Refinement of pharmacophore models for inhibition of 11β-hydroxysteroid dehydrogenases, regulators of intracellular glucocorticoid concentrations

Vuorinen A[1], Fürstenberger C[2], Odermatt A[2], Schuster D[1]

[1]Computer-Aided Molecular Design Group and Center for Molecular Biosciences Innsbruck, Institute of Pharmacy / Pharmaceutical Chemistry, University of Innsbruck, Innrain 80/82, 6020 Innsbruck, Austria

[2]Division of Molecular and Systems Toxicology, Department of Pharmaceutical Sciences, University of Basel, Klingelbergstr. 50, 4056 Basel, Switzerland

11β-Hydroxysteroid dehydrogenases (11β-HSDs) regulate the local concentrations of cortisone and cortisol in human tissues: 11β-HSD1 converts the inactive cortisone to active cortisol and 11β-HSD2 catalyzes the opposite reaction. [1] Selective 11β-HSD1 inhibitors could be used in the treatment of metabolic syndrome and type 2 diabetes, while inhibition of 11β-HSD2 causes hypokalemia and hypertension. [2-3]. We have previously reported pharmacophore models for 11β-HSD inhibition, which are used for virtual screening, drug discovery and toxicological studies. [4-5] Since new 11β-HSD inhibitors are constantly reported, it is important to regularly re-evaluate the performance of the models to confirm good model quality. For the model refinement purposes, all our 11β-HSD models were employed for virtual screening of following databases: Innhouse (own development), Specs (www.specs.net), Maybridge (www.maybridge.com), DrugBank (www.drugbank.ca), Endocrine disrupting chemical library [6] and DIOS [7]. From these screenings, 43 compounds, including endocrine disruptors, natural products and currently used drugs were tested *in vitro* for their 11β-HSD activity. The results of the enzyme activity tests were used for refining the models: all the compounds were fitted to the models and several model refinement steps were taken to increase the model performance. During this study we have discovered new 11β-HSD inhibitors and optimized our 11β-HSD pharmacophore models.

[1] Z. Krozowski, et al. *J. Steroid. Biochem. Mol. Biol.,* **1999**, *69,* 391-401.
[2] H. Masuzaki, et al. *Science,* **2001**, *294,* 2166-2170.
[3] Y. Kotelevtsev Y, et al. *J. Clin. Invest.,* **1999**, *103,* 683-689.
[4] D. Schuster, et al. *J. Med. Chem.,* **2006**, *49,* 3454-3466.
[5] DV. Kratschmar, et al. *J. Steroid. Biochem. Mol. Biol.,* **2011**, *125,* 129-142.
[6] LG Nashev, et al. *Biochem. Pharmacol.,* **2010**, *79,* 1189-1199.
[7] JM Rollinger, et al. *J. Med. Chem.,* **2008**, *51,* 842-851.