Novel Semisynthetic Derivative of Antibiotic Eremomycin Active against Drug-Resistant Gram-Positive Pathogens Including *Bacillus anthracis*†

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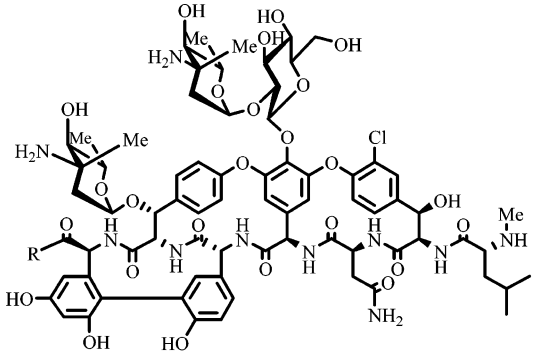
Five adamantyl-containing carboxamides of eremomycin or vancomycin were synthesized and their antibacterial activities against some Gram-positive clinical isolates were investigated in vitro and in vivo. The adamantyl-2 amide of glycopeptide antibiotic eremomycin (**1a** in Chart 1, AN0900) was the most active compound and showed high activity against several Gram-positive pathogens: vancomycin-susceptible staphylococci and enterococci, glycopeptide-intermediate-resistant *Staphylococcus aureus*, and glycopeptide-resistant enterococci. Compound **1a** was equally active in vitro against both Ciprofloxacin-susceptible and -resistant *Bacillus anthracis* strains (MICs 0.25−0.5 μg/mL). It was distinguished by having a 2.8 h half-life ($t_{1/2}$) in mice and a volume of distribution of 2.18 L/kg. Compound **1a** was active against *Staphylococcus aureus* in mice (iv) and provided complete protection against a lethal intravenous challenge with vegetative *B. anthracis* bacilli and also in a murine pulmonary anthrax model in which mice were challenged with *Bacillus anthracis* spores.

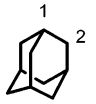
Introduction

The discovery and development of new antibiotics is of crucial importance because our current arsenal of antibiotics is rapidly becoming obsolete. This is due, in large measure, to the spread of drug resistant pathogens that have evolved mechanisms to resist almost all available antibiotics. Furthermore, ease of transportation is creating a "global village" that can result in the potential for the devastating spread of infectious agents. Other bacterial pathogens are being stockpiled by terrorist groups and countries, which increases the threat of biological warfare. The mailing of letters containing *B. anthracis* spores to government officials and members of the media in the fall of 2001 emphasized the need for developing effective countermeasures against potential biowarfare agents such as anthrax. Anthrax is a zoonotic disease caused by the spore forming organism *B. anthracis* and occurs worldwide. The disease can occur in three forms: cutaneous, gastrointestinal, and inhalation. In spite of supportive care, including appropriate antibiotics, inhalation anthrax mortality is very high.[1] The current recommended antibiotic therapy for *B. anthracis* exposure is ciprofloxacin or doxycycline, and these agents are indeed effective against most strains of *B. anthracis*.[2] The ability to create resistant strains of *B. anthracis*, as demonstrated by Athamna et al.,[3] resistant to ciprofloxacin and 17 other antibiotics, including the antibiotic vancomycin (**2**, Chart 1), is of concern. Thus, there is an urgent need for novel antibiotics that could be effective against *B. anthracis*. Antibacterials with a

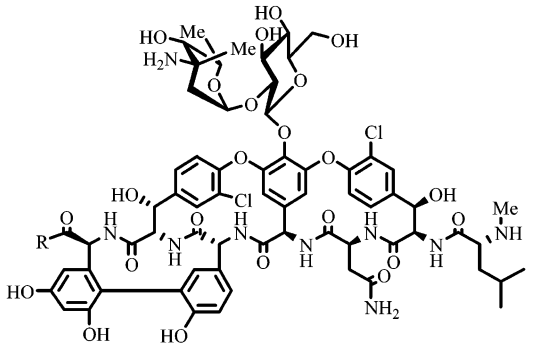
Chart 1. Eremomycin and Vancomycin Adamantyl-Containing Amides



