Published in final edited form as:

Diagn Microbiol Infect Dis. 2011 January ; 69(1): 114–116. doi:10.1016/j.diagmicrobio.2010.08.014.

Novel Bis-Indole Agents Active Against Multidrug-Resistant *Acinetobacter baumannii*

Michael R. Jacobs^{1,*}, Saralee Bajaksouzian¹, Caryn E. Good¹, Michelle M. Butler², John D. Williams², Norton P. Peet², Terry L. Bowlin², Andrea Endimiani³, and Robert A. Bonomo^{3,*}

¹Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, OH

²Microbiotix Inc, Worcester, MA

³Case Western Reserve University and Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH

Abstract

The *in vitro* activity of five novel Microbiotix bis-indole agents (MBXs) against 30 multidrug-resistant (MDR) *A. baumannii* (including 18 resistant to carbapenems) was evaluated. Overall, MIC₉₀s ranged from 1–8 µg/ml, whereas those for imipenem were > 64 µg/ml. MBX 1196 was the most potent (MIC₉₀ 1 µg/ml). MBXs are compounds that are highly effective against MDR *A. baumannii*.

Keywords

bis-indole; multidrug-resistant; MBX; susceptibility; in vitro

Acinetobacter baumannii are commonly associated with serious hospital-acquired infections, particularly in severely ill, immune-compromised hosts (Perez, Hujer et al. 2007; Munoz-Price and Weinstein 2008). Resistance, both intrinsic and acquired, to nearly all classes of antibiotics significantly limits treatment options, making *A. baumannii* one of the most difficult multidrug-resistant (MDR) organisms to treat (Dijkshoorn, Nemec et al. 2007). Unfortunately, there are few active agents available for treating serious infections due to MDR *Acinetobacter* infections, with carbapenems being one of the “last line” treatment agents available. At the present time, the prevalence of carbapenem-resistant *A. baumannii* isolates is increasing (Perez, Hujer et al. 2007; Munoz-Price and Weinstein 2008). Therefore, our therapeutic choices for the treatment of the infections due to *A. baumannii* isolates are limited. Developing new antibiotics that are active against these life-threatening pathogens is an important goal.

Bis-imidazolylindole (or bis-indole) agents are members of a promising new drug class (Panchal, Ulrich et al. 2009). These are diarylamidine derivatives that target DNA synthesis,

© 2010 Elsevier Inc. All rights reserved.

*Corresponding authors: Michael R. Jacobs, MD, PhD, Department of Pathology, University Hospitals Case Medical Center/ CWRU, 11100 Euclid Avenue, Cleveland, Ohio 44106, Phone: 216-844-3484, Fax: 216-844-5239, mrj6@cwru.edu Robert A. Bonomo, MD, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, 10710 East Blvd., Cleveland, Ohio 44106, Phone: 216-791-3800x4399 robert.bonomo@med.va.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

providing a broad-spectrum antibacterial activity. Currently, investigations are underway to establish the mechanism of bacterial killing. The minor structural differences between the compounds correlate with differences in their effects on bacterial macromolecular synthesis and mechanisms of resistance. Several of these agents were shown to be effective in treating mice lethally infected with *Bacillus anthracis*, *Staphylococcus aureus*, or *Yersinia pestis* (Butler, Williams et al. 2008; Panchal, Ulrich et al. 2009).

This study evaluated five novel bis-indole agents, MBX 1158, MBX 1162, MBX 1196, MBX 1337, and MBX 1339 (Microbiotix, Inc, Worcester, MA) (Figure 1) against recently collected *A. baumannii* isolates, more than half of which were carbapenem-, ciprofloxacin-, piperacillin/tazobactam-, cefepime-, and amikacin-resistant. These *A. baumannii* isolates were collected from Iraqi and United States sources (Hujer, Hujer et al. 2006), and were tested by broth microdilution using current procedures outlined by the Clinical and Laboratory Standards Institute (CLSI) (CLSI 2009a). We define “MDR” as strains exhibiting resistance to representatives of three or more of the following classes of antibiotics: quinolones (ciprofloxacin), extended-spectrum cephalosporins (ceftazidime and cefepime), β -lactam/ β -lactamase inhibitor combinations (ampicillin-sulbactam), aminoglycosides (amikacin and tobramycin), and carbapenems (imipenem and meropenem).

These MBX agents were tested at concentrations of 0.03 to 32 μ g/ml; meropenem at 0.25 to 8 μ g/ml, and imipenem at 0.5 to 64 μ g/ml. Carbapenem-resistant strains were defined as isolates with meropenem and/or imipenem MICs of $\geq$ 8 μ g/ml according to CLSI criteria (CLSI 2009b).

