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Review article

Inhibitors of cytochrome P450 (CYP) 1B1

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ABSTRACT

Human cytochrome P450 1B1 (CYP1B1) is involved in the metabolism of various drugs. This enzyme catalyzes the hydroxylation of aryl compounds, thus generating more polar metabolites that can be easily excreted. CYP1B1 is also known for its ability to activate procarcinogens into carcinogens. For example, it can hydroxylate 17β-estradiol (E2) into 4-hydroxy-E2, which can promote tumorigenesis as a potent estrogen, or after being transformed into E2-3,4-quinone. Since elevated expression levels of CYP1B1 have been reported in various cancers, but not in normal tissues, this enzyme represents an interesting therapeutic target. This review put emphasis on different families of inhibitors, especially those reported since 2003.

Contents

1. Introduction

Cytochromes P450 (CYPs) constitute a large family of hemoproteins involved in many reduction and oxidation reactions on both endogenic and xenobiotic molecules of various sizes [1,2]. This enzyme family is primarily made up of monooxygenases which are present in several animals, plants, fungi, bacteria, protists, archaea and also in some viruses [3]. More than 21,000 CYPs have been identified to date, and 18 families, including over 50 enzymes are found in humans [1,4]. Cytochrome P450-mediated diseases are associated with anormal steroidogenesis; defects in cholesterol, fatty and bile acid pathways; vitamin D dysregulation and with retinoid dysfunction during fertilization, implantation, embryogenesis, foetogenesis and neonatal development [5].

The CYP1 subfamily contains three members: CYP1A1, CYP1A2 and CYP1B1. Human CYP1B1 share 41 and 40% amino acid sequence homology with human CYP1A1 and CYP1A2, respectively, while the latter two are 72% identical [6]. Three-dimensional structures of

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human CYP1A1, CYP1A2 and CYP1B1 have been reported and can be consulted in the Protein Data Bank [7–9]. CYP1A1 is expressed in the liver but also in many extrahepatic tissues such as pancreas, thymus, uterus and small intestine, while CYP1A2 is constitutively expressed in the liver [10]. CYP1B1 is mainly expressed in extrahepatic tissues such as breast, prostate and uterus. Furthermore, a low level of CYP1B1 mRNA has been detected in several normal human tissues such as kidney, liver, intestine, eye tissue and brain [6,10,11]. CYP1A1 and CYP1B1 have been widely studied because they are involved in the conversion of a large number of polycyclic aromatic hydrocarbons (PAHs) into carcinogens [12]. Also, it should be emphasized that CYP1 enzymes are involved in the modulation of pro-inflammatory and inflammatory pathways through the metabolism of leukotrienes and eicosanoids [13]. Moreover, it has been shown that some flavonoid-type compounds could act as CYP1 substrates, leading to the formation of more antiproliferative agents within cancer cells [14].

CYP1B1 is the most interesting target among the three CYP1 mentioned above. Indeed, it should be noted that CYP1B1 is the most efficient enzyme catalyzing the hydroxylation of the potent estrogenic C18-steroid 17β-estradiol (E2) (Fig. 1) [15]. Moreover, it is overexpressed in various types of human cancers (breast, lung, colon, esophagus, skin, testis, lymph node and brain), but not in healthy tissues [16]. This enzyme is also a good marker for the prevention of certain cancers, such as breast cancer.

In addition to its involvement in the activation of many PAHs such as benzo[α]pyrene, CYP1B1 has a distinct selectivity for the 4-hydroxylation of E2, whereas CYP1A1 and CYP1A2 are mainly implicated in the 2-hydroxylation of E2 [17]. Unlike 2-hydroxy-E2 and its oxidation product E2-2,3-quinone, 4-hydroxy-E2 can be oxidized into E2-3,4-quinone, which has a high mutagenic potential by interacting covalently with DNA, thus leading to the formation of depurinating adducts [18]. Finally, CYP1B1 is also involved in the metabolism of some anticancer agents such as docetaxel, leading to drug resistance associated with the overexpression of CYP1B1 [19,20]. Therefore, an inhibitor of CYP1B1 could be useful in certain multitherapies. Clearly, the inhibition of CYP1B1 represents a promising therapeutic strategy because it would permit a therapeutic action at three different levels (Fig. 1): (1) by inhibiting the formation of 4-hydroxy-E2, (2) by inhibiting the bioactivation of procarcinogens, and (3) by reducing drug-resistance [1,20]. However, it is important to specifically inhibit CYP1B1 because CYP1A1 plays a significant role in the detoxication of environmental procarcinogens, and contributes also to the metabolic activation of dietary compounds with cancer preventive activity [21].

