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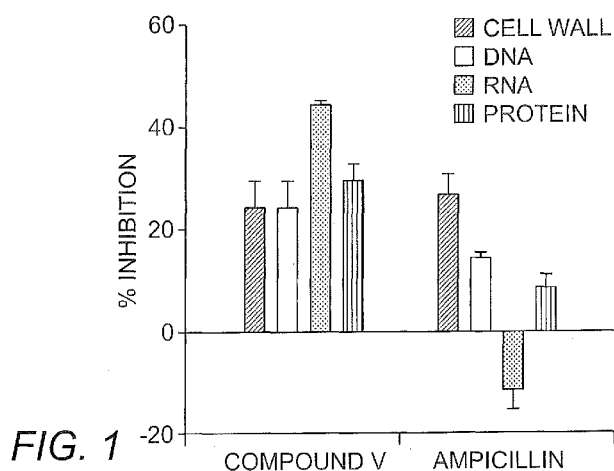
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(54) Title: COMPOUNDS, COMPOSITIONS AND METHODS FOR TREATING BACTERIAL INFECTIONS



(57) Abstract: Thieno [2, 3 -b] thiophene compounds and pharmaceutical compositions containing the same are provided for use in inhibiting or suppressing the growth of bacterial pathogens and in the amelioration and treatment bacterial infections, including drug-resistant bacterial infections. Combination therapies including thieno [2, 3 -b] thiophene compounds and beta-lactam antibiotics are also provided.

COMPOUNDS, COMPOSITIONS AND METHODS FOR
TREATING BACTERIAL INFECTIONS

Background

[0001] Antibiotic-resistant *Staphylococcus aureus* is a common cause of infections in hospitals, emergency rooms and acute-care clinic. Many *S. aureus* bacteria are resistant to methicillin (*i.e.*, methicillin-resistant *S. aureus* or MRSA) and its related antibiotic oxacillin. Therefore, there is a need to identify new antibiotic of use in the treatment of MRSA and other resistant bacteria, which continue to emerge in hospital settings.

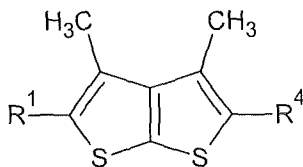
[0002] Penicillin-binding proteins (PBPs) are the enzymes that are required for the biosynthesis of the bacterial cell wall (Ghuysen (1991) *Annu. Rev. Microbiol.* 45:37-67). PBPs catalyze the final steps of the polymerization (transglycosylation) and cross-linking (transpeptidation) of peptidoglycan, an essential component of the bacterial cell wall. PBPs are membrane-bound enzymes and targets of β -lactam antibiotics (Dowson, et al. (1994) *Trends Microbiol.* 2:361-366; Dowson, et al. (1989) *Mol. Microbiol.* 3:95-102; Ghuysen (1991) *Annu. Rev. Microbiol.* 45:37-67; Hakenbeck, et al. (1998) *J. Bacteriol.* 180:1831-40; Munoz, et al. (1992) *Mol. Microbiol.* 6:2461-65; Spratt (1977) *Eur. J. Biochem.* 72:341-352; Tomasz & Munoz (1995) *Microb. Drug Resist.* 1:103-109). Resistance to β -lactam antibiotics in some species has occurred by development of altered high-molecular-mass PBPs which have reduced affinity for the antibiotics (Dowson, et al. (1994) *supra*; Dowson, et al. (1989) *supra*; Ghuysen (1991) *supra*; Hakenbeck, et al. (1998); Munoz, et al. (1992); Neu (1992) *Science* 257:1064-1073; Tomasz & Munoz (1995) *supra*). Extensive molecular and genetic studies have been devoted to the understanding of

the mechanisms of bacterial resistance to β -lactam antibiotics (Dowson, et al. (1994) *supra*; Dowson, et al. (1989) *supra*; Ghuyssen (1991) *supra*; Neu (1992) *supra*; Tomasz & Munoz (1995) *supra*). For example, PBP4, while not essential to growth, is a major factor that confers methicillin/oxacillin resistance to MRSA. Indeed, the antibiotic cefoxitin, which preferentially inactivates PBP4, can render MRSA sensitive to oxacillin (Memmi, et al. (2008) *Antimicrob. Agents Chemother.* 52:3955-66). In this respect, a screening assay for identifying agents that can bind, inactivate or reduce expression of PBP4 has been described for use in treatment MRSA infections (US 2010/0197649).

[0003] Substituted thieno[2,3-*b*]thiophenes have been described for use as anti-glaucoma agents (e.g., EP 0307084 and EP 0375320) and semiconductors (e.g., WO 2006/021277). In addition, US 2010/0279983 describes compounds having thieno[2,3-*b*]thien-2-yl groups for inhibiting β -lactamase activity. Similarly, US 4,581,352 describes cephalosporin derivatives having a thieno[2,3-*b*]thien-2-yl group. Bis-[1,3,4]thiadiazoles having a thieno[2,3-*b*]thiophene moiety have also been described as exhibiting activity against Gram-positive bacteria (Khedar et al. (2012) *Intl. J. Mol. Sci.* 13(3):3661-70; Mobkhot, et al. (2013) *Molecules* 18:4669-4678).

Summary of the Invention

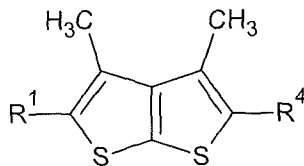
[0004] This invention is a compound having the structure of Formula II, or a pharmaceutically acceptable salt or prodrug thereof:



Formula II

wherein R^1 and R^4 are different; R^1 is a hydrogen, halo, or $-C(=O)OR^{11}$ group; R^4 is an unsubstituted aryl, substituted aryl, or $-C(=O)OR^{11}$ group; and R^{11} is a C_1 - C_2 alkyl, fluorinated alkyl, or benzyl group. A pharmaceutical composition containing the compound either alone or in combination with one or more β -lactam antibiotics is also provided.

[0005] This invention is also a pharmaceutical composition containing a pharmaceutically acceptable carrier and a compound having the structure of Formula II, or a pharmaceutically acceptable salt or prodrug thereof:



Formula II

wherein R^1 and R^4 are independently a hydrogen, halo, cyano, $-C(=O)OR^{11}$, C_1 - C_{10} alkyl, cycloalkyl, aryl, substituted aryl, heteroaryl group; and R^{11} is a hydrogen, C_1 - C_{10} alkyl, fluorinated alkyl or benzyl group. In one embodiment, the pharmaceutical composition also includes one or more β -lactam antibiotics. A kit containing said compound and one or more β -lactam antibiotics is also provided.

