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Synthesis and antibacterial evaluation of macrocyclic diarylheptanoid derivatives

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Abstract

Bacterial infections, caused by *M. tuberculosis* and other problematic bacterial pathogens, continue to pose a significant threat to global public health. As such, new chemotype antibacterial agents are desperately needed to fuel and strengthen the antibacterial drug discovery and development pipeline. As part of our antibacterial research program to develop natural product-inspired new antibacterial agents, here we report synthesis, antibacterial evaluation, and structure-activity relationship studies of an extended chemical library of macrocyclic diarylheptanoids with diverse amine, amide, urea, and sulfonamide functionalities. Results of this study have produced macrocyclic geranylamine and 4-fluorophenethylamine substituted derivatives, exhibiting moderate to good activity against *M. tuberculosis* and selected Gram-positive bacterial pathogens.

Graphical abstract

Keywords

Antituberculosis; Antibacterial; Diarylheptanoid; Macrocycle; SAR

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Supplementary data

Supplementary data (synthetic procedures, compound characterization, ¹H and ¹³C NMR spectra, and HPLC chromatographs) associated with this article can be found, in the online version, at .

The continuing emergence and spread of multidrug resistant bacterial pathogens including *Mycobacterium tuberculosis* is a major global health care concern.^{1, 2} According to the World Health Organization, approximately one third of the world's population is infected with latent *M. tuberculosis*, the bacterium causing tuberculosis (TB).¹ In 2014, there were about 9.6 million new cases of TB and 1.5 million deaths worldwide from this infectious disease.¹ This problem is compounded by mounting bacterial resistance to existing antibiotic chemical classes and the low rate of discovery of new agents.^{3, 4} As such, the discovery and development of new chemotype antibacterial agents are urgently needed to combat clinically problematic bacterial infections.

Natural products represent the most valuable source of novel bioactive molecules in antimicrobial drug discovery, as the majority of clinically used antibiotics are natural products and/or their semisynthetic derivatives in their origin.⁵⁻⁷ Natural and synthetic macrocycles have attracted a growing attention in drug discovery and medicinal chemistry due to their favorable pharmacological properties.⁸⁻¹¹ Among them, the cyclic diarylheptanoids belong to a chemical class of plant secondary metabolites and have been reported to mediate diverse biological activities.^{12,13} As examples, acerogenin A and analogs have been reported to possess osteogenic activity and may serve as potential biomarkers for osteoblast differentiation.^{14, 15} In addition, acerogenins A and B (Fig. 1) were also found to function as Na⁺-glucose co-transporter (SGLT) inhibitors with therapeutic potential for type 2 diabetes.¹⁶ The benzoyl ester derivative of acerogenin C was found to inhibit nitric oxide (NO) production (IC₅₀ = 13 μM) from lipopolysaccharide (LPS)-activated macrophages with no cytotoxicity.¹⁷ The dimethyl ether derivative **7** of engelhardione was reported to function as a micromolar inhibitor (IC₅₀ = 14.3 μM) against NF-κB by Natarajan and coworkers.¹⁸

In our continued efforts to develop natural product-inspired antibacterial agents, we previously reported the synthesis and preliminary structure-activity relationship (SAR) of macrocyclic diarylheptanoids with antibacterial activity.¹⁹ Antibacterial evaluation revealed that the *N*-substituted secondary amine derivatives (**1** in Fig. 1) exhibited moderate antitubercular and antibacterial activities with minimum inhibitory concentrations (MIC) of 12.5-50 μg/mL.¹⁹ In this current study, we explore the further synthesis and optimization of *N*-substituted macrocyclic diarylheptanoids in an effort to obtain compounds with improved antibacterial properties. Specifically, an extended chemical library of macrocyclic amine derivatives **9-35** was synthesized to expand the scope of amine substrates. We also designed and synthesized a series of new macrocyclic derivatives **36-48** with various ester, amide, urea, carbamate, sulfonamide, and sulfonate functionalities. Finally on the basis of a newly obtained antibacterial lead, a focused set of macrocycles **49-53** with different ring systems was also synthesized to expand the SAR.

