Anti-androgenic effects of the UV-filter Benzophenone-1 by inhibition of 17β-hydroxysteroid dehydrogenase type 3

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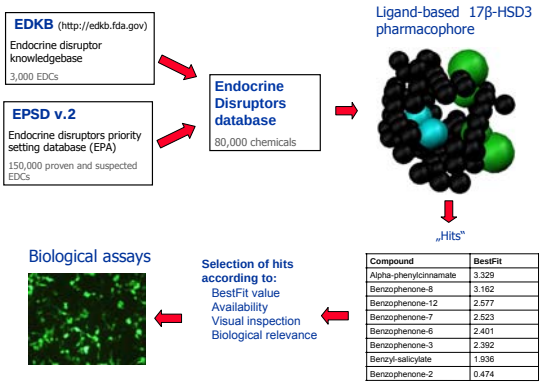
Summary

- We constructed a 3D-chemical database from known and suspected endocrine disrupting chemicals, suitable for screening with pharmacophores.
- Virtual screening of the database with pharmacophores of human 17ß-HSD3 yielded several benzophenone derived UV-filters as hits.
- BP-1 inhibited 17ß-HSD3-dependent testosterone synthesis in intact cells with an IC_{50} of 1 μM.
- Benzophenone-1 exerts anti-androgenic effects both by inhibiting testosterone synthesis via 17ß-HSD3 and by blocking androgen receptor activation. Some UV-filters including OMC did not interfere with androgen action and can be considered safe from this point of view.
- The EDDB allows screening with pharmacophores of any target of interest and should facilitate the identification of target/chemical interactions.

Introduction

Endocrine disruptors are environmental chemicals interfering with the action of natural hormones and causing adverse health effects such as sexual and behavioral disorders, allergic diseases, and certain forms of cancer. We constructed a virtual 3D-chemical database of proven and suspected endocrine disrupting chemicals, prepared it for virtual screening and screened the database using pharmacophore models of the testosterone-synthesizing enzyme 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3).

Fig 1. Scheme of the construction of the Endocrine Disruptor Database (EDDB)



17β-HSD3 is responsible for the synthesis of testosterone from androstenedione. Individuals with mutations in the *17KSR3* gene develop the monogenic disease male pseudohermaphroditism. Blocking the 17β-HSD3 function by environmental chemicals may be harmful especially during development and pre-puberty.

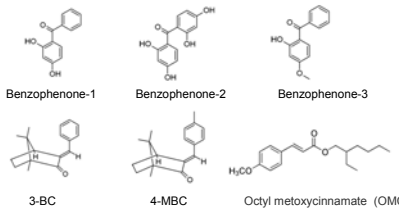
Results

The screening yielded several benzophenone derived UV-filters (Fig.2).

UV-filters are organic UV-absorbing chemicals, widely used in sunscreens, cosmetics and plastic materials for light stabilization. Due to their lipophilic character some UV-filters tend to bio-accumulate as shown in molluscs, fish and humans. Studies using different systems have shown that some UV-filter chemicals can bind and trans-activate estrogen receptors.
However, there is little information on potential interaction of UV-filters with other proteins involved in steroid hormone action.

UV-filters

Fig. 2 Chemical structures of representatives of three classes of organic UV-filters investigated in this project.



Effects on 17β-HSD3

We tested 7 different benzophenone UV-filters for potential inhibition of human 17β-HSD3 in intact transfected HEK-293 cells. Fig 3A shows the effect of different UV-filters (at 20 μM concentration) on the conversion of androstenedione to testosterone. The most potent compound Benzophenone-1 inhibited 17β-HSD3 with an IC_{50} of 1.05 μM (Fig 3B, Table 1). BP-1 also potently blocked testosterone formation in an *ex vivo* whole organ assay in mice (Fig 3C).

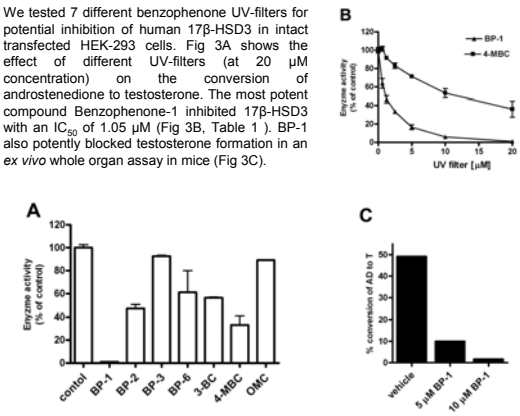


Fig. 3 Effects of different UV-filters on human and mouse 17β-HSD3

Table 1. Inhibitory effect of UV-filters on the activity of different 17β-HSDs (IC_{50} [μM], determined in intact HEK-293 cells).

UV-filter	17β-HSD3	17β-HSD5	17β-HSD2	17β-HSD1*
BP-1	1.05 ± 0.08	ND	> 20	65.2 %
BP-2	18.1 ± 3.8	ND	10.3 ± 2.5	42.2 %
BP-3	ND	ND	ND	97.7 %
3-BC	33.3 ± 7.5	ND	6.3 ± 1.4	72.4 %
4-MBC	10.7 ± 0.9	ND	5.9 ± 1.3	69.5 %

% of enzyme activity at 20 μM, measured in cell lysates. ND – not determined

Effects on the androgen receptor

We determined the antagonistic effect of selected UV-filters on the androgen receptor in transfected HEK-293 cells (Fig. 4A). We measured the potency of BP-1 and other UV-filters to block the activation of human androgen receptor by testosterone. Benzophenones were the most potent AR-antagonists with IC_{50} values of 5.7, 2.2, and 3.1 μM for BP-1, 2, and 3, respectively (Fig. 4B).

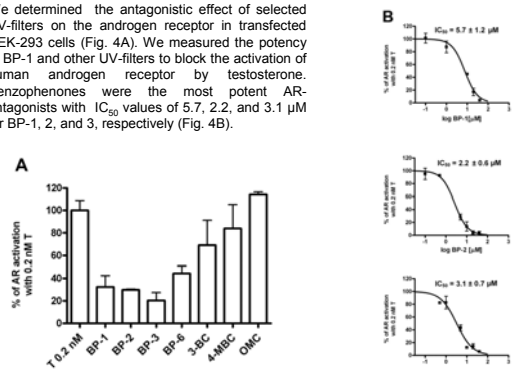


Fig. 4 Effects of different UV-filters on human androgen receptor

Abbreviations:
EDDB *- Endocrine disruptors database*
BP-1 *- Benzophenone 1*
4-MBC *- 4-methylbenzylidene camphor*
17β-HSD *- 17β-hydroxysteroid dehydrogenase*
3-BC *- 3-methyl benzylidene camphor*

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