[0006] This invention also pertains to methods for suppressing the growth of a bacterial pathogen, and ameliorating or treating a bacterial infection with a compound having the structure of Formula II, or a pharmaceutically acceptable salt or prodrug thereof. In some embodiments, the bacterial pathogen is a drug-

resistant bacterial pathogen. In other embodiments, the compound of Formula II is used in combination with one or more β -lactam antibiotics.

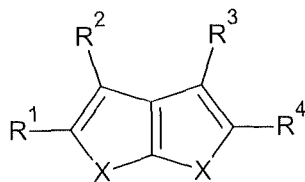
Brief Description of the Drawings

[0007] Figure 1 shows the inhibitory effect of Compound V on the synthesis of cell wall, DNA, RNA and protein (at 30 minutes) as compared to ampicillin.

Detailed Description of the Invention

[0008] It has now been found that compounds with a core thieno[2,3-*b*]thiophene structure exhibit antibacterial activity against Gram positive bacteria and, when used in combination with a beta-lactam, activity against Gram negative bacteria. In particular, 3-(5-bromo-3,4-dimethylthieno[2,3-*b*] thiophen-2-yl)-1H-pyrazole (referred to herein as Compound V or DNAC-1), and derivatives thereof, exhibit broad spectrum activity against Gram positive and Gram bacteria, especially in combination with beta-lactams such as oxacillin (for Gram positive bacteria) and ceftriaxone or cefoxitin (for Gram negative bacteria). Given the activity of the compounds described herein, these compounds find use in the treatment of bacterial infections, in particular bacterial infections, which are resistant to conventional antibiotics.

[0009] Therefore, the present invention provides compounds, pharmaceutical compositions, and methods for reducing the growth of pathogenic bacteria and treating bacterial infections. In one embodiment, the invention provides compounds having the structure of Formula I, or a pharmaceutically acceptable salt or prodrug thereof:



Formula I

wherein each X is the same or different and independently C-(R⁵)_n, O, S or NR⁵, wherein each R⁵ is independently hydrogen, a halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, -R⁶-cycloalkyl, aryl, -NHR⁶, Het, -NHHet, -NHR⁶Het, -OR⁶, -O-aryl, -OHet, -R⁶OR⁷, -NR⁷R⁸, -NR⁷-aryl, -R⁶NR⁷R⁸, -R⁶NR⁷-aryl, -R⁶C(O)R⁷, -C(O)R⁷, -CO₂R⁷, -R⁶CO₂R⁷, -C(O)NR⁷R⁸, -C(O)aryl, -C(O)NR⁷aryl, -C(O)Het, -C(O)NHR⁶Het, -R⁶C(O)NR⁷R⁸, -C(S)NR⁷R⁸, -R⁶C(S)NR⁷R⁸, -R⁶(NH)NR⁷R⁸, -C(NH)NR⁷R⁸, -R⁶C(NH)NR⁷R⁸, -S(O)₂NR⁷R⁸, -S(O)₂N R⁷aryl, -R⁶SO₂NHCOR⁷, -R⁶SO₂NR⁷R⁸, -R⁶SO₂R⁷, -S(O)_mR⁷, cyano, nitro, or azido group; and

R¹, R², R³, and R⁴ are independently hydrogen, a halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, -R⁶-cycloalkyl, aryl, -NHR⁶, Het, -NHHet, -NHR⁶Het, -OR⁷, -O-aryl, -OHet, -R⁶OR⁷, -NR⁷R⁸, -NR⁷-aryl, -R⁶NR⁷R⁸, -R⁶NR⁷-aryl, -R⁶C(O)R⁷, -C(O)R⁷, -CO₂R⁷, -R⁶CO₂R⁷, -C(O)NR⁷R⁸, -C(O)aryl, -C(O)NR⁷aryl, -C(O)Het, -C(O)NHR⁷Het, -R⁶C(O)NR⁷R⁸, -C(S)NR⁷R⁸, -R⁶C(S)NR⁷R⁸, -R⁶(NH)NR⁷R⁸, -C(NH)NR⁷R⁸, -R⁶C(NH)NR⁷R⁸, -S(O)₂NR⁷R⁸, -S(O)₂N R⁷aryl, -R⁶SO₂NHCOR⁷, -R⁶SO₂NR⁷R⁸, -R⁶SO₂R⁷, -S(O)_mR⁷, cyano, nitro, or azido group;

the pairs R¹R², R²R³, R³R⁴, XR⁴, XX and XR¹, can be connected by a chain of any length composed of atoms or groups that are the same or different and are independently C-(R⁵)_n, OR⁵, S or NR⁵, wherein each R⁵ is independently haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, -R⁶-cycloalkyl, aryl, -NHR⁶, Het, -NHHet, -NHR⁶Het, -OR⁷, -O-aryl, -OHet, -R⁶OR⁷, -NR⁷R⁸, -NR⁷-aryl, -

$R^6NR^7R^8$, $-R^6NR^7$ -aryl, $-R^6C(O)R^7$, $-C(O)R^7$, $-CO_2R^7$, $-R^6CO_2R^7$, $-C(O)NR^7R^8$, $-C(O)$ aryl, $-C(O)NR^7$ aryl, $-C(O)$ Het, $-C(O)NHR^6$ Het, $-R^6C(O)NR^7R^8$, $-C(S)NR^7R^8$, $-R^6C(S)NR^7R^8$, $-R^6(NH)NR^7R^8$, $-C(NH)NR^7R^8$, $-R^6C(NH)NR^7R^8$, $-S(O)_2NR^7R^8$, $-S(O)_2N$ R^7 aryl, $-R^6SO_2NHCOR^8$, $-R^6SO_2NR^7R^8$, $-R^6SO_2R^7$, $-S(O)_mR^7$, cyano, nitro, or azido group;

each R^6 is the same or different and is independently selected from an alkylene, cycloalkylene, alkenylene, cycloalkenylene or alkynylene group;

each of R^7 and R^8 are the same or different and are independently selected from the group of hydrogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, $-R^6$ cycloalkyl, $-R^6OH$, $-R^6(OR^6)_w$, or $-R^6NR^9R^{10}$ group;

each of R^9 and R^{10} are the same or different and are independently selected from the group of an alkyl, cycloalkyl, alkenyl, cycloalkenyl, or alkynyl group;

each n independently is 0, 1 or 2;

each m independently is 0, 1 or 2; and

w is 1-10.

[0010] For the groups herein, the following parenthetical subscripts further define the groups as follows: " (C_n) " defines the exact number (n) of carbon atoms in the group. For example, " C_1 - C_{10} -alkyl" designates those alkyl groups having from 1 to 10 carbon atoms (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (e.g., 3-10 carbon atoms)).

[0011] Het represents an optionally substituted 5-, 6-, or 7-membered heterocyclic group or heteroaryl group.