Synthesis of the key macrocycle intermediates **7** and **8** is shown in Scheme 1. Briefly, 3-(benzyloxy)-4-methoxybenzaldehyde was first transformed into **2** via a 3-step sequence. This improved protocol can be easily scaled up in gram scales compared to our previously reported method.²⁰ Next, in the presence of 10% sodium hydroxide solution, the aldol condensation of **2** and **3** yielded **4** as a yellow solid in 74% yield. Subsequent hydrogenation of **4** gave both **5** and **6**, which could be easily separated by flash column chromatography.

Under microwave irradiation, final intramolecular copper-catalyzed Ullmann coupling²¹ of **5** or **6** afforded the corresponding macrocyclic product **7** or **8** in 77% and 80% yields, respectively.

Once the key intermediate **7** was in hand, we next expanded the chemical diversity of macrocyclic amine derivatives by employing various amine substrates (Table 1). The reduction of *in situ* formed imines with NaBH₄ gave their corresponding amine products. Specifically, reduction of **7** in concentrated ammonia solution (7N in methanol) gave primary amine **9** in 50% yield. In the cases of amine derivatives **12**, **15**, **19**, **22**, and **23** (Table 1, entries 4, 7, 11, 14 and 15), low to moderate yields (19-58%) were obtained under this reaction condition due to the simultaneous formation of the reduced alcohol by-product **8** from starting material **7**. We subsequently found that the yield and selectivity of this reductive amination reaction can be greatly improved by using a milder reductant NaBH₃CN, resulting in the desired macrocyclic amine derivatives in good yields with no or only trace amounts of **8** for most primary amine substrates.

With the optimized conditions, compounds **10** and **11** (Table 1, entries 2 and 3), with a 3- and 4-carbon linker, respectively, were designed and synthesized to probe the effect of the spacer length of the alkyl side chain. Compounds **12-18** (Table 1, entries 4-10) were synthesized to evaluate different groups and substitution patterns of the phenyl ring by using substituted phenethyl amines as the substrates. The amine derivatives **19-21** (Table 1, entries 11-13) with different aromatic/heterocyclic ring systems (pyridine, naphthalene, and 1,3-benzodioxole) were also prepared in moderate to good yields. Compounds **19**, **22**, and **32** (Table 1, entries 11, 14, and 22) with two basic nitrogen functionalities on the side chain of the macrocyclic scaffold were also synthesized. Accordingly, reaction of **7** with optically pure (*R*)-(-)-1,2,3,4-tetrahydro-1-naphthylamine or (*S*)-(+)-1,2,3,4-tetrahydro-1-naphthylamine gave a pair of diastereomers **25** and **26** (Table 1, entry 17) or **27** and **28** (Table 1, entry 18), respectively.

In addition, **24** with the geranyl amine motif was also synthesized in 79% yield. Ethylamine was used to synthesize **29** (Table 1, Entry 19) to understand the effect of the phenyl group by comparing to **1a**. Meanwhile, secondary amines diethylamine, diethanolamine, and 1-methylpiperazine were used as substrates to give **30-32** (Table 1, entries 20-22) in 15-40% yields. Overall, secondary amines were found to be less reactive in this reductive amination reaction with generally lower yields presumably due to steric effects.

The reaction of 4-chloroaniline with **7** proceeded smoothly to yield the desired product **33** in 57% yield (Table 1, entry 23). However, the reaction of **7** with bulky amine 1-adamantylamine (Table 1, entry 24) gave no desired product under the optimized reaction conditions.

To further evaluate the effect of phenolic hydroxyl groups in cyclic amine derivatives, two selected amine compounds **1a** and **1b** were demethylated using boron tribromide to give free phenols **34** and **35** in 74 and 26% yields, respectively (Scheme 2).