1. R = OH, **Eremomycin;**
1a. R = NH-(Adam-2)**;**
1b. R = NH-(Adam-1)**;**
1c. R = NH-CH(CH_3)(Adam-1);
1d. R = NH-CH_2(Adam-1)



Adam = adamantyl-



2. R = OH, **Vancomycin;**
2a. R = NH-(Adam-2)

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Table 1. MICs for Adamantyl-Bearing Carboxamides of Glycopeptides **1a**, **1b**, **1c**, **1d**, and **2a**, Comparing with Eremomycin (**1**), Vancomycin (**2**), and Teicoplanin against Staphylococci and Enterococci Clinical Isolates

	MIC (μg/mL)							
strain/isolate	eremomycin (**1**)	vancomycin (**2**)	teicoplanin	**1a**	**1b**	**1c**	**1d**	**2a**
Staphylococcus epidermidis 533	0.25	2	8	0.25	0.5	0.5	0.5	1
Staphylococcus hemeolyticus 602	0.25	2	16	0.25	1	1	0.5	1
Staphylococcus aureus 3793 (GISA)	8	16	16	1	2	4	1	4
Staphylococcus aureus 3798 (GISA)	8	8	8	2	2	2	2	4
Enterococcus faecium 568 (VSE)	0.5	2	0.25	0.5	1	0.5	0.5	0.5
Enterococcus faecalis 559 (VSE)	0.5	1	0.5	0.5	1	1	1	0.5
Enterococcus faecium 569 (GRE)	>128	>128	>128	4	16	16	16	64
Enterococcus faecalis 560 (GRE)	>128	>128	>128	8	16	16	16	64

Table 2. Antibacterial Activity of **1a** in Comparison with Vancomycin (**2**)

	MIC (μg/mL)	
strains/isolate	vancomycin (**2**)	**1a**
Staphylococcus aureus Stau_29213[a]	1	0.78
Staphylococcus aureus Stau_33591[a]	1	0.78
Staphylococcus aureus Stau_b11386[a]	1	0.78
Staphylococcus aureus Stau_Mu50-HIP5406[a]	2	0.4
Staphylococcus aureus Stau_HIP5827[a]	8	1.56
Enterococcus faecalis Enfa_29212[b]	2	0.4
Enterococcus faecalis Enfa_t29862[c]	>64	6.25
Enterococcus faecalis Enfa_vre-2[c]	>64	12.5
Streptococcus pyogenes Stpy_8668	0.5	0.2
Escherichia coli Esco_25922	>50	>50

[a] All staphylococcus strains are MRSA. [b] Vancomycin susceptible strain. [c] Vancomycin resistant strains.

Table 3. MIC of **1a** and Ciprofloxacin against *B. anthracis* Strains and Isolates

B. anthracis strain/isolate[a]	MIC[b] (μg/mL)	
	1a	ciprofloxacin
Ames	0.50	0.06
HH105−5	0.50	8.00
HH105−6	0.50	32.00
HH105-5R	0.25	4.00
HHT105-5R	0.25	8.00
HH113-6R	0.50	4.00

[a] The original *B. anthracis* Ames strain spore stock was obtained from the U.S. Army Medical Research Institute of Infectious Diseases, Frederick, MD. The resistant strains came from the studies using the Ames strain in animals, as described by Lyons et al.[15] [b] The values for all strains were within a well (single dilution) of the parent Ames strain.

Table 4. Mortality and ED_{50} Estimates for **1a** in a *S. aureus* Infection Model

dose (mg/kg)	mortalities	ED_{50}	lower 95% C.I.	upper 95% C.I.
1	5			
5	4			
10	4	20.4	9.8	42.5
25	3			
50	0			

long half-life and deep tissue penetration are needed for effective therapy against multiple infectious agents, including *B. anthracis*. Thus semisynthetic antibiotics, derived from glycopeptides, may have better pharmacokinetic properties and offer therapeutic advantages.

