conjugate (AAC). US 5545721 and US 6660267 describe synthesis of a non-specific immunoglobulin-antibiotic conjugate that binds to the surface of target bacteria via the antibiotic, and uses thereof for treating sepsis. US 7569677 and related patents suggest prophetically antibiotic-conjugated antibodies that have an antigen-binding portion specific for a bacterial antigen (such as SA capsular polysaccharide), but lack a constant region that reacts with a bacterial Fc-binding protein (e.g., staphylococcal protein A).

SUMMARY

The disclosure provides compositions referred to as "antibody-antibiotic conjugates," or "AAC") comprising an antibody conjugated by a covalent attachment to one or more rifamycin-type antibiotic moieties.

Disclosed is an isolated anti-WTA monoclonal antibody, comprising a light chain and a H chain, the L chain comprising CDR L1, CDR L2, and CDR L3 and the H chain comprising CDR H1, CDR H2 and CDR H3, wherein the CDR L1, CDR L2, and CDR L3 and CDR H1, CDR H2 and CDR H3 comprise the amino acid sequences of the CDRs of each of Abs 4461 (SEQ ID NO. 1-6), 4624 (SEQ ID NO. 7-12), 4399 (SEQ ID NO. 13-18), and 6267 (SEQ ID NO. 19-24) respectively, as shown in Tables 6A and 6B.

Disclosed is an isolated anti-WTA (wall teichoic acid) monoclonal antibody comprising a light (L) chain and a heavy (H) chain, wherein: the L chain comprising CDR L1 comprising the sequence of KSSQSIFRTSRNKNLLN (SEQ ID NO:99), CDR L2 comprising the sequence of WASTRKS (SEQ ID NO:100), and CDR L3 comprising the sequence of QQYFSPPYT (SEQ ID NO:101); and the H chain comprising CDR H1 comprising the sequence of SFWMH (SEQ ID NO:102), CDR H2 comprising the sequence of FTNNEGTTTAYADSVRG (SEQ ID NO:103), and CDR H3 comprising the sequence of GEGGLDD (SEQ ID NO:118).

Disclosed is an isolated anti-WTA monoclonal antibody comprising a light (L) chain and a heavy (H) chain, wherein: the L chain comprising CDR L1 comprising the sequence of RASQTISGWLA (SEQ ID NO:33), CDR L2 comprising the sequence of KASTLES (SEQ ID NO:34), and CDR L3 comprising the sequence of QQYKSYSFN (SEQ ID NO:35); and the H chain comprising CDR H1 comprising the sequence of SYDIN (SEQ ID NO:36), CDR H2 comprising the sequence of WMNANSGNTGYAQKFQG (SEQ ID NO:37), and CDR H3 comprising the sequence of SSILVRGALGRYFDL (SEQ ID NO:38).

Disclosed is an isolated anti-WTA monoclonal antibody comprising an amino acid sequence selected from the group consisting of:

Another isolated anti-WTA beta antibody provided by the disclosure comprises a heavy chain and a light, wherein the heavy chain comprises a VH having at least 95% sequence identity to SEQ ID NO. 120. In an additional embodiment, this antibody further comprises a VL having at least 95% sequence identity to SEQ ID NO. 119. In a specific embodiment, the anti-WTA beta antibody comprises a light chain and a heavy chain, wherein the L chain comprises a VL sequence of SEQ ID NO. 119 and the H chain comprises a VH sequence of SEQ ID NO. 120. In a yet more specific embodiment, the isolated antibody that binds WTA beta comprises a L chain of SEQ ID NO. 121 and a H chain of SEQ ID NO. 122.

The anti-WTA beta Cys-engineered H and L chain variants can be paired in any of the following combinations to form full Abs for conjugating to linker-Abx intermediates to generate anti-WTA AACs of the disclosure. In one embodiment, the L chain comprises the sequence of SEQ ID NO.121 and the H chain comprises the sequence of SEQ ID NO. 124. In another embodiment, the isolated antibody comprises a L chain of SEQ ID NO. 123 and a H chain comprising a sequence of SEQ ID NO.124 or SEQ ID NO.157. In a particular embodiment, the anti- WTA beta antibody as well as the anti-WTA beta AAC of the disclosure comprises a L chain of SEQ ID NO. 123.

Disclosed is an antibody that binds to the same epitope as any one of the antibodies described herein. Yet another embodiment is an antibody that binds to the same epitope as each of the anti-WTA alpha Abs of Figure 13A and Figure 13B. Also provided is an antibody that binds to the same epitope as each of the anti-WTA beta Abs of Figure 14, Figures 15A and 15B, Figures 16A and 16B, and Figures 17A and 17B.

In a further embodiment, the anti-WTA beta and anti-WTA alpha antibodies of the present disclosure are antigen-binding fragments lacking the Fc region, preferably $F(ab')_2$ or F(ab). Thus, the present disclosure provides antibody-antibiotic conjugates wherein the WTA antibody is a $F(ab')_2$ or F(ab).

Disclosed is an anti-WTA monoclonal antibody that binds to WTA beta.

Disclosed is an isolated anti-WTA (wall teichoic acid) monoclonal antibody comprising a light (L) chain and a heavy (H) chain, wherein:

(a) the L chain comprising CDR L1 comprising the sequence of RASQTISGWLA (SEQ ID NO:33), CDR L2 comprising the sequence of KASTLES (SEQ ID NO:34), and CDR L3 comprising the sequence of QQYKSYSFN (SEQ ID NO:35); and the H chain comprising CDR H1 comprising the sequence of SYDIN (SEQ ID NO:36), CDR H2 comprising the sequence of WMNANSGNTGYAQKFQG (SEQ ID

In some embodiments, the isolated anti-WTA monoclonal antibody comprising a heavy chain and a light chain, wherein the heavy chain comprises the sequence of SEQ ID NO:146, SEQ ID NO.147, SEQ ID NO.157 or SEQ ID NO.124, and the light chain comprises the sequence of SEQ ID NO.121. In some embodiments, the isolated anti-WTA monoclonal antibody comprising a heavy chain and a light chain, wherein the heavy chain comprises the sequence of SEQ ID NO:146, SEQ ID NO.147, SEQ ID NO.157 or SEQ ID NO.124, and the light chain comprises the sequence of SEQ ID NO.123. In some embodiments, the isolated anti-WTA monoclonal antibody comprising a heavy chain and a light chain, wherein the heavy chain comprises the sequence of SEQ ID NO:146, SEQ ID NO.147, SEQ ID NO.157 or SEQ ID NO.124, and the light chain comprises the sequence of SEQ ID NO.145.

In some embodiments of any of the antibodies described above, the antibody is not an IgM isotype. In some embodiments of any of the antibodies described above, the antibody is an IgG (e.g., IgG1, IgG2, IgG3, IgG4), IgE, IgD, or IgA (e.g., IgA1 or IgA2) isotype. In some embodiments of any of the antibodies described above, the antibody is produced by a host cell in cell culture. In some embodiments, the host cell is a non-human cell. In some embodiments, the host cell is prokaryotic or eukaryotic. In some embodiments, the host cell is a mammalian cell (e.g., a human or non-human mammalian cell). In some embodiments, the host cell is a CHO cell.

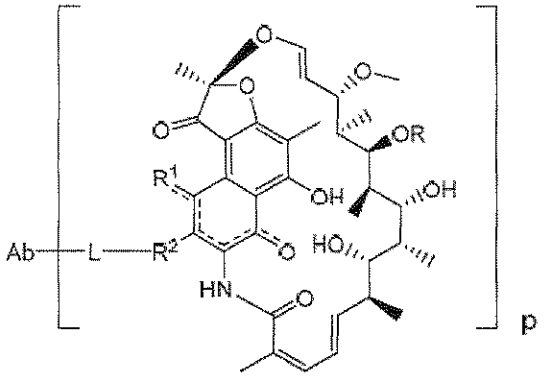
Disclosed is a composition comprising any of the antibodies described herein and a pharmaceutically acceptable carrier. Disclosed is a pharmaceutical composition comprising any of the antibodies disclosed herein, and a pharmaceutically acceptable carrier.

Disclosed is an isolated nucleic acid encoding any of the antibodies disclosed herein. Disclosed is a vector comprising the nucleic acid described herein. Disclosed is a vector comprising a nucleic acid encoding any of the antibodies disclosed herein. In a further embodiment, the vector is an expression vector.

Disclosed is an isolated host cell comprising a nucleic acid encoding any of the antibodies described herein. The disclosure also provides a host cell comprising a nucleic acid encoding any of the antibodies disclosed herein. In a further embodiment, the host cell is prokaryotic or eukaryotic. In some embodiments, the host cell is a mammalian cell (e.g., a human or non-human mammalian cell). In some embodiments, the host cell is a CHO cell.

Disclosed is a method of producing an antibody comprising culturing a host cell described herein under conditions suitable for expression of the nucleic acid; and recovering the antibody produced by the cell. The disclosure further provides a method of producing an antibody comprising culturing a host cell comprising a nucleic acid encoding any of the antibodies disclosed herein under conditions suitable for expression of the nucleic acid; and recovering the antibody produced by the cell. In some embodiments, the method further comprises purifying the antibody.

