



## **21<sup>ST</sup> NATIONAL MEETING ON MEDICINAL CHEMISTRY**



# **BOOK OF ABSTRACTS**

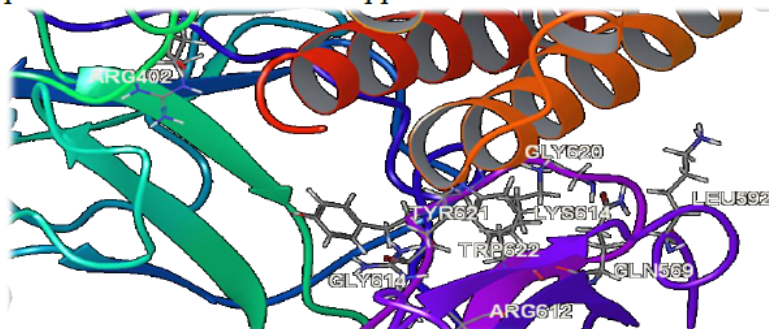
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## Molecular Modelling on Leptin and the Ob Receptor as anti-obesity target

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Obesity is a chronic pathology with multi-factorial aetiology, characterized by extreme body weight due to storing of fat in the adipose tissue, caused by an increase of caloric income, decrease of energetic intake, or both. The body weight control is a mechanism finely regulated by several hormonal, metabolic, and nervous pathways. 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 (1,2). The leptin receptor is critical for energy homeostasis and regulation of food uptake. 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 neurocircuitry 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 interesting challenge in the fight against obesity. Unfortunately only the crystal structure of leptin is available, but not that of the leptin receptor. In this work, first, we build 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 and to identify the guidelines for rational drug design of new agonists of leptin, which could be used in the therapy of obesity.

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