

MS5-P5 Identification of inhibitors for the DEDDh family of exonucleases and a unique inhibition mechanism revealed by crystal structure analysis of CRN-4 bound with MES

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ABSTRACT The DEDDh exonuclease family contains more than 7000 members which play essential roles in nucleic acids metabolism in prokaryotes and eukaryotes. Recently, some DEDDh exonucleases proved to have important functions in viral infection and replication, such as NP exonuclease of Lassa fever virus (LV NP), can serve as antiviral drug targets. However, there is no systematic characterization of inhibitors for the DEDDh exonucleases. Here, we used two DEDDh exonucleases, RNase T and CRN-4, as model systems to identify potential DEDDh exonucleases inhibitors, including PV6R, PCMPS, DTNB and ATA. IC50 value analysis have shown PCMPS, DTNB and ATA, can inhibit the exonuclease activity of LV NP efficiently. Moreover, we determined the crystal structure of CRN-4 in complex with a weak inhibitor, 2-morpholin-4-ylethanesulfonate acid (MES). MES induces a conformational change in the active site of CRN-4, preventing substrate degradation. Combining structural information and molecular docking of inhibitors in CRN-4 help us to identify important inhibitor-binding residues and provide clues to design more effective inhibitors for DEDDh exonucleases. Taken together, both biochemical and structural studies on potential inhibitors of the DEDDh exonucleases are helpful for antiviral therapy.

Keywords: Nuclease, Inhibitors, Protein-inhibitor complex, crystal structure, nuclease inhibitor, antiviral drug.

MS5-P6 Industrial integration at the French national synchrotron facility SOLEIL

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Synchrotron SOLEIL is a French national synchrotron facility, located on the Saclay Plateau in the Paris suburbs. It is a multi-disciplinary instrument and a research laboratory, with the mission to provide research programs, to develop state-of-the-art instrumentations targeted to specific experiments, and to make those available to the scientific community. SOLEIL differentiates itself from other complementary synchrotron facilities as a unique tool for performing both academic research and industrial applications developed on site and across a wide range of disciplines among which physics, biology, and chemistry. Based on a state-of-the-art synchrotron source, both in terms of brilliance and stability, SOLEIL is used by over 5,000 researchers coming from France and abroad.

Industrial applications at SOLEIL have recently been reinforced by the opening of an industrial laboratory specialised in structural biology within SOLEIL, working in the vicinity of the biology village and macromolecular crystallography *PROXIMA* beamlines. Both *PROXIMA-1* and *PROXIMA-2A* end-stations provide with the required instrumentation for high-throughput diffraction measurements on crystallographic samples. The presence of a structural biology unit from the industrial group SERVIER (LBS3) laboratory in close proximity to these instruments offers to SOLEIL's industrial collaborators both rapid access beam time and on site expertise. This proximity allows industrial applications to develop fast and practical solutions to redundant problems in sample preparation for structural studies, reduce their product-to-market downtimes and enhance their R&D programmes.

Keywords: industry, drug design,