Pharmacophore-based identification of chemical tool compounds inhibiting 17β-hydroxysteroid dehydrogenase 14 (17β-HSD14)

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Objective: Steroid-metabolizing enzymes are able to convert a multitude of diverse steroid hormones and other types of substrates (e.g. prostaglandins, fatty acids). Thus, they are also associated with a great variety of diseases in humans. [1] One pivotal enzyme class of steroid-metabolizing enzymes includes the hydroxysteroid dehydrogenases (HSDs). 17β-HSD14 is the latest identified 17β-HSD representing a tetrameric, cytosolic enzyme that catalyzes the inactivation of, for example, estradiol to estrone (due to oxidation in position 17). Although its physiological relevance is largely unknown, its high expression in (but not limited to) several steroidogenic tissues indicates a role in human sex steroid metabolism (e.g. breast cancer) and possibly also other metabolic pathways. [2,3] Except for some non-steroidal pyridine derivatives discovered by Bertoletti *et al.* and Braun *et al.*, no inhibitors on 17β-HSD14 have been reported to date. [4,5,6] Therefore, the aim of this study is to discover further structurally diverse inhibitors of 17β-HSD14 and thus enable a better characterization of the binding site and the enzyme's physiological function.

Methods: For the implementation of this issue, a pharmacophore-based virtual screening workflow was elaborated in LigandScout and the three best performing models were chosen for screening of 13 different chemical databases. The hits were docked into the X-ray crystal structure of 17β-HSD14 (PDB-entry 5ICM) with AutoDockVina implemented in LigandScout. [7,8] Based on the binding mode of the resulting docking poses, the final hit selection was carried out. In the end, the selected hits were biologically evaluated in a fluorimetric in vitro assay on human recombinant 17β-HSD14 at the University of Marburg. [4]

Results and Outlook: Out of 18 compounds, 2 turned out to be active in the low micromolar to nanomolar range, namely Specs compound AO-081/15245155 and nordihydroguaiaretic acid with a K_i of 0.65 µM and 1.30 µM, respectively. [9] Based on the outcome, the pharmacophore models will be refined and used again to screen several databases in order to discover further inhibitors with different scaffolds. Moreover, SAR studies will be carried out on compound AO-081/15245155, since several derivatives occurred in the hitlist.

Conclusions: There are probably several other scaffolds among natural products or synthetic chemicals that can inhibit the enzyme. The discovery of such inhibitors will contribute to a better understanding of 17β-HSD14 and it will guide to assessing the potential health risks associated to its inhibition through natural and/or synthetic sources.

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