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Screening of bisphenol A, triclosan and paraben analogues as modulators of the glucocorticoid and androgen receptor activities

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ABSTRACT

A homeostasis of the glucocorticoid and androgen endocrine system is essential to human health. Their disturbance can lead to various diseases, for example cardiovascular, inflammatory and autoimmune diseases, infertility, cancer. Fifteen widely used industrial chemicals that disrupt endocrine activity were selected for evaluation of potential (anti)glucocorticoid and (anti)androgenic activities. The human breast carcinoma MDA-kb2 cell line was utilized for reporter gene assays, since it expresses both the androgen and the glucocorticoid-responsive reporter. Two new antiandrogens, 4,4′-sulfonylbis(2-methylphenol) (dBPS) and 4,4′-thiodiphenol (THIO), and two new antiglucocorticoids, bisphenol Z and its analog bis[4-(2-hydroxyethoxy)phenyl] sulfone (BHEPS) were identified. Moreover, four new glucocorticoid agonists (methyl paraben, ethyl paraben, propyl paraben and bisphenol F) were found. To elucidate the structure–activity relationship of bisphenols, we performed molecular docking experiments with androgen and glucocorticoid receptor. These docking experiments had shown that bulky structures such as BHEPS and bisphenol Z act as antiglucocorticoid, because they are positioned toward helix H12 in the antagonist conformation and could therefore be responsible for H12 conformational change and the switch between agonistic and antagonistic conformation of receptor. On the other hand smaller structures cannot interact with H12. The results of *in vitro* screening of fifteen industrial chemicals as modulators of the glucocorticoid and androgen receptor activities demand additional *in vivo* testing of these chemicals for formulating any relevant hazard identification to human health.

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1. Introduction

Based on U.S. Environmental Protection Agency (EPA) and Environment Canada data, more than 30,000 chemicals are in wide commercial use (Muir and Howard, 2006). The Registration, Evaluation, and Authorization of Chemicals (REACH) program reported about 140,000 substances that were pre-registered by 1 December 2008 in the European Union (Judson et al., 2009). Several of these chemicals can interfere with functions of the endocrine system (Soto et al., 2009). Such endocrine disrupting compounds (EDCs) were defined by the U.S. EPA as "exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes". EDCs can thus disrupt the endocrine system by numerous mechanisms of action, the most obvious one being modulation of nuclear receptors, including the glucocorticoid and androgen receptors.

Glucocorticoids are essential for the feedback mechanism in the immune system that decreases immune activity, appropriate brain functions and fetal development. They also regulate electrolyte concentration and glucose metabolism (Cooper, 2004; Liu et al., 2010; Rosmond, 2005). Disturbance of these physiological functions can lead to diseases such as obesity, diabetes type 2, osteoporosis and others cardiovascular, inflammatory and autoimmune diseases (Odermatt et al., 2006). Similar exposure to androgen disrupting chemicals is related to reduced sperm counts, decreased fertility, testicular dysgenesis syndrome, testicular and prostate cancers (Luccio-Camelo and Prins, 2011). Fifteen high production volume chemicals (see Fig. 1) that are encountered daily were selected and screened for their (anti)glucocorticoid and (anti)androgenic activities using a reporter gene assay. For the purpose of this study chemicals were sorted into three groups: (1) bisphenol A (BPA) and its analogues, (2) triclosan (TCS) and triclocarban (TCC), and (3) four parabens.

BPA is used as a primary component of polycarbonate plastic used in beverage and food containers or as an additive in other types of plastics. It is also used in dental sealants as one of the building blocks of epoxy resins. It is estimated that more than

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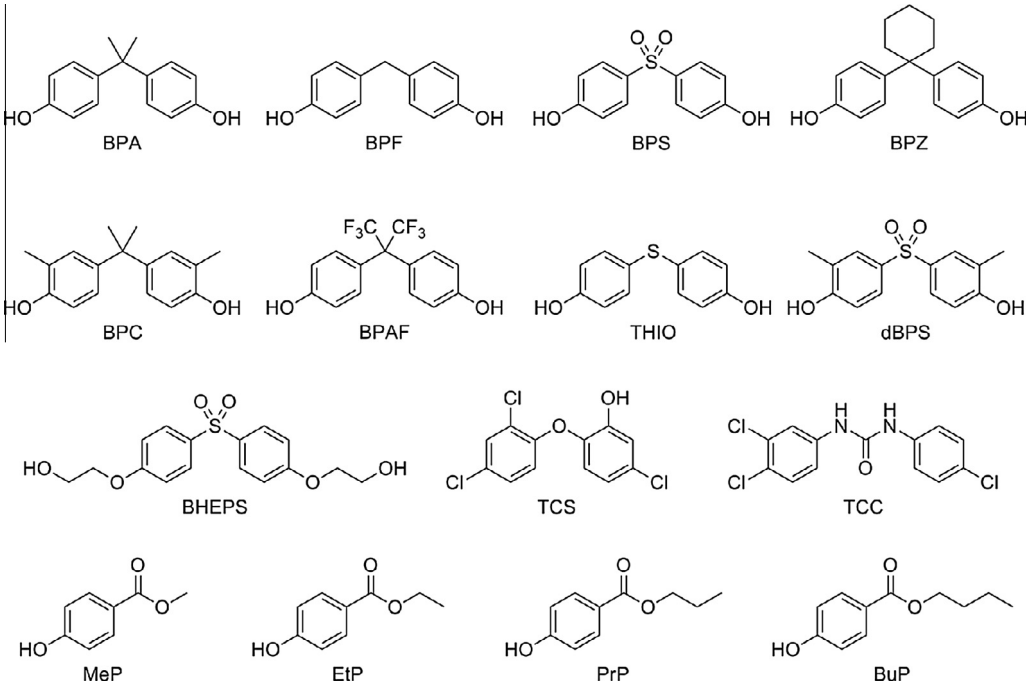

Fig. 1. Structures of tested chemicals. For explanation of abbreviations see Section 2.1.