In a review article published in 2003 [1], Chun and Kim clearly exposed the state of knowledge of CYP1B1 and its inhibitors by grouping them according to several families: synthetic aromatic compounds, naturally occurring coumarins, flavonoids, naturally occurring stilbenes and analogs, anthraquinones and anti-cancer agents. Among these families of compounds, we note that the flavonoids and the stilbenes have been the most studied for the inhibition of CYP1B1. Stilbene family thus provided the best inhibitors in terms of activity and selectivity, particularly with the 2,4,3′,5'-tetramethoxystilbene which is one of the most selective inhibitors of CYP1B1 [22]. Moreover, this compound also specifically inhibits the 4-hydroxylation of E2 by CYP1B1. There are also some exotic compounds which have shown some inhibitory activity against CYP1B1. This is the case, for example, of organoselenium compounds, some anticancer agents (e.g. flutamide) and certain alkaloids (e.g. rutaecarpine) [1,23–27]. Moreover, it should be noted that feedback inhibition of CYP1B1 by methoxyestrogens has been reported [28].

Since 2003, improved versions of known inhibitors or novel inhibitors have been the subject of new publications; we therefore deemed it relevant to write a new review article. It should be emphasized that two review articles were recently published. In 2014, Cui and Li wrote a review of different CYP1 inhibitors and reported several CYP1-activated prodrugs [29]. Their exhaustive review presents a complete listing of the chemicals interacting with CYP1 enzymes and provides key information based on structure-activity relationship (SAR) studies. The second review article, published in 2016 by Dong et al. [30], focuses on flavonoids and naphthoflavonoids as CYP1 substrates and inhibitors. In our mini-review article, we focused on the CYP1B1 inhibition and we presented, across different families, various new CYP1B1 inhibitors published between 2003 and 2017.

2. Stilbenes

Stilbenes have been studied extensively as CYP1B1 inhibitors and they generally represent the most active and selective inhibitors among the different previously mentioned families [1]. The basic structure of stilbenes (Fig. 2) has two aromatic groups on either side of a double bond. For instance, the trihydroxylated *trans*-stilbene resveratrol (**1**) is present in red wine and is a chemopreventive agent due to its antioxidant activity [31]. However, resveratrol is not selective for CYP1B1 because it also inhibits CYP1A1 [32,33] and its activity was quite low in comparison with some other stilbenes, which are much more active inhibitors [1]. Subsequently, several derivatives of resveratrol have been developed, including, for example, compounds **2**–**11** bearing methoxy (CH_3O) or thiomethyl (CH_3S) groups instead of the hydroxy (OH) group generally found in basic scaffold. Among those derivatives without a thiomethyl group, compounds **2**, **3** and **4** appear to be

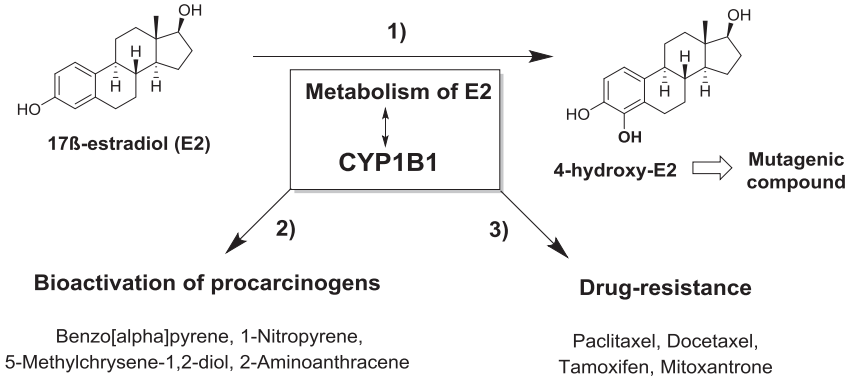

Fig. 1. Involvement of CYP1B1 in the development of cancer.