -169) ^e	(Lin et al. 2006)
Potassium ^f	(Denner et al. 1996; Matsuda et al. 2014)
Tetrabromodibenzo- <i>p</i> -dioxin ^e	(Ding et al. 2007)

Footnotes:

^aCompetitive inhibition, ligand binding^bDecreased/suppressed/inhibited activity/product formation^cReduced/suppressed mRNA and/or protein level/expression and activity^dCompetitive inhibition, binding to enzyme active site^eIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity^fUp-regulation of biosynthesis, increased expression of protein^gIncreased activity, and/or increased product formation

Table 9.

P450 17A1

Properties	References
Physiological substrates: Progesterone, 17 α -hydroxyprogesterone, 17 α -hydroxypregnenolone, 16 α -hydroxyprogesterone	(Pikuleva et al. 2008; Petrunak et al. 2014; Pan et al. 2016; Gonzalez and Guengerich 2017; Yadav et al. 2017; Gonzalez et al. 2018)
Function: Biosynthesis of androgens and estrogens (cortisol), 16 α -hydroxylase, 17 α -hydroxylase, 17,20-lyase (Figs. 4, 11); controls the levels of mineralocorticoids influencing blood pressure, glucocorticoids involved in immune and stress responses, as well as androgens and estrogens involved in development and homeostasis of reproductive tissues	
Inhibition: Lower androgen level and production in prostate cancer, treating diseases caused by cortisol overproduction; increases the pool of precursors for mineralocorticoid production and blocks P450 17A1-mediated production of glucocorticoids (Leroux 2005; Bird and Abbott 2016; Bonomo et al. 2016)	
Inhibitors: (Ahmed 1999; Clement et al. 2003)	
Drugs:	
Abiraterone and analogs ^a (Pinto-Bazurco Mendieta et al. 2008; Ferraldeschi and de Bono 2013; Auchus R. J. et al. 2014; Petrunak et al. 2014; Yin and Hu 2014; Schroeder et al. 2016; Malikova et al. 2017)	
Abiraterone, galeterone, seviteronel, orteronel ^a (Yamaoka et al. 2012; Stein et al. 2014; Bird and Abbott 2016; Petrunak et al. 2017)	
Azole drugs ^a (e.g., ketoconazole, liarozole—weak inhibitors) (Ayub and Levell 1989; Ideyama et al. 1998; Ahmed 1999; Clement et al. 2003; Bird and Abbott 2016) Ketoconazole (at high concentrations) (De Coster et al. 1986; Ayub and Levell 1989; Engelhardt and Weber 1994; Johansson et al. 2002)	
Rifampicin ^b (Kim et al. 2013)	
Valproic acid ^c (at high concentrations) (Glistler et al. 2012)	
Natural compounds:	
1 α ,25-Dihydroxyvitamin D ₃ ^d (Lundqvist et al. 2010)	
Daidzein, hesperitin, resveratrol ^d (Lin et al. 2014)	
Polyphenols ^d (e.g., apigenin, aringenin, eriodictyol, genistein) ^d (Hasegawa et al. 2013)	
Physiological compounds:	
Bone morphogenetic protein 4 ^c (Rege et al. 2015)	
Epidermal growth factor ^c (Doi et al. 2001)	
Interferon- β ^c (van Koetsveld et al. 2013)	
Other compounds, including drug candidates:	
16- and 17-Azolyl steroids ^a (Njar et al. 1998)	
5-(Phenoxymethyl)-1,3-dioxane analogs ^d (Schroeder et al. 2016)	
6-Hydroxy-2,2',4,4'-tetrabromodiphenyl ether ^d , bromodiphenyl ether-183 ^d (Canton et al. 2006; Song et al. 2008)	
Biphenylmethylene 4-pyridines ^d (Hu et al. 2010)	
Bisphenol A ^d (Niwa et al. 2001)	
Imidazole, pyridine, 1,2,4- and 1,2,3-triazole, pyrazine, pyrimidine, pyrazole, oxazole, thiazole, isoxazole, 1,2,3,4- and 1,2,3,5-tetrazole and isothiazole containing compounds ^d (Bonomo et al. 2016)	
Methoxy- and hydroxy-substituted methyleneimidazolyl biphenyls ^a (Hille et al. 2009)	

Properties	References
α -Naphthoflavone ^c	(Lin et al. 2014)
Nitrophenols ^d	(Furuta et al. 2008)
Prochloraz ^d	(Ohlsson et al. 2009)
Steroidal C-17 benzoazoles ^d	(Handratta et al. 2005)
Vioxx (rofecoxib)-related lactones ^d	(van Duursen et al. 2010)
YM116 ^d	(Ideyama et al. 1998)
Induction: stimulation of androgen biosynthesis in man and risk of development of prostate cancer, or enhanced estrogen biosynthesis and risk of breast cancer	
Inducers:	
<u>Drugs:</u>	
Cycloheximide ^e	(Doi et al. 2001)
Valproic acid ^f	(Nelson-DeGrave et al. 2004)
<u>Natural compounds:</u>	
Retinoids ^e	(Wickenheisser et al. 2005)
Forskolin ^e	(Sawetawan et al. 1996; Nelson-DeGrave et al. 2004; Asif et al. 2006; Lin et al. 2014)
<u>Physiological compounds:</u>	
Adrenocorticotrophic hormone (ACTH) ^e	(Di Blasio et al. 1987)
Cardiolipin ^g	(Kisselev et al. 1999)
Cortisol ^e	(Hsu et al. 2001; Auchus R. J. et al. 2014)
Insulin-like growth factors I and II ^e	(Mesiano et al. 1997)
<u>Other compounds:</u>	
PD98059 (MAPK kinase (MEK) inhibitor) ^e	(Doi et al. 2001)
Polybrominated diphenyl ethers ^f	(e.g. 2'-hydroxybromodiphenyl ether-68) (Song et al. 2008)

Footnotes:

^aCompetitive inhibition, ligand binding

^bCompetitive inhibition, binding to enzyme active site

^cReduced/suppressed mRNA and/or protein level/expression and activity

^dDecreased/suppressed/inhibited activity/product formation

^eIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity

^fUp-regulation of biosynthesis, increased expression of protein

^gIncreased activity, and/or increased product formation

Table 10.

P450 19A1

Properties	References
Physiological substrates: Testosterone, androstendione, 16 α -androstendione, 16 β -OH-androstenedione, 17 β -estradiol, dihydrotestosterone	(Zharikova et al. 2007; Pan et al. 2016; Ghosh et al. 2018; Magistrato et al. 2017; Neunzig et al. 2017)
Other substrates:	
<u>Drugs:</u> L- α -Acetylmethadol, methadone, buprenorphine, tiboline, nortestosterone (norethisterone)	
<u>Sex hormone derivatives:</u> 7 α -Methyl-19-nortestosterone (trestolone), androst-5-ene-4,17-dione, androstadiene-3,17-dione, androst-4,6-diene and -1-4-diene-3,17-diones, 6-alkyl- and 6-ether analogs	
<u>Other compounds:</u> Dibenzylfluorescein, 7-methoxy-4-trifluoromethylcoumarin, 6 α -methoxyandrost-1,4-diene-3,17-dione derivatives	
Inhibition: Lowered estrogen levels in breast and endometrial cancers, decreased estradiol secretion, anti-androgen activity (Vanden Bossche et al. 1994; Lønning and Eikesdal 2013; Ahmad and Shagufta 2015; Linardi et al. 2017; Kang et al. 2018)	
Inhibitors: (Yumoto et al. 1976; Zhou et al. 1990; Kelloff et al. 1998; Ahmed and Amanuel 2000; Seralini and Moslemi 2001; Conley et al. 2002; Lønning and Eikesdal 2013; Bois et al. 2017; Sgrignani et al. 2014; Punetha et al. 2011; Caporuscio et al. 2011; Hirani et al. 2004; Hadizadeh et al. 2018)	
<u>Drugs :</u>	
Aminoglutethimide ^a (Ayub and Levell 1988; Kitawaki et al. 1990; Zhou et al. 1990; Campbell and Kurzer 1993; Wang C et al. 1994; White et al. 1999)	
Antiepileptic drugs ^b (lamotrigine, tiagabine, oxcarbazepine, phenobarbital, phenytoin, ethosuximide, valproic acid) ^b (Jacobsen et al. 2008; Glister et al. 2012; Chen Y et al. 2015)	
Cyclooxygenase-1 selective inhibitors ^c (SC-560) (Brueggemeier et al. 2005; Diaz-Cruz et al. 2005)	
Cyclooxygenase-2 selective inhibitors ^c (celecoxib, niflumic acid, nimesulide, NS-398 and N-methyl analog, SC-58125) (Brueggemeier et al. 2005; Diaz-Cruz et al. 2005; Su et al. 2008)	
15-Deoxy-prostaglandin J ₂ (15-dPGJ ₂) ^b (Andrews et al. 2005)	
Exemstane ^d and derivatives (Görlitzer et al. 2006; Hong et al. 2007; Lønning and Eikesdal 2013; Kümler et al. 2016; Chottanapund et al. 2017)	
Fenretinide ^b (Andrews et al. 2005)	
Formestane ^b (Pokhrel and Ma 2011)	
Fulvestrant (Kümler et al. 2016)	
Fungicides, imidazoles ^e (e.g., bifonazole, fadrozole, tioconazole, clotrimazole; anastrozole, econazole, miconazole, isoconazole, ketonazole, letrozole, tinidazole (weak inhibitor), carbimazole (weak inhibitor), metronidazole (weak inhibitor), econazole, miconazole, mebendazole, thiabendazole (weak inhibitor), nimorazole (weak inhibitor), astemizole (weak inhibitor), mebendazole (weak inhibitor), propiconazole, (Ayub and Levell 1988, 1990; Ahmed et al. 1995; Sanderson JT et al. 2002; Zarn et al. 2003; Sanderson JT et al. 2004; Tröskén et al. 2004; Tröskén, Fischer, Volkel, et al. 2006; Kjeldsen et al. 2013; Lønning and Eikesdal 2013; Linardi et al. 2017; Di Nardo et al. 2018; Magistrato et al. 2017)	
Metformin ^c (Takemura et al. 2007; Rice et al. 2009)	
Non-steroidal anti-inflammatory drugs ^c (ibuprofen, piroxicam, indomethacin, nimesulide) (Brueggemeier et al. 2005)	
Norendoxifen (tamoxifen metabolite) ^b (Lu WJ, Desta Z, et al. 2012; Lu WJ, Xu C, et al. 2012)	
Opiates ^a (sufentanil, L-acetylmethadol, methadone, EDDP, (nor)buprenorphine, Oxycodone (weak inhibitor), codeine (very weak inhibitor)	
Pentazocine (very weak inhibitor) (Zharikova et al. 2006; Zharikova et al. 2007)	
Plomestane ^d (19-acetylenic androstenedione) (White et al. 1999)	
Rifampicin ^a (Kim et al. 2013)	

