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# Medicinal Chemistry 2019: Design and Synthesis of DapE Inhibitors as Potential Antibiotics with a New Mechanism of Action: Scientific Opinion-Daniel P. Becker-University of Tripoli

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**Introduction:**

There is an urgent need for antibacterial agents with new cellular mechanisms of action, and the bacterial enzyme N-succinyl-L,L-diaminopimelic acid desuccinylase (DapE) offers an excellent target for the eventual development of new antibiotics. DapE is in the succinylase pathway, which is the primary biosynthetic pathway for producing meso-diaminopimelate (m-DAP) and lysine in all Gram-negative and most Gram-positive bacteria, and is not expressed in mammals, making it a very important bacterial enzyme to study. X-ray crystallography of the DapE enzyme in the presence of our inhibitors has resulted in an atomic resolution (1.3Å) structure. Structural insights from X-ray crystallography have been coupled with molecular dynamics (MD) experiments using NAMD to explore the mechanism of the dramatic enzyme conformational changes that result in substrate binding by DapE and product release, and also using our Products-Based Transition-State Modeling (PBTSM) protocol, as we have recently described. Synthesis of analogs that we have identified from a high-throughput screen including tetrazoles and pyrazoles as well as 6- and 7-indoline sulfonamides will be described, with efforts that have been guided by docking using MOE. Synthetic efforts include methodology to access 7-substituted indolines that have previously eluded synthesis. We will also describe acyl sulfonamides prepared through Click chemistry that have the capacity to interact with both zinc atoms in dimetalloenzymes. DapE enzyme inhibitory potency has been assessed using our recently validated ninhydrin-based assay (Scheme 1) employing N-methyl-L,L-SDAP (succinyl diaminopimelate), synthesized on a large scale via an asymmetric synthesis, as will also be described. The perils of antimicrobial drug resistance are often overcome by finding novel antibiotic targets and corresponding small molecule inhibitors. Microbial enzyme DapE may be a promising antibiotic target thanks to its importance to the bacterial survival. The potency of L-Captopril, a well-known angiotensin-converting enzyme inhibitor, as an inhibitor of DapE enzyme has been evaluated by analyzing its binding modes and binding affinity towards DapE enzyme. L-Captopril is found to bind the metal centers of DapE enzyme either via its etiolate group or through its carboxylate group. While the latter binding mode is found to be thermodynamically favorable, the former binding mode, also seen in the crystal structure, is kinetically favored. To optimize the binding affinity of the inhibitor towards DapE enzyme, a series of L-Captopril-based inhibitors are modeled by changing the side groups of L-Captopril. The introduction of a bipolar functional group at the C4 position of the pyrrolidine ring of L-Captopril and therefore the substitution of the thiol group with a carboxylate group, have been shown to supply excellent enzyme affinity that supersedes the binding affinity of DapE enzyme towards its natural substrate, thus making this molecule a possible inhibitor with great promise. Antibiotic resistance affects quite one or a couple of patients: the worldwide accumulation of resistant bacteria threatens everyone's health. Once a problem associated only with the sickest patients in intensive-care wards, antibiotic-resistant bacteria have become widespread in communities throughout the world. Resistance genes aren't distributed randomly in bacterial populations but are commonly clustered in multiple-drug-resistant strains with resistance spread together. The frequency of international travel, combined with the shortage of worldwide standards of antibiotic use, exacerbates the matter. The result's an acceleration of the spread of resistance round the globe and in every environment. All stakeholders recognize that the present antibiotic-resistance crisis is related to a predictable, inexorable loss of efficacy of our current antimicrobial arsenal, but substantial economic, regulatory, and scientific barriers to the event of latest antimicrobial agents and therapies persist. The goal of the workshop was to spot novel approaches to the event of antimicrobial therapeutics. However,

Workshop discussions made it clear that even the foremost innovative antibiotics are going to be made obsolete, at some point, by the inevitable emergence of resistance. Therefore, the committee concluded that it's worthwhile to spot research that might help to surmount the matter of resistance or a minimum of slow its emergence. The recommendations during this section, although they are doing not lead on to the event of novel antibiotics, might be important in increasing the useful lifespan of current and future antibiotics. Synthetic antibiotics, like the fluoroquinolones, would seem to be less vulnerable to causing resistance, as long as bacteria wouldn't have had millennia of exposure to them. Thus, evolved mechanisms of resistance would be less likely to exist.

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However, ubiquitous and promiscuous efflux systems have evolved to guard microorganisms from diverse toxic small molecules of natural origin, and these systems often provide cross-protection against such non-natural products. As a result, genes that encode resistance elements are embedded within the genomes of virtually all bacteria; these hard-wired resistance genes are inherited in vertical fashion, providing continuous protection against toxic agents in a bacterial species even in the absence of prior exposure. Regulatory T (Treg) cells are essential for preventing autoimmunity and controlling immune homeostasis. They have a remarkable ability to control many different types of immune cells, but it has been difficult to delineate exactly how they mediate these effects in any given tissue context, likely because of overlapping and redundant suppressive mechanisms. An additional consideration is that the vast majority of research into Treg mechanisms to date has focused on their systemic relevance; whether or not unique mechanisms may be at play in disease- or tissue-specific contexts has not been explored. This is particularly true for human Treg cells, where compelling evidence for functionally relevant mechanisms is restricted to the inhibitory co-receptor CTLA-4HPGD, which catabolizes the prostaglandin PGE2 into 15-keto-PGE2, has been studied in the context of reproduction, cancer, and tissue injury but never in the context of adaptive immune cells. To investigate whether expression of HPGD was important for Treg cells, the authors carried out classical in vitro suppression assays with or without addition of the substrate PGE2. Remarkably, human Treg cells were more suppressive in the presence of added PGE2, an effect that was contact-independent and could not be mimicked by simply adding PGE2 to Tconv cells. Using liquid chromatography and mass spectrometry, the authors detected elevated levels of 15-keto-PGE2 in supernatants from Tregcellscultured.

**Biography**

Daniel Becker earned his PhD at Indiana University in Bloomington, Indiana and worked in the pharmaceutical industry in Searle, Pharmacia, and then Pfizer as a Project Leader and Research Fellow developing new treatments for cancer, arthritis, and cardiovascular diseases. He moved from industry to join Loyola University Chicago in 2004 where he serves as a full Professor of Chemistry performing research in synthetic organic and medicinal chemistry, especially in the discovery of new antibiotics and treatments for cancer, as well as in supramolecular chemistry. He has published more than 50 scientific papers in various areas of chemistry and is an inventor on over 50 U.S. patents Conferences on Drug Discovery and Therapy in Dubai, UAE in 2012, 2013 and 2014, and made presentations on low density lipoprotein-cholesterol, cholesterol and diet ,and serum lipid patterns in type 2 diabetes mellitus. Also plenary speaker, (Effects of Dietary Plant Polyunsaturated.

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