Thirty MDR *A. baumannii* strains were assayed, including 18 carbapenem-resistant isolates. Unimodal MIC distributions were obtained for the five MBX agents and bimodal distributions for the two carbapenems tested (data not shown). MIC ranges, MIC₅₀ and MIC₉₀ values are shown in Table 1. With MIC₉₀ values of 1-8 μ g/ml, the MBX compounds had superior *in vitro* potency to either meropenem or imipenem (MIC₉₀ values of $>$ 8 μ g/ml). MBX 1196 was the most potent agent tested, with MIC₅₀ of 0.25 μ g/ml, MIC₉₀ of 1 μ g/ml, and MIC range of 0.06-1 μ g/ml. The MBX compounds had similar activity against carbapenem-resistant isolates to that against all isolates, with MIC₅₀ values varying by up to one doubling dilution and MIC₉₀ values being identical for the two groups (Table 1).

Our results show that the five MBX agents tested had potent *in vitro* activity against the MDR *A. baumannii* isolates tested, with MBX 1196 being the most potent, regardless of carbapenem susceptibility. Previous work reported with MBX 1162 showed a range of activity against *A. baumannii* isolates similar to that found in the present study, as well as good activity against a wide variety of Gram-positive and Gram-negative bacteria, including other non-fermenters such as *Pseudomonas aeruginosa* and *Burkholderia cepacia* (Butler, Williams et al. 2008; Panchal, Ulrich et al. 2009). MBX 1162 was also effective and well-tolerated in a mouse model of *Staphylococcus aureus* bacteremia (Butler, Williams et al. 2008). Should the toxicities and pharmacokinetic and pharmacodynamic parameters of these agents prove favorable, they are potentially useful and needed additions to the antimicrobial armamentarium and should undergo further development for clinical use.

Acknowledgments

This work was supported in part by the Veterans Affairs Merit Review Program (RAB), the National Institutes of Health (RAB), and Geriatric Research Education and Clinical Center VISN 10 (RAB).

REFERENCES

- Butler, MM.; Williams, JD., et al. Novel bis-(imidazoliny lindole) Antibacterials Active Against a Broad Spectrum of Bacteria. Abstract F1-3933. ICAAC; 2008.
- CLSI. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 8th ed. Approved standard M7-A8. National Committee for Clinical Laboratory Standards; Wayne, PA: 2009a.
- CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Nineteenth Informational Supplement. CLSI document M100-S19. Clinical and Laboratory Standards Institute; Wayne, PA: 2009b.
- Dijkshoorn L, Nemec A, et al. An increasing threat in hospitals: multidrug-resistant *Acinetobacter baumannii*. *Nat Rev Microbiol*. 2007; 5(12):939–51. [PubMed: 18007677]
- Hujer KM, Hujer AM, et al. Analysis of antibiotic resistance genes in multidrug-resistant *Acinetobacter* sp. isolates from military and civilian patients treated at the Walter Reed Army Medical Center. *Antimicrob Agents Chemother*. 2006; 50(12):4114–23. [PubMed: 17000742]
- Munoz-Price LS, Weinstein RA. *Acinetobacter* infection. *N Engl J Med*. 2008; 358(12):1271–81. [PubMed: 18354105]
- Panchal RG, Ulrich RL, et al. Novel broad-spectrum bis-(imidazoliny lindole) derivatives with potent antibacterial activities against antibiotic-resistant strains. *Antimicrob Agents Chemother*. 2009; 53(10):4283–91. [PubMed: 19635954]
- Perez F, Hujer AM, et al. Global challenge of multidrug-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother*. 2007; 51(10):3471–84. [PubMed: 17646423]

Figure 1.
Chemical structures of MBX compounds.

Table 1

Results for all isolates (n=30) and for carbapenem-nonsusceptible *A. baumannii* isolates (n=18), defined as meropenem and/or imipenem MICs $\geq 8 \mu\text{g/ml}$ (CLSI 2009b).

Agent	MIC values ($\mu\text{g/ml}$)					
	All isolates (n=30)			Carbapenem-resistant isolates (n=18)		
	Range	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀
MBX 1158	0.5-4	1	2	1-4	1	2
MBX 1162	0.12-4	0.5	2	0.5-2	0.5	2
MBX 1196	0.06-1	0.25	1	0.12-1	0.5	1
MBX 1337	0.25-4	1	2	0.5-4	0.5	2
MBX 1339	0.5-8	2	8	1-8	4	8
Meropenem	0.5 - >8	>8	>8	>8	>8	>8
Imipenem	0.5->64	4	>64	4->64	32	>64