Properties	References
Rogletimide ^b	(Vanden Bossche et al. 1994)
Tamoxifen, raloxifene ^b	(Fiorelli et al. 1999)
Testolactone ^b	(low potency inhibitor) (Dunkel 2006)
Tibolone, 4,7 α -methyl norethisterone metabolite ^a	(Raobaikady et al. 2007)
Tibolone and its 4,7 α -methyl norethisterone metabolite ^b	(Raobaikady et al. 2007)
Troglitazone plus LG100268 ^c	(Mu, Yanase, Nishi, Waseda, et al. 2000; Yanase et al. 2001)
<u>Natural compounds:</u>	
Alkylresorcinols ^c	(Oskarsson and Ohlsson Andersson 2016)
Cree plant extracts ^b	(Tam et al. 2009)
<i>Cicer arietinum</i> seeds extracts ^b	(Zhang et al. 2018)
Depsidones ^b	(unguinol and aspergillusidone A) (Sureram et al. 2012; Chottanapund et al. 2017)
Flavonoids, polyphenols, chalcones ^c	(e.g., biochanin (potent inhibitor), butein, 4-hydroxychalcone, 8-prenylnaringenin, apigenin (at high doses), quercetin (at high doses), genistein (at high doses—or no inhibition), baicalein, biochanin A (at high doses), daidzein (at high doses), naringenin (potent inhibitor), chrysin (potent inhibitor), coumestrol, rotenone (potent inhibitor), luteolin, kaempferol, 7,8-benzoflavone, 7-hydroxyflavones, 7-hydroxyflavanone, 4'-hydroxyflavanone, 7,4'-dihydroxyflavone, flavone (weak inhibitor), flavanone (weak or no inhibition), quercetin (weak inhibitor), genistein 4'-methyl ether (weak inhibitor), formononetin (also no inhibition) (Kellis J.T., Jr. and Vickery 1984; Ibrahim and Abul-Hajj 1990; Campbell and Kurzer 1993; Wang C et al. 1994; Le Bail et al. 1998; Fiorelli et al. 1999; Jeong et al. 1999; Le Bail et al. 2000; Le Bail et al. 2001; Saarinen et al. 2001; Vinh et al. 2001; Almstrup et al. 2002; Sanderson JT et al. 2004; Lacey et al. 2005; Wang Y et al. 2005; Rice et al. 2006; van Meeuwen et al. 2007; van Meeuwen et al. 2008; McNulty et al. 2009; Lu DF et al. 2012)
(-) Gossypol ^b	(Zhong et al. 2010; Dong et al. 2016)
Green tea extract catechins ^b	(Sato et al. 2002)
<i>Isodon excisus</i> var. <i>Coreanus</i> ^b	(Jeong et al. 2000)
Isoflavone derivatives ^b	(Su et al. 2005)
Lignans ^b	(nectandrin-B) (Filleur et al. 2001)
Lignans ^b	(lignan, O-demethylsecoisolariciresinol, demethoxysecoisolariciresinol, didemethylsecoisolariciresinol) (Adlercreutz et al. 1993; Wang C et al. 1994)
Melatonin, resveratrol ^b	(Chottanapund et al. 2014)
Phytoestrogens ^c	(Le Bail et al. 2000; Whitehead and Lacey 2003; Lacey et al. 2005)
Phytoestrogens ^b	(chrysin, biochanin A, naringenin, formononetin; at low concentrations) (Almstrup et al. 2002)
<i>trans</i> -Phytol (SA-20), (22 <i>E</i>)-ergosta-6,9,22-triene-3 β ,5 α ,8 α -triol (SA-48) ^c	(Guo et al. 2014)
Red wine extract ^b	(procyanidin B dimers, resveratrol) (Eng et al. 2001, 2002; Eng et al. 2003; Wang Y et al. 2006; Wang Y and Leung 2007; Linardi et al. 2017)
Sesquiterpene lactones ^a	(guaianolides 10- <i>epi</i> -8-deoxycumambrin B, dehydroleucodin, ludartin (Blanco et al. 1997)
UVA-ursi herbal products ^b	(Chauhan et al. 2007)
White button mushroom phytochemicals ^b	(Grube et al. 2001; Chen S et al. 2006)
Yikun neiyi wan ^c	(Wang Q et al. 2009)
Zaraleone ^b	(Lacey et al. 2005)
<u>Physiological compounds:</u>	

Properties	References
17 β -Estradiol ^c (in women) (Dieudonné et al. 2006)	
4-Hydroxyandrostendione ^f (Abul-Hajj 1983; Ayub and Levell 1988, 1990; Zhou et al. 1990; White et al. 1999; Vinggaard et al. 2000; Almstrup et al. 2002; Numazawa et al. 2002)	
Leptin ^c (in women) (Dieudonné et al. 2006)	
<u>Physiological condition:</u>	
Hypoxia ^c (Jiang et al. 2000; Jiang and Mendelson 2005)	
<u>Other compounds, including drug candidates:</u>	
($\pm$)-Abyssinone II and analogues ^b (Maiti et al. 2007)	
7-(α -Azolylbenzyl)-1 <i>H</i> -indoles and indolines ^b (Marchand et al. 2003)	
4-(Arylheteroaryl)-2-(pyrimidin-2-yl)thiazole derivatives ^b (Ertas et al. 2018)	
3-(1 <i>H</i> -imidazol-1-yl)-2 <i>H</i> -chromen-2-one ^a (Niinivehmas et al. 2018)	
Atrazine ^c (Pogrmic-Majkic et al. 2018)	
1-[(Benzofuran-2-yl)(phenylmethyl)pyridine, -imidazole, and -triazole inhibitors ^b (Saber et al. 2006)	
Bisphenol A, lindane ^b (longer incubation time, up to 18 h) (Almstrup et al. 2002; Nativelle-Serpentini et al. 2003; Benachour et al. 2007; Chu et al. 2018)	
4'- <i>tert</i> -Butyl-quinolin-4-one ^b (Sanderson JT et al. 2004)	
C19 steroidal 17-oxime analogs ^b (Pokhrel and Ma 2011)	
Carbon black nanoparticles ^b (Simon et al. 2017)	
Chlordecone ^b (Benachour et al. 2007)	
Cinnamyl triazoles ^b (McNulty et al. 2014)	
Dibutyl phthalate ^c (Mauger 1989)	
Diethylstilbestrol ^b (Benachour et al. 2007)	
<i>N,N</i> -Disubstituted-5-aminopyrimidine derivatives ^b (Okada et al. 1997)	
Estrone and estradiol derivatives (2-, 4-, or 6-substituted) ^b (Numazawa et al. 2005)	
19-(Ethyldithio)-androst-4-ene-3,17-dione (OrG 30958) ^b (Geelen et al. 1991)	
Fungicides ^b (prochloraz, imazalil, flusilazole, fenbuconazole, propiconazole, difenoconazole, penconazole, fenarimol, triadimenol, triadimefon, toxaphen, heptachlor, dicofol, ziram, vinclozolin, tributyltin oxide, myclobutanil) (Vinggaard et al. 2000; Heneweer et al. 2004; Tröskén et al. 2004; Laville et al. 2006; Tröskén, Fischer, Völkel, et al. 2006; Benachour et al. 2007; Chen L et al. 2017)	
Herbicides ^b (atrazine) (Benachour et al. 2007)	
ICI 182,780 ^c (Almstrup et al. 2002)	
5-Hydroxy-BDE47, 6-hydroxy-BDE47, 6-hydroxy-BDE99) ^b (Cantón et al. 2005; Cantón et al. 2008)	
Imidazole, triazole and pyridine based compounds ^b (Ahmed et al. 1995; Saber et al. 2006)	
1-(1 <i>H</i> -imidazol-1-yl)methyl-6-chloro-9 <i>H</i> -xanthen-9-one, lactones (CRI-7, 8, and 9)	
Insecticides ^b (dieldrin, toxaphenem) (Almstrup et al. 2002; Laville et al. 2006)	
Lactone derivatives ^b (Sanderson T et al. 2008)	

