Arbab Khan et al., J Bacteriol Parasitol 2014, 5:4
http://dx.doi.org/10.4172/2155-9597.S1.008

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Congress on
Bacteriology & Infectious Diseases
November 17-19, 2014 DoubleTree by Hilton Hotel Chicago-North Shore, USA

Evaluation of inhibitory action of novel non β-lactam inhibitor against *Klebsiella pneumoniae* carbapenemase (KPC-2)

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The use of three classical β-lactamase inhibitors (Clavulanic acid, tazobactam and sulbactam) in combination with β-lactam antibiotics is presently the mainstay of antibiotic therapy against Gram-negative bacterial infections. However these inhibitors are unable to inhibit carbapenemase KPC-2 effectively. They being β-lactam derivatives behave as substrates for this enzyme instead of inactivating it. We have initiated our study to check the in vitro inhibition activity of the two novel screened inhibitors (ZINC01807204 and ZINC02318494) in combination with carbapenems against KPC-2 expressing bacterial strain and their effect on purified enzyme KPC-2. The MIC values of meropenem and ertapenem showed maximum reduction (8 folds) in combination with screened compounds (ZINC01807204 and ZINC02318494). CLSM images also depicted their strong antibacterial activity in comparison to conventional β-lactamase inhibitors. Moreover no toxic effect has been shown on HeLa cell line. Though the IC_{50} value of ZINC01807204 was high (200 μM), it exhibited fairly good affinity for KPC-2 (K_i=43.82 μM). With promising results this study identifies ZINC01807204 as a lead molecule for further optimization and development of more potent non β-lactam inhibitors against KPC-2.

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