Molecular modeling and docking of microginin the active site of ACE

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Abstract

Docking studies show a good molecular fit of the MG770 compound in the active site of ACE which corroborates with data from biological inhibiton assays.

Introduction

Microginins, natural producs produced by cyanobacteria, have presented inhibitory activity towards angiotensin converting enzyme (ACE). Such activity indicates that these compounds can be used in the study and in the development of antihypertensive compounds. Nevertheless, the ACE inhibitory activity of these compounds has not been fully elucidated. To evaluate the mechanism of interaction between MG770 and ACE, we performed molecular docking studies. Captopril crystal structure was used in order to validate the molecular docking of MG770 to the ACE structure.

Results and Discussion

To perform the docking studies we have constructed the structure of peptide (MG770). We then ran energy minimization to refine the model (ChemOffice 2004). The crystal structure of human ACE-captopril complex (PDB:2X8Z) was obtained in Protein Data Bank (PDB). Docking studies were performed on the software GOLDv5.0 using the MG770 and ACE structures after validation of the method through captopril redocking. The crystal structure of the ACE presented interactions between the sulfur atom from captopril, and zinc with a distance of 2,1 Å (Figure 1-A). The best docked pose of the peptide have showed the same interactions of captopril in the active site of the ACE. In the docking results it was observed that MG770 presented interactions between zinc and the carbonyl homotyrosine, from microginine, at 1.6 Å (Figure 1-B). These results suggest the correlated interaction between zinc and small molecules, since carbonyl and thiocarbonyl are isosters. On the other hand, the residues Try507 and His337 show hydrogen bonding with captopril and microginine (FIGURE 1).

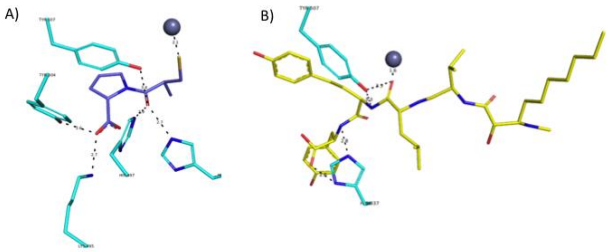

Figure 1. Active site of the ACE and major interactions between: A) captopril co-crystal structure (PDB: 2X8Z); B) Best docked pose of MG770.

In order to analyze the physical chemical properties, the molecular interaction fields (MIFs) were calculated based on the active site of the ACE crystal structurein GRID program v1.2.2 using specific chemical probes (H2O, DRY, C1, C3, N:, N1 and O). The MIFs results suggested that the peptide MG770 present complementary regions to ACE active site.

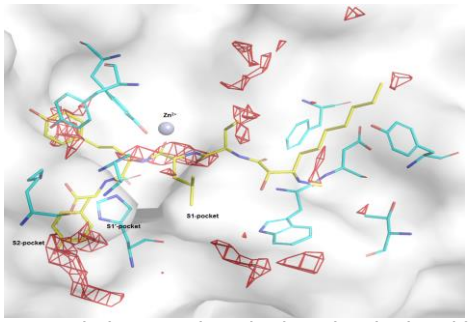

Figura 2. Methyl sp3 carbon (C3) probe depicted in red; MG770 depicted in yellow.

Conclusions

Through the analysis of docking results, we observed significant interactions common to both MG770 and to known ACE. Thus, the molecular docking and analysis of the MIF's, suggested the best pose for possible interactions between MG770 and ACE.

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