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How can we design an inhibitor with an enhanced binding affinity that is selective for MMP12 ?

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Nova Southeastern University Honors Protein Modeling

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PDB File: 3LIK (Inhibitor 36 from the original paper)

Primary Citation: Stura, E.A. "3LIK: Human mmp12 in Complex with Non-Zinc Chelating Inhibitor." *RCSB PDB*, 17 July 2019, www.rcsb.org/structure/3LIK.

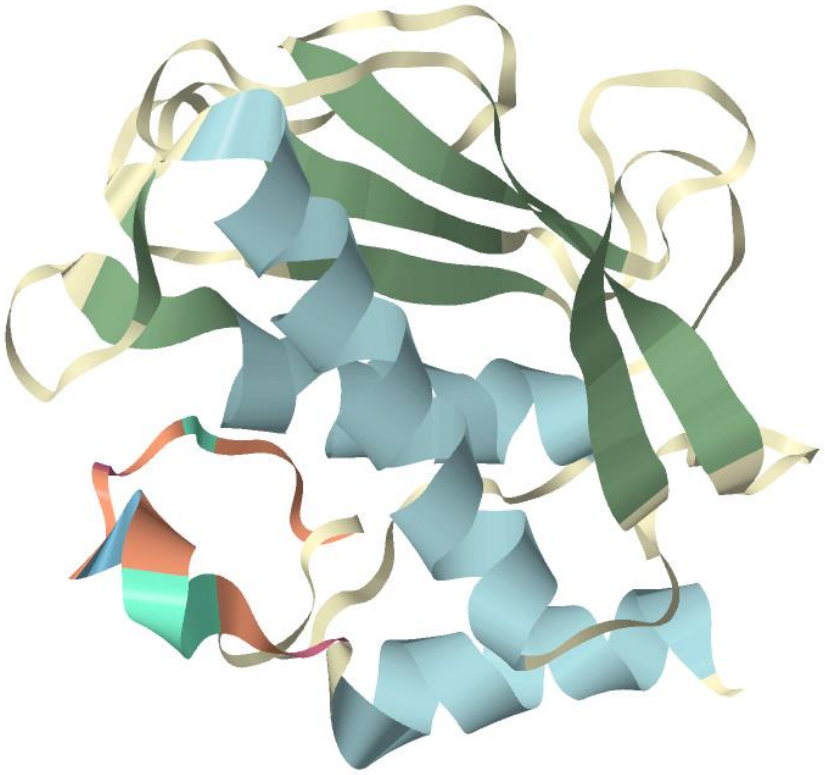
Format: Model based on x-ray diffraction with 1.8 Angstroms

Description:

Matrix metalloproteinase 12 (MMP12) is one of the twenty-three members of the peptidase M10 family which are responsible for the breakdown of the extracellular matrix[3]. MMP12 is a well-studied protease that degrades elastin [1]. In the lungs of smokers, MMP12 digests elastin which acts as a chemokine to recruit a pro-inflammatory immune response. Additionally, MMP12 is a well-studied mediator of arterial stiffening in both acute and chronic settings through the degradation of elastin [2]. This finding makes MMP12 a major therapeutic target in wound healing and scar formation following myocardial infarction. Previous studies have examined ways to selectively inhibit MMP12 to modulate the pro-inflammatory response. An ongoing challenge in creating a clinically useful inhibitor is selectivity. MMP proteins share similar structures and functions therefore, most inhibitors of MMP12 also inhibit other MMP proteins. This has prevented the development of new treatments based on MMP although the evidence does support this as a tool with untapped potential. The protein data bank has an MMP12 protein complexed with the inhibitor called EEG under the code 3LIK[3]. EEG fits into the S1 loop of the protein without disturbing the conformation of the loop conformation. Murine trials were found with corresponding data for another MMP12 inhibitor known as AS111793 which was shown to reduce inflammation associated with cigarette smoke. A series of inhibitors were created using key components of EEG and AS111793. It was found that the hybrid compound created had a higher binding affinity than AS111793, but less affinity than EEG. This may be because a majority of the solvents and elements were removed from the inhibitor which did not allow the docking to occur. The initial goal was to make an inhibitor that has structures that enable it to stick better inside the S1 loop to improve selectivity [3]. We plan to build on this work and modify EEG to create a new inhibitor and test its binding using Py-Rx modeling software.

Specific Model Details: The original paper studied four different models based on four MMP 12 inhibitors. The PDB being used in this research project is 3LIK. It was chosen because it incorporates the inhibitor, EEG, N-{3-[4-(4-phenylthiophen-2-yl)phenyl]propanoyl}-L-alpha-glutamyl-L-alpha-glutamyl-amide.

Model Photo:



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