In addition to introducing the basic amine moieties on the macrocyclic ring, a series of macrocyclic derivatives with other functionalities including ester, amide, urea, carbamate, sulfonamide, and sulfonate were also synthesized from **8** or **9** (Table 2). Briefly, reaction of secondary alcohol **8** with substituted isocyanate gave the corresponding carbamates **36-38**, in which 4-fluorophenyl isocyanate (Table 2, entry 1) gave a higher yield comparing to phenethyl and benzyl isocyanates (Table 2, entries 2 and 3). Accordingly, macrocyclic urea derivatives **39** and **40** were obtained by reacting primary amine **9** and phenethyl or 4-fluorophenethyl isocyanate (Table 2, entries 4 and 5). Furthermore, **8** or **9** reacted with substituted sulfonyl chloride, carbonyl chloride, or carboxylic acid led to the formation of corresponding sulfonate **41**, sulfonamides **42-43**, esters **44-46**, and amides **47-48** in a range of 26-99% yields (Table 2, entries 6-13).

Finally, based on the promising antibacterial activity of **15** (described below), a focused set of structural analogs **49-53** (Fig. 2) with 12, 14, and 15-membered ring systems as well as different methoxy substitution patterns were next prepared to probe the SAR. These compounds were synthesized from their corresponding ketone macrocycles and 4-fluorophenethyl amine under the similar experimental conditions (see Supporting Information for details). In the cases of 12-membered products **52** and **53**, higher reaction temperature and longer reaction time (100 °C, 7-10 days) were required due to higher ring strains.

The synthesized macrocyclic analogs were tested against *M. tuberculosis*, a panel of Gram-positive bacterial pathogens including *Bacillus anthracis*, *Enterococcus faecalis*, *Staphylococcus aureus* (MSSA), *Staphylococcus aureus* (MRSA), *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Bacillus subtilis*, as well as Gram-negative bacterial strains *Escherichia coli* (K12), *Escherichia coli* (efflux deficient, TolC), *Acinetobacter baumannii*, *Burkholderia cepacia*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Proteus vulgaris*, and *Pseudomonas aeruginosa*. Specifically, MIC values were determined against *M. tuberculosis* (H37Rv) and other bacteria using the standard microbroth dilution method exactly as previously described,²² which is based on the methods by the Clinical and Laboratory Standards Institute.^{23, 24} The results are shown in Table 3; and preliminary SARs are summarized below.

Overall, the secondary amine derivatives generally demonstrated the most promising antibacterial activity against *M. tuberculosis* and some of selected Gram-positive bacterial strains. Among them, **24** with the geranylamine motif and the *p*-fluorophenethylamine derivative **51** showed antibacterial activity with MICs ranging from 3.125 to 12.5 µg/mL. In addition, the *para*-halogen substituted phenethylamine derivatives (e.g., **13** with *p*-chlorophenethyl, **14** with *p*-bromophenethyl, and **15** with *p*-fluorophenethyl) and the β -naphthylethyl amine derivative **20** also showed moderate to good antibacterial activities (MICs = 6.25-25 µg/mL). Compared to the *p*-halogenphenethyl substituted derivatives **13-15**, compound **12** with the *p*-hydroxyphenethyl group only showed very weak antitubercular and antibacterial activities (MIC = 50-100 µg/mL), suggesting the importance of *para*-halogen substitution. The *o*- and *m*-fluorosubstituted derivatives **16** and **17** exhibited generally comparable antibacterial activity relative to the *p*-fluoro analog **15**. Notably, consistent with our previous finding,¹⁹ the macrocyclic derivatives **19** and **22** with two basic

nitrogen functionalities were largely inactive when tested at 100 µg/mL likely due to the decreased cellular membrane penetration.²⁵ Compound **32** bearing the methylpiperazine moiety showed weak antibacterial activity with MICs ranging from 50 to 100 µg/mL. In contrast, the macrocycle **9** with primary amine functionality and other macrocycles **29-31** bearing alkyl amine moieties showed weak or no antibacterial activities (MIC > 100 µg/mL). With regard to the two pairs of diastereomers (**25** and **26**; **27** and **28**), no significant antibacterial activities and stereospecific effects were observed among these stereoisomers. Moreover, the free phenol macrocycles **34** and **35** showed weaker antibacterial activity compared to their corresponding methyl ether derivatives.¹⁹