In one aspect, there is provided an antibody-antibiotic conjugate compound comprising an anti-wall teichoic acid (WTA) monoclonal antibody, wherein the anti-wall teichoic acid monoclonal antibody binds to *Staphylococcus aureus,* and covalently attached to a rifamycin-type antibiotic by a protease-cleavable, peptide linker, the antibody-antibiotic conjugate compound having Formula I:



I

wherein:

the dashed lines indicate an optional bond;

R is H, C_1–C_{12} alkyl, or $C(O)CH_3$;

R^1 is OH;

R^2 is CH=N–(heterocyclyl), wherein the heterocyclyl is optionally substituted with one or more groups independently selected from $C(O)CH_3$, C_1–C_{12} alkyl, C_1–C_{12} heteroaryl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_3–C_{12} carbocyclyl;

or R^1 and R^2 form a five- or six-membered fused heteroaryl or heterocyclyl, and optionally forming a spiro or fused six-membered heteroaryl, heterocyclyl, aryl, or carbocyclyl ring,

wherein the spiro or fused six-membered heteroaryl, heterocyclyl, aryl, or carbocyclyl ring is optionally substituted H, F, Cl, Br, I, C_1–C_{12} alkyl, or OH;

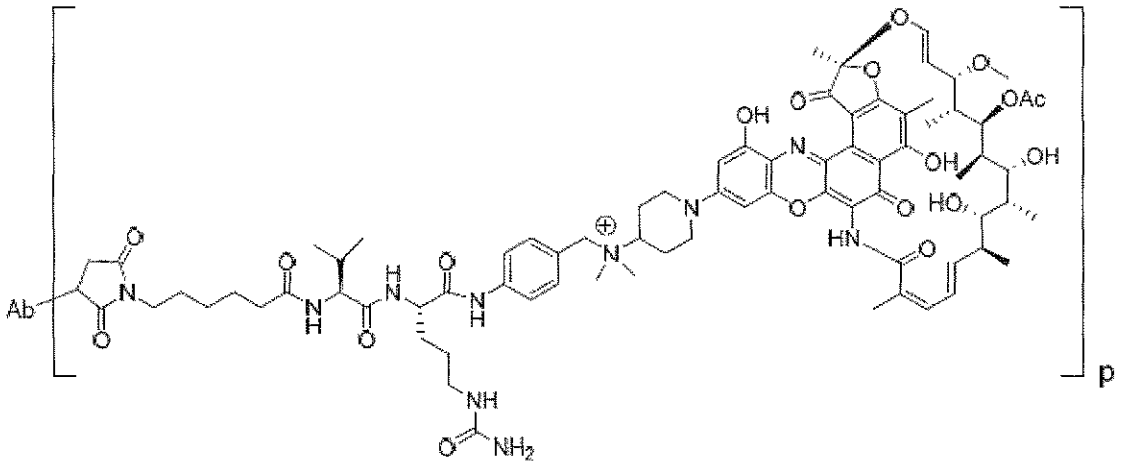
L is the peptide linker attached to R^2 or the fused heteroaryl or heterocyclyl formed by R^1 and R^2;

Ab is the anti-wall teichoic acid monoclonal antibody; and

p is an integer from 1 to 8.

In some embodiments, the anti-wall teichoic acid antibody binds to methicillin-resistant *Staphylococcus aureus* (MRSA).

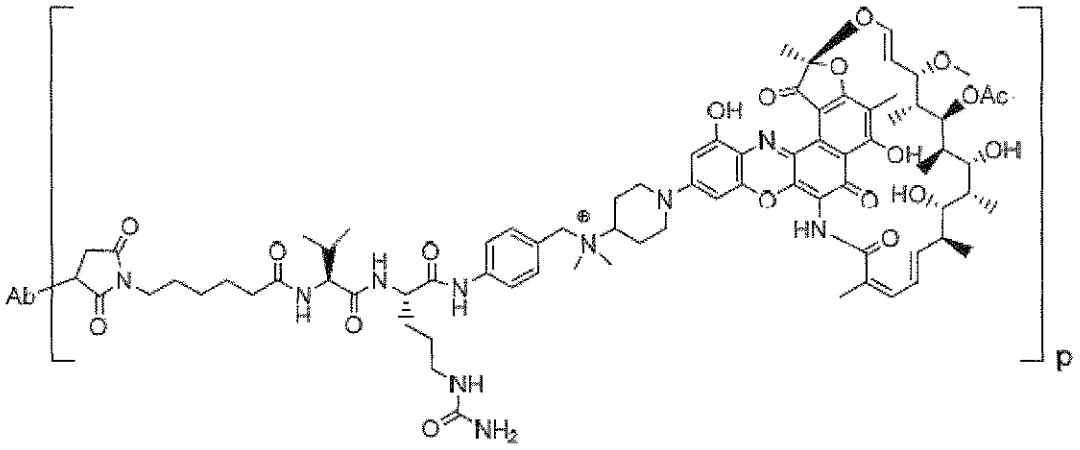
In another aspect, there is provided an antibody-antibiotic conjugate compound having the formula:



wherein Ab is an anti-wall teichoic acid (WTA) monoclonal antibody that binds to *Staphylococcus aureus*, wherein the VL of the anti-wall teichoic acid monoclonal antibody comprises CDR L1 comprising the sequence of KSSQSIFRTSRNKNLLN (SEQ ID NO:99), CDR L2 comprising the sequence of WASTRKS (SEQ ID NO:100), and CDR L3 comprising the sequence of QQYFSPPYT (SEQ ID NO:101); and the VH of the anti-WTA monoclonal antibody comprises CDR H1 comprising the sequence of SFWMH (SEQ ID NO:102), CDR H2 comprising the sequence of FTNNEGTTTAYADSVRG (SEQ ID NO:103), and CDR H3 comprising the sequence of GEGGLDD (SEQ ID NO:118); and

p is an integer from 1 to 8.

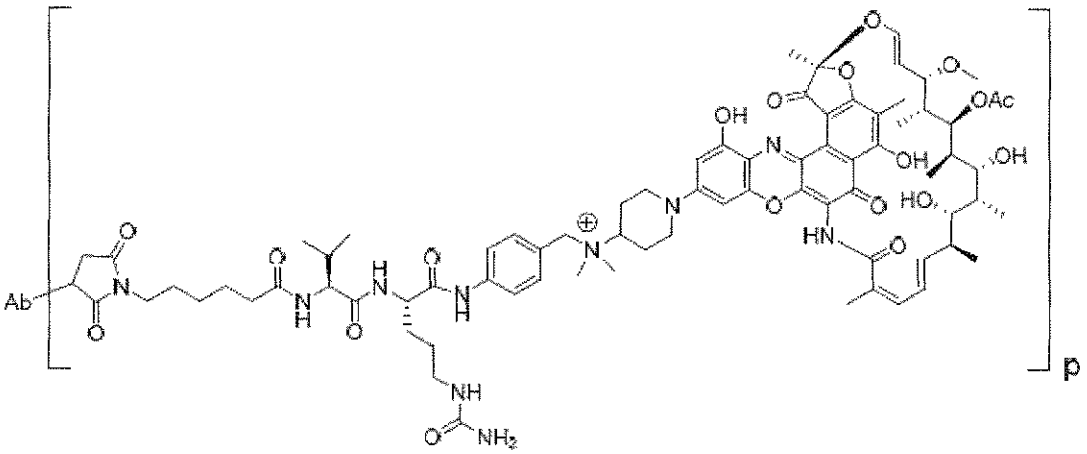
In yet another aspect, there is provided an antibody-antibiotic conjugate compound having the formula:



wherein Ab is an anti-wall teichoic acid (WTA) monoclonal antibody that binds to *Staphylococcus aureus*, and comprises a VL and a VH, wherein the VL comprises the sequence of SEQ ID NO:119 and the VH comprises the sequence SEQ ID NO:156; and

p is an integer from 1 to 8.

In a further aspect, there is provided an antibody-antibiotic conjugate compound having the formula:



wherein Ab is an anti-wall teichoic acid (WTA) monoclonal antibody that binds to *Staphylococcus aureus*, and comprises a VL and a VH, wherein the VL comprises the sequence of SEQ ID NO:119 and the VH comprises the sequence SEQ ID NO:156; and wherein p is an integer of 2.

In some embodiments of the antibody-antibiotic conjugates disclosed herein, the antibody comprises: i) L chain and H chain CDRs of SEQ ID NOs 99-104 or the L chain and H chain CDRs of SEQ ID NOs. 33-38; or ii) the VL of SEQ ID NO.119 or SEQ ID NO. 123 paired with the VH of SEQ ID NO.120 or SEQ ID NO. 156; or iii) the VL of SEQ ID NO.111 paired with the VH of SEQ ID NO.112.

In some embodiments, the rifamycin-type antibiotic is a rifalazil-type antibiotic. In some embodiments, the rifamycin-type antibiotic comprises a quaternary amine attached to the peptide linker. In some embodiments, the antibiotic is attached to the antibody via a peptide linker which is attached to an engineered cysteine of the anti-WTA antibody. The engineered cysteine may be in the L or H chain of the modified antibody. In some embodiments, the cysteine residue is in the L chain. In some embodiments, the cysteine residue is in the H chain.

The antibody-antibiotic conjugate compounds of the disclosure can comprise a peptide linker which is a *S. aureus* cysteine protease cleavable linker; such linkers include a staphopain B or a staphopain A cleavable linker. In one embodiment, the *S. aureus* protease is an endopeptidase. In another embodiment the linker is a host protease cleavable linker preferably a human protease cathepsin B cleavable linker (e.g., a val-cit dipeptide linker).

