

Publication

1PSI: Intact recombined alpha1-antitrypsin mutant PHE 51 to LEU

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4531099

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Year 1996

Title 1PSI: Intact recombined alpha1-antitrypsin mutant PHE 51 to LEU

Journal Worldwide Protein Data Bank

Pages / Article-Number 1PSI

Keywords serine protease inhibitor

Mesh terms Science & TechnologyLife Sciences & BiomedicineBiochemistry & Molecular BiologyBiochemistry & Molecular Biology

The reactive site loop of the serpin family of serine proteinase inhibitors is flexible and can adopt a number of diverse conformations. A 2.9 Å resolution structure of alpha 1-antitrypsin—the principal proteinase inhibitor in human plasma—shows the loop in a stable canonical conformation matching that found in all other families of serine proteinase inhibitors. This unexpected finding in the absence of loop insertion into the body of the molecule favours a two-stage mechanism of inhibition and provides a model for the heparin activation of antithrombin. The beta-pleated strand conformation of the loop also accounts for the polymerization of the serpins in disease and for their association with other beta-sheet structures, most notably the beta-amyloid of Alzheimer's disease.

edoc-URL <https://edoc.unibas.ch/76002/>

Full Text on edoc No;

Digital Object Identifier DOI 10.2210/pdb1psi/pdb

ISI-Number 2012136001729276

Document type (ISI) Data set