From the carbamate, urea, sulfonate, sulfonamide, ester and amide chemical series, all the carbamate **36-38**, urea **39-40**, sulfonate **41**, ester **44-46**, amide **47-48** were inactive (MIC > 100 µg/mL) against *M. tuberculosis* and all the other test bacterial strains, with the exception of carbamate **36** with *p*-fluorophenyl motif showing moderate to weak antibacterial activity against *E. faecalis* and *S. aureus* with MICs of 50 and 25 µg/mL, respectively. In addition, the sulfonamide derivatives **42-43** were largely inactive except that the *p*-trifluoromethylphenyl sulfonamide **43** exhibited weak inhibitory activity (MIC = 50 µg/mL) against *Enterococcus faecalis* and MRSA (NRS70) strains.

Among the 12-15 membered macrocycles **49-53** with the *p*-fluorophenethyl amine motif and different methoxy substitution patterns, **51** showed the most promising antibacterial activity against *M. tuberculosis* and select Gram-positive bacterial strains *B. anthracis*, *E. faecalis*, and *Staphylococcus aureus* (29213, MSSA), with MICs ranging from 6.25-12.5 µg/mL. Compound **49** with the 14-membered ring system and one methoxy substitution also exhibited comparable antibacterial activity against *M. tuberculosis* and these Gram-positive bacterial strains (MICs = 6.25-25 µg/mL). By comparing to **51**, compounds **50** with an additional methoxy group and **53** with the 12-membered ring system generally had 2-4 fold decrease of antibacterial activity. Overall, both **52** and **53** with a smaller 12-membered ring system showed 4-8 fold weaker antibacterial activity relative to **51**, suggesting the smaller ring may be detrimental to antibacterial activity.

Cytotoxicity evaluation^{26, 27} of select compounds showed these compounds possessed narrow therapeutic indices, with mammalian cell growth inhibited (**13**, IC₅₀ = 6.8±0.3 µg/mL; **14**, IC₅₀ = 6.9±0.3 µg/mL; **15**, IC₅₀ = 7.3±0.2 µg/mL; **20**, IC₅₀ = 7.0±0.3 µg/mL; **24**, IC₅₀ = 5.6±0.3 µg/mL; **34**, IC₅₀ = 11.1±0.2 µg/mL; **51**, IC₅₀ = 3.7±0.1 µg/mL), exhibiting cytotoxicity close to MIC levels. These results suggest that further optimization to decrease this level of cytotoxicity is required to further advance this series.

In summary, an extended chemical series of macrocyclic diarylheptanoid analogs **9-48** bearing amine and other diverse functionalities, as well as a focused set of macrocycles **49-53** with *p*-fluorophenethyl amine motif and different ring sizes, were designed and synthesized. These compounds were evaluated for their ability to inhibit bacterial growth against *M. tuberculosis* and a select panel of Gram-positive and -negative bacteria strains. Results of this study have produced the 14-membered macrocyclic geranylamine derivative **24** and the 15-membered *p*-fluorophenethylamine derivative **51**, exhibiting antibacterial activity against *M. tuberculosis* and some of selected Gram-positive bacterial strains with

MICs ranging from 3.125 to 12.5 $\mu\text{g/mL}$. The *para*-halogen substituted phenethylamine derivatives (e.g., **13** with *p*-chlorophenethyl, **14** with *p*-bromophenethyl, and **15** with *p*-fluorophenethyl) and the β -naphthylethyl amine derivative **20** also showed moderate to good antibacterial activities (MICs = 6.25-25 $\mu\text{g/mL}$). Further optimization and advancement of this macrocyclic series will aim to improve the antibacterial activity, decrease cytotoxicity profile, as well as to enhance desirable physiochemical properties such as solubility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Selected examples of bioactive cyclic diarylheptanoids and an overview of library design.

Figure 2.
Macrocyclic amine derivatives **49-53** with different ring systems and methoxy substitution patterns.

