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Biochemical characterization of CTX-M-15 from Enterobacter cloacae and designing a novel non-β-lactam-β-lactamase inhibitor

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The worldwide dissemination of CTX-M type β-lactamases is a threat to human health. Previously, we have reported the spread of $bla_{CTX-M-15}$ gene in different clinical strains of Enterobacteriaceae from the hospital settings of Aligarh in north India. In view of the varying resistance pattern against cephalosporins and other β-lactam antibiotics, we intended to understand the correlation between MICs and catalytic activity of CTX-M-15. In this study, steady-state kinetic parameters and MICs were determined on *E. coli* DH5α transformed with blaCTX-M-15 gene that was cloned from *Enterobacter cloacae* (EC-15) strain of clinical background. The effect of conventional β-lactamase inhibitors (clavulanic acid, sulbactam and tazobactam) on CTX-M-15 was also studied. We have found that tazobactam is the best among these inhibitors against CTX-M-15. The inhibition characteristic of tazobactam is defined by its very low IC_{50} value (6 nM), high affinity (K_i=0.017 μM) and better acylation efficiency (k_{+2}/K9=0.44 $\mu M^{-1}s^{-1}$). It forms an acyl-enzyme covalent complex, which is quite stable (k+3=0.0057 s-1). Since increasing resistance has been reported against conventional β -lactam antibiotic-inhibitor combinations, we aspire to design a non-β-lactam core containing β-lactamase inhibitor. For this, we screened ZINC database and performed molecular docking to identify a potential non-β-lactam based inhibitor (ZINC03787097). The MICs of cephalosporin antibiotics in combination with this inhibitor gave promising results. Steady-state kinetics and molecular docking studies showed that ZINC03787097 is a reversible inhibitor which binds non-covalently to the active site of the enzyme through hydrogen bonds and hydrophobic interactions. Though, it's IC_{50} (180 nM) is much higher than tazobactam, it has good affinity for CTX-M-15 (Ki=0.388 μM). This study concludes that ZINC03787097 compound can be used as seed molecule to design more efficient non-b-lactam containing β -lactamase inhibitor that could evade pre-existing bacterial resistance mechanisms.

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