Kely Medeiros Turra et al., Med Chem 2014, 4:12
http://dx.doi.org/10.4172/2161-0444.S1.011

OMICS Group Conferences
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3rd International Conference on
Medicinal Chemistry & Computer Aided Drug Designing
December 08-10, 2014 DoubleTree by Hilton Hotel San Francisco Airport, USA

Molecular modeling approach to investigate the binding mode of 4-nerolidylcatechol into two subtypes of matrix metalloproteinases

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Matrix metalloproteinases (MMP) are proteinases involved in the extracellular matrix degradation. MMP-2 and MMP-9 subtypes are over expressed in several human cancer types becoming attractive targets to develop novel anticancer agents. A metabolite from the plant Pothomorphe umbellata, named 4-nerolidylcatechol (4-NC), has showed the ability to inhibit both MMP *in vitro* and in vivo. In this regard, molecular docking (Autodock software) and molecular dynamics simulations (MDS; MOLSIM 3.2 program) were performed in order to investigate the binding mode of 4-NC into MMP-2 and MMP-9. Autodock was used to explore the best binding interactions of 4-NC in the active site of each enzyme. The grid box included the entire binding site of each enzyme and a grid spacing of 0.375 Å was set up (AutoGrid). The zinc ions were parameterized as zinc radius (1.48) and well depth (0.550). Thirty docking runs were performed for each complex. The best binding model was chosen regarding the energy rank position and orientation of ligand in the active site. The best complexes from docking approach were energy-minimized and employed as initial structures to perform a short warming-up MDS sampling scheme and, then, a longer simulation (5 ns) at 310 K. The ligand 4-NC was oriented in the catalytic site by accommodating its side chain in an adjacent pocket (S1') to the catalytic site. The hydroxyl groups were near the zinc atom allowing the coordination. The size of S1' pocket has provided changes in the binding mode of 4-NC in MMP-2 and MMP-9.

Biography

Kely Medeiros Turra is a PhD student at the age of 29 years from University of São Paulo. She works in the computer-aided drug design field, applying molecular modeling and QSAR approaches to develop novel metalloproteinases inhibitors as antitumor agents against melanoma.

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