Abstract

Computational methodologies in combination with experimental biological assay represent fundamental key tools in the drug discovery process. The study of ligand-macromolecule interactions has a crucial role for the design, the identification and the development of new chemical platforms as anti-inflammatory and anti-cancer agents. In this project, different aspects of interaction and recognition processes between ligand and targets, and stereostructure assignment of natural compounds has been studied through different *in silico* approaches with the determination of their biological activities, which allow to corroborate the predicted results.

In particular, the strong interconnection between the tumoral and inflammatory pathology has led to the identification of new promising targets involved in essential cellular processes and acting at diverse levels and phases of the tumor and inflammation diseases. In this project, the drug design and identification of new compounds able to inhibit microsomal prostaglandin E synthase mPGES-1, 5-lipoxygenase5-LOX, cicloxygenase-1 COX-1, cicloxygenase-2 COX-2 and G-protein-coupled purinergic receptors $P2Y_{12}R$ will be described. The results obtained during my PhD three years course can be summarized in four main areas of activity, whose relative weight was varied according to the development of the overall project:

1) The support in the design of original scaffolds for the generation of libraries potentially utilizable in therapy. This work was conducted *in silico* by molecular docking technique in order to direct the design of the new molecules basing on the analysis of ligand-target interactions and the synthetic possibilities. This kind of approach was successfully applied leading to the identification of new potential inhibitors for mPGES-1 enzyme. The good qualitative accordance between the calculated and experimental data has made possible the identifications of new lead compounds, rationalizing the molecular basis of the target inhibition.

2) The rationalization of the biological activity of compounds by the study of the drug-receptor interactions. Molecular docking was used for the detailed study of anti-inflammatory and anticancer compounds whose biological activities are known a priori. In fact, thanks to this procedure, in this thesis several rationalizations of binding modes were reported related to a small pool of natural products as mPGES-1 inhibitors, such as carnosol and carnosic acid, and cryptotanshinone and tanshinone IIA as $P2Y_{12}R$ inhibitors. Through the *in silico* methodology the putative binding modes for the reported molecules was described offering a complete rationalization of the observed biological activities, e.g. evaluating the specific influence of the ligand target interactions (e.g. hydrophobic, hydrophilic, electrostatic contacts).

3) The determination of relative configuration of natural products. The complete comprehension of the three dimensional structure of synthetic or isolated molecules is fundamental to design and characterize new platform potentially utilizable in therapy. On this basis, the combined approach basing on the comparison of the predicted NMR parameters (e.g. chemical shifts, computed through quantum mechanical (QM) calculations) and the related experimentally determined values was employed to assigning the relative configuration of giffonins J-P. Moreover, the assignment of relative and absolute configuration of giffonins Q-S is ongoing by a combined approach that consider the quantum mechanical calculations of circular dicroism spectra and quantum mechanical calculations of chemical shifts to be compared with the related experimental data.

4) The biological evaluation and assay systems. The determination of PGE_2 synthase activity in microsomes of A549 cells, the determination of product formation by 5-LOX in the cell-based and cell-free assay and the determination of eicosanoids production by LC-MS/MS in monocytes and polymorphonuclear leucocytes were performed at the Department of Pharmaceutical and Medicinal Chemistry of the Friedrich- Schiller University in Jena. Moreover, the preparation of plasma through isolation of monocytes, polymorphonuclear leucocytes and platelets was carried out.