Scheme 1.

Synthesis of the key macrocycle intermediates **7** and **8**. Reagents and conditions: (a) i. $\text{MeO}_2\text{CCH}_2^+\text{PPh}_3\text{Br}^-$, $t\text{-BuOK}$, CH_2Cl_2 , 0°C -r.t.; ii. DIBAL-H, CH_2Cl_2 , 0°C -r.t.; iii. Dess-Martin oxidation, CH_2Cl_2 , 0°C - r.t., 42% over 3 steps. (b) 10% NaOH (aq), EtOH, 74%. (c) 10% Pd/C, H_2 (1 bar), ethyl acetate, 47% for **5**, 36% for **6**. (d) CuO, K_2CO_3 , pyridine, microwave, 220°C , 35 min, 77% for **7**, 80% for **8**.

Scheme 2.

Synthesis of free phenol macrocycles **34** and **35**. Reagents and conditions: (a) BBr_3 , CH_2Cl_2 , 74% for **34**, 26% for **35**.

Table 1Synthesis of an extended chemical library of macrocyclic amine derivatives **9-33**

Entry	R ($-NR^1R^2$)	Product ^a	Yield (%)	Entry	R ($-NR^1R^2$)	Product ^a	Yield (%)
1		9	50	13		21	78
2		10	78	14		22	19
3		11	71	15		23	32
4		12	26	16		24	79
5		13	83	17		25	18
6		14	80	18		26	33
						27	26
						28	34

Entry	R ($-NR^1R^2$)	Product ^a	Yield (%)	Entry	R ($-NR^1R^2$)	Product ^a	Yield (%)
7		15	58	19		29	75
8		16	86	20		30	35
9		17	86	21		31	15
10		18	87	22		32	40
11		19	31	23		33	57
12		20	60	24		-	0

^aUnless noted below, all compounds were synthesized using procedure A (7, R¹R²NH, AcOH, NaBH₃CN, MeOH, 50 °C, 12 h); For products **30-32**, the reductive amination was done at 100 °C instead of 50 °C, reaction time: 2-6 days. For the synthesis of **9**, **12**, **15**, **19**, **22**, and **23**, procedure B (i. 7, R¹R²NH, 70 °C, overnight; ii. NaBH₄, r.t. -70 °C) was used. See Supporting Information for detailed experimental conditions.

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Table 2Synthesis of macrocyclic carbamate, urea, sulfonate, sulfonamide, ester, and amide derivatives^a

Entry	Reagent	R	X	Product	Yield (%)
1	RNCO, DIPEA, DMAP	4-F-phenyl	O	36	92
2		PhCH ₂ CH ₂	O	37	16
3		PhCH ₂	O	38	42
4	RNCO, NEt ₃	PhCH ₂ CH ₂	NH	39	60
5		4-F-PhCH ₂ CH ₂	NH	40	59
6	RSO ₂ Cl, pyridine, DMAP	Me	O	41	99
7		4-Me-phenyl	NH	42	54
8		4-(CF ₃ O)-phenyl	NH	43	26
9	RCOCl, pyridine, DMAP	Me	O	44	78
10		Ph ₂ CH ₂	O	45	95
11		PhCH ₂ CH ₂	O	46	70
12	RCOCl, NEt ₃	PhCH ₂ CH ₂	NH	47	41
13	4-F-PhCH=CHCOOH, EDC·HCl, NEt ₃	4-F-PhCH=CH-	NH	48	62

^a All reactions were performed at room temperature in dichloromethane, see Supporting Information for detailed experimental conditions.