The glycopeptides (vancomycin **2** and teicoplanin) are traditionally the antibiotics of last choice for serious infections due to Gram-positive pathogens. Eremomycin (**1**, Chart 1) is a glycopeptide in the vancomycin group that is several times more active in vitro and in vivo than vancomycin,[4] although not active against vancomycin-resistant Gram-positive organisms. The search for derivatives of glycopeptide antibiotics active against multidrug-resistant Gram-positive pathogens resulted in the discovery of derivatives of vancomycin, eremomycin, and other members of this group of antibiotics. Many of these compounds are active against methicillin-resistant *S. aureus* (MRSA[a]), glycopeptide intermediately resistant staphylococci (GISA), and vancomycin-resistant enterococci (GRE).[5−7] In addition, a series of *N*′-substituted derivatives of eremomycin or vancomycin bearing hydrophobic moieties of the optimal size are generally active against glycopeptide-resistant enterococci (MICs = 2−16 μg/mL) and act in a manner different from that of the parent antibiotics.[8] It was demonstrated that nonbonded interactions of the hydrophobic substituent at the amide group of eremomycin amide and the L-Ala-D-iso-Glu component of the peptidoglycan chain results in steric hindrance in interaction with the bacterial transglycosylase enzyme.[9] However, some hydrophobic glycopeptides amides, for example, decyl amides, are cytotoxic.[10] One approach to overcome the cytotoxicity of hydrophobic glycopeptide derivatives is the introduction of a hydrophilic moiety into the glycopeptide molecule to compensate for the effects of the hydrophobic substituent. This strategy led to telavancin, a derivative of vancomycin carrying simultaneously both hydrophilic and hydrophobic substituents.[11] An alternative approach to minimize toxicity is to carefully select hydrophobic substituents that will exert only the desired effect on resistant strains and not cause any concomitant toxicological effects.

Adamantane derivatives, such as amantadine, rimantadine, memantine, and some others, are broadly employed as antiviral or neurological drugs and demonstrate good pharmacological properties.[12] Earlier we demonstrated that adamantyl-containing amides of vancomycin and eremomycin aglycons exhibit low cytotoxic effects and are active against staphylococci and enterococci clinical isolates in vitro (2−32 μg/mL).[13] These results prompted us to synthesize and study a series of adamantyl-derived amides of fully glycosylated glycopeptides and to evaluate their antibacterial activity.

Chemistry

Earlier we described the synthesis of several eremomycin carboxamides by a one-step reaction of the antibiotic with the appropriate amine in the presence of a condensing reagent such as DPPA, PyBOP, HBPyU, or HBTU.[8,14] Carboxamides of eremomycin bearing the adamantyl-moiety, 2-amino-adamantane **1a**, 1-amino-adamantane **1b**, 1-(adamantyl-1)ethylamine

[a] Abbreviations: MIC, minimal inhibitory concentration of antibiotic (μg/ml); MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; GISA, staphylococci with an intermediate resistance to vancomycin; GRE, vancomycin-resistant enterococci; DPPA, diphenylphosphoryl azide; PyBOP, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; HBPyU, *O*-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)-uronium hexafluorophosphate; HBTU, *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; DIPEA, di-isopropylethylamine; ESI MS, electrospray ionization mass spectra.

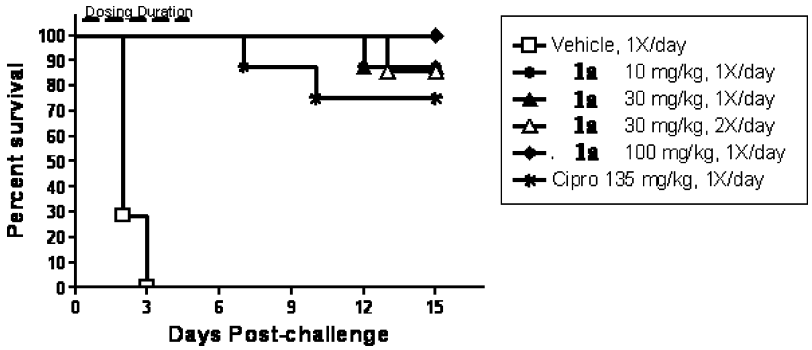

Figure 1. Initial dose−response study showing prevention by **1a** of mortality in mice exposed to a lethal challenge of *B. anthracis* spores by intratracheal instillation.