An exemplary embodiment of an antibody-antibiotic conjugate compound has the formula:

$$Ab–(L–abx)_p$$

wherein:

Ab is the anti-wall teichoic acid antibody;

L is the peptide linker having the formula:

$$–Str–Pep–Y–$$

where Str is a stretcher unit; Pep is a peptide of two to twelve amino acid residues, and Y is a spacer unit;

In another aspect, there is provided a pharmaceutical composition comprising any of the antibody-antibiotic conjugate compounds described herein, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient. Disclosed is a pharmaceutical composition comprising an antibody-antibiotic conjugate compound of the disclosure.

Disclosed is use of an antibody-antibiotic conjugate compound comprising an anti-wall teichoic acid (WTA) antibody covalently attached by a peptide linker to a rifamycin-type antibiotic, in the manufacture of a medicament for treating a bacterial infection in a patient. Disclosed is use of any one of antibody-antibiotic conjugates described herein in the manufacture of a medicament for treating a bacterial infection in a patient. Disclosed is a method of treating a bacterial infection by administering to a patient a therapeutically-effective amount of an antibody-antibiotic conjugate compound of any of the above embodiments. In one embodiment, the patient is a human. In one embodiment the bacterial infection is a *Staphylococcus aureus* infection. In some embodiments, the patient has been diagnosed with a Staph aureus infection. In some embodiments, treating the bacterial infection comprises reducing bacterial load.

The disclosure further provides a method of killing intracellular Staph aureus in the host cells of a staph aureus infected patient without killing the host cells by administering an anti-WTA-antibiotic conjugate compound of any of the above embodiments. Another method is provided for killing persister bacterial cells (e.g, staph A) in vivo by contacting the persister bacteria with an AAC of any of the preceding embodiments.

In another embodiment, the method of treatment further comprises administering a second therapeutic agent. In a further embodiment, the second therapeutic agent is an antibiotic including an antibiotic against Staph aureus in general or MRSA in particular.

In one embodiment, the second antibiotic administered in combination with the antibody-antibiotic conjugate compound of the disclosure is selected from the structural classes: (i) aminoglycosides; (ii) beta-lactams; (iii) macrolides/cyclic peptides; (iv) tetracyclines; (v) fluoroquinolines/fluoroquinolones; (vi) and oxazolidinones.

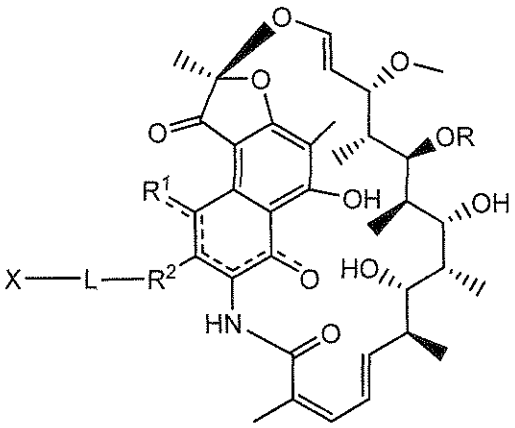
In one embodiment, the second antibiotic administered in combination with the antibody-antibiotic conjugate compound of the disclosure is selected from clindamycin, novobiocin, retapamulin, daptomycin, GSK-2140944, CG-400549, sitafloxacin, teicoplanin, triclosan, napthyridone, radezolid, doxorubicin, ampicillin, vancomycin, imipenem, doripenem, gemcitabine, dalbavancin, and azithromycin.

In some embodiments herein, the bacterial load in the subject has been reduced to an undetectable level after the treatment. In one embodiment, the patient's blood culture is negative after treatment as compared to a positive blood culture before treatment. In some embodiments herein, the bacterial resistance in the subject is undetectable or low. In some embodiments herein, the subject is not responsive to treatment with methicillin or vancomycin.

In another aspect, there is provided a process for making any one of the antibody-antibiotic conjugates described herein comprising the steps of:

a) preparing the anti-wall teichoic acid monoclonal antibody by reduction with DDT (dithiothreitol) or tricarbonylethylphosphine (TCEP); and

b) conjugating an antibiotic-linker intermediate having Formula II:



II

wherein:

the dashed lines indicate an optional bond;

R is H, C_1–C_{12} alkyl, or $C(O)CH_3$;

R^1 is OH;

R^2 is CH=N–(heterocyclyl), wherein the heterocyclyl is optionally substituted with one or more groups independently selected from $C(O)CH_3$, C_1–C_{12} alkyl, C_1–C_{12} heteroaryl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_3–C_{12} carbocyclyl;

or R^1 and R^2 form a five- or six-membered fused heteroaryl or heterocyclyl, and optionally forming a spiro or fused six-membered heteroaryl, heterocyclyl, aryl, or carbocyclyl ring, wherein the spiro or fused six-membered heteroaryl, heterocyclyl, aryl, or carbocyclyl ring is optionally substituted H, F, Cl, Br, I, C_1–C_{12} alkyl, or OH;

L is a peptide linker attached to R^2 or the fused heteroaryl or heterocyclyl formed by R^1 and R^2; and having the formula:

–Str–Pep–Y–

where Str is a stretcher unit; Pep is a peptide of two to twelve amino acid residues, and Y is a spacer unit; and

X is a reactive functional group selected from maleimide, thiol, amino, bromide, bromoacetamido, iodoacetamido, p-toluenesulfonate, iodide, hydroxyl, carboxyl, pyridyl disulfide, and N-hydroxysuccinimide;

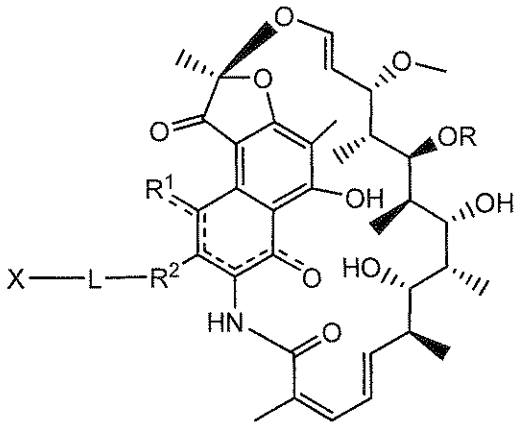
to the anti-wall teichoic acid monoclonal antibody

whereby the antibody-antibiotic conjugate compound is formed.

Disclosed is a process for making an antibody or an antibody-antibiotic conjugate compound of the disclosure comprising conjugating a rifamycin-type antibiotic to an anti-wall teichoic acid (WTA) antibody.

In another aspect, there is provided a kit for treating a bacterial infection comprising a pharmaceutical composition described herein and instructions for use.

Disclosed is an antibiotic-linker intermediate having Formula II:



II

wherein:

the dashed lines indicate an optional bond;

R is H, C_1–C_{12} alkyl, or $C(O)CH_3$;

R^1 is OH;

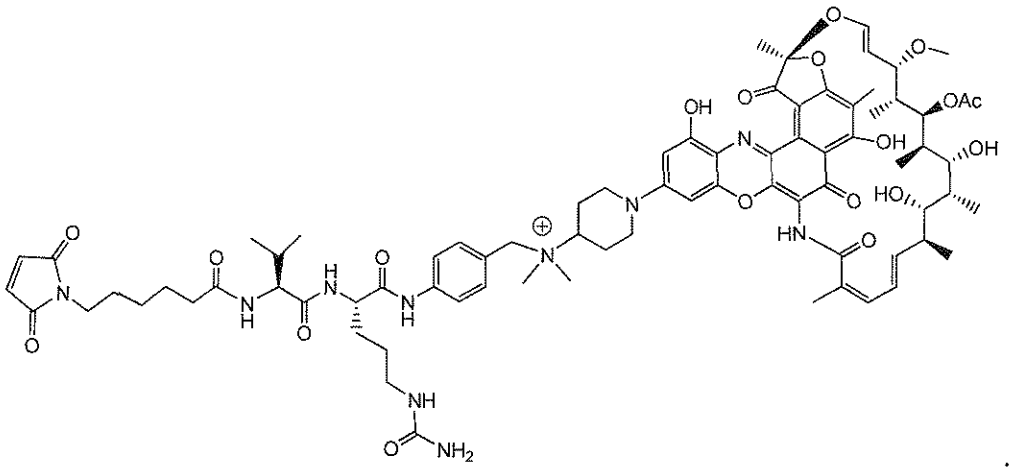
R^2 is CH=N–(heterocyclyl), wherein the heterocyclyl is optionally substituted with one or more groups independently selected from $C(O)CH_3$, C_1–C_{12} alkyl, C_1–C_{12} heteroaryl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_3–C_{12} carbocyclyl;

or R^1 and R^2 form a five- or six-membered fused heteroaryl or heterocyclyl, and optionally forming a spiro or fused six-membered heteroaryl, heterocyclyl, aryl, or carbocyclyl ring, wherein the spiro or fused six-membered heteroaryl, heterocyclyl, aryl, or carbocyclyl ring is optionally substituted H, F, Cl, Br, I, C_1–C_{12} alkyl, or OH;

L is a peptide linker attached to R^2 or the fused heteroaryl or heterocyclyl formed by R^1 and R^2; and having the formula:

$$-Str-Pep-Y-$$

where Str is a stretcher unit; Pep is a peptide of two to twelve amino acid residues, and Y is a spacer unit; and



In one aspect, there is provided use of an anti-antibiotic conjugate compound of any one of claims 1-43 in the manufacture of a medicament for treating a bacterial infection in a patient, wherein the bacterial infection is a *Staphylococcus aureus* infection.