[0012] As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon, preferably having from one to twelve carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl,

propyl, isopropyl, isobutyl, n-butyl, tert-butyl, isopentyl, n-pentyl, and the like.

[0013] The term "alkenyl" refers to a straight or branched chain aliphatic hydrocarbon containing one or more carbon-to-carbon double bonds. Examples include, but are not limited to, vinyl, allyl, and the like.

[0014] As used herein, the term "alkynyl" refers to a straight or branched chain aliphatic hydrocarbon containing one or more carbon-to-carbon triple bonds. Examples include, but are not limited to, ethynyl and the like.

[0015] The term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical, preferably having from one to ten carbon atoms. Alkylene groups as defined herein may optionally be substituted. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene.

[0016] As used herein, the term "alkenylene" refers to a straight or branched chain divalent hydrocarbon radical, preferably having from one to ten carbon atoms, containing one or more carbon-to-carbon double bonds that may be optionally substituted. Examples include, but are not limited to, vinylene, allylene or 2-propenylene, and the like.

[0017] The term "alkynylene" refers to a straight or branched chain divalent hydrocarbon radical, preferably having from one to ten carbon atoms, containing one or more carbon-to-carbon triple bonds that may be optionally substituted. Examples include, but are not limited to, ethynylene and the like.

[0018] As used herein, the term "cycloalkyl" refers to an optionally substituted non-aromatic cyclic hydrocarbon ring, which optionally includes an alkylene linker through which the cycloalkyl may be attached. Exemplary

"cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and substituted versions thereof. As used herein, the term "cycloalkyl" includes an optionally substituted fused polycyclic hydrocarbon saturated ring and aromatic ring system, namely polycyclic hydrocarbons with less than maximum number of non-cumulative double bonds, for example where a saturated hydrocarbon ring (such as a cyclopentyl ring) is fused with an aromatic ring (herein "aryl," such as a benzene ring) to form, for example, groups such as indane.

[0019] As used herein, the term "cycloalkenyl" refers to an optionally substituted non-aromatic cyclic hydrocarbon ring containing one or more carbon-to-carbon double bonds which optionally includes an alkylene linker through which the cycloalkenyl may be attached. Exemplary "cycloalkenyl" groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and substituted versions thereof.

[0020] The term "cycloalkylene" refers to a divalent, optionally substituted non-aromatic cyclic hydrocarbon ring. Exemplary "cycloalkylene" groups include, but are not limited to, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, and the like.

[0021] As used herein, the term "cycloalkenylene" refers to a divalent optionally substituted non-aromatic cyclic hydrocarbon ring containing one or more carbon-to-carbon double bonds. Exemplary "cycloalkenylene" groups include, but are not limited to, cyclopropenylene, cyclobutenylene, cyclopentenylene, cyclohexenylene, cycloheptenylene, and the like.

[0022] As used herein, the term "heterocycle" or "heterocyclyl" refers to an optionally substituted mono- or

polycyclic ring system containing one or more degrees of unsaturation and also containing one or more heteroatoms. Preferred heteroatoms include N, O, and/or S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to twelve-membered and is either fully saturated or has one or more degrees of unsaturation. Such rings may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" groups include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine, tetrahydrothiopyran, and tetrahydrothiophene.

[0023] As used herein, the term "aryl" refers to an optionally substituted benzene ring or to an optionally substituted fused benzene ring system, for example anthracene, phenanthrene, or naphthalene ring systems. Examples of "aryl" groups include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, methylphenyl, (dimethyl)phenyl, ethylphenyl, propylphenyl, methylethylphenyl, vinylphenyl, and the like.

[0024] As used herein, the term "heteroaryl" refers to an optionally substituted monocyclic five to seven membered aromatic ring, or to an optionally substituted fused bicyclic aromatic ring system comprising two of such aromatic rings. These heteroaryl rings contain one or more nitrogen, sulfur, and/or oxygen atoms, where N-oxides, sulfur oxides, and dioxides are permissible heteroatom substitutions. Examples of "heteroaryl" groups used herein include, but should not be limited to, furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole, indazole, benzimidazolyl, imidazopyridinyl,

pyrazolopyridinyl, pyrazolopyrimidinyl groups, and the like.

[0025] As used herein, the term "halogen" refers to fluorine, chlorine, bromine, or iodine. In this respect, the term "haloalkyl" refers to an alkyl group, as defined herein, that is substituted with at least one halogen. Examples of branched or straight chained "haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, and t-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo, and iodo. The term "haloalkyl" should be interpreted to include such substituents as perfluoroalkyl groups and the like.

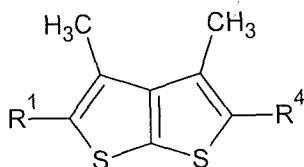
[0026] As used herein, the term "alkoxy" refers to the group -O-alkyl. The term "nitro" refers to the group -NO₂. The term "cyano" refers to the group -CN. The term "azido" refers to the group -N₃. The term "acyl" refers to the group R^aC(O)-, where R^a is alkyl, aryl, heteroaryl, or heterocyclyl, as each is defined herein.

[0027] As used herein throughout the specification, the phrase "optionally substituted" or variations thereof denote an optional substitution, including multiple degrees of substitution, with one or more substituent group. The phrase should not be interpreted so as to be imprecise or duplicative of substitution patterns herein described or depicted specifically. Rather, those of ordinary skill in the art will appreciate that the phrase is included to provide for obvious modifications, which are encompassed within the scope of the appended claims.

[0028] Exemplary optional substituent groups include acyl; alkyl; alkenyl; alkynyl; alkylsulfonyl; alkoxy; alkoxycarbonyl; cyano; halogen; haloalkyl; hydroxy; nitro; aryl, which may be further substituted with acyl, alkoxy,

alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; heteroaryl, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; arylsulfonyl, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; heteroarylsulfonyl, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; aryloxy, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; heteroaryloxy, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro; or aryloxycarbonyl, which may be further substituted with acyl, alkoxy, alkyl, alkenyl, alkynyl, alkylsulfonyl, cyano, halogen, haloalkyl, hydroxy, or nitro.

[0029] In other embodiments, a compound of the invention is a derivative of 3,4-dimethylthieno[2,3-b]thiophene. In particular, the invention provides compounds having the structure of Formula II, or a pharmaceutically acceptable salt or prodrug thereof:

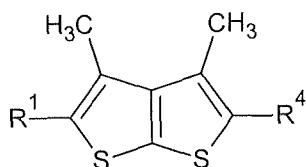


Formula II

wherein R¹ and R⁴ are independently a hydrogen, halo, cyano, -C(=O)OR¹¹, C₁-C₁₀ alkyl, cycloalkyl, aryl, substituted aryl, heteroaryl; and R¹¹ is a hydrogen, C₁-C₁₀ alkyl, fluorinated alkyl or benzyl group. In accordance with this embodiment, preferably an alkyl is a C₁-C₄ alkyl, C₁-C₃ alkyl, or C₁-C₂

alkyl. In some embodiments, R^1 and R^4 are the same. In other embodiments, R^1 and R^4 are different. In still other embodiments, the halo group is a bromo group. In yet other embodiments, the heteroaryl group is imidazolyl, pyridinyl, oxazolyl, or quinolyl.

