

Harnessing the evolvability of tricyclic microviridins to dissect protease-inhibitor interactions.

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Abstract

Understanding and controlling proteolysis is an important goal in therapeutic chemistry. Among the natural products specifically inhibiting proteases microviridins are particularly noteworthy. Microviridins are ribosomally produced and posttranslationally modified peptides that are processed into a unique, cage-like architecture. Here, we report a combined rational and random mutagenesis approach that provides fundamental insights into selectivity-conferring moieties of microviridins. The potent variant microviridin J was co-crystallized with trypsin, and for the first time the three-dimensional structure of microviridins was determined and the mode of inhibition revealed.

Beteiligte Forschungseinheiten

[Biomolekulare Chemie](#) [Christian Hertweck](#) [Mehr erfahren](#)

Leibniz-HKI-Autor*innen



Christian Hertweck

[Details](#)



Keishi Ishida

[Details](#)



Florian Meyer

[Details](#)

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