Antimicrobial Heme Oxygenase Inhibitors and Methods of Use

Summary

Antimicrobials are widely used to treat a variety of infections. However, due to overuse and microbial evolution, many antimicrobials are rendered ineffective as first-line therapies. This invention is a new class of broad-spectrum, small-molecule antimicrobials that target the critical enzyme, heme oxygenase that is required to process heme, an iron carrying small molecule. The inhibition of heme oxygenases could be used for the treatment of microbial infections.

Key Investigator

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Field

Therapeutic
Small molecule

Technology

Antimicrobial

Technology Status

Animal studies underway

Status

Available for licensing
Available for sponsored research

Patent Status

US Patent 8,450,368

UMB Docket Reference

AW-2007-003

External Reference

- J Med Chem. 2007 Aug 9;50(16):3804-13. Epub 2007 Jul 13.
- Biochemistry. 2007 Dec 18;46(50):14391-402. Epub 2007 Nov 20.
- J Am Chem Soc. 2007 Sep 26;129(38):11730-42. Epub 2007 Sep 1.

Market

Nearly 2 million patients in the United States get an infection in the hospital each year and about 90,000 of those patients die as a result of their infection. More than 70 percent of the bacteria that cause hospital-acquired infections are resistant to at least one of the antibiotics most commonly used to treat them. The continuous evolution of bacterial pathogens and the resulting development of drug resistance creates a constant need for the development of new antibiotics. To encourage development the Generating Antibiotics Incentives Now Act (GAIN Act) was passed to potentially provide expedited review and an additional five years of exclusivity for antibiotic and antifungal drugs that qualify. Between the years 2010 – 2015, the U.S. Food and Drug Administration (FDA) has approved eight new antibiotics: ceftaroline, fidaxomicin, bedaquiline, dalbavancin, tedizolid, oritavancin, ceftolozane-tazobactam, and ceftazidime-avibactam. However, seven had similar mechanisms of action to those of previously approved drugs.

Technology

Iron acquisition is a critical function for bacterial pathogens for survival and virulence. Heme oxygenases are required to cleave heme to yield biliverdin, iron, and carbon monoxide. The discovery of heme oxygenase inhibitors offers a novel target and the potential for the development of a new class of antimicrobial agents with broad-spectrum activity. These inhibitors were identified using a computer-aided drug design (CADD) screening approach combined with experimental assays to identify small-molecule inhibitors of the *Neisseria meningitides* HO (nm-HO). Several of the compounds were shown to have *K*D values in the micromolar range for nm-HO and the *Pseudomonas aeruginosa* HO (pa-HO). The compounds also inhibited the growth of *P.aeruginosa* as well as biliverdin formation in *E. coli* cells overexpressing nm-HO. Thus, CADD combined with experimental analysis has been used to identify novel inhibitors of the bacterial heme oxygenases that can cross the cell membrane and specifically inhibit HO activity.

Advantages

- New target
- Broad-spectrum antimicrobial properties
- Small molecule
  - Permeability
  - Blood-brain permeability
  - Reduced immune response
  - Enhanced stability
  - Decreased biomaterial contamination potential
  - Capacity for large-scale manufacturing

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