Properties	References
MDL 18,962 ^d (19-acetylenic androstenedione, and analogs) (Johnston et al. 1990)	
4-Methoxy-androst-4-ene-3,17-dione (White et al. 1999)	
2-Methoxyestrone-3-O-sulfamate ^b (Purohit et al. 2005)	
Mono-(2-ethylhexyl) phthalate ^f (Noda et al. 2007)	
Nonylphenol ^b (Almstrup et al. 2002; Benachour et al. 2007)	
α -Naphthoflavone and derivatives ^b (Kellis J. T., Jr. et al. 1986; Campbell and Kurzer 1993; Sanderson JT et al. 2004)	
Organochlorines ^c (e.g. TCDD, PCB126) (Drenth et al. 1998; Letcher et al. 1999)	
Pesticides ^b (prochloraz (IC ₅₀) <1 μ M), fenbuconazole (IC ₅₀ 1.1 μ M), propiconazole (IC ₅₀ 1.5 μ M) fenarimol (IC ₅₀ 3.3 μ M); toxaphen (10 μ M) and heptachlor (10 μ M) only after 24 h exposure), epoxyconazole, endosulfan (weak inhibitor) (Andersen et al. 2002; Heneweer et al. 2004; Laville et al. 2006)	
Pesticides ^j (<i>i</i> -butyl-, tributyl-, and triphenyltin chloride) (Sanderson JT et al. 2002; Benachour et al. 2007)	
Pesticides ^j (<i>p,p'</i> -DDT, <i>o,p'</i> -DDT, <i>p,p'</i> -DDE, <i>o,p</i> -DDE) (Sanderson JT et al. 2002; Wójtowicz et al. 2007)	
Polybrominated diphenyl ethers, brominated flame retardants ^b , (e.g., 2-hydroxy-BDE, 2,4,6-tribromophenol, 5-hydroxy-BDE47, 6-hydroxy-BDE47, and 6-hydroxy-BDE9) (Cantón et al. 2005; Cantón et al. 2008)	
Polychlorinated biphenyls ^c (Aroclor 1254, PCB39) (Benachour et al. 2007; Li 2007)	
Protein kinase inhibitors PD98059, KN-93m H-89 ^b (Watanabe et al. 2006)	
2-Pyridinyl-substituted γ -naphthoflavones (at concentrations >30 μ M) ^b (Sanderson JT et al. 2004)	
Pyridine-substituted thiazolylphenol derivatives (non-steroidal triazole bioisosteres) ^b (Ertas et al. 2018)	
Pyridoglutethimide ^a (Kitawaki et al. 1990)	
Pyridyl-substituted indanones, indans, and tetralins ^b (Hartmann et al. 1994)	
Pyridyl-substituted tetrahydrocyclopropa[<i>a</i>]naphthalenes ^b (Hartmann et al. 1995)	
Ro41-5253 ^f (RAR α -selective antagonist) (Hartmann et al. 1995)	
RU486 ^c (antiglucocorticoid and antiprogesterin) (Schmidt and Löffler 1997)	
Steroidal derivatives ^d (6-oxoandrostenedione and its 19-hydroxy analog, 10 α -acetoxyestr-5-ene-7,17-dione, androst-5-ene-4,7,17-trione, and 17 α -ethynyl-19-nortestosterone) (Hartmann et al. 1995; Numazawa and Yamaguchi 1998; Numazawa et al. 1998; Numazawa and Yamada 1999; Numazawa and Yamaguchi 1999; Numazawa et al. 2000; Numazawa et al. 2002; Numazawa et al. 2003)	
Sulfonanilide analogues ^c (Su et al. 2006)	
Synthetic lactones (TM-7, TM-8, TM-9) ^b (Cantón et al. 2008)	
Thioglutethimide derivatives ^a (Bednarski and Hartmann 1993)	
Triazole derivatives ^e (CGS 20267, CGS 47645, R 76 713, ICI D1033) (Vanden Bossche et al. 1994)	
Triazolylflavans ^b (Yahiaoui et al. 2004)	
Induction: Over-expression associated with increased risk of developing estrogen-dependent mammary tumors	
Inducers:	
<u>Drugs:</u>	
Dexamethasone ^g (Zhao et al. 1996; Heneweer et al. 2004; Enjuanes et al. 2005; Watanabe et al. 2005)	
Insulin ^h (Rice et al. 2006)	

Properties	References
Mibolerone ⁱ	(Stillman et al. 1991)
Opiates ^g	(morphine, heroin, hydromorphone, oxymorphone, hydrocodone, propoxyphene, meperidine, levorphanol, dextrophan, (–)-pentazocine, naloxone, naltrexone, sufentanil) (Zharikova et al. 2007; Cui et al. 2011)
Pacitaxel (taxol) ⁱ	(Morinaga et al. 2004)
<u>Natural compounds:</u>	
1 α ,25-Dihydroxyvitamin D ₃ (calcitriol) ⁱ	(Yanase et al. 2003; Enjuanes et al. 2005; Lou et al. 2005; Pino et al. 2006; Barrera et al. 2007)
All- <i>trans</i> -Retinoic acid, 9- <i>cis</i> -retinoic acid ^h	(Zhu et al. 2002)
<i>Cordyceps sinensis</i> mycelium ^h	(Huang et al. 2004)
Egonol gentiobioside, egonol gentiotrioside ⁱ	(Lu D et al. 2012)
Epidermal growth factor ^h	(Watanabe et al. 2006)
Flavonoids (quercetin, genistein at 10 μ M) ⁱ	(Sanderson JT et al. 2004)
Forskolin ^g	(Watanabe et al. 2005)
<i>Buthus martensi Karsch</i> (BMK) extract ⁱ	(Jin et al. 2006)
Zeranol ^g	(Zhong et al. 2010)
<u>Physiological compounds:</u>	
Ceramide ^h	(Zhao et al. 1996)
Collagen ^h	(Tan et al. 2015)
Cortisol platelet-derived growth factor BB ^h	(Schmidt and Löffler 1997)
Epidermal growth factor ⁱ	(Jin et al. 2006)
17 β -Estradiol ^g (in men)	(Dieudonné et al. 2006)
Interleukin 6 ⁱ	(Lou et al. 2005)
Leptin ^g (in men)	(Dieudonné et al. 2006; Pino et al. 2006);
Progesterone ^h	(Purohit et al. 2005)
Prostaglandins (PG) A ₁ , PGB ₂ , PGD ₂ , PGE ₁ , PGE ₂ ^h	(Heneweer et al. 2004; Watanabe et al. 2006; Chen D et al. 2007; Tan et al. 2015)
Protein kinase ^h	(Watanabe et al. 2006)
Redox-regulated transcription factor, NRF2 ^h	(Muralimanoharan et al. 2018)
Retinoic acid receptor system RAR-RXR heterodimer ligands combined ^h	(TTNPB and LG100268) (Mu, Yanase, Nishi, Hirase, et al. 2000)
Testosterone, 5 α -dihydrotestosterone ⁱ	(Stillman et al. 1991)
Transforming growth factor- β_1 ⁱ	(Stillman et al. 1991)
Tumor necrosis factor- α ^h	(Zhao et al. 1996)
<u>Physiological conditions and illnesses:</u>	
Bladder cancer (tumor related stroma) ^g	(Nguyen et al. 2017; Wu et al. 2018)
<u>Other compounds, including drug candidates:</u>	

