Structures of Matrix Metalloproteinase - 9 in Complex with Pharmacological Inhibitors

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The matrix metalloproteinases (MMPs) constitute a family of zinc endopeptidases with a metzincin-like catalytic domain [1]. They are involved in tissue remodelling, extracellular matrix degradation and futher biological processes. Under healthy conditions, their proteolytic activity is mainly regulated by the endogeneous tissue inhibitors of metalloproteinases (TIMPs). Disruption of this MMP-TIMP balance results in pathologies such as rheumatoid arthritis and osteoarthritis, atherosclerosis, heart failure, fibrosis, tumor growth and metastasis. MMP-9 is a key enzyme in the pathogenesis of heart failure and cancer [2]. MMP-9 activity could have an impact on the ventricular remodeling following infarction as well as in the blockage of tumor growth. Because the inhibition of MMPs is a promising approach for treatment of those diseases, synthetic MMP-9 inhibitors are developed as potential therapeutic agents for structure-based drug design.

We will describe high resolution crystallographic structures of the mutant (E402->Q) of the catalytic domain of MMP-9 with different synthetic inhibitors. One is based on pyrimidine-2,4,6-trione (RO-206-02222), the second on phosphinic acid (AM-409), the third on propionic acid (R1) and the last one is hydroxamic asid based on (MS-560). All of them possess high affinity towards MMP-9.

[1] Bode W., Maskos K., *Handbook of Metalloproteins,* 2004, **3**, 130-147. [2] Lee P.P.H., Hwang J.J., Murphy G., Ip M.M., *Endocrinology*, 2000, **141**, 3764-3773.

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