

**Crystal Structures of MMP-13 With Non-hydroxamate Inhibitors.** Zhangbao Xu, Junjun Wu, James Wilhem, Karl Malakian, Frank Lovering, Jeremy Levin, Elisabeth Morris, Mark Stahl, Lidia Mosyak, Will Somers. Chemical and Screening Sciences, Structural Biology and Computational Chemistry, WYETH, 85 Bolton St., Cambridge, MA 02140.

Matrix metalloprotease-13 (MMP-13, collagenase-3) is responsible for the breakdown of cartilage. Over expression of MMP-13 within articular cartilage results in the increased incidence of osteoarthritis, the inhibition of MMP-13 should slow the onset of the disease. Our discovery team is searching for non-hydroxamate inhibitors of MMP-13. The co-crystal structures of MMP-13 with compounds **106** and **107** (Figure 1) were solved and the structural information was then used to design significantly more selective inhibitors. The complex of MMP-13 with compound **106** crystallized in the orthorhombic space group P212121 with cell dimensions  $a=51.75 \text{ \AA}$ ,  $b=53.12 \text{ \AA}$ ,  $c=58.43 \text{ \AA}$ . The structure was determined at  $1.70 \text{ \AA}$  resolution. The R-value of the final model was 0.158 ( $R_{\text{free}}=0.182$ ). The complex of MMP-13 with compound **107** crystallized in the space group P21 with cell dimensions  $a=35.94 \text{ \AA}$ ,  $b=135.25 \text{ \AA}$ ,  $c=69.38 \text{ \AA}$ ,  $\beta=104.95^\circ$ . The structure was determined and refined at  $2.0 \text{ \AA}$  resolution. The R-factor of the final model was 0.201 ( $R_{\text{free}}=0.238$ ). In the MMP-13 complexes, the catalytic zinc is coordinated with nitrogen atoms from three histidines (His197, His201, and His207) of the protein and two oxygen atoms from the carboxylate group of the inhibitors. Also conserved waters have been identified in the binding pocket. The knowledge of conformation of the flexible loops and the side chains bound to the inhibitors will provide a molecular basis for the design of more potent and selective MMP-13 inhibitors.

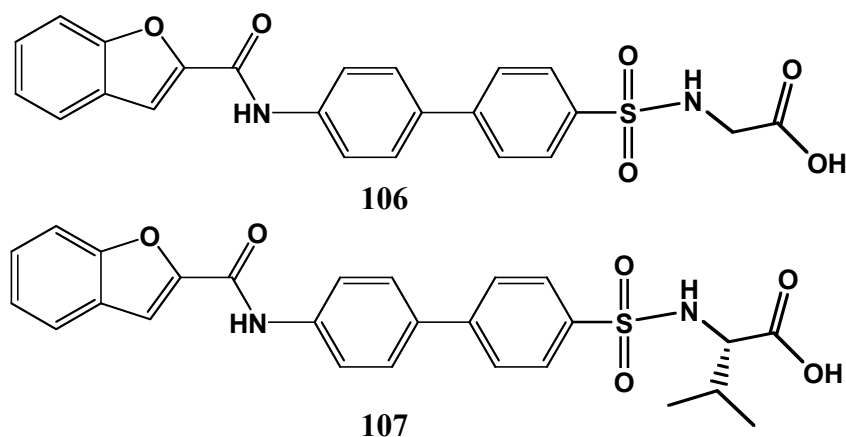


Figure 1