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#### 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

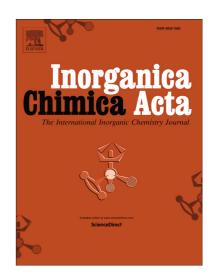
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## **ACCEPTED MANUSCRIPT**

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

Authors: Flavio Di Pisa<sup>a</sup>, Cecilia Pozzi<sup>a</sup>, Manuela Benvenuti<sup>a</sup>, Jean-Denis Docquier<sup>b</sup>, Filomena De Luca<sup>b</sup> and Stefano Mangani<sup>a,c</sup>

#### **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  $\beta$ -lactam antibiotics that can rapidly disseminate worldwide.  $\beta$ lactamase enzymes are the main determinant of bacterial resistance and among them metallo-βlactamases (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 fragmentbased lead-discovery program.

<sup>&</sup>lt;sup>a</sup> Department of Biotechnology, Chemistry and Pharmacy, University of Siena, 53100 Siena, Italy;

<sup>&</sup>lt;sup>b</sup> Department of Medical Biotechnology, University of Siena, 53100, Italy;

<sup>&</sup>lt;sup>c</sup> Magnetic Resonance Center CERM, University of Florence, 50019 Sesto Fiorentino (Fi), Italy.

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