19th EuroQSAR

Knowledge Enabled Ligand Design
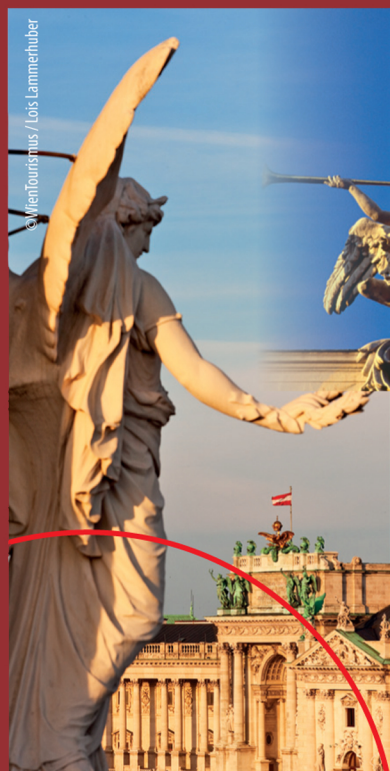
©WienTourismus / Lois Lammerhuber
©WienTourismus / MAXUM
©WienTourismus / Manfred Horvath
©WienTourismus / Willfried Gredler-Oxenbauer

August 26-30, 2012
Vienna, Austria

Abstract Book

www.euroqsar2012.org

EFMC
European Federation
for Medicinal Chemistry

Sponsored by

IN THE SEARCH OF LEPTIN AGONISTS AS ANTI-OBESITY DRUGS: PROTEIN/PROTEIN DOCKING, MOLECULAR DYNAMICS, AND VIRTUAL SCREENING

Marco Tutone, **Licia Pantano, Giuseppe Marino, Antonino Lauria, Anna Maria Almerico**

Università di Palermo, Dipartimento di Scienze e Tecnologie Molecolari e Biomolecolari (STEMBIO)
Sezione di Chimica Farmaceutica e Biologica
Via Archirafi 32, 90123 Palermo
marco.tutone@unipa.it

The body weight control is a mechanism thinly regulated by several hormonal, metabolic, and nervous pathways (1). Recessive homozygous mutations in the *ob/ob* and *db/db* mouse strain cause extreme obesity. The products of the *ob* and *db* genes are leptin and its receptor, respectively. The leptin receptor is crucial for energy homeostasis and regulation of food uptake (2). Leptin is a 16 kDa hormone that is mainly secreted by fat cells into the bloodstream. Under normal circumstances, circulating leptin levels are proportionate to the fat body mass. Sensing of elevated leptin levels by the hypothalamic neurocircutry activates a negative feedback loop resulting in reduced food intake and increased energy expenditure. Decreased leptin concentrations lead to opposite effects.
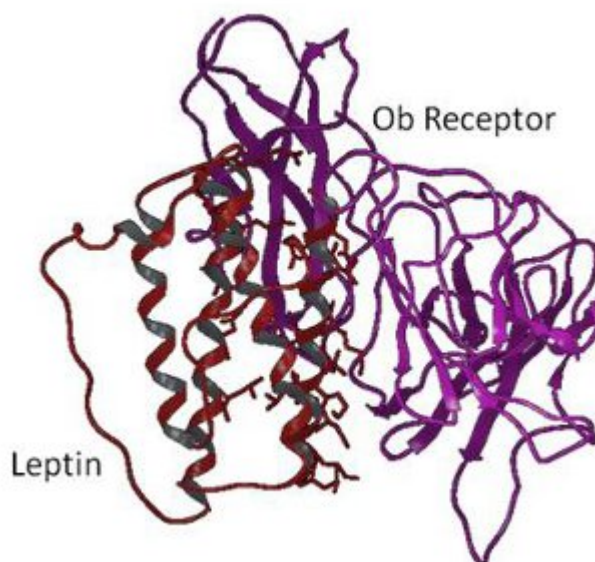
Therefore rational design of leptin agonists could be an appealing challenge in the battle against obesity. Unfortunately only the crystal structure of leptin is available, but not that of the leptin receptor. In this work, first, we built, by homology modelling, the leptin receptor starting from FASTA sequence and the similarity search of templates. The obtained model was used to perform a protein-protein docking with the crystal structure of leptine by means Gramm-X server, with the aim to define the complementary surfaces of the two proteins. The complex of leptin/leptin receptor was then used as starting point to carry out molecular dynamics simulations in water solvent to characterize the key residues involved into the protein-protein interaction. Snapshots of leptin were used as template to build a pharmacophore hypothesis to carry out virtual screening on a large database of compounds.

References

1) Friedman, J. M., Halaas, J. L. Nature 1998, 395, 763-770
2) Tepper, R. I. et al. Cell 1995, 83, 1263-1271