Properties	References	
2-Phenylbenzo[<i>b</i>]furans ^{<i>i</i>}	(Pu et al. 2016)	
Bisphenol A, lindane ^{<i>b</i>}	(shorter time pre-incubation) (Nativelle-Serpentini et al. 2003)	
Brominated flame retardants ^{<i>i</i>}	(2,4,6-tribromophenol) (Cantón et al. 2005)	
8-Bromo-cyclic adenosine monophosphate	(Heneweer et al. 2004)	
Ethanol ^{<i>i</i>}	(Eng et al. 2002; Linardi et al. 2017)	
Fungicides—benzimidazole ^{<i>i</i>}	(benomyl, and metabolite, carbendazim) (Morinaga et al. 2004)	
Fungicides ^{<i>h</i>}	(vinclozolin, prochloraz) (Sanderson JT et al. 2002; Rieke et al. 2014)	
Herbicides, triazines ^{<i>h</i>}	(atrazine, simazine, propazine, and metabolites-atrazine-desethyl, atrazine-desisopropyl) (Sanderson JT et al. 2000; Sanderson JT et al. 2001)	
2-Hydroxy-BDE-123, 2-MeO-BDE-123 ^{<i>i</i>}	(Song et al. 2008)	
Lactones (CRI-1, CRI-4 or Vioxx, CRI-11 and CRI-13) ^{<i>b</i>}	(Sanderson T et al. 2008)	
Lindane, bisphenol A ^{<i>i</i>}	(shorter incubation time, up to 6 h) (Nativelle-Serpentini et al. 2003)	
3-Methylcholanthrene ^{<i>g</i>}	(weak inducer) (Ning et al. 2008)	
1-Methyl-3-isobutylxanthine ^{<i>h</i>}	(Sanderson JT et al. 2002)	
Pesticides ^{<i>h</i>}	(aldrin, chlordane, cypermethrin, parathion-methyl, endosulfan, methoxychlor, oxadiazon, metolachlor and atrazine after 24 h of exposure; tributyltin at 1 nM and 3 nM after 2 h and 24 h of exposure) (Laville et al. 2006)	
Pesticides ^{<i>i</i>}	(terbuthylazine, propiconazole, prothioconazole-weak inducers) and pesticide mixtures ^{<i>i</i>}	(Kjeldsen et al. 2013)
Pesticides, herbicides ^{<i>h</i>}	(atrazine, aldrin, chlordane, cypermethrin, parathion-methyl, endosulfan, methoxychlor, oxadiazon, metolachlor, terbuthylazine, propiconazole, prothioconazole, methomyl, pirimicarb, propamocarb, iprodion) (Andersen et al. 2002; Laville et al. 2006; Kjeldsen et al. 2013)	
Phorbol 12-myristate 13-acetate ^{<i>i</i>}	(Heneweer et al. 2004; Jin et al. 2006)	
Polybrominated diphenyl ethers ^{<i>h</i>}	(<i>e.g.</i> 2-hydroxy-BDE-123, 2-MeO-BDE-123) (Song et al. 2008)	
Polychlorinated biphenyls ^{<i>h</i>}	(PCB126, at high concentrations)(Li 2007)	
2-Pyridinyl-substituted γ -naphthoflavones	(at concentrations <1 μ M) (Sanderson JT et al. 2004)	
Ro40–6055 ^{<i>h</i>}	(retinoic acid receptor α (RAR α)-selective activator) (Zhu et al. 2002)	
Steroidal derivatives (6-oxoandrostenedione)		
2,4,6-Tribromophenol, BDE38 ^{<i>i</i>}	(Cantón et al. 2005)	

Footnotes

^{*a*}Competitive inhibition, binding to enzyme active site^{*b*}Decreased/suppressed/inhibited activity/product formation^{*c*}Reduced/suppressed mRNA and/or protein level/expression and activity^{*d*}Suicide inactivator(s)^{*e*}Competitive inhibition, ligand binding^{*f*}Gene downregulated/suppressed^{*g*}Up-regulation of biosynthesis, increased expression of protein

^hIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity

ⁱIncreased activity, and/or increased product formation

^jAt cytotoxic concentrations

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Table 11.

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Properties	References
Physiological substrates: Progesterone, 17 α -hydroxyprogesterone	(Coulter and Jaffe 1998; Zöllner et al. 2010; Parr et al. 2012; Yoshimoto et al. 2012; Pallan, Wang, et al. 2015; Pan et al. 2016; Wang et al. 2017)
Other substrate(s): Normetandienone, metandienone, 17-fluoroprogestosterone	
Function: Steroid 21-hydroxylase, formation of 11-deoxycorticosterone from progesterone and 11-deoxycortisol from 17 α -hydroxyprogesterone (Figs. 2, 13)	
Inhibition: May lead to congenital adrenal hyperplasia	
<u>Inhibitors:</u>	
<u>Drugs:</u>	
Abiraterone ^a (Malikova et al. 2017)	
Imidazole drugs ^b (e.g. clotrimazole, bifonazole, isoconazole, miconazole, ketoconazole, tioconazole) (Ayub and Levell 1990; Johansson et al. 2002)	
Mitotane ^c (Lin CW et al. 2012)	
Omeprazole ^d (weak inhibitor) (Dowie et al. 1988)	
<u>Natural compounds:</u>	
1 α ,25-Dihydroxyvitamin D ₃ ^d (Lundqvist et al. 2010)	
Alkylresorcinols ^c (Ayub and Levell 1990; Oskarsson and Ohlsson Andersson 2016)	
Polyphenols ^d (e.g., apigenin, genistein, hesperitin, naringenin, apigenin, eriodictyol, daidzein, resveratrol (Hasegawa et al. 2013; Lin CJ et al. 2014)	
<u>Physiological compounds:</u>	
<i>ent</i> -Progesterone ^e (Auchus et al. 2003)	
<u>Other compounds:</u>	
2,3,7,8-Tetrabromodibenzo- <i>p</i> -dioxin ^c (Ding et al. 2007)	
5-(Phenoxymethyl)-1,3-dioxane analogs ^d (Schroeder et al. 2016)	
Brominated flame retardants ^c (2,6-dibromophenol, 2,4,6-tribromophenol, 2,3,7,8-tetrabromodibenzofuran) (Ding et al. 2007)	
Crude sediment extracts ^f (containing high concentrations of polycyclic aromatic hydrocarbons (PAHs) and moderate amounts of polychlorinated biphenyls and organochlorine pesticides) (Blaha et al. 2006)	
Prochloraz ^d (Ohlsson et al. 2009)	
YZ5ay (imidazole biphenyl derivative ^b (Dragan et al. 2006)	
Induction: causes cortisol overproduction	
<u>Inducers:</u>	
<u>Natural compound:</u>	
Forskolin ^g (Asif et al. 2006; Lin CJ et al. 2014)	
<u>Physiological compound:</u>	
Orexin/hypocretin ^h (Wenzel et al. 2009)	

Properties	References
<u>Other compounds:</u>	
Brominated flame retardants ^g (weak inducer) (e.g., pentabromophenol) (Ding et al. 2007)	
Polybrominated diphenyl ethers ^g (e.g., 2'-hydroxy-BDE-68) ^h (Song et al. 2008)	
Polybrominated biphenyls ^g (e.g., 3,3',4,4,5,5''-tetrabromobiphenyl, 3,3',4,4'-tetrabromobiphenyl) (Ding et al. 2007)	

Footnotes:

^a Irreversible binding the iron heme complex, inactivator

^b Competitive inhibition, ligand binding

^c Reduced/suppressed mRNA and/or protein level/expression and activity

^d Decreased/suppressed/inhibited activity/product formation

^e Competitive inhibition, binding to enzyme active site

^f Gene downregulated/suppressed

^g Increased transcription/mRNA/protein expression/levels /and/or catalytic activity

^h Up-regulation of biosynthesis, increased expression of protein

Table 12.