Table 3
Antitubercular and antibacterial activities (MIC, $\mu\text{g}/\text{mL}$) of macrocyclic diarylheptanoid analogs^a

Product	<i>M. tuberculosis</i> (H37Rv) ^b	<i>B. anthracis</i> Sterne (34F2)	<i>E. faecalis</i> (ATCC 33186)	<i>S. aureus</i> (ATCC 29213) (MSSA)	<i>S. aureus</i> (NRS 70) (MRSA)	<i>S. pyogenes</i> (ATCC 700294)	<i>S. pneumoniae</i> (R6)	<i>B. subtilis</i> (ATCC 23857)	<i>A. baumannii</i> (ATCC 19606)	<i>E. coli</i> (K12)	<i>E. coli</i> (Tolc)
9	200	100	200	200	200	200	200	100	200	200	100
10	50	50	25	25	25	50	50	25	50	>100	12.5
11	25	50	25	25	25	12.5	50	12.5	100	>100	12.5
12	100	50	100	>100	100	100	100	50	>100	>100	100
13	25	12.5	12.5	12.5	12.5	12.5	25	6.25	25	>100	6.25
14	25	12.5	12.5	12.5	12.5	50	50	6.25	50	>100	12.5
15	25	25	25	25	12.5	25	50	12.5	25	>100	12.5
16	25	50	25	50	25	50	50	12.5	100	>100	25
17	25	50	25	50	25	50	50	12.5	50	>100	25
18	100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
19	100	>100	>100	>100	>100	>100	100	100	>100	>100	100
20	25	12.5	12.5	12.5	6.25	12.5	25	6.25	>100	>100	6.25
21	25	50	50	50	25	12.5	50	12.5	>100	>100	12.5
22	100	>100	>100	>100	>100	>100	>100	100	>100	>100	>100
23	25	12.5	>100	>100	12.5	50	>100	12.5	>100	>100	6.25
24	12.5	12.5	12.5	12.5	6.25	25	50	3.125	25	50	6.25
25	>100	>100	>100	>100	>100	>100	>100	6.25	>100	>100	100
26	50	>100	>100	>100	>100	>100	50	25	>100	>100	25
27	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
28	50	>100	>100	>100	>100	>100	>100	>100	>100	>100	25
29	100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
30	100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
31	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
32	50	100	100	100	50	>100	100	50	100	>100	50
33	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
34	25	50	50	>100	50	50	50	25	50	100	25

Product	<i>M. tuberculosis</i> (H37Rv) ^b	<i>B. anthracis</i> Sterne (34F2)	<i>E. faecalis</i> (ATCC 33186)	<i>S. aureus</i> (ATCC 29213) (MSSA)	<i>S. aureus</i> (NRS 70) (MRSA)	<i>S. pyogenes</i> (ATCC 700294)	<i>S. pneumoniae</i> (R6)	<i>B. subtilis</i> (ATCC 23857)	<i>A. baumannii</i> (ATCC 19606)	<i>E. coli</i> (K12)	<i>E. coli</i> (<i>Tolc</i>)
35	100	>50	>50	>50	>50	>50	>50	>50	>50	>50	50
36	>100	>100	50	>100	25	>100	>100	>100	>100	>100	>100
37	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
38	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
39	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
40	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
41	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
42	>100	>100	100	>100	100	>100	>100	>100	>100	>100	>100
43	>100	100	50	>100	50	>100	>100	>100	>100	>100	>100
44	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	12.5
45	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
46	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
47	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
48	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
49	25	25	12.5	25	12.5	50	50	6.25	50	>100	12.5
50	25	50	25	25	25	50	25	12.5	100	>100	25
51	12.5	12.5	12.5	12.5	6.25	25	50	6.25	50	>100	6.25
52	50	100	100	50	100	100	100	50	100	>100	50
53	25	50	50	25	25	50	50	25	50	>100	12.5
Chlor amphe nicol		3.125	0.78	6.25	3.125	3.125	1.56	6.25	50	6.25	0.78

^a All compounds were inactive (MIC >100 µg/mL) against Gram-negative bacteria pathogens including *B. cepacia* (ATCC 25416), *K. pneumoniae* (ATCC 33495), *P. mirabilis* (ATCC 25933), *P. vulgaris* (ATCC 33420), and *P. aeruginosa* (PAO1).

^b The MICs of control antibiotics isoniazid and rifampin against *M. tuberculosis* were 0.03 and .5 µg/mL, respectively.