1c, and (adamantyl-1)methylamine **1d** and 2-amino-adamantyl amide of vancomycin (**2a;** Chart 1), were obtained by the condensation of **1** or **2** with the corresponding amines in the presence of PyBOP, HBPyU, or HBTU reagents in DMSO without protection of antibiotic amino groups. The yields of **1a**−**d** and **2a** were ∼60−70%, with HPLC purity at 95−97%. The homogeneity and identity of these compounds were assessed by two systems of HPLC and two systems of TLC, and electrospray ionization mass-spectrometry (ESI MS; Table in Supporting Information).

Biological Evaluation

Comparative in vitro antibacterial activities of adamantane-derived amides of eremomycin and vancomycin against staphylococci and enterococci strains versus eremomycin, vancomycin, and teicoplanin are presented in Table 1. The four amides of eremomycin (**1a**−**d)** were found to be as active as the natural antibiotics against vancomycin-sensitive bacterial strains (MICs 0.25−0.5 μg/mL), more active than the natural antibiotics against GISA staphylococci (1−4 μg/mL), and only **1a** was active (4−8 μg/mL) against vancomycin-resistant enterococci. In contrast to **1a**, (adamantyl-2)-amide of vancomycin (**2a**) was less active against vancomycin-sensitive and especially vancomycin-resistant strains (64 μg/mL). Compound **1a** was further evaluated in vitro against five *Staphylococcus aureus* strains, one *Streptococcus pyogenes* strain, and one vancomycin-sensitive enterococci strain and showed high activity. It was active against two vancomycin-resistant *Enterococcus faecalis* strains (6.25−12.5 mcg/mL; Table 2). Antibiotic susceptibilities were also determined for the Ames strain of *B. anthracis* and five strains isolated from failed-ciprofloxacin-treated mice that had been challenged with the Ames strain. In vitro antibacterial activities of **1a** (against *B. anthracis* strains) in comparison with ciprofloxacin are presented in Table 3. These strains represent a range of decreased susceptibility to ciprofloxacin in vitro. The susceptibility pattern for **1a** was unaffected by the alteration in ciprofloxacin susceptibility. As shown in Table 3, the MICs for **1a** for all strains range within a single dilution of the parent Ames strain (0.25−0.5 μg/mL). Cytotoxicity for **1a** was IC_{50} > 200 μM (CEM0 cells, measured by Balzarini, J. et al. by the method described earlier).[10]

The objective of the pharmacokinetic study was to assess the exposure of female BALB/c mice to **1a** when the test compound was administered by intravenous (iv), subcutaneous (sc), intraperitoneal (ip), and oral (po) routes. The bioavailability of **1a** from sc, ip, and po dosing routes to mice was 78, 95, and 0%, respectively, and the C_{max} (μg/mL) values from iv, sc, and ip dosing were 11.5, 7.2, and 9.7, respectively. The pharmacokinetic parameters of **1a** iv were the following: half-life = 2.8 h, clearance = 536 mL/h/kg, and volume of distribution V_{ss} = 2.18 L/kg. There was no mortality or significant clinical observations noted during the course of this study.

The in vivo efficacy for **1a** was demonstrated in several tests, including survival studies against *Staphylococcus aureus* (*S. aureus*) and *B. anthracis* (Ames strain). Compound **1a** was evaluated for its ability to prevent mortality in mice caused with a lethal dose of *S. aureus* PGO#172 (ATCC#29213). Compound **1a** was administered as an iv bolus at doses 1, 5, 10, 25, or 50 mg/kg to groups of five mice. As shown in Table 4, **1a** provided dose-dependent efficacy with an ED_{50} of 20.4 mg/kg.

