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Profiling of enantiopure drugs towards aryl hydrocarbon (AhR), glucocorticoid (GR) and pregnane X (PXR) receptors in human reporter cell lines

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ABSTRACT

In the past decade, a large number of enantiopure drugs were introduced to clinical practice, since improved therapeutic effects were demonstrated for one of the enantiomers from originally racemic drug. While the therapeutic effects and safety of enantiopure drugs were tested prior to their approval, various biological enantiospecific activities of these, often "old" drugs, remain to be elucidated. In the current paper, we examined enantiospecific effects of clinically used enantiopure drugs containing one chiral center in the structure (i.e. zopiclone, tamsulosin, tolterodine, modafinil, citalopram) towards aryl hydrocarbon (AhR), glucocorticoid (GR) and pregnane X (PXR) receptors in human reporter cell lines.

The cytotoxicity (IC_{50}), agonist (EC_{50}) and antagonist effects (IC_{50}) of R-form, S-form and racemic mixture for each tested drugs were determined and compared in AhR-, GR- and PXR-gene reporter cell lines. Since AhR, GR and PXR are key regulators of drug metabolism, energy metabolism, immunity and play many other physiological functions, the data presented here might be of toxicological significance.

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1. Introduction

Large number of clinically used drugs contains in their chemical structure one or more chiral centers. Therefore, such a drug consists of 2^n chemical entities (where n = number of chiral centers), called enantiomers, and their mixture is called racemic mixture or racemate. The majority of drugs are administered in the form of racemate, i.e. as a mixture of enantiomers. Individual enantiomers of one drug may drastically differ, both qualitatively and quantitatively in their biological activities. An example of quantitative enantiospecific drug effects is a non-selective β/α1 blocker carvedilol, where its S-form is 100× stronger antagonist of β-adrenergic receptors as compared to R-form [1]. An example of qualitatively different effects of enantiomers is thalidomide, when R-form has desired therapeutic activity and it is safe, while S-form exerts serious teratogenic effects [2]. An enantiomer with desired (or significantly pronounced) biological activity is called eutomer, and its opposite enantiomer (antipode) is called distomer. When a ratio (eudysmic ratio) between given biological activity of eutomer and distomer is largely different from 1, such a drug is a candidate for the use in its enantiopure form. A *condition sin qua non* for use of enantiopure drugs is that the enantiomer does not racemize in clinically relevant time (i.e. hours – days). The benefits of enantiospecific drugs are not only higher therapeutic activity, but consequently also attenuation of side effect due to reduced dosing. Indeed, in a past decade, a large number of enantiopure drugs were approved and introduced to the clinical practice. While the therapeutic effects and safety of enantiopure drugs were tested prior to their approval, various biological enantiospecific activities of these, often "*old*" drugs, remain to be elucidated. In the current paper, we examined five structurally and therapeutically different chiral drugs, which contain one chiral atom in the molecule and which are currently used as enantiopure drugs (for structures and properties of drugs see Table 1): i.e. Zopiclone – it is a non-benzodiazepine hypnotic, which binds preferentially to ω1-$GABA_A$ subtype of the GABA receptors family, localized primarily in the brain,

Abbreviations: AhR, aryl hydrocarbon receptor; DEX, dexamethasone; GR, glucocorticoid receptor; PXR, pregnane X receptor; RIF, rifampicin; RU486, mifepristone; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

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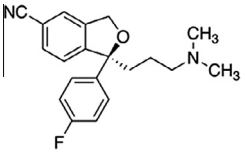
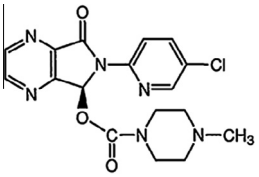
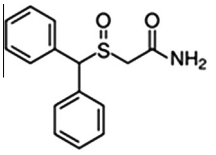
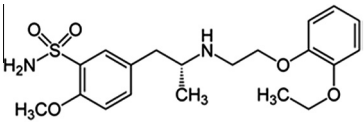
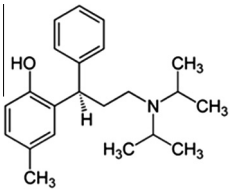
Table 1
Summary information on the enantiopure drugs tested.

