Development of Novel Inhibitors of New Delhi Metallo-beta-lactamase-1 (NDM-1)

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Technology description

Researchers at UC San Diego have successfully designed and synthesized a new class of inhibitors for New Delhi Metallo-betalactamase-1 (NDM-1) and two related beta-lactamases. They exhibit remarkable selectivity as they don’ t hit other Zn(II) metalloenzymes. The inhibitors restored susceptibility to imipenem in three differentE.colistrains, including a clinical isolate expressing blaNDM-1.

Antibiotic-resistance in pathogenic bacteria has become a critical public health threat. A major mechanism of antibiotic resistance is microbial degradation of drugs by enzymes such as β-lactamases which degrade the β-lactam ring of β-lactam antibiotics, namely penicillins, cephalosporins, carbapenems and monobactams, inactivating them. There are four different molecular classes of β-lactamases (A-D). Three classes of β-lactamases (A, C, and D) utilize an active-site serine in covalent mechanisms that can be targeted by β-lactamase inhibitors coformulated with β-lactam drugs. In contrast, class B consists of metallo-β- lactamases (MBLs) that utilize one or two active site Zn(II) ion(s) to catalyze the hydrolysis of the β-lactam ring.The emergence of carbapenemase producing bacteria, especially New Delhi metallo-β-lactamase (NDM-1) and its variants, worldwide, has raised a major public health concern. NDM-1 hydrolyzes a wide range of β-lactam antibiotics, imipenem, meropenem, ertapenem, gentamicin, amikacin, tobramycin, and ciprofloxacin including carbapenems, which are the last resort of antibiotics for the treatment of infections caused by multidrug-resistant bacteria such as carbanenem-resistant Enterobacteriacae and Klebsiella pneumoniae. Currently, there are Inhibitors of NDM-1, both of which have liabilities, either due to adverse effects in mammals or off-target inhibitory activity. Therefore, a new type of NDM-1 inhibitor is needed.

Related Materials

Allie Y. Chen, Pei W. Thomas, Alesha C. Stewart, Alexander Bergstrom, Zishuo Cheng, Callie Miller,Christopher R. Bethel, Steven H. Marshall, Cy V. Credille, Christopher L. Riley, Richard C. Page, Robert A. Bonomo, Michael W. Crowder, David L. Tierney, Walter Fast, and Seth M. Cohen. Dipicolinic Acid Derivatives as Inhibitors of New Delhi Metallo-ß- lactamase 1. J. Med. Chem. 2017

Application area

The new inhibitors for NDM-1 are targeted toward the very pathogenic multidrug-resistant bacteria such as carbapenem-resistant Enterobacteriacae and Klebsiella pneumoniae.

Advantages

This invention represents a major discovery because there are currently no approved drugs to block NDM-1. These discoveries could lead to development of new therapeutics to treat these highly pathogenic and resistant bacteria.

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