Small Molecule Lipid II Inhibitors

Technology Summary

Drug resistance in microorganisms is an urgent and growing concern as more and more microorganisms are found with resistance to commonly used treatments. For bacterial infections alone, approximately 2 million people are infected a year and 23,000 deaths can be directly correlated to drug-resistant bacteria (CDC). There is an urgent need for the development of novel antibiotics to address drug-resistant bacterial infections. A common target of existing antibiotics is Lipid II, an essential precursor for bacterial wall biosynthesis and the target of four different classes of antibiotics, including vancomycin. Currently no synthetic compound(s) exist that interferes with Lipid II and vancomycin and derivatives telavancin and dalbavancin are not active against gram-negative pathogens such as *Acinetobacter baumanii.* This invention is the novel compound BAS00127538 and its analogs for the inhibition of Lipid II. BAS00127538 has shown successful demonstrations against methicillin and vancomycin resistant staphylococcus aureus (MRSA and VRSA); as well as, showing activity against clinical isolates of *Acinetobacter baumannii* (Table 1) and in murine models of infection against S. aureus. BAS00127538 has the potential for a broad application due to its activity against both gram-positive and gram-negative pathogens.

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Field
Anti-infective

Technology
Small Molecule Inhibitors

Advantages
Novel synthetic compound
Active against gram-negative and gram-positive bacteria

Status
Available for licensing
Available for sponsored research

Patent Status
US 16/064,276
EP 16 879 970.8

UMB Docket Reference
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External Reference
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Market

The global antibiotic market generated sales of $42 billion (46% of the global anti-infective market, which includes antiviral drugs and vaccines) in 2009. The two foremost factors that play a significant role in the growth of industry are the continuing worldwide growth of antibiotic resistance, especially among potentially life-threatening pathogens, and generic competition. The Center of Disease Control and Prevention (CDC) listed 18 drug-resistant threats to the United States with clostridium difficile, carbapenem-resistant enterobacteriaceae (CRE), and neisseria gonorrhoeae listed as urgent threats. In March of 2015, an Executive Order was released providing a National Action Plan to address the challenges of antibiotic-resistance over the course of five years to enhance domestic and international capabilities to address antibiotic resistance. Federal investments nearly doubled to more than $1.2 billion. Key players present in the industry include Abbott Laboratories, Daiichii Sankyo Company. Limited, Bayer Health Care, Astellas Pharma, Roche, Bristol-Myers Squibb Co., Cubist Pharmaceuticals, Inc., GlaxoSmithKline Plc, Pliva d.dd, Toyama Chemica Co. Ltd., Takeda Pharmaceutical Company. Ltd, Johnson & Johnson, LG Life Sciences Limited. Inc and Eli Lilly and Co.

Table 1

		MIC (µg/ml)			Synergy (Σ FIC)
Organism:	MMX#-ATCC#	BAS00127538	Colistin	Vancomycin	Colistin/BAS 00127538
Acinetobacter baumanii	19606	2	<0.5	>256	0.15≤0.5
Acinetobacter baumanii (n=12)	clinical isolates	2 to 8	<0.5-2	>256	0.15≤0.5
Staphylococcus aureus (MRSA)	USA300	<1	ND	<1	ND
Staphylococcus aureus (VISA)	ATCC 700699	<1	ND	8	ND
Staphylococcus aureus (VISA)	NRS22	<1	ND	8	ND

Broth microdilution susceptibility testing and synergy for BAS00127538 and comparators. Experiments were carried out according to CLSI standards. Values of Fractionary Inhibitory Concentration Index (FIC) are given in ug/ul.

Technology Status

Using computer-aided drug design and medicinal chemistry, the inventors have generated optimized BAS00127538 derivatives. One compound, termed 6Jc48-1, shows markedly decreased cytotoxicity while retaining potent activity against multi-drug resistant Enterococcus faecium and Enterococcus faecalis in vitro and in vivo. Importantly, compound 6Jc48-1 shows greatly enhanced pharmacokinetic properties in vivo.

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