Therapeutically active form	Chemical structure	Brand names	FDA approval	Cell target	Indication	IC_{50} AhR	GR	PXR
S-citalopram		Cipralex, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen	2002	Selective serotonin reuptake inhibitor	Major depression, anxiety disorders	46.6 ± 20.1 μM	>100 μM	79.4 ± 10.9 μM
S-zopiclone		Estorra, Lunesta	2006	ω1-$GABA_A$ receptor	Insomnia	>100 μM	>100 μM	>100 μM
R-modafinil		Provigil, Modiodal, Modafinil, Nuvigil	2007	Stimulation of histamine, norepinephrine, serotonin, dopamine and orexin systems in the brain – precise mechanism of action remains unclear	Narcolepsy, shift work sleep disorder, ADHD	>100 μM	>100 μM	>100 μM
R-tamsulosin		Flomax, Flomaxtra, Contiflo XL, Urimax,Pradif	1997	α1-adrenoceptor	Benign prostatic hyperplasia	>100 μM	>100 μM	>100 μM
R-tolterodine		Detrol, Detrusitol	1998	Muscarinic receptor	Overactive bladder	>10 μM	>10 μM	>10 μM

notably by binding to their α1 subunit [3]. As enantiopure drug, an eutomer S-zopiclone (eszopiclone) was approved by FDA in 2006 [4,5]. Citalopram – it acts as serotonin-selective re-uptake inhibitor SSRI in serotoninergic neurons in the brain. In its enantiopure form, S-form of citalopram (escitalopram) was approved by FDA in 2002 and 2003 for the treatment of major depression and general anxiety disorder, respectively [6]. Modafinil – it is a CNS stimulant used for the treatment of narcolepsy, shift-work sleep disorder or ADHD. Enantiopure drug R-modafinil (armodafinil) was approved by FDA in 2007 for the treatment of abuse of psychostimulants [7]. Tamsulosin – it is a selective $\alpha 1_a$-blocker used in the symptomatic treatment of benign prostatic hyperplasia. Enantiopure drug R-tamsulosin was approved by FDA in 1997 [8,9]. Tolterodine – it is an antimuscarinic drug used for the treatment of overactive urinary bladder. Enantiopure drug R-tolterodine was approved by FDA in 1998 [10].

In the present paper, the *in vitro* biological assays were performed for R-form, S-form and racemic mixture of each drug. We aimed to estimate enantiospecific potential of tested drugs towards key transcriptional regulators of drug-metabolizing enzymes, i.e. aryl hydrocarbon (AhR), glucocorticoid (GR) and pregnane X (PXR) receptors [11]. Cytotoxicity, agonist and antagonist activities of tested compounds towards AhR, PXR and GR were evaluated in human reporter cell lines, established recently in our laboratory. Briefly, A transcriptional activity of AhR was assayed in a stably transfected gene reporter cell line AZ-AhR, derived from human hepatoma HepG2 cells transfected with a construct containing several AhR binding sites upstream of a luciferase reporter gene, was used for assessment of AhR transcriptional activity [12]. Transcriptional activity of GR was examined in a stably transfected gene reporter cell line AZ-GR, derived from human cervix carcinoma HeLa cells transfected with a construct containing several GR response elements upstream of a luciferase reporter gene, was used for assessment of GR transcriptional activity [13]. Human colon adenocarcinoma cells LS174T, transiently transfected with a chimera *p3A4-luc* reporter construct containing the basal promoter (−362/+53) with proximal PXR response element and the distal xenobiotic responsive enhancer module (−7836/−7208) of the *CYP3A4* gene 5′-flanking region were used for assessment of PXR transcriptional activity. Recently, these reporter cell lines were used for examination of anthocyanins [14], anthocyanidins [15], constituents from non-alcoholic beverages [16,17] etc. Since AhR, GR and PXR are also master regulators of energy metabolism, bile acid and cholesterol homeostasis, cell cycle, immunity and play many other physiological functions, including differentiation and development [18], the data presented here might be of toxicological significance.

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