In one aspect, there is provided use of an anti-antibiotic conjugate compound of any one of claims 1-43 in the manufacture of a medicament for reducing the number of intracellular *Staphylococcus aureus* bacterial cells in the host cells of a *Staphylococcus aureus* infected patient without reducing the number of the host cells.

Disclosed is use of any one of the anti-WTA-antibiotic conjugates described herein in the manufacture of a medicament for killing intracellular *Staphylococcus aureus* in the host cells of a *Staphylococcus aureus*-infected patient without killing the host cells. Also provided is a method of killing intracellular *Staph aureus* in the host cells of a *Staph aureus* infected patient without killing the host cells comprising administering an anti-WTA-antibiotic conjugate detailed herein.

It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present disclosure. These and other disclosures will become apparent to one of skill in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows that exposure to vancomycin or rifampicin kills MRSA gradually. Vancomycin was tested at 2 μg/mL (open square) and 20 μg/mL (closed square). Rifampicin was tested at 0.02 μg/mL (open triangle) and 0.2 μg/mL (closed triangle).

Figure 2 shows infected peritoneal cells were able to transfer infection to osteoblasts in the presence of vancomycin.

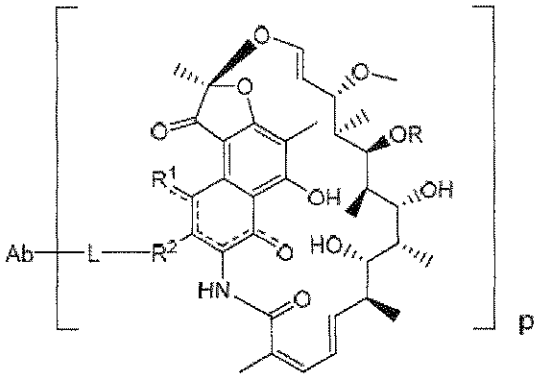
Figure 3 shows the cell wall of Gram-positive bacteria, such as S. aureus with a cartoon representation of wall teichoic acids (WTA), Lipo teichoic acid (LTA) and the Peptidoglycan (PGN) sheaths that stabilize the cell membrane and provide attachment sites.

Figure 4 shows the chemical structure and glycosyl modifications of Wall Teichoic Acid (WTA), described in detail under Definitions.

Figure 5 shows a possible mechanism of drug activation for antibody-antibiotic conjugates (AAC). Active antibiotic (Abx) is released after internalization of the AAC inside mammalian cells.

We Claim:

1. An antibody-antibiotic conjugate compound comprising an anti-wall teichoic acid (WTA) monoclonal antibody, wherein the anti-wall teichoic acid monoclonal antibody binds to *Staphylococcus aureus,* and covalently attached to a rifamycin-type antibiotic by a protease-cleavable, peptide linker, the antibody-antibiotic conjugate compound having Formula I:



I

wherein:

the dashed lines indicate an optional bond;

R is H, C_1–C_{12} alkyl, or $C(O)CH_3$;

R^1 is OH;

R^2 is CH=N–(heterocyclyl), wherein the heterocyclyl is optionally substituted with one or more groups independently selected from $C(O)CH_3$, C_1–C_{12} alkyl, C_1–C_{12} heteroaryl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_3–C_{12} carbocyclyl;

or R^1 and R^2 form a five- or six-membered fused heteroaryl or heterocyclyl, and optionally forming a spiro or fused six-membered heteroaryl, heterocyclyl, aryl, or carbocyclyl ring,

wherein the spiro or fused six-membered heteroaryl, heterocyclyl, aryl, or carbocyclyl ring is optionally substituted H, F, Cl, Br, I, C_1–C_{12} alkyl, or OH;

L is the peptide linker attached to R^2 or the fused heteroaryl or heterocyclyl formed by R^1 and R^2;

Ab is the anti-wall teichoic acid monoclonal antibody; and

p is an integer from 1 to 8.

2. The antibody-antibiotic conjugate compound of claim 1, wherein the VL of the anti-WTA monoclonal antibody comprises CDR L1 comprising the sequence of KSSQSIFRTSRNKNLLN (SEQ ID NO:99), CDR L2 comprising the sequence of WASTRKS (SEQ ID NO:100), and CDR L3 comprising the sequence of QQYFSPPYT

(SEQ ID NO:101); and the VH of the anti-WTA monoclonal antibody comprises CDR H1 comprising the sequence of SFWMH (SEQ ID NO:102), CDR H2 comprising the sequence of FTNNEGTTTAYADSVRG (SEQ ID NO:103), and CDR H3 comprising the sequence of GEGGLDD (SEQ ID NO:118) or GDGGLDD (SEQ ID NO:104).

3. The antibody-antibiotic conjugate compound of claim 2, wherein the antibody comprises a VL comprising the amino acid sequence SEQ ID NO:119.

4. The antibody-antibiotic conjugate compound of claim 2, wherein the antibody comprises a VH comprising the amino acid sequence of SEQ ID NO:156.

5. The antibody-antibiotic conjugate compound of claim 2, wherein the antibody comprises a VL and a VH, wherein the VL comprises the sequence of SEQ ID NO:119 and the VH comprises the sequence SEQ ID NO:156.

6. The antibody-antibiotic conjugate compound of claim 2, wherein the antibody comprises a light chain and a heavy chain sequence of

(a) SEQ ID NO:123 and SEQ ID NO:147, or

(b) SEQ ID NO:145 and SEQ ID NO:147.

7. The antibody-antibiotic conjugate compound of claim 2, wherein the antibody comprises a VH comprising the amino acid sequence of SEQ ID NO:120.

8. The antibody-antibiotic conjugate compound of claim 2, wherein the antibody comprises a VL and a VH, wherein the VL comprises the sequence of SEQ ID NO:119 and the VH comprises the sequence SEQ ID NO:120.

9. The antibody-antibiotic conjugate compound of claim 2, wherein the antibody comprises a light chain (LC) wherein the LC comprises the amino acid sequence of SEQ ID NO:121, and a heavy chain (HC) wherein the HC comprises the amino acid sequence of SEQ ID NO:146.

10. The antibody-antibiotic conjugate compound of claim 2, wherein the antibody comprises a light chain (LC) wherein the LC comprises the amino acid sequence of SEQ ID NO:145, and a heavy chain (HC) wherein the HC comprises the amino acid sequence of SEQ ID NO:157.

11. The antibody-antibiotic conjugate compound of any one of claims 1-10, wherein the rifamycin-type antibiotic comprises a quaternary amine attached to the peptide linker.

12. The antibody-antibiotic conjugate compound of any one of claims 1-11, wherein the peptide linker is attached to a cysteine or an engineered cysteine of the anti-WTA antibody.

13. The antibody-antibiotic conjugate compound of any one of claims 1-12, wherein the peptide linker is a *S. aureus* endopeptidase or cysteine protease cleavable linker.

14. The antibody-antibiotic conjugate compound of claim 13, wherein the peptide linker is a staphopain B or a staphopain A cleavable linker.

15. The antibody-antibiotic conjugate compound of claim 13, wherein the peptide linker is a human protease cathepsin B cleavable linker.

16. The antibody-antibiotic conjugate compound of claim 15, wherein the peptide linker is a val-cit dipeptide linker.

17. The antibody-antibiotic conjugate compound of claim 1, wherein:

L is the peptide linker having the formula:

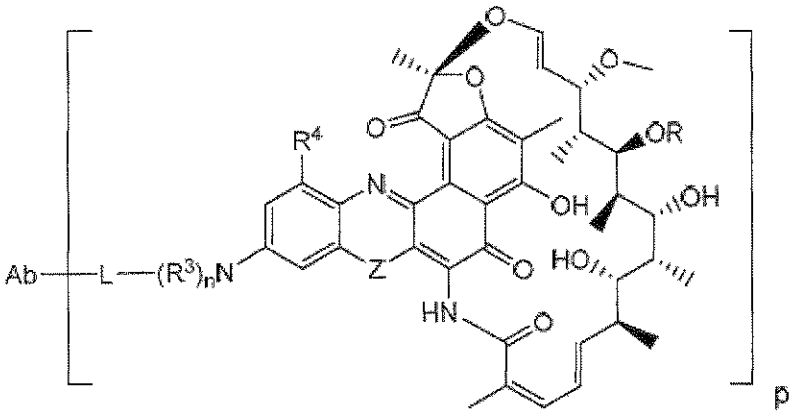
–Str–Pep–Y–

where Str is a stretcher unit; Pep is a peptide of two to twelve amino acid residues, and Y is a spacer unit.

