Computational docking analysis on selective inhibition and binding affinity of synthetic inhibitors towards Matrix Metalloproteinase (MMPs) isoforms

Sudandiradoss C. and Petrek Martin

Palacky University, Czech Republic

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Abstract. The prognostic value of matrix metalloproteinases has been evaluated since many years for its role in tissue remodeling events. The need for selective inhibition of the matrix metalloproteinases is to be of great interest due to the various side effects caused by MMP isoforms. The search for high affinity zinc binding groups that effectively inhibit MMP catalytic site is believed to serve as a template in designing effective inhibitors. In this study, we computationally evaluated the selectivity and binding potential of 16 MMP inhibitors that included tetracycline and its derivatives, doxycycline, minocycline and CMT-3, the hydroxamate derivative marimastat, and corticosteroids retrieved from Drugbank towards the zinc binding catalytic sites of MMP-1, -2, -3, -7, -8, -9, -10, -11, -12, 13 and -16. All docking calculations were carried out using Arguslab 4.0.1 docking software and results were evaluated based on the selectivity, hydrogen bond interactions with the catalytic site residues and zinc chelation ability of the drugs. Our results show the cyclohexane drugs to have an improved selectivity and greater potential to bind at the catalytic site. The corticosteroids show an improved binding affinity and moderate selectivity. The hydroxamate inhibitor marimastat was the only inhibitor observed to form a favorable chelating geometry among the other zinc coordinated drugs. Also atoms like fluorine and chlorine were noted to contribute to selectivity of drugs. These results suggest that a combinatorial design of cyclohexanes analogs bonded to hydroxamic acid with substituted halogens may enhance the selectivity of these drugs both in binding to active site and in metal chelation. Our results further propose the templates and choice of elements in designing multifunctional second generation inhibitors for the targeted inhibition of MMP isoforms.