[0030] In certain embodiments, the invention provides compounds having the structure of Formula II, or a pharmaceutically acceptable salt or prodrug thereof:



Formula II

wherein R^1 and R^4 are different; R^1 is a hydrogen, halo, or $-C(=O)OR^{11}$ group; R^4 is an unsubstituted aryl, substituted aryl, or $-C(=O)OR^{11}$ group; and R^{11} is a C_1 - C_2 alkyl, fluorinated alkyl or benzyl group. In some embodiments, the halo group is a bromo group. In other embodiments, the heteroaryl group is imidazolyl, pyridinyl, oxazolyl, or quinolyl.

[0031] In one embodiment, the invention embraces one or more compounds as disclosed in Table 2. In a further embodiment, the invention embraces one or more of compounds DNAC-6, DNAC-7, DNAC-9, DNAC-10, DNAC-11, DNAC-12, DNAC-13, DNAC-14, DNAC-15, DNAC-16, DNAC-17 or DNAC-19. In yet other embodiments, the invention excludes compounds DNAC-2 (CAS No. 152487-69-9), DNAC-3 (CAS No. 175202-55-8), DNAC-4 (PUBCHEM SID 125518424), DNAC-5 (PUBCHEM SID 16119545), DNAC-8 (PUBCHEM SID 26541135), DNAC-1 (PUBCHEM SID 92269126) and DNAC-18 (PUBCHEM SID 26534179).

[0032] "Pharmaceutically acceptable salts" means salts of compounds of the invention which are pharmaceutically acceptable, and which possess the desired pharmacological

activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, 2-naphthalenesulfonic acid, 3-phenylpropionic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, acetic acid, aliphatic mono- and di-carboxylic acids, aliphatic sulfuric acids, aromatic sulfuric acids, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, heptanoic acid, hexanoic acid, hydroxynaphthoic acid, lactic acid, laurylsulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, o-(4-hydroxybenzoyl)benzoic acid, oxalic acid, p-chlorobenzenesulfonic acid, phenyl-substituted alkanolic acids, propionic acid, p-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid, trimethylacetic acid, and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like. It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable.

Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (Stahl & Wermuth eds., Verlag Helvetica Chimica Acta, 2002).

[0033] Compounds of the invention may also exist in prodrug form. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals, e.g., solubility, bioavailability, manufacturing, etc., the compounds employed in some methods of the invention may, if desired, be delivered in prodrug form. Thus, the invention contemplates prodrugs of compounds of the present invention as well as methods of delivering prodrugs. Prodrugs of the compounds of this invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a patient, cleaves to form a hydroxy, amino, or carboxylic acid, respectively. For example, a compound having a hydroxy group may be administered as an ester that is converted by hydrolysis *in vivo* to the hydroxy compound. Suitable esters that may be converted *in vivo* into hydroxy compounds include acetates, citrates, lactates, phosphates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis- β -hydroxynaphthoate, gentisates, isethionates, di-*p*-toluoyltartrates, methane-sulfonates, ethane-sulfonates, benzenesulfonates, *p*-toluene-sulfonates, cyclohexylsulfamates, quinates, esters of amino acids, and the like.

[0034] Therapeutics including compounds of the invention can be prepared in physiologically acceptable formulations, such as in pharmaceutically acceptable carriers, using known techniques. For example, a thieno[2,3-*b*]thiophene compound of the invention is combined with a pharmaceutically acceptable excipient to form a pharmaceutical composition.

[0035] The compositions of the invention may be administered in the form of a solid, liquid or aerosol. Examples of solid compositions include pills, creams, soaps and implantable dosage units. Pills may be administered orally. Therapeutic creams and anti-bacterial soaps may be administered topically. Implantable dosage units may be administered locally, for example, in the lungs, or may be implanted for sustained release of the therapeutic composition, for example, subcutaneously. Examples of liquid compositions include formulations adapted for injection intramuscularly, subcutaneously, intravenously, intraarterially, and formulations for topical and intraocular administration. Examples of aerosol formulations include inhaler formulations for administration to the lungs.

[0036] A sustained release matrix, as used herein, is a matrix made of materials, usually polymers, which are degradable by enzymatic or acid/base hydrolysis, or by dissolution. Once inserted into the body, the matrix is acted upon by enzymes and body fluids. The sustained release matrix is chosen desirably from biocompatible materials, including, but not limited to, liposomes, polylactides, polyglycolide (polymer of glycolic acid), polylactide co-glycolide (copolymers of lactic acid and glycolic acid), polyanhydrides, poly(ortho)esters, polypeptides, hyaluronic acid, collagen, chondroitin

sulfate, carboxylic acids, fatty acids, phospholipids, polysaccharides, nucleic acids, polyamino acids, amino acids such as phenylalanine, tyrosine, isoleucine, polynucleotides, polyvinyl propylene, polyvinylpyrrolidone and silicone. A preferred biodegradable matrix is a matrix of one of either polylactide, polyglycolide, or polylactide co-glycolide.

[0037] The dosage of the composition will depend on the condition being treated, the particular compound used, and other clinical factors, such as weight and condition of the patient, and the route of administration. A suitable dosage may range from 100 to 0.1 mg/kg. A more preferred dosage may range from 50 to 0.2 mg/kg. A more preferred dosage may range from 25 to 0.5 mg/kg. Tablets or other forms of media may contain from 1 to 1000 mg of one or more thieno[2,3-*b*]thiophene compounds.

