Conference abstract PDD03

# Preparation of Recombinant Human Hydroxysteroid Dehydrogenases and Study of their Inhibitors

**P. BROŽIČ [1], S. GOBEC [2], T. LANIŠNIK RIŽNER [3]**

[1] Sandoz Development Center, Ljubljana, Slovenia (work was performed at [3])
[2] Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia
[3] Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

E-mails: petra.brozic@sandoz.com (P. Brožič), stanislav.gobec@ffa.uni-lj.si (S. Gobec), tea.lanisnik-rizner@mf.uni-lj.si (T. Lanišnik Rižner)

Sci Pharm. 2010; 78: 592 doi:10.3797/scipharm.cespt.8.PDD03

Androgens and estrogens increase the number of cell division and the opportunity for random genetic errors and are thus involved in carcinogenesis of hormone related cancers. Pre-receptor regulatory enzymes interconvert the active forms of hormones with high affinities to corresponding receptors to their less active forms. They represent interesting targets for development of new drugs for prevention and treatment of conditions caused by disturbed hormone action. We have focused our attention to four hydroxysteroid dehydrogenases (HSDs). AKR1C1 converts potent progesterone to a weak 20α-hydroxy-progesterone; AKR1C2 inactivates potent androgen 5α-DHT, and AKR1C3 reduces a weak androgen androstenedione to a potent testosterone. Both AKR1C3 and 17β-HSD type 1 activate weak estrogen estrone to a potent estradiol [1, 2]. We have isolated the recombinant AKR1C1, AKR1C2, AKR1C3 and over-expressed 17β-HSD type 1 in bacterial and mammal cells. Different approaches were used for searching the inhibitors of these enzymes and structurally different compounds were shown to be potent inhibitors (e. g. [3, 4]). Inhibitors with $IC_{50}$ values in micromolar range are good starting points for further design and synthesis of new and improved inhibitors of this important group of enzymes.

*This work was supported by a J3-9448 grant to T.L.R. and a young researcher grant to P.B., both from the Slovenian Research Agency.*

[1] Penning TM. Molecular endocrinology of hydroxysteroid dehydrogenases. Endocr Rev. 1997; 18: 281–305. doi:10.1210/er.18.3.281
[2] Penning TM, Drury JE. Human aldo-keto reductases: Function, gene regulation, and single nucleotide polymorphisms. Arch Biochem Biophys. 2007; 464: 241–250. doi:10.1016/j.abb.2007.04.024
[3] Brozic P,Turk S,Rizner TL,Gobec S. Discovery of new inhibitors of aldo-keto reductase 1C1 by structure-based virtual screening. Mol Cell Endocrinol. 2009; 301: 245–250. doi:10.1016/j.mce.2008.08.002
[4] Stefane B, Brozic P, Vehovc M, Rizner TL, Gobec S. New cyclopentane derivatives as inhibitors of steroid metabolizing enzymes AKR1C1 and AKR1C3. Eur J Med Chem. 2009; 44: 2563–2571. doi:10.1016/j.ejmech.2009.01.028