TECHNOLOGY

Small Molecule Lipid II Inhibitors

OVERVIEW

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.

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.

APPLICATIONS

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.

ADVANTAGES

Novel synthetic compound

Active against gram-negative and gram-positive bacteria

STAGE OF DEVELOPMENT

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.

MW- 2/18/16

LICENSING POTENTIAL

Available for licensing

Available for sponsored research

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PATENT STATUS

U.S.Patent | 10,941,114 issued date 03/09/2021 U.S. Patent | 10,961,214 issued date 03/30/2021

LICENSE STATUS

Available for licensing and/or sponsored research

CATEGORIES

- Therapeutics
- Small molecules

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ATTACHMENTS

- Download UMB ED-2016-042 Summary.pdf

EXTERNAL RESOURCES

- Towards Development of Small Molecule Lipid II Inhibitors as Novel Antibiotics

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