18. The antibody-antibiotic conjugate compound of claim 17, wherein p is 2 to 4.

19. The antibody-antibiotic conjugate compound of claim 1, wherein the formula is selected from the group consisting of:

a)



wherein

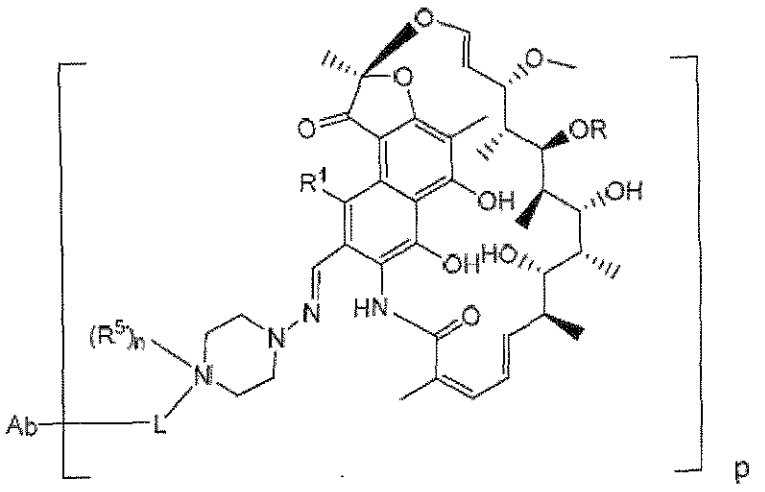
R^3 is independently selected from H and C_1–C_{12} alkyl;

n is 1 or 2;

R^4 is selected from H, F, Cl, Br, I, C_1–C_{12} alkyl, and OH; and

Z is selected from NH, N(C_1–C_{12} alkyl), O and S;

b)

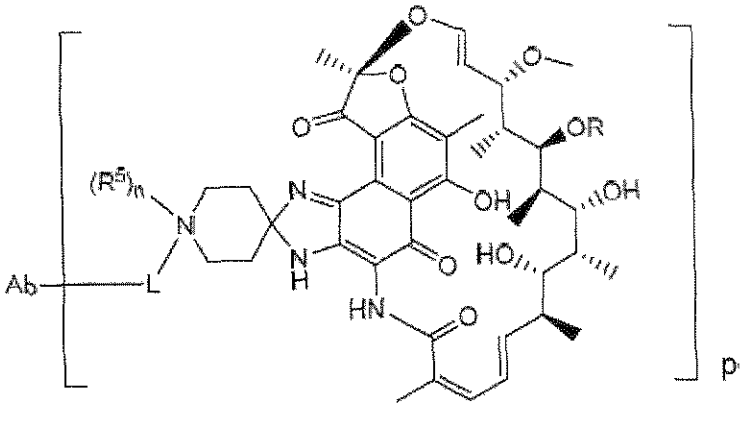


wherein

R^5 is selected from H and C_1–C_{12} alkyl; and

n is 0 or 1;

c)

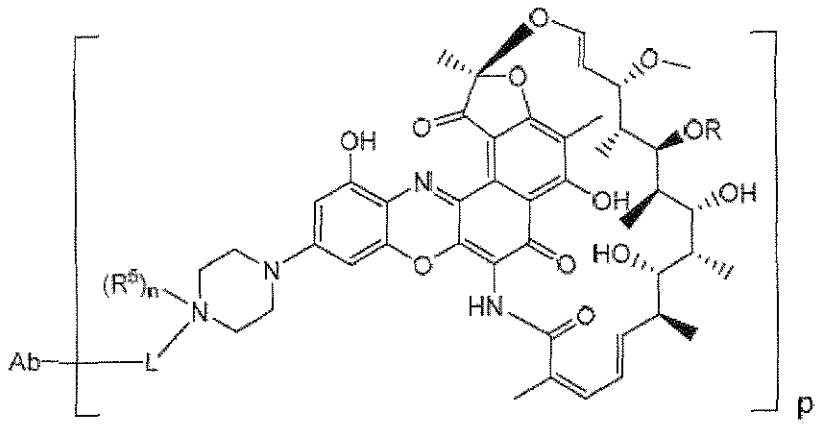


wherein

R^5 is selected from H and C_1–C_{12} alkyl; and

n is 0 or 1;

d)

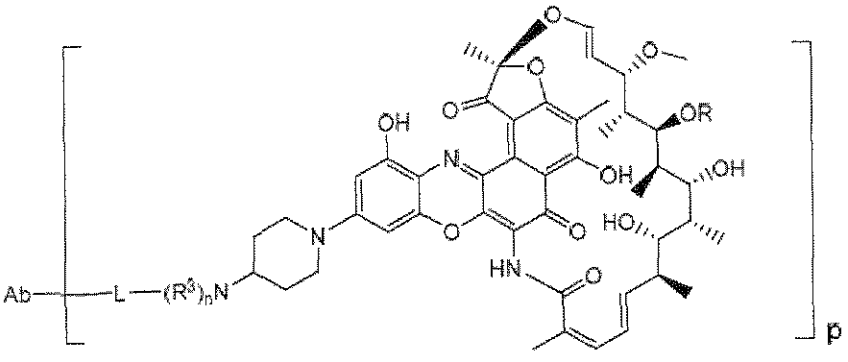


wherein

R^5 is independently selected from H and C_1–C_{12} alkyl; and

n is 0 or 1;

e)

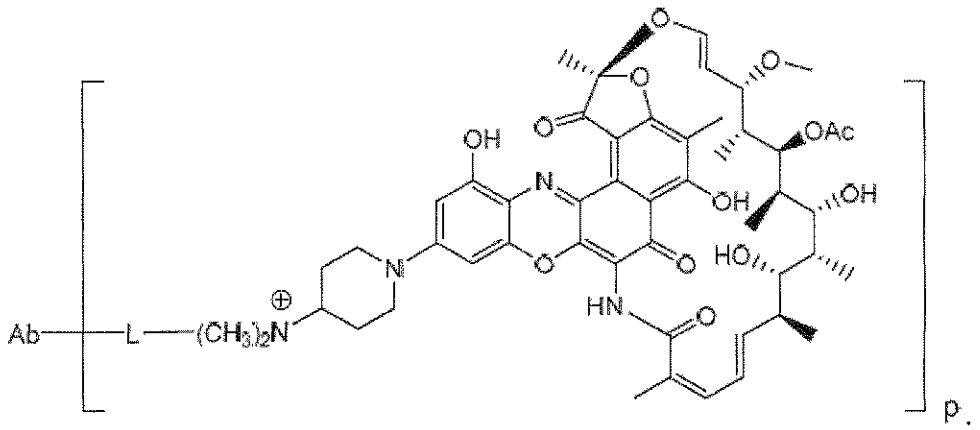


wherein

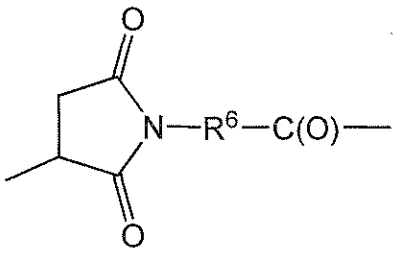
R^3 is independently selected from H and C_1–C_{12} alkyl; and

n is 1 or 2; and

f)



20. The antibody-antibiotic conjugate compound of claim 17, wherein Str has the formula:



wherein R^6 is selected from the group consisting of C_1-C_{10} alkylene-, -C_3-C_8 carbocyclo, -O-(C_1-C_8 alkyl)-, -arylene-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-, -$(CH_2CH_2O)_r$-, and -$(CH_2CH_2O)_r$-CH_2-; and r is an integer ranging from 1 to 10.

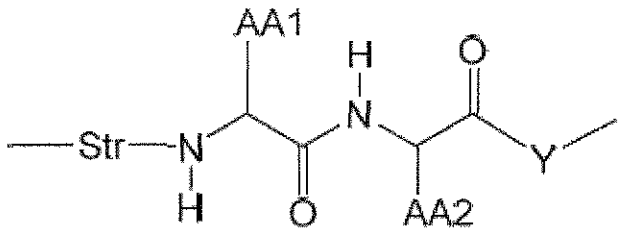
21. The antibody-antibiotic conjugate compound of claim 20, wherein R^6 is -$(CH_2)_5$- .

22. The antibody-antibiotic conjugate compound of claim 17, wherein Pep comprises two to twelve amino acid residues independently selected from glycine, alanine, phenylalanine, lysine, arginine, valine, and citrulline.

23. The antibody-antibiotic conjugate compound of claim 22, wherein Pep is selected from valine-citrulline (val-cit, vc); phenylalanine-lysine (fk); and valine-citrulline-phenylalanine (val-cit-phe).

24. The antibody-antibiotic conjugate compound of claim 17, wherein Y comprises para-aminobenzyl or para-aminobenzyloxycarbonyl.

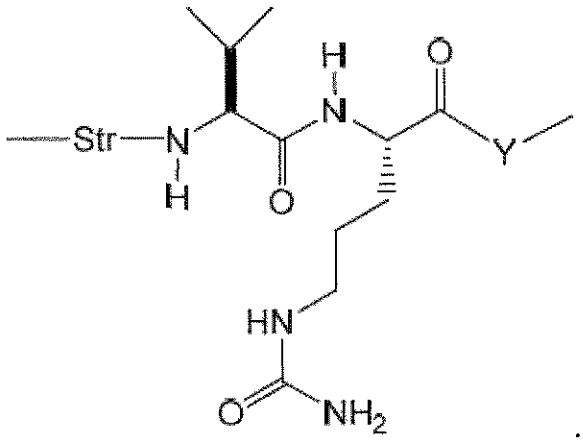
25. The antibody-antibiotic conjugate compound of claim 17 wherein the L is the peptide linker having the formula:



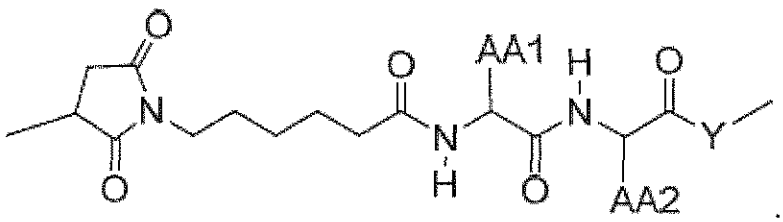
where AA1 and AA2 are independently selected from an amino acid side chain.