With regard to *B. anthracis*, the efficacy of **1a** was first tested against a systemic bacteremia in mice that were inoculated intravenously with a known number of vegetative bacilli. In this study, two single daily intravenous doses of either 25 or 50 mg/kg of compound **1a** were sufficient for complete protection against a lethal *B. anthracis* challenge (data not shown). Ciprofloxacin at 106 mg/kg/day for 3 days also provided complete protection, as expected. Most impressively, **1a** is equivalent or possibly slightly superior in efficacy to ciprofloxacin in preventing mortality in mice infected with lethal doses of *B. anthracis*.

The efficacy of **1a** was then examined in a pulmonary anthrax model in which mice were inoculated with *B. anthracis* (Ames) spores. Daily subcutaneous treatment with 10, 30, or 100 mg/kg of **1a** for 6 days provided significant protection against a lethal pulmonary challenge with *B. anthracis* spores, with 88% survival observed in the mice treated with 10 or 30 mg/kg and 100% survival in the mice treated with the 100 mg/kg dose (Figure 1). In comparison, oral treatment with ciprofloxacin at a daily dose of 135 mg/kg for 6 days resulted in 75% protection in this study. No increase in survival with **1a** was observed by treating the mice with 30 mg/kg twice a day as compared to once a day (86% survival vs 88% survival, respectively; p = 0.96).

In a second study, the treatment dose of **1a** was further reduced, and the efficacy again was tested against a pulmonary challenge with *B. anthracis* spores. As shown in Figure 2, a significant increase in survival was observed at all doses of **1a** as compared to the vehicle-treated mice, and the protection was dose-dependent with 85.7, 62.5, 50, and 12.5% survival observed in the groups treated with **1a** at doses of 10, 3, 1, or 0.3 mg/kg/day, respectively, while 87.5% protection was observed in mice treated orally with Ciprofloxacin at 114 mg/kg.

Discussion

The 2-adamantyl amide of eremomycin **1a** was selected from the series of adamantyl-derived amides of eremomycin and vancomycin as the best compound with antibacterial activity against 17 clinical isolates of Gram-positive bacteria. It was distinguished by having a 2.8 h half-life in mice and a volume

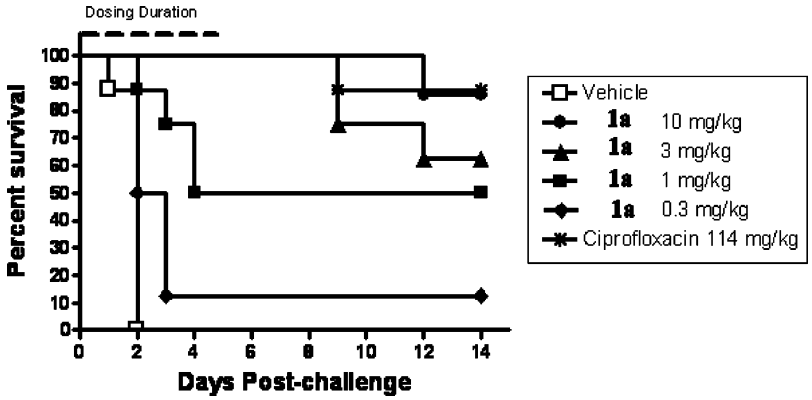

Figure 2. Dose−response study of **1a** showing prevention of mortality in mice exposed to a lethal challenge of *B. anthracis* spores by intratracheal instillation.

of distribution (V_{ss}) of 2.18 L/kg. The V_{ss} of **1a** is much higher than that for marketed glycopeptides (700 mL/kg) and implies excellent deep tissue penetration. This property of **1a** is important since antibacterials with long half-lives and deep tissue penetration may be beneficial for skin and soft tissue infections.