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Properties	References
<p>Physiological substrates: Cholesterol, 4-cholesten-3-one, 7α-ketcholesterol, 7-dehydrocholesterol, lathosterol, zymosterol, zymostenol, desmosterol, 27-hydroxycholesterol, 25-hydroxycholesterol, 5β-cholestane-3α,7α,12α-triol, 7α-hydroxy-4-cholesten-3-one, 4-cholesten-3-one, 24-hydroxy-4-cholesten-3-one, 25-hydroxy-4-cholesten-3-one, 24-hydroxycholesterol</p> <p>Natural substrates: Vitamin D₃ (cholecalciferol), vitamin D₂ (ergocalciferol), 20-hydroxyvitamin D₃, 1α-hydroxyvitamin D₃, 2α-propoxy-1α,25-dihydroxyvitamin D₃, 2α-(3-hydroxypropoxy)-1α,25-dihydroxyvitamin D₃</p> <p>Other compounds: 3β-Hydroxy-24S-methyl-5α-cholesta-8(14),22-dien-15-one, cholesterol 25-hydroperoxide</p> <p>Function: Degradation of cholesterol to bile acids (Fig. 14A), vitamin D₃ 25-hydroxylase (Fig. 14B)</p> <p>Inhibition: May be effective as an adjuvant in the treatment of ER-positive breast cancer</p> <p>Inhibitors: : (Gueguen et al. 2007; Taban et al. 2017)</p> <p>Drugs:</p> <p>Anastrozole, fadrozole, (<i>R</i>)-bicalutamide, dexmedetomidine, ravuconazole, posaconazole^a (Mast et al. 2015)</p> <p>Bezafibrate^b (Honda et al. 2013)</p> <p>Carfilzomib^c (Federspiel et al. 2016)</p> <p>Clevidipine, delaviridine, etravirine, felodipine and analogs, nicardipine, sorafenib, abiraterone, candesartan, celecoxib, dasatinib, nilvadipine, nimodipine, nilotinib, regorafenib^b (Lam et al. 2018)</p> <p>Cyclosporine A, rapamycin^d (Lyons and Brown 2001; Gueguen et al. 2007; Sharanek et al. 2015)</p> <p>SDZ-286907^d (Schuster et al. 2006)</p> <p>Statins (e.g., atorvastatin)^d (Llaverias et al. 2006; Kimbung et al. 2017)</p> <p>Natural compounds:</p> <p>Phorbol 12-myristate 13-acetate^d (Araya et al. 2003; Quinn et al. 2005)</p> <p>Physiological compounds:</p> <p>Bile acids^d (glycochenodeoxycholic acid, glycodeoxycholic acid) (Chen and Chiang 2003; Ellis E et al. 2003)</p> <p>Estrogens^d (17β-estradiol in HepG2 and RWPE-1 prostate cells) (Tang et al. 2007)</p> <p>Luteinizing hormone, human chorionic gonadotropin^{''} (Xu et al. 2018)</p> <p>Sitosterol^e (Nguyen et al. 1998)</p> <p>L-Thyroxine (T₄), triiodothyronine (T₃)^d (Araya et al. 2003; Ellis EC 2006; Norlin and Wikvall 2007)</p> <p>Physiological conditions and illnesses:</p> <p>Prostate cancer^d (Alfaqih et al. 2017; Lutz et al. 2018)</p> <p>Other compounds:</p> <p>GI268267X, GW273297X, GW9662^d (Lyons and Brown 2001; Quinn et al. 2005)</p> <p>Induction: enhanced biosynthesis of bile acids, cholesterol lowering effect</p> <p>Inducers:</p> <p>Drugs:</p>	<p>(Norlin et al. 2003; Abe et al. 2005; Sakaki et al. 2005; Pettersson et al. 2008; Pikuleva et al. 2008; Tieu et al. 2012; van Lier et al. 2015; Acimovic et al. 2016; Pan et al. 2016)</p>

Properties	References
Dexamethasone ^f	(Araya et al. 2003)
Pioglitazone ^g	(Quinn et al. 2005)
Rifampicin ^g	(Li et al. 2007)
Rosiglitazone ^g	(Quinn et al. 2005; Llaverias et al. 2006)
<u>Natural compounds:</u>	
1,25-Dihydroxyvitamin D ₃ , vitamin D ₃ ^g	(Tokar and Webber 2005; Diesing et al. 2006; Yin et al. 2015)
Retinoid X receptor ligands (9- <i>cis</i> -retinoic acid) ^g	(Szanto et al. 2004; Quinn et al. 2005)
<u>Physiological compounds:</u>	
5 α -Dihydrotestosterone ^g	(Tang et al. 2007)
Estrogens ^g (e.g., 17 β -estradiol in LNCaP prostate cancer cells)	(Tang et al. 2007)
Growth hormone ^f	(Araya et al. 2003)
Insulin like growth factor-1, growth hormone ^f	(Araya et al. 2003)
Nuclear factor 4 α ^g	(Chen and Chiang 2003)
<u>Physiological condition and illnesses:</u>	
Breast cancer ^g	(Kimbung et al. 2017)
<u>Other compounds:</u>	
Oleic acid anilide ^g	(An et al. 2008)
Peroxisome-proliferator-activated receptor- γ ligands ^g (e.g., GW1929)	(Szanto et al. 2004; Quinn et al. 2005)

Footnotes:

^aCompetitive inhibition, ligand binding

^bDecreased/suppressed/inhibited activity/product formation

^cIrreversible binding, inactivator

^dReduced/suppressed mRNA and/or protein level/expression and activity

^eCompetitive inhibition, binding to enzyme active site

^fIncreased activity, and/or increased product formation

^gIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity

Table 13.

P450 39A1

Properties	References
Physiological Substrates: 24(<i>S</i>)-Hydroxycholesterol, 25-hydroxycholesterol, and 27-hydroxycholesterol	(Li-Hawkins, Lund, Bronson, et al. 2000; Pan et al. 2016)
Function: Oxysterol 7 α -hydroxylase, C7-hydroxylation of 24-hydroxycholesterol, biosynthesis of bile acids (Figs. 4, 15), downregulated in melanoma	
Inhibition: No information available	
<u>Inhibitors:</u>	
<u>Physiological condition and illness:</u>	
downregulation in melanoma ^a (Sumantran et al. 2016)	
<u>Induction:</u>	
<u>Inducer:</u>	
<u>Drugs:</u>	
carbamazepine ^b (Oscarson et al. 2006)	

Footnotes:

^aGene downregulated/suppressed^bIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity

Table 14.

P450 46A1

Properties	References
Physiological Substrates: Cholesterol, 4 β -hydroxycholesterol, 24(<i>S</i>)-hydroxycholesterol, 7 α -hydroxycholesterol, cortisol, 7-ketocholesterol, 7-dehydrocholesterol, cholestanol, desmosterol, zymostenol, zymosterol, progesterone, testosterone, lanosterol Other substrates: <u>Drugs:</u> Diclofenac, bufuralol, phenacetin, dextromethorphan, clotrimazole <u>Natural compounds:</u> 25-Hydroxyvitamin D ₃ Functions: Cholesterol 24 <i>S</i> -hydroxylase, 25- and 27-hydroxylase (minor extent) (Figs. 4, 16), eliminates cholesterol from brain, metabolizes neurosteroids and drugs that can cross the blood-brain barrier, 27-hydroxylation of 7-ketocholesterol (detoxication) Inhibition: Reduced brain cholesterol excretion <u>Inhibitors:</u> (Mast N. et al. 2010) <u>Drugs:</u> Azole drugs ^a (ketoconazole, posaconazole, clotrimazole, voriconazole) (Mast N. et al. 2010; Shafaati et al. 2010; Mast N. et al. 2013) (<i>E</i>)-Fluvoxamine, bicalutamide, dexmedetomidine ^b (Mast N. et al. 2012) Tranylcypromine, thioperamide ^a (Mast N. et al. 2010) <u>Natural compounds:</u> Okadaic acid ^c (Nunes et al. 2012) Stimulation: Increased activity potentially involved in the pathogenesis of Alzheimer's disease (Testa et al. 2016) <u>Stimulators:</u> (Mast N. et al. 2017) <u>Drugs:</u> Efavirenz (Anderson et al. 2016) Trichostatin A (Nunes et al. 2012) <u>Natural compounds:</u> L-Glutamate, L-aspartate, γ -aminobutyric acid, acetylcholine, 1 α ,25-dihydroxyvitamin D ₃ ^d (Mast N. et al. 2017) <u>Other compounds:</u> -PD98059, U0126 ^e (MEK1 inhibitors) (Nunes et al. 2012)	(Mast N. et al. 2003; Mast N. et al. 2008; Liao et al. 2009; Mast N. et al. 2010; Goyal et al. 2014; Acimovic et al. 2016; Pan et al. 2016)

Footnotes

^aCompetitive inhibition, ligand binding^bCompetitive inhibition, binding to enzyme active site^cReduced/suppressed mRNA and/or protein level/expression and activity^dActivation/stimulation^eIncreased transcription/mRNA/protein expression levels and/or catalytic activity

Table 15.