[0038] The compounds of this invention can be used alone or in combination with conventional antimicrobial agents used in the treatment of infectious disease. In particular, the invention includes a combination therapy composed of one or more thieno[2,3-*b*]thiophene compounds as described herein together with one or more β -lactams, *i.e.*, antibiotic agents containing a β -lactam nucleus in its structure. Examples of β -lactam antibiotics include, but are not limited to, penicillin derivatives, cephalosporins, penems, monobactams, carbapenems, β -lactamase inhibitors and combinations thereof. Examples of penicillin derivatives include aminopenicillins (*e.g.*, amoxicillin, ampicillin, and epicillin); carboxypenicillins (*e.g.*, carbenicillin, ticarcillin, and temocillin); ureidopenicillins (*e.g.*, azlocillin, piperacillin and mezlocillin); mecillinam, sulbenicillin, benzathine penicillin, penicillin G (benzylpenicillin), penicillin V (phenoxymethylpenicillin),

penicillin O (allylmercaptomethylpenicillanic), procaine penicillin, oxacillin, methicillin, nafcillin, cloxacillin, dicloxacillin, flucloxacillin, pivampicillin, hetacillin, becampicillin, metampicillin, talampicillin, co-amoxiclav (amoxicillin plus clavulanic acid), and piperacillion. Examples of cephalosporins include cephalixin, cephalothin, cefazolin, cefaclor, cefuroxime, cefamandole, cefotetan, cefoxitin, ceforanide, ceftriaxone, cefotaxime, cefpodoxime proxetil, ceftazidime, cefepime, cefoperazone, ceftizoxime, cefixime and cefpirome. An example of a penem is faropenem. Examples of monobactams include aztreonam and tigemonam. Examples of carbapenems include biapenenvdoripenem, ertapenem, imipenem, meropenem, and panipenem. Examples of Beta-lactamase inhibitors include tazobactam ([2S-(2 α ,3 β ,5 α)]-3-Methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide sodium salt), sulbactam (2S,5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide sodium), and clavulanic acid ((2R,5R,Z)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid).

[0039] Compounds of the invention are of particular use in inhibiting or suppressing the growth or spread of microorganisms, in particular Gram positive and Gram negative bacteria that cause disease (i.e., pathogenic bacteria). Examples of such pathogenic bacteria include any one or more of *Acinetobacter baumannii*, *Actinobacillus* sp., *Actinomycetes*, *Actinomyces* sp. (such as *A. israelii* and *A. naeslundii*), *Aeromonas* sp. (such as *A. hydrophila*, *A. veronii* biovar *sobria* and *A. caviae*), *Anaplasma phagocytophilum*, *Alcaligenes xylosoxidans*, *Acinetobacter baumannii*, *Actinobacillus actinomycetemcomitans*, *Bacillus* sp. (such as *B. anthracis*, *B. cereus*, *B. subtilis*, *B.*

thuringiensis and *B. stearothermophilus*), *Bacteroides* sp. (such as *B. fragilis*), *Bartonella* sp. (such as *B. bacilliformis* and *B. henselae*), *Bifidobacterium* sp., *Bordetella* sp. (such as *B. pertussis*, *B. parapertussis* and *B. bronchiseptica*), *Borrelia* sp. (such as *B. recurrentis* and *Borrelia burgdorferi*), *Brucella* sp. (such as *B. abortus*, *B. canis*, *B. melintensis* and *B. suis*), *Burkholderia* sp. (such as *B. pseudomallei* and *B. cepacia*), *Campylobacter* sp. (such as *C. jejuni*, *C. coli*, *C. lari* and *C. fetus*), *Capnocytophaga* sp., *Cardiobacterium hominis*, *Chlamydia trachomatis*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, *Citrobacter* sp., *Coxiella burnetii*, *Corynebacterium* sp. (such as *C. diphtheria* and *C. jeikeum*), *Clostridium* sp. (such as *C. perfringens*, *C. difficile*, *C. botulinum* and *C. tetani*), *Eikenella corrodens*, *Enterobacter* sp. (such as *E. aerogenes*, *E. agglomerans* and *E. cloacae*), *Escherichia coli* (including opportunistic *E. coli* such as enterotoxigenic *E. coli*, enteroinvasive *E. coli*, enteropathogenic *E. coli*, enterohemorrhagic *E. coli*, enteroaggregative *E. coli* and uropathogenic *E. coli*), *Enterococcus* sp. (such as *E. faecalis* and *E. faecium*), *Ehrlichia* sp. (such as *E. chaffeensis* and *E. canis*), *Erysipelothrix rhusiopathiae*, *Eubacterium* sp., *Francisella tularensis*, *Fusobacterium nucleatum*, *Gardnerella vaginalis*, *Gemella morbillorum*, *Haemophilus* sp. (such as *H. influenzae*, *H. ducreyi*, *H. aegyptius*, *H. parainfluenzae*, *H. haemolyticus* and *H. parahaemolyticus*), *Helicobacter* sp. (such as *H. pylori*, *H. cinaedi* and *H. fennelliae*), *Kingella kingii*, *Klebsiella* sp. (such as *K. pneumoniae*, *K. granulomatis* and *K. oxytoca*), *Lactobacillus* sp., *Legionella pneumophila*, *Leptospira interrogans*, *Listeria monocytogenes*, *Peptostreptococcus* sp., *Moraxella catarrhalis*, *Morganella* sp., *Mobiluncus* sp., *Micrococcus*

sp., *Mycoplasma* sp. (such as *M. pneumoniae*, *M. hominis* and *M. genitalium*), *Nocardia* sp. (such as *N. asteroides*, *N. cyriacigeorgica* and *N. brasiliensis*), *Neisseria* sp. (such as *N. gonorrhoeae* and *N. meningitidis*), *Pasteurella multocida*, *Plesiomonas shigelloides*, *Prevotella* sp., *Porphyromonas* sp., *Prevotella melaminogenica*, *Proteus* sp. (such as *P. vulgaris* and *P. mirabilis*), *Providencia* sp. (such as *P. alcalifaciens*, *P. rettgeri* and *P. stuartii*), *Pseudomonas aeruginosa*, *Propionibacterium acnes*, *Rhodococcus equi*, *Rickettsia* sp. (such as *R. rickettsii*, *R. akari*, *R. typhi* and *R. prowazekii*), *Orientia tsutsugamushi* (formerly *Rickettsia tsutsugamushi*), *Rhodococcus* sp., *Serratia marcescens*, *Stenotrophomonas maltophilia*, *Salmonella* sp. (such as *S. enterica*, *S. typhi*, *S. paratyphi*, *S. enteritidis*, *S. choleraesuis* and *S. typhimurium*), *Serratia* sp. (such as *S. marcescens* and *S. liquifaciens*), *Shigella* sp. (such as *S. dysenteriae*, *S. flexneri*, *S. boydii* and *S. sonnei*), *Staphylococcus* sp. (such as *S. aureus*, *S. epidermidis*, *S. hemolyticus*, *S. saprophyticus*), *Streptococcus* sp. (such as *S. pneumoniae*, *S. agalactiae*, *S. mutans*, *S. pyogenes*, *S. pyogenes*, *S. agalactiae*, *S. anginosus*, *S. equismilis*, *S. bovis* and *S. anginosus*), *Spirillum minus*, *Streptobacillus moniliformis*, *Treponema* sp. (such as *T. carateum*, *T. petenue*, *T. pallidum* and *T. endemicum*), *Tropheryma whippelii*, *Ureaplasma urealyticum*, *Veillonella* sp., *Vibrio* sp. (such as *V. cholerae*, *V. parahemolyticus*, *V. vulnificus*, *V. parahaemolyticus*, *V. vulnificus*, *V. alginolyticus*, *V. mimicus*, *V. hollisae*, *V. fluvialis*, *V. metchnikovii*, *V. damsela* and *V. fumisii*), *Yersinia* sp. (such as *Y. enterocolitica* and *Y. pestis*) and *Xanthomonas maltophilia*. In certain embodiments, the methods and compositions of this invention are effective in inhibiting or suppressing

the growth or spread of *E. coli*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *S. aureus*, *Enterococcus*, and *Staphylococcus epidermidis*.

