IN SILICO DESIGN AND FOCUSED SOLID PHASE SYNTHESIS OF NEW, SELECTIVE ENZYME INHIBITORS WITH POTENTIAL IN CANCER AND NEUROLOGICAL THERAPIES

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Inhibitors of enzyme targets for cancer therapy. The successful clinical development of selective small-molecule protein kinase inhibitors, such as imatinib (Gleevec), in chronic myeloid leukaemia (CML) and gastrointestinal stromal tumors (GIST), and gefitinib (Iressa), in lung cancer, have established a new paradigm for the treatment of tumors, inaugurating the era of the so-called "molecular targeted cancer therapy". Imatinib, a specific inhibitor of the BCR-ABL tyrosine kinase, is an effective drug in CML, but in many patients with advanced disease a harmful drug resistance frequently develops after an initial positive response. Taking the numerous mutations observed in BCR-ABL into account, which mainly clustered within the ATP binding region, and on the basis of the information obtained from the 3D structures of diverse enzyme-inhibitor complexes, we designed two focused libraries *in silico* and synthesized them through an original and efficient solid phase synthesis (SPS) and a multiple parallel synthesis (MPS) in solution. The results allowed new structure-affinity (SAFIR) and structure-selectivity relationships (SSR) to be established.

Another important and widespread tumor, i.e. breast tumor, was targeted in a study aimed at identifying new aromatase inhibitors, antitumor agents expected to replace estrogen receptor antagonists, like *tamoxifene* and *raloxifene*. A combined application of 3D-QSAR and direct modelling approaches (based on a homology built 3D model of the enzyme) guided the design of new classes of highly potent aromatase inhibitors, prepared through MPS in solution, which showed outstanding selectivity over 17-alpha-hydroxylase/17-20 lyase, another important cytochrome P450 enzyme involved in prostate cancer.

Enzymatic inhibitors with potential for the treatment of neurodegenerative disease. Two large series of *safinamide* and coumarin derivatives were designed, prepared and tested as monoaminoxidase (MAO) inhibitors. The former were prepared through an efficient solid-phase synthesis allowing the introduction of several structural modifications at three different steps of the synthetic pathway. Molecular diversity was properly explored on both series of ligands following the suggestions from both 3D QSAR studies and flexible docking investigation on MAO-A and MAO-B binding sites, recently elucidated by high resolution x-ray crystallography . The comparative analyses of the main interactions governing the MAO inhibition, allowed a ligand-based design of novel, reversible, potent and selective MAO-B inhibitors, with favourable pharmacokinetic profiles for the therapy of Parkinson disease.

Finally, based on the assumption that a suitable modulation of multiple targets can provide improved therapeutic effects and safer toxicological profiles, a new class of molecules, acting as dual MAO-B and acetylcholinesterase enzyme inhibitors, was successfully designed for their potential in the therapy of Alzheimer's disease. Investigations aimed at obtaining inhibitors with differently balanced activities at each targeted enzyme will be discussed and preliminary pharmacological data shown.