Conclusion

The adamantyl amide of eremomycin, **1a**, had excellent activity against a range of clinical isolates, including MSSA, MRSA, and GISA, and moderate activity against GRE. In vivo efficacy for **1a** was demonstrated by its ability to prevent death caused by either *S. aureus* or *B. anthracis*. Compound **1a** is very effective at preventing mortality induced by *B. anthracis*, is significantly more efficacious than ciprofloxacin in this animal model, and is effective in vitro against *B. anthracis* strains shown to be resistant to ciprofloxacin. These compelling results are highly suggestive that **1a** has considerable promise as a development candidate for use as a therapeutic agent for the treatment of a *B. anthracis* infection. Thus, **1a** represents a promising development candidate for use as a therapeutic countermeasure against *B. anthracis* exposure. Further studies are needed to recognize the full potential of this novel compound.

Experimental Section

Chemistry. Synthesis of 1a. Compound **1a** was synthesized by the condensation of antibiotic eremomycin sulfate (1 equiv) with (adamanthyl-2) amine hydrochloride (3 equiv) using PyBOP (1.1 equiv) in DMSO in the presence of DIPEA (pH ∼8) using TLC to monitor reaction progress with UV detection. After 20 min of stirring at 18 °C, 50 mL of Et_2O was added to the reaction mixture and the mixture was shaken intensively to extract DMSO partly. The layer of Et_2O was separated. The DMSO layer was poured into 200 mL of a stirring acetone to precipitate the product of the reaction, which was filtered off, washed with acetone, and dried in vacuum to give a white powder of crude **1a**. Then crude **1a** was dissolved in 9 mL of water and applied to a chromatographic column with silanized silica gel, pre-equilibrated with water (1 g of solid for 70 cm^3 of silica gel). The column was eluted with water. Fractions containing the pure **1a** were combined, acidified with 6 N H_2SO_4 to pH 2, and passed through a column with DOWEX 50WX2 resin (Serva, mesh size 200−400 μm) with 0.25 N NH_4-OH as eluent. The eluates were concentrated in vacuum to the volume ∼50 mL and adjusted to pH 7 with 1 N aqueous solution of H_2SO_4. The solution was evaporated to a volume of 15 mL and 400 mL of acetone was added to precipitate the product. The precipitate was filtered, washed with acetone, and dried in vacuum to give a white powder of 2-adamantylamide of eremomycin sulfate (**1a**) in a yield of 62%. HPLC purity was ∼97%. TLC, HPLC, and ESI MS data are presented in the Supporting Information (SI).

Synthesis of 1b, 1c, 1d, and 2a. The compounds **1b**−**d** and **2a** were obtained by the procedure similar for **1a**. They were purified by column chromatography over silanized silica gel. The yields of **1b**−**d** and **2a** were ∼60−70%, HPLC purity was 95−97%. HPLC, TLC, and ESI MS data for adamantyl-bearing carboxamides of eremomycin (**1b**−**d**) and vancomycin (**2a**) are presented in the SI.

Biological Evaluation. Antibiotic Susceptibilities against Staphylococci and Enterococci (Table 1 and 2). Minimum inhibitory concentrations (MICs) were determined by the microdilution method using Mueller Hinton broth, in 96-well plates, as recommended by NCCLS. Antibiotic stocks were diluted to 250 μg/mL with cation-adjusted Mueller-Hinton broth (CAMHB) and serially diluted 2-fold in 50 μL of CAMHB in the wells. The antibiotic range was 64 to 0.03 μg/mL based on a final well volume of 100 μL after inoculation.

Mortality and ED_{50} for 1a in *S. aureus* Mouse Model. The mice were infected by *S. aureus* PGO#172 (ATCC#29213) strain by intraperitoneal injection and treated with **1a** intravenously (Table 4).

Experimental details for antibiotic susceptibility studies against *B. anthracis* (Table 3), pharmacokinetic studies in BALB/c mice, and mouse efficacy studies (Figures 1 and 2) are presented in the SI.

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Supporting Information Available: Experimental for chemistry, pharmacokinetic study in BALB/c mice, and mouse efficacy studies. This material is available free of charge via the Internet at http//pubs.acs.org.

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