P450 51A1

Properties	References
Physiological substrate: Lanosterol	(Lepesheva and Waterman 2007; Hargrove et al. 2012; Pan et al. 2016; Guengerich 2017)
Other substrates: 24, 25-Dihydrolanosterol, 24-methylenedihydrolanosterol, obtusifoliol, 4 β -desmethyllanosterol, eburicol	
Function: Sterol 14 α -demethylase, 14 α -lanosterol demethylase (Figs. 4, 17), a key step in the biosynthesis of membrane sterols and steroid hormones	
Inhibition: Block biosynthesis of cholesterol in tumors, used for treatment of hypercholesterolemia; fungal enzyme inhibited to treat fungal infections and tropical diseases in humans	
<u>Inhibitors:</u>	
<u>Drugs:</u>	
Antifungal drugs, imidazole and triazole drugs ^a , weak or non-inhibitors of human enzyme, potent inhibitors of protozoal and fungal enzyme, systemic fungicides, e.g. ketoconazole (Pont et al. 1982; Harwood et al. 2005; Trösken et al. 2006; Strushkevich et al. 2010)	
Azalanstat (used for treatment of hyperlipidemia, benzenamine) (Swinney et al. 1994; Burton et al. 1995; Trzaskos 1995)	
Clotrimazole, bifonazole (Trösken et al. 2006)	
CP-320626 ^b (used of treatment of type 2 diabetes, indole-2-carboxamide) and analogs (Harwood et al. 2005)	
Cytostatic drugs ^a : fadrozole, letrozole (Trösken et al. 2006)	
Fluconazole (Harwood et al. 2005; Trösken et al. 2006; Arlt 2007; Krone et al. 2007)	
Itraconazole ((Trösken et al. 2006; Schuster and Bernhardt 2007))	
Miconazole, econazole (Trösken et al. 2004; Trösken et al. 2006; Strushkevich et al. 2010)	
Voriconazole (Trösken et al. 2006)	
<u>Natural compounds:</u>	
Betulafolientriol ^d , holothurin A ^d , teasaponin ^d , capsicoside A ^d (Kaluzhskiy et al. 2014)	
<u>Physiological compounds:</u>	
Oxysterols (e.g., 25-hydroxycholesterol, 15-ketolanosterol ^c) (Swinney et al. 1994; Trzaskos 1995; Lepesheva and Waterman 2007)	
<u>Other compounds and drug candidates:</u>	
15 α -Fluorosterol (Trzaskos et al. 1993)	
Lanosterol analogs ^c : 7-oxo-, 15-oxime, 15-keto, 15-hydroxy, 26-oxo, and 32-carboxylic acid derivatives of lanosterol ^c (Frye and Leonard 1999)	
2-Phenylimidazole ^a (Harwood et al. 2005)	
4-Phenylimidazole ^a (Matsuura et al. 2005)	
SKF 104976, (32-carboxylic acid derivative of lanosterol) (Mayer et al. 1991)	
Triazoles ^a (Lepesheva and Waterman 2007)	
VFV ^a (azole derivative) (Hargrove et al. 2016)	
<u>Induction:</u> Enhanced cholesterol biosynthesis (possible)	
<u>Inducers:</u>	
<u>Physiological compounds:</u>	
Cholesterol deprivation ^c (Stromstedt et al. 1996)	
Growth differentiation factor 9 and follicle-stimulating hormone combined treatment ^c (Nakamura et al. 2015)	

Footnotes:

^aCompetitive inhibition, ligand binding, type II binding

^bDecrease (inhibition) of activity

^cReduced/suppressed mRNA level

^dCompetitive inhibition, binding to enzyme active site

^eIncreased mRNA levels

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Table 16.

P450 24A1

Properties	References
<p>Natural substrates: Vitamin D₃, 1,25-dihydroxy vitamin D₃, 25-hydroxy vitamin D₃, 1α-hydroxyvitamin D₂, 1α,25-dihydroxy vitamin D₃, 1α,25-dihydroxyvitamin D₃, 1α,25-dihydroxy vitamin D₂, 1α,25-dihydroxy-20ϵ-vitamin D₃, 1α,24(<i>R</i>)-dihydroxy vitamin D₃, 1α,4α,25-trihydroxy vitamin D₃, 25-hydroxy vitamin D₃-26,23-lactol, 23(<i>S</i>),25,26-trihydroxy vitamin D₃, 21α-hydroxy vitamin D₂, 1α,25-dihydroxy-19-<i>nor</i>-vitamin D₃, 1α,25-dihydroxy-3-<i>epi</i>-vitamin D₃, 1β25-dihydroxy-3-<i>epi</i>-vitamin D₃, 1α,25-dihydroxycholecalciferol, 1α,24-dihydroxy vitamin D₂, 1α,4β,25-trihydroxy vitamin D₃, 20-hydroxy vitamin D₃, 20,23-dihydroxy vitamin D₃</p> <p>Other substrates: 2α-Propoxy-1α,25-dihydroxy vitamin D₃, 2α-(3-hydroxypropoxy)-1α,25-dihydroxy vitamin D₃, 6,27-hexafluoro-1α,25-dihydroxy vitamin D₃</p> <p>Function: 1,25-Dihydroxyvitamin D₃ 24-hydroxylase (Figs. 3, 19), inactivates the active vitamin D₃ metabolite 1,25-dihydroxyvitamin D₃</p> <p>Inhibition: Elevated level of 1,25-dihydroxyvitamin D₃ active vitamin D metabolite, enhancement of the anti-tumor effect of 1α,25-dihydroxyvitamin D₃</p> <p>Inhibitors: (Schuster, Egger, Astecker, et al. 2001; Taban et al. 2017a)</p> <p><u>Drugs:</u></p> <p>Ketoconazole, liarozole ^a (Schuster, Egger, Bikle, et al. 2001; Vantieghem et al. 2006; Bruno and Njar 2007; Muindi et al. 2010; Luo et al. 2013)</p> <p>Ritonavir, indinavir, nelfinavir (mild inhibitors of activity) ^b (Cuzzolino et al. 2003)</p> <p><u>Natural compounds:</u></p> <p>Isoflavonoids ^b (genistein, dihydroxygenistein, tetrahydroxygenistein) (Farhan and Cross 2002; Lechner and Cross 2003; Swami et al. 2005; Bruno and Njar 2007; Wietrzyk 2007)</p> <p>All <i>trans</i>-Retinoic acid ^b (Lou, Miettinen, et al. 2005)</p> <p><u>Physiological compound:</u></p> <p>5α-Dihydrotestosterone ^b (Lou, Nazarova, et al. 2005)</p> <p><u>Physiological condition and illnesses:</u></p> <p>Cancer ^b (e.g., breast tumor) (Anderson et al. 2006)</p> <p><u>Other compounds:</u></p> <p>Azoles ^c (e.g., VID400) (Schuster, Egger, Nussbaumer, et al. 2003; Schuster, Egger, Reddy, et al. 2003; Schuster et al. 2006; Bruno and Njar 2007)</p> <p>Azoles ^c (e.g., NFP-VAB636, SDZ-89789, SDZ-284814, SDZ-286907, (<i>S</i>)-SDZ 285428), (Schuster, Egger, Nussbaumer, et al. 2003; Schuster et al. 2006)</p> <p>1,25-Dihydroxyvitamin D₃ analogues ^d (Posner et al. 2010)</p> <p><i>N</i>-(2-(1<i>H</i>-Imidazol-1-yl)-2-phenylethyl)arylamides ^a (Muindi et al. 2010)</p> <p>(<i>E</i>)-<i>N</i>-(2-(1<i>H</i>-Imidazol-1-yl)-2-(phenylethyl)-3/4-styrylbenzamides ^a (Taban et al. 2017b)</p> <p>MK-24(<i>S</i>)-S(O)(NH)Ph ^b (Bruno and Njar 2007)</p> <p>QW1624F2-2 ^b (Bruno and Njar 2007; Purnapatre et al. 2008)</p> <p>RC2204 ^d (Muindi et al. 2010)</p>	<p>(Sakaki et al. 1999; Inouye and Sakaki 2001; Kusudo et al. 2004; Abe et al. 2005; Sakaki et al. 2005; Saito et al. 2009; Kaufmann et al. 2011; Jones et al. 2012, 2014; Tieu et al. 2015; Pan et al. 2016)</p>