3.5 million tons of BPA is produced annually, classifying it as one of the high production volume chemicals (Vandenberg et al., 2010b). A recent study on more than 2500 participants showed that BPA is present in 92.6% of urine samples (Calafat et al., 2008). BPA is a known endocrine disruptor, which has been correlated with various diseases and medical conditions (reviewed in Rubin (2011)). From a mechanistic point of view, BPA interacts with a variety of receptors, including the classical nuclear and non-classical membrane estrogen receptors, estrogen-related receptor γ, aryl hydrocarbon receptor, thyroid hormone receptor, androgen receptor and glucocorticoid receptor (Rubin, 2011; Vandenberg et al., 2009). Less is known about BPA analogs such as bisphenols F, S, Z, C, AF, 4,4′-thiodiphenol (THIO), bis[4-(2-hydroxyethoxy)phenyl] sulfone (BHEPS) and 4,4′-sulfonylbis(2-methylphenol)(dBPS). Some of these are already used in industry for the production of paper, dental material and plastics, as a substitute for BPA because of the known toxic pleiotropic effects of the latter (Chen et al., 2002; Gallart-Ayala et al., 2011; Kitamura et al., 2005; Liao et al., 2012). Triclosan (TCS) and triclocarban (TCC) are bactericides widely used in many personal care and household products such as shampoos, soaps, dish detergents, deodorants, hand sanitizers, creams, mouthwash products and toothpastes (Daughton and Ternes, 1999; Masuda et al., 2005). Both agents have been on the market for about 40 years. The annual worldwide production of TCS in 2005 was estimated at 1500 tons (Bester, 2005). TCC is also classified as a high production volume chemical by the U.S. EPA, since its annual production is at least 250 tons in the US alone (Velichko and Trishkin, 1993). Due to their large consumption, widespread use and frequent detection in waste and surface waters (Brausch and Rand, 2011), these compounds have attracted great attention. Like TCS and TCC, parabens are used in personal care products, pharmaceuticals and food as bactericidal and fungicidal preservatives. The presence of parabens, primarily methylparaben and propylparaben, was reported in the majority of body care cosmetics analyzed (Darbre and Harvey, 2008). Intact parabens that escaped from metabolism by esterases have been detected in human urine samples and breast milk (Schlumpf et al., 2010; Ye et al., 2006). Recent studies suggest that parabens are EDCs, because of their binding to estrogen, androgen, thyroid hormone and peroxisome proliferator-activated gamma receptors (Darbre and Harvey, 2008; Taxvig et al., 2012). Potential hazards arising from the use of parabens are still under investigation.

All the above mentioned chemicals are known as EDCs for at least one endocrine system. While they are known to have varying estrogenic and androgenic potencies, their glucocorticoid properties remained poorly characterized. Therefore, the human breast carcinoma MDA-kb2 cell line, which stably expresses an androgen- and glucocorticoid-responsive reporter, was used to evaluate (anti)glucocorticoid or (anti)androgenic activity of the selected compounds. Molecular modeling has been used to explain the structure–activity relationship of bisphenols.

2. Materials and methods

2.1. Chemicals

Bisphenol A (2,2-bis(4-hydroxyphenyl)propane, BPA), bisphenol F (bis(4-hydroxydiphenyl)methane, BPF), bisphenol S (bis(4-hydroxyphenyl)sulfone, BPS), bisphenol Z (1,1-bis (4-hydroxyphenyl)-cyclohexane, BPZ), bisphenol C (2,2-bis(3-methyl-4-hydroxyphenyl)propane, BPC), bisphenol AF (2,2-bis(4-hydroxyphenyl)-hexafluoropropane, BPAF), 4,4′-thiodiphenol (THIO), bis[4-(2-hydroxyethoxy)phenyl] sulfone (BHEPS), 4,4′-sulfonylbis(2-methylphenol) (dBPS), irgasan (triclosan, TCS), 3,4,4′-trichlorocarbanilide (triclocarban, TCC), dihydrotestosterone (DHT), hydrocortisone (HC), flutamide (FLUT) and mifepristone (RU486) were from Sigma–Aldrich. Methyl paraben (MeP) and propyl paraben (PrP) were from Fluka, ethyl paraben (EtP) and butyl paraben (BuP) from CHEMOS GmbH. All the above chemicals are of 95% or better purity as specified by the suppliers.

2.2. Cell line and cell culture conditions

The MDA-kb2 cell line (ATCC, USA) is a stably transformed MDA-MB-453 cell line with the murine mammalian tumor virus

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