Title: 3D GRID-based pharmacophore and Metadynamics approaches for the rational design of N-Methyl β-sheet breaker peptides as inhibitors of the Alzheimer's Aβ-amyloid fibrillogenesis.

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the loss of the cognitive functions and dementia. Several scientific evidences report that a central role in the pathogenesis of AD is played by the brain deposition of insoluble aggregates of β-amyloid protein (Aβ) proteins, thus causing neuronal cell death [1]. For this reason, one of the promising approach is to inhibit the aggregation of Aβ peptides. Because Aβ is self-assembling, one possible strategy to prevent this process is to use short peptide fragments homologous to the full-length wild-type Aβ protein. From this consideration, several short synthetic peptides were designed as beta-sheet breakers (BSB) [2]. In particular, the pentapeptide Ac-LPFFD-NH$_2$ (iAβ5p) exhibited a certain capability to inhibit Aβ fibrillogenesis [3]. iAβ5p analogs [4] were, then, designed by introducing N-Methylation at the amide bond nitrogen were also promising BSB. Here, we describe the methodological approach, which combines 3D GRID-based pharmacophore peptide screening with Well-Tempered Metadynamics simulations aimed to the discovery of novel N-Methylated BSB. This approach led us to identify two promising, cell permeable, N-Methylated peptides that were further evaluated for their BSB properties showing a significant improvement of the fibrillogenesis inhibition with respect to the lead iAβ5p.

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Biography

Dr. Federica Moraca completed her PhD in Pharmaceutical Sciences at the University "Magna Graecia" of Catanzaro (Italy) in 2014, being mostly involved in the discovery of new promising anticancer drugs. During her PhD, she spent one year in the prestigious laboratory of Prof. Michele Parrinello in Lugano, where she learnt about the application of Metadynamics calculations in several molecular systems of biological interest. In 2018, she moved to University "Federico II" in Naples, where she has been involved in the design novel agents addressed to the health improvement.

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