NEW INSIGHTS IN OLIGOPEPTIDASES INHIBITION: MOLECULAR DYNAMICS STUDIES OF SUBSTRATE/INHIBITOR ACCOMMODATION.

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Oligopeptidases are important enzymes in regulating intracellular and extracellular concentration of small peptides, are involved in important physiological processes and it has been an attractive target for drug design due to the critical role in cardiovascular, renal and other disease. In our work X-ray data was combined with modeling, docking and molecular dynamics to study the evolutive conservation of residues that allow the enzyme-substrate/inhibitors contacts in the S2’-S3 positions. Substrates and inhibitors were docked using Autodock 3.0 and obtained complexes were subjected to molecular dynamics using the GROMACS 3.3 package. Rich in proline peptides from 5 to 10 residues with well-defined carboxy-terminal Pro-Pro motif (BPPs) were tested as natural oligopeptidase inhibitors. In the accommodation of the substrate/inhibitor are essential hydrophobic and electrostatic interactions. Substrate/inhibitors are accommodated near the active site by forming a hydrogen bond network with the conserved β-barrel near the catalytic Zn ion. The only selective contacts were detected in S2-S5 positions whereas all the S2’-S1 enzyme-inhibitor contacts were conserved. P1’ position is coordinated by hydrogen bonds. For us is clear that the development of selective oligopeptidase inhibitors with improved pharmacological profile is more feasible based on middle-size carboxy-Pro-Pro peptide-like structures.

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