26. The antibody-antibiotic conjugate compound of claim 25, wherein the amino acid side chain is independently selected from H, $-CH_3$, $-CH_2(C_6H_5)$, $-CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, $-CHCH(CH_3)CH_3$, and $-CH_2CH_2CH_2NHC(O)NH_2$.

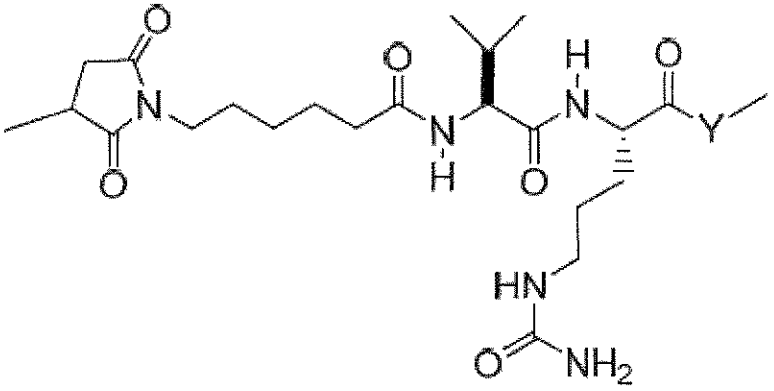
27. The antibody-antibiotic conjugate compound of claim 25 wherein L is the peptide linker having the formula:



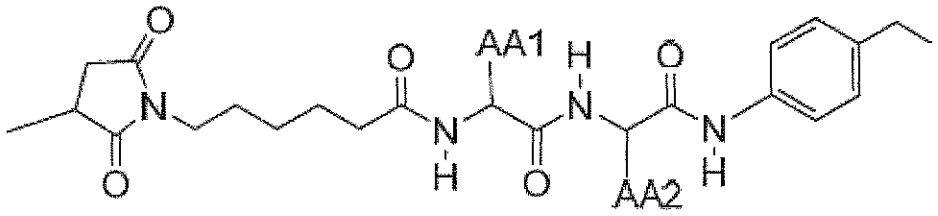
28. The antibody-antibiotic conjugate compound of claim 25 wherein L is the peptide linker having the formula:



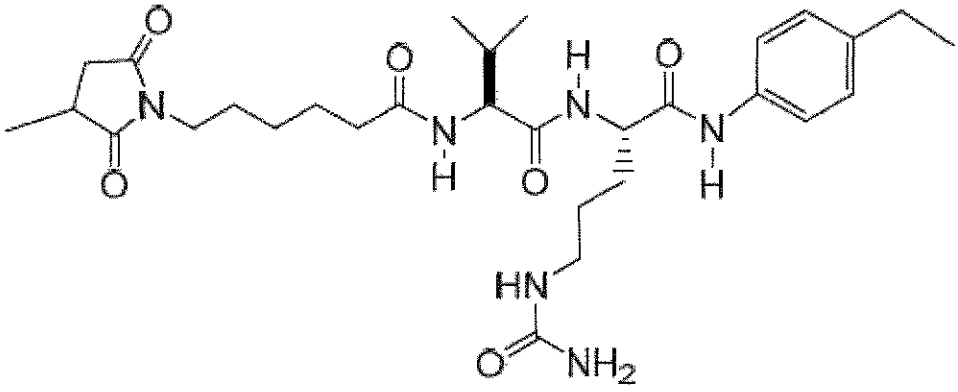
29. The antibody-antibiotic conjugate compound of claim 25 wherein L is the peptide linker having the formula:



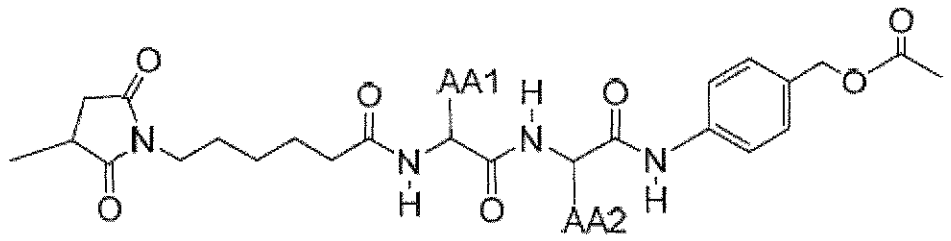
30. The antibody-antibiotic conjugate compound of claim 25 wherein L is the peptide linker having the formula:



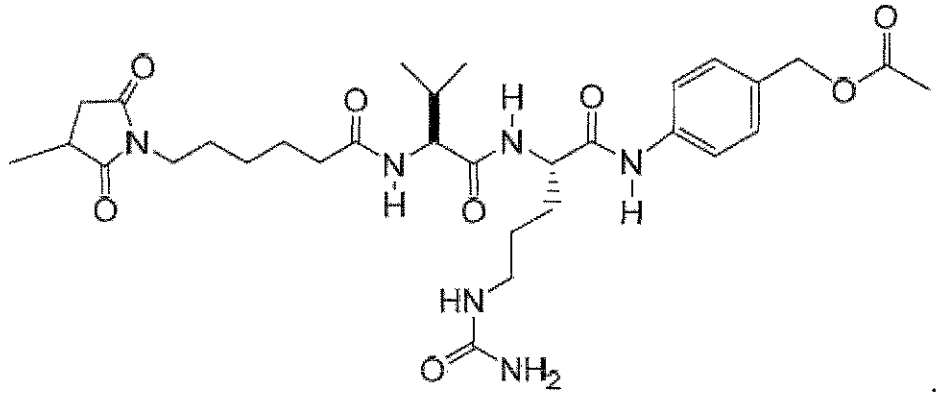
31. The antibody-antibiotic conjugate compound of claim 30 wherein L is the peptide linker having the formula:



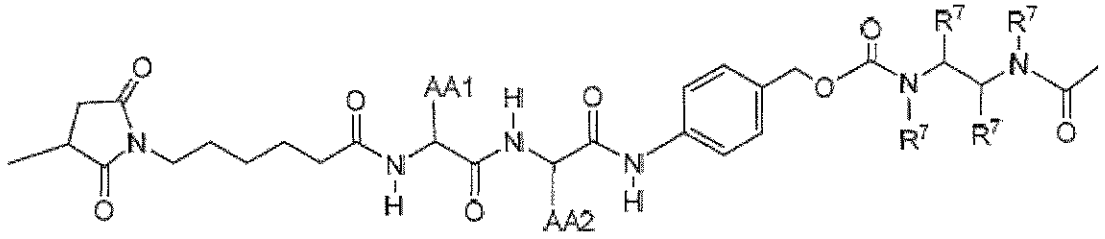
32. The antibody-antibiotic conjugate compound of claim 25 wherein L is the peptide linker having the formula:



33. The antibody-antibiotic conjugate compound of claim 32 wherein L is the peptide linker having the formula:

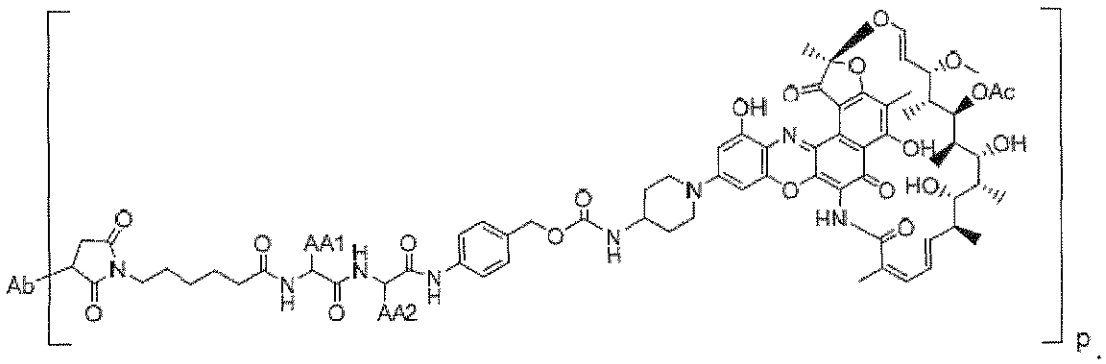


34. The antibody-antibiotic conjugate compound of claim 25 wherein L is the peptide linker having the formula:

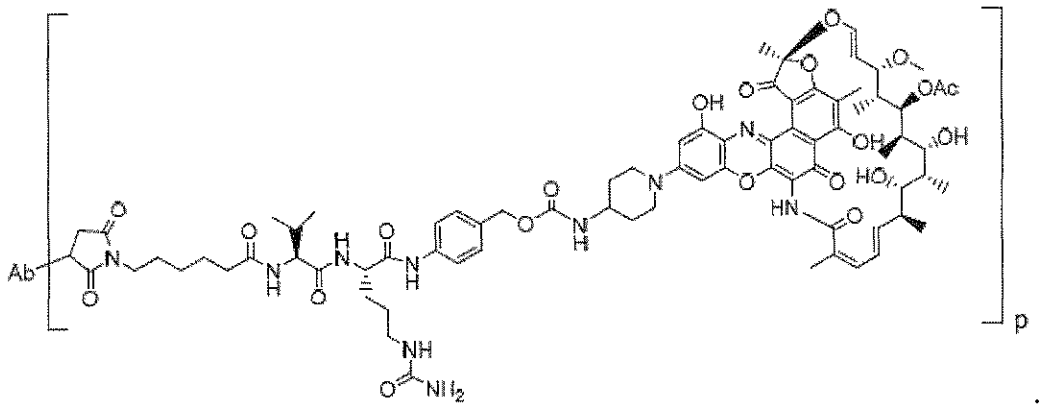


where R^7 is independently selected from H and C_1–C_{12} alkyl.

