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The x-ray crystal structure of microplasmin with a small-molecular active site inhibitor PSI-112

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Plasmin (Plm) is the active form of the zymogen plasminogen (Plg), a serine protease which plays a key role in the fibrinolytic system and several other physiological activities. Physiologically, Plg/Plm activity is regulated by specific inhibitors and activators, making it an attractive therapeutic target for both traumatic bleeding and thrombotic diseases. Here we report the first crystal structure of microplasmin (the catalytic domain of Plm) in complex with a small-molecular active site inhibitor PSI-112 which is highly specific for Plm with IC50 of 0.22 µM. The crystal structure has been determined to 1.62Å, and the inhibitor binds to the substrate binding pocket with extensive additional subsite interactions. This structure may be helpful in developing a more Plm specific inhibitor as a new anti-fibrinolytic agent used to reduce bleeding complications in cardiac surgery or liver transplantation.

Keywords

plasmin; serine protease; inhibitor; therapeutic; crystal structure

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