Properties	References
Styrylbenzamides ^d	(Taban et al. 2017b)
Styrylindoles ^a	(Ferla et al. 2014)
24-Sulfone analogs of the hormone 1 α ,25-dihydroxyvitamin D ₃ ^d	(Posner et al. 2004)
Sulfone and sulfoximine derivatives (CTA018, CTA091) ^d	(Schuster and Bernhardt 2007)
Tetralones ^d (e.g., KD-35)	(Yee and Simons 2004; Aboraia et al. 2010; Kósa et al. 2013; Luo et al. 2013)
Induction: enhanced steroid metabolism, proposed for treatment of congenital adrenal hyperplasia, may cause osteomalacia	
Inducers:	
<u>Drugs:</u>	
Bufalin ^f	(Nakano et al. 2005; Amano et al. 2009)
Carbamezepine (very weak inducer), phenobarbital, phenytoin, rifampicin ^f	(Pascussi et al. 2005; Schuster et al. 2006)
Cycloheximide ^f	(Pascussi et al. 2005)
Efavirenz, stavudine, ritonavir ^f	(Ikezoe et al. 2006; Norlin et al. 2017)
Valproic acid ^f	(Vrzal et al. 2011)
<u>Natural compounds and metabolites:</u>	
1 α ,25-Dihydroxyvitamin D ₃ ^f	(Tashiro et al. 2004; Lou, Nazarova, et al. 2005; Pascussi et al. 2005; Ikezoe et al. 2006; Kemmis et al. 2006; Tuckey et al. 2008; Muindi et al. 2010; Horvath et al. 2012; Kósa et al. 2013; Wegler et al. 2016)
24 R ,25-Dihydroxyvitamin D ₃	(Tashiro et al. 2004)
High glucose levels ^f	(Zhou et al. 2015)
25-Hydroxyvitamin D ₃ ^f	(Kemmis et al. 2006)
Hyperforin ^f	(Pascussi et al. 2005)
<u>Physiological compounds:</u>	
Calcitonin ^f	(Gao et al. 2004)
Lithocholic acid ^f	(Ishizawa et al. 2008)
PXR-ligands	(Pascussi et al. 2005)
Retinoids ^f	(Zou et al. 1997)
Transforming growth factor β ^f	(Solomon et al. 2014)
<u>Physiological conditions and illnesses:</u>	
Cancer ^f (e.g., colon, ovary, prostatic, lung tumors)	(Anderson et al. 2006; King et al. 2010; Luo et al. 2013; Ge et al. 2017)
Chronic kidney disease ^g	(Petkovich and Jones 2011)
Psoriasis ^h	(Sumantran et al. 2016)
UVB irradiation ^f	(Vantieghem et al. 2006)
<u>Other compounds:</u>	
(25 R)-25-Adamantyl-1 α ,25-dihydroxy-2-methylene-22,23-didehydro-19,26,27-trinor-20-epivitamin D ₃ ^f	(Choi et al. 2011)
Benzo[a]pyrene ^f	(Matsunawa et al. 2009)
Non-1 α -hydroxylated vitamin D analogues	(Segersten et al. 2005)

Properties	References
ZK 158222 (vitamin D receptor antagonist) ^f	(Avila et al. 2007)

Footnotes:

- ^aCompetitive inhibition, ligand binding
- ^bReduced/suppressed mRNA and/or protein level/expression and activity
- ^cCompetitive inhibition, binding to enzyme active site
- ^dDecreased/suppressed/inhibited activity/product formation
- ^eGene downregulated/suppressed
- ^fIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity
- ^gIncreased activity, and/or increased product formation
- ^hUp-regulation of biosynthesis, increased expression of protein

Table 17.

P450 27B1

Properties	References
<p>Natural substrates: 25-Hydroxyvitamin D₃, 27-hydroxyvitamin D₃, 24-oxo-, 25-hydroxyvitamin D₃, 25-hydroxy-3-<i>epi</i>-vitamin D₃, 24(<i>R</i>),25-dihydroxyvitamin D₃, 20,24-, 20,25-, and 20,26-dihydroxyvitamin D₃</p> <p>Function: 25-Hydroxyvitamin D₃ 1α-hydroxylase (Figs. 18, 20), synthesizes 1α,25-dihydroxyvitamin D₃, the active form of vitamin D₃, 24(<i>R</i>),25-dihydroxyvitamin D₃ 1α-hydroxylation</p> <p>Inhibition: Decreased plasma 1α,25-dihydroxyvitamin D levels</p> <p>Inhibitors: (Schuster, Egger, Nussbaumer, et al. 2003)</p> <p><u>Drugs:</u></p> <p>Azole drugs ^a (ketoconazole, liarozole) (Frizen and Zhegin 1976; Schuster et al. 2001; Bruno and Njar 2007)</p> <p>Efavirenz ^b (Ellfolk et al. 2009; Wegler et al. 2016)</p> <p>Ritonavir, indinavir, nelfinavir ^c (Cuzzolino et al. 2003)</p> <p><u>Natural compounds:</u></p> <p>17α,20-Dihydroxyvitamin D₃ ^b (Tang et al. 2013)</p> <p>1α,25-Dihydroxyvitamin D₃ ^b (Bland et al. 1999; Xie et al. 2002; Pascucci et al. 2005; Avila et al. 2007; Lechner et al. 2007; Wietrzyk 2007; Wu et al. 2007; Ellfolk et al. 2009)</p> <p>Genistein ^c (Farhan and Cross 2002; Farhan et al. 2003)</p> <p><u>Physiological compounds:</u></p> <p>Short hairpin RNA ^c (Wu et al. 2007)</p> <p>Thyroid hormones ^c (Kozai et al. 2013)</p> <p><u>Physiological condition and illnesses:</u></p> <p>Breast cancer ^d (Zhalehjoo et al. 2017)</p> <p><u>Other compounds:</u></p> <p>Azoles ^a ((<i>R</i>)-VID400 weak inhibitor) (Xie et al. 2002; Schuster, Egger, Reddy, et al. 2003; Bruno and Njar 2007)</p> <p>8-Bromo cAMP ^c (Avila et al. 2004)</p> <p>Calcium ^b (high concentrations) (Bland et al. 1999)</p> <p>Imidazoles ^a (e.g. SDZ-88357, SDZ 89–443, SDZ 284971, SDZ 284814, (<i>R</i>)-SDZ 287871, (<i>R</i>)-SDZ 286907, SDZ 283251, (<i>S</i>)-SDZ 285428, (<i>R</i>)-VAB636) (Schuster et al. 2001; Schuster, Egger, Nussbaumer, et al. 2003; Schuster et al. 2006)</p> <p>Pyridine compounds ^a (Schuster, Egger, Nussbaumer, et al. 2003)</p> <p>Induction: Increased production of 1,25-dihydroxyvitamin D₃</p> <p>Inducers:</p> <p><u>Drugs:</u></p> <p>Raloxifene ^d (Somjen et al. 2005)</p> <p>Ritonavir, dexamethasone ^d (Wegler et al. 2016)</p> <p><u>Natural compounds:</u></p> <p>Carboxy biochainin A, genistein ^d (Somjen et al. 2005; Lechner et al. 2006; Somjen et al. 2007)</p>	<p>(Inouye and Sakaki 2001; Maas et al. 2001; Sakaki et al. 2005; Tang et al. 2013; Pan et al. 2016)</p>

Properties	References
25-Hydroxyvitamin D ₃ , femarelle, daidzein ^d	(Somjen et al. 2017)
Forskolin ^e	(Bland et al. 1999)
<u>Physiological compounds:</u>	
5 α -Dihydrotestosterone ^d	(Somjen et al. 2007)
17 β -Estradiol ^d	(Lechner et al. 2006)
Parathyroid hormone ^d	(Somjen et al. 2005; Somjen et al. 2007)
Spirolactone ^d	(Alesutan et al. 2013)
<u>Physiological condition and illnesses:</u>	
Colonic inflammation ^e	(Du et al. 2017)
Psoriasis ^e	(Sumantran et al. 2016)
Non-small cell lung cancer ^d	(Ge et al. 2017)
<u>Other compounds:</u>	
Calcium ^e (low concentrations)	(Bland et al. 1999)

Footnotes:

^aCompetitive inhibition, ligand binding

^bGene downregulated/suppressed

^cReduced/suppressed mRNA and/or protein level/expression and activity

^dIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity

^eUp-regulation of biosynthesis, increased expression of protein

Table 18.

