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

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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.

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