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PROJECT TITLE

Design of Novel Bioactive Molecules Targeting and/or Mimicking Specific Protein Hot-Spots

Project description

The most functionally important biological processes are regulated by allosteric networks among protein complexes. The proteins controlling these communication networks respond to changes in the cellular environment switching between different conformational states[1]. The involved molecular interactions have shown to have a high degree of plasticity and to occur through small regions, called hot-spots, which are included in binding surfaces or in binding clefts, characterized by a high degree of complementarity with the binding partner[1]. The presence of hot-spots allows small molecules to interfere with biological systems and accounts for the efficacy of most current drugs[2-4].

On this background, the present project aims at the identification/design of molecules able to interact with specific protein structural motifs by mimicking the structural motif/domain of the endogenous binding partner, thus blocking/activating a specific "biological message", i.e., function. At this aim, the structure-function relationships of the molecular target together with the structure-activity relationships of bioactive (natural and synthetic) compounds will be investigated using computational methods. Then, new molecular scaffolds will be designed/identified able to reproduce the pharmacophore shared by conserved structural motifs/domains of bioactive molecules, which can be then rationally modified according to the specific molecular target(s).

Starting from previous results achieved in this field[5-9] and based on the current collaborations, the following molecular targets will be mainly studied: proteasome, amyloidogenic proteins/peptides, corona virus non-structural proteins (nsp10, nsp14 and nsp16), human calcium channels and key enzymes in parasitic diseases.

The research activity will be performed in the context of multi-disciplinary projects integrating computational and experimental (synthesis and structural characterization of peptides and peptidomimetics; spectroscopic studies of interaction with the molecular target; biochemical assays and enzyme kinetics studies; SPR techniques; pharmacological assays). The research activity will be carried out by using all software and facilities present at the Laboratory of Excellence of Molecular Modelling (https://www.farmacia.unina.it/laboratori-di-eccellenza/lmm).

REFERENCES

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FUNDS

1) PRIN – Bando 2022 PNRR: Prot. P2022YRPHS; Title: Multifaced-peptidomimetics as proteasome modulators.
2) PRIN – Bando 2022: Prot. 2022MBK24T; Title: UNmasking VIral RNA: targeting viral RNA capping machinery to tackle COVID-19 and future CoV emergencies (UNVIR-19)
3) PRIN – Bando 2022: Prot. 2022PAAYZE; Title: Modulating confoRmational Equilibria of prion protein and proteaSome to tune protEostasis neTwork (RESET).
4) COST Action CA21111. One Health drugs against parasitic vector borne diseases in Europe and beyond (OneHealthdrugs).