[0040] Compounds of the invention, either alone or in combination with one or more β -lactam antibiotics, are of further use in inhibiting or suppressing the growth or spread of drug-resistant bacterial pathogens. As used herein, a drug-resistant bacterial pathogen refers to a bacterial pathogen that is resistant to one or more anti-microbial agents. Drug-resistance refers to both partial and complete resistance. For example, MRSA is a drug-resistant bacterial pathogen that is resistant to β -lactam antibiotics. A bacterial pathogen may be both drug-resistant and drug-sensitive if it is sensitive to one anti-microbial agent, but resistant to another. In particular embodiments of this invention, the drug-resistant bacterial pathogen is MRSA. As is known in the art, MRSA may also be referred to as multidrug-resistant *S. aureus* (MDSA), oxacillin-resistant *S. aureus* (ORSA) or "Golden Staph." Drug-resistant MRSA can be readily detected using known assays such as the ETEST system (bioMerieux SA, France). Using the ETEST system, a MRSA bacterial pathogen will generally have a MIC for oxacillin of 2 μ g/ml or more (see, e.g., the ETEST Technical Manual (2008)). In some embodiments, contacting a MRSA with a compound of the invention renders the MRSA sensitive to a β -lactam antibiotic that it was resistant to prior to contact with the compound of the invention.

[0041] Whether used alone or in combination with in combination with one or more β -lactam antibiotics, the compounds of this invention can decrease or reduce one or more biological activities, such as growth, reproduction, proliferation, survival rate, metabolism, vitality,

robustness, action, and/or function of a microorganism by at least 10%, at least 20%, at least 50%, or even at least 90%, including between 10% to 95%, 20% to 80%, 30% to 70%, 40% to 50%, such as 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 98%, or 100%. Such decreases can be measured using the methods disclosed herein as well as those known to one of ordinary skill in the art.

[0042] In accordance with the present invention, reducing or suppressing pathogenic bacterial growth finds application in the prevention or treatment of bacterial infections in human, as well as other animals. Thus, this invention also includes a method of ameliorating or treating an infection, disease or condition, for example, in a subject who has or is at risk for developing an infection, such as a bacterial infection. "Treatment" refers to a therapeutic intervention that ameliorates a sign or symptom of a disease or pathological condition after it has begun to develop. As used herein, the term "ameliorating," with reference to a disease, pathological condition or symptom, refers to any observable beneficial effect of the treatment. The beneficial effect can be evidenced, for example, by a delayed onset of clinical symptoms of the infection/disease in a susceptible subject, a reduction in severity of some or all clinical symptoms of the infection/disease, a slower progression of the infection/disease, a reduction in the number of relapses of the infection/disease, an improvement in the overall health or well-being of the subject, or by other parameters well known in the art that are specific to the particular infection/disease, such as a particular bacterial infection.

[0043] In one embodiment, treatment with a compound of this invention provides a detectable inhibition or decrease in

one or more signs of a bacterial infection. A "sign" is any abnormality indicative of disease, discoverable on examination or assessment of a subject. A sign is generally an objective indication of disease. Signs include, but are not limited to any measurable parameters such as tests for detecting a disorder or disease, such as a bacterial infection. In one example, reducing or inhibiting one or more symptoms or signs associated with a bacterial infection, includes reducing or inhibiting bacterial survival by a desired amount, for example by at least 20%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, or even at least 100%, as compared to the bacterial survival in the absence of a compound of the invention.

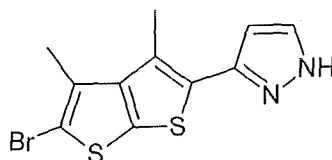
[0044] In another embodiment, a desired effect of a compound of the invention is to reduce or inhibit one or more symptoms associated with a disease, for example symptoms associated with MRSA infection. The one or more symptoms do not have to be completely eliminated for the composition or compound to be effective. For example, a composition or compound can decrease a symptom by a desired amount, for example by at least 20%, at least 50%, at least 80%, at least 90%, at least 95%, at least 98%, or even at least 100%, as compared to the symptom in the absence of the composition or compound.

[0045] The following examples are provided to illustrate certain particular features or embodiments. These examples should not be construed to limit the invention to the particular features or embodiments described.

Example 1: Screening for Antimicrobial Agents

[0046] Small molecules were screened for the ability to inhibit growth of MRSA, in conjunction with oxacillin. From

this screen of over 60,000 compounds, six compounds were identified, two of which possessed broad-spectrum killing activity against various bacteria, especially in combination with beta-lactam such as oxacillin (for Gram positive bacteria) and ceftriaxone or ceftiofur (for Gram negative bacteria). In particular, one compound, designated Compound V, was found to effectively inhibit the growth of a number of resistant Gram positive and Gram negative bacteria in the presence or absence of ceftriaxone or oxacillin at $\frac{1}{4}$ the minimum inhibitory concentration (MIC) (Table 1).



Compound V

(3-(5-bromo-3,4-dimethylthieno[2,3-b]thiophen-2-yl)-1H-pyrazole)

TABLE 1

Resistant Gram+ or Gram- Hospital Isolates	Ceftriaxone or Oxacillin at $\frac{1}{4}$ MIC	MIC Compound V ($\mu\text{g/mL}$)
<i>E. coli</i>	No Ceftriaxone	>32
	Ceftriaxone	<0.03
<i>Acinetobacter baumannii</i>	No Ceftriaxone	>32
	Ceftriaxone	<0.03
<i>Klebsiella pneumoniae</i>	No Ceftriaxone	>32
	Ceftriaxone	<0.03
MRSA	No Oxacillin	1-2*
	Oxacillin	0.5-1*
<i>Enterococcus</i>	No Oxacillin	>32
	Oxacillin	2
<i>Staphylococcus epidermidis</i>	No Oxacillin	16
	Oxacillin	<0.125

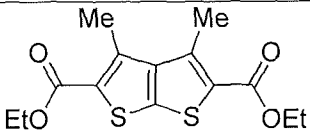
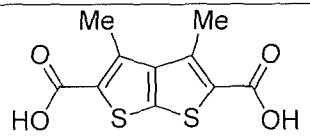
*The range of MIC against both community-acquired and hospital acquired MRSA. Ceftriaxone at $\frac{1}{4}$ MIC (16 $\mu\text{g/mL}$) was ineffective in killing the above-referenced Gram- bacteria. Similarly, oxacillin at $\frac{1}{4}$ MIC was ineffective in killing the above-referenced Gram+ bacteria.