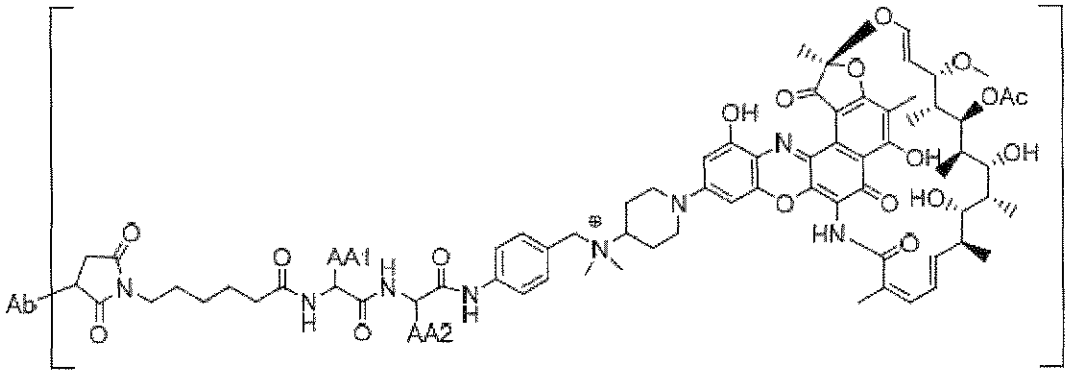
35. The antibody-antibiotic conjugate compound of claim 25 having the formula:



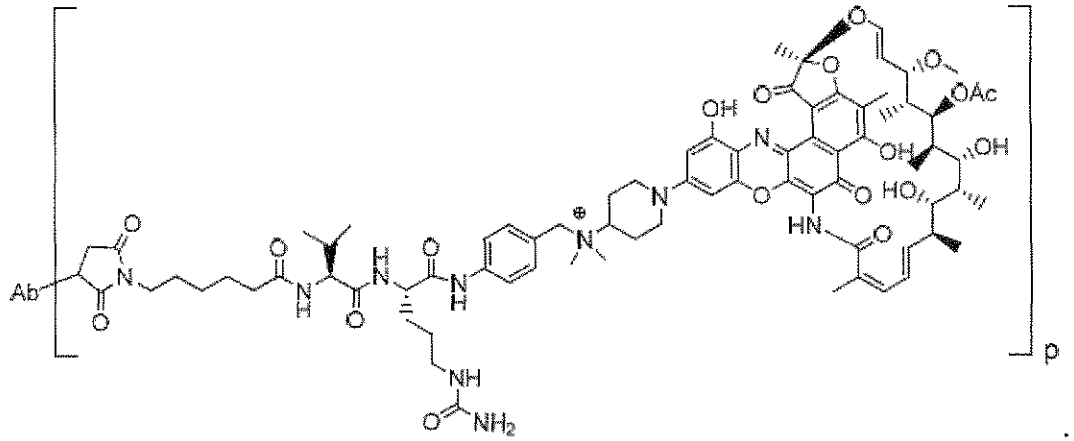
36. The antibody-antibiotic conjugate compound of claim 35 having the formula:



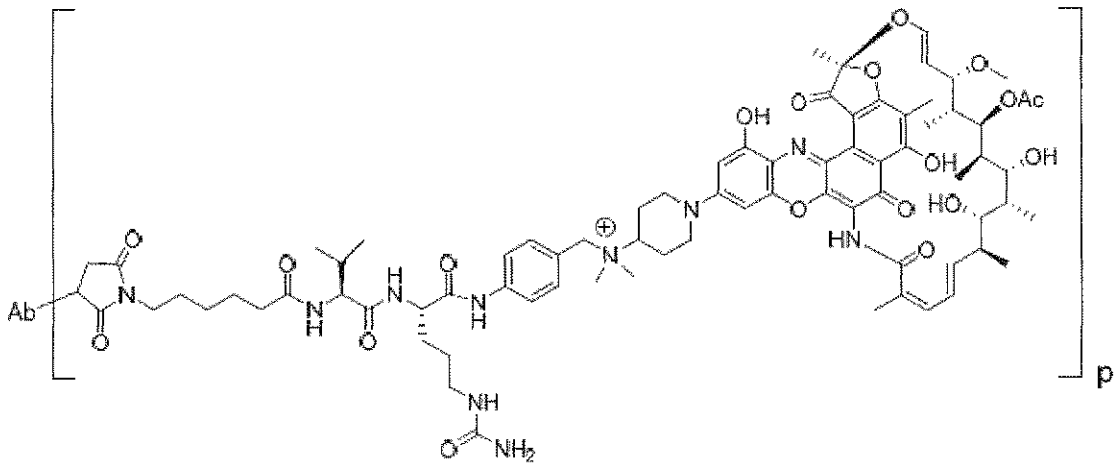
37. The antibody-antibiotic conjugate compound of claim 25 having the formula:



38. The antibody-antibiotic conjugate compound of claim 37 having the formula:



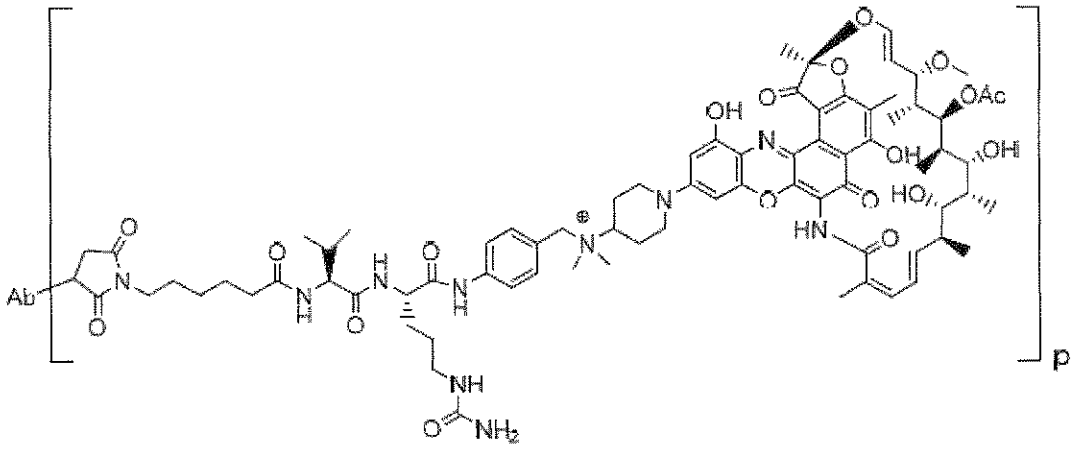
39. An antibody-antibiotic conjugate compound having the formula:



wherein Ab is an anti-wall teichoic acid (WTA) monoclonal antibody that binds to *Staphylococcus aureus*, wherein the VL of the anti-wall teichoic acid monoclonal antibody comprises CDR L1 comprising the sequence of KSSQSIFRTSRNKNLLN (SEQ ID NO:99), CDR L2 comprising the sequence of WASTRKS (SEQ ID NO:100), and CDR L3 comprising the sequence of QQYFSPPYT (SEQ ID NO:101); and the VH of the anti-WTA monoclonal antibody comprises CDR H1 comprising the sequence of SFWMH (SEQ ID NO:102), CDR H2 comprising the sequence of FTNNEGTTTAYADSVRG (SEQ ID NO:103), and CDR H3 comprising the sequence of GEGGLDD (SEQ ID NO:118); and

p is an integer from 1 to 8.

