Sulfonyl Indoline Inhibitors of NDM-1 as an Antibiotic Adjuvant

A Novel Beta-Lactamase Inhibitor

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Field
Medicinal Chemistry

Technology
Antimicrobials/Inhibitors of NDM-1

Key Features
- Novel mechanism inhibiting two zincs
- Broad utility
- Resensitizes bacteria to antibiotics

Key Benefits
- Novel structures
- May overcome antimicrobial resistance
- Multiple derivatives available

Stage of Development
In vitro data

Status
Seeking licensing partner

Patent Status
Provisional Patent

Sulfonyl Indoline Inhibitors of NDM-1

Antimicrobial resistance (AMR) is a major, growing health and economic problem worldwide for humans and animals alike, and the emergence of plasmid-borne resistance to last-resort antibiotics illustrates the pressing need for new antimicrobial drugs. One way to tackle AMR is to develop inhibitors of the resistance-conferring genes.

One resistance gene of immediate concern is New Delhi metallo-β-lactamase-1. NDM-1 was discovered in India in 2008 and has since spread around the world. It is a carbapenemase that confers resistance to a broad range of β-lactam antibiotics (penicillins, cephalosporins, and carbapenems), but, unlike other β-lactamases, it is not inhibited by clavulanic acid, the adjuvant in Augmentin®.

Researchers at Loyola have synthesized and characterized novel compounds that inhibit NDM-1. Experiments suggest that the efficacy of these compounds results from their bridging the two active site zinc ions of NDM-1. *In vitro* IC_{50} values for these compounds are 1 to 10 µM.

Market

With the World Health Organization's recent report that called AMR a global health crisis, the FDA, the EMA (Europe's FDA), Infectious Diseases Society of America, and several others have stepped in to address the issue of industry interest and lobbied to provide market incentives. A few years ago, the GAIN act was signed into law to incentivize new drug development. Drugs that fall under the GAIN provisions receive fast track status and enjoy an added five years of market exclusivity. These changes and the greater demand for more effective drugs have added to the recent upsurge in the antibiotic market. According to a 2012 report by Transparency Market Research, the demand for antibiotics is expected to reach $44.68 B by 2016. Peak sales for Augmentin® were over $1 billion annually before it went off patent.

Opportunity

Loyola University Chicago is looking for commercial research and development partners for this technology and line of research.

Inventors

Daniel P. Becker, Ph.D.
Dr. Becker received his Bachelor's degree in Chemistry from Kalamazoo College and his Ph.D. in Organic Chemistry from Indiana University, and he is presently a tenured member of the faculty as an Associate Professor of Chemistry at Loyola University in Chicago. His academic research encompasses both medicinal chemistry toward the design of novel enzyme inhibitors, and supramolecular chemistry in the construction of new supramolecular scaffolds for host-guest chemistry and analytical detection. Dr. Becker previously served as a Project Team Leader and Research Fellow in the Department of Medicinal Chemistry with Searle Pharmaceuticals and Pharmacia for seventeen years before moving to academia. He has authored over thirty publications in medicinal chemistry and synthetic organic methodology and has been awarded forty-seven U.S. patents for new

pharmaceuticals in the areas of gastrointestinal diseases, cancer, arthritis and cardiovascular disease, and new synthetic organic methods.

Walter Fast, Ph.D.
Dr. Fast is currently an Associate Professor and William I. Dismukes Fellow in Pharmacy in the Division of Chemical Biology & Medicinal Chemistry at the College of Pharmacy, University of Texas at Austin. Professor Fast received his B.S. in Chemistry in 1992 from Wheaton College (Wheaton, IL), started graduate studies in Biochemistry at Brandeis University and completed his Ph.D. at Northwestern University in 1998, studying mechanism-based enzyme inactivators. In 2002, he completed his NIH postdoctoral fellowship at Pennsylvania State University, was awarded an NIH Career Transition Award and started as Assistant Professor at the University of Texas, followed by tenure and promotion as Associate Professor in 2008, and pending Regents' approval, promotion to full Professor effective September 2016. His research interests include the chemistry of enzymes and inhibitors relating to bacterial quorum-sensing, antibiotic resistance, and nitric oxide regulation in cancer and cardiovascular / pulmonary disorders. His work is currently supported by grants from the NIH, NSF, and the Robert A. Welch Foundation.