Indoline Sulfonamide Inhibitors of DapE as an Antibiotic

A Non Strain-Specific Antimicrobial Compound

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Field
Medicinal Chemistry

Technology
Antimicrobials/Inhibitors of DapE

Key Features
- Not thiol dependent
- Non strain-specific
- Allows for combination usage

Key Benefits
- Not prone to oxidation
- May overcome antimicrobial resistance
- Many routes of administration

Stage of Development
In vitro data

Status
Seeking licensing partner

Patent Status
Provisional Patent

Indoline Sulfonamide Inhibitors of DapE

Antimicrobial resistance (AMR) is a major, growing health and economic problem worldwide for humans and animals alike. Researchers at Loyola have synthesized and characterized novel compounds that specifically target N-succinyl-L,L-diaminopimelic acid desuccinylase (DapE), an enzyme that is required for cell wall synthesis. The claimed compounds will be toxic to bacteria by blocking the action of this vital enzyme. Inhibiting cell wall synthesis with these small molecules is a new approach that has the potential to overcome AMR in an array of disease causing bacteria. Broad spectrum effectiveness widens the possibilities for clinical applications of these new antibiotics. An additional advantage over many currently available antimicrobials is that these DapE inhibitors can be used in combination with additional therapeutic agents and can be administered via many different routes. Until now, undesirable oxidation has been a stumbling block for thiol-containing DapE inhibitors but these newly synthesized compounds are non-thiol inhibitors, thus avoiding that problem. In addition, drug toxicity should be of diminished concern since mammals have no comparable enzymatic pathway.

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.[1]

Opportunity

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

Inventors

Daniel P. Becker
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 forty-seven publications in medicinal chemistry and synthetic organic methodology and has been awarded forty-nine U.S. patents for new pharmaceuticals in the areas of gastrointestinal diseases, cancer, arthritis and cardiovascular disease, and new synthetic organic methods.

[1] http://www.transparencymarketresearch.com/antibiotic-market.html

Richard C. Holz

Dr. Holz is Professor and Dean, Helen Way Klingler College of Arts & Sciences, at Marquette University in Milwaukee, Wisconsin. Dr. Holz received a B.S. degree in Chemistry from Bemidji State University with minors in biology and mathematics, an M.S. degree in Chemistry from the University of Minnesota-Duluth, and a Ph.D. in Chemistry from The Pennsylvania State University under the direction of Dr. William DeW. Horrocks, Jr. He was an NIH Postdoctoral Research Fellow at the University of Minnesota under the direction of Dr. Larry Que who is the 3M/Alumni Distinguished Professor of Chemistry. He subsequently joined the faculty at Utah State University before moving to Loyola University Chicago as the Chair of the Chemistry Department, and finally moving to Marquette. Dr. Holz's research group is interested in structure/function studies of metalloenzymes some of which are antimicrobial targets. Within these studies, the Holz group uses a wide variety of biochemical and biophysical methods such as enzyme kinetics, site-directed mutagenesis, isothermal titration calorimetry, UV-Vis, NMR and EPR spectroscopies. Current projects in the Holz group center on an NSF-sponsored project to study the catalytic mechanism of nitrile hydratases (NHases) and an NIH-sponsored project to study the zinc dependent dapE-encoded desuccinylase from Haemophilus influenzae (DapE). Dr. Holz is a member of the American Chemical Society and the Society of Biological Inorganic Chemistry. He has contributed to more than 90 research articles and is co-inventor on two patents.