40. An antibody-antibiotic conjugate compound having the formula:



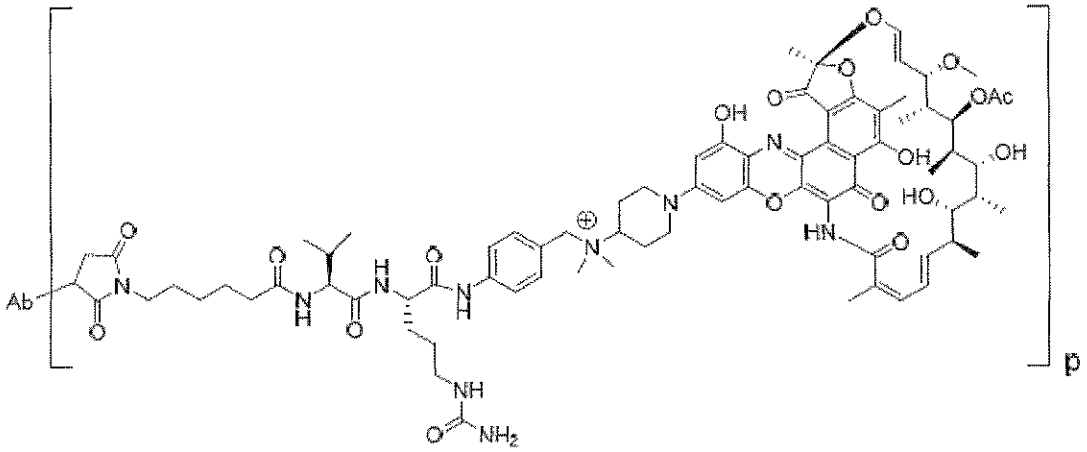
wherein Ab is an anti-wall teichoic acid (WTA) monoclonal antibody that binds to *Staphylococcus aureus*, and comprises a VL and a VH, wherein the VL comprises the sequence of SEQ ID NO:119 and the VH comprises the sequence SEQ ID NO:156; and

p is an integer from 1 to 8.

41. The antibody-antibiotic conjugate compound of claim 40, wherein the antibody comprises a light chain (LC) wherein the LC comprises the amino acid sequence of

SEQ ID NO:145, and a heavy chain (HC) wherein the HC comprises the amino acid sequence of SEQ ID NO:157.

42. An antibody-antibiotic conjugate compound having the formula:



wherein Ab is an anti-wall teichoic acid (WTA) monoclonal antibody that binds to *Staphylococcus aureus*, and comprises a VL and a VH, wherein the VL comprises the sequence of SEQ ID NO:119 and the VH comprises the sequence SEQ ID NO:156; and wherein p is an integer of 2.

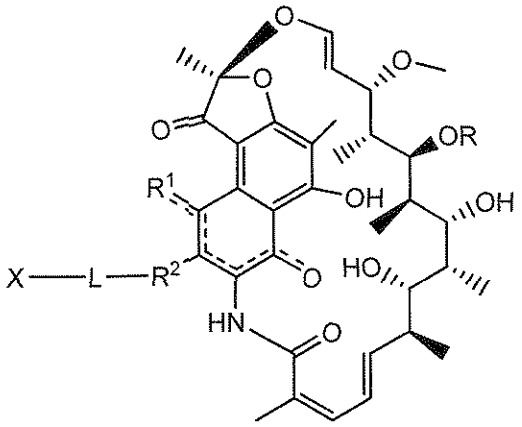
43. The antibody-antibiotic conjugate compound of claim 42, wherein the antibody comprises a light chain (LC) wherein the LC comprises the amino acid sequence of SEQ ID NO:145, and a heavy chain (HC) wherein the HC comprises the amino acid sequence of SEQ ID NO:157.

44. A pharmaceutical composition comprising the antibody-antibiotic conjugate compound of any one of claims 1-43, and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

45. A process for making the antibody-antibiotic conjugate compound of any one of claims 1-43 comprising the steps of:

a) preparing the anti-wall teichoic acid monoclonal antibody by reduction with DDT (dithiothreitol) or tricarbonylethylphosphine (TCEP); and

b) conjugating an antibiotic-linker intermediate having Formula II:



II

wherein:

the dashed lines indicate an optional bond;

R is H, C_1–C_{12} alkyl, or $C(O)CH_3$;

R^1 is OH;

R^2 is CH=N–(heterocyclyl), wherein the heterocyclyl is optionally substituted with one or more groups independently selected from $C(O)CH_3$, C_1–C_{12} alkyl, C_1–C_{12} heteroaryl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_3–C_{12} carbocyclyl;

or R^1 and R^2 form a five- or six-membered fused heteroaryl or heterocyclyl, and optionally forming a spiro or fused six-membered heteroaryl, heterocyclyl, aryl, or carbocyclyl ring, wherein the spiro or fused six-membered heteroaryl, heterocyclyl, aryl, or carbocyclyl ring is optionally substituted H, F, Cl, Br, I, C_1–C_{12} alkyl, or OH;

L is a peptide linker attached to R^2 or the fused heteroaryl or heterocyclyl formed by R^1 and R^2; and having the formula:

–Str–Pep–Y–

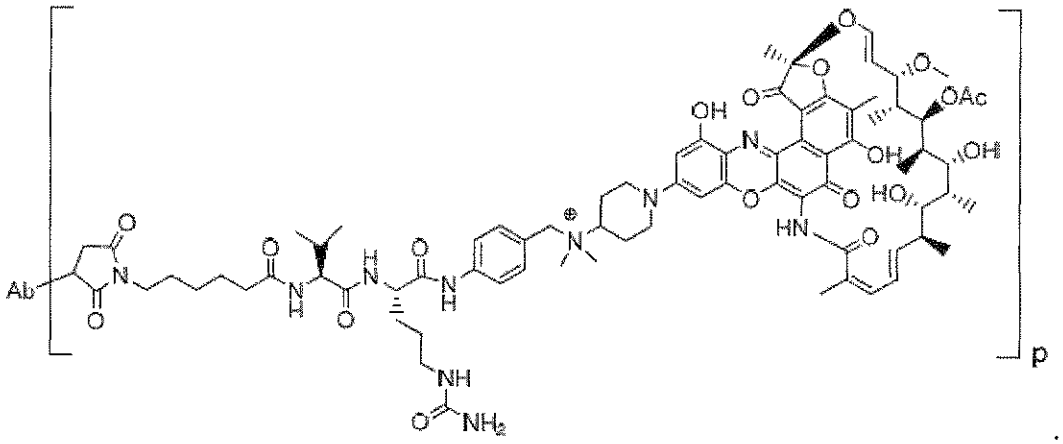
where Str is a stretcher unit; Pep is a peptide of two to twelve amino acid residues, and Y is a spacer unit; and

X is a reactive functional group selected from maleimide, thiol, amino, bromide, bromoacetamido, iodoacetamido, p-toluenesulfonate, iodide, hydroxyl, carboxyl, pyridyl disulfide, and N-hydroxysuccinimide;

to the anti-wall teichoic acid monoclonal antibody

whereby the antibody-antibiotic conjugate compound is formed.

46. The process of claim 45, wherein the antibody-antibiotic conjugate compound has the formula:



47. Use of an anti-antibiotic conjugate compound of any one of claims 1-43 in the manufacture of a medicament for treating a bacterial infection in a patient, wherein the bacterial infection is a *Staphylococcus aureus* infection.

48. The use of claim 47, wherein the antibody-antibiotic conjugate compound comprises an antibody comprising a VL and a VH, wherein the VL comprises the sequence of SEQ ID NO:119 and the VH comprises the sequence SEQ ID NO:156.

49. The use of claim 47, wherein the antibody-antibiotic conjugate compound comprises an antibody comprising a LC and a HC, wherein the LC comprises the sequence of SEQ ID NO:145 and the HC comprises the sequence SEQ ID NO:157.

50. The use of claim 47, wherein bacterial load in the patient is reduced by the treatment.

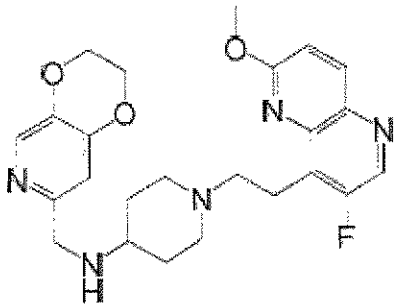
51. The use of claim 47, wherein the patient is a human.

52. The use of any one of claims 47-51, wherein the medicament is to be administered with a second therapeutic agent.

53. The use of claim 52, wherein the second therapeutic agent is an antibiotic.

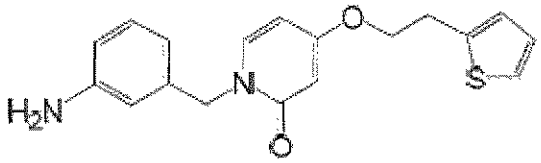
54. The use of claim 53, wherein the antibiotic is selected from the structural class consisting of (i) aminoglycosides; (ii) beta-lactams; (iii) macrolides/cyclic peptides; (iv) tetracyclines; (v) fluoroquinolines/fluoroquinolones; and (vi) oxazolidinones.

55. The use of claim 53, wherein the antibiotic is selected from the group consisting of clindamycin, novobiocin, retapamulin, daptomycin, GSK-2140944 (gepotidacin) having the structure:



GSK-2140944,

CG-400549 having the structure:



CG-400549,

sitafloxacin, teicoplanin, triclosan, napthyridone, radezolid, doxorubicin, ampicillin, vancomycin, imipenem, doripenem, gemcitabine, dalbavancin, and azithromycin.

56. Use of an anti-antibiotic conjugate compound of any one of claims 1-43 in the manufacture of a medicament for reducing the number of intracellular *Staphylococcus aureus* bacterial cells in the host cells of a *Staphylococcus aureus* infected patient without reducing the number of the host cells.

57. The use of claim 56, wherein the number of persistant bacterial cells are reduced.

58. A kit for treating a bacterial infection, comprising:

a) the pharmaceutical composition of claim 44; and

b) instructions for use.