P450 26A1

Properties	References
Natural substrates: all- <i>trans</i> -Retinoic acid, all- <i>trans</i> -dihydroretinoic acid, 9- <i>cis</i> -retinoic acid, 4-hydroxyretinoic acid, 18-hydroxyretinoic acid, 4-oxo-retinoic acid, retinal, and retinol	(Lutz et al. 2009; Thatcher et al. 2010; Helvig et al. 2011; Shimshoni et al. 2012; Topletz et al. 2012; Pan et al. 2016)
Function: Retinoic acid-metabolizing enzyme, inactivation of all- <i>trans</i> -retinoic acid to hydroxylated forms 4-hydroxy- and 4-oxo- all- <i>trans</i> -retinoic acid and 18-hydroxy- all- <i>trans</i> -retinoic acid (Figs. 3, 22)	
Inhibition: Block degradation of endogenous retinoids, application in retinoid therapy, increase the levels of endogenous all- <i>trans</i> -retinoic acid	
Inhibitors: (Njar et al. 2006; Osanai and Lee 2011b; Purushottamachar et al. 2012; Sun, Song, et al. 2015)	
Drugs:	
Azoles (ketoconazole, liarozole, talarozole) (Ocaya et al. 2007; Schuster and Bernhardt 2007; Chang et al. 2008; Pavez Lorie, Chamcheu, et al. 2009; Helvig et al. 2011; Thatcher et al. 2011; Diaz et al. 2016)	
Rosiglitazone, pioglitazone ^a (Thatcher et al. 2011)	
Other compounds:	
(Amide)imidazole derivatives ^c (Sun, Liu, et al. 2015)	
4-Azoly retinoids (Njar 2002; Quere et al. 2007)CD2503 ^d (retinoic acid receptor- α -specific antagonist) (Ozpolat et al. 2002; Thatcher et al. 2011)	
3-(1 <i>H</i> -Imidazol- and triazol-1-yl)-2,2-dimethyl-3-(4-(naphthalen-2-ylamino)phenyl)propyl derivatives ^a (Gomaa, Bridgens, Veal, et al. 2011)	
Imidazole methyl 3-(4-(aryl-2-ylamino)phenyl)propanoates ^c (Gomaa, Bridgens, Aboraia, et al. 2011)	
Imidazole- and triazole-containing inhibitors ^a (Thatcher et al. 2011)	
R116010 ^a (benzoimidazolamine derivative) (Armstrong et al. 2005)	
Tetralones 4-hydroxyphenyl substituted ^b (e.g. KD-35) (Yee et al. 2005; Njar et al. 2006)	
3-{4-[2-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-1,3-dioxolan-2-yl] phenyl}4-propanoic acid ^a (Diaz et al. 2016)	
Induction: increased catabolism of retinoids, diminishing the levels of active all- <i>trans</i> -retinoic acid in the course of therapy	
Inducers:	
Drugs:	
Fenretinide ^e (Ozpolat et al. 2004; Villani et al. 2004)	
Talarozole ^e (Pavez Lorie, Cools, et al. 2009; Pavez Lorie, Li, et al. 2009)	
Natural compounds:	
(4 <i>S</i>)-Hydroxy all- <i>trans</i> -retinoic acid, (4 <i>R</i>)-hydroxy-all- <i>trans</i> -retinoic acid, 4-oxo-all- <i>trans</i> -retinoic acid, 18-hydroxy-all- <i>trans</i> -retinoic acid ^e (Topletz et al. 2015)	
13- <i>cis</i> -Retinoic acid, 9- <i>cis</i> -retinoic acid, all- <i>trans</i> -retinoic acid ^e (Lampen et al. 2000; Ozpolat et al. 2002; Armstrong et al. 2005; Ozpolat et al. 2005; Chang et al. 2008; Pavez Lorie, Chamcheu, et al. 2009; Pavez Lorie, Li, et al. 2009; Wang et al. 2009; Topletz et al. 2015)	
Lithocholic acid ^e (Chang et al. 2008)	
Nicotine ^d (Osanai and Lee 2011b)	
Physiological conditions and illnesses:	
Barrett's associated adenocarcinoma ^e (Chang et al. 2008)	
Breast, colorectal, cervical squamous neoplasia, and head and neck cancers ^e (Brown et al. 2014; Osanai and Lee 2014, 2015)	

Properties	References
Skin from chronically sun-exposed body areas ^e (Osanai and Lee 2011a)	

Footnotes:

^a Decreased/suppressed/inhibited activity/product formation

^b Competitive inhibition, binding to enzyme active site

^c Competitive inhibition, ligand binding

^d Reduced/suppressed mRNA and/or protein level/expression and activity

^e Increased transcription/mRNA/protein expression/levels /and/or catalytic activity

Table 19.

P450 26B1

Properties	References
Natural substrates: all- <i>trans</i> -Retinoic acid, all- <i>trans</i> -dihydroretinoic acid, 9- <i>cis</i> -retinoic acid, 4-hydroxyretinoic acid, 18-hydroxyretinoic acid, 4-oxo retinoic acid, retinal, and retinol	(Helvig et al. 2011; Ross and Zolfaghari 2011; Topletz et al. 2012; Pan et al. 2016)
Function: Retinoic acid-metabolizing enzyme, inactivation of all- <i>trans</i> -retinoic acid to hydroxylated forms 4-hydroxy- and 4-oxo-all- <i>trans</i> -retinoic acid and 18-hydroxy-all- <i>trans</i> -retinoic acid (Figs. 21, 23)	
Inhibition: Application in retinoid therapy, increase the levels of endogenous all- <i>trans</i> -retinoic acid	
Inhibitors: (Njar 2002; Njar et al. 2006)	
Drugs:	
Azoles ^a (ketoconazole, liarozole, talarozole) (Ocaya P et al. 2007; Pavez Lorie, Chamcheu, et al. 2009; Helvig et al. 2011; Kumar et al. 2011; Diaz et al. 2016)	
Natural compounds:	
9- <i>cis</i> -Retinoic acid, 13- <i>cis</i> -retinoic acid, all- <i>trans</i> -retinoic acid ^b (Taimi et al. 2004; Helvig et al. 2011)	
Other compounds:	
4-Azoly retinoids (Njar 2002)	
Induction: May increase the catabolism of retinoids, diminishing the levels of active all- <i>trans</i> -retinoic acid in the course of therapy	
Inducers:	
Drugs:	
Talarozole ^c (Pavez Lorie, Cools, et al. 2009; Ocaya PA et al. 2011)	
Natural compounds:	
9- <i>cis</i> β -Carotene ^c (Bechor et al. 2016)	
all- <i>trans</i> -Retinoic acid ^c (Pavez Lorie, Chamcheu, et al. 2009; Pavez Lorie, Li, et al. 2009)	
Physiological conditions and illnesses:	
Colorectal cancer ^c (Brown et al. 2014)	
Ovarian cancer ^c (Downie et al. 2005)	

Footnotes

^aCompetitive inhibition, ligand binding^bCompetitive inhibition, binding to enzyme active site^cIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity

Table 20.

P450 26C1

Properties	References
<p>Natural substrates: all-<i>trans</i>-Retinoic acid, 9-<i>cis</i>-retinoic acid, 13-<i>cis</i>-retinoic acid, all-<i>trans</i>-4-oxo retinoic acid, all-<i>trans</i>-dihydroretinoic acid</p> <p>Function: Retinoic acid metabolism, conversion of all-<i>trans</i>-retinoic acid to hydroxylated forms (4-hydroxy- and 4-oxo- all-<i>trans</i>-retinoic acid and 18-hydroxy-all-<i>trans</i>-retinoic acid (Figs. 21, 23)). All-<i>trans</i>-4-oxo retinoic acid is oxidized to all-<i>trans</i>-4-oxo-16-hydroxy retinoic acid, and 13-<i>cis</i>-retinoic acid is hydroxylated at the 4 and 16 positions.</p> <p>Inhibition: Increases the levels of endogenous all-<i>trans</i>-retinoic acid</p> <p>Inhibitors:</p> <p>Drugs:</p> <p>Ketoconazole ^a (Taimi et al. 2004; Zhong et al. 2018)</p> <p>Talarozole ^a (Zhong et al. 2018)</p> <p>Induction: May contribute to increase the catabolism of retinoids, diminishing the levels of active all-<i>trans</i>-retinoic acid in the course of therapy</p> <p>Inducers:</p> <p>Natural compounds:</p> <p>all-<i>trans</i>-Retinoic acid, 9-<i>cis</i> retinoic acid ^c (Taimi et al. 2004)</p> <p>Physiological condition and illnesses:</p> <p>Primary breast carcinoma ^c (Osanai and Lee 2016)</p>	<p>(Taimi et al. 2004; Helvig et al. 2011; Pan et al. 2016; Zhong et al. 2018)</p>

Footnotes:

^aCompetitive inhibition, ligand binding^bCompetitive inhibition, binding to enzyme active site^cIncreased transcription/mRNA/protein expression/levels /and/or catalytic activity

Table 21.

P450 27C1

Properties	References
Natural substrates: all- <i>trans</i> Retinol (vitamin A ₁), all- <i>trans</i> retinal and all- <i>trans</i> retinoic acid, 11- <i>cis</i> -retinal, all- <i>trans</i> retinol acetate	(Vahlquist 1980; Törmä and Vahlquist 1985; Kramlinger et al. 2016; Pan et al. 2016; Johnson et al. 2017)
Function: Retinoid 3,4-desaturase, oxidation of all- <i>trans</i> retinol to 3,4-didehydroretinol (vitamin A ₂) (Figs. 21, 24)	
Inhibitors ^a :	
Drugs:	
Acitretin, arotenoid Ro 13–7410, 4-(<i>N</i> -hydroxyphenyl)retinamide, ketoconazole (Törmä et al. 1991)	
Natural product:	
13- <i>cis</i> -Retinoic acid (Rollman et al. 1993; Törmä et al. 1991)	
Citral (Törmä et al. 1991)	
Inducers ^a :	
Physiological compound:	
Cellular retinoid-binding protein (Andersson et al. 1994)	
Physiological condition and illnesses:	
Squamous cell carcinoma and keratoacanthoma (Vahlquist et al. 1996)	
UV light exposure (UVA, UVB) (Tafrova et al. 2012)	

Footnote:

^a Mechanisms have not been investigated. All cited studies were only done at a cellular activity level before the assignment of P450 27C1.

Table 22.

P450 20A1

Properties	References
Natural substrates: function unknown, still considered to be an “orphan” enzyme	(Marek et al. 2007; Stark and Guengerich 2007; Stark et al. 2008; Lemaire et al. 2016)
Inhibition: No information available	
Induction: No information available	

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