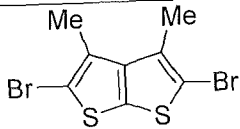
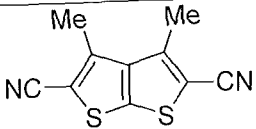
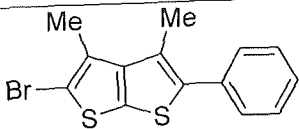
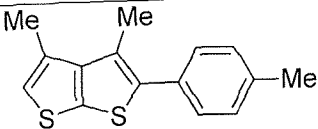
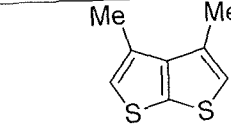
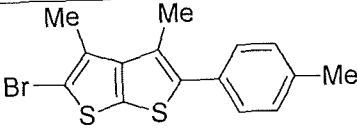
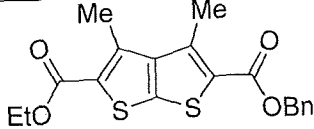
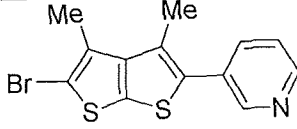
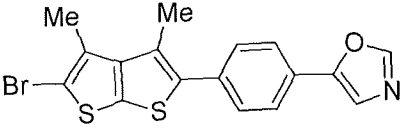
[0047] The effect of Compound V on macromolecular synthesis was also determined and compared to ampicillin. This analysis included measuring the inhibition of the radiolabeled precursors incorporated into synthesis of cell wall (^3H -lysine), DNA (^3H -thymidine), RNA (^3H -uracil) and protein (^3H -leucine). For cell wall synthesis, the incorporation of ^3H -lysine into peptidoglycan was measured in the presence of chloramphenicol, which inhibits protein synthesis. For positive controls, a membrane perturbation agent, hexadecylpyridinium, was used to disrupt DNA, RNA and cell wall synthesis. In addition, ciprofloxacin and rifampin were used as positive controls for inhibition of DNA and RNA synthesis, respectively. All positive controls behaved as expected. The results for compound V and ampicillin are presented in Figure 1 and are reported as % inhibition vs. no compound control.

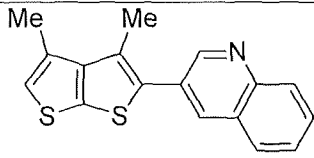
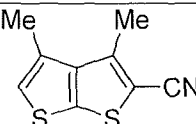
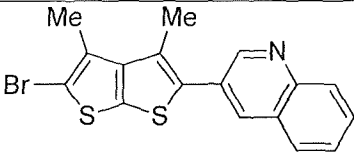
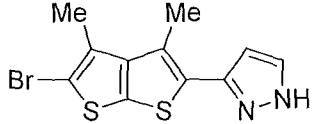
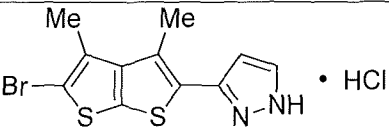
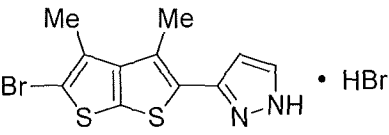
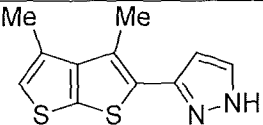
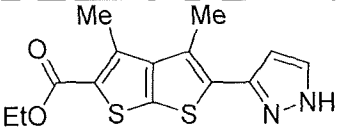
Example 2: Derivatives of Compounds V

[0048] Given the activity of Compound V, derivatives were generated. Activity of the compounds was tested against MRSA USA 300 in the presence or absence of oxacillin. The results of this analysis are presented in Table 2.

TABLE 2

Compound	Activity Alone ($\mu\text{g/mL}$)	Activity + Oxacillin ($\mu\text{g/mL}$)
 DNAC-2 (CAS No. 152487-69-9)	>32	>32
 DNAC-3 (CAS No. 175202-55-8)	>32	>32

 DNAC-4 (PUBCHEM SID 125518424)	>32	>32
 DNAC-5 (PUBCHEM SID 16119545)	>32	>32
 DNAC-6	>32	>32
 DNAC-7	>32	>32
 DNAC-8 (PUBCHEM SID 26541135)	>32	>32
 DNAC-9	>32	>32
 DNAC-10	>32	>32
 DNAC-11	16	16
 DNAC-12	>32	>32

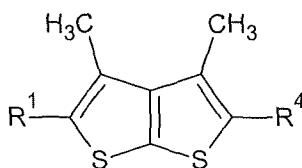
 DNAC-13	>32	>32
 DNAC-14	>32	>32
 DNAC-15	>32	>32
 Compound V (DNAC-1) (PUBCHEM SID 92269126)	1–2 ^a	0.5–1 ^a
	2 ^b	2 ^b
	1 ^c	0.5 ^c
 DNAC-16	8	4
 DNAC-17	2–4	2
 DNAC-18 (PUBCHEM SID 26534179)	>32	>32
 DNAC-19	>32	>32

^aObtained from a commercial source. ^bSynthetic, impure compound. ^cSynthetic, purified compound.

[0049] The data presented in Table 2 indicates that the presence of a nitrogen heterocycle directly attached to the thienothiophene ring (*c.f.*, DNAC-1, DNAC-11, DNAC-16, DNAC-17) and a bromine atom directly attached to the thienothiophene (*c.f.*, DNAC-1, DNAC-16, DNAC-17) impart good inhibitory and/or bactericidal activity.

What is claimed is:

1. A compound having the structure of Formula II, or a pharmaceutically acceptable salt or prodrug thereof:



Formula II

wherein

R^1 and R^4 are different;

R^1 is a hydrogen, halo, or $-C(=O)OR^{11}$ group;

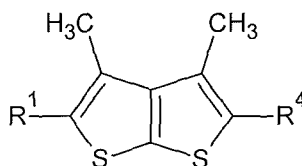
R^4 is an unsubstituted aryl, substituted aryl, or $-C(=O)OR^{11}$ group; and

R^{11} is a C_1 - C_2 alkyl, fluorinated alkyl or benzyl group.

2. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

3. The pharmaceutical composition of claim 2, further comprising one or more β -lactam antibiotics.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound having the structure of Formula II, or a pharmaceutically acceptable salt or prodrug thereof:



Formula II

wherein

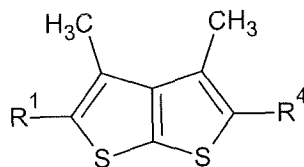
R^1 and R^4 are independently a hydrogen, halo, cyano, $-C(=O)OR^{11}$, C_1-C_{10} alkyl, cycloalkyl, aryl, substituted aryl, heteroaryl group; and

R^{11} is a hydrogen, C_1-C_{10} alkyl, fluorinated alkyl or benzyl group.

5. The pharmaceutical composition of claim 4, further comprising one or more β -lactam antibiotics.

6. A kit comprising

(a) a compound having the structure of Formula II, or a pharmaceutically acceptable salt or prodrug thereof:



Formula II

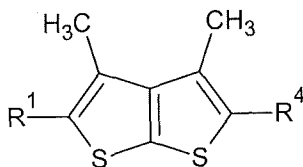
wherein

R^1 and R^4 are independently a hydrogen, halo, cyano, $-C(=O)OR^{11}$, C_1-C_{10} alkyl, cycloalkyl, aryl, substituted aryl, heteroaryl group; and

R^{11} is a hydrogen, C_1-C_{10} alkyl, fluorinated alkyl or benzyl group; and

(b) one or more β -lactam antibiotics.

7. A method for suppressing the growth of a bacterial pathogen comprising contacting a bacterial pathogen with a compound having the structure of Formula II, or a pharmaceutically acceptable salt or prodrug thereof:



Formula II

wherein

R^1 and R^4 are independently a hydrogen, halo, cyano, -C(=O)OR¹¹, C₁-C₁₀ alkyl, cycloalkyl, aryl, substituted aryl, heteroaryl group; and

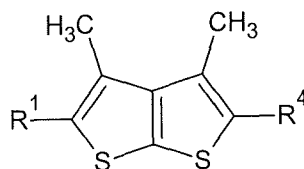
R¹¹ is a hydrogen, C₁-C₁₀ alkyl, fluorinated alkyl or benzyl group,

thereby suppressing the growth of the bacterial pathogen.

8. The method of claim 7, wherein the bacterial pathogen is a drug-resistant bacterial pathogen.

9. The method of claim 7, further comprising contacting the bacterial pathogen with one or more β -lactam antibiotics.

10. A method for ameliorating or treating a bacterial infection comprising administering to a subject in need of treatment an effective amount of a compound having the structure of Formula II, or a pharmaceutically acceptable salt or prodrug thereof:



Formula II

wherein

R^1 and R^4 are independently a hydrogen, halo, cyano, -C(=O)OR¹¹, C₁-C₁₀ alkyl, cycloalkyl, aryl, substituted aryl, heteroaryl group; and

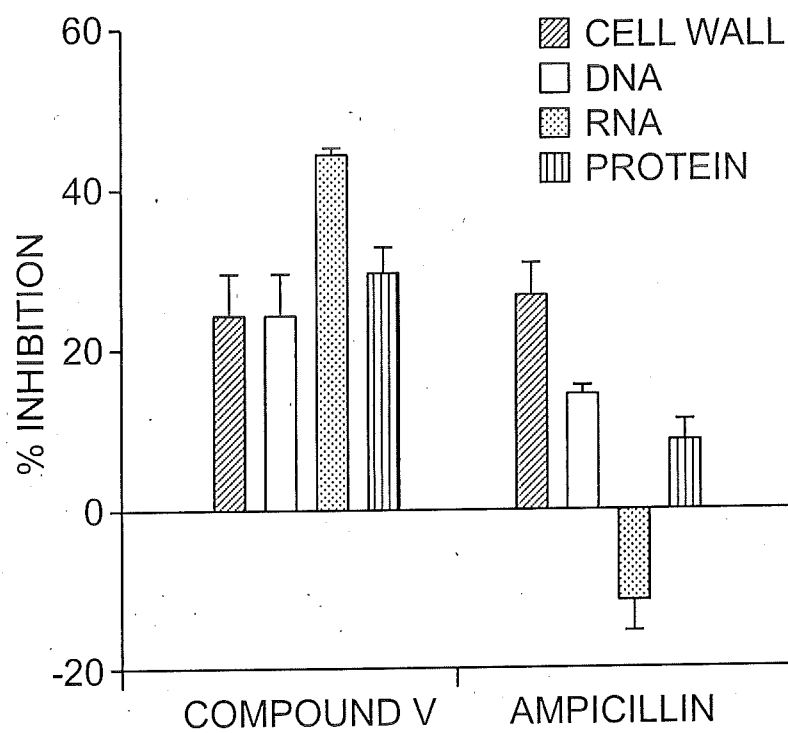
R¹¹ is a hydrogen, C₁-C₁₀ alkyl, fluorinated alkyl or benzyl group,

thereby ameliorating or treating the subject's bacterial infection.

11. The method of claim 10, wherein the bacterial infection is by a drug-resistant bacterial pathogen.

12. The method of claim 10, further comprising administering one or more β -lactam antibiotics.

1/1

*FIG. 1*

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/69242

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 495/04; A61K 31/381; A61P 31/04 (2015.01)

CPC - C07D 495/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): C07D 495/04; A61K 31/381; A61P 31/04 (2015.01)

CPC: C07D 495/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 549/50; 514/443; 514/438

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Scholar, PubWEST, SureChem

thieno[2,3-b]thiophene, antibacterial, anti-bacterial, beta-lactam antibiotic, combination

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PUBCHEM-CID 2778798 Create Date: 19 July 2005 (19.07.2005) pg 3, structure	1
Y	US 5,143,914 A (DININNO et al.) 01 September 1992 (01.09.1992) col 45-46, Table 1, Compound 168; col 51, ln 41-62; col 53, ln 27-36	1-3
Y	KHEDER et al. 'Synthesis and Antimicrobial Studies of Some Novel Bis-[1,3,4]thiadiazole and Bis-thiazole Pendant to Thieno[2,3-b]thiophene Moiety', Int. J. Mol. Sci. 2012, Vol.13, pp. 3661-3670. abstract; pg 3662, Scheme 1, compounds 6a-g; pg 3663, Scheme 2, compound 10; pg 3668, Table 1	1-12
Y	US 2009/0111737 A1 (CHRISTENSEN et al.) 30 April 2009 (30.04.2009) para [0010]-[0011], [0018]-[0022], [0335]-[0338], Table; para [0340], [0345], [0436]-[0439]	4-12



Further documents are listed in the continuation of Box C.



* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

24 January 2015 (24.01.2015)

Date of mailing of the international search report

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