

Computer-aided drug design for the β_2 -adrenergic receptor

Peter Kolb¹, Daniel Rosenbaum², John J. Irwin¹, Brian K. Kobilka², and Brian K. Shoichet¹

¹Department of Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, CA 94158, USA and ²Department of Molecular and Cellular Physiology, Stanford University School of Medicine, Stanford, CA 94305, USA

Email: kolb@blur.compbio.ucsf.edu

Preferred presentation method: oral

G protein-coupled receptors (GPCRs) constitute a large family of membrane receptors with seven transmembrane helices. They sense molecules outside a cell and activate signal transduction pathways, thereby eliciting cellular responses. GPCRs are highly attractive targets in drug design, since they are involved in many diseases ranging from cardiovascular to behaviour-related maladies. Consequently, they are the targets of about half of all present-day drugs [1].

The recently solved high-resolution structure of the β_2 -adrenergic receptor [2, 3] presents a unique opportunity to apply computational methods to the design of small molecule modulators of GPCRs. The program DOCK [4] was used in all docking calculations. In a control calculation, the 1046 molecules of the MDL Drug Data Report (MDDR) were docked to the β_2 -adrenergic structure. Of the 782 molecules for which poses were found, 83 are active against β -adrenergic receptors. Among the top 100 compounds, 47 are assigned β -adrenergic activity, which corresponds to a 4.5-fold enrichment.

In order to identify novel binders, the fragment- and lead-like subsets of the ZINC database [5] were docked. After visual inspection, 26 compounds were tested in a competition assay. Six compounds were active in the low μ M range and below. This represents an extraordinarily high hit rate of 23%. Excitingly, the most potent compound has a K_i of only 17 nM. Moreover, two compounds that do not feature the common β -hydroxy-amine motif (usually found in β_2 -adrenergic receptor antagonists) were identified and demonstrate the potential of docking for scaffold hopping.

References

- [1] FILMORE, D., It's a GPCR world. *Modern Drug Discovery* 7 (2004), 24–28.
- [2] CHEREZOV, V., ROSENBAUM, D. M., HANSON, M. A., RASMUSSEN, S. G. F., THIAN, F. S., KOBILKA, T. S., CHOI, H.-J., KUHN, P., WEIS, W. I., KOBILKA, B. K., AND STEVENS, R. C., High-resolution crystal structure of an engineered human beta(2)-adrenergic G protein-coupled receptor. *Science* 318 (2007), 1258–1265.
- [3] ROSENBAUM, D. M., CHEREZOV, V., HANSON, M. A., RASMUSSEN, S. G. F., THIAN, F. S., KOBILKA, T. S., CHOI, H.-J., YAO, X.-J., WEIS, W. I., STEVENS, R. C., AND KOBILKA, B. K., GPCR engineering yields high-resolution structural insights into beta(2)-adrenergic receptor function. *Science* 318 (2007), 1266–1273.
- [4] MENG, E. C., SHOICHET, B. K., AND KUNTZ, I. D., Automated docking with grid-based energy evaluation. *J. Comp. Chem.* 13 (1992), 505–524.
- [5] IRWIN, J. J. AND SHOICHET, B. K., ZINC – a free database of commercially available compounds for virtual screening. *J. Chem. Inf. Model.* 45 (2005), 177–182.