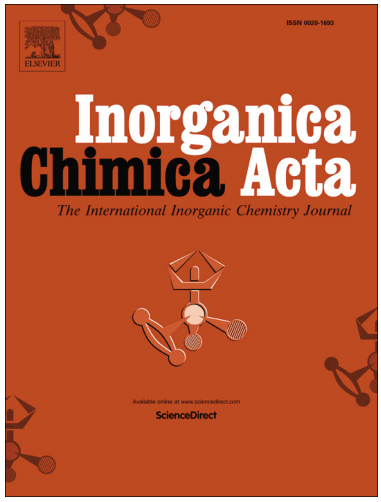

Research paper

Boric acid and acetate anion binding to subclass B3 metallo-β-lactamase BJP-1 provides clues for mechanism of action and inhibitor design

Flavio Di Pisa, Cecilia Pozzi, Manuela Benvenuti, Jean-Denis Docquier, Filomena De Luca, Stefano Mangani

PII: S0020-1693(17)30558-3
DOI: http://dx.doi.org/10.1016/j.ica.2017.07.030
Reference: ICA 17753

To appear in: *Inorganica Chimica Acta*

Received Date: 10 April 2017
Revised Date: 11 July 2017
Accepted Date: 12 July 2017

Please cite this article as: F. Di Pisa, C. Pozzi, M. Benvenuti, J-D. Docquier, F. De Luca, S. Mangani, Boric acid and acetate anion binding to subclass B3 metallo-β-lactamase BJP-1 provides clues for mechanism of action and inhibitor design, *Inorganica Chimica Acta* (2017), doi: http://dx.doi.org/10.1016/j.ica.2017.07.030

Boric acid and acetate anion binding to subclass B3 metallo-β-lactamase BJP-1 provides clues for mechanism of action and inhibitor design.

Authors: Flavio Di Pisa[a], Cecilia Pozzi[a], Manuela Benvenuti[a], Jean-Denis Docquier[b], Filomena De Luca[b] and Stefano Mangani[a,c]

[a] Department of Biotechnology, Chemistry and Pharmacy, University of Siena, 53100 Siena, Italy;

[b] Department of Medical Biotechnology, University of Siena, 53100, Italy;

[c] Magnetic Resonance Center CERM, University of Florence, 50019 Sesto Fiorentino (Fi), Italy.

Abstract

Microbial infections represent a major risk to human health. In this respect, β-lactam antibiotics constitute a key therapeutic resource against such infections. However, we are facing increasing microbial resistance to antibiotic treatment and particularly worrisome is the emergence of resistant bacterial strains towards β-lactam antibiotics that can rapidly disseminate worldwide. β-lactamase enzymes are the main determinant of bacterial resistance and among them metallo-β-lactamases (MBLs) are most threatening, as exemplified by the recent resistance outbreaks due to New Delhi β-lactamase 1 (NDM-1) producing bacteria. MBLs are mono or di-zinc enzymes able to inactivate clinically important β-lactam antibiotics including carbapenems, which are used as a last resort therapy in severe infections. Under this scenery, the discovery of new potent inhibitors of MBLs becomes an urgent need and X-ray crystallography of MBLs in complex with small molecule inhibitors provides the possibility to accelerate the process of drug discovery. We present here the atomic-resolution crystal structures of BJP-1, a di-zinc MBL, in complex with two small molecules and their comparison with other MBL complexes with inhibitors. These structural data, besides providing hints about the mechanism of di-zinc MBLs, might be the starting point for a fragment-based lead-discovery program.